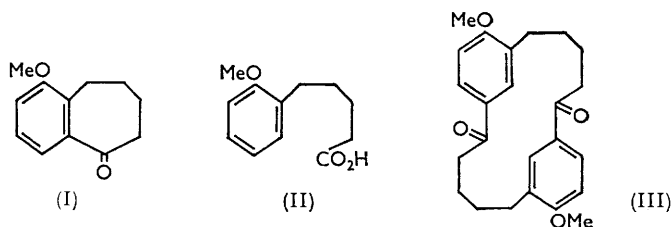


792. *The Preparation of (5,5)-Metacyclophan.*

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Cyclisation of δ -*o*-methoxyphenylvaleric acid by polyphosphoric acid has been shown to be intermolecular, yielding "dimeric" and "trimeric" ketones. The "dimeric" ketone (III) was used to prepare the heretofore unknown (5,5)-metacyclophan (VIII).

SINCE 3'-methoxy-2,3-benzocycloheptenone (I) was desired as a starting material, cyclisation¹ of δ -*o*-methoxyphenylvaleric acid (II) by polyphosphoric acid was investigated. This reaction had been reported² to give "high-melting neutral products, insoluble in the common solvents." In our hands, the neutral product obtained was readily soluble in chloroform and crystallised from benzene and acetone. The structure was therefore investigated. By a careful and tedious chromatographic separation a "dimeric" diketone



was obtained in 30% yield and formulated as (III) as a result of molecular-weight determination and the formation of 4-methoxyisophthalic acid by potassium permanganate oxidation of the reduction product (IV). Two other crystalline compounds, presumably an isomeric "dimer" and a "trimeric" ketone (see p. 4017) were also isolated, in low yield, but have not yet been identified.

That intermolecular rather than intramolecular cyclisation takes place, is not surprising

¹ Horton and Walker, *J. Amer. Chem. Soc.*, 1952, **74**, 758.

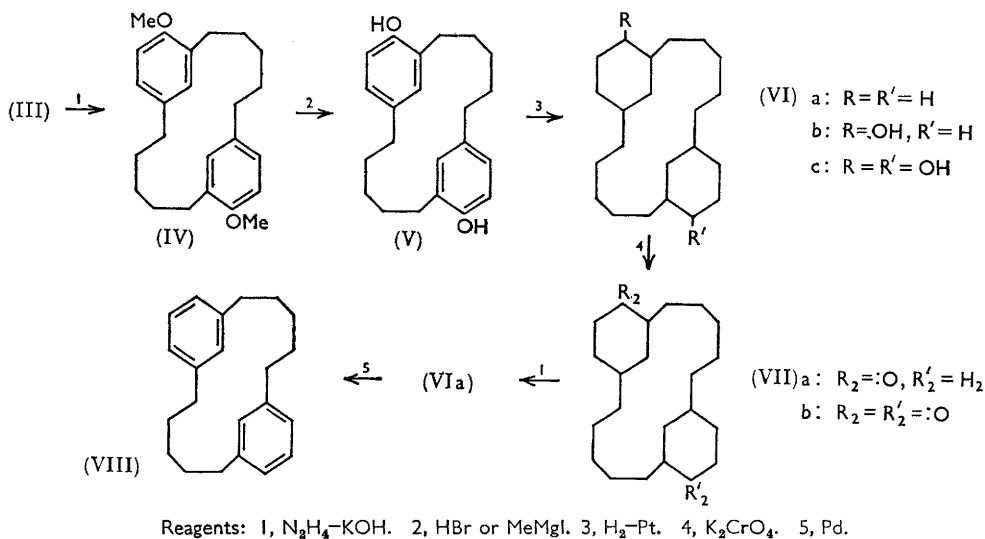
² Gardner, Horton, Thompson, and Twelves, *J. Amer. Chem. Soc.*, 1952, **74**, 5527.

in view of the deactivating effect of the *m*-methoxyl group; this decreases the yield in Friedel-Crafts-type intramolecular cyclisations.³ Dimeric and trimeric ketones were obtained⁴ also in the high-dilution cyclisation of 7-phenylheptanoyl chloride.

The dimer (III) was used to prepare the new (5,5)-metacyclophan (VIII). Huang-Minlon reduction⁵ of this diketone caused partial demethylation,⁶ and the aryl ether (IV) was obtained only after remethylation with methyl sulphate. Demethylation of the ether (IV) was effected with hydrogen bromide or by treatment with methylmagnesium iodide,⁷ giving the phenol (V). Hydrogenation of the phenol over platinum oxide in acetic acid in the presence of a small amount of hydrogen chloride resulted in extensive hydrogenolysis and a mixture of the saturated hydrocarbon (VIa) and the saturated mono- and di-alcohols (VIb and c) and their acetates was obtained. After cleavage of the acetates by lithium aluminium hydride to the alcohols (VIb and c) the synthesis was continued along two routes.

In one the hydrocarbon (VIa) was separated by chromatography from the alcohols and dehydrogenated to the metacyclophan (VIII) with 30% palladised carbon. Oxidation of the combined alcohol fractions with potassium chromate⁸ yielded oily mono- and diketones (VIIa, b) separable by chromatography and identified as their 2,4-dinitrophenylhydrazones.

In the second sequence the crude mixture (VIa, b, and c) was directly oxidised, reduced, and dehydrogenated. Chromatographic purification of the crude product yielded the (5,5)-metacyclophan (VIII), identical with that obtained by the first route.



The infrared spectrum in the 2000—1650 cm.⁻¹ region is characteristic of benzene substitution.⁹ The cyclic ether (IV) and the (5,5)-metacyclophan (VIII) showed analogous absorption patterns to those of the structurally similar 2,4-dimethylanisole and *m*-xylene, respectively, in this frequency range.

The ultraviolet absorption of the metacyclophan was very similar to that of *m*-xylene,

³ Locket and Short, *J.*, 1939, 789. For a discussion see W. S. Johnson in "Organic Reactions," Wiley, New York, 1944, Vol. II, p. 120.

⁴ Schubert, Sweeny, and Latourette, *J. Amer. Chem. Soc.*, 1954, **76**, 5462.

⁵ Huang-Minlon, *J. Amer. Chem. Soc.*, 1946, **68**, 2487.

⁶ Cf. Bien and Boazi, *J.*, 1959, 1727; Gates and Tshudi, *J. Amer. Chem. Soc.*, 1956, **78**, 1380.

⁷ Späth, *Monatsh.*, 1914, **35**, 319; Wilds and Cormack, *J. Amer. Chem. Soc.*, 1948, **70**, 4127; Johnson, Rogier, and Ackerman, *J. Amer. Chem. Soc.*, 1956, **78**, 6322.

⁸ Fieser and Rajagopalan, *J. Amer. Chem. Soc.*, 1950, **72**, 5530; cf. Johnson, Rogier, and Ackerman, *ibid.*, 1956, **78**, 6322.

⁹ Bellamy, "The Infrared Spectra of Complex Molecules," Methuen, London, 1958, p. 67.

which indicates the absence of interaction between the two benzene nuclei. This is analogous to the behaviour of the paracyclophan with the same number of carbon atoms in the aliphatic chains.¹⁰

EXPERIMENTAL

δ-*o*-Methoxyphenylvaleric Acid (II).—The following procedure was kindly communicated by Dr. A. Dreiding. A solution of *o*-methoxybenzaldehyde (13.6 g.) in methyl crotonate (20.0 g.) was added dropwise to a solution from potassium (7.8 g.) in dry *t*-butanol (150 ml.), the temperature being kept at 30°. The solution was left overnight at room temperature, then acidified with 50% acetic acid and extracted with ether (3 × 50 ml.). The crude residue (*ca.* 30 g.) obtained on evaporation of the dried (MgSO₄) extracts was hydrogenated in ethyl acetate (180 ml.) in the presence of 10% palladised carbon at an initial hydrogen pressure of 60 lb./sq. in. The catalyst and solvent were removed and the semicrystalline residue was refluxed with methanolic potassium hydroxide (11 g. in 90 ml.) for 2 hr. The unsaponified material was removed by extraction of the diluted alkaline solution with ether. The aqueous layer was then acidified with hydrochloric acid, and the separated oil removed in ether. Drying (MgSO₄) and evaporation gave the crude acid (20 g.), m. p. 77—79° (from dilute acetic acid) (m. p. 79—81° has been reported for the crude acid²). Several recrystallisations from 2,2,4-trimethylpentane gave the analytically pure sample, m. p. 85° (Found: C, 68.9; H, 7.8; O, 23.35. Calc. for C₁₂H₁₆O₃: C, 69.2; H, 7.75; O, 23.05%).

Cyclisation of δ-*o*-Methoxyphenylvaleric Acid.—To a solution of phosphorus pentoxide (210 g.) in 85% phosphoric acid (140 ml.) the acid (II) (7.5 g.) was added at 90° with stirring. Stirring was continued for 2 hr. at 90°, a red colour developing. The mixture was poured into ice-water, and the precipitate removed, suspended in 10% sodium carbonate solution, refiltered, and washed with water. The dried product (7.1 g.) is dark yellow.

The crude product (2 g.) was chromatographed in chloroform (20 ml.) on alumina (90 g.; Fisher) (prepared in 1:1 in hexane-benzene). Development was started with the named solvent mixture (750 ml.) and continued with pure benzene (5 l.), which eluted the *diketone* (III) (0.5 g.), m. p. 205° (from benzene) (Found: C, 75.9; H, 7.5; O, 16.7; OMe, 16.2%; *M*, 352. C₂₄H₂₈O₄ requires C, 75.8; H, 7.4; O, 16.8; OMe, 16.3%; *M*, 380.5). The *dioxime* had m. p. 261—262° (from 2-methoxyethanol) (Found: C, 69.6; H, 7.45; N, 6.3. C₂₄H₃₀O₄N₂ requires C, 70.2; H, 7.4; N, 6.3%).

The residue was eluted from the column with chloroform and rechromatographed on alumina (90 g.; Fisher) as described above. Benzene (3 l.) eluted more (0.1 g.) of compound (III). Elution was then continued with benzene-chloroform (93:7), yielding a second dimeric *diketone* (*ca.* 0.15 g.), m. p. 198.5—199.5° (from benzene) (Found: C, 75.3; H, 7.45; O, 16.9; OMe, 16.0%; *M*, 400. C₂₄H₂₈O₄ requires C, 75.8; H, 7.4; O, 16.8; OMe, 16.3%; *M*, 380.5). Benzene-chloroform (85:15) eluted a trimeric *triketone* (*ca.* 0.07 g.), m. p. 165—167° (from benzene) (Found: C, 75.1; H, 7.4; O, 17.0%; *M*, 610. C₃₆H₄₂O₆ requires C, 75.8; H, 7.4; O, 16.8%; *M*, 570). Intermediate fractions gave crystalline mixtures, and fractions eluted with solvents of higher chloroform content gave glassy polymers.

Huang-Minlon Reduction of the Diketone (III).—The *diketone* (0.5 g.) was refluxed with diethylene glycol (15 ml.), potassium hydroxide (1 g.), and 95% hydrazine hydrate (1.5 ml.) for 2 hr. The temperature was raised slowly to 190—200° and kept thereat for 4 hr. The cooled solution was acidified with dilute hydrochloric acid and extracted with ether. After the usual working-up a semi-solid residue (0.4 g.) was obtained, infrared absorption of which showed partial demethylation.⁶ The crude product was treated in acetone (15 ml.) with potassium hydroxide solution (3.2 g. in 11 ml. of water) and methyl sulphate (5 ml.) in acetone (4 ml.) at 50° with vigorous stirring. The temperature was slowly raised to 60°, and the acetone removed by distillation. The mixture was stirred at 60° for 30 min. and at 95° for 1 hr. The alkaline solution was diluted with water, and the precipitate removed and washed with dilute hydrochloric acid and with water. The crude material was dried and percolated through alumina (16 g.; Fisher) in benzene-hexane (2:1), giving white crystals (0.4 g.), m. p. 138°. Recrystallisation gave the pure *ether* (IV), m. p. 139—140° (from acetic acid) (Found: C, 81.6; H, 9.0; O, 9.1. C₂₄H₃₂O₂ requires C, 81.8; H, 9.1; O, 9.1%).

Permanganate Oxidation of the Ether (IV).—To the boiling solution of the ether (0.10 g.) in

¹⁰ Cram, Allinger, and Steinberg, *J. Amer. Chem. Soc.*, 1954, **76**, 6132.

pyridine (30 ml.) and 0.1N-sodium hydroxide (30 ml.), potassium permanganate (5 g.) was added during 4 hr. Manganese dioxide was removed, and the solution evaporated to dryness *in vacuo*, acidified with hydrochloric acid, and extracted continuously with ether for 24 hr. The residue obtained on evaporation of the dried (MgSO_4) ether solution gave 4-methoxyisophthalic acid, m. p. and mixed m. p. 269—271° (from water) (0.06 g., 54%), having the correct infrared spectra (in KBr).

Demethylation of the Ether (IV).—(a) The ether (0.4 g.) was demethylated in a boiling mixture of 30% hydrogen bromide in glacial acetic acid (15 ml.), 50% hydrogen iodide (1 ml.), and water (1 ml.) for 3 hr. After dilution with water, a few drops of sulphurous acid solution were added and the mixture was extracted with ether. The residue (0.35 g.) obtained in the usual way was taken up in a few ml. of benzene and chromatographed on silica gel (5 g.). Benzene eluted a small amount of oil, and the cyclic phenol (V) (0.25 g.) was obtained by elution with benzene-chloroform (50 : 50) and chloroform; it had m. p. 159—161° (from carbon tetrachloride) (Found: C, 81.4; H, 8.7; O, 9.9. $\text{C}_{22}\text{H}_{28}\text{O}_2$ requires C, 81.45; H, 8.65; O, 9.9%).

(b) The ether (0.21 g.) was added to a Grignard solution prepared from magnesium (0.1 g.) and methyl iodide (0.3 ml.) in ether (3 ml.). The ether was then removed and the mixture heated at 180°. Gas evolution immediately started and heating was continued for 1.5 hr. The cooled mixture was treated with dilute hydrochloric acid and extracted with ether. The residue (0.2 g.) obtained from the dried ethereal solution gave the cyclic phenol (V) (0.12 g.), identical with that obtained above.

Catalytic Hydrogenation of the Phenol (V).—The phenol (0.35 g.) in glacial acetic acid (30 ml.) was hydrogenated over platinum oxide (0.13 g.) in the presence of 3M-hydrochloric acid (0.2 ml.). After hydrogen absorption had ceased, the catalyst was removed and the solvent evaporated under reduced pressure. The oily residue (0.32 g.) was dissolved in absolute ether (20 ml.) and added dropwise to a slurry of lithium aluminium hydride (2 g.) in ether (50 ml.). The suspension was refluxed for 1 hr., excess of lithium aluminium hydride decomposed with ethyl acetate, and dilute sulphuric acid added. The organic layer was washed first with 10% sodium hydrogen carbonate solution, then with water, dried (MgSO_4), and evaporated, giving an oily residue (0.3 g.).

This residue was taken up in a minimal volume of hexane and chromatographed on alumina (18 g.; Alcoa). Elution with hexane gave the hydrocarbon (VIa) (0.12 g.); further elution with benzene, benzene-chloroform, and chloroform gave the mono- and di-alcohol mixture (VIb, c) (0.15 g.).

The hydrocarbon fraction was dehydrogenated with 30% palladised carbon (0.05 g.) at 250—300°. From the product hexane extracted an oil which was chromatographed in pentane on basic alumina (7.0 g.; Woelm). Fractions 2—6 (each fraction about 5 ml.) gave (5,5)-metacyclophan (VIII) (0.07 g.), m. p. 67° (Found: C, 90.4; H, 9.6. $\text{C}_{22}\text{H}_{28}$ requires C, 90.35; H, 9.65%), λ_{max} . 263, 268.5, 272 μ (ϵ 435, 342, 330 respectively) in EtOH.

The mono- and di-alcohol mixture (VIb, c) (0.15 g.) in acetic acid (6 ml.) was oxidised with potassium chromate (0.25 g.) in water (0.6 ml.), with stirring overnight at room temperature. After the usual working-up, an oil (0.16 g.) was obtained, having λ_{max} . 1706 cm^{-1} (six-membered ring ketone), which was chromatographed in a minimal volume of hexane-benzene (1 : 1) on alumina (15 g.; Alcoa). Elution with the same solvent gave the monoketone (VIIa) (0.08 g.) as an oil, identified as its yellow 2,4-dinitrophenylhydrazone, m. p. 183—184° (from ethyl acetate) (Found: C, 67.4; H, 8.3; N, 11.1. $\text{C}_{28}\text{H}_{42}\text{N}_4\text{O}_4$ requires C, 67.4; H, 8.5; N, 11.2%). Elution with chloroform gave oily diketone (VIIb). Its bis-2,4-dinitrophenylhydrazone decomposed at 325—330° (Found: N, 15.4. $\text{C}_{34}\text{H}_{44}\text{N}_8\text{O}_8$ requires N, 16.2%).

Alternatively the crude mixture of (VIa, b, and c) (0.15 g.) in acetic acid (6 ml.) was oxidised with potassium chromate (0.25 g.) in water (0.6 ml.) as described above. The oily product (0.15 g.) was reduced with 95% hydrazine hydrate (0.5 ml.), potassium hydroxide (0.35 g.), and diethylene glycol (6 ml.). The oily hydrocarbon (0.12 g.) obtained in the usual way was dehydrogenated to (5,5)-metacyclophan (VIII) as described above.

Infrared spectra in the 2000—1650 cm^{-1} region of the cyclic ether (IV) and the (5,5)-metacyclophan (VIII) were taken in concentrated carbon tetrachloride solution (0.04 g. in 0.25 ml.; 0.5 mm. cell thickness) as the characteristic overtone and combination bands are relatively weak.⁹