NITROGEN MUSTARDS RELATED TO BISDEHYDRO-DOISYNOLIC ACID

Thesis for the Degree of Ph. D.
MICHIGAN STATE UNIVERSITY
Sharon K. Slack
1963

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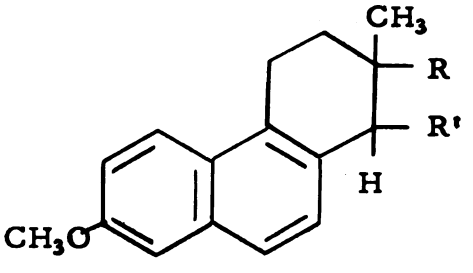
ABSTRACT

NITROGEN MUSTARDS RELATED TO BISDEHYDRO-DOISYNOLIC ACID

by Sharon K. Slack

It has been observed that in several series of closely related nitrogen mustards the trend of oncotoxic activity and chemical reactivity do not correspond (1). These differences may be attributed to the transport characteristics of these compounds. The arrival of a nitrogen mustard molecule at the desired site of action may be effected by the incorporation of a physiological "carrier moiety" (2) into the molecule. An estrogenically active residue, such as bis-dehydrodoisynolic acid, may act as a carrier moiety for a nitrogen mustard molecule. Accordingly, the preparation of certain nitrogen mustards containing a bisdehydrodoisynolic acid-type residue was undertaken.

Both the C_2-carboxy group and the C_1-ethyl group of bisdehydro-doisynolic acid methyl ether (I) were to be replaced by an



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III ($R = -CO_2H$, $R' = -CH_2N(CH_2CH_2Cl)_2 \cdot HCl$)

IV ($R = -CO_2H$, $R' = -N(CH_2CH_2Cl)_2 \cdot HCl$)

N, N-bis(2-chloroethyl)aminomethyl group and the C_1-ethyl group by an N, N-bis(2-chloroethyl)amino group. Thus, the desired compounds were 1-ethyl-2-methyl-2-[N, N-bis(2-chloroethyl)aminomethyl]-7-methoxy-1, 2, 3, 4-tetrahydrophenanthrene hydrochloride (II), 1-[N, N-bis(2-chloroethyl)aminomethyl]-2-carboxy-2-methyl-7-methoxy-1, 2, 3, 4-tetrahydrophenanthrene hydrochloride (III) and 1-[N, N-bis(2-chloroethyl)amino]-2-carboxy-2-methyl-7-methoxy-1, 2, 3, 4-tetrahydrophenanthrene hydrochloride (IV).

In order to explore the sequence of reactions necessary to convert 1-keto-7-methoxy-1, 2, 3, 4-tetrahydrophenanthrene to II, a series of bicyclic model compounds was prepared. 1-Ethyl-2-methyl-2-[N, N-bis(2-chloroethyl)aminomethyl]-1, 2, 3, 4-tetrahydronaphthalene hydrochloride, 1-ethyl-2-methyl-2-[N, N-bis(2-chloroethyl)aminomethyl]-6-methoxy-1, 2, 3, 4-tetrahydronaphthalene hydrochloride, cis-1-ethylidene-2-methyl-2-[N, N-bis(2-chloroethyl)aminomethyl]-1, 2, 3, 4-tetrahydronaphthalene hydrochloride and trans-1-ethylidene-2-methyl-2-[N, N-bis(2-chloroethyl)aminomethyl]-1, 2, 3, 4-tetrahydronaphthalene hydrochloride were the nitrogen mustards resulting from the preparation of these model compounds.

The stereochemistry of 1-ethylidene-2-methyl-2-carboxy-1, 2, 3, 4-tetrahydronaphthalene was investigated. Nuclear magnetic resonance spectra showed the high melting acid to be the trans-isomer and the low melting acid to be the cis-isomer (methyl and phenyl groups were used as reference).

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The reaction sequence developed in the investigation of these model compounds led to the successful preparation of 1-ethyl-2-methyl-2-[N, N-bis(2-hydroxyethyl)aminomethyl]-7-methoxy-1, 2, 3, 4-tetrahydrophenanthrene hydrochloride, but the preparation of the nitrogen mustard from this intermediate proved unsuccessful.

None of the synthetic routes devised for the preparation of III or IV proved to be successful. The preparation of bicyclic model compounds failed in all cases.

The nitrogen mustards prepared in this work were submitted to the Cancer Chemotherapy National Service Center* for screening.

REFERENCES

1) W. C. J. Ross, Ann. N. Y. Acad. Sci., 68, 669 (1958).

2) F. Bergel, Ann. N. Y. Acad. Sci., 68, 1238 (1958).

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*Cancer Chemotherapy National Service Center, National Institutes of Health, Bethesda 14, Maryland.

NITROGEN MUSTARDS RELATED TO BISDEHYDRO-DOISYNOLIC ACID

By

Sharon K. Slack

A THESIS

Submitted to
Michigan State University
in partial fulfillment of the requirements
for the degree of

DOCTOR OF PHILOSOPHY

Department of Chemistry

1963

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ACKNOWLEDGMENTS

The author wishes to express her appreciation to Dr. G. L. Goerner for his willing assistance during this investigation.

Sincere acknowledgment is gratefully extended to my associates, John F. Benner, Paul M. Dupree, Richard L. Titus, and David D. Taft, for their many suggestions and enlightening discussions concerning this problem.

Finally, the author wishes to express her most sincere appreciation to her parents, Mr. and Mrs. Seibert M. Slack, for their unending encouragement and aid extended to her throughout the course of her education.

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HISTORICAL

A. Estrogens

The sexual functions of the female are designed primarily for the process of reproduction. These functions are divided into two major phases: first, the preparation of the feminine body for the process of conception and gestation, and second, the period of gestation itself. Both of these phases are endocrinological, being instituted and controlled by the female sex hormones. Except for a small quantity of female sex hormones secreted by the adrenal gland, these hormones are secreted in the female by the ovaries under the stimulation of proteinoid hormones secreted in the anterior lobe of the pituitary gland.

There are two major types of steroidal female sex hormones--the estrogens and progesterone. The action of progesterone is almost entirely limited to the immediate preparation of the uterus for pregnancy and of the breasts for lactation. The estrogens mainly promote proliferation of specific cells in the body and are responsible for growth of sexual organs and most of the secondary sexual characteristics of the female.

Progesterone (I) is chemically similar to the estrogens and the corticosteroids--such as cortisone (II)--and, in fact, it has some functions in common with the estrogens and with the adrenocortical hormones. Normally, almost all of the progesterone secreted in the body is secreted by the corpus luteum, but during pregnancy progesterone is formed in the placenta, especially after the fourth month of gestation. The major function of progesterone is to promote the

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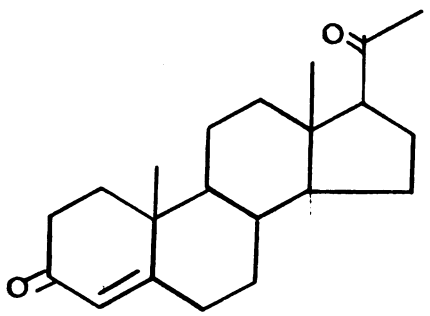

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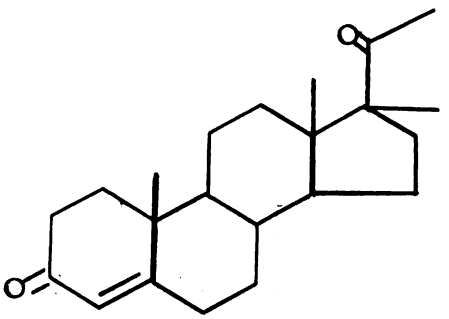

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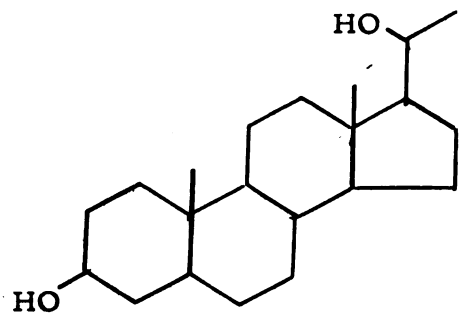

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secretory changes in the uterine endometrium, necessary to prepare the uterus for implantation of the fertilized ovum. Progesterone also inhibits the contractibility of the myometrium which aids in preventing the expulsion of the implanted ovum. Progesterone is normally absorbed into the portal blood and undergoes partial detoxification by the liver. The major end product of progesterone

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detoxification is pregnanediol (III), which no longer exhibits any progesterone effects.

The basic functions of the estrogens are exerted especially on the tissues of the sexual organs and on other tissues related to reproduction. During childhood estrogens are secreted only in small quantities. Following puberty the quantity of estrogens, secreted under the influence of the pituitary gonadotropic hormones, increases some 20-fold causing the female sexual organs to change from those of a child to those of an adult.

During the few years following puberty the size of the uterus increases approximately two times. More important, however, than the increase in size of the uterus are the changes that take place in the endometrium under the influence of estrogens. Estrogens cause marked proliferation of the endometrium with the development of appropriate glands and other characteristics necessary for implantation of the ovum.

Estrogens cause fat deposition in the breasts and also cause the development of an extensive ductile system. The female breast is a secondary sex characteristic rather than a primary sex characteristic. This is because the primordial breasts of both male and female are exactly alike. Under the influence of appropriate hormones the male breast will develop sufficiently to produce milk in the same manner as the female breast.

Estrogens cause increased osteoblastic activity. Subsequent to the onset of puberty the female growth rate becomes rapid for several years. Partially counteracting this increase in growth rate, the estrogens cause the early uniting of the epiphysis with the diaphysis. This results in the growth of the female to become arrested several years earlier than the male. An important by-product of the general

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effects of estrogens on skeletal growth is to broaden the pelvis, changing the pelvis outlet from a narrow, funnel-like outlet to a broad, ovoid outlet. The mechanism by which estrogens cause this change is not clearly understood and may be quite indirect.

Estrogens do not seem to effect the metabolism rate greatly, but they do cause deposition of increased quantities of fat in the subcutaneous tissues. This causes the over-all specific gravity of the female to be considerably less than that of the male. In addition to the general fat deposition in the subcutaneous tissue, the estrogens also cause a marked local deposition of fat producing the characteristic feminine figure.

Estrogens cause the skin to develop a special texture which is quite soft and usually very smooth. This is opposite to the effect of androgens, which causes the skin to become thick and tough. The estrogens also cause the skin of the female to become more vascular than that of the male. This effect is associated with increased resistance to cold and results in greater bleeding of surface cuts than is observed in men.

Estrogens also exert psychological effects which prompt the behavior characteristic of the female.

Research on the hormones secreted by the ovary was stimulated by the development of a biometric determination for estrogenic material by Allen and Doisy in 1923 (1). This convenient test for estrogenic hormones is based upon the ability of such substances to produce an estrus response in castrated or immature rats or mice. A positive reaction is easily recognized by distinct changes in the cell structure of the lining of the vagina. At the height of estrus the lining acquires a characteristic cornified structure easily distinguished from that typical of the resting period, or of the permanent condition of castrated or immature animals. Microscopic examination of

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vaginal smears gives reliable information of the estrus condition of the living animals. The Allen-Doisy assay gives reproducible results and, since the sexual cycle of the mouse has a duration of only 4-6 days, the test can be performed rapidly.

The estrogenic activity of a substance is expressed in terms of rat units (r.u.) or mouse units (m.u.). A mouse unit is the quantity (usually expressed in terms of γ, 10^{-6} g.) of estrogenic material that just suffices to produce estrus in a castrated animal. The international standard of activity has been set as that of 0.1 γ of pure estrone. The ratio of the mouse unit to the rat unit generally varies between 1:5 to 1:7.

Since Allen and Doisy's original procedure there have been many other bioassay methods devised for the quantitative estimation of estrogenic material. Criteria other than vaginal cornification have been used in many of these later methods. Several of the more common critera are: vaginal opening in immature rats (2, 3, 4), disappearance of vaginal leucocytes in ovariectomized female rats (5), increase in uterine weight in female rats (6, 7, 8) and in female rabbits (9), inhibition of comb growth in male chicks when the material is injected simultaneously with 0.4 γ of testosterone (10), nipple stimulation in the male guinea pig (11), reversal of male feathering in castrated hens (12), lengthening of ovipositor in female bitterlings (13), and vaginal mucification in female monkeys (14).

Aschheim and Zondek (15, 16, 17), in 1927, discovered the presence of large amounts of estrogenic material in the urine of pregnant women. This discovery was of enormous value since a simple extraction of pregnancy urine afforded solutions of estrogen of higher biological potency and with a lower content of interfering contaminants than had been obtained by the elaborate processing of tissue extracts.

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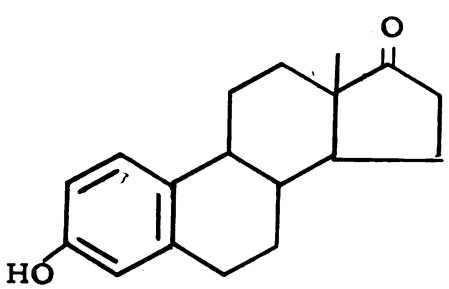
Zondek later observed that estrogenic material is present in large amounts in the genital glands and urine of certain male mammals. The richest source found was the testes of the horse. In fact, the concentration of estrogen in stallion urine is considerably higher than in the urine of the pregnant mare (170,000 m.u./l. vs. 100,000 m.u./l.). This paradoxical excretion of large quantities of estrogen by male animals has been observed only in the case of the equines (horse, zebra, ass, kiang).

Crystalline material, fully identified as estrone, has been isolated from the following sources other than those already mentioned: human male urine (18), human placenta (19), beef adrenal glands (20), bile of pregnant cows (21) and urine of pregnant goats (22). Some plant materials also contain appreciable quantities of estrogens.

The discovery in 1931 by Kober (23) of a sensitive and highly specific color reaction for the natural estrogens was an event of considerable importance since it led to the development of a number of useful methods for the colorimetric determination of estrogens in human and equine pregnancy urine.

Toward the end of 1929 and early in 1930 the substance now known as estrone (IV) had been isolated from human pregnancy urine in a nearly pure crystalline state simultaneously by three groups:



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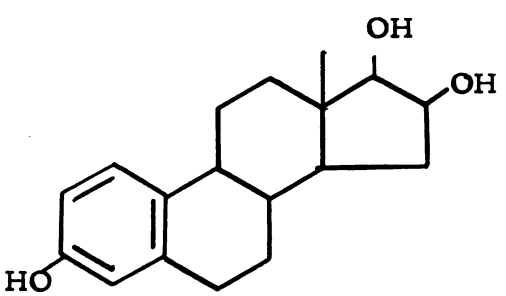

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Doisy and co-workers (24), Butenandt (25), and Dingemanse and his colleagues (26). Several names were given to this first isolated estrogen by the various groups involved in this early work. It was named theelin by Doisy's group, progynon and follicular hormone by Butenandt and his colleagues, oestrin by Marrian's group, menformone by Laqueur and his co-workers and folliculin by Girard and his group. The name oestrin, now modernized to estrone, was accepted at a League of Nations conference in London in 1935.

A few months after the first report of the isolation of estrone the isolation of a second crystalline estrogen was reported by Marrian (27) and by Doisy and co-workers (28). This estrogen was also isolated from human pregnancy urine. It is more water soluble and at first (29) was considered to be a hydrate of estrone. This substance was later shown to be estriol (V) (30, 31).

Although only a small amount of any crystalline estrogen was available, rapid progress was made in several different laboratories toward the elucidation of their structures. This progress was so rapid that, shortly after the sterol-bile acid formula had been advanced by Rosenheim and King in 1932 (32, 33), the possibility of the estrogens also being cyclopentanophenanthrene derivatives was advanced, in the same year, by both Marrian and Haslewood (34) and by Butenandt (35).

The fact that the estrogens were, indeed, phenanthrene derivatives was conclusively proven by Butenandt, Weidlich, and Thompson (36) in 1933.

Tribute must be paid to an important discovery which greatly aided the original work on the elucidation of the structure of the estrogens. Girard and co-workers (37, 38, 39) had devised a simple method for obtaining pure ketonic estrogens from mare's urine in high yield by means of new ketone reagents which they had discovered. The full description of these reagents was not published until 1936 (40), but as

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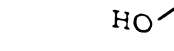

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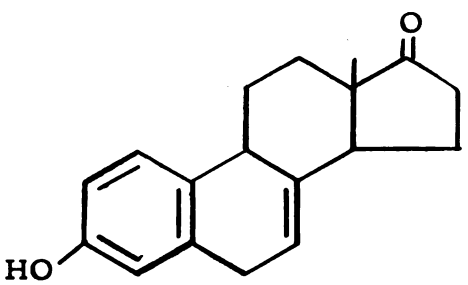
early as 1932 Girard had isolated large quantities of pure estrone and two new ketonic estrogens, equilin (VI) and equilenin (VII). These substances are now known to be the mono- and di-dehydro derivatives of estrone. Girard found that estrone from mare's urine contained traces of equilenin, but none has been found in human urine. They possess a much lower level of estrogenic activity than the benzenoid estrogens.

Girard supplied Cook and co-workers (41, 42, 43) with samples of pure estrogens, which were used by these workers to complete the proof of structure of the natural estrogens, during the years of 1934 and 1935.

Of the estrogenic substances isolated from natural sources before 1935, estrone was found to be the most potent in the Allen-Doisy test. Estrone was soon found to be surpassed in activity by



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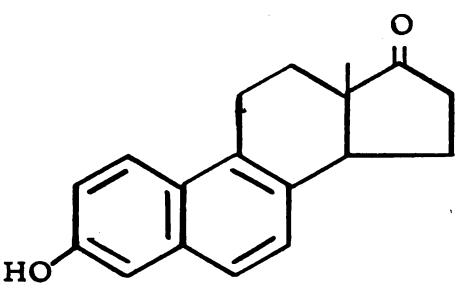

VII

products derivable from it by chemical transformations. The most potent and important is a dihydro derivative first prepared by Schwenk and Hildebrandt (44). This substance is now known to be estradiol (VIII).

The early realization that estradiol is more active than estrone led workers in the field to suspect that even the most potent of the estrogenic materials excreted in the urine may not be the primary estrogens responsible for the physiological changes in the body.

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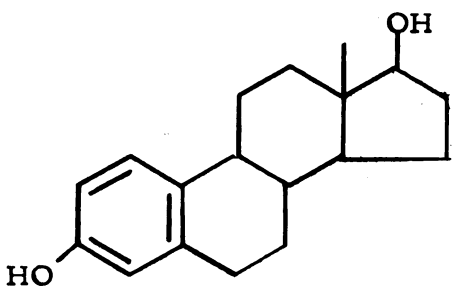
The investigations of the constituents of ovarian tissue presented many difficulties but in 1935 Doisy (45, 46) reported the isolation of crystalline estradiol. Some of the other sources from which estradiol



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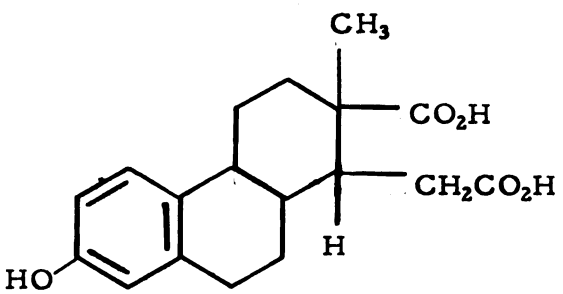

IX

has been isolated are: late human pregnancy urine (47), human placenta (48), horse testes (49), stallion urine (50), and mare pregnancy urine (51). The ovary produces mainly estradiol and progesterone. These are metabolized to a host of products and are largely excreted in the urine as metabolites with reduced, or in some cases with no, biological activity. Thus estrone and estriol are estrogenically active metabolites of estradiol.

In 1932 Marrian and Haslewood (34) obtained a dicarboxylic acid by the fusion of estriol with potassium hydroxide. This same dibasic acid was also obtained by Doisy and co-workers (52) by a similar procedure. This acid has since been shown to have the structure shown in IX and has been named "marrianolic acid" by Miescher (53).

In 1933 Doisy and co-workers (54) subjected estrone to fusion with potassium hydroxide and obtained a monocarboxylic acid. At the time this acid was first reported it was claimed to possess an estrogenic activity several times greater than that of estrone, but this claim was later withdrawn (55).

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In 1937 and 1939, Hohlweg and Inhoffen (56, 57) described the production of the same acid as had been obtained from estrone, or analogous monocarboxylic acids, by the fusion of estradiol, dihydroequilin, equilin or equilenin with potassium hydroxide. These acids were claimed to be hydrophenanthryl-1-acetic acids and the claim was made that they possessed a threshold activity of 1-6 γ (rats, oral) whereas the corresponding value for estrone is 20-30 γ.

These "estrogenolic acids" were systematically investigated by Miescher and his colleagues (58, 59). He named the monobasic acid isolated by Doisy "doisynolic acid." The structure of doisynolic acid (X) and its interrelationship with marrianolic acid and the naturally occurring estrogens is shown in Figure I (60, 61, 62, 63).

The conversion of estrone (IV) to marrianolic acid (IX) by the hypoiodite oxidation of the benzyl ether relates the stereochemistry of these two compounds. It is known that neither the formation of the benzyl ether, the hypoiodite oxidation nor the hydrogenolysis of the benzyl group effects the stereochemistry of the A, B or C rings. The conversion of marrianolic acid (IX) to doisynolic acid (X) by a six step procedure correlates the stereochemistry of the dicarboxylic acid with that of the monocarboxylic acid.

Marrianolic acid is completely inactive as an estrogen. Pure doisynolic acid and its methyl ether are about as active as estrone by subcutaneous injection, but distinctly more active orally (64). This substantiates the original finding of Doisy (54) which had been incorrectly retracted (55).

The alkali fusion of the weakly estrogenic equilenin (VII) or of dihydroequilenin produces a mixture of diastereoisomeric bisdehydrodoisynolic acids (XI and XII). Of the two isomeric acids formed in approximately equal amounts, the levorotatory isomer (XII) is extremely active but the dextrorotatory isomer (XI) is almost devoid of

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Figure 1.

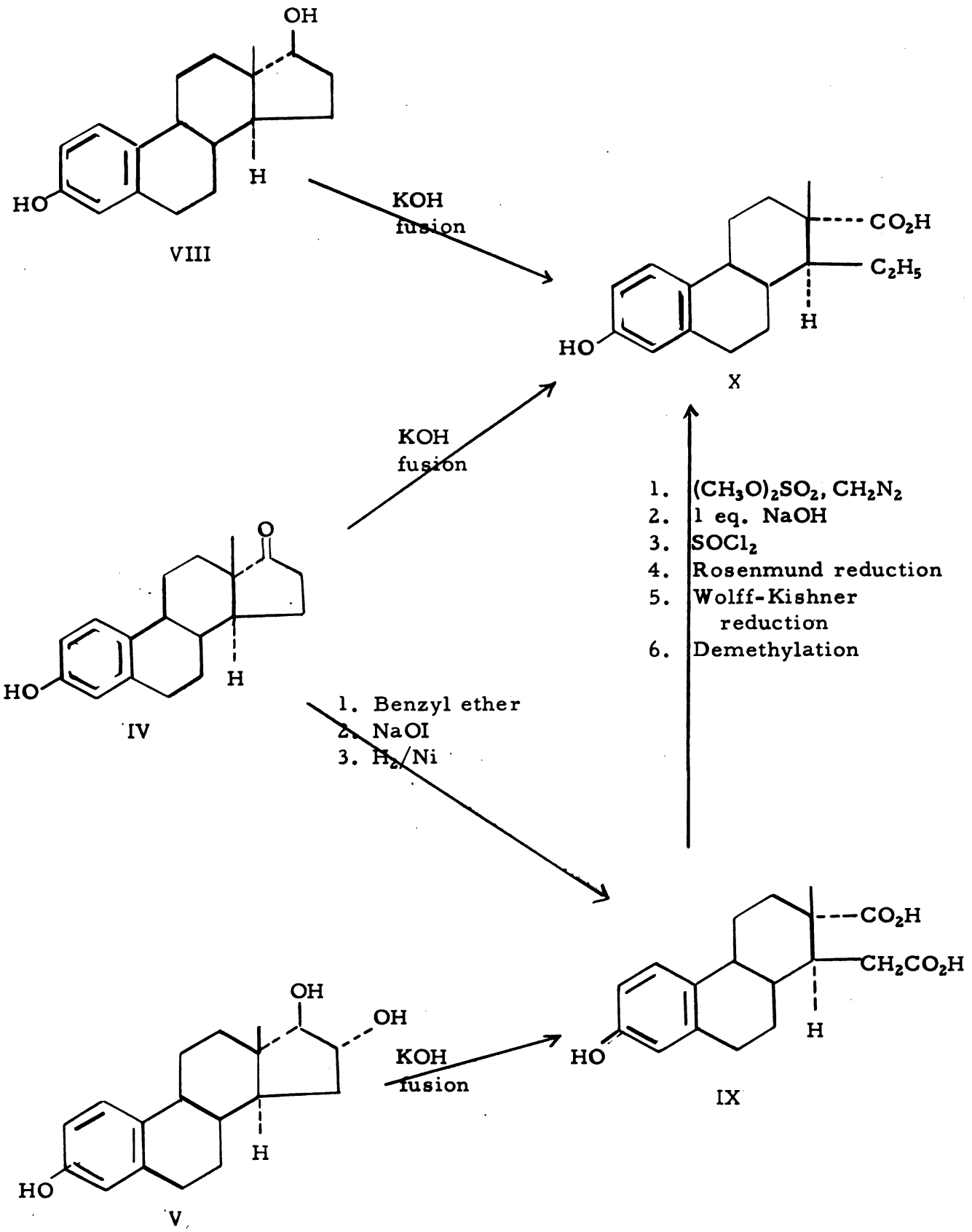

Figure I. Stereochemical relationships between the natural estrogens and the estrogenolic acids.

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estrogenic activity. Miescher and co-workers were able to demonstrate that the estrogenically active bisdehydrodoisynolic acid was the stereoisomer that had formed with an inversion at the site of the ethyl group. The equilibration which takes place during the alkali fusion of equilenin and the absence of inversion in the case of the fusion of estrone is easily rationalized on the basis of the aromatic B ring in equilenin. The hydrogen at C_{14} in equilenin (C_1 in bisdehydrodoisynolic acid) is attached to a carbon atom α to an aromatic system and is therefore easily extractable by the molten alkali causing equilibration about this carbon atom.

As shown in the sequence in Figure II the catalytic dehydrogenation of estrone methyl ether (methyl ether of IV) to d-14-isoequilenin methyl ether (XIII) is known to proceed with inversion at C_1 (62). The hypoiodite oxidation of d-14-isoequilenin methyl ether followed by methylation gives the dimethyl ester of l-cis-bisdehydromarrianolic acid methyl ether (XIV), which can be converted by the series of reactions indicated in Figure II to l-cis-bisdehydrodoisynolic acid (XII). The hypoiodite oxidation and the subsequent reactions are all known to proceed without causing an isomerization at C_1. Thus, the active bisdehydrodoisynolic acid (XII) corresponds to the C_{14}-epimer of estrone.

Horeau and Jacques (65) achieved further structural simplification in the allenolic acids in which the C-ring of bisdehydrodoisynolic acid is replaced by an aliphatic chain. The allenolic acids have the general structure shown in XV. α, α-Dimethyl-β-ethylallenolic acid (XVI), also known as horeau acid, is a very potent estrogen belonging to this series. It is of interest to note that the configuration about the asymmetric center in horeau acid is the opposite to that at C_1 in the active isomer of bisdehydrodoisynolic acid (66, 67, 68). This means

XI

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XII

Figure II

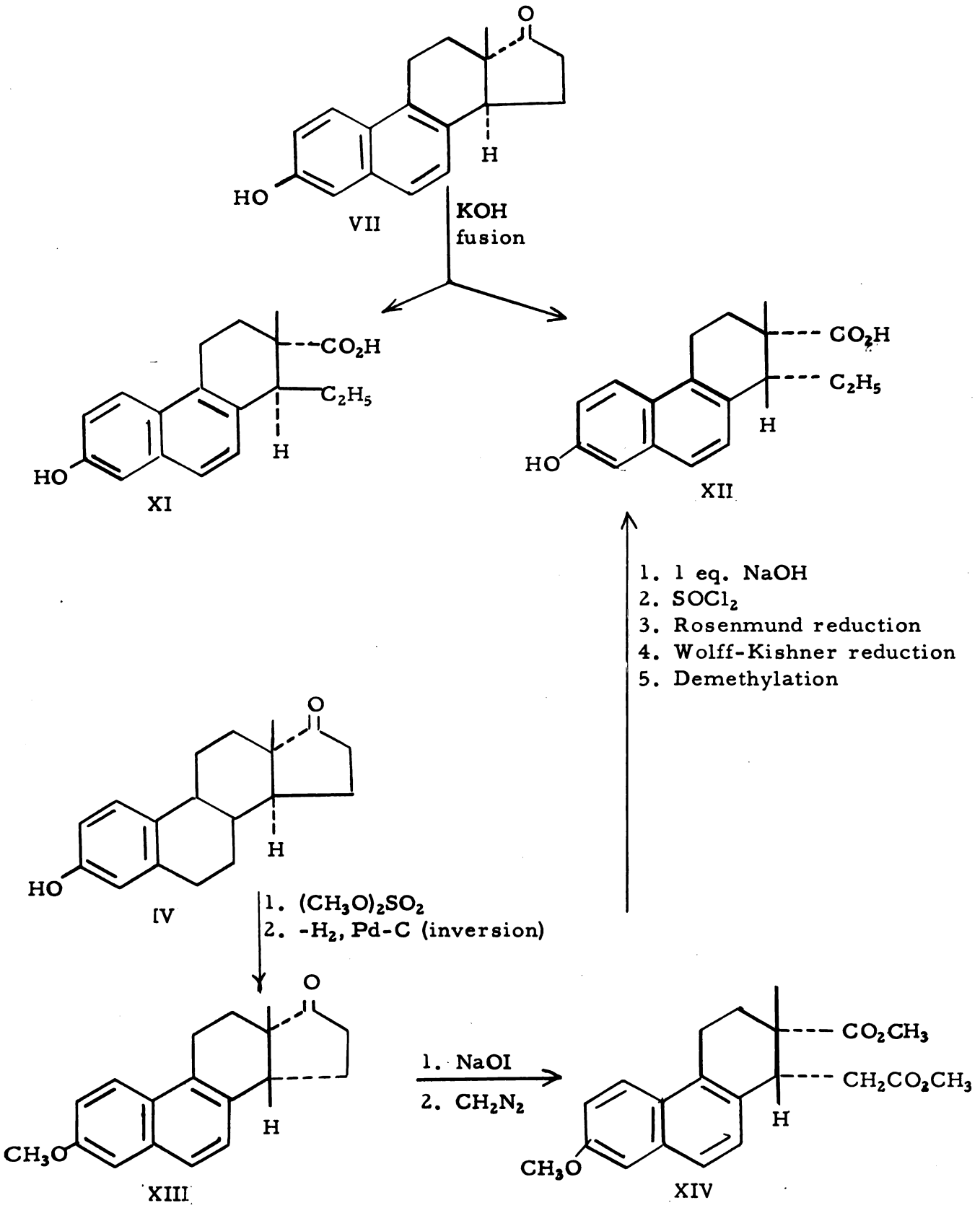
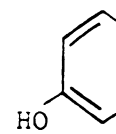


Figure II. Stereochemical relationships between equilenin and estrone and 1-cis-bisdehydrodoisynolic acid.



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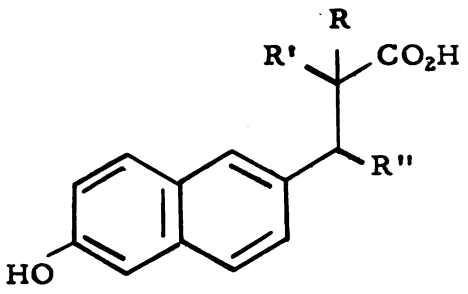

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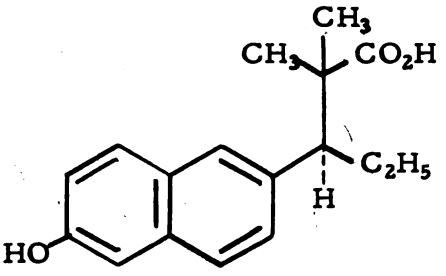


XVI

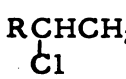
that the estrogenically active l-α, α-dimethyl-β-ethylallenolic acid has the same configuration about the asymmetric carbon as equilenin has about C_{14}.

B. Biological Alkylating Agents

Organic sulfides and amines containing the 2-chloroethyl radical have been the subject of extensive study due to their usefulness as war gases and as alkylating agents for the treatment of certain types of cancer.

Mustard gas, bis(2-chloroethyl)sulfide, was first prepared by Meyer (69) in 1886 by the action of phosphorous trichloride on bis(2-hydroxyethyl)sulfide. The best known method for the preparation of mustard gas is that of Levinstein in which ethylene is combined with sulfur chloride. It has been shown (70, 71) that 2-chloroethylsulfenyl chloride, $ClCH_2CH_2SCl$, is formed as an intermediate in this reaction. During the interim between the two World Wars little research was done on the sulfur mustards. Then, during World War II, the study of the sulfur vesicants was resumed. In the United States and in Great Britain several series of structurally modified sulfur mustards were

prepared by various groups. Some examples are the alkyl 2-chloroethylsulfides (72, 73); the sulfur mustards of the type represented by I, where R is alkyl (74, 75); the type shown in II (76); those containing a 3-chloroallyl group (77); and those represented by III (78). All of these compounds are extremely toxic and therefore are of questionable utility as therapeutic agents.



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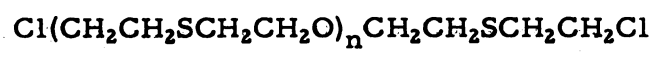


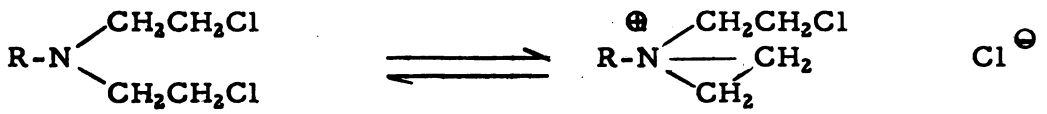
II

III

Research on the "nitrogen mustards" was initiated in 1935 when Ward (79) synthesized several 2-chloroethylamines and discovered their vesicant properties. It was noted that tris(2-chloroethyl)amine and its hydrochloride produced deep blisters which required months to heal and left a dark discoloration. These are the identical effects which result from contact with the sulfur mustards. Much of the wartime research on the nitrogen mustards still remains unpublished. A review by Gilman and Philips (80) summarized some of this research pertaining to the biological and pharmacological properties of methyl bis(2-chlorethyl)-amine. This compound has since found use in the treatment of Hodgkin's disease and certain lymphosarcomas in man. Subsequent to this first report hundreds of compounds containing the bis(2-chloroethyl)amine group have been synthesized and screened as oncotoxic agents (81).

The unique pharmacological properties of the bis(2-chloroethyl)-amines can be attributed to the high chemical reactivity of the 2-chloroethylamino group. Aliphatic nitrogen mustards (IV, R is aliphatic) react, under physiological conditions, through the intermediate ethylene immonium ion (V). This cyclic ion is a true intermediate, having been

isolated and characterized as 1-methyl-1-(2-chloroethyl)ethylenimmonium picrylsulfonate (VI) by Golumbic, Fruton and Bergman (82). The fact that the cyclic immonium ion intermediate is stable and is only weakly



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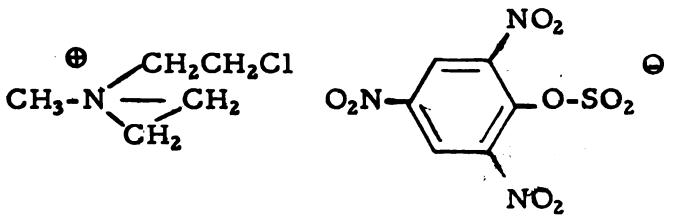
electrophilic results in a pronounced selectivity toward competitive substrates. It is due to this weak electrophilic character that the nitrogen mustards display a much lower general toxicity than the sulfur



VI

mustards. The sulfonium ion intermediate of the sulfur mustards, being much less stable than the immonium ion of the nitrogen mustards, is highly reactive and a totally indiscriminate alkylating agent. The pharmacological action of the sulfur mustard was aptly described by Bacq (83): "des chines affamés se jetant sur n'importe quelle nourriture."

Variation of the third substituent on the nitrogen mustards alters both the chemical and biological reactivity. Ross (84) has shown that a certain degree of chemical reactivity is necessary for biological activity. Electron donating groups enhance both the chemical and biological reactivity while electron withdrawing groups decrease the

reactivity. This trend in the chemical reactivity depends on the base strength of the amine or more specifically on the availability of the electron pair of the nitrogen to participate in the formation of the cyclic immonium ion. Many cases have been noted (85) where the degree of biological activity does not correspond to the chemical reactivity. This discrepancy can be attributed to the transport characteristics of these compounds.

The fact that certain nitrogen mustards do vary in their biological properties independently of the chemical reactivity has led to the search for agents which show some specificity of action. In these investigations it was hoped that by the interaction of a particular "carrier moiety" the nitrogen mustard would be concentrated at the site of action and thus minimize its general toxic side effects. The success of many chemotherapeutic agents can be attributed to the incorporation of a specific carrier moiety into the molecule. Ing (86) distinguished between the pharmocodynamically active portion and the carrier group in several series of physiologically active compounds. Bergel (87) first introduced the concept that biological alkylating agents can be considered as being composed of an alkylating group and a specific carrier moiety.

Several groups of investigators have incorporated a steroid, or steroid-like, group as the carrier moiety in nitrogen mustards. These include 3-β-[bis(2-chloroethyl)amino]-5-cholestene (88), 3-β-[bis-(2-chloroethyl)amino]-5,7,22-ergostatriene (88), bis(2-chloroethyl)-carbamic acid, cholesteryl ester (89), 3-β-[bis(2-chloroethyl)amino]-5,22-stigmastadiene (88), N,N-bis(2-chloroethyl)sulfanilic acid, cholesteryl ester (89,90), 3-β-{p-[bis(2-chloroethyl)amino]-phenyldithio}-5-cholestene (89,90), p-[bis(2-chloroethyl)amino]-carbanilic acid, cholesteryl ester (89,90), N,N-bis(2-chloroethyl)-5-cholesten-3ʃ-amine (91), 3-β-[bis(2-chloroethyl)aminomethyl]-5-cholestene (92),

3β- and 3α-(2-chloroethylamino)cholestane (93), 20ʃ-[bis(2-chloroethyl)amino]-3β-methoxy-5-pregnene (94), 3ʃ-[bis(2-chloroethyl)-amino]-4-androstene-17β-ol (94), and 2-[bis(2-chloroethyl)amino-methylene]-5α-androstan-17β-ol-2-one-17-acetate (95). It is also possible to include the nitrogen mustards incorporating an estrogenic carrier moiety (96) in this general series. Although these compounds do not contain a steroid residue, they do have the structurally related hexesterol and stilbestrol groups as carrier moieties. The members of this series which have been prepared (96) are: N,N-bis(2-chloroethyl)-[erythro-2, 3-di(p-hydroxyphenyl)pentyl]amine and the corresponding dimethyl ether and N, N-bis(2-chloroethyl)-3, 4-di(p-methoxyphenyl-3-hexenylamine.

The present work is a continuation of this series of nitrogen mustards. In place of the hexestrol- and stilbestrol-type carrier moieties an attempt was made to incorporate a bisdehydrodoisynolic acid-type of group into the molecule. The nitrogen mustard hydrochlorides prepared in this work were submitted to the Cancer Chemotherapy National Service Center* for screening.

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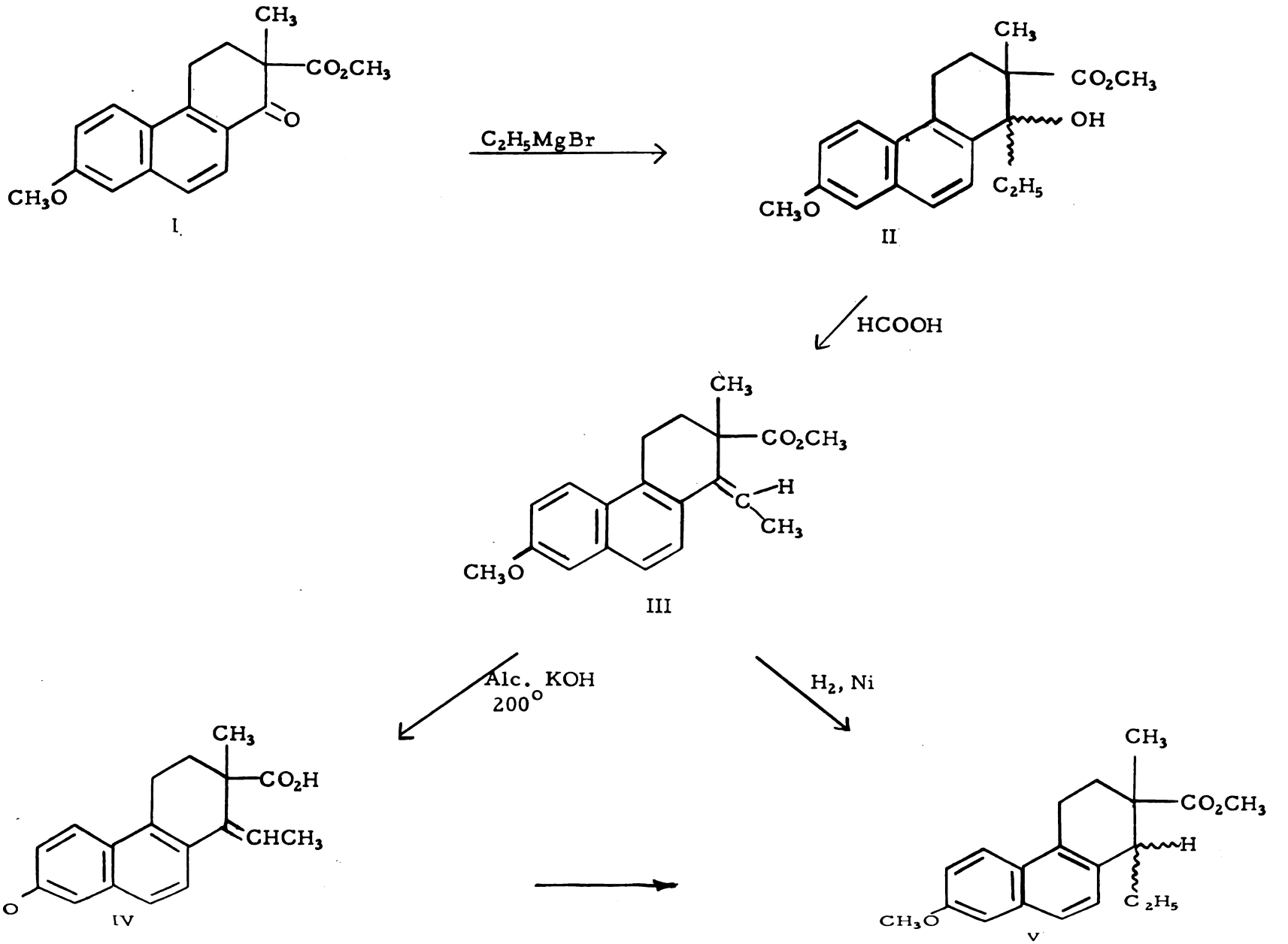
*Cancer Chemotherapy National Service Center, National Institute of Health, Bethesda 14, Maryland.

INTRODUCTION

A. Bisdehydrodoisynolic Acid

Several synthetic routes have been devised for the synthesis of bisdehydrodoisynolic acids. Miescher and co-workers (97) utilized an intermediate (I) in Bachmann's equilenin synthesis as a starting point for the preparation of dl-trans- and dl-cis-bisdehydrodoisynolic acid. As shown in Figure III, the reaction of ethylmagnesium bromide with 1-keto-2-methyl-2-carbomethoxy-7-methoxy-1, 2, 3, 4-tetrahydrophenanthrene (I) gave a mixture of the isomeric cis- and trans-1-ethyl-1-hydroxy-2-methyl-2-carbomethoxy-7-methoxy-1, 2, 3, 4-tetrahydrophenanthrenes (II). Dehydration of either of the carbinols (II) with formic acid afforded a mixture of cis- and trans-1-ethylidene-2-methyl-2-carbomethoxy-7-methoxy-1, 2, 3, 4-tetrahydrophenanthrenes (III). The simultaneous saponification and demethylation of this mixture with alcoholic potassium hydroxide at 200° gave a single isomer of 1-ethylidene-2-methyl-2-carboxy-7-hydroxy-1, 2, 3, 4-tetrahydrophenanthrene (IV). The stereochemistry of this acid was not investigated by Miescher during the course of his work. Hydrogenation of this unsaturated acid (IV) over Rupe nickel gave dl-cis-bisdehydrodoisynolic acid (VIa and VIb). This racemate was resolved (98) into a physiologically inactive d-acid (VIb) and an estrogenically active l-acid (VIa), identical to that obtained by the alkali fusion of equilenin.

When the mixture of unsaturated esters (III) was hydrogenated over Rupe nickel a mixture of diastereomeric saturated esters (V) was obtained. Hydrolysis and demethylation with pyridine hydrochloride gave a mixture of both the dl-cis-bisdehydrodoisynolic acid (VI) and the dl-trans-bisdehydrodoisynolic acid (VIIa and VIIb).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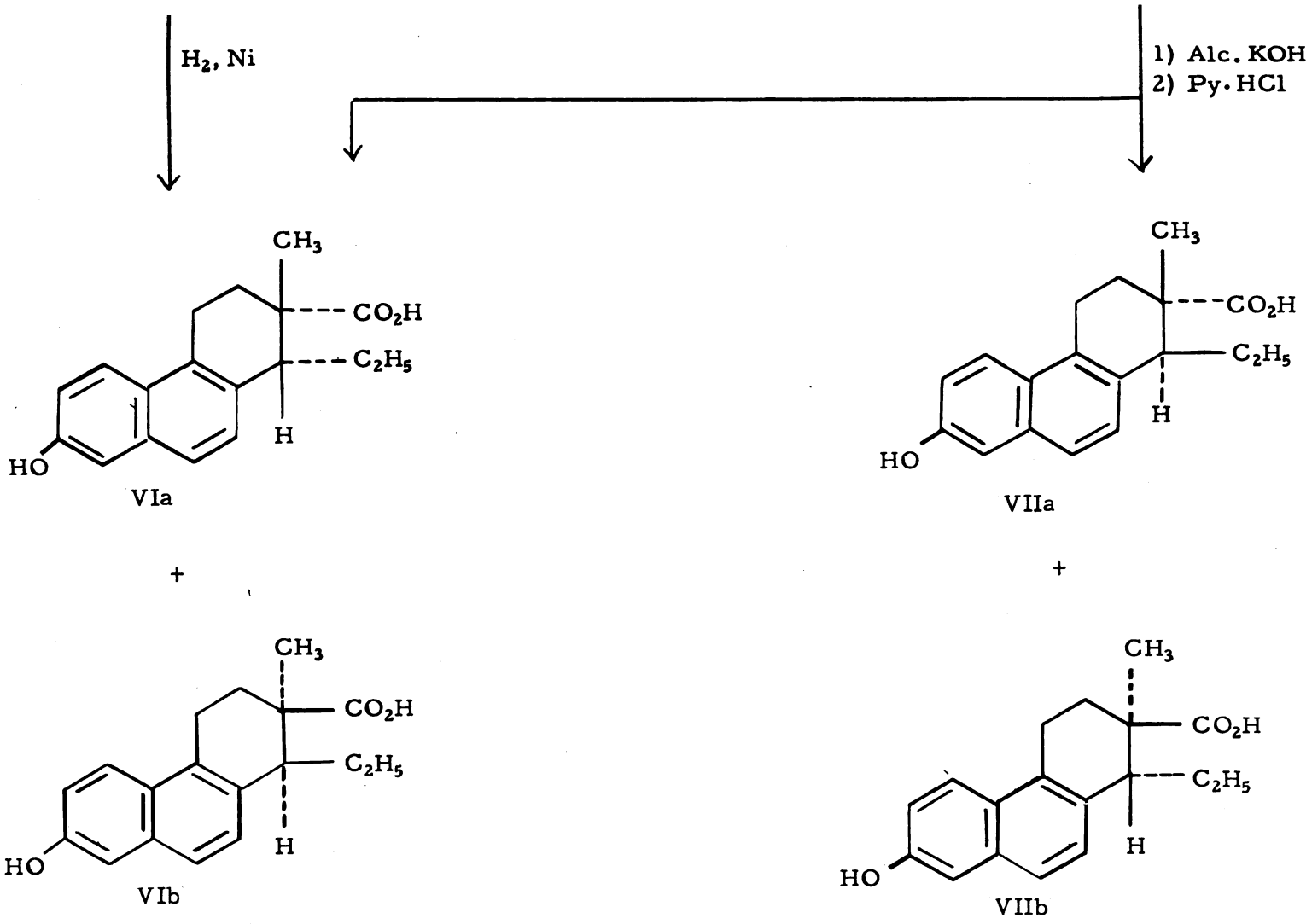
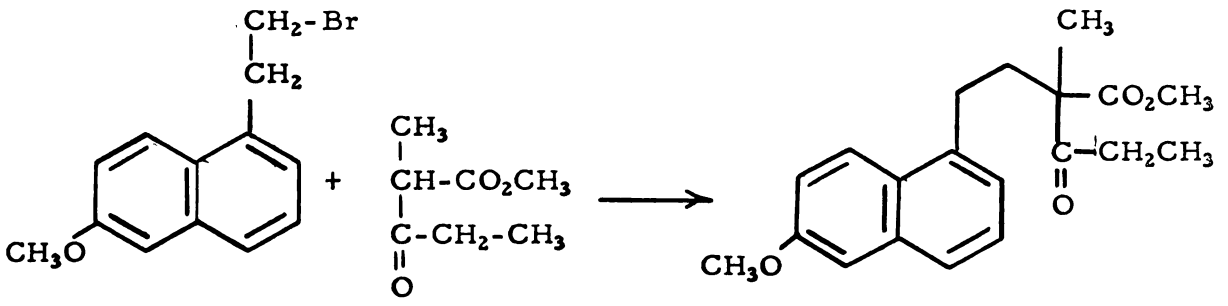


Figure III. Miescher's synthesis of bisdehydrodoisynolic acid.



VIII IX

A second synthesis of bisdehydrodoisynolic acid was developed by Anner and Miescher (99). This involved a more convenient route to the unsaturated ester (III). Alkylation of methyl α-methyl-β-keto-valerate with 1-(2-bromoethyl)-6-methoxynaphthalene (VIII) gave the ketoester (IX). Ring closure with sulfuric acid afforded the same mixture of isomeric hydroxy esters (II) as obtained by the previously described procedure (Figure III).

Johnson and associates (100, 101) developed a third synthesis of dl-cis-bisdehydrodoisynolic acid (Figure IV). 2-Propionyl-6-methoxynaphthalene was condensed with dimethyl succinate via a Stobbe condensation and this product was hydrogenated to the half ester (XI). After the formation of the acid chloride, the ring was closed with stannic chloride and the carbonyl group was reduced by hydrogenation over palladium in the presence of a trace of perchloric acid to give the tricyclic ester (XII). This ester was then methylated at C_2 with triphenylmethyl sodium and methyl iodide. The resulting 1-ethyl-2-methyl-2-carbomethoxy-7-methoxy-1, 2, 3, 4-tetrahydrophenanthrene was hydrolyzed and demethylated to yield dl-cis-bisdehydrodoisynolic acid (VI).

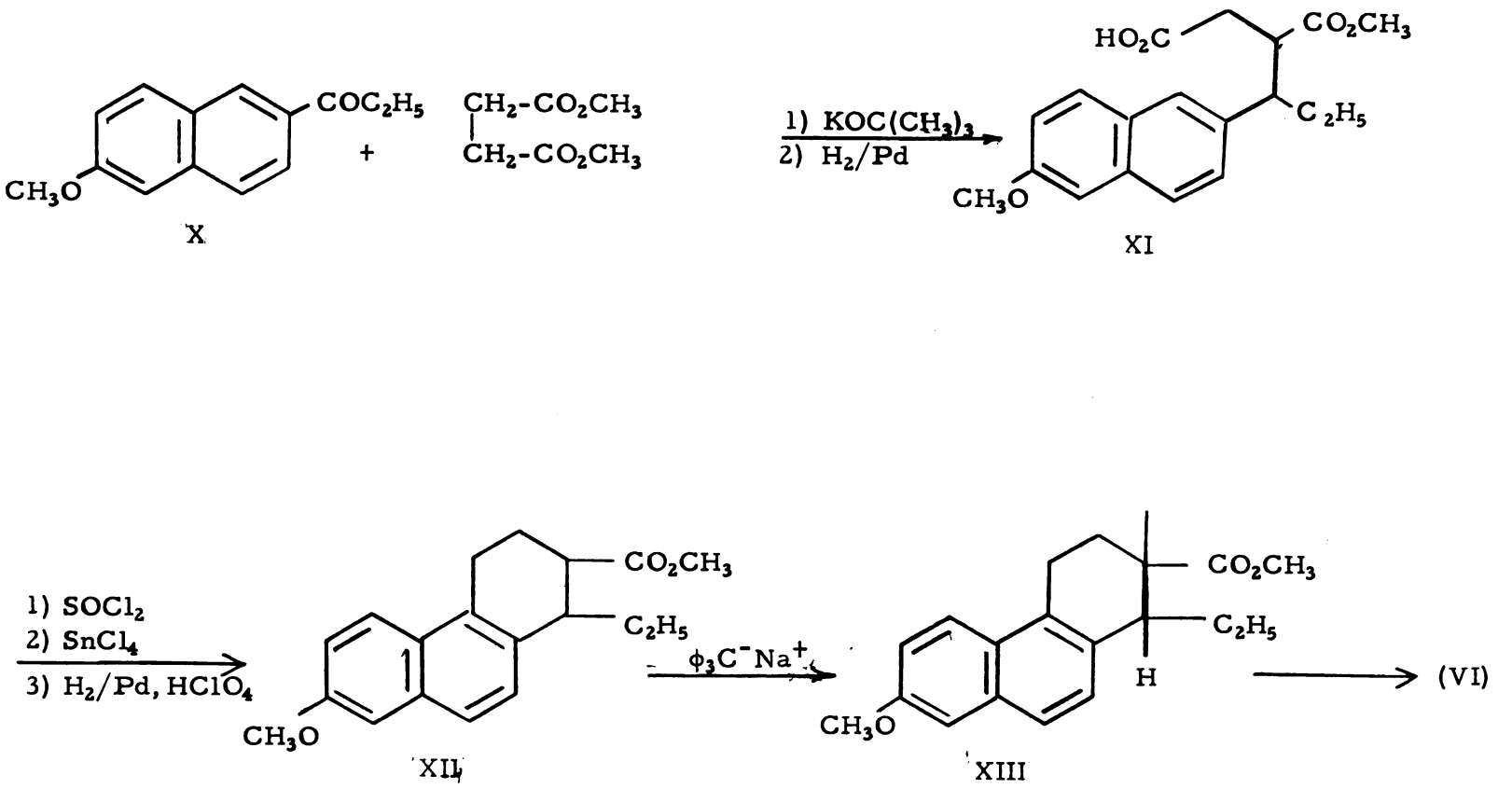


Figure IV. Johnson's synthesis of bisdehydrodoisynolic acid.

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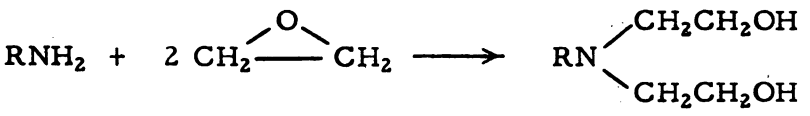
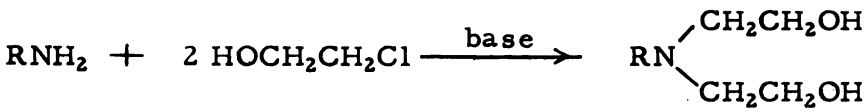
B. Nitrogen Mustards

Almost without exception the nitrogen mustards are prepared from the corresponding N-substituted diethanolamines or their hydrochlorides. Numerous reagents have been successfully employed for this transformation. The use of any particular one depends largely on the type of N-substituent carried by the diethanolamine. Thionyl chloride in refluxing benzene (102, 103, 104, 105) or in chloroform (106, 107) and phosphorous trichloride in chloroform saturated with hydrogen chloride (108) are several of the many reagents which have been successfully employed to replace the β-hydroxyl group with a chlorine atom. Ross (109) considered phosphorous oxychloride to be the most satisfactory reagent for this purpose. Several cases have been reported where this reaction has failed completely (110) or has proceeded in very low yield using the standard reaction conditions. Typical of the latter is the preparation of 5-bis(2-chloroethyl)aminouracil. Lyttle and Petering (111, 112) found that the preparation of the nitrogen mustard from 5-bis(2-hydroxyethyl)aminouracil gave satisfactory yields only when the ethylene glycol dimethyl ether solvent was pretreated with a mixture of ethanol, water and thionyl chloride. The addition of a trace of dimethylformamide has been reported (113, 114) to catalyze this reaction in certain cases.

Several general methods are available for the preparation of the requisite N-substituted diethanolamines. A primary amine can be added to two moles of ethylene oxide. Generally this reaction proceeds in good yield and is limited only by the availability of the primary amine.

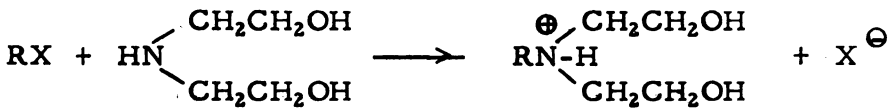


In some cases this reaction has apparently failed because of steric reasons (115) and it is often accompanied by the formation of ethylene oxide polymer (115, 116). Similar to the addition of a primary amine to ethylene oxide is the dialkylation of the amine with two moles of ethylene chlorohydrin in the presence of a base such as calcium carbonate. The formation of ethylene oxide polymers is avoided by



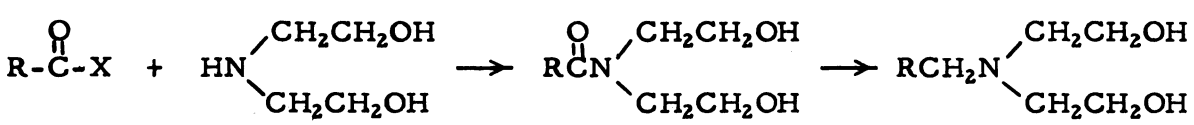
this method, but monoalkylation often limits the utility of this reaction (109).

Diethanolamine can be alkylated by a halide or tosylate to give an N-substituted diethanolamine. This method has been used mainly



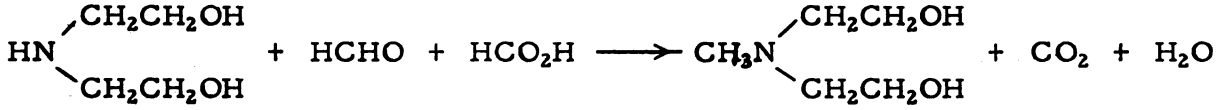
for halides with sterically unhindered R groups and for unusually reactive halides. Many unsuccessful attempts to use this procedure have been reported in the literature (117, 118, 119). The fact that the alkylation of diethanolamine is subject to steric hinderance generally limits the applicability of this synthesis.

Acylation of diethanolamine with an ester or acid halide gives an N, N-bis(2-hydroxyethyl)amide which can be reduced to the corresponding substituted N-methyl diethanolamine (92, 94, 96). There are two obvious limitations to this method. Since the carbonyl group is



reduced to a methylene group the final nitrogen mustard must be an N, N-bis(2-chloroethyl)aminomethyl derivative. Also, the R group cannot contain any functional groups which will be reduced by the lithium aluminum hydride.

According to Hanby and Rydon (104) it is preferable to synthesize methyl bis(2-hydroxyethyl)amine by the method of Clarke, Gillepsie and Weisshaus (120). In this method diethanolamine is treated with formaldehyde and formic acid to give the desired N-methyldiethanolamine.



This reaction has been studied by Forsee and Pollard (121) who have alkylated a large number of secondary amines with aldehydes. However, formaldehyde is the only aldehyde which has been investigated for the alkylation of diethanolamine.

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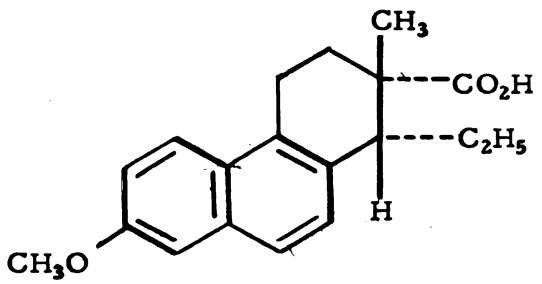
DISCUSSION [1]

In order to continue the investigation (96) of nitrogen mustards with an estrogenic carrier moiety it was decided to prepare nitrogen mustards containing a bisdehydrodoisynolic acid-type residue. Both the C_2-carboxyl group and the C_1-ethyl group of bisdehydrodoisynolic acid methyl ether (I) were to be replaced by a N, N-bis(2-chloroethyl)aminomethyl group and the C_1-ethyl group by a N, N-bis-(2-chloroethyl)amino group.



I

Thus, the desired compounds are 1-ethyl-2-methyl-2-[N, N-bis(2-chloroethyl)aminomethyl]-7-methoxy-1, 2, 3, 4-tetrahydrophenanthrene hydrochloride (II), 1-[N, N-bis(2-chloroethyl)aminomethyl]-2-carboxy-2-methyl-7-methoxy-1, 2, 3, 4-tetrahydrophenanthrene

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[1]Throughout this discussion compounds will be numbered in consecutive order with Roman numerals when no specific reference to a stereoisomeric modification is made, or when other stereoisomeric forms are designated by separate Roman numerals. The designation "I_c" refers to the cis-form of compound I and "I_t" to the corresponding trans-modification. The lower case Roman numerals refer to previously mentioned compounds the stereochemistry of which was not designated in the earlier discussion.

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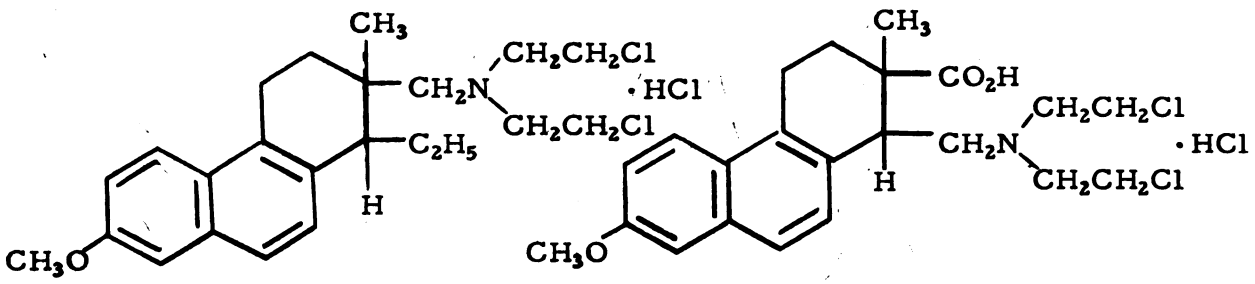
hydrochloride (III) and 1-[N, N-bis(2-chloroethyl)amino]-2-carboxy-2-methyl-7-methoxy-1, 2, 3, 4-tetrahydrophenanthrene hydrochloride (IV).



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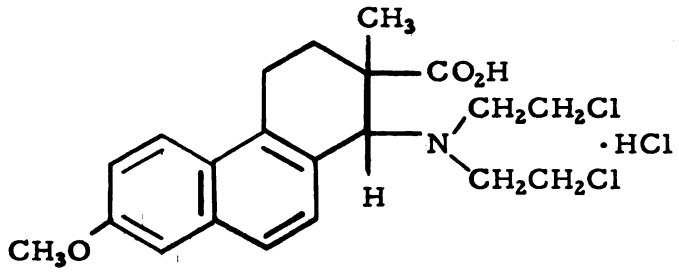
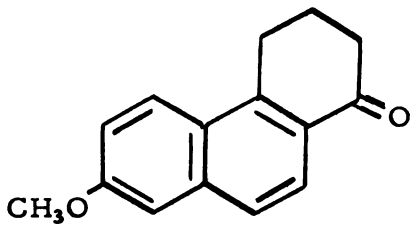


IV

The stereochemical modification corresponding to the most estrogenically active form of the bisdehydrodoisynolic acid methyl ether was to be incorporated as the carrier moiety in the above nitrogen mustards. This aspect of the problem will be discussed concurrently with the preparation of the various compounds.

Based on the preparative methods developed by several groups of workers (122, 123) who have investigated the synthesis of bis-dehydrodoisynolic acid and its derivatives it appeared that the most convenient route to the compounds desired in this work would be by the modification of the C-ring of 1-keto-7-methoxy-1, 2, 3, 4-tetrahydrophenanthrene (V). This intermediate contains the requisite

unsaturation in the A- and B-rings and a conveniently modifiable



V

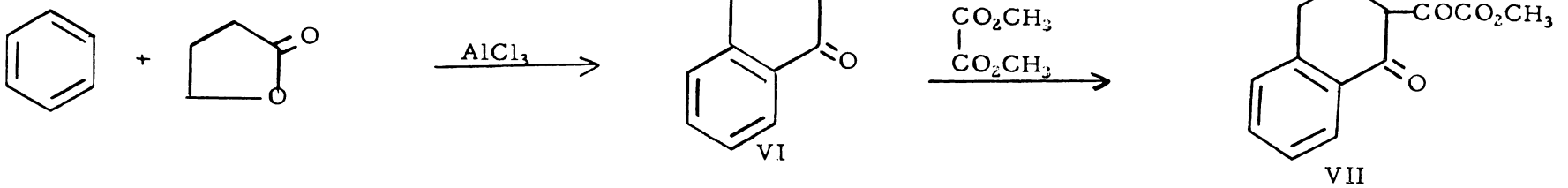
C-ring required for the synthesis of the bisdehydrodoisynolic acid analogs.

A. Unsubstituted Bicyclic Nitrogen Mustards and Stereochemistry of C_1-Ethylidene Intermediate

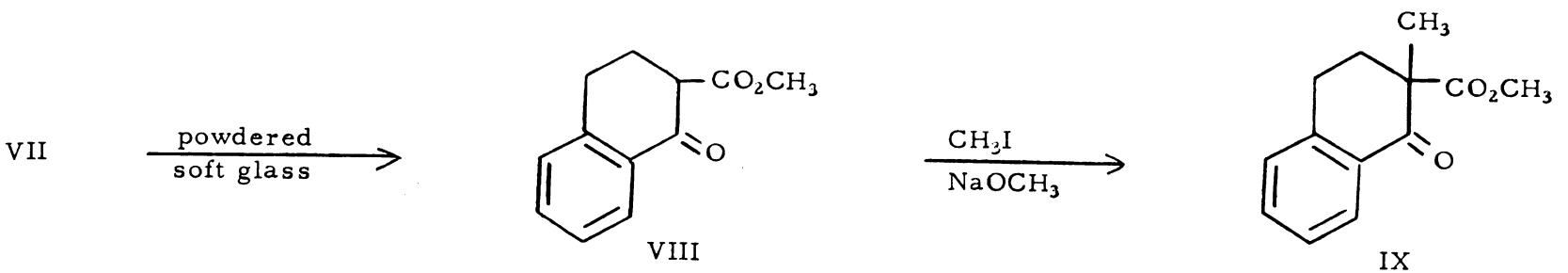
The bicyclic analog, 1-tetralone (VI), was used as a starting point for the synthesis of a model system employed to explore the sequence of reactions necessary to modify the C-ring of the less readily available tricyclic ketone (V) to the desired nitrogen mustards. The possible complications caused by the presence of a methoxy group on the reaction sequence was investigated by repeating the preparation of the model system using 6-methoxy-1-tetralone.

The reaction sequence used to prepare the model compound, 1-ethyl-2-methyl-2-[N, N-bis(2-chloroethyl)aminomethyl]-1, 2, 3, 4-tetrahydronaphthalene hydrochloride (XV), is shown in Figure V.

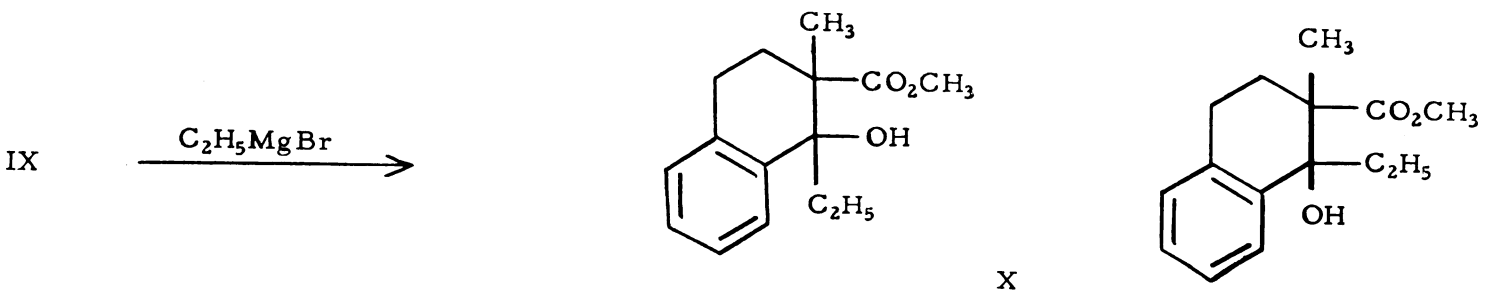
The preparation of 1-tetralone from γ-butyrolactone and benzene using the procedure of Olson and Bader (124) was straightforward. Methyl 1-keto-1, 2, 3, 4-tetrahydronaphthalene-2-glyoxalate (VII) was prepared from 1-tetralone and dimethyl oxalate by a modification of the procedure of Dannenberg and Laufer (125).



VI VII



VIII IX



X

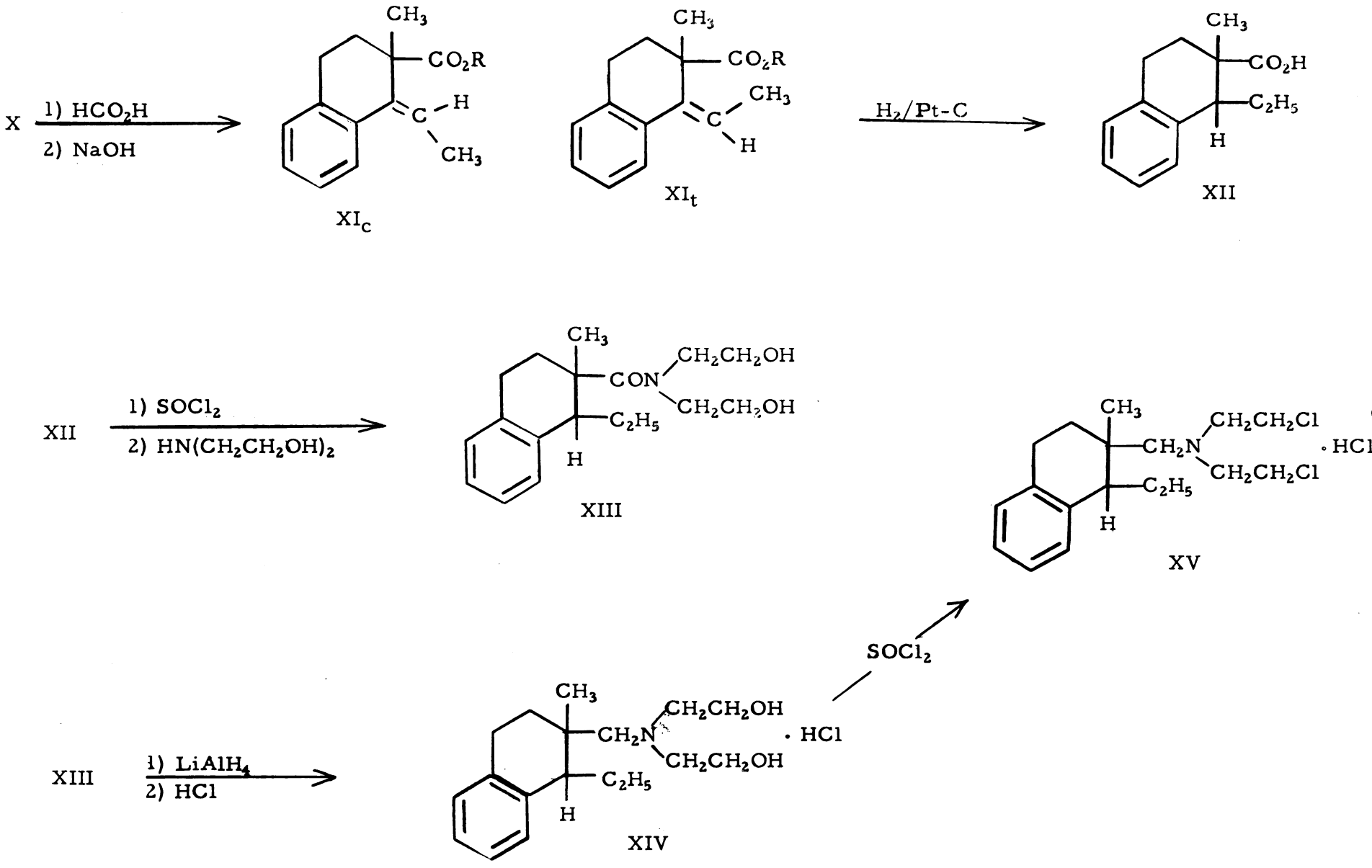


Figure V. The reaction sequence for the preparation of 1-ethyl-2-methyl-2-[N, N-bis-(2-chloroethyl)aminomethyl]-1, 2, 3, 4-tetrahydronaphthalene hydrochloride.

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The yield of glyoxalate obtained by this procedure was fair (75-85%) when the amount of 1-tetralone used was 0.25 mole or less. However, an increase in the amount of 1-tetralone on a scaled-up procedure caused the yield to drop considerably (45-55%).

The glyoxalate was used without extensive purification, other than being treated with Norite followed by a single recrystallization from methanol. It was necessary to carry out the decarbonylation step immediately to prevent decomposition of the impure glyoxalate. A sample of the above glyoxalate which had been carefully purified by repeated recrystallization from methanol could be kept for a period of several months in an evacuated vial without apparent decomposition. Extensive decomposition of the impure glyoxalate was usually evident within 24 hrs.

1-Keto-2-carbomethoxy-1, 2, 3, 4-tetrahydronaphthalene (VIII) was prepared by using the decarbonylation procedure of Bachmann and Thomas,(126), which consists of heating the molten glyoxalate with powdered soft glass. Yields obtained from this reaction were found to be dependent upon the amount of material used. Repeated crystallization of the resulting ester did not give a final product with the purity that could be obtained by distillation. The crude material was, therefore, distilled without fractionation to give a thick yellow sirup which crystallized readily to give a moderate yield (65-75%) to 1-keto-2-carbomethoxy-1, 2, 3, 4-tetrahydronaphthalene.

The angular methyl group was introduced onto the keto ester (VIII) by alkylating the sodio-derivative, formed with sodium methoxide, with methyl iodide. Only one isomer was formed in this alkylation, the angular methyl group being introduced into the pseudo-axial position as shown in ix.* This reaction proceeded in good yield

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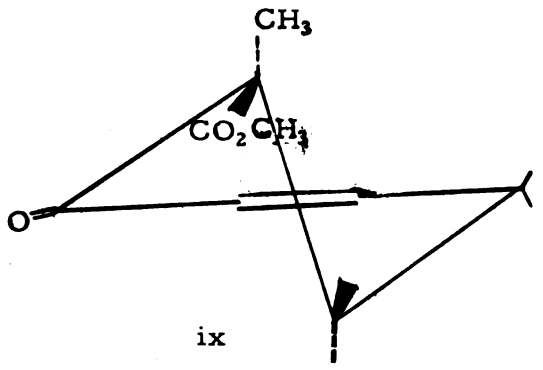
*An explanation of this formula is given in the section of this discussion dealing with the hydrogenation of 1-ethylidene-2-methyl-2-carboxy-7-methoxy-1, 2, 3, 4-tetrahydrophenanthrene.

(85-90%). It was found that passing a solution of the crude product in methylcyclohexane through a bed of alumina removed most of the red-colored impurity permitting the isolation of pure product. The alumina treatment undoubtedly removed a trace amount of unmethylated material capable of enolization. The product from the alumina



ix

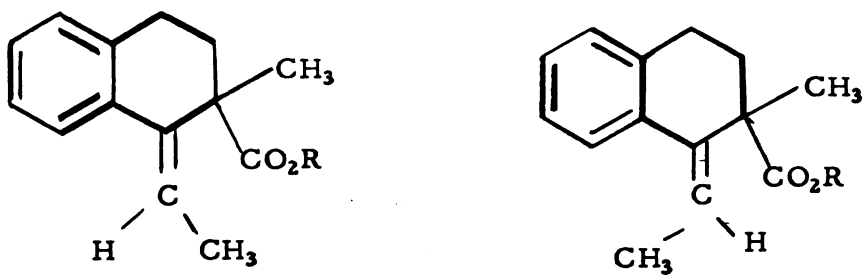
column was treated with Norite and was then recrystallized several times from methanol to give pure 1-keto-2-methyl-2-carbomethoxy-1, 2, 3, 4-tetrahydronaphthalene (IX). This compound became dark red upon standing, although the melting point did not change as the color developed.

A mixture of the isomeric 1-ethyl-1-hydroxy-2-methyl-2-carbomethoxy-1, 2, 3, 4-tetrahydronaphthalenes was obtained by causing the keto ester (IX) to react with one equivalent of ethylmagnesium bromide. Inverse addition was not necessary to effect this selective Grignard addition. It was sufficient to keep the reaction temperature below 10° to prevent the reaction of the Grignard reagent with the carbomethoxy group. Although the reaction of the Grignard reagent with the carbonyl group gave rise to a mixture of diastereoisomeric alcohols it was deemed unnecessary to separate these isomers prior to the dehydration and saponification steps. Dehydration of either pure

isomer would undoubtedly result in the formation of a mixture of unsaturated esters (XI_c and XI_t). Miescher (99) reported that this was the case in the preparation of the analogous 1-ethylidene-2-methyl-2-carbomethoxy-6-methoxy-1, 2, 3, 4-tetrahydronaphthalene. Miescher found that the dehydration of either of the diastereoisomeric 1-ethyl-1-hydroxy-2-methyl-2-carbomethoxy-6-methoxy-1, 2, 3, 4-tetrahydronaphthalenes afforded a mixture of the isomeric cis- and trans-1-ethylidene-2-methyl-2-carbomethoxy-6-methoxy-1, 2, 3, 4-tetrahydronaphthalenes. Hydrolysis of the latter mixture of isomeric esters with alcoholic potassium hydroxide gave a mixture of the two possible 1-ethylidene-2-methyl-2-carboxy-6-methoxy-1, 2, 3, 4-tetrahydronaphthalenes.

Dehydration of the hydroxy esters (X) was achieved with 85% formic acid to give a mixture of the cis- and trans-1-ethylidene-2-methyl-2-carbomethoxy-1, 2, 3, 4-tetrahydronaphthalenes (XI, R=CH_3). Without purification this mixture of esters was saponified with alcoholic potassium hydroxide to give a mixture of the cis- and trans-1-ethylidene-2-methyl-2-carboxy-1, 2, 3, 4-tetrahydronaphthalenes (XI, R= H). These two acids are geometrical isomers resulting from the formation of an exocyclic double bond. The double bond which is formed must be exocyclic since both C_2 and C_9 lack an available hydrogen. The acids were partially separated by repeated crystallization from methylcyclohexane. By this process there was obtained a high melting isomer, m.p. 124-125°, and a low melting isomer, m.p. 84-85°. Both of these acids gave satisfactory analytical data and the neutralization equivalents were in agreement with the proposed formula. The nuclear magnetic resonance spectrum (127) of the high melting isomeric acid is indicative of a pure compound. However, the N.M.R. spectrum of what appeared to be pure low melting isomer shows that it is, in reality, a mixture of the two isomeric acids.

As illustrated in Figure VI the isomeric acid with the benzenoid ring and methyl group opposed has been designated as the trans isomer. Throughout this discussion and the experimental section the aromatic portion of the tetralin nucleus, and later the tetrahydrophenanthrene nucleus, and the methyl group will be used as reference



XI_t, R = H XI_c, R = H

Figure VI. Cis- and trans-1-ethylidene-2-methyl-2-carboxy-1,2,3,4-tetrahydronaphthalene.

groups for the assignment of cis-trans isomers. Examination of the N.M.R. spectra of these two acids shows that the higher melting acid is the isomer with the vinyl hydrogen neighboring to the benzene ring. This corresponds to the trans-structure shown in Figure VI. From the spectra shown in Figures VII and VIII it is seen that the hydrogen (τ = 4.07)* of the high melting isomer is at a lower field than the hydrogen (τ = 4.38) in the low melting isomer. This is analogous to cis- and trans-stilbene (XVI_t and XVI_c) in which the hydrogen (τ = 3.01) in trans-stilbene is at a lower field than the hydrogen (τ = 3.51) in the

*N.M.R. spectra were taken in carbon tetrachloride solution with a Varian associate A-60 nuclear magnetic resonance spectrometer. Tetramethylsilane was used as an internal standard for the determination of the tau values.

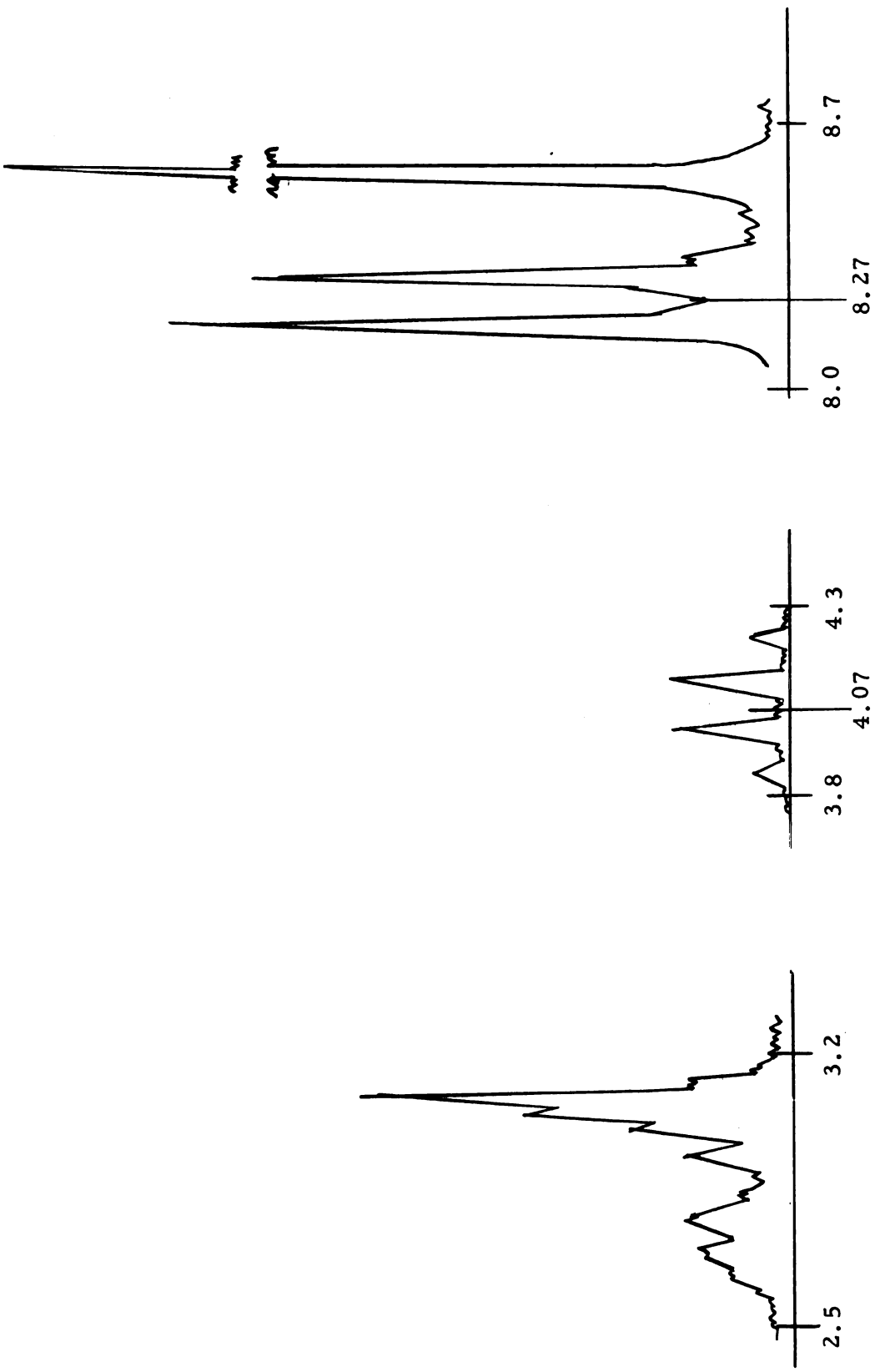


Figure VII. N.M.R. spectrum of trans-1-ethylidene-2-methyl-2-carboxy-1, 2, 3, 4-tetrahydronaphthalene.

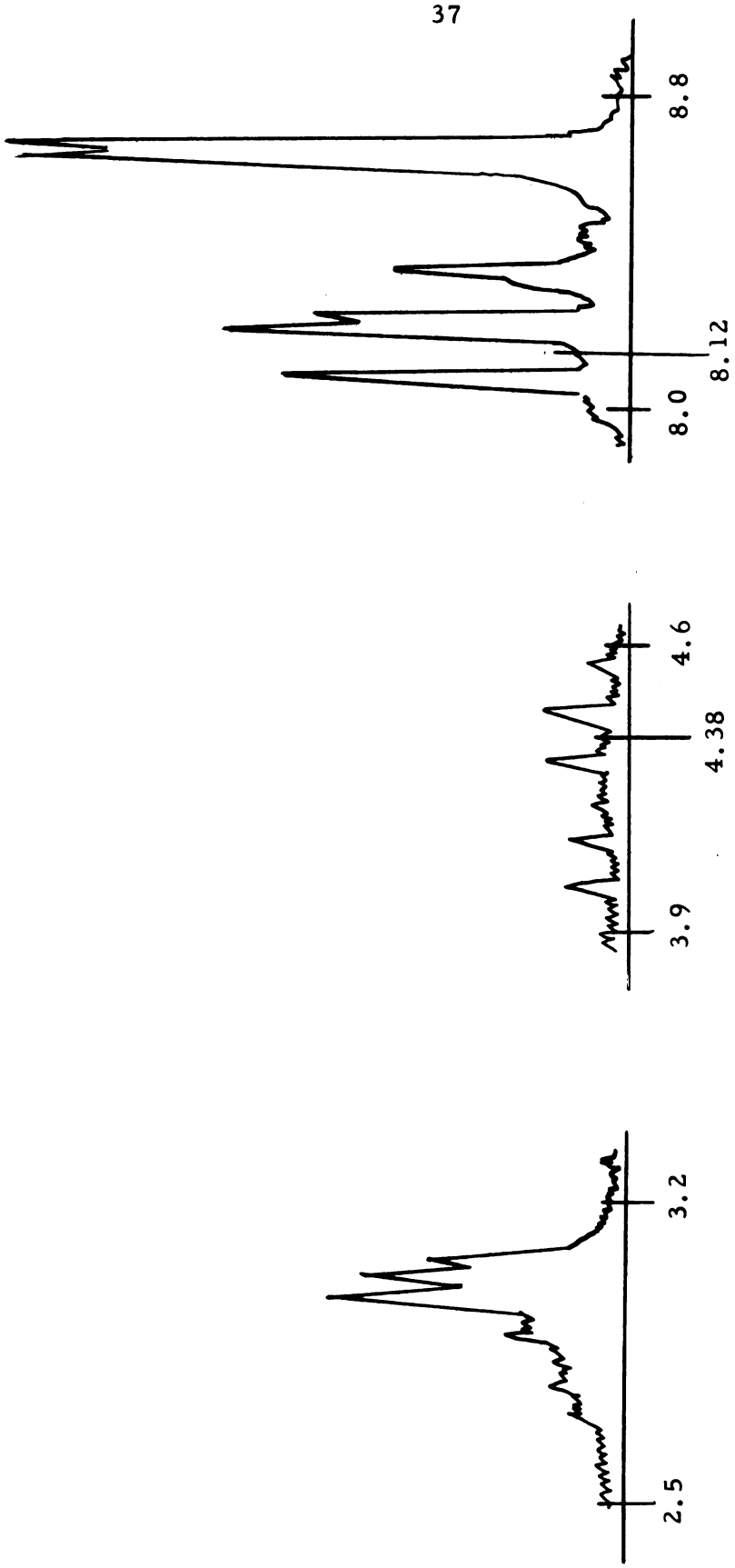
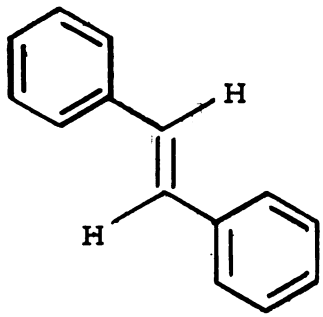
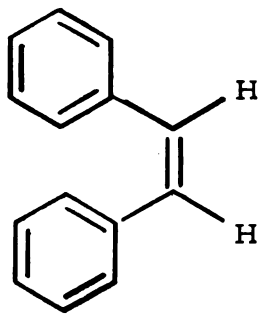


Figure VIII. N.M.R. spectrum of cis-1-ethylidene-2-methyl-2-carboxy-1, 2, 3, 4-tetrahydronaphthalene.



XVI_t



XVI_c

Figure IX. Cis- and trans-stilbene.

corresponding cis-stilbene due to the deshielding effect of the neighboring benzene ring (128). In a similar manner the N.M.R. spectra of cis- and trans-1-ethylidene-2-methyl-2-carboxy-1, 2, 3, 4-tetrahydronaphthalenes (Figures VII and VIII) show that the position of the methyl group is altered by the presence of the benzene ring. The methyl group in the trans-isomer appears at τ = 8.27 whereas in the cis-isomer the methyl group has shifted to a value of τ = 8.12. Therefore, from a comparison of the N.M.R. spectra of these isomeric acids, it has been established that the high melting isomer is the trans-acid and the low melting isomer is the cis-acid.

The next step in the preparation of the model compound as shown in Figure V, was the hydrogenation of the unsaturated acid (XI) to 1-ethyl-2-methyl-2-carboxy-1, 2, 3, 4-tetrahydronaphthalene. Preliminary work showed that the hydrogenation of either cis- or trans-1-ethylidene-2-methyl-2-carboxy-1, 2, 3, 4-tetrahydronaphthalene over 5% platinum on charcoal (15 lb. pressure at ambient temperature) gave the identical single saturated acid (XII). Hydrogenation of a mixture of the isomeric unsaturated acids also gave the same saturated acid. Therefore it was not necessary to separate these geometrical isomers before hydrogenation.

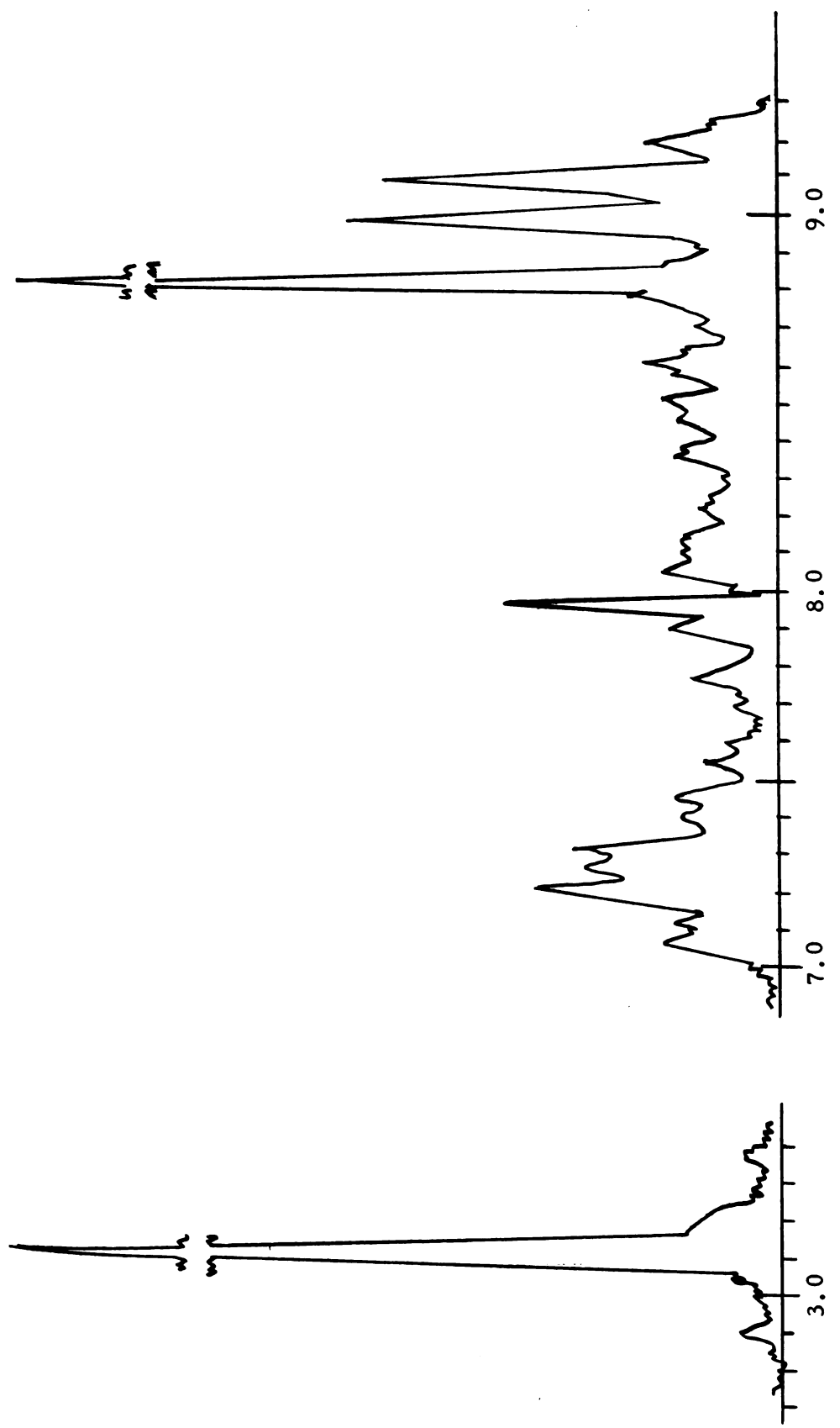
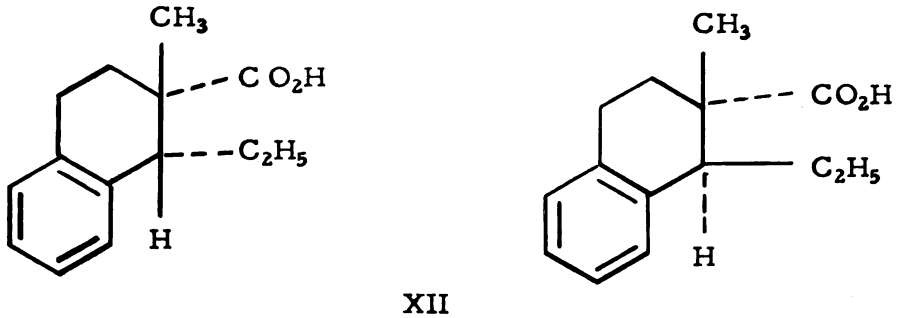


Figure X. N.M.R. spectrum of 1-ethyl-2-methyl-2-carboxy-1,2,3,4-tetrahydronaphthalene.

The N.M.R. spectrum of this saturated acid indicated the absence of the exocyclic double bond. As shown in Figure X the peaks at (τ = 4.07 and τ = 4.38), previously assigned to the vinyl hydrogen in the unsaturated acids, have been eliminated from the spectrum. The two possible diastereoisomeric modifications of this saturated acid are shown in Figure XI. These results with a platinum catalyst



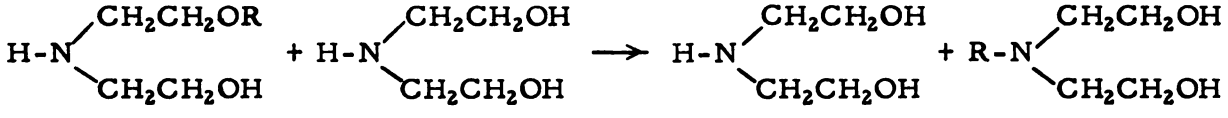
XII

Figure XI. The two possible diastereoisomeric modifications of 1-ethyl-2-methyl-2-carboxy-1, 2, 3, 4-tetrahydronaphthalene.

differed from those reported for the hydrogenation of analogous compounds with a nickel catalyst. Miescher (99) obtained a mixture of dl-cis- and dl-trans-7-methylbisdehydrodoisynolic acids by the hydrogenation of the sodium salt of the analogous 1-ethylidene-2-methyl-2-carboxy-7-methoxy-1, 2, 3, 4-tetrahydrophenanthrene over Rupe nickel in dilute aqueous base. The hydrogenation of these bicyclic acids will be discussed concurrently with the hydrogenation of 1-ethylidene-2-methyl-2-carboxy-7-methoxy-1, 2, 3, 4-tetrahydrophenanthrene.

1-Ethyl-2-methyl-2-[N, N-bis(2-hydroxyethyl)carbamyl]-1, 2, 3, 4-tetrahydronaphthalene (XIII) was prepared by the acylation of diethanolamine with the acid chloride of XII. This acid chloride was prepared

with freshly distilled Matheson, Coleman and Bell thionyl chloride using pyridine as the catalyst. The acid chloride was not purified before use in this acylation other than carefully removing the traces of excess thionyl chloride. It was then dissolved in dry dioxane and was added to a dioxane solution of diethanolamine (92, 94, 96). The product of this acylation was undoubtedly a mixture of N- and O-acylated diethanoamines. Although there is the possibility of the acid chloride reacting with either the nitrogen or the hydroxyl group of the diethanolamine the yields of the desired N, N-bis(2-hydroxyethyl)amide obtained by this procedure were generally very good. The effective concentration of the hydroxyl group is always at least twice that of the nitrogen, but the higher nucleophilicity of the latter more than compensates for the high hydroxyl concentration if the acid chloride is added slowly enough to keep its concentration reasonably low. After the addition of the acid chloride the reaction mixture was heated for at least 10 hrs. During this period amidation takes place thus increasing the amount of N-acylated product at the expense of the O-acylated product. Thus, the ester (i) could react with a molecule of diethanolamine (ii_a) to give the desired diethanolamine (iii) and to regenerate a molecule of diethanolamine (ii_b). Using an excess of diethanolamine the reaction mixture would, theoretically, eventually consist of practically all N-acylated product.



i $\quad$ ii_a $\quad$ ii_b $\quad$ iii

Separation of this mixture of N- and O-acylated diethanolamine is not necessary since the hydride reduction will reduce the ester-linkages to the desired hydroxyl groups.

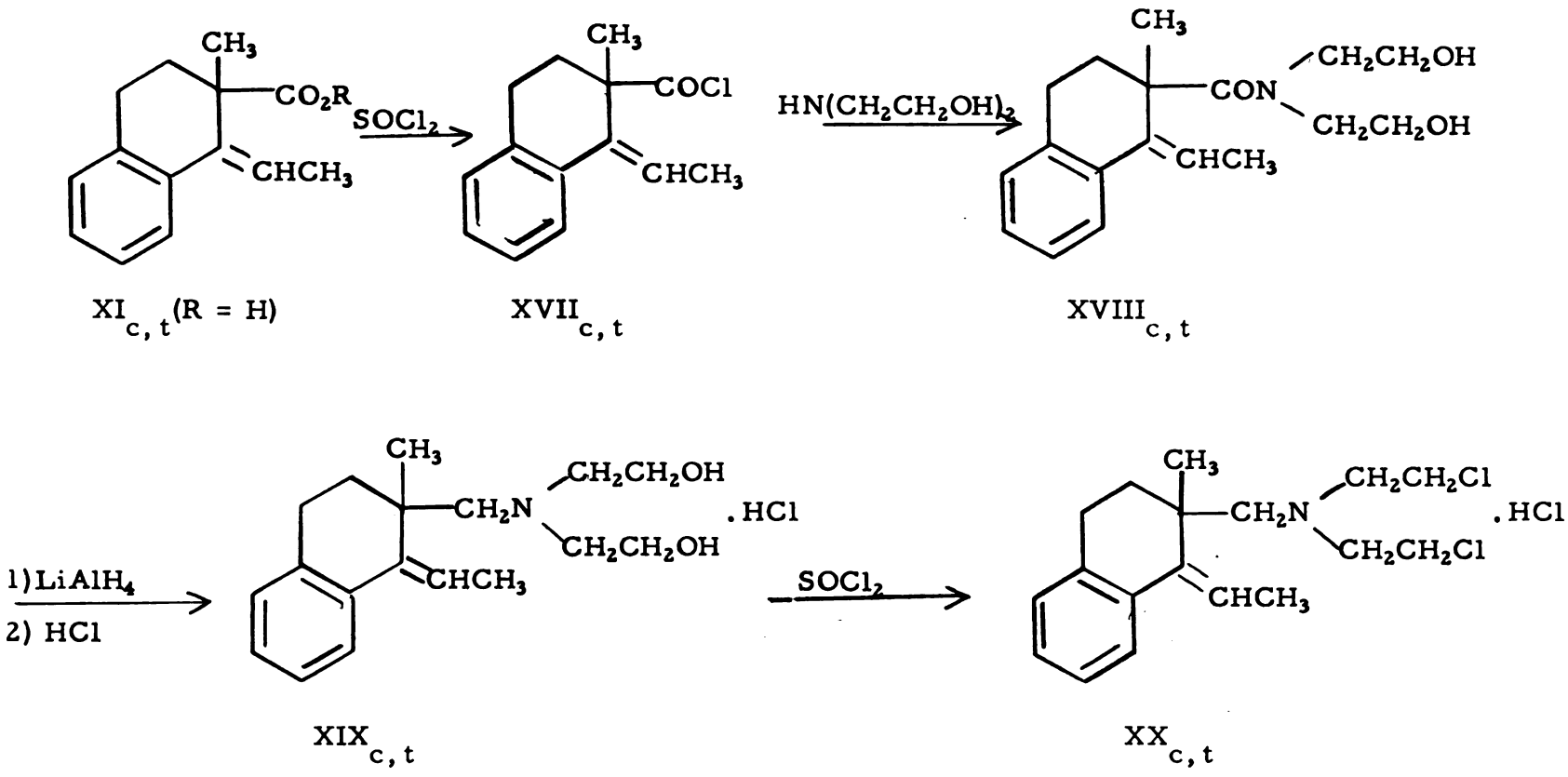
Lithium aluminum hydride reduction of the crude diethanolamide (XIII) gave the desired 1-ethyl-2-methyl-2-[N, N-bis(2-hydroxyethyl)-aminomethyl]-1-2-3-4-tetrahydronaphthalene. The reaction proceeded well when sufficient reagent was used to combine with the free hydroxyl groups (or to reduce the esters) as well as to reduce the amide. After hydrolysis with water the aluminum salts were complexed with an ammonium tartrate solution. The addition of anhydrous hydrogen chloride to an ethereal solution of the amine gave a good yield of colorless amine hydrochloride (XIV). This method of purification effectively separated the amine from the alcohol formed by the reduction of the O-acylated product.

1-Ethyl-2-methyl-2-[N, N-bis(2-chloroethyl)aminomethyl]-1, 2, 3, 4-tetrahydronaphthalene hydrochloride (XV) was prepared by adding freshly distilled thionyl chloride to a chloroform solution of the diethanolamine hydrochloride (XIV) using a trace of dimethylformamide as a catalyst (113, 129, 130). This nitrogen mustard hydrochloride was isolated as a near-colorless, well defined solid which adequately met all analytical requirements.

Since reasonably large quantities of the unsaturated acids (XI_c and XI_t) were available it was decided to prepare the corresponding unsaturated nitrogen mustards (XX) to be submitted for screening as a comparison with the analogous saturated compound (XV).

The reaction sequence employed for the preparation of these compounds is shown in Figure XII. trans-1-Ethylidene-2-methyl-2-[N, N-bis(2-hydroxyethyl)carbamyl]-1, 2, 3, 4-tetrahydronaphthalene ($XVIII_t$) was prepared by the acylation of diethanolamine with the acid chloride (XVII) by the same procedure which has been described for the preparation of the saturated analog.

Lithium aluminum hydride reduction of the crude diethanolamide ($XVIII_t$) gave the desired trans-1-ethylidene-2-methyl-2-[N, N-bis-(2-chloroethyl)aminomethyl]-1, 2, 3, 4-tetrahydronaphthalene (XIX_t).



$XI_{c,t}$ (R = H) $XVII_{c,t}$ $XVIII_{c,t}$

$XIX_{c,t}$ $XX_{c,t}$

Figure XII. Preparation of cis- and trans-1-ethylidene-2-methyl-2-[N, N-bis-(2-chloroethyl)aminomethyl]-1, 2, 3, 4-tetrahydronaphthalene hydrochloride.

The addition of anhydrous hydrogen chloride to an ethereal solution of the amine gave a gummy precipitate of the amine hydrochloride (XIX_t). This amine hydrochloride could then be crystallized from acetone-ether to give a well defined near-colorless solid.

The trans-nitrogen mustard hydrochloride (XX_t) was prepared by adding freshly distilled thionyl chloride to a chloroform solution of the diethanolamine hydrochloride (XIX_t) using a trace of dimethylformamide as a catalyst. The dark brown residue from the reaction work-up was slurried with hot acetone, cooled and filtered to give a light tan solid which could be recrystallized to pure trans-1-ethylidene-2-methyl-2-[N, N-bis(2-chloroethyl)aminomethyl]-1, 2, 3, 4-tetrahydronaphthalene hydrochloride (XX_t).

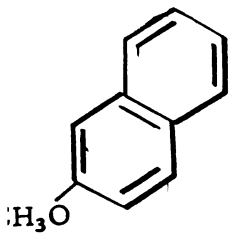
The cis-nitrogen mustard hydrochloride (XX_c) was prepared following the same sequence of reactions as described above for the corresponding trans-isomer. The work-up of the reaction mixture from the preparation of cis-1-ethylidene-2-methyl-2-[N, N-bis(2-chloroethyl)aminomethyl]-1, 2, 3, 4-tetrahydronaphthalene hydrochloride resulted in a dark sirupy residue from which no solid could be isolated. This crude residue was dissolved in the minimum amount of dry chloroform and passed through a column of neutral alumina. This procedure converted the nitrogen mustard hydrochloride to the free amine and removed most of the tar (131). The nitrogen mustard hydrochloride was then obtained as a solid by precipitation of the hydrochloride from an ether solution of the free base by the addition of anhydrous hydrogen chloride. This solid then was recrystallized to give pure cis-1-ethylidene-2-methyl-2-[N, N-bis(2-chloroethyl)aminomethyl]-1, 2, 3, 4-tetrahydronaphthalene hydrochloride (XX_c).

B. Methoxy-Substituted Bicyclic Nitrogen Mustard

The reaction sequence used to convert 1-tetralone to the corresponding nitrogen mustard (XV) was repeated with 1-keto-6-methoxy-1, 2, 3, 4-tetrahydronaphthalene (XXIII). This second model compound was prepared in order to determine the influence, if any, that the methoxy group would have on the reactions necessary to convert the "C" ring of 1-keto-7-methoxy-1, 2, 3, 4-tetrahydrophenanthrene (V) to the desired nitrogen mustard (II). The sequence of reactions employed for the preparation of 1-ethyl-2-methyl-2-[N, N-bis(2-chloroethyl)-aminomethyl]-6-methoxy-1, 2, 3, 4-tetrahydronaphthalene hydrochloride (XXXII) is shown in Figure XIII. This nitrogen mustard was to be submitted for screening as an oncotoxin as a comparison to the tricyclic analog corresponding to a doisynolic acid-type structure.

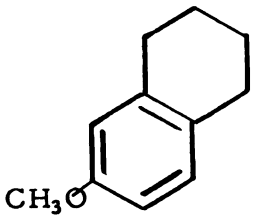
6-Methoxy-1, 2, 3, 4-tetrahydronaphthalene (XXII) was prepared by the hydrogenation of 2-methoxynaphthalene (XXI) over Raney nickel (Mozingo) (132). In this work the high yields reported by Stork (133) for this reduction were not obtained. Stork, using a temperature of 160°, obtained a 91.6% yield of 6-methoxy-1, 2, 3, 4-tetrahydronaphthalene. In this work a temperature of 160° gave a yield of only 68%. It was found that the yield was increased to 87.5% by lowering the hydrogenation temperature to 140°, but by further lowering the temperature to 120° the yield fell to 65%. The quality of the product seemed to be the same in all cases. The activity of the Raney nickel catalyst, although freshly prepared, was probably responsible for these lower yields.

Oxidation of 6-methoxy-1, 2, 3, 4-tetrahydronaphthalene (XXII) with chromic acid gave 1-keto-6-methoxy-1, 2, 3, 4-tetrahydronaphthalene (XXIII). A number of workers have described experimental procedures for performing this oxidation and for the subsequent isolation of the product from the reaction mixture. Burnop, Elliott and



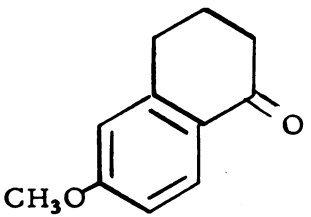
XXI

H_2/Ni



XXII

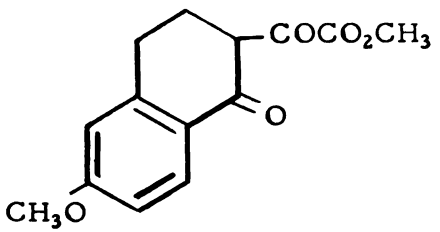
CrO_3



XXIII

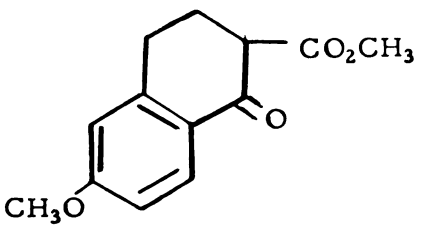
XXIII

CO_2CH_3
CO_2CH_3
$NaOCH_3$



XXIV

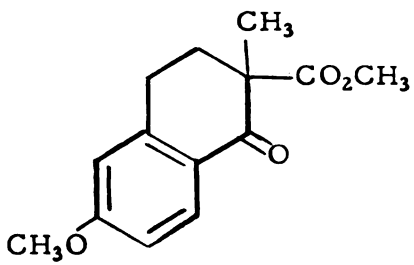
Soft glass



XXV

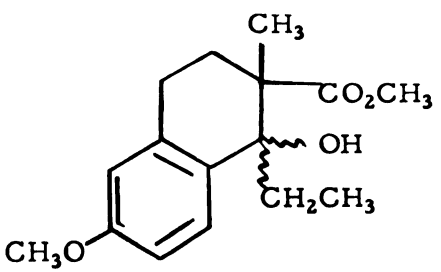
XXV

CH_3I
$NaOCH_3$



XXVI

CH_3CH_2MgBr



XXVII

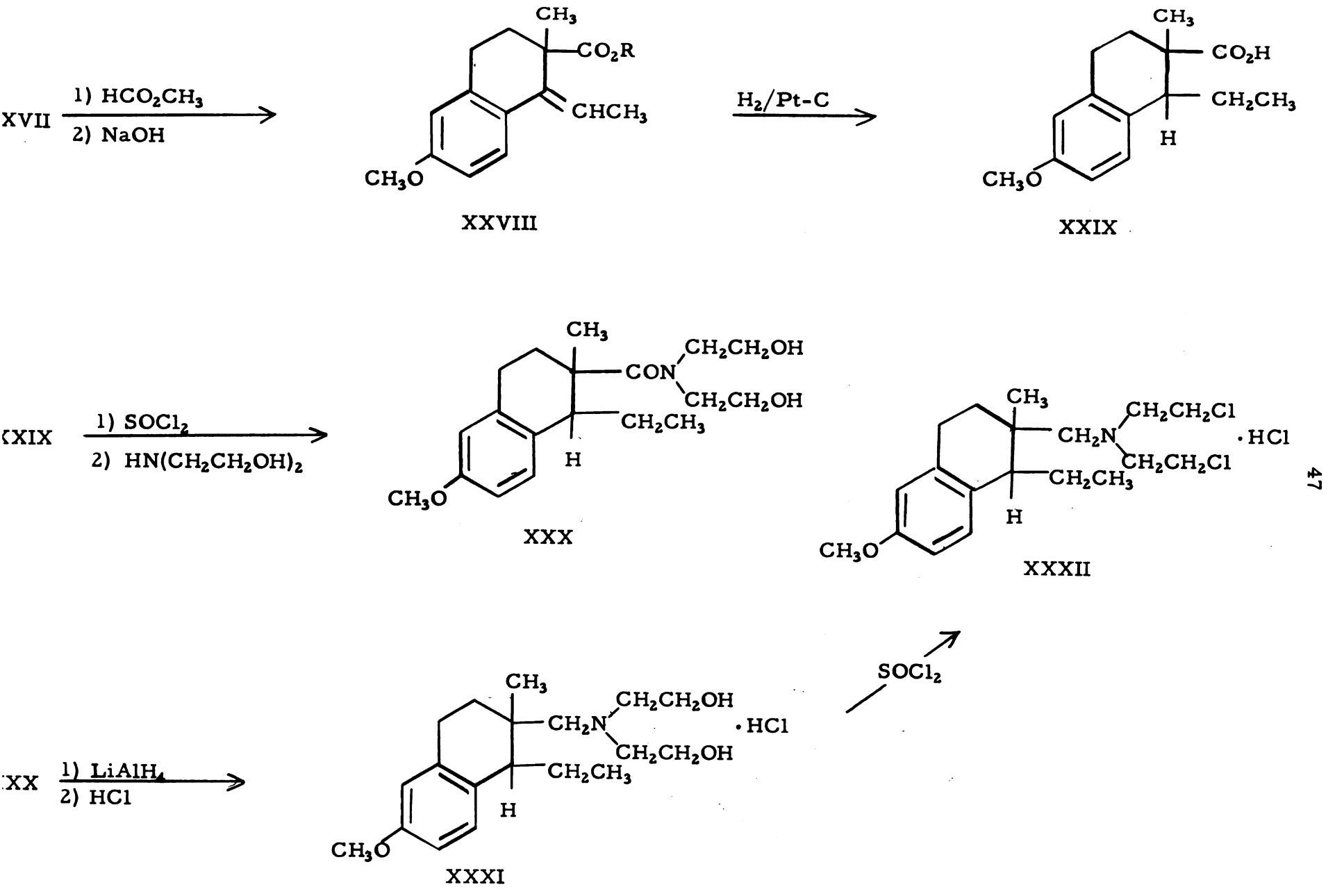


Figure XIII. Reaction sequence for the preparation of 1-ethyl-2-methyl-2-[N, N-bis-2-chloroethyl)aminomethyl]-6-methoxy-1-2-3-4-tetrahydronaphthalene hydrochloride.

Linstead (134) employed a reaction mixture of chromic acid in aqueous acetic acid and isolated the product by steam distillation. These workers claimed that this steam distillation employing superheated steam (220°), was preferable to direct extraction of the reaction mixture for the isolation of the pure ketone. Over 40 l. of distillate had to be collected to recover 110 g. of product. Schwenk and Papa (135) employed essentially the same reaction conditions as Linstead and co-workers, but they extracted the reaction mixture, after a ten-fold dilution with water, with butyl ether rather than carry out a steam distillation. Stork (133) used the reaction conditions of Linstead combined with the work-up procedure of Schwenk and Papa. All of the above workers reported yields in the range of 60-70%. Bachmann and Thomas (136) reported a modification of the procedure of Linstead (134). In this modification the oxidation was carried out by adding a solution of chromic acid in aqueous acetic acid to a solution of the 6-methoxy-1, 2, 3, 4-tetrahydronaphthalene in a mixture of acetic acid and propionic acid. The addition of propionic acid resulted in a homogeneous reaction mixture for the oxidation which could not be obtained by the use of aqueous acetic acid alone. The ketonic product was extracted into ether. After the ether was removed, the residue was dissolved in benzene and the solution was passed through a column of alumina to remove the residual chromium salts. All of these procedures were tried, with some variations, and that of Bachmann was found to be the most expedient despite the lower yields (58.6%). The product obtained after concentration of the effluent solution from the alumina column was of sufficient purity that it could be used in the succeeding step of the reaction sequence without further purification. Although Bachmann's procedure gave slightly lower yields, this was compensated for by both the shorter time involved for the oxidation and isolation and by the avoidance of exceedingly

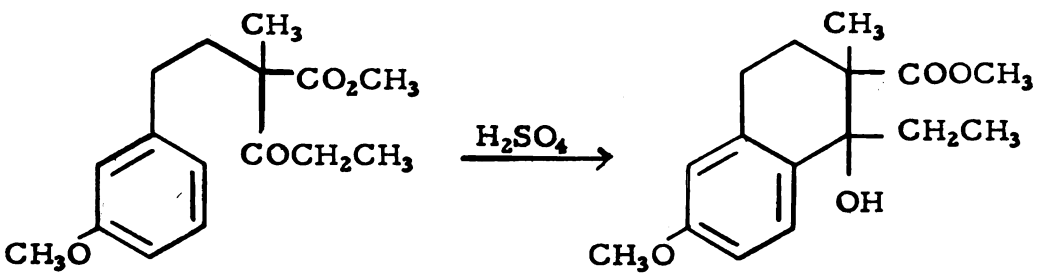
large volumes of steam distillate or butyl ether extract. In an attempt to avoid the large volume of distillate which was obtained Linstead, a continuous extraction-steam distillation (137) was tried, but the time involved limited the use of this procedure. By using steam at atmospheric pressure, this distillation required three weeks of continuous distillation in order to isolate 10 g. of product.

Methyl 1-keto-6-methoxy-1, 2, 3, 4-tetrahydronaphthalene-2-glyoxalate (XXIV) was prepared by the glyoxalation of the sodio-derivative of 1-keto-6-methoxy-1, 2, 3, 4-tetrahydronaphthalene with dimethyl oxalate. The procedure developed for the glyoxalation of 1-tetralone was found to be satisfactory without major change. The presence of the 6-methoxy group did seem to lower the yield for this reaction (76.2% compared to 85% for the unsubstituted analog). It appears that this somewhat lower yield is more readily explained by the difficulties encountered in the work-up procedures than in the actual reaction itself.

Decarbonylation of the above glyoxalate to 1-keto-2-carbomethoxy-6-methoxy-1, 2, 3, 4-tetrahydronaphthalene (XXV) was carried out within 24 hrs. after the isolation of the glyoxalate. Although the stability of the 6-methoxy-glyoxalate was not investigated, the latter was assumed to be fairly unstable based on the experience with the unsubstituted compound. Rather than heating a mixture of the glyoxalate and powdered soft glass, as was done for the decarbonylation of methyl 1-keto-1, 2, 3, 4-tetrahydronaphthalene-2-glyoxalate (VII), it was found that the decarbonylation of the methoxy-substituted analog proceeded more smoothly when the powdered glass was added to the previously fused glyoxalate. When this procedure was used carbon monoxide was evolved rapidly as the glass was added and the reaction was complete within a few minutes, thus decreasing the duration of heating. The reaction temperature was the same as that used with the unsubstituted glyoxalate.

1-Keto-2-methyl-2-carbomethoxy-6-methoxy-1, 2, 3, 4-tetrahydronaphthalene (XXVI) was prepared by methylating the sodio-derivative of the keto ester (XXV) with methyl iodide. The procedure used was the same as that developed for the unsubstituted keto-ester (IX).

A mixture of the diastereoisomeric 1-ethyl-1-hydroxy-2-methyl-2-carbomethoxy-6-methoxy-1, 2, 3, 4-tetrahydronaphthalenes (XXVII) was obtained by the addition of one mole of ethylmagnesium bromide to 1-keto-2-methyl-2-carbomethoxy-6-methoxy-1, 2, 3, 4-tetrahydronaphthalene (XXVI). This diastereoisomeric mixture had a melting point of 100-101°. Miescher (99) observed an identical melting point for this same diastereoisomeric mixture obtained by an entirely different route. Miescher prepared these isomeric hydroxy esters (XXVII) by the ring closure of methyl 2-methyl-2-[2-(2-methoxyphenyl)-ethyl]-3-ketopentanoate (XXXIII) with sulfuric acid.



XXXIII XXVII

In the present work dehydration of the above mixture of hydroxy esters (XXVII) with 85% formic acid gave a mixture of cis- and trans-1-ethylidene-2-methyl-2-carbomethoxy-6-methoxy-1, 2, 3, 4-tetrahydronaphthalenes (XXVIII, R = CH_3). Saponification of this mixture without purification yielded a mixture of the corresponding isomeric acids (XXVIII, R = H). The melting point of 113-115° for this mixture

of cis- and trans-1-ethylidene-2-methyl-2-carboxy-6-methoxy-1,2,3,4-tetrahydronaphthalenes was identical to that reported by Miescher (99). This mixture of isomeric acids was reduced over 5% platinum on charcoal in 95% ethanol to 1-ethyl-2-methyl-2-carboxy-6-methoxy-1,2,3,4-tetrahydronaphthalene (XXIX). As in the case of the unsubstituted acids (XI) this hydrogenation gave only one of the two possible diastereoisomeric saturated acids. The melting point of the isomer obtained is 130-131°. The isolation of a single saturated acid has precedence in the results of Horeau (138), who obtained the identical product (m.p. 130-131°) by the hydrogenation of the same mixture of unsaturated acids over Vavon platinum in anhydrous ether. Miescher (99), by hydrogenating an aqueous solution of the sodium salts of a mixture of the isomeric unsaturated acids over Rupe nickel, obtained a mixture of the diastereoisomeric saturated acids. He reported melting points of 128-130° and 148-150° for the two isomers. The stereochmeistry of this reduction will be discussed concurrently with the comparable hydrogenation involved in the preparation of 1-ethyl-2-methyl-2-[N,N-bis(2-chloroethyl)aminomethyl]-7-methoxy-1,2,3,4-tetrahydrophenanthrene hydrochloride (II).

1-Ethyl-2-methyl-2-[N,N-bis(2-hydroxyethyl)carbamyl]-6-methoxy-1,2,3,4-tetrahydronaphthalene (XXX) was prepared by the acylation of diethanolamine with the acid chloride of the saturated acid (XXIX). This N,N-diethanolamide was isolated as a light amber sirup. No attempt was made to purify this intermediate before reduction with lithium aluminum hydride to 1-ethyl-2-methyl-2-[N,N-bis(2-hydroxyethyl)aminomethyl]-6-methoxy-1,2,3,4-tetrahydronaphthalene. This reduction proceeded in good yield using the identical procedure employed with the unsubstituted analog (XIII). Treatment of an ethereal solution of the crude reaction product with anhydrous hydrogen chloride caused the separation of pure 1-ethyl-2-methyl-2-

[N, N-bis(2-hydroxyethyl)aminomethyl]-6-methoxy-1, 2, 3, 4-tetrahydronaphthalene hydrochloride (XXXI) as a well-defined colorless solid.

1-Ethyl-2-methyl-2-[N, N-bis(2-chloroethyl)aminomethyl]-6-methoxy-1, 2, 3, 4-tetrahydronaphthalene hydrochloride (XXXII) was prepared by treating a chloroform solution of the diethanolamine hydrochloride (XXXI) with freshly distilled thionyl chloride employing a trace of dimethylformamide as a catalyst. The crude nitrogen mustard was a light tan solid which could be recrystallized from ethanol to give a cream-colored product which met all analytical requirements.

C. C_2-Tricyclic Nitrogen Mustard and Stereochemistry of the Hydrogenated C_1-Ethylidene Intermediate

The synthetic route chosen for the preparation of 1-ethyl-2-methyl-2-[N, N-bis(2-chloroethyl)aminomethyl]-7-methoxy-1, 2, 3, 4-tetrahydrophenanthrene hydrochloride (II) was based on the previously described work with the model compounds and on several series of reaction sequences which have been developed by various other workers (122, 123) for the total synthesis of equilenin and related estrogens.

The first step in the synthesis of the doisynolic acid-type nitrogen mustard was the preparation of 1-keto-7-methoxy-1, 2, 3, 4-tetrahydrophenanthrene (V). This intermediate corresponds to the 1-tetralone and to the 1-keto-6-methoxy-1, 2, 3, 4-tetrahydronaphthalene used as a starting point to prepare the model nitrogen mustards (XV and XXXII). The synthetic route utilized for the preparation of this intermediate is shown in Figure XIV.

Methyl 4-[1-(6-methoxy-1, 2, 3, 4-tetrahydronaphthylidene]-crotonate (XXXV) was prepared by the dehydration of the hydroxy-ester obtained from the Reformatsky reaction using methyl γ-bromo-crotonate and 1-keto-6-methoxy-1, 2, 3, 4-tetrahydronaphthalene (XXIII). Although this reaction gave a low yield of the desired product, the

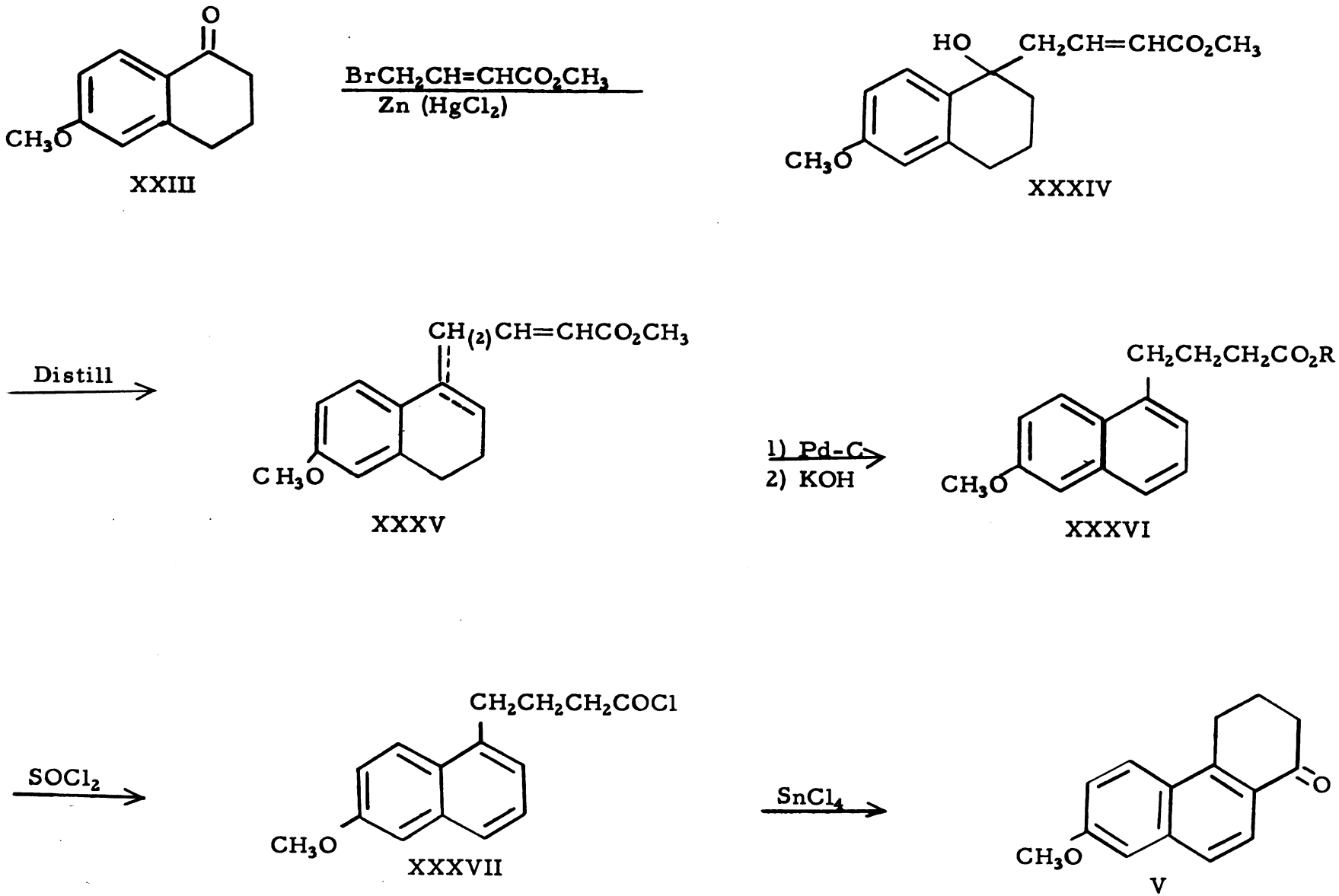


Figure XIV. Reaction sequence for the preparation of 1-keto-7-methoxy-1, 2, 3, 4-tetrahydrophenanthrene.

starting ketone was recoverable and could be reused in succeeding preparations. It was not necessary to isolate the hydroxy-ester intermediate. Separation of the starting ketone (XXIII) and the unsaturated ester (XXXV) was conveniently effected by a simple distillation. Dehydration took place just prior to the distillation of the ketone as evidenced by the accumulation of water in the cold trap of the vacuum system. Stork (139) suggested that the instability of this β-hydroxy ester may be due to the spontaneous loss of water to form a conjugated system. The product formed by this dehydration may be an unsaturated ester containing either an endocyclic or an exocyclic double bond, as indicated in formula XXXV, or a mixture of both of these isomers. The actual ester formed is inconsequential since the subsequent isomerization gives only a single aromatized product.

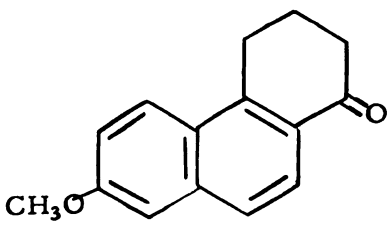
Isomerization of the dehydrated Reformatsky ester to methyl 4-(6-methoxy-1-naphthyl)butanoate (XXXVI, R = CH_3) was effected by heating it to 280-90° with 30% palladium on charcoal under a carbon dioxide atmosphere. The rearranged ester was not purified before saponification with alcoholic potassium hydroxide. Upon acidification of the hydrolysate there was obtained 4-(6-methoxy-1-naphthyl)butanoic acid (XXXVI, R = H) in near-analytical purity. This rearrangement and subsequent hydrolysis proceeded with an overall yield of 81%.

Several procedures are available for the ring closure necessary to form the C-ring in the desired 1-keto-7-methoxy-1,2,3,4-tetrahydrophenanthrene. Bachmann, Cole and Wilds (140) described a procedure for preparing this tricyclic ketone by treating the acid chloride of the intermediate 4-(6-methoxy-1-naphthyl)butanoic acid with stannic chloride. This procedure afforded the ketone in a 91% yield. Stork (139) later developed a procedure for the same cyclization utilizing the free acid and liquid hydrogen fluoride as both the solvent and catalyst. This method required the use of special platinum reaction

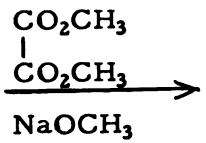
equipment. He prepared the cyclic ketone in 85% yield by this procedure. Bachmann's procedure was the obvious choice since it did not require the use of special equipment and gave higher yields. The major disadvantages of the procedure employing stannic chloride were the necessity of the prior preparation of the acid chloride and the fact that it gives these high yields only when the amount of acid used is 5 g. or less. Stork used .14 g. of the acid.

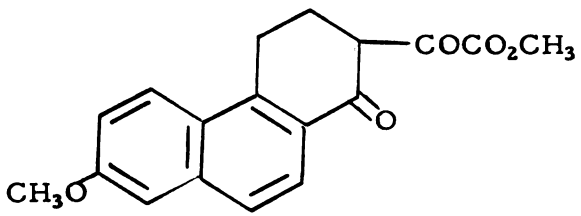
The acid chloride (XXXVII) of 4-(6-methoxy-1-naphthyl)butanoic acid was prepared by adding the acid to an ether solution of freshly distilled thionyl chloride containing a trace of pyridine as a catalyst. After the solvent and the excess thionyl chloride were removed, the acid chloride was dissolved in benzene and was treated with a benzene solution of anhydrous stannic chloride. This reaction gave yields in the neighborhood of 65-80% when quantities of 10 g. or less of the starting acid were employed. The yield dropped to approximately 50% when larger quantities of the acid were used. The tricyclic ketone was sufficiently pure for use in the succeeding step after it was isolated from the reaction mixture.

As shown in Figure XV the reaction sequence employed to synthesize 1-ethyl-2-methyl-2-[N, N-bis(2-chloroethyl)aminomethyl]-7-methoxy-1, 2, 3, 4-tetrahydrophenanthrene hydrochloride from the tricyclic ketone (V) is based on the procedures developed in the synthesis of the model nitrogen mustards from the analogous bicyclic ketones. Methyl 1-keto-7-methoxy-1, 2, 3, 4-tetrahydrophenanthrene-2-glyoxalate (XXXVIII) was prepared by the glyoxalation of the sodio-derivative of 1-keto-7-methoxy-1, 2, 3, 4-tetrahydrophenanthrene (V) with dimethyl oxalate. This reaction proceeded in good yield using the experimental conditions developed with the model compounds. Since the glyoxalate was subject to rapid decomposition upon standing, the decarbonylation step was carried out within 24 hrs. after the isolation of the product.

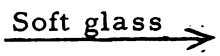


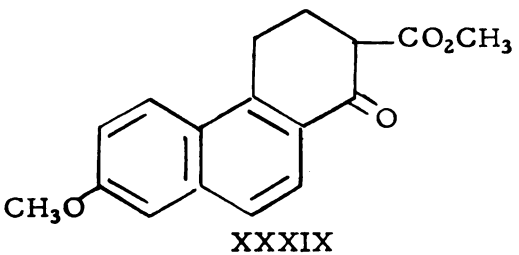
V



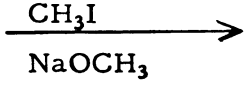


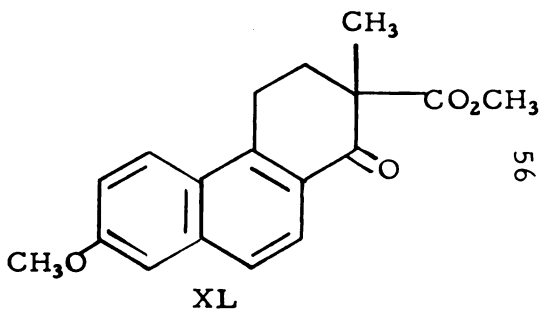
XXXVIII

XXXVIII 



XXXIX





XL

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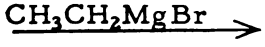
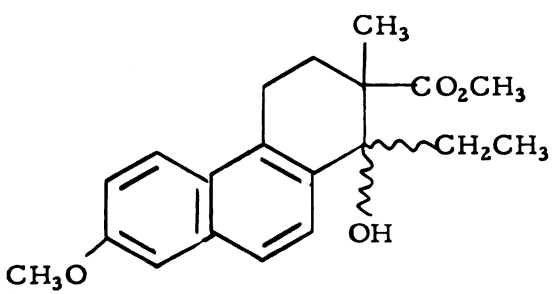
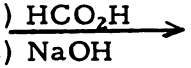
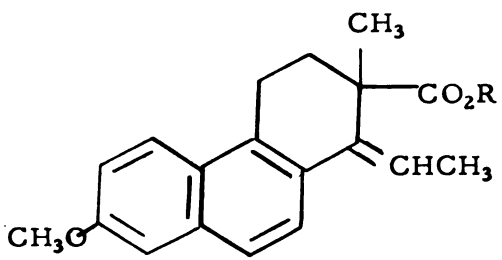
L 



XLI





XLII$_c$ and XLII$_t$

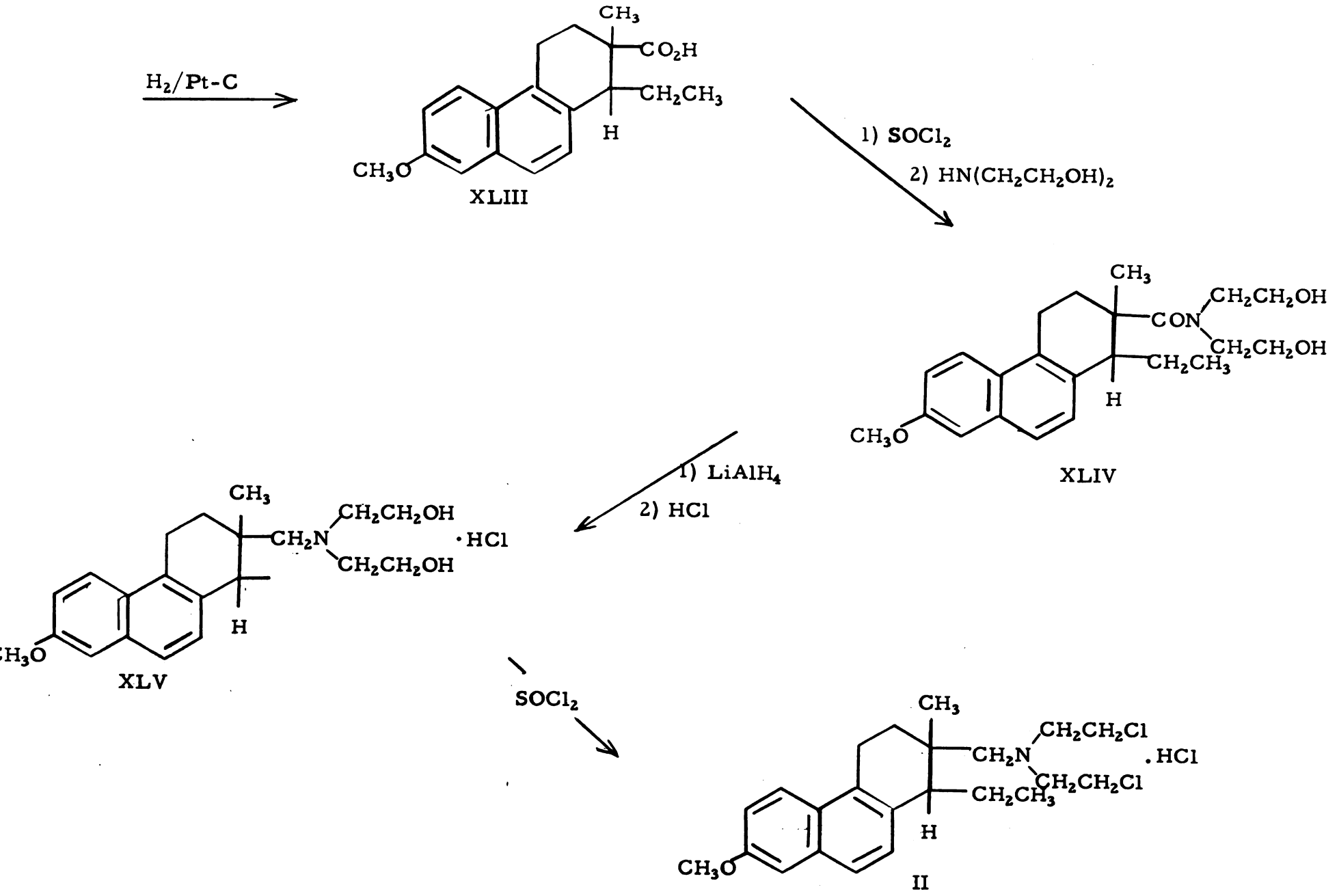


Figure XV. Reaction sequence for the preparation of 1-ethyl-2-methyl-2-[N, N-bis-(2-chloroethyl)aminomethyl]-7-methoxy-1, 2, 3, 4-tetrahydrophenanthrene hydrochloride.

Decarbonylation of the glyoxalate (XXXVIII) to 1-keto-2-carbomethoxy-7-methoxy-1, 2, 3, 4-tetrahydrophenanthrene (XXXIX) was effected by adding powdered soft glass to a melt of the glyoxalate. In the case of the tricyclic glyoxalate, however, it was found that a single treatment of a melt of the compound with powdered glass did not complete the decarbonylation. It was necessary to cool the reaction mixture to 150°, add a second portion of powdered glass and reheat the mixture to 190° in order to obtain 1-keto-2-carbomethoxy-7-methoxy-1, 2, 3, 4-tetrahydrophenanthrene free of starting glyoxalate.

The angular methyl group at C_2 was introduced by the alkylation of the sodio-derivative of 1-keto-2-carbomethoxy-7-methoxy-1, 2, 3, 4-tetrahydrophenanthrene with methyl iodide. The procedure developed with the model compounds was used for this alkylation without modification and gave the methylated product in an 88% yield.

As previously described for the substituted and unsubstituted bicyclic compounds (IX and XXVI), the introduction of the ethyl group at C_1 was effected by the selective addition of one mole of ethylmagnesium bromide to the C_1-carbonyl group of 1-keto-2-methyl-2-carbomethoxy-1, 2, 3, 4-tetrahydrophenanthrene (XL). The product obtained was a mixture of the diastereoisomeric 1-ethyl-1-hydroxy-2-methyl-2-carbomethoxy-7-methoxy-1, 2, 3, 4-tetrahydrophenanthrenes (XLI). This mixture of isomeric alcohols had a melting point of 118-138°. Miescher (97) reported a melting point of 118-130° for this mixture of isomeric alcohols, which he obtained by essentially the same procedure that was used in this work.

Dehydration of the mixture of diastereoisomeric hydroxy esters (XLI) was effected by heating to 100° with 85% formic acid. The mixture of crude cis- and trans-1-ethylidene-2-methyl-2-carbomethoxy-7-methoxy-1, 2, 3, 4-tetrahydrophenanthrenes ($XLII_c$ and $XLII_t$, R = CH_3)

thus obtained was not purified prior to saponification to a mixture of the isomeric 1-ethylidene-2-methyl-2-carboxy-7-methoxy-1,2,3,4-tetrahydrophenanthrenes ($XLII_c$ and $XLII_t$, R = H) with alcoholic potassium hydroxide. No attempt was made to separate the cis- and trans-isomers of this unsaturated acid. Based on the results obtained from the hydrogenation of the model compounds only one saturated product was expected by the hydrogenation of either the cis- or the trans-unsaturated acid. The isomeric mixture had a melting point of 165-174°, which is in fair agreement with that reported by Miescher (99). By using essentially the same procedure as described here he obtained a similar mixture of these unsaturated acids with a melting point of 163-175°.

Due to the limited solubility of the 1-ethylidene-2-methyl-2-carboxy-7-methoxy-1,2,3,4-tetrahydrophenanthrenes ($XLII_c$ and $XLII_t$, R = H) in ethanol the hydrogenation procedure developed for the model compounds (XI and XXVIII, R = H) had to be modified. Ethyl acetate was the only suitable hydrogenation solvent found in which the unsaturated tricyclic acid was soluble to any extent at room temperature. Very dilute solutions had to be used for this hydrogenation since the saturated acid produced was much less soluble and separated from solution during the hydrogenation and occluded the catalyst. Despite the fact that the number of replicate hydrogenations was increased it was felt that the use of dilute solutions was more expedient than increasing the temperature. An increase in temperature could easily alter the favorable stereochemical course observed with the hydrogenation of the model compounds. Except for the use of a dilute ethyl acetate solution instead of an ethanol solution, the procedure employed for the hydrogenation of the tricyclic unsaturated acid was the same as that developed for the model compounds, i.e., 5% platinum on charcoal catalyst, 15 pounds pressure for 20 minutes at ambient temperature.

As in the case of the bicyclic acids (XI and XXVIII, R = H), already discussed, the hydrogenation of a mixture of cis- and trans-1-ethylidene-2-methyl-2-carboxy-7-methoxy-1, 2, 3, 4-tetrahydrophenanthrenes (XLII, R = H) gave only one of the two possible diastereoisomeric saturated acids (XLIII). 1-Ethyl-2-methyl-2-carboxy-7-methoxy-1, 2, 3, 4-tetrahydrophenanthrene (XLIII) was obtained in a 89.4% yield and was of excellent quality when it was isolated from the hydrogenation mixture. The melting point was 228-230°.

Conformational formulas for the two epimeric forms of the cis-unsaturated acid (d-XLII$_c$ and l-XLII$_c$), the two epimeric forms of the cis-diasteroisomeric modification of the saturated acid (d-XLIII and l-XLIII), and a single epimeric form of the trans-diastereoisomeric modification of the saturated acid (XLVI) are shown in Figure XVI. The related conventional formulas, as used throughout this discussion, are also shown for comparison. The conformational formulas are written as cyclohexenes with the double bond representing the junction of the aromatic B-ring with the C-ring. When written in this manner the aromatic AB-rings extend back perpendicular to the plane of the page with the A-ring always being behind and to the right of the B-ring.

Since the compound formed by the hydrogenation of the tricyclic unsaturated acid (XLII) is bisdehydrodoisynolic acid methyl ether it is now possible to correlate the stereochemical course of the hydrogenation with known compounds. Both of the diastereoisomeric modifications of bisdehydrodoisynolic acid methyl ether have been prepared from naturally occurring estrogens of known configuration. Figure II shows the stereochemical relationships between equilenin and l-cis-bisdehydrodoisynolic acid. As seen in this figure cis-bisdehydromarrianolic acid, related to 14-isoequilenin, has been converted to cis-bisdehydrodoisynolic acid by a series of reactions which do not

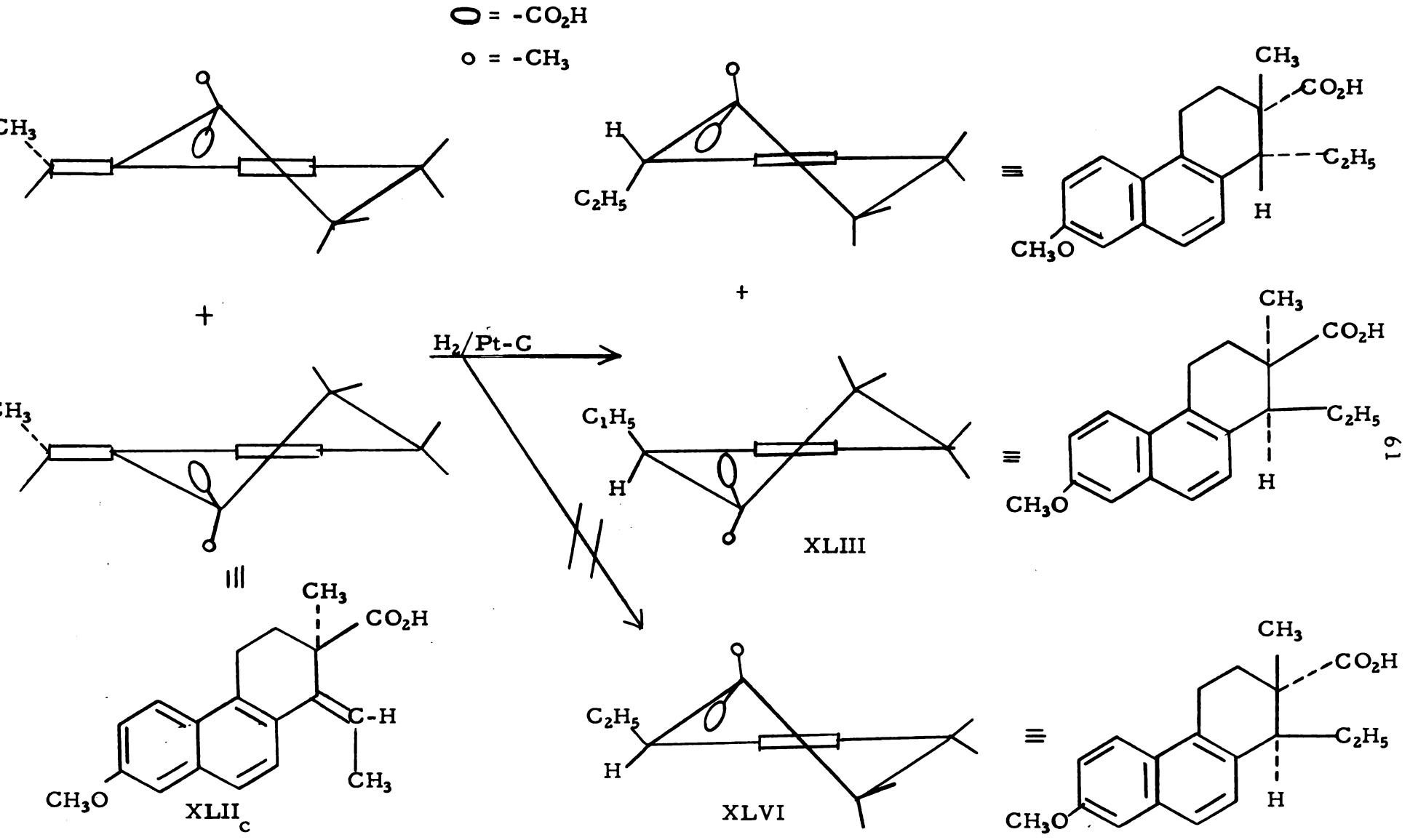


Figure XVI. Stereochemistry of the hydrogenation product from 1-ethylidene-2-methyl-2-carboxy-7-methoxy-1, 2, 3, 4-tetrahydrophenanthrene.

effect either of the asymmetric centers. Biologically inactive trans-bisdehydrodoisynolic acid accompanies the active cis-diastereoisomer in the product obtained from the alkali fusion of equilenin.

dl-cis-Bisdehydrodoisynolic acid methyl ether,* obtained from 14-isoequilenin, has a melting point of 228-230°, compared to the dl-trans-isomer with a melting point of 204-206°. Thus, the product obtained by the hydrogenation procedure developed in this work is the biologically active dl-cis-bisdehydrodoisynolic acid methyl ether.

Miescher and co-workers (99) described a procedure for the hydrogenation of 1-ethylidene-2-methyl-2-carboxy-7-methoxy-1,2,3,4-tetrahydrophenanthrene as the sodium salt in the presence of excess sodium hydroxide over Rupe nickel. This method gave dl-cis-bisdehydrodoisynolic acid methyl ether which was contaminated with a small amount of the isomeric dl-trans-isomer. If this reduction were carried out in the presence of sodium carbonate in place of the excess sodium hydroxide, the dl-cis-and dl-trans-isomers were formed in a ratio of approximately 2:3.

By constructing models (Stuart and Briegleb were used) of the four possible isomeric modifications of the unsaturated acid (XLII), i.e., d- and l-cis and d- and l-trans, it can be readily observed that the C_2-carboxyl group shields the olefinic bond to a much greater extent than does the C_2-methyl group. Since the hydrogen atom and the methyl group of the ethylidene residue are fixed in the same plane as the aromatic rings, the shielding of the double bond due to the methyl group is about the same in either the cis-or the trans-position.

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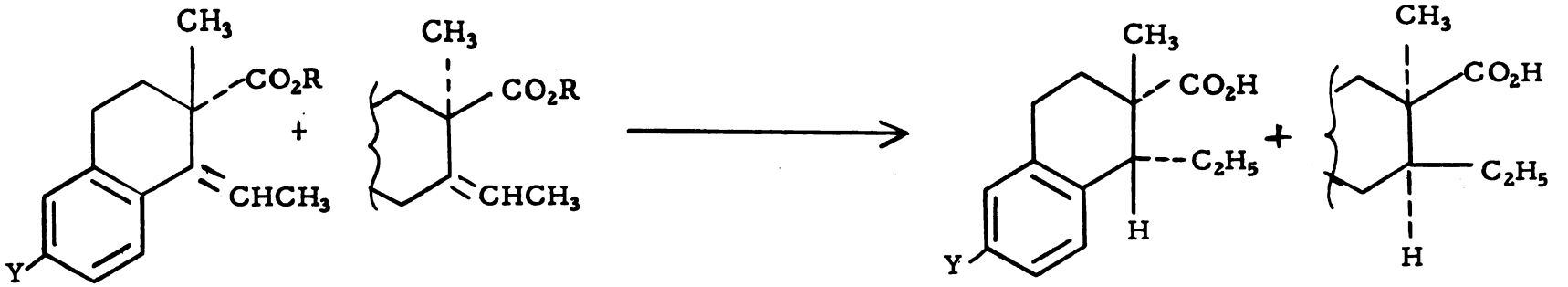
*The cis-isomer is also referred to as "α"- or normal- and the trans-isomer as "β"- or iso-bisdehydrodoisynolic acid. The C_1-ethyl and the C_2-carboxyl groups are used as reference in these designations. These groups correspond to the two acid residues in marrianolic acid, which in turn are related to the carbon atoms forming the five membered D-ring in the natural estrogens. Thus cis- or iso-bisdehydrodoisynolic acid is configurationally related to 14-isoequilenin, in which the juncture of the C and D rings is trans.

Thus, the course of this hydrogenation can be easily rationalized on the basis of the catalyst-hydrogen complex fitting the olefinic bond from the least hindered side of the molecule to give the saturated compound with the ethyl group cis to the carboxyl group. It is of interest to note that, since this hydrogenation gave the desired biologically active cis-bisdehydrodoisynolic acid, it probably would be of no practical use in the preparation of other estrogenic material such as doisynolic acid if the same stereochemical course were followed. This is because only in bisdehydrodoisynolic acid and monodehydrodoisynolic acid is the cis-diastereoisomer the active form. Doisynolic acid and the tetracyclic natural estrogens are active only in the trans-form.

By analogy to the tricyclic acid the stereochemistry of the bicyclic saturated acids, used as model compounds can now be tentatively assigned. Both 1-ethylidene-2-methyl-2-carboxy-6-methoxy-1, 2, 3, 4-tetrahydronaphthalene (XXVIII, R = H) and 1-ethylidene-2-methyl-2-carboxy-1, 2, 3, 4-tetrahydronaphthalene (XI, R = H) were hydrogenated to the isomeric saturated acid which should possess a cis-conformation. Thus, in the nitrogen mustards prepared as model compounds, the bis(2-chloroethyl)aminomethyl group and the ethyl groups should possess a cis orientation. These configurational assignments are shown in Figure XVII.

The acid chloride of 1-ethyl-2-methyl-2-carboxy-7-methoxy-1, 2, 3, 4-tetrahydrophenanthrene (XLIII) was prepared in the usual manner employing a large excess of freshly distilled thionyl chloride and a trace of pyridine as a catalyst. This acid chloride was not purified prior to the acylation of diethanolamine to give 1-ethyl-2-methyl-2-[N, N-bis-(2-hydroxyethyl)carbamyl]-7-methoxy-1, 2, 3, 4-tetrahydrophenanthrene (XLIV). Dioxane was used as the solvent for this acylation but, unlike the acid chlorides prepared during the synthesis of the model compounds,

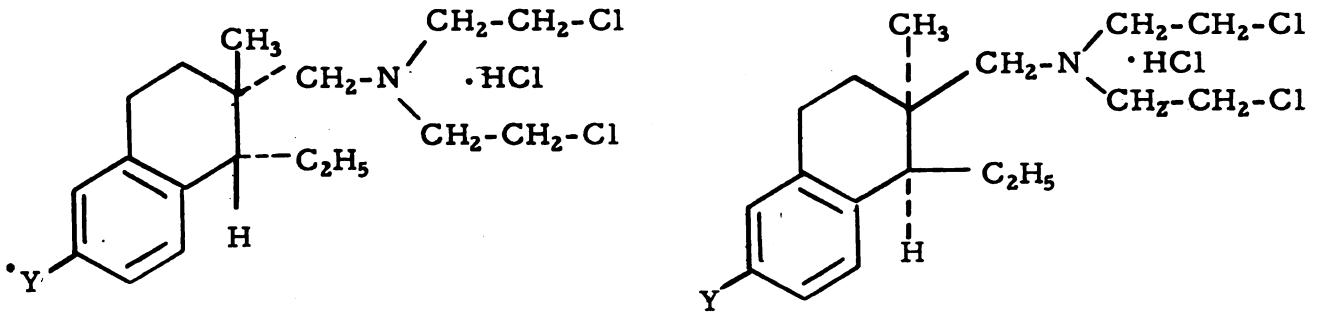


(XI, when R = H and Y = H)

(XXVIII, when R = H and Y = $\cdot OCH_3$

(XII, when Y = H)

(XXIX, when Y= $-OCH_3$)



(XV, when Y = H)

(XXXII, when Y = $-OCH_3$)

Figure XVII. Stereochemistry of 1-ethyl-2-methyl-2-carboxy-1, 2, 3, 4-tetrahydronaphthalene, 1-ethyl-2-methyl-2-carboxy-6-methoxy-1, 2, 3, 4-tetrahydronaphthalene, 1-ethyl-2-methyl-2-[N, N-bis(2-chloroethyl)aminomethyl]-1, 2, 3, 4-tetrahydronaphthalene hydrochloride and 1-ethyl-2-methyl-2-[N, N-bis(2-chloroethyl)aminomethyl]-6-methoxy-1, 2, 3, 4-tetrahydronaphthalene hydrochloride.

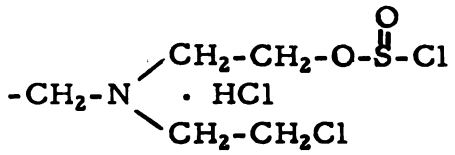
this tricyclic acid chloride was only slightly soluble in it at room temperature. The solution in the addition funnel had to be kept warm to prevent solidification. The crude amide was isolated from the reaction mixture as a yellow sirup and was not purified before reduction to the corresponding amine.

Reduction of the crude diethanolamide to the corresponding amine with lithium aluminum hydride was carried out in the manner previously described for the analogous model compounds. Passing anhydrous hydrogen chloride into an ethereal solution of the crude amine precipitated the pure amine hydrochloride. 1-Ethyl-2-methyl-2-[N,N-bis(2-hydroxyethyl)aminomethyl]-7-methoxy-1,2,3,4-tetrahydrophenanthrene hydrochloride (XLV) was thus obtained as a colorless solid in 90.0% yield (based on starting acid). A sample, recrystallized from methanol, gave satisfactory analytical results.

An attempt was made to prepare the nitrogen mustard hydrochloride by adding thionyl chloride to a slurry of the diethanolamine hydrochloride (XLV) in chloroform containing a trace of dimethylformamide. The experimental procedure followed was identical to that which had been successfully used with the model compounds. After the solvent and the excess thionyl chloride had been removed from the brown, homogeneous reaction mixture, there remained a thick, dark brown tar which was practically insoluble in all solvents except in large volumes of chloroform or of hot acetone. A chloroform solution of this tarry material slowly deposited a small amount of dark yellow solid. The mother liquor was passed through an alumina column, which was then eluted with dry chloroform. After the chloroform was removed from the combined eluates, a brown, ether-insoluble sirup remained. When anhydrous hydrogen chloride was bubbled into this solution, there was obtained a dark brown tar from which no solid could be isolated.

The solid had a melting point of approximately 173-175°. It showed signs of decomposition at 168° and the melt evolved gas at approximately 176°. An analysis of this product showed: C, 55.21%; N, 2.92%; Cl, 21.00%; S, 5.35%; ash, 0.68%. This data is most consistent with a monochlorosulfinate ester (XLVII). A molecular weight was not obtained for this material since in an attempted Rast molecular weight determination it decomposed in both camphor and biphenyl, and since no solution of sufficient concentration for observation of boiling point elevation or of freezing point depression could be obtained.

Chlorosulfinate esters are known to decompose when treated with excess thionyl chloride (141). Attempts to obtain the nitrogen mustard by treating this presumed chlorosulfinate ester with excess thionyl chloride or with a chloroform solution of thionyl chloride were unsuccessful. In both cases the product was a black tar from which no solid could be isolated.



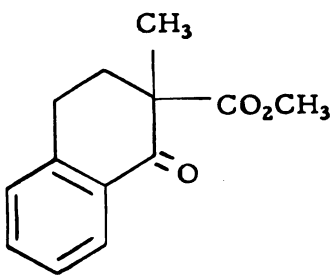
XLVII

D. Attempted Preparation of Model Compounds for C_1-Tricyclic Nitrogen Mustards

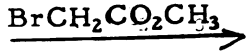
In order to investigate the sequence of reactions necessary to convert 1-keto-7-methoxy-1,2,3,4-tetrahydrophenanthrene (V) to 1-[N,N-bis(2-chlroethyl)aminomethyl]-2-methyl-2-carboxy-7-methoxy-1,2,3,4-tetrahydrophenanthrene hydrochloride (III), the preparation of another model compound was undertaken. 1-Tetralone was used,

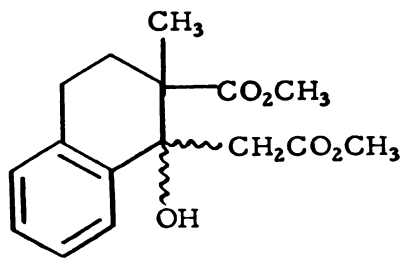
in place of the less readily available tricyclic ketone V, as a starting point for the synthesis of the model compound 1-[N, N-bis(2-chloroethyl)aminomethyl]-2-methyl-2-carboxy-1, 2, 3, 4-tetrahydronaphthalene (LVI, X = Cl). The reaction sequence devised for the synthesis of 1-[N, N[bis(2-hydroxyethyl)aminomethyl]-2-methyl-2-carbomethoxy-1, 2, 3, 4-tetrahydronaphthalene (LVI, X = OH), the immediate precursor of the methyl ester of the model nitrogen mustard, is shown in Figure XVIII.

Methyl (1-hydroxy-2-methyl-2-carbomethoxy-1, 2, 3, 4-tetrahydronaphthyl)acetate (LXVIII) was prepared by the Reformatsky reaction employing 1-keto-2-methyl-2-carbomethoxy-1, 2, 3, 4-tetrahydronaphthalene (IX), the preparation of which has been previously described, and methyl bromoacetate. Treatment of the Reformatsky ester (XLVIII) with a solution of thionyl chloride and pyridine in benzene afforded the tertiary chloride. This β-chloroester was not isolated before dehydrohalogenation and saponification to the dibasic acid (XLIX). A methanolic solution of potassium hydroxide was employed to effect this dehydrohalogenation and then an aqueous solution of potassium hydroxide was added to the reaction mixture to effect the saponification of the dimethyl ester. The stereochemistry of this mixture of unsaturated acids was not investigated. This was to be done if this reaction sequence had proved to be feasible. Since it has been demonstrated (126) that the reduction of either isomeric modification of the unsaturated acid (XLIX) leads to a mixture of the diastereoisomeric (2-methyl-2-carboxy-1, 2, 3, 4-tetrahydronaphthyl)acetic acids (L), no attempt was made to separate this mixture of unsaturated acids prior to reduction. This reduction was effected by treating an aqueous solution of the potassium salts of the unsaturated acids (XLIX) with approximately 20 parts (wt./wt.) of 2% sodium amalgam. Acidification of the basic solution from the reduction medium precipitated a mixture of the

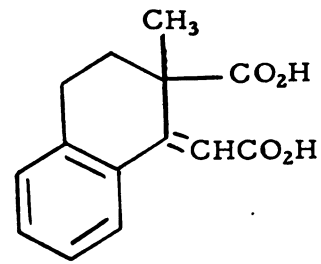


IX

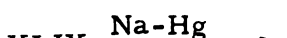


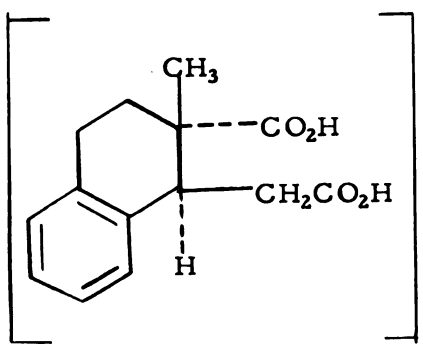


XLVIII



XLIX

XLIX 



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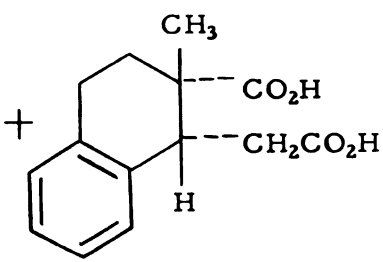

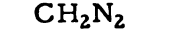

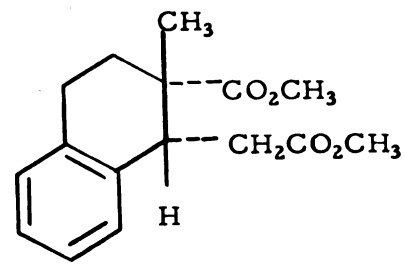

LI

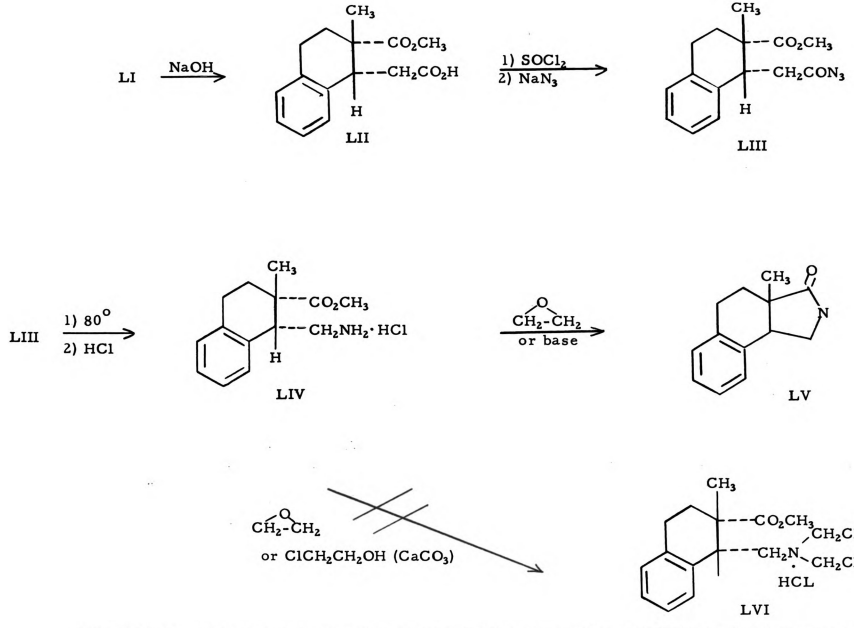

Figure XVIII. Proposed sequence of reactions for the preparation of 1-[N, N-bis(2-chloroethyl)amino-methyl]-2-methyl-2-carbomethoxy-1, 2, 3, 4-tetrahydronaphthalene hydrochloride.

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diastereoisomeric acids (L). The high melting and the low melting diastereoisomers were obtained in an approximately 4:1 ratio. Bachmann and Thomas (126) had previously prepared this same mixture of diastereoisomeric acids which they designated as "α" (high melting) and "β" (low melting), in approximately this same ratio. These workers did not investigate the stereochemistry of these acids. No effort was made in this work to assign configurations to these diastereoisomers.

Esterification of the high melting acid with diazomethane gave methyl (2-methyl-2-carbomethoxy-1, 2, 3, 4-tetrahydronaphthyl)acetate (LI) in near quantitative yield. The less hindered of the two carbomethoxy groups was selectively saponified with one equivalent of methanolic sodium hydroxide. (2-Methyl-2-carbomethoxy-1, 2, 3, 4-tetrahydronaphthyl)acetic acid (LII) was obtained in a 92% yield (after purification). A dry acetone solution of the half-ester acid chloride, prepared from the acid and thionyl chloride, was treated with an aqueous solution of sodium azide and gave (2-methyl-2-carbomethoxy-1, 2, 3, 4-tetrahydronaphthyl)acetyl azide (LIII). A benzene solution of this azide, after refluxing and the addition of concentrated hydrochloric acid, gave 1-aminomethyl-2-methyl-2-carbomethoxy-1, 2, 3, 4-tetrahydronaphthalene hydrochloride (LIV). This amine hydrochloride, when recrystallized to analytical purity, had a melting point of 169-170°. All attempts to obtain the free amine failed due to the facile formation of a five membered lactam (LV). Since 1-aminomethyl-2-methyl-1, 2, 3, 4-tetrahydro-2-naphthoic acid lactam (LV) was formed by the amidation of the methyl ester, it was felt that the free amine might be obtained if the ester were hydrolyzed to the free acid or saponified to the acid salt. Attempted hydrolysis of the ester with concentrated hydrochloric acid led to the isolation of the lactam (LV), as did an attempt to isolate the barium salt (142) of the acid by saponification in refluxing barium hydroxide solution. Although the free amine could

not be isolated, it was hoped that the amine hydrochloride might react with an excess of ethylene oxide to give the desired 1-[N, N-bis-(2-hydroxyethyl)aminomethyl]-2-methyl-2-carbomethoxy-1, 2, 3, 4-tetrahydronaphthalene hydrochloride (LVI). However, the reaction of the amine hydrochloride with ethylene oxide or with ethylene chlorohydrin led to the cyclic lactam as the only product. Attempts to hydrolyze the lactam by several methods also proved to be unsuccessful.

The synthetic route which was devised and investigated leading to 1-[N, N-bis(2-hydroxyethyl)amino]-2-methyl-2-carbomethoxy-1, 2, 3, 4-tetrahydronaphthalene (LX), the immediate precursor for the model nitrogen mustard analogous to the doisynolic acid-type nitrogen mustard 1-[N, N-bis(2-chloroethyl)amino]-2-methyl-2-carboxy-7-methoxy-1, 2, 3, 4-tetrahydrophenanthrene hydrochloride (IV), is shown in Figure XIX.

1-Keto-2-methyl-2-carbomethoxy-1, 2, 3, 4-tetrahydronaphthalene (IX), the preparation of which has already been described, was reduced to 1-hydroxy-2-methyl-2-carbomethoxy-1, 2, 3, 4-tetrahydronaphthalene (LVII) with sodium borohydride. Only one of the two possible diastereoisomeric β-hydroxy esters was obtained by this reduction procedure. No investigation of the stereochemistry of this reduction product was considered pending the success of this synthesis.

Reaction of the β-hydroxy ester (LVII) with phosphorous pentachloride and barium carbonate gave the chloro-ester (LVIII). This chloro-ester was not isolated before use for the attempted alkylation of diethanolamine. No tertiary amine could be isolated from the reaction mixture resulting from this attempted alkylation. Other workers (117, 118, 119) have reported similar difficulties in attempting to alkylate diethanolamine with hindered alkyl halides.

Since the alkylation with diethanolamine proved to be unsuccessful an attempt was made to prepare the primary amine by the Gabriel

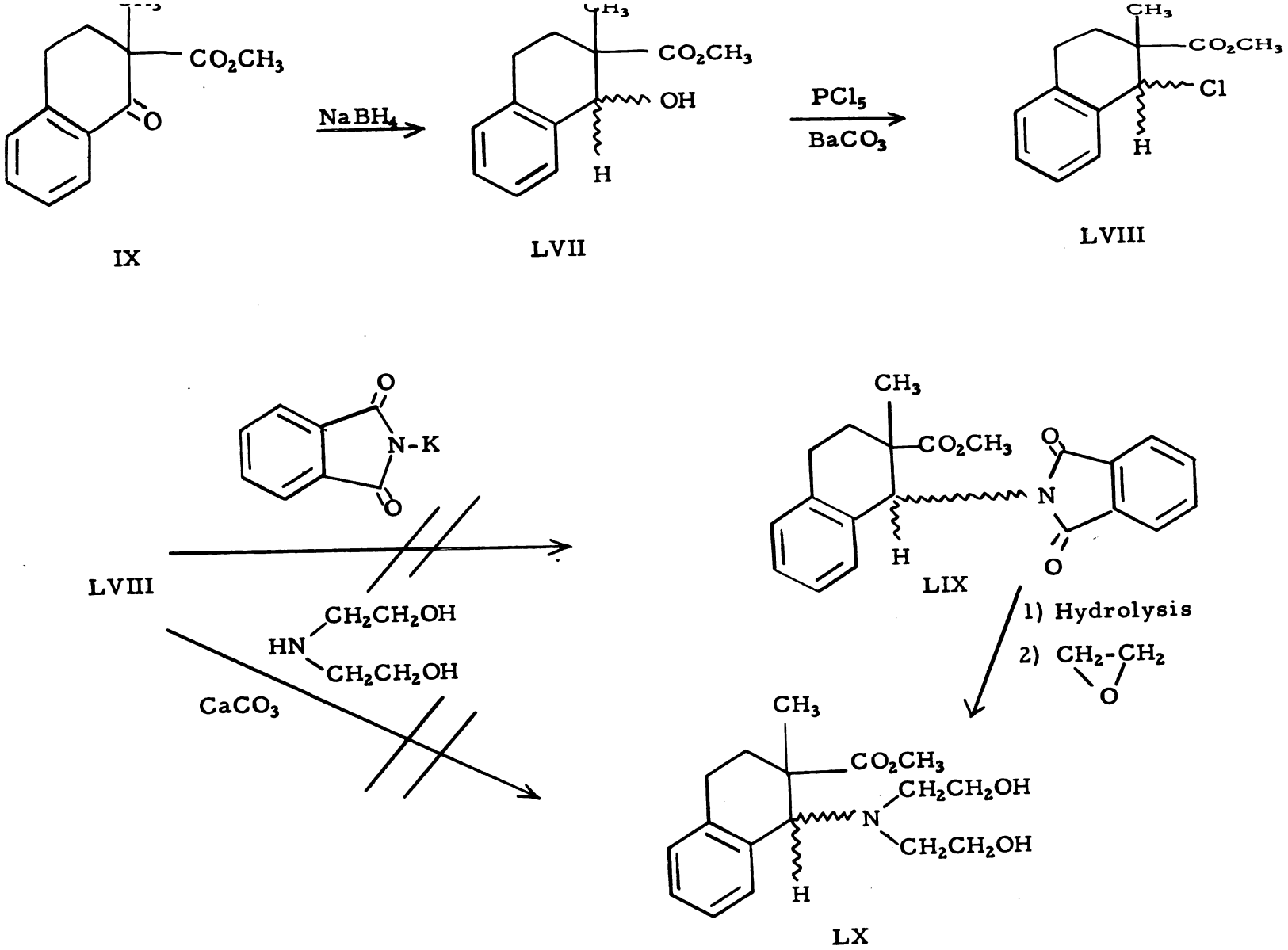

Figure XIX. Proposed sequence of reactions for the preparation of 1-[N, N-bis-(2-chloroethyl)amino]-2-methyl-2-carbomethoxy-1, 2, 3, 4-tetrahydro-naphthalene hydrochloride.

synthesis. The proposed route to the desired intermediate is also shown in Figure XIX. The reaction of the chloride (LVIII) with potassium phthalimide did give evidence of a reaction as shown by the isolation of a small amount of potassium chloride upon dilution of the reaction mixture in chloroform. The attempted hydrolysis of the crude phthalimido-derivative led to a intractable tar from which no primary amine could be isolated. This tar may have been a polyamide polymer since it contained nitrogen (sodium fusion).

EXPERIMENTAL[1,2,3]

1-Keto-1,2,3,4-tetrahydronaphthalene (1-tetralone). A solution of 104 g. (1.2 moles) of γ-butyrolactone in 1-l. of dry benzene was placed in a 3-l. flask equipped with a stirrer, a 20 cm. length of rubber tubing connecting a neck of the flask with the neck of a 1-l. Erlenmeyer flask and a reflux condenser topped with a calcium chloride drying tube. The Erlenmeyer flask was charged with 600 g. (4.5 moles) of anhydrous aluminum chloride. This was added to the stirred reaction mixture, in approximately 10 g. portions, over a period of 2 hrs. During this addition the reaction mixture became dark brown and refluxed slowly. Hydrogen chloride was also evolved. After the addition of the aluminum chloride, the reaction mixture was heated on a steam bath with constant stirring for 16 hrs. At the end of this reflux period the mixture was allowed to cool to room temperature and was then poured onto a mixture of approximately 3-kg. of crushed ice and 500 ml. of concentrated hydrochloric acid. The water layer was separated and was extracted with 500 ml. of toluene. The brown organic layer and the toluene extracts were combined and the solution was washed successively with two 100 ml. portions of water, with 100 ml. of 20% potassium hydroxide and finally with two 100 ml. portions of saturated

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[1]All melting points were taken in open capillary tubes and are uncorrected, unless otherwise noted. Boiling points are all uncorrected.

[2]The compound names used for headings of the experimental section are those recommended by the Chemical Abstracts Service in "The Naming and Indexing of Chemical Compounds," Chemical Abstracts Service, 1957. In some cases the less cumbersome trivial names are used in the text.

[3]Microanalyses by Micro-Tech Laboratories, Skokie, Illinois.

sodium chloride. Flash distillation on the steam bath at aspirator pressure removed the solvents. This distillation was carried out by undersurface addition to prevent foaming. The residue was distilled through a Fenske column and gave the following fractions.

Fraction	B.p., °C. (0.4 mm.)	Grams	n_D^{25}
1	55-65	4.3	-
2	65-74	4.0	-
3	75-77	70.5	1.5663
4	77-77	92.3	1.5665
residue	--	125.0	-

Fractions 3 and 4, assumed to be 1-tetralone, amounted to 162.8 g. (92.2%).

The above procedure is essentially that of Olson and Bader, as described in Organic Syntheses (124). These workers reported a 91-96% yield of 1-tetralone with a boiling point of 75-85° (0.3 mm.), n_D^{25} 1.565-1.568.

Dimethyl oxalate. To a solution of 45.0 g. (0.5 mole) of anhydrous oxalic acid in 50 ml. of anhydrous methanol contained in a 250 ml. flask equipped with a stirrer, a reflux condenser and an addition funnel was added 18.5 ml. of concentrated sulfuric acid over a period of 30 min. When the addition was completed, the reaction mixture was heated to boiling and was then filtered rapidly. The reaction flask was rinsed with 20 ml. of hot methanol which was poured through the filter. After standing in the cold for 24 hrs. the crystals were filtered with suction and air dried. The filtrate was concentrated and, after cooling, a second crop of crystals was collected and combined with the first crop. Recrystallization from anhydrous methanol gave 42.0 g. (71.2%) of dimethyl oxalate, m.p. 51.5-52.5°.

This procedure is a modification of that described in Organic Syntheses (143) by Bowden who reported a 68-76% yield of dimethyl oxalate, m.p. 52.5-53.5°.

Methyl 1-keto-1, 2, 3, 4-tetrahydronaphthalene-2-glyoxalate. A solution of 11.5 g. (0.5 g. atom) of sodium in 80 ml. of anhydrous methanol, to which 100 ml. of dry benzene had been added, was distilled to dryness at reduced pressure. After the dry salt had been heated on a steam bath under a nitrogen atmosphere for 15 min., it was crushed in the flask and was stirred with 100 ml. of refluxing benzene for 15 min. The resulting slurry of alcohol-free sodium methoxide was then cooled to 5° in an ice bath and a solution of 36.5 g. (0.25 mole) of 1-tetralone and 59.0 g. (0.5 mole) of dimethyl oxalate in 100 ml. of dry benzene was added in one portion. After the solution had stood in the ice bath for approximately 45 min., the yellow sodio-derivative of the glyoxalate precipitated from the light green solution. After an additional hour at 5° the ice bath was removed and the reaction mixture was allowed to stand at room temperature for 12 hrs. The reaction mixture was then poured onto 200 g. of ice, the water layer was acidified to Congo red with dilute hydrochloric acid, was separated, and was extracted with four 200 ml. portions of ether. The combined organic solution was extracted eight times with 100 ml. portions of 2% sodium hydroxide solution. These basic extracts were combined, were poured onto ice and were acidified to a pH of 5 (pHydrion paper) with 6N hydrochloric acid. The dark yellow solid was filtered off, was washed twice with cold water and was dried overnight over anhydrous calcium chloride. The dark yellow methyl 1-keto-1, 2, 3, 4-tetrahydronaphthalene-2-glyoxalate, m.p. 58-61°, weighed 49.3 g. (85.2%).

A 5 g. sample of this glyoxalate, after several recrystallizations from methanol, gave 3.3 g. of pure methyl 1-keto-1, 2, 3, 4-tetrahydronaphthalene-2-glyoxalate, m.p. 64-66°, as light yellow crystals. The bulk of this material was not purified before decarbonylation to 1-keto-2-carbomethoxy-1, 2, 3, 4-tetrahydronaphthalene.

This procedure is based on those of Dannenberg and Laufer (125) and Bachmann and Thomas (126). The former reported an 85% yield of the glyoxalate. Bachmann and Thomas obtained the glyoxalate in a yield of 91% and reported a melting point of 65.5-66.5°.

1-Keto-2-carbomethoxy-1,2,3,4-tetrahydronaphthalene. A 100 ml. Florence flask containing a mixture of 9 g. of powdered soft glass and 18 g. (0.078 mole) of methyl 1-keto-1,2,3,4-tetrahydronaphthalene-2-glyoxalate was suspended in an air bath. The temperature of the air bath was raised to 180±5° in approximately 5 min. and was maintained at this temperature for 20 to 25 min. A vigorous evolution of gas commenced as the temperature reached approximately 150° and lasted for about 15 min. Very little gas evolution was observed during the remainder of the heating period. The flask was removed from the air bath and was allowed to cool to room temperature. The organic residue was dissolved in acetone and was filtered to remove the glass. The acetone solution was treated with Norite and the acetone was removed with a rotary evaporator, leaving 19.3 g. of brown, viscous oil. This residue failed to crystallize. The crude product was distilled without fractionation through an ether bridge (bath temperature 140±10°) at 0.6 mm. The clear, straw-colored distillate was crystallized from methanol to give 11.2 g. (70.5%) of 1-keto-2-carbomethoxy-1,2,3,4-tetrahydronaphthalene, m.p. 83-85°.

A 1.5 g. sample of the above product, after recrystallization several times from methanol, gave 1.1 g. of pure 1-keto-2-carbomethoxy-1,2,3,4-tetrahydronaphthalene, m.p. 83-84.5°.

This procedure is a modification of that described by Bachmann and Thomas (126) who reported a 94% yield of 1-keto-2-carbomethoxy-1,2,3,4-tetrahydronaphthalene, m.p. 84.5-86.5°.

1-Keto-2-methyl-2-carbomethoxy-1, 2, 3, 4-tetrahydronaphthalene. To a solution of 0.87 mole of sodium methoxide in 400 ml. of methanol, under a dry nitrogen atmosphere, was added a solution of 40.8 g. (0.2 mole) of 1-keto-2-carbomethoxy-1, 2, 3, 4-tetrahydronaphthalene in a mixture of 200 ml. of dry benzene and 200 ml. of anhydrous methanol. The reaction mixture was refluxed with stirring for 15 min. and was cooled in an ice bath to 5°. To the resulting slurry of the sodio-derivative there was added 60 ml. (136.6 g., 0.96 mole) of methyl iodide in one portion. The ice bath was removed and the mixture was stirred at room temperature for 2 hrs. After being refluxed for 45 min. the reaction mixture was cooled in an ice bath and was neutralized to a pH of 7 (pHydrion paper) with glacial acetic acid. The light orange colored solution was evaporated to near dryness in a rotary evaporator and the residue was partitioned between 300 ml. of water and 200 ml. of benzene. The water layer was separated and extracted with two 100 ml. portions of benzene. The combined organic solution was washed several times with small portions of sodium bicarbonate solution and once with water. After the solution had been dried over anhydrous sodium sulfate, the solvent was removed with a rotary evaporator. The brown, liquid residue was dissolved in the minimum amount of methylcyclohexane and then was diluted to twice its volume with additional solvent. Passing this solution through a fritted glass Büchner funnel (6 cm. diameter) containing 100 g. of alumina (Merck chromatographic grade) removed most of the color. The light yellow solution was then concentrated to approximately one-half its volume in a rotary evaporator. The solid which separated, when the solution was kept at 5° for 10 hrs., was removed by filtration and was dried *in vacuo* over paraffin chips. The colorless solid weighed 33.9 g. and melted at 53-55°. From the filtrate there was isolated an additional 3.1 g. of product, m.p. 53-55°. This raised the total yield to 37.0 g. (84.6%). A 1.5 g. sample,

recrystallized several times from methylcyclohexane, gave 0.9 g. of pure 1-keto-2-methyl-2-carbomethoxy-1,2,3,4-tetrahydronaphthalene, 58-59.5°.

This procedure is a modification of that described by Bachmann and Thomas (126). These workers reported an 88% yield of 1-keto-2-methyl-2-carbomethoxy-1,2,3,4-tetrahydronaphthalene, m.p. 56-57.5°.

1-Ethyl-1-hydroxy-2-methyl-2-carbomethoxy-1,2,3,4-tetrahydronaphthalene. A solution of 0.05 mole of ethylmagnesium bromide (from 1.3 g., 0.054 g. atom of magnesium and 5.9 g., 0.054 mole of ethyl bromide) in 80 ml. of anhydrous ether was prepared in a 300 ml. flask equipped with a stirrer, a thermometer, a reflux condenser, a nitrogen inlet tube, and a pressure equilizing addition funnel. To this Grignard reagent was added a solution of 10.9 g. (0.05 mole) of 1-keto-2-methyl-2-carbomethoxy-1,2,3,4-tetrahydronaphthalene in 50 ml. of dry benzene at such a rate that the temperature did not rise above 10°. After the addition had been completed, the reaction mixture was maintained at 5° for 30 min., at room temperature for 1 hr. and was finally refluxed for 30 min. The mixture was then cooled below room temperature and poured onto 200 g. of ice. Dilute hydrochloric acid was added slowly until the inorganic salts had dissolved. The two layers were separated and the water layer was extracted with two 50 ml. portions of benzene-ether (5:1). The organic solutions were combined and washed successively with 100 ml. of 1N hydrochloric acid, with 100 ml. of water and with 50 ml. of saturated sodium chloride solution. After the organic phase had been dried over anhydrous sodium sulfate, the solvent was removed with a rotary evaporator, leaving 11.65 g. (94.0%, crude yield) of light yellow, solid residue. This product was not further purified before dehydration and saponification.

This procedure is a modifiation of that used by Anner and Miescher (99) for the preparation of the analogous 1-ethyl-1-hydroxy-2-methyl-2-carbomethoxy-6-methoxy-1, 2, 3, 4-tetrahydronaphthalene.

Mixture of the cis and trans-1-ethylidene-2-methyl-2-carbomethoxy-1, 2, 3, 4-tetrahydronaphthalenes. A mixture of 10.82 g. (0.044 mole) of the crude isomeric 1-ethyl-1-hydroxy-2-methyl-2-carbomethoxy-1, 2, 3, 4-tetrahydronaphthalene and 15 ml. of 85% formic acid was warmed on a steam bath for approximately 2 hrs. The reaction mixture turned dark red after 10-15 min. and retained this color throughout the heating period. It was then cooled to room temperature and was dissolved in 250 ml. of benzene. The benzene solution was washed with water, with several 20 ml. portions of 5% sodium hydroxide, with water and finally with saturated sodium chloride solution. After the benzene solution had been dried over anhydrous sodium sulfate the solvent was removed with a rotary evaporator, leaving a dark brown sirup amounting to 9.73 g. (95.4% crude yield). This crude ester was not purified before saponification to the free acid.

This procedure is a modification of that used by Anner and Miescher (99) for the preparation of a mixture of cis- and trans-1-ethylidene-2-methyl-2-carbomethoxy-6-methoxy-1, 2, 3, 4-tetrahydronaphthalenes.

cis and trans-1-Ethylidene-2-methyl-2-carboxy-1, 2, 3, 4-tetrahydronaphthalene. A mixture of 9.6 g. (0.042 mole) of crude 1-ethylidene-2-methyl-2-carbomethoxy-1, 2, 3, 4-tetrahydronaphthalene and 10 g. of potassium hydroxide in 10 ml. of water and 15 ml. of ethanol was refluxed for 4 hrs. The reaction mixture was then cooled to room temperature and the ethanol was removed with a rotary evaporator. The residue was diluted with 200 ml. of water and the resulting

cloudy solution was extracted with three 10 ml. portions of benzene to remove any non-acidic material. The water solution was cooled and acidified with dilute hydrochloric acid to a pH of 2 (pHydrion paper). The dark brown semi-solid which separated from the solution was extracted into four 100 ml. portions of benzene. The benzene extracts were combined and were washed once with 50 ml. of saturated sodium chloride solution. After the solution had been dried over anhydrous sodium sulfate, the solvent was removed with a rotary evaporator leaving a residue which amounted to 6.65 g. (73.8% crude yield). Recrystallization from methylcyclohexane gave 2.60 g. of a high melting acid, m.p. 123-125° and 3.95 g. of a low melting acid, m.p. 83-84°. A 1.0 g. sample of each of these isomeric acids was recrystallized several times from methylcyclohexane. The pure trans-1-ethylidene-2-methyl-2-carboxy-1, 2, 3, 4-tetrahydronaphthalene melted at 124-125° and the cis-1-ethylidene-2-methyl-2-carboxy-1, 2, 3, 4-tetrahydronaphthalene melted at 84-85°.

This procedure is a modification of that described by Anner and Miescher (99) for the preparation of 1-ethylidene-2-methyl-2-carboxy-6-methoxy-1, 2, 3, 4-tetrahydronaphthalene.

Analysis:

Calculated for cis-1-ethylidene-2-methyl-2-carboxy-1, 2, 3, 4-tetrahydronaphthalene, $C_{14}H_{16}O_2$: C, 77.76; H, 7.45.

Found: C, 77.65; H, 7.27.

Calculated for trans-1-ethylidene-2-methyl-2-carboxy-1, 2, 3, 4-tetrahydronaphthalene, $C_{14}H_{16}O_2$: C, 77.76; H, 7.45.

Found: C, 77.70; H, 7.42.

1-Ethyl-2-methyl-2-carboxy-1, 2, 3, 4-tetrahydronaphthalene.

a) By the hydrogenation of pure trans-1-ethylidene-2-methyl-2-carboxy-1, 2, 3, 4-tetrahydronaphthalene. A solution of 1.0 g. of trans-1-ethylidene-2-methyl-2-carboxy-1, 2, 3, 4-tetrahydronaphthalene

in 50 ml. of 95% ethanol was placed in a 500 ml. low pressure bottle with 0.5 g. of 5% platinum on charcoal catalyst. The bottle was placed in a Parr low pressure hydrogenation apparatus and charged with hydrogen to a pressure of 15 lb. The hydrogen pressure was maintained at 15±1 lb. until the consumption of hydrogen had ceased. The reaction required approximately 20 min. at ambient temperature. The catalyst was removed by filtration and the ethanol was evaporated in a current of dry nitrogen at room temperature to give a colorless solid residue weighing 0.92 g. and having a melting point of 132-135°. After two recrystallizations of this residue from ethanol there was obtained 0.78 g. of pure 1-ethyl-2-methyl-2-carboxy-1,2,3,4-tetrahydronaphthalene, m.p. 135-136°.

b) By the hydrogenation of cis-1-ethylidene-2-methyl-2-carboxy-1,2,3,4-tetrahydronaphthalene. A solution of 1.0 g. of cis-1-ethylidene-2-methyl-2-carboxy-1,2,3,4-tetrahydronaphthalene, m.p. 84-85°, in 50 ml. of 95% ethanol was hydrogenated by the same procedure as described for the trans-isomer. Upon evaporation of the solvent there was obtained 0.90 g. of residue which after recrystallization from ethanol gave 0.72 g. of pure 1-ethyl-2-methyl-2-carboxy-1,2,3,4-tetrahydronaphthalene, m.p. 134-135°. The products from the hydrogenation of the cis- and trans-isomeric acids gave a mixed melting point of 135-136°.

Analysis. Calculated for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31.
Found: C, 76.97; H, 8.26.

c) By the hydrogenation of a mixture of cis- and trans-1-ethylidene-2-methyl-2-carboxy-1,2,3,4-tetrahydronaphthalene. A solution of 11.2 g. (0.052 mole) of a mixture of cis- and trans-1-ethylidene-2-methyl-2-carboxy-1,2,3,4-tetrahydronaphthalene in 60 ml. of 95% ethanol was placed in a 500 ml. pressure bottle with 2 g. of 5% platinum on charcoal. The bottle was placed in a Parr low pressure hydrogenation apparatus

and was charged with 15 lb. of hydrogen. The hydrogenation was allowed to proceed for 30 min. at ambient temperature. Previous work with the pure cis- and trans-isomers of this compound have shown that the hydrogenation is complete in 20 min. The catalyst was filtered off and the alcohol solution was concentrated to approximately 20 ml. with rotary evaporator. Upon cooling this alcohol solution, the product separated as a colorless solid. The 1-ethyl-2-methyl-2-carboxy-1,2,3,4-tetrahydronaphthalene, m.p. 132-135°, weighed 9.80 g. (86.5%).

A 1.0 g. sample, of the above compound, after several recrystallizations recrystallized several times from ethanol, gave 0.82 g. of pure 1-ethyl-2-methyl-2-carboxy-1,2,3,4-tetrahydronaphthalene, m.p. 136-136.5°. This compound gave a mixed melting point of 136-136.5° with the 1-ethyl-2-methyl-2-carboxy-1,2,3,4-tetrahydronaphthalene obtained by the hydrogenation of the pure isomeric modifications of cis- and trans-1-ethylidene-2-methyl-2-carboxy-1,2,3,4-tetrahydronaphthalene.

1-Ethyl-2-methyl-2-[N,N-bis(2-hydroxyethyl)carbamyl]-1,2,3,4-tetrahydronaphthalene. A solution of 10.9 g. (0.05 mole) of 1-ethyl-2-methyl-2-carboxy-1,2,3,4-tetrahydronaphthalene and 4 drops of pyridine in 30 ml. of dry benzene was cooled to 5°. To this solution was added 16 ml. (26.5 g., 0.22 mole) of freshly distilled Matheson, Coleman and Bell thionyl chloride over a period of 30 min. with constant stirring. After the addition had been completed, the reaction mixture was stirred at room temperature for 3 hrs. and then was warmed to 40° for 1 hr. Removal of the benzene and excess thionyl chloride with a rotary evaporator left a dark brown residue. A 10 ml. portion of dry benzene was added to the residue and was then evaporated with a rotary evaporator. This process was repeated six times in order

to remove the last traces of thionyl chloride. The odor of thionyl chloride could not be detected after the fourth treatment. The crude acid chloride, amounting to 13.9 g., was dissolved in 50 ml. of purified dioxane (144) and the solution was filtered (to remove the pyridine hydrochloride) into an addition funnel. This solution was added over a period of 2 hrs. to a well-stirred mixture of 52 ml. (0.54 mole) of diethanolamine in 100 ml. of dioxane at room temperature. After the addition had been completed, the reaction mixture was heated to 55° in an oil bath and was maintained at this temperature for 12 hrs. The dioxane was then removed directly from the reaction flask by distillation at 15 mm. pressure. The light yellow liquid residue was cooled to room temperature and was partitioned between 150 ml. of water and 120 ml. of benzene. The layers were separated and the water layer was extracted with three 30 ml. portions of benzene. The benzene extracts were combined and were washed successively with two 15 ml. portions of 2% potassium hydroxide, with 50 ml. of water, with two 15 ml. portions of 1N hydrochloric acid, with 50 ml. of water and finally with saturated sodium chloride solution. After the solution was dried over anhydrous sodium sulfate, the solvent was removed with a rotary evaporator, leaving 16.85 g. of crude 1-ethyl-2-methyl-2-[N, N-bis(2-hydroxyethyl)carbamyl]-1,2,3,4-tetrahydronaphthalene as a thick yellow sirup. No attempt was made to purify this product before its reduction to the corresponding amine.

Benner (145), using a similar procedure, prepared N, N-bis-(2-hydroxyethyl)3, 4-di(p-methoxyphenyl)-3-hexenamide.

1-Ethyl-2-methyl-2-[N, N-bis(2-hydroxyethyl)aminomethyl]-1, 2, 3, 4-tetrahydronaphthalene hydrochloride. A solution of 16.85 g. of crude 1-ethyl-2-methyl-2-[N, N-bis(2-hydroxyethyl)carbamyl]-1, 2, 3, 4-tetrahydronaphthalene in 75 ml. of purified tetrahydrofuran (146)

was added to a well-stirred slurry of 4.56 g. (0.12 mole) of lithium aluminum hydride in 275 ml. of tetrahydrofuran over a period of 2 hrs. After the reaction mixture had been refluxed for 8 hrs., an additional 0.46 g. of lithium aluminum hydride was added and the refluxing was continued for 4 hrs. The reaction mixture was then cooled to 10° and 30 ml. of wet ethyl acetate was added dropwise to destroy the excess lithium aluminum hydride.

Two hundred and fifty milliliters of saturated ammonium tartrate-ammonium sulfate solution and 350 ml. of methylene chloride were then added to the reaction mixture. The layers were separated and the water solution was extracted with three 50 ml. portions of methylene chloride. The combined organic solution was washed with two 50 ml. portions of saturated ammonium tartrate-ammonium sulfate solution and was dried over anhydrous sodium sulfate. The solvent was removed with a rotary evaporator leaving a clear sirup amounting to 14.3 g. This crude product was dissolved in 150 ml. of dry ether and the solution was cooled to 10° in an ice bath. Anhydrous hydrogen chloride was added until the solution was acidic to moist Congo red paper. The ether was decanted from the white semi-solid which had precipitated from the solution. A slurry of the solid in hot anhydrous acetone, after cooling and filtering, gave 12.12 g. (74.0% based on starting acid) of 1-ethyl-2-methyl-2-[N, N-bis(2-hydroxyethyl)aminomethyl]-1, 2, 3, 4-tetrahydronaphthalene hydrochloride.

Benner (147), using a similar procedure, prepared N, N-bis(2-hydroxyethyl)-3, 4-di(p-methoxyphenyl)-3-hexenylamine hydrochloride.

Two recrystallizations of a 2.0 g. sample of the above material from methanol gave 1.5 g. of pure 1-ethyl-2-methyl-2-]N, N-bis(2-hydroxyethyl)aminomethyl]-1, 2, 3, 4-tetrahydronaphthalene hydrochloride, m.p. 136-137.5°.

Analysis. Calculated for $C_{18}H_{30}NO_2Cl$: C, 65.93; H, 9.22; Cl, 10.81.
Found: C, 65.79; H, 9.04; Cl, 11.08.

1-Ethyl-2-methyl-2-[N, N-bis(2-chloroethyl)aminomethyl]-1, 2, 3, 4-tetrahydronaphthalene hydrochloride. A well-stirred slurry of 8.19 g. (0.025 mole) of 1-ethyl-2-methyl-2-[N, N-bis(2-hydroxyethyl)aminomethyl]-1, 2, 3, 4-tetrahydronaphthalene hydrochloride in 150 ml. of dry chloroform containing 8 drops of dimethylformamide (129, 130, 113) was cooled to 10°. As this slurry was vigorously stirred there was added a solution of 50 ml. of freshly distilled thionyl chloride in 50 ml. of dry chloroform over a period of 1 hr. The resulting light yellow solution was then allowed to stand for 12 hrs. at room temperature and was then heated to 60° for 1 hr. The chloroform and excess thionyl chloride were removed with a rotary evaporator. A 10 ml. portion of dry benzene was added to the residue and then removed with a rotary evaporator. This process was repeated five times in order to remove the last trace of thionyl chloride. The dark brown residue was then dissolved in dry acetone and sufficient ether was added to give a cloudy solution. The light brown solid which separated as the solution was maintained at 0° for 2 hrs. was removed by filtration and dried in vacuo. The impure product amounted to 8.31 g. This material was recrystallized from chloroform-methylcyclohexane (Norite). Filtration gave 5.88 g. (64.0%) of 1-ethyl-2-methyl-2-[N, N-bis(2-chloroethyl)aminomethyl]-1, 2, 3, 4-tetrahydronaphthalene hydrochloride, m.p. 135-145°.

This procedure is essentially that of Benner (148) who prepared N, N-bis(2-chloroethyl)-3, 4-di(p-methoxyphenyl)-3-hexenylamine hydrochloride.

Several recrystallizations from ethanol gave an analytical sample of pure 1-ethyl-2-methyl-2-[N, N-bis(2-chloroethyl)aminomethyl]-1, 2, 3, 4-tetrahydronaphthalene hydrochloride, m.p. 144-146°.

Analysis. Calculated for $C_{18}H_{28}NCl_3$: C, 59.24; H, 7.74; Cl, 29.14.
Found: C, 59.46; H, 7.85; Cl, 29.20.

trans-1-Ethylidene-2-methyl-2-[N,N-bis(2-hydroxyethyl)carbamyl]-1,2,3,4-tetrahydronaphthalene. A slurry of 6.49 g. (0.03 mole) of trans-1-ethylidene-2-methyl-2-carboxy-1,2,3,4-tetrahydronaphthalene in 15 ml. of dry benzene containing 4 drops of dry pyridine was cooled to 5°. As this slurry was stirred with a magnetic stirrer there was added 8 ml. (13 g., 0.11 mole) of freshly distilled thionyl chloride over a period of 30 min. The homogeneous reaction mixture was allowed to stand at room temperature for 3 hrs. and was then warmed to 40° for 1 hr. Removal of the benzene and the excess thionyl chloride left a dark brown residue. The residue was dissolved in 20 ml. of dry benzene and the benzene was removed with a rotary evaporator. This process was repeated several times in order to remove the last trace of thionyl chloride. The residue amounted to 7.7 g. of crude acid chloride. This semi-solid residue was then dissolved in 30 ml. of purified dioxane (144). The solution was filtered to remove the pyridine hydrochloride and was added to a well-stirred mixture (partial solution) of 34.65 g. (0.33 mole) of diethanolamine in 100 ml. of dioxane during a period of 2 hrs. After the addition had been completed, the reaction mixture was heated to 55° in an oil bath and maintained at this temperature, with constant stirring, for 10 hrs. The oil bath was removed and the reaction mixture cooled to room temperature. The dioxane and excess diethanolamine were then distilled directly from the reaction flask at 15 mm. pressure. The residue was partitioned between 100 ml. of water and 80 ml. of benzene. The layers were separated and the water solution was extracted with two 20 ml. portions of benzene. The organic solutions were combined and washed successively with 20 ml. portions of the following: 2% potassium hydroxide solution (twice), water (once),

1N hydrochloric acid (twice), water (twice) and then finally with a saturated sodium chloride solution. The organic phase was dried over anhydrous sodium sulfate. Removal of the solvent with a rotary evaporator left a thick yellow sirup which amounted to 10.35 g. of impure trans-1-ethylidene-2-methyl-2-[N, N-bis(2-hydroxyethyl)carbamyl]-1, 2, 3, 4-tetrahydronaphthalene. This product was not purified before reduction to the corresponding amine.

This procedure is based on that described by Benner (145) for the preparation of N, N-bis(2-hydroxyethyl)-3, 4-di(p-methoxyphenyl)-3-hexenamide.

trans-1-Ethylidene-2-methyl-2-[N, N-bis(2-hydroxyethyl)aminomethyl]-1, 2, 3, 4-tetrahydronaphthalene hydrochloride. A solution of 10.35 g. of crude trans-1-ethylidene-2-methyl-2-[N, N-bis(2-hydroxyethyl)carbamyl]-1, 2, 3, 4-tetrahydronaphthalene in 50 ml. of purified tetrahydrofuran (146) was added to a well-stirred slurry of 2.28 g. (0.06 mole) of lithium aluminum hydride in 150 ml. of tetrahydrofuran over a period of 2 hrs. After the addition had been completed, the reaction mixture was refluxed for 8 hrs. An additional 0.23 g. (0.006 mole) of lithium aluminum hydride was added and the refluxing was continued for an additional 4 hrs. The reaction mixture was then cooled to 10° and 20 ml. of water-saturated ethyl acetate was slowly added to destroy the excess lithium aluminum hydride. To the reaction mixture were then added 150 ml. of saturated ammonium tartrate-ammonium sulfate solution and 200 ml. of methylene chloride. The two layers were separated and the salt solution was extracted with four 30 ml. portions of methylene chloride. The organic solutions were combined and washed with two 50 ml. portions of saturated ammonium tartrate-ammonium sulfate solution. The solution was dried over anhydrous sodium sulfate and the solvent was removed with a rotary evaporator.

The crude amine, weighing 8.60 g., was isolated as a thick amber sirup. It was dissolved in 200 ml. of anhydrous ether, the solution was cooled to 10° and anhydrous hydrogen chloride was added until the ether was acidic to moist Congo red paper. The ether was decanted from the gum which separated and the latter was dissolved in boiling anhydrous acetone. The addition of an equal volume of ether to the cool acetone solution precipitated an off-white solid. After several recrystallizations from acetone, there was recovered 4.0 g. (40.0% based on starting acid) of trans-1-ethylidene-2-methyl-2-[N, N-bis(2-hydroxyethyl)aminomethyl]-1, 2, 3, 4-tetrahydronaphthalene hydrochloride, m.p. 150-157°.

This procedure is based on Benner's (147) preparation of N, N-bis(2-hydroxyethyl)-3, 4-di(p-methoxyphenyl)-3-hexenylamine hydrochloride.

A 0.5 g. sample, recrystallized several times from ethanol, gave 0.3 g. of pure trans-1-ethylidene-2-methyl-2-[N, N-bis(2-hydroxyethyl)aminomethyl]-1, 2, 3, 4-tetrahydronaphthalene hydrochloride, m.p. 157-159°.

Analysis. Calculated for $C_{18}H_{28}NO_2Cl$: C, 66.33; H, 8.66; Cl, 10.89.

Found: C, 64.13; H, 8.29; Cl, 10.83; ash, 2.67.

trans-1-Ethylidene-2-methyl-2-[N, N-bis(2-chloroethyl)aminomethyl]-1, 2, 3, 4-tetrahydronaphthalene. A slurry of 4.0 g. (0.012 mole) of trans-1-ethylidene-2-methyl-2-[N, N-bis(2-hydroxyethyl)aminomethyl]-1, 2, 3, 4-tetrahydronaphthalene in 100 ml. of purified chloroform (149) containing 2 drops of dimethylformamide was cooled to 5°. To this slurry there was added 25 ml. (41 g., 0.35 mole) of freshly distilled thionyl chloride over a period of 30 min. with constant stirring.

After 30 min. at 5°, the reaction mixture was allowed to stand at room temperature for 2 hrs. and then was warmed to 60° for 1 hr. The chloroform and excess thionyl chloride were removed with a rotary evaporator. The residue was repeatedly suspended in small portions of dry benzene and the benzene was evaporated from the slurry after each addition. This procedure was repeated several times until the odor of thionyl chloride was no longer noticeable. The dark residue thus obtained weighed 7.3 g. This residue was well triturated with dry acetone and gave a light brown solid. After recrystallization from absolute alcohol there was obtained 2.15 g. (49.2%) of trans-1-ethylidene-2-methyl-2-[N, N-bis(2-chloroethyl)aminomethyl]-1, 2, 3, 4-tetrahydronaphthalene hydrochloride, m.p. 137-140°.

Benner (148), using a similar procedure, prepared N, N-bis(2-chloroethyl)-3, 4-di(p-methoxyphenyl)-3-hexenylamine hydrochloride.

Analysis. Calculated for $C_{18}H_{26}NCl_3$: C, 59.59; H, 7.23; Cl, 29.32.
Found: C, 59.43; H, 7.20; Cl, 29.42.

cis-1-Ethylidene-2-methyl-2-[N, N-bis(2-hydroxyethyl)carbamyl]-1, 2, 3, 4-tetrahydronaphthalene. A solution of 8.64 g. (0.04 mole) of cis-1-ethylidene-2-methyl-2-carboxy-1, 2, 3, 4-tetrahydronaphthalene in 30 ml. of dry benzene containing 4 drops of pyridine was cooled to 5°. To this solution there was added 15 ml. (25 g., 0.21 mole) of freshly distilled thionyl chloride over a period of 30 min. The reaction mixture was allowed to stand at 5° for an additional 30 min., at room temperature for 2 hrs. and was finally warmed to 40° for 1 hr. The excess thionyl chloride and benzene were removed with a rotary evaporator. In order to remove the final traces of thionyl chloride the solid was suspended repeatedly in 10 ml. portions of dry benzene and the benzene was evaporated from the slurry with a rotary evaporator after each addition. The crude acid chloride weighed 10.02 g. It was dissolved in

30 ml. of purified dioxane (144) and the solution was filtered into an addition funnel. This solution was then added over a period of 2 hrs. to a well-stirred mixture (partial solution) of 42 ml. (0.044 mole) of diethanolamine and 100 ml. of dioxane contained in a 100 ml. flask equipped with a reflux condenser, thermometer, paddle stirrer and an addition funnel. After the addition had been completed, the reaction mixture was heated to 50° in an oil bath and was maintained at this temperature for 10 hrs. The reflux condenser was replaced with a Claisen head and the dioxane and excess diethanolamine were distilled directly from the reaction flask at 15 mm. pressure. The cool residue was partitioned between 100 ml. of water and 80 ml. of benzene. The two layers were separated and the water layer was extracted with three 30 ml. portions of benzene. The organic solutions were combined and washed successively with two 20 ml. portions of 10% sodium hydroxide, with 30 ml. of water, with three 20 ml. portions of 1N hydrochloric acid, with 30 ml. of water and finally with 10 ml. of saturated sodium chloride solution. After the solution had been dried over anhydrous sodium sulfate, the solvent was removed with a rotary evaporator. The light yellow sirupy residue consisted of 13.47 g. of crude cis-1-ethylidene-2-methyl-2-[N, N-bis(2-hydroxyethyl)carbamyl]-1, 2, 3, 4-tetrahydronaphthalene. This product was not purified prior to its reduction to the corresponding amine.

This procedure is based on that described by Benner (145) for the preparation of N, N-bis(2-hydroxyethyl)-3, 4-di(p-methoxyphenyl)-3-hexenamide.

cis-1-Ethylidene-2-methyl-2-[N, N-bis(2-hydroxyethyl)amino-methyl]-1, 2, 3, 4-tetrahydronaphthalene hydrochloride. A solution of 13.47 g. of crude cis-1-ethylidene-2-methyl-2-[N, N-bis(2-hydroxyethyl)carbamyl]-1, 2, 3, 4-tetrahydronaphthalene in 50 ml. of purified tetrahydrofuran (146) was added to a well-stirred slurry of 3.04 g.

(0.08 mole) of lithium aluminum hydride in 150 ml. of tetrahydrofuran over a period of 1 hr. The reaction mixture was then brought to reflux temperature and maintained at this temperature for 8 hrs. An additional 0.304 g. (0.008 mole) of lithium aluminum hydride was added and the refluxing was continued for an additional 4 hrs. The reaction mixture was then cooled to 10° and 20 ml. of water-saturated ethyl acetate was slowly added to destroy the excess lithium aluminum hydride. To the reaction mixture there was then added 150 ml. of saturated ammonium tartrate-ammonium sulfate solution followed by 200 ml. of methylene chloride. The water layer was separated and was extracted with three 30 ml. portions of methylene chloride. The combined organic solutions were washed with two 25 ml. portions of saturated ammonium tartrate-ammonium sulfate solution. After the solution was dried over anhydrous sodium sulfate, the solvent was removed with a rotary evaporator. There remained 11.30 g. of a thick yellow sirup. This crude amine was dissolved in 200 ml. of dry ether. The ether solution was cooled to 10° and anhydrous hydrogen chloride was passed into it until the ether was acidic to moist Congo red paper. A colorless semi-solid separated from the ether solution. A small quantity of the amine hydrochloride was saved for the preparation of an analytical sample and the remainder was dissolved in chloroform and the ether removed by distillation at atmospheric pressure. Additional small portions of chloroform were added and evaporated until all of the ether had been removed. The chloroform solution (total volume approximately 100 ml.) was immediately used for the preparation of cis-1-ethylidene-2-methyl-2-[N, N-bis(2-chloroethyl)aminomethyl]-1, 2, 3, 4-tetrahydronaphthalene hydrochloride.

This procedure is based on that described by Benner (147) for the preparation of N, N-bis(2-hydroxyethyl)-3, 4-di(p-methoxyphenyl)-3-hexenylamine hydrochloride.

The semi-solid sample, after several recrystallizations from alcohol, gave pure cis-1-ethylidene-2-methyl-2-[N, N-bis(2-hydroxyethyl)aminomethyl]-1, 2, 3, 4-tetrahydronaphthalene hydrochloride, m.p. 155-156.5°.

Analysis. Calculated for $C_{18}H_{28}NO_2Cl$: C, 66.33; H, 8.66; Cl, 10.89.

Found: C, 66.40; H, 8.72; Cl, 10.92.

cis-1-Ethylidene-2-methyl-2-[N, N-bis(2-chloroethyl)aminomethyl]-1, 2, 3, 4-tetrahydronaphthalene hydrochloride. The chloroform solution of cis-1-ethylidene-2-methyl-2-[N, N-bis(2-hydroxyethyl)-aminomethyl]-1, 2, 3, 4-tetrahydronaphthalene hydrochloride (described immediately above), to which four drops of dimethylformamide were added, was cooled to 5°. To this a solution of 30 ml. (49.1 g., 0.41 mole) of freshly distilled thionyl chloride in 20 ml. of chloroform was added with constant stirring over a period of 30 min. The reaction mixture was allowed to stir for an additional 3 hrs. at room temperature and was then warmed to 50° for 1 hr. Excess thionyl chloride and chloroform were removed with a rotary evaporator, leaving a dark brown residue. The latter was repeatedly dissolved in 10 ml. portions of dry benzene and the benzene evaporated after each addition until all traces of thionyl chloride had been completely removed. No solid could be isolated from the dark sirupy residue. A solution of the residue in 50 ml. of dry chloroform was passed through a 2.5 x 10 cm. column of neutral alumina. The column was eluted with 250 ml. of chloroform. Evaporation of the chloroform from the eluate with a rotary evaporator left a light yellow residue, which was dissolved in 150 ml. of dry ether and the solution cooled to 5°. Anhydrous hydrogen chloride was passed into the solution to precipitate the amine

hydrochloride. The light tan solid, after two recrystallizations from absolute ethanol, gave 3.83 g. (27.5%, based on starting acid) of cis-1-ethylidene-2-methyl-2-[N, N-bis(2-chloroethyl)aminomethyl]-1, 2, 3, 4-tetrahydronaphthalene hydrochloride, m.p. 141-143.5°.

This procedure is a modification of that described by Benner (148) for the preparation of N, N-bis(2-chloroethyl)-3, 4-di(p-methoxyphenyl)-3-hexenylamine hydrochloride.

Analysis. Calculated for $C_{18}H_{26}NCl_3$: C, 59.59; H, 7.23; Cl, 29.32.
Found: C, 59.38; H, 7.03; Cl, 29.15.

6-Methoxy-1, 2, 3, 4-tetrahydronaphthalene. A mixture consisting of 189.8 g. (1.2 mole) of 2-methoxynaphthalene, 5 ml. of glacial acetic acid and approximately 20 g. of Raney nickel was placed in a 1-l. high pressure hydrogenation bomb (no glass liner was used) which was charged with hydrogen at 3400 psi. The temperature was slowly raised to 160°. The shaker was started when the temperature had reached 100°. The consumption of hydrogen ceased within 1 hr. after the temperature reached 160°. Ethanol was added to the liquid product before it was poured from the bomb. After the Raney nickel had been removed by filtration, the solvent was removed with a rotary evaporator. Distillation of the orange colored residue gave the following fractions.

Fraction	B.p., °C. (13 mm.)	Grams	n_D^{25}
1	102-115	12.5	1.4955
2	115-123	8.6	1.5248
3	123-123	25.5	1.5342
4	123-124	35.8	1.5364
5	124-125	40.2	1.5360
6	125-127	30.5	1.5415
residue(solid)	---	50.2	---

Fractions 3-6, selected as 6-methoxy-1, 2, 3, 4-tetrahydronaphthalene, amounted to 132.0 g. (68%).

The hydrogenation was repeated using the same quantities of 2-methoxynaphthalene and catalyst as above. The bomb was charged with hydrogen at 3400 psi, and the temperature was raised to 140°. Again the shaker was started when the temperature reached 100°. The reduction product was poured from the bomb, filtered and worked up as before. The following fractions were obtained upon distillation.

Fraction	B.p., °C. (13 mm.)	Grams	n_D^{25}
1	85-95	11	1.5245
2	96-118	1.2	1.5360
3	119-123	37.5	1.5369
4	123-125	72.3	1.5390
5	125-128	60.0	1.5412
residue(solid)	---	43.5	---

Fractions 3-5 yielded 169.8 g. (87.5%) of 6-methoxy-1, 2, 3, 4-tetrahydronaphthalene.

The hydrogenation was repeated a third time using the same quantity of 2-methoxynaphthalene and catalyst. This time the temperature was raised to 120° for the hydrogenation. Distillation of the residue gave the following fractions.

Fraction	B.p., °C. (13mm.)	Grams	n_D^{25}
1	110-115	8.2	1.5295
2	115-124	3.5	1.5345
3	124-124	30.2	1.5380
4	124-125	52.4	1.5385
5	125-127	22.8	1.5395
6	127-130	21.0	1.5408

Fractions 3-6 gave 126.4 g. (65%) of 6-methoxy-1, 2, 3, 4-tetrahydronaphthalene.

This procedure is based on that described by Stork (133), who obtained 6-methoxy-1, 2, 3, 4-tetrahydronaphthalene in a 91.6% yield. He reported a boiling point of 134-137° (17 mm.) for the compound.

1-Keto-6-methoxy-1, 2, 3, 4-tetrahydronaphthalene.

Procedure A. A solution of 113 g. (0.7 mole) of 6-methoxy-1, 2, 3, 4-tetrahydronaphthalene in 583 ml. of glacial acetic acid containing 50 ml. of water was placed in a 3-l. flask equipped with a stirrer, an addition funnel and a thermometer. This solution was cooled to 5° in an ice-salt bath. A solution of 125 g. (1.25 mole) of chromic oxide in 633 ml. of water was then added over a period of 2 hrs. with constant stirring. The rate of addition was such that the temperature of the reaction mixture did not rise above 20°. The reaction mixture was then allowed to stand at room temperature for two weeks. At the end of this period, 50 ml. of methanol and 85 ml. of concentrated hydrochloric acid were added to the reaction mixture and the resulting solution was then concentrated on a steam bath (100 mm. pressure) to a dark, thick sirup. To this residue was added 500 ml. of hot water and the water solution was extracted (no shaking) with two 300 ml. portions of benzene. It was extracted with two additional 300 ml. portions of benzene, with shaking. This procedure was necessary due to the formation of emulsions and to the difficulty in distinguishing the two layers. The benzene extracts were combined and were washed with 100 ml. of each of the following in succession: 5% hydrochloric acid, water, and saturated sodium chloride. Removal of the solvent with a rotary evaporator left a dark residue which was distilled (without fractionation) through an ether bridge at 0.05 mm. pressure with a bath temperature of 140°. The distillate solidified in the receiver and was recrystallized from 80% methanol, yielding 46.5 g. (37.7%) of 1-keto-6-methoxy-1, 2, 3, 4-tetrahydronaphthalene, m.p. 76-77°.

This procedure is based on that described by Stork (133) and Reusch (150) for the preparation of 1-keto-6-methoxy-1, 2, 3, 4-tetrahydronaphthalene. These workers reported a yield of 60-65% and a melting point of 78-79°.

Procedure B. A solution of 338 g. (2.09 moles) of 6-methoxy-1,2,3,4-tetrahydronaphthalene in 1750 ml. of acetic acid and 150 ml. of water was cooled to 5° in an ice-salt bath. To this reaction mixture was then added, with constant stirring, a solution of chromic acid prepared by dissolving 375 g. (3.75 moles) of chromic oxide in 150 ml. of water and then diluting to 1750 ml. with additional water. The addition was maintained at such a rate that the temperature did not rise above 20°. After the addition had been completed, the reaction mixture was allowed to stand at room temperature for 24 hrs. The reaction mixture was then divided equally between three 2-l. beakers. To each beaker was added 50 ml. of methanol and 85 ml. of concentrated hydrochloric acid and the solutions were concentrated individually on a steam bath (atm. pressure) to a thick dark liquid. This process required approximately 72 hrs. The residue was then continuously extracted with benzene for one week. The benzene extracts were combined, the solvent was removed on a rotary evaporator and the residue was distilled (without fractionation) through an ether bridge and gave 128.35 g. of product. Recrystallization from 80% methanol gave 111.8 g. of ketone, m.p. 77-78°.

The water solution was then steam distilled with a steam distillation-continuous extraction apparatus (137). Ether was used for the organic phase. At the end of three weeks the ether solutions were combined and the solvent was removed on a rotary evaporator leaving a clear sirup amounting to 12.3 g. Recrystallization from methanol gave an additional 10 g. of ketone, m.p. 78-79°. This made a total of 121.8 g. (33.0%) of 1-keto-6-methoxy-1,2,3,4-tetrahydronaphthalene obtained from this oxidation.

This procedure is based on that described by Burnop, Elliott and Linstead (134) for the preparation of 1-keto-6-methoxy-1,2,3,4-tetrahydronaphthalene. These workers obtained the ketone in a 70% yield and reported a melting point of 77.5°.

Procedure C. To a solution of 275 g. (1.7 moles) of 6-methoxy-1,2,3,4-tetrahydronaphthalene in 1444 ml. of acetic acid and 124 ml. of water was added a solution of chromic acid prepared by dissolving 310 g. (3.10 moles) of chromic oxide in 124 ml. of water and then diluting to a volume of 1450 ml. The reaction conditions were identical to those described in procedure B above. After standing for 24 hrs. at room temperature, there was added 123 ml. of methanol and 205 ml. of concentrated hydrochloric acid and the reaction mixture was concentrated on a steam bath (atm. pressure) to a thick sirup. Water was added to the residue and the resulting solution was extracted with a steam distillation-continuous extraction apparatus (137) using ether as the organic phase. After a period of one week the ether solutions (the extraction apparatus had been charged with 100 ml. of ether each 24 hr. period) were combined and the solvent was removed with a rotary evaporator, giving 28.5 g. of product, m.p. 79-79.5°. The water solution was then continuously extracted with ether for a period of several days using the lighter than water extractor. The ether extracts were combined and the ether was removed with a rotary evaporator to give 120 g. of residue. This residue was distilled (without fractionation) through an ether bridge to give 80 g. of product, m.p. 77.5-79°. The total yield of 1-keto-6-methoxy-1,2,3,4-tetrahydronaphthalene amounted to 108 g. (35.6%).

This procedure, like Procedure B above, is based on the work of Elliott and Linstead (134).

Procedure D. A solution of 122 g. (1.22 mole) of chromic oxide in 50 ml. of water and 350 ml. of acetic acid was added dropwise to a stirred cold (5-10°) solution of 124 g. (0.76 mole) of 6-methoxy-1,2,3,4-tetrahydronaphthalene in 125 ml. of propionic acid and 563 ml. of acetic acid. After the addition had been completed, the

reaction mixture was allowed to come to room temperature and was stirred for 16 hrs. The solvents were then removed at aspirator pressure leaving a dark viscous residue. This residue was heated with 1250 ml. of water for 1 hr. After the reaction mixture had cooled to room temperature, it was extracted with a total of 1750 ml. of ether. The ether solution was washed with two 100 ml. portions of sodium carbonate and with one 100 ml. portion of water. The ether was removed from the dried solution (anhydrous sodium sulfate) with a rotary evaporator, leaving a dark-colored residue. A solution of the residue in approximately 500 ml. of benzene was decolorized passing it through a 2.5 x 60 cm. column of alumina. The column was eluted with an additional 2 l. of benzene. The combined effluent was concentrated under reduced pressure and gave 78.8 g. (58.6%) of 1-keto-6-methoxy-1, 2, 3, 4-tetrahydronaphthalene, m.p. 77-78°.

Bachmann (136), using a similar procedure, prepared 1-keto-6-methoxy-1, 2, 3, 4-tetrahydronaphthalene in 62.0% yield and reported a melting point of 78-79°.

Methyl 1-keto-6-methoxy-1, 2, 3, 4-tetrahydronaphthalene-2-glyoxalate. Eight-tenths of a mole of alcohol-free sodium methoxide was prepared by dissolving 18.4 g. (0.8 g. atom) of sodium in 200 ml. of anhydrous methanol, adding 100 ml. of dry benzene and removing the solvents at reduced pressure. After heating the dry salt for 15 min. under an atmosphere of dry nitrogen, it was crushed in the flask and was then stirred with 100 ml. of dry benzene to obtain a fine slurry. To this slurry was added 94.4 g. (0.8 mole) of dimethyl oxalate in one portion, followed by an additional 300 ml. of dry benzene. The reaction mixture was then refluxed for 15 min. in order to dissolve most of the solid. After the reaction mixture had been cooled to 5°, a solution of 70.4 g. (0.4 mole) of 1-keto-6-methoxy-1, 2, 3, 4-tetrahydronaphthalene in 200 ml. of dry benzene was added, with vigorous

stirring, over a period of 30 min. When this addition had been completed the ice bath was removed and the stirring was continued at room temperature. After approximately 30 min. the sodio-derivative of the product began to separate from the light green solution making further stirring impossible. After standing for 4 hrs. at room temperature, the reaction mixture was hydrolyzed by pouring the thick paste onto approximately 500 g. of ice. The addition of a small amount of sodium hydroxide produced two distinct layers. The benzene solution was separated and extracted with four 75 ml. portions of 2% sodium hydroxide. The combined water layer and basic extracts were cooled in an ice bath and then acidified to a pH of 5 (pHydrion paper) with dilute hydrochloric acid. The light yellow crystalline glyoxalate was separated and dried in a desiccator over calcium chloride. The dry solid, after digestion with a warm mixture of acetone-methanol (1:1), cooling and filtration weighed 71.5 g. Another 8.53 g. of product was isolated from the filtrate, making a total of 80.03 g. (76.2%) of methyl 1-keto-6-methoxy-1, 2, 3, 4-tetrahydronaphthalene-2-glyoxalate.

Several recrystallizations of a small sample from methanol gave pure methyl 1-keto-6-methoxy-1, 2, 3, 4-tetrahydronaphthalene-2-glyoxalate, m.p. 77-78°.

Bachmann and Thomas (151) obtained this glyoxalate, using this procedure, in a 92% yield. The reported melting point was 76.5-77.5°.

1-Keto-2-carbomethoxy-6-methoxy-1, 2, 3, 4-tetrahydronaphthalene. Decarbonylation of methyl 1-keto-6-methoxy-1, 2, 3, 4-tetrahydronaphthalene-2-glyoxalate was accomplished by heating 24 g. of the glyoxalate contained in a 100 ml. flask to 150° in an oil bath and then by adding 12 g. of powdered soft glass to the melt. The temperature of the oil bath was quickly raised to 180 ± 5° and was maintained at this temperature for 30 min. A vigorous evolution of

gas commenced as the temperature reached approximately 160° and appeared to be complete at the end of the heating period. The cool organic residue was dissolved in benzene and the solution was filtered to remove the glass. The benzene was removed with a rotary evaporator and the residue distilled (free flame at 0.15 mm.) through an ether bridge without fractionation, giving 17.9 g. (82.6%) of light yellow 1-keto-2-carbomethoxy-6-methoxy-1,2,3,4-tetrahydronaphthalene.

A sample, after several recrystallizations from methylcyclohexane containing a small amount of acetone, formed colorless crystals at 1-keto-2-carbomethoxy-6-methoxy-1,2,3,4-tetrahydronaphthalene, m.p. 85-86°.

This procedure is based on that described by Bachmann and Thomas (151). They reported the preparation of 1-keto-2-carbomethoxy-6-methoxy-1,2,3,4-tetrahydronaphthalene, m.p. 88-89.5°, in 96% yield.

1-Keto-2-methyl-2-carbomethoxy-6-methoxy-1,2,3,4-tetrahydronaphthalene. To a solution of 1.0 mole of sodium methoxide in 450 ml. of anhydrous methanol, under an atmosphere of dry nitrogen there was added 46.8 g. (0.2 mole) of finely powdered 1-keto-2-carbomethoxy-6-methoxy-1,2,3,4-tetrahydronaphthalene, followed by 250 ml. of dry benzene. The resulting deep red reaction mixture was refluxed for 30 minutes and was then cooled to 5° in an ice bath. Thirty-five milliliters of methyl iodide was added in one portion and the reaction mixture was stirred at room temperature for 1 hour. An additional 35 ml. of methyl iodide was then added and the dark purple solution was refluxed for another hour. After standing at room temperature for 12 hrs. the reaction mixture was cooled to 5° and was neutralized to a pH of 7 (pHydrion paper) with glacial acetic acid. The solution was evaporated almost to dryness with a rotary evaporator

and the residue partitioned between 300 ml. of benzene and 300 ml. of water. The layers were separated and the water layer was extracted with three 50 ml. portions of benzene. The organic solutions were combined and washed with 75 ml. of water, with 10 ml. portions of 5% sodium hydroxide solution until no color appeared in the extract, and finally with 75 ml. of saturated sodium chloride. The solution was dried over anhydrous sodium sulfate and decolorized with Norite and the solvents were removed with a rotary evaporator. The residue was dissolved in methylcyclohexane containing a small amount of acetone and the solution was maintained at 5° overnight. The product was removed by filtration and was dried in a desiccator over paraffin chips. The light yellow 1-keto-2-methyl-2-carbomethoxy-6-methoxy-1, 2, 3, 4-tetrahydronaphthalene, m.p. 88-90°, amounted to 37.5 g. (75.5%).

A sample was recrystallized several times from methylcyclohexane containing a small amount of acetone. The colorless crystals of pure 1-keto-2-methyl-2-carbomethoxy-6-methoxy-1, 2, 3, 4-tetrahydronaphthalene melted at 91.5-92°.

This procedure is a modification of that described by Bachmann and Thomas (151). These workers prepared the last mentioned product in 84% yield and reported a melting point of 91-92.5°.

1-Ethyl-1-hydroxy-2-methyl-2-carbomethoxy-6-methoxy-1, 2, 3, 4-tetrahydronaphthalene. A solution of approximately 0.1 mole of ethylmagnesium bromide in 100 ml. of anhydrous ether was prepared from 2.6 g. (0.11 g. atom) of magnesium and 11.99 g. (0.11 mole) of ethyl bromide. This reaction was carried out in a 500 ml. flask equipped with a stirrer, reflux condenser, thermometer, a pressure equilizing addition funnel and a nitrogen inlet tube. The Grignard solution was cooled to 5° before a solution of 24.8 g. (0.1 mole) of 1-keto-2-methyl-2-carbomethoxy-6-methoxy-1, 2, 3, 4-tetrahydronaphthalene was added at such a rate that the temperature did not rise above 10°.

This addition required approximately 1 hr. After the addition had been completed, the reaction mixture was stirred at 5° for 30 min., at room temperature for 1 hr. and then at reflux temperature for 30 min. The reaction mixture was then poured onto approximately 200 g. of crushed ice and sufficient dilute hydrochloric acid was added to effect solution of the inorganic salts. The two layers were separated and the water solution was extracted with two 50 ml. portions of benzene-ether (5:1). The combined organic solution was washed successively with 100 ml. of 1N hydrochloric acid, 75 ml. of water and finally with saturated sodium chloride solution. This solution was then dried over anhydrous sodium sulfate and the solvent was removed with a rotary evaporator. A sirupy residue amounting to 30.0 g. (92.0% crude yield) of a diastereoisomeric mixture of crude hydroxy esters remained. This residue crystallized upon standing. A 2.0 g. sample was recrystallized from methanol and gave 1.4 g. of diastereoisomeric 1-ethyl-1-hydroxy-2-methyl-2-carbomethoxy-6-methoxy-1, 2, 3, 4-tetrahydronaphthalenes, m.p. 100-101°.

This procedure is based on that described by Anner and Miescher (99) for the preparation of 1-ethyl-1-hydroxy-2-methyl-2-carbomethoxy-6-methoxy-1, 2, 3, 4-tetrahydronaphthalene. These workers reported a melting point of 99-100° for this isomeric mixture.

1-Ethylidene-2-methyl-2-carbomethoxy-6-methoxy-1, 2, 3, 4-tetrahydronaphthalene. A mixture of 30.0 g. (0.092 mole) of the crude isomeric 1-ethyl-1-hydroxy-2-methyl-2-carbomethoxy-6-methoxy-1, 2, 3, 4-tetrahydronaphthalenes and 35 ml. of 85% formic acid was warmed on a steam bath for 2 hrs. The reaction mixture, after being cooled to room temperature, was added to 400 ml. of benzene. The layers were separated and the formic acid layer was extracted with two 25 ml. portions of benzene. The benzene solutions were combined and washed with two 50 ml. portions of 5% sodium hydroxide, with

75 ml. of water and then with saturated sodium chloride solution. After the solution was dried over anhydrous sodium sulfate, the solvent was removed with a rotary evaporator leaving a residue amounting to 25.5 g. This crude 1-ethylidene-2-methyl-2-carbomethoxy-6-methoxy-1, 2, 3, 4-tetrahydronaphthalene was not purified before it was saponified to the free acid.

This procedure is based on that described by Anner and Miescher (99) for the preparation of 1-ethylidene-2-methyl-2-carbomethoxy-6-methoxy-1, 2, 3, 4-tetrahydronaphthalene.

1-Ethylidene-2-methyl-2-carboxy-6-methoxy-1, 2, 3, 4-tetrahydronaphthalene. A mixture of 25.5 g. (0.098 mole) of the crude isomeric 1-ethylidene-2-methyl-2-carbomethoxy-6-methoxy-1, 2, 3, 4-tetrahydronaphthalenes and 25 g. (0.45 mole) of potassium hydroxide in 25 ml. of water and 40 ml. of ethanol was refluxed for 4 hrs. The reaction mixture was cooled to room temperature and the ethanol was removed with a rotary evaporator. The residue was diluted with 200 ml. of water and the solution was extracted with three 20 ml. portions of benzene to remove any nonacidic material. Removal of the benzene with a rotary evaporator left a residue weighing 0.8 g.). The cool water solution was acidified to a pH of 2 (pHydrion paper) with dilute hydrochloric acid, causing a dark brown semi-solid to precipitate. This was extracted into four 100 ml. portions of benzene. The benzene extracts were combined and washed with 25 ml. of water and then with 25 ml. of saturated sodium chloride. After the solution was dried over anhydrous sodium sulfate, the solvent was removed with a rotary evaporator leaving a residue of 22.5 g. Recrystallization from methanol gave 22.5 g. (91.5%, based on hydroxy ester from Grignard reaction) of a mixture of the isomeric 1-ethylidene-2-methyl-2-carboxy-6-methoxy-1, 2, 3, 4-tetrahydronaphthalenes, m.p. 113-115°.

This procedure is based on that described by Anner and Miescher (99) for the preparation of the same mixture of isomeric 1-ethylidene-2-methyl-2-carboxy-6-methoxy-1, 2, 3, 4-tetrahydronaphthalenes. These workers reported a melting point of 113-115° for this mixture.

1-Ethyl-2-methyl-2-carboxy-6-methoxy-1, 2, 3, 4-tetrahydronaphthalene. A solution of 4.9 g. (0.02 mole) of the isomeric 1-ethylidene-2-methyl-2-carboxy-6-methoxy-1, 2, 3, 4-tetrahydronaphthalenes in 100 ml. of ethanol was placed in a 500 ml. low pressure hydrogenation bottle with 1 g. of 5% platinum on charcoal. The low pressure bottle was then placed in a Parr low pressure hydrogenation apparatus and charged with 15 lb. of hydrogen pressure. The hydrogen pressure was maintained at 15 ± 1 lb. while the reaction proceeded for 20 min. at ambient temperature. After the catalyst was removed by filtration, the alcohol solution was evaporated to a volume of approximately 20 ml. From the cooled solution there was filtered 4.53 g. (91.5%) of 1-ethyl-2-methyl-2-carboxy-6-methoxy-1, 2, 3, 4-tetrahydronaphthalene, m.p. 132-133°.

Anner and Miescher (99) hydrogenated the sodium salts of this same isomeric mixture of acids over Rupe nickel and obtained a mixture of the two diastereoisomeric 1-ethyl-2-methyl-2-carboxy-6-methoxy-1, 2, 3, 4-tetrahydronaphthalenes. They reported melting points of 128-130° and 148-150° for these two isomeric modifications.

Horeau (138) hydrogenated the same isomeric mixture with Vavon platinum in anhydrous ether and obtained the isomeric acid melting at 130-131° as the sole product.

1-Ethyl-2-methyl-2-[N, N-bis(2-hydroxyethyl)carbamyl]-6-methoxy-1, 2, 3, 4-tetrahydronaphthalene. A slurry of 9.92 g. (0.04 mole) of finely powdered 1-ethyl-2-methyl-2-carboxy-6-methoxy-1, 2, 3, 4-tetrahydronaphthalene in 35 ml. of dry benzene containing 4 drops of

pyridine was cooled to 5°. To this there was added 20 ml. (32.8 g., 0.28 mole) of freshly distilled thionyl chloride over a period of 30 min. as the reaction mixture was stirred with a magnetic stirrer. After the addition had been completed, the reaction mixture was stirred at room temperature for 3 hrs. and then at 40° for 1 hr. The solvent and excess thionyl chloride was removed with a rotary evaporator. To the residue was added a 10 ml. portion of benzene and the solution was again evaporated to dryness. This process was repeated until the last trace of thionyl chloride had been removed. The dark brown residue weighed 13.3 g. The crude acid chloride was dissolved in 50 ml. of purified dioxane (144) and the solution was filtered (to remove the pyridine hydrochloride) into an addition funnel. This solution was added over a period of 2 hrs. to a well-stirred mixture (partial solution) of 42 ml. (0.42 mole) of diethanolamine and 20 ml. of dioxane contained in a 100 ml. flask equipped with a reflux condenser, thermometer, a paddle stirrer and an addition funnel. When the addition had been completed, the reaction mixture was slowly heated to 55° and maintained at this temperature for 18 hrs. The reaction mixture was allowed to cool to room temperature and the reflux condenser was replaced with a Claisen head. The excess diethanolamine and dioxane were removed at aspirator pressure. The residue was then partitioned between 150 ml. of water and 120 ml. of benzene and the two layers were separated. The water solution was extracted with three 50 ml. portions of benzene. The organic solutions were combined and washed successively with three 15 ml. portions of 2% potassium hydroxide, with 30 ml. of water, with two 15 ml. portions of 1N hydrochloric acid, with 30 ml. of water and finally with 50 ml. of saturated sodium chloride solution. After the solution had been dried over anhydrous sodium sulfate, the solvent was removed with a rotary evaporator. The thick yellow sirup, consisting of crude 1-ethyl-2-methyl-2-[N, N-bis(2-hydroxyethyl)carbamyl]-6-methoxy-1, 2, 3, 4-tetra-

hydronaphthalene weighed 15.16 g. This intermediate was not purified before reduction to 1-ethyl-2-methyl-2-[N, N-bis(2-hydroxyethyl)aminomethyl]-6-methoxy-1, 2, 3, 4-tetrahydronaphthalene hydrochloride.

This procedure is based on that described by Benner (145) for the preparation of N, N-bis(2-hydroxyethyl)-3, 4-di(p-methoxyphenyl)-3-hexenamide.

1-Ethyl-2-methyl-2-[N, N-bis(2-hydroxyethyl)aminomethyl]-6-methoxy-1, 2, 3, 4-tetrahydronaphthalene hydrochloride. To a well-stirred slurry of 3.42 g. (0.09 mole) of lithium aluminum hydride in 250 ml. of purified tetrahydrofuran (146) was added a solution of 15.16 g. of crude 1-ethyl-2-methyl-2-[N, N-bis(2-hydroxyethyl)carbamyl]-6-methoxy-1, 2, 3, 4-tetrahydronaphthalene in 100 ml. of tetrahydrofuran over a period of 1 hr. After the addition had been completed, the reaction mixture was refluxed for 8 hrs. An additional 0.38 g. (0.01 mole) of lithium aluminum hydride was added and the refluxing was continued for an additional 4 hrs. The reaction mixture was then cooled in an ice bath and 30 ml. of water-saturated ethyl acetate was slowly added to destroy the excess lithium aluminum hydride.

There was then added 250 ml. of saturated ammonium tartrate-ammonium sulfate solution followed by 350 ml. of methylene chloride. The two layers were separated and the water solution was extracted with two 50 ml. portions of methylene chloride. The organic solutions were combined and washed with two 50 ml. portions of saturated ammonium tartrate-ammonium sulfate solution. After the solution was dried over anhydrous sodium sulfate, the solvent was removed with a rotary evaporator, leaving a thick sirup which weighed 12.85 g. This residue was dissolved in 250 ml. of anhydrous ether, cooled to 5° and anhydrous hydrogen chloride was added until the ether was acidic to moist Congo red paper. The ether was decanted from the colorless

precipitate and the solid suspended in hot acetone. After cooling, the product was filtered from the cool slurry, giving 9.85 g. (69.0% based on starting acid) of 1-ethyl-2-methyl-2-[N, N-bis(2-hydroxyethyl)aminomethyl]-6-methoxy-1, 2, 3, 4-tetrahydronaphthalene hydrochloride, m.p. 142-147.5°.

Benner (147), using a similar procedure, prepared N, N-bis(2-hydroxyethyl)-3, 4-di(p-methoxyphenyl)-3-hexenylamine hydrochloride.

A 1.65 g. sample, recrystallized several times from ethanol, gave 0.97 g. of pure 1-ethyl-2-methyl-2-[N, N-bis(2-hydroxyethyl)aminomethyl]-6-methoxy-1, 2, 3, 4-tetrahydronaphthalene hydrochloride, m.p. 149.5-151°.

Analysis. Calculated for $C_{19}H_{32}NO_3Cl$: C, 63.75; H, 9.01; Cl, 9.91.

Found: C, 63.93; H, 9.09; Cl, 10.04.

1-Ethyl-2-methyl-2-[N, N-bis(2-chloroethyl)aminomethyl]-6-methoxy-1, 2, 3, 4-tetrahydronaphthalene hydrochloride. A well-stirred slurry of 7.15 g. (0.02 mole) of 1-ethyl-2-methyl-2-[N, N-bis(2-hydroxyethyl)aminomethyl]-6-methoxy-1, 2, 3, 4-tetrahydronaphthalene hydrochloride in 150 ml. of purified chloroform (149) containing 4 drops of dimethylformamide was cooled to 5°. To this slurry was added a solution of 14 ml. (23.6 g., 0.2 mole) of freshly distilled thionyl chloride in 30 ml. of chloroform over a period of 45 min. After the addition had been completed, the reaction mixture was stirred at 5° for 1 hr., at room temperature for 3 hrs. and was finally warmed to 60° for 1 hr. The excess thionyl chloride and the chloroform were removed with a rotary evaporator, leaving a dark brown residue. Ten milliliter portions of benzene were added to the residue and the solvent was completely removed with a rotary evaporator after each addition until the last trace of thionyl chloride had been removed. The residue

was then dissolved in acetone and the product precipitated by the addition of an equal volume of ether. Filtration gave 5.79 g. of light tan solid. From the filtrate an additional 0.73 g. of product was isolated, making a total of 6.52 g. (82.5%) of 1-ethyl-2-methyl-2-[N, N-bis(2-chloroethyl)-aminomethyl]-6-methoxy-1, 2, 3, 4-tetrahydronaphthalene hydrochloride, m.p. 156-162°.

This procedure is based on that described by Benner (148) for the preparation of N, N-bis(2-chloroethyl)-3, 4-di(p-methoxyphenyl)-3-hexenylamine hydrochloride.

An analytical sample was prepared by recrystallizing a 1 g. portion of the above product several times from absolute ethanol, giving 0.72 g. of pure 1-ethyl-2-methyl-2-[N, N-bis(2-chloroethyl)aminomethyl]-6-methoxy-1, 2, 3, 4-tetrahydronaphthalene hydrochloride, m.p. 157.5-159°.

Analysis. Calculated for $C_{19}H_{30}NOCl_3$: C, 57.77; H, 7.66; Cl, 26.97.
Found: C, 57.71; H, 7.51; Cl, 26.77.

Methyl crotonate from crotonic acid and methanol. A solution of 1032 g. (12.0 moles) of commercial crotonic acid and 70 g. of concentrated sulfuric acid in 1600 ml. of anhydrous methanol was refluxed for 12 hrs. The solution was cooled to room temperature and diluted with 1500 ml. of water. The resulting two layers were separated and the water solution was extracted with five 200 ml. portions of ether. The organic solutions were combined and washed with sodium carbonate until effervescence had ceased. After being dried over anhydrous magnesium sulfate, the solvent was removed by distillation at atmospheric pressure. Distillation of the residue through a 40 cm. Fenske column gave the following fractions at atmospheric pressure.

Fraction	B.p., °C	Grams	n_D^{25}
1	33-34	-	-
2	46-48	-	-
3	76-86	-	-
4	86-114	25.0	1.4221
5	114-114.5	123.5	1.4221
6	114.5-114.5	220.0	1.4220
7	114.5-114.5	275.0	1.4220
8	115-115	35.0	1.4220

Fractions 4-8, assumed to be methyl crotonate, amounted to 678.5 g. (56.5%).

According to Vogel (152) this procedure should give a 70.7% yield of methyl crotonate, b.p. 118-120°.

Methyl crotonate from crotonic acid, methanol and 2,2-dimethoxypropane. To a solution of 861 g. (10 moles) of technical crotonic acid and 520 g. (5 moles) of 2,2-dimethoxypropane in 2-l. of absolute methanol there was added, in one portion, 10 ml. of absolute methanol which had been saturated with anhydrous hydrogen chloride. After being swirled for several seconds to insure uniform distribution of the catalyst the reaction mixture was allowed to stand at room temperature for 24 hrs. in a stoppered 5-l. flask. The reaction mixture was then divided into three parts by pouring it into three 2-l. beakers, each containing approximately 200 g. of finely pulverized ice. Several drops of phenolphthalein were added to the contents of each beaker and the solutions were then carefully neutralized with dilute sodium bicarbonate. The water layers were quickly separated and the ester layers were individually washed with a 50 ml. portion of saturated sodium chloride solution. The combined water layers and washings were extracted with 50 ml. of ether which was added to the combined ester fractions. After being dried briefly over anhydrous sodium sulfate, the product was distilled through a 6 in. Vigreux column. The distillation was

started at atmospheric pressure to remove the ether and the residual methanol (a volume of approximately 50 ml. was collected) and then the pressure was reduced to 100 mm. for the distillation of the ester. The product was collected in three fractions.

Fraction	B.p., °C. (100mm.)	Grams
1	94-94	310
2	94-96	346
3	95-96	326
residue	---	< 1

The total weight of the methyl crotonate was 982 g. (98%).

This procedure is based on the methylation procedure for dehydrated castor oil acids described by Lorette and Brown (153).

Methyl γ-bromocrotonate. A mixture of 80.0 g. (0.8 mole) of methyl crotonate, 72 g. (0.4 mole) of N-bromosuccinimide and 120 ml. of purified carbon tetrachloride (149) in a 500 ml. flask was refluxed for 12 hrs. The reaction mixture was cooled to room temperature and the succinimide which had risen to the surface of the liquid was removed by filtration. The filtrate was distilled through a Vigreux column to give the following fractions.

Fraction	B.p., °C. (mm.)	Grams	n_D^{25}
1	20-28(124)	60	-
2	28-38(124)	92.5	-
3	38-40(124)	37.5	-
4	86-91(15)	3.46	1.4960
5	91-91(15)	32.44	1.4980
6	91-96(15)	20.68	1.4985

Fractions 4-6, assumed to be methyl γ-bromocrotonate, amounted to 56.58 g. (39.5%).

Fractions 2 and 3 consisted of recovered methyl crotonate and carbon tetrachloride which were reused in succeeding preparations of the bromo-ester.

According to Vogel (152) this procedure should give a 43.2% yield of methyl γ-bromocrotonate, b.p. 77-78°(8mm.).

Methyl 4[1-(6-methoxy-1,2,3,4-tetrahydronaphthylidene)]-crotonate. A mixture of 90 g. of 30-mesh zinc (cleaned by successive washings with dilute hydrochloric acid, water, acetone and then drying at 100° just prior to use) and 6 g. of dry mercuric chloride was covered with 220 ml. of dry benzene and allowed to stir for 30 min. To the resulting amalgamated zinc there was added a solution of 85.8 g. (0.48 mole) of methyl γ-bromocrotonate and 84.5 g. (0.48 mole) of 1-keto-6-methoxy-1,2,3,4-tetrahydronaphthalene in a solvent mixture of 220 ml. of anhydrous ether and 60 ml. of dry benzene in one portion followed by a crystal of iodine. The reaction mixture, which turned dark green within 15 min., was refluxed for 90 min. Another 44 g. of zinc, 27 g. of methyl γ-bromocrotonate and a second crystal of iodine was added and the refluxing continued for an additional 90 min. Two additional portions of 44 g. of zinc, 27 g. of methyl γ-bromocrotonate and a crystal of iodine were added at 90 min. intervals as the reaction mixture was vigorously stirred under reflux. Refluxing was continued for 3 hrs. after the last addition. The reaction mixture was then cooled and poured onto approximately 600 g. of crushed ice and the resulting water layer acidified with acetic acid. The layers were separated and the water solution was extracted with four 75 ml. portions of ether. The benzene-ether solution was combined with the ether extracts and washed successively with several 25 ml. portions of 5% ammonium hydroxide (until the washings became light yellow), with water and finally with saturated sodium chloride solution. After being dried over anhydrous sodium sulfate, the solvent was removed with a rotary evaporator. The residue was distilled through a 6 in. Vigreux column. A forerun, distilling at 125-145° (0.1 mm.), solidified and proved to be recovered 1-keto-6-methoxy-1,2,3,4-tetrahydronaphthalene.

After recrystallization from methanol this material, m.p. 78-79°, weighed 37 g. (43.8% recovery). The next fraction, a thick yellow sirup, b.p. 160-178° (0.1 mm.), was methyl 4-[1-(6-methoxy-1,2,3,4-tetrahydronaphthylidene)]crotonate. The ester weighed 59.8 g. (48.6% or 86.9% based on unrecovered starting material). The sirup solidified upon standing. A sample of this product was recrystallized several times from absolute ethanol, giving methyl 4[1-(6-methoxy-1,2,3,4-tetrahydronaphthylidene)]crotonate, m.p. 80-81°, as light yellow crystals.

Stork (139), using this procedure, prepared methyl 4-[1-(6-methoxy-1,2,3,4-tetrahydronaphthylidene)]crotonate in 93% yield (based on unrecovered starting material). He reported a melting point of 79-80° and boiling point of 182-188° (1.3 mm.).

4-(6-Methoxy-1-naphthyl)butyric acid. A mixture of 19 g. (0.074 mole) of methyl 4-[1-(6-methoxy-1,2,3,4-tetrahydronaphthylidene)]-crotonate and 1 g. of 30% palladium on charcoal* was heated at 285 ± 5° for 4 hrs. under a dry carbon dioxide atmosphere. This reaction was carried out in a 100 ml. three necked flask equipped with a reflux condenser, an all-glass paddle stirrer and a gas inlet tube. The carbon dioxide was obtained by allowing dry ice to sublimate in a 250 ml. filter flask. It was passed through concentrated sulfuric acid before being introduced into the reaction flask. After the reaction mixture had cooled to room temperature under the carbon dioxide atmosphere, sufficient ether was added to dissolve the product. The catalyst was removed by filtration. The solvent was removed with a rotary evaporator leaving a reddish-brown, viscous sirup which weighed 17.05 g. Hydrolysis of this residue to the desired acid was accomplished by refluxing it under a nitrogen atmosphere for 4 hrs. with a solution of 10 g. of potassium hydroxide in 220 ml. of 50% ethanol. After the -

*Commercial product of Engelhard Industries, Inc.

reaction mixture had cooled to room temperature, the alcohol was removed with a rotary evaporator. Two hundred milliliters of water was added to the residue and the resulting solution was extracted with three 50 ml. portions of ether to remove any non-acidic material. The water solution was then poured slowly into a mixture of 20 ml. of concentrated hydrochloric acid and 100 g. of crushed ice to precipitate the free acid. The light tan acid was removed by filtration and, after being air dried, weighed 16.53 g. Recrystallization from aqueous methanol gave 14.75 g. (81.6% based on starting unrearranged ester) of pure 4-(6-methoxy-1-naphthyl)butyric acid, m.p. 150-151°.

This procedure is a modification of that described by Stork (139) for the preparation of 4-(6-methoxy-1-naphthyl)butyric acid, m.p. 151°. He reported a 77.0% yield from this rearrangement.

It was noted during the preliminary investigation of this reaction that the catalyst settled to the bottom of the reaction vessel. The apparatus described above was constructed in order to effect an even distribution of the catalyst throughout the melt during the heating period. This stirring gave a much better contact with the catalyst and is probably responsible for the slightly higher yields obtained for this arrangement.

1-Keto-7-methoxy-1,2,3,4-tetrahydrophenanthrene. To a slurry of 10 g. (0.04 mole) of finely powdered 4-(6-methoxy-1-naphthyl)butyric acid in 50 ml. of anhydrous ether containing 3 drops of pyridine there was added 4.8 ml. (7.86 g., 0.066 mole) of freshly distilled thionyl chloride in one portion. The reaction mixture was allowed to stand at room temperature with occasional swirling until the mixture became homogeneous. This usually required approximately 3 hrs. The solution was then warmed to 35° for 10 min. and the solvent and excess thionyl chloride were removed with a rotary evaporator. To the residue there

was then added a 10 ml. portion of benzene and the solution was again evaporated. This process was repeated until all trace of thionyl chloride was removed. The acid chloride was dissolved in 200 ml. of dry benzene and the solution was filtered into a 500 ml. flask to remove the pyridine hydrochloride. This solution was then cooled in an ice-salt bath until the benzene began to crystallize. To this a solution of 11.0 g. (0.04 mole) of stannic chloride in 40 ml. of benzene was then added in one portion. The reaction mixture was swirled until a uniform yellow slurry was obtained. The reaction mixture was cooled in an ice bath for several min. and was then poured onto a mixture of 50 g. of crushed ice, 60 ml. of concentrated hydrochloric acid and 60 ml. of ether. This mixture was then allowed to stand until most of the solid had gone into solution. An additional 100 ml. of ether was added and the two layers were separated. The ether-benzene solution was washed successively with three 30 ml. portions of cold 10% hydrochloric acid, 50 ml. of water, two 30 ml. portions of 10% sodium hydroxide, and again with water. The solution was dried over anhydrous sodium sulfate and the solvent was removed with a rotary evaporator. The residue was dissolved in benzene and the solution was passed through a 2.5 x 10 cm. column of neutral alumina which removed most of the color. The benzene was evaporated and the residue crystallized from methylcyclohexane. There was obtained 6.57 g. (72.5%) of 1-keto-7-methoxy-1,2,3,4-tetrahydrophenanthrene, m.p. 102-102.5°.

This procedure is essentially that of Bachmann, Cole and Wilds (140) who prepared 1-keto-7-methoxy-1,2,3,4-tetrahydrophenanthrene, m.p. 98-100°, in a 90-95% yield.

Methyl 1-keto-7-methoxy-1,2,3,4-tetrahydrophenanthrene-2-glyoxalate. Two-tenths of a mole of alcohol-free sodium methoxide was prepared by dissolving 4.6 g. (0.2 g.-atom) of sodium in 50 ml. of

anhydrous methanol, adding 50 ml. of dry benzene and removing the solvents at reduced pressure. After the dry salt had been heated for 15 min. on a steam bath it was then crushed to a coarse powder with a Teflon paddle stirrer. To the dry sodium methoxide was then added 23.6 g. (0.2 mole) of finely powdered dimethyl oxalate, followed by 100 ml. of dry benzene. This mixture was then refluxed for 15 min. in order to obtain a fine slurry. The mixture was then cooled to 5° in an ice bath and a solution of 22.6 g. (0.1 mole) of 1-keto-7-methoxy-1,2,3,4-tetrahydrophenanthrene in 150 ml. of dry benzene was added in one portion. The reaction mixture turned dark green immediately and within 20 min. a light yellow solid began to deposit on the sides of the flask. The ice bath was removed and the mixture was allowed to stand at room temperature for 4 hrs. All of the above operations were carried out under an atmosphere of dry nitrogen. The reaction mixture was hydrolyzed by pouring it over 200 g. of crushed ice. A small amount of 5% sodium hydroxide was added to give two distinct layers. The layers were separated and the benzene solution was extracted with two 30 ml. portions of 2% sodium hydroxide. The water solution and the basic extracts were combined, cooled to 10° and acidified to a pH of 5 (pHydrion paper) with cold 6N hydrochloric acid. The yellow glyoxalate was removed by filtration and desiccated over anhydrous calcium chloride. The dry solid was digested with 700 ml. of methanol-acetone (1:1), cooled and filtered, giving 29.65 g. (94.8%) of methyl 1-keto-7-methoxy-1,2,3,4-tetrahydrophenanthrene-2-glyoxalate. The bright yellow product had a melting point of 134-135.5°.

This procedure is a modification of Bachmann, Cole and Wilds (140) who prepared methyl 1-keto-7-methoxy-1,2,3,4-tetrahydrophenanthrene-2-glyoxalate in 96.0% yield and reported a melting point of 134-35°.

1-Keto-2-carbomethoxy-7-methoxy-1,2,3,4-tetrahydrophenanthrene. Ten grams (0.032 mole) of methyl 1-keto-7-methoxy-1,2,3,4-tetrahydrophenanthrene-2-glyoxalate was placed in an 8 in. test tube and the tube flushed with dry nitrogen. The tube was then kept in a preheated oil bath ($160 \pm 5^{\circ}$) until the glyoxalate melted. Five grams of powdered soft glass was then added to the melt and the temperature of the oil bath was quickly raised to 190°. There was a rapid evolution of carbon monoxide as the temperature of the reaction mixture reached 175°. Heating was continued at 180° for 20 min. and then the temperature was raised to 200°. The evolution of gas appeared to be complete after 15 min. at 180° and the originally bright orange reaction mixture had become dark orange-brown. The reaction mixture was allowed to cool to 150° and an additional 5 g. of powdered soft glass was added. The temperature was again raised to 180° and maintained for 20 min. There was further evolution of gas during this period of heating with the second portion of soft glass. At the end of the heating period the reaction mixture was dark brown with no visible orange or red coloration. The test tube was removed from the oil bath and allowed to cool to 90°. Ten milliliters of benzene and 3 g. of Norite were added directly to the reaction mixture. This mixture was heated with stirring and was filtered into a round bottom flask. The benzene was removed from the light yellow solution with a rotary evaporator, leaving a thick yellow sirup. This residue was dissolved in methanol. The product was recovered by filtration from the cool methanol and was air dried. The 1-keto-2-carbomethoxy-7-methoxy-1,2,3,4-tetrahydrophenanthrene amounted to 8.02 g. (87.5%). This product, as obtained from the methanol recrystallization, melted first at $108\text{-}110^{\circ}$; the melt then resolidified and remelted at $125\text{-}126.5^{\circ}$.

Bachmann, Cole and Wilds (140), using a similar procedure, prepared 1-keto-2-carbomethoxy-7-methoxy-1,2,3,4-tetrahydrophenanthrene in a 90-94% yield. These workers reported a melting point

of 110-111° and a second melting point of 125-126.5° for the resolidified solid.

In this work it was found that by re-heating the reaction mixture with a second portion of powdered soft glass a much purer product was obtained. The completeness of the decarbonylation seems to be shown by the loss of the red or orange coloration in the reaction product.

1-Keto-2-methyl-2-carbomethoxy-7-methoxy-1,2,3,4-tetrahydrophenanthrene. To a solution of 0.2 mole of sodium methoxide in 90 ml. of anhydrous methanol was added 11.35 g. (0.04 mole) of finely powdered 1-keto-2-carbomethoxy-7-methoxy-1,2,3,4-tetrahydrophenanthrene and 50 ml. of dry benzene. As this mixture was refluxed, with constant stirring, the solid partially dissolved and then reappeared as the sodio-derivative. After 30 min. of refluxing, the light red reaction mixture was cooled in an ice bath and 14 ml. (32 g., 0.25 mole) of methyl iodide was added in one portion. The ice bath was removed and the slurry was stirred at room temperature for one hour. An additional 14 ml. of methyl iodide was then added and stirring at room temperature was continued for another 2 hrs. The resulting red-orange solution was then refluxed for 45 min., cooled to 5° and neutralized with glacial acetic acid. After the solution had been evaporated almost to dryness with a rotary evaporator, the residue was partitioned between 150 ml. of benzene and 150 ml. of water. After the separation of the two layers, the water solution was extracted with two 50 ml. portions of benzene. The combined organic solution was washed with three 30 ml. portions of 5% sodium hydroxide, with 100 ml. of water, and finally with 100 ml. of saturated sodium chloride solution. After being dried over anhydrous sodium sulfate the solution was treated with Norite and the solvent was removed with a rotary evaporator. The residue was a thick yellow sirup weighing 12.07 g. Crystallization from methanol gave

11.52 g. (97.5%) of 1-keto-2-methyl-2-carbomethoxy-7-methoxy-1,2,3,4-tetrahydrophenanthrene, m.p. 84-85°.

Bachmann, Cole and Wilds (140), using a similar procedure, prepared 1-keto-2-methyl-2-carbomethoxy-7-methoxy-1,2,3,4-tetrahydrophenanthrene, m.p. 84-86°, in an 89-92% yield.

1-Ethyl-1-hydroxy-2-methyl-2-carbomethoxy-7-methoxy-1,2,3,4-tetrahydrophenanthrene. A solution of approximately 0.05 mole of ethylmagnesium bromide was prepared by adding 5.7 g. (0.052 mole) of ethyl bromide in 25 ml. of dry ether over a period of 45 min. to 1.25 g. (0.052 g. atom) of magnesium covered with 50 ml. of ether. The resulting solution was refluxed for 1 hr. and was then cooled to 5° in an ice bath. To the cold Grignard reagent was added a solution of 12.0 g. (0.04 mole) of 1-keto-2-methyl-2-carbomethoxy-7-methoxy-1,2,3,4-tetrahydrophenanthrene in 50 ml. of dry benzene at such a rate that the temperature did not rise above 10°. After the addition had been completed, the reaction mixture was stirred at 5° for 30 min., at room temperature for 1 hr. and finally refluxed for 30 min. The mixture was then cooled to approximately 15° and poured over 200 g. of crushed ice, to which sufficient dilute hydrochloric acid was added to dissolve the inorganic salts. The two layers were separated and the water solution was extracted with two 50 ml. portions of benzene-ether (5:1). The organic solutions were combined and washed with 100 ml. of 1N hydrochloric acid, 100 ml. of water and finally with 50 ml. of saturated sodium chloride solution. After the solution had been dried over anhydrous sodium sulfate, the solvent was removed with a rotary evaporator, leaving a thick yellow sirup which amounted to 13.59 g. This residue solidified upon standing. Recrystallization from methanol gave 12.5 g. (95.0%) of 1-ethyl-1-hydroxy-2-methyl-2-carbomethoxy-7-methoxy-1,2,3,4-tetrahydrophenanthrene, m.p. 118-138°.

This melting point is indicative of the mixture of diastereoisomeric alcohols obtained. No attempt was made to separate these isomers before dehydration to 1-ethylidene-2-methyl-2-carbomethoxy-7-methoxy-1,2,3,4-tetrahydrophenanthrene.

This procedure is based on that described by Heer and Miescher (97). These workers prepared 1-ethyl-1-hydroxy-2-methyl-2-carbomethoxy-7-methoxy-1,2,3,4-tetrahydrophenanthrene, m.p. 118-130°, in an 80% yield.

1-Ethylidene-2-methyl-2-carbomethoxy-7-methoxy-1,2,3,4-tetrahydrophenanthrene. A mixture of 6.39 g. (0.02 mole) of 1-ethyl-1-hydroxy-2-methyl-2-carbomethoxy-7-methoxy-1,2,3,4-tetrahydrophenanthrene and 8 ml. of 85% formic acid was heated on a steam bath for 2 hrs. As the reaction mixture cooled to room temperature, two layers separated. The reaction mixture was added to 300 ml. of benzene and the resulting solution was washed with 50 ml. of water, with three 30 ml. portions of 5% sodium hydroxide and finally with 50 ml. of saturated sodium chloride solution. After the solution had been dried over anhydrous sodium sulfate, the solvent was removed from the solution with a rotary evaporator. The residue, consisting of a mixture of crude cis- and trans-1-ethylidene-2-methyl-2-carbomethoxy-7-methoxy-1,2,3,4-tetrahydrophenanthrenes, weighed 6.02 g. (99.4%). This product was not purified before saponification to the free acid.

This procedure is based on that described by Heer and Miescher (97). These workers prepared 1-ethylidene-2-methyl-2-carbomethoxy-7-methoxy-1,2,3,4-tetrahydrophenanthrene for which they reported a 102% yield of crude product.

1-Ethylidene-2-methyl-2-carboxy-7-methoxy-1,2,3,4-tetrahydrophenanthrene. A solution of 6.02 g. (0.02 mole) of 1-ethylidene-2-methyl-2-carbomethoxy-7-methoxy-1,2,3,4-tetrahydrophenanthrene

and 33 g. of potassium hydroxide in 10 ml. of water and 20 ml. of alcohol was refluxed for 2 hrs. The reaction mixture was cooled to room temperature and most of the alcohol was removed with a rotary evaporator. After the residue had been dissolved in 200 ml. of water, any non-acidic material was removed by extraction with three 30 ml. portions of benzene. Acidification of the cooled solution to a pH of 2 (pHydrion paper) with cold 6N hydrochloric acid caused the separation of a light brown gum which was extracted into 300 ml. of benzene. After this solution had been dried over anhydrous sodium sulfate, the benzene was removed with a rotary evaporator. The semi-solid residue weighed 5.46 g. Treatment with Norite and recrystallization from acetone gave 4.42 g. (78.9%) of a mixture of the cis- and trans-1-ethylidene-2-methyl-2-carboxy-7-methoxy-1,2,3,4-tetrahydrophenanthrenes, m.p. 165-174°. No attempt was made to separate these cis- and trans- acids before hydrogenation to 1-ethyl-2-methyl-2-carboxy-7-methoxy-1,2,3,4-tetrahydrophenanthrene.

Heer and Miescher (99) obtained 1-ethylidene-2-methyl-2-carboxy-7-methoxy-1,2,3,4-tetrahydrophenanthrene, m.p. 163-175°. These workers started with a purified diastereoisomeric modification of the hydroxy ester obtained from the ring closure of 6-(6'-methoxy-1'-naphthyl)-4-methyl-4-carbomethoxy-3-hexanone with sulfuric acid.

1-Ethyl-2-methyl-2-carboxy-7-methoxy-1,2,3,4-tetrahydrophenanthrene. A mixture of 1.12 g. (0.0037 mole) of 1-ethylidene-2-methyl-2-carboxy-7-methoxy-1,2,3,4-tetrahydrophenanthrene in 50 ml. of ethyl acetate and 0.3 g. of platinum on charcoal catalyst was placed in a 500 ml. hydrogenation bottle. The bottle was placed in a Parr low pressure hydrogenation apparatus and charged with hydrogen at 15 p.s.i. The hydrogenation was allowed to proceed for 40 min. at ambient temperature. The catalyst was removed by filtration and

the filtrate was evaporated to dryness with a rotary evaporator. The residue was recrystallized from 10 ml. of ethanol, and weighed 1.05 g., m.p. 218-222°. A second recrystallization left 0.93 g. of product, m.p. 228-230°. From the combined filtrates an additional 0.08 g. of product, m.p. 227-229°, was obtained. The total yield of 1-ethyl-2-methyl-2-carboxy-7-methoxy-1,2,3,4-tetrahydrophenanthrene was 1.01 g. (89.4%).

Anner and Miescher (99) by the hydrogenation of a mixture of the sodium salts of the unsaturated acids over Rupe nickel obtained a mixture of the two isomeric 1-ethyl-2-methyl-2-carboxy-7-methoxy-1,2,3,4-tetrahydrophenanthrenes, m.p. 228-230° and 204-206°.

1-Ethyl-2-methyl-2-[N,N-bis(2-hydroxyethyl)carbamyl]-7-methoxy-1,2,3,4-tetrahydrophenanthrene. A well-stirred slurry of 5.86 g. (0.02 mole) of 1-ethyl-2-methyl-2-carboxy-7-methoxy-1,2,3,4-tetrahydrophenanthrene in 50 ml. of dry benzene and 4 drops of pyridine was cooled to 5°. To the above slurry was added 16 ml. (26.2 g., 0.14 mole) of freshly distilled thionyl chloride over a period of 30 min. The reaction mixture was stirred at room temperature for 3 hrs. and then at 40° for 1 hr. After cooling the resulting solution to room temperature, the solvent and excess thionyl chloride were removed with a rotary evaporator. To the residue there was added a small portion of dry benzene and the solution was evaporated. This process was repeated several times until all of the thionyl chloride had been removed. The bright yellow residue weighed 10.7 g. This crude acid chloride was dissolved, with difficulty, in 150 ml. of purified dioxane and the solution was filtered (to remove the pyridine hydrochloride) into an addition funnel. This solution was added to a well-stirred mixture (partial solution) of 20 ml. (0.2 mole) of diethanolamine and 100 ml. of dioxane over a period of 2 hrs. After the addition had been

completed the reaction mixture was heated to 55° and stirred at this temperature for 12 hrs. The reflux condenser was then replaced with a Claisen head and the dioxane and the excess diethanolamine were removed at aspirator pressure directly from the reaction flask. The yellow residue was partitioned between 100 ml. of benzene and 80 ml. of water. The two layers were separated and the water solution was extracted with three 25 ml. portions of benzene. The benzene solutions were combined and washed successively with two 15 ml. portions of 2% sodium hydroxide, with 30 ml. of water, with two 15 ml. portions of 1N hydrochloric acid, with 30 ml. of water and finally with 30 ml. of saturated sodium chloride. The solvent was removed from the dried solution (anhydrous sodium sulfate) with a rotary evaporator. The residual thick sirup consisted of 8.31 g. of crude 1-ethyl-2-methyl-2-[N, N-bis(2-hydroxyethyl)carbamyl]-7-methoxy-1, 2, 3, 4-tetrahydrophenanthrene. This crude product was not purified before reduction to the corresponding amine.

No starting acid was recovered upon acidification of the basic extract, obtained from extracting the crude product with 2% sodium hydroxide, with 6N hydrochloric acid.

Benner (145), using a similar procedure, prepared N, N-bis(2-hydroxyethyl)-3, 4-di(p-methoxyphenyl)-3-hexenamide.

1-Ethyl-2-methyl-2-[N, N-bis(2-hydroxyethyl)aminomethyl]-7-methoxy-1, 2, 3, 4-tetrahydrophenanthrene hydrochloride. To a well-stirred slurry of 1.52 g. (0.04 mole) of lithium aluminum hydride in 150 ml. of purified tetrahydrofuran (146) was added over a period of 2 hrs. a solution of 8.31 g. of crude 1-ethyl-2-methyl-2-[N, N-bis(2-hydroxyethyl)carbamyl]-7-methoxy-1, 2, 3, 4-tetrahydrophenanthrene in 100 ml. of tetrahydrofuran. After the addition had been completed, the reaction mixture was refluxed for 8 hrs. An additional 0.15 g.

(0.004 mole) of lithium aluminum hydride was added and the refluxing was continued for another 4 hrs. The reaction mixture was cooled to 5° and 40 ml. of water-saturated ethyl acetate was slowly added to destroy the excess lithium aluminum hydride. Two hundred and fifty milliliters of saturated ammonium tartrate-ammonium sulfate solution was added to the reaction mixture followed by 250 ml. of methylene chloride. The two clear layers were separated and the water layer was extracted with two 50 ml. portions of methylene chloride. The organic solutions were combined and washed with three 30 ml. portions of saturated ammonium tartrate-ammonium sulfate solution. After the solution had been dried over anhydrous sodium sulfate, the solvent was removed with a rotary evaporator, leaving 7.97 g. of crude amine. This residue was dissolved in 250 ml. of dry ether. The ethereal solution was cooled to 5° and anhydrous hydrogen chloride was added until the solution became acidic to moist Congo red paper. A colorless solid precipitated and was allowed to stand at 5° for one week. The solid was recovered and after drying in vacuo amounted to 7.29 g. (89.5% based on starting acid) of 1-ethyl-2-methyl-2-[N,N-bis(2-hydroxyethyl)-aminomethyl]-7-methoxy-1, 2, 3, 4-tetrahydrophenanthrene hydrochloride, m.p. 201-210°.

One gram of the amine hydrochloride was recrystallized several times from methanol, giving an analytical sample of 1-ethyl-2-methyl-2-[N, N-bis(2-hydroxyethyl)aminomethyl]-7-methoxy-1, 2, 3, 4-tetrahydrophenanthrene hydrochloride, m.p. 214.5-216.5°.

This procedure is based on that described by Benner (147) for the preparation of N, N-bis(2-hydroxyethyl)-3, 4-di(p-methoxyphenyl)-3-hexenylamine hydrochloride.

Analysis. Calculated for $C_{23}H_{34}NO_3Cl$: C, 67.71; H, 8.40; Cl, 8.69.
Found: C, 67.63; H, 8.47; Cl, 8.55.

Attempted preparation of 1-ethyl-2-methyl-2-[N, N-bis(2-chloroethyl)aminomethyl]-7-methoxy-1, 2, 3, 4-tetrahydrophenanthrene hydrochloride. To a well-stirred slurry of 6.29 g. (0.0154 mole) of 1-ethyl-2-methyl-2-[N, N-bis(2-hydroxyethyl)aminomethyl]-7-methoxy-1, 2, 3, 4-tetrahydrophenanthrene hydrochloride in 100 ml. of purified chloroform (149) containing 5 drops of dimethylformamide at 5° was added 35 ml. (47 g., 0.4 mole) of thionyl chloride in 15 ml. of chloroform over a period of 1 hr. The reaction mixture was allowed to come to room temperature and was then stirred for 12 hrs. During this time the light yellow solution had become dark brown. The excess thionyl chloride and solvents were removed with a rotary evaporator. To the residue there was added a 10 ml. portion of benzene which was then removed with a rotary evaporator. This process was repeated until all traces of thionyl chloride had been removed. There remained a dark sirupy residue amounting to 12.90 g. This residue was partially dissolved in chloroform and the chloroform solution was decanted from a small amount of black insoluble tar. Upon cooling, a yellow solid (approximately 4 g.) separated from the chloroform solution and was removed by filtration. A sample of this solid material which had been recrystallized several times from acetone had a melting point of 173-175°, with darkening at 155°, decomposition at 168° and evolution of gas at 176°. The mother liquor was passed through an alumina column, 5 x 20 cm., and was eluted with dry chloroform. Removal of the chloroform with a rotary evaporator left a thick brown sirup. Anhydrous hydrogen chloride was passed through this ethereal solution until it was acidic to moist Congo red paper. A dark brown tar was the only material which separated from the ethereal solution. No solid crystalline product could be isolated from this material.

A 0.5 g. sample of the yellow solid was dissolved in 100 ml. of dry chloroform and 20 ml. (33 g., 0.27 mole) of thionyl chloride was

added. The reaction mixture was refluxed for 2 hrs. The solvent and excess thionyl chloride were removed with a rotary evaporator leaving a dark brown intractable tar. No other product could be isolated from the reaction mixture. A sodium fusion of the brown tar showed the presence of sulfur.

A mixture of 0.5 g. of the yellow solid and 10 ml. of thionyl chloride containing 1 drop of water was heated at 50° for 2 hrs. in a water bath. A dark brown intractable tar was the only material isolated from the reaction mixture.

An attempt was made to determine the molecular weight of the yellow solid but a solution of sufficient concentration could not be obtained for a freezing point depression or boiling point elevation. An attempted Rast molecular weight determination with camphor gave a black sirup that would not resolidify.

The desired nitrogen mustard, $C_{23}H_{32}ONCl_3$, would require: C, 62.09; H, 7.25; N, 3.18; Cl, 23.91. Found: C, 55.21; H, 6.53; N, 2.92; Cl, 21.00; S, 5.33; ash 0.68.

Methyl (1-hydroxy-2-methyl-2-carbomethoxy-1,2,3,4-tetrahydronaphthyl)acetate. Thirty-five grams of clean (126) 20-mesh zinc was covered with a solution of 21.8 g. (0.1 mole) of 1-keto-2-methyl-2-carbomethoxy-1,2,3,4-tetrahydronaphthalene and 0.2 g. iodine in a solvent mixture of 150 ml. of anhydrous ether and 150 ml. of dry benzene. To this mixture there was added 16 ml. (24.2 g.) of methyl bromoacetate in one portion. As the reaction mixture was stirred at reflux temperature, under a dry nitrogen atmosphere, the iodine color gradually disappeared and a light yellow solid was deposited on the sides of the reaction flask. After the reaction mixture had been refluxed for 30 min., an additional 35 g. of zinc and a crystal of iodine were added and the refluxing was continued for another hour.

A third 35 g. portion of zinc, a second 16 ml. portion of methyl bromoacetate (making a total of 0.32 mole) and a crystal of iodine was then added. Three more portions of fresh zinc (making a total of 210 g.) were added to the reaction mixture at 45 min. intervals. The total reflux time was 6 hrs. The addition product was dissolved by adding a minimum amount of glacial acetic acid and methanol (1:1) to the reaction mixture and the homogeneous solution was then decanted from the zinc into water which had been acidified with acetic acid. After the ether-benzene layer had been separated, the water solution was extracted with three 25 ml. portions of benzene. The organic solutions were combined and washed with dilute ammonium hydroxide until no color appeared in the extract, with 75 ml. of water and finally with 75 ml. of saturated sodium chloride solution. After the solution had been briefly dried over anhydrous sodium sulfate, the solvents were removed by flash distillation. This left a light, orange-colored sirup which solidified upon standing. Two recrystallizations from methanol gave 27.88 g. (95.5%) of product with a melting point of 54-56°. This material was considered sufficiently pure for the succeeding step.

A 5.0 g. sample of this material was recrystallized several times from methanol-acetone (20:1) to give 3.73 g. of pure methyl (1-hydroxy-2-methyl-2-carbomethoxy-1, 2, 3, 4-tetrahydronaphthyl)acetate, m.p. 63-64°.

Bachmann and Thomas (126) using a similar procedure, prepared methyl (1-hydroxy-2-methyl-2-carbomethoxy-1, 2, 3, 4-tetrahydronaphthyl)acetate, m.p. 63.5-64.5°, in a 97% yield.

(2-Methyl-2-carboxy-1, 2, 3, 4-tetrahydronaphthylidene)acetic acid. A mixture of 29.2 g. (0.1 mole) of methyl (1-hydroxy-2-methyl-2-carbomethoxy-1, 2, 3, 4-tetrahydronaphthyl)acetate in 50 ml. of dry benzene and 12.5 ml. of pyridine was cooled to 5° in an ice bath.

To this mixture there was then added 25 ml. of freshly distilled thionyl chloride. After the immediate reaction had ceased, the reaction flask was removed from the ice bath and allowed to stand at room temperature for 30 min. The homogeneous reaction mixture was again cooled to 5° and transferred to a separatory funnel containing 100 ml. of ice water. After the excess thionyl chloride had reacted, the two layers were separated and the water layer was extracted with three 25 ml. portions of benzene. The benzene solutions were combined and added to a solution of 28 g. (0.5 mole) of potassium hydroxide in 500 ml. of methanol. The resulting solution was refluxed for 15 min. on a steam bath. The reaction mixture was then cooled and 100 ml. of 45% aqueous potassium hydroxide was added. After this mixture had been refluxed for approximately 45 min., a large amount of insoluble material had separated from the reaction mixture. Sufficient water was added to dissolve this precipitate while approximately 250 ml. of the organic solvents were being removed by distillation. Refluxing was then continued for an additional 4 hrs. After the remainder of the benzene and methanol had been distilled, the reaction mixture was cooled and the excess potassium hydroxide was carefully neutralized to pH 8 (pHydrion paper) with dilute hydrochloric acid. The solution was then treated with Norite and the filtrate acidified to pH 2 (pHydrion paper). Filtration gave 16.40 g. of a light yellow product. The water solution was extracted with three 75 ml. portions of ether. The combined ether extract was dried over anhydrous magnesium sulfate and the ether was removed from this solution with a rotary evaporator, giving an additional 3.55 g. of product. The total yield was 19.45 g. (81.1%). This product is a mixture of cis- and trans-(2-methyl-2-carboxy-1,2,3,4-tetrahydronaphthylidene)acetic acids. Since prior investigators (140) have shown that each isomer yields the same mixture of diastereoisomeric acids on

reduction, it was considered unnecessary to separate these unsaturated acids prior to reduction.

This procedure is adapted from that described by Bachmann and Thomas (126) who prepared this same mixture of unsaturated acids in an 86% yield.

2% Sodium amalgam. A 1-l. flask equipped with a reflux condenser, an addition funnel and a gas inlet tube was thoroughly dried by brushing with a luminous flame as a stream of nitrogen was passed through the flask. After the flask had cooled, it was charged with 30.0 g. of clean sodium which was covered with 50 ml. of dry toluene and 1500 g. of mercury was placed in the addition funnel. After the sodium had been melted by heating the flask with a free flame a few drops of mercury was added to the contents of the flask. After the initial reaction had subsided the remainder of the mercury was added at such a rate that the toluene slowly refluxed. At the end of the reaction the reflux condenser was replaced by a distilling head and the flask evacuated to 100 mm. The toluene was removed by gently heating the flask with a free flame. The amalgam was allowed to cool slightly before it was transferred to 10 ml. screw capped bottles while still molten.

This preparation is based on that described by Vogel (154).

(2-Methyl-2-carboxy-1,2,3,4-tetrahydronaphthyl)acetic acid. A solution of 3 g. of a mixture of cis- and trans-(2-methyl-2-carboxy-1,2,3,4-tetrahydronaphthylidene)acetic acids in 36 ml. of 7.5% potassium hydroxide was shaken vigorously ("precision" equipoise shaker) with 60 g. of 2% sodium amalgam for 30 min. After the residual mercury had been removed by filtration, the nearly colorless filtrate was cooled and acidified to pH 2 (pHydrion paper) with dilute hydrochloric acid. The colorless solid was removed and air dried, giving 2.17 g. of product.

An oil, recovered by ether extraction of the filtrate, was crystallized from carbon tetrachloride, giving an additional 0.86 g. of product. Recrystallization of the combined solid from carbon tetrachloride-acetone (10:1) gave a first crop of crystals amounting to 2.30 g. of (2-methyl-2-carboxy-1,2,3,4-tetrahydronaphthyl)acetic acid, m.p. 167-168° and a second crop amounting to 0.53 g. of the second diastereoisomeride, m.p. 100-115°.

Bachmann and Thomas (126), using a similar procedure, prepared the same diastereoisomeric (2-methyl-2-carboxy-1,2,3,4-tetrahydronaphthyl)acetic acids, m.p. 167.5-169° and 100-115°.

p-Tolylsulphonylmethylnitrosamide. A 5-l. flask was equipped with a reflux condenser, paddle stirrer, thermometer, a graduated addition funnel and a standard taper glass powder funnel which was closed with an inverted 50 ml. Erlenmeyer flask. This flask was placed in a water bath which was maintained at 70° during the course of the reaction by the addition of ice or hot water as required. The flask was charged with 210 ml. of 33% aqueous methylamine and 110 ml. of 50% sodium hydroxide solution (equivalent to approximately 70 g. of sodium hydroxide) was placed in the addition funnel. When the methylamine solution in the flask had reached 70° there was added a 30 g. portion of p-toluenesulfonyl chloride and the solution was stirred until the reaction mixture became acidic (pH 6- pHydrion paper). Ten milliliters of the sodium hydroxide solution was then added at such a rate that the temperature of the reaction mixture did not exceed 85° (this addition required approximately 3 min.). This sequence--the addition of 30 g. of p-toluenesulfonyl chloride, allowing the reaction to proceed until the solution became acidic and the addition of 10 ml. of 50% sodium hydroxide solution--was repeated ten times. A total of 320 g. (1.7 moles) of p-toluenesulfonyl chloride was added to an excess of methylamine.

The walls of the flask were washed with sufficient water to remove the adhering solid and the reaction mixture was heated to 90° for 1 hr. with gentle stirring. The water bath was cooled to 2° by the addition of ice, and 1700 ml. of glacial acetic acid was added to the reaction mixture. A solution of 125 g. of sodium nitrite in 250 ml. of water was placed into the addition funnel. When the reaction mixture had been cooled to 5°, the sodium nitrite solution was added at such a rate as to maintain the temperature below 8°. Vigorous stirring was maintained throughout this addition, which required approximately 5 hrs. After the reaction mixture had been stirred at 10° for an additional hour, it was then diluted with 1-l. of ice water. The solid reaction product was collected on a large Buchner funnel and washed with two 500 ml. portions of cold water. After being dried over concentrated sulfuric acid, the product was dissolved in 500 ml. of ether and precipitated by the addition of 500 ml. of pentane. The dried p-tolylsulphonylmethylnitrosamide, m.p. 59-60°, amounted to 358 g. (96%).

This procedure is a modification of that of H. J. Backer as described by Vogel (155). The addition of the p-toluenesulfonyl chloride and sodium hydroxide in eleven portions, rather than in three as described by Vogel, allows better temperature control which prevents the loss of methylamine from high reaction temperatures and the formation of solids at lower temperatures.

Methyl (2-methyl-2-carbomethoxy-1, 2, 3, 4-tetrahydronaphthyl)-acetate. An ethereal solution of approximately 0.15 mole of diazomethane was distilled from an all-glass apparatus (155) in the usual manner. It was prepared from a solution of 33 g. (0.15 mole) of p-tolylsulphonylmethylnitrosamide in 200 ml. of ether and a solution of 7.5 g. of potassium hydroxide in 40 ml. of methanol and 12 ml. of water. A solution of 7.55 g. (0.03 mole) of (2-methyl-2-carboxy-1, 2, 3, 4-tetrahydronaphthyl)acetic acid in 50 ml. of ether and 100 ml. of methanol was added

to the above diazomethane solution over a period of 1 hr. The solution was cooled in an ice bath and stirred with a magnetic stirrer during this addition. The reaction mixture was stirred at 5° for 2 hrs. and then at room temperature overnight. The solvent was then removed with a rotary evaporator. The semi-solid residue was dissolved in 250 ml. of benzene and the benzene and the benzene solution was extracted with several 10 ml. portions of sodium bicarbonate solution. Acidification of the bicarbonate extracts with dilute hydrochloric acid gave no recovered acidic material. The benzene solution was dried briefly over anhydrous sodium sulfate and the benzene was removed with a rotary evaporator leaving a light yellow sirup which solidified upon standing. Recrystallization from petroleum ether (60-90°) gave 8.14 g. (98.3%) of methyl (2-methyl-2-carbomethoxy-1,2,3,4-tetrahydronaphthyl)acetate, m.p. 63.5-64°.

Bachmann and Thomas (126), using a similar procedure, prepared methyl (2-methyl-2-carbomethoxy-1,2,3,4-tetrahydronaphthyl)acetate, m.p. 62-63.5°, in a 94% yield.

(2-Methyl-2-carbomethoxy-1,2,3,4-tetrahydronaphthyl)acetic acid. A mixture of 10.66 g. (0.38 mole) of methyl (2-methyl-2-carbomethoxy-1,2,3,4-tetrahydronaphthyl)acetate and 38.6 ml. of 0.984 N sodium hydroxide in 127 ml. of methanol was refluxed for 1 hr. and 45 min. After the methanol had been removed with a rotary evaporator, the residue was dissolved in water and filtered to remove a small quantity of insoluble material. The filtrate was then cooled and acidified with dilute hydrochloric acid. The colorless solid was removed by filtration and air-dried to give 10.5 g. of product. Recrystallization from methylcyclohexane gave 9.25 g. (92.1%) of (2-methyl-2-carbomethoxy-1,2,3,4-tetrahydronaphthyl)acetic acid, m.p. 113.5-114°.

This procedure is similar to that described by Bachmann and Thomas (126) for the preparation of (2-methyl-2-carbomethoxy-1,2,3,4-tetrahydronaphthyl)acetic acid, m.p. 113.5-114.5°. These workers obtained the product in a 96.6% yield.

1-Aminomethyl-2-methyl-2-carbomethoxy-1,2,3,4-tetrahydronaphthalene hydrochloride. A solution of 5.24 g. (0.02 mole) of (2-methyl-2-carbomethoxy-1,2,3,4-tetrahydronaphthyl)acetic acid in 20 ml. of dry benzene containing 2 drops of pyridine was cooled to 5° and 8 ml. of freshly distilled thionyl chloride was added over a period of 10 min. After the addition of the thionyl chloride had been completed, the reaction mixture was allowed to stand at room temperature for approximately 30 min. and was then warmed to 40° for 15 min. The benzene and excess thionyl chloride were removed with a rotary evaporator leaving a light tan solid. Four milliliters of benzene was added to the residue and then removed with a rotary evaporator. This process was repeated several times until there was no noticeable odor of thionyl chloride in the residue. The crude acid chloride was then dissolved in 80 ml. of anhydrous acetone and filtered into a three-neck flask equipped with a drying tube and alcohol thermometer. The acetone solution was cooled to 0° and a solution of 5.2 g. (0.08 mole) of sodium azide in 36 ml. of water was added in one portion as the mixture was stirred with a magnetic stirrer. The reaction mixture was stirred at 0° for 30 min. and was allowed to come to room temperature with constant stirring. The reaction mixture was then diluted with 140 ml. of water and the stirring was continued for an additional 10 min. The solid azide was filtered, washed twice with water and then dissolved in 100 ml. of benzene. This benzene solution of the azide was then refluxed for 16 hrs. with a water separator (which had been filled with benzene to maintain a volume of 100 ml. of benzene in the flask). A "U" tube was attached to the top of the condenser and was filled with ethylene glycol

monomethyl ether to detect the evolution of nitrogen. The evolution of gas appeared to have ceased after 14 hrs. Forty milliliters of concentrated hydrochloric acid was then added and the refluxing was continued for an additional 4 hrs. During this time a colorless solid separated from solution. This solid was removed from the reaction mixture and the benzene solution returned to the flask. After one recrystallization the 1-aminomethyl-2-methyl-2-carbomethoxy-1,2,3,4-tetrahydronaphthalene hydrochloride, m.p. 169-170°, amounted to 3.44 g. (63.8%, based on starting acid). The benzene solution was refluxed until all of the water had been removed and the benzene was then removed with a rotary evaporator. After one recrystallization from ether there was obtained 2.15 g. (53.5%, based on free acid) of 1-aminomethyl-2-methyl-1,2,3,4-tetrahydro-2-naphthoic acid lactam, m.p. 134-136°.

A small quantity of the amine hydrochloride was dissolved in water and 5% sodium hydroxide was added until the solution was basic. The basic solution was then extracted several times with small portions of ether. The ether extracts were combined and the ether was removed with a rotary evaporator. Crystallization of the residue from ether gave a colorless solid, m.p. 134-135°.

This procedure is based on that described by Drefahl (156), as modified by Benner (157) for the preparation of erythro-2,3-di(p-methoxyphenyl)pentylamine.

Analysis. Calculated for 1-aminomethyl-2-methyl-2-carbomethoxy-1,2,3,4-tetrahydronaphthalene hydrochloride, $C_{14}H_{20}NO_2Cl$: C, 62.32; H, 7.47; N, 5.19. Found: C, 63.53; H, 7.51; N, 5.01.

Calculated for 1-aminomethyl-2-methyl-1,2,3,4-tetrahydro-2-naphthoic acid lactam, $C_{13}H_{15}NO$: C, 77.57; H, 7.51; N, 6.96. Found: 77.36; H, 7.46; N, 6.77.

Attempted hydrolysis of 1-aminomethyl-2-methyl-1, 2, 3, 4-tetrahydro-2-naphthoic acid lactam.

a) With concentrated hydrochloric acid. A mixture of 0.2 g. (0.0009 mole) of 1-aminomethyl-2-methyl-1, 2, 3, 4-tetrahydro-2-naphthoic acid lactam and 20 ml. of concentrated hydrochloric acid was refluxed for 4 hrs. The reaction mixture was cooled to room temperature and a small amount of acetone was added. After standing in a dry ice bath for a period of 1 hr., the solid which had separated was removed by filtration. After drying, the product, which amounted to 0.2 g., was found to be recovered starting material, m.p. 135-136° and had a mixed melting point with the starting lactam of 135-136°.

b) With methanolic potassium hydroxide. A solution of 0.1 g. of 1-aminomethyl-2-methyl-1, 2, 3, 4-tetrahydro-2-naphthoic acid lactam and 5 g. of potassium hydroxide in 20 ml. of methanol was refluxed for 12 hrs. After the reaction mixture had been cooled to room temperature, the methanol was removed with a rotary evaporator. The residue was vigorously stirred with 30 ml. of water and the water solution was extracted with several 10 ml. portions of ether. Removal of the ether with a rotary evaporator left a colorless residue weighing 0.078 g. and melting at 133-134°. This residue and the starting lactam gave a mixed melting point of 134-136°. The water solution was acidified with dilute hydrochloric acid and the potassium chloride was removed by filtration. The water solution was concentrated with a rotary evaporator causing the separation of a minute (less than 0.01 g.) amount of solid which was not further investigated.

c) With sodium hydroxide in ethylene glycol. A solution of 0.78 g. of the lactam and 2 ml. of 50% sodium hydroxide in 10 ml. of ethylene glycol was refluxed for 8 hrs. After the reaction mixture had cooled to room temperature, it was diluted with 10 ml. of acetone.

No solid precipitated. The solution was cooled in an ice-salt bath and neutralized with cold concentrated hydrochloric acid. A colorless solid precipitated and was removed by filtration. This material did not char on fusion and was assumed to be inorganic salts. The solution was then extracted with several small portions of ether and the ether was removed with a rotary evaporator. The colorless residue weighed 0.65 g. and had a melting point of 132-133°, a mixed melting point with the original lactam was 133-134°. No further solid material could be isolated from the water solution other than inorganic salts.

d) With barium hydroxide. A mixture of 4.6 g. of barium hydroxide, 0.4 g. of the lactam and 20 ml. of water contained in a 50 ml. flask with a condenser topped with an ascarite filled drying tube, was refluxed for 5 hrs. The reaction mixture was then allowed to cool to room temperature and the solution was filtered to remove the solid that had formed during the reflux period. The solid was washed with a small amount of ether to remove any organic material that might be present. Ignition of this residue showed it to be an inorganic salt containing little, if any, organic material. The filtrate was then extracted several times with 10 ml. portions of ether. The ether was removed with a rotary evaporator, leaving a solid residue which amounted to 0.33 g. and which had a melting point of 133-134°. The mixed melting point with the starting material was 134-135°. Carbon dioxide was bubbled through the water solution until no more solid appeared to form. The solid barium carbonate was removed by filtration. Evaporation of the water left a small amount of solid residue. Ignition of a small quantity of this solid indicated that it was inorganic material with little or no organic material present.

Attempted hydrolysis of 1-aminomethyl-2-methyl-2-carbomethoxy-1,2,3,4-tetrahydronaphthalene hydrochloride. A mixture of 0.4 g. (0.0015 mole) of 1-aminomethyl-2-methyl-2-carbomethoxy-1,2,3,4-tetrahydronaphthalene hydrochloride and 25 ml. of concentrated hydrochloric

acid was refluxed for 10 hrs. The reaction mixture was cooled to room temperature and concentrated to one-half its volume with a rotary evaporator. The residue was diluted with 15 ml. of acetone and the resulting solution was allowed to stand at 5° for several weeks to induce crystallization. The solid was removed by filtration, giving 0.26 g. of 1-aminomethyl-2-methyl-1,2,3,4-tetrahydro-2-naphthoic acid lactam, m.p. 134-135°. No additional material could be isolated from the filtrate by extraction with chloroform or by cooling in dry ice-acetone for several days.

Attempted preparation of 1-[N,N-bis(2-hydroxyethyl)amino]-2-methyl-2-carbomethoxy-1,2,3,4-tetrahydronaphthalene hydrochloride.

a) With ethylene oxide. A mixture of 0.4 g. (0.0015 mole) of 1-aminomethyl-2-methyl-2-carbomethoxy-1,2,3,4-tetrahydronaphthalene hydrochloride in 30 ml. of benzene and 3 ml. of distilled ethylene oxide was placed in a 200 ml. stainless steel bomb. The reaction was allowed to proceed in the sealed bomb for 6 hrs. at 150°. After the bomb had been allowed to cool to room temperature the pressure was slowly vented and the residual solution was treated with Norite and filtered into a tared flask. The benzene was removed with a rotary evaporator leaving a residue amounting to 0.43 g. Recrystallization from benzene-ether gave 0.4 g. of 1-aminomethyl-2-methyl-1,2,3,4-tetrahydro-2-naphthoic acid lactam, m.p. 132-134°.

b) With ethylene chlorohydrin. A solution of 0.1 g. (0.0004 mole) of 1-aminomethyl-2-methyl-2-carbomethoxy-1,2,3,4-tetrahydronaphthalene hydrochloride and 0.129 g. (0.0016 mole) ethylene chlorohydrin in 5 ml. of dimethylformamide was placed in a glass liner of a 200 ml. stainless steel bomb. The temperature was gradually raised to 170° and the reaction mixture was maintained at this temperature for 4 hrs. The reaction mixture was allowed to cool to room temperature

and then poured onto approximately 5 g. of crushed ice. This residue was extracted several times with 10 ml. portions of chloroform. The combined chloroform extracts were washed once with water and the solution dried over anhydrous sodium sulfate. The solvent was removed with a rotary evaporator, leaving a residue weighing 0.098 g. The residue had a melting point of 133-135°, and a mixed melting point with 1-aminomethyl-2-methyl-1,2,3,4-tetrahydro-2-naphthoic acid lactam of 134-136°.

1-Hydroxy-2-methyl-2-carbomethoxy-1,2,3,4-tetrahydronaphthalene. To a well-stirred solution of 1.2 g. (0.033 mole) of sodium borohydride in 24 ml. of 85% methanol was added a solution of 6.4 g. (0.03 mole) of 1-keto-2-methyl-2-carbomethoxy-1,2,3,4-tetrahydronaphthalene in 40 ml. of methanol over a period of 1 hr. The reaction mixture was then stirred at room temperature for an additional 12 hrs. After acidification of the reaction mixture with approximately 1 N hydrochloric acid, the methanol was removed with a rotary evaporator. The water solution was then extracted with five 15 ml. portions of methylene chloride. After this solution had been dried over anhydrous sodium sulfate, the solvent was removed with a rotary evaporator, leaving a thick colorless sirup. This residue, which amounted to 6.55 g. (99% crude yield), was distilled through a 10 cm. Vigreux column to give the following fractions.

Fraction	B.p., °C. (0.2 mm.)	Grams
1	78-86	0.35
2	86-86	2.08
3	86-89	3.22
4	89-98	0.87
residue	-	<0.1

Fractions 2 and 3 solidified and were recrystallized from a 1:1 mixture of acetone-petroleum ether (40-60°), giving 1-hydroxy-2-methyl-2-carbomethoxy-1,2,3,4-tetrahydronaphthalene, m.p. 63-64° (with previous softening).

This is a modification of the procedure described by Dauben (158) for the reduction of cholestenone enol acetate.

Analysis. Calculated for $C_{13}H_{16}O_3$: C, 70.88; H, 7.32.
Found: C, 70.77; H, 7.31.

1-Chloro-1-methyl-2-carbomethoxy-1,2,3,4-tetrahydronaphthalene. A mixture of 11.0 g. (0.05 mole) of 1-hydroxy-2-methyl-2-carbomethoxy-1,2,3,4-tetrahydronaphthalene and 19.8 g. (0.1 mole) of barium carbonate in 200 ml. of purified chloroform (149) was cooled to 0° in an ice-salt bath. To the above mixture was then added 20.7 g. (0.1 mole) of phosphorous pentachloride in small portions over a period of 2.5 hr. During this addition the reaction mixture was constantly stirred with a magnetic stirrer. Stirring was continued for 30 min. after the addition had been completed. Thirty-five milliliters of a cold saturated sodium bicarbonate solution was then added to the reaction mixture and stirring was continued for an additional 30 min. The reaction mixture was then filtered to remove the inorganic salts and the filtrate was dried over anhydrous sodium sulfate. Evaporation of the solvent with a rotary evaporator left a brown residue which amounted to 11.5 g. (96.0%crude yield). No attempt was made to purify this crude 1-chloro-2-methyl-2-carbomethoxy-1,2,3,4-tetrahydronaphthalene before its use in an attempted alkylation of diethanolamine.

The I.R. spectrum of the crude chloride indicated the complete loss of the hydroxyl group which was well resolved in the spectrum of the starting alcohol.

A 2 g. portion of the crude chloride was distilled at 0.005 mm. (bath temperature of 54° in a Hickman still giving a clear, colorless liquid. A sodium fusion showed the presence of chlorine in this distilled and the I. R. spectrum indicated the absence of the hydroxyl group.

This procedure is a modification of that described by Wintersteiner (159) for the preparation of 3β-acetoxycholestane chloride-7.

Attempted preparation of 1-[N, N-bis(2-hydroxyethyl)amino]-2-methyl-2-carbomethoxy-1, 2, 3, 4-tetrahydronaphthalene hydrochloride. A mixture of 17 g. (0.07 mole) of crude 1-chloro-2-methyl-2-carbomethoxy-1, 2, 3, 4-tetrahydronaphthalene and 80 g. (0.76 mole) of diethanolamine was heated under a nitrogen atmosphere at 180° for 6 hrs. The reaction mixture was allowed to cool to room temperature and was then diluted with 200 ml. of water and 8 ml. of 0.1 N sodium hydroxide. The brown oil which separated from the water solution was extracted with four 50 ml. portions of benzene. The organic solutions were combined and dried over anhydrous sodium sulfate. The solvent was removed with a rotary evaporator leaving a thick, brown sirup amounting to 10.0 g. This residue was dissolved in anhydrous ether and anhydrous hydrogen chloride was passed into the solution until it was acidic to moist Congo red paper. Very little hydrogen chloride was required. No material separated from this solution as it was kept at -78° for 48 hrs. After the ether solution had been washed with several portions of dilute base, the solvent was removed and the residue was analyzed for nitrogen (sodium fusion). No nitrogen was present in the product.

The water solution was acidified to pH 2 with dilute hydrochloric acid and was continuously extracted with chloroform in a heavier than water extractor for 48 hrs. The small amount of residue remaining upon evaporation of the chloroform extract did not contain nitrogen (sodium fusion).

This procedure is a modification of that described by Friedman and Seligman (160) for the preparation of 1, 2-benzanthranyl-10-methyl-bis(β-hydroxyethyl)amine hydrochloride.

Attempted preparation of 1-amino-2-methyl-2-carbomethoxy-1,2,3,4-tetrahydronaphthalene. A mixture of 11.9 g. (0.05 mole) of crude 1-chloro-1-methyl-2-carbomethoxy-1,2,3,4-tetrahydronaphthalene, 10 g. (0.054 mole) of potassium phthalimide (161), 0.2 g. of potassium iodide and 40 ml. of dimethylformamide was heated at 140±5° for 48 hrs. The reaction mixture was cooled to room temperature and then poured into 100 ml. of ice water. An additional 50 ml. of water was used to rinse the reaction flask. There were two distinct types of solid present at this time--a light yellow well defined solid and a light brown semi-solid. Extraction with four 50 ml. portions of chloroform removed the semi-solid material leaving the solid residue suspended in the water phase. The chloroform solutions were combined and successively washed with 20 ml. of water, 20 ml. of 2% sodium hydroxide and again with 20 ml. of water. The chloroform was removed with a rotary evaporator leaving a dark brown sirup. Sodium fusion of this residue indicated the presence of nitrogen.

The solid remaining in the water solution was removed by filtration and, after being allowed to air dry, had a melting point of 218-225°. This solid also gave a positive nitrogen test.

Approximately 0.5 g. of the semi-solid residue obtained from the chloroform extraction was dissolved in a mixture of 10 ml. of glacial acetic acid and 10 ml. of concentrated hydrochloric acid. This solution was warmed on a steam bath for 1 hr. and a small portion was withdrawn and tested for primary amine (162). No primary amine was present. After the solution had been refluxed for several hours, it was poured over ice and the dark brown residue was extracted into three 15 ml. portions of chloroform. The residue obtained by removing the chloroform did not give a test for primary amine. Anhydrous hydrogen chloride passed into an ethereal solution of this material did not lead to the separation of an insoluble hydrochloride.

A second 0.5 g. portion of this semi-solid residue was dissolved in 25 ml. of absolute ethanol containing 0.2 ml. of hydrazine hydrate. After being refluxed for 3 hrs., the solution was cooled and acidified with dilute hydrochloric acid. No solid was present--as a rule solid phthalyl hydrazide separates from solution at this point (163). The reaction mixture was diluted with water until a dark brown gum had separated and was then extracted with chloroform. No primary amine could be isolated from the residue obtained from this chloroform extract.

The solid material obtained from the original reaction mixture was treated as has been described for the non-crystalline material. No primary amine could be isolated from the tarry residues obtained from either the hydrochloric acid or the hydrazine hydrolysis.

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