1.25 hr., the solution was cooled, diluted with water (150 ml.), and the ester extracted into a benzene-ether (1:1) mixture (100 ml.). The organic layer was washed with water, with dilute sulfuric acid, and then again with water. Distillation of the organic layer afforded the *trans* ester (23.0 g.; 87%), b.p. 68–69° at 0.2 mm. On cooling, the distillate solidified m.p. 29.5–30°, lit.[19] b.p. 119–120° at 4 mm., m.p. 37–39°. The infrared spectra (10% chloroform solution) of the *cis* and *trans* esters showed notable differences:

cis Ester (in cm.$^{-1}$): 3000 (s); 1742 (vs); 1430 (s); 1358 (m); 1335 (s); 1250 (s); 1195 (s); 1165 (s); 1118 (w); 1092 (w); 1075 (m); 1040 (m); 942 (w); 908 (m); 848 (w).

trans Ester (in cm.$^{-1}$): 3000 (s); 1732 (vs); 1430 (s); 1368 (m); 1310 (s); 1260 (s); 1242 (w); broad absorption between 1210–1170 (s); 1110 (s); 1070 (w); 1022 (s); 990 (w); 910 (m); 878 (w); 862 (m).

5-Norbornene-endo-trans-2,3-dicarbo(benzoylhydroxamic) acid. The *trans* ester (21.0 g.; 0.1 mole) was treated with hydroxylamine and sodium ethoxide as described above. As the salt did not precipitate after 3 hr., the solvents were removed *in vacuo*. The residual sodium salt was dissolved in water (200 ml.) containing sodium acetate trihydrate (16.2 g.) and treated dropwise with benzoyl chloride (40 ml.) at 0°. After 2.0 hr. the mixture was acidified, with concentrated hydrochloric acid (20 ml.) and the solid filtered, washed with water, then with benzene (100 ml.) and then with ether (20 ml.). The crude solid (22.5 g.) was recrystallized from 80% ethanol (250 ml.) and it formed fine needles which weighed 21.0 g. (50%) m.p. 187° with dec.

Anal. Calcd. for $C_{23}H_{20}N_2O_6$ (420.2): C, 65.71; H, 4.77; N, 6.67. Found: C, 65.32; H, 4.78, N, 6.98.

The *cis* ester when carried through this reaction sequence afforded only 30% of the *trans*-benzoylhydroxamic acid.

Rearrangement of trans-benzoylhydroxamic acid, VI. The hydroxamic acid (4.2 g.; 0.01 mole) was dissolved in potassium hydroxide solution (1.12 g. in 26.4 ml. of water). The solution was warmed on a steam bath and within 5 min. a solid commenced to precipitate. After 1 hr. the product (2.25 g.) was collected, washed with water. It decomposed above 300°. The product was boiled with methanol (100 ml.) and refiltered. The solid decomposed above 340°.

Anal. Calcd. for $C_8H_{10}N_2O$: C, 64.00; H, 6.66; N, 18.66. Found: C, 63.71; H, 6.87; N, 18.32.

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(19) The *trans* ester was prepared by refluxing the anhydride in methanol in the presence of dry hydrogen chloride. A. T. Blomquist and E. C. Winslow, *J. Org. Chem.*, **10**, 149 (1945).

[Contribution from the Department of Chemistry, University of Delaware]

The Synthesis of 6-Hydroxy-1,3,4,5-tetrahydrobenz [cd] indole[1]

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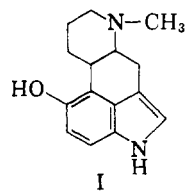
5,8-Dimethoxy-1-tetralone (IV) was converted to the aminomethyltetralin (VIII) *via* the cyanohydrin (V) and nitrile (VII). Demethylation and ferricyanide oxidation led to the 6-hydroxytetrahydrobenzindole (IX).

The importance of both 5-hydroxytryptamine (serotonin) and of lysergic acid derivatives in pyschopharmacology, and the biochemical interactions of these substances,[2] suggest that derivatives of 12-hydroxyergoline (I) might be of considerable pharmacological interest. This possibility has prompted us to undertake synthetic efforts designed to furnish access to the 12-hydroxyergoline system.



I

Most of the previous synthetic approaches to reduced benz[*cd*]indole or ergoline derivatives have involved the elaboration of rings C and D on a preformed indole nucleus[3]; an exception has very recently been described by Walker and Weaver.[4] The presence of the 12-hydroxy group in II, however, lends a rather broader scope to the synthetic possibilities. One attractive approach permitted by this substituent is embodied in the elegant synthesis of 5-hydroxyindole, described by Cromartie and Harley-Mason,[5] in which β-(2,5-dihydroxyphenyl)ethylamine is cyclized directly to the indole by mild oxidation. As an initial stage in the adaptation of this route to the ergoline system I, the preparation of the model tricyclic compound IX has been accomplished and is described in the present paper.

The required aminomethyltetralin was obtained from 5,8-dimethoxy-1-tetralone (IV)[6] by the reaction sequence shown in Fig. 1. In the preparation of the ketone IV, the procedure of Momose *et*

(1) Supported by a grant from the Geschickter Fund for Medical Research.

(2) For a review, *cf. Ann. N. Y. Acad. Sci.*, **66**, 417–480 (1957).

(3) *Inter alia:* F. C. Uhle and W. A. Jacobs, *J. Org. Chem.* **10**, 76 (1945); A. Stoll and J. Rutschmann, *Helv. Chim. Acta* **33**, 67 (1950); E. C. Kornfeld, E. J. Fornefeld, G. B. Kline, M. J. Mann, D. E. Morrison, R. G. Jones, and R. B. Woodward, *J. Am. Chem. Soc.* **78**, 3087 (1956); H. Plieninger, M. Schach v. Wittenau and B. Kiefer, *Chem. Ber.* **91**, 2095 (1958).

(4) G. N. Walker and B. N. Weaver, *J. Org. Chem.* **35**, 484 (1960).

(5) R. J. T. Cromartie and J. Harley-Mason, *J. Chem. Soc.* 2525 (1952).

(6) T. Momose, H. Oya, Y. Ohkura, and M. Iwasaki, *Pharm. Bull.* (Tokyo), **2**, 119 (1954); *Chem. Abstr.* **50**, 911 (1956).

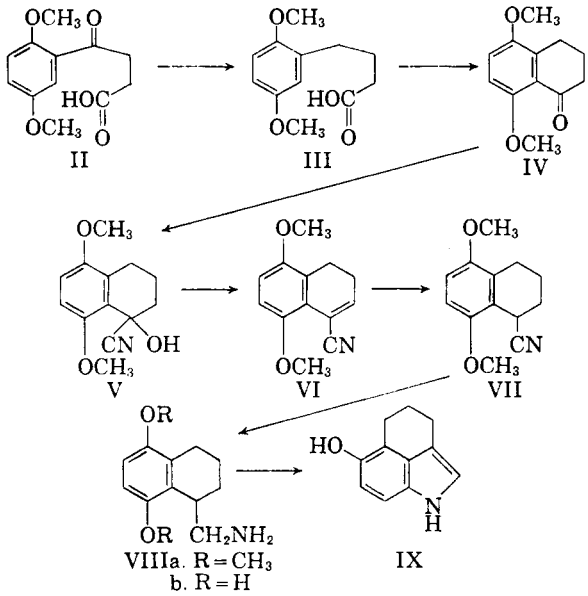


Fig. 1 Preparation of the aminomethyltetralin, IX

al.[6] starting with β-(2,5-dimethoxybenzoyl)propionic acid was followed with two modifications. Instead of a two-stage sequence of electrolytic reduction to the lactone and subsequent hydrogenolysis, the arylbutyric acid (III) was obtained directly in 66% yield by Wolff-Kishner reduction. Cyclization of III was accomplished with polyphosphoric acid. The crystalline cyanohydrin V was obtained in the usual way in 75% yield and was then dehydrated with thionyl chloride in pyridine. Although catalytic reduction of the unsaturated nitrile in the presence of acid furnished the amine VIIIa in moderate yield, hydrogenation to the saturated nitrile followed by hydride reduction was more satisfactory for larger-scale preparations of VIIIa. Demethylation was effected with constant-boiling hydrobromic acid, giving the hydrobromide of VIIIb in 70% yield.

The oxidation of the dihydroxyamine, as the hydrochloride, was carried out according to the procedure described for the phenethylamine.[5] The crude indole could be crystallized directly after extraction with ether, but was very unstable until purified by passage over a column of alumina. The material was then sublimed and recrystallized to give a colorless product in 52% yield. The ultraviolet spectrum was very similar to that of 5-hydroxyindole.

The 6-hydroxy-1,3,4,5-tetrahydrobenz[*cd*]indole formulation for the oxidation product is quite firmly established by this straightforward reaction sequence. It seemed desirable, nevertheless, to confirm the structure by conversion to the known 1,3,4,5-tetrahydrobenz[*cd*]indole,[7] particularly since it was anticipated that such a transformation would be required in the structure proof of more complex tetracyclic members of the series which are currently in preparation. The similar removal of a hydroxyl group in the indole benzenoid ring was accomplished in the structure proof of 6-hydroxyyohimbyrine by Raney nickel detosylation,[8] and an attempt was made to apply this procedure to IX. The tosylate was obtained in good yield, but neither this compound nor 5-tosyloxyindole could be converted to the corresponding unsubstituted indole, the unchanged tosylates being recovered after vigorous treatment with Raney nickel.

(7) W. A. Jacobs and G. Gould, *J. Biol. Chem.*, 120, 141 (1937); F. C. Uhle, C. G. Vernick, and G. L. Schmir, *J. Am. Chem. Soc.* 77, 3334 (1955).

EXPERIMENTAL[9]

β-(2,5-Dimethoxybenzoyl)propionic acid[6] was prepared from 125 g. of succinic anhydride, 333 g. of aluminum chloride and 155 g. of *p*-dimethoxybenzene in 2 l. of nitrobenzene. The mixture was allowed to warm from 5° to 29° during 3.5 hr. at which time the color changed from orange to green, and the solution was then promptly poured into iced hydrochloric acid. After extraction with bicarbonate and reacidification, 218 g. (81%) of colorless product, m.p. 101–102°, was obtained.

α-(2,5-Dimethoxyphenyl)butyric acid (III). A solution of 17.6 g. of the keto acid II in 200 ml. of triethylene glycol containing 10 g. of sodium hydroxide, 10 ml. of 85% hydrazine hydrate and 10 ml. of water was refluxed for 3 hr. and then was heated further without a condenser until the temperature rose to 210°. After another hour sufficient water was added to lower the temperature to 190° and heating was continued for 4 more hours. The solution was then cooled and poured into a mixture of 50 ml. of concd. hydrochloric acid and 500 g. of ice. The precipitated acid was washed and dried, 11.0 g. (66%), m.p. 64–65°; after recrystallization from ether, m.p. 68–69°.

5,8-Dimethoxy-1-tetralone (IV). To polyphosphoric acid prepared from 500 g. of 85% phosphoric acid and 455 g. of phosphoric anhydride was added 22.9 g. of III. After warming on the steam bath for 1.5 hr. the orange solution was poured onto ice and the ketone extracted with ether. The ether solution was washed with base, dried, and evaporated. Two crops of colorless prisms were obtained, total 15 g., m.p. 58–62°.

The *2,4-dinitrophenylhydrazone* was obtained as orange-red needles from ethyl acetate, m.p. 245–246°.

Anal. Calcd. for $C_{18}H_{18}O_6N_4$: C, 55.95; H, 4.70; N, 14.50. Found: C, 56.14; H, 4.73; N, 14.24.

5,8-Dimethoxy-1-tetralone cyanohydrin (V). Solutions of 3.74 g. of the ketone IV in 300 ml. of ether and 60 g. of sodium cyanide in 300 ml. of water were stirred and treated dropwise with a solution of 34 ml. of concd. sulfuric acid in 80 ml. of water. After 1 hr. the ether layer was washed with water, dried with sodium sulfate, decolorized with charcoal, and concentrated to a syrup. The cyanohydrin crystallized as colorless prisms, m.p. 97–98°. Recrystallization from ethanol furnished 3.1 g., m.p. 103–104°, λ^{KBr} 2.86 μ, 4.48 μ (weak).

4-Cyano-5,8-dimethoxy-1,2-dihydronaphthalene (VI). To a solution of 38 g. of the cyanohydrin V in 19 ml. of pyridine at 0° was added 10 ml. of thionyl chloride. The yellow solution was then heated for 1 hr. on the steam bath, cooled

(8) L. Dorfman, A. Furlenmaier, C. F. Huebner, R. Lucas, H. B. Mac Phillamy, J. M. Mueller, E. Schlittler, R. Schwyzer, and A. F. St. Andre, *Helv. Chim. Acta* 37, 59 (1954).

(9) Infrared spectra were obtained in potassium bromide discs for all new compounds; selected bands are recorded for the more important compounds.

and treated with ice water. The product separated as a yellow solid, m.p. 81–86°. Recrystallization from ethanol gave 28 g. (80%) of colorless needles, m.p. 85–86°, λ^{KBr} 4.49 μ (med.).

Anal. Calcd. for $C_{13}H_{15}O_2N$: C, 72.54; H, 6.09; N, 6.51. Found: C, 72.82; H, 6.15; N, 6.31.

1-Cyano-5,8-dimethoxy-1,2,3,4-tetrahydronaphthalene (VII). A solution of 28 g. of the unsaturated nitrile VI in 100 ml. of methanol was shaken with 1 g. of 10% palladium-carbon catalyst for 10 hr. at 3 atm. hydrogen pressure. After removal of the catalyst and concentration the product crystallized as colorless plates, 23 g. (82%), m.p. 98–99°. Recrystallization from methanol raised the m.p. to 104–105°, λ^{KBr} 4.46 (med).

Anal. Calcd. for $C_{13}H_{16}O_2N$: C, 71.86; H, 6.96. Found: C, 72.06; H, 6.91.

1-Aminomethyl-5,8-dimethoxy-1,2,3,4-tetrahydronaphthalene (VIIIa). A. From VII. A solution of 23 g. of the saturated nitrile VIII in ether was refluxed for 5 hr. with excess lithium aluminum hydride. The excess reagent was decomposed with water and the inorganic solid filtered and washed with ether. The combined ether solutions were concentrated to a syrup which crystallized to give 19 g. of white needles, m.p. 86–87°.

B. From VI. A solution of 215 mg. of the unsaturated nitrile in 25 ml. of ethanol containing 0.16 ml. of concd. hydrochloric acid was stirred with 10% palladium-carbon catalyst for 10 hr. in a hydrogen atmosphere. The catalyst was filtered and the solution evaporated to a syrup which was dissolved in hydrochloric acid, decolorized and then made alkaline. The amine separated in white crystals, m.p. and mixed m.p. 83–85°.

1-Aminomethyl-5,8-dihydroxy-1,2,3,4-tetrahydronaphthalene hydrobromide (VIIIb). A solution of 15 g. of the dimethoxyamine in 350 ml. of 48% hydrobromic acid was refluxed for 2 hr. On cooling the salt of VIIIb crystallized as violet plates, which were recrystallized twice from ethanol to give 13 g. of nearly colorless crystals which decomposed above 150° without melting.

Anal. Calcd. for $C_{11}H_{16}O_2NBr$: C, 48.18; H, 5.88, N, 5.11. Found: C 48.53; H, 5.82; N, 5.38.

6-Hydroxy-1,3,4,5-tetrahydrobenz[cd]indole (IX). A solution of 1.23 g. of hydrobromide VIIIb in 100 ml. of water was shaken for 30 min. with freshly precipitated silver chloride and then filtered. To this solution of the hydrochloride of VIIIb was added in one portion a solution of 3.11 g. of potassium ferricyanide and 5 g. of sodium bicarbonate in 50 ml. of water. The solution immediately became magenta, and carbon dioxide was evolved for 2–3 min. The solution was then extracted with four 50-ml. portions of ether and the combined extracts were dried with magnesium sulfate; the drying agent immediately developed a brilliant azure color. The ether was then evaporated *in vacuo* to give 701 mg. of brown crystalline residue. A solution of this material in benzene was passed over a 1.5 x 20 cm. column of alumina. A band of dark violet material was retained at the top of the column; after elution of a small amount of oily material, increasing concentrations of chloroform eluted the indole, which crystallized as pale tan prisms, 452 mg., m.p. 117–118°. Sublimation furnished 406 mg. of sparkling white material. m.p. 125–126°, $\lambda_{max}^{C_2H_5OH}$ 276 μ (6000), 301 μ (4700). The Ehrlich reaction with *p*-dimethylaminobenzaldehyde gave a violet color.

Anal. Calcd. for $C_{11}H_{11}ON$: C, 76.27; H, 6.40; N, 8.09. Found: C, 76.25; H, 6.80; N, 8.41.

The *tosylate* was prepared by heating a solution of 100 mg. of IX and 300 mg. of *p*-toluenesulfonyl chloride in 5 ml. of pyridine at 50° for 26 hr. After pouring onto iced hydrochloric acid the product precipitated. It was recrystallized from ethanol-ether to give 121 mg. of colorless prisms, m.p. 164–165° and 25 mg., m.p. 162–163°.

Anal. Calcd. for $C_{18}H_{17}O_3NS$: C, 66.05; H, 5.24. Found: C, 66.15; H, 5.25.

In an attempted reduction, 100 mg. of the tosylate was refluxed with Raney nickel in ethanol with a stream of hydrogen for 6 hr. After removing the catalyst, evaporation of the solution furnished 65 mg. of the tosylate, m.p. 157–161°. None of the reduced indole was obtained by distillation of the mother liquor.

NEWARK, DEL.

[CONTRIBUTION FROM THE RESEARCH DEPARTMENT, HOFFMANN LAROCHE, INC.]

Quinazolines and 1,4-Benzodiazepines. II.[1] The Rearrangement of 6-Chloro-2-chloromethyl-4-phenylquinazoline 3-Oxide into 2-Amino Derivatives of 7-Chloro-5-phenyl-3H-1,4-benzodiazepine 4-Oxide

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On treatment with ammonia or primary amines, 6-chloro-2-chloromethyl-4-phenylquinazoline 3-oxide (I) rearranges into 2-amino derivatives of 7-chloro-5-phenyl-3H-1,4-benzodiazepine 4-oxide (II, IX). Reaction of I with secondary amines proceeds without rearrangement with formation of the expected 6-chloro-2-aminomethyl-4-phenylquinazoline 3-oxides.

The structure determination of quinazoline 3-oxides was described in a preceding communication.[1] This paper is concerned with further reactions of these compounds.

In attempts to prepare secondary amino derivatives of quinazoline 3-oxides we treated 6-chloro-2-chloromethyl-4-phenylquinazoline 3-oxide (I)[1] with primary amines. In a few cases the expected products were formed, but in addition we obtained in all reactions compounds of a different character whose infrared and ultraviolet absorption spectra[2a] indicated a structural change. A closer study of the "abnormal" reaction products showed that a ring enlargement[2b] had occurred and that these compounds were 2-amino derivatives of 7-chloro-5-phenyl-3H-1,4-benzodiazepine 4-oxide.

For the structure determination we chose the product formed on treatment of 6-chloro-

(1) Paper I. L. H. Sternbach, S. Kaiser, and E. Reeder, *J. Am. Chem. Soc.* 82, 475 (1960).