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SYNTHESIS AND SYNTHETIC APPLICATIONS OF
GAMMA BROMINATED BETA DICARBONYLS

presented by

ERIC JOHN LIND

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MASTER degree in SCIENCE

Eugene E. Hoff
Major professor

Date Sept. 7, 1984

SYNTHESIS AND SYNTHETIC APPLICATIONS OF GAMMA BROMINATED BETA DICARBONYLS

By

Eric John Lind

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ABSTRACT

SYNTHESIS AND SYNTHETIC APPLICATIONS
OF GAMMA BROMINATED BETA DICARBONYLS

By

Eric John Lind

The gamma brominations of beta-dicarbonyl compounds were investigated. The initial compound of interest, γ,γ'-dibromoacetylacetone , was produced by treating acetylacetone with tetramethylammonium tribromide (TMAT) in ether. In this reaction α,α'-dibromoacetylacetone formed first, but the bromine would rearrange to give the more stable γ,γ'-dibromoacetylacetone isomer in good yield. This alpha-gamma bromine rearrangement was also observed in other beta-dicarbonyl systems when brominated in this manner. The synthetic utility of γ,γ'-dibromoacetylacetone was demonstrated in making its new pyrazole derivative, 3,5-bis(bromomethyl) pyrazole. In conclusion there is a brief discussion of possible reactions of 3,5-bis(bromomethyl)pyrazole with pyrrole derivatives.

To my wife Donna, who gives me much happiness.

ACKNOWLEGEMENT

I would like to thank Professor Eugene LeGoff for making this research enjoyable. His enthusiasm and chemical experience are greatly acknowledged.

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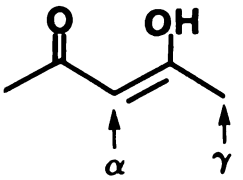
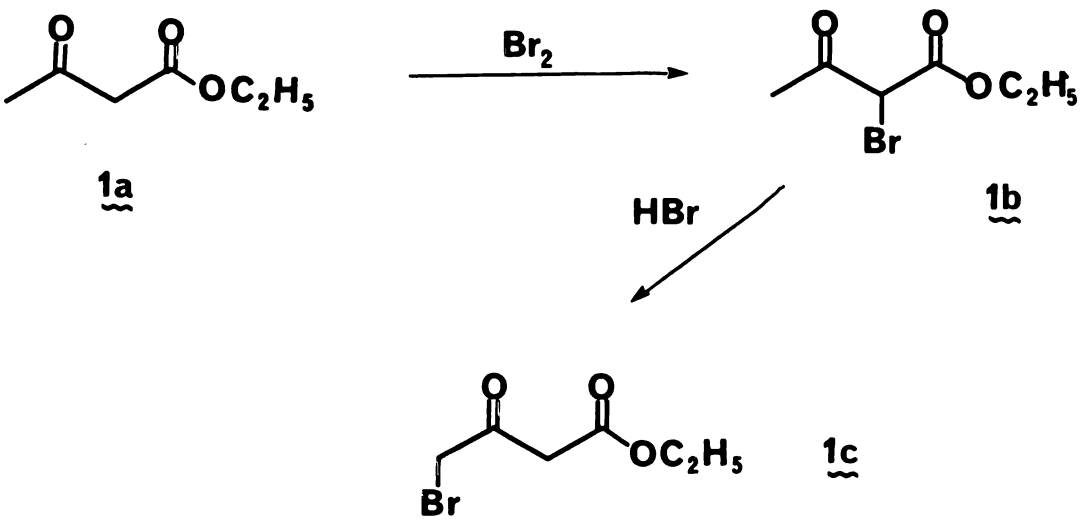
INTRODUCTION

The brominations of beta-dicarbonyls have been extensively studied. Most of these deal with bromination at the alpha carbon. In an effort to produce



γ,γ'- dibromoacetylacetone the opportunity to explore gamma brominations of beta-dicarbonyls arose. The apparent difficulty with this reaction is that the alpha carbon is more reactive then the gamma carbon. The key to gamma brominations lies in the observations made by Hantzsch.[1] He noticed that the bromine, in ethyl-α-bromoacetoacetate (1b) he had prepared, would slowly rearrange in the presence of acid to give the gamma brominated compound 1c (Scheme 1).

Scheme 1



Later Smith established the importance of acid in this rearrangement.[2] Ethyl acetoacetate was brominated while sweeping out the hydrogen bromide with a stream of air. He found no bromine rearrangement had occurred. The sole product in the reaction was the alpha-bromo-ester.

At about the same time Hirst and Macbeth observed an alpha-gamma bromine shift in the production of ethyl-γ-bromoacetylsuccinate.[3] They suggested that bromine at the alpha position of beta-dicarbonyl compounds is labile and that under acidic conditions it can rearrange to the gamma position.

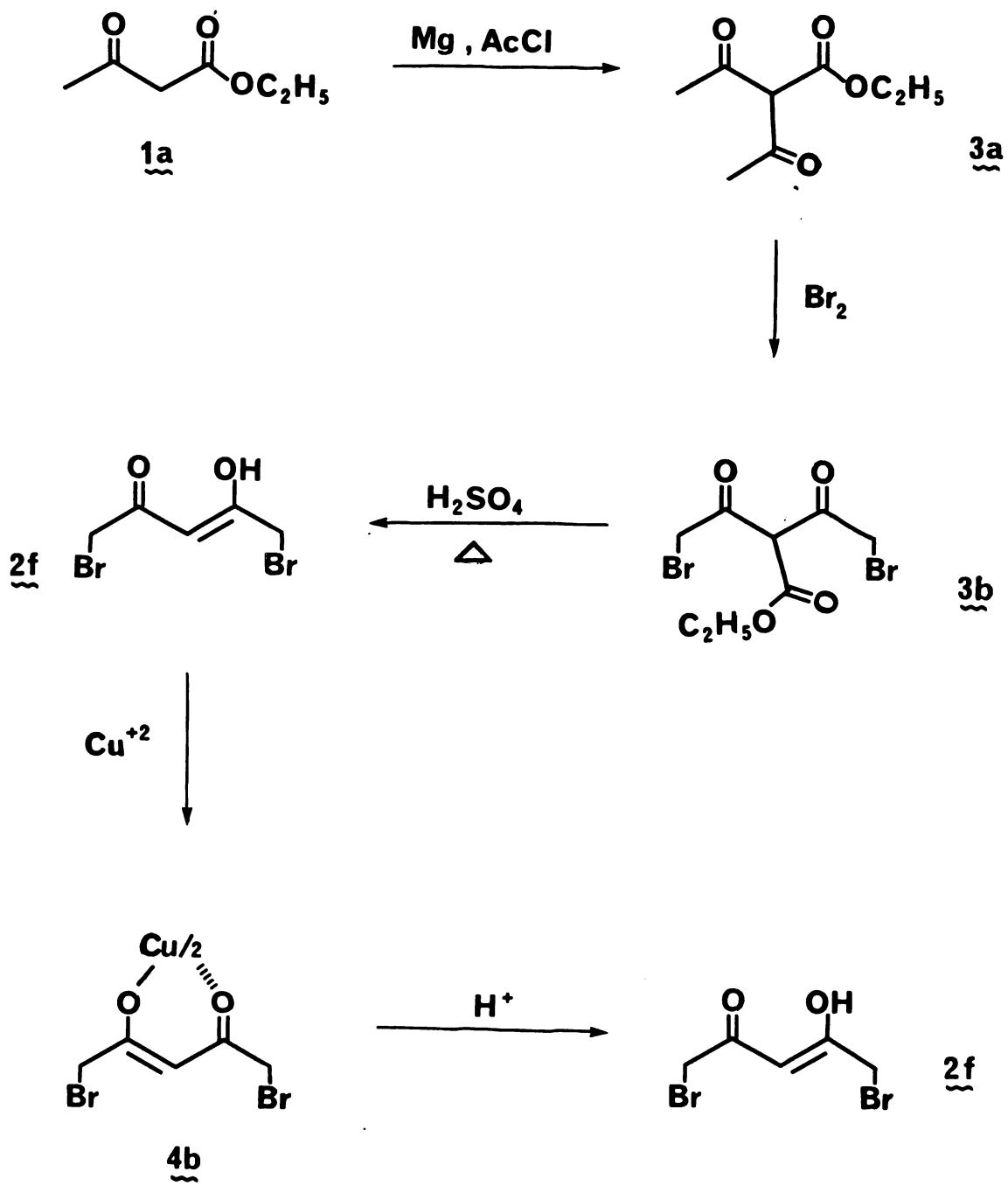
In this thesis the gamma brominations of beta-dicarbonyls is examined further. Two literature preparations have been reported for making the desired compound, γ,γ'-dibromoacetylacetone. Both of these reactions were tried and will be discussed. An improved procedure for making γ,γ'-dibromoacetylacetone and other gamma brominated beta-dicarbonyls is described. Subsequent sections deal with synthetic applications of the gamma-bromo-beta-dicarbonyls.

A. GAMMA BROMINATIONS OF BETA DICARBONYLS

The approach used in the production of gamma brominated beta-dicarbonyls involves the rearrangement of the bromine from the more reactive alpha position to the more stable gamma position. In the literature there have been two methods reported for making the compound of interest, γ,γ'- dibromoacetylacetone 2f.

The first method that was tried for making 2f had been put forth by Becker,[4a,b] and is shown in Scheme 2. In the first step the starting material ethyl acetoacetate 1a was acylated using the technique of Spassow[5] to give 3-carbethoxy-2,4-pentanedione 3a. Now three carbonyl groups exerted their electron withdrawing affect on the alpha position. This makes a bromine atom in this position highly reactive and it would more readily rearrange to the gamma position. The compound 3a was treated with bromine in ether to give 3b. The bromine had rearranged from the alpha to the gamma position. Compound 3b proved to be a potent lachrymator making it difficult to work with. Following decarboxylation of 3b, the crude product was purified by forming its copper complex which was converted to 2f by treatment with acid. The pure product 2f was a green oily liquid. The overall yield of only 7% in this five step synthesis was discouraging.

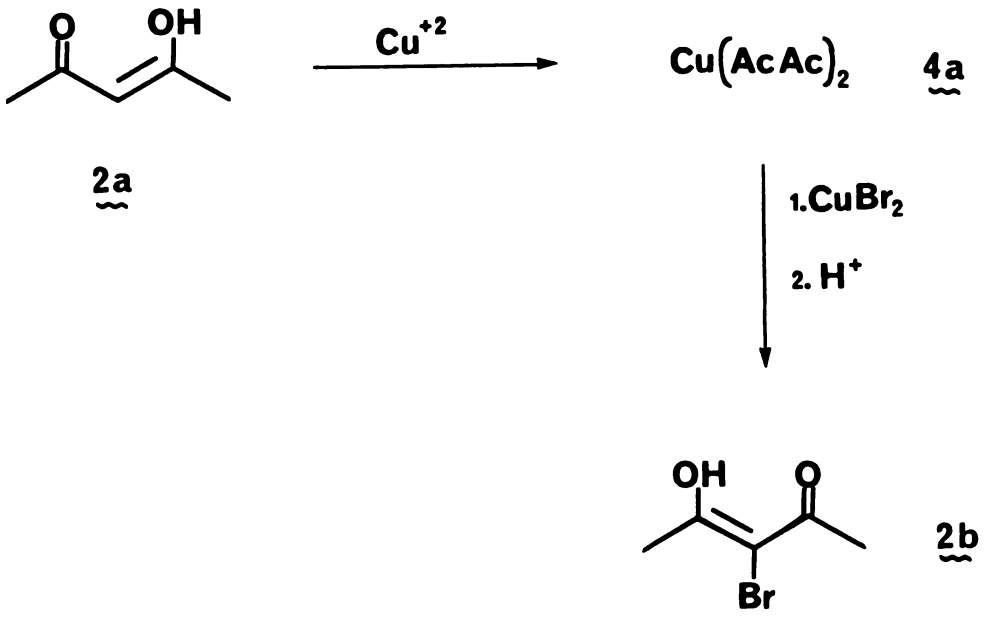
Scheme 2



In retrospect probably the biggest problem with the procedure in Scheme 2 is the decarboxylation step. Compound 3b is heated with sulfuric acid to 90^{0}C for fifteen minutes. After ten minutes the solution would turn from brown to black. This is probably a combination of unwanted polymer and condensation products. As a result there is a substantial loss of compound 2f, which contributed to the poor overall yield. Even though the pure γ,γ'-dibromoacetylacetone (2f) product was obtained, the poor yields and many steps made it desirable to look for an alternate route.

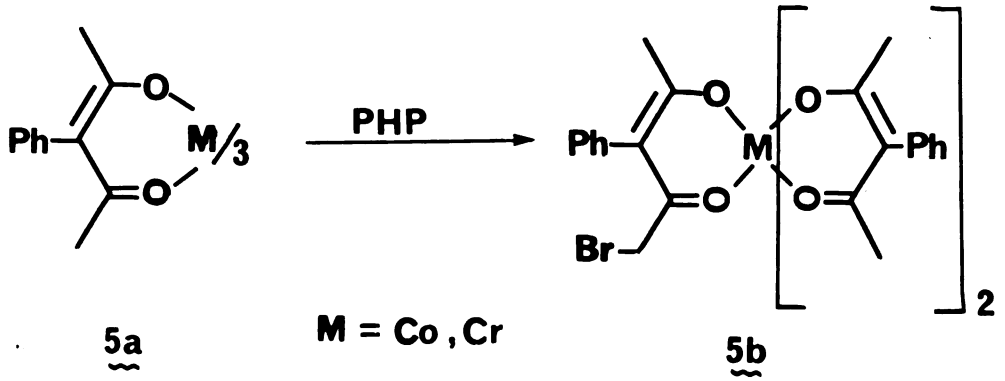
The second method reported in the literature to make 2f involved brominating a metal complex of acetylacetone. Before discussing this reaction, an overview of previous brominations of metal acetylacetonates is presented. The alpha brominations of several different metal complexed acetylacetonates including Cu, Ni, Al, Co and Cr to name a few have been reported.[6,7,8] These are straight forward brominations and one was tried using copper acetylacetonate (4a), (Scheme 3). The copper complex can be formed by adding acetylacetone to a cupric nitrate solution.[9] Any number of brominating agents could have been used. In this case cupric bromide was employed.[10] The alpha-brominated product, 2b, was obtained in good yields.

Scheme 3



Murakami and Nakamura while studying the electrophillic brominations of tris(3-phenyl-2,4-pentanediono) cobalt III and chromium III observed that bromination was taking place to a certain extent at the gamma position.[11] Pyridinium hydrobromide perbromide (PHP) had been used as a brominating agent (Scheme 4, yields were not reported[12]). The monobrominated chelate was fully characterized by the author. The explanation they gave was that the steric hindrance of the phenyl group at the alpha position prevents the bromine atom from entering there.

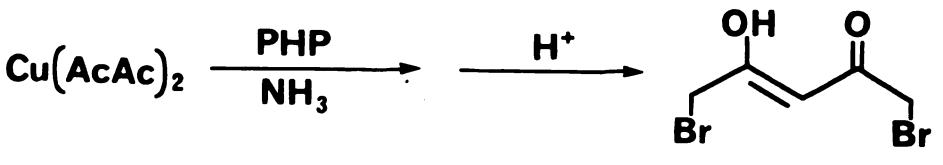
Scheme 4



5a 5b

A second method of forming 2f from the PHP bromination of 4a was reported in a Russian patent abstract.[13] While no reaction conditions were reported it was claimed that 4a was brominated at the gamma positions. From previous experimentation done on brominated metal acetylacetonate complexes (Schemes 3 and 4) this

Scheme 5

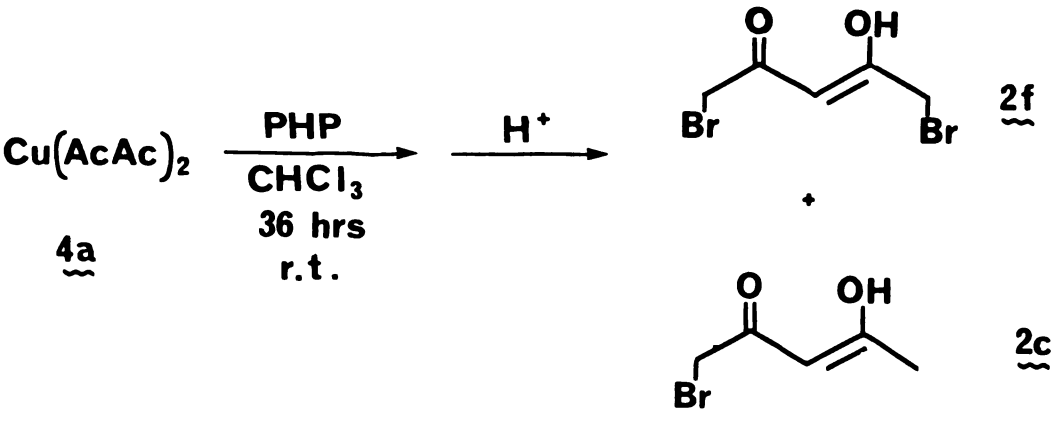


4a 2f

reaction would not appear to be feasible. A metal acetylacetonate complex would be expected to brominate in the alpha position unless there was a bulky group blocking the attack of bromine.

This reaction was tried with PHP as the brominating agent using the conditions shown below (Scheme 6).

Scheme 6



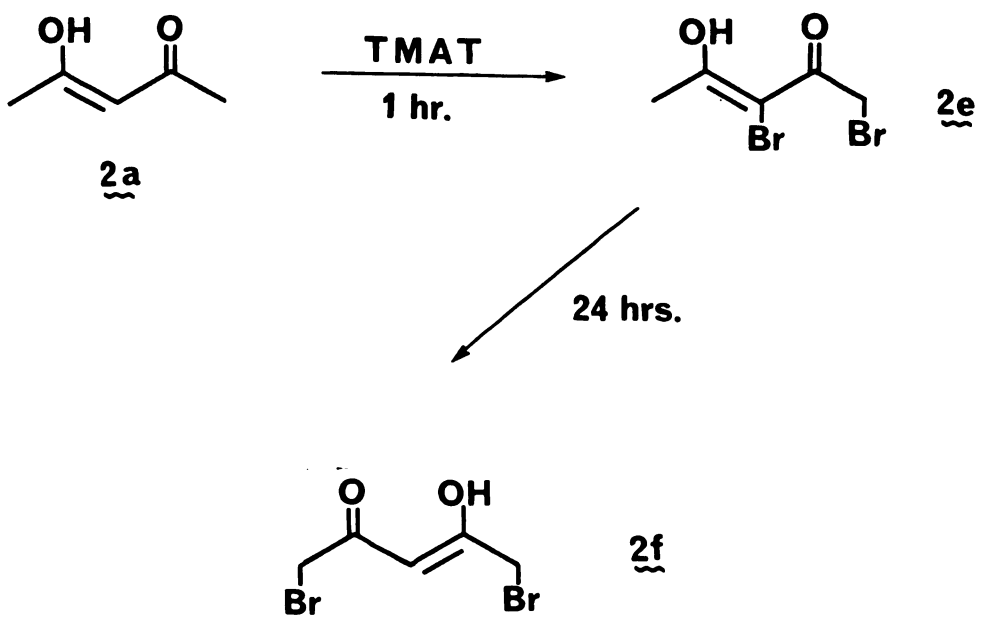
Surprisingly this procedure worked to give 38% (by NMR) of γ,γ'- dibromoacetylacetone 2f along with 15% of the gamma monobromo compound 2c. Similar results were obtained using Al or Ni as the metal in the acetylacetonate complex. This is an improvement over the first method (Scheme 2) as far as the yield and the number of steps in the reaction. The only problem with the second method is that 2c, which is formed as the minor product, could not be separated from 2f. The attempts to separate

the two compounds using flash chromatography, crystallization and purification through the copper complex failed. Using an excess of the brominating agent did not lead to increased yields of 2f at the expense of 2c.

The explanation given by Murakami and Nakamura that the steric hindrance of the phenyl group in the phenyl acetylacetone complex blocks alpha bromination could be questioned now. The gamma bromination occurred in copper acetylacetonate where there is not a bulky group at the alpha position. What appears to be happening in this bromination (Scheme 6) is that the bromine is rearranging from the alpha to gamma position. This will be discussed in the context of the following improved reaction where the same rearrangement was taking place as confirmed by a comparison of their NMR's.

An improved method of producing the desired γ,γ'-dibromoacetylacetone was developed (Scheme 7). In this reaction acetylacetone was brominated with tetramethylammonium tribromide (TMAT) to give a 79% yield (by NMR) of 2f along with 15% of 2c. The bromine at the alpha position in the initially brominated product was shown to rearrange to the gamma position. The NMR of the product, taken after the reaction, (Figure 1) shows 2e to be the major component. The peaks at 4.38 ppm ($-CH_2Br$) and 2.42 ppm ($-CH_3$) are in the ratio of 2:3 and are consistent with the structure 2e. Even after only one

Scheme 7



hour a small amount of 2f has formed as shown by the peaks at 3.9 ppm ($-CH_2Br$) and 6 ppm (vinyl proton) in the ratio 4:1. After twenty four hours at room temperature the peaks attributed to 2e have disappeared, and now 2f can be seen to be the major component (Figure 2). Compounds 2e and 2f are almost completely in their enol form and the enol peak seen at the top of the NMR's has shifted downfield in Figure 2.

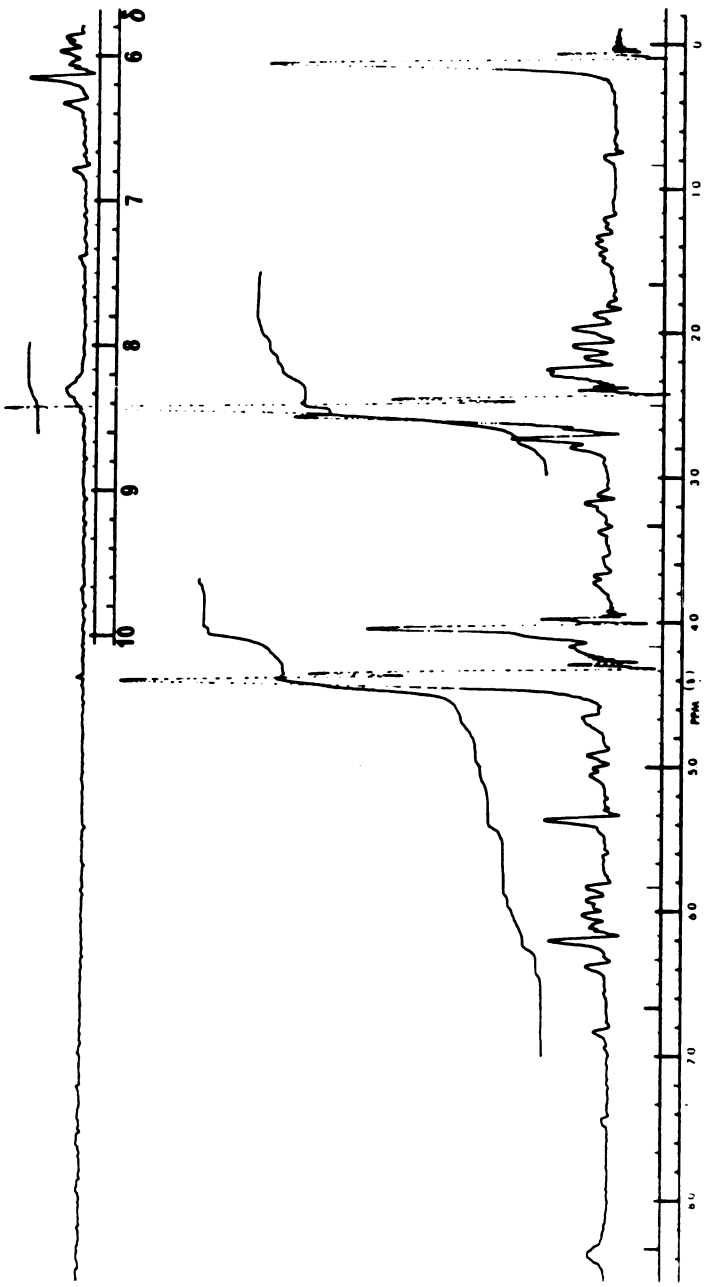


Figure 1. 60 MHz ^{1}H NMR spectrum of a mixture with major product being 1,3-dibromo-2,4-pentanedione 2e.

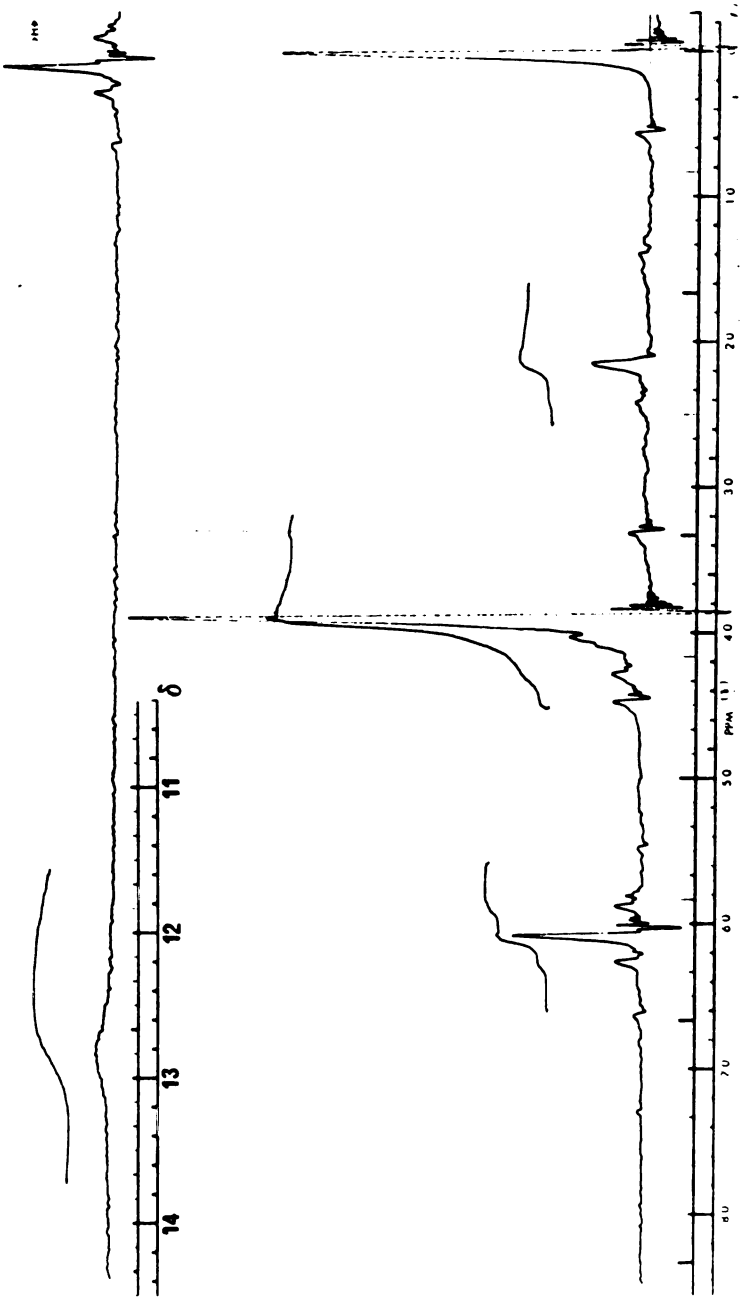
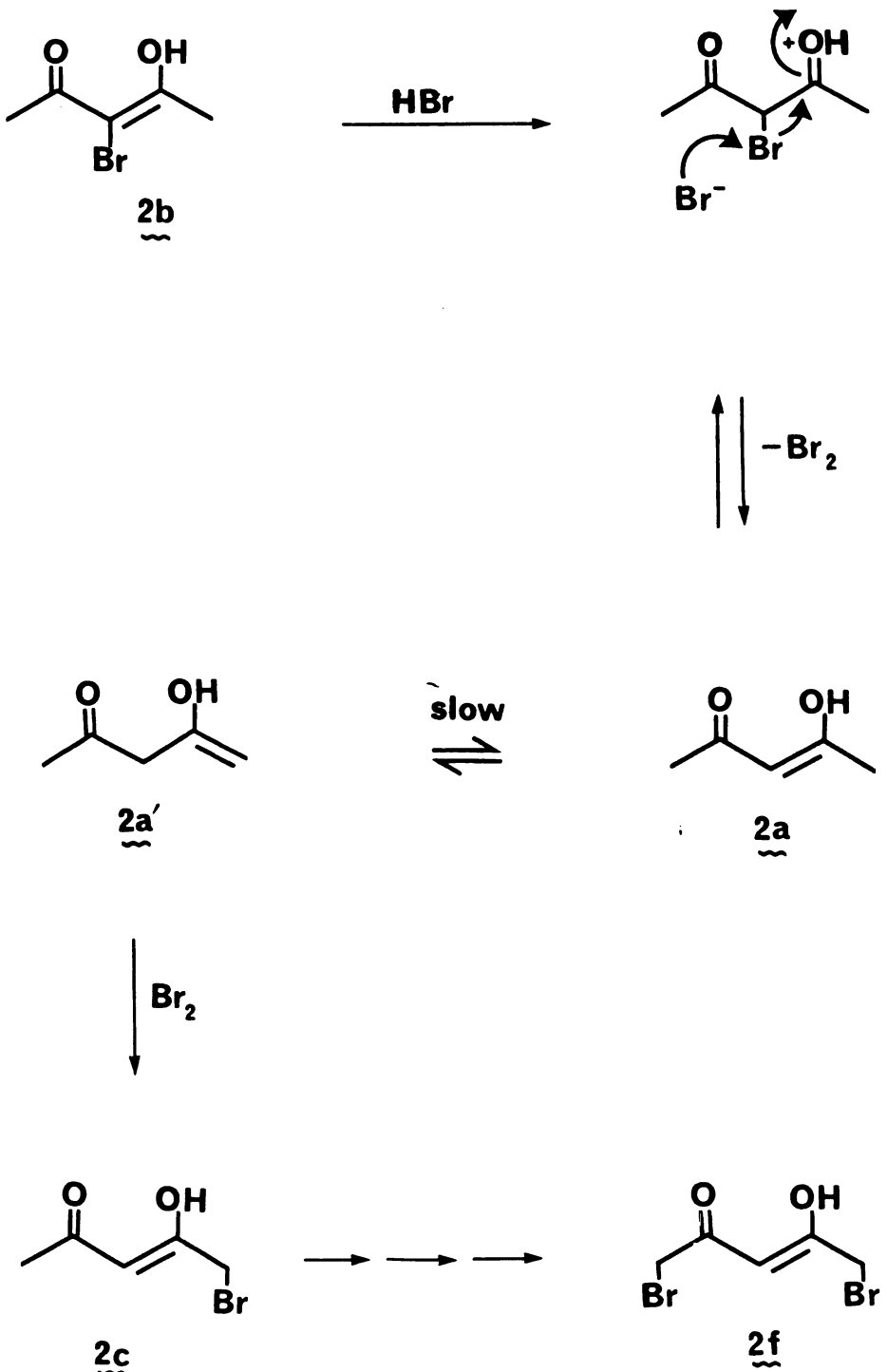


Figure 2. 60 MHz ^{1}H NMR spectrum of a mixture with major product being 1,5-dibromo-2,4-pentanedione 2f.

A mechanism that accounts for this bromine rearrangement is seen in Scheme 8. A similar explanation is given by House[14] for the rearrangement of bromine in monoketones. Initially bromination can take place at the more reactive alpha position to give 2b. In the presence of hydrogen bromide the alpha bromination is reversible. An alpha bromine can be abstracted with a bromide ion which leads to molecular bromine and 2a. Compound 2a can slowly isomerize to its β-γ enol 2a'. Then bromination of 2a' produces the more stable γ-bromoacetylacetone 2c. Once bromination occurs at the gamma position it does not appear to be reversible to any extent. The formation of 2c has been previously observed when brominating in acidic media.[15,16] If another equivalent of brominating agent is used the process can be repeated to give the gamma dibromo product 2f.

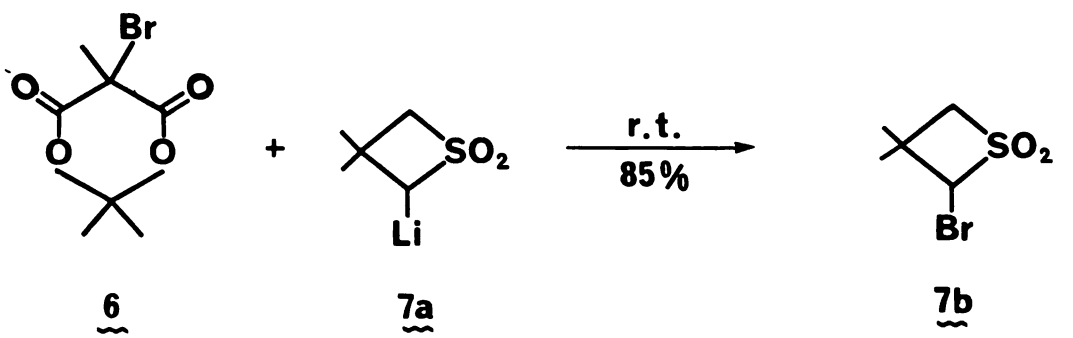
Various brominating agents were tried while experimenting with this reaction (Scheme 7). Among these were TMAT[17], PHP, pyrrolidone hydrotribromide (PHT)[18], NBS[19] and Br_2. The TMAT was the reagent of choice since there was the least amount of the gamma mono bromo product 2c formed and it, with the exception of Br_2, brominated the fastest. The other perbromides released bromine slower which was apparent by the rate of hydrogen bromide evolution. The NBS brominated more completely at the alpha position of acetylacetone and took the longest for the bromine to rearrange from the alpha to the gamma position since there was less hydrogen bromide present.

Scheme 8

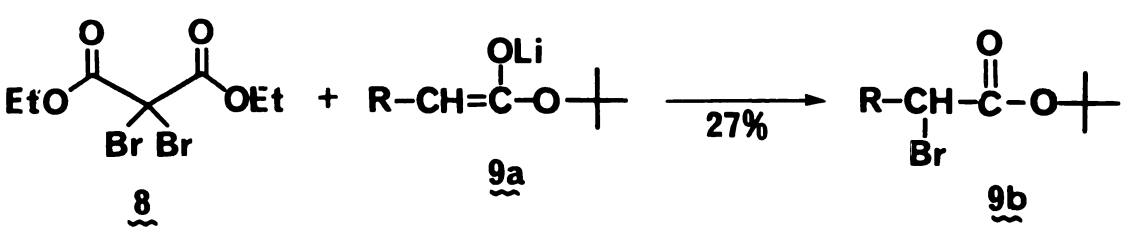

O
OH
Br
2b
HBr
O
+OH
Br
Br⁻
−Br₂
O
OH
2a′
slow
O
OH
2a
Br₂
O
OH
Br
2c
O
OH
Br
Br
2f

In this bromination there is also the possibility that any of the bromoacetylacetone compounds with bromine at the alpha position could themselves be brominating agents. Other alpha-bromo-beta-dicarbonyls have been used in this regard (Scheme 9). The alpha-bromo meldrums acid derivative 6 has been used to brominate 3,3-dimethylthietan-1,1-dioxide 7a.[20] Diethyl dibromomalonate 8 was also used as a brominating agent in the production of 2-bromo-cis-8,cis-11,cis-14-eicosatrienoic acid 9b.[21]

Scheme 9



6 7a 7b



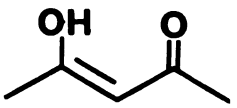
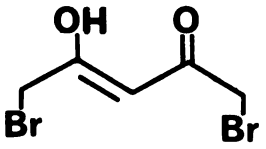
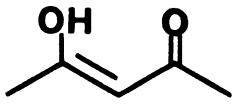
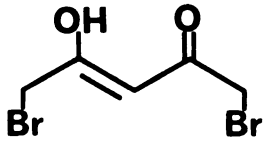
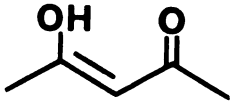
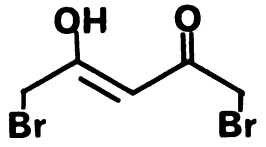
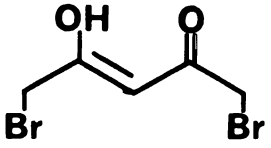
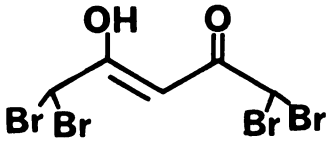
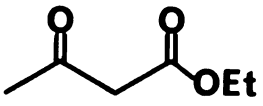
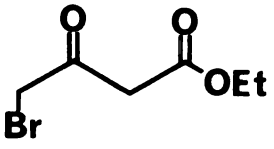
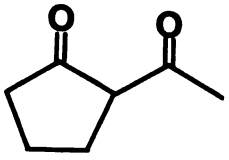
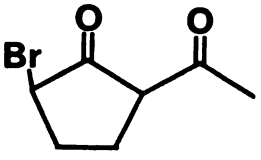
8 9a 9b

$$R = CH_3(CH_2)_4-\left[C{=}CCH_2\right]_3-(CH_2)_4$$

The bromination of acetylacetone to give γ,γ'-dibromoacetylacetone using the different methods is summarized in Table 1. Some gamma brominations of other beta-dicarbonyls that were done are shown. Further bromination of 2f with 2 equivalents of TMAT produced $\gamma,\gamma,\gamma',\gamma'$-tetrabromoacetylacetone as the major product. Monobromination of ethyl acetoacetate and 2-acyl-cyclopentanone with TMAT gave the gamma-bromo products 1c and 10c respectively. The products 1c and 10c were both obtained in high yields with little evidence of other compounds present (TLC & NMR).

This alpha-gamma bromine rearrangement appears to be fairly general in beta-dicarbonyls, but some beta-dicarbonyls tried did not rearrange. One compound that failed to show this rearrangement was dimedone. The bromination of dimedone was previously studied by Voitila[22] and later by Irie and Arakawa.[23] They did not report the direct production of the gamma bromo compound 4-bromo-5,5-dimethyl-1,3-cyclohexanedione which was what we attempted to do. When the bromination of dimedone was tried with one equivelent of TMAT, bromination took place at the alpha or 2 position and no rearrangement to the gamma or 4 position was detected. Even when two equivelents of TMAT were used no rearrangement occurred and the only product isolated was 2,2-dibromo-5,5-dimethyl-1,3-cyclohexanedione.

Table 1. Gamma brominations of beta-dicarbonyls.

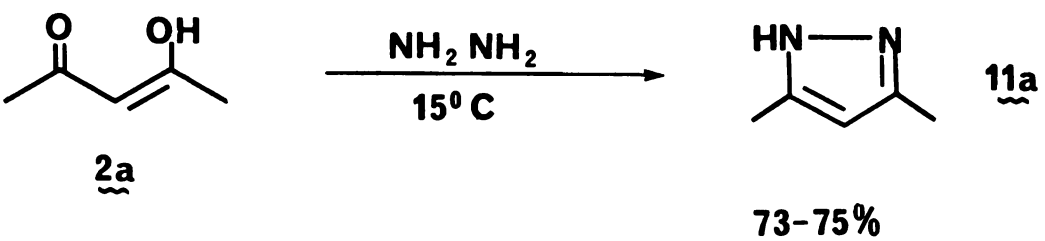
Substrate	Product	Method used Scheme#	%Yield[a]	Time (hrs)
 2a	 2f	2	7	-
		6	38[b]	36
		7	79[b]	24
 2f	 2g	7	75[b]	48
 1a	 1c	7	94[c]	30
 10a	 10c	7	95[c]	24

[a] isolated yield; [b] not separated from minor products, yield based on NMR integration; [c] crude yield, TLC showed one spot.

B. APPLICATIONS OF GAMMA BROMINATED BETA DICARBONYLS

The most general and widely applicable method for the preparation of pyrazoles consist of the addition of hydrazine to beta-dicarbonyl compounds. Symmetrical heterocyclic compounds can be produced efficiently in this manner (Scheme 10).[24]

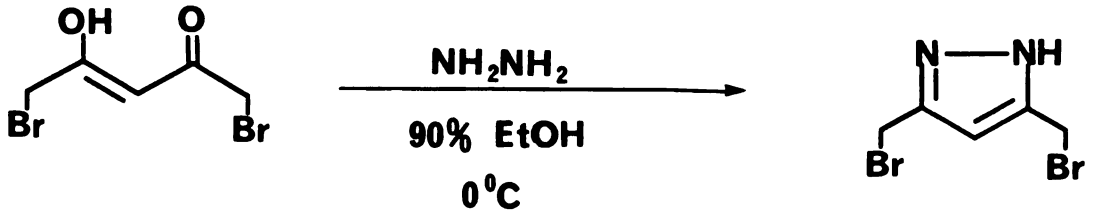
Scheme 10



This method was chosen for making 3,5-bis(bromomethyl) pyrazole 11b. The beta-dicarbonyl used, γ',γ'-dibromo-acetylacetone 2f is now readily available (Scheme 7). In Scheme 11 hydrazine hydrate was added to a solution of 2f in 90% ethanol at ice bath temperatures. The reaction was tried in absolute ethanol but the product was too soluble and did not crystallize out of solution. On cooling, the new compound 11b crystallized out of solution as white needles in 66% yield.

There was the question before trying this reaction of whether the hydrazine would add at the carbonyl

Scheme 11

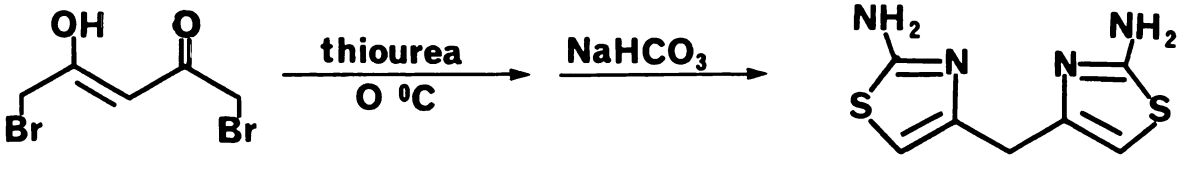


2f 11b

carbons or undergo a substitution reaction at the gamma carbons to displace the bromines. Under these conditions (Scheme 11) the carbonyl carbons were found to be more reactive.

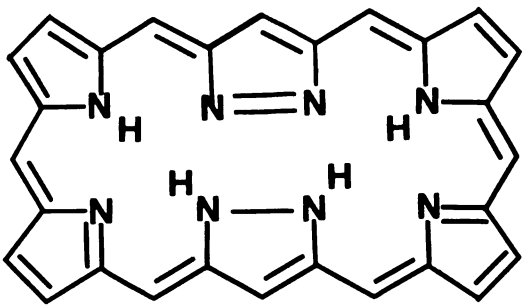
The compound 2f also showed utility in the synthesis of the thiazole derivative 12 (Scheme 12).[25] In this reaction both addition at the carbonyl carbons and nucleophillic substitution occurred. When this reaction was tried the hydrobromide salt was obtained in good yield. Subsequent formation of the free amine was not accomplished here, but was previously formed and characterized elsewhere.[25]

Scheme 12



2f 12

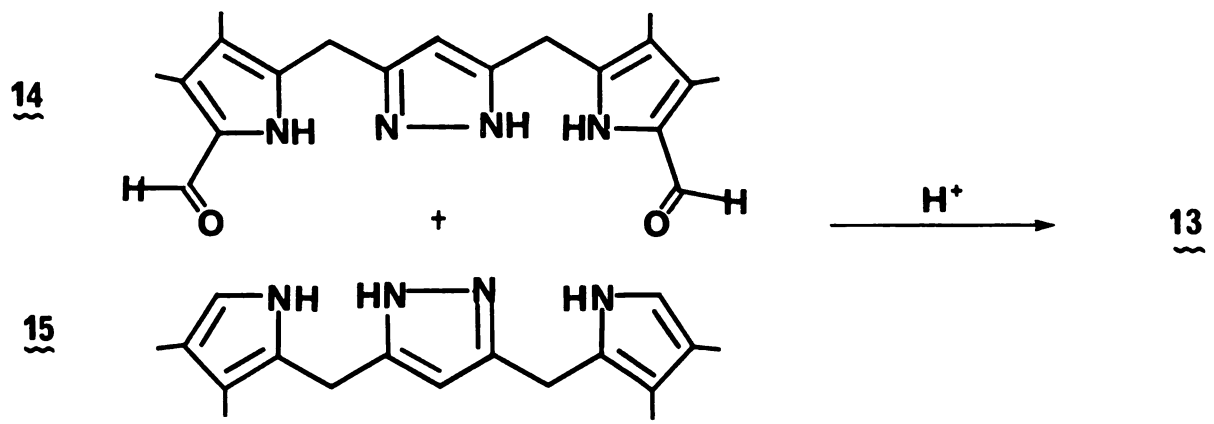
A future consideration is to explore reactions of 3,5-bis(bromomethyl)pyrazole with pyrrole derivatives. This could lead to the formation of the potentially interesting macrocycle octaaza-(26)-annulene 13.



13

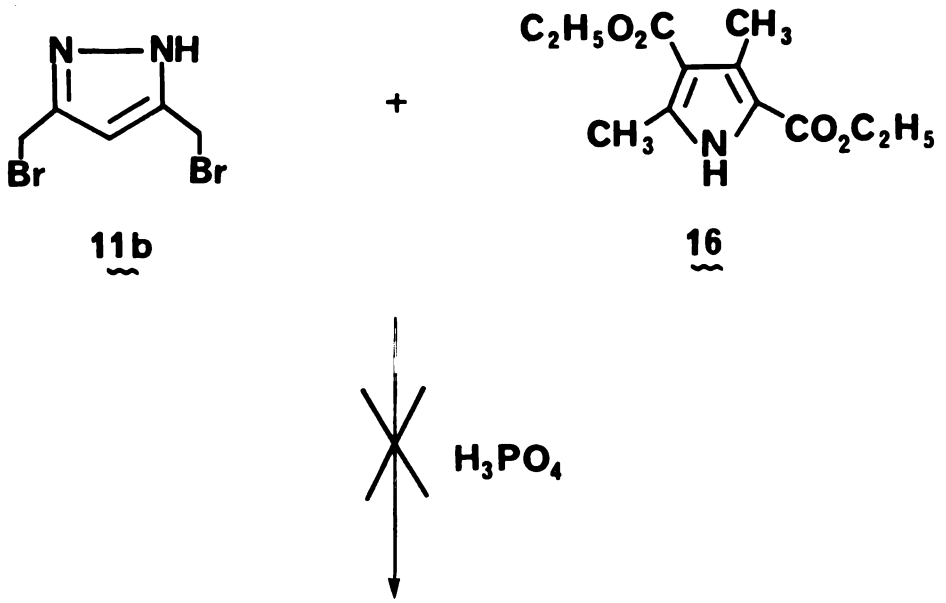
The strategy that would be used in the formation of this expanded porphine is based on known pyrrole chemistry. One possibility can be seen in Scheme 13 where the two halves 14 and 15 could couple to form the macrocycle.[25]

Scheme 13



In an effort to form a compound similar to 15 the 3,5-bis(bromomethyl)pyrazole 11b was added to Knorr pyrrole in a preliminary study (Scheme 14). The purpose of this reaction was to test the reactivity of the benzyllic-like bromines in the pyrazole derivative. In this reaction a dark tar-like material was formed after heating which contained no identifiable products. Further work is planned in this area.

Scheme 14



11b

16

17

EXPERIMENTAL

General Methods

All melting points were determined using a Thomas-Hoover capillary melting point apparatus and are uncorrected. Unless otherwise noted, all NMR spectra were obtained in chloroform-d_1 solution with the chemical shifts reported in parts per million downfield from the tetramethylsilane standard. Proton NMR spectra were obtained on Varian T-60 and Bruker WM-250 spectrometers at 60 MHz and 250 MHz, respectively. Infrared spectra were obtained on a Perkin-Elmer 237 grating spectrometer and were calibrated using the polystyrene 1601 cm^{-1} peak. Mass spectra were obtained on a Finnigan 4000 instrument at 70 eV or using ionized methane. Galbraith Laboratories, Inc. provided elemental analysis data. Flash column chromatography refers to the method of Still, Kahn and Mitra.[27] All reactions were done under N_2 atmosphere unless otherwise noted.

3-Carbethoxy-2,4-pentanedione (3a).

According to the procedure of Spassow[5] 0.2 moles of ethyl-acetoacetate is diluted with 50 mL of benzene and then 0.1 moles of Mg shavings are added. Then 0.3 moles of acetyl chloride is added. During the addition of acetyl chloride there is a slow evolution of gas. Then warm to 80-85 °C for 1 h. Cool the reaction mixture to 25 °C, decant from unreacted Mg. Wash the unreacted Mg with ether. Combine the ether layers and wash several times with water. Then separate the ether layer and dry it over anhydrous Na_2SO_4. The remaining liquid was vacuum distilled bp 93-94/11mm Hg to produce 68% yield of 3a. This appeared pure (by NMR) and was used directly in the preparation of 3b. ^{1}H NMR: δ1.37(3H,t), 2.40(6H,s), 4.27(2H,q), 15.9(1H,s).

1,5-Dibromo-3-carbethoxy-2,4-pentanedione (3b).

According to Becker[4a] in a 500 mL round bottom flask 50 g of 3a in 150 mL of absolute ether and 93 g of dry bromine is stirred at -15 °C for 1½ h. After this the reaction mixture is allowed to warm to 25 °C. After approximately 17 h the reaction is complete. One pours it into 250 mL of ice water. Then the mixture is extracted with ether, dried with anhydrous

Na_2SO_4 and the ether is distilled off. Upon cooling to -15 °C one obtains .24 g of crystals and 21 g oil. Recrystallization from 30 mL alcohol produces 17 g of pure white product. Cooling the oil to -15 °C produces an additional 3-4 g of crystals. The yield is 21% of 3b; mp 52-53 °C (lit. mp 54-55 °C).[4a] This appeared pure by the melting point and was used directly in the preparation of 2f.

1,5-Dibromo-2,4-pentanedione (2f).

The decarboxylation[4b] involves taking 10 g of 3b and dissolving it in 35 mL of conc. H_2SO_4. Heat this solution to 90 °C. At about 65 °C CO_2 begins to evolve. After about 15 min at 85-90 °C the solution is cooled to 25 °C, then poured slowly over 200 g of ice. The dark oil ppt. is extracted with two 75 mL portions of ether. Then the volume of ether is reduced to about 30 mL. This can be purified by shaking with a cupric diacetate solution to obtain the copper salt; mp 149-152 °C with decomposition. To decompose the copper salt, first take 5 g of 4b and suspend it in 30 mL of ether. This mixture is shaken for 10 min with 30 mL of 20% H_2SO_4. The ether layer is separated and dried over anhydrous Na_2SO_4. The ether is distilled off and a dark green oil (2f) is recovered in 47% yield from 3b; mp 6-7 °C.

This appeared pure (by NMR) and was used directly in the production of 11b. ^{1}H NMR: δ3,9(4H,s), 4.02(2H,t), 6.04(1H,s). M.S.: m/e=258 (parent)triplet isotope cluster, 163 (base peak). IR (neat): 3445, 1720, 1600 cm^{-1}.

Copper acetylacetonate (4a)

Using the method of Jones[9] cupric nitrate trihydrate (10 g) was dissolved in distilled water (100 mL) and conc. aqueous ammonia (15 mL) was added. To the resulting solution of $Cu(NH_3)_2^{+2}$, acetylacetone (11 mL) was added dropwise while stirring. A light blue precipitate was obtained. Jones obtained a 98% yield of 4a.

3-Bromo-2,4-pentanedione (2b)

The purpose of this reaction was to verify bromination at the alpha position. An excess of cupric bromide was added to 1 g of 4a in 30 mL of a 1:1 EtOAc/$CHCl_3$ solution at 25 °C. The solution turned to a blue color upon addition. After approximately 1 h the white CuBr began to ppt. out of solution. After 2 h the reaction is done. The CuBr is filtered from the solution. The solution is washed with water and the organic layer is dried and put in the refrigerator. Within a period of a few hours green needles crystallize out of the solution

and are collected and dried. After decomposition of the complex with acid an NMR was taken. The NMR indicated bromination had taken place at the alpha position. ^{1}H NMR: δ2.4(6H,d), 4.77(1H,m).

1,5-Dibromo-2,4-pentanedione (2f).

The second method of producing 2f involves taking 1.0 g of copper acetylacetonate and dissolving in 30 mL of $CHCl_3$. Then 4.9 g of PHP is added. The solution is stirred for 36 h at 25 °C. Then the solution is treated with 20% H_2SO_4 to decompose what copper complex is remaining. After this the solution is washed several times with water and then dried over anhydrous Na_2SO_4. Then the $CHCl_3$ is distilled off. The yield is 38% of the green oil 2f (by NMR) with 15% of 2c. These compounds could not be separated. Data of compound 2f; ^{1}H NMR: δ3.9(4H,s), 4.02(2H,t), 6.04(1H,s). M.S.: m/e=258 (parent) triplet isotope cluster, 163 (base peak). IR: 3445, 1720, 1600 cm^{-1}.

1,5-Dibromo-2,4-pentanedione (2f).

The third method of producing 2f proceeds as follows: 2 g of acetylacetone was added to 13.2 g of TMAT[26] in 50 mL of anhydrous ether. Then the solution is stirred

at 25 °C. Hydrogen bromide is given off immediately. The solution goes from the orange color of TMAT to the white color of tetramethylammonium bromide (TMAB) within 1 h. The TMAB is filtered off from the solution. Then the solution is washed several times with water. The ether layer is separated and dried over anhydrous Na_2SO_4. The ether is distilled off at 0.5 mm Hg. The solution is put in the refrigerator for approximately 24 h to allow the bromine to rearrange. The yield is 79% of the green oil 2f, (by NMR) along with 15% of 2c. These compounds could not be separated. Data of compound 2f; ^{1}H NMR: δ 3.9(4H,s), 4.02(2H,t), 6.04(1H,s). 12.82(1H,bs). M.S.: m/e=258, 163 (base peak). IR: 3445, 1720, 1600 cm^{-1}.

1,1',5,5'-Tetrabromo-2,4-pentanedione (2g).

To a mixture of 3.83 g TMAT in 40 mL of ether was added 1.5 g of 2f. The solution was stirred at 25 °C for 48 h. Then the white TMAB is filtered off from the solution. The dark bronze filtrate is washed several times with water. The ether layer is dried over anhydrous Na_2SO_4. The ether is distilled off to give a dark brown oil. The yield is 75% (by NMR) of 2g along with approximately 17% of lower brominated products. These compounds could not be separated. Data of compound 2g; ^{1}H NMR: δ 5.87(2H,d), 6.32(1H,d), 12.5(1H,bs).

M.S.: m/e=416 (parent) quintuplet isotope cluster, 243 (base peak). IR: 3410, 1735, 1585 cm^{-1}.

Ethyl-γ-bromoacetoacetate (1c).

In a 250 mL flask 3.29 g of TMAT is added to 30 mL of anhydrous ether. Then 1.24 g of ethyl acetoacetate is added. The reaction is stirred for 1 h at 25 °C. Then the TMAB is filtered off. The solution is washed several times with water. The ether layer is dried over anhydrous Na_2SO_4 and then the ether is distilled off. The solution is allowed to stand in the refrigerator for approximately 30 h. The oily liquid appeared fairly pure (by TLC). The crude yield was 94%. ^1H NMR: δ1.31(3H,t), 3.70(2H,s), 4.07(2H,s), 5.27(1H,s), 8.33 (1H,s). M.S.: m/e=209 doublet isotope cluster, 43 (base peak). IR: 3410, 1720 cm^{-1}.

2-Acetyl-5-bromocyclopentanone (10c).

In a 250 mL round bottom flask was added 2.3 g of TMAT in 30 mL ether. Added to this was 1 g of 2-acetyl-cyclopentanone. This solution was stirred at 25 °C for 1 h. Then the TMAB was filtered from the reaction mixture. The filtrate was washed several times with water. The ether layer is dried over anhydrous Na_2SO_4. The solution is allowed to stand in the refrigerator for

approximately 24 h. The oily liquid appeared fairly pure (by TLC). The crude yield was 95%. ^{1}H NMR: δ 2.1 (3H,s), 2.37(2H,t), 2.6(2H,m), 4.6(1H,t), 12.66(1H,s). M.S.: m/e=205 (parent) doublet isotope cluster, 43 (base peak). IR: 3405, 1710, 1610 cm^{-1}.

2-Bromo-5,5-dimethyl-1,3-cyclohexanedione

In a 250 mL round bottom flask 2.67 g of NBS was added to 25 mL of CCl_4. Then 2 g of dimedone was added. The solution was stirred at 25 °C for 3½ h. At that time all of the succinimide had floated to the top of the CCl_4. The reaction mixture was washed several times with water. The white solid that ppt. was collected. The yield was 85%; mp 174-175 °C (lit. mp 175-176 °C).[22] ^{1}H NMR: δ1.10(6H,s), 2.47(4H,s). M.S.: m/e=220 (parent) doublet isotope cluster, 162 (base peak).

2,2-Dibromo-5,5-dimethyl-1,3-cyclohexanedione

In a 250 mL round bottom flask 2.67 g of NBS was added to 25 mL of CCl_4. Then 1 g of dimedone was added. This was stirred at 25 °C for 4 h. At that time all of the succinimide had floated to the top of the CCl_4. The reaction mixture was washed several times with water. The white solid that ppt. was collected. The yield was 75%; mp 146-148 °C (lit. mp 148-149 °C).[22] ^{1}H NMR:

δ1.03(6H,s), 3.0(4H,s). M.S.: m/e=298 (parent) triplet isotope cluster, 83 (base peak).

3,5-Bis(bromomethyl)pyrazole (11b).

In a 25 mL flask was added 1.45 g of 1,5-dibromo-2,4-pentanedione to 5 mL of 90% ethanol. This solution was cooled to ice bath temperature. Then 0.281 g of hydrazine hydrate was added dropwise while stirring the mixture. The reaction was not run under nitrogen. After addition was complete the solution was allowed to stir an additional 10 min. Then the solution is put in the freezer. White crystals are collected in 66% yield; mp 78-79 °C. ^{1}H NMR: δ 4.43(4H,s), 6.32(1H,s). M.S.: m/e=254 (parent peak) triplet isotope cluster, 173 (base peak).

Anal. Calcd. for $C_5H_6N_2Br_2$: C, 23.62; H, 2.36; N, 11.02 Br, 62.99.

Found: C, 23.84; H, 2.52; N, 11.38 Br, 62.27.

Hydrobromide salt of 2,2'-diamino-dithiazolyl-4,4'-methane (12).

In a flask 0.93 g of thiourea was dissolved in 30 mL of EtOH/ether (2:1). This was cooled to 0 °C. Then 1.5 g of 1,5-dibromo-2,4-pentanedione was added dropwise. After addition the solution was stirred for 15 more min.

Then this was put in the freezer. Within 2 h a tan solid was collected. The crude yield was 91%; decomp. mp 269-271 °C. ^{1}H NMR: δ 4.05(2H,s), 4.8(6H,s), 6.76(2H,s).

3,5-Bis(pyrrole methylene)pyrazole (17).

In a three necked flask fitted with a condenser, 0.75 g of Knorrs pyrrole was added to phosphoric acid.[18] This was heated to 120-130 °C for 15 min . Then the reaction mixture was cooled to 40 °C. Then 0.9 g of 11b was added to the solution. The solution turned from yellow to brown. After stirring the mixture for 5 h it was washed several times with water. The solution was extracted with ether. The ether layer was dried over anhydrous Na_2SO_4. Then the ether was distilled off. There were no identifiable products (by NMR) from this reaction.

APPENDIX

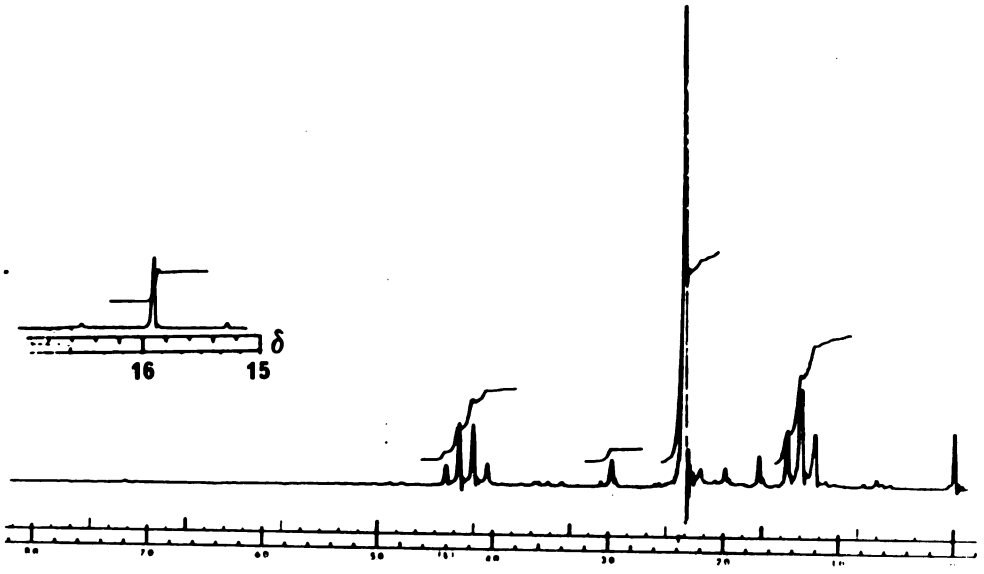


Figure A1. 60 MHz ^{1}H NMR spectrum of 3-carbethoxy-2,4-pentanedione 3a.

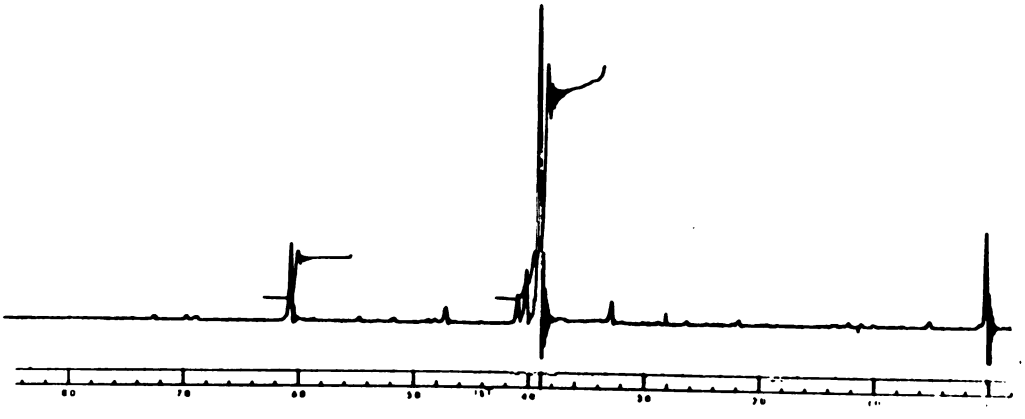


Figure A2. 60 MHz ^{1}H NMR spectrum of 1,5-dibromo-2,4-pentanedione 2f.

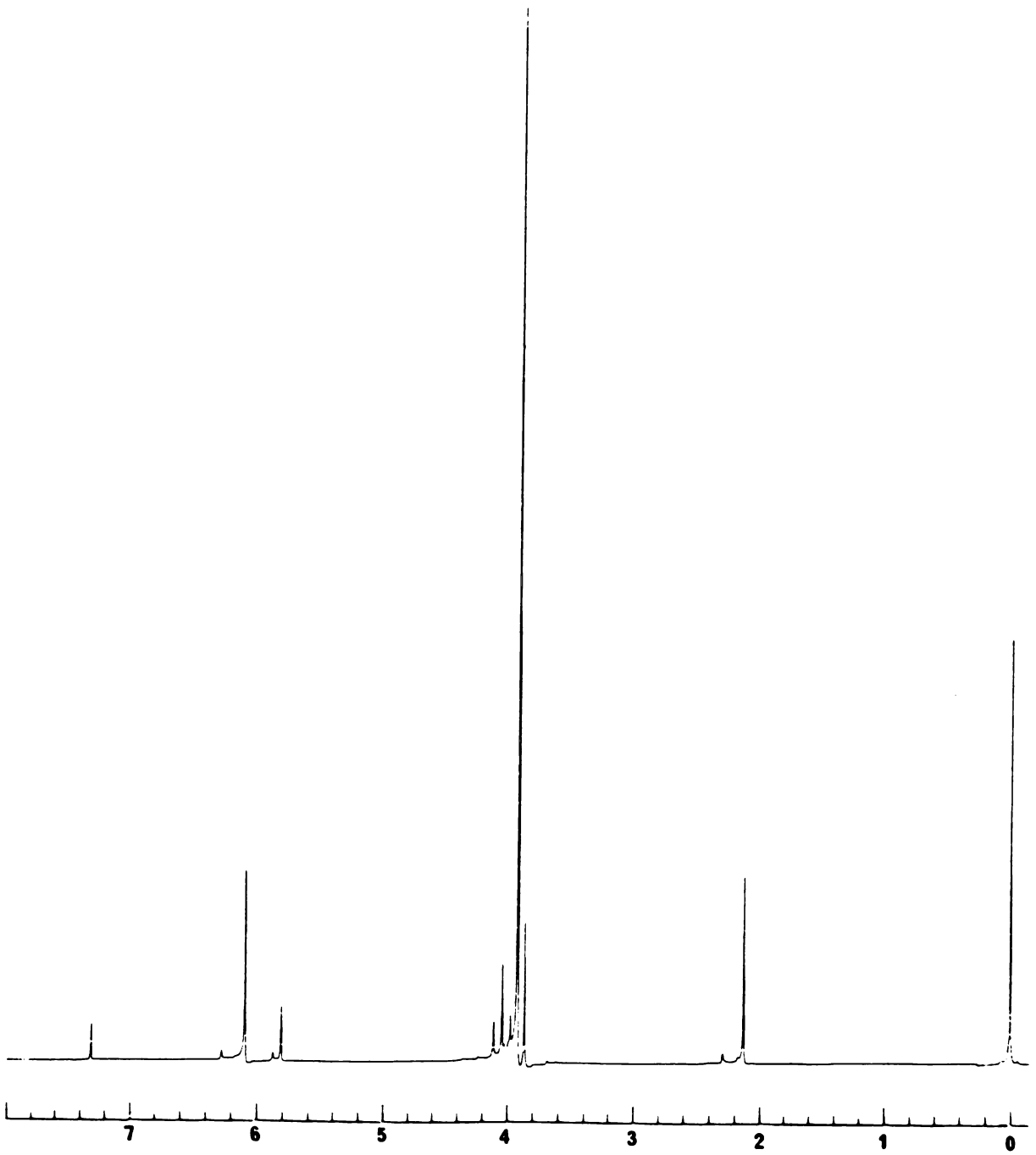


Figure A3. 250 MHz ^{1}H NMR spectrum of a mixture of 1,5-dibromo-2,4-pentanedione 2f and 1-bromo-2,4-pentanedione 2c.

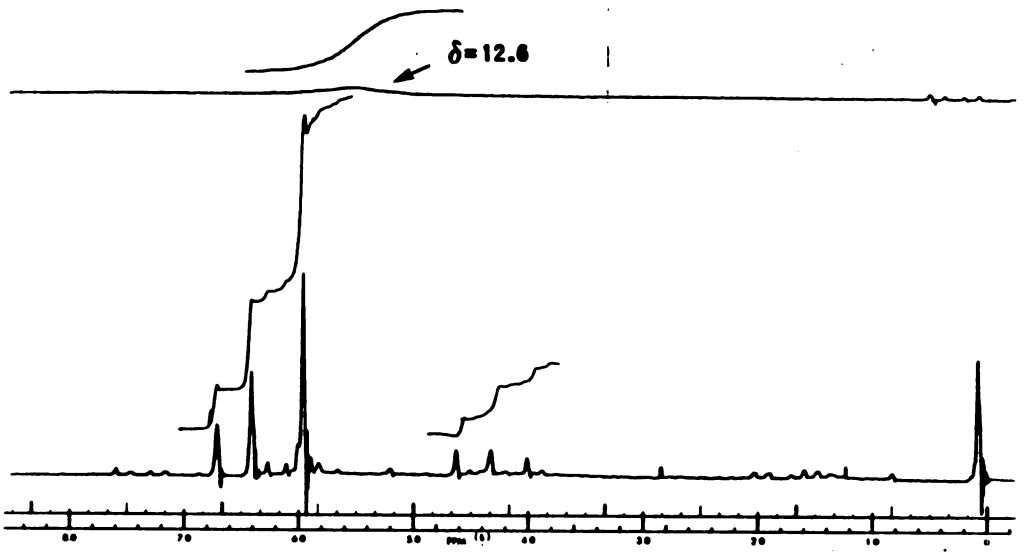


Figure A4. 60 MHz ^{1}H NMR spectrum of a mixture of 1,1',5,5'-tetrabromo-2,4-pentanedione 2g. and lower bromination products.

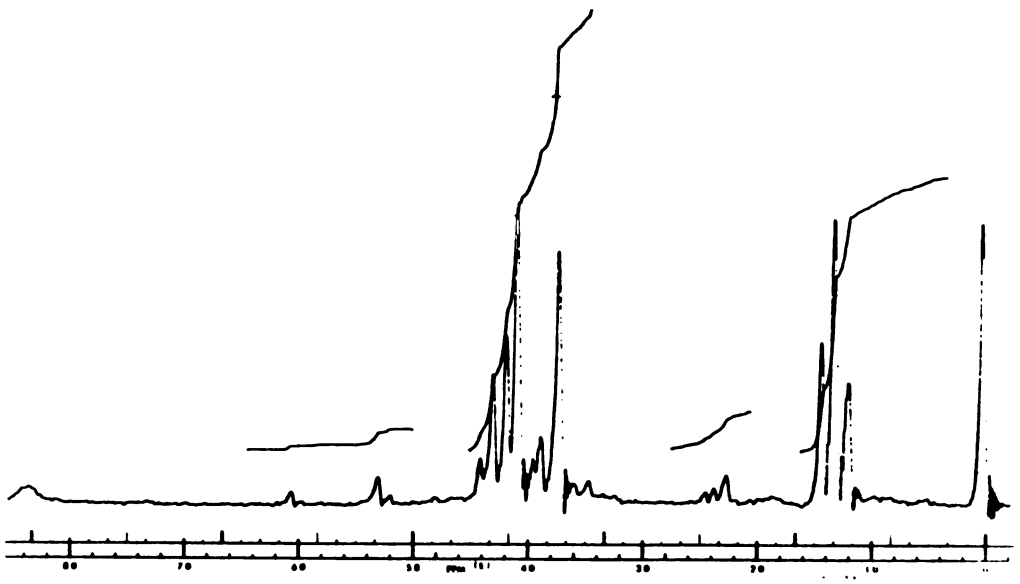


Figure A5. 60 MHz ^{1}H NMR spectrum of ethyl-γ-bromo-acetoacetate 1c.

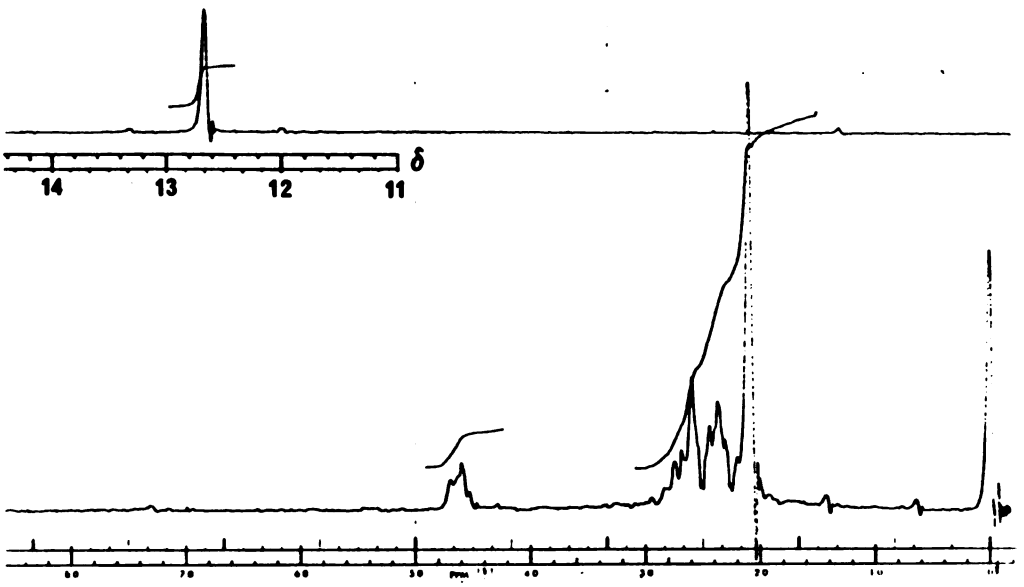


Figure A6. 60 MHz ^{1}H NMR spectrum of 2-acetyl-5-bromocyclopentanone 10c.

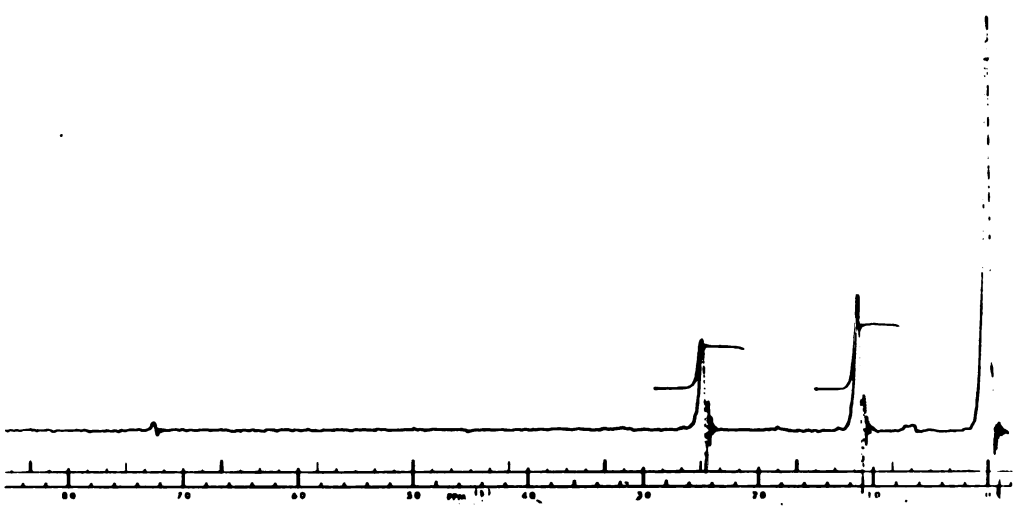


Figure A7. 60 MHz ^{1}H NMR spectrum of 2-bromo-5,5-dimethyl-1,3-cyclohexanedione.

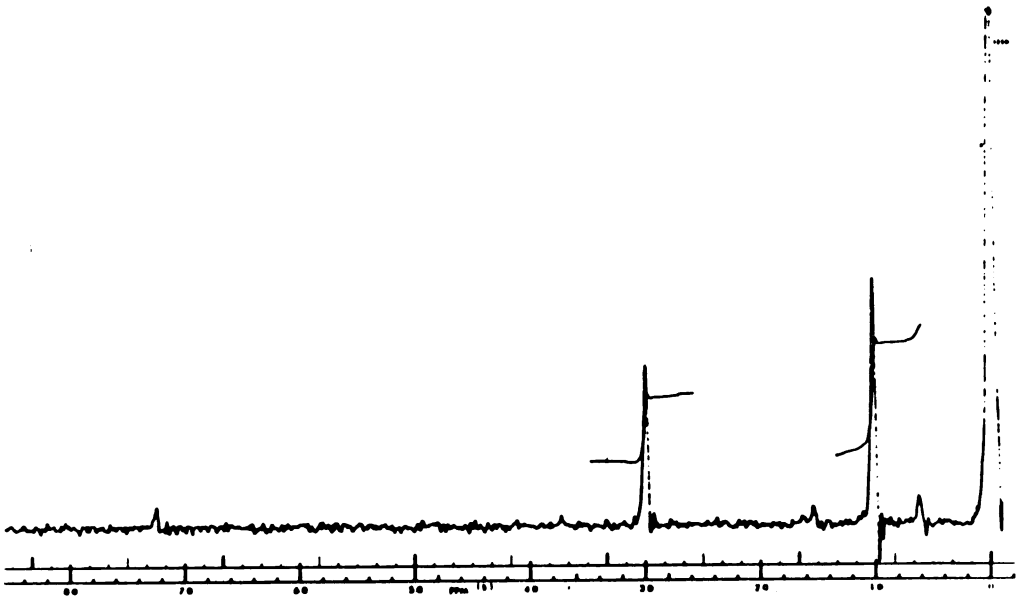


Figure A8. 60 MHz ^{1}H NMR spectrum of 2,2'-dibromo-5,5-dimethyl-1,3-cyclohexanedione.

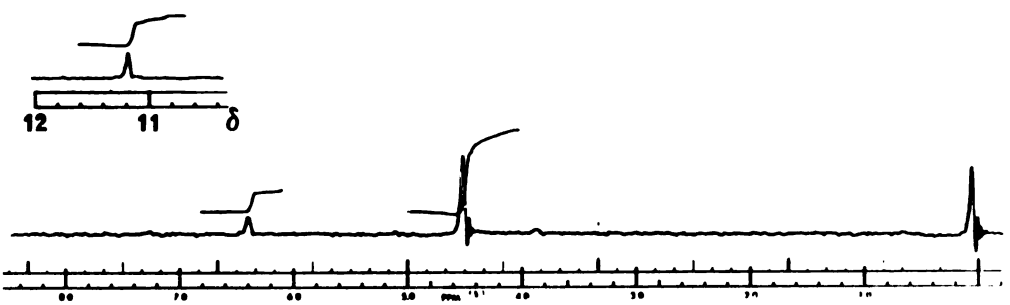


Figure A9. 60 MHz ^{1}H NMR spectrum of 3,5-bis(bromomethyl)pyrazole 11b.

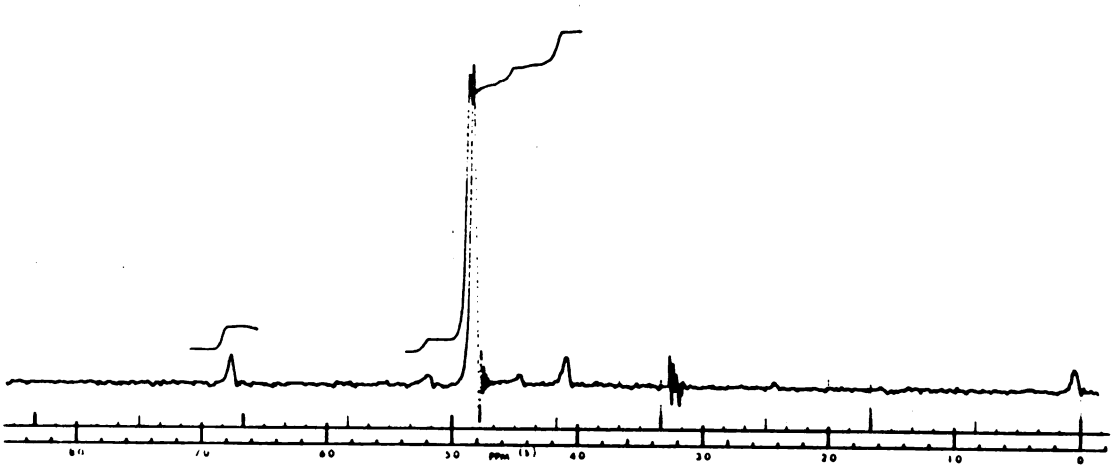


Figure A10. 60 MHz ^{1}H NMR spectrum of hydrobromide salt of 2,2'-diamino-dithiazolyl-4,4'-methane 12.

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