180° for 16 hr. and at 200° for 10 min. The cooled solution was treated with water and ether. The dried ether layer was evaporated to give 0.5 g. (98%) of VIIb, m.p. 85–90°; plates from methanol-water, m.p. 93–94°.

Anal. Calcd. for $C_{18}H_{25}NO$: C, 79.66; H, 9.29 Found: C, 79.45; H, 9.02.

The methiodide crystallized from methanol in prisms of m.p. 265–267° (froth).

Anal. Calcd. for $C_{19}H_{28}INO$: C, 55.21; H, 6.83. Found: C, 54.99; H, 6.62.

The hydrochloride crystallized from alcohol-ether in needles which appear to be the hemihydrate.

Anal. Calcd. for $C_{18}H_{26}ClNO \cdot {}^1/_2H_2O$: C, 68.21; H, 8.59. Found: C, 68.02; H, 8.81.

1,2,3,9,10,10a-Hexahydro-6-hydroxy-1-methyl-1,4a(4H)-iminoethanophenanthrene (VIIc). A mixture of 0.4 g. of VIIb and 3 ml. of 48% hydrobromic acid was refluxed for 0.5 hr. and evaporated to dryness *in vacuo*. The residue, digested with 3–5 ml. of absolute alcohol and cooled to 5°, gave 0.4 g. (83%) of VIIc hydrobromide (m.p. 268–272°) which was converted to the base with aqueous ammonium hydroxide; prisms from methanol, m.p. 246–248° (froth).

Anal. Calcd. for $C_{17}H_{23}NO$: C, 79.34; H, 9.01. Found: C, 79.48; H, 9.00.

The *hydrobromide*[13] crystallized from 95% ethanol in small prisms (m.p. 150–155°, froth) which apparently contain one molecular equivalent of solvate ethanol.

Anal. Calcd. for $C_{17}H_{24}NO + C_2H_5OH$: C, 59.37; H, 7.87; Br, 20.80; C_2H_5OH, 11.98. Found: C, 58.75; H, 7.70; Br, 21.45; C_2H_5OH (determined as ethoxyl), 11.73.

4a-(2-Dimethylaminoethyl)-6-methoxy-1,2,3,4,4a,9,10,10a-octahydrophenanthrene (VI) *picrate.* (a) *From* Vb. (±)-3-Methoxy-*N*-methylmorphinan (Vb) hydrobromide[5] (0.2 g.) was converted to Vb (aqueous ammonium hydroxide–ether) which in turn gave 0.15 g. of the methiodide (methyl iodide–methanol-ether). This methiodide and 5 ml. of 10% sodium hydroxide were refluxed 1–2 hr. and the resultant base (after drying in ether) was hydrogenated in methanol (5 mg. of platinum oxide) during 10 min. The filtered solution was evaporated to dryness *in vacuo*, and the residue was treated with saturated alcoholic picric acid to give 0.15 g. (79%) of the picrate of m.p. 158–159°. A recrystallization from alcohol did not alter the melting point.

Anal. Calcd. for $C_{25}H_{32}N_4O_8$: C, 58.13; H, 6.25. Found: C, 57.77, 57.91; H, 6.13, 5.95.

(*b*) *From* VIIb. The methiodide of VIIb (0.09 g.), 0.4 g. of potassium hydroxide, 4 ml. of water, and 1 ml. of triethylene glycol were kept at 135–140° (bath temperature)[14] for 3 hr. and treated with water and ether. The residue from the dried ether layer was distilled at 0.5 mm. (bath temperature 150°). The distillate was hydrogenated as described in the previous experiment. The product gave 35 mg. (31%) of picrate, m.p. 145–150°. Careful recrystallization from alcohol yielded 25 mg. of picrate, m.p. 156–157.5°, indistinguishable in crystal form, melting phenomena, and infrared spectrum, from that prepared from Vb.

Acknowledgment. I am indebted to Mr. J. Harrison Ager for valuable assistance in the chemical work and to Dr. Nathan B. Eddy, Chief, section on analgesics, for the pharmacological results.

BETHESDA, MD.

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(13) This material was quantitatively convertible to VIIc.

(14) Unlike Vb methiodide, this methiodide (of VIIb) was unaffected by boiling 10% sodium hydroxide.

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

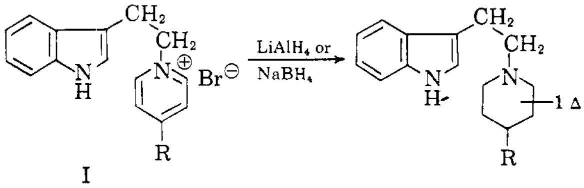
Alstonia Alkaloids. IX. Synthesis of Alstonilinol and Analogs by Reductive Ring Closure[1]

ROBERT C. ELDERFIELD AND BALTHASAR A. FISCHER

Received March 21, 1958

Tetrahydroalstonilinol has been synthesized by reductive ring closure of 2-[β-(6-methoxy-3-indolyl)ethyl]-5-carbomethoxyisoquinolinium bromide. Dehydrogenation of tetrahydroalstonilinol gave alstonilinol.

In a preceding paper the action of lithium aluminum hydride and sodium borohydride upon a series of β-(3-indolylethyl)-1-pyridinium bromides (I) was reported.[2] It was shown that, although two double bonds in the pyridine ring were reduced, no ring closure to a tetracyclic β-carboline resulted. In the present paper we present the results of a study of the action of the two hydrides on β-(3-indolylethyl)-2-isoquinolinium bromides which led to a total synthesis of alstonilinol (XXII). This interesting ring closure to a pentacyclic β-carboline was first described by Robinson and Potts[3] and a preliminary note dealing with our experiences has already appeared.[4]



I

Inasmuch as the ultimate objective was a synthesis of alstoniline itself which carries a carbomethoxyl group in the 16 position of the parent yohimbane carbon skeleton (disregarding unsatu-

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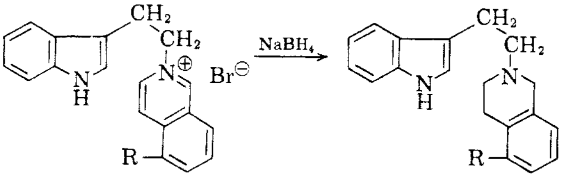
(1) The work here reported was done in part under Research Grant H-1733 from the National Heart Institute and in part under Research Grant CY-2961 from the National Cancer Institute.

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

(3) Sir Robert Robinson and K. T. Potts, *J. Chem. Soc.*, 2675 (1955). *cf.* B. Belleau, *Chem. & Ind.* (*London*), 229 (1955).

(4) R. C. Elderfield and B. Fischer, *J. Org. Chem.*, **23**, 332 (1958).

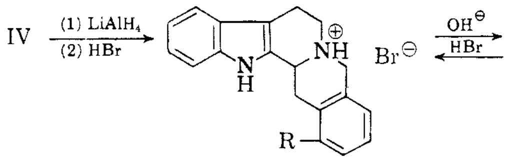
ration in Rings D and E) initial experiments involved a study of the action of sodium borohydride on β-(3-indolylethyl)-2-isoquinolinium bromides carrying a carbomethoxyl function, or some group potentially convertible to such a function, in the 5 position of the isoquinoline system. For this purpose the quaternary salts resulting from condensation of β-(3-indolyl)ethyl bromide with isoquinoline (II), 5-cyanoisoquinoline (III),[5] and the methyl ester of isoquinoline-5-carboxylic acid (IV) were selected. Reduction of all three bromides in methanol gave products (V, VI, and VII) which arose by reduction of two double bonds in the pyridine ring of the isoquinoline system without ring closure to a pentacyclic β-carboline. The structure of VII was shown by its identity with the substance obtained by catalytic reduction of IV over platinum and the structures of V and VI are assigned by analogy and on the basis of analytical data. Further, V, VI, and VII all gave a positive Ehrlich color test[6] which is characteristic for indoles in which the α-position is unsubstituted and failed to undergo dehydrogenation with iodine and potassium acetate. The latter reaction is characteristic of reduced pentacyclic β-carbolines.



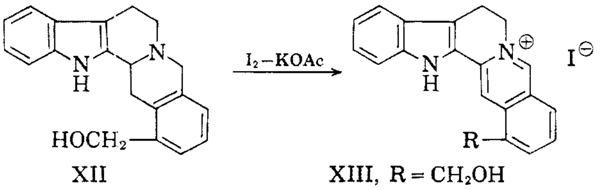
II, R = H
III, R = CN
IV, R = COOCH$_3$

V, R = H
VI, R = CN
VII, R = COOCH$_3$
VIII, R = CH$_2$OH

However, when IV was reduced with sodium borohydride in 95% ethanol reduction of the carbomethoxy group also occurred to give VIII. Although it has been noted previously that reduction of an ester in the analogous pyridinium compounds may take place, the striking effect of merely a change of solvent in the present case is noteworthy. VIII was also obtained by reduction of VII with lithium aluminum hydride.



IX, R = CH$_2$OH
X, R = CH$_2$OCOCH$_3$
XI, R = CHO



XII

XIII, R = CH$_2$OH
XIV, R = CH$_2$OCOCH$_3$
XV, R = CHO

With lithium aluminum hydride III gave an unstable base which has resisted all attempts at purification. On the other hand, IV on reduction with lithium aluminum hydride in a mixture of ether and tetrahydrofuran gave a base (IX) which was isolated as the hydrobromide. IX formed an acetate (X) and the free base (XII) underwent dehydrogenation with iodine and potassium acetate to XIII which in turn gave an acetate (XIV). However, when X was dehydrogenated a compound differing from XIV in melting point was obtained. Only minor differences in the infrared spectra of this substance and XIV were noted. The dehydrogenation product of X also gave analytical data corresponding to those demanded by XIV plus an additional iodine.

Oxidation of IX and XIII with regeneration of the carboxyl group was attempted. With chromic anhydride under various conditions XIII gave an oxygen-free compound. This is under further investigation. With manganese dioxide IX gave a poor yield of the aldehyde (XI) which was very difficult to purify. XI gave a positive test with 2,4-dinitrophenylhydrazine and could be dehydrogenated to XV. The infrared spectra of both XI and XV clearly demonstrated the presence of an aldehyde group.

For the synthesis of alstoniline or derivatives of it by the above general method 6-methoxytryptophol (XVIII) is required. Application of the Japp-Klingemann reaction using *m*-methoxybenzenediazonium chloride and diethyl α-acetoglutarate should give 2-carboxy-6-methoxyindole-3-acetic acid from which XVIII can be prepared by successive decarboxylation and reduction. However, instead of the expected indole derivative, a good yield of a green base which gave analytical data corresponding to $C_9H_{12}N_2O_2$ and which showed an amide band in the infrared was obtained. It formed a yellow salt from which the base could be recovered. The nature of this substance is under further study.

Application of the gramine synthesis as a route to 6-methoxyindole-3-acetic acid using 6-methoxyindole resulted in the formation of a high-melting salt which was not investigated further.

Finally, condensation of 6-methoxyindole with oxalyl chloride[7] to give 6-methoxyindole-3-glyoxalyl chloride (XVII) followed by reduction of XVII with lithium aluminum hydride gave XVIII. Reduction of XVII with sodium borohydride gave the expected

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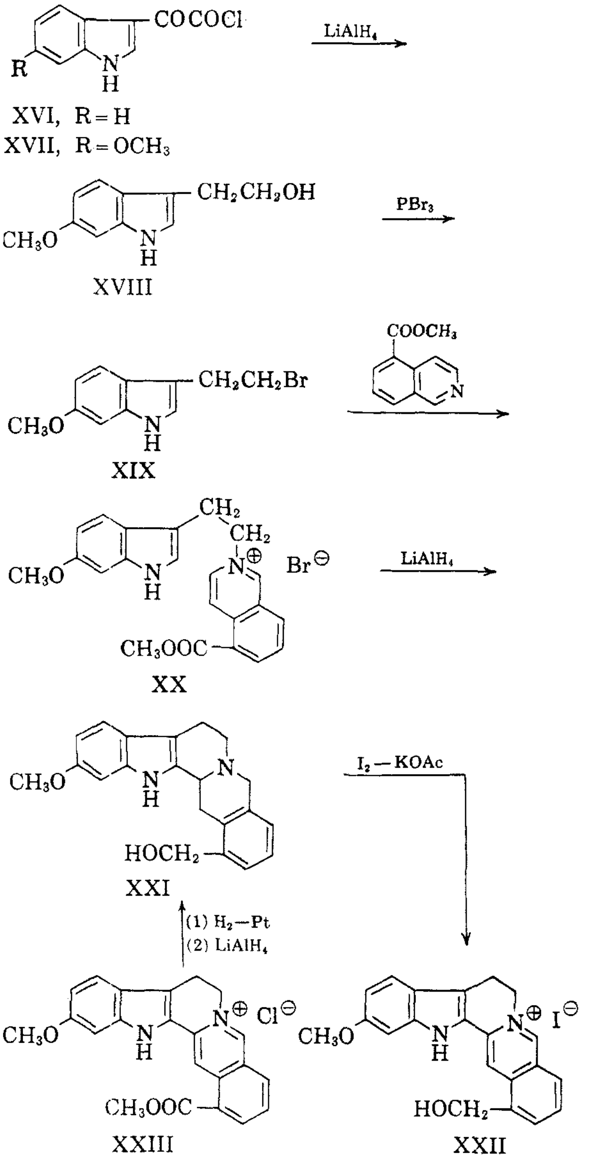
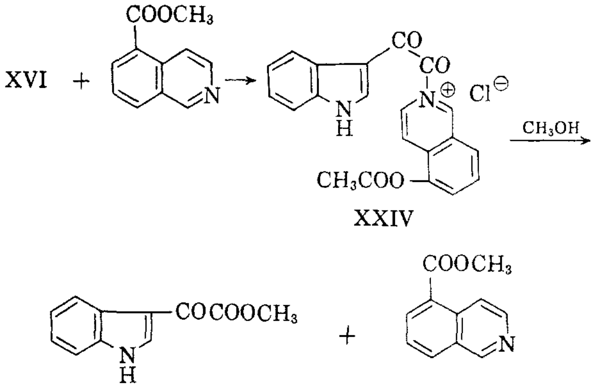
(5) A study of the preferred methods for the preparation of 5-cyanoisoquinoline has been reported by R. C. Elderfield, J. M. Lagowski, O. L. McCurdy, and S. L. Wythe, *J. Org. Chem.*, **23**, 435 (1958).

(6) F. C. Happold and L. Hoyle, *Biochem. J.*, **28**, 1171 (1934). F. Blumenthal, *Biochem. J.*, **19**, 527 (1909).

(7) F. A. Hochstein and A. M. Paradies, *J. Am. Chem. Soc.*, **79**, 5735 (1957).





diol, 6-methoxy-3-(1,2-dihydroxyethyl)indole. The remaining steps to alstonilinol (XXII) are shown in the sequence XVIII–XXII. Alstonilinol as thus prepared was identical in all respects to a sample of the substance prepared from alstoniline (XXIII). The structure previously assigned to alstoniline[8,9] is thus confirmed.

In an effort to accomplish the synthesis in one step, indole-3-glyoxalyl chloride (XVI) was condensed with 5-carbomethoxyisoquinoline. The resulting product (XXIV) underwent methanolysis during recrystallization and this approach was abandoned.

EXPERIMENTAL[10,11]

2-[β-(3-Indolyl)ethyl]-1,2,3,4-tetrahydroisoquinoline (V). To a solution of 3 g. of sodium borohydride in 100 ml. of absolute ethanol one gram of 2-[β-(3-indolyl)ethyl]isoquinolinium bromide[3] was added in small portions. The color of the bromide was discharged immediately. After stirring for 30 min. at room temperature the mixture was refluxed for an additional 30 min. and diluted with 50 ml. of water. After addition of 10 ml. of concentrated hydrochloric acid, the ethanol was removed under reduced pressure. The aqueous solution was made basic with 0.1*N* sodium hydroxide and extracted with ether. After drying over anhydrous sodium sulfate, removal of the ether left 0.61 g. (86%) of material which formed colorless needles, m.p. 124–125°, after recrystallization from acetone. The substance is sensitive to light and moisture. The hydrochloride is an oil, but the picrate, prepared in and recrystallized from aqueous acetone, formed orange needles, m.p. 169° (dec.). Reported m.p. 167–168°.[12] The picrate of the pentacyclic base which would have resulted from ring closure melts at 173° and the free base melts at 188°.[3]

2-[β-(3-Indolyl)ethyl]-5-cyanoisoquinolinium bromide (III). A solution of 2.23 g. of β-(3-indolyl)ethyl bromide, prepared by the action of phosphorus tribromide on tryptophol,[13] and 1.5 g. of 5-cyanoisoquinoline[5] in 50 ml. of methanol was refluxed for 5 min. After standing overnight the yellow solution was concentrated to 20 ml. to give 2.75 g. (73%) of III, m.p. 257° after recrystallization from aqueous ethanol.

Anal. Calcd. for $C_{20}H_{16}BrN_3$: C, 63.49; H, 4.30; N, 11.11. Found: C, 63.51; H, 4.30; N, 11.01.

2-[β-(3-Indolyl)ethyl]-5-carbomethoxyisoquinolinium bromide (IV). A solution of 2.23 g. of β-(3-indolyl)ethyl bromide and 1.87 g. of 5-carbomethoxyisoquinoline[14] in 25 ml. of methanol was refluxed for 5 min. On standing overnight 3.1 g. (75%) of IV, m.p. 248° after recrystallization from a large volume of methanol, separated.

Anal. Calcd. for $C_{21}H_{19}BrN_2O_2$: C, 61.3; H, 4.7; N, 6.8; Br, 19.4. Found: C, 61.2; H, 4.6; N, 6.8; Br, 19.4.

Attempts to condense β-(3-indolyl)ethyl bromide with isoquinoline-5-carboxylic acid failed.

2-[β-(3-Indolyl)ethyl]-5-cyano-1,2,3,4-tetrahydroisoquinoline (VI). Reduction of 1 g. of III with 3 g. of sodium borohydride in 100 ml. of ethanol for 16 hr. at room temperature gave 0.62 g. (77%) of VI as white prisms, m.p. 185–187° after recrystallization from acetone-ether.

Anal. Calcd. for $C_{20}H_{19}N_3$: C, 79.70; H, 6.35; N, 13.94. Found: C, 79.68; H, 6.31; N, 14.02.

The *hydrobromide* of VI, m.p. 222–255° (dec.), was prepared in acetone and recrystallized from methanol.

Anal. Calcd. for $C_{20}H_{20}BrN_3$: C, 62.82; H, 5.27; N, 10.99. Found: C, 62.78; H, 5.30; N, 11.00.

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

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

(10) All melting points are corrected except as noted.

(11) Microanalyses by Spang Microanalytical Laboratory, Ann Arbor, Mich.

(12) E. S. Shaw and D. W. Wooley, *J. Biol. Chem.*, **203**, 979 (1953).

(13) B. Jeiteles, *Monatsh.*, **15**, 807 (1894).

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

The *picrate* of VI, m.p. 184–187°, was prepared in acetone and recrystallized from ethanol.

Anal. Calcd. for $C_{26}H_{22}N_6O_7$: C, 58.86; H, 4.18; N, 15.84. Found: C, 58.85; H, 4.12; N, 15.75.

Reduction of IV *with sodium borohydride. A. In methanol. 2-[β-(3-Indolyl)ethyl]-5-carbomethoxy-1,2,3,4-tetrahydroisoquinoline* (VII). Reduction of IV in methanol for 4 hr. as in the reduction of VI gave 80% of VII as slightly yellow prisms from acetone, m.p. 130–131°.

Anal. Calcd. for $C_{21}H_{22}N_2O_2$: C, 75.42; H, 6.63; N, 8.38. Found: C, 75.32; H, 6.71; N, 8.39.

The *hydrobromide* of VII formed white needles, m.p. 204–206°, from ethanol.

Anal. Calcd. for $C_{21}H_{23}BrN_2O_2$: C, 60.71; H, 5.58; N, 6.74. Found: C, 60.63; H, 5.70; N, 6.65.

The *picrate* of VII was recrystallized from acetone-ethanol. It melted at 186° or 194° depending on the solvent mixture.

Anal. Calcd. for $C_{27}H_{25}N_5O_9$: C, 57.54; H, 4.47; N, 12.34. Found: C, 57.76; H, 4.16; N, 12.34.

VII was also obtained when the reduction was done in 50% methanol.

B. In 95% ethanol. 2-[β-(3-Indolyl)ethyl]-5-hydroxymethyl-1,2,3,4-tetrahydroisoquinoline (VIII). One gram of IV was added in three portions to a stirred solution of 3 g. of sodium borohydride in 100 ml. of 95% ethanol. The yellow color of the bromide was discharged immediately and the temperature of the mixture rose considerably. After 15 hr. the mixture was worked up as in the preceeding cases giving 0.66 g. (87%) of VIII as fine white needles, m.p. 173–174°, from acetone.

Anal. Calcd. for $C_{20}H_{22}N_2O$: C, 78.40; H, 7.24; N, 9.14. Found: C, 78.17; H, 7.11; N, 9.11.

The *acetate* of VIII was prepared with acetic anhydride in pyridine. It was isolated as the hydrobromide which formed fine white needles, m.p. 214–216°, from methanol.

Anal. Calcd. for $C_{22}H_{25}BrN_2O_2$: C, 61.52; H, 5.86; N, 6.53. Found: C, 61.41; H, 5.84; N, 6.41.

When the reduction was done in absolute ethanol a mixture of VII and VIII was obtained.

VII *By hydrogenation of* IV. Hydrogenation of IV in ethanol over platinum oxide resulted in the uptake of 2 equivalents of hydrogen in 70 min. with the formation of the hydrobromide of VII in 95% yield.

VIII *By reduction of* VII. Reduction of VII with excess lithium aluminum hydride in ether gave VIII, m.p. 173–174°, in 83% yield. The infrared spectra of the free base and its acetate were identical with those of the substances obtained above.

Reduction of IV *with lithium aluminum hydride. 1-Hydroxymethyl-5,7,8,14-tetrahydro-13H-benzo[g]indolo[2,3-a]-quinolizine hydrobromide* (IX). To a suspension of 3 g. of IV in a mixture of 300 ml. of anhydrous ether and 300 ml. of anhydrous tetrahydrofuran 3 g. of lithium aluminum hydride was added. After 5 min. white flocks separated. After 30 min. a second portion of 5 g. of lithium aluminum hydride was added and the mixture was stirred for 5 hr. at room temperature and allowed to stand overnight. Excess hydride was decomposed by careful addition of water. After addition of 50 g. of anhydrous sodium sulfate, the salts were filtered off and thoroughly washed with dry ether. The filtrate and washings were concentrated to 15 ml. Addition of hydrobromic acid precipitated the hydrobromide (IX) which formed pale yellow prisms, m.p. 300–301° (dec.), after recrystallization from methanol. The yield was 2.5 g. (67%).

Anal. Calcd. for $C_{20}H_{21}BrN_2O$: C, 62.33; H, 5.49; N, 7.27. Calcd. for $C_{20}H_{23}BrN_2O$: C, 61.99; H, 5.98; N, 7.23. Found: C, 62.24; H, 5.53; N, 7.31.

Attempted hydrogenation of IX over platinum or palladium resulted in no uptake of hydrogen.

1-Hydroxymethyl-5,7,8,14-tetrahydro-13H-benzo[g]indolo-[2,3-a]quinolizine (XII). A suspension of 2 g. of IX in 50 ml. of 50% methanol and 10 ml. of *N* sodium hydroxide was shaken for 15 min. The slightly brown suspension was filtered, the filter cake was washed thoroughly with water and dried over phosphorus pentoxide. The white powder, 1.5 g. (90%), melted at 230° (dec.). It could not be recrystallized without decomposition. On treatment with alcoholic hydrobromic acid it was reconverted to IX.

The acetate of XII (X) was prepared by allowing 300 mg. of crude XII to stand with a mixture of 10 ml. of acetic anhydride and 10 ml. of pyridine at room temperature for 48 hr. After removal of the solvent at reduced pressure alcoholic hydrobromic acid was added to a solution of the residue in acetone. Recrystallization of the precipitate from methanol gave 295 mg. (75%) of X as colorless prisms which did not melt at 320°. The same compound could also be prepared directly from IX.

Anal. Calcd. for $C_{22}H_{23}BrN_2O_2$: C, 61.82; H, 5.43; N, 6.56. Found: C, 61.84; H, 5.48; N, 6.59.

Dehydrogenation of XII. *1-Hydroxymethyl-7,8-dihydro-13H-benzo[g]indolo[2,3-a]quinolizinium iodide* (XIII). A solution of 40 mg. of XII in 3 ml. of methanol was added to a solution of 200 mg. of potassium acetate and 100 mg. of iodine in 3 ml. of ethanol. After refluxing for 5 min. the brown precipitate was collected and dissolved in methanol. After addition of a few crystals of sodium sulfite, the hot orange solution was filtered. XIII (22 mg.), m.p. 308° (dec.), slowly crystallized as orange needles.

Anal. Calcd. for $C_{20}H_{17}IN_2O$: C, 55.95; H, 4.00; N, 6.53; I, 29.80. Found: C, 56.07; H, 4.11; N, 6.32; I, 29.54.

Acetate of XIII (XIV). A solution of 200 mg. of XIII in 15 ml. of pyridine and 15 ml. of acetic anhydride was shaken for 18 hr. After removal of the solvent under reduced pressure, the residue was suspended in 5 ml. of acetone and the insoluble material was collected. Recrystallization from methanol gave 170 mg. (77%) of fine yellow needles, m.p. above 320° with darkening around 260°.

Anal. Calcd. for $C_{22}H_{19}IN_2O_2$: C, 56.14; H, 4.07; N, 5.95; I, 27.16. Found: C, 56.01; H, 4.00; N, 5.98; I, 26.91.

Dehydrogenation of X. When 40 mg. of X were dehydrogenated as above 27 mg. of brown needles, m.p. 263° (dec.), were obtained. Analysis indicated the presence of two iodine atoms in the compound.

Anal. Calcd. for $C_{22}H_{18}I_2N_2O_2$: C, 44.16; H, 3.03; N, 4.68; I, 41.37. Found: C, 44.91; 44.96; H, 3.27, 3.19; N, 4.61, 4.72; I, 43.01, 42.94.

The infrared spectrum shows a band corresponding to an acetate band, but otherwise the spectrum does not resemble that of XIV.

Oxidation of XIII. Oxidation of the carbinol (XIII) to an aldehyde or acid was attempted with chromic oxide in pyridine, acetone, and aqueous acetone. The product was difficult to purify and decomposed around 325°. The infrared spectrum showed no absorption in the carbonyl or hydroxyl region. Further, analyses confirmed the absence of oxygen in the substance. It is under further investigation.

Anal. Found: C, 66.42; H, 7.29; N, 7.29; I, 20.73.

6-Methoxytryptophol (XVIII). 6-Methoxy-3-indoleglyoxalyl chloride[7,15] (2.06 g.) was added in four portions to a suspension of 4 g. of lithium aluminum hydride in 60 ml. of tetrahydrofuran previously dried over calcium hydride. After standing overnight the excess hydride was destroyed by careful addition of water. The suspension was filtered through Celite and the filter cake was washed thoroughly with ether. After removal of the solvent, the residue was taken up in benzene, dried over sodium sulfate, and recrystallized from benzene to give 1.3 g. (79%) of white plates, m.p. 96–97°.

Anal. Calcd. for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85; N, 7.33. Found: C, 69.27; H, 6.91; N, 7.16.

β-(6-Methoxy-3-indolyl)ethyl bromide (XIX). To a solution of 1.91 g. of XVIII in 150 ml. of absolute ether 0.9 g. of phosphorus tribromide in 5 ml. of absolute ether was added

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(15) 6-Methoxyindole was prepared by a procedure placed at our disposal by Professor R. B. Woodward. We express our appreciation to Professor Woodward for his courtesy.

at 0°. After 15 hr. the supernatant ether solution was decanted, washed once with sodium bicarbonate solution, then with water and dried over anhydrous potassium carbonate. Removal of the ether in a stream of dry air left the bromide which is very sensitive to heat and moisture. It was used directly for the next step.

2-[β-(6-Methoxy-3-indolyl)ethyl]-5-carbomethoxyisoquinolinium bromide (XX). Condensation of XIX with 5-carbomethoxyisoquinoline as in the preparation of IV gave XX as clusters of orange needles, m.p. 270°, with a color change about 220°. The yield was 61% from XIX.

Anal. Calcd. for $C_{22}H_{21}BrN_2O_3$: C, 59.85; H, 4.77; N, 6.35. Found: C, 59.57; H, 4.78; N, 6.35.

Tetrahydroalstonilinol (XXI). To a solution of 441 mg. of XX in 20 ml. of anhydrous tetrahydrofuran and 20 ml. of anhydrous ether was added 1 g. of lithium aluminum hydride. After standing overnight at room temperature with occasional shaking the excess hydride was carefully decomposed with a few drops of water. After filtering through Celite and thorough washing of the filter cake, the solvent was removed under reduced pressure and the residue was recrystallized from chloroform–petroleum ether to yield 210 mg. (64%) of XXI as fine white needles, m.p. 220–224°.

Anal. Calcd. for $C_{21}H_{22}N_2O_2$: C, 75.42; H, 6.63; N, 8.38. Found: C, 75.28; H, 6.77; N, 8.09.

The *hydrochloride* of XXI, prepared in and recrystallized from absolute ethanol, formed white needles, m.p. 278° (dec.) with previous darkening about 250°.

Anal. Calcd. for $C_{21}H_{23}ClN_2O_2$: C, 68.03; H, 6.29; N, 7.51. Found: C, 67.97; H, 6.01; N, 7.29.

The infrared spectra of tetrahydroalstonilinol and its hydrochloride were identical with those of the substances prepared from natural alstoniline (XXIII) according to Elderfield and Wythe.[8]

Alstonilinol (XXII). Dehydrogenation of XXI with iodine and potassium acetate as in the case of XIII gave alstonilinol iodide as orange needles, m.p. 310° (dec.), from methanol. The yield was 90%.

Anal. Calcd. for $C_{21}H_{19}IN_2O_2$: C, 54.90; H, 4.17; N, 6.10; I, 27.86. Found: C, 55.02; H, 4.20; N, 6.07; I, 27.52.

Reaction of β-(3-indole)glyoxalyl chloride (XVI) *with 5-carbomethoxyisoquinoline* (XXIV). To a solution of 2.08 g. of XVI[16] in 15 ml. of tetrahydrofuran was added a solution of 1.87 g. of 5-carbomethoxyisoquinoline in 10 ml. of tetrahydrofuran. When recrystallization of the yellow precipitate from methanol-ether was attempted solvolysis occurred. The crystalline material which separated first as white needles, m.p. 200° (dec.), was identified as the hydrochloride of 5-carbomethoxyisoquinoline by infrared comparison with a known sample.

Anal. Calcd. for $C_{11}H_9NO_2$: C, 59.10; H, 4.48; N, 6.28; Cl, 15.86. Found: C, 59.47; H, 4.49; N, 6.22; Cl, 15.51.

The mother liquors from the above hydrochloride were concentrated and the residue was recrystallized from methanol-benzene to give 1.45 g. (72%) of white prisms, m.p. 226°.

Anal. Calcd. for $C_{11}H_9NO_3$: C, 65.02; H, 4.43; N, 6.85. Found: C, 64.71; H, 4.21; N, 6.64.

Hydrolysis of the above ester with 0.2*N* sodium hydroxide gave an acid, m.p. 214°, after recrystallization from methanol. Indole-3-glyoxylic acid is reported as melting at 216° and its methyl ester at 225°.[17]

Attempted Japp-Klingemann Reaction with m-methoxybenzenediazonium chloride and diethyl α-acetogluturate. To a solution of 24 g. of diethyl α-acetylgluturate[18] in 200 ml. of ethanol and 200 ml. of 20% sodium hydroxide solution at 5° a solution of *m*-methoxybenzenediazonium chloride prepared from 13 g. of *m*-anisidine,[19] 7 g. of sodium nitrite, and 61 ml. of 18% hydrochloric acid was added. The mixture was kept in an ice-salt bath for 3 hr. and allowed to come to room temperature. Green needles, m.p. 130° (14.2 g., 79%), were collected and recrystallized from ethanol.

Anal. Calcd. for $C_9H_{12}N_2O_2$: C, 59.98; H, 6.71; N, 15.55. Found: C, 59.64; H, 6.83; N, 15.66.

The *acid sulfate*, prepared in and recrystallized from 90% ethanol, formed long yellow needles, m.p. 180° (dec.).

Anal. Calcd. for $C_9H_{12}N_2O_2 \cdot H_2SO_4$: C, 38.85; H, 5.07; N, 10.07. Found: C, 38.55; H, 5.10; N, 9.83.

The structure of this green compound is under investigation.

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(16) M. S. Kharasch, S. S. Kane, and H. C. Brown, *J. Am. Chem. Soc.*, 62, 2243 (1940).

(17) J. N. Baker, *J. Chem. Soc.*, 459 (1940).

(18) The ester, b.p. 134–138° (2 mm.), was prepared in 69% yield by refluxing the product of the condensation of pyrrolidine and ethyl acetoacetate with ethyl acrylate. (Private communication from Dr. R. E. Ireland of these Laboratories.)

(19) P. K. Kadaba and S. P. Massie, *J. Org. Chem.*, 22, 333 (1957).

[CONTRIBUTION FROM THE MERCK SHARP & DOHME RESEARCH LABORATORIES, MERCK & CO., INC.]

Transformations in the D-Homosteroid Series. The Isomeric 17α,17a-Glycols[1]

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The formation and various transformations of the isomeric 17α,17a-dihydroxy-3α-acetoxy-17β-methyl-D-homoetiocholan-11-ones are described.

The formation and structure elucidation of two 3α-acetoxy-17α-17a-diols isomeric at position 17a arising from reduction of 3α-acetoxy-17α-hydroxy-17β-methyl-D-homoetiocholane-11,17a-dione (I) were reported recently.[1,2a] Reduction of I with aluminum isopropoxide affords in good yield a glycol, m.p. 213–15° which reverted to I on chromic acid oxidation. When I was refluxed in ethanol solu-

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(1) Presented in part at the Symposium on Steroids and Related Natural Products, The Gordon Research Conferences, New Hampton, N. H., July 30–August 3, 1956.

(2) (a) N. L. Wendler, D. Taub, S. Dobriner, and D. K. Fukushima, *Chem. & Ind.* (*London*), 1259 (1955); (b) *J. Am. Chem. Soc.*, 78, 5027 (1956).