59. *Phthalans. Part I. The Preparation of Phthalan-4-carboxylic Acid.*

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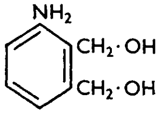
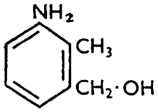
Phthalan-4-carboxylic acid was prepared from dimethyl 3-aminophthalate.

Following earlier studies on the formation of phthalan-4-carboxylic acids, substituted in the benzene ring, by isomerisation of the corresponding 4-hydroxymethylphthalides [1,2] it was desired to synthesise the unknown phthalan-4-carboxylic acid (III). The route envisaged required 3-aminophthalyl alcohol (I) as starting material.



(I)



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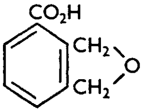
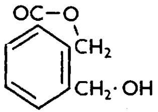


(III)



(IV)

Dimethyl 3-aminophthalate [3] was treated with boiling ethereal lithium aluminium hydride; two products, separated by crystallisation and chromatography, were isolated. The first was the expected 3-aminophthalyl alcohol (I), which was formed in only slightly higher yield at 0°, while the other product, $C_8H_{11}ON$, had m. p. 106—107°. The alcohol (I) was partly converted into the compound $C_8H_{11}ON$ by more vigorous treatment with lithium aluminium hydride. Conover and Tarbell [4] have shown that while reduction by lithium aluminium hydride of benzenoid carbonyl compounds with *o*- or *p*-amino-groups gives the corresponding alcohol under normal conditions, prolonged reaction results in the formation of the corresponding deoxy-compound. The conditions used by these authors were much more drastic than those described in this paper. It therefore appeared that the compound, $C_8H_{11}ON$, must be formulated as 3-amino-2-methylbenzyl alcohol (II), whose preparation as an oil has been described by Erlenmeyer and his collaborators [5] from 2-methyl-3-nitrobenzoic acid by successive conversion into the acyl chloride and the thiobenzyl ester followed by nickel desulphurisation. An unambiguous preparation of the alcohol (II) was therefore desirable; we have accomplished this by catalytically hydrogenating methyl 2-methyl-3-nitrobenzoate and then reducing the resulting amino-ester with lithium aluminium hydride, the compound $C_8H_{11}ON$ (II) then being obtained in good yield. The Swiss workers' product was probably insufficiently purified.

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[1] Brown and Newbold, *J.*, 1952, 4878.

[2] Blair and Newbold, *J.*, 1954, 3935; Blair, Logan, and Newbold, *J.*, 1956, 3608; Logan and Newbold, *J.*, 1957, 1946.

[3] Twiss and Heinzelmann, *J. Org. Chem.*, 1950, **15**, 496.

[4] Conover and Tarbell, *J. Amer. Chem. Soc.*, 1950, **72**, 3586.

[5] Sorkin, Krähenbühl, and Erlenmeyer, *Helv. Chim. Acta*, 1948, **31**, 65.

Replacement of the amino-group of 3-aminophthalyl alcohol (I) by the cyano-group followed by alkaline hydrolysis gave in small yield an acid product, $C_9H_8O_3$, which we regard as phthalan-4-carboxylic acid (III). This acid has presumably been formed by the base-catalysed isomerisation of 4-hydroxymethylphthalide (IV), formed initially. We did not obtain the phthalide (IV) from the uncrystallisable neutral fraction of the hydrolysis. Brown and Newbold[1] have shown that 5 : 6-dimethoxyphthalan-4-carboxylic acid is converted into 4-hydroxymethylmeconin (4-hydroxymethyl-6 : 7-dimethoxyphthalide) when heated with acid. This method being used phthalan-4-carboxylic acid gave a neutral solid, not obtained pure, but whose infrared spectrum in Nujol showed hydroxyl (3390 cm.$^{-1}$) and phthalide-carbonyl (1770 cm.$^{-1}$) peaks, indicating that the product was crude 4-hydroxymethylphthalide (IV).

EXPERIMENTAL

Ultraviolet-light absorptions were determined in ethanol.

Methyl 2-Methyl-3-nitrobenzoate.—An ice-cooled solution of 2-methyl-3-nitrobenzoic acid[5] (2·55 g.) in methanol (30 c.c.) was treated with excess of an ethereal solution of diazomethane, and the reaction solution kept overnight. Methyl 2-methyl-3-nitrobenzoate (2·2 g.) formed felted needles, m. p. 65—66° (from aqueous methanol) (Found: C, 55·3; H, 4·6. Calc. for $C_9H_9O_4N$: C, 55·4; H, 4·65%). The m. p. of the ester obtained[6] from the acid chloride is 66°.

3-Aminophthalyl Alcohol.—Dimethyl 3-aminophthalate (2·56 g.), prepared from dimethyl 3-nitrophthalate (3·12 g.) by catalytic reduction in ethyl acetate with Raney nickel catalyst[7] (1·2 g.; W-2), was dissolved in ether (100 c.c.) and added dropwise during 15 min. to a stirred refluxing solution of lithium aluminium hydride (2 g.) in ether (200 c.c.). After 2½ hr. at the boiling point the mixture was cooled to 0° and excess of hydride decomposed by addition of crushed ice. The ethereal layer was separated and the aqueous phase extracted with ether (100 c.c.). The combined ethereal solution was washed with water, dried (Na_2SO_4), and evaporated. Crystallisation of the residue (0·90 g.) from benzene–ethyl acetate–light petroleum (b. p. 60—80°) gave material (0·36 g.; mother liquor *A*) which after several crystallisations from benzene gave *3-aminophthalyl alcohol* (0·25 g.; 14%) as needles, m. p. 96—97° (Found: C, 63·0; H, 6·7. $C_8H_{11}O_2N$ requires C, 62·7; H, 7·2%); $\lambda_{max.}$ 2080 (ε = 29,000), 2410 (ε = 6000), and 2960 Å (ε = 2300). Acetic anhydride–pyridine treatment on the steam-bath for 3 hr. gave the *triacetate* as needles, m. p. 122—122·5° [from benzene–ether–light petroleum (b. p. 60—80°)] (Found: C, 60·5; H, 5·8. $C_{14}H_{17}O_5N$ requires C, 60·2; H, 6·1%); $\lambda_{max.}$ 2075 (ε = 29,800) and 2340 (ε = 6300), $\lambda_{infl.}$ 2700 Å (ε = 1000).

When this reduction was carried out at 0° during 40 hr. the yield of pure 3-aminophthalyl alcohol was 16%.

3-Amino-2-methylbenzyl Alcohol.—(*a*) Mother liquor *A* (see above) was concentrated to half-bulk, and light petroleum (b. p. 60—80°) added. The crystals (0·41 g.) which separated on cooling were chromatographed in benzene (30 c.c.) on alumina (12 g.). Elution with benzene (100 c.c.) and ether (100 c.c.) followed by evaporation of the combined eluates and crystallisation of the residue from benzene gave *3-amino-2-methylbenzyl alcohol* as needles, m. p. 106—107° (Found: C, 70·1; H, 7·8; N, 10·3. $C_8H_{11}ON$ requires C, 70·0; H, 8·1; N, 10·2%); $\lambda_{max.}$ 2070 (ε = 26,800), 2355 (ε = 6300), and 2900 Å (ε = 2000). The *diacetate*, prepared as described for the triacetate above, formed felted needles, m. p. 147·5—148° [from benzene–light petroleum (b. p. 60—80°)] (Found: C, 65·6; H, 6·4; N, 6·7. $C_{12}H_{15}O_3N$ requires C, 65·1; H, 6·8; N, 6·3%); $\lambda_{max.}$ 2110 (ε = 21,500), $\lambda_{infl.}$ 2310 Å (ε = 6400). Further elution of the column with ether–methanol and methanol gave 3-aminophthalyl alcohol, m. p. 96—97° (108 mg.).

(*b*) Methyl 3-amino-2-methylbenzoate (1·53 g.), prepared by catalytic hydrogenation of the corresponding nitro-compound over Raney nickel at room temperature and atmospheric pressure, was added in ether (50 c.c.) during 20 min. to a stirred, refluxing suspension of lithium aluminium hydride (0·8 g.) in ether (100 c.c.). After 2½ hours' refluxing the product was isolated *via* ether. Evaporation gave a solid (1·28 g.) which after crystallisation and sublimation at 75°/10^{-3} mm. had m. p. 106—106·5° alone or on mixing with preparation (*a*) The infrared spectra of preparations (*a*) and (*b*) in Nujol mull were identical.

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[6] van Scherpenzeel, *Rec. Trav. chim.*, 1901, **20**, 149.

[7] Cf. ref. 3.

(*c*) A solution of 3-aminophthalyl alcohol (0·4 g.) in tetrahydrofuran (30 c.c.) was added to a stirred, refluxing suspension of lithium aluminium hydride (0·3 g.) in ether (75 c.c.). After $2\frac{1}{2}$ hr. the product was isolated and purified by chromatography as in (*a*). 3-Amino-2-methylbenzyl alcohol (246 mg.) formed felted needles (from benzene), m. p. 106—107·5° undepressed on mixing with preparation (*a*). Elution of the column with chloroform–methanol (19 : 1) gave unchanged 3-aminophthalyl alcohol (140 mg.), m. p. and mixed m. p. 93—97·5°.

Phthalan-3-carboxylic Acid.—3-Aminophthalyl alcohol (1·0 g.) in hydrochloric acid (1·86 c.c.; *d* 1·16) and water (18 c.c.) was diazotised. Meanwhile a solution of anhydrous nickel chloride (1·32 g.) and potassium cyanide (1·62 g.) in water (10 c.c.) was boiled for 2 min., cooled, and neutralised with sodium carbonate (0·36 g.). To this solution, at $<5°$, was added the diazonium solution which had been neutralised with sodium carbonate. After being kept at room temperature overnight the mixture was filtered (residue *B*) and the filtrate extracted with ether (3 × 50 c.c.). The combined ethereal extracts were washed with water, dried (Na_2SO_4), and evaporated to a brown gum (222 mg.). Residue *B* was extracted with chloroform (2 × 50 c.c.) to yield a gum (246 mg.). The combined gums were heated under reflux with aqueous potassium hydroxide (25 c.c.; 10%) for 3 hr. The cooled solution was acidified (Congo red) with hydrochloric acid (*d* 1·16), and the precipitate extracted with chloroform (3 × 25 c.c.). The combined extracts were washed with aqueous sodium hydrogen carbonate (2 × 50 c.c.; 10%) and water and dried (Na_2SO_4). Evaporation gave an intractable red gum (72 mg.). The alkaline washings were acidified (Congo-red) with hydrochloric acid (*d* 1·16) and extracted with chloroform. The dried (Na_2SO_4) extract on evaporation gave a solid (114 mg.) which on crystallisation from benzene (charcoal) gave *phthalan-4-carboxylic acid* as needles, m. p. 195·5—199° (Found: C, 65·5; H, 5·2. $C_9H_8O_3$ requires C, 65·85; H, 4·9%); $\lambda_{max.}$ 2065 (ε = 19,600), 2300 (ε = 9500), and 2850 Å (ε = 2200).

Attempted Preparation of 4-Hydroxymethylphthalide.—Phthalan-4-carboxylic acid (32 mg.) was heated under reflux for 3 hr. with hydrochloric acid (10 c.c.; 5N). The cooled solution was diluted with water (30 c.c.) and extracted with chloroform (3 × 40 c.c.); the combined extracts were washed with aqueous sodium hydrogen carbonate (2 × 25 c.c.) and water and dried (Na_2SO_4). Evaporation of the solvent, sublimation of the residue at $70°/10^{-3}$ mm. and trituration of the sublimate with a little dry ether gave a white solid, m. p. 103—105·5° (2 mg.).

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