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CONFORMATIONAL STUDIES ON THE DIASTEREOMERS OF PHENYL-ISOPROPYL PINACOL

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Abstract—The *meso* and DL configurations assigned to the diastereomers of 2,5-dimethyl-3,4-diphenyl-3,4-hexanediol have been based on the IR and PMR spectra. The DL isomer (II) is interpreted as being represented mainly by the conformer with the OH groups *gauche* and the isopropyl groups *anti*, while the *meso* isomer (I) is a mixture of the two possible conformers. For the *gauche* conformer of I an OH...π-electrons H-bond is proposed in addition to the OH O H-bond. The magnetic nonequivalence of the isopropyl methyls is solvent independent for II and proportional to the logarithm of the dielectric constant of the solvent for I. An interpretation of these findings in terms of conformational preferences is proposed. The Δτ value of the isopropyl methyls of the DL isomer II is the largest reported (0·84–0·90 ppm in various solvents).

THE subject of the present investigation is the assignment of the *meso* and DL configuration to the diastereomers of 2,5-dimethyl-3,4-diphenyl-3,4-hexanediol (phenyl-isopropyl pinacol) by IR and PMR spectroscopy and the rationalization of some features of the spectra in terms of conformational preferences. 2,5-Dimethyl-3,4-diphenyl-3,4-hexanediol formerly obtained by reduction of isobutyrophenone with zinc powder and alcoholic potassium hydroxide, was not separated in its diastereomers.[1] We prepared the compound by reducing isobutyrophenone with aluminium amalgam.[2] The PMR spectrum of the crude product showed that it was a mixture of about 60% of the diastereomer assigned structure I and 40% of that assigned structure II. The separation was performed by chromatography on a column of silica gel with benzene as eluent.

The IR and PMR spectral characteristics of I and II (Table 1 and 2) permitted the assignment of the configurations. In fact, the IR spectra in dilute CCl_4 solutions

TABLE 1. FREQUENCY OF THE O—H STRETCHING ABSORPTIONS (νOH) IN CCl_4 SOLUTION

Products	Free OH (cm^{-1})	Bonded OH (cm^{-1})	Δ (cm^{-1})
I *meso*	3610 (s)	3575 (m) 3550 (m)	35 60
II DL	3610 (s)	3565 (s)	45
IV *meso*	3610 (s)	3575 (m) 3535 (m)	35 75
V DL	3610 (s)	3565 (s)	45

m = medium; s = strong.

of the diastereomers of some aryl-alkyl pinacols [HO·CRPh·CRPh·OH with R = Me, Et and n-Pr] were recently studied and "free" and "bonded" νOH absorptions typical of *meso* and DL forms were found.[3] The IR spectrum of I in CCl_4 solution exhibits strong "free" and medium "bonded" νOH absorptions while that of II shows strong "free" and strong "bonded" νOH absorptions (Fig. 1). Frequency and relative intensity of these bands are concentration independent, showing that only intramolecular H-bonds are involved. The comparison of the intensities and frequencies of these bands with those of the previously described aryl-alkyl pinacols[3] indicates that I is the *meso* and II is the DL isomer. Such spectral characteristics were interpreted[3] as due to the fact that the intramolecular H-bond is enhanced in the DL form and not favoured in the *meso* form. Furthermore, the different strength of the intramolecular hydrogen-bonding as derived by the chemical shift of the OH protons in the PMR spectra of I and II in various solvents and concentrations (Table 2) is parallel to that observed for *meso* and DL phenyl-methyl pinacol.[4]

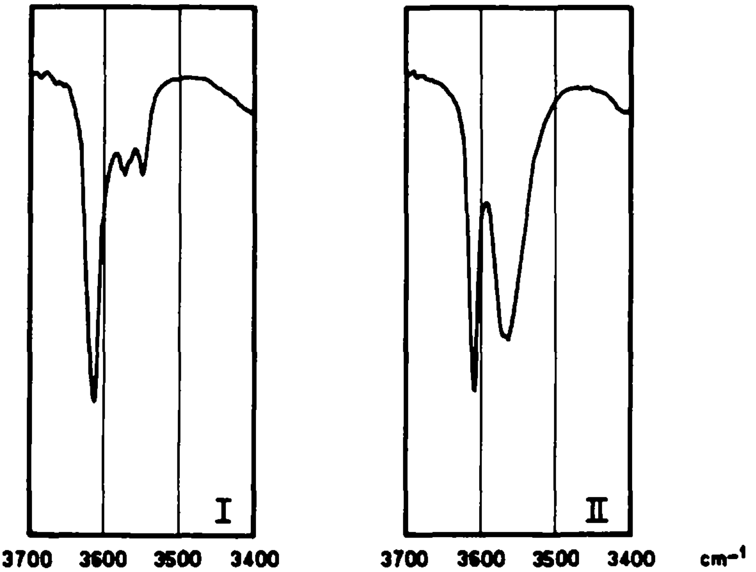


FIG. 1. IR spectra of I and II (2% soln in CCl_4).

Attempts to obtain the acetonides of I and II, in order to check the above assignments by PMR spectra of the derivatives,[5–6] were unsuccessful. This is probably due to the low reactivity of the tertiary hydroxyls and also to the strong non-bonded interactions between the two couples of bulky substituents (phenyls and isopropyls). In fact the acetonides of DL and *meso* hydrobenzoin were easily obtained.[6]

No attempts were made to resolve the DL isomer II, obtained as a racemate.

TABLE 2. CHEMICAL SHIFTS, τ VALUES (ppm) OF THE Me AND OH SIGNALS IN DIFFERENT SOLVENTS

Solvent	ε (Dielectric constant)	Me (doublet)												OH (singlet)			
		I (*meso*)			II (DL)			IV (*meso*)			V (DL)			I (*meso*)	II (DL)	IV (*meso*)	V (DL)
		CH_3	CH'_3	$\Delta\tau$	CH_3	CH'_3	$\Delta\tau$	CH_3	CH'_3	$\Delta\tau$	CH_3	CH'_3	$\Delta\tau$				
(1) Dioxan	2·21[a]	9·52	9·35	0·17	9·68	8·80	0·88	9·53	9·35	0·18	9·69	8·86	0·83	*b*	*b*	*b*	*b*
(2) Carbon tetrachloride	2·24[a]	9·33	9·33	0·00	9·66	8·79	0·87	9·35	9·32	0·03	9·66	8·86	0·80	7·92	7·29	8·08	7·49
(3) Benzene	2·28[a]	9·37	9·27	0·10	9·67	8·77	0·90	9·14	9·07	0·07	9·48	8·63	0·85	8·02	7·39	7·87	7·35
(4) Ethylene glycol dimethyl ether	3·49[c]	—	—	—	—	—	—	9·44	9·32	0·12	9·66	8·82	0·84	—	—	*b*	*b*
(5) Chloroform	5·05[a]	9·33	9·27	0·06	9·63	8·77	0·86	9·32	9·22	0·10	9·62	8·81	0·81	7·73	7·10	7·83	7·24
(6) Tetrahydrofuran	7·39[c]	—	—	—	—	—	—	9·49	9·31	0·18	9·66	8·83	0·83	—	—	*b*	*b*
(7) Pyridine	12·5[a]	—	—	—	—	—	—	9·07	8·90	0·17	9·30	8·41	0·89	—	—	5·04	4·53
(8) Acetone	21·4[a]	9·44	9·29	0·15	9·63	8·78	0·85	9·44	9·28	0·16	9·63	8·82	0·81	6·45	5·91	6·86	6·16
(9) N,N-Dimethylformamide	36·7[a]	9·52	9·30	0·22	9·63	8·79	0·84	9·50	9·27	0·23	9·62	8·82	0·80	*b*	*b*	*b*	*b*
(10) Dimethylsulfoxide	48·9[d]	9·57	9·33	0·24	9·68	8·84	0·84	9·63	9·38	0·25	9·72	8·91	0·81	5·49	5·27	5·98	5·63

[a] Values from *Handbook of Chemistry and Physics* (46th Ed.) Chemical Rubber Publishing Co., Cleveland, Ohio (1965–1966).

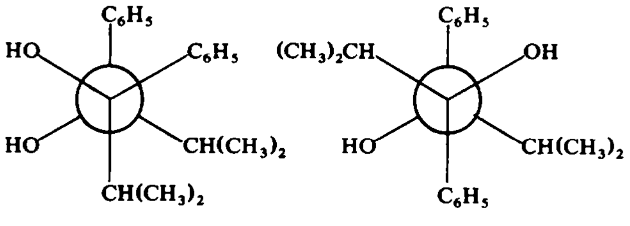
[b] Value not measured.

[c] Values from *Landolt-Börnstein—Zahlenwerte und Funktionen* (6th Ed.) Vol. II, Springer-Verlag, Berlin (1959).

[d] Value from H. L. Schlafer and W. Schaffernicht, *Angew. Chem.* **72**, 618 (1960).

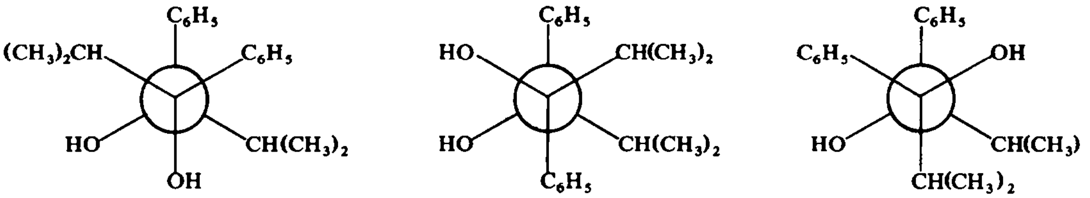
Some features of the IR and PMR spectra of I and II are more extensively discussed in terms of steric effects (Newman projections shown in Chart 1). The IR spectrum of the DL isomer II shows νOH absorptions equal to those of the DL homologs previously described.[3] For this isomer, the E conformer is not present in an appreciable amount as the IR spectrum shows only intramolecular H-bonding. No choice between C and D conformers can be made *a priori*, because the known values of conformational free energy differences[7] for phenyl and isopropyl groups describe the size only in a very qualitative manner due to the difference between the cyclohexane ring and the structure of compound II.[8] However, the independence of IR and PMR characteristics of II from variations of solvent and concentration indicates that only one conformer is present in prevailing amount. On the contrary, the IR spectrum of the *meso* isomer I differs from the described homologs[3] showing two "bonded" νOH absorption of about equal intensity (medium) at 3575 and 3550 cm^{-1}, in addition to the "free" νOH band (strong) at 3610 cm^{-1} (Table 1 and Fig. 1). The assignment of these νOH bands was confirmed by deuteration; in fact the corresponding νOD bands were found at 2670 ("free") and at 2640 and 2623 ("bonded") cm^{-1}, in satisfactory agreement with the calculated values. The "free" νOH band corresponds to the hydroxyl of the *anti* conformer B which is predominant, being favoured by the smaller non-bonded interactions between the bulky substituents. As the frequencies and the intensities of the bands at 3575 and 3550 cm^{-1} do not vary by changing the concentration, they must be due to intramolecular H-bonds. Consequently, it can be assumed that the *gauche* conformer A is present in lower concentration and that one peak is due to one OH which is H-bonded to the O atom of the second OH and that the other peak

Chart 1



A (*Gauche*) B (*Anti*)

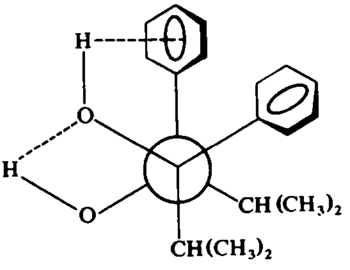
meso series (I)



C D E

DL series (II)

corresponds to the association between the second OH and the Ph ring (see III). A similar intramolecular association has been reported for 1,2-di-α-hydroxyethylferrocene.[9]



III

The hypothesis of an OH...π-electrons H-bonding was further worked out on the basis of the fact that electron releasing substituents (e.g. the dimethylamino group) in the *para* position of the phenyl make the aromatic ring more able to interact with the hydroxyl hydrogen.[10] Accordingly, *meso* IV and DL V 2,5-dimethyl-3,4-di-(*p*-dimethylamino)phenyl-3,4-hexanediol were prepared. The IR absorptions of IV and V in the region 3700–3400 cm^{-1} are reported in Table 1 and Fig. 2. It appears

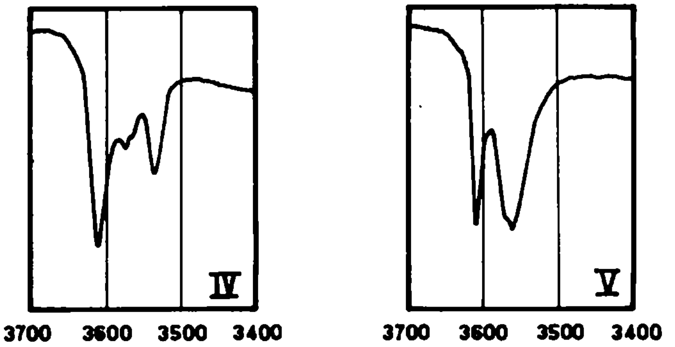


FIG. 2. IR spectra of IV and V (2% soln in CCl$_4$).

that the νOH absorptions of II and V are practically identical and those of I and IV show significant difference. In fact the IR spectrum of IV shows peaks at 3610, 3575 and 3535 cm^{-1}. As the introduction of the *p*-dimethylamino group does not affect the strength of the H-bond OH···O, as shown by the DL series, a similar behaviour is expected for the *meso* series. Consequently, the band at 3575 cm^{-1} in I and IV is attributed to the OH···O association, while the band at 3550 cm^{-1} in I, which shifts to 3535 cm^{-1} in IV indicating that this absorption corresponds to a H-bonding strengthened by the introduction of the *p*-dimethylamino group, is attributed to the association OH···π. Moreover this result indicates that C is the favoured conformer in the DL series; in fact conformer D, if present in appreciable amount would also show (as in the *meso* series) an $OH \cdots \pi$ association beside that $OH \cdots O$. But, this possibility is ruled out by the observation of only one "bonded" νOH absorption in the IR spectra of II and V. Considerations on IR absorption intensities could give further information about conformational populations, but a larger number of derivatives should be studied in order to obtain unequivocal data.

Concerning PMR spectra, the effect of the solvents on the magnetic nonequivalence of the isopropyl groups was studied. The isopropyl groups of the DL isomers II and V give two doublets whose chemical shift difference ($\Delta\tau$) is practically independent of the solvent (Table 2) and, to our knowledge, the largest one reported (0·80–0·90 ppm).[11] On the contrary, the *meso* isomers I and IV show a different behaviour as $\Delta\tau$ was found to be proportional to the logarithm of the dielectric constant (ε) of the solvent (Table 2 and Fig. 3).* The magnetic nonequivalence concerns the two methyls of every isopropyl and not the two isopropyls; this is shown by the fact that only one multiplet is displayed in all solvents by the isopropyl methine protons.† We have tentatively interpreted the above results (Table 2) in terms of the conformational assignments made by the IR studies, although being aware of the oversimplification made by not considering the further conformational possibilities due to the rotation of the isopropyl groups. For the DL isomers the preferred conformation is C. In

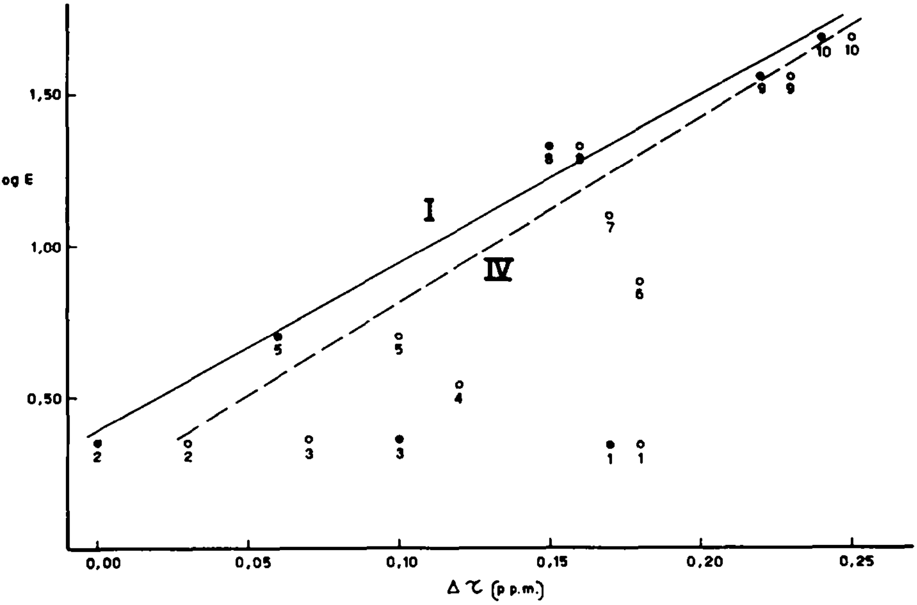


FIG. 3. Plot of log ε (logarithm of the dielectric constant of the solvent) against $\Delta\tau$ (chemical shift difference between the nonequivalent isopropyl methyls) for I (●, full line) and IV (○, dashed line). Numbers refer to the solvents listed in Table 2.

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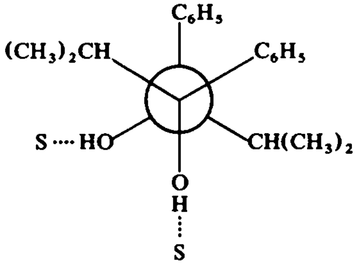
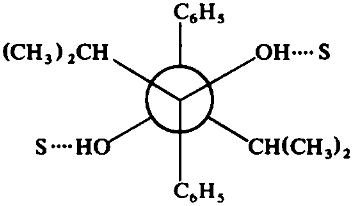
* The relationship is to be considered approximate as ε values are at 20° or 25° while PMR spectra were obtained at 38°.

† The coupling constant values of methyl and methine protons are in the range 6·0–6·8 c/s, as normally found in isopropyl groups.

the case of low ε value solvents, the intramolecular H-bonding is not broken, while in the case of high ε value the solvent (S) associates with the hydroxyls of the pinacol (see VI). But, no variation of the Δτ values can be observed because the conformers D and E are not present. In the case of *meso* isomer the solvents with high ε value break the intramolecular H-bonding, which stabilizes the conformer A, and give intermolecular association with the hydroxyls of the preferred conformer B (see VII), and the amount at the equilibrium is thus enhanced. This happens in a way proportional to the value of ε. Consequently, the isopropyl methyls of the conformer B can be considered more nonequivalent than those of conformer A, if the two nonequivalences have the same sign. The exceptions to the relationship of Fig. 3 are benzene, dioxan, tetrahydrofuran, and ethylene glycol dimethyl ether, which show Δτ values higher than expected. Such effect can be explained for benzene by its high magnetic anisotropy, which, in the collision complex[12] between the pinacol and the benzene molecules, is probably responsible for the larger difference of chemical shift. On the other hand and surprisingly, the Δτ value in pyridine is almost on the straight line. Concerning the anomalous behaviour of the ether solvents no explanation is at present available.



VI



VII

EXPERIMENTAL

IR spectra were run on a Perkin–Elmer mod. 125 grating spectrophotometer, in CCl_4 and $CHCl_3$ solns. OH deuteration was according to a described procedure.[13] PMR spectra were run on a Varian A-60 spectrometer, at 38°, in different solvents (10% w/w), with TMS as internal reference ($\tau = 10{\cdot}00$ ppm). The study of the H-bonding was made examining CCl_4 solns of I, II, IV, and V at different concentrations in the ranges 0·2–5% (IR) and 2–30% (PMR). M.ps are uncorrected.

meso I *and* DL II *2,5-Dimethyl-3,4-diphenyl-3,4-hexanediol*

To 14·5 g of isobutyrophenone in 50 ml anhyd EtOH and 50 ml anhyd benzene, 0·1 g $HgCl_2$ and, under stirring, 1·5 g small pieces of Al foil were added. The mixture was warmed at 50° and an exothermic reaction started, and when complete, the mixture was refluxed until all the Al was completely dissolved. 50 ml benzene and 120 ml 5% HCl aq were added maintaining the temp below 20°. After separation of the organic layer, the aqueous phase was extracted with benzene. The organic layers were combined, washed with 10% HCl aq, then with 10% Na_2CO_3 aq and finally with water to neutrality. The soln, dried over Na_2SO_4, was concentrated *in vacuo* to give 14·95 g of an oil product. Crystallization from hexane gave 6·5 g (44·5% yield) of a product (m.p. 93–94°) whose PMR spectrum was consistent with a mixture of about 60% *meso* I and 40% DL II.

Separation of I *and* II. A soln of 2 g of the mixture in 5 ml benzene was chromatographed with benzene as eluent on a column of silica gel (100 g, 3 cm dia.) collecting fractions of 35 ml. The separation was followed by TLC. Fractions 6–9 were combined, concentrated and crystallized from hexane to give 0·50 g of I, m.p. 107–108°. (Found: C, 80·70; H, 8·53. $C_{20}H_{26}O_2$ requires: C, 80·49; H, 8·78%). Fractions 12–17 similarly treated gave 0·37 g of II, m.p. 124°. (Found: C, 80·79; H, 8·52%).

meso IV *and* DL V *2,5-Dimethyl-3,4-di-(p-dimethylamino)phenyl-3,4-hexanediol*

p-Dimethylamino-isobutyrophenone[14] was obtained as described[15] m.p. 52–53° (hexane). To 25 g *p*-dimethylamino-isobutyrophenone in 250 ml anhyd EtOH and 250 ml anhyd benzene, 21·3 ml 22·6% ethanolic HCl,* 0·15 g $HgCl_2$ and, under stirring, 7·85 g small pieces of Al foil were added. The mixture was warmed at 50° and an exothermic reaction started and when complete, another 7·85 g Al foil were added and the mixture heated under reflux until all the Al was completely dissolved. After cooling, the soln was treated with 500 ml 10% NaOH aq and extracted with benzene. The organic layer was washed with water, dried over Na_2SO_4 and concentrated to give a solid residue. Crystallization from hexane gave 6·85 g (27·4% yield) of a product (m.p. 170–190°) whose PMR spectrum was consistent with a mixture of about 55% *meso* IV and 45% DL V. The mixture was recrystallized from EtOH (m.p. 181–195°).

Separation of IV *and* V. A soln of 2·5 g of the mixture in 50 ml $CHCl_3$ was separated by preparative TLC using 25 plates (20 × 20 cm; 1 mm layer of silica gel HF) twice developed with chloroform–acetone (98:2). The separation was checked examining the plates under UV light. The silica gel of the spots corresponding to IV and V was separately collected from all plates, combined and eluted with $CHCl_3$. After concentration and crystallization from EtOH, 0·55 g of IV, m.p. 206–208° (Found: C, 74·83; H, 9·14; N, 7·27. $C_{24}H_{36}N_2O_2$ requires: C, 74·96; H, 9·44; N, 7·29%), and 0·42 g of V, m.p. 213–215°. (Found: C, 74·64; H, 9·07; N, 7·49%) were obtained.

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[11] See for example: T. S. Sorensen, *Canad. J. Chem.* **45**, 1585 (1967) and M. Kajtár and L. Radics, *Chem. Comm.* 784 (1967).

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* The reduction to pinacol was obtained only in presence of HCl. The lack of reduction in absence of HCl is likely due to the contribution of the quinonoid form, which does not exist in the ammonium salt formed by HCl.

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