yield 60% of the theoretical amount of the cyclic silylamide, mp 140–145° dec. The major by-products were bis(acetamido)diphenylsilane and cyclic diphenylsiloxanes. These by-products predominated when procedure A was used or when the reaction was run without external cooling.

Dimethylbis(2,6-diphenylphenoxy)silane. A solution of 115 mg (0.5 mmol) of cyclobis(acetamidodimethylsilane) and 500 mg (2 mmol) of 2,6-diphenylphenol in 2 cc of dry pyridine was prepared. The nmr spectrum of the solution after 30 min at room temperature showed no indication of the original signals (acetyl absorptions at δ 2.12 and 2.16 ppm; CH_3–Si absorptions at 0.46 and 0.52 ppm); instead, two new signals had arisen at 1.64 and −0.03 ppm (upfield of TMS), respectively, presumably due to dimethyl(2,6-diphenylphenoxy)acetamidosilane. These signals disappeared on heating at 100° overnight and two new absorptions formed at 2.03 ppm (acetamide) and −1.05 ppm. On cooling, colorless crystals formed, mp 156–157° after recrystallization from benzene–ethanol. The compound in deuteriochloroform solution has a CH_3–Si signal 79 cps upfield of tetramethylsilane.

Anal. Calcd for $C_{38}H_{32}O_2Si$: C, 83.1; H, 5.9; Si, 5.1; mol wt, 549. Found: C, 83.4; H, 6.2; Si, 5.2; mol wt, 536.

Acknowledgment. The author is indebted to Dr. J. B. Bush, Jr., for many helpful discussions.

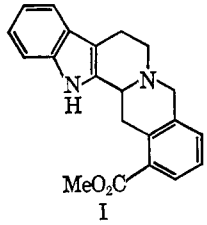
General Methods of Synthesis of Indole Alkaloids. VII. Syntheses of *dl*-Dihydrogambirtannine and Aspidosperma–Strychnos Alkaloid Models[1,2]

Ernest Wenkert, K. G. Dave, C. T. Gnewuch, and P. W. Sprague

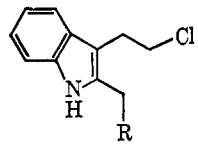
Contribution from the Department of Chemistry, Indiana University, Bloomington, Indiana 47401. *Received March 28, 1968*

Abstract: The synthesis of dimethyl isoquinoline-4,5-dicarboxylate and its four-step conversion into the indole alkaloid dihydrogambirtannine are reported. The preparation of methyl 3-(β-chloroethyl)-2-indoleacetate, its N-alkylation of several β-acylpyridines, and hydrogenation of the salts are described. The use of the resultant 2-piperideines and related 2-methylindole compounds in a study of the rarely observed β-indole cyclization process and the synthesis of Aspidosperma and Strychnos alkaloid models are portrayed.

In continuation of our studies of the synthesis of indole alkaloids by the scheme of hydrogenation and cyclization of 1-alkyl-3-acylpyridinium salts[2] syntheses of dihydrogambirtannine (I) and of tetracyclic models of the Aspidosperma and Strychnos alkaloids were undertaken. This exercise was devised principally to determine whether the synthesis scheme was applicable to the 4-acylisoquinoline area and to β-indole cyclization, all cyclizations heretofore having been of the α-indole type.

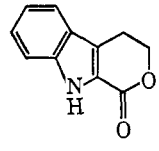


I

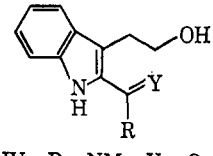


IIa, R = CN
b, R = CO_2Me

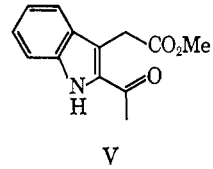
The latter problem required the preparation of methyl 3-(β-chloroethyl)-2-indoleacetate (IIb) which was accomplished by two routes of synthesis. One, reminiscent of the mode of preparation of 2-indoleacetic ester,[3] involved the following reaction sequence: (a) treatment of lactone III[4] with dimethylamine, (b) lithium aluminum hydride reduction of the resultant amide IVa, (c) methylation of the amine IVb, (d) cyanide displacement of the salt IVc, and (e) treatment of the resultant nitrile IVd with methanolic hydrochloric acid. A second route involved (a) lithium aluminum hydride reduction of methyl 2-acetyl-3-indoleacetate (V),[5,6] (b) manganese dioxide oxidation of the diol IVe, (c) Willgerodt rearrangement of the ketone IVf, (d) consecutive treatments of the hydroxyamide IVg with acetic anhydride, phosphorus oxychloride and aqueous base, and (e), as before, exposure of the resultant hydroxynitrile IVd to methanolic hydrochloric acid.



III



IVa, R = NMe_2; Y = O
b, R = NMe_2; Y = H_2
c, R = N^+Me_3; Y = H_2
d, R = CN; Y = H_2
e, R = Me; Y = HOH
f, R = Me; Y = O
g, R = $CONH_2$; Y = H_2

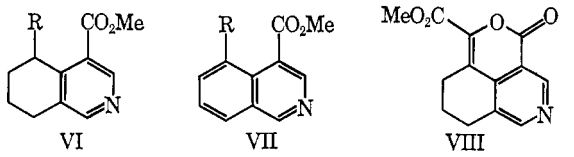


V

Dihydrogambirtannine (I). This alkaloid is one of several yohimboid constituents of the tanning material gambir, isolated from *Uncaria gambier* Roxb.,[7,8] as

(1) This work was supported by the U. S. Department of Health, Education and Welfare (grant GM-11571).
(2) Part VI: E. Wenkert, K. G. Dave, R. G. Lewis, and P. W. Sprague, *J. Am. Chem. Soc.*, **89**, 6741 (1967).
(3) W. Schindler, *Helv. Chim. Acta*, **40**, 2156 (1957).
(4) H. Plieninger, *Chem. Ber.*, **83**, 271 (1950).
(5) H. Plieninger, W. Müller, and K. Weinerth, *Chem. Ber.*, **97**, 667 (1964).
(6) This reaction was carried out first by Dr. L. D. Antonaccio.
(7) L. Merlini, R. Mondelli, G. Nasini, and M. Hesse, *Tetrahedron*, **23**, 3129 (1967), and references cited therein.
(8) L. Merlini and G. Nasini, *Gazz. Chim. Ital.*, **97**, 1915 (1967), reported the synthesis of oxogambirtannine, a relative of I.

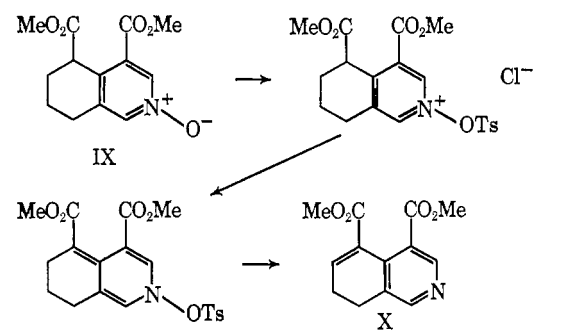
well as coincidentally the enantiomer of a product of degradation of the natural base deserpideine.[9] In analogy with the recent conversions of methyl 5,6,7,8-tetrahydroisoquinoline-4-carboxylate (VIa) into *dl*-epialloyohimbane[10] and of methyl 4-methyl-5-ethylnicotinate into *dl*-corynantheidol[10] and *dl*-corynantheidine[2] a simple route to dihydrogambirtannine (I) from dimethyl isoquinoline-4,5-dicarboxylate (VIIb) could be envisaged. Since heretofore no isoquinoline derivative had been empolyed in the hydrogenation–cyclization scheme of indole alkaloid synthesis,[2,10-12] the construction of the gambir alkaloid I by this method held special attraction.



VI VII VIII

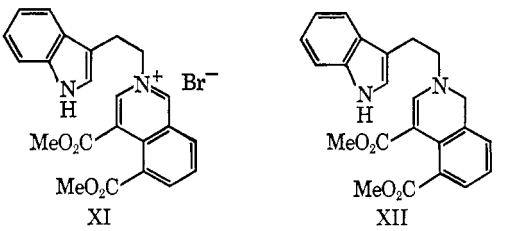
a, R = H
b, R = CO_2Me

Base-induced condensation of VIa with dimethyl oxalate[10] yielded a salt whose acidification led to the lactone ester VIII. However, treatment of the diester salt with alkaline hydrogen peroxide, followed by esterification with methanolic hydrogen chloride gave the diester VIb. Since catalytic dehydrogenation of the latter proved difficult, the pyridine derivative VIb was oxidized to the isoquinoline diester VIIb by consecutive treatments with N-bromosuccinimide and with collidine.[13] Alternatively, VIIb could be prepared from the dihydroisoquinoline X, a compound needed for the synthesis of complex yohimboid alkaloids. In contrast to the behavior of pyridines VI, substance X underwent facile palladium-catalyzed dehydrogenation. Its synthesis involved the oxidation of VIb with *m*-chloroperbenzoic acid and treatment of the resultant N-oxide (IX) with *p*-toluenesulfonyl chloride in pyridine under heating. The following represents the probable reaction sequence in the transformation of the amine oxide into X.



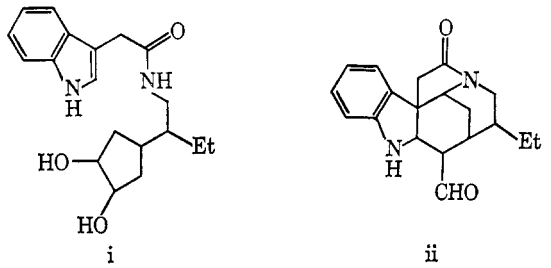
IX X

Alkylation of the isoquinoline derivative VIIb with tryptophyl bromide and palladium-catalyzed hydrogenation of the resultant salt XI produced a dihydroisoquinoline (XII). Thus in the isoquinoline as in the pyridine series N-alkyl-β-acyl compounds are hydrogenated to the oxidation level in which the stable vinylogous amide moiety is unmasked. Heating of XII with aqueous alkali, a reaction known from previous experience[2,10] to cause hydrolysis, decarboxylation, and cyclization, led to *dl*-dihydrogambirtannine (I).

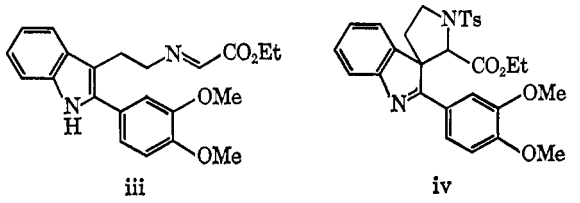


XI XII

Aspidosperma–Strychnos Alkaloid Models. The synthesis as well as possibly biosynthesis of the majority of indole alkaloids of the tetrahydrocarboline structure type incorporate as crucial step the Pictet–Spengler cyclization represented by the transformation of the immonium salt XIII into the tetracycle XIV (*e.g.*, XII → I). Even though the alternate mode of cyclization, XIII → XV, might be expected to be preferred in view of the high nucleophilicity of the β site of the indole ring, and while according to early views it constituted a step on route of the biosynthesis of the Strychnos alkaloids,[14] no simple examples of this reaction are on record.[15] Recently this void has been interpreted in terms of the instability of indolenines (XV) and their facile rearrangements to indoles (XIV).[16] Since the formation of tetrahydrocarbolines (XIV) from α-substituted indole equivalents of XIII is precluded, the latter are ideal substrates for the study of cyclizations of the XIII → XV type.[17] In view of the



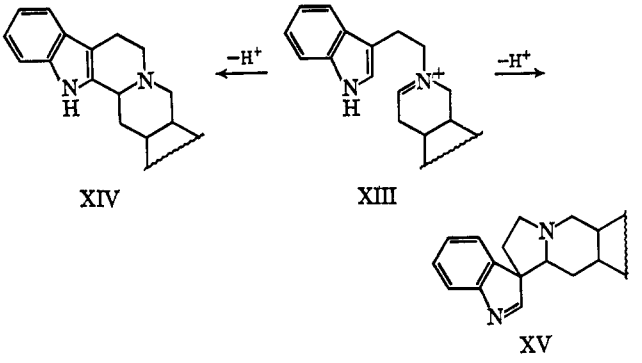
i ii



iii iv

(9) E. Smith, R. S. Jaret, R. J. Shine, and M. Shamma, *J. Am. Chem. Soc.*, **89**, 2469 (1967).
(10) E. Wenkert, K. G. Dave, and F. Haglid, *ibid.*, **87**, 5461 (1965).
(11) E. Wenkert and B. Wickberg, *ibid.*, **87**, 1580, 5810 (1965).
(12) E. Wenkert, K. G. Dave, F. Haglid, R. G. Lewis, T. Oishi, R. V. Stevens, and M. Terashima, *J. Org. Chem.*, **33**, 747 (1968).
(13) This oxidative procedure was first applied to the conversion of VIa into methyl isoquinoline-4-carboxylate (VIIa) (see Experimental Section). Substance VIa also was quite resistant to catalytic dehydrogenation.
(14) R. Robinson, "The Structural Relations of Natural Products," Oxford University Press, Oxford, England, 1955.
(15) The sole case of β-cyclization of an α-unsubstituted indole is the conversion of i into ii on periodate oxidation [E. E. van Tamelen, L. J. Dolby, and R. G. Lawton, *Tetrahedron Letters*, No. **19**, 30 (1960)]. Rigorous proof of the structure of the product and reasons for the success of this fascinating reaction will have to await disclosure of the details of this observation.
(16) (a) A. H. Jackson and A. E. Smith, *Tetrahedron*, **24**, 403 (1968); (b) A. H. Jackson and P. Smith, *ibid.*, **24**, 2227 (1968).
(17) The lone example of β-cyclization of an innocuously β-substituted indole is the transformation of iii into iv on treatment with *p*-toluenesulfonyl chloride in pyridine [R. B. Woodward, M. P. Cava, W. D. Ollis, A. Hunger, H. U. Daeniker, and K. Schenker, *ibid.*, **19**, 247 (1963)]. The oxidative cyclizations of dihydroclevamine and related compounds [J. P. Kutney and E. Piers, *J. Am. Chem. Soc.*, **86**, 953 (1964), and subsequent publications] illustrate double-ring formations through the interactions of 1-piperideinium salt moieties held in close proximity to indole rings by α and β two-carbon bridges.

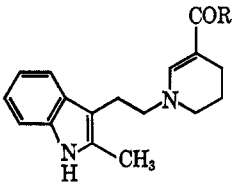
availability of direct precursors of proper derivatives of XIII[12] a study of the β-indole cyclization was undertaken.



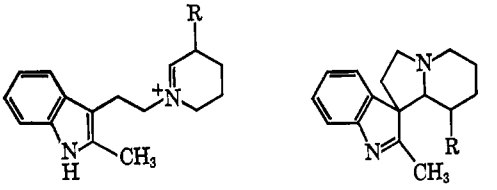
XIV XIII XV

The interaction of acid with the tetrahydropyridines XVI whose preparation was described recently[12] was investigated. Exposure of XVIa or XVIb to mineral acid under a variety of conditions led to tar or recovery of starting material. This result was anticipated in view of the stability of the intermediate conjugate acids, the O-protonated forms of the vinylogous amides derived from aldehydes or ketones,[12] hence their low reactivity and their probable preference at equilibrium (XIII ⇄ XV under forcing conditions). Treatment of XVIc with acid under conditions which in an α-unsubstituted indole case had led to decarbalkoxylated tetracycle[10] yielded intractable material and some decarboalkoxylated dimer which was not investigated further.[18] Thus the intermediate 1-alkyl-1-piperideinium salt XVIIa, unencumbered by a 3-acyl substituent, underwent external condensation more rapidly than intramolecular cyclization to XVIIIa or, more likely, an equilibrium between the two species resulted in the slow removal of the acyclic form through decomposition. Finally, treatment of the methyl ester XVId with hydrobromic acid gave a material whose spectral properties indicated the presence of the desired product XVIIIb. Since despite much effort the latter could not be isolated, the material was reduced with sodium borohydride. This procedure afforded starting compound XVId, some piperidine XIX, the product of reduction of XVIIb, and XXa, the product of reduction of the desired tetracycle XVIIIb. Acetylation of the indoline yielded XXb. The ester XVId thus possessed all the structural features necessary for successful β-indole cyclization: (a) an α-indole blocking group; (b) a vinylogous amide unit which in acid medium undergoes C-protonation;[12] (c) an acyl side chain which protects the intermediate N-alkylpiperideinium salt XVIIb from dimerization or polymerization while destabilizing the immonium moiety and thus facilitating cyclization.

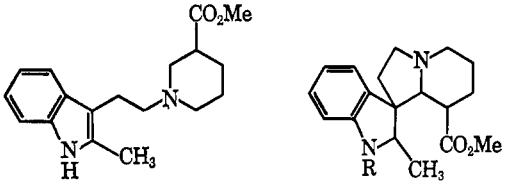
Stereochemistry and functional groups permitting, compounds of structure type XVIII appeared ideally suited for conversion into pentacyclic systems characteristic of Aspidosperma alkaloids, *e.g.*, vincadifformine (XXI). However, for such purpose more appropriate side chains were needed. For this reason the synthesis of a compound related to XVIII was undertaken. Treatment of methyl nicotinate with the



XVIa, R = H
b, R = Me
c, R = O-*t*-Bu
d, R = OMe

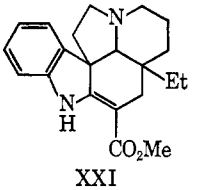


XVII XVIII
a, R = H
b, R = CO_2Me

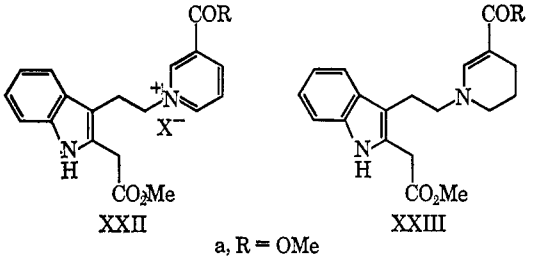


XIX XXa, R = H
b, R = Ac

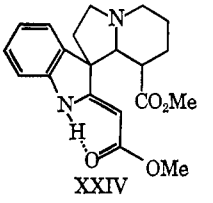
chloro ester IIb produced a salt (XXIIa) whose hydrogenation yielded the tetrahydropyridine XXIIIa. Exposure of the latter to methanolic hydrochloric acid led to the tetracyclic substance XXIV.[19] This cyclization was striking in its high speed, selectivity, and yield. While the stereochemistry of the product has not been determined, it probably is such as to make the



XXI



XXII XXIII
a, R = OMe
b, R = O-*t*-Bu
c, R = Me



XXIV

(18) This reaction was carried out first by Dr. F. Haglid. Preliminary data suggested the dimer to be of the hydroanabasine type, one formed by the self-condensation of 1-piperidines.[10]

(19) A similar series of reactions starting with *t*-butyl nicotinate and the preparation of β-acetylpyridine derivatives are described in the Experimental Section.

ester side chains quite distant from each other thus preventing their interaction in a cyclization leading to the Aspidosperma alkaloid nucleus. The anomalously high-field methyl signals in the proton magnetic resonance spectra of the carbomethoxypiperidines XXa, XXb, and XXIV show that the ester functions of these compounds are proximate to the high electron density of a π-bond system.[20] Since this implies juxtaposition of the ester groups and the benzene rings in the compounds XX, derived from the cyclization product XVIIIb, it may be assumed by analogy that a similar stereochemical relationship exists in the cyclization product XXIV. In view of the latter constituting a product of kinetic control it will be of interest to investigate its equilibration.

Experimental Section

Melting points were determined on a Reichert micro hot stage and are uncorrected. Unless otherwise stated, proton magnetic resonance spectra of deuteriochloroform solutions with tetramethylsilane acting as internal standard were recorded on a Varian A-60 spectrometer. Neutral alumina of activity IV was used for chromatography. Silica gel G was used for thin layer chromatography.

2-Dimethylaminomethyltryptophol (IVb). A solution of 40.0 g of 2-carboxytryptophol lactone (III)[4] in 800 ml of absolute methanol saturated with anhydrous dimethylamine gas was kept stirring at room temperature for 7 days. (Completion of the reaction was checked by infrared spectral analysis of the solutes of aliquots of the solution.) Removal of the solvent under vacuum, washing of the residue with ether, and crystallization from benzene yielded 38.6 g of amide IVa, mp 125–126°; infrared spectrum (Nujol) OH, NH 3.17 (s, broad), C=O 6.28 (s) μ. No satisfactory elemental analysis could be obtained. Sublimation converted the substance into starting lactone, mp and mmp 199–200°.

A solution of 27.0 g of hydroxyamide IVa in 350 ml of freshly distilled tetrahydrofuran was added slowly to a stirring suspension of 22.0 g of lithium aluminum hydride in 500 ml of tetrahydrofuran at 0°. The stirring mixture was refluxed for 12 hr and then treated with a moist sodium sulfate slurry. The salts were filtered and washed with hot ethyl acetate. Evaporation of the combined filtrates and crystallization of the residue from ethyl acetate gave 19.1 g of the amino alcohol IVb, mp 138–140°; spectra: [infrared (Nujol)] OH, NH 3.14 (s) μ; (pmr) six-proton singlet 2.18 (NMe_2), two-proton multiplets 3.05, 3.83 (β-indolylmethylene and oxymethylene, respectively), and a two-proton singlet 3.46 ppm (α-indolylmethylene).

Anal. Calcd for $C_{13}H_{18}ON_2$: C, 71.53; H, 8.31; N, 12.83. Found: C, 71.76; H, 8.28; N, 12.88.

The amino alcohol IVb, 18.5 g, was dissolved in 550 ml of hot ethyl acetate and the solution cooled to room temperature. A solution of 14.7 g of methyl iodide in 50 ml of ethyl acetate was added and the mixture kept at 50° for 1 hr and then cooled in an ice bath. The precipitate was filtered, washed with ether, and dried. Crystallization from ethanol yielded 27.8 g of methiodide IVc, mp 163–165° dec; infrared spectrum (Nujol) OH, NH 2.95 (s) and 3.08 (s) μ.

Anal. Calcd for $C_{14}H_{21}ON_2I$: C, 46.67; H, 5.88; N, 7.78. Found: C, 46.18; H, 5.84; N, 8.26.

2-(α-Hydroxyethyl)tryptophol (IVe). A mixture of 4.0 g of keto ester V[5] and 3.8 g of lithium aluminum hydride in 80 ml of tetrahydrofuran was stirred and refluxed for 3 hr. Ethyl acetate and moist sodium sulfate slurry were added, and the suspension was filtered through Super-Cel. The solid cake was washed with hot ethyl acetate, and the combined filtrates were evaporated. Crystallization of the residue, 3.2 g, from chloroform afforded crystalline diol IVe, mp 124–125°.

Anal. Calcd for $C_{12}H_{15}O_2N$: C, 70.22; H, 7.37; N, 6.82. Found: C, 70.37; H, 7.47; N, 6.70.

2-Acetyltryptophol (IVf). A mixture of 300 mg of diol IVe and 3.5 g of manganese oxide B in 100 ml of chloroform was stirred at room temperature for 18 hr. The suspension was filtered and the precipitate washed with hot chloroform. The combined filtrates were evaporated. Crystallization of the residue from benzene yielded 220 mg of ketol IVf, mp 132–133°; spectra: [infrared (Nujol)] OH, NH 2.99 (s), 3.05 (s), and C=O 6.10 (s) μ; (pmr) three-proton singlet 2.62 (Me) and two-proton multiplets *ca.* 3.3 and 3.83 ppm (β-indolylmethylene and oxymethylene, respectively).

Anal. Calcd for $C_{12}H_{13}O_2N$: C, 70.92; H, 6.45; N, 6.89. Found: C, 71.21; H, 6.48; N, 6.94.

3-(β-Hydroxyethyl)-2-indoleacetamide (IVg). A mixture of 200 mg of ketol IVf, 320 mg of sublimed sulfur, and 0.4 ml of ammonium hydroxide in 2 ml of freshly distilled dioxane was shaken in a sealed tube at 120° for 18 hr. The red-orange reaction mixture was poured onto ice and taken to dryness under vacuum. The residue was extracted with hot water and the extract concentrated under reduced pressure. Crystallization of the remaining solid from ethyl acetate produced 95 mg of hydroxyamide IVg, mp 180–182°; infrared spectrum (Nujol) OH 2.80 (m), NH 2.95, and 3.12 (s), C=O 5.96 (s), and 6.13 (m) μ.

Anal. Calcd for $C_{12}H_{14}O_2N_2$: C, 66.03; H, 6.46; N, 12.84. Found: C, 65.86; H, 6.33; N, 13.02.

2-Cyanomethyltryptophol (IVd). a. A mixture of 20.0 g of salt IVc and 14.5 g of anhydrous potassium cyanide in 750 ml of acetonitrile, distilled from phosphorus pentoxide, was stirred and refluxed under nitrogen until the evolution of trimethylamine had ceased (*ca.* 18 hr). The cooled mixture was filtered; the precipitate was washed with methylene chloride, and the combined filtrates were evaporated. A benzene solution of the residue was filtered through a short alumina column and taken to dryness. Crystallization of the residual solid from benzene produced 8.6 g of cyanoalcohol IVd, mp 108–109°; spectra: [infrared (Nujol)] OH 2.77 (m), NH 3.00 (s), C≡N 4.41 (m), and C=C 6.15 (w) μ; (pmr) two-proton multiplets 2.93 and 3.80 (β-indolylmethylene and oxymethylene, respectively) and a two-proton singlet 3.82 ppm (α-indolylmethylene).

Anal. Calcd for $C_{12}H_{12}ON_2$: C, 71.97; H, 6.04; N, 13.99. Found: C, 71.73; H, 6.04; N, 13.99.

b. A suspension of 90 mg of the hydroxyamide IVg and 10 mg of sodium acetate in 2 ml of acetic anhydride was stirred at room temperature for 12 hr. The clear solution was evaporated under vacuum and the residue washed with a saturated solution of sodium bicarbonate and extracted with chloroform. The extract was dried over sodium sulfate and evaporated. Crystallization of the residue from ether yielded 85 mg of IVg acetate, mp 123–126°; spectra: [infrared (Nujol)] NH 2.94 (s), 3.05 (s), C=O 5.80 (s), 5.95(s), and 6.13 (m) μ; (pmr) a three-proton singlet 1.98 (Me), two-proton triplets 3.02 (J = 7.0 cps), 4.26 (J = 7.0 cps) (β-indolylmethylene and oxymethylene, respectively), and a two-proton singlet 3.68 ppm (α-indolylmethylene). A mixture of 80 mg of the latter and 100 mg of phosphorus trichloride in anhydrous chloroform was refluxed with stirring under nitrogen for 18 hr. The mixture was evaporated and treated with ice and the suspension basified with 20% sodium hydroxide and stirred for 2 hr. Dry Ice was added and the mixture extracted with chloroform. The extract was dried and evaporated. Crystallization of the residue from benzene yielded 45 mg of IVd, mp 108–109°; spectra identical with those of the above sample; pmr spectrum (deuterioacetone): two-proton triplets 2.99 (J = 7.0 cps), 3.77 (J = 7.0 cps) (β-indolylmethylene and oxymethylene, respectively), and a two-proton singlet 4.10 ppm (α-indolylmethylene).

Methyl 3-(β-Chloroethyl)-2-indoleacetate (IIb). An ice-cold solution of 5.0 g of hydroxynitrile IVd and 1 ml of water in 100 ml of methanol was saturated with hydrogen chloride gas. After stirring at room temperature for 48 hr the solution was taken to dryness under vacuum and the residue treated with saturated sodium bicarbonate solution and extracted with methylene chloride. The extract was washed with water and dried over anhydrous potassium carbonate. The solvent was removed, and a cyclohexane solution of the residual oil was chromatographed on alumina. Elution with cyclohexane–benzene and crystallization from cyclohexane afforded 4.2 g of chloro ester IIb, mp 61–62°; spectra: [infrared (Nujol)] NH 2.92 (s) and C=O 5.78 (s) μ; (pmr) two-proton triplets 3.18 (J = 7.0 cps), 3.70 (J = 7.0 cps) (β-indolylmethylene and chloromethylene, respectively), three-proton singlet 3.72 (OMe), and a two-proton singlet 3.80 ppm (α-indolylmethylene).[21]

(20) E. Wenkert, A. Afonso, P. Beak, R. W. J. Carney, P. W. Jeffs, and J. D. McChesney, *J. Org. Chem.*, **30**, 713 (1965); M. P. Cava, S. K. Talapatra, J. A. Weisbach, B. Douglas, and G. O. Dublek, *Tetrahedron Letters*, 53 (1963).

(21) An alternate preparation of IIb involved the conversion of the hydroxynitrile IVd to the chloronitrile IIa [mp 122–124°; spectra: infrared (Nujol), NH 3.00 (s) and C≡N 4.45 (m) μ; pmr (deuterioacetone), two-proton triplets 3.26 (J = 7.0 cps), 3.80 (J = 7.0 cps) (β-indolylmethylene and chloromethylene, respectively), and a two-proton singlet [4.16 ppm (α-indolylmethylene)] with phosphorus trichloride in toluene and methanolysis of IIa by the above procedure.

Anal. Calcd for $C_{13}H_{14}O_2NCl$: C, 61.90; H, 5.55; N, 5.55. Found: C, 61.70; H, 5.68; N, 5.54.

Lactone VIII. A mixture of potassium *t*-butoxide (from 364 mg of potassium), 478 mg of the ester VIa,[10] and 443 mg of dimethyl oxalate in 3 ml of *t*-butyl alcohol was stirred under nitrogen at room temperature for 4 hr. Anhydrous ether, 50 ml, was added and the precipitate filtered under nitrogen and washed with ether. The dry solid was added to 25 ml of cold concentrated hydrochloric acid. After the solution had cleared, its pH was adjusted to 5 by the addition of base. The mixture was extracted with methylene chloride and the extract dried over sodium sulfate and evaporated. Crystallization of the residue from hexane gave 222 mg of lactone VIII, mp 148°; infrared spectrum (Nujol) C=O 5.73 (s), 5.80 (s), C=C 6.30 (m), and 6.45 (m) μ.

Anal. Calcd for $C_{13}H_{11}O_4N$: C, 63.67; H, 4.52; N, 5.71. Found: C, 63.99; H, 4.58; N, 5.89.

Dimethyl 5,6,7,8-Tetrahydroisoquinoline-4,5-dicarboxylate (VIb). A mixture of potassium *t*-butoxide (from 272 mg of potassium), 1.00 g of ester VIa,[10] and 936 mg of dimethyl oxalate in 15 ml of *t*-butyl alcohol was stirred at room temperature under nitrogen for 8 hr. The mixture was poured into 200 ml of anhydrous ether and the precipitated salt filtered and washed with ether. The combined filtrates were evaporated, and the residue was extracted with methylene chloride. The extract was washed with water, dried over anhydrous potassium carbonate, and evaporated. The residual oil, 180 mg, was identified as a mixture of starting material VIa and its *t*-butyl ester analog by infrared and pmr analyses. A solution of the above salt precipitate and 1.0 g of potassium hydroxide in 30 ml of water was stirred at room temperature for 4 hr, then cooled in an ice bath and treated with 3 ml of 30% hydrogen peroxide at three equal intervals over a 12-hr period. The solution was evaporated by freeze drying and the residue treated with 75 ml of methanol saturated with hydrogen chloride gas. The solution was stirred at room temperature for 2 days and then poured slowly into a stirring suspension of excess sodium bicarbonate in methylene chloride. The inorganic salts were filtered and the filtrate dried over potassium carbonate and evaporated. Chromatography of the residue on alumina and elution with hexane produced 250 mg of solid whose crystallization from hexane yielded the diester VIb, mp 115–116°, spectra: [infrared (Nujol)] C=O 5.75 (s), and 5.82 (s) μ; (pmr) two-proton multiplet 2.83 [C(8) hydrogens] three-proton singlets 3.67 [OMe of C(5) ester], 3.83 [OMe of C(4) ester], one-proton triplet 4.50 (J = 5.5 cps) [C(5)–H], and one-proton singlets 8.52 [C(1)–H] and 8.98 ppm [C(3)–H].

Anal. Calcd for $C_{13}H_{15}O_4N$: C, 62.64; H, 6.07; N, 5.62. Found: C, 62.91; H, 6.23; N, 5.78.

Methyl Isoquinoline-4-carboxylate (VIIa). A mixture of 1.90 g of ester VIa and 3.60 g of N-bromosuccinimide in 75 ml of carbon tetrachloride was refluxed with stirring for 4 hr. Succinimide was filtered and washed with carbon tetrachloride. The combined solutions were evaporated, and the residue was extracted with chloroform. The extract was washed with ice-cold 5% sodium hydroxide solution and with water and evaporated. The residue crystallized on standing but was dissolved in 10 ml of collidine without purification. The solution was refluxed with stirring for 4 hr, then diluted with chloroform and washed with ice-cold 5% sodium hydroxide solution and with water. It was dried over potassium carbonate and evaporated under vacuum. Sublimation of the residue at 65–70° (0.05 mm) yielded 1.25 g of ester VIIa, mp 82° (lit.[22] mp 81°); spectra: [infrared (Nujol)] C=O 5.81 (s) μ; (pmr) three-proton singlet 3.98 ppm (OMe).

Anal. Calcd for $C_{11}H_9O_2N$: C, 70.58; H, 4.81; N, 7.48. Found: C, 70.56; H, 4.96; N, 7.57.

Dimethyl 5,6,7,8-Tetrahydroisoquinoline-4,5-dicarboxylate Oxide (IX). A solution of 157 mg of diester VIb and 142 mg of 80% *m*-chloroperbenzoic acid in 30 ml of methylene chloride was kept at room temperature for 3 days. The solution was washed with 10% sodium bicarbonate solution and with water, dried over sodium sulfate, and evaporated. Crystallization of the residual oil from benzene–hexane afforded 120 mg of N-oxide IX, mp 119–120°; spectra: [infrared (Nujol)] C=O 5.79 (s) and C=C 6.24 (m) μ; (pmr) two-proton multiplet 2.78 [C(8) hydrogens], three-proton singlets 3.70 and 3.88 (methoxyls), one-proton broad triplet 4.46 (J = 5.0 cps) [C(5)–H], and one-proton multiplets 8.12 [C(1)–H] and 8.56 ppm [C(3)–H].

Anal. Calcd for $C_{13}H_{15}O_5N$: C, 58.86; H, 5.70; N, 5.28. Found: C, 58.99; H, 5.74; N, 5.52.

(22) F. T. Tyson, *J. Am. Chem. Soc.*, **61**, 183 (1939).

Dimethyl 7,8-Dihydroisoquinoline-4,5-dicarboxylate (X). A mixture of 274 mg of N-oxide IX and 201 mg of freshly crystallized *p*-toluenesulfonyl chloride in 20 ml of dry pyridine was refluxed for 4 hr. The mixture was evaporated under vacuum and the residue mixed with 20% sodium bicarbonate solution. After cessation of gas evolution the solution was extracted with methylene chloride. The extract was dried over sodium sulfate and evaporated. The residual oil, 236 mg, crystallized on standing producing diester X, mp 89.5–90.5°; spectra: [infrared (Nujol)] C=O 5.79 (s), C=C 6.16 (m), 6.34 (m), and 6.46 (w) μ; (pmr) three-proton singlets 3.77 and 3.85 (methoxyls) and a one-proton triplet 7.37 ppm (J = 5.0 cps) [C(6)–H].

Anal. Calcd for $C_{13}H_{13}O_4N$: C, 63.15; H, 5.30; N, 5.66. Found: C, 63.43; H, 5.42; N, 5.70.

Dimethyl Isoquinoline-4,5-dicarboxylate (VIIb). a. Bromination of 1.20 g of diester VIb with 1.80 g of N-bromosuccinimide and subsequent dehydrobromination with 5 ml of collidine under conditions of the above conversion of VIa into VIIa led to a product whose sublimation gave 800 mg of diester VIIb, mp 136–138°; spectra: [infrared (Nujol)] C=O 5.81 (s) μ; (pmr) three-proton singlets 4.03 and 4.09 ppm (methoxyls).

Anal. Calcd for $C_{13}H_{11}O_4N$: N, 5.71. Found: N, 5.64.

b. A mixture of 236 mg of X and 200 mg of 10% palladium–charcoal in 15 ml of xylene was refluxed under nitrogen for 24 hr. It was filtered and the filtrate evaporated. A benzene solution of the residue was passed through a short alumina column and evaporated. Sublimation of the residue, 210 mg, gave VIIb.

Salt XI. A solution of 250 mg of the diester VIIb and 250 mg of tryptophyl bromide in 1 ml of methanol was stirred at room temperature for 48 hr. Crystallization of the precipitated salt from methanol–benzene led to 370 mg of XI, mp 245° dec; infrared spectrum (Nujol) NH 3.11 (w) and C=O 5.78 (s) μ.

Anal. Calcd for $C_{23}H_{21}O_4N_2Br$: C, 58.85; H, 4.51; N, 5.97. Found: C, 58.75; H, 4.20; N, 6.29.

***dl*-Dihydrogambirtannine (I).** Hydrogenation of a mixture of 235 mg of salt XI in 10 ml of methanol in the presence of 0.06 ml of triethylamine as well as a work-up followed the usual procedure.[12] A solution of the unpurified product XII in 10 ml of a 20% sodium hydroxide solution in 1:1 methanol–water was refluxed under nitrogen for 24 hr. The solution was evaporated under vacuum and the residual salt dried and dissolved in 50 ml of methanol saturated with hydrogen chloride gas. The solution was left standing at room temperature for 48 hr and then was poured slowly into a suspension of sodium bicarbonate in 200 ml of methylene chloride. The inorganic salts were filtered and washed with methylene chloride. Evaporation of the combined filtrates and chromatography of a benzene solution of the gummy residue on alumina led to a product whose crystallization from benzene–hexane afforded 60 mg of I, mp 176–178°; infrared and pmr spectra and thin-layer chromatographic behavior identical with the published data[7] and with the data of an authentic sample.[9,23]

Anal. Calcd for $C_{21}H_{20}O_2N_2$: C, 75.88; H, 6.07; N, 8.43. Found: C, 76.04; H, 6.35; N, 8.25.

The hydrochloride of dihydrogambirtannine, mp 248–250° dec, crystallized from methanol–acetone, had an infrared spectrum identical with that of the deserpideine degradation product[9] hydrochloride, mp 258–260° dec.[24]

Tetracycles XX. A solution of 700 mg of XVId[12] in 7 ml of 48% hydrobromic acid was left stirring under nitrogen for 3 days. The solution was evaporated under vacuum on a steam bath. Benzene was added and the mixture reevaporated. A solution of the residue and 1.0 g of sodium borohydride in 30 ml of methanol was stirred for 12 hr, diluted with water, and extracted with methylene chloride. The extract was washed with water, dried over potassium carbonate, and evaporated. A hexane solution of the semisolid residue was chromatographed on alumina. While most fractions were oily and thus combined, the 1:1 benzene–hexane eluate was crystalline. Its crystallization from hexane yielded 97 mg of XXa, mp 76–76.5°; spectra: [infrared (CCl_4)] NH 2.98 (w), C=O 5.81 (s) μ; [ultraviolet (95% EtOH)] λ_{max} 247 (3.88) and 300 mμ (log ϵ 3.47); (pmr) three-proton doublet 1.35 (J = 7.0 cps) (C–Me), three-proton singlet

(23) The authors are indebted to Professor Shamma for samples of the deserpideine degradation product[9] and its hydrobromide.

(24) Methyl isoquinoline-4-carboxylate (VIIa) was converted into decarbomethoxydihydrogambirtannine by a similar reaction sequence. Hydrogenation of the N-tryptophyl perchlorate, mp 194–195°, followed by base treatment yielded the pentacyclic product, mp 119–121° [*cf.* J. W. Huffman, *J. Am. Chem. Soc.*, **80**, 5193 (1958)].

3.42 (ester Me), one-proton doublet 3.76 ppm (J = 7.0 cps) [C-(2)–H].

Anal. Calcd for $C_{18}H_{24}O_2N_2$: C, 71.97; H, 8.05. Found: C, 71.63; H, 7.97.

Chromatography of the combined oily eluates on silica gel and elution with chloroform led to 138 mg of starting material (XVId), while 20:1 chloroform–methanol yielded 150 mg of liquid XIX; spectra: [infrared (CCl_4)] NH 2.95 (w) and C=O 5.80 (s) μ; (pmr) three-proton singlets at 2.30 (C–Me) and 3.68 ppm (O–Me).

Anal. Calcd for $C_{18}H_{24}O_2N_2$: C, 71.97; H, 8.05; N, 9.33. Found: C, 71.71; H, 8.22; N, 9.10.

The amine XIX picrate, orange needles, mp 173–174°.

Anal. Calcd for $C_{24}H_{27}O_9N_5$: C, 54.44; H, 5.14; N, 13.23. Found: C, 54.45; H, 5.33; N, 13.33.

A mixture of 375 mg of methyl N-(α-methyltryptophyl)nicotinate[12] and 300 mg of prereduced 10% palladium–charcoal in 70 ml of methanol was hydrogenated at atmospheric pressure and room temperature. After the uptake of 3 mol of hydrogen the catalyst was filtered and the solution evaporated. A benzene solution of the residue was passed through a short alumina column. Evaporation of the eluate yielded 290 mg of liquid XIX, identical in spectra and picrate with the above sample.

A solution of 25 mg of XXa in 0.3 ml of acetic anhydride was stirred at room temperature for 25 hr. Water and sodium bicarbonate were added successively, and the mixture was extracted with ether. The extract was dried over potassium carbonate and evaporated. Crystallization of the solid residue yielded 25 mg of crystalline XXb, mp 141–141.5°; spectra: [infrared (Nujol)] C=O 5.81 (s), 6.02 (s), and C=C 6.27 (m) μ; [ultraviolet (95% EtOH)] λ_{max} 208 (4.42) and 254 mμ (log ε 4.18); (pmr) three-proton doublet 1.57 (J = 7.0 cps) [C(2)–Me], three-proton singlets 2.31 (acetyl Me), 3.37 (OMe), and a one-proton doublet 4.21 ppm (J = 7.0 cps) [C(2)–H].

Salts XXII. A solution of 0.70 g of methyl nicotinate and 1.25 g of chloro ester IIb in 3 ml of methanol was refluxed under nitrogen for 18 hr. The solvent was removed and the residue extracted several times with hot water. A saturated solution of sodium perchlorate was added to the extract and the precipitate filtered and washed with water. Crystallization of the salt from methanol yielded 1.31 g of XXIIa (X = ClO_4), mp 208°.

Anal. Calcd for $C_{20}H_{21}O_8N_2Cl$: C, 53.00; H, 4.63; N, 6.40. Found: C, 52.71; H, 4.91; N, 6.25.

A solution of 0.90 g of t-butyl nicotinate and 1.37 g of chloro ester IIb in 1.5 ml of methanol was kept at room temperature for 18 hr. Work-up as above and crystallization of the product from methanol afforded 1.90 g of XXIIb (X = ClO_4), mp 206–208°, after gas evolution and softening at 170°.

Anal. Calcd for $C_{23}H_{27}O_8N_2Cl$: N, 5.65. Found: N, 5.80.

A solution of 0.60 g of β-acetylpyridine and 1.37 g of chloro ester IIb in 5 ml of methanol was refluxed under nitrogen for 18 hr. Work-up as above and crystallization of the product from methanol afforded 1.40 g of XXIIc (X = ClO_4), mp 192°.

Anal. Calcd for $C_{20}H_{21}O_7N_2Cl$: C, 54.92; H, 4.80; N, 6.41. Found: C, 55.21; H, 4.53; N, 6.19.

Tetrahydropyridines XXIII. A mixture of 450 mg of XXIIa (X = ClO_4), 0.1 ml of triethylamine and 100 mg of 10% palladium–charcoal in 10 ml of methanol was hydrogenated at atmospheric pressure. Work-up according to a previous procedure[12] and crystallization of the product from ether yielded 290 mg of XXIIIa mp 93–94°; spectra: [infrared (Nujol)] NH 3.05 (s), C=O 5.79 (s), 6.10 (s), and 6.29 (s) μ; (pmr) six-proton broad singlet 3.62 ppm (OMe).

Anal. Calcd for $C_{20}H_{24}O_4N_2$: C, 67.39; H, 6.79; N, 7.86. Found: C, 67.25; H, 6.71; N, 7.75.

Similar hydrogenation of 500 mg of XXIIb (X = ClO_4) and crystallization of product from ether led to 310 mg of XXIIIb, mp 108–110°; spectra: [infrared (Nujol)] NH 3.05 (s), C=O 5.82 (s), 6.13 (s), and 6.28 (s) μ; (pmr) nine-proton singlet 1.46 (t-butyl) and a three-proton singlet 3.70 ppm (OMe).

Anal. Calcd for $C_{28}H_{30}O_4N_2$: C, 69.32; H, 7.59; N, 7.03. Found: C, 69.19; H, 7.38; N, 6.81.

Like hydrogenation of 430 mg of XXIIc (X = ClO_4) and crystallization of the product from benzene–hexane afforded 290 mg of XXIIIc, mp 166–167°; spectra: [infrared (Nujol)] NH 3.16 (m), C=O 5.78 (s), 6.16 (s), and 6.38 (s) μ; (pmr) three-proton singlets 1.84 (acetyl Me) and 3.71 ppm (OMe).

Anal. Calcd for $C_{20}H_{24}O_8N_2$: C, 70.56; H, 7.11; N, 8.23. Found: C, 70.72; H, 6.97; N, 8.49.

Tetracyclic Base XXIV. A solution of 100 mg of XXIIIa in 5 ml of methanol saturated with hydrogen chloride gas was kept at room temperature for 4 hr. (The ultraviolet spectrum of aliquots indicated the reaction to be complete within minutes.) The solvent was removed under vacuum and a chloroform solution of the residue shaken with solid sodium bicarbonate. The mixture was filtered and the filtrate taken to dryness. Crystallization of the residue from benzene–hexane yielded 82 mg of XXIV, mp 119–120°; spectra: [infrared (Nujol)] NH 2.99 (m), C=O 5.82 (s), 6.02 (s), and 6.24 (s) μ; [ultraviolet (MeOH)] λ_{max} 224 (3.99), 297 (3.98), and 332 mμ (log ε 4.10); (pmr) three-proton singlets 3.30 and 3.70 (OMe) and a one-proton singlet 4.93 ppm (olefinic H).