[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF MICHIGAN]

Alstonia Alkaloids. VIII. Synthesis of Tetra- and Pentacyclic Quaternary Carboline Analogs of Alstoniline by Fischer Indole Ring Closure.[1,2,3]

ROBERT C. ELDERFIELD, JEANNE M. LAGOWSKI, ORVILLE L. McCURDY,[4] AND STEPHEN L. WYTHE[5]

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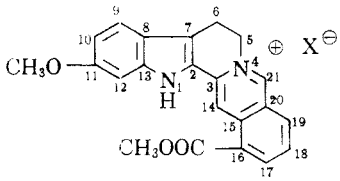
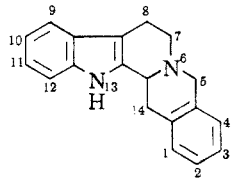
Synthesis of a series of penta- and tetra-cyclic β-carbolines by application of the Fischer indole synthesis to 1-keto-1,2,3,4-tetrahydroquinolizinium salts is described. Nitration and sulfonation of 3-methylisoquinoline has been shown to occur primarily at the 5 position.

The structure of alstoniline, a minor alkaloid of *Alstonia constricta*, F. Muell., has been shown to be represented by I.[6,7] The unsaturation of the ring



I



II

system of alstoniline is unique among the naturally occurring pentacyclic β-carbolines and appears to offer certain advantages from the synthetic point of view which are absent in other members of this general class of substances. Thus, the lack of an asymmetric center eliminates configurational problems and the possibility of introduction of functional groups into the molecule combined with the possibility of varying the degree of unsaturation in Rings C, D, and E are attractive from the standpoint of the synthesis of compounds which may possess hypertensive or tranquilizing properties. In the present communication we wish to report an investigation of the synthesis of tetra- and pentacyclic quaternary β-carbolines by application of the Fischer indole synthesis to ketones derived from pyridine and isoquinoline.

When this work was started no reports of the synthesis of tetra- or penta-cyclic quaternary β-carbolines in which Ring C is saturated and Ring D (and Ring E) is aromatic had appeared. The synthesis of sempervirine in which Rings C and D are aromatic, by Woodward and McLamore[8] represents the only reported example of the synthesis of a quaternary carboline of this type by methods other than those involving dehydrogenation of saturated systems. After the present investigation was substantially complete, Sugasawa, Terashima, and Wanaoka[9] described the synthesis of 6,7-dihydro-12*H*-indolo[2.3-*a*]quinolizinium bromide by a different route than the one here reported.

Several examples of the application of the Fischer indole synthesis to the preparation of compounds related to the pentacyclic β-carbolines but with ring C open have appeared.

Julian and coworkers[10] prepared tetrahydroyobyrine by cyclization of the phenylhydrazone of *n*-propyl-3-isoquinolyl ketone and analogs of alstoniline with Ring C open have been prepared by the same general route.[11] Clemo and Swan[12] have synthesized II by ring closure of the phenylhydrazone of the appropriate tricyclic ketone.

In order to gain experience in the application of the Fischer method attention was first turned to the synthesis of substances related to alstoniline but which did not carry the carbomethoxy group in position 16.[13] The general synthetic scheme followed for the preparation of these compounds is represented by the sequence illustrated. 3-Methylisoquinoline (III) was oxidized to isoquinoline-3-carboxaldehyde (IV) with selenium dioxide essentially according to Teague and Roe.[14] Reaction of IV with

(1) For paper VII in this series see H. Boaz, R. C. Elderfield, and E. Schenker, *J. Am. Pharm. Assoc. Sci. Ed.*, **46**, 510 (1957).

(2) This work was supported in part by Research Grant H-1733 from the National Heart Institute of the Public Health Service.

(3) Portions of this paper are taken from doctoral dissertations submitted by Jeanne M. Lagowski, Orville L. McCurdy, and Stephen L. Wythe.

(4) Eli Lilly Fellow in Chemistry 1954–55.

(5) Eli Lilly Fellow in Chemistry 1952–53.

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

(7) R. C. Elderfield and O. L. McCurdy, *J. Org. Chem.*, **21**, 295 (1956).

(8) R. B. Woodward and W. M. McLamore, *J. Am. Chem. Soc.*, **71**, 379 (1949).

(9) S. Sugasawa, M. Terashima, and Y. Wanaoka, *Pharm. Bull., Pharm. Soc. Japan.*, **4**, 16 (1956).

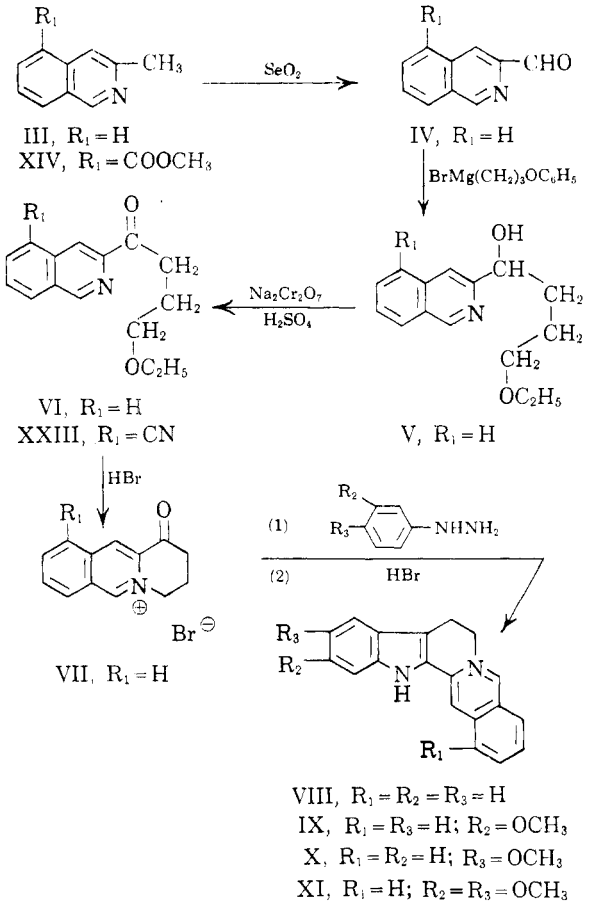
(10) P. L. Julian, W. J. Karpel, A. Magnani, and E. W. Meyers, *J. Am. Chem. Soc.*, **70**, 180 (1948).

(11) R. C. Elderfield and S. L. Wythe, *J. Org. Chem.*, **19**, 693 (1954).

(12) G. R. Clemo and G. A. Swan, *J. Chem. Soc.*, 617 (1946); 487 (1949).

(13) The numbering in the skeleton represented by alstoniline (I) is confusing. Common practice has led to the adoption of the numbering scheme shown in I for alkaloids derived from the parent system. On the other hand the systematic name, benzo[g]indolo[2.3-*a*]quinolizine and the numbering system shown in II is approved by the Ring Index. In this paper the system shown in II will be used.

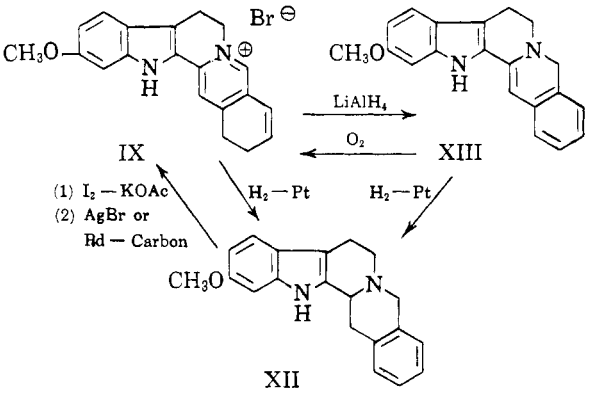
(14) C. E. Teague, Jr., and A. Roe, *J. Am. Chem. Soc.*, **73**, 688 (1951).



γ-ethoxypropylmagnesium bromide gave γ-ethoxypropyl-3-isoquinolinemethanol (V) which was in turn oxidized to the ketone (VI). Treatment of VI with hydrobromic acid resulted in cleavage of the ether and cyclization to give 1-keto-1,2,3,4-tetrahydrobenzo[*b*]quinolizinium bromide (VII). Reaction of VII with phenylhydrazine, *m*- and *p*-methoxyphenylhydrazine, and 3,4-dimethoxyphenylhydrazine gave the corresponding phenylhydrazones which were cyclized with hydrobromic acid to give 7,8-dihydro-13*H*-benzo[*g*]indolo[2.3-*a*]quinolizinium bromide (VIII) and the 11-methoxy (IX), the 10-methoxy (X), and the 10,11-dimethoxy (XI) derivatives of VIII, respectively.

Ring closure of the *m*-methoxyphenylhydrazone of VII can conceivably lead to the formation of two isomers. However, no evidence for the presence of a second isomer was noted. It thus appears that this ring closure follows the general rule in quinoline and indole syntheses involving a methoxyl group *meta* to the ring nitrogen that closure occurs exclusively *para* to the methoxyl group.[15]

The colors of the indoloquinolizinium bromides are of some interest. VIII and IX are orange, X is yellow, and XI is brick red. The ultraviolet spectrum of IX is nearly identical with that of alstoniline hydrochloride whereas the spectra of X and XI differ considerably from the spectrum of IX. A similar effect of the position of methoxyl substituents on the ultraviolet spectra of other indoles has been noted previously.[16] Catalytic reduction of VIII gave 5,7,8,13,13*b*,14-hexahydrobenzo[*g*]indolo[2.3-*a*]quinolizine (II) which has previously been prepared by a number of routes.[12,17,18] Conversion of VIII to II furnishes a convenient proof for the structure assigned to VIII. Further, certain of the reactions undergone by IX furnish confirmation for the unsaturated system previously assigned to alstoniline. Thus, IX was reduced to 11-methoxy-5,7-,8,13,13*b*,14-hexahydrobenzo[*g*]indolo[2.3-*a*]quinolizine (XII) which is analogous to tetrahydroalstoniline. The ultraviolet curves of tetrahydroalstoniline and XII are very similar.



Dehydrogenation of XII with iodine and potassium acetate or catalytically with palladium resulted in aromatization of ring D and regeneration of IX. An analogous dehydrogenation of II has been noted by Swan.[19] Inasmuch as alloyohimbane, in which rings C, D, and E are saturated, undergoes dehydrogenation in Ring C to give tetradehydroalloyohimbane[20] it appears that the tetrahydroisoquinoline ring system is dehydrogenated more readily to an isoquinoline than the tetrahydro-β-carboline is to a carboline. Dehydrogenation of XII to IX was accomplished also slowly with air. Reduction of IX with lithium aluminum hydride gave a dihydro compound, presumably XIII, by reduction of the quaternary azomethine linkage. XIII was readily oxidized back to IX by atmospheric oxygen and absorbed one mole of hydrogen on catalytic reduction to give XII. It is noteworthy that neither the free bases of XII or XIII underwent oxidation by air to give a compound of the type of alstoniline oxide.[7] The influence of the carbomethoxyl group in alstoniline in promoting formation of alstoniline oxide is some-

(15) C. Mentzer, *Compt. rend.*, **222**, 1176 (1946); L. Bradford, T. J. Elliot, and F. M. Rowe, *J. Chem. Soc.*, 437 (1947); W. O. Kermack, W. H. Perkin, Jr., and R. Robinson, *J. Chem. Soc.*, **119**, 1602 (1921).

(16) N. Neuss, H. E. Boas, and J. W. Forbes, *J. Am. Chem. Soc.*, **76**, 2463 (1954).

(17) J. Jost, *Helv. Chim. Acta*, **32**, 1297 (1949).

(18) K. T. Potts and Sir Robert Robinson, *J. Chem. Soc.*, 2675 (1955).

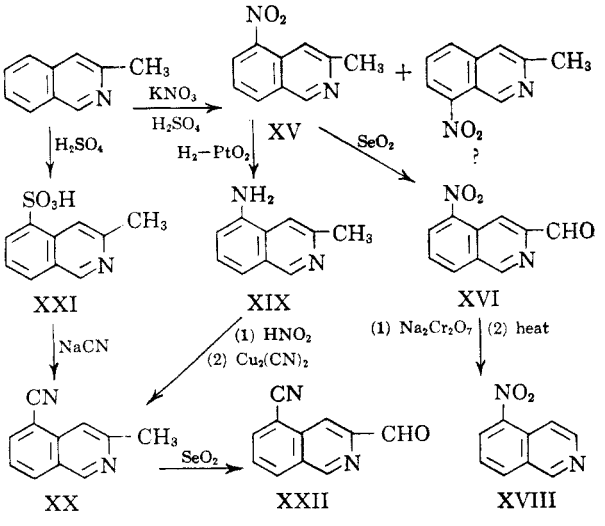
(19) G. A. Swan, *J. Chem. Soc.*, 1720 (1949).

(20) A. LeHir, M. M. Janot, and R. Goutarel, *Bull. soc. chim. France*, 1027 (1953).

what unexpected. It is known that a nitro group in the 5 position of isoquinoline promotes pseudo base formation by increasing the electrophilic strength of the carbon atom at the 1 position.[21] A similar effect of the electron-attracting carbomethoxyl group may be operative in alstoniline.

For the synthesis of alstoniline itself, substantially the same series of reactions as those used for the synthesis of IX was contemplated. Rather than starting from III, the isoquinoline, XIV, carrying a carbomethoxyl group or some group potentially convertible to a carbomethoxyl group was required. Two routes to the desired intermediate were explored.

Isoquinoline itself nitrates in the 5 position[22] and a methyl group in the 3 position would not be expected to alter the orientation appreciably. Bergstrom and Patterson[23] nitrated 3-methylisoquinoline with fuming nitric and sulfuric acids and obtained a major and a minor product but did not prove the structure of either. On nitration with potassium nitrate in sulfuric acid 3-methylisoquinoline gives a major product, m.p. 109–110°, and a minor one, m.p., 85–90°. The major product was shown to be the desired 3-methyl-5-nitroisoquinoline (XV) as follows. Oxidation with selenium dioxide gave 5-nitroisoquinoline-3-carboxaldehyde (XVI) which was not purified but rather was oxidized in the crude state to 5-nitroisoquinoline-3-carboxylic acid (XVII) with sodium dichromate in dilute sulfuric acid. Oxidation of XV stepwise in this fashion gives much better over-all yields of XVII than direct one-step oxidation. When heated above its melting point XVII gave 5-nitroisoquinoline (XVIII) identical with a known sample. The lower melting nitro compound is presumably 3-methyl-8-nitroisoquinoline although its structure



(21) R. C. Elderfield, *Heterocyclic Compounds*, Vol. 4, John Wiley and Sons, Inc., New York, 1952, p. 469.

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

(23) F. W. Bergstrom and R. E. Patterson, *J. Org. Chem.*, **10**, 479 (1945).

was not proved. A route was thus opened to the desired potential isoquinolinecarboxylic acid.

Catalytic reduction of XV over platinum oxide gave 5-amino-3-methylisoquinoline (XIX) from which a poor yield of 5-cyano-3-methylisoquinoline (XX) was obtained on application of the Sandmeyer reaction. Substitution of nickel cyanide[24] for cuprous cyanide did not improve the yield of XX. In view of the discouraging yield of XX, attention was devoted to the preparation of XX from 3-methylisoquinoline-5-sulfonic acid (XXI). Sulfonation of 3-methylisoquinoline occurs in the 5 position as shown by conversion of the sulfonic acid (XXI) to XX on fusion with sodium cyanide. Although the yield of XX by this route is only about 15%, it still is to be preferred to the Sandmeyer procedure.

Oxidation of XX with selenium dioxide gave 5-cyanoisoquinoline-3-carboxaldehyde (XXII). At this point the reaction of XXII with γ-ethoxypropylmagnesium bromide was attempted paralleling the similar reaction of IV. It was hoped that the aldehyde group of XXII would react selectively faster with the Grignard reagent than the cyano group.[25] The cyano group could then be converted to the carbomethoxyl group at some later stage of the reaction sequence. However, oxidation of the crude reaction product failed to yield any of the desired 5-cyano-3-isoquinolyl-γ-ethoxypropyl ketone (XXIII).

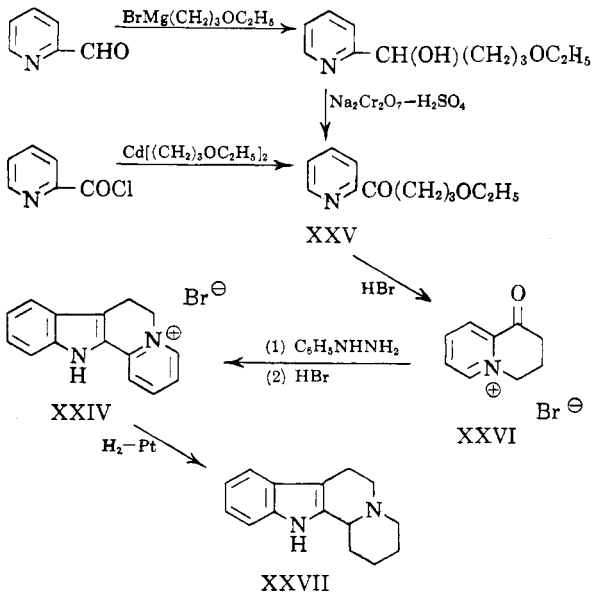
The Grignard reaction of γ-ethoxypropylmagnesium bromide was then attempted on isoquinoline-3-carboxaldehyde-5-carboxylic acid which was in turn prepared by hydrolysis of the cyano group in XXII. The thought was that an extra mole of reagent would merely react with the hydrogen of the carboxyl group which would then be regenerated during decomposition of the Grignard addition compound. Oxidation of the crude reaction product with dichromate did, indeed, give a poor yield of the desired ketone as the 2,4-dinitrophenylhydrazone. However, the yields in this series of reactions were so discouragingly low that this approach was abandoned.

In another attempt to obtain the ketone (XXIII) the acid chloride of 5-cyanoisoquinoline-3-carboxylic acid was brought into reaction with both γ-ethoxypropylmagnesium bromide and γ-ethoxypropylcadmium chloride. In neither case could any XXIII be isolated from the reaction products.

We have also investigated the application of the general synthesis discussed above to the preparation of quaternary tetracyclic β-carbolines preparatory to the preparation of such compounds carrying various functional groups in the molecule. Specifically, 6,7-dihydro-12*H*-indolo[2.3-*a*]quinolizinium bromide (XXIV) has been prepared as follows.

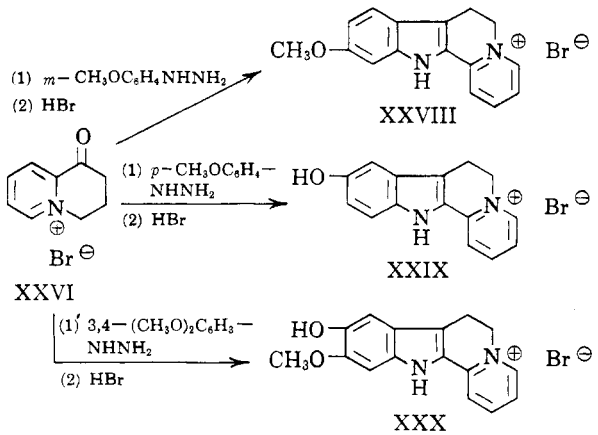
(24) J. A. McRae, *J. Am. Chem. Soc.*, **52**, 4550 (1930).

(25) H. Gilman, *Organic Chemistry, An Advanced Treatise*, 2nd Ed., Vol. 2, John Wiley and Sons, Inc., New York, 1943, p. 501.



The ketone (XXV) was prepared both from pyridine-2-carboxaldehyde *via* the carbinol and from picolinic acid chloride and di(γ-ethoxypropyl)cadmium, a method which failed with an isoquinoline aldehyde. Catalytic hydrogenation of XXIV gave 1,2,3,4,6,7,12,12*b* - octahydroindolo[2.3 - *a*]quinolizine (XXVII) which had previously been prepared by other methods.[26,27] While this work was in progress, Sugasawa, Terashima, and Wanaoka[9] reported the synthesis of XXIV by another method. The physical constants for XXIV reported by them are in agreement with ours.

When the ketone (XXVI) was subjected to the Fischer indole synthesis with *m*-methoxy-, *p*-methoxy- and 3,4-dimethoxyphenylhydrazine, certain departures from the behavior displayed by the isoquinoline ketone (VII) were noted. Reaction with *m*-methoxyphenylhydrazine, proceeded normally to give 6,7-dihydro-10-methoxy-12*H*-indolo[2.3-*a*]-quinolizinium bromide (XXVIII).



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

(27) W. A. Reckhow and D. S. Tarbell, *J. Am. Chem. Soc.*, **74**, 4961 (1952).

However during the course of the analogous reaction with *p*-methoxyphenylhydrazine the ether was cleaved. The product, 6,7-dihydro-9-hydroxy-12*H*-indolo[2.3-*a*]quinolizinium bromide (XXIX), gave analytical data consistent with loss of a methyl group. No ether absorption was present in the infrared spectrum but a hydroxyl band was. Similarly, with 3,4-dimethoxyphenylhydrazine, XXVI underwent cleavage of one methoxyl group to give 6,7-dihydro-9-hydroxy-10-methoxy-12*H*-indolo[2.3-*a*]-quinolizinium bromide (XXX). The structure of XXX is assigned on the basis of analytical data, the infrared spectrum, which showed both hydroxyl and methoxyl absorption, and summation of the ultraviolet curves of XXVIII and XXIX[28] (Fig. 1).

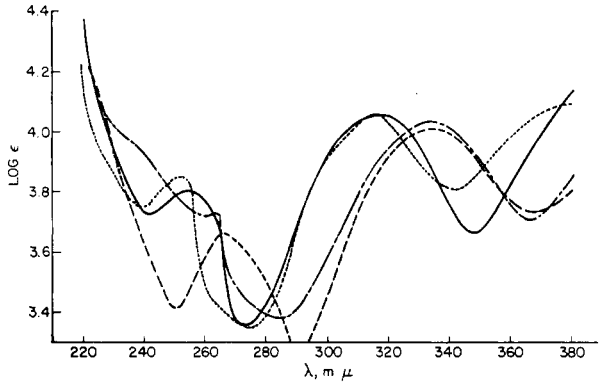


Fig. 1. Ultraviolet absorption curves. ——— 6,7-Dihydro-9-hydroxy-12*H*-indolo[2,3-*a*]quinolizinium bromide (XXIX), - - - - 6,7-Dihydro-10-methoxy-12*H*-indolo[2,3-*a*]quinolizinium bromide (XXVIII), ... 6,7-Dihydro-12*H*-indolo[2,3-*a*]quinolizinium bromide (XXIV), —·—·— 6,7-Dihydro-9-hydroxy-10-methoxy-12*H*-indolo[2,3-*a*]quinolizinium bromide (XXX).

A possible explanation for this difference in behavior in the two series may be found in the fact that whereas, in the isoquinoline series, the quaternary salts crystallized from the reaction mixture, the analogous salts derived from the pyridine derivatives remained in solution and were therefore subject to the action of hydrobromic acid for the entire reaction period.

EXPERIMENTAL[29,30]

γ-Ethoxypropyl-3-isoquinolinemethanol (V). A solution of 40 g. of isoquinoline-3-carboxaldehyde[11] in 1200 ml. of absolute ether was added gradually with stirring to the Grignard reagent prepared from 50 g. of γ-ethoxypropyl bromide[31] and 8.4 g. of magnesium turnings in 400 ml. of absolute ether. It was necessary to activate the magnesium

(28) See ref. 16 for another example of the summation of ultraviolet absorption in the indole series.

(29) All melting points are corrected unless otherwise noted. Boiling points are uncorrected.

(30) Microanalyses by Spang Microanalytical Laboratory, Ann Arbor, Mich. or by Mrs. Anna Griffin, University of Michigan.

(31) L. I. Smith and J. A. Sprung, *J. Am. Chem. Soc.*, **65**, 1276 (1943).

with methyl iodide for the successful preparation of the Grignard reagent. After addition of the aldehyde the mixture was stirred at room temperature for 16 hr., then cooled in an ice bath and decomposed with 1 l. of saturated ammonium chloride solution. The ether layer was separated, washed with water, and dried over anhydrous sodium sulfate. Removal of the solvent left the carbinol as a dark red viscous oil which could not be crystallized. It was used without purification for the next step.

For characterization a picrate was prepared in ethanol. It formed bright yellow crystals, m.p. 122–123°, on recrystallization from absolute ethanol.

Anal. Calcd. for $C_{21}H_{22}N_4O_9$: C, 53.2; H, 4.7. Found: C, 52.8; H, 4.6.

γ-Ethoxypropyl-3-isoquinolyl ketone. (VI). To a stirred solution of 35 g. of the above carbinol in 175 ml. of concentrated sulfuric acid and 1 l. of water a solution of 26.8 g. of sodium dichromate dihydrate in 175 ml. of water was added slowly at room temperature. After stirring for 18 hr. the solution was made basic with sodium hydroxide, the precipitate was collected, dried, and extracted in a Soxhlet extractor. The alkaline filtrate was also extracted with ether. The combined ether extracts were concentrated somewhat and extracted with 10% hydrochloric acid. The acid extract was made basic with sodium hydroxide and the brown precipitate was collected, dried, and extracted in a Soxhlet extractor with 40–60° petroleum ether to yield 15.2 g. of crystalline ketone. After recrystallization from petroleum ether it melted at 79–81°. The yield from isoquinoline-3-carboxaldehyde was 24%.

Anal. Calcd. for $C_{15}H_{17}NO_2$: C, 74.1; H, 6.9. Found: C, 73.8; H, 7.0.

1-Keto-1,2,3,4-tetrahydrobenzo[b]quinolizinium bromide. (VII). A solution of 15.2 g. of the ketone (VI) in 100 ml. of 48% hydrobromic acid was refluxed for 3 hr. After cooling, the hydrobromic acid was removed under reduced pressure. Addition of ether to a solution of the residue in absolute ethanol precipitated white crystals. In some runs cyclization did not occur in the acid solution and a compound, m.p. 157°, which is probably γ-bromopropyl-3-isoquinolyl ketone, was isolated. This was converted to VII by refluxing it in absolute ethanol with ether. VII melted at 244° and the yield was quantitative.

Anal. Calcd. for $C_{13}H_{12}BrNO$: C, 56.1; H, 4.4. Found: C, 55.8; H, 4.7.

Phenylhydrazone of VII. A mixture of 3 g. of VII, 3 g. of phenylhydrazine, and 50 ml. of absolute ethanol was refluxed for 30 min. On cooling 3.5 g. (88%) of the phenylhydrazone of VII separated. On recrystallization from absolute ethanol it formed orange needles which darkened at 285° and melted at 351° (dec.).

Anal. Calcd. for $C_{19}H_{18}BrN_3$: C, 62.0; H, 4.9; N, 11.4. Found: C, 61.9; H, 4.8; N, 11.2.

m-Methoxyphenylhydrazone of VII. This was prepared in 76% yield from 7.5 g. of VII and 4 g. of *m*-methoxyphenylhydrazine as in the preceding case. It crystallized from absolute ethanol as clusters of small orange-yellow needles, m.p. 254° (dec.).

Anal. Calcd. for $C_{20}H_{20}BrN_3O$: C, 60.3; H, 5.1; N, 10.5; Br, 20.1. Found: C, 60.3; H, 5.3; N, 10.3; Br, 20.3.

7,8-Dihydro-13H-benzo[g]indolo[2,3-a]quinolizinium bromide. (VIII). A rapid stream of hydrogen bromide was passed into a solution of 2 g. of the phenylhydrazone of VII in 200 ml. of 95% ethanol. After 30 min. a yellow precipitate formed. Passage of hydrogen bromide was continued for an additional 20 min. and the mixture was cooled. The precipitate was collected and recrystallized from absolute ethanol yielding 1.7 g. (89%) of light orange needles, m.p. 350–351° (dec.).

Anal. Calcd. for $C_{19}H_{15}BrN_2$: C, 65.0; H, 4.3; N, 8.0. Found: C, 65.2; H, 4.5; N, 7.8.

11-Methoxy-7,8-dihydro-13H-benzo[2,3-a]quinolizinium bromide. (IX). This was prepared from 5 g. of the *m*-methoxyphenylhydrazone of VII in 500 ml. of methanol as in the preceding case. The yield of bright orange needles, m.p. 311–312° (dec.) after recrystallization from absolute ethanol, was 4.5 g. (94%).

Anal. Calcd. for $C_{20}H_{17}BrN_2O$: C, 63.0; H, 4.5; N, 7.4. Found: C, 62.9; H, 4.7; N, 7.5.

10-Methoxy-7,8-dihydro-13H-benzo[2,3-a]quinolinizium bromide. (X). The intermediate phenylhydrazone was not isolated. A mixture of 4 g. of VII, 2.2 g. of *p*-methoxyphenylhydrazine and 100 ml. of methanol was refluxed for 30 min. After cooling hydrogen bromide was passed through the mixture as in the above cases. The yield of yellow needles, m.p. 326–327° (dec.) after recrystallization from absolute ethanol, was 3.6 g. (65%).

Anal. Calcd. for $C_{20}H_{17}BrN_2O$: C, 63.0; H, 4.5; N, 7.4. Found: C, 62.8; H, 4.7; N, 7.4.

10,11-Dimethoxy-7,8-dihydro-13H-benzo[2,3-a]quinolizinium bromide (XI). This was prepared by the same method as was X without isolation of the phenylhydrazone from VII and 3,4-dimethoxyphenylhydrazine. The yield of light red needles, m.p. 306–307° (dec.), was 54%.

Anal. Calcd. for $C_{21}H_{19}BrN_2O$: C, 60.7; H, 5.6; N, 6.8. Found: C, 60.8; H, 5.6; N, 6.8.

5,7,8,13,13b,14-Hexahydrobenzo[g]indolo[2,3-a]quinolizine hydrochloride. A suspension of 1.0 g. of VIII in 100 ml. of methanol was shaken with 100 mg. of Adams' platinum oxide catalyst at room temperature and atmospheric pressure. After uptake of 2 equivalents of hydrogen in 15 min. during which the color of the solution changed from orange to light yellow-green, hydrogen absorption ceased. The catalyst was filtered off under nitrogen and the filtrate was concentrated at reduced pressure to 30 ml. After addition of 30 ml. of water, addition of a few drops of sodium hydroxide solution precipitated the free base. The yield of white needles, m.p. 190° (dec.) after recrystallization from ethyl acetate, was 0.8 g. (90%). The reported m.p. is 196–197°,[12] 192°[17] and 188–189° (dec.).[18]

The hydrochloride precipitated when dry hydrogen chloride was passed into a solution of the free base in methanol. It forms yellow platelets, m.p. 282–284° (dec.). The reported m.p. is 298° (dec.),[12] 290° (dec.),[17] and 288–289° (dec.).[18]

Anal. Calcd. for $C_{19}H_{18}N_2 \cdot HCl$: C, 73.4; H, 6.2; N, 9.0. Found: C, 73.0; H, 6.2; N, 8.8.

11-Methoxy-5,7,8,13,13b,14-hexahydrobenzo[g]indolo[2,3-a]quinolizine hydrochloride. (XII). Reduction of IX as in the preceding case gave XII as clusters of tan crystals, m.p. 230° after recrystallization from ethyl acetate. The yield was 93%. In the presence of air and moist catalyst XII oxidizes rapidly to orange products. The hydrochloride of XII, m.p. 248° (dec.), formed long white needles from methanol.

Anal. Calcd. for $C_{20}H_{20}N_2O.HCl$; C, 70.6; H, 6.2; N, 8.2. Found: C, 70.4; H, 6.6; N, 8.1.

Dehydrogenation of XII. A. with iodine. A warm solution of 1.4 g. of potassium acetate and 0.7 g. of iodine in 20 ml. of absolute ethanol was added to 140 mg. of XII in 4 ml. of absolute ethanol. The mixture was warmed on the steam bath for 5 min. during which a copious orange precipitate formed. This was collected and suspended in 50 ml. of hot water. Sulfur dioxide was passed through the suspension for 10 min. After cooling, the solid was collected and recrystallized from absolute ethanol to give 120 mg. of the iodide corresponding to IX as orange-red needles, m.p. 310° (dec.).

The above iodide was converted to the bromide (IX) by refluxing it with 1 g. of freshly prepared silver bromide in 150 ml. of ethanol and 50 ml. of water. Evaporation to dryness and recrystallization of the residue from ethanol after filtering from silver salts gave IX, m.p. 312° (dec.). The infrared spectrum was identical with that of an authentic sample of IX.

B. with palladium. A solution of 700 mg. of maleic acid and 500 mg. of XII in 150 ml. of hot water was refluxed with 250 mg. of 20% palladium-on-charcoal under nitrogen for 22 hr. The filtrate from the catalyst was concentrated under

nitrogen until crystallization began. After cooling, the precipitate was collected, suspended in 75 ml. of methanol, and treated with dry hydrogen bromide. The precipitate dissolved and, on cooling, 340 mg. of IX, m.p. 311–312° (dec.), separated. The ultraviolet spectrum was identical with that of an authentic sample of IX.

C. with air. A slow stream of air was passed through a refluxing solution of 500 mg. of XII and 2 ml. of 48% hydrobromic acid for 4 days. On concentration and cooling 80 mg. of IX, m.p. 311–312° (dec.), separated. It was further identified by ultraviolet and infrared spectra.

Action of lithium aluminum hydride on IX. (XIII). To a stirred suspension of 1 g. of IX in 100 ml. of absolute ether 0.76 g. of lithium aluminum hydride was slowly added. Reduction occurred immediately and the color of the suspension changed from orange to light yellow-green. After refluxing for 2 hr. excess hydride was destroyed by cautious addition of 10 ml. of ethyl acetate. After addition of 50 ml. of 5% hydrobromic acid, the ether was removed in a stream of nitrogen leaving a white precipitate which slowly began to turn orange even under nitrogen. Part of the precipitate was filtered and hydrogenated in methanol over platinum oxide. One equivalent of hydrogen (calculated on the amount of XII isolated) was absorbed. After working up, 380 mg. of XII, m.p. 230°, was obtained. Identification was by mixture m.p.'s and identity of the infrared spectrum with that of an authentic sample of XII.

The other portion of the suspension was allowed to stand exposed to air and the precipitate rapidly turned orange. The precipitate was collected and recrystallized from ethanol yielding 350 mg. of IX, m.p. 311–312°. The ultraviolet and infrared spectra were identical with those of a known sample of IX.

10-Methoxy-5,7,8,13,13b,14-hexahydrobenzo[g]indolo[2,3-a]quinolizine hydrochloride. Reduction of X over platinum oxide by the same procedure as that used in the reduction of IX gave 90% of the quinolizine hydrochloride, m.p. 275–277° (dec.).

Anal. Calcd. for $C_{20}H_{20}N_2O.HCl$: C, 70.6; H, 6.2; N, 8.2. Found: C, 70.8; H, 6.5; N, 8.5.

3-Methyl-5-nitroisoquinoline. (XV). This procedure was adapted from one for the preparation of 5-nitroisoquinoline.[32] A solution of 55 g. of potassium nitrate in 300 ml. of concentrated sulfuric acid was added with stirring to a solution of 72 g. of 3-methylisoquinoline in 400 ml. of concentrated sulfuric acid, chilled in an ice-salt bath, at such a rate that the temperature of the mixture did not exceed 4°. The addition required 2.5 hr. The solution was stirred for an additional 2 hr. during which it was allowed to come to room temperature. It was then poured into a mixture of 4 l. of water and 4 kg. of chopped ice. After neutralization by cautious addition of ammonia, the suspension was cooled and the solid was collected and recrystallized from ethanol yielding 28 g. of yellow needles, m.p. 105–108.5°. The mother liquor was concentrated and water was added to the hot solution to the point of incipient crystallization. On cooling, 14 g. of needles, m.p. 105–108°, separated. A third crop, m.p. 102–107°, obtained by the same procedure weighed 18 g., and finally, a fourth crop, m.p. 85–90°, weighed 2.5 g. The total recovery was 85 g. (90%). The first crop on recrystallization from ethanol gave pale yellow needles, m.p. 109.5–110.5°, in good recovery. Additional material was obtained from the first three fractions. Bergstrom and Patterson[23] nitrated 3-methylisoquinoline by a different procedure and obtained 55% of a nitro derivative, m.p. 108–110°, and 14% of a second isomer, m.p. 90–91°.

Oxidation of 3-methyl-5-nitroisoquinoline. A solution of 3.16 g. of the major product, m.p. 109.5–110.5°, of the above nitration in 30 ml. of nitrobenzene was added slowly with stirring to a suspension of 2.2 g. of selenium dioxide (purified by sublimation) in 100 ml. of nitrobenzene. During the addition the suspension was slowly brought to boil. After the addition was complete the mixture was refluxed for 1 hr. during which the color changed from yellow to deep red-brown. After cooling the solution was washed successively with 50 ml. of 5% sodium hydroxide solution and 100 ml. of water and then extracted with several portions of 10% hydrochloric acid until the extracts gave no precipitate with alcoholic 2,4-dinitrophenylhydrazine reagent. The acid extracts were combined and made basic with sodium hydroxide solution, chilled, and the solid was collected. The filtrate was extracted with ether. Removal of the ether left a solid residue which was combined with the first filter cake and recrystallized from 90–100° petroleum ether with carbon. The first crop, m.p. 165–172°, weighed 0.7 g. A second crop, m.p. 159–163°, weighed 0.6 g. Both crops gave positive tests with 2,4-dinitrophenylhydrazine. Recrystallization raised the m.p. to 173–178°. The aldehyde (XVI) was not purified further since the contaminant, 3-methyl-5-nitroisoquinoline was not attacked in the next step and could easily be separated from the resulting acid.

A solution of 0.5 g. of sodium dichromate heptahydrate in 5 ml. of water was added to a solution of 0.45 g. of the crude aldehyde (XVI) in 15 ml. of water and 5 ml. of concentrated sulfuric acid. After standing 2 hr., the solution was diluted with 50 ml. of water, filtered, and brought to *p*H 4 with ammonia. After boiling a few minutes, the solid was collected. The combined filter cakes, m.p. 260–263° (dec.), weighed 200 mg. The material was dissolved in 10% sodium hydroxide solution, the solution was extracted with ether, and the acid was precipitated with acetic acid.

When the above acid was heated above its melting point carbon dioxide was evolved and a yellow volatile product distilled and solidified, m.p. 102–104°. After recrystallization from water it was identified by m.p. (108–110°) and mixture m.p.'s as 5-nitroisoquinoline.

5-Amino-3-methylisoquinoline (XIX). Reduction of XV in methanol over platinum oxide catalyst at room temperature and atmospheric pressure gave a quantitative yield of 5-amino-3-methylisoquinoline, m.p. 213–216°. Bergstrom and Patterson[23] report m.p. 219.5–221° for the amine prepared by reduction with stannous chloride.

3-Methylisoquinoline-5-sulfonic acid. (XXI). 3-Methylisoquinoline (28.6 g.) was added slowly with cooling to 110 g. of 50% fuming sulfuric acid and the mixture was allowed to stand at room temperature for 48 hr. After pouring onto 500 g. of ice and water and standing until crystallization was complete, the sulfonic acid was collected. It formed white needles, m.p. 420–430° (dec.), after recrystallization from water. The yield was 39 g. (88%).

Anal. Calcd. for $C_{10}H_9NO_3S$: C, 53.8; H, 4.1; S, 14.4. Found: C, 53.8; H, 4.1; S, 14.4.

5-Cyano-3-methylisoquinoline. (XX). *A. from 5-amino-3-methylisoquinoline.*[33] A solution of 8.3 g. of 5-amino-3-methylisoquinoline in 56 ml. of concentrated hydrochloric acid and 120 ml. of water was chilled to 0°. A chilled solution of 4.9 g. of sodium nitrite in 25 ml. of water was added slowly and the resulting solution was allowed to stand 5 min. It was then cautiously neutralized with sodium carbonate and added slowly with stirring to a chilled solution of 11.4 g. of potassium cyanide and 10.2 g. of cuprous cyanide in 80 ml. of water. The solution was allowed to come to room temperature and stirred overnight. It was necessary to add a few drops of octyl alcohol to prevent excessive foaming. The mixture was steam distilled for 24 hr. using a combination steam distillation and liquid-liquid extraction apparatus[34] with chloroform as the extractant. The chloroform extracts were exhaustively extracted with 10% hydrochloric acid. The combined acid extracts were made basic with sodium hydroxide solution, chilled and 1.2 g. (15%) of XX

(32) Private communication from Dr. R. L. Shriner.

(33) *Cf.* L. F. Fieser and E. B. Hershberg, *J. Am. Chem. Soc.*, **62**, 1640 (1940).

(34) A. I. Vogel, *Practical Organic Chemistry*, 2nd Ed., Longmans, Green and Co., Ltd., London, 1951, p. 223.

separated. After recrystallization from 90–100° petroleum ether it melted at 127–129°.

Anal. Calcd. for $C_{11}H_8N_2$: 3, 78.5; H, 4.8. Found: C, 78.3; H, 4.7.

B. from 3-methylisoquinoline-5-sulfonic acid. An intimate mixture of 56 g. of XXI, 12 g. of sodium cyanide, 32 g. of potassium cyanide, and 10 g. of anhydrous sodium acetate was placed over 10 g. of anhydrous sodium acetate in a 500-ml. Monel metal flask. The flask was connected to a condenser set downward for distillation which was in turn connected to a filter flask chilled in ice and connected to an aspirator. The metal flask was heated with a Meker burner at water pump pressure and the nitrile distilled and partially solidified in the condenser. The distillate was extracted with ether and the extract was dried over anhydrous potassium carbonate. Distillation of the residue after removal of the ether gave a forerun of 1.5 g. of 3-methylisoquinoline, b.p., 65–70° (0.07 mm.), m.p. 52–53°, followed by 6.4 g. of XX, b.p. 115–120° (0.05 mm.). After recrystallization from methanol it formed white needles, m.p. 128°. The m.p. was not depressed on admixture with XX prepared from 5-amino-3-methylisoquinoline thus proving that sulfonation had occurred in the 5 position.

5-Cyanoisoquinoline-3-carboxaldehyde. (XXII). A solution of 12 g. of XX in 150 ml. of nitrobenzene was added slowly to a suspension of 10.8 g. of freshly prepared and sublimed selenium dioxide in 850 ml. of nitrobenzene at 180° with stirring. After refluxing for one hour, the solution was cooled and extracted with three 300 ml. portions of 10% hydrochloric acid. After extraction of the combined acid extracts with ether they were made basic with ammonia. The precipitated aldehyde was collected and recrystallized from benzene–petroleum ether. The yield of fine white needles, m.p. 208–210°, was 5.3 g. (41%). Analytical data indicated that partial hydrolysis of the cyano group had occurred since the carbon figures were consistently low.

Anal. Calcd. for $C_{11}H_6N_2O$: C, 72.5; H, 3.3. Found: C, 71.6; H, 3.3.

A 2,4-dinitrophenylhydrazone, m.p. 275–276° (dec.) was prepared. Again the analytical data were unsatisfactory. However, the acid prepared by hydrolysis of the nitrile gave satisfactory figures.

Isoquinoline-3-carboxaldehyde-5-carboxylic acid. A solution of 5.3 g. of XXII in 50 ml. of 48% hydrobromic acid was refluxed for 3 hr. After cooling the *p*H of the solution was adjusted to 5 and it was extracted with ether in a continuous extractor. The aldehydo acid was recrystallized from dioxane giving 5.2 g. (89%) of long white needles, m.p. 249–250° (dec.). It retained 0.5 mole of dioxane of crystallization.

Anal. Calcd. for $C_{11}H_7NO_3 \cdot 0.5\ C_4H_8O_2$: C, 63.7; H, 4.5; N, 5.7. Found: C, 63.9; H, 4.3; N, 5.8.

γ-Ethoxypropyl-5-carboxyisoquinolyl ketone. γ-Ethoxypropylmagnesium bromide (prepared from 8.35 g. of γ-ethoxypropyl bromide in 50 ml. of absolute ether) was added slowly to a stirred solution of 3.5 g. of the above aldehydo acid in 300 ml. of dry tetrahydrofuran. A copious yellow precipitate formed immediately. After refluxing for 5 hr., the mixture was cooled and hydrolyzed with saturated ammonium chloride solution. The tetrahydrofuran was removed by distillation and, after adjusting the *p*H to 5, the solution was extracted with ether. After drying the extract over anhydrous magnesium sulfate, removal of the solvent left about a gram of viscous oil. This was dissolved in a mixture of 5 ml. of concentrated sulfuric acid and 30 ml. of water and a solution of 2 g. of potassium dichromate in 15 ml. of water was added. After 18 hr. at room temperature the *p*H was adjusted to 5 and the solution was extracted with ether. After drying over anhydrous magnesium sulfate, removal of the ether left a viscous oil. This was refluxed with 200 mg. of 2,4-dinitrophenylhydrazine in absolute ethanol for 30 min. On cooling 70 mg. of a 2,4-dinitrophenylhydrazone, m.p. 249° (dec.) after recrystallization from ethanol, crystallized.

Anal. Calcd. for $C_{22}H_{21}N_5O_7$: C, 56.5; H, 4.5; N, 15.0 Found: C, 56.6; H, 4.6; N, 14.9.

γ-Ethoxypropyl-2-pyridinemethanol. To a solution of γ-ethoxypropylmagnesium bromide prepared from 53.4 g. of γ-ethoxypropyl bromide and 8.0 g. of magnesium in 400 ml. of absolute ether a solution of 30.4 g. of freshly distilled pyridine-2-carboxaldehyde, b.p. 63° (14 mm.), in 500 ml. of absolute ether was added with powerful stirring as rapidly as possible. A gummy yellow precipitate formed almost immediately. After stirring and refluxing, for 2 hr., the complex was hydrolyzed by boiling with 400 ml. of 15% ammonium chloride solution for 1 hr. The ether layer was separated and the aqueous layer was extracted with four 250-ml. portions of ether. After drying over anhydrous magnesium sulfate, removal of the ether left a brown oil which was distilled through a 13-cm. Vigreux column at reduced pressure to give 34.2 g. (62%) of very hygroscopic yellow oil, b.p. 121–126° (1.5 mm.). An analytical sample, b.p. 130° (4 mm.), n_D^{29} 1.5002, was analyzed immediately after distillation. The infrared spectrum showed bands at 3400 cm.$^{-1}$ (OH) and 1100 cm.$^{-1}$ (saturated —O—).

Anal. Calcd. for $C_{11}H_{17}NO_2$: C, 67.7; H, 8.8. Found: C, 67.7; H, 8.5.

The picrate, m.p. 92–93°, formed yellow rhomboids from ether.

Anal. Calcd. for $C_{17}H_{20}N_4O_9$: C, 48.1; H, 4.7. Found: C, 47.9; H, 4.8.

γ-Ethoxypropyl-2-pyridyl ketone, (XXV). *A. by oxidation of the carbinol.* To a solution of 24.8 g. of γ-ethoxypropyl-2-pyridinemethanol in 123 ml. of concentrated sulfuric acid and 740 ml. of water was added slowly a solution of 24.6 g. of sodium bichromate dihydrate in 123 ml. of water. After standing 24 hr. at room temperature, the solution was made strongly basic with sodium hydroxide and filtered on a large Buchner funnel. The air-dried filter cake was extracted with ether in a Soxhlet extractor for 10 hr. The aqueous filtrate was exhaustively extracted with ether. Removal of the solvent from the combined dried ether extracts left a brown oil which was distilled at reduced pressure under nitrogen through a 13-cm. Vigreux column to give 12.3 g. (50%) of very hygroscopic colorless oil, b.p. 109–114° (1.3 mm.). An analytical sample, b.p. 114° (1.2 mm.), n_D^{29} 1.4978, was analyzed immediately after distillation. The ketone, or solutions of it, cause a very irritating skin eruption.

Anal. Calcd. for $C_{11}H_{15}NO_2$: C, 68.4; H, 7.8. Found: C, 68.1; H, 8.2.

The infrared spectrum of XXV indicates that it exists in the enol form to a considerable extent. It shows strong bands at 1700 cm.$^{-1}$ (C=O) and at 1100 cm.$^{-1}$ (saturated —O—). There are less intense bonds at 3400 cm.$^{-1}$ (OH), 1580 cm.$^{-1}$ (aromatic absorption), and 990 cm.$^{-1}$ (vinyl or trans C=C). Further, XXV gave a dark green color with ferric chloride in ethanol.

The *p*-nitrophenylhydrazone, m.p. 94–96°, formed fine, orange needles from dilute methanol.

Anal. Calcd. for $C_{17}H_{20}N_4O_3$: C, 62.2; H, 6.1; N, 17.1. Found: C, 62.2; H, 6.2; N, 17.1.

B. via the cadmium reagent. Picolinic acid chloride was prepared by heating 5.0 g. of picolinic acid with 19 ml. of freshly distilled thionyl chloride under reflux for 20 min. The excess thionyl chloride was removed under reduced pressure; 20 ml. of dry benzene was added to the residue and removed by distillation. The dark green residue was dissolved in 25 ml. of absolute ether and used directly without further purification.

To a solution of γ-ethoxypropylmagnesium bromide prepared from 1.6 g. of magnesium and 13.3 g. of γ-ethoxypropyl bromide in 100 ml. of absolute ether was added 13.1 g. of anhydrous cadmium chloride. After stirring for 30 min. the above ethereal solution of picolinic acid chloride was added dropwise with stirring. The mixture was stirred and refluxed for 3 hr. After cooling, the complex was hydrolyzed by stirring with a solution of 10 g. of ammonium chloride and 10 ml. of concentrated hydrochloric acid in 50 ml. of water for

5 hr. The ether layer was separated and the aqueous layer was refluxed for an additional 5 hr., made basic to litmus with sodium hydroxide and extracted with four 50-ml. portions of ether. Removal of the ether from the dried combined extracts and distillation under reduced pressure gave 1.15 g. (15% based on picolinic acid) of XXV. The refractive index and infrared spectrum were identical with those of the ketone prepared by procedure A.

1-Keto-1,2,3,4-tetrahydroquinolizinium bromide (XXVI) A mixture of 12.25 g. of XXV and 255 ml. of 48% hydrobromic acid was refluxed for 3 hr. Removal of the acid left a red-brown oil. The product was very difficult to purify if the excess hydrobromic acid was not completely removed at this point. The oil was heated under reflux with 20 ml. of absolute ethanol for 8 hr. Concentration of the solution under reduced pressure and dropwise addition of absolute ether to the concentrate induced crystallization of XXVI. After chilling for several hours, the product was filtered in a dry atmosphere, washed with 2 ml. of anhydrous ether, and desiccator dried. The yield of very hygroscopic bromide was 6.3 g. (48%). An analytical sample crystallized as light tan needles, m.p. 204.5–206° (dec., uncorr.) with preliminary darkening, from absolute ethanol–anhydrous ether.

Anal. Calcd. for $C_9H_{10}BrNO$: C, 47.4; H, 4.4; N, 6.1. Found: C, 47.4; H, 4.4; N, 6.1.

The *p*-nitrophenylhydrazone crystallized as fine orange needles, m.p. 291–292° (uncorr.) after sintering at 280°, from absolute ethanol.

Anal. Calcd. for $C_{15}H_{15}BrN_4O_2$: C, 49.6; H, 4.2. Found: C, 49.6; H, 4.1.

The phenylhydrazone (85% yield) formed fine yellow-orange needles, m.p. 264–265° (dec.), from absolute ethanol.

Anal. Calcd. for $C_{15}H_{16}BrN_3$: C, 56.6; H, 5.1; N, 13.2. Found: C, 56.4; H, 5.2; N, 13.3.

6,7-Dihydro-12H-indolo[2.3-a]quinolizinium bromide (XXIV). A stream of dry hydrogen bromide was bubbled through a solution of 0.71 g. of the phenylhydrazone of XXVI in 50 ml. of absolute ethanol at such a rate that gentle refluxing was maintained. The color changed from golden yellow to yellow-green. The mixture was concentrated under reduced pressure, chilled, and the precipitate was collected in a dry atmosphere and dried in a desiccator. The yield was 0.60 g. (91%). The bromide formed bright yellow needles from absolute ethanol and melted at 335–337° (dec., uncorr.). Sugasawa and coworkers[9] report m.p. 327–330° (dec.) for XXIV prepared by another method.

Anal. Calcd. for $C_{15}H_{13}BrN_2$: C, 59.8; H, 4.4; N, 9.3. Found: C, 59.8; H, 4.3; N, 9.3.

The ultraviolet spectrum of an ethanolic solution of XXIV showed maxima at 252 (log ϵ 3.85), 315 (log ϵ 4.06), and 3.85 (log ϵ 4.09) mμ and minima at 240 (log ϵ 3.75), and 275 (log ϵ 3.35), and 340 (log ϵ 3.80) mμ.

Hydrogenation of XXIV. *1,2,3,4,6,7,12,12b-octahydroindolo-[2.3-a]quinolizine.* (XXVII). A solution of 0.254 g. of XXIV in 80 ml. of absolute methanol containing 3 drops of ammonium hydroxide was shaken with 0.1 g. of platinum oxide under hydrogen at room temperature and atmospheric pressure. Three equivalents of hydrogen were absorbed in 20 min. and the color changed from red to colorless. The filtrate from the catalyst was made basic with 5% sodium carbonate solution and concentrated to dryness under reduced pressure. The yellow residue was extracted with ether. Recrystallization of the residue after evaporation of the ether from hexane (Norite) gave 0.18 (95%) of stout, white needles, m.p. 153–154°. Reported m.p.'s for XXVII prepared by other routes are 148–151°[27] and 147–147.5°.[26] The m.p. of XXVII was not depressed on admixture with an authentic sample,[35] and the infrared spectra of the two samples were superimposable.

The ultraviolet spectrum of an ethanolic solution of XXVII showed maxima at 226 (log ϵ 4.58), 283 (log ϵ 3.91), a shoulder at 290 (log ϵ 3.84), and a minimum at 247 (log ϵ 3.42) mμ. Groves and Swan[25] report a maximum at 279 (log ϵ 3.89) and a minimum at 247 (log ϵ 3.33) mμ.

10-Methoxy-6,7-dihydro-12H-indolo[2.3-a]quinolizinium bromide. XXVIII. The *m*-methoxyphenylhydrazone of XXVI, prepared in and recrystallized from absolute ethanol, formed fine orange-yellow needles, m.p. 261–262° (dec.).

Anal. Calcd. for $C_{16}H_{15}BrN_2O$: C, 55.2; H, 5.2; N, 12.1. Found: C, 55.1; H, 5.0; N, 11.9.

Cyclization was effected by passing dry hydrogen bromide through a solution of 0.75 g. of the above phenylhydrazone in 60 ml. of absolute ethanol for 1 hr. Concentration of the mixture and chilling gave 0.63 (86%) of XXVIII. It formed yellow-orange needles, m.p. 306–307° (dec., uncorr.), from absolute ethanol.

Anal. Calcd. for $C_{16}H_{15}BrN_2O$: C, 58.0; H, 4.6; N, 8.5. Found: C, 58.0; H, 4.7; N, 8.4.

9-Hydroxy-6,7-dihydro-12H-indolo[2.3-a]quinolizinium bromide. (XXIX). The *p*-methoxyphenylhydrazone of XXVI, prepared in and recrystallized from absolute ethanol, formed orange needles, m.p. 269–271° (dec., uncorr.) after darkening at about 255°.

Anal. Calcd. for $C_{16}H_{15}BrN_2O$: C, 55.2; H, 5.2; N, 12.1. Found: C, 55.3; H, 5.1; N, 12.1.

Cyclization was carried out as in the case of XXVIII. XXIX formed fine orange needles, m.p. 304–306° (dec. uncorr.) after darkening at 290°, from absolute ethanol. The yield of very hygroscopic material was 61%.

The infrared spectrum taken as a Nujol mull showed a weak band at 3400 cm.$^{-1}$ (OH) and there were no prominent bands in the region associated with an ether linkage (1100 cm.$^{-1}$).

Anal. Calcd. for $C_{16}H_{15}BrN_2O$: C, 58.0; H, 4.6; N, 8.5. Calcd. for $C_{15}H_{13}BrN_2O$: C, 56.8; H, 4.1; N, 8.8. Found: C, 56.6; H, 4.3; N, 8.7.

9-Hydroxy-10-methoxy-6,7-dihydro-12H-indolo[2.3-a]-quinolizinium bromide. (XXX). The 3,4-dimethoxyphenylhydrazone of XXVI, prepared as in the preceding cases formed brown-orange needles, m.p. 265° (dec., uncorr.), after softening and darkening at 255°.

Anal. Calcd. for $C_{16}H_{20}BrN_3O_2$: C, 54.0; H, 5.3; N, 11.1. Found: C, 54.0; H, 5.4; N, 11.1.

Cyclization was accomplished as in the preceding cases to give 67% of XXX as fine red-orange needles, m.p. 302–303° (dec., uncorr.) after darkening at 290°. The compound is very hygroscopic.

The infrared spectrum (Nujol) showed a weak band at 3400 cm.$^{-1}$ (OH) and a stronger band at 1100 cm.$^{-1}$ (ether).

Anal. Calcd. for $C_{17}H_{17}BrN_2O_2$: C, 56.5; H, 4.7; N, 7.8. Calcd. for $C_{16}H_{15}BrN_2O_2$: C, 55.3; H, 4.4; N, 8.1. Calcd. for $C_{15}H_{13}BrN_2O_2$: C, 54.0; H, 3.9; N, 8.4. Found: C, 55.2; H, 4.6; N, 8.2.

The ultraviolet spectra for XXVIII, XXIX, and XXX are shown in Fig. 1.

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