The Synthesis of (±)-Hexahydropronuciferine and Related Compounds[1]

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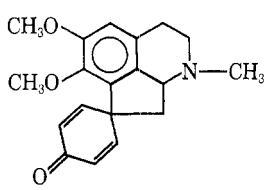
In an effort to develop a new synthetic approach to the proaporphine alkaloids, a method for effecting the conversion of a suitably substituted 1-indanone to a hexahydrocyclopent[*ij*]isoquinoline has been developed. Bobbitt's modification of the Pomeranz–Fritsch reaction applied to 4,5-dimethoxy-1-indanone affords the corresponding cyclopentisoquinoline (**5**) in acceptable yield. By the same procedure demethoxydeoxystepharine (**11**) was prepared from spiroindanone (**7**), which was in turn synthesized in three steps from 2-bromoanisole and ethyl cyanocyclohexylidineacetate. This procedure was extended to the total synthesis of (±)-hexahydrostepharine (**26**) by subjecting spiroindanone (**12**) to the modified Pomeranz–Fritsch reaction. The indanone was prepared from 4-cyano-2,3-dimethoxycyclohexanone (**14**) by reduction to the hydroxy aldehyde (**19**), homologation, and oxidation to the requisite acetic acid (**24**) followed by polyphosphoric acid cyclization. Methylation of **26** gave (±)-hexahydropronuciferine (**27**).

The proaporpine alkaloids, of which pronuciferine (**1**) is a typical example, constitute a relatively small, but important, group of alkaloids.[2] The structural features of the basic skeleton of these alkaloids pose two



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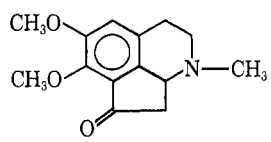

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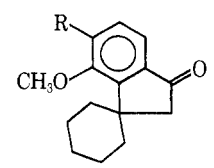
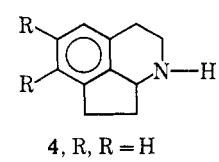
major obstacles to their synthesis, which are, first, the formation of a suitably substituted C-7a quaternary carbon atom[3] and, second, the synthesis of the requisite hexahydrocyclopent[*ij*]isoquinoline. Both these problems were overcome simultaneously in the biogenetic type syntheses of these alkaloids by the oxidation of appropriate benzylisoquinoline precursors;[4] however, the yields are very low. The stepwise total synthesis of pronuciferine reported by Bernauer[5] utilized the cyclopentisoquinolone **2** as a starting material, with the cyclohexadienone ring constructed by more or less standard techniques.

In an effort to devise an alternative synthetic approach to these alkaloids, it was felt that a reversal of Bernauer's route, namely synthesis of an appropriately substituted indanone (for example **3**) containing the quaternary C-7a carbon but lacking the heterocyclic ring, might prove promising. Since compounds related to **3** appeared *a priori* to be less than readily available, and in view of the inherent perversity of the Pomeranz–Fritsch reaction,[6] various model syntheses directed toward the conversion of simple indan derivatives to compounds **4** and **5** were undertaken.

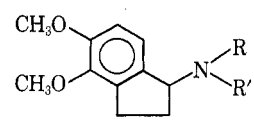
The successful conversion of *N*-benzylglycine derivatives to 4-oxotetrahydroisoquinolines has been reported;[7] however, the attempted cyclization of a number of N-substituted *N*-(4,5-dimethoxyindanyl)glycine derivatives (**6**) failed to yield any identifiable products.[8]



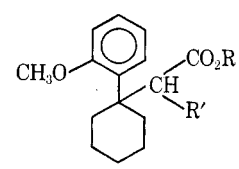
3, R = OCH_3
7, R = H



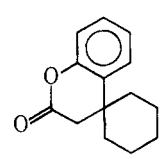
4, R, R = H
5, R, R = OCH_3



6, R = $CH_2C_6H_5$ or CHO;
R′ = CH_2CO_2H or CN



8, R = C_2H_5; R′ = CN
9, R; R′ = H



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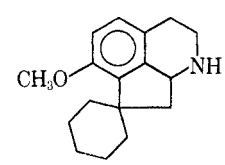

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The desired conversion of 4,5-dimethoxy-1-indanone to **5** in 54% yield was finally accomplished by means of Bobbitt's modification of the Pomeranz–Fritsch reaction.[9] Initial attempts to carry out this reaction failed; however, when the reaction was carried out under scrupulously anhydrous conditions with the exclusion of oxygen the conversion of the indanone to **5** proceeded smoothly.[10] The nmr spectrum of **5** was in accord with the assigned structure, with the aromatic proton appearing as a singlet at δ 6.45. The benzyl and methylene protons adjacent to nitrogen appeared as a complex multiplet in the δ 2.2–3.2 region. The benzylic methine proton adjacent to nitrogen was a triplet at δ 3.77, partially obscured by the methoxyl singlets.

With a method in hand for converting indanones to cyclopent[*ij*]quinolines, approaches to the preparation of an indanone containing an appropriate spirocyclo-

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(1) (a) A preliminary communication describing a portion of this work appeared in *Tetrahedron Lett.*, 5243 (1969). (b) Abstracted in part from the Ph.D. Dissertation of C. E. Opliger, Clemson University, Dec 1969. (c) This work was supported in part by Career Development Award GM-5433 from the National Institutes of Health.

(2) K. L. Stuart and M. P. Cava, *Chem. Rev.*, **68**, 321 (1968).

(3) The numbering system is that suggested by the authors in ref 2.

(4) (a) D. H. R. Barton and T. Cohen, *Festschr. Prof. Dr. Arthur Stoll Siebzigsten Geburtstag*, 117 (1957); (b) A. H. Jackson and J. A. Martin, *J. Chem. Soc. C*, 2222 (1966).

(5) (a) K. Bernauer, *Experientia*, **20**, 380 (1964); (b) K. Bernauer, *Helv. Chim. Acta*, **51**, 1120 (1968).

(6) W. J. Gensler, *Org. React.*, **6**, 191 (1951).

(7) (a) G. Grethe, H. L. Lee, M. Uskokovic, and A. Brossi, *J. Org. Chem.*, **33**, 491 (1968); (b) B. Umezawa, O. Hoshino, and Y. Yamanashi, *Tetrahedron Lett.*, 933 (1969).

(8) The preparation and reactions of these compounds are described in ref 1b.

(9) J. M. Bobbitt, A. S. Steinfeld, K. H. Weisgrabber, and S. Dutta, *J. Org. Chem.*, **34**, 2478 (1969), and earlier papers in this series.

(10) W. H. Perkin and R. Robinson, *J. Chem. Soc.*, **105**, 2376 (1914), have found that Schiff bases of various indanones are exceedingly sensitive to water.

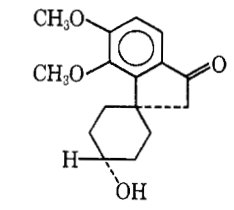
hexane system were explored. The obvious approach to this system is the preparation of an appropriately substituted 1-arylcyclohexaneacetic acid. A method which has been used successfully for the formation of quaternary centers similar to this is the cuprous chloride catalyzed reaction of a Grignard reagent with an unsaturated ester.[11] In an effort to utilize this route, attempts were made to prepare the Grignard reagent derived from 2,3-dimethoxybromobenzene. Although it has been stated that this compound forms a Grignard reagent in a normal manner,[12] this work could not be repeated.[13] Since the immediate goal was the development of a general synthetic method, an attempt was made to prepare the demethoxy derivative of **3** (**7**), which appeared to be available from the reaction of 2-methoxyphenylmagnesium bromide and ethyl cyclohexylideneacetate. However, even in the presence of cuprous chloride, the only product isolated from this reaction had the formula $C_{22}H_{26}O_3$, with the infrared spectrum showing the absence of carbonyl absorption. The nmr showed the presence of a vinyl proton and six methoxyl protons, indicating that instead of adding 1–4 to the conjugated system, a normal reaction with the ester had occurred.

When, however, the cuprous chloride catalyzed reaction of 2-methoxyphenylmagnesium bromide with ethyl cyanocyclohexylideneacetate was carried out, a compound $C_{18}H_{23}NO_3$ was obtained in 73% yield which had the spectral characteristics expected for **8**. Prolonged, vigorous, basis hydrolysis with concomitant decarboxylation afforded 1-(2-methoxyphenyl)cyclohexaneacetic acid (**9**).[14]

Polyphosphoric acid cyclization of **9** gave a mixture of two compounds, one of which was soluble in hot, 10% base and was recovered on acidification. This, the major product of the reaction (63% yield), showed carbonyl absorption at 5.68 μ in the infrared, and the nmr spectrum indicated the lack of a methoxyl peak and the presence of four aromatic protons. On the basis of these data, and a formula of $C_{14}H_{16}O_2$, this compound must be the lactone **10** resulting from demethylation and cyclization. Chromatography of the base insoluble portion of the reaction mixture gave 11% yield of a compound, $C_{15}H_{18}O_2$, which showed carbonyl absorption at 5.85 μ in the infrared and the nmr spectrum was that predicted for a compound of structure **7**. Bobbitt's modification of the Pomeranz–Fritsch reaction again proceeded smoothly to afford 2-methoxy-10-deoxo-8,9,11,12-tetrahydrostepharine (**11**) in 64% yield.[15]

This synthetic approach to the proaporphine alkaloids successfully overcomes the conversion of an indanone to the requisite hexahydrocyclopent[*ij*]-isoquinoline synthesis, but owing to the failure of 2,3-dimethoxybromobenzene in the Grignard reaction, an alternative synthesis of the requisite indanone (**12**) had to be developed.

Utilizing steps paralleling those reported,[16] 2,3-dimethoxyphenylacetonitrile (**13**)[17] was converted to



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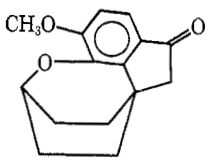

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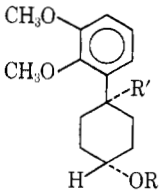
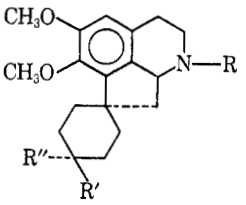


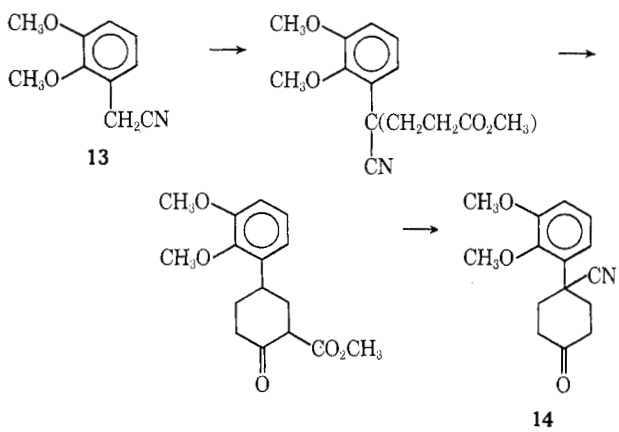
15, R = H; R′ = CN
16, R = $C_6H_5CH_2$; R′ = CN
17, R = $CH_2C_6H_5$; R′ = HC = NH
18, R = $CH_2C_6H_5$; R′ = CHO
19, R = H; R′ = CHO
20, R = H; R′ = CH_2NH_2
21, R = $OCOCH_3$; R′ = CHO
22, R = $OCOCH_3$; R′ = CH = $CHOCH_3$
23, R = $OCOCH_3$; R′ = CH_2CHO
24, R = $OCOCH_3$; R′ = CH_2CO_2H



26, R; R′ = H; R″ = OH
27, R = CH_3; R′ = H; R″ = OH
28, R = CH_3; R′ = OH; R″ = H

4-cyano-4(2,3-dimethoxyphenyl)cyclohexanone (**14**) by the sequence outlined in Scheme I.

SCHEME I



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14

The various reactions leading to **12** required the protection of the carbonyl group in **14**, and reduction to the alcohol appeared to be a most promising method of accomplishing this goal. Treatment of **14** with sodium borohydride gave **15** as the only isolable product in 72% yield. The assignment of stereochemistry for the hydroxyl group is based on the nmr spectrum which shows the carbinol proton as a broad multiplet at δ 3.57, indicating an equatorial hydroxyl. Since $-\Delta G_{C_6H_5}$ is in excess of 2 kcal/mol while $-\Delta G_{CN}$ is less than 0.3 kcal/mol,[18] the dimethoxyphenyl group in **15** should exist largely in the equatorial conformation, while the nitrile would be axial.[19] The attempted conversion of **15** to the benzyl ether **16** by conventional methods[20]

(11) J. W. Huffman and T. W. Bethea, *J. Org. Chem.*, **30**, 2956 (1965).
(12) G. Holmberg, *Acta Chem. Scand.*, **8**, 728 (1954).
(13) J. A. Barltrop and J. S. Nicholson, *J. Chem. Soc.*, 2524 (1951), also report the failure of this halide to react normally with magnesium.
(14) Less vigorous hydrolysis of **8** gave the amide corresponding to **9**.
(15) As in the case of 4,5-dimethoxyindanone, the classical Pomeranz–Fritsch reaction failed to afford any of the desired product.
(16) N. Hazama, H. Irie, T. Mizutani, T. Shingu, M. Takada, S. Uyeo, and A. Yoshitake, *J. Chem. Soc. C*, 2947 (1968).
(17) R. Delaby, G. Tsatsas, and M. C. Jendrot, *Bull. Soc. Chim. Fr.*, 1830 (1956).
(18) E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," Interscience, New York, N. Y., 1965, pp 435–444.
(19) In the isomer of **15** with the hydroxyl cis to the aromatic ring, the phenyl group would still be equatorial since $-\Delta G_{OH}$ = 0.6 kcal/mol and $-\Delta G_{OH} + -\Delta G_{CN}$ = 0.8 kcal/mol, still significantly less than $-\Delta G_{C_6H_5}$.
(20) (a) D. A. Prins, *Helv. Chim. Acta*, **40**, 1621 (1957); (b) R. L. Whistler and S. Hirase, *J. Org. Chem.*, **26**, 4600 (1961).

failed, apparently due to solubility factors; however, treatment of the alcohol with benzyl bromide, potassium *tert*-butoxide, *tert*-butyl alcohol, and dimethylformamide smoothly afforded the desired ether.

In an effort to prepare a suitable precursor for **12**, the controlled lithium aluminum hydride reduction of **16** to the imine **17** followed by hydrolysis to the aldehyde **18** was attempted. This sequence afforded **18**; however, reduction was incomplete and the isolation of the product difficult. In order to circumvent this problem, the direct reduction of **14** with lithium aluminum hydride was carried out to give, after hydrolysis, aldehyde **19** in 55% yield, accompanied by 4% of the primary amine **20**. The assignment of stereochemistry to this compound is based on the same nmr arguments employed in the discussion of **15**; however, subsequent experiments (*vide infra*) indicate that there may well have been a small percentage of the isomeric alcohol present in the reduction product.

The acetate of **19** (**21**) smoothly underwent the Wittig reaction with methoxymethylenetriphenylphosphorane to give the enol ether **22**. The nmr spectrum of **22** showed two overlapping AB quartets, one at δ 4.17 and 5.86 (J = J Hz), the other at δ 5.14 and 6.21 (J = 13 Hz), corresponding to the cis and trans isomers, respectively, of **22**. The mixture of isomeric enol ethers on treatment with perchloric acid in ether[21] gave the requisite aldehyde **23**. Oxidation of **23** with Jones reagent[22] in acetone afforded the substituted phenylpropionic acid **24**, the direct precursor of ketone **12**.

Although some lactonization of **24** under acidic cyclization conditions was predicted by analogy to the model synthesis described previously, the presence of a methoxyl group para to the site for cyclization to the indanone was expected to increase the relative amount of **12** in the reaction mixture. This was indeed the case, and it was found that on treatment of **24** with polyphosphoric acid at 65°, **12** was obtained in 40% yield. The use of more vigorous cyclization conditions led to the formation of a compound which showed only a single carbonyl peak in the infrared at 5.88 μ and was devoid of hydroxyl absorption. The nmr spectrum of this material showed an aromatic AB quartet, indicating cyclization to an indanone, but only one methoxyl peak at δ 4.00. On the basis of these spectral data, this compound was assigned the cyclic ether structure **25**, analogous to that suggested by Pfeifer for a compound obtained by reaction of oreoline with acid.[23]

Conversion of **12** to (±)-10-hydroxy-8,9,11,12-tetrahydrostepharine (**26**) was effected as described above using Bobbitt's modification of the Pomeranz–Fritsch reaction. The crude product from the isoquinoline synthesis was a mixture of three compounds, all with very similar R_f values on tlc, but with one of three components of the mixture predominating. The nmr spectrum of the crude product was consistent with that predicted for **26** and showed an aromatic singlet at δ 6.77, a one proton triplet at 4.12 for the benzylic methine proton, a six proton methoxyl singlet at δ 3.80, and the axial carbinol proton as a broad multiplet centered at δ 3.67. Although some efforts were made to purify this material (see Experimental Section), they were not successful on a small scale, and it was converted to the known *N*-methyl derivative[5,24] (**27**) for characterization. Eschweiler–Clarke methylation gave a mixture of several compounds; however, the recently reported N-methylation procedure of Cava and Buck[25] gave (±)-10-hydroxy-8,9,11,12-tetrahydropronuciferine (**27**), identical with a sample prepared by Bernauer.[5,24] Although both the free base and hydrochloride of **27** prepared by the above procedure and that prepared by Bernauer are identical, tlc of our material showed a trace of a second compound with an R_f value identical with that of the 10 epimer of **27** (**28**). This may be due to a small quantity of an impurity in **27**, which coincidentally has the same R_f value as **28**, but is probably due to the presence of a small amount of **28**, which arises from the reduction of **14** to the stereoisomer of **19** (see above) at an earlier stage in the synthesis. Although there was no direct evidence for the presence of isomeric compounds in the precursors of **27**, the possibility that small amounts of C-10 epimers are present cannot be precluded.

Experimental Section[26]

4,5-Dimethoxy-1-indanone.—4,5-Dimethoxy-1-indanone was prepared after the method of Koo.[27] From 17.2 g of 2,3-dimethoxydihydrocinnamic acid was obtained 10.4 g (67.0%) of 4,5-dimethoxy-1-indanone, sublimed at 105–115° (0.04 mm): mp 74° (lit.[10] 74–75° and 82°); nmr 2.62, 3.10 (m, 4 H, CH_2-CH_2), 3.95 and 3.98 (s, 6 H, OCH_3), 7.04 (d, J = 9 Hz, 1 H, H-7), 7.55 (d, J = 9 Hz, 1 H, H-8).

5,6-Dimethoxy-1,2,3,7,8,8a-hexahydrocyclopent[*ij*]isoquinoline (5).—A mixture of 0.398 g of 4,5-dimethoxy-1-indanone, 5 ml of dry toluene, and 0.840 g of aminoacetal was stirred and heated at reflux for 42 hr under a water separator in a system flushed with nitrogen. A positive pressure of nitrogen was maintained during the entire reaction. A second portion of 0.271 g of aminoacetal was added to the reaction mixture, and heating was continued for 24 hr. After the reaction mixture was evaporated and dried *in vacuo*, the brown oily residue was dissolved in 10 ml of absolute ethanol (3A molecular sieves). To a mixture of 50 mg of platinum oxide in 5 ml of absolute ethanol (3A molecular sieves), which was prereduced, was added the dissolved oily residue. The reduction was carried out at room temperature and pressure with hydrogen passed through a Dry Ice–acetone condenser and was completed in 2.5 hr. After the catalyst was collected on a Celite pad and washed with ethanol, the filtrate was evaporated *in vacuo* at room temperature. The dried residue was dissolved in 15–20 ml of ether and was added to 20 ml of ice cold 10 *N* hydrochloric acid. The cold mixture was extracted with ether and stored at room temperature overnight. After the dissolved ether was removed *in vacuo*, 0.206 g of 5% palladium on carbon was added to the acidic solution, which was reduced to room temperature and pressure for 24 hr or until reduction was completed. The catalyst was collected on a Celite pad, and the filtrate was evaporated *in vacuo* at 40–50°, giving a yellow viscous mass. After the mass was dissolved in ethanol and evaporated to dryness several times, it solidified. The residue was dissolved

(21) G. W. Wittig, W. Boll, and K. Kruck, *Chem. Ber.*, **95**, 2514 (1962).

(22) L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis," Wiley, New York, N. Y., 1967, pp 143–144.

(23) (a) I. Mann and S. Pfeifer, *Pharmazie*, **22**, 124 (1967). (b) Compound **25** was characterized only by spectral means, since it was obtained in very small quantities while efforts were being made to find optimum conditions for the cyclization of **24** to **12**.

(24) We would like to thank Dr. Bernauer for comparison samples of compounds **27** and **28**.

(25) M. P. Cava and K. T. Buck, *Tetrahedron*, **25**, 2795 (1969).

(26) All melting points were determined on a Kofler hot stage and au uncorrected. Infrared spectra were taken as potassium bromide disks or liquid films on sodium chloride plates using a Perkin-Elmer Model 137 spectrophotometer and are reported in microns. Ultraviolet spectra were taken in 95% ethanol using a Perkin-Elmer Model 202 spectrophotometer and are reported as λ_{max} in millimicrons (log ϵ) except where the units are specified. Nuclear magnetic resonance spectra were obtained from a Varian Associates A-60 nuclear magnetic resonance spectrophotometer in deuteriochloroform unless stated otherwise. All spectra are reported in ppm relative to tetramethylsilane. Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn.

(27) J. Koo, *J. Amer. Chem. Soc.*, **75**, 189 (1953).

in water, and the solution was extracted with methylene chloride, made basic with concentrated ammonium hydroxide, filtered, and extracted with methylene chloride. The organic extract was washed with water, 10% sodium hydroxide, and water, dried over sodium sulfate, evaporated, and dried *in vacuo* giving 0.25 g (54.5%) of **5**, mp 81–93°. The free base could not be induced to crystallize satisfactorily from any of several solvent systems and purification was effected through the picrate. A portion of the picrate was dissolved in sodium hydroxide and extracted with methylene chloride. The washed and dried extract was evaporated and dried *in vacuo*, giving the free base: mp 90–95°; ir 3.11; uv (neutral) 208 (4.69), 230 (4.15), 2.85 (3.49); uv (base) 284 (3.49); uv (acid) 208 (4.76), 228 (4.30), 253 (3.83), 285 (3.57); nmr (C_6D_6) 1.52 (t, J = 10 Hz, 2 H, Ar CH_2CH_2CH), 2.53 (m, 6 H, Ar CH_2CH_2N– and Ar CH_3), 3.52, 3.77 (s, 6 H, OCH_3), 3.77 (t, 1 H, NHCH), 6.45 (s, 1 H, Ar H). The analytical sample was characterized as the picrate and crystallized from ethanol as yellow-brown needles, mp 230–235° dec.

Anal. Calcd for $C_{19}H_{20}N_4O_9$: C, 50.90; H, 4.50; N, 12.50. Found: C, 50.70; H, 4.50; N, 12.37.

Cyclohexylidenebis(2-methoxyphenyl)carbinol.—In a dry system a mixture of 0.058 g of magnesium, a crystal of iodine, and 0.448 g of *o*-bromoanisole in 2 ml of dry ether was warmed until the magnesium was consumed. The reagent was transferred to an addition funnel and diluted with 8–10 ml of dry ether. The Grignard solution was added dropwise over 10 min to a stirred mixture of 0.336 g of ethyl cyclohexylideneacetate[28] and 0.30 g of cuprous chloride in 5 ml of dry ether. The reaction mixture was heated at reflux for 2 hr and then hydrolyzed with 10% ammonium chloride solution and extracted with ether. The ether extract was washed with saturated sodium bicarbonate and water, and dried. Removal of the solvent gave a mixture of oil and crystals which on trituration with ether–petroleum ether gave 0.104 g (25%) of solid, mp 131–133.5°. The analytical sample crystallized from ether–hexane as white needles: mp 132.5–133.5°; ir 2.30; nmr 1.52, 2.18 [m, 10 H, $(CH_2)_5$], 3.62 (s, 6 H, OCH_3), 4.75 (s, 1 H, OH), 5.78 (s, 1 H, =CH–), 7.25 (m, 8 H, Ar H). After the sample was shaken with deuterium oxide, the peak at 4.75 disappeared.

Anal. Calcd for $C_{22}H_{26}O_3$: C, 78.07; H, 7.74. Found: C, 78.23; H, 7.52.

Ethyl α-Cyano-1-(2′-methoxyphenyl)cyclohexaneacetate (8).—To a mixture of 7.36 g of magnesium turnings, 100 ml of dry ether, and a crystal of iodine was added 11.9 g of *o*-bromoanisole. After the reaction had started, the mixture was diluted with 100 ml of dry ether. A solution of 44.2 g of *o*-bromoanisole in 60 ml of dry ether was added dropwise to maintain reflux and the resulting mixture was heated at reflux for 60 min. The cooled *o*-methoxyphenylmagnesium bromide solution was filtered into an addition funnel and added dropwise over 75 min to a stirred heterogeneous mixture of 48.7 g of ethyl cyanocyclohexylideneacetate,[29] 0.84 g of cuprous chloride, and 300 ml of dry ether. The gummy mixture was heated at reflux for 60 min, cooled to 0°, and hydrolyzed with 600 ml of 10% ammonium chloride. After the aqueous layer was extracted with ether, the combined extracts were washed with 1 *N* hydrochloric acid and with water. Evaporation of the dried solvent *in vacuo* gave a yellow semisolid residue. Crystallization from methanol gave 54.4 g (73.4%) of crystalline product, mp 89–96°, in two crops. The analytical sample, mp 97–98°, was recrystallized from methanol: ir 4.50, 5.78; nmr 0.93 (t, J = 7 Hz, 3 H, CH_3CH_2), 3.82 (s, 3 H, OCH_3), 3.83 (q, J = 7 Hz, 2 H, CH_3CH_2O), 3.60 [s, $CH(CO_2)$-CH], 7.20 (m, 4 H, Ar H).

Anal. Calcd for $C_{18}H_{23}NO_3$: C, 71.73; H, 7.69; N, 4.65. Found: C, 71.69; H, 7.53; N, 4.57.

1-(2′-Methoxyphenyl)cyclohexaneacetic Acid (9).—To a stirred, heated mixture of 48.8 g of potassium hydroxide and 190 ml of diethylene glycol flushed continuously with a slow stream of nitrogen was added 33.5 g of ethyl α-cyano-1-(2′-methoxyphenyl)cyclohexaneacetate (**8**). The mixture was heated at 175–185° for 35 hr, cooled, poured into an ice–water slurry, and extracted with ether. The cold aqueous basic solution was acidified with concentrated hydrochloric acid and extracted with ether. The extract was washed, dried, and evaporated *in vacuo*, giving 26.0 g (98.8%) of crude acid, mp 95–105°. The analytical sample crystallized from ether–hexane: mp 106–107°; ir 5.88, 5.99 sh, 6.29, 6.38; nmr 1.17, 2.08 [m, 10 H, $(CH_2)_5$], 2.90 (s, 2 H, CH_2CO_2H), 3.84 (s, 3 H, OCH_3), 7.16 (m, 4 H, Ar H).

Anal. Calcd for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12. Found: C, 72.56; H, 8.16.

When the reaction mixture was heated less than 20 hr, partial hydrolysis was observed. The basic ether extract was washed and dried. Removal of the solvent gave crude 1-(2′-methoxyphenyl)cyclohexaneacetamide, mp 96–98°. The analytical sample crystallized from ethanol–hexane: mp 100–101°; ir 3.03, 3.21, 6.04; nmr 1.30, 2.08 [10 H, $(CH_2)_5$], 2.87 (s, 2 H, CH_2CONH_2), 3.92 (s, 3 H, OCH_3), 7.23 (m, 4 H, Ar H).

Anal. Calcd for $C_{15}H_{21}NO_2$: C, 72.84; H, 8.56; N, 5.66. Found: C, 72.86; H, 8.61; N, 5.70.

Spiro[cyclohexane-1,3′-(4′-methoxyindan-1′-one)] (7).—To 320 g of polyphosphoric acid at 90–100° was added 20.0 g of pulverized 1-(2′-methoxyphenyl)cyclohexaneacetic acid, and the mixture was stirred at 90–100° for 1.5 hr. The dark red mixture was poured into 1200 ml of ice–water slurry and extracted with ether. The ether extract was washed with water, and the ether was removed *in vacuo*. To the tarry residue were added 40 g of potassium hydroxide, 340 ml of methanol, and 60 ml of water. The mixture was heated at reflux for 3–4 hr in a nitrogen atmosphere, cooled, and diluted with water. The methanol was removed *in vacuo*, and the aqueous mixture was extracted with ether. The organic layer was washed, dried, and evaporated *in vacuo*, giving 4.86 g (27.0%) of residue, which was dissolved in benzene–hexane, 1:1, and chromatographed on alumina. Elution with benzene gave 1.92 g of spiro[cyclohexane-1,3′-(4′-methoxyindan-1′-one)]. The analytical sample crystallized from ether as colorless rectangular crystals: mp 119°; ir 5.85; uv (neutral) 211 (4.17), 226 (4.30), 256 (3.81), 312 (3.42); uv (base) 256 (3.85), 310 (3.57); nmr 2.60 (s, 2 H, $CH_2C{=}O$), 3.92 (s, 3 H, OCH_3), 7.17 (m, 3 H, Ar H).

Anal. Calcd for $C_{15}H_{18}O_2$: C, 78.23; H, 7.83. Found: C, 78.22; H, 7.86.

The aqueous basic layer was acidified and extracted with ether. The ether extract was washed, dried, and evaporated *in vacuo*, giving 11.6 g (63.0%) of the δ-lactone of 1-(2′-hydroxyphenyl)-cyclohexaneacetic acid (**10**). The analytical sample was obtained by distillation as a viscous colorless oil: bp 117–120° air bath, (0.07 mm); $n^{23.5}D$ 1.5569; ir 5.68; nmr 1.67 [m, 10 H, $(CH_2)_5$], 2.78 (s, 2 H, CH_2CO), 7.20 (m, 4 H, Ar H).

Anal. Calcd for $C_{14}H_{16}O_2$: C, 77.75; H, 7.46. Found: C, 77.68; H, 7.58.

Almost complete lactone formation was observed with polyphosphoric acid at room temperature for 1.5 hr and at 150° for 3 min, as well as with a mixture of phosphorus oxychloride, phosphoric acid, and phosphorus pentoxide heated at reflux for 1.5 hr.

2-Demethoxy-10-deoxo-8,9,11,12-tetrahydrostepharine (11).—A mixture of 0.247 g of spiro[cyclohexane-1,3′-(4′-methoxyindan-1′-one)], 0.858 g of distilled aminoacetal, and 5 ml of dry toluene was stirred and heated at reflux over a water separator for 48 hr in a system flushed and maintained under a slight positive pressure of nitrogen. A second portion of 0.570 g of aminoacetal was added, and heating was continued for 24 hr. The light yellow solution was evaporated and dried *in vacuo* at room temperature, giving a viscous oil. This oil was dissolved in 10 ml of absolute ethanol (3A molecular sieves) and added to a mixture of 5 ml of absolute ethanol and 0.037 g of platinum oxide which was prereduced. The reduction was carried out with hydrogen passed through a Dry Ice–acetone condenser at room temperature and pressure. After 11.2 ml of hydrogen was consumed in 3.25 hr, the reduction ceased and a coating was observed on the catalyst. An additional 0.040 g of platinum oxide was added, and reduction was completed in 3 hr. The reduction mixture was filtered through a Celite pad, and the filtrate was evaporated and dried *in vacuo* at 35–60°. The residue was dissolved in 15 ml of ether, cooled to 0°, and added to 20 ml of 6 *N* hydrochloric acid at 0°. The mixture was stirred and allowed to stand at room temperature overnight. The aqueous–ether mixture was filtered, and the ether was concentrated *in vacuo* at room temperature to 15 ml. To the solution were added 15 ml of ethanol and 0.210 g of 5% palladium on charcoal and the mixture was reduced at room temperature and pressure for 6 hr or until the theoretical uptake of hydrogen was observed. After the catalyst was collected on a Celite pad, the filtrate was concentrated *in vacuo* at room temperature to approximately 3 ml. The white precipitate which formed was collected, washed with water, and dried *in vacuo* giving 0.186 g (63.7%) of 2-demethoxy-10-deoxy-8,9,11,12-tetra-

(28) C. Ruchardt, S. Eichler, and P. Panse, *Angew. Chem.*, **75**, 858 (1953).

(29) A. C. Cope, C. M. Hoffman, C. Wycoff, and E. Hardenbergh, *J. Amer. Chem. Soc.*, **63**, 3452 (1941).

hydrostepharine hydrochloride (11 hydrochloride), mp 244–256° dec. The methylene chloride extract from the acidic filtrate was evaporated, giving an additional 0.053 g (19.3%), mp 245–264° dec. A 0.073-g portion of the salt was stirred with 5–10 ml of water, adjusted to pH 10 with sodium hydroxide, and extracted with methylene chloride. The organic layer, which was washed and dried with sodium sulfate, was evaporated and dried *in vacuo*, giving 61 mg of free base which solidified after standing: mp 93–100°; ir 3.09, 6.20, 6.30; uv (neutral) 208 (4.43), 230 (3.85), 280 (3.17); uv (acid) 208 (4.43), 230 (3.83), 280 (3.17); uv (base) 280 (3.17); nmr (hexadeuteriobenzene), 2.88 (m, 6 H, Ar CH_2CH_2N- and CH_2CHN), 3.48 (s, 3 H, OCH_3), 3.90 (t, 1 H, NCHAr), 6.60 (d, J = 9 Hz, 1 H, H-2), 6.93 (d, J = 8 Hz, 1 H, H-1). The analytical sample of the hydrochloride was recrystallized from methylene chloride by dilution with dry ether, giving white needles, mp 254–259°.

Anal. Calcd for $C_{17}H_{24}NOCl$: C, 69.49; H, 8.25; N, 4.77; Cl, 12.01. Found: C, 69.26; H, 8.47; N, 5.03; Cl, 12.31.

2,3-Dimethoxyphenylacetonitrile.—2,3-Dimethoxyphenylacetonitrile was prepared by a modification of the method used for the preparation of 3-ethoxy-3-methoxybenzonitrile.[16] To a mixture of 86.0 g of 2,3-dimethoxybenzyl alcohol and 150 ml of dry benzene in a dry system was added a solution of 140 ml of thionyl chloride in 150 ml of dry benzene over 20 min at room temperature. After the reaction mixture was heated at reflux for 3 hr, the benzene and excess thionyl chloride were removed *in vacuo*. To the azeotropically dried residue in 300 ml of ethanol was added a solution 96.5 g of potassium cyanide in 300 ml of water at room temperature. The mixture was heated at reflux for 8 hr. After the solution was evaporated *in vacuo* at 100° to one-half the original volume, the aqueous layer was extracted with benzene. The organic extract was washed, dried over 4A molecular sieves, and evaporated *in vacuo* to a black viscous oil. Distillation of the crude nitrile gave 63.1 g (69.8%) of colorless liquid: bp 82–95° (0.13–0.15 mm) [lit.[17] 154–161° (13 mm)]; ir 4.46; nmr 3.65 (s, 2 H, CH_2), 3.80 (s, 6 H, OCH_3), 7.50 (m, 3 H, Ar H).

Dimethyl 4-Cyano-4-(2′,3′-dimethoxyphenyl)pimelate.—To a mixture of 60 g of 2,3-dimethoxyphenylacetonitrile, 160 ml of methyl acrylate, and 160 ml of dry *tert*-butyl alcohol heated at reflux under a nitrogen atmosphere was added rapidly a solution of 67.5 ml of 35% methanolic Triton B and 75 ml of dry *tert*-butyl alcohol. After heating the reaction mixture at reflux for 4.5 hr, 100 ml of solvent was distilled off. The remaining solvent was removed *in vacuo* at 100°, and the residue was dissolved in methylene chloride. After the organic mixture was washed with 1.5 *N* hydrochloric acid and water and dried over 4A molecular sieves, evaporation of the methylene chloride *in vacuo* gave 110 g (93.0%) of light yellow viscous oil. Distillation of an 80-g portion of the crude pimelate gave 73.7 g (91.9%) of fluorescent blue-green syrupy oil [bp 175–220° (0.10–035 mm)] which eventually crystallized. The analytical sample was obtained by distillation and crystallized during transfer: bp 187–192° air bath (0.10–0.12 mm); mp 55–57°; ir 4.50 w, 5.77; nmr 2.38 (m, 8 H, CH_2) 3.58 (s, 6 H, CH_3OCO), 3.83, 3.88 (s, 6 H, Ar OCH_3), 6.95 (m, 3 H, Ar H).

Anal. Calcd for $C_{18}H_{24}NO_6$: C, 61.88; H, 6.64; N, 4.01. Found: C, 62.06; H, 6.74; N, 3.87.

Methyl 5-Cyano-5-(2′,3′-dimethoxyphenyl)-2-oxycyclohexanecarboxylate.—To a stirred mixture of 31.2 g of 50% sodium hydride washed with dry toluene in a dry nitrogen atmosphere in 1.9 l. of dry toluene was added 69.7 g of dimethyl 4-cyano-4-(2′,3′-dimethoxyphenyl)pimelate in 400 ml of dry toluene. The mixture was stirred vigorously with a mechanical stirrer and heated at reflux for 5 hr. The cooled mixture was diluted cautiously with 200 ml of 6 *N* acetic acid and 200 ml of water. After the toluene layer was collected, the aqueous layer was extracted with toluene. The combined extracts were washed with aqueous sodium bicarbonate and then with water. The dried toluene extract was evaporated *in vacuo*, giving 57.1 g (85.5%) of a crystalline residue, mp 99–100°. The analytical sample was crystallized from absolute ethanol, giving colorless crystals: mp 103–104°; ir 4.48 w, 5.98, 6.15; uv (neutral) 222 (3.95), 255 (3.94); uv (acid) 221 (3.97), 254 (3.97); uv (base) 283 (4.19); nmr 2.37 (m, 6 H, CH_2), 3.19 (d, J = 15.5 Hz, 1 H, CHCO), 3.67 (s, 3 H, CH_3OCO), 3.79 (s, 3 H, Ar OCH_3), 3.93 (s, 3 H, Ar OCH_3), 6.84 (m, 3 H, Ar H).

Anal. Calcd for $C_{17}H_{19}NO_5$: C, 64.34; H, 6.03; N, 4.41. Found: C, 64.61; H, 6.14; N, 4.38.

1-(2′,3′-Dimethoxyphenyl)-4-oxocyclohexanecarbonitrile (14).—A mixture of 57.1 g of crude methyl 5-cyano-5-(2′,3′-dimethoxyphenyl)-2-oxocyclohexanecarboxylate, 900 ml of glacial acetic acid, and 500 ml of 10% sulfuric acid was heated at reflux for 7 hr. After the acidic mixture was extracted with benzene, the extract was washed with saturated sodium bicarbonate and with water and the benzene distilled off. Crystallization of the crude product from methanol gave 34.3 g (77.5%) of colorless crystals, mp 132–135°. The analytical sample crystallized from absolute ethanol: mp 136–137°; ir 4.50, 5.83; uv (neutral and acid) 218 sh (3.90), 278 (3.31); nmr 2.38 (m, 8 H, CH_2), 3.84, 4.00 (s, 6 H, OCH_3), 6.95 (m, 3 H, Ar H).

Anal. Calcd for $C_{15}H_{17}NO_3$: C, 69.48; H, 6.61; N, 5.40. Found: C, 69.52; H, 6.69; N, 5.34.

1-(2′,3′-Dimethoxyphenyl)-4-hydroxycyclohexanecarbonitrile (15).—To a stirred mixture of 10.0 g of **14** and 700 ml of absolute ethanol was added 3.50 g of sodium borohydride over 5–10 min at room temperature. The mixture was stirred for 3.5 hr at room temperature, diluted with 200 ml of water, and stirred for 0.5 hr. After the ethanol was removed *in vacuo* at elevated temperature, the residue was diluted with water and extracted with methylene chloride. Evaporation of the washed and dried extract and crystallization from acetone–hexane, 1:1, gave 7.2 g (72.0%) of crystals in two crops, mp 169–171°. The analytical sample crystallized from acetone–hexane as white crystals: mp 171–172°; ir 3.08, 4.48; uv (neutaal) 218 sh (3.98), 278 (3.33); uv (acid) 218 sh (3.95), 278 (3.39); uv (base) 278 (3.50); nmr 1.97 (s, 1 H, OH), 2.08 (m, 8 H, CH_2), 3.57 (m, 1 H, CHOH), (s, 6 H, OCH_3), 6.93 (m, 3 H, Ar H); with the addition of D_2O the peak at 1.97 disappeared.

Anal. Calcd for $C_{15}H_{19}NO_3$: C, 68.94; H, 7.33; N, 5.36. Found: C, 69.09; H, 7.32; N, 5.33.

4-Benzyloxy-1-(2′,3′-dimethoxyphenyl)cyclohexanecarbonitrile (16).—A stirred solution of 5.7 g of potassium *tert*-butoxide and 40 ml of dry *tert*-butyl alcohol was cooled to 2–4° in a system protected from atmospheric moisture and flushed with dry nitrogen. When the mixture began to freeze, 10 ml of dry *N*,*N*-dimethylformamide was added at 2–4°, and then a mixture of 6.5 g of 1-(2′,3′-dimethoxyphenyl)-4-hydroxycyclohexanecarbonitrile and 50 ml of *N*,*N*-dimethylformamide was added. To the mixture was added a solution of 6.0 ml of benzyl bromide in 30 ml of *N*,*N*-dimethylformamide at 2–4° over 25 min, and the mixture was stirred at 2–4° for an additional 40 min. The light yellow mixture was gradually warmed to room temperature and stirred for 3.5 hr. The mixture was poured into 250 g of ice–water and the precipitate was collected, washed, and dried *in vacuo*, mp 87–89°. Crystallization from methanol gave 7.8 g (87.8%) of white needles: mp 93–94°; ir 4.47 w; nmr 2.25 (m, 8 H, CH_2), 3.43 (m, 1 H, OCH), 3.87 (s, 3 H, OCH_3), 4.02 (s, 3 H, OCH_3), 4.61 (s, 2 H, $C_6H_5CH_2O$), 6.98 (m, 3 H, Ar H), 7.36 (m, 5 H, C_6H_5).

Anal. Calcd for $C_{22}H_{25}NO_3$: C, 75.19; H, 7.17; N, 3.99. Found: C, 75.22; H, 7.06; N, 3.92.

4-Benzyloxy-1-(2′,3′-dimethoxyphenyl)cyclohexanecarboxaldehyde (18).—To a mixture of 10 ml of dry tetrahydrofuran and 10.7 mg of lithium aluminum hydride were added 0.221 g of 4-benzyloxy-1-(2′,3′-dimethoxyphenyl)cyclohexanecarbonitrile (**16**) and 3 ml of tetrahydrofuran and the reaction mixture was heated at reflux for 5.75 hr. Tlc showed starting material present in an aliquot of the reaction mixture. After an additional 0.010 g of lithium aluminum hydride was added, the mixture was heated at reflux for 3.75 hr. The excess hydride was decomposed with 1 *N* sodium hydroxide, and the tetrahydrofuran was removed *in vacuo*. The residue was partially dissolved in 1 *N* sodium hydroxide and extracted with chloroform. The chloroform extract was washed with ice-cold 1 *N* hydrochloric acid, saturated sodium bicarbonate, and water, dried, and evaporated *in vacuo*, giving 172 mg (76.0%) of a brown oil containing starting material and aldehyde. After the acidic wash solution was made basic and extracted with chloroform, the chloroform extract was evaporated *in vacuo*. The residue was hydrolyzed with 5 ml of 50% acetic acid containing 0.15 ml of concentrated sulfuric acid at 100° for 40 min. The mixture was diluted with water and extracted with chloroform. Evaporation of the washed and dried chloroform gave 0.025 g (11.1%) of an oil. An infrared spectrum shows the oil to be a mixture of aldehyde (5.73 μ) and aldimine (6.03 μ). The extracted hydrolysis solution was made basic and extracted with chloroform. Negligible residue was found in the chloroform extract. The aldehyde was characterized as the 2,4-dinitrophenylhydrazone derivative, which was prepared and isolated from the 0.172 g of the crude material. After repeated recrystallizations from ethanol–water, mp 135–

136° was obtained: ir 3.02, 6.16; nmr 1.77, 2.62 (m, 8 H, CH_2), 3.43 (m, 1 H, CHO), 3.73, 3.78 (s, 6 H, OCH_3), 4.54 (s, 2 H, $C_6H_5CH_2O$), 6.94 (m, 3 H, ArH), 7.25 (s, 5 H, C_6H_5), 7.70, 7.75, 8.14, 8.19 [doublet of doublets, J = 7 or 8 Hz, J = 10 Hz, 3 H, 2,4-$(NO_2)_2$ArH], 10.95 (s, 1 H, C=H).

Anal. Calcd for $C_{28}H_{30}N_4O_7$: C, 62.91; H, 5.66; N, 10.48. Found: C, 62.74; H, 5.74; N, 10.36.

1-(2′,3′-Dimethoxyphenyl)-4-hydroxycyclohexanecarboxaldehyde (19).—A mixture of 0.708 g of lithium aluminum hydride and 300 ml of dry 1,2-dimethoxyethane (glyme) was stirred and cooled to 10° in a system protected from atmospheric moisture and continuously purged with dry nitrogen. To the cold mixture was added a mixture of 5.50 g of 1-(2′,3′-dimethoxyphenyl)-4-oxocyclohexanecarbonitrile (**14**) in 100 ml of glyme over 7 min. A white precipitate formed 15 min after heating was started, and the heterogeneous mixture was heated at reflux for 5 hr. The mixture was cooled to 10°, decomposed with 2.5 N sodium hydroxide, and stirred 30 min at 10°. The supernatant liquid was decanted and evaporated *in vacuo* at 35–40° and the residue dissolved in chloroform. After the chloroform solution was extracted with 400 ml of ice-cold 1 N hydrochloric acid, the washed and dried organic layer was evaporated *in vacuo* giving 2.09 g of an oil.

Residual chloroform in the hydrochloric acid wash layer was removed *in vacuo* at 30–45°, and after the mixture was stored at room temperature overnight, a precipitate was observed in the acidic solution. The acidic mixture was made basic and cooled to 10°, and the white precipitate was collected, washed, and dried, giving 2.89 g (51.7%) of 1-(2′,3′-dimethoxyphenyl)-4-hydroxycyclohexanecarboxaldehyde (**19**), mp 143–146°. The analytical sample crystallized from methylene chloride–ether: mp 141–146°; ir 3.09, 3.71 w, 5.82; nmr, 1.85 (m, 8 H, CH_2), 3.50 (m, 1 H, CHOH), 3.68 and 3.76 (s, CH_3, OCH_3), 6.85 (m, 3 H, Ar H), 9.60 (s, 1 H, CH=O).

Anal. Calcd for $C_{15}H_{20}O_4$: C, 68.16; H, 7.63. Found: C, 68.45; H, 7.84.

After extraction of the basic filtrate with chloroform, the extract was evaporated, and the residue was heated in 300 ml of 50% acetic acid containing 30 drops of concentrated sulfuric acid at 100° for 2 hr. The acidic mixture was diluted with water and extracted with chloroform. The washed and dried extract was evaporated *in vacuo* giving 0.16 g (3.0%) of recrystallized **19**, mp 144–148°.

After the acidic layer was made basic and extracted with chloroform, the washed and dried extract was evaporated giving 0.23 g (4.1%) of crude 4-aminomethyl-4-(2′,3′-dimethoxyphenyl)cyclohexanol (**20**), mp 109–117°. The amine was characterized as its picrate. The analytical sample crystallized from ethanol as yellow needles: mp 204–205°; ir 3.20, 6.12.

Anal. Calcd for $C_{21}H_{26}N_4O_{10}$: C, 51.01; H, 5.30; N, 11.33. Found: C, 51.21; H, 5.44; N, 11.30.

Considerable reduction of the nitrole to the amine was observed when glyme distilled from lithium aluminum hydride was used in the preceding procedure.

1-(2′,3′-Dimethoxyphenyl)-4-acetoxycyclohexanecarboxaldehyde (21).—A mixture of 2.17 g of 1-(2′,3′-dimethoxyphenyl)-4-benzyloxycyclohexanecarboxaldehyde (**18**), 10.8 ml of pyridine, and 3.6 ml of acetic anhydride was stirred at room temperature for 12 hr. The light tan solution was diluted with 36 ml of methanol, stirred for 2 hr, and evaporated *in vacuo* giving 2.44 g (97.3%) of **21**, mp 103–106°. The analytical sample crystallized from methanol: mp 109–111°; ir 3.64 w, 5.79; uv (neutral, acid, and base) 278 (3.43); nmr 1.97 (s, 3 H CH_3CO), 2.02 (m, 8 H, CH_2), 3.67, 3.77 (5,6 H, OCH_3), 4.76 (m, 1 H, $CHOCOCH_3$), 6.82 (m, 3 H, Ar H), 9.55 (s, 1 H, CH=O).

Anal. Calcd for $C_{17}H_{22}O_5$: C, 66.65; H, 7.24. Found: C, 66.49; H, 7.19.

1-(2′,3′-Dimethoxyphenyl)-4-acetoxycyclohexaneacetaldehyde (23).—A suspension of 15.3 g of methoxymethyltriphenylphosphonium chloride[30] and 324 ml of freshly distilled tetrahydrofuran was stirred vigorously in a system previously dried and flushed with dry nitrogen. After the protected mixture was cooled to −10°, 28.3 ml of *n*-butyllithium (1.6 N) was added over 30 min. The deep red mixture was gradually warmed to room temperature and stirred for 2.6 hr. After the deeply colored solution was cooled to −10°, a solution of 5.84 g of 1-(2′,3′-dimethoxyphenyl)-4-acetoxycyclohexanecarboxaldehyde (**21**) in 60 ml of freshly distilled tetrahydrofuran was added over 15 min. The mixture was stirred at −10° for 30 min, room temperature for 8 hr, and at reflux for 5 hr. The cooled solution was evaporated and dried *in vacuo*. The foamy residue was triturated with eight 100-ml portions of dry ether. After the decantate was filtered and washed with water, 0.1 N hydrochloric acid, water, and dried over 4A molecular sieves, the ether was evaporated, giving 8.2 g of a viscous brown mass which contained the partially deacetylated enol-ether. To a stirred solution of 32 ml of dry pyridine and 8.2 g of the crude enol-ether was added 10.5 ml of acetic anhydride at room temperature, and the mixture was stirred overnight. The mixture was diluted with 100 ml of methanol and stirred at room temperature for 2 hr. After removal of the solvents *in vacuo* at 60–80°, the residue was dissolved in ether. The organic layer was washed with water, 0.1 N hydrochloric acid, saturated sodium bicarbonate, and water, and dried over 4A molecular sieves, evaporated, and dried *in vacuo*, giving 7.6 g of crude, fully acetylated enol-ether (**22**). To a column of alumina packed in hexane was added a solution of the crude enol-ether in benzene–hexane, 1:1. The desired product was found in the fractions eluted with benzene–hexane, 1:1, and benzene. After the solvents were removed *in vacuo*, 3.88 g of **22** was obtained as a light yellow oil: ir 5.78, 6.04; nmr 2.05 (s, 3 H, CH_3CO_2–), 3.40 and 3.55 (s, 3 H = $CHOCH_3$), 3.83, 3.85, and 3.99 (s, 6 H, Ar OCH_3), 4.17 and 5.14 (d, J = 7 and 13 Hz, 1 H, =CH–), 5.86 and 6.21 (d, J = 7 and 13 Hz, 1 H, =CH), 6.96 (m, 3 H, Ar H).

To a stirred solution of 3.31 g of enol-ether in 100 ml of ether was added 20 ml of 40% perchloric acid at room temperature, and the solution was heated at reflux for 30 min. The reaction mixture was diluted with water and extracted with ether. After the organic layer was washed with saturated sodium bicarbonate and water and was dried, the ether was evaporated giving 2.75 g (86.0%) of 1-(2′,3′-dimethoxyphenyl)-4-acetoxycyclohexaneacetaldehyde (**23**) as a light yellow viscous oil, which was converted to the acid without purification. The aldehyde was characterized as the 2,4-dinitrophenylhydrazone which crystallized from ethanol: mp 183–184°; ir 3.03, 5.76; nmr 2.07 (s, 3 H, CH_3CO_2, and m, 8 H, CH_2), 3.00 (d, J = 6 Hz, 2 H, CH_2C=N), 3.85 and 3.88 (s, 6 H, OCH_3), 4.73 (m, 1 H, CHO), 7.00 (m, 3 H, Ar H), 7.77 (d, J = 9 Hz, 1 H), 8.20, 8.25 (doublet of doublets, J = 9 Hz, 1 H), 9.00 (d, J = 3 Hz, 1 H), 10.73 (singlet, 1 H, CH=N).

Anal. Calcd for $C_{24}H_{28}N_4O_8$: C, 57.59; H, 5.64; N, 11.19. Found: C, 57.58; H, 5.69; N, 11.18.

1-(2′,3′-Dimethoxyphenyl)-4-acetoxycyclohexaneacetic Acid (24).—To a solution of 2.16 g of 1-(2′,3′-dimethoxyphenyl)cyclohexaneacetaldehyde (**23**) and 150 ml of reagent grade acetone at 10° was added a slight excess of Jones reagent. The mixture was stirred for 5 min, warmed to 15–20°, and stirred for 35 min. After the mixture was diluted with 50 ml of water, 10% aqueous sodium sulfite was added until the yellowish-red color was discharged. The aqueous acetone layer was decanted evaporated *in vacuo* at 30–35° until most of the acetone was removed. The residue was taken up in methylene chloride and then washed with four 25-ml portions of 5% sodium hydroxide, followed by water. After drying, the organic extracts were evaporated and dried *in vacuo* giving 0.88 g (38.2%) of an unidentified viscous yellow oil.

The 5% sodium hydroxide and water wash solutions were combined, back-washed with methylene chloride, acidified at 0° with concentrated hydrochloric acid, and extracted with methylene chloride. The organic extract was washed with water, dried, evaporated, and dried *in vacuo*, giving 0.94 g (41.3%) of partially hydrolyzed crystalline acid, mp 136–160°. The acid was dissolved in 15 ml of dry pyridine, 6 ml of acetic anhydride were added at room temperature, and the solution was stirred at room temperature for 17 hr. After the mixture was hydrolyzed with 1.5 ml of water at 0° for 1 hr, it was evaporated *in vacuo* at room temperature giving an oily brown residue. The residue was dissolved in methylene chloride, and the solution was washed with 1 N hydrochloric acid and water, dried, evaporated, and dried *in vacuo*, giving 1.02 g (49.3%) of **24** as a foamy solid. The foamy mass crystallized from ether–hexane, giving 0.67 g of 1-(2′,3′-dimethoxyphenyl)-4-acetoxycyclohexaneacetic acid as white crystals, mp 114–120°. The analytical sample crystallized from hexane–ether as white needles: mp 121–123°; ir 5.78; nmr 2.07 (s, 3 H, CH_3CO_2), 2.88 (s, 2 H, CH_2CO_2N), 3.87, 3.90 (s, 6 H, OCH_3), 4.83 (m, 1 H, CHO), 6.95 (m, 3 H, Ar H).

Anal. Calcd for $C_{18}H_{24}O_6$: C, 64.27; H, 7.19. Found: C, 64.13; H, 7.25.

(30) G. Wittig and M. Schlosser, *Chem. Ber.*, **94**, 1373 (1961).

Spiro[4-hydroxycyclohexane-1,3′-(4′,5′-dimethoxyindan-1′-one] (12).—To 20 g of polyphosphoric acid was added 0.348 g of pulverized 1-(2′,3′-dimethoxyphenyl)-4-acetoxycyclohexaneacetic acid. After the solid was thoroughly dispersed in the polyphosphoric acid, the mixture was heated in an oil bath at 64–65° for 30 min. The mixture was stirred every 4–5 min and gradually turned a brownish red. The mass was cooled in an ice bath and hydrolyzed with 150 ml of an ice–water slurry. After the mixture was extracted with methylene chloride, the organic layer was washed with water, dried, and evaporated to a viscous residue. The residue was heated at reflux with a mixture of 36 ml of methanol, 12 ml of water, and 4.8 g of potassium hydroxide for 2 hr in a system continuously flushed with nitrogen. After the methanol was removed from the cooled solution *in vacuo*, the aqueous mixture was diluted with 20 ml of water and was extracted with methylene chloride. The washed and dried extract was evaporated and dried *in vacuo*, giving 0.115 g (40.2%) of indanone as a greenish-brown amorphous mass. One crystallization from ether–hexane gave 0.068 g (24.5%) of pure material, mp 166–168°. The analytical sample was obtained by filtration through a column containing 2 g of alumina and elution with benzene–ethyl acetate, 1:1. Recrystallization from ether–hexane gave the analytical sample: mp 167–169°; ir 2.88, 5.78, 6.24, 6.34; uv (neutral) 203 (4.18), 231 (4.24), 281 (4.04); uv (acid) 199 (4.34), 231 (4.24), 281 (4.04); uv (base) 281 (4.04); nmr 1.33–2.50 (m, 8 H, CH_2), 2.62 (s, 2 H, CH_2CO), 3.67, 3.83 (m, 1 H, CHOH), 3.95, 3.98 (s, 6 H, OCH_3), 7.02 (d, J = 9 Hz, 1 H, Ar H), 7.56 (d, J = 9 Hz, 1, H, Ar H).

Anal. Calcd for $C_{16}H_{20}O_4$: C, 69.55; H, 7.30. Found: C, 69.33; H, 7.25.

The aqueous basic layer was acidified and extracted with methylene chloride. The organic extract was washed with water, dried, and evaporated. The residue was dried *in vacuo*, giving 0.116 g (40.6%) of crude lactone (ir 2.91, 5.63) which was not characterized in detail.

(±)-10-Hydroxy-8,9,11,12-tetrahydrostepharine (26).—A mixture of 0.063 g of spiro-4-hydroxycyclohexane-1,3′-(4′,5′-dimethoxyindan-1′-one) (24), 1.1 g of distilled aminoacetal, and 4 ml of dry toluene (excluding the water separator volume) was heated at reflux for 72 hr in a system previously dried and flushed with dry nitrogen. A slight positive nitrogen pressure was maintained during the reaction. The excess reagent and solvent were removed *in vacuo*, and the viscous residue was dried *in vacuo* overnight. After 0.027 g of platinum oxide in 5 ml of absolute ethanol was reduced with hydrogen passed through a Dry Ice condenser, the Schiff base was dissolved in 12 ml of absolute ethanol and added to the prereduced catalyst. The mixture was reduced at room temperature and pressure until the theoretical uptake of hydrogen was observed. Usually, the reduction was completed in 4–6 hr. After the reduction mixture was filtered through a Celite pad, the filtrate was evaporated *in vacuo* at 30–40° to an oily residue. The light brown residue was dissolved in 10–15 ml of dry ether and cooled in an ice bath. The cold ether solution was added to 15 ml of ice-cold 6 N hydrochloric acid, and the mixture was stored at room temperature overnight. After the mixture was extracted with three 5-ml portions of ether, the dissolved ether was removed *in vacuo*, first with a water aspirator, and then with an oil pump connected to two sets of Dry Ice and sodium hydroxide traps. When the volume had been reduced to approximately 10 ml, 10 ml of 1:1 ethanol–concentrated hydrochloric acid was added. To this solution was added 0.077 g of 5% palladium on charcoal, and reduction was carried out at room temperature and pressure. Reduction was stopped when the theoretical uptake of hydrogen was observed (6 hr). After the reaction mixture was filtered through a Celite pad, the filtrate was concentrated *in vacuo* at room temperature. The concentrated solution was diluted with 10–20 ml of water, cooled to 0°, and made basic with concentrated sodium hydroxide. The basic solution was extracted with methylene chloride. After the methylene chloride was washed with water, dried over anhydrous sodium sulfate, and evaporated, the residue was dried *in vacuo* giving 0.055 g (81.2%) of **26** as a light yellow foam: mp 30–66°; ir 2.95; nmr (CD_3CN) 1.35–2.00 [m, 8 H, (CH_2)], 2.70 (m, 6 H, $ArCH_2CH_2N$ and CH_2CHN), 3.58–3.75 (m, 1 H, CHOH), 3.80 (s, 6 H, OCH_3), 4.12 (t, J = 7 Hz, 1 H, CH_2CHN), 6.77 (s, 1 H, Ar H). Tlc showed two minor spots in addition to one major component.

Attempts were made to purify a portion of the free base or hydrochloride for analysis but were unsuccessful. Tlc showed two or three spots still present in the free base after chromatography.

(±)-10-Hydroxy-8,9,11,12-tetrahydropronuciferine (27).—To a mixture of 0.030 g of 10-hydroxy-8,9,11,12-tetrahydrostepharine (26), 1.2 ml of chloroform, and 0.2 ml of dry pyridine at 0° was carefully added 0.14 ml of ethyl chloroformate in a system protected from atmospheric moisture. The mixture was heated at reflux on a steam bath for 5 min and evaporated to a viscous residue. After the residue was dissolved in methylene chloride, the organic solution was washed with 10% hydrochloric acid, 10% sodium bicarbonate, and water, and dried over anhydrous sodium sulfate. Evaporation of the solvent gave 0.039 g (95.1%) of red residue.

To a slurry of 0.050 g of lithium aluminum hydride in 1.5 ml of tetrahydrofuran (freshly distilled from lithium aluminum hydride) at 0° was added the crude amide dissolved in 1.5 ml of dry tetrahydrofuran.

After the mixture was heated at reflux for 2 hr, it was cooled to 0°, and the excess hydride was destroyed at 0° with 10% sodium hydroxide. The granular mixture was filtered and washed with tetrahydrofuran. After the tetrahydrofuran was removed *in vacuo*, at 35–50°, the residue was dissolved in methylene chloride, and the solution was washed with water and dried over anhydrous sodium sulfate. The solvent was removed and the residue dried *in vacuo*, giving 0.020 mg (64.7%) of **27** as a foamy solid, mp 48–58°. Tlc showed a mixture of four components. The mixture, 0.017 g, was purified by column chromatography on 3.3 g of Biorad neutral alumina (activity II). The product was eluted from the column with a 2% methanol–ether solution. After 7 ml was collected in six fractions, the remaining 100 fractions were collected in 0.2-ml portions. Tlc was used to monitor the elution products. From fractions 16–56 was obtained 0.0055 g of **27**. An infrared spectrum of this material was identical with that of Bernauer's sample of the free base (hydroxyl, 2.95 μ).[5,24] The R_f value on tlc was identical with the R_f value of Bernauer's sample; however, there was a trace of a faster moving component present which had an R_f value identical with that of the 10 epimer of **41** (**42**). Fractions 26–56 (0.00238) were converted to the hydrochloride and recrystallized twice from methanol–ether, mp 209–219° dec, mmp with Bernauer's sample 203–214°. The decomposition point of this compound is indefinite at best and appears to be a function of the rate of heating. The material prepared in this work was not obtained in sufficient quantity to permit exhaustive purification of the base hydrochloride. An infrared spectrum of the hydrochloride (hydroxyl, 2.95 μ), was identical with that of Bernauer's sample of (±)-10-hydroxy-8,9,11,12-tetrahydropronuciferine hydrochloride.[5,24]

Registry No.—**5**, 26709-68-2; **5** picrate, 26679-48-3; **7**, 26709-69-3; **8**, 26709-70-6; **9**, 26709-71-7; **9** amide, 26709-72-8; **10**, 26709-73-9; **11**, 26697-49-4; **11** HCl, 26697-50-7; **12**, 26681-39-0; **14**, 26709-74-0; **15**, 26681-40-3; **16**, 26686-05-5; **18** 2,4-DNP, 26686-06-6; **19**, 26686-07-7; **20**, 26681-41-4; **20** picrate, 26681-42-5; **21**, 26681-43-6; **22**, 26681-44-7; **23**, 26681-45-8; **24**, 26681-46-9; **26**, 26681-47-0; **27**, 25926-57-2; 4,5-dimethoxy-1-indanone, 6342-80-9; cyclohexylidenebis(2-methoxyphenyl)carbinol, 26709-76-2; 2,3-dimethoxyphenylacetonitrile, 4468-57-9; dimethyl 4-cyano-4-(2′,3′-dimethoxyphenyl)pimelate, 26709-78-4; methyl 5-cyano-5-(2′,3′-dimethoxyphenyl)-2-oxocyclohexenecarboxylate, 26709-79-5; **23** 2,4-DNP, 26686-09-9.