[CONTRIBUTION FROM THE AYERST RESEARCH LABORATORIES]

Central Stimulants. Cyclized Diphenylisopropylamines

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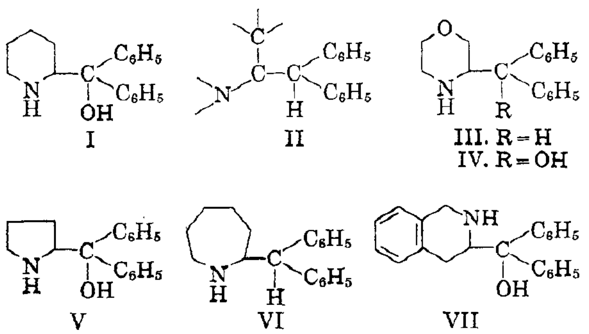
A series of cyclized diphenylisopropylamines (III–VII) have been synthesized for evaluation as central nervous system stimulants.

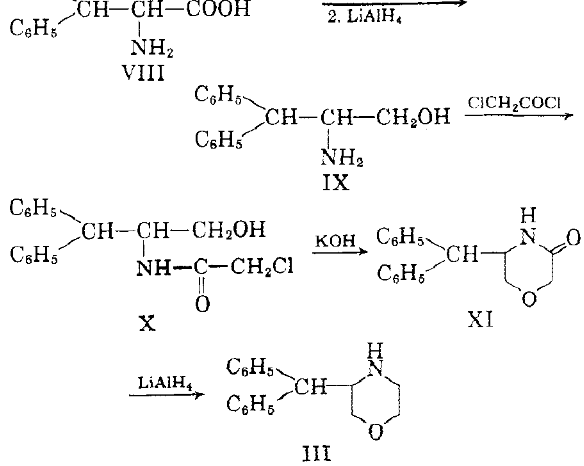
Several reports have appeared recently describing the central stimulant activity of various diarylmethylpiperidines, diarylpiperidinemethanols, and diarylthiamorpholinemethanols.[1] One of these compounds, α,α-diphenyl-2-piperidinemethanol[1a](I) has found clinical application as a central stimulant.



I, II, III. R = H, IV. R = OH, V, VI, VII

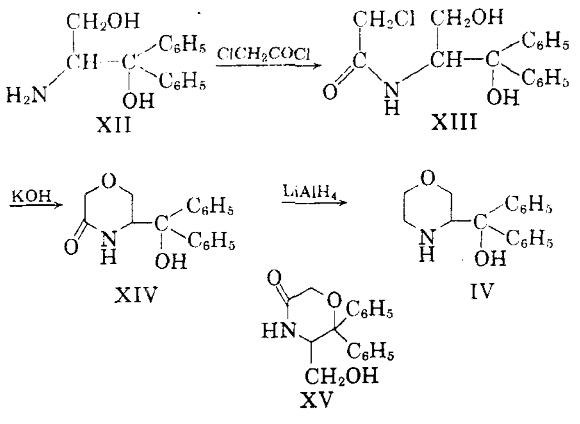
A common feature of all these compounds is the presence of a diphenylisopropylamine moiety (II). In our investigation, a series of related compounds were prepared containing the diphenylisopropylamine moiety incorporated into various heterocyclic nuclei. They have structures III–VII.

3-Benzhydrylmorpholine (III) was prepared in a five-step synthesis from β,β-diphenylalanine. Initially the amino acid was obtained by alkylation of ethylacetamidocyanoacetate with benzhydryl chloride followed by hydrolysis of the *N*-acetyl group.[2] This procedure was found to give low yields and for preparative purposes the method of Anatol[3] was used. This method involves the hydrolysis of the hydantoin prepared from diphenylacetaldehyde and, although longer, it gave better yields and required less expensive starting materials. The required aldehyde was prepared from benzophenone by the Darzens glycidic ester synthesis.[4] The amino acid VIII was esterified, reduced with lithium aluminum hydride to the alcohol IX and condensed with chloracetylchloride to yield the 2-chloracetamido-2-benzhydrylethanol (X) which on treatment with alkali readily formed the keto-1,4-oxazine XI. The desired morpholine was then obtained by a lithium aluminium hydride reduction.



VIII, IX, X, XI, III

α-(3-Morpholyl)benzhydrol[5] (IV) was prepared in three steps from the known 1,1-diphenyl-2-amino-1,3-propanediol.[6] Condensation of the pro-



XII, XIII, XIV, XV, IV

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panediol XII with chloracetylchloride yielded 1,1-diphenyl - 2 - (α - chloroacetamido) - 1,3 - propanediol (XIII). Cyclization to the keto-1,4-oxazine XIV takes place with alkali and the desired amine was readily obtained by reduction. The possibility of the cyclization occurring with the tertiary hydroxyl group to yield the oxazine XV is remote. Steric hindrance and the lowered acidity of the tertiary hydroxyl group would tend to prohibit this type of cyclization. It was further ruled out by the observation that the hydroxyl group of the final product was not acetylated with acetic anhydride and pyridine.

α-(2-Pyrrolidyl)benzhydrol (V) was prepared from *dl*-proline ethyl ester and phenylmagnesium bromide according to the method of Kapfhammer.[7]

α-[3-(1,2,3,4-Tetrahydroisoquinolyl)]benzhydrol (VII) was prepared in a one-step synthesis with phenylmagnesium bromide from the known 3-carbethoxy-1,2,3,4-tetrahydroisoquinoline.[8]

3-Benzhydrylhexamethyleneimine (VI) was obtained in three steps from the known 2-benzylidenecyclohexanone[9] (XVI). The benzylidenecyclohexanone (XVI) on treatment with phenyl Grignard in the presence of a cuprous chloride[10] yielded the 1,4-addition product, 2-benzhydrylcyclohexanone (XVII) in 35% yield after chromatography. Under the conditions of the Schmidt reaction and using a trichloroacetic acid solvent, a good yield of the 7-benzhydrylcaprolactam (XVIII) was obtained. The lithium aluminum hydride reduction of the caprolactam did not proceed readily; only in a dioxane-ether solvent was the hexamethyleneimine (VI) obtained.

Most of the compounds reported showed central stimulant activity when administrered parenterally as their hydrochloride salts. The degree of stimulation was measured in an activity cage.[11] The most active compounds of this series were benzhydrylmorpholine (III) and the morpholylbenzhydrol (IV). They both antagonized bulbocapnine induced catatonia and potentiated pentobarbital induced hypnosis.

EXPERIMENTAL

Ethyl-β,β-diphenylalaninate hydrochloride. β,β-Diphenylalanine (40 g.) and 600 ml. of 10% ethanolic hydrogen chloride were heated at reflux for 4 hr. The ethanol was stripped off, leaving 46 g. of hydrochloride, m.p. 195–196° dec. One recrystallization from ethanol-ether raised the melting point to 200–201° dec.

Anal. Calcd. for $C_{17}H_{20}NO_2Cl$: N, 4.58; Cl, 11.60. Found: N, 4.54; Cl, 11.48.

3,3-Diphenyl-2-amino-1-propanol. Ethyl β,β-diphenylalaninate hydrochloride (46 g., 0.15 mole) was dissolved in water, neutralized with sodium carbonate and the free base taken up in ether and dried. The ether solution (400 ml.) was added dropwise with stirring to lithium aluminum hydride (11.4 g., 0.3 mole) in 200 ml. of ether. The addition was complete in 30 min. and refluxing was continued for another hour. Water (50 ml.) was added and the aluminum hydroxide removed by filtration and washed with acetone. The combined ether and acetone filtrates were stripped leaving an oil residue. Triturating with hexane gave 14 g. of product, m.p. 117–119°. One recrystallization from benzene gave m.p. 120–121°.

Anal. Calcd. for $C_{15}H_{17}NO$: C, 79.26; H, 7.54; N, 6.17. Found: C, 79.38; H, 7.74; N, 6.20.

3,3-Diphenyl-2-(α-chloroacetylamino)-1-propanol. 3,3-Diphenyl-2-amino-1-propanol (8.9 g., 0.039 mole) was added to a mixture of 107 ml. of ethylene dichloride and 71 ml. of water containing 2.3 g. (0.057 mole) of sodium hydroxide. The mixture was stirred and cooled to 0°. Chloroacetyl chloride (6.4 g., 0.057 mole) was then added dropwise, the reaction temperature maintained around 0°. The addition was complete in 30 min. and the reaction mixture was then allowed to warm up to room temperature and stirred for an additional 3 hr. The ethylene dichloride layer was dried and stripped to yield a gummy residue which crystallized from benzene-hexane, m.p. 106–108°, 7.4 g.

Anal. Calcd. for $C_{17}H_{18}NO_2Cl$: N, 4.61; Cl, 11.67. Found: N, 4.40; Cl, 11.86.

5-Benzhydryl-3-morpholone. 3,3-Diphenyl-2-(α-chloroacetylamino)-1-propanol (1.7 g., 0.0056 mole) was dissolved in 20 ml. of absolute ethanol containing 0.32 g. (0.0056 mole) of powdered, dried potassium hydroxide. The solution was stirred at room temperature for 4 hr. after which the precipitated potassium chloride (0.38 g.) was removed. The ethanol filtrate was stripped and the oil residue triturated with ether to give 1.0 g. of product, m.p. 133–135°. One recrystallization from methanol raised the melting point to 135–136°.

Anal. Calcd. for $C_{17}H_{17}NO_2$: C, 76.37; H, 6.42; N, 5.24. Found: C, 75.67; H, 6.21; N, 5.19.

3-Benzhydrylmorpholine hydrochloride. 5-Benzhydryl-3-morpholone (3.9 g., 0.0146 mole) was dissolved in 150 ml. of tetrahydrofuran and the solution added dropwise with stirring to lithium aluminum hydride (1.6 g., 0.0292 mole) in 50 ml. of tetrahydrofuran. The addition was completed in 20 min. and the reaction mixture was then refluxed for an additional 2 hr. The hydride complex was then hydrolyzed with 4.7 ml. of water. After filtration, the ether filtrate was dried and hydrogen chloride was introduced to precipitate 1.55 g. of product, m.p. >260° dec. One recrystallization from isopropyl alcohol gave analytically pure material.

Anal. Calcd. for $C_{17}H_{20}NOCl$: N, 4.83; Cl, 12.23. Found: N, 4.87; Cl, 12.47.

1,1-Diphenyl-2-(α-chloroacetamido)-1,3-propanediol. 1,1-Diphenyl-2-amino-1,3-propanediol[6] (30 g., 0.124 mole), chloroacetyl chloride (14.7 g., 0.13 mole), sodium hydroxide (5.2 g., 0.13 mole), 400 ml. ethylene dichloride, and 200 ml. of water gave 38 g. of product, m.p. 166–168°. The procedure was as described above. One recrystallization from isopropyl alcohol gave m.p. 167–169°.

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Anal. Calcd. for $C_{17}H_{18}NO_3Cl$: C, 63.90; H, 5.68; N, 4.38; Cl, 11.08. Found: C, 63.60; H, 6.13; N, 4.47; Cl, 11.04.

5-(α-Hydroxybenzhydryl)-3-morpholone. 1,1-Diphenyl-2-(α-chloroacetamino)-1,3-propanediol (35 g., 0.11 mole) was dissolved in 400 ml. of absolute ethanol containing 6.2 g., 0.11 mole of powdered, dried potassium hydroxide. The solution was stirred at room temperature for 3 hr., then warmed to 40° for 30 min. Potassium chloride, 6 g., was removed and the filtrate was stripped down to yield an oily residue which solidified on trituration with acetone to give 9.5 g. of product, m.p. 218–220°. One recrystallization from methanol did not change the melting point.

Anal. Calcd. for $C_{17}H_{17}NO_3$: C, 72.06; H, 6.05; N, 4.94. Found C, 72.10; H, 6.22; N, 5.05.

α-(3-Morpholyl)benzhydrol hydrochloride. 5-(α-Hydroxybenzhydryl)-3-morpholone (9 g., 0.032 mole) was added portionwise to lithium aluminum hydride (2.4 g., 0.064 mole) in 300 ml. of ether. The addition was complete in 20 min. and refluxing was continued for 2 hr. The excess hydride and complex was carefully destroyed by adding 10.3 ml. of water. After removal of the aluminum hydroxide, the ether solution was dried and hydrogen chloride bubbled in yielding the product as its hydrochloride, 7.4 g., m.p. 242–244° dec. It was analytically pure without any further treatment.

Anal. Calcd. for $C_{17}H_{20}NO_2Cl$: N, 4.58; Cl, 11.60. Found: N, 4.63; Cl, 11.32.

α-(2-Pyrrolidyl)benzhydrol hydrochloride. dl-Proline ethyl ester (4.7 g.) was added dropwise at room temperature to a solution of phenylmagnesium bromide (4 equivalents) in ether. After addition of all the ester, the mixture was refluxed for 2 hr. and then hydrolyzed with dilute ammonium chloride. The ether layer was separated and the aqueous solution extracted thrice with benzene. The combined extracts were washed with water, dried (sodium sulfate), and evaporated *in vacuo* to yield an oil (4.5 g.). It was converted to the hydrochloride which crystallized from methanol-ether. It had m.p. >250°.

Anal. Calcd. for $C_{17}H_{20}ONCl$: N, 4.83. Found: N, 4.89.

An aliquot of the hydrochloride was converted to the free base. It was crystallized from ethanol-water and had m.p. 81–82°, (lit.[7] m.p. 83°).

Anal. Calcd. for $C_{17}H_{19}ON$: C, 80.60; H, 7.56; N, 5.53. Found: C, 80.31; H, 7.84; N, 5.48.

2-Benzhydrylcyclohexanone. To a solution of phenylmagnesium bromide (1.47 mole) in ether (1000 ml.), was added cuprous chloride (1.2 g., 1 mole %). Benzylidenecyclohexanone (230 g., 1.23 moles) dissolved in a mixture of ether (1000 ml.), and benzene (30 ml.) was added at room temperature over a period of 4 hr. to the Grignard solution. The mixture was refluxed for 1 hr. and allowed to stir overnight at room temperature.

The reaction was worked up by pouring onto cracked ice and acidifying with dilute hydrochloric acid. The ether layer was separated, washed free of acid and the ether evaporated to yield a light yellow oil (350 g.), which did not crystallize. The oil was chromatographed on alumina. The benzene-petroleum ether (1:1) eluate yielded 2-benzhydrylcyclohexanone in 35% yield. The ketone was crystallized from benzene-petroleum ether (b.p. 30–60°) and had m.p. 105°. The infrared spectrum showed a single high intensity peak in the carbonyl region at 1714 cm.$^{-1}$

Anal. Calcd. for $C_{19}H_{20}O$: C, 86.3; H, 7.63. Found: C, 85.46; H, 7.65.

2-Benzhydryl-6-ketohexamethyleneimine. 2-Benzhydrylcyclohexanone (12 g.), was dissolved in molten trichloroacetic acid (60 g.). To this solution was added, at 66°, sodium azide (4.56 g.), all at once resulting in a brisk evolution of nitrogen. The mixture was stirred at 66° for 4 hr. then water was added and the mixture made alkaline with concentrated ammonium hydroxide (10 ml.). The organic material was extracted with chloroform to yield 13.7 g. of material which contained *ca.* 15% of starting material as indicated by the infrared spectrum. The ketonic material was removed by treating with Girards reagent T. The crude reaction product (13.7 g.) was dissolved in methanol (170 ml.) and an excess of Girard reagent (20 g.) in glacial acetic acid (10 ml.) was added. The mixture was refluxed for 1 hr. the poured into ice cold water (1700 ml.) containing sodium hydroxide (6.3 g.) and extracted with chloroform (4 × 200 ml.) to yield a dark oil (11.8 g.) which contained no ketonic carbonyl peak in the infrared.

2-Benzhydryl-6-ketohexamethyleneimine was obtained as colorless crystals m.p. 133–134° from ethyl acetate. The infrared spectrum exhibited a single high intensity peak in the carbonyl region at 1673 cm.$^{-1}$

Anal. Calcd. for $C_{19}H_{21}ON$: C, 81.71; H, 7.58; N, 5.02. Found: C, 81.08; H, 7.11; N, 4.68.

2-Benzhydrylhexamethyleneimine. A solution of 2-benzhydryl-6-ketohexamethyleneimine (7.6 g.), dissolved in a mixture of ether (200 ml.) and dioxane (50 ml.), was added over a period of 10 min. to lithium aluminum hydride (2.06 g.) in ether. The mixture was refluxed for 2 hr. then water (9.2 ml.) was added cautiously. The solid material was removed by filtration and the dried filtrate was evaporated and dissolved in benzene. Anhydrous hydrochloric acid was bubbled into the benzene solution of the reduction product and on addition of an equal volume of ether and cooling, a crude hydrochloride salt (3.5 g.) was obtained. The free base was liberated from the water insoluble salt by prolonged shaking with aqueous sodium carbonate and chloroform.

The free base was chromatographed on alumina. The chloroform eluate yielded a hydrochloride which was obtained crystalline from acetone-ether. It had m.p. 200–202° and its infrared spectrum was in agreement with the expected structure.

Anal. Calcd. for $C_{19}H_{24}NCl$: C, 75.6; H, 8.01; Cl, 11.75. Found: C, 75.2; H, 7.56; Cl, 12.55.

α-[3-(1,2,3,4-Tetrahydroisoquinolyl)]benzhydrol hydrochloride. Crystalline 3-carbethoxytetrahydroisoquinoline hydrochloride[8] (4.7 g., 0.023 mole) was added slowly to an ethereal solution of phenylmagnesium bromide (0.28 mole, 10 eqs.). The mixture was refluxed for 3 hr. then allowed to stir at room temperature overnight. The reaction was decomposed by adding a 20% solution of ammonium chloride. Benzene was added to increase the solubility of the product and the benzene-ether layer was separated, washed (water), dried (sodium sulfate), and evaporated to dryness *in vacuo* to yield an oil (6.6 g.), which was converted to its hydrochloride salt. The hydrochloride was obtained as colorless crystals from absolute ethanol and had m.p. >250°.

Anal. Calcd. for $C_{23}H_{22}NOCl$: N, 3.98; Cl, 10.08. Found: N, 3.95; Cl, 10.02.

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