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

---

[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

---

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

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

iodine. For example, corresponding experiments using equivalent amounts of iodine and hydriodic acid gave 75 and 76%, respectively, of 2-acetylthiophene from equimolar amounts of thiophene and acetic anhydride.

Iodic anhydride (I_2O_5) failed to catalyze acylation. Other halogens such as bromine and chlorine failed as catalysts, probably because they are consumed in halogenating thiophene. Similarly, hydrochloric and hydrobromic acids failed to catalyze the acylation of thiophene.

A more complete literature survey on the acylation of thiophene in the recent book by Steinkopf[3] lists more than 50 references.

Due to the tendency of furan to polymerize or undergo ring rupture in the presence of most acylating catalysts, the yields reported are considerably lower than in the thiophene series.[4,5] Stannic chloride appears to be the preferred catalyst and 64% yields of 2-acetylfuran are reported from acetic anhydride and furan.[6]

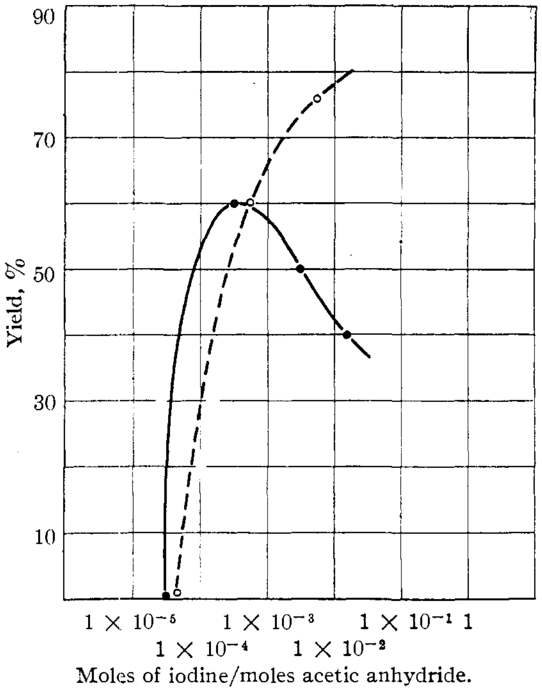

Fig. 1. —●— 2-Acetylfuran obtained using equimolar quantities of furan and acetic anhydride; - -O- - 2-acetylthiophene obtained using equimolar quantities of thiophene and acetic anhydride.

Furan can also be acylated easily with iodine and hydriodic acid. While 4×10^{-5} mole of iodine per mole of acetic anhydride failed to catalyze the acylation of furan with acetic anhydride, the use of 4×10^{-4} mole resulted in an exceptionally rapid reaction and gave a 60% yield of 2-acetylfuran (2-furyl methyl ketone). 4×10^{-3} mole of iodine gave only a 50% yield while 1.5×10^{-2} mole gave only a 40% yield.

Figure 1 shows the relationship between the moles of iodine catalyst employed and the percentage yield of 2-acetylfuran and 2-acetylthiophene.

Hydriodic acid (55.8%) in quantities of the order of 1×10^{-2} mole per mole of acetic anhydride gave the best results, a 76% yield, obtained in our work or in any reported work on 2-acetylfuran. Still better results might be expected if the quantity of hydriodic acid were reduced, since the amount used produced such a rapid reaction that a Dry Ice-bath was necessary to keep it under control.

In general the use of aliphatic acyl chlorides resulted in poorer results than did the corresponding anhydrides. With furan the yields were negligible when iodine was employed. With benzoyl chloride yields of 90% were obtained with thiophene when iodine was used. The uncatalyzed reaction between benzoyl chloride and thiophene under reflux produces approximately 1% of 2-benzoylthiophene per hour, at least during the first six hours studied.

The reaction of the anhydrides and chlorides of polybasic acids with thiophene and furan is under investigation and will be reported at a later date.

We hope to propose a comprehensive mechanism in a later paper after reporting experimental data on other catalysts for the acylation of heterocyclics.

Experimental

2-Acetylthiophene.—To a mixture of 168 g. (2 moles) of thiophene and 197 g. (1 mole) of 95% acetic anhydride was added 2 g. (0.008 mole) of iodine with agitation. The mixture immediately turned purple and within a few seconds changed to brown. It was heated for one hour, the reflux temperature rising from 100 to 107° (a longer heating period leads to decomposition of thiophene with evolution of hydrogen sulfide and results in lower yields). The reaction mixture was cooled, diluted with 200 ml. of water and agitated for fifteen minutes. The organic lower layer was drawn off and the aqueous layer washed twice with 50 ml. of chloroform. The organic layers were combined, washed with 10% sodium carbonate, and then thoroughly with 10% sodium thiosulfate solution. The material was dried over sodium sulfate, filtered, and the chloroform and thiophene distilled off at atmospheric pressure from a Vigreux-modified Claisen flask. The distillation was continued under vacuum and 108 g. (86% yield) was collected, b. p. 77–78° (4 mm.), $n^{20}D$ 1.5666.

The oxime melted at 112–113°. A mixture melting melting point of this and an authentic sample[7] showed no depression. The semicarbazone melted at 191–192°, the 2,4-dinitrophenylhydrazone at 245°.

2-Benzoylthiophene.—To an agitated mixture of 168 g. (2 moles) of thiophene and 141 g. (1 mole) of benzoyl chloride was added 2 g. of iodine. The purple solution was heated at 97° for two hours during which time little hydrogen chloride was evolved and the mixture turned brown. The hydrogen chloride evolution became rapid and the reaction mixture was boiled under reflux for seven hours more until the hydrogen chloride evolution had practically ceased. The cooled reaction mixture was mixed

---

(3) Steinkopf, "Die Chemie des Thiophene," Verlag von Theodor Steinkopff, Dresden and Leipzig, 1941, pp. 70–81.

(4) Reichstein, *Helv. Chim. Acta*, **13**, 356 (1930).

(5) Gilman and Calloway, THIS JOURNAL, **55**, 4197 (1933).

(6) Gol'dfarb and Smorgonskii, *J. Gen. Chem. U.S.S.R.*, **8**, 1523–1526 (1938); *C. A.*, **33**, 4593 (1939).

(7) "Organic Syntheses," Coll. Vol. II, 8 (1943).

with 20% sodium hydroxide and mechanically agitated for thirty minutes, washed with 10% sodium thiosulfate solution, filtered and distilled to remove unreacted thiophene. The product boiled at 113–117° (1.5 mm.); yield 169 g. (90%). The distillate had a green cast that was removed by three recrystallizations from a mixture of equal parts of petroleum ether and absolute ether; m. p. 56–57°; the mixed melting point with an authentic sample[8] was 56–57°.

The oxime melted at 92.5–93°.[9]

2-Acetylfuran.—To an agitated mixture of 58 g. (0.85 mole) of furan and 107 g. (1 mole) of 95% acetic anhydride cooled to 0° was added 2.5 g. of 56% hydriodic acid. The reaction proceeded very rapidly and the mixture was maintained at 0–25° by means of the Dry Ice–acetone-bath. After the reaction ceased, the mixture was allowed to warm to room temperature and stirred thirty minutes longer. After the addition of 200 ml. of water, the mixture was stirred for fifteen minutes. The organic layer was drawn off and the aqueous layer washed twice with 50-ml. portions of chloroform. The organic layers were combined and washed with 10% sodium carbonate solution until neutral and finally washed thoroughly with a 10% solution of sodium thiosulfate. The organic layer was dried over anhydrous sodium sulfate and then filtered into a Vigreux-modified Claisen flask, the chloroform removed at atmospheric pressure. The product boiled at 45–48° (5 mm.), m. p. 30–32°.[10] Three grams of crystalline residue was not identified but may have been 2,5-diacetylfuran.

The 2,4-dinitrophenylhydrazone melted at 219–220°.[11]

Acknowledgment.—The authors are very grateful to Dr. Darwin E. Badertscher for his advice and interest in this problem. The authors wish to thank Miss Josephine Sidoni and Mr. John J. Sardella for their coöperation in carrying out some of the laboratory preparations.

Summary

1. Catalytic quantities of iodine and hydriodic acid have been shown to promote the acylation of furan and thiophene.

2. Yields of 2-acetylthiophene as high as 86% are reported when 8×10^{-3} mole of iodine per mole of acetic anhydride is employed with thiophene and acetic anhydride. 2-Benzoylthiophene has been obtained in yields of the order of 90% from benzoyl chloride and thiophene.

3. 2-Acetylfuran has been prepared from furan and acetic anhydride in yields of 60 and 76% when iodine and hydriodic acid, respectively, are used as catalysts.

PAULSBORO, N. J. RECEIVED JULY 2, 1946

---

(8) Stadnikoff and Goldfarb, *Ber.*, **61B**, 2341 (1928).

(9) Stadnikoff and Rakovski (*ibid.*, **61B**, 268 (1928)) reported 93°.

(10) Reichstein (ref. 4) reported 30–32°.

(11) Chute, Orchard and Wright [*J. Org. Chem.*, **6**, 165 (1941)] found 223°.

[CONTRIBUTION FROM THE NOYES LABORATORY OF CHEMISTRY, UNIVERSITY OF ILLINOIS]

The Preparation of Unsymmetrical Diaryl Amines. 5-Phenylamino-6-methoxy-8-(3-diethylaminopropylamino)-quinoline[1]

BY H. R. SNYDER AND NELSON R. EASTON

There are several known examples of the reaction of aromatic nitroso compound with a phenol or an aromatic amine to form the anil of a quinone. For example, Euler[2] reported that nitrosobenzene reacts with α- or β-naphthol to give the phenylanil of the corresponding naphthoquinone, and Kaufler and Suchannek[3] have described a similar reaction between *p*-nitrosodimethylaniline and 9-anthrol or 9-anthramine. Thus it would appear that certain phenols and primary aromatic amines might be converted to their *o*- or *p*-arylamino derivatives by condensation with the appropriate nitroso compound and reduction of the resulting anil. This possibility was particularly attractive in connection with the application to the synthesis of 5-phenylamino-6-methoxy-8-aminoquinoline (II) from 6-methoxy-8-aminoquinoline; the diethylaminopropyl derivative (III) of the base II was desired for testing as an antimalarial agent.

The anil (I) was obtained in about 60% yield when the reaction was carried out in aqueous *i*-propyl alcohol under mild conditions. When the reaction was attempted in glacial acetic acid solution none of the product (I) was obtained; the dark-colored, tarry material that formed in this experiment may have contained some of the isomeric azo compound (6-methoxy-8-benzeneazoquinoline). The reduction of the anil to the diaminoquinoline (II) could be effected with phenylhydrazine, stannous chloride and hydrochloric acid, or hydrogen and platinum oxide catalyst. The desired drug (III) was obtained by the treatment of II with 3-diethylaminopropyl chloride.

Because of the possibility that the initial condensation might have produced 6-methoxy-8-benzeneazoquinoline rather than the anil (I), rigorous proof of the structure of the product was sought. The reduction product (II) underwent cleavage of the phenylamino group on treatment with hot dilute hydrochloric acid, yielding 5-hydroxy-6-methoxy-8-aminoquinoline (IV). The base (IV) was found to have approximately the same melting point as that reported by Jacobs and Heidelberger[4] for a sample prepared by a similar hydrolysis of 5,8-diamino-6-methoxyquinoline; for confirmation, the diacetyl derivative of IV was prepared and compared, by means of melting

---

(1) 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 the University of Illinois.

(2) Euler, *Ber.*, **39**, 1037, 1040, 1042 (1906).

(3) Kaufler and Suchannek, *ibid.*, **40**, 518 (1907).

(4) Jacobs and Heidelberger, THIS JOURNAL, **44**, 1073 (1922).