THE PREPARATION OF SOME 3,6- AND 3,4-DISUBSTITUTED THIANAPHTHENES

Thesis for the Degree of Ph. D.

MICHIGAN STATE UNIVERSITY

Richard Lee Titus

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ABSTRACT

THE PREPARATION OF SOME 3,6- AND
3,4-DISUBSTITUTED THIANAPHTHENES

by Richard Lee Titus

The original goal of the investigation was to prepare the alkaloid reserpine with a thianaphthene ring in place of the indole ring.

One of the compounds essential to this synthesis was β(6-methoxythianaphthyl-3)ethylamine. Attempts to prepare this intermediate were not successful. One method involved an attempted substitution on the number three carbon of the 6-methoxythianaphthene ring. Subsequent work showed that the presence of the 6-methoxy group directs the substitution away from the number three carbon. A second attempt involved the preparation of 6-bromothianaphthene. It was found that 6-bromothianaphthene could not be prepared by the method used in a desirable state of purity. Large amounts of 4-bromothianaphthene were also formed. The third attempt involved the preparation of 6-methoxythianaphthyl-3-acetamide. This compound was prepared in a pure state but the reduction of it to β(6-methoxythianaphthyl-3)ethylamine was unsuccessful.

Since the preparation of the desired amine was unsuccessful to this point it was decided to prepare a model compound having some of the gross structure of reserpine so that its physiological properties could be investigated.

This was done by reacting piperidine with 6-methoxythianaphthyl-3-acetyl chloride which was prepared from 6-methoxythianaphthyl-3-acetic acid which in turn was obtained by the hydrolysis of the above amide. The tertiary amide obtained was reduced using lithium aluminum hydride to an amine, N[2(6-methoxythianaphthyl-3)ethyl]piperidine, which was isolated and purified as its hydrochloride. This compound was submitted for testing regarding its physiological properties.

Several other compounds were prepared as a result of this investigation, viz. ethyl (6-methoxythianaphthyl-3)-acetate, 4-methoxythianaphthyl-3-acetamide, 4-methoxythianaphthyl-3-acetic acid, and 2(4-methoxythianaphthyl-3)-ethanol.

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By

Richard Lee Titus

A THESIS

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The plant growth assays for 4-methoxythianaphthyl-3-acetic acid and 6-methoxythianaphthyl-3-acetic acid were performed by her and Mr. Roger Ritzert.

VITAE

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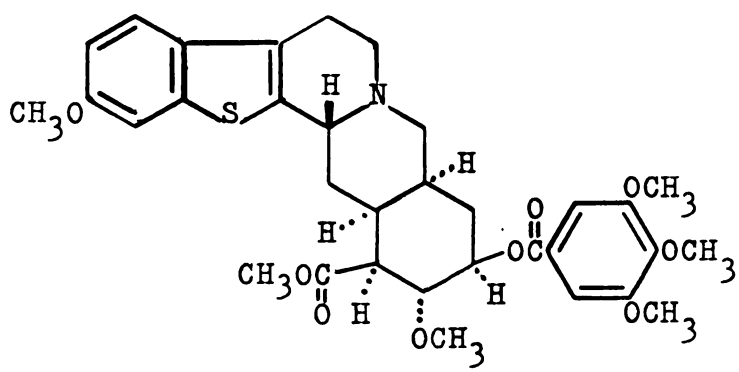
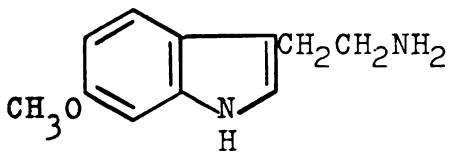
INTRODUCTION AND HISTORICAL

The total synthesis of reserpine (1)(2)(3) and yohimbane (4) suggested simple direct synthetic routes to their sulfur analogs wherein a thianaphthene nucleus would replace the indole ring in these naturally occurring alkaloids. The aim of the present study was to investigate the physiological properties of such a molecule, i.e. of "thioreserpine" I.



I

The total synthesis of reserpine involved the preparation of three large fragments of the molecule and combination of them to form the desired structure. The three fragments employed in the total synthesis of reserpine were 6-methoxytryptamine II, 3,4,5-trimethoxybenzoyl chloride III, and finally, ring E of the reserpine molecule in a form suitable for further reaction IV.



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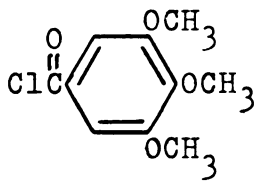

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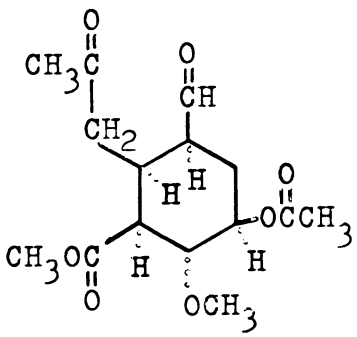
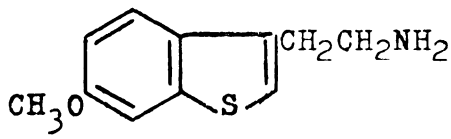


IV

The synthesis of "thioreserpine" then required the development of synthetic routes to the unknown sulfur analog of the 6-methoxytryptamine or β(6-methoxythianaphthyl-3)ethylamine V.



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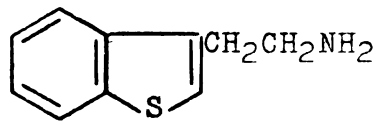
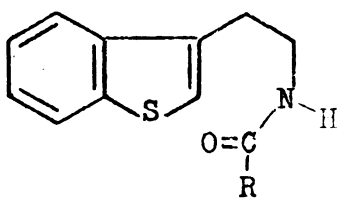


VI

Similar thianaphthene derivatives have been described, e.g. Werner Herz (5) prepared VI, VII, and VIII, while



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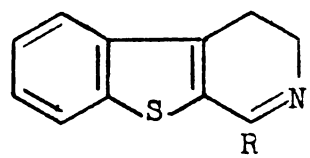
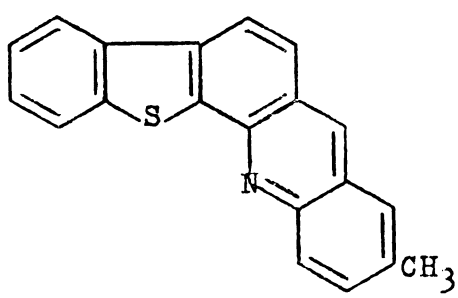


VIII

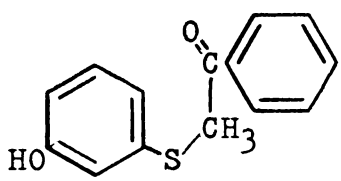
P. Cagniant et al. (6) prepared IX. The latter contains



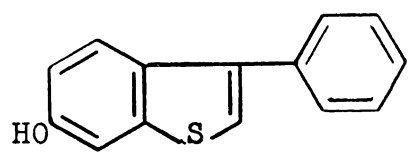
IX

a ring system similar to that of reserpine even though structurally it is quite dissimilar.

A literature search revealed no description of a suitable 3,6-disubstituted thianaphthene from which the β(6-methoxythianaphthyl-3)ethylamine might be synthesized. Further, the literature examination showed only a few 3,6-disubstituted thianaphthenes had ever been prepared and the majority of these had only been investigated as intermediates in the synthesis of dyes. The 6-methoxythianaphthenes described had been prepared by the ring closure of an appropriately substituted sulfide (7), e.g. X to XI.

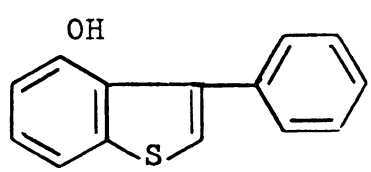


X



XI

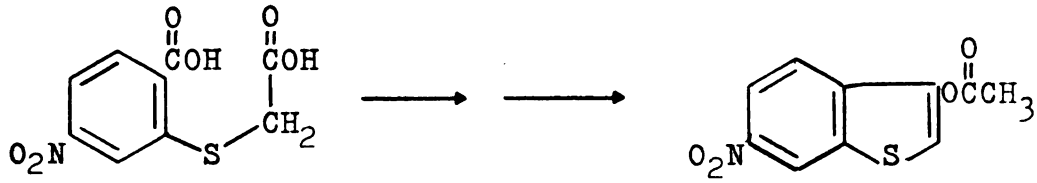
Such a ring closure would seem to depend upon the steric hinderance of the meta substituent on the benzene ring to prevent formation of a large amount of the 4-substituted thianaphthene, i.e. XII.



XII

Other 6-substituted thianaphthenes prepared by this procedure are 6-methoxythianaphthene (8), 6-chlorothianaphthene (9), and 6-methylthianaphthene (9)(10).

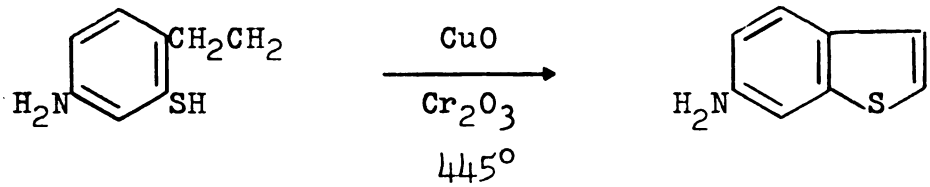
Another widely used synthesis of 3,6-disubstituted thianaphthenes has the advantage that the ring closure can occur one way as in XIII to XIV (11), employing an aromatic dicarboxylic sulfide.



XIII XIV

However, a disadvantage of the latter method is the general difficulty of obtaining the appropriately substituted benzene.

Another ring closure procedure to obtain 6-substituted thianaphthenes starts with an ortho mercapto alkyl benzene which is pyrolyzed at 445° in the presence of a copper oxide-chromium oxide catalyst supported on charcoal, e.g. XV to XVI (12).



XV XVI

EXPERIMENTAL

Preparation of Sodium meta-Hydroxybenzenesulfonate

A solution containing 97.6 g. (0.5 mole) of sodium meta-aminobenzenesulfonate (metanilic acid, sodium salt; Eastman Practical) and 37 g. (0.536 mole) of $NaNO_2$ dissolved in 600 ml. of water was cooled to 5° and poured into a stirred mixture of 100 ml. of conc. HCl and 500 g. of ice. The chilled solution was then diluted with 500 ml. of water and heated slowly with stirring on a steam bath to 60°. When nitrogen evolution had ceased, the solution was heated to 70-80° for an hour and then made alkaline with 20% NaOH solution to a pH of approximately 8. The resulting dark red solution was heated on a steam bath under a stream of air until a crust of NaCl began to form. The mixture was then cooled and an equal volume of absolute alcohol added to precipitate the NaCl. This was removed by vacuum filtration and the filtrate evaporated to dryness under a stream of air on a steam bath. The residue was dried at 130° in an oven, and ground to pass a 40 mesh screen. The product was used without further purification.

Preparation of Sodium meta-Methoxybenzenesulfonate

A 150 g. (0.76 mole) quantity of sodium meta-hydroxybenzenesulfonate and 150 g. of a 20% NaOH solution were

stirred in a two-liter three-necked round bottom flask fitted with a reflux condenser while being heated on a steam bath under a stream of air to obtain a syrupy consistency. The mixture was cooled to room temperature and 72 ml. (0.76 mole) of dimethyl sulfate added with vigorous stirring. Stirring was continued until the mixture hardened, shortly after which it swelled quickly to several times its original volume. It was reheated on a steam bath for two hours. A 190 ml. volume of water was added and the solution was heated on a steam bath to dissolve the product. The hot solution was transferred to an Erlenmeyer flask and sufficient absolute alcohol added to make the solution turbid. The mixture was set aside in a refrigerator to allow crystallization of the product. The light yellow solid was removed by vacuum filtration, dried in an oven at 130°, and ground to pass a 40 mesh screen. The product was used without further purification.

Preparation of meta-Methoxybenzenesulfonyl Chloride

A 200 g. (0.95 mole) quantity of sodium meta-methoxybenzenesulfonate, previously dried overnight at 135° in an oven, was placed in a round bottom flask fitted with a reflux condenser. A 70 ml. (0.76 mole) volume of $POCl_3$ was then added and the mixture shaken well. The mixture was placed in an oil bath and heated at 165° for 3-4 hours. At the end of this time an additional 40 ml. (0.40 mole) of

$POCl_3$ was added and the mixture shaken thoroughly to break up the caked solids. The reaction mixture was held at 165° for a day with occasional shaking. It was then cooled in an ice bath and pieces of ice were added to decompose excess $POCl_3$. Sufficient water was added to dissolve inorganic salts. The dark organic layer was separated and the aqueous layer extracted with three 100-ml. portions of benzene. The combined product and benzene extracts were washed with 100 ml. of water and dried over anhydrous $MgSO_4$. The drying agent was removed by filtration and the benzene was removed under reduced pressure. The dark oily residue was distilled in vacuo, with the majority of the material (light yellow) distilling at 155°/1.2 mm. Hg; yield 70% of theory.

Preparation of meta-Methoxythiophenol

A 160 ml. volume of absolute alcohol and 80 g. (1.22 gr. at.) of zinc dust were placed in a two-liter three-necked round bottom flask fitted with condenser, stirrer, and dropping funnel. The mixture was heated to boiling on a steam bath, and 78 g. (0.38 mole) of meta-methoxybenzenesulfonyl chloride were added dropwise at a rate sufficient to maintain the mixture at its reflux temperature. Following addition of the acid chloride the mixture was stirred a half hour and 50 ml. of conc. HCl was added to the reaction mixture. Following a modest induction period a vigorous reaction

ensued and the stirrer was started. An additional 190 ml. of the acid (HCl) was added at a rate to maintain reflux temperature. When all the acid had been added the stirred reaction mixture was heated on a steam bath for 3-4 hours. The mixture was cooled to room temperature and 1.2 l. of water was added. The reaction mixture was transferred to a two-liter separatory funnel and the organic layer separated. The aqueous layer was extracted with three 100-ml. portions of ether. The product and combined ether extracts were washed with three 50-ml. portions of water. The ether solution was dried over anhydrous $MgSO_4$, filtered, and the ether removed by distillation. The light yellow oily product was vacuum distilled; b.p. 95°/9 mm. Hg - 110°/9 mm. Hg; yield 83% of theory.

Preparation of meta-Methoxyphenyl ω-Diethoxyethyl Sulfide

A 19.8 g. (0.86 gr. at.) quantity of sodium was added in portions to 400 ml. of absolute alcohol in a liter three-necked round bottom flask fitted with a reflux condenser and dropping funnel. When all the sodium had reacted, 120 g. (0.86 mole) of meta-methoxythiophenol was added, in portions, to the sodium alkoxide solution with shaking to insure thorough mixing. After the addition of the methoxythiophenol was complete the reaction mixture was heated on the steam bath for a half hour and then 12.9 g. (0.096 mole) of NaI was added with shaking, followed by the addition, in

small portions with intermittent shaking, of a solution of 170 g. (0.86 mole) of bromoacetaldehyde diethy acetal dissolved in 30 ml. of absolute alcohol. Heat was evolved after an induction period of several minutes and a white precipitate of NaBr formed. Following complete addition of the acetal the reaction mixture was heated on the steam bath for 16 hours. The alcohol was removed under reduced pressure and 600 ml. of water was added to the residue to dissolve the inorganic salts. The mixture was transferred to a separatory funnel and the layers separated, the aqueous layer being extracted with three 100-ml. portions of ether. The product and ether extracts were combined and washed with two 50-ml. portions of water. The ether solution was dried over anhydrous $MgSO_4$, filtered, and the ether removed by distillation. The light orange residue was distilled <u>in vacuo</u> using a Fenske column. The pure product collected boiled at 104-119°/< 1 mm. Hg; yield 153.4 g. which was 70% of theory.

The 2,4-dinitrophenylhydrazone of the product was prepared; m.p. 122-124°; literature value (8) 123-124°.

Preparation of 6-Methoxythianaphthene

A 48 ml. volume of 85% H_3PO_4 and 80 g. (0.56 mole) of P_2O_5 were placed in a 500 ml. three-necked round bottom flask fitted with a thermometer extending below the surface of the flask contents and a dropping funnel, the tip of

which was drawn out to a fine capillary extending below the surface of the polyphosphoric acid. The reaction flask was connected to a receiver using a short path connection and the entire system was evacuated to a pressure of 2.2 mm. Hg. The reaction flask was heated to 160° in an oil bath and 16.5 g. (0.64 mole) of meta-methoxyphenyl ω-diethoxyethyl sulfide was placed in the dropping funnel, and added in small amounts to the reaction mixture. The sulfide on contact with the acid mixture initiated a very vigorous reaction resulting in the simultaneous direct distillation of the product, 6-methoxythianaphthene, into the receiver. When the reaction had subsided another portion of sulfide was added, and so on until all of the sulfide had been added. At this point the pressure in the reaction flask was reduced to 0.07 mm. Hg for 15 minutes to collect the final quantity of product. The crude 6-methoxythianaphthene was redistilled; b.p. 60°/0.07 mm. Hg - 64°/0.03 mm. Hg; yield 60% of theory.

The picrate of the product melted from 104.4-105.8°; literature value (8) 105-106°.

Attempted Preparation of 3-Chloromethyl-6-methoxythianaphthene

A mixture containing 8.2 g. (0.05 mole) of 6-methoxythianaphthene, 4.8 ml. of conc. HCl, 4.2 g. of 37% formalin, and 10 ml. of 95% ethanol was placed in a 50 ml. round bottom flask fitted with a two-hole stopper containing a gas inlet tube reaching to the bottom of the flask and an outlet tube

leading to a water trap to absorb excess HCl. The reaction mixture, stirred with a magnetic stirrer, was cooled to 0° and dry HCl gas was bubbled through it for 15 minutes. At this point the stirred mixture was allowed to warm up to room temperature while passing a gentle stream of HCl through it. The reaction mixture was then set aside for three hours, at which time it had become a solid dark blue mass. Methylene chloride was added to dissolve the dark blue mass and the layers were separated. The methylene chloride solution was washed first with water, then with sodium bicarbonate solution, and finally again with water. The light yellow solution was dried for three hours over anhydrous $MgSO_4$, filtered, and poured slowly into a large excess of ice cold alcohol. The almost white precipitate, weighing 5.2 g., was recovered by filtration and dried.

Attempted Preparation of 3-Cyanomethyl-6-methoxythianaphthene

A 5.2 g. (0.024 mole) quantity of what was assumed to be 3-chloromethyl-6-methoxythianaphthene, 2.4 g. (0.049 mole) of NaCN, 0.5 g. (0.0033 mole) of NaI, and 17 ml. (0.23 mole) of anhydrous acetone were placed in a 50 ml. round bottom flask. The mixture was heated to 55° and stirred vigorously for 36 hours with a magnetic stirrer, in which time it darkened somewhat. The solid salts were removed by filtration and the acetone was removed from the filtrate by evaporation. An orange solid remained which, however, failed

to give a positive test for nitrogen or chlorine after being fused with sodium.

Attempted Preparation of 3-Bromo-6-methoxythianaphthene

A 10.0 g. (0.061 mole) quantity of 6-methoxythianaphthene, 10 g. (0.12 mole) of sodium acetate, and 80 ml. (1.4 mole) of glacial acetic acid were placed in a 250 ml. round bottom flask fitted with an addition tube, having a dropping funnel on top and a second tube connected from it to a sodium hydroxide trap at the side. A solution of 9.6 g. (0.06 mole) of bromine dissolved in 50 ml. of glacial acetic acid was placed in the dropping funnel. The contents of the flask were maintained at 20° and stirred magnetically while the bromine solution was added dropwise. Following the addition of the bromine, the reaction mixture was poured onto crushed ice and dilute $NaHSO_3$ solution to destroy excess bromine. About 50 ml. of methylene chloride was added to dissolve the product and the mixture was transferred to a separatory funnel and the layers were separated. The methylene chloride was removed under reduced pressure at room temperature. The residue was quickly distilled <u>in vacuo</u> and the fraction collected which boiled at 90°/0.06 mm. Hg - 103°/0.07 mm. Hg. This material was used immediately in the next step of the synthetic reaction sequence to prepare the acid.

Attempted Preparation of 3-Carboxy-6-methoxythianaphthene

A 2.43 g. (0.10 gr. at.) quantity of magnesium turnings was placed in a 300 ml. three-necked round bottom flask fitted with dropping funnel, stirrer, and a condenser with attached drying tube. A solution containing 2.57 ml. (0.034 mole) of ethyl bromide, 70 ml. of absolute ether, and the entire yield of the 6-methoxybromothianaphthene obtained from the previous bromination was placed in the separatory funnel. A solution of 2 ml. (0.026 mole) of ethyl bromide and 10 ml. of absolute ether was added to the flask. After initiating the reaction, the alkyl bromide ether solution in the separatory funnel was added at a rate to maintain the mixture at its reflux temperature. After adding the alkyl halide the reaction mixture was set aside for 20 minutes, followed by heating it under reflux on a steam bath for 30 minutes. It was then cooled to room temperature, and poured quickly with stirring over 150 g. of crushed dry ice. After the excess carbon dioxide evolved, 100 g. of ice was added to the mixture followed by 150 ml. of water and 35 ml. of conc. HCl. The mixture was transferred to a separatory funnel and repeatedly extracted with ether. The combined ether extracts were extracted with four 100-ml. portions of saturated $NaHCO_3$ solution. The combined bicarbonate extracts were decolorized with Norite and acidified to Congo red. The faintly pink precipitate was recovered by filtration

dried, and weighed (3.43 g.). The melting point of the crude acid was 221-224°, softening at 218°. After repeated recrystallizations from 95% alcohol a small quantity of material (approx. 0.1 g.) was obtained which melted at 279-280.5° (decomp.). An equivalent weight determination gave a value of 207. Calculated equivalent weight for a carboxymethoxythianaphthene is 208.

Anal. Calcd. for $C_{10}H_8O_3S$: C, 56.90; H, 3.93; S, 14.7. Found: C, 57.7; H, 3.87; S, 15.4.

Preparation of a Bromo-6-methoxythianaphthene

A 10 g. (0.061 mole) quantity of 6-methoxythianaphthene, 10.8 g. (0.061 mole) of N-bromosuccinimide, and 100 ml. of carbon tetrachloride were placed in a 250 ml. round bottom flask fitted with condenser and drying tube. The reaction mixture was heated at its reflux temperature for 24 hours, cooled, filtered, and the solvent removed under reduced pressure. The dark orange residue was distilled *in vacuo*. The product distilling at 88-90°/0.07 mm. Hg was collected. The yield was 11.3 g. (0.047 mole), 77% of theory.

Desulfurization of the Carboxy-6-methoxythianaphthene

An 8.20 g. (0.039 mole) quantity of the carboxy-6-methoxythianaphthene was refluxed with 20 g. of Raney nickel and 250 ml. of ethyl alcohol in a 500 ml. round bottom flask for 20 hours. The mixture was filtered and the alcohol

removed by distillation. The melting point of the crude product was 201-233° (decomp.). The crude product was desulfurized again as described until no further depression in melting point (88-92°) of the product was observed.

Preparation of Sodium meta-Bromobenzenesulfonate

An 83 g. (0.48 mole) quantity of sodium metanilate and 34.5 g. (0.50 mole) of $NaNO_2$ were dissolved in 850 ml. of distilled water. The solution was cooled to 10° and filtered into a stirred mixture of 250 ml. of conc. HCl and 100 g. of ice contained in a four-liter beaker. Ice was added, as needed, to maintain a temperature of 0-5°. This solution was added slowly to a stirred suspension of 160 g. (0.56 mole) of Cu_2Br_2 in 200 ml. of water and 75 ml. of 48% HBr. After adding the diazonium salt solution the reaction mixture was stirred at room temperature for 2 hours, heated to 75° on a steam bath for an hour, and then cooled and the Cu_2Br_2 removed by vacuum filtration. The filtrate was adjusted to pH 9-10 with 20% NaOH solution. Norite, 5 g., and Celite, 6 g., were added to the alkaline filtrate and the mixture was filtered through a Büchner funnel. The filtrate was then concentrated by heating it on a steam bath under a stream of air, until a crust of solid material had formed on the inner surface of the container. The mixture was heated to its reflux temperature to dissolve solid material then cooled to room temperature to crystallize the product,

which was recovered by vacuum filtration. Yield, 93.3 g. (0.36 mole), 75% of theory.

Preparation of meta-Bromobenzenesulfonyl Chloride

Sodium meta-bromobenzenesulfonate, 93.3 g. (0.36 mole), and 26 ml. (0.28 mole) of $POCl_3$ were placed in a 500 ml. round bottom flask fitted with a reflux condenser and heated to 175° for a half hour. An additional 15 ml. (0.16 mole) of $POCl_3$ was then added; the mixture was shaken thoroughly and again heated for another 14 hours. The reaction mixture was cooled by immersion in an ice water bath and excess $POCl_3$ destroyed by adding pieces of ice to the mixture. The semisolid material was transferred to a liter separatory funnel and sufficient water was added to dissolve the inorganic salts. The dark oil was separated and the aqueous layer extracted with two 100-ml. portions of benzene. The benzene extracts and dark oily product were combined and the benzene was removed under reduced pressure. The residual oil was distilled in vacuo. The light yellow colored product distilling at 82.5-91°/0.6 mm. Hg was collected. The yield was 58.0 g. (0.23 mole), 63% of theory. The meta-bromobenzenesulfonamide after two recrystallizations from water melted at 153-154.5°.

Preparation of meta-Bromothiophenol

A 50.0 g. (0.76 gr. at.) quantity of zinc dust and

100 ml. of absolute alcohol were placed in a two-liter three-necked flask fitted with a dropping funnel, stirrer, and condenser. The stirred mixture was initially brought to its reflux temperature on a steam bath and 55 g. (0.23 mole) of meta-bromobenzenesulfonyl chloride was added at a rate to maintain reflux. After addition of the acid chloride the gray mixture was stirred an additional 15 minutes and 150 ml. of conc. HCl was added dropwise. There was an induction period before a vigorous reaction with HCl was initiated. Following the acidification the reaction mixture was heated for 4 hours on a steam bath, cooled to room temperature and transferred to a 500 ml. separatory funnel and the layers were separated. The aqueous layer was diluted with 500 ml. of water and extracted with three 100-ml. portions of methylene chloride. The combined product and methylene chloride extracts were washed with three 100-ml. portions of water and dried over anhydrous $MgSO_4$. The drying agent was removed by filtration and the solvent by distillation. The oily residue was distilled under reduced pressure, collecting the product boiling from 92-100°/10 mm. Hg. The yield was 32.0 g. (0.17 mole), 74% of theory.

Preparation of meta-Bromophenyl ω-Diethoxyethyl Sulfide

Metallic sodium, 13.1 g. (0.57 gr. at.), was added in portions to 285 ml. of absolute alcohol contained in a liter

three-necked round bottom flask fitted with a reflux condenser, a drying tube and a dropping funnel. When the sodium had dissolved, 106.8 g. (0.56 mole) of meta-bromothiophenol was added, with shaking, in portions to the sodium alkoxide solution. Then 0.85 g. (0.057 mole) of NaI was added and the mixture thoroughly shaken. Following the addition of the iodide, 112 g. (0.57 mole) of bromoacetal was added, with vigorous shaking, in 10-15 ml. portions. External cooling was necessary to control the reaction. The mixture was set aside for a half hour then heated on a steam bath for eight hours. The alcohol was removed by distillation and 300 ml. of water was added. The mixture was transferred to a separatory funnel and the aqueous layer was separated and extracted with three 100-ml. portions of ether. The crude product and combined ether extracts were washed with 100 ml. of water, and dried over anhydrous $MgSO_4$. The drying agent was removed by filtration and the ether by distillation. The residual yellow colored oil was distilled <u>in vacuo</u> using a Fenske column. The product distilling in the range 104-116.5°/0.08 mm. Hg was collected. The yield was 87.6 g. (0.29 mole), 51% of theory.

The 2,4-dinitrophenylhydrazone of the product was prepared and purified by recrystallizing from 95% alcohol. It melted from 94.8-95.5° then immediately recrystallized and again melted from 113-114.2°.

Ring Closure of meta-Bromophenyl ω-Diethoxyethyl Sulfide

The procedure used was identical to that described for the ring closure of meta-methoxyphenyl ω-diethoxyethyl sulfide. A mixture of 23.2 g. (0.076 mole) of the sulfide, 56.2 ml. of 85% H_3PO_4 and 94 g. (0.66 mole) of P_2O_5 was used to effect the ring closure at a reaction temperature of 165° and a system pressure of 2.6 mm. Hg. The yield of crude product was 12.2 g. (0.056) mole, 74% of theory. The crude product, 31 g., was fractionated, using a 16-inch tantalum spiral column, into two fractions. The first was collected in the range 42-50°/0.07 mm. Hg, n_D^{25} 1.6440, 5.2 g. The second fraction was collected from 50-57.5°/0.07 mm. Hg, n_D^{25} 1.6688, 14.9 g. By setting fraction I inside a refrigerator for several days a white solid which melted from 38-43° was obtained. This was purified by sublimination at reduced pressure to a white solid melting from 44.8-45°. By cooling fraction II in a refrigerator for several days a white solid which melted from 53-56.5° was obtained. After sublimation at 50°/0.06 mm. Hg a pure white solid melting from 54.8-55.8° was obtained.

A 1.98 g. (0.0092 mole) quantity of the bromothianaphthene, melting at 55°, was converted to its Grignard reagent by placing the halide, magnesium metal, and dry tetrahydrofuran in a round bottom flask, and after adding several drops of ethyl bromide to initiate the reaction, refluxing the reaction

mixture for 5 hours. The solution was then cooled to room temperature and poured over crushed dry ice, hydrolyzed and the product isolated in the usual manner. The melting point of the crude product was 185-196°. After several recrystallizations from alcohol-water the acid melted from 200-203°.

A Grignard reagent was prepared from the noncrystalline residue of fraction I of the bromothianaphthene distillation by refluxing the halide and magnesium turnings in tetrahydrofuran for 5 hours, after initiating the reaction with a few drops of ethyl bromide. The reaction mixture was then cooled to room temperature and poured over crushed dry ice, hydrolyzed and the product isolated in the usual manner. Melting range of the crude material was 131-150°. This material was dissolved in base and precipitated by acidifying to Congo red. After drying, the precipitate was sublimed at reduced pressure to yield a product which melted from 139-155°. Fractional recrystallization failed to further purify the material.

A Grignard reagent was prepared from the noncrystalline material of fraction II of the bromothianaphthene distillation by refluxing it with magnesium turnings in tetrahydrofuran for 5 hours after initiating the reaction with a few drops of ethyl bromide. The reaction mixture was cooled to room temperature, poured over crushed dry ice, hydrolyzed and the product isolated in the usual way. The melting range of the crude product was 155-160°. Sublimation of the crude acid

at 130°/0.03 mm. Hg changed its melting point to 142-157°.

Extensive fractional recrystallization failed to purify this crude acid appreciably. The majority of the fraction had a melting range of 155-162°. However, a few milligrams of an acid melting from 188-189° were also obtained. The equivalent weight of this acid was determined to be 185; the calculated equivalent weight for a thianaphthylcarboxylic acid is 178.

Anal. Calcd. for $C_9H_6O_2S$: C, 60.65; H, 3.39. Found: C, 60.28; H, 3.65.

A gram of the acid fractions melting from approximately 150-155° was desulfurized by refluxing it with Raney nickel for several hours. The catalyst was removed by filtration and the alcohol by distillation. The melting point of the acid residue was determined and the acid was again desulfurized as described. This process was repeated until no further depression of the melting point of the product occurred. The acid finally obtained was a semi-solid which melted from 60-70°.

Preparation of Ethyl γ-Chloroacetoacetate

A gram of $HgCl_2$ (0.0037 mole) and 24.0 g. (1.0 gr. at.) of magnesium were placed in a two liter three-necked flask fitted with stirrer, condenser, and dropping funnel. A solution of 245.2 g. (2.0 mole) of ethyl chloroacetate dissolved in 173 ml. of dry ether was placed in the dropping funnel. A

small amount of the ester solution was added to the magnesium which was broken with a stirring rod to initiate the reaction. The remainder of the ester solution was added at a rate to maintain reflux temperature in the reaction mixture. A precipitate soon formed and the reaction became a pale green in color.

After adding the haloester the reaction mixture was refluxed with stirring on a steam bath for four hours, and hydrolyzed by pouring it onto crushed ice. Sufficient dilute H_2SO_4 was then added to dissolve the magnesium salts. The ether layer was separated and the aqueous layer extracted with three 100-ml. portions of ether. The combined ether extracts were washed with 50 ml. of dilute H_2SO_4, then with two 100-ml. portions of water. The ether solution was dried over anhydrous $MgSO_4$ and filtered. The ether was removed by distillation. The oily residue was distilled under reduced pressure. Unreacted ethyl chloroacetate was obtained in the fraction distilling at 25-79°/9 mm. Hg and the product was collected in the boiling range from 75-100°/9 mm. Hg. The yield was 48% of theory.

Preparation of Ethyl 4-(meta-Methoxyphenylmercapto)-3-oxobutyrate

A 60.0 g. (0.43 mole) quantity of meta-methoxythiophenol was dissolved in 300 ml. of pyridine in a liter three-necked round bottom flask fitted with a stirrer, thermometer supported in a slotted cork, and a dropping funnel. To this

stirred solution was added dropwise 70.0 g. (0.43 mole) of ethyl γ-chloroacetoacetate while holding the reaction temperature between 25-30° by means of an ice bath. When the haloester had been added the mixture was set aside for 15 minutes, then heated to 70-80° for 15 minutes on a steam bath, and cooled to room temperature. The pyridine was dissolved by slowly adding 600 ml. of 8 N HCl. The layers were separated and the aqueous layer extracted with two 100-ml. portions of ether. The product and ether extracts were combined and washed with two 50-ml. portions of water. The ether solution was dried over anhydrous $MgSO_4$, filtered, and the ether removed by distillation. The residue was distilled *in vacuo*. Decomposition occurred during distillation as evidenced by the continually rising pressure in the distillation system. The product boiling from 100°/0.2 mm. Hg to 170°/0.5 mm. Hg was collected. The yield was 88.6 g. (0.33 mole), 77% of theory.

Preparation of Ethyl 6-Methoxythianaphthyl-3-acetate and Ethyl 4-Methoxythianaphthyl-3-acetate

A 48 ml. volume of 85% H_3PO_4, 96 g. (0.68 mole) of P_2O_5, and a solution containing 28.8 g. (0.107 mole) of ethyl 4-(meta-methoxyphenylmercapto)-3-oxobutyrate dissolved in 200 ml. of chlorobenzene were placed in a liter round bottom flask fitted with a condenser. The reaction mixture was heated at its reflux temperature for three hours. The chlorobenzene solution was

then decanted from the semisolid reaction mass and 200 ml. of benzene was added and the mixture was again heated at its reflux temperature for three hours. The benzene layer was then decanted and combined with the chlorobenzene solution. The combined aromatic solutions were washed with 50 ml. of dilute $NaHCO_3$, followed by two 50-ml. portions of saturated NaCl solution. The benzene and chlorobenzene were removed under reduced pressure and the residue was distilled. The crude product was collected distilling from 90-155°/0.1 mm. Hg; yield 22.4 g. (0.090 mole); 83% of theory. The crude product was fractionated using a small heated Vigreaux column, and a small forerun boiling from 50-120°/0.07 mm. Hg was discarded. The combined 4- and 6-methoxy esters were collected in the temperature range from 120-164°/0.07 mm. Hg.

Preparation of 6-Methoxythianaphthyl-3-acetamide

A 10.0 g. mixture of the crude ethyl 4- and 6-methoxythianaphthyl-3-acetate and 200 ml. of conc. NH_4OH were placed in a 500 cc. Paar bottle and shaken at room temperature for a week. At the end of this time the solid product was recovered by filtration. The yield of the crude amide after drying was 6.6 g. (0.030 mole), 75% of theory. Pure 6-methoxythianaphthyl-3-acetamide was obtained by crystallizing the crude amide from 95% alcohol and it melted at 192.8-193.3°.

Pure 4-methoxythianaphthyl-3-acetamide was obtained by chromatographing the residue obtained by removing the alcohol

from the filtrates obtained from the purification of 6-methoxythianaphthyl-3-acetamide. A 0.4 g. quantity of the above residue was dissolved in the minimum quantity of chloroform and then placed on a 1" x 16" alumina column. The eluent used was chloroform. The first band obtained contained the 6-methoxy isomer and the second band contained the 4-methoxy isomer. After removal of the eluent the separated amides were purified by recrystallization from 95% alcohol. The pure 4-methoxythianaphthyl-3-acetamide melted at 200.0-200.5°. Approximately 1 g. of the 4-methoxy isomer was obtained from 20 g. of the crude amide which had been obtained from the ammonolysis of the ester mixture.

Anal. Calcd. for $C_{11}H_{11}O_2NS$: C, 59.72; H, 5.01; N, 6.36; S, 14.47. Found: 6-Methoxy amide: C, 60.21; H, 5.14; N, 6.22; S, 14.37. 4-Methoxy amide: C, 59.83; H, 5.08; N, 6.47; S, 14.42.

Preparation of 6-Methoxythianaphthyl-3-acetic Acid

A mixture containing 0.5 g. (0.0023 mole) of 6-methoxythianaphthyl-3-acetamide, 13 ml. of 10% NaOH, and 5 ml. of 95% alcohol was heated at its reflux temperature for two hours. The reaction mixture was cooled, filtered, and acidified with HCl to Congo red. The white precipitate which formed on acidification was recovered by filtration and dried. After several recrystallizations from alcohol-water the acid melted at 141-142°. Its equivalent weight was found to be

228; calculated 222.

Anal. Calcd. for $C_{11}H_{10}O_3S$: C, 59.43; H, 4.54; S, 14.39. Found: C, 59.37; H, 4.76; S, 14.33.

Preparation of 4-Methoxythianaphthyl-3-acetic Acid

A mixture containing 0.5 g. (0.0023 mole) of 4-methoxythianaphthyl-3-acetamide, 13 ml. of 10% NaOH, and 5 ml. of 95% ethanol was heated at its reflux temperature for two hours. The reaction mixture was cooled, filtered, and acidified with HCl to Congo red. The white precipitate which formed on acidification was recovered by filtration and dried. After several recrystallizations from alcohol-water the acid melted at 159.5-160.5°.

Anal. Calcd. for $C_{11}H_{10}O_3S$: C, 59.43; H, 4.54; S, 14.39. Found: C, 59.11; H, 4.71; S, 14.33.

Structure Determination of 6-Methoxythianaphthyl-3-acetic Acid

Approximately 1.5 g. (0.0068 mole) of 6-methoxythianaphthyl-3-acetic acid was desulfurized by heating an absolute alcohol solution of it overnight under reflux with 10-15 g. of Raney nickel. The spent catalyst was removed by filtration and the alcohol by evaporation under a stream of air. To the greenish oily residue was added 40 ml. of water, 2 g. of $KMnO_4$, and 8 drops of 20% NaOH solution. The oxidizing mixture was heated at its reflux temperature until

the permanganate color had disappeared. The insoluble MnO_2 was removed by filtration and the filtrate was evaporated to dryness. The residue was dissolved in 20 ml. of water and the solution acidified with HCl to Congo red. The small quantity of precipitate was recovered by filtration and dried. After recrystallization from water, the material melted at 181-184°. A mixed melting point, with an authentic sample of anisic acid, showed no depression in the melting point of anisic acid.

Preparation of 6-Methoxythianaphthyl-3-acetyl Chloride

A 2.25 g. (0.01 mole) quantity of 6-methoxythianaphthyl-3-acetic acid, 22 ml. of absolute ether, and two drops of pyridine were placed in a 50 ml. round bottom flask and cooled to 0°. A 2 ml. (0.028 mole) volume of freshly distilled thionyl chloride was added to the reaction mixture which was set aside, at room temperature, for five hours, and then heated to its reflux temperature for 15 minutes on a steam bath. The ether was removed under vacuum and, to insure the complete removal of thionyl chloride, 20 ml. of dry benzene was added to the mixture to dissolve the product and then removed under reduced pressure. The red residue was used in subsequent reactions without further purification.

Preparation of Ethyl 6-Methoxythianaphthyl-3-acetate

To the acid chloride obtained from 2.25 g. (0.01 mole)

of 6-methoxythianaphthyl-3-acetic acid was added 25 ml. of absolute ethanol. The esterification mixture was set aside for a few minutes and then warmed gently on the steam bath, cooled, and the excess alcohol removed under reduced pressure. The residue was distilled twice to obtain an oil boiling at 140-145°/0.07 mm. Hg; n_D^{25} 1.5811.

Preparation of β(6-Methoxythianaphthyl-3)ethanol and β(4-Methoxythianaphthyl-3)ethanol

A 5.28 g. (0.14 mole) quantity of the reducing agent $LiAlH_4$ and 100 ml. of anhydrous ether were placed in a 300 ml. three-necked round bottom flask fitted with a condenser, dropping funnel, and stirrer. A solution containing 30 g. (0.12 mole) of crude ethyl (4- and (6-methoxythianaphthyl-3)acetate dissolved in 30 ml. of anhydrous ether was added dropwise to the stirred reaction mixture at a rate which maintained it at its reflux temperature. When the ester had been added the mixture was stirred at room temperature for two hours and a dilute solution of H_2SO_4 (15 ml. of conc. H_2SO_4 in 90 ml. of water) was added dropwise to hydrolyze the reaction mixture. It was then transferred to a separatory funnel where the aqueous layer was separated and extracted with two 50-ml. portions of ether. The ether solutions and product were combined and washed with 50 ml. of dilute $NaHCO_3$ solution and then with 50 ml. of water. The ether was removed and the oily residue was fractionated with

difficulty and did not give a good separation. The fractions obtained were set aside for several weeks in which time some crystallization had started in the lower boiling fractions. The crystals were isolated and purified by crystallizing from benzene. The melting point of this solid material was 97.8-98.5°. It was concluded after comparison of the infrared spectrum of this solid alcohol with those of the corresponding acids and amides that this compound was β(4-methoxythianaphthyl-3)ethanol. The melting point of its 3,5-dinitrobenzoyl derivative was 194.5-199.5°.

Anal. Calcd. for $C_{11}H_{12}O_2S$: C, 63.43; H, 5.81; S, 15.40. Found: C, 63.59; H, 5.98; S, 15.12.

The other isomer, β(6-methoxythianaphthyl-3)ethanol, was not obtained in a very pure condition, and was obtained as an oil in spite of many attempts to crystallize it. The melting point of its 3,5-dinitrobenzoyl derivative was 167.5-168°.

Attempted Preparation of β(6-Methoxythianaphthyl-3)ethylamine

A small amount, 2.7 g. (0.012 mole), of (6-methoxythianaphthyl-3)acetamide was placed in a Sohxlet extractor attached to a 500 ml. three-necked round bottom flask which in turn had been fitted with a stirrer and dropping funnel. A 1.39 g. (0.037 mole) quantity of $LiAlH_4$ and 200 ml. of dry ether were placed in the reaction flask and the reaction

mixture was heated at its reflux temperature for a day and a half. Then, 1.4 ml. of water was added dropwise to the stirred reduction solution followed by 1.4 ml. of 15% NaOH, and finally by 4.2 ml. of water. The alkaline mixture was stirred vigorously for a half hour. The white precipitate was removed by filtration and washed with two 100-ml. portions of ether. The combined ether extracts were dried over anhydrous $MgSO_4$, filtered, and dry hydrogen chloride gas was passed into the ether solution. Only a very small white precipitate was observed to form. After filtering the ether solution, the ether was removed and the oily residue distilled, collecting the material boiling in the range 150-202°/0.07 mm. Hg. The product was a light yellow, viscous oil, insoluble in hydrochloric acid.

Preparation of N(6-Methoxythianaphthyl-3-acetyl)piperidine

The acid chloride prepared from 2.5 g. (0.011 mole) of 6-methoxythianaphthyl-3-acetic acid as described above was dissolved in 10 ml. of dry benzene. To the acid chloride solution was added a second solution containing 2 ml. (0.02 mole) of piperidine dissolved in 20 ml. of dry benzene. Addition of the base solution to the acid chloride solution gave a color change of the reaction mixture to straw yellow and the formation of a gelatinous precipitate of piperidine hydrochloride. The contents of the flask were transferred to a separatory funnel and the benzene reaction solution was

given several successive washings; first with two 20-ml. portions of 5% HCl, then with two 20-ml. portions of water, followed by 20 ml. of saturated $NaHCO_3$ solution, and finally with two 20-ml. portions of water. The benzene solution was then dried over anhydrous $MgSO_4$, filtered, and the benzene was removed by evaporation. The residue of amide was reduced directly to the amine without further purification.

Preparation of N [β(6-Methoxythianaphthyl-3)-ethyl]piperidine Hydrochloride

The N(6-methoxythianaphthyl-3-acetyl)piperidine prepared from 2.5 g. (0.11 mole) of 6-methoxythianaphthyl-3-acetic acid as described above was dissolved in 30 ml. of anhydrous ether. This latter solution was added dropwise to a stirred suspension of 0.68 g. (0.018 mole) of $LiAlH_4$ suspended in 30 ml. of stirred anhydrous ether contained in a three-necked round bottom flask fitted with condenser, stirrer, and dropping funnel. When the reducing agent had been added the resulting mixture was stirred an additional half hour, then heated to its reflux temperature for half an hour, cooled to room temperature, and 0.68 ml. of water was added dropwise to the stirred solution, followed by 0.68 ml. of 15% NaOH solution and finally by 2.04 ml. of water. After stirring the mixture half an hour the granular precipitate was recovered by filtration, and the ether solution was saturated with anhydrous hydrogen chloride gas. The flocculent white precipitate

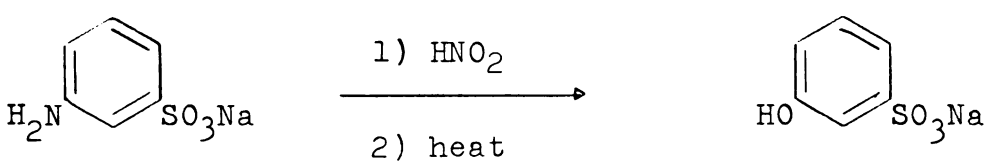
after two crystallizations from absolute alcohol, melted at 224.5-225.5°.

Anal. Calcd. for $C_{16}H_{22}ONSCl$: C, 61.61; H, 7.11; N, 4.49; S, 10.28; Cl, 11.37. Found: C, 61.77; H, 7.26; N, 4.23; S, 10.30; Cl, 11.10.

DISCUSSION

The initial objective of this investigation was to prepare an appropriately substituted thianaphthene which could then be attached to the D and E ring system of the reserpine molecule. The thianaphthene needed was β(6-methoxythianaphthyl-3)ethylamine V.

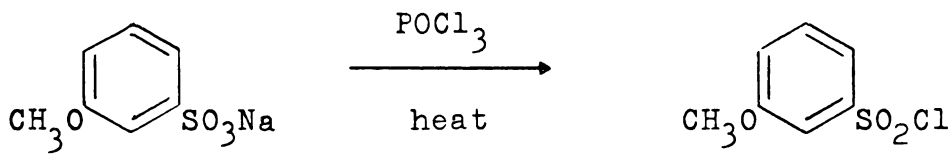
The starting material for this synthesis was sodium meta-aminobenzenesulfonate XVII (sodium metanilate). This was diazotized and the solution of the diazonium salt was warmed to produce sodium meta-hydroxybenzenesulfonate XVIII. The hydroxy compound was methylated using dimethyl sulfate to obtain sodium meta-methoxybenzenesulfonate XIX (13).



XVII XVIII

XIX

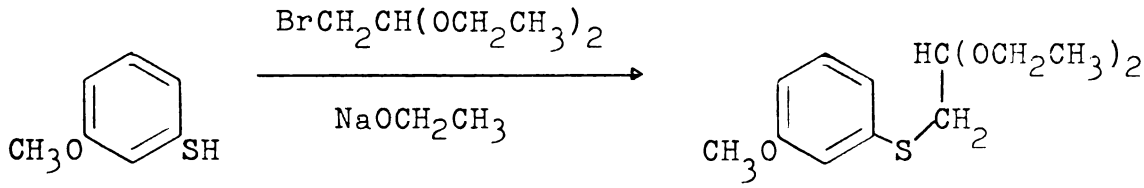
The meta-methoxybenzenesulfonyl chloride XX was prepared by treating the sodium meta-methoxybenzenesulfonate with an excess of phosphorus oxychloride at 165° (14). Reduction of meta-methoxybenzenesulfonyl chloride using zinc dust and hydrochloric acid produced meta-methoxythiophenol XXI.



XIX XX

XXI

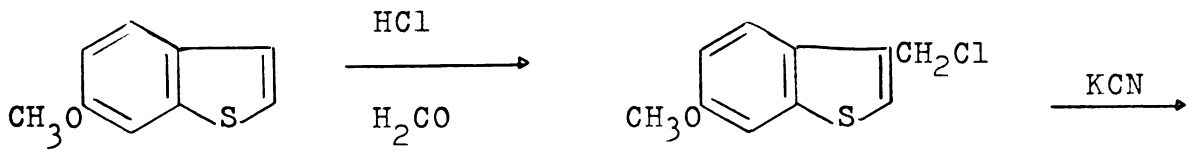
The meta-methoxythiophenol was then alkylated (8) using bromoacetaldehyde diethyl acetal (bromoacetal) (15) in the presence of sodium ethoxide to produce meta-methoxyphenyl ω-diethoxyethyl sulfide XXII. The sulfide was converted to 6-methoxythianaphthene XXIII by the procedure of Sunthankar and Tilak (8).



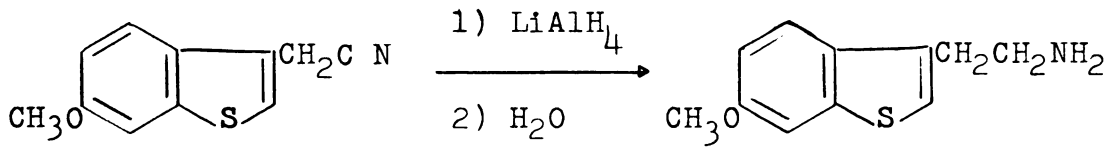
XXI XXII

XXIII

The proposed synthesis of V from 6-methoxythianaphthene was based on the following sequence of reactions.

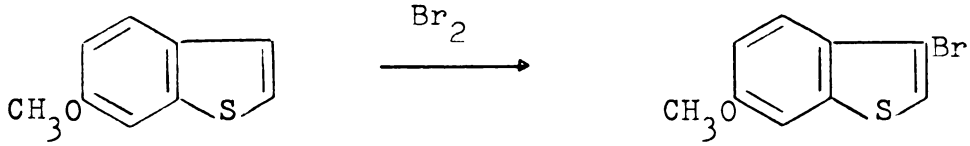


XXIII XXIV

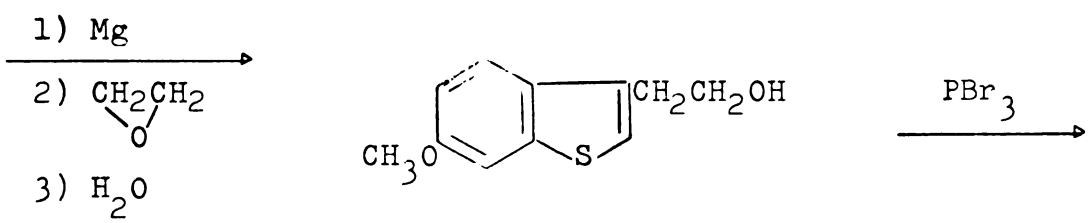


XXV V

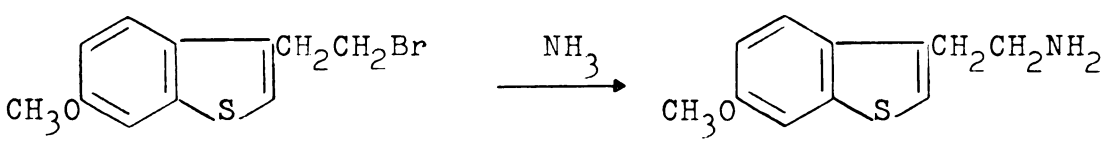
Chloromethylation of 6-methoxythianaphthene was attempted using the procedure of Avakian, Moss, and Martin (16). The off-white powder obtained gave only a weak test for chloride after fusion with sodium. However, an attempt was made to convert it to the nitrile XXV. Upon working up the reaction mixture after removal of the sodium cyanide by filtration only starting material was recovered. Characterization of the product obtained from the chloromethylation of 6-methoxythianaphthene was not undertaken. Instead, an alternate method of synthesizing V starting with 6-methoxythianaphthene was initiated, based on the following sequence of reactions.



XXIII XXVI



XXVIII



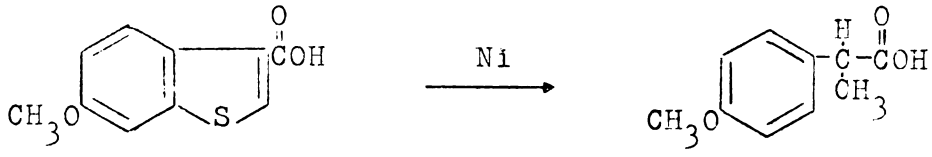
XXIX V

Bromination of 6-methoxythianaphthene yielded material which turned out to be largely 2-bromo-6-methoxythianaphthene. Two experimental procedures were used; bromination with elemental bromine in glacial acetic acid in the presence of anhydrous sodium acetate, and free radical bromination with N-bromosuccinimide. Both procedures gave excellent results; however, the product was quite unstable and had to be used before it decomposed. The freshly distilled 2-bromo-6-methoxythianaphthene was a light yellow solid which, when set aside, soon turned to a dark green or black intractable material with the evolution of hydrogen bromide. To determine the structure of this material it was converted into the corresponding Grignard reagent by entrainment, using ethyl bromide as the other halide, followed by carbonation with dry ice. Isolation of the product yielded a crude acid which had a melting point range of 221-224° with softening at 218°. Several recrystallizations failed to give a purer product. However, several milligrams of a product melting at 279-280.5°, which had an equivalent weight of 207, were obtained from the recrystallizations. The equivalent weight of a carboxymethoxythianaphthene is 208.

For determination of structure, the crude product obtained from the Grignard reaction was desulfurized by repeated treatment with Raney nickel in boiling alcohol until no further depression was noted in the melting point of the desulfurized product. The crude material from the desulfurization

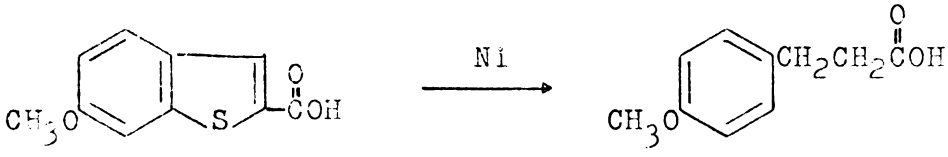
melted in the range 88-92°.

3-Carboxy-6-methoxythianaphthene XXXI would desulfurize to produce 2-(4-methoxyphenyl)propionic acid XXXII which melts



XXXI XXXII

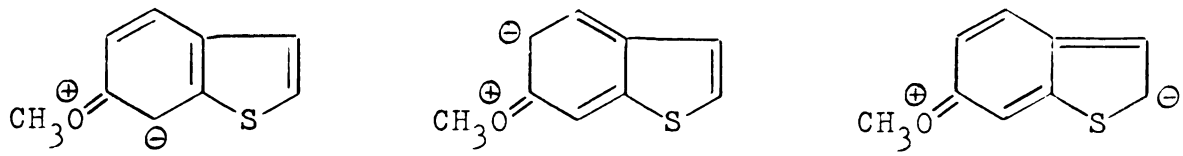
at 57° (17), while 2-carboxymethoxythianaphthene XXXIII would



XXXIII XXXIV

desulfurize to produce 3-(4-methoxyphenyl)propionic acid XXXIV melting at 104-5° (18). Since the crude product from the desulfurization melted from 88-92° it was evident that a large portion of the acid obtained was not the desired isomer XXXI.

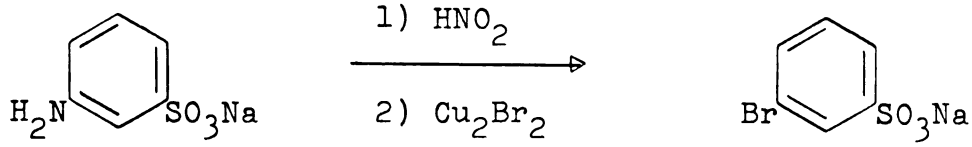
From the work of Campaigne (19) on the substitution of 6-ethoxythianaphthene it seems reasonable to assume that the bromination did occur predominantly in the 2-position. The reason for this would seem to be the strong electron release of the methoxy group upon demand of an attacking electrophile. In this case then the active sites on 6-methoxythianaphthene could be depicted as:



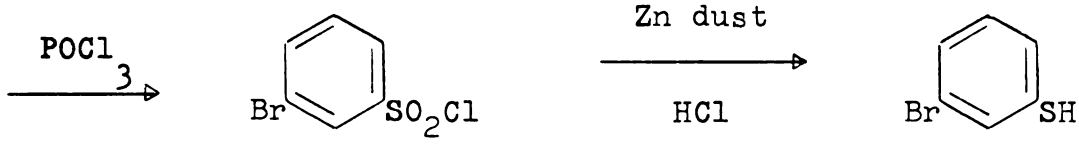
Based on this it was assumed that if a thianaphthene could be prepared possessing a group less activating than methoxy in the 6-position the normally enhanced reactivity of the 3-position might again predominate over any activation the 2-position might receive. Accordingly, it was decided to prepare 6-bromothianaphthene XXXIX in the anticipation that further substitution would occur in the 3-position.

The method of synthesis of 6-bromothianaphthene was by a sequence similar to that used to prepare 6-methoxythianaphthene. Sodium metanilate was diazotized and converted via the Sandmeyer reaction to sodium meta-bromobenzenesulfonate XXXV. The meta-bromobenzenesulfonyl chloride was prepared by heating XXXV to 165° with an excess of phosphorus oxychloride. The meta-bromothiophenol XXXVII was prepared by reduction of XXXVI with zinc and hydrochloric acid. The bromothiophenol XXXVII was then alkylated with bromoacetal to produce meta-bromophenyl ω-diethoxyethyl sulfide XXXVIII.

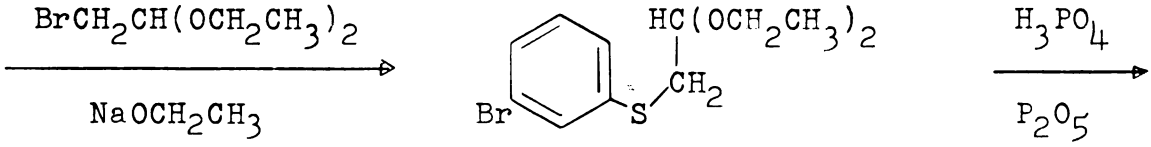
The method of ring closure of the sulfide was identical to that utilized for the preparation of 6-methoxythianaphthene.



XVIII XXXV



XXXVI XXXVII



XXXVIII

XXXIX XL

The sulfide was introduced below the surface of a mixture of phosphorus pentoxide and phosphoric acid at a temperature of 165° under a system pressure of 2.6 mm. Hg. The bromothianaphthene was collected by distillation into a receiver as it formed.

It was necessary to prove the structure of the ring closure product since it had been shown by Hansch (12) that meta-chlorophenyl ω-diethoxyethyl sulfide closes to give predominantly 4-chlorothianaphthene and not 6-chlorothianaphthene as Sunthankar and Tilak (9) had assumed. Since there are two alternate paths by which ring closure may occur, either 4-bromothianaphthene XL, 6-bromothianaphthene XXXIX, or both could be obtained. The crude bromothianaphthene product was fractionated using a 30-cm. tantalum spiral column. Two fractions were obtained. The first, 25% of the material, was collected from 42-50°/0.07 mm. Hg; n_D^{25} approximately 1.644. The second was collected from 50-57.5°/0.07 mm. Hg; n_D^{25} approximately 1.669. After being set aside for several days in a refrigerator the first fraction crystallized to a white solid which, after sublimation, melted at 44.8-45°.

When the second fraction was also set aside for several days in a refrigerator a white solid was obtained which, after sublimation, melted at 54.8-55.8°. A melting point of 56° has been reported for 6-bromothianaphthene (2). The reliability of this melting point is in question, however, since these workers converted the bromothianaphthene to what they considered 6-carboxythianaphthene and report its melting point as 162°. Hansch (12) has also prepared a 6-carboxythianaphthene by a seemingly unambiguous route and gives a melting point of 215-216°. The identities of the bromothianaphthenes were not determined since at this juncture the objective was to establish whether enough

6-bromothianaphthene was present in the ring closure product to make continuing the synthetic reaction sequence feasible.

A portion of each of the two noncrystalline bromothianaphthene fractions was converted to the carboxylic acid via its Grignard reagent. In each case an acid mixture was obtained which had a broad melting range of about 145-160° indicating that the bromothianaphthene fractions were not pure. An unsuccessful attempt was made to purify these mixtures by fractional recrystallization from alcohol/water. However, a few milligrams of an acid melting from 188-189° was obtained which had an equivalent weight of 185. The equivalent weight of a thianaphthenecarboxylic acid is 178.

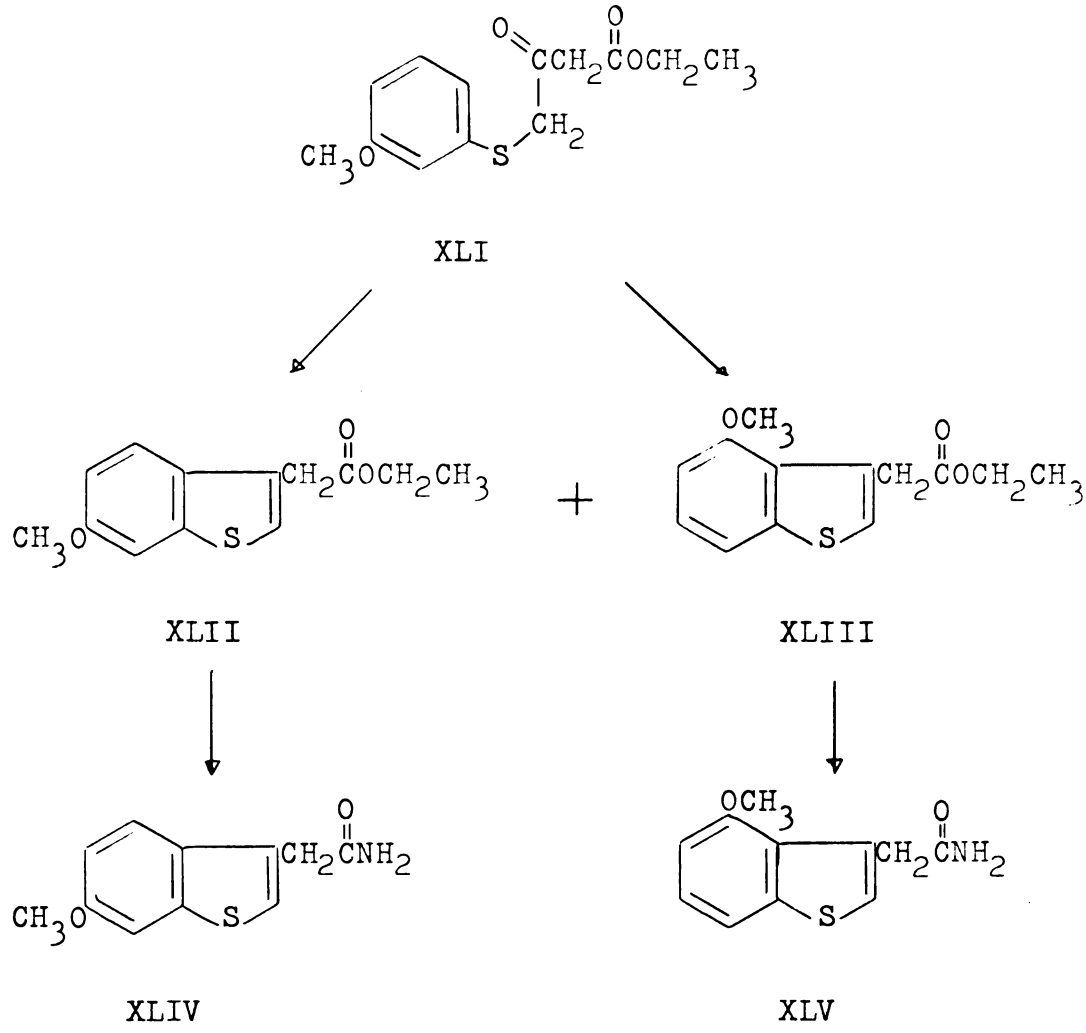
The acid mixtures were then desulfurized using Raney nickel. The melting range of the desulfurized acid was 60-70°. 6-Bromothianaphthene would give 6-carboxythianaphthene which upon desulfurization would yield para-ethylbenzoic acid having a melting point of 110-111°. 4-Bromothianaphthene would give 4-carboxythianaphthene which upon desulfurization would give ortho-ethylbenzoic acid with a melting point of 68°. The melting point of the product from the desulfurization indicates that it was predominantly the ortho isomer, thus showing that the starting bromothianaphthene was predominantly the 4-bromo isomer.

This conclusion was further substantiated by the determination and examination of the substitution pattern of the infrared spectrum of the desulfurized product.

As a further confirmation, 2 g. of the bromothianaphthene melting at 54.8-55.8° was converted to its corresponding acid. After several recrystallizations a pure sample of acid which melted at 200-203° was obtained. This melting point agrees with neither of the values cited above for 6-carboxythianaphthene.

Since the mixture of isomeric bromothianaphthenes obtained from the ring closure did not contain enough of the desired 6-isomer a new synthetic reaction sequence was started at this juncture using an approach similar to that used by Tilak et al. (21) to obtain a suitable 3,6-disubstituted thianaphthene. Meta-methoxythiophenol was alkylated with ethyl γ-chloroacetoacetate, prepared by the procedure of Hamel (22), in pyridine (21) to obtain ethyl 4-(meta-methoxyphenylmercapto)-3-oxobutyrate XLI. The latter compound (XLI) was then cyclized to a thianaphthene derivative by heating it with phosphorus pentoxide and 85% phosphoric acid using chlorobenzene (21) as a reaction solvent. The ring closure produced both ethyl (6-methoxythianaphthyl-3)acetate XLII and ethyl (4-methoxythianaphthyl-3)acetate XLIII. However fractional distillation using a Fenske column failed to separate the mixture of the esters XLII and XLIII.

The ester mixture of XLII and XLIII was shaken with concentrated aqueous ammonia for a week to produce 6-methoxythianaphthyl-3-acetamide XLIV and 4-methoxythianaphthyl-3-acetamide XLV. The isomeric amides were easily separated



by crystallization and chromatography. The reaction mixture containing the amides was first crystallized from alcohol. The solid obtained was 6-methoxythianaphthyl-3-acetamide. The filtrate from the crystallization, containing both the 6-methoxy and 4-methoxy isomers, was evaporated to dryness and the residue chromatographed on alumina using chloroform as the eluent. The 6-methoxythianaphthyl-3-acetamide was removed from the column first followed by the 4-methoxy-thianaphthyl-3-acetamide.

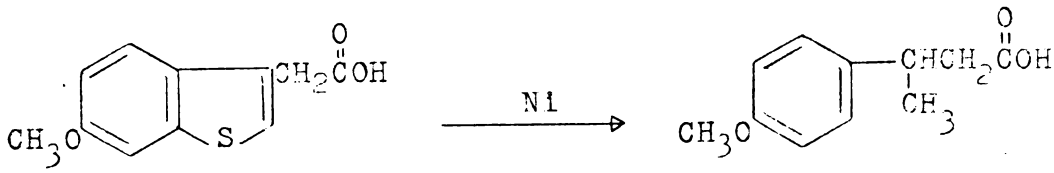
The next step in the reaction sequence was reduction of 6-methoxythianaphthyl-3-acetamide to the amine (V) using lithium aluminum hydride. This reduction was tried several times in diethyl ether and in tetrahydrofuran as reaction solvents and in each case only a trace of an amine was obtained.

At this point in the study it was apparent that the original goal of synthesizing "thioreserpine" could not be realized in a reasonable period of time. Thus, it was decided to prepare structurally simpler thioreserpine type compounds which could be tested for potential physiological activity. While not giving a definite answer regarding the physiological activity of thioreserpine, these simpler thianaphthenes having the basic ring structure of reserpine would give some indication of the physiological properties of the basic ring system devoid of the functional groups present in reserpine. These compounds would be similar to those prepared by Werner Herz (5) and P. Cagniant (6).

The simplest and most direct route to this alternate objective was to obtain more easily reducible amides and convert these to their corresponding amines.

The structures of the amides had to be proven first. Each amide was hydrolyzed to the corresponding acid, i.e. XLIV was hydrolyzed to 6-methoxythianaphthyl-3-acetic acid XLVI and XLV was hydrolyzed to give 4-methoxythianaphthyl-3-acetic acid XLVII. XLVI was shown to be the 6-methoxy

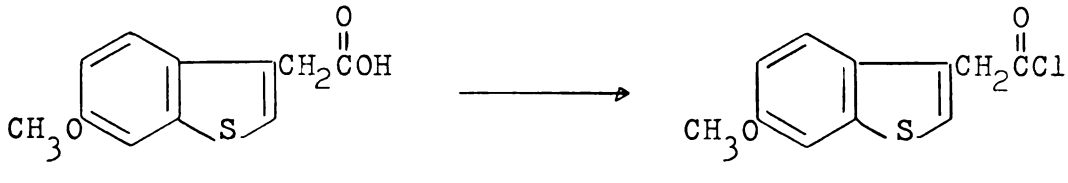
isomer by desulfurization using Raney nickel followed by oxidation of the oily desulfurization product with potassium permanganate to obtain para-anisic acid *viz*.



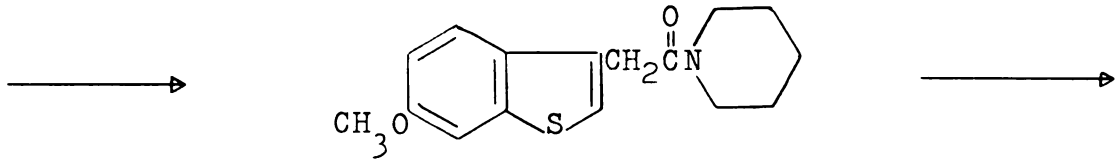
XLVI

The para-anisic acid obtained did not depress the melting point of an authentic sample of para-anisic acid.

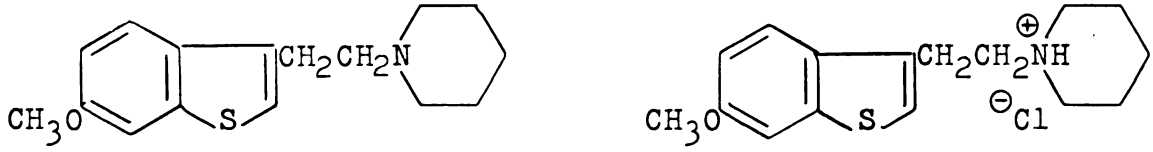
The 6-methoxythianaphthyl-3-acetic acid was then converted to its acid chloride using thionyl chloride. The acid chloride was not isolated but was immediately treated with an excess of piperidine to obtain the amide *N*(6-methoxythianaphthyl-3-acetyl)piperidine XLIX which, without further purification, was reduced to the amine L. This was isolated as the hydrochloride LI, *N* [β(6-methoxythianaphthyl-3)ethyl]piperidine hydrochloride. The amine salt (LI) after purification by several recrystallizations was submitted for physiological evaluation.



XLVI XLVIII



XLIX

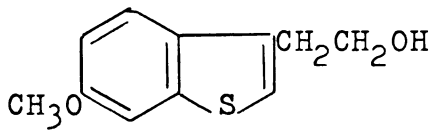


L LI

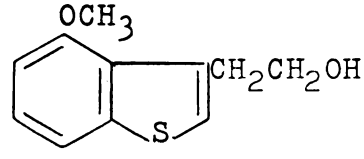
A sample of pure ethyl (6-methoxythianaphthyl-3)acetate was prepared by treating the acid chloride XLVIII with absolute ethyl alcohol.

Some of the ester mixture of XLII and XLIII obtained from the ring closure reaction described was reduced using lithium aluminum hydride to a mixture of the alcohols β(6-methoxythianaphthyl-3)ethanol LII and β(4-methoxythianaphthyl-3)ethanol LIII. These could not be separated satis-

factorily by distillation. After being set aside several weeks in the laboratory, however, some of the fractions from the distillation did crystallize partially. When these crystals were separated and recrystallized a solid alcohol was obtained which melted from 97.8-98.5°. By comparing the substitution bands in the infrared spectrum with those in the spectra of the other 3,4- and 3,6-disubstituted thianaphthenes it was established that this alcohol was β(4-methoxythianaphthyl-3)ethanol. The other isomer, β(6-methoxythianaphthyl-3)ethanol, did not crystallize. Several distillations of alcohol gave an oil which did not give the infrared pattern of the 4-methoxy alcohol. The oil was not purified further.



LII



LIII

SUMMARY

While the original objectives, i.e. the total synthesis of "thioreserpine" or the preparation of β(6-methoxythianaphthyl-3)ethylamine V, were not realized, it is felt that the preparation of the amine V from 6-methoxythianaphthyl-3-acetamide is entirely possible. This can be accomplished either by using a different reducing medium, e.g. sodium in alcohol, or by carrying out repeated reductions with lithium aluminum hydride since the initial aluminum complex formed might be too sterically hindered for complete reduction.

While somewhat short of its original aims this investigation gained several important goals. First, a compound of a structure grossly similar to rings A, B, C, and D of reserpine was obtained which was submitted for testing for its physiological activity; secondly, a sound synthetic route for the preparation of 6-substituted thianaphthyl-3-acetic acids was developed using a procedure similar to Sunthankar and Tilak; thirdly, several 3,6- and 3,4-disubstituted thianaphthenes previously undescribed were prepared and characterized.

Somewhat as an aside from the main theme of the study the 6-methoxythianaphthyl-3-acetic acid and 4-methoxythianaphthyl-3-acetic acid were submitted for testing as plant growth regulators using Avena coleoptile sections. Qualitatively the 4-methoxy isomer was only slightly less active

than indole-3-acetic acid while the 6-methoxy isomer was inhibitory at concentrations up to 10^{-5} molar, at which concentration it was then slightly active as a growth promoter.

There are several facets of the present problem which require further investigation. The identities of the isomeric bromothianaphthenes were not established due to limitations of time and the very conflicting literature reports on the preparation of 6-carboxythianaphthene.

Several additional pure compounds should also be prepared to complete the series reported in the present work, e.g. ethyl (4-methoxythianaphthyl-3)acetate and β(6-methoxythianaphthyl-3)ethanol were not prepared in a pure state. The preparation of β(6-methoxythianaphthyl-3)ethanol would give an alternate route to the preparation of the amine V. The alcohol could be converted to 6-methoxy-3-(β-bromoethyl)-thianaphthene using phosphorus tribromide. The bromide could then be interacted with a large excess of ammonia to produce the amine V following neutralization. An additional objective of value would be the preparation of either a 6-nitro- or 6-aminothianaphthyl-3-acetic acid since both groups could readily be converted to other functional groups via diazotization of the amine, thus enabling a wide variety of 3,6-disubstituted products to be synthesized.

Finally, the complete synthesis of "thioreserpine" or of "thioyohimbane" would be of value in determining to what

extent the difference between the nitrogen and sulfur heteroatom affects the physiological activities of a specific alkaloid.

BIBLIOGRAPHY

1. Woodward, R. B., Bader, F. E., Bickel, H., Frey, A. J., and Kierstead, R. W., Journal of the American Chemical Society 78, 2023 (1956).

2. Woodward, R. B., Bader, F. E., Bickel, H., Frey, A. J., and Kierstead, R. W., Tetrahedron 2, 1-57 (1958).

3. Woodward, R. B., Bader, F. E., Bickel, H., Frey, A. J., and Kierstead, R. W., Journal of the American Chemical Society 78, 2657 (1956).

4. van Tamelen, E., and Shamma, M., Journal of the American Chemical Society 76, 950 (1954).

5. Herz, Werner, Journal of the American Chemical Society 72, 4999 (1950).

6. Cagniant, P., and Caignant, Mrs. P., Bulletin de la Société Chimique de France, 340 (1952).

7. Fries, K., Heering, H., Hemmecke, E., and Siebert, G., Annalen der Chemie 527, 83-114 (1936).

8. Sunthankar, A. V., and Tilak, B. D., Proceedings of the Indian Academy of Science 33A, 35-41 (1951).

9. Sunthankar, A. V., and Tilak, B. D., Proceedings of the Indian Academy of Science 32A, 396-401 (1950).

10. Tarbell, D. S., and Fukushima, D. K., Journal of the American Chemical Society 68, 1456-1460 (1946).

11. Martani, A., Annali di Chimica (Rome) 47, 885-891 (1957).

12. Hansch, C., and Schmidhalter, B., Journal of Organic Chemistry 20, 1056 (1955).

13. Fries, K., and Engelbertz, E., Annalen der Chemie 407, 211 (1915).

14. Organic Syntheses, Coll. Vol. I, Second Ed., John Wiley & Sons, Inc., New York, 1958, p. 85.

15. Organic Syntheses, Coll. Vol. III, John Wiley & Sons, Inc., New York, 1955, p. 123.

16. Avakian, S., Moss, J., and Martin G., Journal of the American Chemical Society 70, 3075 (1948).

17. Bougault, M., Annales de Chimie et de Physique [7] 25, 521 (1902).

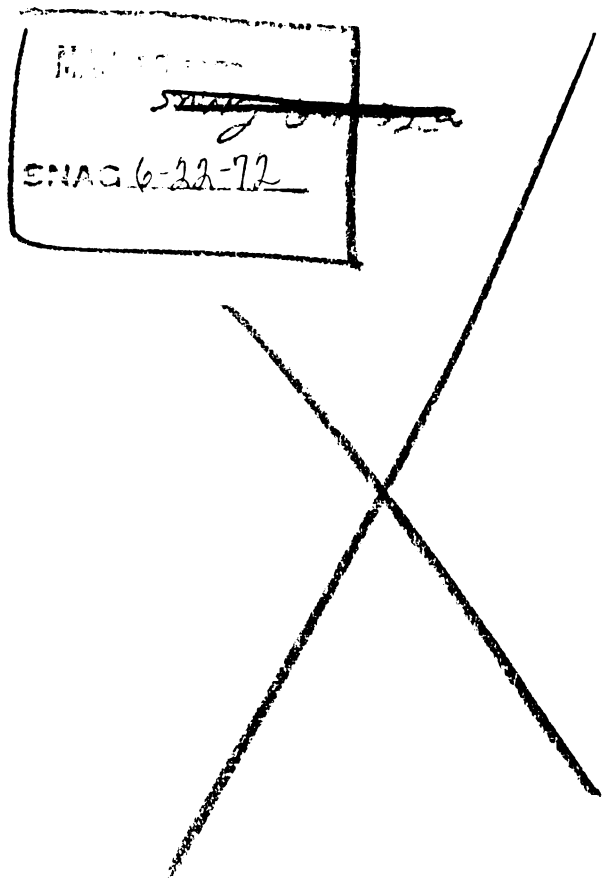
18. Barger, G., and Walpole, G. S., Journal of the Chemical Society 95, 1723 (1909).

19. Campaigne, E., and Kreighbaum, W. E., Journal of Organic Chemistry 26, 363 (1961).

20. Badger, G. M., Clark, D. J., Davies, W., Farrer, K. T. H., and Kefford, N. P., Journal of the Chemical Society 1957, 2624.

21. Bhattacharjie, M. K., Mitra, R. B., Tilak, B. D., and Vankiteswaren, M. R., Tetrahedron 10, 215 (1960).

22. Hamel, J. F., Bulletin de la Société Chimique de France 29, 390 (1921).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