526. *Synthesis of Gentianine.*

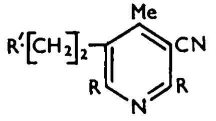
By T. R. Govindachari, K. Nagarajan, and S. Rajappa.

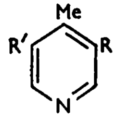
Treatment of 4-methyl-5-vinylnicotinic acid (IIa) with formaldehyde yields gentianine (III).

The alkaloid, gentianine, was recently[1] assigned structure (III) by degradation and by synthesis of its dihydro-derivative (IIIa). The synthesis of gentianine by an analogous method is reported in this paper.

The condensation product (I)[2,3] of α-aceto-γ-butyrolactone with cyanoacetamide was converted by phosphoryl chloride into 2 : 6-dichloro-5-2′-chloroethyl-3-cyano-4-methylpyridine (Ia) and thence into 5-2′-chloroethyl-4-methylnicotinonitrile (Ib) by hydrogenation over palladium. Attempts to prepare 4-methyl-5-vinylnicotinic acid (IIa) from the nitrile by alcoholic alkali, by dehydrochlorination,[2] and hydrolysis of the nitrile group[4] failed: the claim by McElvain and Goese[4] to have effected alkaline hydrolysis of 4-methylnicotinonitrile to 4-methylnicotinic acid could not be confirmed by Webb and Corwin.[5] Acid hydrolysis of the nitrile (Ib) yielded intractable products. With excess of diethylamine the nitrile (Ib) yielded two products: the higher-boiling fraction gave analyses correct for the diethylamino-compound (Ic) which, however, could not be hydrolysed to the acid (IIb). Analyses of the lower-boiling product were correct for 4-methyl-5-vinylnicotinonitrile (II), and this structure was unambiguously proved by preparation from the nitrile (Ib) on treatment with trimethylamine, partly by direct dehydrochlorination and partly by Hofmann degradation of the quaternary compound. Acid hydrolysis of the nitrile (II) gave a satisfactory yield of 4-methyl-5-vinylnicotinic acid (IIa), its structure being confirmed by identity of its dihydro-derivative with the known 5-ethyl-4-methylnicotinic acid.[1]

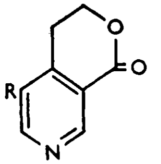
(I): R = R′ = OH.
(Ia): R = R′ = Cl.
(Ib): R = H, R′ = Cl.
(Ic): R = H, R′ = NEt$_2$.

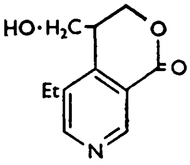




(II): R = CN, R′ = CH:CH$_2$.
(IIa): R = CO$_2$H, R′ = CH:CH$_2$.
(IIb): R = CO$_2$H, R′ = [CH$_2$]$_2$·NEt$_2$.

(III): R = CH:CH$_2$.
(IIIa): R = Et.





(IV)

Treatment of the sodium salt of the acid (IIa) with the calculated quantity of formaldehyde, under conditions employed for the synthesis of dihydrogentianine,[1] yielded only minute amounts of gentianine (isolated as the picrate). That the vinyl group has a deactivating effect on the adjacent 4-methyl group in the reaction with formaldehyde was confirmed by substantial recovery of gentianine after it had been heated with excess of formaldehyde under conditions which convert dihydrogentianine into the lactone (IV). Finally treatment of the sodium salt of the acid (IIa) with excess of formaldehyde gave a moderate yield of gentianine (III) identical with the natural substance.

Experimental

5-2′-Chloroethyl-4-methylnicotinonitrile.—3-Cyano-2 : 6-dihydroxy-5-2′-hydroxyethyl-4-methylpyridine[2,3] (4 g.) was heated with phosphorus oxychloride (10 ml.) at 200—210° for 4 hr., then poured on crushed ice. The solution was allowed to come to room temperature and

---

[1] Govindachari, Nagarajan, and Rajappa, *J.*, 1957, 551.

[2] Stevens, Beutel, and Chamberlin, *J. Amer. Chem. Soc.*, 1942, **64**, 1093.

[3] Ritchie, *Austral. J. Chem.*, 1956, **9**, 244.

[4] McElvain and Goese, *J. Amer. Chem. Soc.*, 1943, **65**, 2233.

[5] Webb and Corwin, *ibid.*, 1944, **66**, 1456.

extracted twice with ether. The combined extracts were washed with water and dried (Na_2SO_4) and the solvent was distilled off, yielding the crude trichloro-compound (3·7 g.). The combined product from 2 such batches was hydrogenated in methanol (50 ml.) containing potassium acetate (6 g.) and palladium chloride (0·45 g.) at 2 atm. till no more hydrogen was absorbed. The solution was filtered and the residue washed with methanol. The filtrate was evaporated and the residue treated with water (50 ml.), saturated with sodium hydrogen carbonate, and extracted repeatedly with ether. Evaporation of the dried (Na_2SO_4) ether extract and vacuum-distillation of the residual solid gave 5-2′-chloroethyl-4-methylnicotinonitrile (5·4 g.), b. p. 144—145°/3 mm., solidifying in the receiver, and yielding a *picrate* (from water), m. p. 143—144° (Found: C, 43·7; H, 3·0. $C_{15}H_{12}O_7N_5Cl$ requires C, 44·0; H, 2·9%).

4-*Methyl*-5-*vinylnicotinonitrile*.—(*a*) The preceding nitrile (4 g.) in alcohol (7 ml.) was heated with excess of diethylamine (8 ml.) in a bomb at 120° for 8 hr. The alcohol was then evaporated, and the residue diluted with water, basified with 2N-sodium hydroxide, and extracted repeatedly with ether. The dried (Na_2SO_4) ether extract on evaporation and fractionation under reduced pressure gave 4-methyl-5-vinylnicotinonitrile (1·8 g.), b. p. 98°/2 mm., yielding a *picrate*, m. p. 141—143° (from water) (Found, after drying at 30° for 24 hr.: C, 48·6; H, 2·7. $C_{15}H_{11}O_7N_5$ requires C, 48·3; H, 2·9%), and 5-2′-diethylaminoethyl-4-methylnicotinonitrile (1 g.), b. p. 134°/2 mm., yielding a *monopicrate* (prepared in aqueous acid), m. p. 172—173° (from alcohol) (Found: C, 51·2; H, 4·6. $C_{13}H_{19}N_3,C_6H_3O_7N_3$ requires C, 51·1; H, 4·9%), and a *dipicrate* (prepared in alcohol), m. p. 126—127° (from acetic acid–alcohol) (Found: C, 44·7; H, 3·6; N, 18·8. $C_{13}H_{19}N_3,2C_6H_3O_7N_3$ requires C, 44·4; H, 3·7; N, 18·7%).

(*b*) 5-2′-Chloroethyl-4-methylnicotinonitrile (1 g.) was heated in a bomb with trimethylamine (25% solution in methanol; 5 ml.) at 130° for 7 hr. The solvent was evaporated and the residue digested with dry ether. Evaporation of the extract and distillation of the residue (0·5 g.) gave an oil, b. p. 98°/2 mm., yielding a picrate, m. p. and mixed m. p. with 4-methyl-5-vinylnicotinonitrile picrate, m. p. 141—143°. The ether-insoluble residue was dissolved in water (100 ml.) and shaken with silver oxide (from 5 g. of silver nitrate) for 3 hr. The mixture was filtered and the residue washed with water. The total filtrates (200 ml.) were concentrated in a vacuum. When the last 10 ml. of the solution were evaporating, a solid (100 mg.) distilled with the steam. The picrate after crystallisation from water was identical with the picrate of 4-methyl-5-vinylnicotinonitrile.

4-*Methyl*-5-*vinylnicotinic Acid*.—4-Methyl-5-vinylnicotinonitrile (2 g.) was heated with 70% sulphuric acid (20 ml.) at 125—130° for 4 hr. The mixture was poured on crushed ice, and the solution treated with calcium hydroxide to pH 5—6 and filtered. The residue was repeatedly washed with boiling water. The combined filtrates were evaporated to dryness, extracted thoroughly with boiling alcohol, and filtered. The filtrate was evaporated to dryness and the residual amino-acid sulphate passed in aqueous solution through De-acidite-E (Permutit). Evaporation of the eluate and recrystallisation of the residue from alcohol–ether gave 4-*methyl*-5-*vinylnicotinic acid* (0·8 g.), m. p. 178—180° (decomp.) (Found after drying at 70°: C, 60·0; H, 6·0. $C_9H_9O_2N,H_2O$ requires C, 59·7; H, 6·1%).

The above acid (50 mg.) in methanol (10 ml.) was hydrogenated at 50 lb. per sq. in. for 3 hr. after the addition of Adams catalyst (20 mg.). Filtration, evaporation, and crystallisation of the residue from alcohol gave 5-ethyl-4-methylnicotinic acid[1] (10 mg.), m. p. and mixed m. p. 163—165°.

Synthesis of Gentianine.—4-Methyl-5-vinylnicotinic acid (0·5 g.) in water (5 ml.) was treated with sodium hydrogen carbonate (0·3 g.) and 40% aqueous formaldehyde (5 ml.) and heated in a sealed tube at 100° for 10 hr. Excess of formaldehyde was then removed in steam. The solution was acidified, basified with solid sodium hydrogen carbonate after 1 hr., and extracted with chloroform. The dried (Na_2SO_4) extract was evaporated. Crystallisation of the residue (50 mg.) from light petroleum (b. p. 40—60°) gave *gentianine*, m. p. and mixed m. p. 80—81° (Found: C, 68·8; H, 4·9. $C_{10}H_9O_2N$ requires C, 68·6; H, 5·1%).

Gentianine (0·2 g.) in water (2 ml.) was heated with sodium hydrogen carbonate (0·2 g.) and 40% aqueous formaldehyde (3 ml.) at 100° for 15 hr. Working up as before resulted in the recovery of gentianine (0·1 g.), m. p. and mixed m. p. 80—81°.

We thank Mr. S. Selvavinayakam for microanalyses and the Government of India for the award of a senior scholarship (to S. R.).

PRESIDENCY COLLEGE, MADRAS, INDIA.

[*Received, January 28th*, 1957.]