n_D^{25} 1.479, equivalent to an 81% yield of benzyl chloride and ethyl dimethylcarbamate. This crude mixture was very similar to an equimolar mixture, n_D^{25} 1.475, of known ethyl dimethylcarbamate and benzyl chloride, when examined in the vaporfractometer and by comparison of infrared absorption curves. These compounds were further identified by comparing the infrared absportion curves of the products of fractional distillation with known standards.

Acknowledgment. We are indebted to Mr. L. Brancone and associates for the microanalyses, to Mr. W. Fulmor and coworkers for the infrared absorption data, and to Mr. A. Mistretta for the chromatography.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF ILLINOIS COLLEGE OF PHARMACY]

Stereospecific Synthesis of A Reserpine Analog[1a,b]

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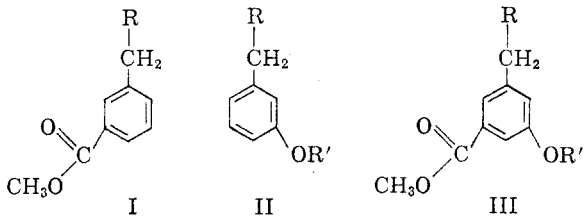
Received January 6, 1961

The stereospecific synthesis of *cis*-*N*-(3-hydroxycyclohexylmethyl)-β-phenylethylamine hydrochloride is described. This compound may be considered to be an analog of reserpine which contains ring E and a part of rings C and D of the naturally occurring alkaloid. The substituents on the cyclohexyl ring have similar configuration to those found in the reserpine molecule.

The discovery by Miller and Weinberg[2] that the γ-diethylaminopropyl ester of 3,4,5-trimethoxybenzoic acid possesses tranquillizing properties may indicate that the indole ring system of the reserpine molecule is not necessary for its pharmacological activity. Earlier attempts in this laboratory to prepare reserpine analogs[3] without the indole ring system resulted in three series of compounds that were devoid of biological activity. These compounds, which may be considered to contain the E ring and a portion of the D and C rings of the reserpine molecule were methyl 3-(*N*-substituted aminomethyl)benzoates (I), 3-(*N*-substituted aminomethyl)phenylacetates (*II*), and methyl 3-acetoxy-5-(*N*-substituted aminomethyl)benzoates (III).



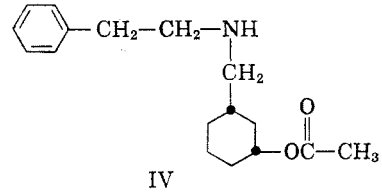
I II III

R = Piperidino or diethylamino
R′ = Acetyl, benzoyl or 3,4,5-trimethoxybenzoyl

While these compounds resemble a portion of the reserpine molecule, the ring is aromatic, while the E ring of reserpine is not. Furthermore, the substituents on the ring of the synthetic compounds are planar with the ring while the substituents on the E ring of reserpine have been shown to be present in the *cis* configuration. Since the carbon to carbon bonds of the aliphatic chain of β-diethylaminopropyl-3,4,5-trimethoxybenzoate possess free rotation, the compound could assume any spacial arrangement necessary for tranquillizing activity.

In order to evaluate the importance of stereochemical configuration upon the pharmacological activity of reserpine analogs of this type, it appeared desirable to investigate possible synthetic approaches to reserpine analogs similar to compound II in which the ring is cyclohexyl and whose substituents are in the *cis* configuration.

This report describes the stereospecific synthesis of *cis*-*N*-(3-acetoxycyclohexylmethyl)-β-phenylethylamine hydrochloride (IV).



IV

For this synthesis it appeared logical to utilize as the starting compound the lactone of 3-hydroxycyclohexanecarboxylic acid. This compound not only possessed the proper configuration but had functional groups capable of undergoing the necessary chemical reactions without inversion or epimerization. The desired lactone was prepared by heating *cis* 3-hydroxycyclohexanecarboxylic acid. 3-Hydroxycyclohexanecarboxylic acid was conveniently synthesized from 3-hydroxybenzoic acid which was prepared by the fusion of 3-sulfobenzoic acid with sodium hydroxide.[4] The catalytic hydrogenation of this compound to 3-hydroxycyclohexanecarboxylic acid with Raney Nickel at high temperatures and pressures has been reported to yield

(1)(a) Presented at the Frederick F. Blicke Symposium of the Division of Medicinal Chemistry at the 138th National Meeting of the American Chemical Society, New York, N. Y., September, 1960. (b) This paper comprises a portion of a thesis presented by Paul B. LeVine in partial fulfillment of the requirements for the M.S. degree at the University of Illinois.

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both the *cis* and *trans* stereoisomers.[5,6] Similar results have been reported from the reduction with sodium and alcohol.[5] While the hydrogenation has been carried out using platinum oxide as the catalyst, the presence or absence of the *trans* compound was not reported.[7]

In the hope that hydrogenation with platinum oxide catalyst would yield only the thermodynamically more stable *cis* isomer, 3-hydroxybenzoic acid was reduced with platinum oxide at room temperature under two atmospheres of hydrogen pressure. Slightly less than the theoretical quantity of hydrogen was consumed. After removal of the alcohol employed as a solvent and conversion of the resulting acid to the lactone, a yield of 56% of the lactone of 3-hydroxycyclohexane carboxylic acid was obtained. In an attempt to determine if only the *cis* isomer was produced, the residue after distillation of the lactone was fractionated. Only unreacted 3-hydroxybenzoic acid was obtained. Fractionation of the solvent, which had been removed on a flash evaporator revealed the presence of ethyl cyclohexanecarboxylate. The hydrogenation, therefore, produced only the *cis* isomer, and the low yield appears to be due to hydrogenolysis and incomplete hydrogenation.

The lactone of 3-hydroxycyclohexane carboxylic acid was treated with a number of amines. It failed to react with such secondary amines as diethylamine, pyrrolidine, piperidine and tetrahydroisoquinoline. However, aniline reacted to give the expected amide. The yield of the anilide, however, was not high. While the reaction should proceed through the attack of the amine on the carbon atom of the carbonyl group and therefore not cause inversion, there did remain the possibility that the amine might have abstracted a proton from the carbon *alpha* to the carbonyl group. This would permit epimerization. The low yield might therefore be the result of the isolation of a single stereoisomer. Since this created some doubt concerning the stereochemistry of the isolated amide, it seemed desirable to use a more reactive amine in the hope that a single product of high yield could be obtained. β-Phenylethylamine was employed since it not only provided a more nucleophilic amino group but also placed an aromatic ring in a position analogous to the indole ring system of reserpine. When treated with the lactone, β-phenylethylamine gave a 92% yield of the expected amide. No other isomer could be isolated. Since the accepted mechanism for amide formation does not involve attack at the *alpha* carbon atom, inversion could not have taken place. The presence of a single amide rules out the possibility of epimerization, and the isolated amide must have the *cis* configuration.

Reduction of this amide with lithium aluminum hydride in tetrahydrofuran gave a single amine in 70% yield. Previous syntheses with this reagent in the reduction of compounds possessing known configuration has shown that the reaction proceeds without epimerization or inversion.[8,9]

The reaction of *cis*-*N*-(3-hydroxycyclohexylmethyl)-β-phenylethylamine with acid chlorides to form either the desired esters or the amides was not successful and led to a mixture of compounds. Even with an excess of acetylchloride a single compound could not be obtained. *cis*-*N*-(3-Hydroxycyclohexylmethyl)-β-phenethylamine was, therefore, esterified with glacial acetic acid in the presence of a small quantity of sulfuric acid. A high yield of *cis*-*N*-(3-acetoxycyclohexanemethyl)-β-phenylethylamine was isolated as the hydrochloride salt. No other ester could be isolated.

cis-*N*-(3-Acetoxycyclohexanemethyl)-β-phenylethylamine hydrochloride, while showing some sedative action, possessed a poor therapeutic index and showed side reaction incompatible with its sedative action. The pharmacological activity, however, appears to indicate the importance of the stereochemistry of the cyclohexyl ring to its therapeutic activity.

EXPERIMENTAL[10]

Lactone of cis-3-hydroxycyclohexanecarboxylic acid. A solution of 69.0 g. (0.5 mole) of *m*-hydroxybenzoic acid in 200 ml. of 95% ethanol was hydrogenated at 3 atm. using 2.0 g. platinum oxide catalyst. The hydrogenation required about 30 hr. The solution was filtered and the ethanol removed by distillation *in vacuo*. The residue remaining after removal of the alcohol weighed 44.5 g. (61%). Fractionation of the solvent employed in the hydrogenation yielded ethyl cyclohexanecarboxylate.

The crude hydrogenation product was heated at 180° in an oil bath for 45 min. and then subjected to distillation under reduced pressure. A small amount of ethyl cyclohexanecarboxylate was collected at 85–90°/15 mm. (lit.[6] b.p. 84–90°/16 mm.). The major fraction distilling from 126 to 140°/15 mm. afforded 36.8 g. (56%) of crude lactone. Redistillation of this higher boiling fraction yielded 27.2 g. (43%) of pure lactone with b.p. 122–123°/15 mm. (lit.,[5] b.p. 120–123°/19 mm.).

The residues from several lactone distillations were combined and the temperature of the pot slowly raised while under reduced pressure until it reached 250°. A small amount of lactone b.p. 120–122°/10 mm., and a sublimate which proved to be *m*-hydroxybenzoic acid, m.p. 198–200° (lit.[4], m.p. 200–201°) were the only products obtained.

cis-N-Phenyl-3-hydroxycyclohexylcarboxamide. A mixture of 6.0 g. (0.048 mole) of the lactone of *cis*-3-hydroxycyclohexanecarboxylic acid and 22.8 g. (0.25 mole) of freshly distilled aniline was heated to 180° under reflux in an oil bath

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(10) All melting and boiling points are uncorrected. Microanalyses were performed by Micro-Tech Laboratories, Skokie, Ill., and Weiler and Strauss Analytical Laboratory Oxford, England.

for 24 hr. The excess aniline was removed by distillation at reduced pressure and the residue allowed to cool to room temperature. This residue was transferred to a Buchner funnel with the aid of ether, filtered and washed with the same solvent. The washed reaction product weighed 3.7 g. (35%) and melted at 157–160°. After recrystallization from water the compound melted at 159.5–160.5°.

Anal. Calcd. for $C_{13}H_{17}NO_2$: C, 71.20%; H, 7.82%; N, 6.39%. Found: C, 71.37%; H, 7.58%; N, 6.58%.

cis-N-(β-Phenylethyl)-3-hydroxycyclohexanecarboxamide. A mixture of 6.0 g. (0.048 mole) of the lactone of 3-hydroxycyclohexanecarboxylic acid and 13.0 g. (0.107 mole) of freshly distilled β-phenylethylamine was heated at 180° in an oil bath under reflux for 24 hr. The excess amine was removed by distillation at reduced pressure and the residue cooled to room temperature. The resulting product was washed with a small amount of ether, transferred to a Buchner funnel and filtered. The solid weighed 10.8 g. (92.5%) and melted at 113–116°. A sample after recrystallization from ether melted 119–120°.

Anal. Calcd. for $C_{15}H_{21}NO_2$: C, 72.84%; H, 8.56%; N, 5.66%. Found: C, 72.84%; H, 8.41%; N, 5.61%.

cis-N-(3-Hydroxycyclohexylmethyl)-β-phenylethylamine hydrochloride. A slurry, prepared by adding 75 ml. of dried tetrahydrofuran to 2.0 g. of lithium aluminum hydride, was contained in a 500 ml. round bottom flask equipped with a reflux condenser, dropping funnel and calcium chloride tube. To this slurry was added dropwise a solution of 2.5 g. (0.01 mole) of *cis-N-(β*-phenylethyl)-3-hydroxycyclohexanecarboxamide (XXII) in 150 ml. of dried tetrahydrofuran. The addition required approximately 20 min. After the solution was added, the reaction mixture was heated under reflux for 12 hr., and then 150 ml. of tetrahydrofuran was removed by distillation. The remaining mixture was cooled in an ice bath and 5 g. of chipped ice added in small pieces. When the reaction subsided, 100 ml. of 95% ethanol was cautiously added in small portions. The resulting mixture was removed from the ice-bath, heated to the boiling point on a steam bath and then allowed to cool to room temperature. The alcohol-tetrahydrofuran solution was decanted and the residue washed twice with 75-ml. portions of alcohol and the alcohol added to the supernatent liquid previously decanted. The alcohol and tetrahydrofuran were then evaporated on a steam bath, the residue cooled and extracted with 100 ml. portions of ether, which were combined and treated with dry hydrogen chloride. The hydrochloride precipitated and was removed by filtration. It weighed 1.6 g. (70%). After recrystallization from isopropyl alcohol it melted at 250–252° dec. after careful drying.

Anal. Calcd. for $C_{15}H_{24}ClNO \cdot \frac{1}{2}H_2O$: C, 64.61%; N, 9.04%; N, 5.02%. Found: C, 64.60%; H, 8.94%; N, 5.55%.

cis-N-(3-Acetoxycyclohexanemethyl)-β-phenylethylamine hydrochloride (IV). A solution of 1.5 g. of crude *cis-N-*(3-hydroxycyclohexylmethyl)-β-phenylethylamine in 9 ml. of glacial acetic acid was treated with 6 drops of concd. sulfuric acid and heated to reflux for 15 hr. The reaction mixture was cooled to 0° and an excess of 10% sodium hydroxide solution added with constant stirring. The alkaline mixture was extracted two times with 100-ml. portions of ether and the ethereal solutions were combined. After drying over sodium sulfate, the ethereal solution was filtered, cooled in an ice-bath and saturated with dry hydrogen chloride. The resulting precipitate (IV), 1.3 g. (75%), was filtered and after several recrystallizations from isopropyl alcohol melted at 201–202° dec.

Anal. Calcd. for $C_{17}H_{26}Cl\,NO_2$: C, 65.48%; H, 8.41%; N, 4.4%. Found: C, 65.65%; H, 8.17%; N, 4.48%.

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[CONTRIBUTION FROM THE DEPARTMENT OF MEDICINAL CHEMISTRY, GEIGY RESEARCH LABORATORIES AND THE DEPARTMENT OF PHARMACOLOGY, UNIVERSITY OF ILLINOIS COLLEGE OF MEDICINE]

Centrally Active 2-(Substituted phenyl)-β-alanines[1]

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Received January 6, 1961

Carbethoxylation of substituted phenylacetonitriles gave ethyl substituted phenylcyanoacetates which were reduced to the correspondingly substituted β-alanine esters. A number of the latter were reductively methylated. Hydrolysis of the esters proceeded easily to yield β-alanines. The pharmacological properties of these substances are briefly discussed.

γ-Aminobutyric acid (GABA), one of most abundant amino acids in the brain,[3] has been identified[4] as one of the active agents in the extracts (Factor I) of mammalian brain and spinal cord which inhibit impulse transmission in stretch receptor neurons of the crayfish, and block synaptic transmission in autonomic ganglia and monosynaptic spinal reflexes of mammals. These observations led to the suggestion that γ-aminobutyric acid may have an important function in the control of neurophysiological activity.[4] One other natural amino acid, β-alanine, possesses Factor I activity; it is however, only one-twentieth as active as γ-aminobutyric acid.[4] Purpura, Girado, and Gundfest studied the central inhibitory and excitatory actions of the homologous series of ω-amino acids from C_2 to C_8 by topical application of these substances to the cerebral cortex of cats.[5] β-Alanine was found to be slightly more potent that γ-aminobutyric acid as a cortical synaptic inhibitor in this test system.

None of the simple substitution products of γ-aminobutyric acid or of β-alanine have been studied

(1) Presented at the Frederick F. Blicke Symposium of the Division of Medicinal Chemistry at the 138th National Meeting of the American Chemical Society, New York, N. Y. September, 1960.

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