rate can only be due to a much smaller attraction for electrophilic centers.

Summary

1. The rates of reaction of a series of primary aliphatic amines with methyl acetate, in the presence of ethylene glycol, have been determined.

2. The order of activity found for the series is: methylamine > ethylenediamine > ethanolamine > ethylamine > *n*-butylamine > *n*-amylamine > *n*-propylamine > isobutylamine > β-phenylethylamine > allylamine > benzylamine > ammonia > isopropylamine > *s*-butylamine > *t*-butylamine.

3. These results are discussed from the standpoints of the basicities and steric bulks of the amines.

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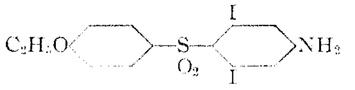
[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF TOLEDO]

Oxidation of a Di-*o*-substituted Diphenyl Sulfide

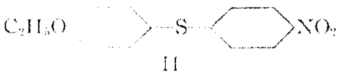
BY PAUL BLOCK, JR., AND JEAN L. BALMAT[1]

In an attempt to prepare a thyroxine-like molecule in which the oxygen atom linking the two benzene rings of thyroxine would be replaced by the sulfone grouping, the substituted 2,6-diiododiphenyl sulfone (I) has been synthesized, and the effect of iodine atoms ortho to the sulfide linkage on the oxidation of sulfide to sulfoxide and sulfone has been investigated. The hope of converting such an oxidized molecule to a thyroxine analog by standard procedures[2] has not yet been realized.

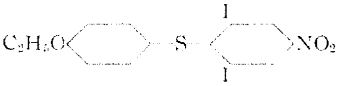
For comparison of their behavior toward oxidizing agents, and as an aid in proof of structure, the uniodinated 4′-ethoxy-4-nitrodiphenyl sulfide[3] (II) and its 2-monoiodo derivative (X) were oxidized. The uniodinated compound readily yielded both a sulfoxide and a sulfone under the usual conditions for such oxidations. One molar-equivalent of hydrogen peroxide in acetic acid at 25° caused the sulfoxide to form, whereas excess hydrogen peroxide at 25° or at 90° gave the sulfone. While no attempt was made to obtain the sulfoxide of the monoiodinated diphenyl sulfide (X), this compound also readily yielded the sulfone.



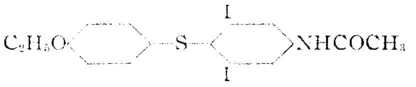
I



II



III



IV

Compounds having two iodine atoms adjacent to the sulfide linkage of a diphenyl sulfide have been synthesized,[4] but oxidation of this configuration was not studied. It has now been found that the presence of two iodine atoms ortho to the sulfide linkage gives rise to two anomalies in the oxidation of such a molecule. In the case of 4′-ethoxy-2,6-diiodo-4-nitrodiphenyl sulfide (III), no reaction occurred either with hydrogen peroxide at 25°, or with potassium permanganate at the temperature of boiling acetone. At higher temperatures, hydrogen peroxide gave the sulfoxide (XI) in good yield, but oxidized it no further. The sulfoxide could be converted to the sulfone (XIII), however, even at lower temperatures, by potassium permanganate. The use of chromic acid was less satisfactory.

Oxidation of the sulfide (III) to the sulfone (XIII) in one step could be effected by potassium permanganate in boiling acetic acid, but except in very dilute solution the oxidation was accompanied by formation of more or less of a partially deiodinated substance. This deiodination also occurred when the sulfoxide was prepared (under the optimum conditions for its formation) in hot acetic acid with hydrogen peroxide, and the reaction subsequently cooled and treated with potassium permanganate.

Oxidation of the compound in which the nitro group had been reduced and acetylated, 4′-ethoxy-2,6-diiodo-4-acetamidodiphenyl sulfide (IV), also did not proceed at 25°, and, as in the case of the nitro compound (III), could not be carried beyond the sulfoxide stage by hydrogen peroxide in acetic acid at higher temperatures. However, in the case of (IV), no conditions were found which gave rise to the desired sulfone, although a partially deiodinated product was occasionally isolated in small yield. This sulfone could be synthesized, however, by acetylation of the amine (I).

The two amino sulfones (I) and (IX) gave evidence of the modification of the usual properties

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(1) From a thesis by J. L. Balmat submitted in partial fulfillment of the requirements for the degree of Master of Science, 1948.

(2) C. R. Harington, *Biochem. J.*, **21**, 169 (1927).

(3) G. H. Law and T. B. Johnson, THIS JOURNAL, **52**, 3625 (1930).

(4) S. L. Bass and T. B. Johnson, *ibid.*, **52**, 1146 (1930).

TABLE I

UNIODINATED AND MONOIODINATED COMPOUNDS

Name, 4′-ethoxy-	No.	Starting material	Method	Yield, %	M. p.,[l] °C.	Empirical formula	Analyses, % Calcd.	Analyses, % Found
4-Nitrodiphenyl sulfide	II	[a]	III[b]	95	94–95[c]	$C_{14}H_{13}O_3NS$		
4-Aminodiphenyl sulfide	VI	II, VII[j]	XIV	90	51[d]	$C_{14}H_{15}ONS$		
4-Acetamidodiphenyl sulfide	V	VI	IV	90	128–129	$C_{16}H_{17}O_2NS$	C, 66.90	66.84
							H, 5.92	5.84
4-Nitrodiphenyl sulfoxide	VII	II	[e]	95[f]	148–149	$C_{14}H_{13}O_4NS$	S, 11.0	10.8
4-Nitrodiphenyl sulfone	VIII	II, VII	[g]	95	210.5[h]	$C_{14}H_{13}O_5NS$	S, 10.4	10.4
4-Aminodiphenyl sulfone	IX	VIII, XI[j]	[i]	85	215.5–217	$C_{14}H_{15}O_3NS$	S, 11.55	11.3
2-Iodo-4-nitrodiphenyl sulfide	X	[k]	[b]	95	152	$C_{14}H_{12}O_3NSI$	I, 31.6	31.9
2-Iodo-4-nitrodiphenyl sulfone	XI	X	[g]	95	139	$C_{14}H_{12}O_5NSI$	S, 7.4	7.1

[a] *p*-Chloronitrobenzene and *p*-ethoxythiophenol. [b] Using only sufficient ethanol to dissolve the nitro compound. [c] Law and Johnson[3] give m. p. 96°. [d] Law and Johnson[3] give m. p. 53°. [e] A saturated acetic acid solution of II was oxidized by 1 mole of 30% hydrogen peroxide for four days. A precipitate of impure sulfone was removed and the sulfoxide precipitated by dilution with water. [f] Deducting weight of sulfone. [g] Excess 30% hydrogen peroxide was added to a solution containing sufficient acetic acid to prevent precipitation of the starting material. Oxidation was effected in four days at 25° or in several hours at 90°. [h] From acetic acid. [i] One g. of starting material in 10 ml. of acetic acid was treated with excess zinc dust for 30 minutes on a steam-bath with agitation. [j] To confirm the structure of the compound reduced. [k] *p*-Ethoxythiophenol and 3,4-diiodonitrobenzene synthesized from 2-iodo-4-nitroaniline (Willgerodt and Arnold, *Ber.*, **34**, 3344 (1901)) by the method employed for 3,4,5-triiodonitrobenzene.[7] [l] After recrystallization from 95% ethanol.

of the amino group by the sulfone group. This was particularly true of the diiodinated compound (I), which was found to possess properties peculiarly reminiscent of sulfanilic acid although the generally accepted explanation of the properties of sulfanilic acid could hardly be applicable here. It had a higher melting point than the parent nitro sulfone (XIII) and was considerably less soluble in benzene, chloroform and ethanol. It could be dissolved in absolute methanol by adding a high concentration of dry hydrogen chloride; addition of water reprecipitated the free amine. An acetyl derivative was not readily formed in pyridine with acetic anhydride under conditions which easily gave an acetate in the case of other amines in this series when unsubstituted ortho to the amino group. When formed by heating in acetic anhydride containing a trace of sulfuric acid, the acetyl derivative, unlike the free amine, could be recrystallized from the usual solvents. On attempted diazotization by a method[5] available for amines whose hydrochlorides cannot be isolated, an insoluble product was obtained rather than the clear solution of a diazonium salt found in other syntheses of thyroxine analogs. Such insolubility characterizes the diazonium salts of sulfanilic acid.

The attempt to synthesize a sulfone-containing thyroxine by this classical method was abandoned when the compound to which the nitrile structure had been tentatively assigned was found to undergo fission at the sulfone linkage under the conditions of the Stephen aldehyde synthesis, an indispensable link in the chain leading to the amino acid by this general route.

The iodine compounds herein reported were deiodinated with zinc and acetic acid to relate their skeletal structures to the compounds synthesized initially without iodine. This reducing agent simultaneously served to distinguish between sulfoxide and sulfone, since the former is readily reduced to the sulfide. Reduction of sulfoxide and nitro groups without deiodination was effected by iron and acetic acid.

Experimental[6]

4′-Ethoxy-2,6-diiodo-4-nitrodiphenyl Sulfide (III).—Finely ground 3,4,5-triiodonitrobenzene[7] (10 g.) was suspended in 375 ml. of ethanol at 23°. *p*-Ethoxythiophenol[8] (3.1 g.) was added, followed by 1.3 g. of potassium hydroxide dissolved in about 1 ml. of water. A deep yellow, bulky precipitate appeared after a few seconds. The reaction mixture was shaken until, on standing, there was no further settling of the heavy, sandy starting-material on the botton of the reaction vessel. After several hours, the almost quantitative yield of product was filtered off, dried and crystallized from benzene (1 g. in 4.5 ml.). The yield of pure material, m. p. 174–175°, was 90%.

Anal. Calcd. for $C_{14}H_{11}O_3NSI_2$: I, 48.2; mol. wt., 527. Found: I, 48.0; mol. wt. (Rast) 525.

4′-Ethoxy-2,6-diiodo-4-nitrodiphenyl Sulfoxide (XII).—The sulfide (III) (10 g.) was suspended in 200 ml. of acetic acid, 8 ml. of hydrogen peroxide (30%) was added, and the suspension heated under a condenser until gentle refluxing began. As soon as the solid had gone into solution, a further 8 ml. of hydrogen peroxide was added in small portions, while continuing the heating until the gold-colored solution became light yellow. With oxidations on a larger scale, it was found convenient to compare the shade of yellow with that of solution taken from a small-scale reaction mixture, adding more peroxide if necessary, to ensure completion of the oxidation. Hot water (130 ml.) was added, and the solution cooled. The sulfoxide which crystallized (9 g., 90%) melted at 137–138°. Recrystallization from ethanol gave a golden-yellow product melting at 143–145.5°, darkening on prolonged exposure to light.

Reduction of 1 g. of (XII) with powdered iron in 10 ml. of 90% acetic acid after warming on the steam-bath with agitation for 30 minutes, gave the amine of the sulfide

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[5] C. Niemann and C. E. Redemann, *ibid.*, **63**, 1549 (1941).

[6] All melting points corrected.

[7] R. B. Sandin and T. L. Cairns, "Organic Syntheses," Collected Volume II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 604.

[8] C. M. Suter and H. L. Hansen, THIS JOURNAL, **54**, 4100 (1932).

(XIV), isolated as its acetyl derivative (IV); m. p. 231–233°.

Anal. Calcd. for $C_{14}H_{11}O_4NSI_2$: S, 5.9; I, 46.7. Found: S, 5.85; I, 46.8.

4′-Ethoxy-2,6-diiodo-4-nitrodiphenyl Sulfone (XIII).—The sulfoxide (XII) (8 g.) was dissolved in 320 ml. of acetone, and 14.5 g. of potassium permanganate was added in several portions over a 30-minute period while the reaction was stirred and heated under reflux. After cooling, the mixture was poured into 400 ml. of water containing 20 ml. of concentrated hydrochloric acid, and solid sodium bisulfite was added until only a light yellow precipitate remained. This amounted to 5.6 g. (70%). Crystallization from amyl acetate gave an 85% recovery of a product, m. p. 190–192°.

Anal. Calcd. for $C_{14}H_{11}O_5NSI_2$: I, 45.4. Found: I, 45.2.

Reduction with zinc and acetic acid (0.5 g. in 10 ml.) gave an amine identical with (IX) above.

4′-Ethoxy-2,6-diiodo-4-aminodiphenyl Sulfone (I).—The nitro sulfone (XIII) (10 g.) was added to 100 ml. of acetic acid in which 14 g. of stannous chloride dihydrate had been dissolved by passing dry hydrogen chloride into the suspension heated on a boiling water-bath. Stirring and heating was continued for 45 minutes while a stream of this gas was bubbled through. The precipitate was filtered off, washed with a little cold glacial acetic acid, and triturated with 200 ml. of 3 *N* sodium hydroxide solution. The residue was washed with water and dried. For purification, it was dissolved in 350 ml. of dry methanol by passing through a rapid stream of dry hydrogen chloride. The solution was filtered, and the amine precipitated by adding an equal volume of water. The yield was 8.5 g. (90%) m. p. 241–242°. Crystallization from dioxane raised the melting point to 248–249°.

Anal. Calcd. for $C_{14}H_{13}O_3NSI_2$: I, 48.0. Found: I, 47.8.

Treatment of the amine with acetic anhydride plus 1 drop of sulfuric acid gave an acetyl derivative m. p. 243–244° after recrystallization from acetic acid. The melting point of a mixture of this and the free amine was depressed to 218–221°.

Anal. Calcd. for $C_{16}H_{15}O_4NSI_2$: C, 33.62; H, 2.63. Found: C, 33.29; H, 2.76.

4′-Ethoxy-2,6-diiodo-4-aminodiphenyl Sulfide (XIV).—Fifty grams of the nitro sulfide (III) was suspended in 1000 ml. of ethanol, and 75 g. of stannous chloride dihydrate and 75 ml. of concentrated hydrochloric acid were added. The reaction mixture was refluxed for 30 minutes after the nitro compound had gone completely into solution. A solution of 150 g. of potassium hydroxide in 1000 ml. of water was added slowly with cooling, and the amine which precipitated was allowed to stand in the refrigerator overnight. The yield of crude amine was 90%, m. p. 151–152°. It was purified by dissolving in benzene, filtering if necessary, and precipitating the hydrochloride with dry hydrogen chloride. For analysis, the amine was recrystallized from ethanol; m. p. 152°.

Anal. Calcd. for $C_{14}H_{13}ONSI_2$: I, 51.1; S, 6.4. Found: I, 50.75; S, 6.4.

4′-Ethoxy-2,6-diiodo-4-acetamidodiphenyl Sulfide (IV).—The amine (XIV) (10 g.) was dissolved in 20 ml. of pyridine and treated with 2.5 g. of acetic anhydride. After warming for 15 minutes on the steam-bath, water was added to precipitate the product; m. p. 236–237°, unchanged by further recrystallization.

Anal. Calcd. for $C_{16}H_{15}O_2NSI_2$: I, 47.1; S, 5.9. Found: I, 47.0; S, 5.7.

4′-Ethoxy-2,6-diiodo-4-acetamidodiphenyl Sulfoxide (XV).—The acetamido compound (IV) (1 g.) was suspended in 50 ml. of glacial acetic acid, and 1.5 ml. of hydrogen peroxide (30%) was added. The reaction mixture was refluxed gently for 10 minutes after the starting material had completely dissolved and the color of the solution had changed to light orange. After cooling, the salmon-colored product was precipitated by the addition of water; m. p. 202°. The yield was virtually quantitative.

Anal. Calcd. for $C_{16}H_{15}O_3NSI_2$: S, 5.8; I, 45.7. Found: S, 5.6; I, 45.85.

When 0.5 g. of this compound was treated with zinc dust in 5 ml. of acetic acid a product was obtained which was identical with the acetamido sulfide (V).

Summary

1. Two di-*o*-substituted diphenyl sulfides, 4′-ethoxy-2,6-diiodo-4-nitrodiphenyl sulfide and 4′-ethoxy-2,6-diiodo-4-acetamidodiphenyl sulfide, have been oxidized to their sulfoxides by hydrogen peroxide in acetic acid at the reflux temperature.

2. The sulfoxide of one of these, 4′-ethoxy-2,6-diiodo-4-nitrodiphenyl sulfoxide, has been further oxidized to a sulfone by potassium permanganate in acetone. The other sulfoxide, in which an acetamido group replaces a nitro group, could not be oxidized to the sulfone.

3. Where only one iodine atom is ortho to the sulfide linkage, oxidation proceeds in a manner similar to that of the uniodinated molecule.

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