280. *A Synthesis of 2-(2 : 3-Dimethoxyphenyl)*cyclo*hexanone.*

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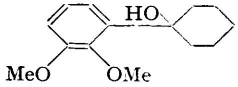
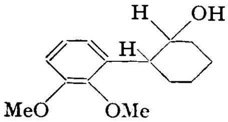
2-(2 : 3-Dimethoxyphenyl)*cyclo*hexanone is prepared, starting from 2 : 3-dimethoxyphenyl-lithium and *cyclo*hexanone or epoxy*cyclo*hexane. Intermediates are elucidated.

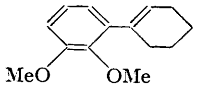
For a synthetic project, relatively large quantities of 2-(2 : 3-dimethoxyphenyl)*cyclo*hexanone (IV) were required. The methods chosen may be of interest in connection with the results recently communicated by Mueller and May (*J. Amer. Chem. Soc.*, 1949, **71**, 3313). ' 2 : 3-Dimethoxyphenyl-lithium, which is obtained from veratrole and butyl-lithium (Gilman, Swiss, and Cheney, *ibid.*, 1940, **62**, 1965), gave with 2-chloro*cyclo*hexanone rather intractable mixtures containing only traces of ketonic material, probably because of the multiplicity of possible simultaneous reactions (Newman and Booth, *J. Org. Chem.*, 1947, **12**, 737; Orchin, *J. Amer. Chem. Soc.*, 1948, **70**, 495). The following two alternative methods gave overall yields of 21%.

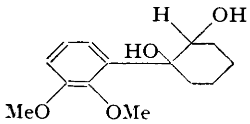
Condensation of 2 : 3-dimethoxyphenyl-lithium with *cyclo*hexanone or with *cyclo*hexene oxide (cf. Cook, *J.*, 1936, 71) yielded (I*a*) and 2-(2 : 3-*dimethoxyphenyl)*cyclo*hexan*-1-*ol* (I*b*), respectively.

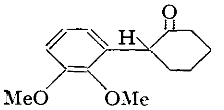
(I*b*) was oxidised directly to 2-(2 : 3-*dimethoxyphenyl*)cyclo*hexanone* (IV) with chromic acid in glacial acetic acid, but for the conversion of (I*a*) into (IV) the following more devious route was used: (I*a*) split off water easily upon treatment with oxalic acid in boiling toluene. The hydroxylation of 1-(2 : 3-*dimethoxyphenyl*)cyclo*hexene* (II) so obtained led to the *glycol* (III), both when performic acid and when osmium tetroxide was used. The same glycol also resulted from the direct interaction of the carbinol (I*a*) with performic acid. Oxalic acid caused transformation of the glycol into the desired ketone (IV). The direct oxidative transformation of (I*b*) into (IV) proves the constitution of the former.

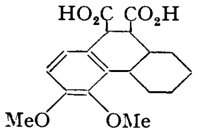

(I*a*.)


(I*b*.)


(II.)


(III.)


(IV.)


(V.)

The ketone (IV) proved identical with the substance synthesized by Horning, Horning, and Platt (*J. Amer. Chem. Soc.*, 1947, **69**, 2929) from 2 : 3-dimethoxybenzaldehyde by a much longer route and in an overall yield of 6·4%. The olefin (II) gave a very unstable dibromide; it is, however, easily characterised by the reaction with maleic anhydride which yields a crystalline *dicarboxylic acid* (V). This reaction conforms with the results of Szmuszkovicz and Modest (*J. Amer. Chem. Soc.*, 1948, **70**, 2542) but it is smoother than that of 1-phenyl*cyclo*hexene studied by these authors.

It is perhaps surprising that the osmium tetroxide and the performic acid method of hydroxylation generally believed to give *cis*- and *trans*-glycols, respectively, should lead to the same glycol (III). This is by no means characteristic for the *cyclo*hexene system, as English and Gregory (*ibid.*, 1947, **69**, 2120) have obtained without difficulty the *trans*-diol from *cyclo*hexene itself.

Neither the treatment with aluminium *tert.*-butoxide and acetone or *cyclo*hexanone, nor the interaction with *N*-bromosuccinimide (following a suggestion by Prof. L. F. Fieser), caused the expected dehydrogenation of the secondary hydroxyl group in (III), but the structure of the glycol appears firmly established by the rearrangement to (IV). Indeed, in the case of 1-phenyl*cyclo*hexane-1 : 2-diol, too, only one form is stable, which rearranges to 2-phenyl*cyclo*hexanone; it has been shown to be the *cis*-compound (Nametkin and Iwanoff, *Ber.*, 1923, **56**, 1806; Nametkin, *Chem. Zentr.*, 1925, I, 222; 1926, I, 2686; Böeseken, *Ber.*, 1923, **56**, 2409; Verkade, *Annalen*, 1928, **467**, 232). It is reasonable to assume that the glycol (III) also has the *cis*-configuration.

EXPERIMENTAL.

(All b. p.s and m. p.s are uncorrected.)

1-(2 : 3-*Dimethoxyphenyl*)cyclo*hexanol* (I*a*).—A solution of 2 : 3-dimethoxyphenyl-lithium was prepared from ethereal butyl-lithium [from 164 g. (1·2 mols.) of butyl bromide and 18·5 g. of lithium wire] and veratrole (200 g., 1·5 mols.) in ether (1200 c.c.). The reaction was interrupted after 24 hours at room temperature (stirring); it was desirable to protect the reacting mixture from autoxidation by a slow current of nitrogen.

To this solution, *cyclo*hexanone (110 g., 1·1 mols.) in anhydrous ether (150 c.c.) was added at —10° to 0°, with stirring. After 12 hours, the reaction product was treated with ice-water, and hydrochloric acid added until reaction was neutral. The ethereal solution was then washed with water, 10% sodium hydroxide solution, and water, and then concentrated and the residue was subjected to vacuum-distillation (b. p. 130—145°/0·03 mm.) (120 g.). The very viscous oily *alcohol* crystallised spontaneously. After recrystallisation from light petroleum the substance melted at 51—51·5°. The yield was 90 g. (Found : C, 71·0, 71·4; H, 8·9, 8·7. $C_{14}H_{20}O_3$ requires C, 71·2; H, 8·5%).

From the fore-run, veratrole (113 g.) could be recovered by renewed fractionation. Calculated on veratrole reacting, the yield of (I*a*) is 60%.

2-(2 : 3-*Dimethoxyphenyl*)cyclo*hexanol* (I*b*).—The solution of 2 : 3-dimethoxyphenyl-lithium was prepared as above [from 90 g. (0·66 mol.) of butyl bromide, 9 g. of lithium wire, and 100 g. (0·75 mol.) of veratrole in 300 c.c. of ether]. At 5°, *cyclo*hexene oxide (50 g., 0·50 mol.) was added. When the spontaneous reaction had subsided, the mixture was refluxed for 2 hours and the product hydrolysed by addition of cold water. From the ethereal solution 2-(2 : 3-*dimethoxyphenyl*)cyclo*hexanol* (I*b*) was isolated by fractionation (b. p. 140—150°/0·02 mm.) as a very viscous liquid which crystallised on trituration with methyl*cyclo*hexane. The alcohol (55 g.) crystallised from the same solvent in well-shaped crystals, m. p. 67—68°. Based on the veratrole not recovered (46 g.), the yield amounted to 70% (Found : C, 70·8 ; H, 8·5. $C_{14}H_{20}O_3$ requires C, 71·2 ; H, 8·5%).

1-(2 : 3-*Dimethoxyphenyl*)cyclo*hexene* (II).—Dehydration of (I*a*) (15 g.) was effected by heating it with anhydrous oxalic acid (2 g.) in boiling toluene (50 c.c.), until no more water collected in the azeotropic separator (~30 minutes). The yield of colourless cyclo*hexene*, m. p. 14·2°, b. p. 145—150°/0·01 mm., was quantitative (Found : C, 77·4 ; H, 8·6. $C_{14}H_{18}O_2$ requires C, 77·1 ; H, 8·3%).

The dehydration of (I*a*) with formic acid according to Sherwood, Short, and Stansfield (*J.*, 1932, 1832) was unsatisfactorily slow and gave rise to highly coloured tars.

The *dibromide*, prepared in light petroleum at −5°, crystallized spontaneously. It decomposes readily even at only slightly elevated temperature. It melts at 130° (decomp.) if brought into a bath preheated at 128° (Found : Br, 42·3, 42·6. $C_{14}H_{18}O_2Br_2$ requires Br, 42·4%).

Reaction of (II) *with Maleic Anhydride*.—A mixture of (II) (3 g.) and maleic anhydride (10 g.) was refluxed for 3 hours in the presence of a few crystals of *N*-phenyl-*α*-naphthylamine (the same result was achieved by heating the mixture at 120° for 48 hours). The reaction product was dissolved in 10% aqueous sodium hydroxide and precipitated with hydrochloric acid. Recrystallised from glacial acetic acid 3 : 4-*dimethoxy*-5 : 6 : 7 : 8 : 9 : 10 : 13 : 14-*octahydrophenanthrene*-9 : 10-*dicarboxylic acid* (X) had m. p. 173—175° (decomp.) It contained no olefinic double bonds (titration with perbenzoic acid) (Found : C, 65·1, 65·3 ; H, 6·4, 6·4% ; equiv., 168·5. $C_{18}H_{22}O_6$ requires C, 64·6 ; H, 6·3% ; equiv., 167).

1-(2 : 3-*Dimethoxyphenyl*)cyclo*hexane*-1 : 2-*diol* (III).—(*a*) To a solution of (II) (10·8 g.) in 90% formic acid (33 c.c.), 30% hydrogen peroxide (6 g.) was added with stirring, the temperature being kept below 40°. The mixture became homogeneous after 15 minutes. After 2 hours, the formic acid was removed *in vacuo* and the residue refluxed for 1 hour with potassium hydroxide (9 g.) in methanol (50 c.c.). The methanol was distilled off ; the *product*, taken up with water, extracted with ether, and recrystallised from methyl*cyclo*hexane, had m. p. 104—105° (7·3 g.) [Found : C, 66·5 ; H, 8·6 ; active H, 1·8 (Zerewitinoff). $C_{14}H_{20}O_4$ requires C, 66·6 ; H, 8·0% ; active H, 2·0]. From the mother-liquor, a second crop (0·4 g.) of the same substance, and 1·5 g. of unchanged starting material could be recovered by fractionation *in vacuo*. The total yield was 70%. In subsequent runs the yield varied from 70 to 80%.

(*b*) From (II) (0·8 g.) and osmium tetroxide (1·0 g.), 0·8 g. of (III), m. p. 104—105°, was obtained by Wieland's procedure (*Ber.*, 1942, **75**, 1708). Mixed m. p. of samples formed by procedure (*a*) and (*b*) showed no depression.

Reaction of (III) *with* N-*Bromosuccinimide*.—A solution of (III) (2 g.) and the reagent (2 g.) in a mixture of dioxan (20 c.c.) and water (2 c.c.) gave, after 24 hours at room temperature, a quantitative yield of a *monobromo*-compound, m. p. 118—120°, instead of the expected oxidation product (Found : Br, 24·2, 24·3. $C_{14}H_{19}O_4Br$ requires Br, 24·2%). The bromine atom probably entered the benzene nucleus.

2-(2 : 3-*Dimethoxyphenyl*)cyclo*hexanone* (IV).—(*a*) A mixture of the diol (III) (25·2 g.) and anhydrous oxalic acid (10 g.) was heated at 110—120° for 30 minutes. The product was isolated by treatment with aqueous sodium hydroxide and ether; after removal of the solvent, it crystallised spontaneously and was recrystallised from light petroleum (yield, 11 g., m. p. 70—71°). The 2 : 4-dinitrophenylhydrazone melted at 125—127°, and the oxime at 139—140°. According to Horning, Horning, and Platt (*loc. cit.*), the three m. p.s are 67—68·5°, 123—124°, and 137—138° (all corrected), respectively.

(*b*) When (I*b*) was oxidised with chromic acid in glacial acetic acid, according to Cook (*loc. cit.*), a 30% yield of (IV) was obtained. The substance and its 2 : 4-dinitrophenylhydrazone proved identical with the corresponding products prepared according to procedure (*a*).

This paper represents part of a thesis submitted by Raphael Pappo to the Hebrew University, Jerusalem, in partial fulfilment of the requirements for the degree of Doctor of Philosophy.

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