229. *An Attempted Synthesis of Perhydro-2 : 8-methylenepyridocoline.*

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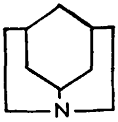
Attempts to prepare the compound named in the title, from 5-nitro*iso*phthalaldehyde, failed.

THE non-indole part of the 1954 formula for ajmaline[1] contained the cyclic system, perhydro-2 : 8-methylenepyridocoline (1-aza*tricyclo*[4 : 4 : $1^{4:8}$]undecane) (I), which has not yet been prepared. Some routes for its realisation have been examined, but without success.

A possible route appeared to be from 5-nitro*iso*phthalaldehyde to 1 : 3-di(carboxymethyl)-5-nitrobenzene and then cyclisation and reduction. *iso*Phthalaldehyde was prepared by the Sommelet reaction in good yield from *m*-xylylene dibromide and in poor yield from *m*-xylylenebishexaminium dibromide. It afforded 5-nitro*iso*phthalaldehyde in 67% yield. The Rosenmund reaction gave a tar, and the McFayden–Stevens and the Grundmann reaction gave polymers.


(I)

Attempts were then made to secure 1 : 3-di(carboxymethyl)-5-nitrobenzene from 5-nitro*iso*phthalaldehyde; the Erlenmeyer azlactone synthesis gave 5-nitro*iso*phthalylidenebis-(2-phenyloxazolone) and thence only 5-nitrophenylene-1 : 3-bis-ββ'-(α-benzamidoacrylic acid)—the methyl analogue yielded an uncrystallisable oil; the oxadiazine route[2] gave polymers at an early stage; and the rhodanine route gave a tar. Treatment of 5-nitro*iso*phthaloyl dichloride under the usual Arndt–Eistert conditions also gave a tar.

A different approach was an adaptation of Cronyn's path[3] to morphan, but 5-nitrophenylene-1 : 3-bis(ethyl benzoyloxyacetate) was obtained in very low overall yield, and the route was abandoned.

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[1] Anet, Chakravarti, Robinson, and Schlittler, *J.*, 1954, 1242.
[2] Jennings, *J.*, 1957, in the press.
[3] Cronyn, *J. Org. Chem.*, 1949, **14**, 1013.

EXPERIMENTAL

M. p.s are corrected.

iso*Phthalaldehyde.*—Hexamine (112 g.), *m*-xylylene dibromide [4] (53 g.), and 50% acetic acid (400 ml.) were refluxed together for 2 hr., becoming homogeneous after 10 min. Concentrated hydrochloric acid (200 ml.) was added, and refluxing was continued for 10 min. When cool, the solution was poured into excess of aqueous sodium carbonate; collection and drying gave crude *iso*phthalaldehyde (11·4 g.), m. p. 78—81°. The aqueous medium was extracted with chloroform, and the crude product already obtained added to the extracts. These, after washing with water, drying (Na_2SO_4), concentration, and dilution with ether, gave the pure product (23·5 g., 88%), m. p. 88—90° (Johnston *et al.*[5] give m. p. 89°). *iso*Phthalaldehyde, in MeOH, has maxima at 2250, 2400, 2900, and 3300 Å (ε 14,200, 13,060, 1520, and 230 respectively).

m-*Xylylenebishexaminium Dibromide.*—*m*-Xylylene dibromide (26·4 g.) was added to a solution of hexamine (30 g.) in chloroform (330 ml.). After 6 hr. at room temperature the precipitate was filtered off and dried at room temperature, to give m-*xylylenebishexaminium dibromide* (57 g., 100%), m. p. 178—180° (decomp.) (Found: Hal, 39·6, 39·4. $C_{20}H_{32}N_8Br_2,CHCl_3$ requires Hal, 40·1%). In MeOH, it has maxima at 2080 and 2400 Å (ε 12,050 and 1610 respectively).

5-*Nitro*iso*phthalaldehyde.*—A mixture of ammonium sulphate (4 g.), concentrated sulphuric acid (12 g.), and nitric acid (2 g.; *d* 1·5) was cooled to −50°, and a solution of *iso*phthalaldehyde (1 g.) in concentrated sulphuric acid (12 g.) added, the whole allowed to attain room temperature during 12 hr. and kept thereat for a similar period. Pouring the mixture on ice gave a light yellow precipitate, which after being washed with water afforded 5-*nitro*iso*phthalaldehyde* (0·9 g., 67%), m. p. 105—108°. This is pure enough for use. Recrystallisation from ether gave short fawn needles, m. p. 128—129° (Found: C, 53·8; H, 3·0. $C_8H_5O_4N$ requires C, 53·65; H, 2·8%). In EtOH, it has one maximum at 2300 Å (ε 13,000) and inflections at 2400 and 1650 Å (ε 13,060 and 1955 respectively). The *dioxime* had m. p. 207·5—208° (Found: C, 45·9; H, 3·4. $C_8H_7O_4N_3$ requires C, 45·9; H, 3·4%).

5-*Nitro*iso*phthaloyl Dichloride.*—5-Nitro*iso*phthalic acid [6] (15 g., dried at 100°/15 mm. for 1 hr. before use) was refluxed with thionyl chloride (200 g.), until all had dissolved (about 48 hr.). The excess of thionyl chloride was removed *in vacuo*. The residual oil, on cooling, gave off-white needles of 5-*nitro*iso*phthaloyl dichloride* (17·6 g., 100%), m. p. 67·5—68° (Found: N, 5·55. $C_8H_3O_4Cl_2N$ requires N, 5·65%).

*Dimethyl 5-Nitro*iso*phthalate.*—To ice-cold ethereal diazomethane (from methyl-*N*-nitrosourea, 20 g.) was added 5-nitro*iso*phthalic acid (9·8 g.), in small portions, during a few minutes. Decolorisation was complete in 10 min., and the white precipitate was filtered off, to give dimethyl 5-nitro*iso*phthalate (10·4 g., 93%), m. p. 122—124°. Müller [7] reported m. p. 123°.

5-*Nitro*iso*phthaldihydrazide.*—Dimethyl 5-nitro*iso*phthalate (6·85 g.) was refluxed in 100% hydrazine hydrate (3·7 g.) and ethanol (50 ml.) for 70 min. After cooling, filtration gave the *dihydrazide* (6·7 g., 98%), m. p. 237—239°. Recrystallisation from ethanol gave granules, m. p. 249—250° (Found: N, 29·0. $C_8H_9O_4N_5$ requires N, 29·3%). The *diethylidene derivative* had m. p. 243—244° (Found: C, 49·8; H, 4·7; N, 24·0. $C_{12}H_{13}O_4N_5$ requires C, 49·45; H, 4·8; N, 24·05%).

5-*Nitro*-sym-*di*-N-*toluene*-p-*sulphonyl*iso*phthalhydrazide.*—5-Nitro*iso*phthaldihydrazide (7·0 g.), and toluene-*p*-sulphonyl chloride (11·9 g.) in pyridine (120 ml.) were refluxed for 4 hr., filtered, and treated with water (500 ml.). An oil which separated solidified at 0° and on being washed, afforded 5-*nitro*-sym-*di*-N-*toluene*-p-*sulphonyl*iso*phthaloylhydrazide* (7·5 g., 47%), m. p. 243—243·5° (decomp.). Recrystallisation from acetone–ethanol gave fawn crystals, m. p. 248—248·5° (Found: C, 48·5; H, 3·7; N, 12·8. $C_{22}H_{21}O_8N_5S_2$ requires C, 48·3; H, 3·9; N, 12·8%). In EtOH, it has maxima at 2080 and 2180 Å (ε 18,860 and 20,100 respectively).

NN′-*Ditoluene*-p-*sulphonylhydrazine.*—100% Hydrazine hydrate (22 g.) and crushed ice (11 g.) were kept at 0° while, with vigorous stirring, toluene-*p*-sulphonyl chloride (37·6 g.) was added, in small portions, during 45 min. Stirring was continued for 1 hr., then filtration gave NN′-*ditoluene*-p-*sulphonylhydrazine* (26·4 g., 39%). Recrystallisation from acetone–water

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[4] Kipping, *J.*, 1888, 26.

[5] Johnston and Williams, *J. Amer. Chem. Soc.*, 1947, **69**, 2065.

[6] Meyer and Wesche, *Ber.*, 1917, **50**, 444.

[7] Müller, *Ber.*, 1909, **42**, 433.

gave white feathery needles, m. p. 219—220° (decomp.) (Found: C, 49·6; H, 4·8; N, 8·3; S, 18·5. $C_{14}H_{16}O_4N_2S_2$ requires C, 49·4; H, 4·7; N, 8·2; S, 18·8%). In EtOH, it has maxima at 2310, 2560, 2635, 2690, and 2745 Å (ε 32,000, 1530, 1700, 1600, and 1490 respectively). It is soluble in aqueous sodium hydroxide amd insoluble in hydrochloric acid, which proves the position of the acyl groups.

1 : 3-*Bisdiazoacetyl*-5-*nitrobenzene*.—To ice-cold ethereal diazomethane (from methyl-*N*-nitrosourea, 12 g.) was added powdered 5-nitro*iso*phthaloyl dichloride (3·0 g.), in small portions, in 1 min. Immediate effervescence occurred, and the product was precipitated. After a few minutes 1 : 3-bisdiazoacetyl-5-nitrobenzene (2·4 g., 77%) was filtered off, washed with ether, and dried, and thus had m. p. 143—145°. It could not be satisfactorily analysed.

3 : 5-*Bisacetoxyacetylnitrobenzene*.—The bisdiazoacetylnitrobenzene (6·4 g.) was heated in acetic acid (125 ml.) in a boiling-water bath for 2 hr. On cooling, the entire product crystallised. After being washed with water and dried, 1 : 3-*bisacetoxyacetyl*-5-*nitrobenzene* (5·4 g., 68%) had m. p. 176—177°. Recrystallisation from methanol yielded white needles, m. p. 178—179° (Found: C, 51·8; H, 4·1; N, 4·55. $C_{14}H_{13}O_8N$ requires C, 52·0; H, 4·05; N, 4·3%). In EtOH, it has one maximum at 2290 Å (ε 13,700).

5-*Nitro*iso*phthalylidenebis*-(2-*methyloxazolone*).—A mixture of 5-nitro*iso*phthalaldehyde (1·8 g.), aceturic acid (2·2 g.), fused sodium acetate (1·65 g.), and acetic anhydride (5·5 g.) was heated in a boiling-water bath for 4 hr., with occasional shaking. Water (10 ml.) was added, to the cooled solution, and the dark yellow cake filtered off and washed with hot water and hot ethanol, to give the *bisoxazolone* (3·17 g., 93%), m. p. >350°; this is insoluble in the usual solvents. Before analysis, it was washed with ethanol and ether (Found: C, 55·9; H, 3·25; N, 12·0. $C_{16}H_{11}O_6N_3$ requires C, 56·3; H, 3·25; N, 12·3%). It has, in MeOH, one maximum at 2900 Å (ε 5020).

5-*Nitro*iso*phthalylidenebis*-(2-*phenyloxazolone*).—5-Nitro*iso*phthalaldehyde (1·8 g.), hippuric acid (3·6 g.), fused sodium acetate (1·64 g.), and acetic anhydride (5·5 g.) at 100° for ½ hr. gave 5-*nitro*iso*phthalylidenebis*-(2-*phenyloxazolone*) (3·57 g., 77%), m. p. 269—271° (Found: C, 67·1; H, 3·2; N, 9·0. $C_{26}H_{15}O_6N_3$ requires C, 67·1; H, 3·2; N, 9·0%). In MeOH, it has maxima at 2400, 2600, 3000, and 3500 Å (ε 1040, 1060, 690, and 860 respectively).

5-*Nitrophenylene*-1 : 3-*bis*-ββ′-(α-*benzamidoacrylic Acid*).—5-Nitro*iso*phthalylidenebis-(2-phenyloxazolone) (3·0 g.) was heated with 10% aqueous sodium hydroxide (30 ml.) until dissolution was complete (about 5 min.). Water (20 ml.) was then added, and the solution made acid to Congo-red with hydrochloric acid. The precipitate was filtered off, washed with water, and dried. 5-*Nitrophenylene*-1 : 3-*bis*-ββ′-(α-*benzamidoacrylic acid*) (3·1 g., 100%) thus obtained had m. p. 247—248° (Found: C, 61·6; H, 4·1; N, 8·0. $C_{26}H_{19}O_8N_3,\frac{1}{2}H_2O$ requires C, 61·2; H, 3·9; N, 8·2%). In MeOH, it has maxima at 2350, 2500, 2650, 2750, 2850, and 2950 Å (ε 45,100, 37,500, 38,500, 38,000, 34,560, and 33,250 respectively).

5-*Nitro*iso*phthaloylidenebisrhodanine*.—5-Nitro*iso*phthalaldehyde (1·8 g.), rhodanine (2·66 g.), fused sodium acetate (4·92 g.), and glacial acetic acid (12 g.) were heated together at 100° for 15 min. The mixture soon became homogeneous, and then deposited the orange product. Water (25 ml.) was added to the cooled mixture, and the solid filtered off, washed, and dried to give the *bisrhodanine* (3·5 g., 85%), m. p. >300°. Recrystallisation from acetone gave yellow needles (Found: C, 41·5; H, 2·15; N, 10·1. $C_{14}H_7O_4N_3S_4$ requires C, 41·1; H, 1·7; N, 10·2%). In $CHCl_3$, it has maxima at 2650, 3000, 3650, and 3900 Å (ε 8400, 7500, 26,000, and 26,000 respectively).

m-*Nitrobenzylidenerhodanine*.—*m*-Nitrobenzaldehyde (15·1 g.), rhodanine (13·3 g.), fused sodium acetate (24·6 g.), and acetic acid (60 ml.), as above, gave m-*nitrobenzylidenerhodanine* (20·0 g., 80%), yellow needles, m. p. 270·5—271° (Found: N, 10·6. $C_{10}H_6O_3N_2S_2$ requires N, 10·5%).

5-*Nitrophenylene*-1 : 3-*bis*(*benzoyloxyacetonitrile*).—5-Nitro*iso*phthalaldehyde (1·8 g.) and benzoyl chloride (3·2 g.) were mixed together, and potassium cyanide (1·3 g.) in water (4 ml.) was added. The mixture became slightly brown and very hot. After 1 hr., hot water (10 ml.) was added, and, when cool, the whole was extracted with ether and then with chloroform. The two organic layers were combined and washed with aqueous sodium hydrogen carbonate (to remove benzoic acid), and then with water. After drying (Na_2SO_4), the solvents were removed, and the resultant yellow oil was treated with aqueous-ethanolic sodium hydrogen sulphite [8] (22 + 18 ml.) to remove unchanged dialdehyde. The remaining oil was washed with water and

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[8] Vogel, " Practical Organic Chemistry," Longmans, London, 1948, p. 330.

dried by distillation with methanol and benzene. In 3 weeks at room temperature, it changed to pink plates of crude 5-nitrophenylene-1 : 3-bis(benzoyloxyacetonitrile) (2·25 g., 51%), m. p. 51·5—55·5°. The infrared spectrum of this preparation was almost identical with that of pure *O*-benzoyl-*m*-nitromandelonitrile.[9] This sample could not be purified.

*5-Nitrophenylene-*1 : 3-*bis(ethyl benzoyloxyacetate)*.—Crude 5-nitrophenylene-1 : 3-bis(benzoyloxyacetonitrile) (1·65 g.) was refluxed with hydrogen chloride (0·9 g.) in absolute ethanol (5·4 ml.) for ½ hr. The precipitate was filtered off, and removal of the solvent gave an oil, which on addition of ether afforded *5-nitrophenylene-*1 : 3-*bis(ethyl benzoyloxyacetate)* (0·15 g., 7·5%) as granular crystals, m. p. 146—150°. Recrystallisation from methanol–water gave material of m. p. 156—157·5° (Found : C, 62·4; H, 5·0; N, 2·7. $C_{28}H_{25}O_{10}N$ requires C, 62·8; H, 4·7; N, 2·6%). In EtOH, it has one maximum at 2300 Å (ε 17,300).

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[9] Ref. 4, p. 1017.