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Syntheses in the Thiophene Series

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Syntheses In The Thiophene Series

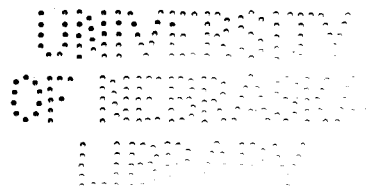
by

ALFRED WILLIAM WEITKAMP

A Thesis

PRESENTED TO THE FACULTY OF
THE GRADUATE COLLEGE IN THE UNIVERSITY OF
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IN PARTIAL FULFILLMENT OF REQUIREMENTS FOR
THE DEGREE OF DOCTOR OF PHILOSOPHY
DEPARTMENT OF CHEMISTRY

LINCOLN, NEBRASKA
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The writer wishes to thank Dr.
Cliff S. Hamilton for his many
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INTRODUCTION

The importance of organic arsenicals in therapy is too well known to require more than passing mention. Many heterocyclic types have been studied. Prominent in this group are the arsenic derivatives of thiophene prepared by Finzi^{1,2,3,4,5} and Steinkopf⁶. In these cases arsenic is substituted in one of the alpha positions whereas the other alpha position is occupied by H, Br, I, or CH₃, all positive groups. It is of interest to note that in no case has a negatively substituted thiophene been arsenated. Finzi failed in his attempts to apply the reactions of Béchamp and Bart to aminothiophene. The Grignard reaction cannot be applied to carbonyl derivatives of thiophene, such as the aldehydes, ketones, acids and esters on account of secondary reaction with the carbonyl group. As a consequence, the known arsenicals with but one exception have been prepared from the corresponding mercurials. Steinkopf and coworkers^{7,8} state that negative substituents hinder mercuration and under conditions of their experiments 2-nitrothiophene did not react. In a later publication Steinkopf⁶ reports the mercuration of thiophenic acid. Volhard⁹ obtained a double compound of acetothienone, with mercuric chloride, but no true mercurials.

The purpose of this investigation was to consider the mercuration of negatively substituted thiophenes as a means of getting to the corresponding arsenicals. Benzothienone and to a lesser degree acetothienone and nitrothiophene have been studied.

DISCUSSION

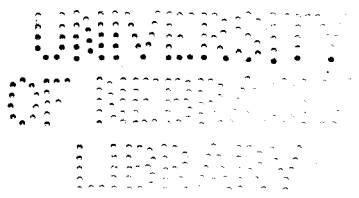
A. Mercuration of Benzothienone

Benzothienone mercurated very slowly at room temperature in a buffered alcoholic solution of mercuric chloride. The results were completely unsatisfactory.

Mercuration proceeded rapidly by fusion of the ketone with mercuric acetate. There was produced a complex substance (3) whose constitution has been made the subject of considerable investigation. It appears that a monoacetoxymercuri derivative formed first but reacted rapidly to form the "complex." Small amounts of the monomercurated derivative (4) were always isolated. Its structure was established by conversion to the corresponding iodo compound by cleavage with iodine and potassium iodide. Gilman's work on superaromaticity¹⁰ made it seem probable that mercuration had occurred in the alpha or 2 position. Unfortunately the physical

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constants of 2-iodo-5-benzothienone are not found in the literature. However, it was conveniently synthesized from 2-iodothiophene and benzoyl chloride by means of the Friedel-Crafts reaction (6). Both this product and the one obtained from the mercurial melt at 129.5-130° C. and the melting point shows no depression when the two are mixed. This not only establishes the position of monomercuration but brings mercuration into line with the other superaromatic properties of benzothienone.

The complex mercurial was studied in greater detail. Purification is best accomplished by recrystallization from glacial acetic acid. The substance crystallizes in characteristic lenticular plates which melt sharply at 202° C. Analysis indicates a ratio of two atoms of sulfur to three atoms of mercury, and furthermore this ratio is unchanged by repeated recrystallizations. In other words, the molecular complex consists of two benzothienone nuclei substituted with three acetoxymercuri groups. There can be no doubt that it is a compound rather than a fortuitous mixture. It may be considered as being a double compound of one mole of a monomercurial with one mole of a dimercurial.

The "complex" was subjected to cleavage with iodine and potassium iodide yielding a mixture of iodobenzothienones. By prolonged fractional crystallization from alcohol this mixture was separated into pure, crystalline, 2-iodo-5-benzothienone and a gummy residual mixture. Apparently the monomercurial, 2-acetoxymercuri-5-benzothienone, is one component of the "complex." It was observed that when the "complex" was refluxed for several hours in methyl cellosolve solution in the presence of excess mercuric acetate the mercury content was increased to that required by theory for a diacetoxymercuribenzothienone. (8). From this, by cleavage with iodine and potassium iodide, was produced the corresponding diiodide (9) as a clear amber, viscous, gummy oil, identical with the second component of the above mixture, but more nearly pure. Since it has been demonstrated that one of the mercury atoms occupies the alpha or 2 position, the number of possible structures for the dimercurial or analogous diiodide is limited to five. Whereas the concept of superaromaticity¹⁰ anticipated the location of the first entering substituent, it did not suggest the next most aromatic position of the benzothienone nucleus, that is to say, the location of the second entering group. With almost equal probability it could have been expected that mercuration had occurred in any one of the five different available positions, two of which are ortho, two meta, and one para to the carbonyl group. The benzene analogue, benzophenone, is reputed to mercurate ortho, although the carbonyl group normally directs

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meta. The possibility of para substitution must not be overlooked because mercuration is often at variance with the usual rules of orientation.

It was possible to synthesize independently three of the five necessary isomeric diiodobenzothienones. The three isomeric iodobenzoyl chlorides were condensed with thiophene by means of the Friedel-Crafts reaction. The three monoiodobenzothienones (15, 20, 23) thus obtained were mercurated (16, 21, 24) by fusion with mercuric acetate yielding monomercurials only. From these by cleavage with iodine and potassium iodide were produced the three isomeric diiodides (17, 22, 25). It is worthy of note that in each instance the presence of iodine on the benzene nucleus prevented the formation of any complex mercurials or dimercurials as in the case of benzothienone, mercuration occurring in the 2 position exclusively. This is suggestive that in the case of benzothienone the second atom of mercury enters the benzene nucleus and that one of the three diiodides would prove to be identical with the product obtained from the dimercurial. The meta and para isomers are well defined crystalline solids. The ortho isomer is a clear amber, viscous, gummy oil, identical in appearance with the one to which we have already referred. In the absence of physical constants comparison of physical properties is meaningless. Hence it was necessary to prepare derivatives.

The synthetic product on nitration (18) yielded a crystalline mononitro derivative, while bromination produced an oil. The product from the mercurial would not nitrate under identical conditions (Note 1), but reacted with bromine to produce a mixture of crystalline substances. It would seem that the two substances are isomeric rather than identical. It was beyond the scope of this investigation to synthesize independently the two lacking diiodides.

NOTE 1.

On one occasion a trace of a crystalline nitro compound melting at 168° C. was isolated. This was shown to be the nitro derivative of 2-iodo-5-benzothienone (19) which was present as an impurity.

At this point the line of attack was shifted from iodo to bromo derivatives. A check of the literature revealed that 2,3-dibromo-5-benzothienone had been synthesized by Steinkopf¹¹ from 2,3-dibromothiophene and benzoyl chloride, and also by direct bromination of benzothienone. It is a crystalline solid melting at 80° C.

On account of the great tendency for bromine to substitute in the thiophene nucleus, it was necessary to determine the conditions under which it could be used safely as a cleavage agent. A sample of 2-chloromercuri-5-benzothienone was

cleaved with the calculated amount of bromine in a solution containing three molar proportions of potassium bromide. 2-Bromo-5-benzothienone (7) formed quantitatively. The amounts of bromine and potassium bromide were doubled and yet only the monobromide formed. Obviously such a solution could be used safely. A sample of benzothienone was treated with excess bromine in chloroform solution. Under these conditions monobromination occurred, yielding 2-bromo-5-benzothienone identical with the product from the mercurial. The product from both sources, alone or mixed, melts at 76° C. Its physical constants have not yet appeared in the literature. Treatment of the monobromide with liquid bromine without a solvent gave rise to a dibromide (10) melting at 80° C. which was identical with Steinkopf's¹¹ 2,3-dibromo-5-benzothienone.

Cleavage of the dimercurial with bromine and potassium bromide under the conditions discussed above produced a dibromide (10) melting at 80° C. Admixture with Steinkopf's dibromide caused no depression of the melting point.

Thus it has been shown that the dimercurial is 2,3-diacetoxymercuri-5-benzothienone. Furthermore the complex mercurial has a molar proportion of 2-acetoxymercuri-5-benzothienone and of 2,3-diacetoxymercuri-5-benzothienone.

The gummy oil obtained from the dimercurial by cleavage with iodine and potassium iodide is 2,3-diiodo-5-benzothienone. Since this fails to undergo nitration it follows reasonably but not rigorously that the nitration product of the isomeric gummy oil, 2-iodo-5-o-iodobenzothienone, is 2-iodo-3-nitro-5-o-iodobenzothienone.

Finally, the superaromaticity of the beta or 3 position of alpha substituted benzothienones has been established by nitration, bromination, and mercuriation reactions.

In the search for ways and means to purify 2-acetoxymercuri-5-benzothienone it was observed that it was converted into the corresponding chloride (5) by addition of calcium chloride to the acetone solution of the mercurial. The chloride is practically insoluble in most organic solvents but recrystallizes readily from ethyl cellosolve. This suggested the use of ethyl cellosolve as a reaction medium. Instead of using the customary mercuric chloride buffered with sodium acetate, it was more convenient to buffer with mercuric acetate and use a correspondingly smaller amount of mercuric chloride. A mixture of the ketone with the mercury salts was refluxed for about an hour in ethyl cellosolve solution. The yield of mercurial was 40% of the calculated amount. Repeated use of the same sample of solvent built up a considerable concentration of acetic acid. Since this did not affect the yields appreciably,

glacial acetic acid was substituted and the reaction carried out according to the equation



The yield was practically quantitative. This mercurial was used in the preparation of arsenicals.

B. Arsenation of Benzothienone

Some of the usual methods of arsenation were considered briefly in the introduction. The arsenicals of benzothienone were prepared from 2-chloromercuri-5-benzothienone by action of arsenic trichloride. This was the method which Finzi and his coworkers have applied successfully to the mercurials of thiophene and of the positively substituted thiophenes. It appears that the presence of a negative substituent does not seriously affect the reactivity of the mercurial.

First attempts to carry out the reaction were made using arsenic trichloride in benzene and in xylene solution. This procedure had been found to work well with certain furan mercurials. However, in the case of 2-chloromercuri-5-benzothienone there was no evidence of reaction even after prolonged heating at the reflux temperature. In the absence of a solvent, arsenic trichloride was found to react rapidly at moderate temperatures. At 50-70° C. the reaction was complete within a few minutes and the yield of arsenicals was quantitative as calculated from the amount of mercuric chloride precipitated. Presumably all three of the arsines were formed but only the dichloroarsine and the tertiary arsine have been isolated. Due to the large excess of arsenic trichloride used the dichloroarsine (11) was the predominant product. The tertiary arsine was isolated by virtue of its being an alkali insoluble residue so that even very small amounts were easily detected. The diarylchloroarsine was never present in sufficiently large amounts to be separated from the dichloroarsine by fractional crystallization.

These negatively substituted thiophene arsenicals stand intermediate between benzene arsenicals and furan arsenicals in the strength of the carbon-arsenic bond. Scission of arsenic from 5-benzothienyl-2-dichloroarsine is easily accomplished by dilute mineral acids. Unlike the α furan arsenicals this carbon-arsenic bond is sufficiently stable to permit hydrolysis to the corresponding arsineoxide (12) and oxidation to the arsonic acid (13). The arsonic acid loses a molecule of water at 140° C. (14).

C. Mercuration of Acetothienone

On account of the toxicity of the unsubstituted benzene nucleus it was desirable to consider the possibility of the

preparation of an arsonated aliphatic thiophene ketone. 2-Iodo-5-acetothienone was treated with arsenic trichloride and sodium in xylene solution. Deep-seated decomposition occurred at the melting point of sodium. No arsenicals were isolated.

As in the case of benzothienone, mercurials of acetothienone were hitherto unknown with the exception of the double compound with mercuric chloride reported by Volhard.⁹

The action of mercuric chloride and mercuric acetate, singly or in combination, on acetothienone and 2-iodo-5-acetothienone under widely varying conditions failed to produce adequate yields of a monomercorial. In most cases insoluble, powdery precipitates were obtained, which were shown by analytical or chemical evidence to be dimercurials. In general the structures have not been established. The conditions employed were fusion with mercuric acetate, refluxing with a mixture of mercuric acetate and mercuric chloride in glacial acetic acid or ethylene glycol diethyl ether and reaction with a buffered alcoholic solution of mercuric chloride either at room temperature or at the boiling point of ethyl alcohol.

It has been shown that in the buffered alcoholic solution (30, 33) mercuration occurred by replacement of two of the alpha hydrogens of the side chain. When the mercurials thus obtained from acetothienone and 2-iodo-5-acetothienone were cleaved with iodine and potassium iodide, ω -diiodoacetothienone (31) and 2-iodo-5- ω -diiodoacetothienone (34) were formed. The respective structures were established by hydrolysis with 5 N alkali which yielded 5-thiophenic acid and 2-iodo-5-thiophenic acid. The other product, methylenediiodide, was not isolated but the characteristic odor gave ample indication of its presence.

Mercuration of the side chain leads to mercurials of little interest. Due to enolization, the hydrogen atoms adjacent to a carbonyl group are very reactive and the reactivity is roughly in inverse proportion to the acidity of the medium. However, there is a limit beyond which increase of the hydrogen ion concentration completely inhibits mercuration. In glacial acetic acid enolization is sufficiently repressed for the alpha hydrogen of the thiophene nucleus to react competitively with the alpha hydrogens of the side chain. By use of this solvent, a mixture of mercurials was formed from acetothienone. A methyl cello-solve soluble fraction containing considerable 2-chloromercuri-5-acetothienone (28) was extracted from the mixture. The presence of this mercurial was demonstrated by the fact that cleavage with iodine and potassium iodide yielded a mixture of iodoacetothienones from which 2-iodo-5-acetothienone was isolated by steam distillation.

A second method of repressing enolization depends on the

use of a solvent with a low dielectric constant. The diethyl ether of ethylene glycol permitted mercuration (29) but unfortunately dimercuration occurred. The structure of this dimercurial has not been established. Its iodine cleavage product is an oil comparable to 2,3-diiodo-5-benzothienone and may be the acetothienone analogue.

It seems likely that in order to mercurate an aliphatic thiophene ketone in the 2 position the alpha hydrogens of the side chain will need to be protected.

D. Mercuration of Nitrothiophene

It was formerly believed by some investigators^{7,8} that nitrothiophene could not be mercurated. However, nitrothiophene has been found to react with a mixture of mercuric chloride and mercuric acetate. In glacial acetic acid a dimercurial (35) was formed. When ethyl alcohol was used as the solvent a monomercurial (36) resulted. These reactions were carried out at the respective boiling points. The structures were not proved but by analogy with benzothienone it seems reasonable to suppose that mercuration has occurred in the 2,3 and 2 positions respectively.

E. The Friedel-Crafts Synthesis

The substitution of tin tetrachloride for aluminum chloride in the classical Friedel-Crafts synthesis of thiophene ketones by Stadnikov and his coworkers^{12,13} increased the yield from approximately 50% to about 90%. The original investigators described the acetylation and benzoxylation of thiophene by the use of acetyl chloride and benzoyl chloride.

The reaction has been indispensable in this investigation, both from the standpoint of the preparation of starting materials and of reference compounds.

It has been of interest to note some of the limitations of the reaction. Iodothiophene can be acetylated (32) and benzoxyated (6) in the available alpha position. It is advantageous to substitute acetic anhydride for acetyl chloride in this acetylation. The yields are on the order of 75% of the theoretical. Substituted benzoyl chlorides react normally with thiophene. In the case of the three isomeric iodobenzoyl chlorides (15, 20, 23) the yields of ketone are excellent. Since iodine is an ortho-para directing group the meta iodobenzoyl chloride reacts a bit sluggishly.

Ethylchloroacetate, chloroacetic acid and benzenesulfonyl chloride do not react with thiophene in the presence of tin tetrachloride, in benzene solution at room temperature.

EXPERIMENTAL

1. Thiophene

The general procedure outlined in Org. Syn.¹⁴ for the reduction of sodium succinate with phosphorous trisulfide was followed with excellent results. Two modifications were introduced; (a) the reaction mixture was diluted with an equal weight of fine dry sand; (b) the phosphorous trisulfide was reduced to a suitable state of subdivision by use of a kitchen sized food grinder.

The yield of product boiling at 82.5-84.5° C. was 46% of the theoretical on 14 runs. The literature reports 25-30%.

2. Benzothienone^{12,13}

To 67.2 g. (0.8 mol) of thiophene in 700 cc. dry benzene was added 112.4 g. (0.8 mol) of benzoyl chloride. The mechanically stirred mixture was cooled (Note 1) with tap water during the dropwise addition of 208.4 g. of tin tetrachloride. After addition was completed the mixture was allowed to come to room temperature for several hours and then left in the refrigerator over night. Water was added to decompose the crystalline addition product. The benzene layer containing the ketone was washed several times to insure the complete removal of tin tetrachloride and then steam distilled to remove the benzene. The residue consisted of crude ketone, which, after two crystallizations from alcohol melted at 55° C.; the yield, 90% of the theoretical.

NOTE 1.

If the temperature was allowed to rise much above room temperature, some tarring occurred. Cooling with ice retarded the reaction unnecessarily.

3. Sesquiacetoxymercuribenzothienone

“The Complex Mercurial”

A mixture of 18.8 g. (0.1 mol) of benzothienone with 48 g. (0.15 mol) of mercuric acetate was heated on the steam bath for 10 hours. The crude product was washed with acetone to remove acetic acid and some gummy impurities and then recrystallized from glacial acetic acid. This mercurial is soluble in the cellosolves but difficultly soluble in the other organic solvents. It crystallizes from glacial acetic acid in lenticular plates which melt sharply at 202° C. The yield under these conditions was about 90%. The substance formed over wide ranges of temperature and concentrations. In fact, it was not possible to modify the procedure to obtain good yields of 2-acetoxymercuri-5-benzothienone.

Analysis: Subs., 0.1969, 0.2952 g.; BaSO₄, 0.0815, 0.1220 g. Subs., 0.0905, 0.0831 g.; HgS, 0.0551, 0.0503 g. Calcd. for C₂₅H₂₂O₃S₂Hg₂: S, 5.57%; Hg, 52.24%. Found: S, 5.69, 5.68%; Hg, 52.49, 52.19%.

4. 2-Acetoxymercuri-5-Benzothienone

This substance was present in the acetone washings from the preceding preparation and could be recovered by evaporation. Larger amounts were formed when molecular proportions of benzothienone and mercuric acetate were fused on the oil bath for 20 minutes at 150°. The melt thus obtained was cooled, extracted with cold acetone to remove gummy impurities and then extracted repeatedly with hot acetone. Dilution of the hot acetone extracts with water precipitated the mercurial. After recrystallization from methyl cellosolve, it melts without darkening but with apparent decomposition at 187° C.

Analysis: Subs., 0.1048, 0.1029 g.; HgS, 0.0544, 0.0538 g. Calcd. for C₁₃H₁₀O₃SHg: Hg, 44.90%. Found: 44.76, 45.08%.

5. 2-Chloromercuri-5-Benzothienone

To a solution of 9.5 g. (0.05 mol) of benzothienone in 100 cc. of glacial acetic acid (Note 1) was added 8 g. (0.025 mol) of mercuric acetate and 6.8 g. (0.025 mol) of mercuric chloride. The mixture was refluxed gently. Within a few minutes a precipitate began to form and after one hour the reaction was complete. The precipitate was removed, dried, and recrystallized from ethyl cellosolve. By using the same samples of solvent repeatedly nearly quantitative yields are obtained of a product that is sufficiently pure for other syntheses. This mercurial crystallizes in bronze leaflets from ethyl cellosolve. It is very soluble in methyl cellosolve, practically insoluble in acetone, alcohol, acetic acid, benzene and the usual organic solvents. It melts sharply at 242°.

Analysis: Subs., 0.0888, 0.1117 g.; HgS, 0.0487, 0.0620 g. Calcd. for C₁₁H₇O₃ClHg: Hg, 47.41%. Found: 47.29, 47.85%.

NOTE 1.

Ethyl cellosolve may be used as the reaction medium but the yield drops to about 40%.

6. 2-Iodo-5-Benzothienone. (Note 1)

A. To a suspension of 4.23 g. (0.01 mol) 2-chloromercuri-5-benzothienone in 10 cc. of water was added 10 cc. of a normal (Note 2) iodine-potassium iodide solution. The mixture was warmed gently until the iodine color had disappeared. After cooling, the supernatant solution of potassium iodomercurate was removed by decantation. The residue was washed with water and then boiled with dilute potassium iodide solution to

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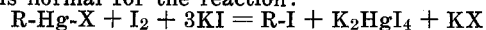
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insure complete removal of mercury salts. (Note 3.) The crude product was recrystallized from 95% ethanol. It crystallizes in long yellow needles melting at 129.5-130°. The yield is almost quantitative.

NOTES

1. In sections 7, 9, 10, 17, 22, 25, 31, and 34 this same general procedure was followed and will not be repeated in detail.

2. The iodine-potassium iodide solution contained one mol of iodine and three mols of potassium iodide per liter. A solution prepared in this way is normal for the reaction:



3. Many investigators have used alcoholic solutions of iodine for the cleavage of mercurials and have encountered difficulty in separating mercuric iodide from the organic iodine compounds due to similar solubilities in organic solvents. This procedure accomplishes cleavage and separation in a single operation.

B. Friedel-Crafts Synthesis.

To a solution of 10.5 g. (0.05 mol) of iodothiophene and 7 g. (0.05 mol) of benzoyl chloride in 40 cc. of dry benzene was added dropwise with stirring 13 g. (0.05 mol) of tin tetrachloride. A dark colored crystalline addition product separated slowly and after two hours at room temperature was removed by filtration and decomposed with water. The ketone was extracted with ether, decolorized with charcoal and evaporated to dryness. It was purified by crystallization from ethanol. The melting point, alone and mixed with the product from the mercurial, is 129.5-130°; yield, 60% of the theoretical.

Analysis: Subs., 0.2103, 0.2238 g.; AgI, 0.1565, 0.1666 g. Calcd. for $\text{C}_{11}\text{H}_7\text{OSI}$: I, 40.41%. Found: 40.23, 40.24%.

7. 2-Bromo-5-Benzothienone

A. This substance was prepared by cleavage of 2-chloro-mercuri-5-benzothienone with a normal bromine-potassium bromide solution by the procedure described in section 6 A. When prepared in this way it has a brownish color which is removed with difficulty by repeated recrystallizations from ethanol. The yield is practically quantitative; m.p. 76°.

B. An alternative method of preparation is the direct bromination of benzothienone.

To a solution of 18.8 g. (0.1 mol) of benzothienone in 50 cc. of chloroform was added 16 g. (0.1 mol) of bromine. The mixture was left at room temperature for one hour and then boiled under reflux for 15-20 minutes. The solution was shaken with sodium thiosulfate and then with dilute alkali. After removal of the solvent chloroform by steam distillation the crude product was purified by recrystallization from 95% ethanol. It crystallizes in cream colored elongated parallelograms. The melting point, alone and mixed with the product

from the mercurial, is 76°. The yield is 65-70% of the theoretical.

Analysis: Subs., 0.2235, 0.2197 g.; AgBr, 0.1579, 0.1548 g.
Calcd. for $C_{11}H_7OSBr$: Br, 29.93%. Found: 30.06, 29.98%.

8. 2,3-Diacetoxymercuri-5-Benzothienone

A mixture of 11.5 g. (0.01 mol) of the "complex" mercurial with 6.4 g. (0.02 mol) of mercuric acetate (Note 1) and 50 cc. of methyl cellosolve was refluxed for three hours. The solution was filtered hot and refrigerated over night. The precipitate was removed, washed with hot water and recrystallized from methyl cellosolve. It crystallizes in indefinitely shaped micaeous plates which do not melt below 300° C. The yield is about 60% of the theoretical.

Analysis: Subs., 0.0808, 0.0897 g.; HgS, 0.0529, 0.0587 g.
Calcd. for $C_{15}H_{12}O_5SHg_2$: Hg, 56.88%. Found: 56.45, 56.42%.

NOTE 1.

Double the theoretically required amount of mercuric acetate was used. Some of the excess was reduced to free mercury.

9. 2,3-Diiodo-5-Benzothienone

This was obtained from the preceding mercurial by cleavage with iodine and potassium iodide. A mixture of 14 g. (0.02 mol) of the mercurial with 20 cc. of the normal iodine-potassium iodide solution was diluted with 20 cc. of water and heated until the color of iodine had disappeared. After thorough washing, the residue was dissolved in hot alcohol and filtered repeatedly through a charcoal mat. On cooling, the ketone separated as a viscous, gummy oil (Note 1). It was dried at 140° C. Since additional purification was not possible the purity of the ketone depended on the purity of the mercurial from which it was obtained.

Analysis: Subs., 0.1791, 0.2302 g.; AgI, 0.1792, 0.2302 g.
Calcd. for $C_{11}H_6OSI_2$: I, 57.70%. Found: 54.08, 54.03%.

NOTE 1.

The oil is metastable and will persist for months. Crystallization was first induced by spontaneous evaporation of a methyl cellosolve solution. By seeding and frequent stirring the oil can be made to crystallize more or less completely within a week or two. The crystals melt in the range of 80-90°C. On account of the slowness with which equilibrium is reached and the questionable purity of the sample the melting point could not be determined more accurately.

10. 2,3-Dibromo-5-Benzothienone

A. This was obtained from the corresponding mercurial by use of a normal bromine-potassium bromide solution in exactly the same manner as the iodine analogue described in the preceding section. The yield is practically quantitative. It

happens to be a solid which crystallizes in cream colored plates melting at 80° C.

B. Steinkopf¹¹ prepared this compound by direct bromination of benzothienone. It was more conveniently prepared by direct bromination of 2-bromo-5-benzothienone.

Five and four tenths g. (0.02 mol) of 2-bromo-5-benzothienone in a small flask was barely covered with liquid bromine. The mixture was left in the fume hood for 20 minutes at room temperature. The crude product, after washing with sodium thiosulfate solution, was recrystallized from ethanol. It melts at 80° C.; yield, about 70% of the theoretical. Since a mixed melting point with the product from the mercurial shows no depression, these are proved to be identical.

11. 5-Benzothienyl-2-Dichloroarsine

To 8.4 g. (0.02 mol) of 2-chloromercuri-5-benzothienone in a small flask was added 20 cc. (0.24 mol) of arsenic trichloride. The mixture was warmed gently for 2-3 minutes and then cooled. After removal of the precipitated mercuric chloride the excess of arsenic trichloride was distilled off on the water bath at 15 mm. The residue was dissolved in hot carbon tetrachloride and on cooling the dichloroarsine crystallized in greenish yellow prisms melting at 113° C.

Analysis: Subs., 0.1268, 0.1270 g.; AgCl, 0.1075, 0.1077 g. Calcd. for $C_{11}H_7OSAsCl_2$: Cl, 21.30%. Found: 20.97, 20.97%.

12. 5-Benzothienyl-2-Arsineoxide

Eight tenths g. of 5-benzothienyl-2-dichloroarsine was dissolved in 2 N sodium hydroxide, filtered through a charcoal mat and carefully acidified with dilute hydrochloric acid. The precipitate was repeatedly washed by decantation, filtered, washed with methyl alcohol and acetone and dried at 140° C. It is a white powder which does not melt or decompose below 300° C. The yield was 0.52 g. or 78% of the theoretical.

Analysis: Subs., 0.1244, 0.1244 g.; 17.90, 17.87 cc. of bromate solution. (1 cc. = 0.001866 g. As) Calcd. for $C_{11}H_7O_2SAs$: As, 26.94%. Found: 26.85, 26.81%.

13. 5-Benzothienyl-2-Arsonic Acid

To a solution of 3.33 g. (0.01 mol) of 5-benzothienyl-2-dichloroarsine in 2 N sodium hydroxide was added an excess of 3% hydrogen peroxide. After 15-20 minutes the solution was acidified with dilute hydrochloric acid. The precipitated acid was recrystallized once from ethyl carbitol and several times from boiling water. It crystallizes in large lustrous pearly flakes which melt at 360° C. and immediately decompose. It is practically insoluble in all available organic solvents

except ethyl carbitol, in which it is extremely soluble. It loses water readily.

Analysis: Subs., 0.1244, 0.1244 g.; 16.08, 16.14 cc. bromate solution (1 cc. = 0.001866 g. As). Calcd. for $C_{11}H_9O_4SAs$: As, 24.01%. Found: 24.12, 24.21%.

14. 5-Benzothienyl-2-Arsenic Oxide

This was prepared by dehydration of the arsonic acid at 140° C.

Dehydration: Subs., 0.2032, 0.2032 g.; loss of H_2O , 0.0121, 0.0120 g. Calcd. for $C_{11}H_7O_3SAs.H_2O$: H_2O , 5.77%. Found: 5.95, 5.91%.

15. o-Iodobenzothienone

This substance was prepared from o-iodobenzoyl chloride and thiophene by the procedure described in section 2. It crystallizes from dilute alcohol (75-85%) in long cream colored needles melting at 61°; yield, 89% of the theoretical.

Analysis: Subs., 0.1077, 1049 g.; AgI, 0.0805, 0.0780 g. Calcd. for $C_{11}H_7OSI$: I, 40.41%. Found: 40.40, 40.19%.

16. 2-Chloromercuri-5-o-Iodobenzothienone

An intimate mixture of 12.4 g. (0.04 mol) of o-iodobenzothienone with 12.8 g. (0.04) of mercuric acetate was heated on an oil bath at 125° for an hour. The gummy mass, thus obtained, was dissolved in acetone and the mercurial converted to the chloride salt by addition of excess of a concentrated aqueous solution of calcium chloride. This mixture was poured into water to complete precipitation of the mercurial and at the same time to remove calcium acetate. The crude product was dissolved in hot methyl cellosolve from which it crystallized in fine microscopic needles melting at 225° C.; yield, 70% of the theoretical.

Analysis: Subs., 0.1173, 0.0887 g.; HgS, 0.0509 0.0381 g. Calcd. for $C_{11}H_6OSiClHg$: Hg, 36.53%. Found: 37.41, 37.04%.

17. 2-Iodo-5-o-Iodobenzothienone

This was prepared by cleavage of the preceding mercurial in the usual manner with iodine and potassium iodide. It is a clear amber, viscous, gummy oil.

Analysis: Subs., 0.1356, 0.1113 g.; AgI, 0.1428, 0.1164 g. Calcd. for $C_{11}H_6OSI_2$: I, 57.70%. Found: 56.93, 56.53%.

18. 2-Iodo-3-Nitro-5-o-Iodobenzothienone

To an ice cold solution of 2-iodo-5-o-iodobenzothienone in concentrated sulfuric acid was slowly added an excess of a

mixture of concentrated nitric acid (sp. g. 1.4) and concentrated sulfuric acid. The mixture was shaken occasionally during fifteen minutes and then poured over cracked ice. Purification was accomplished by recrystallization from methyl alcohol. The purified product crystallizes in bronze prisms which melt at 138-9°.

Analysis: Subs., 0.2099, 0.2202 g.; AgI, 0.2046, 0.2136 g.
Calcd. for $C_{11}H_5O_3SNI_2$: 52.35% I. Found: 52.69, 52.43%.

19. 2-Iodo-3-Nitro-5-Benzothienone

This was made for use as a reference compound by nitration of 2-iodo-5-benzothienone. The reaction was carried out by the procedure described in the preceding section. This nitro compound crystallizes from methyl alcohol in clusters of yellow needles which melt at 168° C.

Analysis: Subs., 0.1169, 0.1222 g.; AgI, 0.0764, 0.0794 g.
Calcd. for $C_{11}H_6O_3SNI$: I, 35.35%. Found: 35.33, 35.12%

20. m-Iodobenzothienone

This was prepared with good yield from m-iodobenzoyl chloride and thiophene by the Friedel-Crafts reaction. It crystallizes from ethanol in glistening leaflets which melt at 48° C.; yield, 75% of the theoretical.

Analysis: Subs., 0.1146, 0.1130 g.; AgI, 0.0860, 0.0850.
Calcd. for $C_{11}H_7OSI$: I, 40.41%. Found: 40.56, 40.66%.

21. 2-Chloromercuri-5-m-Iodobenzothienone

The preparation by fusion of m-iodobenzothienone with mercuric acetate was exactly analogous to that of the ortho isomer. (16). This mercurial crystallizes from methyl cellosolve in microscopic needles which melt at 252°.

Analysis: Subs., 0.1045, 0.0996 g.; HgS, 0.0445, 0.0427 g.
Calcd. for $C_{11}H_6OSIClHg$: Hg, 36.53%. Found: 36.72, 36.96%.

22. 2-Iodo-5-m-Iodobenzothienone

This was obtained by cleavage of the preceding mercurial with iodine and potassium iodide. It crystallizes from ethanol in clusters of yellowish needles which melt at 109° C. The yield is nearly quantitative.

Analysis: Subs., 0.2128, 0.1959 g.; AgI, 0.2260, 0.2084 g.
Calcd. for $C_{11}H_6OSI_2$: I, 57.70%. Found: 57.41, 57.50%.

23. p-Iodobenzothienone

This was prepared with very good yield from p-iodobenzoyl chloride and thiophene by the Friedel-Crafts reaction. It

crystallizes from 95% ethanol in yellow needles which melt at 106.5° C.

Analysis: Subs., 0.0709, 0.0831 g.; AgI, 0.0529, 0.0620 g. Calcd. for $C_{11}H_7OSI$: I, 40.41%. Found: 40.33, 40.33%.

24. 2-Chloromercuri-5-p-Iodobenzothienone

This was produced by action of a mixture of mercuric chloride and mercuric acetate on p-iodobenzothienone in glacial acetic acid solution. The same procedure was followed as in section 5. The yield did not exceed 50% of the theoretical. This substance crystallizes from diacetone alcohol in microscopic needles which melt at 285° C. with decomposition.

Analysis: Subs., 0.0796, 0.0856 g.; HgS, 0.0352, 0.0378 g. Calcd. for $C_{11}H_6OSiClHg$: Hg, 36.53%. Found: 38.22, 38.08%.

25. 2-Iodo-5-p-Iodobenzothienone

Cleavage of the preceding mercurial gave almost quantitative yields of this substance. It crystallizes from ethanol in yellow needles melting at 153° C.

Analysis: Subs., 0.0404, 0.0451 g.; AgI, 0.0432, 0.0482 g. Calcd. for $C_{11}H_6OSI_2$: I, 57.70%. Found: 57.80, 57.77%.

26. Acetothienone^{12,13}

To a solution of 16.8 g. (0.2 mol) of thiophene and 15.6 g. (0.2 mol) of acetyl chloride in 170 cc. of benzene was added dropwise with stirring 52 g. (0.2 mol) of tin tetrachloride. The mixture was cooled with tap water during the addition. At the end of two hours the crystalline addition product was decomposed with water. After removal of benzene by steam distillation, the ketone was steam distilled, dried over calcium chloride and redistilled. A product boiling at 213-214° C. was obtained in 90% yield.

27. ??-Diacetoxymmercuri-5-Acetothienone

Four g. (0.032 mol) of acetothienone was fused with 20 g. (0.064 mol) of mercuric acetate at 150° C. for 30 minutes. Extraction with acetone left a yellowish brown powder; yield, 80% of the theoretical.

Analysis: Subs., 0.0622, 0.0620 g.; HgS, 0.0447, 0.0446 g. Calcd. for $C_{10}H_{10}O_5SHg_2$: Hg, 62.37%. Found: 61.97, 62.02%.

28. 2-Chloromercuri-5-Acetothienone

A solution of 6.3 g. (0.05 mol) of acetothienone, 6.8 g. (0.025 mol) of mercuric chloride and 8 g. (0.025 mol) of mercuric acetate in 50 cc. of glacial acetic acid was refluxed for 30 minutes. Considerable insoluble precipitate formed and

was filtered off. On standing over night more precipitate formed. This was partially soluble in methyl cellosolve. The soluble part was recrystallized from a mixture of methyl cellosolve and ethanol. It was probably a mixture of monomercurials. Cleavage with iodine and potassium iodide yielded some 2-iodo-5-acetothienone, which was steam distilled from the mixture and identified by means of its melting point and a mixed melting point with an authentic sample.

Analysis: Subs., 0.1170 g.; HgS, 0.0784 g. Calcd. for $C_6H_5OSClHg$: Hg, 55.54%. Found: 57.78%.

29. η,η -Dichloromercuri-5-Acetothienone

A solution of 3.15 g. (0.025 mol) of acetothienone, 6.8 g. (0.025 mol) of mercuric chloride and 8 g. (0.025 mol) of mercuric acetate in 30 cc. of ethylene glycol diethyl ether was refluxed for two hours. The mercurial separated as an insoluble precipitate; yield, 85% of the theoretical. Cleavage with iodine and potassium iodide gave an amber oil of unknown structure. The ϕ -diiodide (Sec 31) is a crystalline solid.

Analysis: Subs., 0.1257 g.; HgS, 0.1019 g. Calcd. for $C_6H_4OSCl_2Hg_2$: Hg, 67.29%. Found: 67.34%.

30. ϕ -Dichloromercuriacetothienone

A white, insoluble precipitate formed when a solution containing 6.3 g. (0.05 mol) of acetothienone, 68 g. (0.25 mol) of mercuric chloride and 41 g. (0.5 mol) of sodium acetate in 500 cc. of ethanol was left at room temperature for six weeks. The crude product weighed 57 g. Purification was not possible. The mercury content was approximately that required for a trichloromercuri derivative. It was shown by cleavage with iodine and potassium iodide that there were only two carbon-mercury linkages.

31. ϕ -Diiodoacetothienone

This was obtained from the foregoing mercurial by cleavage with iodine and potassium iodide. It crystallizes from ethanol in yellow prisms which melt at 88-89° C. The substance is rather unstable and eventually decomposes.

Analysis: Subs., 0.1111, 0.1751 g.; AgI, 0.1387, 0.2188 g. Calcd. for $C_6H_4OSI_2$: I, 67.17%. Found: 67.48, 67.54%.

32. 2-Iodo-5-Acetothienone

This was prepared by the Friedel-Crafts reaction. To a solution of 10.5 g. (0.05 mol) of iodothiophene and 6 g. (0.05 mol) of acetic anhydride in 22 cc. of benzene was added dropwise 13 g. (0.05 mol) of tin tetrachloride diluted with 8 cc. of

benzene. The mixture was stirred and cooled during the addition. After standing over night at room temperature, ice was added to decompose the addition complex. The mixture was neutralized with 60 cc. of 5 N sodium hydroxide and steam distilled. The yield was 9.5 g. or 75% of the theoretical. The product melts at 129° C., in agreement with the accepted melting point.

33. 2-Iodo-5- ω -Dichloromercuriacetothienone

Mercuration of 2-iodo-5-acetothienone in a buffered alcoholic solution was carried out by the procedure described in section 30. The mercurial is nearly white when prepared in the dark but turns yellow when exposed to the light. It decomposes at 246° C. The mercury content is approximately that required by theory for a trichloromercuri derivative. It has been shown by cleavage with iodine and potassium iodide that there are only two carbon-mercury linkages.

34. 2-Iodo-5- ω -Diiodoacetothienone

This was prepared by cleavage of the preceding mercurial with iodine and potassium iodide. It crystallizes from ethanol in yellow brown prisms which melt at 132-3° C. It is unstable and slowly decomposes on standing.

Analysis: Subs., 0.1761, 0.2147 g.; AgI, 0.2434, 0.2960 g. Calcd. for $C_6H_3OSI_3$: I, 75.57%. Found: 74.71, 74.53%.

35. ??-Dichloromercuri-5-Nitrothiophene

A solution of 2.6 g. (0.02 mol) of nitrothiophene, 3.2 g. (0.01 mol) of mercuric acetate and 2.7 g. (0.01 mol) of mercuric chloride in 30 cc. of glacial acetic acid was refluxed for two hours. A yellow brown precipitate formed which darkened on exposure to light.

Analysis: Subs., 0.0633 g.; HgS, 0.0495 g. Calcd. for $C_4H_2SNCl_2Hg_2$: Hg, 66.94%. Found: 67.43%.

36. ?-Chloromercuri-5-Nitrothiophene

A solution of 6.5 g. (0.05 mol) of nitrothiophene, 8 g. (0.025 mol) of mercuric acetate and 6.9 g. (0.025 mol) of mercuric chloride in 100 cc. of ethanol was refluxed for two hours. The solution was filtered hot and diluted with water. After standing over night the crystalline precipitate was filtered off and extracted with diethyl ether to remove the unchanged nitrothiophene. Yield, 25%.

Analysis: Subs., 0.0924 g.; HgS, 0.0595 g. Calcd. for $C_4H_2O_2SNClHg$: Hg, 55.08%. Found: 55.52%.

ANALYTICAL

Arsenic was determined by the potentiometric method of Cislak and Hamilton¹⁵.

Ionizable chlorine of the dichloroarsine was determined gravimetrically by precipitating silver chloride from an alcoholic solution of the arsenical.

Nuclear halogen was determined gravimetrically by the Carius¹⁶ method. This gave reasonably good results with all types of halogen compounds. The sample was oxidized with fuming nitric acid in the presence of silver nitrate in a sealed pyrex tube heated to 300° C.

The method of Willard and Thompson¹⁷ gave erratic results with compounds having halogen attached to the thiophene nucleus. In these cases a sublimate formed in the neck of the digestion bask and could not be decomposed with fuming sulfuric acid.

A similar sublimate formed during the digestion of the arsenicals but apparently no arsenic was lost.

Sulfur was determined gravimetrically as barium sulfate by the Carius¹⁸ method.

Mercury was determined as follows: Approximately one-tenth of a gram sample was weighed accurately and transferred to a 125 cc. conical flask. The sides of the flask were washed down with 5 cc. of ethanol and 1 cc. of concentrated hydrobromic acid was added. The mixture was warmed gently until all was in solution, care being taken not to boil the solution too vigorously since mercury salts are volatile with alcohol. The solution was diluted with ethanol and water to a volume of 40 cc., saturated with hydrogen sulfide, and the mercury weighed as mercuric sulfide. The amount of ethanol in the solution varied from 50 to 80%, depending on the solubility of the organic part of the substance being analyzed. This method gave good results only if the mercurial was easily cleaved by hydrobromic acid.

The thermometer used in the determination of melting points was compared with a 200 degree Bureau of Standards thermometer. The correction was found to be negligible.

SUMMARY

The Friedel-Crafts reaction has been used in the preparation of thiophene ketones, some of which were hitherto unknown. Certain limitations of the reaction have been noted.

The mercuration of thiophene ketones has been systematically investigated for the first time. Many new halogen derivatives of benzothienone have been synthesized. These were employed in the elucidation of the structure of a complex mercurial derived from this ketone.

A new modification of an old reaction has been developed whereby benzothienone can be mercurated quickly and almost quantitatively. Interesting derivatives of this little known ketone have been synthesized. Chief among these are the previously inaccessible arsenicals, reasonably stable, well defined substances, which should merit further consideration.

The mercuration of acetothienone is complicated by the presence of the reactive alpha hydrogens of the side chain. Although several mercurials have been obtained, true aromatic substitution has not been achieved successfully.

The fact that two mercurials have been prepared from nitrothiophene is contrary to the observation of an earlier investigator who said, "2-Nitrothiophen mit Sublimat reagieren nicht."

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