mixture of 50% dry ether and 50% petroleum ether (b. p. 60–70°) was added to the mixture and the colorless crystals filtered onto a Büchner funnel having a sintered glass plate, and washed with a mixture of 50% ether and 50% petroleum ether. The product was vacuum dried, wt. 39 g. (73% yield), m. p. 134–136°.[6]

Reaction of (V) with Piperidine and Formaldehyde to Give (IV).—A mixture of 16.5 g. (0.1 mole) of the amide (V), 30 ml. of absolute alcohol and 25 ml. of the stock solution[5] containing approximately 0.1 mole of $C_2H_5OCH_2$-NC_5H_{10} was heated on the steam-bath for two hours without reflux. The remaining solvent was removed by vacuum distillation from a water-bath. On standing in the ice chest overnight the residual mass partially solidified and was readily recrystallized from 30% alcohol to give 16 g. (61% yield) of colorless crystals, m. p. 123–125°, identical with the amide (IV). Further recrystallization did not change the m. p. This product (IV) was soluble in both dilute sodium hydroxide and dilute hydrochloric acid and gave a pale yellow-green color with ferric chloride solution.

A similar experiment using the stock solution[5] containing C_2H_5O-$CH_2N(C_2H_5)_2$ gave a product which would not crystallize, and which gave only an oily hydrochloride.

Summary

p-Hydroxybenzaldehyde and N-(*p*-hydroxybenzyl)-acetamide both readily undergo the Mannich reaction with formaldehyde and secondary amines. The substituted amino methyl group enters the same relative position on the benzene ring in both compounds.

LINCOLN, NEBRASKA RECEIVED JULY 30, 1946

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[6] Helferich, Günther and Winkler, *Ann.*, **508**, 192 (1934).

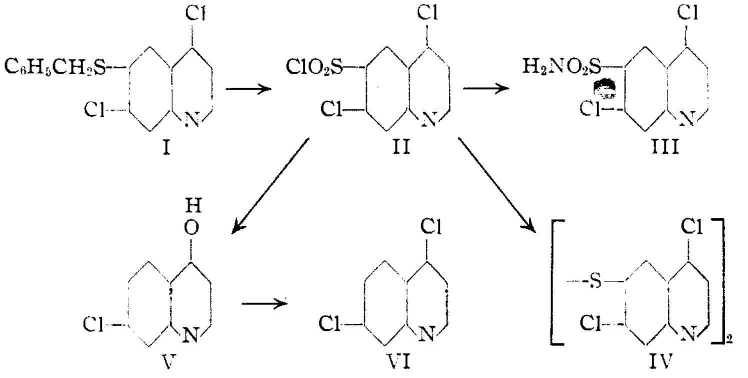
[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NORTHWESTERN UNIVERSITY]

The Cleavage of Organic Sulfides with Chlorine[1]

BY ROBERT H. BAKER, R. M. DODSON[2] AND BYRON RIEGEL

In connection with the antimalarial program a synthesis of 4,7-dichloro-6-quinolinesulfonamide, III, and bis-(4,7-dichloro-6-quinolyl) disulfide, IV, was desired. Attempts to prepare these compounds by means of the ethoxymethylenemalonic ester (EMME) synthesis on bis-(4-amino-2-chlorophenyl) disulfide were unsuccessful.[3] The condensation of EMME and the aminodisulfide and the necessary ring-closure were successfully accomplished, but the decarboxylation of the resulting bis-(3-carboxy-4-hydroxy-7-chloro-6-quinolyl) disulfide could not be effected. Since the EMME synthesis on sulfanilamide was also unsuccessful, any approach analogous to this was excluded. The low temperature sulfonation of 4,7-dichloroquinoline was not attempted because of the fact that the sulfonic acid group enters both 4- and 7-chloroquinoline at the 8 position.[4,5] The high temperature reaction used by Georgievics[6] to prepare 6-quinolinesulfonic acid failed when applied to the dichloroquinoline because excessive decomposition occurred upon heating with sulfuric acid at 300°.

It was finally decided to synthesize 4,7-dichloro-6-benzylthioquinoline, I, by means of the EMME synthesis on 4-benzylthio-3-chloroaniline and then to cleave the sulfide, I, by one of the better known methods. Zincke and Rose[7] have reported the cleavage of 4-methylthio-3-nitrotoluene with chlorine in wet acetic acid with the resulting formation of 3-nitrotoluene-4-sulfonyl chloride. More recently, Lee and Dougherty[8] have cleaved and oxidized dibutyl and dibenzyl sulfides to the corresponding alkylsulfonyl chlorides and alkyl chlorides by the same method.



The oxidative cleavage of 4,7-dichloro-6-benzylthioquinoline, I, with chlorine in acetic acid resulted in the formation of 4,7-dichloro-6-quinolinesulfonyl chloride, II. The sulfonyl chloride was then converted to the desired sulfonamide, III; the over-all yield from I was 67%. The sulfonyl chloride, II, was also reduced by means of stannous chloride and hydrochloric acid to the mercaptan which in turn was oxidized by means of sodium hypoiodite to the desired bis-(4,7-dichloro-6-quinolyl) disulfide, IV.

The structure of 4,7-dichloro-6-benzylthioquinoline had been surmised by analogy with the products of other EMME syntheses.[3] Since the posi-

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[1] Part of the work described in this paper was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and Northwestern University.

[2] National Research Council Predoctoral Fellow, 1946–1947.

[3] B. Riegel, G. R. Lappin, B. H. Adelson, R. I. Jackson, C. J. Albisetti, Jr., R. M. Dodson and R. H. Baker, THIS JOURNAL, **68**, 1264 (1946).

[4] B. Riegel, G. R. Lappin, C. J. Albisetti, Jr., B. H. Adelson, R. M. Dodson, L. G. Ginger and R. H. Baker, *ibid.*, **68**, 1229 (1946).

[5] A. Claus and R. Kayser, *J. prakt. Chem.*, **156**, 270 (1893).

[6] G. Georgievics, *Monatsh.*, **8**, 577 (1888).

[7] Th. Zincke and H. Rose, *Ann.*, **406**, 127 (1914).

[8] S. W. Lee and G. Dougherty, *J. Org. Chem.*, **5**, 81 (1940).

tion of the chlorine atom in the benzenoid ring could be either 5 or 7, it was felt desirable to definitely prove its position. To accomplish this, 4,7-dichloro-6-quinolinesulfonyl chloride was hydrolyzed by means of hydrochloric acid in a sealed tube at 285° to 4-hydroxy-7-chloroquinoline, V, which was then chlorinated to the known 4,7-dichloroquinoline, VI.[9]

In order to further investigate the value of the oxidative cleavage of sulfides to sulfonyl chlorides as a preparative method and in order to throw some light on the mechanism of the cleavage, a series of aryl benzyl sulfides was made. All of the sulfides were prepared by the addition of alcoholic potassium hydroxide to an alcoholic solution of equivalent amounts of benzylthiouronium chloride and the aryl halide. This method of preparation resulted in high yields and avoided the handling of the mercaptan. The results on the preparation of the sulfides are summarized in Table I.

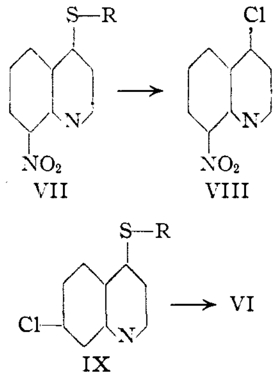
TABLE I

Aryl benzyl sulfide	Formula	Yield, %	M. p., °C. Found	M. p., °C. Reported
4-(8-Nitroquinolyl)-	VII	83	166–168	168–169[14]
4-(7-Chloroquinolyl)-	IX[a]	89	140–141	..
4-Nitrophenyl-	X	79	120–122.5	123[b]
2-Chloro-4-nitrophenyl	XII[c]	81	110–111	..
2,4-Dinitrophenyl	XIV	82	129–130	130[d]

[a] *Anal.* Calcd. for $C_{16}H_{12}ClNS$: N, 4.90. Found: N, 4.90. [b] W. R. Waldron and E. Emmet Reid, THIS JOURNAL, **45**, 2399 (1923). [c] *Anal.* Calcd. for $C_{13}H_{10}ClNO_2S$: N, 5.01. Found: N, 5.35. [d] R. W. Bost, J. O. Turner and R. D. Norton, THIS JOURNAL, **54**, 1985 (1932).

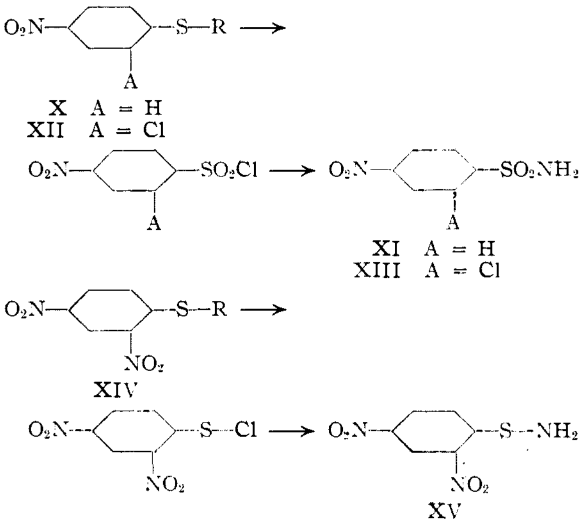
The oxidative cleavage of these sulfides was accomplished by bubbling chlorine into an acetic acid solution of the sulfide containing 2.5% water. The cleavage of 4-benzylthio-8-nitroquinoline, VII, and 4-benzylthio-7-chloroquinoline, IX, resulted in the formation of the corresponding 4-chlorocompounds rather than the expected 4-sulfonyl chlorides.

$R = C_6H_5CH_2—$



VII VIII

IX



X A = H
XII A = Cl

XI A = H
XIII A = Cl

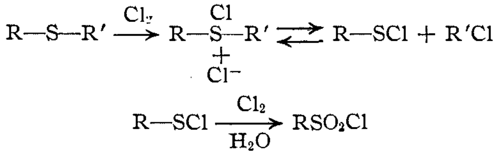
XIV

XV

Results similar to these were obtained by Sprague and Johnson[10] on the cleavage of 2-ethylthio-4-chloro-5-carbethoxypyrimidine in water suspension with chlorine. They obtained ethanesulfonyl chloride and 2,4-dichloro-5-carbethoxypyrimidine as the products. However, the cleavage of 4-benzylthio-7-chloroquinoline appeared to result in the formation of benzyl chloride rather than α-toluenesulfonyl chloride, but this was not definitely established.

4-Benzylthionitrobenzene, X, and 4-benzylthio-3-chloronitrobenzene, XII, were oxidatively cleaved in the expected way to the respective sulfonyl chlorides, which were then converted to the sulfonamides. The over-all yields on these reactions ranged from 70 to 80%. On the other hand, 4-benzylthio-1,3-dinitrobenzene, XIV, was cleaved to 2,4-dinitrobenzenesulfenyl chloride, under the conditions used. Because of the difficulty experienced in the purification of this compound, it was converted to the corresponding sulfenamide, XV, and identified as such.

Lee and Dougherty[8] have shown that the cleavage of the sulfide in this reaction may occur after oxidation to the sulfoxide stage but that it must occur before oxidation to the sulfone stage. In view of the isolation of 2,4-dinitrobenzenesulfenyl chloride from the reaction of 4-benzylthio-1,3-dinitrobenzene, XIV, with chlorine, it appears highly probable that sulfides are first cleaved to the sulfenyl chlorides, then oxidized further. The course of the reaction may be formulated as follows



$$R—S—R' \xrightarrow{Cl_2} R—\underset{\underset{Cl^-}{+}}{\overset{Cl}{S}}—R' \rightleftarrows R—SCl + R'Cl$$

$$R—SCl \xrightarrow[H_2O]{Cl_2} RSO_2Cl$$

This mechanism is further substantiated by the work of Zincke and Rose.[7] They have made a

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[9] C. C. Price, N. J. Leonard and R. H. Reitsema, THIS JOURNAL, **68**, 1256 (1946).

[10] J. M. Sprague and T. B. Johnson, *ibid.*, **57**, 2252 (1935).

thorough study of the action of chlorine on 4-methylthio-3-nitrotoluene in various solvents. In dry carbon tetrachloride the expected chlorosulfonium chloride was first obtained; if the reaction was allowed to proceed further, the sulfide was split, and nitrotolylsulfenyl chloride, along with a small amount of the "disulfoxide," was obtained. If the reaction was carried out in chloroform, the nitrotolylsulfenyl chloride plus a small amount of "disulfoxide" were the products. If wet acetic acid was used as the solvent, the only product was the sulfonyl chloride. However, if the reaction was carried out in wet chloroform, two products were formed, the expected 3-nitrotolyl-4-sulfonyl chloride and methyl 2-chloro-3-nitrotolyl sulfoxide. It is significant here that no chlorinated sulfonyl chloride was obtained. It appears that the sulfonyl chloride and the sulfoxide were formed by different reaction mechanisms and that the sulfoxide was not converted to the sulfonyl chloride under the conditions of this experiment. Zincke has also cleaved 4-ethylthio-3-nitrotoluene and its benzyl analog to the nitrotolylsulfenyl chloride using chlorine in chloroform. The mechanism proposed by Ray and Levine[11] to explain the products of the reaction between an organic sulfide and an alkyl halide is very similar to the one proposed above. They also propose an intermediate sulfonium halide, which can then disproportionate in various ways.

The course that the further oxidation of the sulfenyl chloride follows is, as yet, unknown. Also the factors determining which products are formed on cleavage of an unsymmetrical sulfide are not known. Future work should be able to clarify these problems.

Acknowledgment.—We wish to thank Dr. Norman Kharasch for many useful discussions on the preparation and behavior of sulfenyl halides.

Experimental[12]

Benzyl Aryl Sulfides.—A solution of benzylthiouronium chloride (0.1 mole) and of an aryl chloride (0.1 mole), in which the halide is activated, in 100 ml. of ethanol was heated under reflux on a steam-bath. Then a solution of 14 g. (0.25 mole) of potassium hydroxide in 70 ml. of ethanol was cautiously added through the condenser. An immediate reaction took place, and the benzyl aryl sulfide started to precipitate from the solution. The resulting suspension was heated under reflux for two hours in order to ensure complete reaction. After being cooled to −5°, the suspension was filtered, and the product washed on the filter with two 10-ml. portions of cold alcohol. To free the product from potassium chloride, it was resuspended in 200 ml. of warm water, and the suspension refiltered. The product so obtained was usually pure enough to be used directly in the next experiment. The results of these preparations are summarized in Table I.

4,7-Dichloro-6-quinolinesulfonamide, III.—A suspension of 20.0 g. of 6-benzylthio-4,7-dichloroquinoline,[3] I, in 120 ml. of glacial acetic acid containing 2 ml. of water was cooled in an ice-bath. Chlorine was bubbled into the suspension at such a rate that the temperature of the solution did not at any time exceed 30°. The compound first appeared to go into solution, then most of the compound precipitated from the solution; on continued chlorination, however, all of the solid material dissolved. The resulting clear solution, after standing at room temperature for fifteen minutes, was diluted with five volumes of ice water. The precipitated sulfonyl chloride was filtered from the solution and was washed thoroughly with cold water. The sulfonyl chloride was then suspended in 250 ml. of acetone, and the acetone was saturated with gaseous ammonia. The precipitate was filtered, then suspended in boiling water and refiltered; the sulfonamide was washed on the filter with cold acetone. On dilution of the acetone mother liquors, another crop of sulfonamide was obtained. From this reaction 11.6 g. of 4,7-dichloro-6-quinolinesulfonamide (67% yield) decomposing at *ca.* 250° was obtained. A sample purified by crystallization from ethanol softened, but did not melt or decompose, below 280°.

Anal. Calcd. for $C_9H_6Cl_2N_2O_2S$: N, 10.11. Found: N, 10.42.

4,7-Dichloro-6-quinolinesulfonyl Chloride,[13] II.—A portion of the sulfonyl chloride, prepared as described above, melted after recrystallization from Skellysolve C (petroleum ether, b. p. 85–100°) at 157.5–158.5°.

Anal. Calcd. for $C_9H_4Cl_3NO_2S$: N, 4.73. Found: N, 4.77.

bis-(4,7-Dichloro-6-quinolyl) disulfide, IV.—The sulfonyl chloride, II, prepared from 3 g. of 6-benzylthio-4,7-dichloroquinoline as described above, was dissolved in 20 ml. of a solution of 1:1 glacial acetic acid and concentrated hydrochloric acid. This solution was slowly added to a solution of 8 g. of stannous chloride in 20 ml. of concentrated hydrochloric acid. The solution became warm and deposited yellow crystals. After standing overnight, the suspension was filtered; the crystalline compound was added to 100 ml. of 10% sodium hydroxide and the solution filtered from any undissolved material. To the solution of the sodium mercaptide was added an excess of a solution of sodium hypoiodite. The precipitate that formed was filtered from the solution and crystallized from benzene. From this reaction 0.66 g. (31%) of disulfide, m. p. 236.5–237°, was obtained.

Anal. Calcd. for $C_{18}H_8Cl_4N_2S_2$: N, 6.12. Found: N, 6.18.

Proof of Structure of 4,7-Dichloro-6-quinolinesulfonyl Chloride.[13]—A mixture of 1 g. of 4,7-dichloro-6-quinolinesulfonyl chloride with 20 ml. of 20% hydrochloric acid was heated in a sealed tube for fifteen hours at 285°. The resulting reaction solution was filtered and the filtrate was made alkaline with concd. ammonium hydroxide. Filtration of the suspension yielded 0.42 g. (69%) of 7-chloro-4-quinolinol, m. p. 270–275°. This was converted to 4,7-dichloroquinoline by treatment with phosphorus oxychloride[3] in the usual way. After recrystallization from Skellysolve C, the product melted at 84–85° and did not depress the melting point of an authentic sample of 4,7-dichloroquinoline.[9]

Oxidative Cleavage of the Sulfides.—A suspension of 2 g. of the sulfide in 20 ml. of glacial acetic acid containing 0.5 ml. of water was cooled in an ice-bath. The solution was saturated with chlorine, care being taken that the temperature never exceeded 30°. After standing at room temperature for ten to fifteen minutes, the resulting solution was poured into 60–80 ml. of ice water.

Cleavage of 4-Benzylthio-8-nitroquinoline, VII.—Two grams of 4-benzylthio-8-nitroquinoline was cleaved as described above. The water suspension was filtered, and the product was crystallized from dilute ethanol. From this reaction, 1.08 g. (77%) of 4-chloro-8-nitroquinoline, VIII, m. p. 127–128°, was obtained. A mixed melting point with an authentic sample of 4-chloro-8-nitroquinoline[14] showed no depression.

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[11] F. E. Ray and I. Levine, *J. Org. Chem.*, **2**, 267 (1937).

[12] All melting points were taken on a Fisher–Johns melting point apparatus. Microanalyses by Margaret Ledyard.

[13] We wish to thank L. T. Sherwood, Jr., for carrying out these experiments.

[14] R. H. Baker, C. J. Albisetti, Jr., R. M. Dodson, G. R. Lappin and B. Riegel, This Journal, **68**, 1532 (1946).

Cleavage of 4-Benzylthio-7-chloroquinoline, IX.—Two grams of the sulfide, IX, was cleaved as described above. The major product formed was basic enough to remain in solution in the dilute acid, and only a small amount of benzyl chloride separated. The solution was extracted with two 10-ml. portions of ether to free it from benzyl chloride; it was then made basic to phenolphthalein with dilute sodium hydroxide and the product separated by filtration. From this reaction, 1.19 g. (86%) of 4,7-dichloroquinoline, VI, m. p. 85–86°, was obtained. A mixed melting point with an authentic sample of 4,7-dichloroquinoline[3] showed no depression.

Cleavage of 4-Benzylthionitrobenzene, X.—Two grams of the sulfide, X, was cleaved as before. The sulfonyl chloride was extracted from the aqueous suspension with ether, and the ether solution was washed with water and dilute sodium bicarbonate solution to free it from acid. The ether was then removed under a stream of air, and the residue was shaken periodically for one-half hour with 20 ml. of concd. ammonium hydroxide. The resulting solution, after dilution with ice water, was neutralized with concentrated hydrochloric acid. The product was filtered and thoroughly washed with ice water. From this reaction 1.28 g. (78%) of 4-nitrobenzenesulfonamide, XI, m. p. 178–180°, was obtained. The reported m. p. of the compound is 179–180°.[15]

In another reaction the sulfonyl chloride from 2 g. of the sulfide, X, was filtered from the aqueous suspension and recrystallized from Skellysolve B (b. p. 60–70°). From this reaction, 1.04 g. (58%) of 4-nitrobenzenesulfonyl chloride, m. p. 77.5–78.5°, was obtained. The melting point reported for this compound is 80°.[15]

Cleavage of 4-Benzylthio-3-chloronitrobenzene, XII.—Two grams of the sulfide, XII, was cleaved as described above. The heavy sulfonyl chloride layer was separated from the aqueous layer by means of a separatory funnel then washed once with cold water. The sulfonyl chloride was then shaken for fifteen minutes with five volumes of concentrated ammonium hydroxide. On acidifying the resulting solution, the product precipitated. From this reaction, 1.19 g. (70%) of 2-chloro-4-nitrobenzenesulfonamide, XIII, m. p. 143.5–144.5°, was obtained. On recrystallization from 15% ethanol, its m. p. was raised to 148–149°.

Anal. Calcd. for $C_6H_5ClN_2O_4S$: N, 11.84. Found: N, 11.76.

Cleavage of 4-Benzylthio-1,3-dinitrobenzene, XIV.—The sulfide, 1.82 g., was cleaved as before. When the reaction solution was poured into ice water, a semi-solid product settled out. The water was decanted from the product and the product dissolved in 35 ml. of chloroform. This chloroform solution was then shaken for twenty minutes with 50 ml. of concentrated ammonium hydroxide. The chloroform was then separated from the aqueous solution, dried over sodium sulfate, filtered, and evaporated to dryness. The residual oil was then triturated with Skellysolve A (b. p. 28–38°) and the solid that formed filtered from the solution. The 2,4-dinitrobenzenesulfenamide, XV, so obtained (0.80 g., 60%) melted over a rather wide range, 103–113°. However, the melting point was readily raised to 119.5–120.5° by repeated crystallizations from 60% methanol.

Anal. Calcd. for $C_6H_5N_3O_4S$: C, 33.49; H, 2.34; N, 19.53. Found: C, 33.54; H, 2.49; N, 19.72.

Summary

1. A synthesis of 4,7-dichloro-6-quinolinesulfonamide and of bis-(4,7-dichloro-6-quinolyl) disulfide has been described.

2. The structure of 4,7-dichloro-6-quinolinesulfonyl chloride, obtained from 6-benzylthio-4,7-dichloroquinoline, has been proved.

3. A very convenient synthesis for aryl benzyl sulfides has been described.

4. A number of aryl benzyl sulfides have been cleaved with chlorine in acetic acid to give various products.

5. A mechanism for the oxidative cleavage of organic sulfides by means of chlorine in wet acetic acid solution has been proposed.

EVANSTON, ILLINOIS RECEIVED AUGUST 18, 1946

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[15] J. Obermiller, *J. prakt. Chem.*, **197**, 70 (1914).

[CONTRIBUTION FROM SOCONY-VACUUM LABORATORIES (A DIVISION OF SOCONY-VACUUM OIL CO., INC.) RESEARCH AND DEVELOPMENT DEPARTMENT]

Acylation Studies in the Thiophene and Furan Series. I. Iodine and Hydriodic Acid Catalyts

BY HOWARD D. HARTOUGH AND ALVIN I. KOSAK[1]

Stevens[2] reported that acetyl iodide and thiophene, in the absence of a catalyst, gave a low yield of 2-acetylthiophene. This fact led us to investigate the action of iodine as a catalyst for the acylation of thiophene.

The addition of catalytic amounts of iodine to an equimolar mixture of thiophene and acetyl chloride produced a 16% yield of 2-acetylthiophene. Considerable amounts of unidentified decomposition products were obtained.

When acetic anhydride was used instead of acetyl chloride, yields as high as 86% of 2-acetylthiophene were obtained using 8×10^{-3} mole of iodine per mole of acetic anhydride. When amounts of iodine of the order of 4×10^{-2} mole were used, rapid uncontrollable reactions set in. Traces of ketone have been produced with 7×10^{-5} mole of iodine per mole of acylating agent.

2-Acetylthiophene can be produced at temperatures as low as −30°. Below that temperature iodine is insoluble in the acylating mixture and no ketone is produced.

It is desirable to use an excess of one of the reactants, preferably thiophene. For example, if a molar excess of thiophene is used with acetic anhydride and 8×10^{-3} mole of iodine per mole of acetic anhydride an 85% yield of 2-acetylthiophene is produced. When equimolar quantities are employed with the same amount of iodine only 76% yields are obtained.

Hydriodic acid gave yields in the same order as

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[1] Present address: Dept. of Chemistry, Ohio State University, Columbus, Ohio.

[2] Stevens, THIS JOURNAL, **56**, 451 (1934).