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INTRAMOLECULAR HYDROGEN-BONDING AND THE CONFORMATION OF ± *THREO*-1-(2,6-DIMETHOXYPHENYL)-1-HYDROXY-2-NITROPROPANE AND RELATED COMPOUNDS

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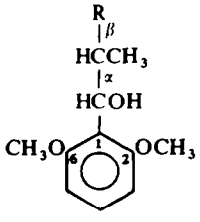
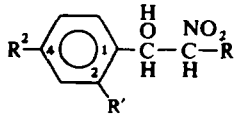
Abstract—IR and NMR studies indicate that a strong intramolecular H-bond in ± *threo*-1-(2,6-dimethoxyphenyl)-1-hydroxy-2-nitropropane, **1**, is maintained in several solvents. The magnitude of *J* HCOH is unusually large. Work on suitable related compounds shows that the bonding is between the OH group and the *ortho* OMe functions and indicates how the nature of the side-chain affects the conformational features of compounds such as **1**.

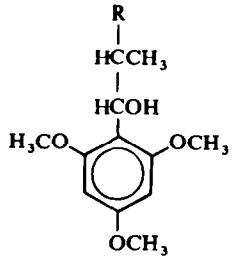
SEVERAL attempts have been made to relate the degree of psychotropic activity of the methoxyamphetamines to physical and chemical features.[1–4] The HMO energy correlates well with hallucinogenic potency[2,3] except that 2,4,6-trimethoxyamphetamine appears to have anomalously high activity.[3,4] Recently, Bryson[5] suggested that the metabolism of amphetamines by β-hydroxylation (at benzylic carbon, furnishing norephedrines) is critical in the study of psychotomimetic effects, and Antun *et al*[4] surmised that 2,6-disubstitution offered protection against metabolic breakdown by amine β oxidase. We have observed that 2,6-dimethoxy- and 2,4,6-trimethoxyamphetamine have NMR spectra differing from their isomers in that the benzylic



1: R = NO_2
2: R = NH_2



3: $R^1 = CH_3O$, $R^2 = R^3 = H$
4: $R^1 = R^3 = H$, $R^2 = CH_3O$
5: $R^1 = CH_3O$, $R^2 = H$, $R^3 = CH_3$
6: $R^1 = R^2 = H$, $R^3 = CH_3$
7: $R^1 = H$, $R^2 = Cl$, $R^3 = CH_3$



8: R = NO_2
9: R = CH_3

protons are more nearly isochronous.[6] This work describes an IR and NMR study of ± *threo* 1-(2,6-dimethoxyphenyl)-1-hydroxy-2-nitropropane (1) and structurally similar compounds in which the OMe and OH groups could adopt similar relative dispositions to those in the 2,6-dimethoxy and 2,4,6-trimethoxynorephedrines, presumed metabolites of the corresponding amphetamines. The results reveal interesting conformational and intramolecular H-bonding effects.

The compound **1** was obtained in 15% yield as a byproduct in the reaction of 2,6-dimethoxypropenylbenzene with tetranitromethane, using the working-up procedure described.[7] The expected 2,6-dimethoxy-β-methyl-β-nitrostyrene (22%) and 2,6-dimethoxybenzaldehyde (14%) were also obtained.

The molecular formula and structure of **1** were indicated by elemental analysis and NMR spectral data (Table 1). The configurational assignment *threo* to the product is made on the basis of the large vicinal Hα–Hβ coupling,[8] the position of the β-CH_3 at δ 1·30 and the observation of a very weak doublet (J = 6 Hz) at δ 1·58 ppm (in $CDCl_3$) which is assigned to the β-CH_3 of a trace of the *erythro* isomer (compare

TABLE 1. DATA[a] FROM THE NMR SPECTRA OF ± THREO-1-(2,6-DIMETHOXYPHENYL)-1-HYDROXY-2-NITROPROPANE **1**.

Solvents	$CDCl_3$	Acetone	DMSO-d_6	Pyridine-d_5
βMe	1·30 d (6·5)	1·20 d (6·5)	1·12 d (6·5)	1·29 d (6·5)
OMe	3·87	3·88	3·81	3·65
β-H	5·07 m	5·18 m	5·30 m	5·75 m
α-H	5·61 dd (9·5, 11·5)	5·58 dd (10·3, 10·3)	5·53 dd (9·2, 6·0)	6·16 d (10·0)
3,5-H	6·61 t	6·71 t	6·70t	6·63 t
4-H	7·30 q	7·30 q	7·30 q	7·29 q
OH	3·91 d (11·5)	4·21d (10·3)	5·22 d (5·5)	7·75–7·30

[a] δ-values in ppm measured with a Varian A-60A spectrometer at 40°C using solutions *ca* 15% in solvents containing TMS as internal standard. Signals were singlets except when d = doublet, t = triplet, q = quartet, and m = multiplet, with first-order coupling constants (Hz) indicated. The OH signal exchanged with D_2O and the α-H signal then became a doublet. The aromatic protons at 3, 4 and 5 gave a typical AB_2 pattern.

Table 2). The β-CH_3 signals correspond well with those for *threo* and *erythro* 1-(4-methoxyphenyl)-1-methoxy-2-nitropropanes.[9] The amount of *erythro* isomer (*ca* 5%) was too small to interfere with the analysis of the NMR spectra.

In samples dissolved in $CDCl_3$ of ordinary spectroscopic grade, there are usually impurities which catalyze OH proton exchange, but this process is slowed by the formation of intramolecular H-bonds, permitting the observation of HCOH coupling in this solvent.[10]* In $CDCl_3$, acetone, and DMSO-d_6 the OH signal of **1** is a doublet. This disappears on adding D_2O and the Hα multiplet collapses to a doublet. The results in DMSO-d_6 are tentative because the chemical shift differences between the coupled α, β, and OH protons are small, and assignments were made by comparison

* We noted that HCOH coupling (5·6 Hz) was observed with samples of 3,5-dimethoxybenzyl alcohol and of piperonyl alcohol although not with samples of 2,6-di- or 2,4,6-trimethoxybenzyl alcohol in the batch of $CDCl_3$ used here. The observation of HCOH coupling without regard to its magnitude is not a sufficient indication of intramolecular H-bonding.

TABLE 2. DATA[a] FROM THE NMR SPECTRA OF ALCOHOLS 3–9

Compound	β-CH_3	OMe	βH	αH	OH
3		3·86	*ca* 4·59 *ca* 4·59[b]	5·62 m[b]	3·37 $w_{\frac{1}{2}}$ 8·0
4		3·79	4·55 dd (−13·0, 9·15) 4·45 dd (−13·0, 3·65)[f]	5·39 dd (9·15, 3·65)[f]	3·20 $w_{\frac{1}{2}}$ 7·5
5 *threo*	1·31 d (6·4)	3·87	*ca* 4·90 m[d]	5·20 d (8·5)	3·36 $w_{\frac{1}{2}}$ 3·5
5 *erythro*	1·45 d (6·8)	3·87	*ca* 4·90 m[d]	5·54 d (4·0)	
6 *threo*	1·25 d (6·5)		*ca* 4·66 m[d]	5·00 d (8·8)	2·88 $w_{\frac{1}{2}}$ 8·0
6 *erythro*	1·45 d (7·0)		*ca* 4·66 m[d]	5·32 d (3·8)	
7 *threo*	1·27 d (6·5)		*ca* 4·65 m[d]	5·00 d (8·8)	2·98 $w_{\frac{1}{2}}$ 3·5
7 *erythro*	1·44 d (7·0)		*ca* 4·65 m[d]	5·33 d (3·8)	
8 *threo*	1·29 d (6·5)	3·86 (×2), 3·82 (×1)	5·04 dq (9·5, 6·5)	5·50 dd (9·5, 11·0)[e]	3·70 d (11·0)
9	0·70 d (6·5), 1·08 d (6·5)	3·79 (×3)	2·08 m	4·65 dd (8·8, 11·5)[e]	3·38 d (11·5)

[a] δ-values measured at 40°C for solutions *ca* 15% in $CDCl_3$ containing TMS. For abbreviations see footnote [a], Table 1; the indicated coupling constants and band-widths at half-heights ($w_{\frac{1}{2}}$) are in Hz.

[b] Degenerate ABX system.

[c] System solved as ABX.

[d] Complex of overlapping multiplets.

[e] Collapses to a doublet on adding D_2O.

with the spectra measured in $CDCl_3$ and acetone. The splitting measured directly from the spectra is equated with the coupling constants *J*.

The magnitude of the HCOH coupling in $CDCl_3$ and acetone (*ca* 11 Hz) shows that an intramolecular H-bond is maintained in these solvents. It is probably broken in DMSO ($J \simeq 6$ Hz) although OH proton exchange is still relatively slow. The presence of a strong intramolecular H-bond in CCl_4 solutions of **1** was shown by an IR dilution study: in the concentration range 4%–0·02% a single sharp peak of invariant extinction coefficient (Experimental) was found at 3570 cm^{-1}, typical for such systems.[11] In pyridine-d_5 the intramolecular H-bond is broken, and the addition of D_2O destroys the broad ill-defined OH signal and sharpens the α-H doublet. Molecular association of pyridine with the solute, suggested by the changed chemical shift of the OMe signals in this solvent, may be responsible for the disruption of the OH bond, and rapid exchange of the OH proton then occurs. In all of the solvents, the α-H—β-H coupling is about 10 Hz, showing that the side chain adopts a conformation with these two protons predominantly *trans*.[12]

The OH-proton could be bonded to an oxygen from the nitro or a OMe group, since both allow a conformationally favourable 6-membered ring. The magnitude of the HCOH coupling and application of the Karplus-type equation determined by Fraser *et al*[13] show that the HCOH dihedral angle is close to 180°.* Models indicate that considerable deviation from the *trans* dihedral angle requirement would be necessary were the OH bonded to the nitro group, but not if it were bonded to the

* For *J* HCOH = 11·5 Hz in $CDCl_3$, the calculated angle is 167°.[13] This may be a low estimate, since *trans*-vicinal couplings of the HCCH type are lowered by electronegative substitution (nitrogen in the present case) and similar effects probably operate here. Fraser *et al*[13] caution against using their equation to a very refined degree.

OMe group. Further, whereas intramolecular H-bonding is maintained in acetone here and in a study by Neville and Awang,[10] intramolecular H-bonding seemed to be absent in acetone solutions of 2-methyl-2-nitropropane-1,3-diol.[14] Experimental work was therefore designed to distinguish between the two possibilities.

For comparison purposes the five similar nitroalcohols **3–8** were prepared; three (**5–7**) are diastereomeric pairs obtained as roughly 1:1 mixtures and whose relative configuration was established as before,[9] but **8** was obtained almost entirely as the *threo* diastereoisomer (β-CH_3 at δ 1·29) containing a trace of the *erythro* form (β-CH_3 at δ 1·58 ppm, about 2%). Data from NMR spectra are recorded in Table 2, and it is evident that the same conformational effects obtain in *threo* **1** and *threo* **8**. The OH signal of **3–7** was a singlet, the α-H a double-doublet for **3** and **4** and a doublet for **5–7** indicating rapid OH proton exchange. The similar broad $w_{\frac{1}{2}}$ (8 Hz) for the OH of **3**, **4**, and the *erythro/threo* mixture **6** might suggest that the *ortho* OMe is not here concerned with the magnitude of the HCOH coupling. However, the changed $w_{\frac{1}{2}}$ (3 Hz) for the *erythro/threo* mixtures **5** and **7** suggested an investigation by IR dilution studies in CCl_4: exchange of the OH proton being slow on the IR time-scale obviates difficulties possibly associated with impurities catalyzing this exchange. As described above, compound **1** shows one sharp absorption band at 3570 cm^{-1} of invariant extinction coefficient, and the same situation was found for **8**. In the same solvent and concentration range, 3,5-dimethoxybenzyl alcohol shows absorption at 3620 cm^{-1} and 3430–3500 cm^{-1} due to free and intermolecularly H-bonded OH groups, the last band disappearing at concentrations less than 0·6% w/w. Both 2,6-di and 2,4,6-trimethoxybenzyl alcohol have very weak bands at 3500 cm^{-1}, even at 4% concentration, and strong absorption at 3610 cm^{-1} but none around 3570 cm^{-1} showing that 2,6-dimethoxy groups effectively protect the OH from intermolecular H-bonding and, surprisingly, apparently do not lead to intramolecular bonding. Compounds **3** and **5** at 4% concentration show a band at 3410 cm^{-1} which disppears on dilution, a band at 3625 cm^{-1} with increasing relative intensity on dilution, and a band at 3570 cm^{-1} of constant extinction coefficient evidently arising from the intramolecularly H-bonded species. Compounds **4** and **6** show bands at 3620 and *ca* 3500 cm^{-1} due to free and intermolecularly H-bonded species.

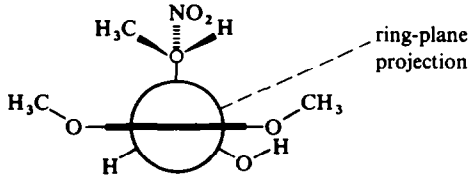


FIG 1. Conformation of **1** viewed along C_4–C_1 axis.

These results indicate that it is the OMe group to which the OH is bonded and since intramolecular H-bonding is complete for **1** and **8**, partial for **3** and **5**, and seemingly non existent for 2,6-di and 2,4,6-trimethoxybenzyl alcohol, suggest that the side chain exerts a rôle in forcing the OH group into proximity with the OMe functions.

Alternatively, it could be that two flanking *ortho* OMe groups force the OH and NO_2 into proximity, and a stabilizing H- bond is formed between them. This possibility seemed unlikely, because the second-order α,β coupling constants of **4** (9·15 and 3·65 Hz) and its methyl ether (8·95 and 3·17 Hz) are nearly the same, revealing a similar population of rotamers about the α–β link.[6] The OH and NO_2 of **4** are therefore not sufficiently H- bonded to affect the side chain conformation significantly. Examination of the alcohol **9**, in which the nitro group of **8** is replaced by Me, demonstrates that it is indeed the OMe to which the OH group H-bonds intramolecularly: an IR dilution study in CCl_4 shows a narrow band at 3570 cm^{-1} of invariant extinction coefficient, and no evidence of intermolecularly H-bonded or of free OH species in the concentration range 4–0·02%; the NMR spectrum (Table 2) is also analogous to **1** and **8**, with HCOH coupling of 11·5 Hz.*

The results define the geometries of **1**, **8**, and **9** in deuterochloroform solution rather strictly: the side-chain has the $HC_\alpha C_\beta H$ and the HCOH dihedral angles about 180°, and the $O\underline{H}\ldots\underline{O}CH_3$ distance is less than 24 nm.[15] The plane of the benzene ring accordingly takes up the position depicted in Fig 1, eclipsed and other steric interactions, with the requirements above, allow only this conformation or slight distortions of it. The low-field β-CH_3 signal of **9** presumably belongs to that group in the position depicted for NO_2 in Fig 1.

The steric requirements of an NO_2 group are less than those of an NH_2 group in $CDCl_3$.[6] Thus, the conformation of 2,6-dimethoxy-nor-ψ-ephedrine, **2**, is probably analogous to that of **1**; the side chain of ephedrines is known to be stabilised in the conformation having the NH_2 and OH groups *gauche*[16] as are the NO_2 and OH here, and the conformation determined experimentally here is in accord with that proposed by Kier[17] for the ephedrines on the basis of HMO theory.

In the case of 2,6-dimethoxybenzyl alcohol, the Me groups may freely rotate about the bond to the benzene ring if the αC-OH bond is perpendicular to the benzene ring-plane, or there could be suitable synchronisation of their rotation with that of the —CH_2OH group. In the case of **1**, **8**, and **9**, rotation of the —OMe link, the benzylic link, and the Cα–Cβ link would have to be suitably synchronized to avoid prohibitive non-bonded interactions.

EXPERIMENTAL

The nitroalcohols **3–8** were obtained by general methods.[18] and **9** by the reaction of 2,4,6-trimethoxybenzaldehyde with i-PrMgBr. The extinction coefficients of the OH stretching frequencies were not measured absolutely, but relative to the C–H stretching band at 2840 cm^{-1} in all of the nitroalcohols.

± threo-1-(2,6-*Dimethoxyphenyl*)-1-*hydroxy*-2-*nitropropane* **1**

The reaction of 2,6-dimethoxypropenylbenzene with tetranitromethane was carried out as described.[7] On working up, the organic product was filtered from a yellow inorganic salt [$KC(NO_2)_3$?] which decomposed spontaneously (and violently) on standing. The organic product was chromatographed on silica-gel, elution with benzene giving 2,6-dimethoxy-β-methyl-β-nitrostyrene (identical with a sample prepared from 2,6-dimethoxy-benzaldehyde by Dr. A. W. By and Mr. K. C. Graham of these laboratories) (22%). Later fractions (2·3 g) were eluted with MeOH and rechromatographed on silica gel using chloroform to give a little of the nitrostyrene followed by **1** m.p. 79–80° (15% yield; Found: C, 54·70; H, 6·33; N, 5·73. Calcd. for $C_{11}H_{15}NO_5$: C, 54·77; H, 6·26; N, 5·81%), and then 2,6-dimethoxybenzaldehyde (14%).

* The OMe signal in the NMR spectra of **1** was sharp and narrow, $w_{\frac{1}{2}}$ 2 Hz, but it is incorrect to infer that the OMe groups are really equivalent; thus in compound **9** all three methoxyls appear at 3·79 ppm, $w_{\frac{1}{2}}$ 0·8 Hz.

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