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STERIC EFFECTS IN FIVE-MEMBERED RINGS—V

SYNTHESIS, PROPERTIES, CONFIGURATION AND CONFORMATION OF 3,3- AND 3,4-DIPHENYLCYCLOPENTANOLS

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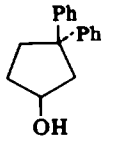
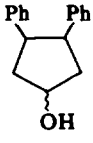
Abstract—The synthesis and characterization of the stereoisomers of the title compounds, their partially deuterated analogues and corresponding dicyclohexyl derivatives are presented. Assignments of configuration and attempts of conformational analysis are made based on the outcome of various reduction procedures, intramolecular H-bond and NMR spectroscopic studies. Oxidation rate measurements of the alcohols and equilibration of stereoisomers are also described.

As a sequel to a study of the stereochemical features of five-membered rings,[1] the investigation of a series of diphenyl-substituted cyclopentanols and their parent ketones was undertaken. As before,[1] spurious 1,2-steric hindrance of the centre under examination was to be prevented. This was achieved by substituting the 3,4-positions and studying the behaviour of a carbonyl or a carbinol function at position 1; the latter centres would then be affected only by bond angle strain, torsional strain and non-bonded interaction, as exhibited in a five-membered ring. The phenyl group was chosen to accentuate the differences between isomers; in the alkyl-substituted series,[1a–c, 2] stereoisomers were shown to exhibit very similar physical and chemical properties, making their analysis and resolutions (as well as their stereochemical study) very difficult. The synthesis of the following cyclopentanols through their ketonic precursors was carried out: 3,3-diphenylcyclopentanol (I), *cis*-3,4-diphenylcyclopentan-*cis*- and *trans*-ol (IIa and b), *trans*-3,4-diphenylcyclopentanol (III) and *cis*-3,4-dicyclohexylcyclopentan-*cis*- and *trans*-ol (IVa and b). The latter were included in the study because of their ready availability and provided an additional and convenient link to the alkyl-substituted series. These relatively simple alcohols were not known in a pure state and a defined configuration; some of them are mentioned in early literature as intermediates or by-products only.



I



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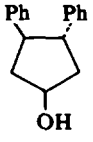

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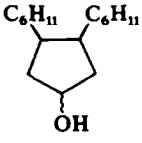

IV

* Taken in part from the M.Sc. Thesis of A.W., Haifa, 1967.

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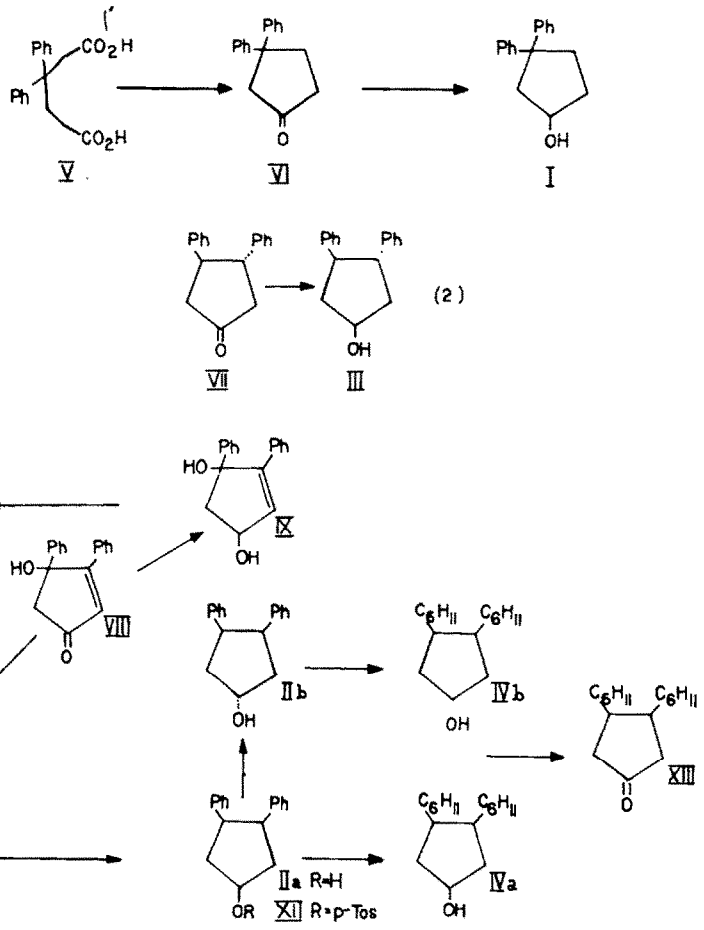
REACTION SCHEMES.



3,3-Diphenylcyclopentanol (I) (see Table 1 and subsequent discussion) was obtained by $LiAlH_4$ reduction of the heretofore unknown ketone (VI). The latter was prepared by pyrolysing the Ba salt of 3,3-diphenyladipic acid[3]* (see Table and subsequent discussion).

trans-3,4-Diphenylcyclopentanol (III) (see Table 1 and subsequent discussion) was obtained by LAH reduction of the parent ketone (VII).[5,6]

Cis-3,4-diphenylcyclopentanol has been mentioned in early literature.[5a]. No attempt, however has been made to resolve the mixture of pure stereoisomers, characterize and assign configuration (cf. though ref. 5*b* for the menthoxyacetic esters). Our results, (Table 1 and subsequent discussion), indicate that in the mentioned report,[5a] they dealt largely with the *cis–cis*-isomer (IIa).

* An alternative path, namely the acyloin (Na|NH_3) closure of dimethyl-3,3-diphenylglutarate[4] had to be abandoned owing to the formation of several by-products in appreciable yields.

TABLE 1

	Physical properties		
	m.p. (°C)	*p*-nitrobenzoate	ν_{max}, cm^{-1}
Cyclopentanol:			
3,3-Diphenyl-(I)	55– 57	112·5–113	1060
cis-3,4-Diphenyl-*cis*-(IIa)	85– 86	118 –119	1035, 1067
cis-3,4-Diphenyl-*trans*-(IIb)	99–101	171 –172	1028
trans-3,4-Diphenyl-(III)	70– 71	160 –162	1030, 1062, 1018
cis-3,4-Dicyclohexyl-*cis*-(IVa)	74– 75		1030, 1065
cis-3,4-Dicyclohexyl-*trans*-(IVb)	111–112		1015
Cyclopentanone:		DNP, m.p. (°C)	
3,3-Diphenyl-(VI)	87– 88	243	1740
cis-3,4-Dicyclohexyl-(XIII)	76– 77	208·5–211	1740

A superior synthesis of both stereoisomers, and supporting evidence for configurational assignment, were an absolute prerequisite for the study of the system.

Sodium borohydride reduction of 5-hydroxy-1,5-diphenylcyclopenten-3-one[7] (VIII) was found to be solvent—and temperature-sensitive to a high degree. Thus under two different, strictly controlled sets of conditions the diol (IX)* or the α,β-unsaturated ketone (X) is formed. The former (IX) is transformed into (X) by dehydration with acid catalysis. These actually constitute a very convenient synthesis of the ketone (X).[5a, 7b, 8] Catalytic reduction of (X) under various conditions usually yielded a mixture of *cis*-alcohol (IIa), saturated ketone (XI) and small amounts of hydrocarbons. A far better method for preparation of *cis*-3,4-diphenylcyclopentanone (XI) was found to be direct catalytic hydrogenation of (VIII) itself, again under strictly controlled conditions, namely Pd/C in *anhydrous* ethanolic KOH. Various reduction methods of the ketone (XI) were subsequently investigated. Pure *cis*-3,4-diphenylcyclopentan-*cis*-ol (IIa) (Table 1 and subsequent discussion) was thus readily obtained and the *cis*, *trans*-epimer (IIb) (Table 1 and subsequent discussion) was secured by inversion of the *p*-tosylate (XII) on basic alumina.

The pure stereomeric *cis*-3,4-dicyclohexylpentanol (IV) (see Table 1 and subsequent discussion; also cf. ref. 9 where this is mentioned as a by-product, but again configurational assignment and homogeneity were not dealt with), were prepared by catalytic reduction of the pure epimeric *cis*-3,4-diphenylcyclopentanols (IIa and b) with PtO_2 in acetic acid.

We next sought means for securing reliable evidence for configurational assignments. The relative configuration of the phenyl groups in the 3,4-diphenylsubstituted compounds is unambiguously known,[10] and spectral implications have been discussed.[11, 12] The steric relationship of the hydroxyl group in the alcohols was

* The configuration is not established.

therefore the only configurational problem to be dealt with. For the alcohols this was done on the basis of their yields from various reductions and from an IR study of the intramolecular hydrogen bond (O—H ... π) which should exist only in the *cis*-isomer. The chemical shifts of the 3-, 4- and (acetate) methyl protons as affected by the magnetic anisotropy of the phenyl groups provided also useful information.

The reduction of *cis*-3,4-diphenylcyclopentanone (XI) by various procedures where kinetic control may be assumed was stereospecific. On this basis the *cis* configuration was assigned to the major product from LiAl H_4 reduction (95%), from Meerwein–Ponndorf–Verley reduction (94%) and from H_2/Pt hydrogenation (99%). By using Na/H_2O, a procedure where thermodynamic control has to be invoked, only 62% *cis*-3,4-diphenylcyclopentan-*cis*-ol was obtained.

The O—H ... π intramolecular interaction has been extensively studied,[13] especially in α- and β-aryl alcohols.[14–18] Following studies of open-chain compounds, frequent inferences have been made[15,16] to the effect that no measurable intramolecular hydrogen bond exists when more than two carbon atoms ($n > 2$) separate the hydroxyl from the π-system. This, however, turns out to be an over-simplification; if the structure is a fixed one, and the hydroxyl and π-system are in favourable geometric juxtaposition, the interaction is observed for $n = 3$ or even $n = 4$.

TABLE 2. CHEMICAL SHIFTS OF METHYL PROTONS IN ACETATES

Compound	δ, c/s*	Δ, c/s†
Cyclopentylacetate	119	0
cis-3-Phenyl-‡	125	6
trans-3-Phenyl-‡	123	4
cis-3,4-Diphenyl-*cis*	130	11
cis-3,4-Diphenyl-*trans*	125	6
trans-3,4-Diphenyl-	126	7
3,3-Diphenyl-	116	−3

* In $CDCl_3$ ca. 10% soln, downfield from TMS as internal reference.

†As compared to cyclopentylacetate. Positive or negative values represent shifts to lower or higher field respectively.

‡ For the sake of comparison the data for the monophenyl derivatives are included in the table.

Our β,β'-substituted cyclopentanols exhibit characteristic measurable absorption bands in the 3 μ region of the IR spectrum of dilute solutions (Fig. 1), indicating definite, albeit weak, intramolecular hydrogen bonding. These results fully support our configurational assignment (*vide supra*). Various degrees of interaction are observed between hydroxyl and *cis* positioned phenyl groups but none when the relationship is *trans*. Moreover, it has been shown[14,18] that in OH...π interactions it is not the frequency shift ($\nu_{bonded} - \nu_{free}$) but rather the intensity ratio $\varepsilon_b/\varepsilon_f$ that correlates with the hydrogen-bonded population. Qualitative comparison (Fig. 1) shows that the 3,3-diphenyl compound exhibits the largest relative absorption coefficient (ε_b) in the series.

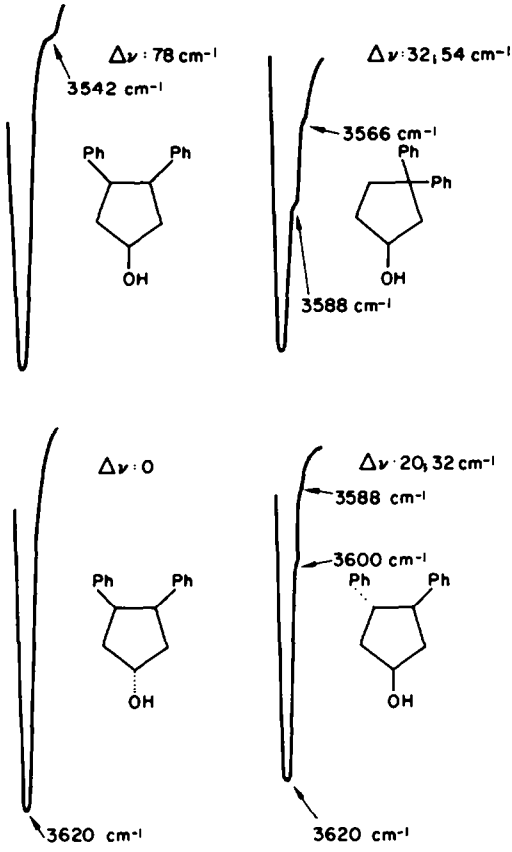


FIG. 1. IR absorption bands of dilute solutions of the alcohols in the 3μ range

We also found the chemical shifts of the methyl protons to be informative (Table 2).[19] Obviously, the latter are deshielded in all the phenyl-substituted acetates except for 3,3-diphenyl-cyclopentylacetate, which exhibits a clearly shielded methyl group. The paramagnetic shift is—as expected—highest in *cis*-3,4-diphenyl-cyclopentyl-*cis*-acetate.*

These results are attributable to inhibition of free rotation of the phenyl groups, especially in the 3,3- and *cis*-3,4-diphenyl-substituted compounds.† Thus, preferred conformations can be envisaged, where (o—o') steric interactions of two phenyl groups are prevented by attaining a parallel (or almost parallel) geometric relationship. In the *cis–cis*-3,4-diphenyl compounds this is tantamount to a preferred conformation with the 1-substituent located *in the ring* plane, or nearly so. Obviously,

* Interestingly enough, the *trans*-acetate exhibits also a paramagnetic shift. Inspection of models reveals indeed the possibility to populate a conformation with the acetate–methyl group being still in the periphery of a *trans*-phenyl group.

† Curtin *et al.*[11] first concluded to that effect, in similar substrates, on the strength of alleged temperature dependence of the chemical shifts of the aromatic protons, but this was retracted later after an investigation of *p,p'*-substituted compounds which do not behave similarly. While their data did not prove a restricted rotation, they do not disprove it either.

this leads to less populated hydrogen-bonded species in the alcohol (IIa) and to deshielded methyl protons in its acetate. In the 3,3-diphenyl compounds one may conclude a preferred conformation with the 1-substituent near the sixfold axis, i.e. *facing the plane* of the phenyl group. As a result, the hydrogen bond in the alcohol (I) is a more efficient one and the acetate-methyl protons are shielded. The *trans*-3,4-diphenyl derivatives, on the other hand, should display all but complete freedom of rotation of the phenyl groups and, accordingly, only slight inflections of medium intensity are observed in the hydrogen bond IR absorption spectrum (Fig. 1) and the acetate–methyl protons are deshielded to an intermediate extent (Table 2).*

Support for our above interpretation is provided by additional NMR data on the α-hydrogens (benzylic) and β-hydrogens to the phenyl groups. These have been obtained—from the otherwise very complex spectra—in a more detailed NMR investigation of deuterated derivatives as an attempt of ring-conformational studies in the

TABLE 3. CHEMICAL SHIFTS AND COUPLING CONSTANTS*

	Chemical shifts, τ (ppm)		Coupling constants, J (δ), (Hz)		
	3-H	4-H	*gem*† 2,2 = 5,5	*vic* 2,3 = 4,5	*vic* 3,4
-Cyclopentanone:					
3,3-Diphenyl-(VI)		7·28			
trans-3,4-Diphenyl-(VII)	6·52				0 (0)
cis-3,4-Diphenyl-(XI)	6·15		−12−−16	‡	0 (0)
-Cyclopentanol:					
3,3-Diphenyl-(I)		7·60§			
cis-3,4-Diphenyl-*cis*-(IIa)	6·57		−14·0 (21·0)	9·0 (52); 7·0 (73)‖	0 (0)
cis-3,4-Diphenyl-*trans*-(IIb)	6·42		−14·5 (21·5)	6·1 (98); 4·9 (77)‖	
trans-3,4-Diphenyl-(III)	6·92	6·54			11·4 (23)

* The values are given to their significant figures.

† The geminal coupling constants are assigned negative signs.[24, 25]

‡ $\frac{1}{2}(J_{2,3} + J_{2',3}) = 6{\cdot}5$ Hz; $\delta_{2,3} \cong \delta_{2,3} \cong 69$ Hz. The latter value was confirmed in a double irradiation experiment.

§ The singlet absorption is attributed to a fortuitous similarity of the chemical shifts of the geminal unequivalent protons. Albeit, the half-width is, ~4 Hz and lack of optimum resolution might be due to deuterium broadening.

‖ Long range coupling is detectable in the fine structure but was not evaluated.

series. Exchange of the 2 and 5 protons was achieved by repeated deuterolysis of the enamine derivatives of the ketones[20] whereas $LiAlD_4$ reduction of the latter provided the 1-deutero compounds. Thus, straightforward analysis became possible revealing chemical shifts and coupling constants of certain sets of protons (see Table 3 and Figs. 2 and 3). In both ketones and alcohols, a shift to a higher field is observed in going from *cis*- to the *trans*-3,4-diphenyl derivatives, i.e. the benzylic protons in the former are relatively deshielded (for an early attempt at analogous—albeit little

* The 3-phenyl substituted analogs behave similarly, corroborating these assignments; results unpublished as yet.

substantiated inferences—see ref. 21). One can explain this by again postulating the preferred "face-to-face" conformation of the phenyls in the *cis*-3,4-derivatives, whereby the benzylic protons are confined to the periphery of the rings and therefore resonate at lower fields. The 4-protons in the 3,3,-diphenyl derivatives are appreciably deshielded (cf. ref. 1*d*) again in accord with a preferred "face-to-face" conformation of the phenyls. It is worth recalling that in the methyl-substituted series, strong

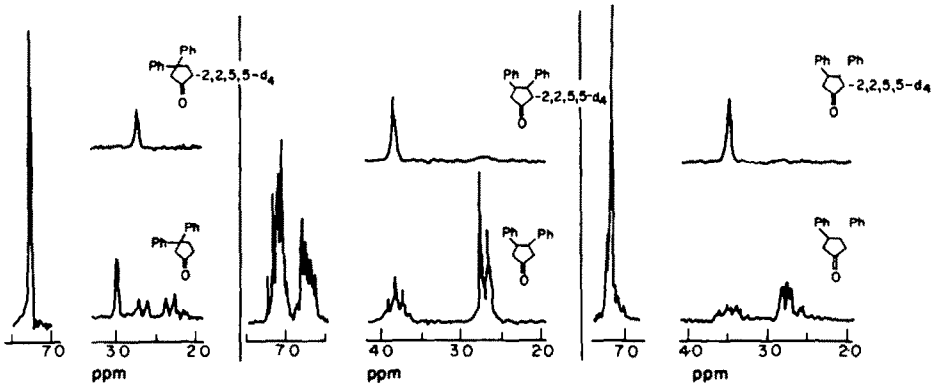


FIG. 2. NMR spectra of the substituted cyclopentanones and their deuterated derivatives.

shielding by *cis-vic* methyl groups has been reported.[1d, 22] In the present series, protons *cis* and adjacent to phenyl groups are deshielded, the extent of this effect depending on the degree of free rotation and the relative conformation of the phenyls vis-a-vis the protons. Similar considerations apply to the benzylic protons.* The coupling constants we were able to extract in this study (see Table 3 and Figs. 2 and 3) provide some, admittedly limited, insight in the ring conformational aspects of these molecules. It should be mentioned at this point that our anticipation of proton averaging due to extensive ring mobility, was largely confirmed by experiment. Thus singlet signals were recorded for the pairs of 3,4- or 4,4-protons in (IIa), (VI), (XI) and (VII). This can be understood in terms of the last being a set of enantiotopic protons while the three first ones constitute sets of equivalent protons.[23] But this is so only if we refer to planar structures which can of course only be derived from conformational time-averaging. This interpretation is supported by further analysis of the NMR spectra of the I-deuterated alcohols IIa and b in terms of two equivalent (2,2,3 and 5,5,4) systems present in each molecule which give rise to degenerate ABK spectra. The geminal as well as the vicinal coupling constants are in good agreement with published values in comparable systems.[1d, 24, 25]

Examination of models reveals indeed the necessity for the *cis*-diphenyl substituted ring to invert rapidly between the extremes of *pseudo*-equatorial:*pseudo*-axial phenyl

* A brief search for benzylic proton resonances in Appendix B of ref. 19*a* yields illuminating data. Thus the τ values for the benzylic protons in 2,2-*p*-cyclophane, 1,2-diphenylethane, tetralin and ethyl benzene are 6·95, 7·13, 7·30 and 7·38, respectively. We regard this trend as providing support for our interpretation as presented above. The unusually low-field signal in the first compound is obviously due to the strong deshielding of the *coplanar* protons by the adjacent phenyl group. On the other hand, in tetralin the benzylic protons librate in a plane *perpendicular* to that of the adjacent phenyl group, and are therefore less deshielded by the latter.

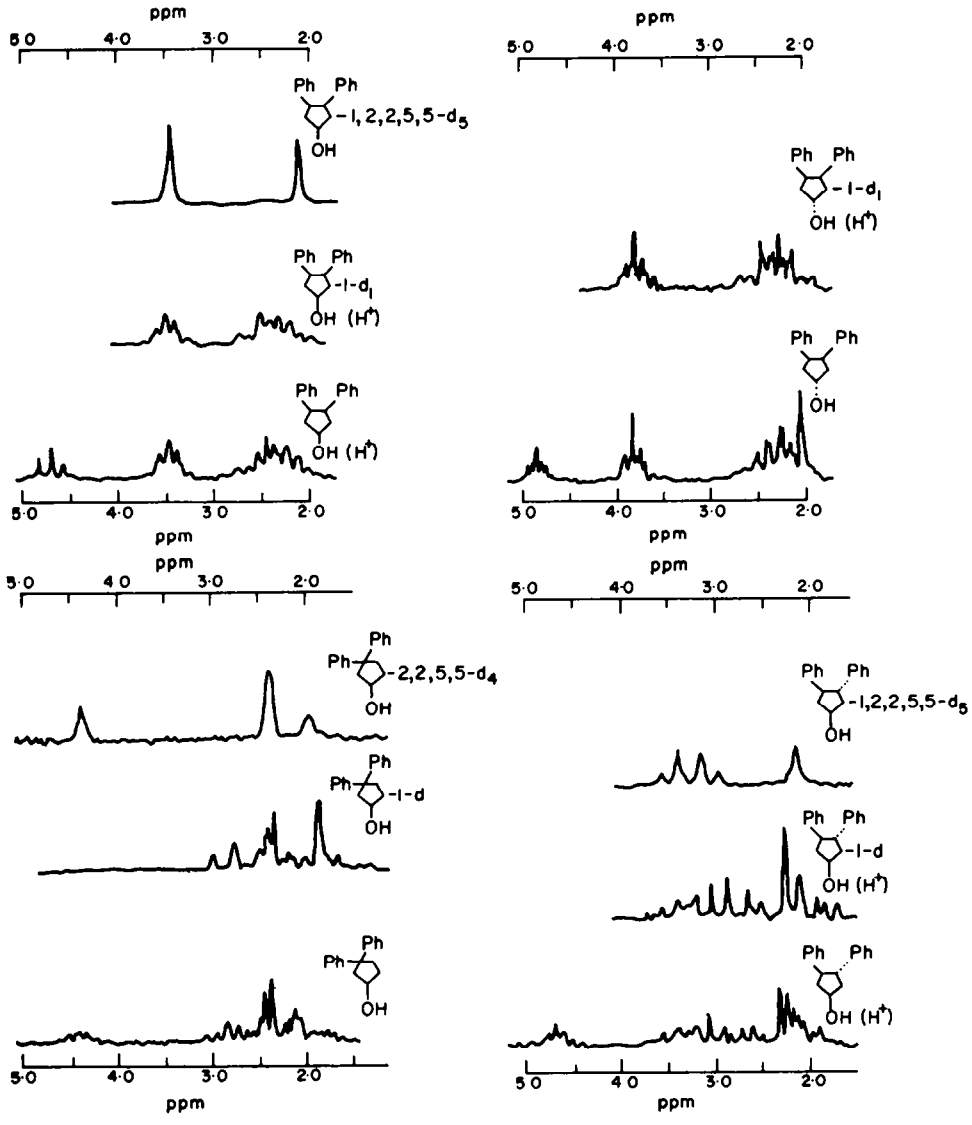


FIG. 3. NMR spectra of the substituted cyclopentanols and their deuterated derivatives.

conformations.* No energetically preferred conformation (out of five probable ones for IIa and eight probable ones for IIb) can indeed be pointed at. On the other hand in *trans*-3,4-diphenylcyclopentanol, the magnitude of $J_{3,4}$ points to two possible half-chair conformations (1-OH, 3-Ph, 4-Ph and 2-Ph, 3-Ph, 5-OH),† where the 3 and 4 protons are *nearly* axial. However, one cannot exclude entirely two additional envelope conformations (2-Ph, 3-Ph, 5-OH and 1-Ph, 2-Ph, 4-OH)‡ which, incident-

* The reader unfamiliar with cyclopentane conformations is referred to one of the available reviews, see for example ref. 26, for further details and numbering of the carbons in the different conformers see for example ref. 27.

† The numbering in the parentheses refer to the cyclopentane conformations,[26] i.e. where position 1 is on the symmetry element of the particular conformation.

ally, appear to be the next neighbours in the pseudorotation itinerary between the two above mentioned half-chairs.[27] It should be expected that the barriers in these inversions be low and indeed in preliminary low-temperature measurements down to *ca.* −60°, no detectable conformational freezing could be observed, implying the occurrence of intermediate conformations via fast interconversion.

A chromic acid oxidation-rate study of the alcohols in the series was carried out, including temperature dependence and isotope effects.[28] The simple oxidation rates are worthy of note and mention (Table 4). Again,[1b] all rates fall in a narrow range of less than one order of magnitude and in the case of epimeric alcohols the results are surprisingly similar.

TABLE 4. OXIDATION RATES*

Compound	k_2, (l. mole^{-1} min^{-1})	Relative rate
Cyclopentanol	67·8	1·0
trans-3,4-Diphenyl-	43·6	0·64
cis-3,4-Diphenyl-*trans*-	52	0·8
cis-3,4-Diphenyl-*cis*-	118	1·75
3,3-Diphenyl-	92	1·35
cis-3,4-Dicyclohexyl-*cis*-	204	3·0
cis-3,4-Dicyclohexyl-*trans*-	236	3·5

* Measured at 30°C, in 90% acetic acid, following spectrophotometrically the disappearance of Cr^{VI}; the constants are averages of three runs and are given to the significant figure.

This trend appears to be characteristic of substituted cyclopentanes and comes into display in their physical as well as chemical properties (both in the kinetic and product analysis).* We attribute this to the flexibility of the five-membered ring even when heavily substituted. The conformational-analytic implications drawn so far, are: in *mobile*† cyclopentanes the labeling of exocyclic bonds (e.g. equatorial, pseudo-axial, bisectional) is largely over-simplified and does not stand up to critical scrutiny. The symmetric ring-conformations cannot be taken for granted‡ and intermediate forms may prevail. Conformational interconversion, either by pseudorotation or by ring-flipping, exhibits very low barriers. Bulky substituents are not imposed by the ring energetics into certain preferred conformations‡ and quite the opposite happens; in a given process, the substituent undergoing the change, brings about the whole structure to assume the conformation of lowest possible energy in the particular reaction profile. Non-bonded interactions (namely 1,3 ones) appear to be relatively unimportant in the total strain-energy expression of substituted cyclopentanes.

Equilibration of the stereomeric pairs of alcohols by the Al $(i\text{-PrO})_3$-*i*-PrOH-acetone method proved instructive (Table 5). In the *cis*-3,4-diphenyl pair, the *trans*-isomer is found to be the more stable of the two by a large margin, whereas in the *cis*-3,4-dicyclohexyl pair the direction is reversed and the difference is only slight.

* cf. also preceding papers in this series[1b,c] and references cited therein.

† As opposed to *rigid* ones, the geometry of which is forcefully imposed and so is the conformation of the substituents, for ex. in bicyclo (2.2.1) heptane derivatives.

‡ In striking contrast to the state of affairs in six-membered rings.

TABLE 5. RELATIVE STABILITY OF STERBOISOMERS

Substituted cyclopentanols	Equilibrium $cis \rightleftarrows trans$ K, $\frac{trans}{cis}$	$\Delta F°$, (kcal/mole)	Oxidation rates $\frac{k_2, trans}{k_2, cis}$	ΔF_{ox}, (kcal/mole)
cis-3,4-Dicyclohexyl-	$\frac{42}{58} = 0{\cdot}7$	0·2	$\frac{3{\cdot}49}{3{\cdot}01} = 1{\cdot}16$	0·1
cis-3,4-Diphenyl-	$\frac{79}{21} = 3{\cdot}8$	−0·9	$\frac{0{\cdot}76}{1{\cdot}74} = 0{\cdot}44$	−0·5

The relative stabilities as obtained from equilibration studies are qualitatively corroborated by the results of the oxidation-rate measurements (cf. 1*b* and references therein). The hydrogen bond apparently contributes only negligibly to the stabilization of the *cis*-isomer in the alcohols IIa and b. This is understandable if one considers in general the low energy of the OH . . . π interaction,[29] and in particular our cases in which the hydrogen bond is weak and scarcely populated. Still we find it difficult at this stage to interpret the differences in relative stabilities between the diphenyl- and dicyclohexyl substituted pairs of isomers (as well as the methyl substituted pair).[1c]

EXPERIMENTAL

M.ps are uncorrected (Büchi immersion apparatus). IR spectra were performed on a Perkin–Elmer 237 grating spectrophotometer, in $CHCl_3$ unless otherwise specified. The analysis in the 3 μ region was done on CCl_4 solutions (ca. 0·005M in alcohol) in 10 cm quartz cells. In the 10 μ region, analysis of mixtures of stereomeric alcohols was performed by using the base-line method and calibration curves from synthetic mixtures, with an estimated error of $\pm 4\%$; the characteristic absorption bands used are given in Table 1.

NMR spectra were measured on a Varian A-60 instrument, in $CDCl_3$ ca. 10% soln (unless otherwise specified) with TMS as internal standard. The estimated accuracies are ± 1 Hz for chemical shifts and $\pm 0{\cdot}4$ Hz for coupling constants.

3,3-*Diphenylcyclopentanone* (VI)

3,3-Diphenyladipic acid (V)[3] (13 g) was heated to 200° in the presence of Ba $(OH)_2$ (1 g). The pyrolysate was collected at reduced pressure (30 mm Hg) in a cooled receiver. The oily distillate was taken up in methylene chloride, washed with cold base and water and dried. Evaporation of the solvent left a residue (7·0 g; 68%) which solidified upon redistillation. Crystallization from hexane gave the analytically pure ketone (VI) (3·1 g; 30%), see Table 1 and subsequent discussion. (Found: C, 86·49; H, 6·76; O, 6·70. Calc. for $C_{17}H_{16}O$: C, 86·40; H, 6·83; O, 6·77%).

The dinitrophenylhydrazone derivative melts at 243° (from nitromethane). (Found: N, 13·86%. Calc. for $C_{23}H_{20}N_4O_4$: N, 13·46%).

3,3-*Diphenylcyclopentanol* (I)

A solution of the ketone (VI) (0·80 g) in dry ether (10 ml) was added dropwise to a stirred solution of $LiAlH_4$ in dry ether (25 ml). After 20 hr of stirring, the excess reagent was destroyed by adding a 10% solution of ethyl acetate in ether. This was followed by water and hydrochloric acid (3N). After separation, the aqueous layer was thoroughly extracted with ether. The combined ethereal solutions were washek, dried and the ether evaporated. The residue was crystallized from hexane to give the pure alcohol (I) (0·68 g; 85%) (see

Table 1 and subsequent discussion). (Found: C, 85·51; H, 7·64; O, 6·81. Calc. for $C_{17}H_{18}O$: C, 85·67; H, 7·61; O, 6·71%).

The *p*-nitrobenzoate derivative melts at 112·5–113° (from methanol). (Found: C, 74·43; H, 5·45; N, 3·84. Calc. for $C_{24}H_{21}NO_4$: C, 74·40; H, 5·46; N, 3·62%).

trans-3,4-*Diphenylcyclopentanol* (III)

An ethereal solution of *trans*-3,4-diphenylcyclopentanone (VII)* (1·0 g), as obtained from a soxhlet extractor, was added to a suspension of $LiAlH_4$ (0·2 g) in dry ether (200 ml). After the usual work up, the alcohol (III) (0·85 g, 85%) was obtained and crystallized from hexane, m.p. 70·5–71·5° (see Table 1 and subsequent discussion). (Found: C, 85·29; H, 7·69; O, 7·01. Calc. for $C_{17}H_{18}O$: C, 85·67; H, 7·61; O, 6·71%).

The *p*-nitrobenzoate derivative melts at 160–162° (from methanol). (Found: C, 74·36; H, 5·82; N, 3·46. Calc. for $C_{24}H_{21}NO_4$: C, 74·40; H, 5·46; N, 3·62%).

1,5-*Diphenylcyclopent*-1-*ene*-3,5-*diol* (IX)

$NaBH_4$ (0·4 g) was added in small portions to a stirred solution of 5-hydroxy-1,5-diphenylcyclopenten-3-one[7] (VIII) (5 g) in methanol (50 ml) and ether (20 ml). The stirring was continued for 30 min. The reaction mixture was then acidified with 3N HCl and the organic solvents were removed *in vacuo*. The aqueous residue was extracted with methylene chloride and the organic solution was washed, dried and concentrated. Upon cooling, colourless crystals were obtained (2·4 g; 48%) m.p. 147–148°. TLC of the mother liquor shows the latter and several other by-products present). Recrystallization from benzene gave the pure diol (IX); m.p. 149–150°. ν_{max} 1030, 1065, 3600 cm^{-1}.
(Found: C, 80·94; H, 6·41; O, 12·69. Calc. for: $C_{17}H_{16}O_2$: C, 80·92; H, 6·39; O, 12·68%.)

1,5-*Diphenylcyclopent*-1-*en*-3-*one* (X)

(a) The hydroxyketone[7] (VIII) (15 g) was suspended in aqueous methanol (96%; 50 ml) and ether (ca. 20 ml) was added until a clear solution was obtained. The latter was ice cooled and treated with $NaBH_4$ (1·0 g) in small portions for 45 min. Stirring was continued for 90 min followed by acidification with dilute HCl and evaporation of the organic solvents *in vacuo*. The aqueous residue was extracted with methylene chloride. The extract was washed, dried and the solvent was evaporated to dryness. The residue (10·5 g) was chromatographed on basic alumina (520 g; Merck). Hexane–methylene chloride (1:1) eluted the pure ketone (X) (3·9 g; 29% m.p. 107–108°). Chloroform eluted the starting material (VIII) (2·2 g) and another compound, m.p. 215–220 which was not further investigated.

(b) A solution of the diol (IX) (2 g) in benzene (100 ml) was azeotropically distilled overnight in the presence of a catalytic amount of *p*-toluenesulphonic acid. The solution was subsequently washed, dried and the solvent evaporated to dryness. Crystallization from isopropanol gave a product, m.p. 217–219° (0·2 g) which was not investigated further. The mother liquor yielded the unsaturated ketone (X) m.p. 107–109° (1·01 g; 52%.)

Hydrogenation of the unsaturated ketone (X) catalyzed by Pd or Pt in various solvents, invariably led to mixtures of a hydrocarbon, the saturated ketone (XI) and the alcohol (IIa).

cis-3,4-*Diphenylcyclopentanone* (11)[5a]

5-Hydroxy-1,5-diphenylcyclopenten-3-one[7] (VIII) (10 g) was hydrogenated in *absolute* ethanol (200 ml), in the presence of 30% palladized carbon (0·4 g) and a few drops of ethanolic KOH, at an initial pressure of 54 psi of hydrogen. After 8 days the catalyst and the solvent were removed. The residue was chromatographed on basic alumina (200 g; Merck). Pentane–methylene chloride (3:1) eluted the ketone (XI) (8·0 g; 85%), crystallized from ethanol, m.p. 108–110·5°. Methylene chloride eluted the alcohol (IIa) (0·7 g; 7·3%).

Reductions of the ketone (XI)

(a) $LiAlH_4$. A solution of the ketone (XI) (0·5 g) in dry ether (25 ml) was added to a suspension of $LiAlH_4$ (0·1 g) in dry ether (50 ml). The stirring was continued for 6 hr and then the excess reagent was decomposed by 10% ethyl acetate in ether followed by water and 3N sulphuric acid. After separation the aqueous layer was extracted with ether. The combined ethereal solutions were washed, dried and the solvent evaporated.

* The original synthetic procedure of Totton *et al.*[6a] had to be modified. The decarboxylation of 2-carbethoxy-3,4-diphenylcyclopentanone occurred smoothly only by boiling it in a mixture of HBr (46–48%) and ethanol (1:1).

Crystallization from hexane gave a product m.p. 79–82° (88%), 95% *cis* (IR). On repeated recrystallization the pure *cis*-alcohol (IIa m.p. 83–84°) was obtained.

(b) *Meerwein–Ponndorf–Verley*. The ketone (XI) (0·45 g) in dry isopropanol was refluxed for 6 hr in the presence of aluminium isopropoxide. The acetone formed was removed by continuous distillation (altogether 15 ml of solvent being removed). The reaction mixture was concentrated and the residue was taken up in methylene–chloride and acidified with 3N sulphuric acid. After separation, the aqueous phase was extracted with methylene chloride. The combined organic layers were subsequently washed, dried and evaporated. The residue was recrystallized from hexane to yield colourless crystals m.p. 78–82·5° (0·26 g; 58%), 94% *cis*- (IR).

(c) Na/H_2O. To a solution of the ketone (XI) (0·5 g) in ether (16 ml), a sodium bicarbonate solution (3 g in 10 ml water) was added. The two phase system was treated with sodium metal (0·7 g) in small pieces for 1 hr. TLC showed some ketone still present but addition of more sodium bicarbonate solution and sodium metal did not appreciably alter the composition. After separation, the aqueous phase was extracted with ether. The combined ethereal solutions were dried and the ether removed. The oily residue (0·47 g) was chromatograahed on basic alumina (Merck; 15 g) Hexane–CH_2Cl_2 (1:1) eluted the ketone (XI) (50 mg; 10%) followed by a mixture of the epimeric alcohols (296 mg; 59%), 62% *cis*-(IR), which was recrystallized from hexane m.p. 56–64°.

(d) H_2/PtO_2. cis-3,4 *Diphenylcyclopentan*-cis-*ol* (IIa). The ketone (XI) (2·69 g) was hydrogenated in absolute ethanol (200 ml) in the presence of platinum oxide (0·447 g) at atmospheric pressure, for 2 hr. After removal of the catalyst and solvent, the residue was recrystallized from hexane to yield the pure alcohol (IIa) (1·92 g; 89%) 99% *cis*-(IR), m.p. 84–86°, see Table 1 and subsequent discussion.

(Found : C, 85·57; H, 7·82; O, 6·84. Calc. for $C_{17}H_{18}O$: C, 85·67; H, 7·61; O, 6·71%.)

The *p*-nitrobenzoate derivative melts at 118–119° (from methanol).

(Found: C, 73·91; H, 5·41; N, 3·65. Calc. for $C_{23}H_{21}NO_4$: C, 74·40; H, 5·46; N, 3·62%.)

cis-3,4-*Diphenylcyclopentan-trans-ol* (IIb)

(a) cis-3,4-*Diphenylcyclopentyl*-cis-*p-toluenesulphonate* (XII). An ice-cooled solution of *p*-toluenesulphonyl chloride (0·5 g) in dry pyridine (2·5 ml) was added to an ice-cooled solution of the *cis–cis* alcohol (IIa) (0·3 g) in dry pyridine (2·5 ml). After 16 hr in the refrigerator, the mixture was poured on ice and HCl (3N; 25 ml). The aqueous mixture was extracted with methylene chloride and the organic extract was washed, dried and evaporated. The crude *p*-tosylate (0·47 g; 93%) was recrystallized four times from hexane m.p. 90·5–91·5°, ν_{max} 1370, 1172, 890 cm^{-1}.

(Found: C, 73·41; H, 6·24; S, 8·21. Calc. for: $C_{24}H_{24}O_3S$: C, 73·45; H, 6·16; S, 8·15%.)

(b) *Displacement with inversion of the* p-*tosylate* (XII). The above tosylate (XII) in methylene chloride was applied to a column of basic alumina (activated, Merck, 80 g) and left overnight. Elution with the same solvent gave a hydrocarbon (0·15 g). Methanol in chloroform (15%) gave *cis*-3,4-diphenylcyclopentan-*trans*-ol (IIb) recrystallized from hexane, m.p. 99–101° (0·17 g; 43%) mixed m.p. with (IIa); 55–67°, see Table 1 and subsequent discussion.

(Found: C, 85·75; H, 7·49; O, 6·67. Calc. for $C_{17}H_{18}O$: C, 85·67; H, 7·61; O, 6·71%.)

The *p*-nitrobenzoate derivative melts at 171–172° (from methanol).

(Found: C, 74·21; H, 5·43; N, 3·77. Calc. for $C_{24}H_{21}NO_4$: C, 74·46; H, 5·45; N, 3·62%.)

cis-3,4-*Dicyclohexylcyclopentan*-cis-*ol* (IVa)

A solution of *cis*-3,4-diphenylcyclopentan-*cis*-ol (IIa) (0·88 g) in glacial acetic acid (25 ml) was hydrogenated in the presence of platinum oxide (81·5%; 0·13 g) at atmospheric pressure for 2 days. After removal of the catalyst and solvent, TLC showed two spots: the desired alcohol (IVa) and its acetate derivative. Attempts to hydrolyze the acetate with alcoholic potassium hydroxide (2·5 g in 50 ml 95% ethanol) also caused partial oxidation to the corresponding ketone. The aqueous layer was extracted with ether, and the combined ethereal solution was washed with water and dried over anhydrous magnesium sulphate. After removing the solvent the residue was chromatographed on basic alumina (Merck). Hexane eluted *cis*-3,4-dicyclohexylcyclopentanone (XIII) re-crystallized from hexane m.p. 76–77° (0·14 g: 16%), see Table 1 and subsequent discussion.

(Found: C, 82·20; H, 11·29; O, 6·45. Calc. for $C_{17}H_{28}O$: C, 82·18; H, 11·29; O, 6·47%.)

The dinitrophenylhydrazone melts at 208·5–211 (from methanol).

(Found: N, 13·21. Calc. for $C_{23}H_{32}N_4O_4$: N, 13·08%.)

Methylene–chloride–hexane (1·9) eluted *cis*-3,4-dicyclohexylcyclopentan-*cis*-ol (IVa) (0·32 g; 36%) m.p. 74–75 C, see Table 1 and subsequent discussion.

(Found: C, 81·26; H, 11·87; O, 6·76. Calc. for $C_{17}H_{30}O$: C, 81·53; H, 12·08; O, 6·39%.)

In a repeated experiment, chromatographic separation was performed following the hydrogenation. The alcohol (IVa) and its acetate were isolated. The acetate was identical with the authentic acetate.

cis-3,4-*Dicyclohexylcyclopentan*-trans-*ol* (IVb)

cis-3,4-Diphenylcyclopentane-*trans*-ol (IIb) (0·3 g) was hydrogenated in glacial acetic acid (15 ml) in the presence of platinum oxide for 24 hr. After removal of the solvent and catalyst, the residue was chromatographed on basic alumina (Merck). Hexane eluted the acetate derivative of (IVb), methylene chloride eluted *cis*-3,4-dicyclohexylcyclopentan-*trans*-ol (IVb) (0·12 g; 40%), recrystallized from hexane m.p. 111–112°, see Table 1 and subsequent discussion.

(Found: C, 81·88; H, 11·86; O, 6·10. Calc. for $C_{17}H_{30}O$: C, 81·53; H, 12·08; O, 6·39%.)

Equilibration experiments (*See Table* 5)

The equilibrations of the alcohols were performed in all cases in two parallel experiments starting with both epimers. With the *cis*-3,4-diphenylcyclopentanols (II) equilibrium was reached after 15 days and the products analysed for 21% *cis* isomer. With the dicyclohexyl stereomeric alcohols (IV) equilibrium was reached after 10 days and the products analysed for 58% *cis* isomer. The reproducibility was better than ±3%.

50 mg alcohol in 5 ml dry *i*-propanol, 0·2 g. Al (*i*-PrO)$_3$ and 0·2 ml acetone were refluxed (81°C). The cooled mixture was then acidified (10% HCl) and the aqueous solution extracted with ether. The organic solution was washed, dried and the solvents removed. The residue was then analysed as described in the opening remarks of the Experimental section.

Deuteration experiments.

Exchange of the 2- and 5- protons of the ketones (VI), (VII) and (XI) by deuterium was accomplished in a continuous process whereby formation of the ene-pyrrolidino derivative followed by its deuterolysis[20] was repeated until completion. The reduction of the ketones by $LiAlD_4$ in a standard procedure provided 1-deutero alcohols. The extent of deuteration was always determined by NMR and mass spectrometric analysis.

REFERENCES

1 [a] B. Fuchs and R. G. Haber *Bull. Res. Counc. Israel*, **11A**, 30 (1962);
[b] *Tetrahedron Letters* 1323 (1966);
[c] *Ibid.* 1447 (1966);
[d] B. Fuchs, *Israel J. Chem.* **3**, 52 (1965).

2 [a] W. Hückel and R. Bross, *Liebigs Ann* **664**, 1 (1963);
[b] J. C. Richer and C. Gilardeau, *Can. J. Chem.* **43**, 3418 (1965);
[c] I. Lillien and K. Khaleeluddin, *Chem. & Ind.* 1028 (1964);
[d] A. P. Krapcho and D. E. Horn, *Tetrahedron Letters* 6107 (1966).

3 W. Herz and G. Caple, *J. Org. Chem.* **29**, 1691 (1964).

4 T. C. Bruice and W. C. Bradbury, *Ibid.* **28**, 3403 (1963).

5 [a] H. Burton and C. W. Shoppee, *J. Chem. Soc.* 567 (1939);
[b] R. J. Hovart and C. R. Noller, *J. Org. Chem.* **22**, 353 (1957).

6 [a] E. L. Totton, R. C. Freeman, H. Powel and T. L. Yarboro, *Ibid.* **26**, 343 (1961);
[b] cf. also P. T. Lansbury and E. J. Nienhous, *J. Am. Chem. Soc.* **88**, 4290 (1966).

7 [a] F. R. Japp and G. D. Lander, *J. Chem. Soc.* **71**, 123 (1897);
[b] C. F. H. Allen and J. A. Van Allan, *J. Am. Chem. Soc.* **72**, 5266 (1950);
[c] *Ibid.* **77**, 2315 (1955).

8 P. Yates, N. Yoda, W. Brown and B. Mann, *Ibid.* **80**, 202 (1958).

9 H. Burton and C. W. Shoppee, *J. Chem. Soc.* 1408 (1939).

10 [a] H. A. Weidlich, *Chem. Ber.* **71** II, 1601 (1938);
[b] *Ibid.* **74B**, 1195 (1941).

11 [a] D. Y. Curtin, H. Gruen, Y. G. Hendrickson and H. E. Knipmeyer, *J. Am. Chem. Soc.* **83**, 4838 (1961);
[b] D. Y. Curtin and S. Dayagi, *Can. J. Chem.* **42**, 867 (1964).

12 D. J. Cram, N. L. Allinger and H. Steinberg, *J. Am. Chem. Soc.* **76**, 6132 (1956).

[13] M. Tichy in *Advances in Organic Chemistry*, (Edited by R. A. Raphael, E. C. Taylor and H. Wynberg). Interscience, New York (1965) and leading refs. there.
[14] P. von R. Schleyer, C. Wintner, D. S. Trifan and R. Bacskai, *Tetrahedron Letters* No. 14, 1 (1959).
[15] M. Oki and H. Iwamura, *Bull. Chem. Soc. Japan* **32**, 1135 (1959).
[16] N. Mori, S. Omura and Y. Tsuzuki, *Ibid.* **38**, 1632 (1965).
[17] [a] P. Von R. Schleyer, D. S. Trifan and R. Bacskai, *J. Am. Chem. Soc.* **80**, 6691 (1958);
[b] cf. also footnote 6 cited in Ref. 19*a*.
[18] J. Sicher, M. Cherest, Y. Gault and H. Felkin, *Coll. Czecch. Chem. Commun.* **28**, 72 (1963).
[19] [a] J. W. Emsley, J. Feeney and L. H. Sutcliffe, *High Resolution Nuclear Magnetic Resonance Spectroscopy*, Pergamon Press, Oxford (1966);
[b] L. M. Jackman, *Applications of Nuclear Magnetic Resonance Spectjoscopy in Organic Chemistry*. Pergamon Press, Oxford (1959).
[20] F. Guinot and G. Lamaty, *C.R. Acad. Sci., Paris* C **263**, 549 (1966).
[21] D. Y. Curtin, H. Gruen and B. A. Shoulders, *Chem. & Ind.* 1205 (1958); cf. also, discussion in ref. 19*b*, p. 126.
[22] E. Pretsch, H. Immer, C. Pascual, K. Schaffner and W. Simon, *Helv. Chim. Acta* **50**, 105 (1967) and refs. cited there (cf. also Ref. 19*b*, p. 119).
[23] K. Mislow and M. Raban in *Topics in Stereochemistry* (Edited by N. L. Allinger and E. L. Eliel). Vol. I, Ch. 1. Interscience, New York (1967).
[24] R. N. Johnson, J. B. Lowry and N. V. Riggs, *Tetrahedron Letters* 5113 (1967); see also *Ibid.* 2911 (1964).
[25] R. C. Cookson, J. J. Frankel, J. Hudec and T. A. Crabb, *Tetrahedron*, Suppl. No. 7, 355 (1966).
[26] E. L. Eliel, N. L. Allinger, S. J. Angyal and G. A. Morrison, *Conformational Analysis* p. 200. Interscience, New York (1966).
[27] C. Ouannes and J. Jacques, *Bull. Soc. Chim.* 3601 (1965).
[28] A. Warshawsky, M.Sc. Thesis, Haifa Israel Institute of Technology, Haifa, (1967).
[29] P. J. Krueger and H. D. Mettee, *Tetrahedron Letters* 1587 (1966).