An Assignment of *threo–erythro* Configurations Based on a Nuclear Magnetic Resonance Investigation

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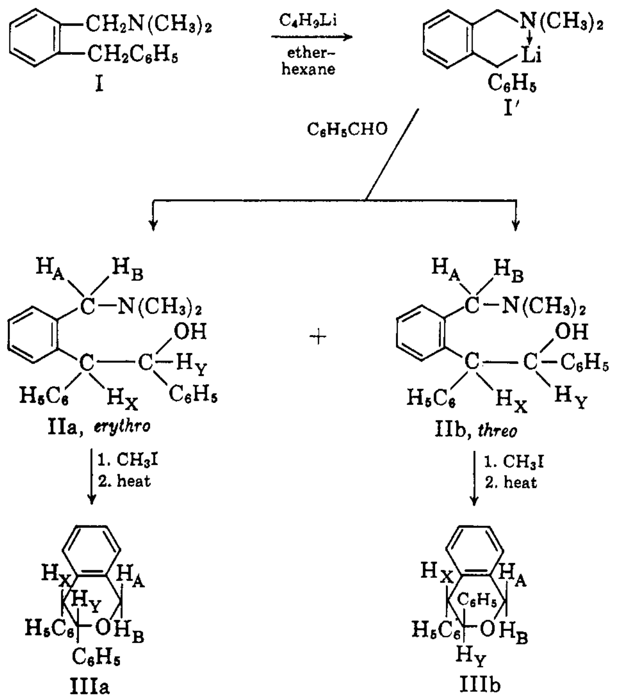
The *threo* and *erythro* isomers of 2-(*o*-dimethylaminomethylphenyl)-1,2-diphenylethanol can be conveniently and separately converted to cyclic isochromans. The relative configurations of the protons on the adjacent asymmetric carbons of the cyclic isochromans can be identified by n.m.r. However, to relate the isochromans to the *threo* and *erythro* configurations requires that no chemical bonds with the asymmetric carbons be involved in the cyclization process. Substantiating evidence for the assignment of *threo* and *erythro* isomers was obtained from the n.m.r. spectra.

N.m.r. has been valuable in the analysis of molecular structure. In the present investigation, n.m.r. was used as substantiating evidence for certain proposed molecular structures and in assignment of configurations for *erythro–threo* isomers.

Scheme I



The isomers investigated were prepared as shown in Scheme I. 2-Benzylbenzyldimethylamine (I) was metalated with *n*-butyllithium to form lithio intermediate I′,[2] which, after condensation with benzaldehyde, yielded a mixture of the *erythro* and *threo* isomers IIa and IIb, respectively. These isomers were separated, and each was converted to its methiodide, which was then cyclized thermally to give the isomeric isochromans IIIa and IIIb.

The structures of the condensation products IIa and IIb were supported by elemental analysis and absorption spectra. A band in the infrared spectra at 840 cm.$^{-1}$ is associated with the dimethylaminomethyl group[3] and bands in the regions 743–746 and 706–697 cm.$^{-1}$ are attributed to out-of-plane deformations of four and five adjacent aromatic hydrogens.[4] The n.m.r. spectra at 32° of IIa and IIb are reproduced in Figure 1. The results of an investigation of the effect of temperature on the spectra of IIa and of IIb in carbon tetrachloride are given in Table I.

Table I

N.m.r. Spectra in Carbon Tetrachloride Solution and AB Analyses of Protons A–B and X–Y of the *threo* (IIb) and *erythro* (IIa) Isomers[a]

Isomer	Temp., °C.	ν_{OH}	δ_{AB}	J_{AB}	$\frac{\nu_A + \nu_B}{2}$	δ_{XY}	J_{XY}	$\frac{\nu_X + \nu_Y}{2}$
threo	105	−255	33.1	13.2	−196.0	19.9	8.5	−298.1
	85	−265	36.4	12.5	−197.2	20.7	8.6	−295.9
	65	−274	39.7	12.5	−197.8	22.0	9.1	−295.9
	45	−296	44.3	12.3	−198.2	23.2	8.9	−292.5
	36	...[b]	46.9	12.0	−197.9	23.3	9.0	−290.0
	34	−316	47.8	12.3	−199.1	23.3	9.1	−291.8
	20	...[b]	51.6	12.3	−199.5	23.9	9.2	−288.3
	0	...[b]	56	12	−200	24.5	9.4	−285.2
	−10	...[b]	58	13	−200	24.9	9.4	−283.3
	−20	...[b]	65	13	−204	25	9.5	−282
	−30	...[b]	67	12	−205	23	9.5	−280
erythro	105	−160	14.3	12.5	−183	14.5	7.0	−308.5
	85	−166	14.3	12.5	−181.2	15.5	7.0	−309.0
	71	−169	15.1	12.8	−181.4	14.8	7.0	−309.7
	61	−176	15.7	12.5	−179.6	14.4	6.8	−308.0
	40	−194	17.9	12.1	−178.4	14.9	6.8	−306.3
	33	−195	18.2	13.0	−178.0	14.4	7.0	−306.5
	20	−212	19.9	12.6	−178.1	15.0	7.1	−306.2
	0	−249	21.7	12.8	−177.5	15.2	7.1	−304.5
	−10	−257	22.2	12.8	−176.2	16.9	6.8	−302.5
	−20	−276	23	13.2	−175	15.9	7.0	−300.2
	−30	−304	24	13.0	−174	...[c]	...[c]	...[c]

[a] All data are in c.p.s. and were obtained on a Varian A-60 spectrometer; δ is the chemical shift difference of the indicated atoms; ν is the chemical shift referred to a TMS internal standard. [b] The -OH peak was obscured due to broadening and spin–spin interaction. [c] The four-peak AB system of protons X and Y was masked almost completely by the broad -OH peak.

The structures of the isochromans IIIa and IIIb were supported by elemental analysis and absorption spectra. Strong bands at 1106 and 1103 cm.$^{-1}$, which are in the spectral region characteristic of six-membered cyclic ethers,[5] and aromatic substitution bands were observed. The n.m.r. spectra of IIIa and IIIb showed an AB quartet for protons H_X and H_Y and a singlet for the methylene protons. The coupling constant J_{XY} for IIIa was found to be 3.0 c.p.s. and for IIIb 9.0 c.p.s.

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[2] R. L. Vaulx, F. N. Jones, and C. R. Hauser, *J. Org. Chem.*, **29**, 1387 (1964).

[3] W. Q. Beard, Jr., and C. R. Hauser, *ibid.*, **25**, 334 (1960).

[4] L. J. Bellamy, "The Infrared Spectra of Complex Molecules," 2nd Ed., John Wiley and Sons, Inc., New York, N. Y., 1958, pp. 76, 78.

[5] See ref. 4, p. 115.

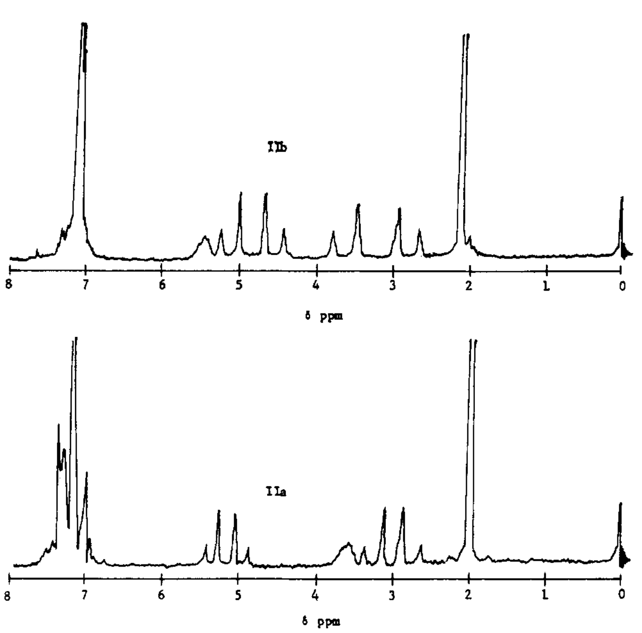
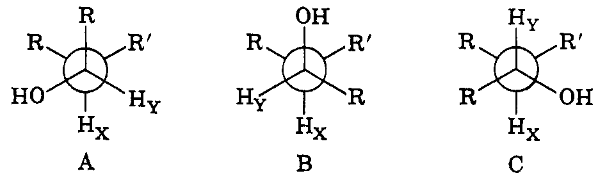


Figure 1.—N.m.r. spectra of compounds IIa and IIb at 32° and 60 Mc.

Discussion

An inspection of possible configurations of isochromans IIIa and IIIb, obtained from IIa and IIb, respectively, is useful in evaluating the significance of the coupling constant differences observed for the isochromans. The cyclic products formed will have the *erythro–threo* type configurations of the amine–alcohols if no bonds of the asymmetric carbons are ruptured in the cyclization process.[6] The *threo* isomer can yield an isochroman that has conformations in which protons H_X and H_Y are approximately *trans*, or approximately *gauche*, whereas the *erythro* isomer can produce cyclic products that have approximately *gauche* orientations for protons H_X and H_Y. In view of this, if J_{XY} for one of the isochromans exceeds that normally expected for *gauche* conformations,[7–9] it would be reasonable to infer that the isochroman resulted from the *threo* isomer.[10] On this basis IIb is assigned the *threo* configuration since J_{XY} for IIIb is 9.0 c.p.s., whereas J_{XY} for IIIa is only 3.0 c.p.s. It may be noted that an approximate *trans* orientation for protons H_X and H_Y in IIIb is sterically favorable since the phenyl groups would likely occupy nearly "equatorial" positions.

Substantiating evidence for the *erythro–threo* assignments was obtained from the n.m.r. spectra of the amine–alcohols IIa and IIb. The observed values for J_{XY} of 9.1 c.p.s. (34°) for IIb and 7.0 c.p.s. (33°) for IIa and the observed effect of temperature changes on their n.m.r. spectra can be used to infer their configurations independently of the assignment based on the cyclic derivatives.



$R = C_6H_5$, $R' = C_6H_4CH_2N(CH_3)_2$

Figure 2.

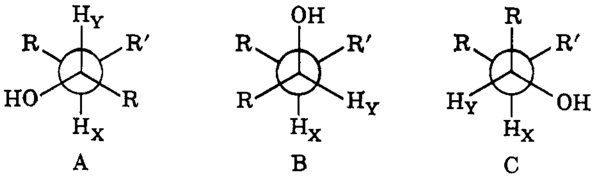


Figure 3.

The observed value of 9.1 c.p.s. for J_{XY} in the amine–alcohol IIb confirms a predominately *trans* orientation of protons H_X and H_Y in this isomer. By inspection of models of conformations of the *threo* isomer a *trans* orientation of protons H_X and H_Y is most favorable for an intramolecular hydrogen bond between the hydroxyl group and the dimethylamine group. The effect of an intramolecular hydrogen bond on the relative orientations of protons H_X and H_Y is illustrated in Figure 2 for the *threo* isomer. By selecting, as preferred intramolecularly hydrogen-bonded forms, those conformers having –OH adjacent to R′ in the staggered conformations conformers B (H_X, H_Y *gauche*) and C (H_X, H_Y *trans*) appear favorable for the *threo* isomer. Conformer C, on the basis of the molecular models, appears less sterically hindered than B. Conformer C, as the preferred conformation, could account for the observed J_{XY} value of 9.1 c.p.s. since protons X and Y are *trans*.

Examination of the staggered conformers for the *erythro* isomer (Figure 3) shows that the *trans* conformation for protons H_X and H_Y is unfavorable for an intramolecular hydrogen bond, yet is probably the most favorable sterically (see conformer A in Figure 3). If the three conformer populations of IIa are approximately the same, one might anticipate the observed 7.0-c.p.s. coupling constant for J_{XY}.[11]

Evidence that isomer IIb is more extensively hydrogen bonded than isomer IIa is supplied by the chemical shift and the temperature effect on the chemical shift[12] of the hydroxyl hydrogens of IIa and IIb at equal concentrations in carbon tetrachloride. At 34° for isomer IIb, the OH chemical shift is −346 c.p.s. with respect to an internal TMS standard, whereas the OH chemical shift at 33° for isomer IIa is −195 c.p.s. The difference between the two isomers is more strongly emphasized by observing that at 105° the chemical shift, ν_{OH}, for IIb is −255 c.p.s. and that a temperature of −10° is required to effect a roughly equal

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[6] It seems reasonable to assume that the configurations of the "X" and "Y" carbons are not affected by the cyclization reaction. If any of the bonds of the asymmetric carbons were ruptured, one would expect to obtain mixtures of the two isomeric isochromans from each of the amine–alcohols. The ease of purification, sharp melting point, and n.m.r. spectrum indicate that only one isomer of the isochromans was obtained in each cyclization.

[7] H. S. Gutowsky, G. E. Belford, and P. E. McMahon, *J. Chem. Phys.*, **36**, 3353 (1962).

[8] A. A. Bothner-By and C. Naar-Colin, *J. Am. Chem. Soc.*, **84**, 743 (1962).

[9] R. V. Lemieux, R. K. Kullmit, H. J. Bernstein, and W. G. Schneider, *ibid.*, **80**, 6098 (1958).

[10] Recently Vickars [*Tetrahedron*, **12**, 2873 (1964)] has reported somewhat similar coupling constants for protons in *cis-trans* systems of some flavan-3,4-diol diacetates. Also H. Finegold [*J. Chem. Phys.*, **41**, 1809 (1964)] has confirmed earlier findings of a coupling constant of about −1.5 c.p.s. for a *gauche* configuration of vicinal protons and +15.5 c.p.s. for *trans* vicinal protons in ethanic systems. Although the signs of the coupling constants were not determined in our investigation, the findings of Vickars and of Finegold support the assignment of the *threo* structure to compounds IIb and IIIb.

[11] R. E. Glick and A. A. Bothner-By, *J. Chem. Phys.*, **25**, 362 (1956).

[12] J. A. Pople, W. G. Schneider, and H. J. Bernstein, "High-Resolution Nuclear Magnetic Resonance," McGraw-Hill Book Co., Inc., New York N. Y., 1959, p. 419 ff.

chemical shift, −257, in isomer IIa. As the temperature increases, the chemical shifts of the hydroxyl hydrogens move to higher field values as expected for hydrogen-bonded systems. It was also observed that J_{XY} and δ_{XY} were somewhat temperature dependent for isomer IIb, whereas for isomer IIa both J_{XY} and δ_{XY} were nearly constant over the temperature interval investigated. The observed chemical shift effects are consistent with intramolecular hydrogen bonding, and the effect of temperature on ν_{OH} seems to indicate a greater degree of hydrogen bonding in IIb, probably intramolecular, than in IIa.

The data presented for the amine–alcohols are consistent with the specific assignments of the *threo* and *erythro* structures of the individual alcohols, but the basis for the assignments is strengthened by the fact that the alcohol data lend support to the much stronger case of assignments made for the individual isochromans; thus the latter mutually support the amine–alcohol structure assignments.

Experimental[13]

Synthesis of *erythro* and *threo* Isomers IIa and b.—To 15.8 g. (0.07 mole) of 2-benzylbenzyldimethylamine (I) was added 55 ml. (0.08 mole) of approximately 1.5 *M* *n*-butyllithium in hexane, followed by ether; the metalation mixture was allowed to stand at room temperature for 6 hr. as described recently.[2] The resulting dark red solution of lithioamine I′ was poured into a boiling ether solution of 9.55 g. (0.09 mole) of benzaldehyde. After standing at room temperature for 6 hr., the reaction mixture was decomposed with 150 ml. of water, and the layers were separated. The ether layer was dried over anhydrous magnesium sulfate, and the solvent was removed. The resulting yellow oil was stirred with pentane to precipitate white crystals, which were collected on a funnel and washed free of the oil with pentane. After drying, 6.4 g. (28%) of *threo*-2-(*o*-dimethylaminomethylphenyl)-1,2-diphenylethanol (IIb), m.p. 131–137°, was obtained. Recrystallization of the product from pentane–absolute ethanol raised the melting point to 139–140°, which was not changed on further recrystallization.

Anal. Calcd. for $C_{23}H_{25}NO$: C, 83.34; H, 7.60; N, 4.23. Found: C, 83.43; H, 7.78; N, 4.23.

The combined pentane filtrate and washings was cooled to precipitate a sticky oil, which failed to crystallize. The mixture was dissolved in 250 ml. of ether and extracted three times with 2 *M* hydrochloric acid. The combined acid extracts were cooled and made basic with 6 *M* sodium hydroxide. The basic mixture was extracted with ether and the combined extracts were dried over anhydrous magnesium sulfate. Removal of the solvent afforded an oil which was crystallized from pentane. The crystals were collected and dried to give 7.0 g. (30%) of *erythro*-2-(*o*-dimethylaminomethylphenyl)-1,2-diphenylethanol (IIa), m.p. 71–78 and 77–79° after recrystallization from pentane containing a few drops of absolute ethanol.

Anal. Calcd. for $C_{23}H_{25}NO$: C, 83.34; H, 7.60; N, 4.23. Found: C, 83.59; H, 7.74; N, 4.41.

Conversion of IIa and b to Isochromans IIIa and b through the Methiodides.—These reactions were effected by adaptations of earlier procedures for related reactions.[2]

erythro isomer IIa (3.3 g., 0.01 mole) was refluxed with excess methyl iodide in 100 ml. of acetonitrile for 1 hr. After cooling, the solution was added dropwise to 500 ml. of ice-cold anhydrous ether to precipitate 4.2 g. (89%) of the corresponding methiodide (slightly hygroscopic). This methiodide (3.95 g., 0.084 mole) was cyclized at 200–210° under nitrogen[2] (30 min.). After cooling, the reaction mixture was boiled with several portions of anhydrous ether to remove the soluble isochroman from the insoluble trimethylammonium iodide. The combined ether extract was dried over anhydrous magnesium sulfate, and the solvent was removed. The residue was recrystallized from absolute ethanol to give 2.4 g. (75%) of *erythro*-3,4-diphenylisochroman (IIIa), m.p. 113–115°.

Anal. Calcd. for $C_{21}H_{18}O$: C, 88.08; H, 6.34. Found: C, 88.30; H, 6.13.

threo isomer IIb (4.4 g., 0.013 mole) was refluxed with excess methyl iodide in 150 ml. of acetonitrile for 1.5 hr. The solution was cooled, and 6.05 g. (99%) of the methiodide was precipitated by dropwise addition of 750 ml. of anhydrous ether. This methiodide (6.00 g., 0.012 mole) was cyclized as described above for the *erythro* isomer to give, after recrystallization from ethanol, 3.0 g. (81%) of *threo*-3,4-diphenylisochroman (IIb), m.p. 118–120°.

Anal. Calcd. for $C_{21}H_{18}O$: C, 88.08; H, 6.34. Found: C, 88.11; H, 6.31.

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[13] Melting points are uncorrected. Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn. Infrared spectra were recorded using a Perkin-Elmer Infracord 137. Nuclear magnetic resonance spectra were obtained on a Varian A-60 n.m.r. spectrometer equipped with a variable-temperature probe. The concentrations of the samples used for n.m.r. studies were 0.4–0.5 *M* in carbon tetrachloride.

Equilibration of *para*-Substituted Styrenes to Produce *p*-Xylylenes

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P.m.r. and infrared data are presented for the formation of α-cyano-α-phenyl-α′-methyl-*p*-xylylene and its subsequent trapping through polymerization upon basic equilibration of *p*-(vinylphenyl)phenylacetonitrile. This reactive intermediate was also produced and isolated as its polymer in the basic 1,6-elimination of hydrogen chloride from α-cyano-α-phenyl-α′-methyl-α′-chloroxylene.

para-Substituted styrenes such as I and corresponding substituted *p*-xylylenes II[1b] are isomeric and in theory can be interconverted by a simple proton shift. Although analogous systems are known in which at equilibrium the quinoid form can be detected,[2] no evidence for conversion of a *para*-substituted styrene to the corresponding xylylene has been reported. A reason for this can be obtained by making a crude estimate of the equilibrium constant in the simplest styrene–xylylene system. Based on the calculated resonance energy differences of styrene (2.43β)[3] and *p*-xylylene (1.93β),[4] an equilibrium constant of 10^6 is obtained. This large equilibrium constant helps to account for the absence of evidence for the formation of α-methyl-*p*-xylylene in studies on the *p*-vinylbenzyl anion, al-

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[1] (a) Correspondence regarding this paper should be sent to the Library, Union Carbide Corp., Plastics Division, Bound Brook, N. J. 08805. (b) Indexed as *p*-quinomethans or substituted 1,4-cyclohexadienes.

[2] J. A. Berson and M. Pomerantz, *J. Am. Chem. Soc.*, **86**, 3896 (1964); W. R. Roth, *Tetrahedron Letters*, **No. 17** 1009 (1964); D. F. Vaber and W. Lwowski, *J. Am. Chem. Soc.*, **85**, 646 (1963); R. B. Davis, L. C. Pizzini, and J. D. Benigni, *ibid.*, **82**, 2913 (1960).

[3] G. Berthier and B. Pullman, *Bull. soc. chim. France*, 554 (1948).

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