

PREPARATION AND CONFIGURATION OF SOME CYCLOHEXANOLS

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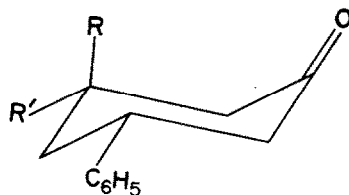
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KINETIC (1) and infrared (1,2) studies on some phenyl substituted 4-piperidinols showed that some of these probably exist as an equilibrium mixture of chair and boat conformations (3). This prompted us to prepare analogous cyclohexanols and study their properties. The compounds chosen for the study were expected to exist predominantly in one chair conformation, the alternative chair form being excluded due to unfavourable steric interactions. However, this would not preclude any contribution by the boat or twist conformation. In this communication we report the preparation of the cyclohexanols and the assignment of configuration.

Reduction of cyclohexanones I to IV should lead to epimeric cyclohexanols with the hydroxyl group cis or trans to the phenyl group. If the chair conformation is assumed for the cyclohexanols, hydroxyl would be equatorial in the cis and axial in the trans isomer.

Except 3-t-butyl-5-phenylcyclohexanone (III), the other cyclohexanones were obtained essentially by methods described

in the literature. Reaction of *t*-butyl styryl ketone (benzalpinacolone) with ethyl acetoacetate in the presence of



- I $R=R'=H$
 II $R=H, R'=C_6H_5$
 III $R=H, R'=C(CH_3)_3$
 IV $R=R'=CH_3$

sodium ethoxide followed by hydrolysis and decarboxylation of the product afforded 3-*t*-butyl-5-phenylcyclohex-2-en-1-one, b.p. 1.5 mm 160-162°, n_D^{30} 1.5449; oxime, m.p. 142-143°; semicarbazone, m.p. 164-165°. Hydrogenation of the cyclohexenone with Pd/C gave the saturated ketone (III), m.p. 74-75°; oxime, m.p. 167-168°; semicarbazone, m.p. 186-187°. Hydrogenation of 3,5-diphenylcyclohex-2-en-1-one, under identical conditions, gave cis-3,5-diphenylcyclohexanone (II), m.p. 139-140°, the configuration of which follows from its reduction to two epimeric 3,5-diphenylcyclohexanols (see below). Since the *t*-butylcyclohexanone melting at 74-75° was obtained under similar conditions, it was expected to have a cis orientation of the phenyl and *t*-butyl groups. Such a configuration is also supported by the stereoisomeric composition of the products formed in the reduction of this ketone by different methods.

The cyclohexanones were reduced by (1) sodium and n-butanol, (2) lithium aluminium hydride, (3) catalytic hydrogenation in neutral and acidic media and (4) Meerwein-Ponndorf-Verley method. The reduction products were purified by column chromatography on alumina. The cyclohexanols prepared and their acetates are listed in Table 1.

Each of the cyclohexanone I to IV, on reduction with sodium and n-butanol, afforded a single cyclohexanol in a high yield. Reduction of the unhindered ketones I to III with LiAlH_4 also gave the same product, no other isomer could be isolated. However, LiAlH_4 reduction of the hindered ketone, 3,3-dimethyl-5-phenylcyclohexanone (IV) with an axial 3-methyl group afforded a cyclohexanol melting at $87-88^\circ$ as the major product together with an epimer, m.p. $49-50^\circ$ which was identical with that obtained in the sodium/n-butanol reduction. According to the generalization due to Barton (4), sodium and alcohol reduction of a cyclohexanone should lead to the cyclohexanol with an equatorial hydroxyl. Reduction with LiAlH_4 of unhindered cyclohexanones generally leads to predominantly equatorial alcohols and the reduction of hindered ketones gives the axial alcohols as the major product (4,5,6). Therefore, the cyclohexanols formed in the sodium/n-butanol reduction might be expected to have the equatorial hydroxyl. Consequently, the hydroxyl should be cis with respect to the phenyl group in these compounds. The 3,3-dimethyl-5-phenylcyclohexanol melting at $87-88^\circ$ might be expected to have the trans arrangement of these groups. Such an assignment is also confirmed by the catalytic hydrogenation of the cyclohexanones.

Table 1

Cyclohexanol	M.p., °C	B.p. or m.p. of the acetate, °C
<u>cis</u> -3-Phenyl	79-80 ^a (Lit (7), 83-84)	120/0.9 mm
<u>trans</u> - ---	63-64 ^a (Lit (7), 64)	109-110/0.4 mm
<u>cis-cis</u> -3,5-Di-phenyl	125-126 ^b (Lit (8), 127)	140 ^c
<u>cis-trans</u> ---	88-89 ^a	99 ^c
<u>cis-cis</u> -3-t-Butyl-5-phenyl	109-110 ^a	59 ^c
<u>cis-trans</u> ----	76-78 ^a	145-146/0.6 mm
<u>cis</u> -3,3-Dimethyl-5-phenyl	49-50 ^a	110-112/0.5 mm
<u>trans</u> - ---	87-88 ^a	112-113/0.5 mm

Recrystallised from ^alight petroleum (b.p. 40-60°),
^bligroin and ^cethanol

Hydrogenation in strongly acid medium of both hindered and unhindered cyclohexanones normally leads to predominantly the axial alcohol (4). As expected, hydrogenation of cyclohexanones I to IV with Pt in acetic acid-hydrochloric acid led to a mixture of isomeric cyclohexanols, the major component of which was different from the alcohol obtained by method 1. On the

other hand, hydrogenation of ketones I to III in neutral medium afforded a mixture containing greater proportions of the cis isomer. However, the hindered ketone IV gave predominantly the trans isomer by this method also, as is to be expected (4). Reduction by the Meerwein-Ponndorf-Verley method also afforded a mixture of the cis and trans isomers.

The configuration assigned to the cyclohexanols is further confirmed by the observation that, on chromatography over alumina, the trans alcohols with a hindered hydroxyl were eluted earlier than the corresponding cis alcohols. The trans isomers were also isomerized to the cis alcohols on equilibration with sodium ethoxide in refluxing xylene.

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