Tetrahydrochloride Monohydrate.—To a stirred mixture of 15.5 g. (102 mmoles) of 2,2′-dithiobisethylamine,[31] 9.90 g. (73.4 mmoles) of potassium carbonate, and 25 ml. of *N,N*-dimethylformamide heated to 80° was added drop by drop over a period of 2 hr. a solution of 14.9 g. (67.0 mmoles) of 8-(bromomethyl)quinoline[38] in 50 ml. of *N,N*-dimethylformamide. The resulting mixture was heated at 80° for an additional 5 hr. and then cooled. The thick slurry thus obtained was poured into 750 ml. of water. The pH of the cloudy mixture was adjusted from 11 to 8–9 with concentrated hydrochloric acid, and the dark oil that separated was extracted from the mixture with benzene (3 × 250 ml.). The benzene extract was washed with water (3 × 50 ml.), treated with Norit, filtered through Celite, dried over magnesium sulfate, and evaporated to dryness under reduced pressure. The residual orange oil, washed down with ethyl alcohol (3 × 25 ml.), was dried for 1 hr. at 60° *in vacuo;* yield 12.6 g. (87%). A 7.7-g. sample of the oily free base was dissolved in 65 ml. of 1 *N* hydrochloric acid and the solution evaporated to dryness under reduced pressure. The solid residue, after trituration in ethyl alcohol (2 × 25 ml.), was collected and dried *in vacuo* over phosphorus pentoxide; yield of a crude hydrochloride 6.81 g. An analytically pure sample (740 mg.) of the tetrahydrochloride monohydrate was obtained in the following manner: A solution of 1.0 g. of the crude hydrochloride in 75 ml. of boiling methyl alcohol was filtered, cooled, and diluted with an equal volume of ethyl ether. The cream-colored solid that precipitated was dried *in vacuo* over phosphorus pentoxide; it decomposed without melting above 200°.

Anal. Calcd. for $C_{24}H_{28}N_4S_2 \cdot 4HCl \cdot H_2O$: C, 48.16; H, 5.39; S, 10.71; Cl, 23.70. Found: C, 47.78; H, 5.40; S, 10.64; Cl, 23.36.

***S*-2-[(8-Quinolylmethyl)amino]ethyl Thiosulfuric Acid (XI).** 1. **From the Disulfide Tetrahydrochloride Monohydrate.**—To a mixture of 600 mg. (1.00 mmole) of 2,2′-dithiobis[*N*-(8-quinolylmethyl)ethylamine] tetrahydrochloride monohydrate and 545 mg. (4.00 mmoles) of sodium acetate trihydrate was added 1.5 ml. of aqueous 10% solution of sulfur dioxide. *p*-Dioxane (0.5 ml.) was added to make the reaction mixture homogeneous. After 2 days the tan needles that had precipitated were collected and dried *in vacuo* over phosphorus pentoxide; yield 450 mg. (76%), m.p. 214° dec.[30] Two recrystallizations from water, followed by drying for 6 hr. at 100° *in vacuo* over phosphorus pentoxide, gave colorless crystals that melted at 193–194° dec.; yield 42%, $\bar{\nu}_{max}^{KBr}$ 1240, 1195, 1175, 1025, 635 cm.$^{-1}$ (SO_3^-).

Anal. Calcd. for $C_{12}H_{14}N_2O_3S_2 \cdot {}^1/_4H_2O$: C, 47.58; H, 4.82; S, 21.17. Found: C, 47.50; H, 4.57; S, 21.55.

2. **From the Disulfide Free Base.**—The free base X in *p*-dioxane was treated with aqueous sulfur dioxide in a manner similar to that described under 1. After 6 days the product had precipitated in 51% yield as pale yellow needles, m.p. 220° dec.[30] Recrystallization from water with the aid of Norit afforded colorless needles that melted at 197–198° dec. after being dried as described above; yield 43%.

Anal. Calcd. for $C_{12}H_{14}N_2O_3S_2$: C, 48.30; H, 4.73; S, 21.49. Found: C, 47.87; H, 4.73; S, 21.60.

Acknowledgment.—The authors are indebted to Mr. Carl R. Stringfellow, Jr., for technical assistance; to Dr. W. C. Coburn, Jr., for aid in the interpretation of the infrared spectra; and to members of the Analytical Section of Southern Research Institute, who performed the spectral and analytical determinations under the direction of Dr. W. J. Barrett.

Investigations in Heterocycles. XI. Tetracyclic and Pentacyclic Indolo[2,3-*a*]quinolizines

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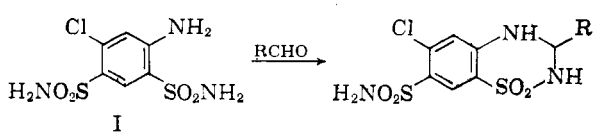
Various procedures have been developed for the synthesis of tetracyclic and pentacyclic indolo[2,3-*a*]quinolizines containing hetero atoms in ring D and ring E, respectively.

In several previous publications from our laboratories[1–4] it was demonstrated that some new and biologically interesting heterocycles could be prepared through application of an intramolecular Mannich reaction. In particular, 4-amino-6-chloro-1,3-benzenedisulfonamide (I) was allowed to react with a wide variety of aldehydes, acetals, and ketones to give rise to dihydrobenzothiadiazine 1,1-dioxides. The chemical and biological significance (*i.e.*, diuretics) of this class of compounds has recently been the subject of an extensive review.[5]



I

It had also been shown that the modified Mannich reaction was useful in the preparation of the new heterocyclic seven-membered ring system 1,2,4,5-tetrahydro-3-methyl-1,3-benzodiazepine.[4]

It was thus considered of interest to extend this investigation to other systems and, in particular, to the indoles. The indoles were selected primarily because of their teleological significance. Moreover, the pharmacological importance of indolic com-

(1) G. deStevens, L. H. Werner, A. Halamandaris, and S. Ricca, Jr., *Experientia*, **14**, 463 (1958).

(2) L. H. Werner, A. Halamandaris, S. Ricca, Jr., L. Dorfman, and G. deStevens, *J. Am. Chem. Soc.*, **82**, 1161 (1960).

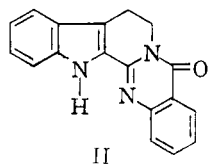
(3) G. deStevens, L. H. Werner, W. E. Barrett, J. J. Chart, and A. A. Renzi, *Experientia*, **16**, 113 (1960).

(4) G. deStevens and M. Dughi, *J. Am. Chem. Soc.*, **83**, 3087 (1961).

(5) E. Schlittler, G. deStevens, and L. H. Werner, *Angew. Chem.*, 1962, in press.

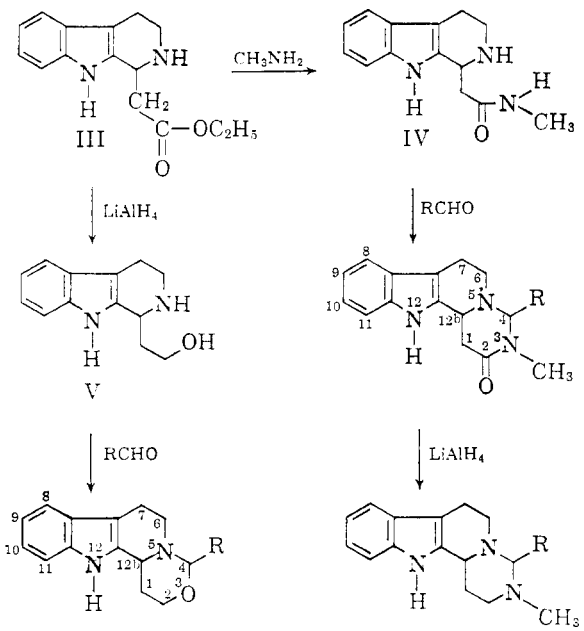
pounds, both of synthetic[6] and natural[7] origin, has been well documented.

Our efforts were directed initially toward the preparation of tetracyclic indoles with a hetero atom in ring D other than the bridgehead nitrogen. Compounds of this type would then bear some similarity to the alkaloid Rutecarpine (II). Moreover, the preparation and properties of such heterocyclic substances have not been heretofore described.



II

The general sequence of reactions leading to these compounds is outlined in Scheme I. Table I lists the various compounds prepared according to this scheme.

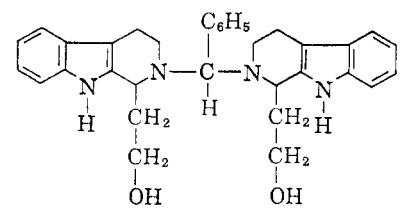


Scheme I

Thus, compounds with hetero atoms at position 3 in ring D were readily synthesized from a common intermediate, namely, 1-carbethoxymethyl-1,2,3,4-tetrahydro-β-carboline (III), which was prepared according to the method described by Kline.[8] It was observed in our laboratory that this ester could be converted in virtually quantitative yields to the corresponding *N*-methylamide (IV) merely by saturating an ethyl alcohol solution of the ester with methylamine. Compound IV was now chemically disposed for an intramolecular Mannich reaction.

Condensation of IV with formaldehyde in refluxing ethyl alcohol with a trace of alkaline catalyst gave rise to a 72% yield of 3-methylaza-1,2,3,4,6,7,-12,12b-octahydro-2-oxoindolo[2,3-*a*]quinolizine. A number of aromatic aldehydes also were used successfully in this condensation reaction. However, it was found that the condensation with aromatic aldehydes could only be effected in refluxing diethylene glycol dimethyl ether. At lower temperatures only starting material was obtained. The reduction of the cyclic amides with lithium aluminum hydride proceeded smoothly to yield compounds with a saturated D ring.

The preparation of compounds in which the hetero atom in ring D other than N_b was oxygen was accomplished through lithium aluminum hydride reduction of III to 1-β-hydroxyethyl-1,2,3,-4-β-carboline (V) followed by treatment of this γ-amino alcohol with formaldehyde to form 1,2,3,4,-6,7,12,12b-octahydro-3-oxaindolo[2,3-*a*]quinolizine (See Table I). It is worthy of note that condensation of the amino alcohol V with benzaldehyde yielded not the expected oxazine derivative but a dimeric substance formulated as VI. The structure of the dimer rests on elemental analysis and spectral data. The preparation of the 6-methyl- and the 9-bromoindolo[2,3*a*]quinolizines outlined in Table I follows similar reaction sequences.



VI

Another modification of ring D was concerned with the synthesis of a tetracyclic compound in which the oxygen atom was now at position 2 (see Scheme II).

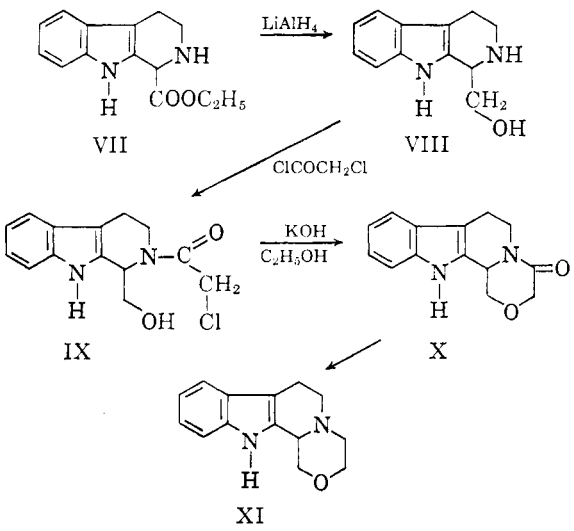
1 - Carbethoxy - 1,2,3,4-tetrahydro - β - carboline (VII) was reduced with lithium aluminum hydride to 1 - hydroxymethyl - 1,2,3,4 - tetrahydro - β - carboline (VIII).[9] Acetylation of compound VIII with chloroacetyl chloride yielded predominantly *N*-acylated substance IX which could be easily separated from the small amount of *O*-acyl impurity. The amide IX was dissolved in ethyl alcohol containing powdered potassium hydroxide and the solution stirred for several hours. The desired product, 1,2,-3,4,6,7,12,12b-octahydro-4-oxo-2-oxaindolo[2,-was 3-*a*]quinolizine (X), was obtained in almost quantitative yield. It should be noted that X is a highly insoluble white crystalline substance. Because of

(6) R. V. Heinzelman, W. C. Anthony, D. A. Lyttle, and J. Szmuszkovicz, *J. Org. Chem.*, **25**, 1548 (1960).

(7) R. E. Woodson, Jr., H. W. Youngken, E. Schlittler, and J. A. Schneider, "Rauwolfia: Botany, Pharmacognosy, Chemistry and Pharmacology," Little, Brown and Co., Boston, 1957,

(8) G. B. Kline, *J. Am. Chem. Soc.*, **81**, 2251 (1959).

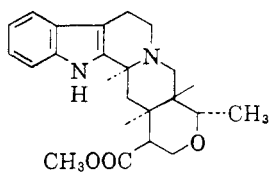
(9) Z. J. Vejdelek, V. Treka, and M. Protiva, *J. Med. and Pharm. Chem.*, **3**, 427 (1961).



Scheme II

this characteristic, its conversion to XI *via* hydride reduction in tetrahydrofuran proceeded only in low yields.

Now it appeared that an obvious extension to this work would be to prepare pentacyclic indoles containing hetero atoms in ring E. There are several members of the indole alkaloid class which are known to contain oxygen in ring E and an example of such a compound is ajmalicine[10] (XII).



XII

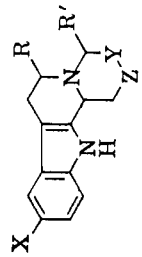
Although these naturally occurring substances do not exhibit any important pharmacological effects, it was hoped that various alterations in ring E might lead to biologically active compounds. In our synthetic approach to this problem, it was felt that the gross structural features associated with ajmalicine should be retained. These included unchanged rings A, B, C, and D, the 19 methyl group, and at least one hetero atom in ring E. For this purpose it was necessary to arrive at a versatile intermediate with which ring E could be readily elaborated. Once again the Mannich reaction was used with good advantage (see Scheme III).

1-Carbethoxymethyl-1,2,3,4-tetrahydro-β-carboline hydrochloride readily condenses with formaldehyde in excess acetone to afford the Mannich base XIII. This substance in turn undergoes base catalyzed ring closure to the desired β-diketone XV. 3-Acetyl-1,2,3,4,6,7,12,12b-octahydro-2-oxoindolo-[2,3-*a*]quinolizine[11] proved to be a versatile plat-

(10) E. Wenkert, B. Wickberg, and C. L. Leicht, *J. Am. Chem. Soc.*, **83**, 5037 (1961).

(11) K. B. Prasad and G. A. Swan, *J. Chem. Soc.*, 2045 (1958).

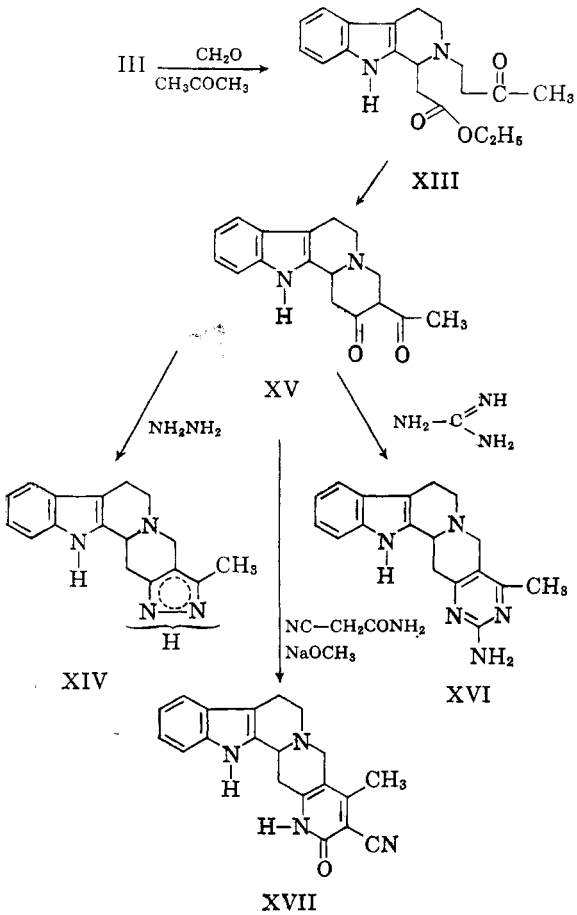
TABLE I. TETRACYCLIC INDOLO[2,3-*a*]QUINOLIZINES



No.	X	Y	Z	R	R′	M.p., °C.	Yield, %	Empirical formula	Calcd., % C	Calcd., % H	Calcd., % N	Found, % C	Found, % H	Found, % N
1	H	N—CH_3	C=O	H	H	167–169	72	$C_{15}H_{17}N_3O^a$	70.56	6.71	16.46	70.44	6.70	16.67
2	H	N—CH_3	CH_2	H	H	156–158	45	$C_{15}H_{19}N_3{}^c$	74.65	7.94	17.42	74.27	8.06	17.47
3	H	N—CH_3	C=O	H	C_6H_5	264–265	60	$C_{21}H_{21}N_3O^a$	76.11	6.39	12.69	75.82	6.30	12.73
4	H	N—CH_3	CH_2	H	C_6H_5	239–240 dec.	55	$C_{21}H_{23}N_3{}^c$	79.44	7.30	13.24	79.42	7.33	13.20
5	H	N—CH_3	C=O	H	*p*-Cl-C_6H_4	277–280	63	$C_{21}H_{20}ClN_3O^a$	68.94	5.51	11.48	68.62	5.52	11.40
6	H	N—CH_3	CH_2	H	*p*-Cl-C_6H_4	231–232 dec.	50	$C_{21}H_{22}ClN_3{}^c$	71.67	6.30	11.94	72.34	6.55	12.21
7	H	N—CH_3	C=O	H	3,4,5-$(CH_3O)_3C_6H_2$	239–241	60	$C_{24}H_{27}N_3O_4{}^a$	68.39	6.46	9.97	68.24	6.50	9.86
8	H	N—CH_3	C=O	CH_3	H	273–275 dec.	77	$C_{16}H_{16}N_2O^b$	71.33	7.11	15.59	71.55	7.32	15.79
9	H	N—CH_3	CH_2	CH_3	H	178–179	60	$C_{16}H_{21}N_3{}^c$	75.24	8.29	16.46	75.38	8.45	16.20
10	Br	N—CH_3	C=O	CH_3	H	277–279 dec.	75	$C_{16}H_{18}BrN_3O^a$	55.18	5.21	12.07	55.32	5.26	11.77
11	Br	N—CH_3	CH_2	CH_3	H	215.5–217	52	$C_{16}H_{20}BrN_3{}^c$	57.49	6.04	12.57	57.93	6.25	13.00
12	H	O	CH_2	H	H	192–193	83	$C_{14}H_{16}N_2O^d$	73.65	7.06	12.28	73.67	7.22	12.42
13	H	O	CH_2	CH_3	H	164–165	78	$C_{15}H_{18}N_2O^d$	74.35	7.49	11.57	74.53	7.70	11.40

Recrystallization solvent: [a] Ethyl alcohol. [b] Methyl alcohol. [c] Ethyl acetate. [d] Acetone–hexane.

form on which to construct a wide variety of pentacyclic compounds, some of which are herein outlined. Hydrazine condensed with XV to form 3a,-4,6,7,12b,13-hexahydro-3-methyl-12*H*-indolo[2,3-*a*]-pyrazolo[4,3-*g*]quinolizine, whereas guanidine carbonate gave rise to 2-amino-5,6,7,8,13b,14-hexahydro-4-methyl-13*H*-indolo[2,3-*a*]pyrimido[5,4-*g*]-quinolizine (XVI). Treatment of the β-diketone with cyanoacetamide in methanol containing two equivalents of sodium methoxide yielded 3-cyano-1,2,5,6,7,8,13b,14-octahydro-4-methyl-13*H*-2-oxoindolo[2,3-*a*]pyrido[3,2-*g*]quinolizine. This structure is preferred to the alternative 1-cyano-2,4,5,6,-7,8,13,*b*,14-octahydro-4-methyl-13*H*-2-oxo-indolo-[2,3-*a*]pyrido[3,2-*g*]quinolizine on the basis of data presented by Walker[12] and Weaver on similar condensation reactions.



Scheme III

Spectral Data.—The ultraviolet absorption maxima of compounds 1 to 13 are listed in Table II. These data preclude the possibility that ring closure by aldehyde condensation could have occurred on Na since the major maximum for such substituted indole nitrogen compounds would be from 236–238 mμ.[13]

(12) G. Walker and B. Weaver, *J. Org. Chem.*, **26**, 4441 (1961).

Table II

Ultraviolet Absorption Data of Tetracyclic Indolo-[2,3-*a*]quinolizines

No. of Compound	λ_{max}, mμ	ε
1	224	37,660
	282	7,600
	289	6,220
2	225	35,930
	280	7,290
	290	6,421
3	223	43,320
	283	8,660
	289	7,100
4	226	40,700
	282	7,780
	290	6,600
5	224	54,060
	282	8,030
	289	6,410
6	226	49,990
	282	7,980
	290	6,915
7	224	52,470
	281	8,730
	289	6,500
8	224	37,500
	282	7,940
	289	6,530
9	226	36,870
	283	7,600
	290	6,410
10	229	39,710
	290	7,630
	299	6,130
11	229	37,140
	290	7,460
	300	6,160
12	226	36,740
	280	7,520
	290	6,160
13	225	36,320
	282	7,570
	290	6,330

The compounds reported in this communication exhibit at least one and in many cases three absorption bands or plateaus in the 2700–2800-cm.$^{-1}$ region of the infrared. Bohlmann[14] has demonstrated that in the quinolizidines the presence of absorption bands in this region are associated with an axial hydrogen at the bridgehead carbon adjacent to the basic nitrogen. Rosen[15] recently has confirmed and expanded upon this rule in the reserpine series. Thus, in the present case the axial conformation of the hydrogen at C-12b or C-13b is confirmed by infrared spectroscopic data, although this assignment was made intuitively on thermodynamic grounds.

Experimental

5-Bromo-3-(2-nitropropenyl)indole.[6]—A mixture of 13.7 g. of ammonium acetate dissolved in 12.5 ml. of acetic acid and 3.8 ml. of acetic anhydride was heated with stirring for

(13) J. Pecher, R. H. Martin, N. Defay, M. Kaisin, J. Peeters, G. van Binst, N. Veryele, and F. Alderweireldt, *Tetrahedron Letters*, **8**, 270 (1961).

(14) F. Bohlmann, *Angew. Chem.*, **69**, 641 (1957).

(15) W. Rosen, *Tetrahedron Letters*, **14**, 481 (1961).

20 min., whereupon a mixture of 23.6 g. (0.112 mole) of 5-bromoindole-3-carboxaldehyde, 63 ml. of nitroethane, and 75 ml. of acetic acid was added with continued stirring. As the solution approached the reflux temperature, 8.8 g. of anhydrous sodium acetate was added followed by dropwise addition of 12.5 ml. of acetic anhydride. After a 2-hr. reflux, the mixture was allowed to cool while 28 ml. of water was added slowly. After standing overnight at room temperature, the precipitate was collected on a filter, washed with dilute acetic acid, and air dried. After one recrystallization from ethyl alcohol 15 g. of pure substance was obtained, m.p. 219–220°.

Anal. Calcd. for $C_{11}H_9BrN_2O_2$: C, 46.99; H, 3.23; N, 9.96. Found: C, 46.93; H, 3.40; N, 10.11.

5-Bromo-α-methyltryptamine Hydrochloride.[6]—A 7.7-g. sample (0.027 mole) of 5-bromo-3-(2-nitropropenyl)indole dissolved in 100 ml. of tetrahydrofuran was added dropwise and with stirring over a 2-hour period to a mixture of 5.3 g. of lithium aluminum hydride in 50 ml. of tetrahydrofuran. The reaction was slowly brought to the reflux temperature duringthis addition and then was refluxed for an additional 2 hr. After standing overnight at room temperature 10 ml. ofwater and 30 ml. of tetrahydrofuran were added with stirring followed by 5 ml. of 5% sodium hydroxide solution. Seventy-five milliliters of ether was then added and the heterogeneous mixture filtered. The ethereal extract was dried over anhydrous potassium carbonate and then filtered. Isopropyl alcohol saturated with dry hydrogen chloride was added to the dry extract until a precipitate ceased to form. The white powder was recrystallized from ethyl alcohol–ether to give a 63% yield of pure compound, m.p. 249–250°.

Anal. Calcd. for $C_{11}H_{14}BrClN_2$: C, 45.61; H, 4.87; N, 9.67. Found: C, 46.19; H, 4.75; N, 9.86.

The α-methyltryptamine hydrochloride used in these studies was prepared in essentially the same manner.[6]

1-(*N*-Methylcarboxyamidomethyl)-1,2,3,4-tetrahydro-β-carboline (IV).—1-Carbethoxymethyl-1,2,3,4-tetrahydro-β-carboline[8] (17.5 g.) was dissolved in 250 ml. of ethyl alcohol and this solution was saturated over a 4-hr. period with methylamine. The reaction temperature was not allowed to exceed 65°. The solution was concentrated to one-half its volume on the water bath *in vacuo* whereupon crystalline amide began to separate from solution. After standing in the refrigerator overnight the crystals were collected on a Buchner funnel and washed with a small amount of cold ethyl alcohol. The yield of crude amide, m.p. 213–215°, was 13.5 g. (82%). The material was substantially pure enough to use in other transformations. One gram recrystallized from ethyl alcohol gave analytically pure substance, m.p. 215°.

Anal. Calcd. for $C_{14}H_{17}N_3O$: C, 69.25; H, 6.98; N, 17.31. Found: C, 69.18; H, 6.93; N, 17.38.

1-Carbethoxymethyl-3-methyl-1,2,3,4-tetrahydro-β-carboline hydrochloride was synthesized according to the method outlined by Kline.[8]

A solution of 16.6 g. (0.10 mole) of carbethoxypyruvic acid dissolved in 50 ml. of ethyl alcohol was added in three equal portions over a period of 24 hr. to a solution of 16.2 g. (0.073 mole) of α-methyltryptamine hydrochloride dissolved in 300 ml. of ethyl alcohol maintained under reflux with vigorous stirring. After refluxing the yellow solution for an additional 24 hr., during which time crystalline product separated, the reaction mixture was chilled for 2 days. The product was collected and recrystallized from ethyl alcohol to give 6.5 g. of white crystals, m.p. 239–240°.

Anal. Calcd. for $C_{16}H_{21}ClN_2O_2$: C, 62.24; H, 6.86; N, 9.08. Found: C, 62.59; H, 7.03; N, 9.03.

5-Bromo-1-carbethoxymethyl-3-methyl-1,2,3,4-tetrahydro-β-carboline hydrochloride, m.p. 260–261°, was prepared similarly in 55% yield.

Anal. Calcd. for $C_{16}H_{20}BrClN_2O_2$: C, 48.21; H, 4.85; N, 7.49. Found: C, 48.58; H, 5.00; N, 7.68.

5-Bromo-1-(*N*-methylcarboxamidomethyl)-3-methyl-1,2,3,4-tetrahydro-β-carboline, m.p. 217–218°, was prepared in this way in 50% yield. It was recrystallized from ethyl acetate.

Anal. Calcd. for $C_{15}H_{18}BrN_3O$: C, 53.58; H, 5.40; N, 12.50. Found: C, 53.81; H, 5.48; N, 12.50.

1-(*N*-Methylcarboxamidomethyl)-3-methyl-1,2,3,4-tetrahydro-β-carboline, m.p. 219–221°, was also prepared as previously described in 61% yield. It was recrystallized from acetone–hexane.

Anal. Calcd. for $C_{15}H_{19}N_3O$: C, 70.00; H, 7.44; N, 16.33. Found: C, 69.86; H, 7.54; N, 16.31.

General Method for the Preparation of 3-Methylaza-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizines. The following example will serve to illustrate the procedure when formaldehyde was used as the condensing agent.

(a) **3-Methylaza-1,2,3,4,6,7,12,12b-octahydro-2-oxoindolo[2,3-*a*]quinolizine.**—To 9.6 g. (0.04 mole) of 1-(*N*-methylcarboxamidomethyl)-1,2,3,4-tetrahydro-β-carboline (IV) dissolved in 180 ml. of ethyl alcohol, there were added 4 ml. of 37% formaldehyde solution and 20 ml. of water containing 2 pellets of sodium hydroxide. The reaction mixture was heated at 60° for 30 min. after which time the solution was cooled and neutralized with dilute hydrochloric acid. The solvent was removed on a steam bath *in vacuo* and the remaining semisolid residue was triturated with a small amount of ethyl alcohol and allowed to stand at room temperature overnight. The tan precipitate was collected and recrystallized from ethyl alcohol or methyl alcohol containing a small amount of water. It was also found that the condensation with formaldehyde could be carried out without sodium hydroxide catalyst.

(b) **Condensation with Aromatic Aldehydes.** A mixture of 2.43 g. (0.01 mole) of IV and 1.06 g. (0.01 mole) of benzaldehyde was dissolved in 20 ml. of diethylene glycol dimethyl ether and the solution was refluxed for 2 hr. After chilling the solution overnight, the crystalline precipitate was collected and recrystallized from chloroform.

Lithium Aluminum Hydride Reduction of Amides in Table I.—The reduction of Compound 1 to 2 will serve as the general example.

3-Methylaza-1,2,3,4,6,7,12,12b-octahydro-2-oxoindolo-[2,3-*a*]quinolizine (6.1 g.; 0.024 mole) was dissolved in 300 ml. of tetrahydrofuran and the clear solution was added quite rapidly with stirring to a mixture of 1.9 g. of lithium aluminum hydride in 250 ml. of tetrahydrofuran. After refluxing for 2 hr. an additional 1 g. of lithium aluminum hydride was added and refluxing was continued overnight. The salt was decomposed with 16.5 ml. of ice water. The mixture was then filtered and the yellow colored tetrahydrofuran solution was separated and dried over magnesium sulfate. After filtering off the drying salt, the filtrate was evaporated to dryness *in vacuo*. A viscous oil was obtained which became crystalline after triturating several times with dry ether. The white powder was recrystallized from ethyl acetate.

1,2,3,4,6,7,12,12b-Octahydro-3-oxaindolo[2,3-*a*]quinolizine.—Five grams (0.02 mole) of 1-carbethoxymethyl-1,2,3,4-tetrahydro-β-carboline was dissolved in 100 ml. of tetrahydrofuran and then added dropwise with efficient stirring to a mixture of 2.5 g. of lithium aluminum hydride in 50 ml. of tetrahydrofuran. The mixture was refluxed for 18 hr. After decomposing the excess lithium aluminum hydride with 15 ml. of ice water, the mixture was filtered, the salts were washed with tetrahydrofuran, and the filtrate was dried over magnesium sulfate. The dried extract was concentrated *in vacuo* on the steam bath to yield a brown oil which slowly crystallized. Recrystallization from benzene afforded 2.2 g. of 1-(β-hydroxyethyl)-1,2,3,4-tetrahydro-β-carboline, (V), m.p. 135–136°.

Anal. Calcd. for: $C_{13}H_{16}N_2O$: C, 72.19; H, 7.46; N, 12.95. Found: C, 72.49; H, 7.50; N, 12.69.

One gram (0.0046 mole) of the amino alcohol V and 0.14 g. of paraformaldehyde were added to 50 ml. of ethyl alcohol containing 1 ml. of glacial acetic acid. The

mixture was refluxed for 5 hr. whereupon complete solution was obtained. The solvent was then removed *in vacuo* affording a yellow viscous residue which was treated with 50 ml. of water containing 1.3 g. of sodium bicarbonate. On standing overnight the residue became crystalline. It was collected on a filter and washed well with water. After two recrystallizations from acetone-hexane containing Norite, an 85% yield of white crystalline 1,2,3,4,6,7,12,12b-octahydro-3-oxaindolo[2,3-*a*]quinolizine was obtained.

The preparation of **1-(β-hydroxyethyl)-3-methyl-1,2,3,4 tetrahydro-β-carboline** was similar to that described for compound V. It was recrystallized from ethyl acetate to give a white powder, m.p. 181–183°.

Anal. Calcd. for $C_{14}H_{18}N_2O$: C, 72.99; H, 7.88; N, 12.16. Found: C, 72.95; H, 8.01; N, 12.07.

6-Methyl-1,2,3,4,6,7,12,12b-octahydro-3-oxaindolo[2,3-*a*] quinolizine was prepared from the above amino alcohol in the usual manner.

Condensation of 1-(β-Hydroxyethyl)-1,2,3,4-tetrahydro-β-carboline with Benzaldehyde.—One gram (0.0046 mole) of compound V and 0.7 g. (0.0069 mole) of benzaldehyde were dissolved in 30 ml. of benzene and the resulting solution was refluxed for 16 hr. with a water separator attached to the apparatus. After removal of the benzene *in vacuo*, the residual oil crystallized on standing (1.6 g.). This substance after several recrystallizations from cyclohexane, was obtained in analytically pure form, m.p. 143–150°. The elemental analysis corresponds very closely to a dimer with 2 moles of benzene of crystallization. Infrared absorption shows one strong band at 3390 cm.$^{-1}$ for —OH. Bonded —NH of indole at 3050(w) cm.$^{-1}$. $\lambda_{max}^{C_2H_5OH}$ 226 mμ ($E_{1cm}^{1\%}$ = 1,204.2); 282 mμ ($E_{1cm}^{1\%}$ = 228.1); 290 mμ ($E\,1_{1cm}^{1\%\,-1}$ = 188.1).

Anal. Calcd. for: $C_{45}H_{48}N_4O_2$: C, 79.85; H, 7.25; N, 8.30. Found: C, 79.68; H, 7.36; N, 8.20.

2-Chloroacetyl-1-hydroxymethyl-1,2,3,4-tetrahydro-β-carboline (IX).—To a mixture of 84 ml. of ethylene dichloride and 1.9 g. of sodium hydroxide dissolved in 56 ml. of water there was added 6.5 g. (0.0032 mole) of 1-hydroxymethyl-1,2,3,4-tetrahydro-β-carboline. The reaction mixture was chilled to 0° and treated dropwise with 5.3 g. of chloroacetylchloride. During the addition (35 min.) the reaction temperature was not allowed to rise above 0°. After addition of the acid chloride, the temperature was allowed to rise slowly (3 hr.) to room temperature and the ethylene dichloride layer was then separated. This extract was dried over sodium sulfate, filtered, and the solvent removed *in vacuo* to afford a powder which was recrystallized several times from petroleum ether (b.p. 40–60°). Even after several recrystallizations the substance contained a slight amount of *O*-acetyl derivative impurity as evidenced by the weak 1735 cm.$^{-1}$ absorption band in the infrared. However, the compound, m.p. 172–175°, was substantially pure enough to carry on to the next step.

Anal. Calcd. for: $C_{14}H_{15}ClN_2O_2$: C, 60.32; H, 5.43; N, 10.05. Found: C, 59.53; H, 5.46; N, 9.52.

1,2,3,4,6,7,12,12b-Octahydro-4-oxo-2-oxaindolo[2,3-*a*]-quinolizine (X).—2-Chloroacetyl-1-hydroxymethyl-1,2,3,4-tetrahydro-β-carboline (0.5 g.) was dissolved in 15 ml. of absolute ethyl alcohol containing 0.20 g. of powdered potassium hydroxide. The solution was stirred at room temperature for 4 hr. The product plus potassium chloride began to separate out of solution within 15 min. The precipitate was collected on a filter, washed with a small amount of water, and air dried. One recrystallization from excess ethyl alcohol afforded 0.32 g. of white felted needles, m.p. 250–251°.

Anal. Calcd. for $C_{14}H_{14}N_2O_2$: C, 69.41; H, 5.83; N, 11.56. Found: C, 69.25; H, 6.03; N, 11.33.

1,2,3,4,6,7,12,12b-Octahydro-2-oxaindolo[2,3-*a*]quinolizine Hydrochloride (XI).—Compound X (0.5 g.) was heated under reflux for 24 hr. in 300 ml. of tetrahydrofuran containing 0.6 g. of lithium aluminum hydride. After decomposing the excess hydride with 5 ml. of water, the mixture was filtered, the salts washed with tetrahydrofuran, and the filtrate dried over $MgSO_4$. The dried extract was filtered, and the filtrate was concentrated *in vacuo* on the steam bath to yield a powder which was dissolved in 5 ml. of ethyl alcohol and then treated with 2 ml. of ethyl alcohol containing hydrogen chloride. The solution was treated with ether. A white powder was obtained which was recrystallized from ethyl alcohol to yield a white crystalline substance, m.p. 278–280°.

Anal. Calcd. for $C_{14}H_{16}N_2O\cdot HCl$: C, 63.51; H, 6.47; N, 12.28. Found: C, 63.16; H, 6.80; N, 12.15.

3a,4,6,7,12b,13-Hexahydro-3-methyl-12*H*-indolo[2,3-*a*]-pyrazolo[4,3-*g*]quinolizine (XIV). Four grams (0.014 mole) of 3-acetyl-1,2,3,4,6,7,12,12b-octahydro-2-oxoindolo[2,3-*a*]-quinolizine dissolved in 200 ml. of ethyl alcohol was allowed to react under reflux with 1 ml. of 99% hydrazine hydrate. A precipitate was formed during the reflux period. The reaction mixture was kept at 0° overnight and then filtered. Two recrystallizations from ethyl alcohol–water gave a 75% yield of product, m.p. 310–314°.

Anal. Calcd. for $C_{17}H_{18}N_4$: C, 73.35; H, 6.52; N, 20.13. Found: C, 72.85; H, 6.68; N, 19.90.

2-Amino-5,6,7,8,13b,14-hexahydro-4-methyl-13*H*-indolo-[2,3-*a*]pyrimido[5,4-*g*]quinolizine (XVI).—The β-diketone XV (2.84 g., 0.01 mole) and guanidine carbonate (0.95 g., 0.01 mole) were dissolved in 200 ml. of ethyl alcohol and the resulting solution was heated under reflux for 18 hr. After chilling the solution overnight, the precipitate was collected and recrystallized from ethyl alcohol. A light tan powder, m.p. 278° was obtained whose elemental analysis indicated that the substance contained 1 mole of ethyl alcohol of crystallization.

Anal. Calcd. for $C_{18}H_{19}N_5\cdot C_2H_5OH$: C, 68.83; H, 6.80. Found: C, 69.01; H, 6.83.

The maleic acid salt was prepared by dissolving the indolic compound in ethyl alcohol and then adding 1 mol. equiv. of maleic acid dissolved in ethyl alcohol. On standing, crystals were obtained which were recrystallized from ethyl alcohol, m.p. 234–235°.

Anal. Calcd. for $C_{18}H_{19}N_5\cdot C_4H_4O_4$: C, 62.70; H, 5.51; N, 16.62. Found: C, 62.82; H, 5.75; N, 16.34.

3-Cyano-1,2,5,6,7,8,13b,14-octahydro-4-methyl-2-oxo-13*H*-indolo[2,3-*a*]pyrido[3,2-*g*]quinolizine (XVII).—A solution of 1.42 g. (0.005 mole) of XV dissolved in 50 ml. of methyl alcohol containing 0.50 g. (0.01 mole) of sodium methoxide was treated with 0.45 g. (0.005 mole) of cyanoacetamide and the whole was refluxed on the steam bath for 4 hr. The solution was then chilled and neutralized with acetic acid. The resulting precipitate was collected on a filter and recrystallized from ethyl alcohol to afford a 50% yield of yellow crystals, m.p. 340°.

Anal. Calcd. for $C_{20}H_{18}N_4O$: C, 72.61; H, 5.49; N, 16.94. Found: C, 72.83; H, 5.77; N, 16.65.

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