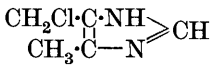
LXXVIII.—*The Action of Alkaline Arsenites on Some Halogenated Organic Compounds.*

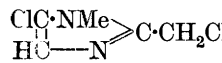
By Isidore Elkanah Balaban.

It is well known that sulphonic acids, both aliphatic and aromatic, may be obtained by the action of alkali sulphites on some halogenated organic compounds. In view of the chemotherapeutic importance of arsinic acids, it was thought worth while to investigate the action of alkali arsenites on a series of halogenated organic compounds of varying degrees of reactivity, in order, if possible, to delimit the applicability of the method. Meyer (*Ber.*, 1883, **16**, 1440) first employed the method to prepare methyl- and ethylarsinic acids, and it was extended to *n*-propyl-, *iso*amyl-, and benzylarsinic acids by Dehn and McGrath (*J. Amer. Chem. Soc.*, 1906, **28**, 351). Quick and Adams (*ibid.*, 1922, **44**, 809) applied it successfully

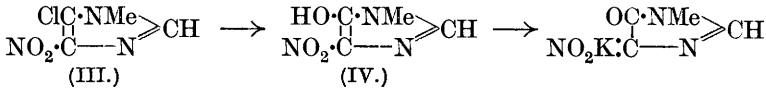
to butyl bromide and allyl bromide, whilst Palmer (*ibid.*, 1923, **45**, 3023) applied it to chloroacetic acid. In the aromatic series, Rosenmund (*Ber.*, 1921, **54**, 438) obtained *o*-benzarsinic acid by the action of potassium arsenite on *o*-bromobenzoic acid.

Two glyoxaline derivatives have now been examined containing highly reactive halogen atoms, 4(5)-methyl-5(4)-chloromethylglyoxaline (I) and 5-chloro-1-methyl-2-chloromethylglyoxaline (II), but only the corresponding alcohols could be isolated in poor yield.

(I.) 

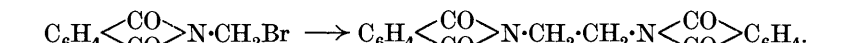
 (II.)

A less reactive glyoxaline compound, 5-chloro-4-nitro-1-methylglyoxaline (III), which had previously been shown to give a sulphonic acid (Balaban and Pyman, J., 1924, **125**, 1564), when heated with potassium arsenite in absolute alcohol gave 4-*nitro*-5-*hydroxy*-1-*methylglyoxaline* (IV), a very unstable nitroamide resembling in general properties the nitroacetone and nitroacetophenone of Lucas (*Ber.*, 1899, **32**, 600) and Henry (*ibid.*, 1899, **32**, 865).



(III.) (IV.)

The nitroamide is, however, stable as its *potassium* and *sodium* salts. 2 : 4-Dinitrobromobenzene, which resembles the foregoing in containing a halogen atom activated by a nitro-group, yielded 2 : 4-dinitrophenol, whereas by the action of sodium sulphite in aqueous alcoholic solution it is known to yield 1 : 3-dinitrobenzene-4-sulphonic acid (D.R.-P. 65240). When 8-chlorocaffeine is heated with potassium arsenite in alcohol at 140—180°, a mixture of 8-hydroxy- and 8-ethoxy-caffeine is obtained. Under somewhat parallel conditions (D.R.-P. 74045), 8-chlorocaffeine is known to yield a sulphonic acid when treated with aqueous sodium sulphite. In the foregoing cases where reaction had taken place, the halogen atom was replaced by hydroxyl or ethoxyl. An unexpected result was, however, obtained on examining the action of alkali arsenite on phthalbromomethylimide in acetone solution, as ethylenediphthalimide was isolated.



When it was boiled with 20% aqueous sodium sulphite, *phthalimidomethanesulphonic acid* was obtained in a yield of 13·2% of the theoretical, the main product being phthalic acid (yield 62%), together with a small amount of phthalimide. An attempt to hydrolyse the sulphonic acid to the unknown aminomethanesulphonic

acid proved unsuccessful. Delépine and Demars also failed to obtain this compound by the action of ammonia on chloromethanesulphonic acid (*Bull. Soc. Pharmacol.*, 1922, **29**, 14).

In none of the above cases, although special search was made, was any organic arsinic acid found. If this result be contrasted with the much more general formation of sulphonic acids by the action of alkali sulphite, one is compelled to attribute it to the difference in alkalinity of sulphite and arsenite.

EXPERIMENTAL.

The action of alkali arsenites was examined on the following halogenated organic compounds: 4(5)-*Methyl*-5(4)-*chloromethylglyoxaline* (I). To a mechanically stirred solution of potassium arsenite (24 g.; 10 mols.) in water (30 c.c.) below 0°, 4(5)-methyl-5(4)-chloromethylglyoxaline hydrochloride (2 g.) in absolute alcohol (50 c.c.) was run in during ½ hour. After removal of much arsenic trioxide the mother-liquor was evaporated to dryness in a vacuum, the residue extracted with absolute alcohol, and the extract added to aqueous picric acid; 4(5)-methyl-5(4)-hydroxymethylglyoxaline picrate (1·1 g.; yield, 27·5%) was the sole product obtained. It melted at 180°, alone or mixed with an authentic specimen.

The experiment was repeated in absolute alcohol, but no definite organic products could be isolated.

5-*Chloro*-1-*methyl*-2-*chloromethylglyoxaline* (II), treated as in the above two experiments, yielded 5-chloro-1-methyl-2-hydroxymethylglyoxaline picrate (3 g.; yield, 64%), m. p. 148—149°, and 0·8 g., m. p. 148°, respectively, but no trace of other organic material.

5-*Chloro*-4-*nitro*-1-*methylglyoxaline* (III). The nitro-compound (2 g.) was boiled under reflux with potassium arsenite (5 g.) in absolute alcohol (50 c.c.) for 8 hours, together with a crystal of potassium iodide. On keeping, clusters of yellow needles crystallised (4·2 g.). This product was extracted with water (20 c.c.), and after removal of arsenic trioxide the filtrate was acidified (Congo-paper); 1·07 g. of solid crystallising in fine, colourless needles and decomposing at 106° were then obtained.

4-*Nitro*-5-*hydroxy*-1-*methylglyoxaline* (IV) is soluble in water, alcohol, dilute acids and alkalis, and the usual organic solvents. It cannot be recrystallised, as the solution rapidly becomes dark red, and acquires a strong odour of oxides of nitrogen. It was unsuitable for combustion, as it decomposed very rapidly. In alcoholic solution, the nitroamide gives with ferric chloride an intense brown coloration. It also gives the Liebermann nitroso-reaction. The *potassium* salt, prepared by carefully neutralising the nitro-amide

with dilute potassium hydroxide and evaporating the solution to dryness over sulphuric acid, crystallised in fine, long, yellow needles, decomp. 292°, containing $\frac{1}{2}H_2O$, which was very gradually lost at 95° (Found in air-dried substance: H_2O, 4·7; K, 20·4, 20·6. $C_4H_4O_3N_3K,\frac{1}{2}H_2O$ requires H_2O, 4·7; K, 20·5%). The *sodium* salt, obtained in a similar manner, crystallised in minute, yellow, anhydrous prisms, decomp. 320° (Found: Na, 13·6. $C_4H_4O_3N_3Na$ requires Na, 13·9%).

2 : 4-*Dinitrobromobenzene*. The nitro-compound (2·5 g.), potassium arsenite (8 g.), and absolute alcohol (50 c.c.) were heated under reflux on the water-bath for 8 hours. The product having been worked up as in the previous experiments, 2 : 4-dinitrophenol (1 g.), m. p. 113—114°, alone or mixed with an authentic specimen, was isolated. A further crop (0·5 g.), m. p. 110°, was also obtained.

8-*Chlorocaffeine*. Potassium arsenite (5 g.), 8-chlorocaffeine (2·3 g.), and absolute alcohol (50 c.c.) were similarly heated for 7 hours. The alcoholic mother-liquor gave 0·75 g., m. p. 160°, which after recrystallisation proved to be unchanged material; no products were isolated. The experiment was repeated in aqueous solution, ammonia or methylamine being evolved. After keeping, 0·85 g. of a substance, m. p. 186° alone or mixed with 8-chlorocaffeine, was collected, no other organic matter being obtained. A third experiment was carried out with absolute alcohol in a sealed tube at 140—180° for 8 hours. The alcohol-insoluble portion (0·4 g.) was hydroxycaffeine (m. p. *ca.* 335°), and later crops (0·55 g.), which did not melt at 340°, were hydroxycaffeine contaminated with arsenic trioxide. The residual alcohol-soluble extract (0·45 g.), m. p. 140—142°, was identical with a prepared specimen of 8-ethoxycaffeine, the melting point of the mixture not being depressed.

8-*Hydroxycaffeine*, m. p. 335°, was readily prepared by heating 8-ethoxycaffeine with 16% hydrochloric acid for 10 minutes in the boiling-water bath. It was not obtainable directly from 8-chlorocaffeine by Fischer's process (*Ber.*, 1885, **28**, 2486).

8-*Ethoxycaffeine* was prepared by heating 8-chlorocaffeine (1·5 g.) with potassium hydroxide (1 g.) and absolute alcohol (15 c.c.) under reflux on the water-bath for 6 hours. After removal of the solvent and extraction with water, 8-ethoxycaffeine (0·93 g.; yield, 62%), m. p. 140—142°, was collected; it crystallised in dense, colourless, waxy prisms.

Phthalbromomethylimide. When phthalbromomethylimide (2·4 g.) was heated with potassium arsenite (5 g.) in absolute alcohol (50 c.c.) under reflux for 7 hours, 0·9 g., m. p. *ca.* 210° (alone or mixed with phthalic acid), was collected, no other products being obtained. The experiment was repeated in acetone solution (50 c.c.) from

which 0·95 g. of product, m. p. 230°, was collected. This crystallised in colourless, rectangular prisms from glacial acetic acid, was very sparingly soluble in boiling water, and insoluble in ether (Gabriel, *Ber.*, 1887, **20**, 2225, gives m. p. 232° for ethylenediphthalimide) (Found: N, 8·8 by the Kjeldahl method. $C_{18}H_{12}O_4N_2$ requires N, 8·7%).

Action of Sodium Sulphite on Phthalbromomethylimide.—The bromo-compound (9·1 g.) was boiled under reflux with sodium sulphite (75 c.c. of 20% aqueous solution; 2 mols.) until complete solution was effected (1¾ hours) and kept, when phthalimide (0·35 g., m. p. 232°) was collected. The mother-liquor, on being acidified (Congo-paper), deposited phthalic acid (3·15 g., m. p. 200°), whilst on concentration a further crop (0·85 g., m. p. 200°; total yield 62%) was obtained. From the mother-liquors, by further concentration, phthalimidomethanesulphonic acid was obtained (1·2 g., m. p. 270° with decomp.; yield, 13·2%).

Phthalimidomethanesulphonic acid crystallises from water in long, fine, colourless, rectangular prisms, m. p. *ca.* 295° with decomposition according to the rate of heating; these contain $2{\cdot}5H_2O$. After being dried at 120°, it does not melt even at 320°. It is very soluble in water, but almost insoluble in absolute alcohol (Found in air-dried substance: loss at 120°, 15·8. $C_9H_7O_5NS,2{\cdot}5H_2O$ requires H_2O, 15·7%. Found in substance dried at 120°: N, 5·9 by the Kjeldahl method. $C_9H_7O_5NS$ requires N, 5·8%). The *barium* salt crystallises in long, fine needles which are sparingly soluble in water.

Hydrolysis of the Sulphonic Acid.—The sulphonic acid (0·5 g.) was heated with 20% hydrochloric acid (10 c.c.) for 2½ hours under reflux. On keeping, phthalic acid (0·3 g., m. p. 214°; yield 91%) was obtained, whilst the mother-liquor on concentration gave less than 0·1 g. of ammonium chloride.

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THE NATIONAL INSTITUTE FOR MEDICAL RESEARCH,
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