59. p-*Xylylarsonic Acid.*

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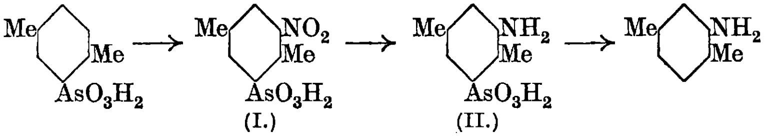
p-XYLYLARSONIC acid was first prepared by Michaelis (*Annalen*, 1902, **320**, 302) by a standard procedure which he applied to a large number of allied substances. Bromo-*p*-xylene on treatment with sodium and arsenic trichloride in ethereal solution gave tri-*p*-xylylarsine, which when heated under pressure with arsenic trichloride in excess gave *p*-xylyldichloroarsine. The latter on oxidation in aqueous suspension with chlorine gave *p*-xylylarsonic acid. In a recent communication (Cohen, King, and Strangeways, J., 1931, 3237) we found that *p*-xylylarsonic acid prepared by the Bart–Schmidt reaction from *p*-xylidine melted at 192°, which is 31° below the m. p. given by Michaelis, and *p*-xylyldichloroarsine, whilst having approximately the same m. p. as that recorded by Michaelis, crystallised from low-boiling petroleum in large plates, whereas Michaelis records his product as crystallising from the same solvent in needles. The present work was undertaken to clear up these discrepancies.

According to Michaelis (*loc. cit.*) *p*-xylylarsonic acid on solution at a low temperature in 100% nitric acid gives nitroxylylarsonic acid, m. p. 205°. Our *p*-xylylarsonic acid under similar conditions, but in 93% nitric acid, gives a nitroxylylarsonic acid, m. p. 242°. Jacobs, Heidelberger, and Rolf (*J. Amer. Chem. Soc.*, 1918, **40**, 1589) obtained 5-nitro-*p*-xylyl-2-arsonic acid, m. p. 290°, by the Bart–Schmidt reaction on 5-nitro-*p*-2-xylidine and for that reason we regard our compound as 6-*nitro*-p-*xylyl*-2-*arsonic acid* (I). On reduction it gives 6-*amino*-p-*xylyl*-2-*arsonic acid* (II), which when heated at 130° with water gives *p*-xylidine, characterised as acet-*p*-xylidide, identical with our starting material.



On repetition of Michaelis's procedure tri-*p*-xylylarsine is obtained with the same m. p. 157° as that recorded by him, and this when heated with excess of arsenious chloride gives *p*-xylyldichloroarsine, which on oxidation with hydrogen peroxide gives *p*-xylylarsonic acid identical with that obtained by us from *p*-xylidine by the Bart–Schmidt reaction. Some error must therefore have crept into the transcription by Michaelis of the melting points of *p*-xylylarsonic acid and its mononitro-derivative.

6-Amino-*p*-xylyl-2-arsonic acid and its N-*acetyl* derivative were practically devoid of trypanocidal action when tested on an experimental infection of *Trypanosoma equiperdum* in mice.

EXPERIMENTAL.

Preparation of p-*Xylylarsonic Acid from Bromo*-p-*xylene*.—A mixture of bromo-*p*-xylene (12·2 g.), arsenious chloride (4·0 g.), dry ether (100 c.c.), and sodium wire (6 g.) was digested on the water-bath for 2 days, and the filtered solution evaporated to dryness. The crystalline residue, treated with absolute alcohol, left a mixture of substances (3 g.). It was recrystallised from absolute alcohol and gave a uniform crop of needles (1 g.), m. p. 157°. This was heated with arsenious chloride (10 c.c.) at 230° for 5·5 hours, and the resulting dark-coloured liquid fractionated under reduced pressure. The higher-boiling fraction, suspended in sodium hydrogen carbonate solution, oxidised with hydrogen peroxide, and acidified, gave crude *p*-xylylarsonic acid (0·13 g.). It contained a small quantity of a less soluble substance, probably the secondary arsonic acid, which was readily removed by fractional crystallisation. *p*-Xylylarsonic acid was then isolated, m. p. 192°, unchanged by further crystallisation and showing no depression of m. p. with *p*-xylylarsonic acid prepared by the Bart–Schmidt reaction from *p*-xylidine.

6-*Nitro*-p-*xylyl*-2-*arsonic Acid*.—*p*-Xylylarsonic acid (4 g.) prepared from *p*-xylidine was added slowly to 20 c.c. of fuming nitric acid (*d* 1·5) at −5°. When the mixture was poured on ice, a crude *nitro-acid* separated (2·5 g.), which decomposed at 227° after shrinking considerably at 200°. Recrystallised from 165 c.c. of boiling water, it separated in double chisel-ended prisms (1·7 g.), m. p. 237° (decomp.). It was identical with a product obtained in better yield by the following process.

p-Xylylarsonic acid (2·3 g.) in sulphuric acid (10 c.c.) was treated with nitric acid (0·9 g., *d* 1·42) in sulphuric acid (2·5 c.c.) at −10°. The solid (2·35 g.) obtained on pouring on ice required 130 c.c. of boiling water for its solution and crystallised in thin prisms (1·9 g.) with a faint yellow colour, m. p. about 242° (decomp.) [Found : N (micro), 5·0; As, 27·4; equiv., 138·2. $C_8H_{10}O_5NAs$ requires N, 5·1; As, 27·3%; equiv., 137·5].

6-*Amino*-p-*xylyl*-2-*arsonic Acid*.—The preceding nitro-compound (13·75 g.) was reduced with ferrous chloride and alkali by the method used by King and Murch (J., 1924, **125**, 2595). When the combined alkaline extracts were acidified and concentrated, an *azoxy*-compound separated as a brick-red powder (0·3 g.) [Found : N (micro), 5·6. $C_{16}H_{20}O_7N_2As_2$ requires N, 5·6%]. The mother-liquors on further concentration gave the required *amino*-compound (10·4 g.). It was dissolved in warm dilute hydrochloric acid, and on addition of sodium acetate it separated in stout, clear, boat-shaped crystals (9·1 g.), m. p. about 255° (decomp.) [Found : N (micro), 5·9. $C_8H_{12}O_3NAs$ requires N, 5·7%]. The hydrochloride is very readily soluble in water and crystallises in small plates.

The amino-acid (1·0 g.) was heated at 135° for 4·5 hours with water (10 c.c.), and the solution basified and extracted with ether. The ethereal extract was acetylated and on crystallisation from dilute alcohol gave acet-*p*-xylidide (0·075 g.), m. p. 142°, alone or in admixture with an authentic specimen. The original alkaline liquors on neutralisation to Congo-paper gave unchanged arsonic acid (0·6 g.).

6-*Acetamido*-p-*xylyl*-2-*arsonic Acid*.—The foregoing amino-acid (2·0 g.) in *N*-sodium hydroxide (12 c.c.; 1·5 mols.) was chilled and shaken with three successive 1 c.c.-portions of acetic anhydride. On acidification to Congo-paper the required *acetyl* derivative rapidly separated in fine needles (1·95 g.). When boiled with 13 volumes of water, which is just sufficient to dissolve the needle form, it became transformed into a more stable, less soluble form crystallising in hexagonal plates or blades [Found : N (micro), 4·8; equiv., 144·6. $C_{10}H_{14}O_4NAs$ requires N, 4·9%; equiv., 143·6]. The more stable plate form is undecomposed at 300°, but the needles may decompose at temperatures between 238° and 258° depending on the mode of heating.

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