STUDIES ON THE REDUCTION OF SOME SUBSTITUTED CYCLOHEXANONES¹

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Abstract—Five different cyclohexanones, with at least one Ph group at position 3, have been reduced by different methods and the stereochemical course of these reductions discussed. 3,3,5-Trimethyl-S-phenyl-cyclohexanone (V) has been shown to exist in a non-chair conformation, probably in one or more of the flexible forms. Configurations have been assigned to the epimeric cyclohexanols obtained in the reductions.

INVESTIGATIONS have shown that phenyl substituted piperidin-4-ols such as α -1,3,5trimethyl-2,6-diphenylpiperidin-4-ol^{2,3} exist as an equilibrium mixture of flexible and chair conformations. Catalytic reduction of some 4-piperidones also shows that they may react in the flexible form.⁴ Consequently, some phenyl substituted cyclohexanones and the corresponding cyclohexanols have been studied and the results are presented in this paper.

The reduction of cyclohexanones I to V was studied with sodium-n-butanol, aluminium isopropoxide-isopropanol, LAH and catalytically in the presence of Adams' platinum oxide using neutral and acidic media. Each of the cyclohexanones gave a *cis*-cyclohexanol (VI) with an equatorial OH and a *trans*-cyclohexanol (VII) with an axial OH. The configurations assigned were confirmed by the stereochemistry of reduction, equilibration with aluminium isopropoxide-isopropanol, adsorption on alumina, IR spectra⁵ and kinetic measurements.⁵



Preparation of cyclohexanones. 3-Phenylcyclohex-2-en-1-one was prepared according to the method of Johnson⁶ and hydrogenated to 3-phenylcyclohexanone (I) in the presence of 10% Pd C. *cis*-3,5-Diphenylcyclohexanone (II) and *cis*-3-t-butyl-5-phenylcyclohexanone (III) were obtained in accordance with Scheme 1. The *cis* configuration of II follows from its conversion to two epimeric 3,5-diphenyl-

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cyclohexanols (see below). Since the t-butylcyclohexanone (III), m.p. 74–75° was obtained under identical conditions as II, it might be expected to have a *cis* orientation of the phenyl and t-butyl groups. Such a configuration is also supported by the stereo-isomeric composition of the products formed in the reduction of III by different methods. The cyclohexanones II and III, on reduction with LAH and on catalytic hydrogenation (see under reduction) yield almost identical mixtures of products, which means they have the same configuration. Since if the t-butyl-cyclohexanone, m.p. 74–75° has the *trans* configuration, these reductions should yield entirely different mixtures of the products. The reactivity⁵ of the epimeric cyclohexanols obtained from V further confirms the *cis* orientation of the phenyl and the t-butyl groups.



3,3-Dimethyl-5-phenylcyclohexanone (IV) was obtained by the hydrogenation of 5,5-dimethyl-3-phenylcyclohex-2-en-1-one.⁷ Conjugate addition of phenylmagnesium bromide to 3,5,5-trimethylcyclohex-2-en-1-one (isophorone) in the presence of anhydrous cuprous chloride afforded 3,3,5-trimethyl-5-phenylcyclohexanone (V).

Reduction of cyclohexanones. The results obtained in the reduction of the cyclohexanones with various reducing agents are recorded in Table 1. The sodium-nbutanol reduction afforded a single cyclohexanol from each of the cyclohexanones. Since this reduction always leads to the more stable of the two epimers,⁸ the cyclohexanol obtained should have the equatorial OH, *cis* with respect to the phenyl. The Meerwein-Ponndorf-Verley (MPV) reduction afforded a mixture of the two epimeric cyclohexanols. Of these, the epimer which was more strongly adsorbed on alumina was identical with the one obtained in sodium-n-butanol reduction. Since cyclohexanols with an equatorial OH are more strongly adsorbed on alumina than those with an axial OH,^{8,9} this further shows that the cyclohexanols obtained in the sodium-alcohol reduction have an equatorial OH. The epimers that are less strongly adsorbed on alumina should, therefore, have an axial OH, *trans* to the Ph group. The assignment of configuration was further confirmed by equilibration of the cyclohexanols with aluminium isopropoxide-acetone in refluxing isopropanol.

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The *cis* isomers predominated in the equilibrated mixtures to an extent of 75% and above (Table 1).

Considering the steric course of the MPV reduction, it will be seen from Table 1 that no simple correlation is possible. Whereas 3-phenylcyclohexanone gives predominantly the *cis*-cyclohexanol, others lead to more or less equal amounts of the two epimers. On the basis of cyclic transition states involved in this reduction, it was shown¹⁰ that a greater amount of the axial alcohol should be produced as has been observed in many cases.^{10,11} Even though the kinetically controlled product will be the axial alcohol, equilibration under the influence of aluminium isopropoxide could lead to considerable quantities of the more stable equatorial alcohol. Indeed, it was observed that heating the less stable *trans*-cyclohexanols for a short period of 2.5 hr with aluminium isopropoxide–acetone (which is the usual time taken for MPV reduction) resulted in 20–25% isomerization. Therefore, it is not surprising that equatorial alcohols are obtained predominantly in this reduction.*

Cyclohexanones I to III, on reduction with LAH afforded chiefly the *cis* isomer, whereas 3,3-dimethyl-5-phenylcyclohexanone (IV) gave a mixture of epimers with a preponderance of the trans-cyclohexanol. The results are in accord with the earlier work,^{8, 13, 14} the unhindered cyclohexanones I to III giving the equatorial alcohol and the hindered cyclohexanone (IV) with an axial Me group β to the carbonyl yielding the axial alcohol predominantly. These results are also comparable with those obtained in the reduction of the 4-piperdinones.¹⁰ It may be noted that the axial alcohol predominates to an extent of 55–60% when there is one β -axial Me troup (*trans*-3,3,5-trimethylcyclohexanol:¹⁴ 55%, β -1,2,2-trimethyl-6-phenylpiperidin-4-ol:¹⁰ 60% and trans-3,3-dimethyl-5-phenylcyclohexanol: 58%). 3,3,5-Trimethyl-5-phenylcyclohexanone (V) with two axial β -Me groups therefore should yield an even greater preponderance of the axial alcohol in the hydride reduction. The two axial Me groups in V should hinder reduction from the axial side, thereby precluding the formation of the equatorial alcohol. Attempts at the purification of the reduction products by chromatography failed; the several fractions obtained were found to be inseparable mixtures. Repeated crystallization from light petroleum afforded only one of the epimeric cyclohexanols, m.p. 93-94° (yield, 56%) which was identical with cis-3,3,5-trimethyl-5-phenylcyclohexanol (VI, R = R' = R'' = CH_3) obtained in the sodium-n-butanol reduction. The IR absorption spectra⁵ and studies on the rate of acetylation⁵ further confirm that the OH is not hindered and therefore, it should have the cis configuration.

It is significant that, even though the carbonyl in V is severely hindered, the cyclohexanone yields the equatorial alcohol. This shows that the compound should exist in a non-chair conformation, the chair form being destabilized by 1,3-diaxial Me-Me interaction. The regular boat conformations should be excluded from consideration because of severe non-bonded steric interactions involved. An examination of Courtald scale models shows that two of the twist conformations (VIII and IX) have the least non-bonded steric interactions. The hydride reductions of either form

[•] Hardy and Wicker¹² report a 75% yield of *cis*-3,3,5-trimethylcyclohexanol from dihydroisophorone and 63% of the *trans* alcohol from 2-methylcyclohexanone (both with an e-OH).

from the least hindered side (shown by arrow) would lead to the *cis*-cyclohexanol as shown below:



The reduction product will have 1,4–OH,H interaction in the twist form. This probably causes the molecule to take a distorted chair conformation in which the OH is unhindered as shown by kinetic studies.⁵ The existence of 3,3,5-trimethyl-5-phenylcyclohexanone in a non-chair conformation is also shown by dipole moment measurements.¹⁵

Catalytic reduction of cyclohexanones. The cyclohexanones were catalytically reduced with Adams' platinum oxide employing neutral, weakly acidic and strongly acidic media. When strongly acid conditions were used, any acetate formed was hydrolysed during preliminary treatment. Subjecting the less stable *trans*-cyclohexanols to this treatment showed that no epimerization occurred. The composition of the reduction product was determined by column chromatography on alumina. The results are recorded in Table 2.

The early work of Skita led to his rule that the catalytic reduction of substituted cyclohexanones in acid media affords products rich in *cis* isomer, whereas reduction in neutral or alkaline media affords products rich in *trans* isomer.¹⁶⁻¹⁸ The Skita rule was modified by Barton,⁸ on the basis of conformational analysis. Accordingly, hydrogenation of both hindered and unhindered ketones in strongly acid media affords a mixture rich in the axial alcohol and in neutral media leads to a mixture rich in the equatorial alcohol, if the carbonyl is not hindered and the axial alcohol, if it is strongly hindered. It is generally accepted that catalytic hydrogenation occurs by the *cis* addition of hydrogen to that side of the molecule which presents least steric hindrance to adsorption on the catalyst surface.^{18,19} The least hindered arrangement of the cyclohexanone ring over the catalyst surface will be one in which the hydrogen is added from the equatorial side resulting in the formation of an axial alcohol.²⁰ On this basis, a 3-substituted cyclohexanone of the type investigated in the present work should lead to a *trans*-cyclohexanol:



The results recorded in Table 2 are in accord with this view. All the cyclohexanones investigated yield more of the *trans*-cyclohexanol irrespective of the medium. The exclusive formation of the *trans*-cyclohexanol from 3,3-dimethyl-5-phenylcyclohexanone (IV) is to be expected on the basis of Barton's generalization.⁸ The presence of an axial Me group β to the carbonyl would completely hinder addition of hydrogen from the axial side even in the neutral medium. The formation of the equatorial alcohol in neutral medium is attributed to the equilibrium of the following type brought about by the hydrogenation catalysts:²⁰

Axial alcohol Ketone Equatorial alcohol

Wicker²⁰ considers that platinum, containing alkali (Adams' catalyst in neutral medium) is an effective dehydrogenation catalyst, whereas platinum oxide which has been acid-washed (or in acidic medium) is inefficient for dehydrogenation. The present work indicates that the equilibria of the above type do not contribute greatly to the composition of the reduction product. The results obtained in the reduction of these cyclohexanones are in contrast with the reduction of the 4-piperidones⁴ which are similarly constituted, the 4-piperidones yielding exclusively the equatorial hydroxyl in the acid medium. These studies indicate that one must exercise great caution in arriving at the configuration of a cyclic alcohol on the basis of hydrogenation studies.

Equilibration of cyclohexanols. The results on the equilibration (Table 1) can be used to obtain the free energy difference between the axial and equatorial hydroxyl. The *cis* orientation of the two Ph groups in the 3,5-diphencyclohexanols and the phenyl and t-butyl in the 3-t-butyl-5-phenylcyclohexanols should restrain the cyclohexane ring in one chair conformation in which the two bulky groups are equatorial. Therefore, the free energy difference of the hydroxyl can be calculated from the equilbrium constant, K of the following equilibrium:



The equilibrium composition of 3,5-diphenylcyclohexanols and 3-t-butyl-5-phenylcyclohexanols leads, respectively, to K values of 3.0 and 3.6 at 84° corresponding to a free energy of 0.79 and 0.91 kcal/mole for the OH group. These values are in good agreement with the value (0.96 kcal/mole) obtained²¹ under identical conditions from the equilibration of *cis* and *trans*-4-t-butylcyclohexanol.

EXPERIMENTAL

All m.ps are uncorrected. E. Merck's Brockmann grade alumina was used for chromatography. Ethereal solns were dried with Na₂SO₄. Light petroleum used had b.p. $40-60^{\circ}$.

3-Phenylcyclohexanone (I). 3-Phenylcyclohex-2-en-1-one⁶ (5 g) in EtOAc (40 ml) was hydrogenated at an initial H₂ press of 22 lb/sq in. using Pd-C (10%, 0.5 g) as catalyst. After 4 hr, the catalyst was filtered off and the liquid distilled to obtain a colourless liquid (3.8 g), b.p. 136-140°/6-7 mm; n_D^{30} 1-5399; d_A^{30} 1-049. Johnson⁶ reports b.p. 145-149°/11-12 mm. The semicarbazone crystallized from aqueous EtOH as shining needles, m.p. 168°. Johnson⁶ records m.p. 167.5-169°.

Cyclohexanone reduced	Yield of th cycloh	Composition of the cis-cyclohexanol			
	cis-form	trans-form	mixture ^e		
	%	%	%		
	Reduction by so	dium/n-butanol			
I	90		89		
II	89	_	75		
III	83	_	78		
IV	73	_	85		
v	70	_			
	Reduction by th	e MPV method			
I	69	31			
II	48	52			
III	54	46			
IV	48	52			
V ^b	_	_			
	Reduction by L.	АН			
I	88	_			
II	92	—			
III	90	_			
IV	32	58			
v	> 56'				

TABLE 1. COMPOSITION OF THE PRODUCTS FROM THE REDUCTION OF CYCLOHEXANON	ES
AND THE EQUILIBRATION OF THE CYCLOHEXANOLS	

^a Equilibrium was effected by heating under reflux (130 hr) the *trans*-cyclohexanol with aluminium isoproxide-acetone in isopropanol.

^b Reduction afforded a liquid, probably a mixture of the epimers, inseparable by chromatography.

' Yield obtained after crystallization from light petroleum.

	Cyclohexanone	Medium	Total - recovery	Composition of the product			
No.				cis-cyclo- hexanol	trans-cyclo- hexanol		
			%	%	%		
1	3-Phenyl	AcOH-HCl	88	20	80		
2	3-Phenyl	AcOH	83	32	68		
3	3-Phenyl	EtOAc	96	29	71		
4	cis-3,5-Diphenyl	AcOH-HCl	90	30	70		
5	cis-3,5-Diphenyl	AcOH	76	35	65		
6	cis-3,5-Diphenyl	EtOAc	90	38	62		
7	cis-3-t-Butyl-5-phenyl	AcOH-HCI	84	11	89		
8	cis-3-t-Butyl-5-phenyl	AcOH	89	12	88		
9	cis-3-t-Butyl-5-phenyl	EtOAc	98	26	74		
10	3,3-Dimethyl-5-phenyl	AcOH-HCl	94		100		
11	3,3-Dimethyl-5-phenyl	AcOH	94	_	100		
12	3,3-Dimethyl-5-phenyl	EtOAc	96	—	100		

TABLE 2. CATALYTIC REDUCTION OF CYCLOHEXANONES

			Solvent for	Analyses			
No.	Compound	М.р./b.р.	crystalliza-	Found		Calc.	
		(°C)	tion	С	н	С	н
1	cis-3-Phenylcyclohexanol	79 –80⁴	Р	81.51	9-05	81.75	9.15
2	cis-3-Phencyclohexyl acetate	120/0·9 mm		77.38	8.56	77-00	8-31
3	trans-3-Phenylcyclohexanol	6364°	Р	81·49	9.24	81.75	9.15
4	trans-3-Phencyclohexyl acetate	109-110/0-4 mm		76-59	8.66	77.00	8 ·31
5	cis-3-cis-5-Diphenylcyclohexanol	125-126	L	85·99	8-21	85 ·70	7·99
6	cis-3-cis-5-Diphenylcyclohexyl acetate	140	Ε	81-49	7·89	81.60	7.53
7	trans-3-trans-5-Diphenyl- cyclohexanol	88–89	Р	85·39	8·24	85 ·70	7-99
8	trans-3-trans-5-Diphenyl- cyclohexyl acetate	99	Е	81·26	7.19	81.60	7.53
9	cis-3-t-Butyl-cis-5-phenylcyclo- hexanol	109 –110	Р	82 44	10-60	82·69	10.41
10	cis-3-t-Butyl-cis-5- phenylcyclohexyl acetate	59	Е	78-98	9 ∙37	78·79	9.55
11	trans-3-t-Butyl-trans-5- phenylcyclohexanol	76–78	Ρ	82.57	10.54	82.69	10-41
12	trans-3-t-Butyl-trans-5- phencyclohexyl acetate	145–146/0•6 mm		78-48	9.82	78·79	9 ·55
13	cis-3,3-Dimethyl-5-phenyl- cyclohexanol	49–50	Р	82 ·10	10.10	82·30	9.87
14	cis-3,3-Dimethyl-5-phenyl- cyclohexyl acetate	110-112/0·5 mm	_	78-30	9.24	78-03	9-01
15	trans-3,3-Dimethyl-5-phenyl- cyclohexanol	87–88	Р	82·35	9.87	82·30	9.87
16	trans-3,3-Dimethyl-5-phenyl- cyclohexyl acetate	112–113/0-5 mm	-	77.56	9-03	78-03	9-01

Solvents: P, light petroleum; L, ligroin; E, ethanol.

" Curtin and Harder²⁵ report m.p 82-83°.

^b Lit.²⁵ 64°.

^c Petrow²³ records m.p. 127°.

3,5-Diphenylcyclohex-2-en-1-one. A soln of NaOEt (prepared from 2 g Na and 60 ml EtOH) was mixed with freshly distilled ethyl acetoacetate (20 g) and benzalacetophenone (20 g) dissolved in abs EtOH (20 ml) and the mixture was heated at 70-80° (water bath, 1.5 hr). Allowing the reaction mixture to cool and crystallization of the ppt from EtOH afforded 6-ethoxycarbonyl-3,5-diphenylcyclohex-2-en-1-one (25 g) m.p. 107-108°. Knoevenagel²² records m.p. 109°. This was heated under reflux (9 hr) with a mixture of glacial AcOH (250 ml) and conc HCl (125 ml) and mixed with crushed ice. 3,5-Diphenylcyclohex-2-en-1-one was obtained as an oil which soon solidified to a yellow solid (18.5 g), m.p. 83-84° after crystallization from aqueous EtOH. Petrow²³ reports m.p. 82-83°.

cis-3,5-Diphenylcyclohexanone. The above unsaturated ketone (12 g in 50 ml EtOAc) was hydrogenated at 22 lb/sq in. using Pd-C (10%, 1·2 g). Removal of the catalyst and the solvent left a residue (11·5 g) which after two crystallizations from MeOH was obtained as colourless plates (8 g) m.p. 139-140°, lit.²³ 139-140°.

3-t-Butyl-5-phenylcyclohex-2-en-1-one. Ethyl acetoacetate (98 g) was added to NaOEt (from 11-6 g Na) in EtOH (200 ml) followed by t-butyl styryl ketone²⁴ (benzalpinacolone, 85 g) in EtOH (100 ml). The mixture was warmed on a water bath at $60-70^{\circ}$ (1 hr) and then heated under reflux (4 hr) with stirring.

EtOH was removed under diminished press, the residue was mixed with water, extracted with ether and dried. After stripping off the ether, the liquid distilling at 180–185°/2.5 mm was collected (95 g). It gave a positive rest for unsaturation, a greenish-brown colouration with ethanolic FeCl₃, but failed to give a satisfactory carbon-hydrogen analysis. The analysis and the subsequent purification showed it to be a mixture of 3-t-butyl-6-ethoxycarbonyl-5-phenylcyclohex-2-en-1-one and 3-t-butyl-5-phenylcyclohex-2-en-1-one. The liquid was dissolved in a mixture of glacial AcOH (800 ml) and cone HCI (400 ml) and heated under reflux (9 hr) to effect hydrolysis and decarboxylation of the ester. The solvents were removed (diminished press), the residue was taken up in ether, washed and dried. Distillation afforded the unsaturated ketone as a colourless liquid (69.5 g), b.p. 160–162°/1.5 mm; n_D^{30} 1.5449. (Found: C, 84.47; H, 9.12. C₁₆H₂₀O requires: C, 84.18; H, 8.83%).

The 2,4-dinitrophenylhydrazone of the cyclohexenone prepared in the usual way crystallized from dioxane-ethanol as orange-red crystals, m.p. 158–160°. (Found : C, 64·80; H, 6·26. $C_{22}H_{24}N_4O_4$ requires : C, 64·69; H, 5·92%).

The semicarbazone crystallized from MeOH as colourless plates, m.p. 164–165°. (Found: C, 72-04; H, 8-32. $C_{17}H_{23}N_3O$ requires: C, 71-55; H, 8-12%).

The oxime crystallized from MeOH as colourless shining needles, m.p. 142-143°. (Found: C, 78.75; H, 9.02. $C_{16}H_{21}NO$ requires: C, 79.00; H, 8.70%).

The thiosemicarbazone was obtained from MeOH as lemon yellow needles, m.p. 192–194°. (Found: C, 68.05; H, 7.45. $C_{17}H_{23}N_3S$ requires: C, 67.74; H, 7.69%).

cis-3-t-Butyl-5-phenylcyclohexanone (III). 3-t-Butyl-5-phenylcyclohex-2-en-1-one (9 g) was dissolved in EtOAc (25 ml) and hydrogenated at 22 lb/sq in. (4 hr) in the presence of 10% Pd-C (0-9 g). Removal of the catalyst and the solvent left a residue (8-5 g, m.p. 60-65°) which crystallized from MeOH as colourless needles (6-5 g), m.p. 74-75°. (Found : C, 83-79; H, 9-73. C₁₆H₂₂O requires: C, 83-45; H, 9-63%).

The semicarbazone crystallized from MeOH as colourless plates, m.p. 186–187°. (Found: C, 71·20; H, 8·93. $C_{17}H_{25}N_3O$ requires: C, 71·06; H, 8·77%).

The oxime obtained as colourless needles from MeOH had m.p. 167–168°. (Found: C, 78.66; H, 9.51. $C_{16}H_{23}NO$ requires: C, 78.30; H, 9.45%).

The 2,4-dinitrophenylhydrazone, after crystallization from MeOH-CH₂Cl₂, was obtained as orangeyellow crystals, m.p. 198-200°. (Found : C, 64·10; H, 6·07. C₂₂H₂₆N₄O₄ requires: C, 64·36; H, 6·39%).

3,3-Dimethyl-5-phenylcyclohexanone (IV). 5,5-Dimethyl-3-phenylcyclohex-2-en-1-one⁷ (4.5 g) in EtOAc (25 ml) was hydrogenated in the usual way to give IV (4.2 g) m.p. 44-45°. Crystallization from light petroleum furnished colourless flakes, m.p. 46°, lit.⁷ 46-47°.

3,3,5-Trimethyl-5-phenylcyclohexanone (V). A soln of PhMgBr in ether (400 ml), prepared from Mg turnings (30 g) and bromobenzene (158 g), was filtered in an atmosphere of N₂, mixed with freshly prepared Cu_2Cl_2 (2·4 g) and stirred at room temp (1 hr). The bluish-green mixture was cooled to 5° and a soln of isophorone (69 g) in dry ether (100 ml) was added during 1 hr with stirring. The reaction mixture was stirred at room temp (5 hr), heated under reflux (1 hr), cooled and treated with cold, HClaq. The ethereal layer was separated and the aqueous layer was extracted with ether. The combined extracts were washed, dried and distilled to afford a liquid, b.p. 130–140°/5 mm. This liquid was treated with an aqueous ethanolic solution of semicarbazide hydrochloride and NaOAc. The precipitated semicarbazone was washed several times with light petroleum (40–60°) and crystallized from dioxan-ethanol to constant m.p. The purified semicarbazone (40 g) of V melted at 198–199°. (Found: C, 70.52; H, 8.69. C₁₆H₂₃N₃O requires: C, 70-30; H, 8.48%).

The above semicarbazone was hydrolysed with aqueous oxalic acid (20%, 600 ml) by heating under reflux (4 hr). The resulting liquid was taken up in ether, dried and distilled to give 3,3,5-*trimethyl*-5-*phenyl-cyclohexanone* (V, 26 g) b.p. 149–150°/11 mm; n_D^{30} 1.5254; d_4^{30} 1.019. (Found : C, 82.96; H, 9.19. C₁₅H₂₀O requires : C, 83.32; H, 9.33%).

The oxime of V crystallized from MeOH as shining needles, m.p. 147–149°. (Found: C, 78·11; H, 9·02. $C_{15}H_{21}NO$ requires: C, 77·91; H, 9·15%).

Reduction of cyclohexanones

With sodium and n-butanol. A soln of the cyclohexanone in n-butanol (100 ml for every gram of the ketone) was heated to boiling and Na (25 equivts) was added in small pieces at such a rate that the soln was kept refluxing. After the addition, the mixture was heated to reflux externally (1 hr), allowed to cool and any unreacted Na was destroyed by the addition of MeOH. Water was added and the n-butanol

layer was separated. The aqueous layer was acidified (conc. HC!) and extracted with ether. The extracts were combined with the n-butanol soln, washed with water and dried. Removal of the solvents under diminished press (water-pump) left a residue which was purified by chromatographic adsorption on alumina.

The Meerwein-Ponndorf-Verley reduction. The reaction was carried out as described,¹⁰ using 0.02 mole of the cyclohexanone. After the reaction, most of the isopropanol was removed by distillation under diminished press, the residue was treated with cold HCl aq and extracted with ether. The ethereal extract were washed, dried and stripped of ether. The residue was subjected to chromatography.

With lithium aluminum hydride. A soln of the cyclohexanone in dry ether (100 ml for 1 g of the ketone) was added dropwise (1 hr) to a well stirred slurry of LAH (2-3 equivts) in ether. The mixture was heated under reflux (1 hr), cooled and the excess hydride was destroyed by dropwise addition of ice-cold water. After acidifying with cold HClaq, the ethereal layer was separated, washed and dried. The residue left after removal of the solvent was purified by chromatography.

Catalytic hydrogenation of cyclohexanones

Neutral medium. The cyclohexanone (500 mg) was dissolved in EtOAc (20 ml), mixed with Adams' PtO_2 (60 mg) and hydrogenated at an initial H₂ press of 35 lb/sq in. in a low pressure Parr hydrogenator. At the end of the reaction (2 hr), the catalyst was filtered off and the solvent was removed by distillation. The residue was subjected to chromatography.

Weakly acidic medium. The reduction was carried out as above using glacial AcOH as the solvent. After removal of the catalyst, the solvent was distilled off (diminished press) and the residue was taken up in ether, washed, dried, stripped of the solvent and subjected to chromatography.

Strongly acidic medium. The cyclohexanone (500 mg) dissolved in a mixture of glacial AcOH (20 ml) and conc. HCl (20 ml) was hydrogenated as described. The residue which was mixed with ethanolic \tilde{KOH} (3%, 10 ml) was heated under reflux (7 hr) to hydrolyse any acetate that might have been formed. After the addition of water, the reaction mixture was extracted with ether, washed, dried and the solvent removed to leave a residue suitable for chromatography.

Chromatography of the epimeric cyclohexanols. This was carried out as described,¹⁰ employing 25 g of alumina for 1 g of the reduction product. The *trans*-cyclohexanol (axial OH) was obtained from the light petroleum eluates and the *cis*-cyclohexanol (equatorial OH) from the benzene and benzene-ether eluates. The cyclohexanols are listed in Table 3.

Acetates of the cyclohexanols. A soln of the cyclohexanol in pyridine (500 mg/2 ml) was treated with Ac_2O (1 ml), left over-night, heated on a water bath (3 hr), cooled, mixed with ice-cold water and extracted with ether. The ethereal extract was washed successively with dil HCl, NaHCO₃ aq and water. After drying and removal of ether, the acetate was either distilled or crystallized from a suitable solvent. The details are recorded in Table 3.

cis-3,3,5-*Trimethyl-5-phenylcyclohexanol.* Compound V (6-0 g) was reduced with Na-n-BuOH as described. The product (4-6 g) was chromatographed on alumina. The fractions obtained from benzene-light petroleum, benzene and benzene-ether eluates melted in the range 75-84°. The combined fractions (4-2 g), after 3 crystallizations from light petroleum, afforded the *cyclohexanol* (3-2 g) melting at a constant temp 93-94°. The earlier fractions (400 mg) eluted with light petroleum remained as a thick liquid. (Found: C, 82-77; H, 10-32. $C_{15}H_{22}O$ requires: C, 82-54; H, 10-16%).

The reduction of V (560 mg) with LAH afforded a viscous liquid (500 mg) which on chromatography gave fractions (benzene-light petroleum and benzene eluates) melting in the range 65-75°. These were combined and repeatedly crystallized (light petroleum) until constant m.p., 93-94° (yield, 280 mg), undepressed on admixture with the cyclohexanol obtained in the Na-n-BuOH reduction.

Attempts to obtain the *trans*-cyclohexanol in the MPV and catalytic reductions failed as the reaction products could not be purified satisfactorily either by chromatography or by crystallization.

Equilibration of the cyclohexanols. The trans-cyclohexanol (150-250 mg) and acetone (0.2 ml) were added to a soln of freshly distilled aluminium isopropoxide in isopropanol (25%, 10 ml) and heated under reflux (130 hr, water bath). After treatment with cold HClaq, the product was isolated in the usual way and chromatographed on alumina (10 g for 200 mg of the equilibrated mixture). Pure cis alcohol was isolated from benzene and benzene-ether eluates. The earlier fractions eluted with light petroleum and light petroleum-benzene were found to be mixtures of the two epimers. The composition of these was deduced from m.p.—composition curves.

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REFERENCES

- ¹ Part of this work has appeared as a preliminary communication in *Tetrahedron Letters* No. 27, 1891 (1963).
- ² M. Balasubramanian and N. Padma, Tetrahedron Letters No. 2, 49 (1963).
- ³ C. Y. Chen and R. J. W. Le Fèvre, J. Chem. Soc. 3467 (1965).
- ⁴ M. Balasubramanian and N. Padma, Tetrahedron 24, 5395 (1968).
- ⁵ M. Balasubramanian and A. D'Souza, unpublished results.
- ⁶ W. S. Johnson, J. S. Belew, L. J. Chinn and R. H. Hunt, J. Am. Chem. Soc. 75, 4995 (1953).
- ⁷ G. F. Woods, J. Am. Chem. Soc. 69, 2549 (1947).
- ⁸ D. H. R. Barton, J. Chem. Soc. 1027 (1953).
- ⁹ S. Winstein and N. J. Holness, J. Am. Chem. Soc. 77, 5562 (1955).
- ¹⁰ M. Balasubramanian and N. Padma, Tetrahedron 19, 2135 (1963).
- ¹¹ L. M. Jackman, A. K. Macbeth and J. A. Mills, J. Chem. Soc. 2641 (1949).
- ¹² K. D. Hardy and R. J. Wicker, J. Am. Chem. Soc. 80, 640 (1958).
- ¹³ W. G. Dauben, G. J. Fonken and D. S. Noyce, *Ibid.* 78, 2579 (1956).
- ¹⁴ H. Haubenstock and E. L. Eliel, *Ibid.* 84, 2363, 2368 (1962).
- ¹⁵ A. D'Souza, Ph.D. Thesis, Annamalai Univ. (1964).
- ¹⁶ A. Skita, Liebigs Ann. 431, 1 (1923).
- ¹⁷ A. Skita and W. Faust, Ber. Dtsch. Chem. Ges. 64, 2878 (1931).
- 18 A. Farkas and L. Farkas, Trans. Faraday Soc. 33, 837 (1937).
- ¹⁹ R. P. Linstead, W. E. Doering, S. B. Davis, P. Levine and R. R. Whetstone, J. Am. Chem. Soc. 64, 1985 (1942).
- ²⁰ R. J. Wicker, J. Chem. Soc. 2165 (1956).
- ²¹ E. L. Eliel and R. S. Ro, J. Am. Chem. Soc. 79, 5995 (1957).
- ²² E. Knoevenagel, Liebigs Ann. 281, 47 (1894).
- ²³ A. D. Petrow, Ber. Dtsch. Chem. Ges. 62, 642 (1929).
- ²⁴ D. Vorländer and F. Kalkow, Ber. Dtsch. Chem. Ges. 30, 2269 (1897).
- ²⁵ Y. Curtin and R. Harder, J. Am. Chem. Soc. 82, 2357 (1960).