SYNTHESIS OF 2, 4-DIAMINO-5-PHENYLTHIAZOLE HYDROCHLORIDE

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(*Received* 28 *Oct.*, 1967)

A process for the synthesis of 2,4-diamino-5-phenylthiazole hydrochloride starting from α chloro α phenyl acetonitrile has been developed. Alternative method for the synthesis of 2, 4-diamino-5-phenylthiazole hydrochloride from α-cyanobezyl benzenesulphonate has also been developed. The drug is known in trade as "Daptazole".

"Daptazole" the 2, 4-diamino-5-phenylthiazole hydrochloride is used in clinical practice as a respiratory stimulant for treatment of barbiturate poisoning and side effects such as respiratory depression, nausea, and as antagonist to respiratory depression produced by large doses of narcotics. A review of the literature revealed that the synthesis of 4-and-5-aminothiazoles has attracted the attention of several workers in the past[1–4]. These aminothiazoles are intermediates for the synthesis of 4-and-5-sulphanilamido derivatives of thiazole. Ganapati and Venkataramani[5] obtained 2, 4-diaminothiazole hydrochloride by condensing α-chloroacetonitrile with thiourea in alcohol but reported difficulty in liberating the free base on treatment with ammonium hydroxide. As a result of these studies, they concluded that the free base is unstable. Dodson and turner[6] synthesised 2, 4-diamino-5-phenylthiazole benzenesulphonate by condensing α-cyanobenzyl benzenesulphonate with thiourea. They also experienced difficulty in liberating the free base from its benzenesulphonate following the procedure of Dodson and Turner. We also encountered the same difficulty in liberating the free base from the benzenesulphonate in good yield, presumably due to aerial oxidation. However, on carrying out the hydrolysis of the benzenesulphonate with ammonium hydroxide under nitrogen and subsequent neutralisation of the product with ethereal hydrochloric acid gave 2, 4-diamino-5-phenylthiazole hydrochloride in 60 per cent yield.

The synthesis of 2, 4-diamino-5-phenylthiazole hydrochloride has been achieved by an alternative method by condensing α-chloro-phenyl acetonitrile with thiourea in acetone in 70 per cent yield. The two samples thus synthesised by the above two methods were found to be identical in all respects *viz* melting point, mixed melting point and infra-red spectra.

EXPERIMENTAL

α-Chloro-phenyl-acetonitrile

A saturated solution of sodium bisulphite (150 ml) (prepared by dissolving 250 gm sodium bisulphite in 335 ml water) was added in small proportion to freshly distilled benzaldehyde (15 gm) with constant vigorous shaking. The crystalline bisulphite compound was filtered off under suction, twice washed with ice cold water and finally with a small quantity of alcohol. The bisulphite compound was made into a thick slurry by suspension in ice cold water (10 ml). An ice cooled solution of protassium cyanide (12·5 gm) potassium cyanide in 25 ml water) was added to the slurry with constant shaking during an interval of 30 minutes. α-Hydroxy-phenyl-acetonitrile was extracted by shaking with benzene (3×50 ml). The benzene extract was dried over anhydrous sodium sulphate and was added dropwise to a suspension of phosphorus pentachloride (17 gm) in dry benzene (250 ml) during an interval of 30 minutes with constant shaking and warmed on water bath till all phosphorus pentachloride dissolved. It was then poured over crushed ice. The benzene layer was separated, washed with water and dried over anhydrous sodium sulphate. On distilling under reduced pressure (120 mm) it gave a greenish yellow liquid α-chloro-phenyl-acetonitrile, which is highly lacrymatory. b. p. 160-170°C yield 40 per cent.

2, 4-Diamino-5-phenylthiazole hydrochloride

α-chloro-phenyl-acetonitrile (8·4 gm) thiourea (4·2 gm) in dry acetone (20 ml) was kept at room temperature for 3 days. The reaction mixture, 2,4-Diamino-5-phenylthiazole hydrochloride separated out which was filtered and crystallised from methyl alcohol ethylacetate mixture in hexagonal plates m.p. 272°C (Yield 60%) Found : C. 47·43; H. 4·05; N, 18·47; S, 14·05% Calc. for $C_9H_{10}N_3SCl$: C, 47·5; H, 4·08; N. 18·50; and S, 14·09%.

SECOND METHOD

α-Cyanobenzyl benzenesulphonate

Benzeldehyde (25 gm), benzenesulphonylchloride (44 gm) and sodiumcyanide (12·5 gm) in water (50 ml) were allowed to stand for 4 hours at 0·5°C with occasional shaking. The cream coloured solid, separated out was filtered off and dissolved in a mixture of acetone, alcohol and ether (2 : 2 : 1) 125 ml). The undissolved material was filtered off and discarded. The solution when poured on crushed ice gave pure α-cyanobenzyl benzenesulphonate, mp. 54°C (Yield 70%).

2, 4-Diamino-5-phenylthiazole benzenesulphonate

A mixture of α-cyanobenzyl benzenesulphonate (30 gm) thiourea (8·4 gm) and acetone (50 ml) was shaken at room temperature until a clear solution was obtained; it was kept overnight at room temperature and then diluted with water and again kept for 48 hours when 2, 4-diamino-5-phenylthiazole benzenesulphonate precipitated out; on recrystallisation from alcohol—ether mixture, pure product had m.p. 261-262°C (Yield 70%).

2, 4-Diamino-5phenylthiazole hydrochloride

The benzenesulphonate (5 gm) was decomposed with ammonium hydroxide (1:1:30 ml) under nitrogen and a portion of the liberated base on crystallisation from dilute alcohol in flakes had m.p. 153—164°C. The crude product was immediately taken up in anhydrous ether (30 ml) and dry ethereal hydrogenchloride added to it until acidic. 2, 4-Diamino-5-phenylthiazole hydrochloride (3·6 gm) which precipitated out was filtered and crystallised from dilute alcohol, m.p., 270°C (decomp.) above 250°C (Yield 55%) Found : C, 47·43; H, 4·05; N, 18·47; S, 14·05% Calc. C, 47, 5; H, 4·08; N, 18·50 and S, 14·09%.

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