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.

Acknowledgment.—The authors wish to thank Professor G. M. Badger for his constant interest and encouragement throughout this work.

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

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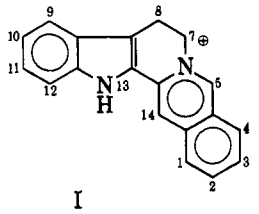
9*H*-[3,4-*b*]Pyridoindole-1-carboxaldehyde has been synthesized and quaternized with benzyl halides. Cyclization of the crude quaternary salts in acidic media has afforded indolo[2,3-*a*]acridizinium salts.

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).

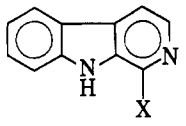
(4) (a) R. M. Jacob and J. Fouché, 16th Congress, Union of Pure and Applied Chemistry, Paris, 1957; Resumés des Comm., Vol. II, p. 316. (b) R. C. Elderfield, J. M. Lagowski, O. L. McCurdy, and S. L. Wythe, *J. Org. Chem.*, **23**, 435 (1958). (c) E. E. Glover and G. Jones, *J. Chem. Soc.*, 1750 (1958).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

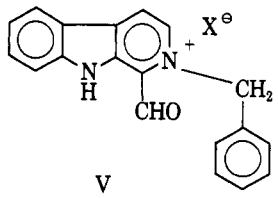
(6) C. K. Bradsher, *Chem. Rev.*, **38**, 447 (1946).

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

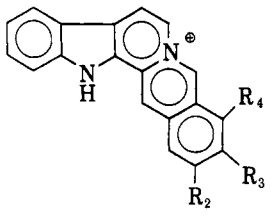
(8) We are indebted to Dr. Hans Berger who developed this procedure for the synthesis of 9*H*-[3,4-*b*]pyridoindole-1-carboxaldehyde in this laboratory.

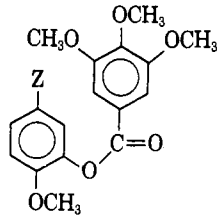


II, X = CH_2OCH_3
III, X = CH_2OH
IV, X = CHO



V





VIII. Since the methoxyl groups facilitate cyclization, heating in concentrated hydrochloric acid for 15 min. on the steam bath was sufficient.[9] The quaternary salt from 3-(3,4,5-trimethoxybenzoxy)-4-methoxybenzyl bromide (XII) proved more difficult to cyclize, but did afford a product IX having the expected composition, and some of the features of the gross reserpine skeleton.

Experimental

All analyses were by Dr. I. A. Schoeller, Mikroanalytisches Laboratorium, Kronach, West Germany. Unless otherwise indicated all infrared absorption spectra were determined by use of potassium bromide pellets. Unless otherwise indicated ultraviolet absorption spectra were made with the Cary Model 14 PM spectrophotometer using acetonitrile as the solvent. Wave lengths marked with an asterisk (*) represent shoulders rather than clearly defined peaks.

1-Methoxymethyl-9*H*-[3,4-*b*]pyridoindole (II).[7]—A mixture containing 2 g. of *dl*-tryptophan, 1.5 g. of methoxyacetaldehyde[10] in 80 ml. of water, and 1 ml. of ethanol was heated at 60° for 22 hr. The solution was then diluted to 500 ml. and boiled for a few minutes, and then 96 ml. of 10% potassium dichromate solution and 20 ml. of acetic acid were added. Heating was continued for only 2–3 min. and then the brown suspension was cooled under the water tap. After the addition of sodium sulfite to destroy excess oxidant, the mixture was made alkaline with solid sodium carbonate, and extracted repeatedly with ether. Evaporation of the ether left 1.57 g. of crude methoxyharman suitable for the next step. An analytical sample was prepared by recrystallization from dilute ethanol, m.p. 129–130°.

Anal. Calcd. for $C_{13}H_{12}N_2O$: C, 73.55; H, 5.70; N, 13.22. Found: C, 73.21; H, 5.92; N, 13.51.

1-Hydroxymethyl-9*H*-[3,4-*b*]pyridoindole (III).—Two grams of crude methoxyharman was dissolved in 60 ml. of 48% hydrobromic acid and the mixture refluxed for 1.5 hr. The red solution was evaporated to near dryness, 60 ml. of water was added, and refluxing was continued for two additional hours. The hot solution was filtered to remove a small amount of tar, cooled, and made alkaline with sodium carbonate. The crude grayish precipitate, m.p. 218–220°, yield 1.9 g. (93%), was pure enough for further reactions. Recrystallization was difficult because the substance was nearly insoluble in most of the common organic solvents. Further purification could be effected if the carbinol was dissolved in hot 10% hydrochloric acid (Norite) and precipitated by addition of solid potassium carbonate to the cooled solution. The grayish white precipitate, when collected, washed with water, and dried, melted at 220–223°. The analytical sample was obtained as colorless needles by crystallizing 325 mg. from 700 ml. of water, m.p. 228–229°.

Anal. Calcd. for $C_{12}H_{10}N_2O$: C, 72.71; H, 5.09; N, 14.13. Found[11]: C, 72.92; H, 5.27; N, 14.19.

The ultraviolet absorption spectrum of this compound, as well as that of the related methoxymethylpyridoindole II closely resembles the spectrum of harman.

9*H*-[3,4-*b*]Pyridoindole-1-carboxyaldehyde (IV).—One gram of the hydroxyharman III and 10 g. of specially prepared manganese dioxide[12] were suspended in 350 ml. of tetrachloroethane and were stirred for 16 hr. by means of a magnetic stirrer. The temperature went as high as 39° because of the heat from the stirrer motor. The reaction mixture was filtered through filter-aid, the residue washed with chloroform, and the combined solutions evaporated to dryness. The product was recrystallized from ethanol affording 0.51 g. (52%) of yellow aldehyde as a microcrystalline powder, m.p. 198–200°. The analytical sample was recrystallized from benzene, m.p. 202–202.5°.

Anal. Calcd. for $C_{12}H_8N_2O$: C, 73.46; H, 4.08; N, 14.28. Found: C, 73.68; H, 3.66; N, 13.95.

The oxime crystallized from ethanol as almost colorless needles, m.p. 264–266° dec.

Anal. Calcd. for $C_{12}H_9N_3O$: C, 68.24; H, 4.29. Found: C, 68.14; H, 4.47.

1-Formyl-2-benzyl-9*H*-[3,4-*b*]pyridoindolium Perchlorate (V).—The pyridoindolecarboxaldehyde IV was usually dissolved in the minimum quantity of dimethylformamide and an excess of benzyl bromide added and the mixture was allowed to stand for 7 days. The crude bromide salt precipitated by the addition of ether was satisfactory for further reactions, but a small sample was converted to the perchlorate by the addition of 20% perchloric acid to an ethanol solution. The orange product precipitated from acetonitrile–ethyl acetate as a powder, m.p. 223–224° dec. The alcohol solution had a blue fluorescence.

Anal. Calcd. for $C_{19}H_{15}N_2O_5Cl$: C, 58.99; H, 3.91; N, 7.24. Found: C, 58.86; H, 3.93; N, 7.32.

Indolo[2,3-*a*]acridizinium Perchlorate (VI).—The crude pyridoindolium V bromide (1.0 g.) was mixed with polyphosphoric acid (20 g.) and heated for about 24 hr. at 120°. The mixture was next cooled and stirred and water was added, causing the precipitation of the product as a phosphate salt. The grayish brown solid was collected, washed with water, and dried. The dry salt was dissolved in methanol acidified with a small quantity of hydrochloric acid, and ion exchanged through an Amberlite IRA-401 chloride column. The alcoholic solution was concentrated and 20% perchloric acid added to the hot solution. The precipitate was collected, washed with cold water–ethanol, and dried. The brownish product which decomposed starting at 275°, (0.72 g., 72%) was recrystallized from acetonitrile–ether, affording an analytical sample as yellow-orange crystals, m.p. 307–310° dec., which showed a strong yellow-green fluorescence in solution. The infrared absorption spectrum showed a peak at 2.96 μ (assigned to indole NH) but no significant absorption in the carbonyl region; λ_{max}[13] (log ϵ) 209 (4.29), 255 (4.44), 280 (4.19), 288* (4.17), 346 (4.24), 401 (3.83), and 443 mμ (3.71).

Anal. Calcd. for $C_{19}H_{13}N_2O_4Cl$: C, 61.88; H, 3.55; N, 7.60. Found: C, 62.14; H, 3.90; N, 7.57.

3-Methoxyindolo[2,3-*a*]acridizinium (VII) Perchlorate.—The pyridoindole carboxaldehyde (0.5 g.) was quaternized with *m*-methoxybenzyl bromide in the usual way. The quaternary salt which formed was precipitated from solution as an oil or impure solid by the addition of ether. The solvent was decanted and the residue was taken up in a small quantity of methanol. Ten milliliters of concentrated hydrochloric acid was added and the mixture heated on the steam bath for 15 min. A yellowish precipitate formed, and after cooling the mixture, it was collected and washed with cold water. To a hot alcoholic solution of the salt, 20% perchloric acid was added dropwise, and after cooling the mixture, the precipitated perchlorate salt was collected, washed with water, and dried. The yellowish product (0.81 g., 80%) decomposed slowly when heated above 280°. The analytical sample, obtained by recrystallization from aceto-

(9) Spectrographic evidence indicates that the activated (methoxy)-benzyl salts may undergo some cyclization at room temperature during the quaternization period.

(10) C. D. Hurd and J. L. Abernethy, *J. Am. Chem. Soc.*, **63**, 1966 (1941); the initial distillate obtained by the Hurd and Abernethy procedure was usually used *without* fractionation.

(11) Analysis by D. C. Daessle, Montreal, Quebec, Canada.

(12) *Cf.* R. J. Highet and W. C. Wildman, *J. Am. Chem. Soc.*, **77**, 4399 (1955); J. Attenburrow, A. F. B. Cameron, J. H. Chapman, R. M. Evans, B. A. Hems, A. B. A. Jensen, and T. Walker, *J. Chem. Soc.*, 1094 (1952). In later experiments it was found more convenient to use 350–700 ml. of acetone or chloroform as the solvent since subsequent concentration of the solution was made easier.

(13) This measurement made in 95% ethanol solution using the Perkin-Elmer Model 202 spectrophotometer.

nitrile or acetonitrile–ether, decomposed at temperatures above 300°, but did not melt below 400°.

Anal. Calcd. for $C_{20}H_{15}N_2O_5Cl$: C, 60.23; H, 3.79; N, 7.02. Found: C, 60.51; H, 3.92; N, 6.96.

The infrared absorption spectrum showed the absence of any significant absorption in the carbonyl region and a definite absorption at 2.94 μ assigned to the indole NH; λ_{max} (log ϵ) 258 (4.36), 268* (4.33), 330 (4.29), 405 (3.82), and 440* mμ (3.49).

3,4-Dimethoxyindolo[2,3-*a*]acridizinium (VIII) Perchlorate.—Starting with 0.8 g. of the pyridoindolecarboxaldehyde and using 2,3-dimethoxybenzyl bromide[14] instead of 3-methoxybenzyl bromide, but otherwise following the procedure used for making the 3-methoxy derivative VII, the desired 3,4-dimethoxyindoloacridizinium perchlorate VIII was obtained as a red-brown product, m.p. about 290° dec.; yield, 1.41 g. (81%). An analytical sample, prepared by recrystallization from acetonitrile or acetonitrile–ether, was orange, m.p. 313–314°; λ_{max} (log ϵ) 260 (4.53), 290 (4.37), 359 (4.50), 385* (4.17) and 480 mμ (3.90).

Anal. Calcd. for $C_{21}H_{17}N_2ClO_6$: C, 58.82; H, 4.00; N, 6.53. Found: C, 58.93; H, 4.05; N, 6.53.

The infrared absorption spectrum showed no significant absorption in the carbonyl region but a strong absorption at 2.96 μ, assigned to indole NH.

3-(3,4,5-Trimethoxybenzoxy)-4-methoxybenzaldehyde (X).—Isovanillin[15] (3.0 g.) was dissolved in freshly distilled pyridine and the solution cooled and stirred vigorously while a slight excess of 3,4,5-trimethoxybenzoyl chloride[16] was added slowly in small portions. After the solution had been kept for several hours at room temperature, the pasty mixture was poured into 2 l. of 3 *N* hydrochloric acid containing some ice. The precipitate was collected, washed with water, and dried, giving 5.5 g. (81%) of a slightly yellow colored solid, m.p. 145–150°, that was pure enough for the next step. The analytical sample formed irregular crystals, m.p. 158–160°, from benzene–petroleum ether (60–90°).

Anal. Calcd. for $C_{18}H_{18}O_7$: C, 62.42; H, 5.24. Found: C, 62.88; H, 5.17.

(14) R. D. Haworth and W. H. Perkin, Jr., *J. Chem. Soc.*, **127**, 1434 (1925).

(15) A. Lovecy, R. Robinson, and S. Sugasawa, *ibid.*, 817 (1930).

(16) W. H. Perkin, Jr., and C. Weizmann, *ibid.*, **89**, 1649 (1906).

3-(3,4,5-Trimethoxybenzoxy)-4-methoxybenzyl Alcohol (XI).—A pasty suspension of 3.0 g. of the aldehyde in methanol was added in small portions to a cooled solution (5%) containing 1 g. of sodium borohydride in methanol. After the reaction was complete the excess hydride was destroyed by dropwise addition of dilute sulfuric acid. The precipitated alcohol was collected, washed with water, and dried; yield, 2.5 g. (82%); m.p. 120–125°. The colorless alcohol formed irregular crystals from benzene–petroleum ether, m.p. 128–129°.

Anal. Calcd. for $C_{18}H_{20}O_7$: C, 62.06; H, 5.79. Found: C, 62.46; H, 5.70.

3-(3,4,5-Trimethoxybenzoxy)-4-methoxybenzyl Bromide (XII). A well stirred suspension of the alcohol XI (2.0 g.) in dry ether (100 ml.) was maintained at 0° and treated dropwise with 1.0 g. of phosphorus tribromide. The mixture was allowed to stand overnight at room temperature, and then shaken repeatedly with cold water until free from acid. The ethereal solution was dried, the ether evaporated, and the residue crystallized from benzene–petroleum ether as colorless nodules; m.p. 112–113°; yield, 1.7 g. (74%).

Anal. Calcd. for $C_{18}H_{19}O_6Br$: C, 52.57; H, 4.66. Found: C, 52.56; H, 4.71.

2-Methoxy-3-(3,4,5-trimethoxybenzoxy)indolo[2-3-*a*]acridizinium (IX) Perchlorate.—One gram of the pyridoindole carboxaldehyde IV was quaternized with XII in the usual way. To the crude quaternary salt in 25 ml. of methanol, 10 ml. of concentrated hydrochloric acid was added, and cyclization carried out as usual, except that heating was continued for 1 hr. instead of the usual 15 min. The acid was evaporated, the resulting oil taken up in methanol and precipitated as the perchlorate by the addition of 20% perchloric acid. The oily perchlorate was washed with water and recrystallized from acetonitrile–ether. The product which showed some signs of decomposition during recrystallization consisted of a red-brown powder; m.p. 203–209° dec.; yield, 2.26 g. (73%). Alcoholic solutions of the product showed a very strong yellow-green fluorescence, and the infrared spectrum showed an absorption in the carbonyl region at 5.75 μ and another absorption in the 2.90-μ region attributed to the NH peak.

Anal. Calcd. for $C_{30}H_{25}N_2ClO_{10} \cdot H_2O$: C, 57.47; H, 4.34; N, 4.47; OCH_3, 19.80. Found: C, 57.41; H, 4.30; N, 4.49; OCH_3, 20.43.

The Solvolysis of 4α- and 4β-Methylcholesteryl *p*-Toluenesulfonate[1a]

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Received April 25, 1963

The hydrolysis of 4α-methylcholesteryl *p*-toluenesulfonate (IX) in 60% aqueous acetone in the presence of potassium acetate yields 55% of 3α,5α-cyclo-4α-methylcholestan-6β-ol (XVIII) together with minor amounts of diene and unrearranged parent alcohol X. The type and distribution of products obtained indicate that this solvolytic reaction is completely analogous to that of cholesteryl *p*-toluenesulfonate. In contrast, under the same conditions, 4β-methylcholesteryl *p*-toluenesulfonate (XVI) yields 80% of 4-methyl-$\Delta^{3,5}$-cholestadiene (XX), 5–7% of the ring-contracted alcohol 3β-(1β-hydroxyethyl)-Δ^5-A-norcholestene (XIX) and a trace of unrearranged parent alcohol (XVII); no 3α,5α-cyclosterol is obtained. Elucidation of the structures of these products and a discussion of factors which may account for the striking difference in solvolytic behavior of IX and XVI are presented.

The 3β-hydroxy-Δ^5 system of steroids represents a useful substrate for the study of homoallylic participation in solvolytic reactions. Under nonacidic conditions, the solvolysis of ester derivatives of this system yields the corresponding homoallylic rearrangement product, namely, a 3α,5α-cyclo-6β substituted steroid.[2] Substantial rate enhancement also is observed[3]; for example, the relative rates of acetolysis at 100° of cholestanyl and cholesteryl *p*-toluenesulfonates are 1:100. Rate acceleration and stereospecific formation of products in the cholesteryl system may be explained in terms of an activation process involving ionization at C-3 facilitated by participation of the C-5–C-6 double bond. The extent of participation in the transition state for ionization depends upon how effectively the p-orbital at C-5 of the double bond can overlap with the developing p-orbital at C-3. Simonetta and Winstein[4] have applied semiempirical molecular orbital calculations to the cholesteryl cation with the important results that (a) at a normal C-3–C-5

(1)(a) Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society for support of this project under Grant 1347-A4; (b) taken in part from the doctoral dissertation of R. M. de Sousa, The Catholic University of America, 1963.

(2) E. S. Wallis, E. Fernholtz, and F. T. Gephardt, *J. Am. Chem. Soc.*, **59**, 137 (1937).

(3) S. Winstein and R. Adams, *ibid.*, **70**, 838 (1948).

(4) M. Simonetta and S. Winstein, *ibid.*, **76**, 18 (1954).