General Methods of Synthesis of Indole Alkaloids. V. Syntheses of *d,l*-Corynantheidol and *d,l*-Epialloyohimbane[1,2]

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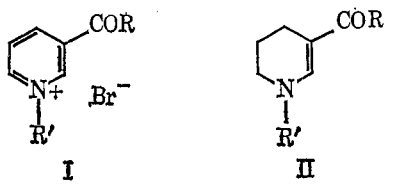
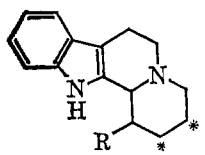
A variety of N-alkylnicotinic ester salts is shown to be transformed into tetrahydropyridines on hydrogenation. The development of simple procedures of alkaloid synthesis based on the hydrogenation and subsequent acid-catalyzed, intramolecular cyclization of the reduction products is portrayed. Three methods for removal of the β-carbalkoxy "handle" of the tetrahydropyridines are discussed and their use in the syntheses of d,l-corynantheidol and d,l-epialloyohimbane is illustrated.

A recent synthesis of the alkaloid eburnamonine featured an unusual hydrogenation (the conversion of the pyridinium salt Ia into the tetrahydropyridine IIa) as well as an acid-induced cyclization (IIa to IIIa) as a crucial, two-step reaction sequence in the construction of the alkaloidal indoloquinolizidine skeleton.[2] The novelty of the reduction process and the ease of synthesis of the fairly complex ring system demanded an investigation of the general applicability of the procedure to other indole alkaloid syntheses. As a consequence a study of the hydrogenation of 1-alkyl-3-carbalkoxypyridinium salts and the utilization of the reduction products for alkaloid synthesis was initiated.



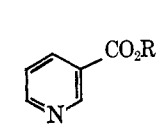
I II

a, R = Me; R′ = β-(3-indolyl)ethyl
b, R = OMe; R′ = β-(3-indolyl)ethyl
c, R = O-*t*-Bu; R′ = β-(3-indolyl)ethyl
d, R = O-*t*-Bu; R′ = Me
e, R = O-*t*-Bu; R′ = H

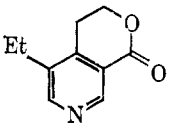


IIIa, R = Ac
b, R = CO_2Me
c, R = H

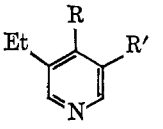
While much of the work was based on methyl nicotinate as starting compound, several pyridines had to be prepared for the present investigation. Ester interchange on methyl nicotinate (IVa) with sodium *t*-butoxide yielded *t*-butyl nicotinate (IVb).[4] Dihydrogentianine (V), initially obtained by hydrogenation of gentianine,[5] was synthesized by a variation of the Govindachari procedure.[5] Hydrolysis of nitrile VIa and subsequent esterification yielded VIb. Condensation of the latter with dimethyl oxalate afforded ester lactone VII[6] whose alkaline hydrolysis, alkaline hydrogen peroxide treatment, and esterification led to diester VIc. Lithium aluminum hydride reduction of the diester gave diol VId whose manganese dioxide oxidation produced dihydrogentianine (V). Finally, 4-carbo-*t*-butoxy-5,6,7,8-tetrahydroisoquinoline (IXd), yet one more pyridine needed for the present investigation, was prepared in the following manner. Phosphorus oxychloride treatment of glutaconimide VIII[7] yielded IXa whose hydrogenation gave IXb.[8] Acid hydrolysis of the latter and subsequent esterification afforded ester IXc, and ester interchange with sodium *t*-butoxide produced the desired ester IXd.

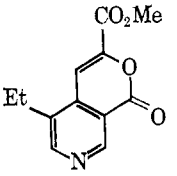


IVa, R=Me
b, R=*t*-Bu



V





VII

VIa, R = Me; R′ = CN
b, R = Me; R′ = CO_2Me
c, R = CH_2CO_2Me; R′ = CO_2Me
d, R = $(CH_2)_2OH$; R′ = CH_2OH

N-Alkylnicotinic ester salts Ib, c, and d were prepared by standard means (see the Experimental Section) and their palladium-induced hydrogenation in methanol in the presence of triethylamine catalyst led to tetrahydropyridines IIb, c, and d, respectively. Thus the change from a β-acetylpyridine in the eburna-

(1) Part of this work was supported by the U. S. Department of Health, Education, and Welfare (Grant MY-5815) and presented for the first time in the course of a series of lectures by E. W. at the Institut de Chimie des Substances Naturelles (C.N.R.S.), Gif-sur-Yvette, France, in April–May 1963.

(2) Part IV: E. Wenkert and B. Wickberg, *J. Am. Chem. Soc.*, 87, 1580 (1965).

(3) Van Leer Visiting Fellow, Weizmann Institute of Science, April–July 1965.

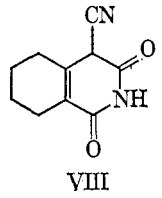
(4) *Cf.* C. T. Kyte, G. H. Jeffery, and A. I. Vogel, *J. Chem. Soc.*, 4454 (1960).

(5) The authors are indebted to Dr. Govindachari (*cf.* T. R. Govindachari, K. Nagarajan, and S. Rajappa, *ibid.*, 551 (1957)) and to Drs. D. Lavie and R. Taylor-Smith (*cf. Chem. Ind.* (London), 781 (1963)), for samples of gentianine (*cf.* also M. Plat, M. Koch, A. Bouquet, J. Le Men, and M.-M. Janot, *Bull. soc. chim. France*, 1302 (1963)).

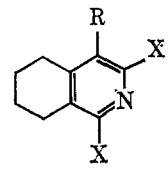
(6) *Cf.* E. Wenkert, D. B. R. Johnston, and K. G. Dave, *J. Org. Chem.*, 29, 2534 (1964).

(7) U. Basu, *J. Indian Chem. Soc.*, 8, 319 (1931).

(8) A. Zeitlin, Ph.D. Dissertation, University of New South Wales, Sydney, Australia, 1964.



VIII



IXa, X = Cl; R = CN
b, X = H; R = CN
c, X = H; R = CO_2Me
d, X = H; R = CO_2-*t*-Bu

monine synthesis[2] to β-carbalkoxypyridines in the present cases had no ill effect on the hydrogenation.[9] In view of the recent, successful, partial hydrogenation of β-acetylpyridine[10] and methyl nicotinate (IVa)[11] a similar reduction was attempted on *t*-butyl nicotinate (IVb). It led to the tetrahydro product (IIe) in high yield.

While representing the pivotal reaction in the construction of the indole alkaloid ring system, the conversion of the tetrahydropyridine IIa into the tetrahydrocarboline derivative IIIa in the eburnamonine synthesis[2] served also the purpose of introducing a necessary two-carbon side chain in the form of an acetyl group. Unfortunately such a substituent is out of place (side chains existing only at the starred positions in formula III) in the majority of alkaloids of structure type III. Consequently methods of removal of the acyl "handle" had to be devised. Compounds IIb and, thereafter, IIc served as models for this study.

Acid treatment of IIb yielded the tetracyclic ester IIIb. Hydrolysis of the latter, followed by dehydrogenation with palladium in maleic acid solution,[12] yielded a decarboxylated tetradehydro product which could be isolated as a perchlorate salt (Xa)[13] and reduced by sodium borohydride to the unsubstituted tetracycle IIIc.[14] Decarboxylation during the dehydrogenation was anticipated because of the instability of the α-pyridylacetic acid salt moiety in the intermediate Xb.[15] Thus a three-step, high-yielding method of extrusion of the frequently undesirable acyl side chain was on hand. A procedure accomplishing the same task but by the use of three less reactions was encountered in a study of the alkaline hydrolysis of IIb. The reaction product proved to be IIIc. This surprising result can be interpreted best on the mechanistic basis shown in Scheme I.

While the second scheme of deacylation was distinctly more attractive than the three-step procedure, it suffered from low reaction yields. Hence an efficient method of ester hydrolysis (the alkaline hydrolysis of IIb having been slow) and decarboxylation, prior to cyclization, had to be designed. Acid hydrolysis of *t*-butyl esters seems to fit this requirement and was tested

(9) (a) Hydrogenation of N-alkylnicotinaldehyde, N-alkylnicotinamide, and N-alkylnicotinonitrile salts also have yielded tetrahydro products: E. Wenkert, K. G. Dave, and T. Oishi, unpublished observations. (b) An attempted Raney nickel induced hydrogenation of methyl nicotinate methiodide to its piperidine reduction product has been reported to yield also appreciable quantities of the tetrahydro compound II (R = OMe, R′ = Me): C. A. Grob and F. Ostermayer, *Helv. Chim. Acta*, **45**, 1119 (1962).

(10) M. Freifelder, *J. Org. Chem.*, **29**, 2895 (1964).

(11) E. Wenkert and M. Terashima, unpublished observation.

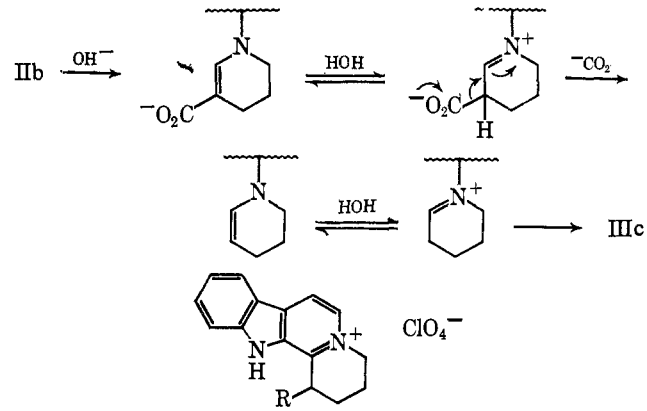
(12) E. Wenkert and D. K. Roychaudhuri, *J. Am. Chem. Soc.*, **80**, 1613 (1958).

(13) E. Wenkert and J. Kilzer, *J. Org. Chem.*, **27**, 2283 (1962).

(14) E. Wenkert, R. A. Massy-Westropp, and R. G. Lewis, *J. Am. Chem. Soc.*, **84**, 3732 (1962).

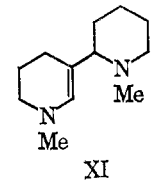
(15) *Cf.* W. von E. Doering and V. Z. Pasternak, *ibid.*, **72**, 143 (1950).

Scheme I

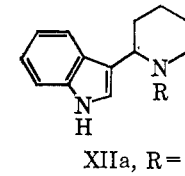


Xa, R = H
b, R = CO_2H

first on *t*-butyl tetrahydronicotinate (IIe) and its N-methyl derivative (IId). Acid hydrolysis of the latter gave 1-methyl-2-piperideine dimer (XI),[16] while acid hydrolysis of IId and e in the presence of indole produced XIIa[17] and b,[17] respectively, in high yields. These reactions represented not only a good omen for the possible synthesis of compounds of structure type III but also one of the best processes of *in situ* preparation of 1- or 2-piperideines.[18] Finally, acid treatment of the tetrahydropyridine IIc afforded IIIc in excellent yield. With three methods of deacylation thus available, consideration could now be given to their application in the synthesis of corynantheioid and yohimboid systems.[19]



XI



XIIa, R = Me
b, R = H

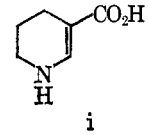
The structural simplicity of the alkaloid dihydrocorynantheol (XVIa)[20] made its synthesis or that of its stereoisomers inviting. The choice of dihydrogentianine (V) as starting compound limited the synthesis to the use of the first two deacylation schemes. Hydrogenation of the salt XIII, prepared from V by standard

(16) N. J. Leonard and F. P. Hauck, Jr., *ibid.*, **79**, 5279 (1957).

(17) E. E. van Tamelen and G. G. Knapp, *ibid.*, **77**, 1860 (1955).

(18) *Cf.* ref. 16; F. Galinovsky, A. Wagner, and R. Weiser, *Monatsh.*, **82**, 551 (1951); C. Schöpf, A. Komzak, F. Braun, and E. Jacobi, *Ann.*, **559**, 1 (1948); C. Schöpf, G. Herbst, and G. Schröder, *Angew. Chem.*, **69**, 391 (1957).

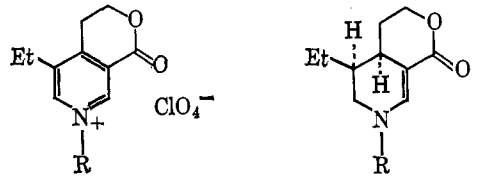
(19) The above data on hydrogenation of alkyl nicotinates and their N-alkyl salts as well as on reactions of the reduction products on acid treatment offer a clue to the heretofore puzzling behavior of nicotinic acid on hydrogenation. While both picolinic and isonicotinic acids are transformed to their respective piperidinecarboxylic acids, hydrogenation of nicotinic acid affords both piperidine and the proper amino acid: M. Freifelder, *J. Org. Chem.*, **28**, 1135 (1963), and references therein. Presumably, hydrogenation stops to a certain extent at the tetrahydro stage (i) and continues upon decarboxylation of the imino tautomer of i.



i

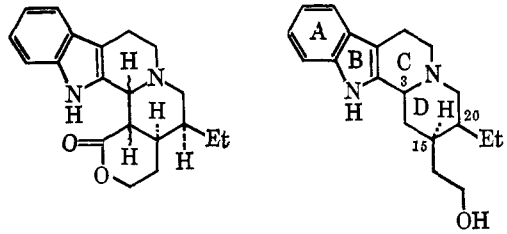
(20) B. Gilbert, L. D. Antonaccio, and C. Djerassi, *J. Org. Chem.*, **27**, 4702 (1962). Its naturally occurring N_b-methyl derivative has been described by M. F. Bartlett, B. Korzun, R. Sklar, A. F. Smith, and W. I. Taylor, *ibid.*, **28**, 1445 (1963).

means (see the Experimental Section) yielded the tetrahydropyridine XIV whose acid treatment led to lactone XV. Application of the acid hydrolysis and oxidation–reduction procedure to the lactone product afforded isomer A of XVI, while base treatment of XIV yielded isomer B of XVI. The two alcohols could be expected to be C-3 epimers in view of their common derivation from XIV, a compound of already definite C-5, C-20 stereochemistry. This configurational relationship was confirmed by the conversion of isomer B into A by ring C dehydrogenation with palladium and maleic acid, followed by sodium borohydride reduction. Furthermore, isomer A could be assigned structure XVIb, *i.e.*, that of *d,l*-corynantheidol, and hence isomer B structure XVIc, *d,l*-3-isocorynantheidol, on the assumption of hydrogenation of the salt XIII having led to *cis* product (XIV) and on the basis of the known preference of formation of 3,15-*cis* products on hydride reduction of ring C tetradehydro compounds.[12] These structure assignments were corroborated by the establishment of identity of the spectral properties of XVIb and of authentic corynantheidol.[21]



XIII XIV

R = β-(3-indolyl)ethyl



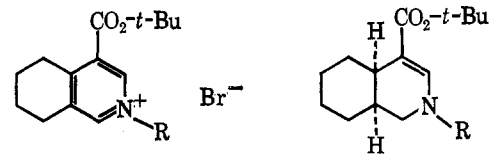
XV

XVIa, 3α-H, 20β-H
b, 3α-H, 20α-H
c, 3β-H, 20α-H

The tetrahydroisoquinoline derivative IXd appeared ideally suited for a rapid synthesis of the yohimbane skeleton by application of the third deacylation scheme (*vide supra*). Consequently it was converted to the salt XVII (see the Experimental Section) and hydrogenated. Acid treatment of the product (XVIII) afforded *d,l*-epialloyohimbane (XIXa), characterized by direct comparison with an authentic sample as well as by conversion to alloyohimbane (XIXb) on exhaustive ring C dehydrogenation and borohydride reduction.[12] Transformation of the octahydroisoquinoline XVIII into epialloyohimbane (XIXa) confirmed the expected *cis* configuration of compound XVIII.

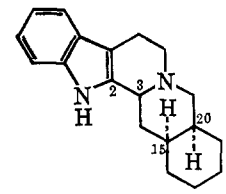
Both corynantheidol and epialloyohimbane syntheses possess interesting features worthy of comment. They

(21) Authentic alcohol was prepared from corynantheidine by the known route of degradation: M.-M. Janot, R. Goutarel, and J. Chabasse-Massoneau, *Bull. soc. chim. France*, 1033 (1953); C. Vamvacas, W. v. Philipsborn, E. Schlittler, H. Schmid, and P. Karrer, *Helv. Chim. Acta.*, 40, 1793 (1957). Compound XVIb was compared also with dihydrocorynantheiol (XVIa) (E. Wenkert and N. V. Bringi, *J. Am. Chem. Soc.*, 81, 1474, 6553 (1959)) but found to be different. The authors are indebted to Dr. Goutarel for a gift of corynantheine and corynantheidine samples.



XVII XVIII

R = β-(3-indolyl)ethyl



XIXa, 3β-H
b, 3α-H

both indicate that the introduction of further nuclear substituents on N-alkyl-β-acylpyridinium salts exert no ill effect on the partial hydrogenation of these compounds. Further, both syntheses illustrate high specificity in the stereodeterminant steps of the over-all hydrogenation–cyclization scheme. The stereospecificity of the formation of the C-3 asymmetry is of special interest.[22] Finally, the present work has cleared a path for new routes of synthesis toward a variety of indole alkaloids.

Experimental Section[23]

Melting points were determined on a Reichert microhot stage and are uncorrected. Neutral alumina of activity IV was used for chromatography. Proton magnetic resonance spectra of deuteriochloroform solutions with tetramethylsilane acting as internal standard were recorded on a Varian A-60 spectrometer.

Methyl 4-Methyl-5-ethylnicotinate (*VIb*). A solution of 6.0 g. of 4-methyl-5-ethylnicotinonitrile (VIa)[5] in 60 ml. of 20% aqueous potassium hydroxide was refluxed for 4 days. Upon cessation of the evolution of ammonia the solution was concentrated to dryness under vacuum and the residue was dried in a vacuum desiccator for 18 hr. It then was treated with 100 ml. of methanol saturated with hydrogen chloride gas and the solution was left standing at room temperature for 24 hr. The resultant precipitate was filtered and washed with methylene chloride. The washings and filtrate were combined and evaporated under vacuum. The residue was suspended in methylene chloride and shaken with solid sodium bicarbonate. The mixture was filtered, the filtrate was evaporated, and a hexane solution of the remaining residue was filtered through a short alumina column. The solution was evaporated and the residual oil was distilled at a bath temperature of 85–90° (0.05 mm.) leading to 4.8 g. of the methyl ester VIb: infrared (Nujol) C=O 5.78 (s) μ; p.m.r. three-proton triplet 1.20 (J = 7 c.p.s.) (ethyl Me), three-proton singlets 2.50 (CMe), 3.89 (OMe), two-proton quartet 2.68 (J = 7 c.p.s.) (ethyl methylene), one-proton singlets 8.78 (C-2–H) and 8.41 p.p.m. (C-6–H).

(22) The uniform formation of 3,15-*trans* compounds in the cyclization of 2,3-*seco*-3-dehydro substances is consistent with a similar observation in the case of a 15,20-*trans* compound: E. E. van Tamelen, M. Shamma, A. W. Burgstahler, J. Wolinsky, R. Tamm, and P. E. Aldrich, *J. Am. Chem. Soc.*, 80, 5006 (1958).

(23) The authors acknowledge the able, technical assistance of Mrs. Gabriella Fischer.

Anal. Calcd. for $C_{10}H_{13}NO_2$: C, 67.02; H, 7.31; N, 7.82. Found: C, 66.98; H, 7.52; N, 7.70.

Lactone VII. A mixture of 6.2 g. of methyl 4-methyl-5-ethylnicotinate (VIb), 6.2 g. of dimethyl oxalate, and dry potassium *t*-butoxide (prepared from 1.8 g. of potassium) in 60 ml. of anhydrous benzene was stirred at room temperature. After *ca.* 15 min. a yellow salt started precipitating and soon caused the entire mixture to become solid. The solid was washed several times with anhydrous ether and then used in the oxidation experiment below. A solution of the salt in a minimum amount of water was neutralized by the addition of Dry Ice. Crystallization of the resultant precipitate from methanol yielded lactone VII, m.p. 123–124°, infrared spectrum (Nujol) C=O 5.70 (s), 5.78 (s), C=C 6.14 (m), and 6.29 (m) μ.

Anal. Calcd. for $C_{12}H_{11}NO_4$: C, 61.80; H, 4.75; N, 6.01. Found: C, 61.73; H, 4.79; N, 5.86.

Methyl 4-Carbomethoxymethyl-5-ethylnicotinate (VIc). A solution of the above salt and 5.6 g. of potassium hydroxide in 50 ml. of water was kept at room temperature for 0.5 hr. Upon cooling the solution to 5° 1.4 ml. of 30% hydrogen peroxide was added and followed by another 1.4 ml. of peroxide after 2 hr. After a total reaction time of 4 hr. the solution was concentrated to dryness under vacuum and at 55–60°. The residue was dried in a vacuum desiccator and treated with 300 ml. of methanol saturated with hydrogen chloride. After 48 hr. the reaction was worked up as above and the product was distilled at 135–145° (0.5 mm.). This led to 2.9 g. of the diester VIc, m.p. 39–40° (crystallized from hexane): infrared (CCl_4) C=O 5.76 (s) and 5.80 (s) μ; p.m.r. three-proton triplet 1.19 (J = 7.5 c.p.s.) (ethyl Me), three-proton singlet 3.67 (aliphatic ester OMe), 3.87 (aromatic ester OMe), two-proton quartet 2.68 (ethyl methylene), two-proton singlet 4.06 (C-4 methylene), one-proton singlets 8.46 (C-6–H) and 8.88 p.p.m. (C-2–H).

Anal. Calcd. for $C_{12}H_{15}NO_4$: C, 60.75; H, 6.37; N, 5.90. Found: C, 60.45; H, 6.10; N, 5.93.

3-Hydroxymethyl-4-(β-hydroxyethyl)-5-ethylpyridine (VId). A solution of 2.2 g. of the diester VIc in 50 ml. of ether was added dropwise to a suspension of 0.40 g. of lithium aluminum hydride in 200 ml. of ether and the mixture was refluxed for 4 hr. Upon cooling the mixture was treated with moist sodium sulfate and filtered, and the residue was washed with hot ethyl acetate. The combined filtrate and washings were evaporated. Crystallization of the residue, 1.9 g., yielded the diol VId: m.p. 97°; infrared (Nujol) OH 3.00 (m), 3.21 (m), and C=C 6.26 (m) μ; p.m.r. three-proton triplet 1.18 (J = 7.5 c.p.s.) (ethyl Me), two-proton quartet 2.62 (J = 7.5 c.p.s.) (ethyl methylene), two-proton singlet 8.06 p.p.m. (C-2–H and C-6–H).

Anal. Calcd. for $C_{10}H_{15}NO_2$: C, 66.27; H, 8.34; N, 7.73. Found: C, 65.88; H, 8.36; N, 7.88.

Dihydrogentianine (V). A mixture of 1.9 g. of the diol VId and 20 g. of active manganese dioxide in 600 ml. of ether was stirred vigorously at room temperature for 24 hr. The suspension was filtered, the residue was washed with hot benzene, and the combined filtrate and washings were evaporated to dryness. Crystallization of the residue from hexane yielded 0.91 g. of V, m.p. and m.m.p. 76–78°; infrared spectrum (Nujol) identical with that of an authentic sample.

1,3-Dichloro-4-cyano-5,6,7,8-tetrahydroisoquinoline, (IXa). The preparation of the glutaconimide VIII followed a procedure by Bobbitt and Scola.[24] A solution of 19.4 g. of potassium hydroxide in 25 ml. of methanol was added over 1 hr. at room temperature to a stirring mixture of 57.0 g. of α-carbethoxycyclohexanone and 28.0 g. of cyanoacetamide in 250 ml. of methanol and the mixture heated for 8 hr. Upon cooling the suspension the precipitated salt was filtered, washed with methanol, and dissolved in hot water. The hot solution was filtered and immediately brought to pH 2–3 with concentrated hydrochloric acid. After 2 hr. the resultant precipitate was filtered, washed with water, and dried, yielding 56.0 g. of VIII: m.p. 280–282° (lit.[7] m.p. 278°); infrared spectrum (KBr) NH 3.03 (m), C≡N 4.54 (m), C=O 6.23 (s), and 6.33 (s) μ.

A mixture of 8.0 g. of VIII and 22 ml. of phosphorus oxychloride was heated in a closed glass ampoule of 70-ml. volume at 180° for 6 hr. After opening of the ampoule, its contents was poured onto ice and the inorganic chlorides were permitted to hydrolyze below 40°. The mixture then was extracted with methylene chloride and the extract was dried over potassium carbonate and filtered through a short alumina column. Concentration of the filtrate and crystallization of the resultant residue from hexane–cyclohexane yielded 7.7 g. of IXa, m.p. 74–75° (lit.[8] m.p. 76°), infrared spectrum (KBr) C≡N 4.47 (w) and C=C 6.45 (m) μ.

Anal. Calcd. for $C_{10}H_8Cl_2N_2$: C, 52.89; H, 3.55; N, 12.34. Found: C, 53.07; H, 3.51; N, 12.69.

4-Cyano-5,6,7,8-tetrahydroisoquinoline (IXb). A mixture of 13.4 g. of IXa, 9.7 g. of anhydrous sodium acetate, and 150 mg. of finely powdered palladium chloride in 60 ml. of absolute methanol was hydrogenated at 50 p.s.i. of hydrogen for 18 hr. The mixture was filtered through Celite and the filter cake was washed with ethanol. The combined washings and filtrate were acidified with concentrated hydrochloric acid and evaporated. The residue was dissolved in 30 ml. of water, solid sodium bicarbonate was added, and the mixture was extracted with methylene chloride. The extract was dried over magnesium sulfate and evaporated. Crystallization of the residue from hexane yielded 8.2 g. of IXb: m.p. 38–40° (lit.[8] m.p. 38–40°), infrared (KBr) C≡N 4.50 (m) and C=C 6.36 (m) μ, p.m.r. four-proton multiplets 1.25–1.55 and 2.15–2.60 and one-proton broad singlets 7.97 and 8.07 p.p.m. (C-1–H and C-3–H).

Anal. Calcd. for $C_{10}H_{10}N_2$: C, 75.92; H, 6.37. Found: C, 75.90; H, 6.46.

Methyl 5,6,7,8-Tetrahydroisoquinoline-4-carboxylate (IXc). A solution of 13.0 g. of the nitrile IXb in 300 ml. of concentrated hydrochloric acid was refluxed for 3 days and then taken to dryness. The residue was dissolved in 75 ml. of water and the solution was brought to pH 9 by the addition of solid potassium carbonate, extracted with methylene chloride, and evaporated to dryness. After being dried under high vacuum the residue was suspended in 100 ml. of absolute methanol, 45 ml. of concentrated sulfuric acid was added dropwise, and the mixture was refluxed with stirring for 12 hr. The cooled mixture was poured onto 500 g. of ice, 100 g. of potassium car-

(24) J. M. Bobbitt and D. A. Scola, *J. Org. Chem.*, 25, 560 (1960).

bonate was added, and the mixture was filtered. The filtrate was saturated with sodium bicarbonate and extracted with methylene chloride. The extract was dried over magnesium sulfate and evaporated. Distillation of the residue yielded 11.2 g. of the ester IXc, b.p. 116–118° (0.3 mm.), infrared spectrum (film) C=O 5.77 (s), C=C 6.30 (m), and 6.36 (m) μ.

Anal. Calcd. for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85. Found: C, 69.20; H, 6.89.

Transesterifications. Methyl nicotinate, 34.3 g., was added to a sodium *t*-butoxide solution, prepared from 12.0 g. of sodium hydride and 400 ml. of *t*-butyl alcohol, and the mixture was refluxed for 40 min. (A voluminous, white precipitate formed immediately which set into a thick paste within 15 min.) Excess solvent, 300–350 ml., was removed immediately at a bath temperature of 60° (20 mm.) with the aid of a rotatory evaporator. (Evaporation to dryness lowered the yield drastically.) Finely divided ice (75 g.) and 50 ml. of methylene chloride were added to the cooled mixture, and the reaction flask was stoppered and vigorously shaken until complete dissolution of the mixture. (During this operation the temperature of the mixture dropped to −8 to −10°.) Upon separation of the layers the aqueous solution was extracted with methylene chloride and the combined organic solutions were dried over magnesium sulfate and evaporated. Distillation of the residue gave 36.5 g. of a mixture of esters containing 7% of starting methyl ester (IVa), as determined by gas phase chromatography[25]; retention time of *t*-butyl nicotinate (IVb) 1.16 relative to methyl nicotinate (IVa) 1.00 (column temperature 140°, inlet pressure 18 p.s.i.). Purification of the mixture by distillation yielded *t*-butyl nicotinate (IVb): b.p. 77–80° (2 mm.) (lit.[4] b.p. 99° (2 mm.)); infrared (film) C=O 5.81 (s) and C=C 6.29 (m) μ; p.m.r. nine-proton singlet 1.66 (Me), one-proton eight-line signal 7.36 ($J_{5,2}$ = 1 c.p.s., $J_{5,6}$ = 5 c.p.s., $J_{5,4}$ = 8 c.p.s.) (C-5–H), one-proton six-line signal 8.22 ($J_{4,2 \text{ or } 6}$ = 2 c.p.s., $J_{4,5}$ = 8 c.p.s.) (C-4–H), one-proton four-line signal 8.72 ($J_{6,4 \text{ or } 2}$ = 2 c.p.s., $J_{6,5}$ = 5 c.p.s.) (C-6–H), one-proton four-line signal 9.39 p.p.m. ($J_{2,5}$ = 1 c.p.s., $J_{2,4 \text{ or } 6}$ = 2 c.p.s.) (C-2–H).

Anal. Calcd. for $C_{10}H_{13}NO_2$: C, 67.02; H, 7.31. Found: C, 66.96; H, 7.35.

A mixture of 2.0 g. of the ester IXc and a sodium *t*-butoxide solution, prepared from 245 mg. of sodium and 150 ml. of *t*-butyl alcohol, was refluxed for 40 min. (no precipitate had formed) and the reaction then was worked up in the above manner. The crude product, 2.1 g., contained 9% starting ester as shown by gas phase chromatography[25]; retention time of the *t*-butyl ester 1.79 relative to the methyl ester 1.00 (column temperature 177°, inlet pressure 18 p.s.i.). Distillation yielded *t*-butyl 5,6,7,8-tetrahydroisoquinoline-4-carboxylate (IXd): b.p. 128–130° (0.7 mm.); m.p. 59–61°; infrared (KBr) C=O 5.87 (s), C=C 6.35 (m), and 6.41 (m) μ; p.m.r. nine-proton singlet 1.61 (Me), and one-proton singlets 8.44 (broad) (C-1–H) and 8.77 (broad) p.p.m. (C-3–H).

Anal. Calcd. for $C_{14}H_{19}NO_2$: C, 72.07; H, 8.21. Found: C, 72.18; H, 8.27.

(25) Gas phase chromatograms were obtained on a Pye Argon Chromatograph; 4 ft. × 1/8 in. column with a stationary phase of 25% silicone SE-30 on 60–80 mesh Gaschrom P.

Pyridinium Salts. A mixture of the pyridine and alkyl halide in a minimum amount of methanol was stirred at room temperature under a nitrogen atmosphere for 12 hr. The solvent was evaporated and the residue was washed with dry ether and crystallized from methanol–ether.

Methyl nicotinate (IVa, 3.7 g.) and 4.5 g. of tryptophyl bromide[26] gave 7.0 g. of salt Ib, m.p. 212–213°.

Anal. Calcd. for $C_{17}H_{17}BrN_2O_2$: C, 56.78; H, 4.71; N, 7.75. Found: C, 56.72; H, 4.78; N, 7.99.

t-Butyl nicotinate (IVb, 4.0 g.) and 5.0 g. of tryptophyl bromide afforded 5.9 g. of salt Ic, m.p. 167–168°.

Anal. Calcd. for $C_{20}H_{23}BrN_2O_2$: N, 6.95. Found: N, 6.85.

Dihydrogentianine (V, 0.10 g.) and 0.15 g. of tryptophyl bromide underwent reaction only without solvent (although being mixed in ether solution). Since their salt could not be induced to crystallize, its aqueous solution was treated with excess sodium perchlorate. Crystallization of the precipitate from methanol yielded 0.13 g. of salt XIII, m.p. 193–194°.

Anal. Calcd. for $C_{20}H_{21}ClN_2O_6$: N, 6.65. Found: N, 6.36.

Ester IXd (1.0 g.) and 0.96 g. of tryptophyl bromide produced 1.4 g. of salt XVII, m.p. 190–191°.

Anal. Calcd. for $C_{24}H_{29}BrN_2O_2$: C, 63.02; H, 6.39. Found: C, 62.90; H, 6.42.

A mixture of 3.2 g. of *t*-butyl nicotinate (IVb) and 2.5 g. of methyl bromide in a closed ampoule was left standing for 12 hr. Upon opening of the ampoule the excess methyl bromide was evaporated and the residue was washed with dry ether. This led to 4.8 g. of crystalline salt Id which appeared to undergo a change at 158–162° and melted at 239–241° dec.[27a] The salt was used in the hydrogenation below without further purification.

A mixture of 2.2 g. of *t*-butyl nicotinate (IVb) and 2 ml. of methyl iodide was treated in a similar manner, yielding 3.8 g. of *t*-butyl N-methylnicotinate iodide, mp. 140–142° (with gas evolution), 218–220° dec.[27b]

Anal. Calcd. for $C_{11}H_{16}INO_2$: C, 41.14; H, 5.02. Found: C, 41.28; H, 4.91.

Tetrahydropyridines. A suspension of 10% palladium–charcoal (20 weight % of the salt to be reduced) and 1.2 equiv. of triethylamine (distilled from calcium hydride) in absolute methanol was saturated with hydrogen. A methanolic solution of pyridinium salt was added and the mixture was hydrogenated at atmospheric pressure. One mole of hydrogen was taken up usually within 3 hr. while the second required as much as 8–16 hr. Upon completion of 2-mole uptake of hydrogen, the catalyst was filtered and the filtrate was evaporated to dryness. Benzene was added to the residue and the mixture was filtered. The filtrate was passed through a short alumina column and evaporated.

Hydrogenation of 3.6 g. of the salt Ib yielded 2.15 g. of oil which solidified on trituration with benzene. Crystallization from benzene–hexane gave colorless needles of IIb: m.p. 117–118°; infrared (Nujol) NH 3.04 (m), C=O 6.02 (s), and C=C 6.31 (s) μ; ultraviolet

(26) T. Hoshino and K. Shimodaira, *Ann.*, 520, 19 (1935).

(27) (a) The m.p. 239–241° is that of trigonelline hydrobromide, as indicated by mixture melting point with an authentic sample and by comparison infrared spectra; (b) the m.p. 218–220° is that of trigonelline hydroiodide, as determined by similar means.

(95% ethanol) λ_{max} 228 mμ (log ε 4.53) and 295 mμ (log ε 4.41), λ_{min} 250 mμ (log ε 3.68); p.m.r. three-proton singlet 3.66 (OMe), one-proton doublet 6.96 (J = 2.5 c.p.s.) (indolyl α-H), and a one-proton singlet 7.40 p.p.m. (tetrahydropyridyl olefinic H).

Anal. Calcd. for $C_{17}H_{20}N_2O_2$: C, 71.80; H, 7.09; N, 9.85. Found: C, 72.01; H, 7.17; N, 9.78.

Hydrogenation of 2.8 g. of salt Ic gave 2.0 g. of a solid whose crystallization from benzene–hexane led to IIc: m.p. 177–178°; infrared (KBr) NH 3.03 (m), C=O 6.03 (s), and C=C 6.18 (s) μ; p.m.r. nine-proton singlet 1.45 (Me), one-proton doublet 6.95 (J = 2.5 c.p.s.) (indolyl α-H), and one-proton singlet 7.22 p.p.m. (tetrahydropyridyl olefinic H).

Anal. Calcd. for $C_{20}H_{26}N_2O_2$: C, 73.59; H, 8.03. Found: C, 73.71; H, 8.11.

Hydrogenation of 2.5 g. of salt Id yielded 1.6 g. of IId, distilled at a bath temperature 100–110° (0.3 mm.) and purity confirmed by gas phase chromatography[25]; retention time 2.58 relative to *t*-butyl nicotinate (IVb) 1.00 (column temperature 148°, inlet pressure 18 p.s.i.); infrared (film) C=O 5.93 (s) and C=C 6.12 (s) μ; ultraviolet (95% ethanol) λ_{max} 295 mμ (log ε 4.25); p.m.r. nine-proton singlet 1.48 (CMe), three-proton singlet 2.92 (NMe), and a one-proton singlet 7.21 p.p.m. (olefinic H).

Anal. Calcd. for $C_{11}H_{19}NO_2$: C, 66.97; H, 9.71. Found: C, 67.32; H, 9.46.

Hydrogenation of 0.86 g. of salt XIII gave 0.56 g. of solid whose crystallization from benzene yielded colorless needles of XIV: m.p. 155–156°; infrared (Nujol) NH 3.18 (m), C=O 6.05 (s), and C=C 6.35 (s) μ; p.m.r. one-proton doublet 6.88 (J = 2.5 c.p.s.) (indolyl α-H) and one-proton doublet 7.52 p.p.m. (J = 1 c.p.s.) (tetrahydropyridyl olefinic H).

Anal. Calcd. for $C_{20}H_{24}N_2O_2$: C, 74.04; H, 7.46; N, 8.64. Found: C, 73.91; H, 7.46; N, 8.83.

Hydrogenation of 875 mg. of salt XVII gave 637 mg. of solid whose crystallization from hexane–cyclohexane afforded XVIII: m.p. 133–134°; infrared (KBr) NH 3.15 (m), C=O 6.05 (s), and C=C 6.32 (s) μ; p.m.r. nine-proton singlet 1.46 (Me), one-proton doublet 6.97 (J = 2.5 c.p.s.) (indolyl α-H), and a one-proton singlet 7.21 p.p.m. (tetrahydropyridyl olefinic H).

Anal. Calcd. for $C_{24}H_{32}N_2O_2$: C, 75.75; H, 8.48; N, 7.36. Found: C, 75.84; H, 8.27; N, 7.37.

t-Butyl 1,4,5,6,-Tetrahydronicotinate (IIe). A mixture of 2.44 g. of *t*-butyl nicotinate (IVb) and 230 mg. of 10% palladium–charcoal was hydrogenated at 45 p.s.i. and room temperature. After a 2-mole hydrogen uptake at the end of 5 hr. the mixture was filtered and evaporated. The residual oil (2.31 g.) solidified and was crystallized from hexane yielding crystalline IIe: m.p. 91–92°; infrared (KBr) NH 3.03 (s), C=O 6.11 (s), and C=C 6.23 (s) μ; ultraviolet (95% EtOH) λ_{max} 286 mμ (log ε 4.04); p.m.r. nine-proton singlet 1.47 (Me), one-proton doublet 7.37 (J = 2 c.p.s.) (olefinic H).

Anal. Calcd. for $C_{10}H_{17}NO_2$: C, 65.54; H, 9.35; N, 7.64. Found: C, 66.08; H, 9.36; N, 7.28.

Amino Ester IIIb. A solution of 1.00 g. of IIb in 10 ml. of anhydrous methanol saturated with hydrogen chloride gas was left standing at room temperature for 12 hr. The solvent was removed under vacuum and the residue was basified carefully with ammonia and extracted with methylene chloride. The extract was dried over potassium carbonate and evaporated. A benzene solution of the residue was passed through a short alumina column and evaporated. Crystallization of the residual solid (0.78 g.) from ether yielded IIIb: m.p. 133–134°; infrared (Nujol) NH 2.80 (w) and C=O 5.84 (s) μ; p.m.r. three-proton singlet 3.79 (OMe) and a one-proton doublet 3.81 p.p.m. (J = 10 c.p.s.) (axial C-3–H).

Anal. Calcd. for $C_{17}H_{20}N_2O_2$: C, 71.80; H, 7.09. Found: C, 71.79; H, 7.18.

Compound IIIc. A solution of 0.40 g. of IIIb in 15 ml. of 10% hydrochloric acid was refluxed for 2 hr. and then evaporated to dryness. A mixture of the residue, 0.7 g. of maleic acid, and 0.6 g. of 10% palladium–charcoal in 10 ml. of water was refluxed for 12 hr., then filtered while hot, and the residue was washed with hot acetic acid. The combined filtrate and washings were taken to dryness under vacuum and the residue was extracted with water, neutralized with sodium bicarbonate, and treated with excess sodium perchlorate. Filtration of the resultant precipitate and crystallization from methanol yielded 0.27 g. of Xa, m.p. and m.m.p. 242–246°.[13]

Sodium borohydride (0.30 g.) reduction of 0.25 g. of Xa in 30 ml. of methanol was complete in 5 min. Usual work-up and crystallization of the product from hexane produced 0.18 g. of IIIc, m.p. and m.m.p. 153–155°.[14]

A solution of 150 mg. of IIb in 15 ml. of (1:4) aqueous, methanolic 10% potassium hydroxide was refluxed under nitrogen with stirring for 14 hr. The mixture was concentrated under vacuum, water was added, and the separated solid was extracted with methylene chloride. The extract was washed with water, dried over potassium carbonate, and evaporated. Filtration of a benzene solution of the residue through a short alumina column, evaporation of the solvent, and crystallization of the residual solid yielded 58 mg. of IIIc, m.p. and m.m.p. 153–155°,[14] infrared spectrum identical with that of an authentic sample.

A solution of 357 mg. of IIc in 5 ml. of methanol was added in small portions over a 2-hr. period to a refluxing 5% acetic acid solution (75 ml.). The intermittent addition was timed so as to permit cloudiness to disappear from the solution. After a 4-hr. reaction period the solution was concentrated to small volume, basified, and extracted with methylene chloride. The extract was dried over magnesium sulfate and evaporated. Crystallization of the residue from hexane yielded 219 mg. of IIIc, m.p. 152.5–153.5°; infrared spectrum identical with that of an authentic specimen.

Amines XII. An acid-induced reaction between 405 mg. of IId and 287 mg. of indole followed the above procedure and led to 277 mg. of product which on crystallization from cyclohexane yielded XIIa, m.p. 157–158° upon gradient sublimation (lit.[17] m.p. 154–156°); infrared (KBr) NH 3.00 (w) and C=C 6.20 (m) μ; p.m.r. three-proton singlet 2.11 (NMe), and one-proton doublet 7.06 p.p.m. (J = 2.5 c.p.s.) (indolyl α-H).

An acid-catalyzed reaction between 608 mg. of IIe and 450 mg. of indole by the above procedure and crystallization of the product from cyclohexane led to 505 mg. of XIIb, m.p. 121–122° after gradient subli-

mation (lit.[17] 121.5–122°); infrared (KBr) NH 2.95 (m), 3.05 (w), 3.17 (m), and C=C 3.15 (w) μ.

1,1'-Dimethyl-1,4,5,6-tetrahydroanabasine (XI). The ester IId (1.7 g.) was added in small portions over a 30-min. period to a refluxing mixture of 5 ml. of concentrated hydrochloric acid in 100 ml. of 1:1 aqueous methanol. After refluxing for 3 hr. the solution was concentrated to smaller volume under reduced pressure and the remaining solution was cooled in an ice bath, carefully basified with solid potassium carbonate, and extracted immediately with ether. The extract was dried over magnesium sulfate and evaporated. Distillation of the crude product (0.7 g.) gave XI: b.p. 74–75° (0.45 mm.) (lit.[16] b.p. 128–129° (18 mm.)); infrared (film), C=C 6.01 (m) μ; p.m.r. three-proton singlets 2.11, 2.55 (NMe) and a one-proton near-doublet 5.75 p.p.m. (olefinic H).

Lactone XV. A solution of 0.50 g. of XIV in 200 ml. of ether saturated with hydrogen chloride was left standing at room temperature for 12 hr. The solvent was evaporated and the residue was extracted with methylene chloride. The extract was treated with solid sodium bicarbonate and then filtered. The filtrate was dried over sodium sulfate and evaporated leaving an oil which solidified on trituration with methanol. Crystallization of the solid (0.38 g.) from dilute methanol yielded colorless needles, m.p. 179–180°; infrared spectrum (Nujol) NH 2.98 (m) and C=O 5.82 (s) μ.

Anal. Calcd. for $C_{20}H_{24}N_2O_2$: C, 74.04; H, 7.46; N, 8.64. Found: C, 73.81; H, 7.31; N, 8.62.

d,l-Corynantheidol (XVIb). A mixture of 200 mg. of lactone XV, 600 mg. of maleic acid, and 400 mg. of 30% palladium–charcoal in 5 ml. of water was refluxed under nitrogen with stirring for 50 hr. Work-up of the dehydrogenation and sodium borohydride reduction of the perchlorate salt followed the procedure described above for the conversion of IIb into IIIc. The final crude solid product (58 mg.) was crystallized from ether yielding XVIb, m.p. 158–162°; infrared spectrum identical with that of authentic corynantheidol.[21]

Anal. Calcd. for $C_{19}H_{26}N_2O$: N, 9.39. Found: N, 9.37.

d,l-3-Isocorynantheidol (XVIc, 0.10 g.) was dehydrogenated and thereafter reduced in the same manner. The product (30 mg.) was indistinguishable from XVIb.

d,l-3-Isocorynantheidol (XVIc). A mixture of 200 mg. of XIV and 5 ml. of 10% alcoholic potassium hydroxide solution was refluxed under nitrogen with stirring for 26 hr. The solvent was removed under vacuum and the residue was extracted with methylene chloride. The extract was dried over potassium carbonate and evaporated. The residue (87 mg.) was crystallized from ether yielding the alcohol XVIc, m.p. 191–192°.

Anal. Calcd. for $C_{19}H_{26}N_2O$: C, 76.47; H, 8.78; N, 9.39. Found: C, 76.30; H, 9.09; N, 9.67.

Stirring of a mixture of 20 mg. of XVIc and 1 ml. of acetic anhydride at room temperature for 48 hr., followed by usual work-up and crystallization of the product, 15 mg., from hexane yielded XVIc acetate: m.p. 146–148°; infrared (Nujol) NH 3.03 (m) C=O 5.86 (s) μ; p.m.r. three-proton unsymmetrical triplet 0.91 (ethyl Me), three-proton singlet 2.06 (acetate Me), and two-proton multiplet 4.20 p.p.m. (acetoxymethylene).

Anal. Calcd. for $C_{21}H_{28}N_2O_2$: C, 74.08; H, 8.29; N, 8.29. Found: C, 73.64; H, 8.27; N, 8.28.

d,l-Epialloyohimbane (XIXa). A solution of 461 mg. of XVIII in 9 ml. of methanol was added in small portions over a 2-hr. period to a refluxing 5% acetic acid solution (100 ml.). The reaction and subsequent work-up followed the procedure described above for the conversion of IIc to IIIc. Crystallization of the crude product, 330 mg. from hexane, yielded needles, m.p. 177–179°, which on gradient sublimation gave XIXa, m.p. and m.m.p. 188–189°; infrared spectrum identical with that of an authentic sample.

Dehydrogenation of 64 mg. of *d,l*-epialloyohimbane with 72 mg. of palladium black and 261 mg. of maleic acid in 10 ml. of water for 24 hr. and work-up as described above gave tetradehydroalloyohimbane perchlorate, m.p. 207–209° (lit.[12] m.p. 207–208°). Borohydride reduction of 41 mg. of perchlorate in the usual manner yielded 17 mg. of *d,l*-alloyohimbane (XIXb), m.p. and m.m.p. 145–147°; infrared spectrum identical with that of an authentic sample.