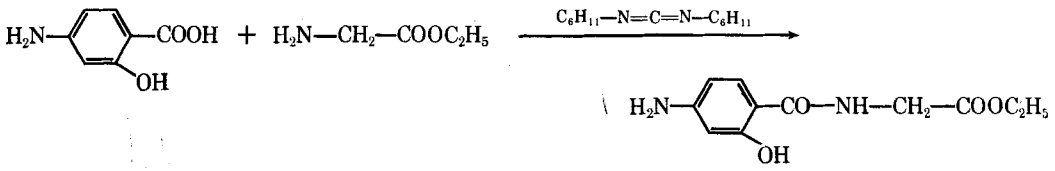

Scheme I

(one of them is the prepared derivative) in blood serum as a consequence of the application of *p*-aminosalicylic acid derivatives to patients, the availability of *p*-aminosalicylglycine ester was necessary.

This compound, which is only described by Foye and Hull (1) as its benzyl ether derivative, can easily be obtained from 4-aminosalicylic acid (PAS) and aminoacetic ethyl ester by using dicyclohexylcarbodiimide as a condensing agent (3). (Scheme I.)

The desired amine, isolated as its hydrochloric acid salt, is a hygroscopic but stable compound. The product gave a correct elemental analysis and showed a positive test for an aromatic amine (coupling of the diazonium salt with β-naphthol).

Chromatography on Whatman No. 4 paper, with butanol–acetic acid–water, showed one spot with $R_f = 0.5$. Some tailing, probably due to hydrolysis of the hydrochloric acid salt, was observed.

It is clear that this method can in principle be extended to the preparation of other amino acid esters.[1]

[1] One of the referees pointed out that the 5-aminosalicylic acid derivatives are rapidly converted to quinonimines and that suitable protection should be taken in this series.

EXPERIMENTAL

To a solution of 7.3 Gm. (0.071 mole) of aminoacetic ester and 10.7 Gm. (0.070 mole) of *p*-aminosalicylic acid in a mixture of 45 ml. of dimethylformamide and 20 ml. of acetonitrile, 18 Gm. (0.085 mole) of dicyclohexylcarbodiimide was added. After 24 hr., the reaction mixture was acidified with 2 ml. of acetic acid and the precipitated dicyclohexylurea filtered off; yield, 11.3 Gm. = 70%.

The filtrate was immediately treated with an excess of absolute ether saturated with gaseous hydrochloric acid. After decanting the supernatant liquid, the residue was dissolved in absolute ethanol and precipitated with absolute ether. After drying in vacuum over potassium hydroxide, 12.0 Gm. (63%) of a slightly colored product was collected which softened at about 90° and decomposed at about 110°.

Anal.—Calcd. for $C_{11}H_{14}N_2O_4$: C, 48.09; H, 5.51; Cl, 12.90. Found: C, 48.1; H, 5.9; Cl, 13.1.

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cis- and *trans*-2-(3,4,5-Trimethoxyphenyl)cyclohexylamine

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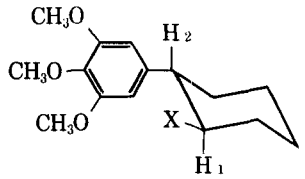
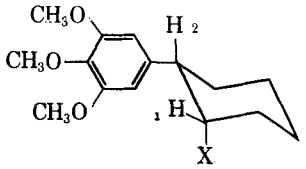
trans- and _cis_-2-(3,4,5-Trimethoxyphenyl)-cyclohexylamine have been prepared for evaluation of psychotropic activity. The synthesis and characterization by NMR spectroscopy are reported.

TRANS- and *cis*-2-(3,4,5-trimethoxyphenyl)cyclohexylamine (III and IV) were obtained by catalytic hydrogenation in acetic acid of *trans*- and *cis*-2-(3,4,5-trimethoxyphenyl)nitrocyclohexane (I and II), respectively, prepared by the general scheme previously reported for the synthesis of *cis*- and *trans*-2-arylnitrocyclohexanes (1).

The NMR spectra were determined with a Varian HR-60 spectrometer at 23° with tetramethylsilane as internal reference. Deuterated chloroform was used as solvent for the nitro compounds, and tetrachloroethylene was used for the amines. The spectra of the four compounds are consistent with structures in which the cyclohexane ring is in a chair conformation with the aromatic group in an equatorial orientation. The NMR signals of H-1 and H-2 in



I, X = NO_2
III, X = NH_2



II, X = NO_2
IV, X = NH_2

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each set of isomers afford easy differentiation between *cis* and *trans* isomers. The interpretation is the same as previously discussed for analogous compounds (1).

The nitro compound I gives a singlet at τ 3.60 for the two aromatic protons; a singlet at τ 6.19 for the six methoxy protons at 3,5-positions and a singlet at τ 6.22 for the 4-methoxy protons; a sextet at τ 5.32 for H-1 with apparent coupling constants of Jaa = 10.9 and Jae = 4.3; and a broad unresolved multiplet at τ 6.93 for H-2. The sextet at τ 5.32 indicates that H-1 has an axial orientation and is adjacent to two axial and one equatorial proton. The lack of resolution of the multiplet of H-2 results from virtual coupling complications. Long-range virtual coupling with the axial proton on C-4 is a probable contributing factor. The nitro compound II, obtained from isomerization of I, gives a singlet at τ 3.56 for the aromatic protons; a singlet at τ 6.20 for the nine methoxy protons; an unresolved signal of half-width of 9 c.p.s. at τ 5.03 for H-1; and a poorly resolved sextet appearing as a main doublet with apparent coupling of Jaa = 11.9 c.p.s., each component of which is split essentially in a triplet at τ 7.02 for H-2. The narrow signal of H-1 indicates that it has the equatorial orientation, and the signal of H-2 indicates that H-2 has an axial orientation and is adjacent to one axial and two equatorial protons. The slight difference in chemical shift of the aromatic protons of I and II afforded a very convenient method of determining the extent of conversion of I to II in the isomerization reaction.

The amine obtained from hydrogenation of I (compound III) gave a singlet at τ 3.62 for the aromatic protons; a singlet at τ 6.22 for the six 3,5-methoxy protons and a singlet at τ 6.26 for the three 4-methoxy protons; and a broad poorly resolved sextet with half-width of about 23 c.p.s. at τ 7.27 for H-1. The signal of H-2 is partially overlapped with signals of other ring hydrogens. The width of the signal of H-1 indicates that H-1 has an axial orientation. The amine IV, obtained from hydrogenation of II, gave a singlet at τ 3.63 for the aromatic protons; a singlet at τ 6.23 for the 3,5-methoxy protons and a singlet at τ 6.28 for the 4-methoxy protons; an unresolved signal of half-width of 9 c.p.s. at τ 6.78 for H-1; and a signal which appears as a main doublet with separation of 12.2 c.p.s. with each component of the doublet poorly resolved in a triplet, at τ 7.38 for H-2. The narrow signal of H-1 indicates that H-1 has an axial orientation and the signal of H-2 indicates that H-2 is axial and adjacent to one axial and two equatorial protons.

EXPERIMENTAL

trans - 3,4,5 - Trimethoxy - β - nitrostyrene.—This compound was obtained in 65% yield by the method of Worral (2), m.p. 122–123°, after crystallization from ethanol. [Reported m.p. 120–121 (3).]

trans - 4 - Nitro - 5-(3,4,5-trimethoxyphenyl)cyclohexene.—This compound was obtained in 87% yield by the condensation of *trans*-3,4,5-trimethoxy-β-nitrostyrene with butadiene as previously described for analogous compounds (1), m.p. 143–144°, after crystallization from isopropyl alcohol.

Anal.—Calcd. for $C_{15}H_{19}NO_5$: C, 61.42; H, 6.53; N, 4.74. Found: C, 61.09; H, 6.13; N, 4.93.

trans - 2 - (3,4,5 - Trimethoxyphenyl)nitrocyclohexane (I).—This compound was obtained quantitatively by low pressure hydrogenation of *trans*-4-nitro-5-(3,4,5-trimethoxyphenyl)cyclohexene in ethyl acetate using 10% palladium-on-carbon as catalyst. Hydrogen uptake stopped after rapid uptake of 1 mole equivalent, m.p. 142–144°, crystallized from methanol.

Anal.—Calcd. for $C_{15}H_{21}NO_5$: C, 61.00; H, 7.17; N, 4.74. Found: C, 60.78; H, 7.34; N, 4.83.

cis - 2 - (3,4,5 - Trimethoxyphenyl)nitrocyclohexane (II).—This compound was obtained by isomerization of the *trans* isomer (I) by the method of Zimmerman and Nevins (4) using a modification of the procedure described in *Reference 1*. The *aci* form of I did not precipitate out under conditions described (1), so the salt of the nitro compound, instead of the aci-nitro compound was added to the buffered solution.

A sodium methoxide solution prepared from 0.357 Gm. (0.0155 mole) of sodium and 25 ml. of methanol was heated with 2.23 Gm. (0.0075 mole) of *trans*-2-(3,4,5-trimethoxyphenyl)nitrocyclohexane until solution was complete. The resulting solution was cooled in a refrigerator for 30 min., then added all at once to a buffer solution prepared from 220 ml. of 95% ethanol 18.7 Gm. (0.137 mole) of sodium acetate trihydrate, and 2.2 ml. of glacial acetic acid (about 0.038 mole). After 10 min. at room temperature the mixture was diluted with 1 L. of water and extracted with three portions of ether and benzene. The combined organic extracts were washed to neutrality with water and dried by filtering through anhydrous sodium sulfate followed by Drierite treatment. Solvent removal yielded 2.22 Gm. of crude product, m.p. 121.5–125°, the composition of which was 84% *cis* and 16% *trans*, as estimated by integration of NMR signals of the respective aromatic protons.

The product was crystallized from ethanol and isopropyl alcohol, m.p. 128–128.5°.

Anal.—Calcd. for $C_{15}H_{21}NO_5$: C, 61.00; H, 7.17; N, 4.74. Found: C, 61.13; H, 7.21; N, 4.56.

trans - 2 - (3,4,5 - Trimethoxyphenyl)cyclohexylamine (III).—This compound was obtained in 90% yield by low-pressure hydrogenation of I in acetic acid for 66 hr. with 10% palladium-on-carbon as catalyst, m.p. 78–79°, after crystallization from benzene. The hydrochloride salt was prepared by bubbling HCl gas in a solution of the amine in a mixture of benzene and hexane, m.p. 246–250°, after crystallization from a mixture of isopropyl alcohol and hexane.

Anal.—Calcd. for $C_{15}H_{24}ClNO_5$: C, 59.69; H, 8.02; N, 4.64. Found: C, 59.60; H, 7.90; N, 4.50.

cis - 2 - (3,4,5 - Trimethoxyphenyl)cyclohexylamine (IV).—This compound was obtained by hydrogenation of II in acetic acid as described for III. The free base was distilled under reduced pressure, b.p. 142° at 0.4 mm. The hydrochloride salt was prepared and crystallized from isopropyl alcohol, m.p. 270–275° dec.

Anal.—Calcd. for $C_{15}H_{24}ClNO_5$: C, 59.69; H, 8.02; N, 4.64. Found: C, 59.72; H, 8.01; N, 4.45.

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