cis- and *trans*-2-(3,4,5-Trimethoxyphenyl)cyclohexylamines: *N*-Methyl and *N,N*-Dimethyl Derivatives

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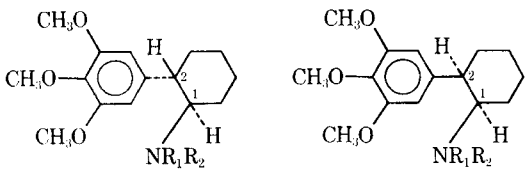
Abstract □ The *N*-methyl and *N,N*-dimethyl derivatives of *cis*- and *trans*-2-(3,4,5-trimethoxyphenyl)cyclohexylamines were prepared for evaluation of psychotropic activity. Synthesis by catalytic reductive methylation and characterization by NMR spectroscopy are reported. Magnetic nonequivalence of the methyl groups was observed in the *trans-N,N*-dimethyl derivative under acidic conditions where inversion of the nitrogen atom is suppressed.

Keyphrases □ 2-(3,4,5-Trimethoxyphenyl)cyclohexylamines, *cis* and *trans*—*N*-methyl and *N,N*-dimethyl derivatives, synthesis as potential psychotropic agents □ TLC—analysis □ NMR—structure

N-Methyl and *N,N*-dimethyl derivatives of *cis*- and *trans*-2-(3,4,5-trimethoxyphenyl)cyclohexylamines were prepared from known (1) *cis*- and *trans*-2-(3,4,5-trimethoxyphenyl)cyclohexylamines (II and I) by catalytic reductive alkylation with formaldehyde (2)[1]. The rate of the reductive alkylation is sufficiently faster on the primary than the secondary amines to afford predominance of the secondary amines III and IV when about 1 equivalent of formaldehyde is used. The use of excess formaldehyde produced the tertiary amines V and VI in good yields. A greater degree of monomethylation selectivity was obtained with the *cis*-amine II than with the *trans*-isomer I. This indicates a greater difference in the energy of activation for the reductive methylation of the primary *versus* secondary amine in the *cis*-isomer than in the *trans*-isomer, presumably because of steric factors.

An alternative two-step synthesis of *trans* secondary amine III by lithium aluminum hydride reduction of the formamide gave a lower overall yield than the reductive alkylation. The tertiary amine VI was also prepared in comparable yields by the less convenient sequence involving preparation of the methiodide from II, followed by dequaternization with sodium thiophenoxide in butanone (3). The Clark–Eschweiler preparation of V and VI utilizing formaldehyde and formic acid was not applicable in this system because of the highly activated aromatic ring which favors Pictet–Spengler cyclization. Cyclic derivatives of I and II will be reported elsewhere. The direct preparation of tertiary amines from 2-(3,4,5-trimethoxyphenyl)nitrocyclohexanes by catalytic reductive alkylation with formaldehyde, as reported for aromatic nitro compounds (2), was unsuccessful with these alicyclic compounds. Only a trace amount of V was obtained from the *trans*-nitro compound by this method.



I: $R_1 = R_2 = H$
III: $R_1 = H$, $R_2 = CH_3$
V: $R_1 = R_2 = CH_3$

II: $R_1 = R_2 = H$
IV: $R_1 = H$, $R_2 = CH_3$
VI: $R_1 = R_2 = CH_3$

Table I—60-MHz. NMR Spectra of 2-(3,4,5-Trimethoxyphenyl)-cyclohexylamine Hydrochlorides in 88% HCOOH [Chemical Shift, τ (p.p.m.)]

Compound	ArH	OCH_3 (3,5)	OCH_3 (4)	H-1	H-2	N-CH_3[a]
I	3.28	6.10	6.16	~6.28	~7.2	–
II	3.30	6.10	6.14	~6.1	~6.8	–
III	3.22	6.06	6.12	~6.45	~7.16	7.19 t
IV	3.25	6.06	6.11	~6.2	~6.7	7.21 t
V	3.23	6.09	6.15	~6.26	~7.15	7.01 d 7.13 d
VI	3.15	6.07	6.12	~6.30	~6.30	7.08 d

[a] t and d stand for triplet and doublet, respectively.

The extent of methylation was readily determined by NMR through integration of the methylamino protons. The multiplicity of the signals of the *N*-methyl protons in highly acidic media provided additional NMR differentiation between monomethylamino and dimethylamino compounds. Under highly acidic conditions, the rate of N—H proton exchange is greatly decreased, and coupling can be seen between the ammonium and *N*-methyl protons, giving distinctive triplets or doublets for the signals of the *N*-methyl groups for the secondary and tertiary amines, respectively. The entire series was, therefore, characterized by NMR as the hydrochloride salts in 88% formic acid.

The spectral data are summarized in Table I, including the data of the nonmethylated precursors I and II for reference. The N—CH_3 signals of the secondary amines III and IV accounted for three protons and occurred as triplets with J = 5.2–5.5 Hz. Products of exhaustive reductive alkylations were characterized as the dimethylamine derivatives by the N—CH_3 signals accounting for six protons and their occurrence as doublets with peak separations of 5.2 Hz. The two methyl groups had identical chemical shifts in the *cis*-isomer VI but were nonequivalent in the *trans*-isomer V, in which two sets of doublets occurred (τ 7.01 and 7.13). The nonequivalence results from a time-average unequal population of rotamers about the C_1—N bond causing the two methyl groups to be affected differently by the long-range shielding effects of the magnetic anisotropy of the aromatic ring. Suppression of the inversion of the nitrogen atom[2]

[1] The compounds were submitted to Eli Lilly and Co. for pharmacological evaluation, January 1969.

[2] This suppression of inversion in the acidic medium is indicated from the observed coupling between the ammonium and N–CH_3 protons which requires a slow N–H proton exchange on the NMR time scale.

(on the NMR time scale) is required for the observed nonequivalence. As expected, the nonequivalence is not seen in the spectra of the free amine in deuteriochloroform or pyridine. The chemical shifts of the two 3,5-methoxy groups were equivalent in all cases but different from the group at position 4. The two aromatic hydrogens were equivalent in all cases. The signals of H-1 were broad unresolved multiplets, sometimes partially overlapped with the signals of the methoxy groups, and their chemical shifts could not always be assigned with certainty. Coupling of H-1 with the N—H protons contributes to the broadening of these signals. Likewise, accurate assignment of chemical shifts to signals of H-2 was not possible in all cases because of partial overlapping by other signals.

The NMR spectra of the tertiary amines V and VI were also examined in deuteriochloroform and pyridine solution. In deuteriochloroform, V gave a singlet at τ 3.56 for two aromatic protons, a singlet at τ 6.15 for all methoxyl protons, a singlet at τ 7.81 for methylamino protons, and a broad signal centered at τ 7.40 representing overlapping H-1 and H-2 signals. Similarly, VI exhibited a singlet at τ 3.28 for the two aromatic protons, a singlet at τ 6.17 for the nine methoxyl protons, and a singlet at τ 7.88 for the six *N*-methyl protons. The signal of H-2 was partially overlapped by signals of cyclohexane protons on unsubstituted positions. The signal of H-1 gave an unresolved multiplet of half-width of about 11 Hz. at τ 6.88. The width of the signal of this equatorial H-1 was slightly wider than for the corresponding *cis* primary amine II measured in tetrachloroethylene (1). This suggests that in deuteriochloroform the *cis*-*N*,*N*-dimethylamino compound, VI, may not be entirely in a single chair conformation. In Compound II, the high predominance of a single chair conformation was verified from the signal of H-2 (1). The same analysis is not possible for VI because of partial overlapping of the signal of H-2. In the *cis*-isomers, deviation from preponderance of a single chair conformation with the aromatic group in an equatorial orientation is not unexpected because the bulkiness of the substituted amino group is increased. This deviation will be greater for the protonated form where inversion of the nitrogen atom is suppressed and where nitrogen has the sp^3 hybridization. In the present series the deviation should be greatest for Compound VI in strongly acidic medium. The broad signal of H-1 for VI in formic acid is consistent with this interpretation. The signal of H-2 is also partially overlapped in formic acid.

EXPERIMENTAL[3]

The NMR spectra were recorded either on a Varian A-60 or Varian T-60 spectrometer at an operating temperature of about 37°. The melting points were determined on a Kofler micro hot stage unless otherwise indicated.

[3] Elemental analyses were done by A. Bernhardt, Mulheim, Germany, or Huffman Laboratories, Wheatridge, Colo.

The *cis*- and *trans*-2-(3,4,5-trimethoxyphenyl)cyclohexylamines, I and II, were prepared by the method reported earlier (1). The free base II, previously described as a liquid, was obtained as a crystalline solid, m.p. 45–47°, upon crystallization from hexane.

General Methylation Procedure—A solution of 1–4 mmoles of primary amine I or II in 50–100 ml. 95% ethanol was treated with aqueous 37% formaldehyde solution and then hydrogenated on a Parr apparatus at an initial pressure of 30 p.s.i. in the presence of 10% palladium on charcoal until hydrogen uptake ceased. For monomethylation, 1.1–1.2 equivalents of formaldehyde was employed, while a large excess (about 60 mmoles) of the aqueous solution was used for dimethylation. About 5–10% of the catalyst was used based on weight of the amine. The catalytic reductive methylation of I was rapid, but was much slower with II, presumably due to slow formation of the imine intermediate. Following removal of catalyst by filtration, the solution was acidified with acetic acid and evaporated. The free base was regenerated with KOH and extracted with benzene, and the resulting solution was dried (anhydrous Na_2SO_4) and evaporated under reduced pressure to give the crude amine.

Hydrochloride salts were prepared by saturation of a benzene–petroleum ether solution of the amine with HCl gas and isolated by evaporation and crystallization of the residue from an appropriate solvent.

***N*-Methyl-*trans*-2-(3,4,5-trimethoxyphenyl)cyclohexylamine (III)**—TLC of crude III indicated contamination with small amount of I and V. Separation was effected by chromatography on silica gel with acetone and acetone–methanol, whereupon III eluted last. A benzene–petroleum ether solution of this amine was filtered and converted to the hydrochloride in the usual manner. Crystallization yielded 52% of III hydrochloride, m.p. 190–192.5° dec., from isopropanol–ethyl acetate, and m.p. 202–202.5° dec. from isopropanol–hexane.

Anal.—Calcd. for $C_{16}H_{26}ClNO_3$: C, 60.84; H, 8.30; N, 4.44. Found: C, 60.76; H, 8.07; N, 4.47.

***N*-Methyl-*cis*-2-(3,4,5-trimethoxyphenyl)cyclohexylamine (IV)**—TLC of crude IV indicated little contamination. The product was readily isolated as the free base in 83.5% yield by crystallization from hexane and had m.p. 65.5–67.5° (Fisher-Johns). IV hydrochloride had m.p. 241–241.5° dec. upon crystallization from ethanol.

Anal.—Calcd. for $C_{16}H_{26}ClNO_3$: C, 60.84; H, 8.30; N, 4.44. Found: C, 60.53; H, 8.05; N, 4.45.

***N*,*N*-Dimethyl-*trans*-2-(3,4,5-trimethoxyphenyl)cyclohexylamine (V)**—Isolation of the product afforded 86.1% as the hydrochloride, m.p. 247–248° dec., upon crystallization from isopropanol.

Anal.—Calcd. for $C_{17}H_{28}ClNO_3$: C, 61.90; H, 8.56; N, 4.25. Found: C, 61.89; H, 8.54; N, 4.27.

The free base V was crystallized from hexane, giving colorless plates, m.p. 75–76.5°.

***N*,*N*-Dimethyl-*cis*-2-(3,4,5-trimethoxyphenyl)cyclohexylamine (VI)**—Isolation afforded 76.7% of VI hydrochloride, m.p. 210–210.5° dec., on crystallization from isopropanol–ethyl acetate.

Anal.—Calcd. for $C_{17}H_{28}ClNO_3$: C, 61.90; H, 8.56; N, 4.25. Found: C, 62.06; H, 8.53; N, 4.29.

Free amine VI crystallized from hexane, m.p. 75.5–77.0°.

REFERENCES

(1) W. F. Trager and A. C. Huitric, *J. Pharm. Sci.*, **54,** 1552 (1965).

(2) R. E. Bowman and H. H. Stroud, *J. Chem. Soc.*, **1950,** 1342.

(3) M. Shamma, N. C. Deno, and J. F. Remar, *Tetrahedron Lett.*, **1966,** 1375.

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