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NEW METHODS FOR THE PREPARATION OF 1-PHENYL-*TRANS*-CYCLOHEXANE-1,2-DIOL

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Abstract—In contrast with previous reports, it was found that the reaction of 1-phenylcyclohexene with peroxyformic acid is not entirely stereospecific, but gives some *trans*-1-phenylcyclohexane-1,2-diol (IV) beside the *cis*-isomer (III). The reaction of 1-phenylcyclohexene oxide (II) with formic acid yielded a similar mixture of III and IV, while addition of trichloroacetic acid in benzene was entirely *cis*-stereospecific. Reaction of the epoxide II with potassium hydroxide took place only under very drastic conditions to give a small yield of III, while sodium 2-dimethylaminoethoxide added exclusively in a *trans* way, leading to the amino ether X, which was easily transformed into the *trans*-glycol IV. The latter compound was also the main product of the borohydride reduction of 2-hydroxy-2-phenylcyclohexanone (IX). Possible explanations of the observed stereochemical results are discussed.

The literature concerning 1-phenylcyclohexene oxide (II) and the corresponding *cis* and *trans* glycols III and IV is rather confused, and, in some instances, contradictory. The oxide (II) has been prepared by reaction of 1-phenylcyclohexene (I) with peroxybenzoic acid, but, while in earlier reports[1–3] there appears not have been any difficulty in the purification of the product by vacuum distillation, recent papers point out that during the distillation the epoxide is transformed partly[4] or completely[5] into 2-phenylcyclohexanone. There may therefore be some doubt about the purity of the earlier products.

We found that it is possible to obtain II pure simply by distilling the crude reaction product of I with peroxybenzoic acid over powdered potassium hydroxide. While the epoxide is very sensitive to acids, it is remarkably stable towards bases. The method has the further advantage to prevent co-distillation of the small amounts of carbonylic rearrangement products which are present in the crude II, probably because the alkali catalyses aldol type condensations to higher-boiling materials. The previous contrasting results were certainly due to the presence of small amounts of acidic impurities and not to thermal instability of II.

The confusion existing about the two glycols (III and IV) may be due in part to the similarity in their m.ps, and in part to the misconception that additions to the epoxide ring usually take a *trans* course. It is now well established that phenyl-substituted epoxides very often open in a *cis* way.[6] Furthermore, if large groups are

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[1] P. E. Verkade, J. Coops Jr., Chr. J. Maan and A. Verkade-Sandbergen, *Liebig's Ann.* **467**, 217 (1928).

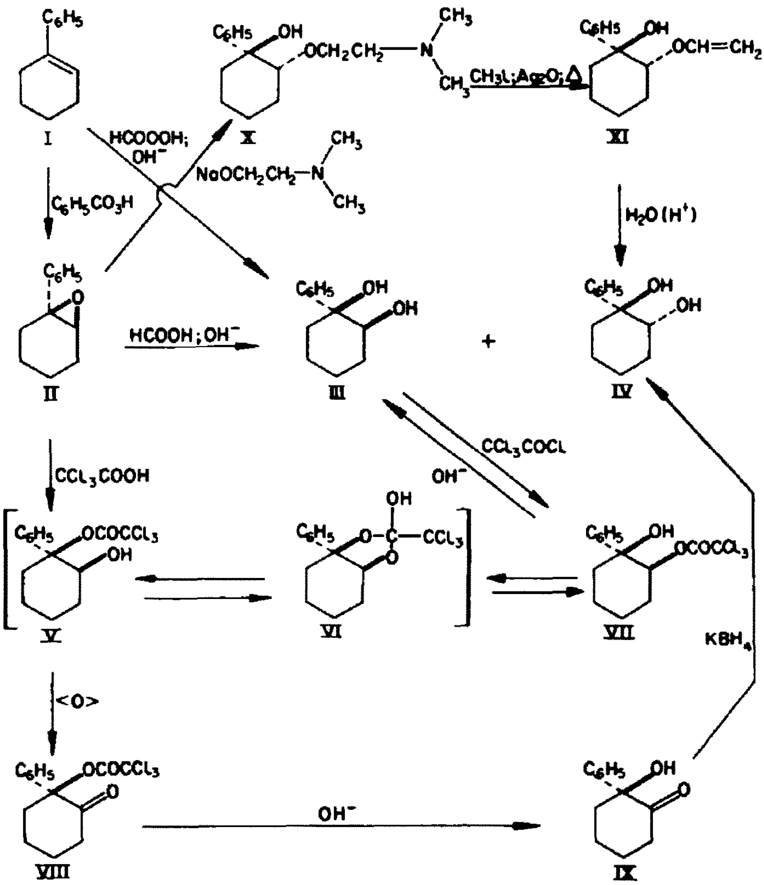
[2] S. Nametkin and N. Iwanoff, *Ber. Dtsch. Chem. Ges.* **56**, 1805 (1923).

[3] J. Lèvy and J. Sfiras, *C.R. Acad. Sci., Paris* **187**, 45 (1928).

[4] D. Y. Curtin and S. Schmukler, *J. Amer. Chem. Soc.* **77**, 1105 (1955).

[5] R. Filler, B. R. Camara and S. M. Naqvi, *J. Amer. Chem. Soc.* **81**, 658 (1959).

[6a] J. H. Brewster, *J. Amer. Chem. Soc.* **78**, 4061 (1956); [b] D. Y. Curtin, A. Bradley and Y. G. Hendrickson, *Ibid.* **78**, 4064 (1956); [c] R. C. Cookson and J. Hudec, *Proc. Chem. Soc.* 24 (1957); [d] G. Berti and F. Bottari, *J. Org. Chem.* **25**, 1286 (1960); [e] G. Berti, F. Bottari and B. Macchia, *Gazz. Chim. Ital.* **90**, 1783 (1960); [f] G. Berti, F. Bottari and B. Macchia, *Tetrahedron* **20**, 545 (1964).



present in the 1-position of cyclohexane-1,2-diol, the *cis*-glycol is more stable than its *trans*-isomer.[7] It is, therefore, quite logical that III is formed in preference to IV.

The dihydroxylation of 1-phenylcyclohexene (I) with potassium permanganate, first reported to give the *trans*-glycol IV,[2] was later shown to produce the *cis*-glycol (III),[3,8,9] which was also prepared from I with osmium tetroxide.[10] Lyle and Lyle[11] obtained the monoacetate of a glycol of non-specified configuration from I and peroxyacetic acid, while the report[5] that I gives exclusively IV with peroxyphtalic acid was later found wrong,[10] III being the only product. Only III was isolated also in the reaction with peroxyformic acid.[10,12] The *trans*-glycol IV appears to be rather elusive, as Davies *et al.*[12] were not able to obtain it in several attempts by different methods. There are, however, substantiated reports on its formation as the minor product in the hydrolytic splitting of the epoxide II. Thus, while reaction with water

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[7] P. R. Jefferies and B. Milligan, *J. Chem. Soc.* 4384 (1956).

[8] J. Böeseken, *Ber. Dtsch. Chem. Ges.* **56**, 2409 (1923); *Rec. Trav. Chim.* **47**, 683 (1928).

[9] C. J. Maan, *Rec. Trav. Chim.* **48**, 332 (1929).

[10] D. C. Kleinfelter and P. von R. Schleyer, *J. Amer. Chem. Soc.* **83**, 2329 (1961).

[11] R. E. Lyle and G. G. Lyle, *J. Org. Chem.* **18**, 1058 (1953).

[12] M. T. Davies, D. F. Dobson, D. F. Hayman, G. B. Jackman, M. G. Lester, V. Petrow, O. Stephenson and A. A. Webb, *Tetrahedron* **18**, 751 (1962).

at 110° apparently gives only III,[2] acid-catalysed hydrolysis was shown to produce mixtures of III and IV.[8,9,13] As we needed a certain amount of the *trans*-glycol (IV) for our work on the stereochemistry of reactions of epoxides and glycols with acids, we reinvestigated some of the previous results and looked for other methods for the preparation of IV. We found in contrast with the previous results[10,12] that in the reaction of 1-phenylcyclohexene (I) with peroxyformic acid, followed by hydrolysis of the formic esters, some IV is formed together with the main product (III); they can be separated fairly well by fractional crystallization. When the reaction was carried out at 30° about 95% III and 5% IV were formed while at 15° the amounts were about 91% III and 9% IV.

The reaction of the epoxide II with formic acid at 0° yielded a mixture of esters which was hydrolysed to a product consisting of about 80% III and 20% IV, while the same reaction, carried out at room temperature, gave 90% III and 10% IV. These results show that in both types of reactions, I with peroxyformic acid and II with formic acid, a lower temperature causes an increase in the amount of the *trans*-compound IV; it is very likely that the former reaction proceeds through the primary formation of epoxide II, followed by addition of formic acid, rather than by a direct addition of peroxyformic acid. The decrease in the amounts of IV in the reactions carried out at higher temperatures is not due to an epimerization to III, as IV is stable to formic acid.

A complete retention of configuration was observed in the reaction of II with trichloroacetic acid in benzene, which gave exclusively the ester VII and, after hydrolysis, the *cis*-glycol III. Such a steric course is what would be expected for the reaction of a phenyl-substituted epoxide[6] in a non-polar solvent and is likely to involve reaction within an ion-pair (XIII) in a cage of solvent.[6a] The lower stereospecificity observed in the reactions carried out in formic acid or in water[8,9,13] should be due to the greater availability of attacking molecules and to the higher polarity of the media, which allows for the presence of free ions and produces stronger solvation of the cationic intermediate. The formation of the *trans* adduct could involve an attack to the protonated epoxide (XII) either on the α carbon atom to give XV, or on the β carbon atom to give XVI. While the latter hypothesis would be in agreement with the rule of diaxial opening of epoxide rings, we think that the former may be more probable in this case, for additions of acids to phenyl-substituted epoxides usually involve the cleavage of the weaker benzylic bond, as was shown in the case of styrene oxide.[14,15] The fact that the amount of the *trans* glycol is smaller in the reactions carried out at higher temperatures could be explained by an increase in thermodynamic control of the reaction, favouring the more stable *cis* isomer.

The product obtained from II with trichloroacetic acid was assigned structure VII, instead of V, because it was also obtained in the esterification of III with trichloroacetyl chloride, which should react preferentially with the secondary, rather than with the tertiary hydroxyl. Furthermore, the ester was stable to oxidation under conditions which easily transform secondary alcohols into ketones; only under very drastic conditions was it possible to transform it into the keto ester (VIII). Such a behaviour is completely similar to that observed in the reactions of styrene oxide[14]

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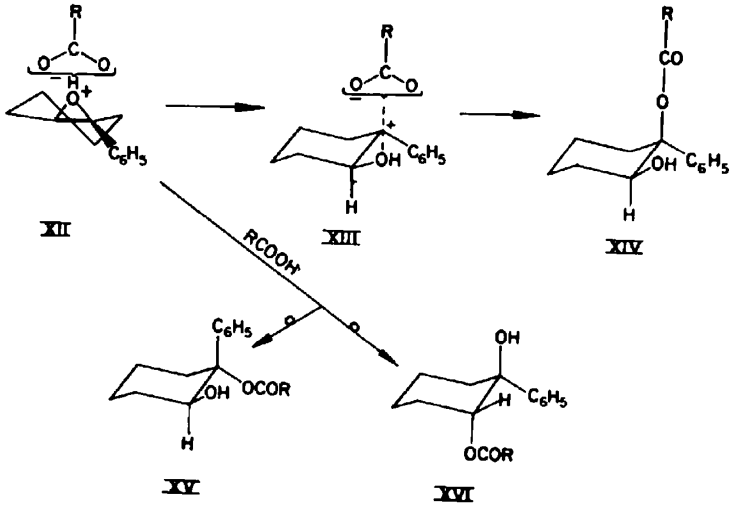
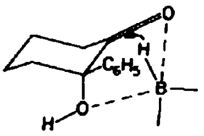
[13] E. Gálantay, *Tetrahedron* **19**, 319 (1963).

[14] G. Berti, F. Bottari and B. Macchia, *Ann. chim., Rome* **52**, 1101 (1962).

[15] T. Cohen, M. Dughi, V. A. Notaro and G. Pinkus, *J. Org. Chem.* **27**, 814 (1962).





XVII

and α-methylstilbene oxide[6f] with trichloroacetic acid; it is therefore very likely that the primary product is V and that it is rapidly transformed into the more stable form VII, through VI. Similarly, the oxidation of VII to VIII is possible because of slow equilibration between VII and V.

The ketol IX, m.p. 69–70°, was obtained by saponification of VIII. It has been reported by Tomboulian[16] as a liquid, and by Elphimoff-Felkin *et al.*[17] as a solid, m.p. 68–69·5°. Repetition of the preparation after Tomboulian (reaction of 2-hydroxy-2-cyclohexene-1-one with phenyllithium) gave a liquid, which solidified on seeding with our product, and was found to be identical to IX.

Reduction of IX with potassium borohydride gave a mixture consisting of about 80% of the *trans*-glycol (IV) and 20% of the *cis*-glycol (III). The steric course of this reaction, that can be employed as a useful method for the preparation of IV, is interesting. The formation of an excess of the *trans*-glycol (IV) is in contrast with both the "steric approach control" and "product development control" theories.[18] It can be assumed that the more stable conformation of IX is that in which the phenyl group is equatorial. Attack by the hydride would be much less hindered from the side opposite to the hydroxyl group and should lead preferentially to the *cis*-glycol; product development control should favour the formation of the same isomer, which is the more stable one. The steric results may, however, be explained by a model

[16] P. Tomboulian, *J. Org. Chem.* **26**, 2652 (1961).

[17] I. Elphimoff-Felkin, G. le Ny and B. Tchoubar, *Bull. Soc. Chim. Fr.* 522 (1958).

[18] W. G. Dauben, G. J. Fonken and D. S. Noyce, *J. Amer. Chem. Soc.* **78**, 2579 (1956); A. V. Kamernitzky and A. A. Akhrem, *Tetrahedron* **18**, 705 (1962).

similar to the rigid model proposed by Cram[19] for open-chain systems containing a polar group α to the carbonyl group, that can complex with the organometallic reagent before the reduction. As shown in XVII such a model would involve hydride attack *cis* to the hydroxyl group and therefore give the *trans*-glycol.

In a further attempt to find new methods for the preparation of the *trans*-glycol (IV) the opening of the epoxide II with bases was investigated, as in all known cases oxirane rings open in *trans*-way in basic media.[20] The reaction of II with alkali required very drastic conditions, and even by heating it 48 hr at 150° with potassium hydroxide in dioxan–water, only 10% of glycol was obtained. This consisted, however, only of the *cis*-form (III). It was found that under the same conditions IV does not isomerize to III: therefore, this appears to be the first case of *cis*-opening of an epoxide ring under basic conditions.

A different approach,[21] however, led to pure IV, although with low overall yield. The oxide (II) was reacted with sodium 2-dimethylaminoethoxide. In this case the reaction was entirely *trans*-stereospecific, giving compound X, as expected for an SN_2-type addition. X was transformed into the corresponding quaternary hydroxide, pyrolysis of which yielded the vinyl ether XI, which was easily hydrolysed to IV. This is, so far, the only method which gives IV in a completely stereospecific way.

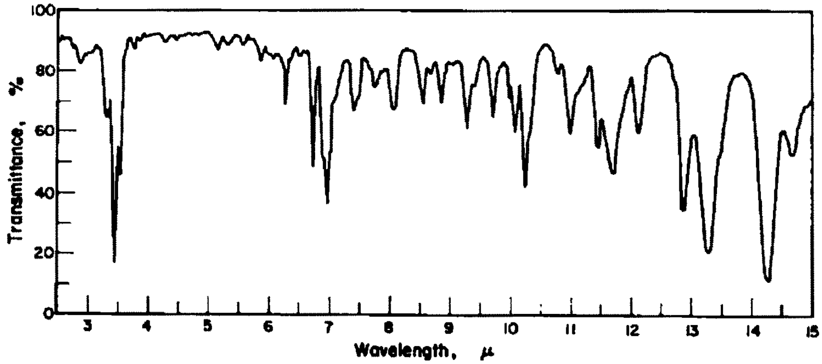


FIG. 1. IR spectrum of 1-phenylcyclohexene oxide (neat).

EXPERIMENTAL

M.ps were determined on a Kofler apparatus. IR spectra were taken, if not indicated differently, on paraffin oil mulls with a Perkin–Elmer Infracord Mod. 137. All comparisons between compounds were made on the basis of IR spectra and mixed m.ps. Pet ether refers to the fraction, b.p. 40–70°. 1-*Phenylcyclohexene oxide* (II). A solution of 15·8 g (0·1 mole) I[22] in 70 ml $CHCl_3$ was cooled at −10° and treated drop-wise with 235 ml (0·12 mole) of a cooled 0·51M solution of peroxybenzoic acid in $CHCl_3$,[23] at such a rate as to keep the temp below 0°. After 50 hr at 0° the solution was washed with 10% Na_2CO_3aq, dried over $MgSO_4$ and the solvent was evaporated under red. press. at room temp to give 16·8 g crude II whose IR spectrum (neat) showed a weak CO band at 5·82 μ. Distillation produced an increase in the intensity of this band. However, when 6·0 g crude II was distilled from 0·5 g powdered KOH it gave 4·8 g pure II (IR spectrum; Fig. 1), b.p. 118°/0·5 mm; n_D^{19} 1·5430 (lit.[8] b.p. 136°/15–16 mm, n_D^{17} 1·5434).

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[19] D. J. Cram and K. R. Kopecky, *J. Amer. Chem. Soc.* **81**, 2748 (1959).

[20] R. E. Parker and N. S. Isaac, *Chem. Revs.* **59**, 737 (1959).

[21] B. Macchia, *Ann. Chim., Rome* **54**, 1131 (1964).

[22] E. W. Garbisch Jr., *J. Org. Chem.* **26**, 4165 (1961).

[23] I. M. Kolthoff, T. S. Lee and M. A. Mairs, *J. Polymer Sci.* **2**, 199 (1947).

Reaction of 1-*phenylcyclohexene* (I) *with peroxyformic acid.*[12] A mixture of 30 ml 99% formic acid, 11 ml (0·128 mole) 35% H_2O_2 and 1·0 g anhydrous potassium acetate was treated, under external cooling to keep the temp below 30°, with 10·0 g (0·063 mole) I in 10 ml ether. After being left overnight at room temp the mixture was almost neutralized with 50% NaOHaq and extracted with ether. The extract was washed with 10% NaOHaq and evaporated, the residue was saponified by 30-min reflux with 13 g KOH in 17 ml water and 30 ml MeOH, the MeOH evaporated *in vacuo* and the residue extracted with ether; the extract was washed with 10% NaOHaq, dried, concentrated to a small volume and diluted with pet ether, to give 8·0 g of a white solid. Fractional crystallization gave 7·0 g 1-phenyl-*cis*-cyclohexane-1,2-diol (III), m.p. 94–96°, identical with a sample prepared according to Gálantay.[18] Concentration of the mother liquor produced 0·4 g of a mixture of III and IV, from which, by crystallization from $CHCl_3$–hexane, it was possible to isolate 0·25 g pure 1-phenyl-*trans*-cyclohexane-1,2-diol (IV), m.p. 98·5–100° (lit.[13]: m.p. 97·7–98·2°). IR analysis (based on bands at 13·2 μ for the *cis*-glycol and at 9·59 μ for the *trans*-glycol) of the crude mixture of glycols obtained in a similar run showed that it was composed of about 95% III and 5% IV.

When the reaction was carried out as above, but with more efficient cooling, in order to keep the temp below 15° during the addition, a mixture of glycols which was composed of about 91% III and 9% IV was obtained. (IR analysis). Fractional crystallization gave 6·0 g III, m.p. 94–96°, 0·45 g IV, m.p. 98·5–100° and 0·57 g of an about 1/1 mixture of III and IV.

Reaction of 1-*phenylcyclohexene oxide* (II) *with formic acid.* A solution of 0·5 g II in 1 ml ether was added to 5 ml 99% formic acid, cooled at 0° and left at this temp for 7 hr. The mixture was treated as described above, except that $CHCl_3$ instead of ether was used for the extraction. The solid crude residue (0·52 g) formed of about 80% III and 20% IV (IR) gave on fractional crystallization 0·38 g III, m.p. 94–96° and 0·09 g IV, m.p. 98·5–100°.

A similar run, in which the addition of II to formic acid was carried out at 0°, but the mixture was then left at room temp for 30 hr, led to 90% III and 10% IV. Compound IV (0·25 g) in 2 ml 99% formic acid was left 9 hr at room temp. Neutralization with 40% NaOHaq, extraction with $CHCl_3$ and evaporation gave a residue whose IR spectrum indicated that it was composed of IV, slightly impure with 2-phenylcyclohexanone, and that no III had formed.

1-*Phenyl*-cis-2-(*trichloroacetoxy*)*cyclohexanol* (VII). (a) A solution of 8·0 g (0·046 mole) epoxide II in 20 ml benzene was treated with 98 ml (0·056 mole) of a 0·575 M solution of trichloroacetic acid in benzene, left at room temp for 24 hr, washed with 10% Na_2CO_3aq and evaporated; the residue was crystallized from EtOH–water to give 8·2 g VII, needles, m.p. 97–99° λ_{OH} 2·80 μ, λ_{CO} 5·70 μ. (Found: C, 50·12; H, 4·48. $C_{14}H_{15}O_3Cl_3$ requires: C, 49·80; H, 4·48%.) Saponification by 30-min reflux with 2M KOH in EtOH gave pure *cis*-glycol (III), m.p. 94–96°.

(b) A mixture of 0·4 g (5 mmole) pyridine, 0·9 g (5 mmole) trichloroacetyl chloride and 8 ml benzene was slowly added to 0·96 g (5 mmole) III in 25 ml benzene. After 30 min the solution was washed with dil. HCl and 10% Na_2CO_3aq, evaporated and taken up with aqueous EtOH: 1·3 g VII, m.p. 97–99°, was obtained.

2-*Phenyl*-2-*hydroxycyclohexanone* (IX). Several attempts to prepare this compound by careful oxidation of the glycol III failed, 5-benzoylvaleric acid, m.p. 77–78° (lit.[24] m.p. 78°), being always formed as the main product. Treatment of the ester VII (0·5 g) in 10 ml acetic acid with 2 ml 5% chromic acid in acetic acid at room temp for 30 min, led to complete recovery of VII; also when the solution was heated 15 or 30 min at 100° only mixtures of VII and of the keto ester VIII were obtained. The latter compound was obtained free from VII in the following way: a solution of 1·0 g VII in 20 ml acetic acid was heated on a steam-bath and treated at 10-min intervals with three 4-ml portions 5% chromic acid in acetic acid, the heating was continued for 40 min, then the solution was diluted with water, extracted with ether and the washed and dried ether solution evaporated to give 0·67 g crude oily 2-*phenyl*-2-(*trichloroacetoxy*)*cyclohexanone* (VIII), λ_{CO} 5·64, 5·78 μ. This was dissolved in 15 ml EtOH, heated 5 min at 50° with 2 ml of 2 M KOH in EtOH, then immediately diluted, acidified with HClaq and extracted with ether. The washed and dried ether extract, on evaporation, left IX as an oily residue (0·30 g), λ_{OH} 2·90 μ, λ_{CO} 5·84 μ. It crystallized only after several days in the refrigerator, and was recrystallized from pet ether to give prisms m.p. 69–70° (lit.[17], m.p. 68–69·5°); oxime,[25]

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[24] B. Eistert, W. Reiss and H. Wurzler, *Liebig's Ann.* **650**, 133 (1961).

[25] R. L. Shriner, R. C. Fuson and D. Y. Curtin, *The Systematic Identification of Organic Compounds* (4th Edition) p. 255. J. Wiley, New York, N.Y. (1956).

m.p. 174–176° (lit.[17], m.p. 174–175°). The oil, obtained according to Tomboulian[16] from 2-hydroxycyclohex-2-en-1-one, recrystallized when seeded with our crystals and gave an identical IR spectrum. Treatment of IX with 2,4-dinitrophenylhydrazine reagent[26] gave an amorphous precipitate, which slowly changed into orange crystals of 2-phenylcyclohex-2-en-1-one 2,4-dinitrophenylhydrazone, m.p. 164–165°.[16]

Reduction of 2-phenyl-2-hydroxycyclohexanone (IX). A solution of 1·1 g (5·8 mmole) IX in 30 ml EtOH was treated with 0·5 g (9·3 mmole) KBH_4 in 2·0 ml water and 0·5 ml 2 N NaOH and left overnight, the excess hydride was decomposed with dil. H_2SO_4, water was added, the precipitate extracted with $CHCl_3$ and the solvent evaporated to give a residue, which, on fractional crystallization from pet ether, yielded 0·50 g of the *trans*-glycol IV, m.p. 98–100°; concentration of the mother liquor gave 0·35 g of a mixture consisting of III and IV in about equal amounts (IR).

Alkaline hydrolysis of 1-phenylcyclohexene oxide (II). A mixture of 1·0 g II, 10 ml 10% KOHaq and 30 ml dioxan was heated 48 hr at 150° in a 200 ml autoclave. Dilution with water and extraction with ether gave an oily product, which after two crystallizations from pet ether yielded 0·11 g (10%) III. The mother liquor contained much unchanged II, small amounts of carbonylic compounds, but no IV (IR). When the same reaction was carried out by heating 46 hr under reflux, III was obtained in only 6% yield. The *trans*-glycol (IV) was recovered completely unchanged after 46-hr reflux with 5% KOH in 1/1 dioxan–water.

1-*Phenyl*-trans-2-(2-*dimethylaminoethoxy*)*cyclohexanol* (X). Sodium (0·35 g, 15 mmole) was heated with 5·3 g 2-dimethylaminoethanol until it dissolved completely, then 2·61 g (15 mmole) II was added and the solution was refluxed 8 hr, then poured into 50 ml water, acidified with conc. HCl. Neutral by-products were extracted with ether and the aqueous solution made alkaline with 10% NaOHaq. The precipitate was crystallized from hexane to give 0·80 g X, needles, m.p. 106–108°, λ_{OH} 3·29 μ (Found: C, 72·51; H, 9·52. $C_{16}H_{25}NO_2$ requires: C, 72·96; H, 9·57%.)

The corresponding methiodide was obtained quantitatively by refluxing 0·53 g X and 1·0 g MeI in 10 ml MeOH. It crystallized from acetone–ether in prisms, m.p. 141–143° (Found: I, 31·15. $C_{17}H_{28}INO_2$ requires: I, 31·31%.)

Transformation of X *methiodide into* 1-*phenyl*-trans-*cyclohexane*-1,2-*diol* (IV). A solution of 0·4 g of the methiodide in 15 ml water was shaken 4 hr with Ag_2O (freshly prepared from 1·2 g $AgNO_3$), left overnight and filtered. The filtrate was evaporated to dryness *in vacuo* and the solid residue of the quaternary hydroxide was slowly heated under a pressure of 40 mm. Decomposition started at 140° and was complete after 10 min at 150°. The residue was extracted with ether to give the crude oily vinyl ether XI, which was directly hydrolysed by shaking it 30 min in 2 ml MeOH and 0·5 ml 1N H_2SO_4; dilution with water, saturation with NaCl, extraction with ether and crystallization from hexane gave 0·10 g IV, m.p. 98·5–100°.

Acknowledgement—This work was supported by a grant from the Consiglio Nazionale delle Ricerche (Rome).

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[26] R. L. Shriner, R. C. Fuson and D. Y. Curtin, Ref. 25, p. 219.