Synthetic Experiments Related to the Indole Alkaloids. III. The Reductive Cyclization of 1-[2-(3-Indolyl)-2-oxoethyl]pyridinium Salts to Quinolizine Derivatives Related to the Indole Alkaloids[1]

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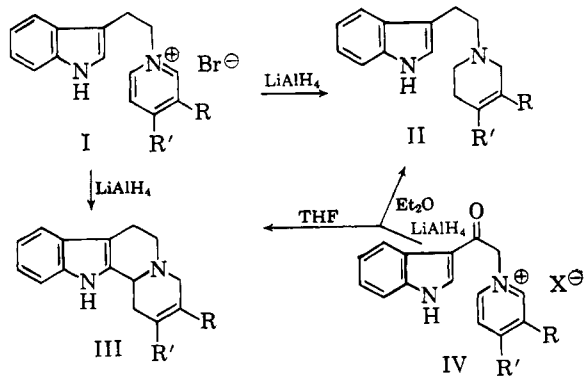
Reduction of 1-[2-(3-indolyl)-2-oxoethyl]pyridinium salts IV with lithium aluminum hydride in tetrahydrofuran solution gave indolo[2,3-*a*]quinolizine derivatives III, whereas in diethyl ether solution 1-[2-(3-indolyl)-ethyl]-1,2,5,6-tetrahydropyridines II were obtained. This method presents a convenient route to these quinolizines and has been utilized in a synthesis of *dl*-$\Delta^{15(20)}$-yohimbene, which has previously been converted into sempervirine and *dl*-alloyohimbane, and also in a synthesis of flavopereirine.

In previous papers in this series,[4] the reduction of a 2-[2-(3-indolyl)ethyl]- or 2-[2-(3-indolyl)-2-oxoethyl]-isoquinolinium salt with lithium aluminum hydride was shown to be a ready means of obtaining in good yield the basic ring skeleton of the yohimbine alkaloids. We now wish to report the extension of our original investigations to the use of pyridinium salts and the utilization of the reaction as a means of obtaining simple quinolizine derivatives related to the indole alkaloids.[5] This same "reductive cyclization" approach to the α-indole alkaloids also has been described recently by Wenkert.[6] The main difference in the two reaction sequences is our choice of 1-[2-(3-indolyl)-2-oxoethyl]-pyridinium salts as starting materials and an interesting solvent effect upon the course of the reduction. Since the final products from several of the examples chosen to illustrate the two methods are the same, we report those of our results not anticipated by Professor Wenkert's publication, or results that are necessary for structural proof.

Early attempts at the reductive cyclization of indolylethylpyridinium salts with lithium aluminum hydride were unsuccessful. Elderfield,[7] as well as K.T.P.,[8] found several years ago that the reduction of 1-[2-(3-indolyl)ethyl]pyridinium bromide (I, R = R′ = H) with lithium aluminum hydride or sodium borohydride gave only the tetrahydropyridine derivative II; no cyclization to the indolo[2,3-*a*]quinolizine system III was observed. The conditions under which the cyclization of salts of type I can be effected have been determined recently by Wenkert.[6]

The intermediate pyridinium salts IV used in our reaction sequence were obtained by condensation of 3-acetylindole with the appropriate pyridine in the presence of iodine or from the reaction of ω-bromoacetylindole, itself easily prepared from 3-acetylindole and bromine,[9] and the pyridine.



In initial experiments the parent salt (IV, R = R′ = H) was subjected to lithium aluminum hydride reduction in ether and in tetrahydrofuran solutions. The general procedure for the work-up of the reaction mixture involved decomposition of the excess hydride and treatment of the solutions with dilute hydrochloric acid, followed by basification, and chromatography of the mixtures of the crude bases. Rather surprisingly, different products were obtained when the reduction of 1-[2-(3-indolyl)-2-oxoethyl]pyridinium iodide (IV, R = R′ = H) was carried out in ether and in tetrahydrofuran solutions. When ether was the solvent employed, 1-[2-(3-indolyl)ethyl]-1,2,5,6-tetrahydropyridine (II, R = R′ = H) was isolated in 33% yield. Verification of this structure was obtained by absorption of one mole of hydrogen in the presence of Adams' catalyst with the formation of 1-[2-(3-indolyl)-ethyl]piperidine, the identity of the latter being established by comparison with authentic material obtained by lithium aluminum hydride reduction of 1-[1,2-dioxo-2-(3-indolyl)ethyl]piperidine prepared from indole-3-glyoxyloyl chloride and piperidine.[10] However, when the reduction of IV (R = R′ = H) was carried out in tetrahydrofuran solution the tetracyclic product, 1,4,6,7,12,12b-hexahydroindolo[2,3-*a*]quinolizine (III, R = R′ = H), was formed in 56% yield. Hydrogenation of this material gave 1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine, a compound well characterized in the literature. The yields of both products were found to vary with length of reaction time (see Table I). The position of the double bond in III (R = R′ = H) was not established directly, but rather the structure (instead of the alternative 3,4,6,7,12,12b-hexahydro product) was formulated by analogy with products formed in

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(4) Part II, D. R. Liljegren and K. T. Potts, *J. Org. Chem.*, **27**, 377 (1962).

(5) This investigation was supported in part by PHS Grant H-6475 from the National Heart Institute, Public Health Service.

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

(7) R. C. Elderfield, B. Fischer, and J. M. Lagowski, *J. Org. Chem.*, **22**, 1376 (1957).

(8) K. T. Potts, unpublished observations (1954).

(9) K. Bodendorf and A. Walk, *Arch. Pharm.*, **294**, 484 (1961).

(10) T. Nogradi, *Monatsh. Chem.*, **88**, 768 (1957).

TABLE I

PRODUCTS ISOLATED FROM THE LITHIUM ALUMINUM HYDRIDE REDUCTIONS OF SALTS OF STRUCTURE IV

Parent pyridine	Solvent	Reaction time, hr.	% II	% III
Pyridine	Ether	6	33	
Pyridine	Ether	3	42	
Pyridine	THF[a]	4.5		44
Pyridine	THF	2		56
3-Ethylpyridine	Ether	4	35	5
3-Ethylpyridine	THF	4.5		48
3-Ethylpyridine	THF	2		52
3-Ethyl-4-methylpyridine	THF	3.5		62
5,6-Tetramethylenepyridine	THF	3		67

[a] THF = tetrahydrofuran.

similar reductions of substituted pyridinium salts where definite assignments could be made on the basis of n.m.r. spectral data (see Experimental[11]).

A similar solvent effect on the course of the lithium aluminum hydride reduction was observed with 3-ethyl-1-[2-(3-indolyl)-2-oxoethyl]pyridinium iodide (IV, R = Et; R′ = H) in ether and in tetrahydrofuran solutions. When the former solvent was employed, 3-ethyl-1-[2-(3-indolyl)ethyl]-1,2,5,6-tetrahydropyridine (II, R = Et; R′ = H) was isolated together with a small amount of 3-ethyl-1,4,6,7,12,12b-hexahydroindolo[2,3-*a*]quinolizine (IV, R = Et; R′ = H). The latter compound was the sole product when tetrahydrofuran was the solvent for the reaction, and the small variations in yield with reaction time are summarized in Table I.

Both the tetrahydropyridine (II, R = Et; R′ = H) and the quinolizine (III, R = Et; R′ = H) absorbed one mole of hydrogen on catalytic reduction, demonstrating the presence of the isolated double bond. Definitive proof of the structures assigned to these compounds was obtained from their nuclear magnetic resonance spectral data which are reported in the Experimental. The quinolizine III was converted into the alkaloid flavopereirine,[12] from *Geissospermum laeve* or *vellosi*, by a reaction sequence reported in the literature[13] involving reduction of III (R = Et; R′ = H) to octahydroflavopereirine, oxidation with mercuric acetate to 3-ethyl-1,2,3,4,6,7-hexahydro-12*H*-indolo[2,3-*a*]quinolizinium perchlorate, followed by dehydrogenation of this salt with palladium–carbon. The flavopereirine, isolated as the perchlorate, was identical with the natural product.

Further extensions of this reaction sequence in the pyridinium series were next investigated with the aim of ultimately obtaining pentacyclic compounds possessing rings D and E in the fully reduced state. We first chose a disubstituted pyridine, β-collidine, as a model. This readily gave the intermediate pyridinium salt (IV, R = Et; R′ = CH_3) which was reduced in the usual manner with lithium aluminum hydride in tetrahydrofuran solution and gave a base with properties similar to those of the products described by formula III previously.

The assignment of structure III (R = Et; R′ = CH_3), 2-methyl-3-ethyl-1,4,6,7,12,12b-hexahydroindolo[2,3-*a*]quinolizine, was on the basis of analytical data, as well as the absence of absorption due to olefinic protons and also the α-proton of the indole nucleus in its n.m.r. spectrum. It is interesting that the reduction and cyclization of the pyridine nucleus occurs predominantly in the way shown, a fact which was also noted by Wenkert.[6] By using 3,4-diethylpyridine one would have an easy method of obtaining a product related to dihydrocorynantheane and flavocoryline.

The use of 5,6,7,8-tetrahydroisoquinoline in this reaction offered an interesting route to the alloyohimbanes. The intermediate salt (IV, R = R′ = $-(CH_2)_4-$) was obtained in poor yield from the reaction of 3-acetylindole, iodine, and the tetrahydroisoquinoline. The low yield was due to mechanical loss in the isolation procedure. An excellent yield of the salt was obtained, however, from the reaction of ω-bromoacetylindole and the isoquinoline. Reduction of this salt with lithium aluminum hydride in tetrahydrofuran solution gave 1,2,3,4,5,7,8,13,13b,14-decahydrobenz[*g*]indolo[2,3-*a*]quinolizine (III, R = R′ = $-(CH_2)_4-$) [$\Delta^{15(20)}$-yohimbene]. The physical characteristics of this product agreed with those described in the literature[14] and the structure was supported by the absence of olefinic proton and α-indole proton absorption in the n.m.r. spectrum. Attempts to reduce the isolated double bond in $\Delta^{15(20)}$-yohimbine by the usual methods were unsuccessful[14]; even the highly active platinum catalyst recently described by Brown[15] did not effect reduction, nor did the conditions used by Janot and coworkers[16] in the preparation of alloyohimbane from sempervirine prove effective. $\Delta^{15(20)}$-Yohimbene has been converted into sempervirine and also *dl*-alloyohimbane and *dl*-epialloyohimbane, and its synthesis thus constitutes syntheses of these products.[17]

$\Delta^{15(20)}$-Yohimbene was a satisfactory intermediate for resolving an interesting point in sempervirine chemistry reported in the literature. Sodium borohydride reduction of N-methylsempervirinium salts V gave a hexahydro base formulated as VI, though the alternative position for the double bond (C-3–C-14) was also considered.[18] Methylation of $\Delta^{15(20)}$-yohimbene should give a base identical with that obtained from the sodium borohydride reduction, and on treatment with sodamide and methyl iodide in liquid ammonia solution $\Delta^{15(20)}$-yohimbene gave such a product.[19] This directly confirmed the correctness of structure VI.

The instability of members of this series of compounds is worthy of mention. Without exception those quinolizines or 1,2,5,6-tetrahydropyridines containing an isolated double bond in ring D or at the junction of rings D and E rapidly decomposed in air and light. During recrystallizations, solutions obtained colorless

(11) The spectra were recorded from a Varian V-4302 dual purpose, 60-Mc., n.m.r. spectrometer, and chemical shift values are reported in τ units, using tetramethylsilane as internal standard. We are indebted to Dr. T. H. Crawford for his assistance in the determination of these spectra.

(12) Numerous syntheses of flavopereirine have been effected: see ref. 6, 24, and among others, A. Le Hir, M.-M. Janot, and D. van Stolk, *Bull. soc. chim. France*, 551 (1958); K. B. Prasad and G. A. Swan, *J. Chem. Soc.*, 2024 (1958); H. Kaneko, *J. Pharm. Soc. Japan*, **80**, 1374 (1960); Y. Ban and M. Seo, *Tetrahedron*, **16**, 5 (1961).

(13) A. Le Hir, M.-M. Janot, and D. van Stolk, *Bull. soc. chim. France*, 551 (1958). We are indebted to Professor H. Rapoport for authentic samples of flavopereirine and its perchlorate.

(14) E. Wenkert and R. Roychaudhuri, *J. Am. Chem. Soc.*, **80**, 1613 (1958).

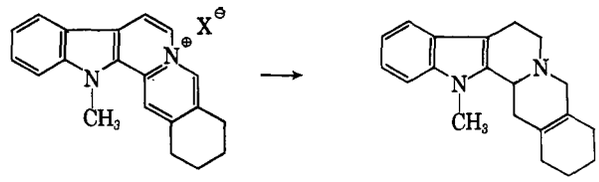
(15) H. C. Brown and C. A. Brown, *ibid.*, **84**, 1494 (1962).

(16) A. Le Hir, R. Goutarel, and M.-M. Janot, *Compt. rend.*, **235**, 63 (1952).

(17) See reference quoted in ref. 14.

(18) B. Witkop, *J. Am. Chem. Soc.*, **75**, 3361 (1953).

(19) We are indebted to Dr. B. Witkop for his gift of 1-methyl-$\Delta^{15(20)}$-yohimbene picrate to carry out direct comparisons.



V VI

after treatment with charcoal became yellow within a few minutes, and this effect was most noticeable in hydrocarbon solvents. This phenomenon is undoubtedly connected with an oxidative process involving the double bond, for when this was removed by reduction the bases were found to be stable and more easily purified.

Experimental[20]

3-Ethyl-1-[2-(3-indolyl)-2-oxoethyl]pyridinium Iodide (IV, R = Et; R′ = H; X = I).—3-Ethylpyridine (2.8 g., 0.03 mole) and 3-acetylindole (1.6 g., 0.01 mole) were warmed together on a water bath. Iodine (2.54 g., 0.01 mole) was added and the mixture heated at 95–100°. The product began to crystallize after several minutes, and heating was continued for 1 hr. The solid product was triturated with ethanol (*ca.* 20 ml.) and the cream powder collected. The iodide (3.1 g., 80%) crystallized from water as a mixture of fawn plates and needles, m.p. 257° dec., with darkening from 248°. Both of these crystalline forms of the iodide separated from ethanol as fine colorless needles, m.p. 260–262° dec. with darkening from 255°.

Anal. Calcd. for $C_{17}H_{17}N_2OI$: C, 52.1; H, 4.4; N, 7.1. Found: C, 52.0; H, 4.5; N, 7.2.

Solutions of the iodide in ethanol gradually became deep yellow on standing at room temperature for several hours.

3-Ethyl-1-[2-(3-indolyl)-2-oxoethyl]pyridinium Bromide (IV, R = Et; R′ = H; X = Br).—A mixture of 3-bromoacetylindole[9] (0.48 g., 0.002 mole) and 3-ethylpyridine (0.28 g., 0.003 mole) was gently warmed on a water bath for a few minutes. The solid product was rubbed with a little ethanol and the colorless powder that precipitated was collected and washed with ether. The bromide separated from water as colorless needles, m.p. 268–271° dec.

Anal. Calcd. for $C_{17}H_{17}N_2OBr$: C, 59.1; H, 5.0; N, 8.2. Found: C, 58.7; H, 4.7; N, 8.2.

Conversion into the Iodide.—The addition of an aqueous solution of potassium iodide to an aqueous solution of the bromide in hot water produced an immediate precipitate of 3-ethyl-1-[2-(3-indolyl)-2-oxoethyl]pyridinium iodide that crystallized from water as colorless needles, m.p. and m.m.p. 259–261° dec. with a sample prepared using the same procedure.

2-[2-(3-Indolyl)-2-oxoethyl]-5,6,7,8-tetrahydroisoquinolinium Chloride (IV, R, R′ = $-(CH_2)_4-$; X = Cl).—5,6,7,8-Tetrahydroisoquinoline[21] (2.7 g., 0.02 mole) and 3-chloroacetylindole[22] (1.7 g., 0.009 mole) were mixed together in a flask protected by a drying tube, and then warmed on a water bath. A pink solution formed and after 1–2 min. the reaction mixture solidified to a cream mass. Titration with ethanol (6–7 ml.) yielded a colorless powder, m.p. 269–270°. The chloride (2.9 g., quant.) crystallized from methanol as colorless plates, m.p. 270–272° dec.

Anal. Calcd. for $C_{19}H_{19}N_2OCl$: C, 69.8; H, 5.9; N, 8.6. Found: C, 69.3; H, 6.1; N, 8.7.

Conversion into the Iodide.—This was carried out as described previously, the iodide crystallizing from water as cream needles, m.p. 249–251° dec. The melting point was not depressed on admixture with a sample of the iodide prepared by the following method.

2-[2-(3-Indolyl)-2-oxoethyl]-5,6,7,8-tetrahydroisoquinolinium Iodide (IV, R,R′ = $-(CH_2)_4-$; X = I).—3-Acetylindole (0.8 g., 0.005 mole) and 5,6,7,8-tetrahydroisoquinoline (2.0 g., 0.015 mole) were heated together on a steam bath with iodine (1.25 g., 0.005 mole) for 40 min. The cooled melt was extracted with boiling water (charcoal) and on cooling a yellow oil was deposited. The mother liquor was decanted and when the oil was rubbed with a little ethanol a pale yellow powder precipitated. The iodide (84 mg., 4%) crystallized from water as fine cream needles, m.p. 251–252° dec.

Anal. Calcd. for $C_{19}H_{19}N_2OI$: C, 54.6; H, 4.6; N, 6.7. Found: C, 54.7; H, 4.6; N, 6.8.

1-[2-(3-Indolyl)ethyl]-1,2,5,6-tetrahydropyridine (II, R = R′ = H).—1-[2-(3-Indolyl)-2-oxoethyl]pyridinium iodide[4] (2.7 g., 0.0075 mole) was added portionwise over a period of 30 min. to a stirred solution of lithium aluminum hydride (1.0 g., 0.025 mole) in anhydrous ether (*ca.* 200 ml.) while a stream of dry nitrogen was passed into the reaction vessel. The mixture was heated under gentle reflux for 6 hr. and as the reaction progressed the yellow starting material dissolved and a flocculant white substance precipitated. At the end of the reaction period the excess hydride was decomposed by the addition of hydrated sodium sulfate and the precipitated inorganic material removed by filtration under nitrogen. The etheral filtrate was pale green with a blue fluorescence. Dilute hydrochloric acid was added with the immediate precipitation of a yellow gum. After removal of the ether on a water bath, the acidic solution was allowed to stand for 2 hr. Making basic with aqueous potassium hydroxide solution precipitated the bases, which were extracted into ether and dried (sodium sulfate). The yellow oil obtained on removal of the solvent was absorbed onto 8 g. of neutral alumina which was then added to a column of alumina (65 g.). Elution with a 1:1 mixture of benzene–petroleum ether yielded a pale yellow crystalline material. 1-[2-(3-Indolyl)ethyl]-1,2,5,6-tetrahydropyridine (0.52 g., 33%) crystallized from hexane as colorless needles, m.p. 152–153° (lit.[7] m.p. 152–153°).

Anal. Calcd. for $C_{15}H_{18}N_2$: C, 79.6; H, 8.0; N, 12.4. Found: C, 79.5; H, 8.1; N, 12.4.

The mixture melting point of this sample with 1,4,6,7,12,12b-hexahydroindolo[2,3-*a*]quinolizine was 114–116°. Further development of the column with benzene and a mixture of benzene–ether (4:1) yielded a few milligrams of yellow oily material that could not be characterized.

The **picrate**, prepared in ethanol, crystallized from ethanol as orange needles, m.p. 174–175°.

Anal. Calcd. for $C_{21}H_{21}N_5O_7$: C, 55.4; H, 4.7; N, 15.4. Found: C, 54.9; H, 4.7; N, 15.1.

Platinum oxide (15.4 mg.), suspended in absolute alcohol (10 ml.), was reduced and saturated with hydrogen. 1-[2-(3-Indolyl)ethyl]-1,2,5,6-tetrahydropyridine (30.0 mg.) was added and hydrogen (3.12 ml., theoretical 3.21 ml.) was absorbed over a period of 20 min. The colorless, crystalline residue of 1-[2-(3-indolyl)ethyl]piperidine separated from hexane as small, colorless needles, m.p. 149–150° (lit.[7], m.p. 151–152°), not depressed on admixture with an authentic specimen prepared by reduction of 1-[1,2-dioxo-2-(3-indolyl)ethyl]piperidine.[10] The infrared spectra of the samples were identical.

1,2,6,7,12,12b-Hexahydroindolo[2,3-*a*]quinolizine (III, R = R′ = H).—1-[2-(3-Indolyl)-2-oxoethyl]pyridinium iodide (1.7 g., 0.0047 mole) was added portionwise over a period of 15 min. to a stirred solution of lithium aluminum hydride (0.6 g., 0.015 mole) in tetrahydrofuran (120 ml.). Marked effervescence occurred, and the solution developed a pale green color with a green fluorescence. After 2 hr. heating in a stream of dry nitrogen, the reaction mixture was worked up as described previously. The residual brown gum from the ether extract was absorbed onto neutral alumina (8 g.) and transferred to the top of a column of alumina (50 g.). Elution with a 1:1 mixture of benzene–petroleum ether yielded 1,4,6,7,12,12b-hexahydroindolo-[2,3-*a*]quinolizine (0.58 g., 56%) m.p. 144–146°. It crystallized from hexane or petroleum ether as clusters of thick, colorless plates, m.p. 147–148° (lit.[6] m.p. 144–144.5°).

Anal. Calcd. for $C_{15}H_{16}N_2$: C, 80.3; H, 7.2; N, 12.5. Found: C, 79.7; H, 7.2; N, 12.6.

Ultraviolet absorption: λ_{max} 2260, 2830, 2910 Å.; log ϵ 4.61, 3.92, 3.84; λ_{min} 2470, 2390 Å.; log ϵ 3.30, 3.81.

The crystalline base or its solutions in hydrocarbon or alcoholic solvents rapidly changed from colorless to pale yellow-green in the presence of air and light.

(20) Petroleum ether refers to the fraction b.p. 60–80° unless otherwise stated. Evaporations were under reduced pressure on a water bath and melting points were determined in capillaries. Ultraviolet spectra were recorded in 95% ethanol solution, using an Optica CF4 spectrophotometer, and analyses were performed by the C.S.I.R.O. Microanalytical Service, Melbourne. Woelm neutral alumina, activity 4, was found most successful in the chromatography experiments.

(21) R. Grewe and A. Mondon, *Ber.*, **81**, 279 (1948).

(22) R. Majima and M. Kotake, *ibid.*, **55B**, 3865 (1922).

The **picrate** formed in ethanol, crystallized from aqueous methanol as clusters of orange needles, m.p. 119–121°.

Anal. Calcd. for $C_{21}H_{19}N_5O_7 \cdot H_2O$: C, 53.5; H, 4.5; N, 14.9. Found: C, 53.7; H, 4.5; N, 15.1.

Further development of the column with benzene and a 4:1 mixture of benzene–ether gave 55 mg. of a yellow oil that could not be induced to crystallize or form a crystalline derivative.

Adams' catalyst (20 mg.) was suspended in ethanol (10 ml.) and saturated with hydrogen. The preceding base (40 mg.) was added, and hydrogen (4.6 ml., theoretical 4.4 ml.) was absorbed over a period of 10 min. 1,2,3,4,6,7,12,12b-Octahydroindolo[2,3-*a*]quinolizine separated from hexane as small colorless prisms, m.p. 152–153° (lit.[23] m.p. 147–147.5°).

Anal. Calcd. for $C_{15}H_{18}N_2$: C, 79.6; H, 8.0. Found: C, 79.3; H, 8.1.

The mixture melting point of the product with 1-[2-(3-indolyl)-ethyl]piperidine was 119–121°.

3-Ethyl-1-[2-(3-indolyl)ethyl]-1,2,5,6-tetrahydropyridine (II, R = Et; R′ = H).—Dried, powdered 3-ethyl-1-[2-(3-indolyl)-2-oxoethyl]pyridinium iodide (IV, R = Et; R′ = H) (3.44 g. 0.0087 mole) was added to a stirred solution of lithium aluminum hydride (1.2 g., 0.03 mole) in ether (300 ml.) under an atmosphere of dry nitrogen and the pale green mixture was heated under reflux for 3 hr.

Using the previous general work-up procedure, the final oily product obtained was absorbed onto alumina (10 g.) and transferred to the top of a column of alumina (100 g.) and eluted with a 1:4 mixture of benzene–petroleum ether. The first two fractions (800 ml.) contained 3-ethyl-1,4,6,7,12,12b-hexahydroindolo[2,3-*a*]quinolizine (0.111 g., 5%), m.p. 143–145°. (The characterization of this product is described fully subsequently.) Further development of the column with a 1:1 mixture of benzene–petroleum ether gave pale yellow, crystalline material, m.p. 117–120°. The 3-ethyl-1-[2-(3-indolyl)ethyl]-1,2,5,6-tetrahydropyridine (0.879 g., 40%) crystallized from a colorless solution in hexane as very pale yellow, irregular prisms, m.p. 121–123° (lit.[6] m.p. 119–122°).

Anal. Calcd. for $C_{17}H_{22}N_2$: N, 11.0. Found: N, 10.9.

N.m.r. spectrum (deuteriochloroform): ind-α-H, 3.22; olefinic CH, 4.62; ethyl CH_3, 9.00 τ (triplet, J = 7.0 c.p.s.).

The **picrate**, prepared in alcohol, separated as orange-red needles, m.p. 155–157°, and successive crystallizations from methanol raised this value to 165–167° (lit.[6] m.p. 161–163°).

Anal. Calcd. for $C_{23}H_{25}N_5O_7$: C, 57.1; H, 5.2; N, 14.5. Found: C, 57.0; H, 5.3; N, 14.1.

Palladium on carbon (20 mg., 20% catalyst) was suspended in ethanol (10 ml.) and saturated with hydrogen. The unsaturated base prepared previously (37.4 mg.) was added, and hydrogen (3.84 ml., theor. 3.63 ml.) was absorbed over a period of 4 hr. The oily base was very soluble in hexane and petroleum ether (b.p. 40–60°) and could not be obtained crystalline.

Ultraviolet absorption: λ_{max} 2230,2830, 2920 Å.; λ_{min} 2440, 2890 Å. It was characterized as the **picrate** which was formed in ethanol and crystallized from methanol–water in the form of fine, orange needles, m.p. 127–128°.

Anal. Calcd. for $C_{23}H_{27}N_5O_7$: C, 56.9; H, 5.6; N, 14.4. Found: C, 56.8; H, 5.6; N, 14.2.

3-Ethyl-1,4,6,7,12,12b-hexahydroindolo[2,3-*a*]quinolizine (III, R = Et; R′ = H).—The finely powdered iodide (5.88 g., 0.015 mole) was added in small portions over a period of 15 min. to a stirred solution of lithium aluminum hydride (2.0 g., 0.05 mole) in tetrahydrofuran (300 ml.). Marked effervescence occurred, and the solution became pale green with a green fluorescence. After 2 hr. heating in a nitrogen atmosphere, the reaction mixture was worked up as before. The residual yellow fluorescent glass was absorbed onto alumina (10 g.) and transferred to the top of a column of alumina (100 g.). Elution with a 1:1 mixture of benzene–petroleum ether gave a crystalline product, m.p. 143–145°. The 3-ethyl-1,4,6,7,12,12b-hexahydroindolo-[2,3-*a*]quinolizine (1.32 g., 52%) crystallized from hexane as colorless plates, m.p. 146–148° (lit.[6] m.p. 143–145°).

Anal. Calcd. for $C_{17}H_{20}N_2$: C, 80.9; H, 8.0; N, 11.1. Found: C, 80.2; H, 7.9; N, 11.4.

Ultraviolet absorption: λ_{max} 2260, 2830, 2910 (sh.) Å.; log ε 4.52, 3.83, 3.75; λ_{min} 2450 Å.; log ε 3.17. N.m.r. spectrum (deuteriochloroform): olefinic CH, 4.62; ethyl CH_3, 8.97 τ (triplet, J = 7.3 c.p.s.).

The crystalline base or its solutions very rapidly became yellow on exposure to air and light.

The **picrate** was formed in ethanol and crystallized from an ethanol–petroleum ether mixture as small, yellow needles, m.p. 184–186° dec.

Anal. Calcd. for $C_{23}H_{23}N_5O_7$: C, 57.4; H, 4.8; N, 14.6. Found: C, 56.9; H, 4.4; N, 14.5.

Adams' catalyst (10 mg.), suspended in ethanol (10 ml.), was reduced and saturated with hydrogen. The previous unsaturated base (25.2 mg.) was added and hydrogen (2.42 ml., theoretical 2.36 ml.) was absorbed over a period of 80 min. The colorless 3-ethyl-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine (octahydroflavopereirine) could not be obtained crystalline (Thesing and Festag[24] report an oil; Hughes and Rapoport[25] and Wenkert[6] report m.p. 163–164°). The **picrate** was prepared in ethanol and crystallized from methanol as small, irregular orange prisms, m.p. 208–210° dec., alone and when mixed with authentic octahydroflavopereirine picrate, kindly supplied by Dr. J. Thesing. The infrared spectra of the two samples were superimposable.

2-Methyl-3-ethyl-1,4,6,7,12,12b-hexahydroindolo[2,3-*a*]quinolizine (III, R = Et; R′ = CH_3). **A.**—Finely powdered 3-ethyl-1-[2-(3-indolyl)-2-oxoethyl]-4-methylpyridinium iodide (IV, R = Et; R′ = CH_3; X = I) (1.2 g., 0.003 mole) was added to a solution of lithium aluminum hydride (0.7 g., 0.018 mole) in dry tetrahydrofuran (100 ml.) and the mixture heated under reflux for 3.5 hr. in a nitrogen atmosphere. After cooling the reaction mixture, water was cautiously added to decompose the excess hydride. Treatment with dilute hydrochloric acid gave a yellow solution containing suspended grey inorganic matter. This was removed as described previously and tetrahydrofuran evaporated from the filtrate at 30–40° under reduced pressure. As the solution concentrated a yellow product separated and was collected by filtration. Further concentration of the mother liquor precipitated a yellow oil that solidified on standing. This was identified as the quinolizinium hydroiodide (0.7 g., 61%) which crystallized from methanol as colorless needles, m.p. 296–298° dec.

Anal. Calcd. for $C_{18}H_{23}N_2I$: C, 54.8; H, 5.8; N, 7.1. Found: C, 54.8; H, 5.8; N, 7.1.

No coloration was obtained with Ehrlich's reagent. The **free base** was obtained by the addition of ammonia to an aqueous solution of the hydroiodide. It separated from aqueous methanol as colorless needles, m.p. 171–173°.

Anal. Calcd. for $C_{18}H_{22}N_2$: C, 81.2; H, 8.3; N, 10.5. Found: C, 80.7; H, 8.3; N, 10.5.

Ultraviolet absorption: λ_{max} 2260, 2820, 2900 Å.; log ε 4.39, 3.92, 3.83; λ_{min} 2470, 2880, Å.; log ε 3.34, 3.82. N.m.r. spectrum (deuteriochloroform): methyl of $(CH_3)C{=}C$, 8.33; ethyl methyl, 9.00 τ; (triplet, J = 7.0 c.p.s.); no olefinic proton.

B.—In another reduction it was possible to isolate the quinolizine as its crystalline hydrochloride. After decomposition of the reaction mixture with hydrated sodium sulfate and removal of the inorganic salts, the filtrate was acidified with dilute hydrochloric acid and the volume of the solution reduced by heating on the water bath. On cooling, colorless crystals of 2-methyl-3-ethyl-1,4,6,7,12,12b-hexahydroindolo[2,3-*a*]quinolizinium hydrochloride (0.85 g., 43%) separated. It crystallized from methanol as long, colorless needles, m.p. 281–282° with frothing.

Anal. Calcd. for $C_{18}H_{23}N_2Cl$: N, 9.3. Found: N, 9.0.

From the acidic mother liquors, by a process involving basification, ether extraction, and chromatography as described in the previous experiments, a further 325 mg. (18%) of the free base was obtained, m.p. 171–172°. Further development of the chromatography column with a 4:1 mixture of benzene–ether gave 170 mg. of a brown oil that could not be induced to crystallize or to form a crystalline picrate or hydrochloride.

1,2,3,4,5,7,8,13,13b,14-Decahydrobenz[*g*]indolo[2,3-*a*]quinolizine (III, R,R′ = $-(CH_2)_4-$).—2-[2-(3-Indolyl)-2-oxoethyl]-5,6,7,8-tetrahydroisoquinolinium chloride (IV, R, R′ = $-(CH_2)_4-$; X = Cl) (2.4 g., 0.0076 mole) was added in small portions to lithium aluminum hydride (1.0 g., 0.025 mole) suspended in dry tetrahydrofuran (150 ml.). Vigorous effervescence occurred and a yellow-green solution with an intense pale green fluorescence was formed. After 3 hr. reflux with stirring in a nitrogen atmosphere, hydrated sodium sulfate was added and the reaction mixture worked up as previously described. The final brown oil was

(23) L. H. Groves and G. A. Swan, *J. Chem. Soc.*, 650 (1952).

(24) J. Thesing and W. Festag, *Experientia*, **17**, 127 (1959).

(25) N. A. Hughes and H. Rapoport, *J. Am. Chem. Soc.*, **80**, 1604 (1958).

absorbed onto alumina (10 g.) and transferred to the top of a column of alumina (80 g.). The column was eluted with a 1:1 mixture of benzene–petroleum ether and 200-ml. fractions taken. Fractions 2,3 and 4 were combined and on removal of the solvent a pale yellow crystalline residue was obtained. 1,2,3,4,5,7,8,-13,13b,14-Decahydrobenz[*g*]indolo[2,3-*a*]quinolizine, $\Delta^{15(20)}$-yohimbene, (1.42 g., 67%) separated from benzene as colorless needles, m.p. 196–197° with darkening (lit.[14] m.p. 196–197°). N.m.r. spectrum (deuteriochloroform): methylene, 6.99–8.34 τ; no olefinic proton.

Anal. Calcd. for $C_{19}H_{22}N_2$: C, 82.0; H, 8.0; N, 10.1. Found: C, 81.6; H, 7.9; N, 10.2.

The base, or its solutions, rapidly became yellow on exposure to air and light.

The **picrate**, formed in ethanol, separated from aqueous methanol as fine yellow needles, m.p. 178–180° dec., with previous darkening.

Anal. Calcd. for $C_{25}H_{25}N_5O_7$: C, 59.2; H, 5.0; N, 13.8. Found: C, 59.5; H, 5.1; N, 13.6.

Further development of the column with a 4:1 mixture of benzene–ether gave a small amount of a brown oily material which could not be characterized.

1,2,3,4,5,7,8,13,13b,14-Decahydro-1′-methylbenz[*g*]indolo-[2,3-*a*]quinolizine (N-Methyl-$\Delta^{15(20)}$-yohimbene) (VI).—Liquid ammonia (*ca.* 15 ml.) was distilled from sodium and collected in a small flask immersed in a Dry Ice–ethanol bath. A crystal of ferric nitrate was added, followed by sodium (22 mg.). The mixture was stirred for several minutes, $\Delta^{15(20)}$-yohimbine (225 mg.) was added, and after a further 10 min. methyl iodide (150 mg.) was introduced. Stirring was continued at room temperature until all the ammonia had evaporated, and then water was added and the product collected (230 mg., m.p. 112–115°). N-Methyl-$\Delta^{15(20)}$-yohimbene crystallized from aqueous methanol as fine, colorless needles, m.p. 137–138° (lit.[18] m.p. 137–139°). N.m.r. spectrum (deuteriochloroform): ind-N methyl, 6.37; methylene, 6.85–8.15 τ.

Anal. Calcd. for $C_{20}H_{24}N_2$: C, 82.1; H, 8.3; N, 9.6. Found: C, 81.9; H, 7.9; N, 9.7.

The **picrate**, prepared in alcohol solution, crystallized from methanol as yellow needles, m.p. 182–185° (lit.[18] m.p. 188–192°).

Anal. Calcd. for $C_{26}H_{27}N_5O_7 \cdot CH_3OH$: C, 58.6; H, 5.6; N, 12.7. Found: C, 58.5; H, 5.4; N, 13.0.

The melting point of the picrate was not depressed on admixture with an authentic sample kindly provided by Dr. B. Witkop, and the infrared spectra of the two samples were identical.

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Aromatic Cyclodehydration. LIV.[1] Indolo[2,3-*a*]acridizinium Salts

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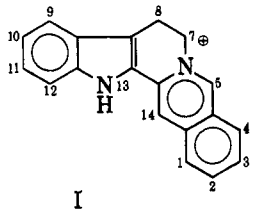
9*H*-[3,4-*b*]Pyridoindole-1-carboxaldehyde has been synthesized and quaternized with benzyl halides. Cyclization of the crude quaternary salts in acidic media has afforded indolo[2,3-*a*]acridizinium salts.

The indolo[2,3-*a*]acridizinium[2] (VI) nucleus may be considered as the parent system of the yohimbine, reserpine, and alstoniline[3] alkaloids. A near approach to the synthesis of VI has been made by four different research groups,[4a–d] each of which prepared 7,8-dihydroindolo[2,3-*a*]acridizinium salts (I). Two of these groups[4c,4d] have recorded their attempts to dehydrogenate the 7,8-dihydro system (I) to the fully aromatic



I

nucleus (VI). Glover and Jones[4c] report that their experiments were unsuccessful. Swan,[4d] using tetrachloro-*o*-benzoquinone as the dehydrogenating agent, isolated (as the iodide) a chocolate brown powder. This substance "was probably not obtained pure" and no analysis was reported. The reported absorption spectrum was simpler (only two maxima) than that of any known acridizinium compound, and the ultimate absorption maximum was at 345 mμ as against 399 mμ for the acridizinium ion.[5]

It appeared probable that the methods of aromatic cyclodehydration[6] might provide a direct route to the aromatic system without recourse to dehydrogenation of a quaternary salt. The preparation of 1-methoxymethyl-9*H*-[3,4-*b*]pyridoindole (methoxyharman, II) from methoxyacetaldehyde and tryptophan[7] was followed by cleavage of the ether linkage by hydrobromic acid, affording the carbinol III. The carbinol was oxidized to the aldehyde IV[8] using activated manganese dioxide.

Quaternization of the pyridoindolecarboxaldehyde with benzyl bromide was carried out in dimethylformamide at room temperature, and the crude salt (V, X = Br) was used directly in the cyclization. Cyclodehydration was brought about by heating the quaternary salt V for 24 hr. in polyphosphoric acid at 120°, and the orange-yellow product had the properties which would be expected of an indoloacridizinium system.

Quaternary salts derived from 3-methoxybenzyl bromide and 2,3-dimethoxybenzyl bromide were cyclized to the expected indoloacridizinium salts VII and

(1) For the preceding communication of this series, see *J. Org. Chem.*, **28**, 1669 (1963). This research was supported by a research grant (H-2170) from the National Heart Institute of the National Institutes of Health, presented before the XIXth Meeting of the International Union for Pure and Applied Chemistry, London, England, July, 1963.

(2) The name acridizinium has been proposed for the benzo[*b*]quinolizinium system: *J. Am. Chem. Soc.*, **77**, 4812 (1955). The *Chemical Abstracts* name for VI is 13*H*-benz[*g*]indolo[2,3-*a*]quinolizinium.

(3) R. C. Elderfield and S. L. Wythe, *J. Org. Chem.*, **19**, 683 (1954).

(4) (a) R. M. Jacob and J. Fouché, 16th Congress, Union of Pure and Applied Chemistry, Paris, 1957; Resumés des Comm., Vol. II, p. 316. (b) R. C. Elderfield, J. M. Lagowski, O. L. McCurdy, and S. L. Wythe, *J. Org. Chem.*, **23**, 435 (1958). (c) E. E. Glover and G. Jones, *J. Chem. Soc.*, 1750 (1958). (d) G. A. Swan, *ibid.*, 2038 (1958).

(5) An additional complication is that, in the text of Swan's paper, (ref. 4d) the dehydrogenation of 7,8-dihydroindolo[2,3-*a*]acridizinium (I) is discussed, while, in the experimental part, only the dehydrogenation of the 13-methyl derivative of I is described.

(6) C. K. Bradsher, *Chem. Rev.*, **38**, 447 (1946).

(7) *Cf.* H. R. Snyder, S. M. Parmenterer, and L. Katz, *J. Am. Chem. Soc.*, **70**, 222 (1948).

(8) We are indebted to Dr. Hans Berger who developed this procedure for the synthesis of 9*H*-[3,4-*b*]pyridoindole-1-carboxaldehyde in this laboratory.