

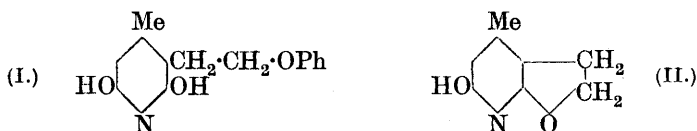
281. 2 : 6-*Dihydroxy-3- β -phenoxyethyl-4-methylpyridine.*

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THIS substance has been prepared by an application of Thorpe and Rogerson's method (J., 1905, **87**, 1685; compare also Kon and Nanji, J., 1931, 566; Ruzicka and Fornasir, *Helv. Chim. Acta*, 1919, **2**, 338) in the hope that it might prove to be a suitable intermediate for the

synthesis of quinine derivatives, *e.g.*, meroquinenine, which contain the vinyl group as a side chain. Very poor results followed an attempt to introduce the β-phenoxyethyl group at too early a stage : the condensation of ethyl acetoacetate with the potassium derivative of ethyl sodio-β-phenoxyethylcyanoacetate was fruitless. On the other hand, the phenoxyethyl group, best as the iodide, could be introduced into ethyl α-cyano-β-methylglutaconate, a carbethoxyl group being extruded.

On hydrolysis with concentrated hydrochloric acid, the condensation product yielded the *dihydroxyphenoxyethylmethylpyridine* (I) together with a by-product which, from its analysis, properties, and method of formation, we consider to have the constitution (II).



Phenoxyethyl bromide (120 g.) ("Organic Syntheses," IX, 72) and a 15% solution of NaI in Me₂CO (650 c.c.) were refluxed for 2 hrs., the filtered solution concentrated to $\frac{1}{3}$ vol., the residue added to H₂O, and β-phenoxyethyl iodide collected by means of Et₂O and distilled; b. p. 128°/12 mm. (yield, 85—90%) (Found : I, 51.0. Calc. : I, 51.2%). This is an improvement on von Braun's method (*Ber.*, 1913, **46**, 1788).

Interaction of the Potassio-derivative of Ethyl α-Cyano-β-methylglutaconate with β-Phenoxyethyl Bromide and Iodide.—Ethyl α-cyano-β-methylglutaconate (22.5 g.) was added to KOEt (3.9 g. of K) in abs. EtOH (70 c.c.) and after the introduction of β-phenoxyethyl bromide (20.1 g.) and KI (2 g.) the mixture was refluxed on the steam-bath for 8 hrs. The oil liberated by dil. HCl was taken up, washed (Na₂CO₃ aq.), and dried in Et₂O and distilled; b. p. 180—190°/2—3 mm. (12.3 g. or 45%). A portion redistilled, b. p. 170—172°/0.2 mm., gave analytical results indicating that it consisted chiefly of ethyl γ-cyano-γ-phenoxyethyl-β-methylcrotonate, mixed with a small proportion of ethyl α-cyano-α-phenoxyethyl-β-methylglutaconate (Found : C, 69.5; H, 6.9; N, 4.5. C₁₆H₁₉O₃N requires C, 70.3; H, 7.0; N, 5.1%).

The yields in later experiments were 40% and 37%, but an improvement followed by the use of the ready-formed phenoxyethyl iodide. The quantities employed were ethyl α-cyano-β-methylglutaconate (22.5 g.), K (3.9 g.), EtOH (70 c.c.), phenoxyethyl iodide (24.5 g.), and the mixture was refluxed for 4—5 hrs. and worked up as before. The yield of the distilled oil was 16 g. or 59%, and almost the same yield was obtained when an equiv. of Na was used instead of K. A redistilled fraction gave analytical results identical with those previously obtained.

2 : 6-Dihydroxy-3-β-phenoxyethyl-4-methylpyridine (I).—Hydrolysis of the condensation product with alc. KOH was unsatisfactory. The distilled condensation product (25 g.) was boiled under reflux with HCl (300 c.c.) for 10—12 hrs. The undissolved oil, which solidified on cooling, was the hydrochloride of the dihydroxypyridine *derivative*. The solution was decanted and concentrated to 50 c.c.; on cooling, the hydrochloride separated in colourless crystals.

The whole product was dissolved in NH_3 aq. and recovered from the filtered solution by acidification with AcOH, the dihydroxyphenoxyethylmethylpyridine separating as a greenish, almost white, mass of microscopic crystals. The HCl filtrate was rendered alkaline with NH_3 aq., the crystals (A, see below) removed, and the filtrate acidified with AcOH; more of the dihydroxy-pyridine derivative was thus obtained (total yield, 4.6 g. or 20%). The substance crystallised from EtOH (charcoal) in microscopic elongated prisms, m. p. 161° (Found: C, 68.7, 68.4; H, 6.1, 6.0; N, 5.9. $\text{C}_{14}\text{H}_{15}\text{O}_2\text{N}$ requires C, 68.6; H, 6.1; N, 5.7%). It has the properties typical of its class, developing a reddish-purple coloration with alc. FeCl_3 , is readily sol. in alkaline solutions, and decomposes carbonates. The ammoniacal solution becomes green on exposure to air.

Anhydro-2 : 6-dihydroxy-3-(β -hydroxyethyl)-4-methylpyridine (II). — The crystals (A), flat plates, had m. p. $249\text{--}250^\circ$ after recrystn. from much EtOH (Found: C, 63.7; H, 6.2; N, 9.1. $\text{C}_8\text{H}_9\text{O}_2\text{N}$ requires C, 63.6; H, 5.9; N, 9.3%). The substance is insol. in weak alkalis; its phenolic character is, however, shown by the reddish-purple coloration developed with alc. FeCl_3 . Unlike the dihydroxypyridine derivative, this substance exhibits no tendency to yield greenish-black oxidation products on exposure of its solutions to air.

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[Received, June 9th, 1932.]
