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

ALSTONIA ALKALOIDS. V. SYNTHESIS OF AN OPEN RING ANALOG OF ALSTONILINE[1]

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In the preceding paper (1) evidence obtained from degradation studies which enabled advancing a tentative structure (I) for alstoniline as its salts was presented. The location of the methoxyl group in the indole portion of the molecule was based largely on analogy to harmine and on spectrographic similarities between alstoniline and 6-methoxyindole.

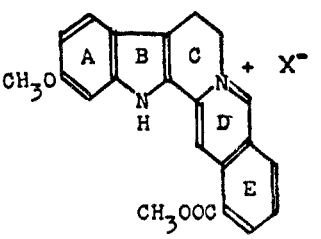
In order to provide more definite confirmation for the structure I, we have investigated syntheses leading to the skeleton of I with the difference that ring C is open. 7,8-Dihydrobenz[*g*]indolo[2,3-*a*]quinolizinium iodide (II), which has the same chromophore group as alstoniline with the exception of the presence of the methoxyl and carbomethoxy groups has been prepared by Swan (2). Its ultraviolet spectrum is quite similar to that of alstoniline. However, since the ultraviolet spectra of tetrahydroalstoniline suggested the presence of a methoxyl group in the indole portion of the molecule, model compounds with methoxyl groups in the 5 and 6 positions of the indole system were desired. For this purpose 3-(6-methoxy-3-methyl-2-indolyl)-2-methylisoquinolinium iodide (III) and 3-(5-methoxy-3-methyl-2-indolyl)-2-methylisoquinolinium iodide (IV) and their tetrahydro derivatives (V and VI) were selected. Since the syntheses of III and IV could be expected to proceed more readily than that of the analog in which ring C is closed, and since both III and IV contain the conjugated system under consideration it was felt that they would be suitable model compounds.

3-Methylisoquinoline (VII) was oxidized to 3-isoquinolinecarboxaldehyde (VIII) according to Teague and Roe (3). Reaction of VIII with ethylmagnesium bromide gave ethyl-3-isoquinolylcarbinol (IX) which on oxidation with chromic oxide gave ethyl 3-isoquinolyl ketone (X). Application of the Fischer indole synthesis to X with *m*-methoxyphenylhydrazine gave the desired indole (XI) which was converted to III by refluxing with methyl iodide in alcohol solution. The ease with which the Fischer indole ring closure occurs with the *m*-methoxyphenylhydrazone of X is remarkable. It is necessary only to pass hydrogen chloride through an alcoholic solution of the hydrazone on which ring closure occurs spontaneously. Reduction of III to V proceeded readily and is formulated as shown since isoquinolinium salts are generally preferentially reduced in the Py ring (4).

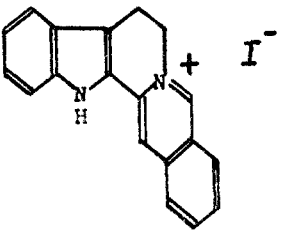
The ring closure of the *m*-methoxyphenylhydrazone of X can conceivably lead to an indole carrying the methoxyl group in the 4 position rather than to the

[1] The material presented in this paper is taken from a dissertation submitted by Stephen L. Wythe in partial fulfillment of the requirements for the degree of Doctor of Philosophy in Columbia University. At the time the work was done Dr. Wythe was in residence at the University of Michigan on leave of absence from Columbia University.

[2] Eli Lilly and Company Fellow.



I.



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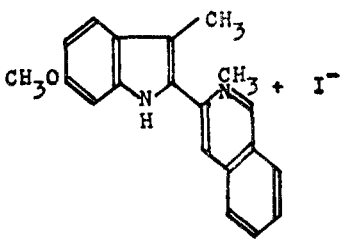

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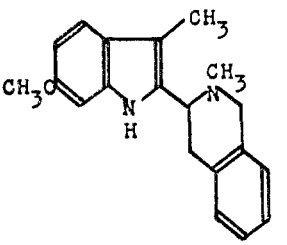

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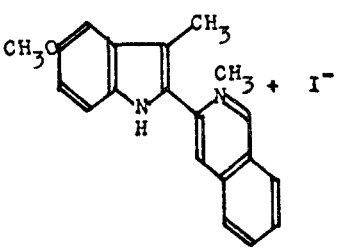

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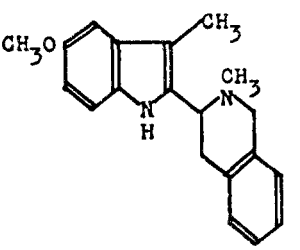
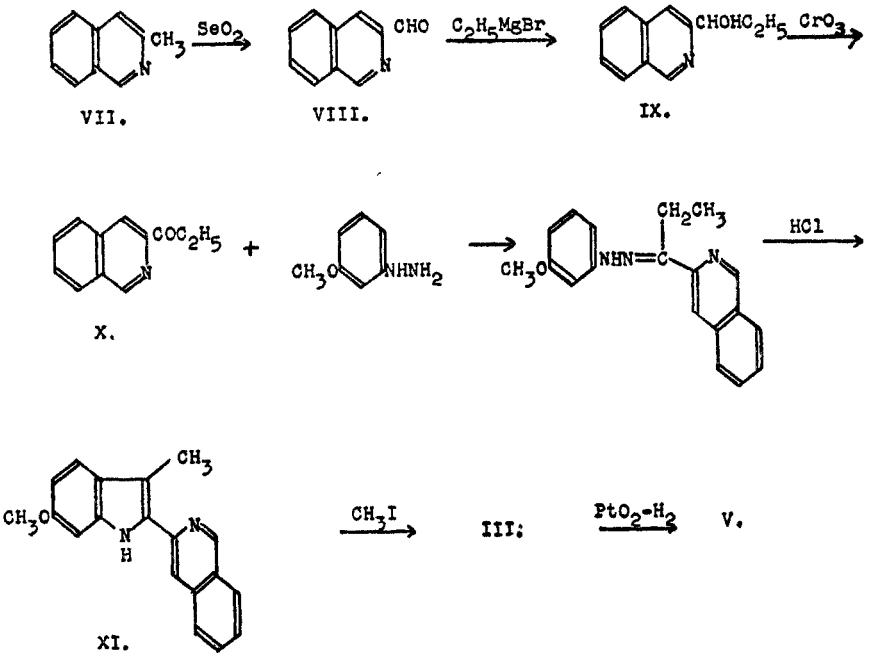


VI.

6-methoxyindole shown. The methoxyl group is *ortho, para*-directing in electrophilic substitution reactions and the Fischer indole synthesis has been postulated as involving electrophilic attack on the benzene ring (5, 6). However, in every instance of ring closure in both indole and quinoline syntheses involving a methoxyl group *meta* to the ring nitrogen of which we are aware, closure occurs exclusively *para* to the methoxyl group. More specifically, Mentzer (7) noted that the *m*-methoxyphenylhydrazone of *p*-methoxypropiophenone gave only the 6-methoxyindole and none of the 4 isomer. Similarly, Kermack, Perkin, and Robinson (8) obtained only the 6-methoxyindole from the reaction of *m*-methoxyphenylhydrazine with α-ketoglutaric acid in alcoholic hydrogen chloride. We therefore believe that III indeed has the structure assigned to it.

In contrast to the extremely facile ring closure of the *m*-methoxyphenylhydrazone of X, the *p*-methoxyphenylhydrazone of X has resisted all attempts at conversion to the 5-methoxyindole.

The ultraviolet spectra of III and of alstoniline hydrochloride are roughly similar (Fig. 1). It is to be expected that one of the peaks in the spectrum of alstoniline would be found at a longer wave length than the corresponding peak



of III due to the presence of the carbomethoxy group. Much better agreement is found between the spectra of tetrahydroalstoniline and V as shown in Fig. 2 in which the curves for 5- and 6-methoxyindole (9) are also included.

Although the case is by no means conclusive, we feel that the weight of the available evidence warrants assignment of structure I to the salts of alstoniline. Syntheses leading to the incorporation of the carbomethoxy group in III and of alstoniline itself are underway and will be reported shortly.

EXPERIMENTAL[3, 4]

Ethyl-3-isoquinolylcarbinol (IX). To a solution of ethylmagnesium bromide prepared from 3.5 g. (0.032 mole) of ethyl bromide and 0.8 g. (0.032 mole) of magnesium in 50 ml. of absolute ether was added a solution of 5 g. (0.032 mole) of 3-isoquinolinecarboxaldehyde (3) in 30 ml. of absolute ether slowly with stirring. The mixture was refluxed one hour after addition of the aldehyde. The Grignard complex was decomposed by refluxing with 20 ml. of 5% sodium hydroxide solution for 20 minutes. The ether layer was drawn off and filtered and the aqueous layer was extracted several times with ether. After drying the combined ether extracts over sodium sulfate and removal of the solvent a light yellow-brown oil remained which solidified on standing. After recrystallization from petroleum ether (b.p. 90–100°) the carbinol formed white needles, m.p. 85–87°. The yield was 3 g. (50%).

Anal. Calc'd for $C_{12}H_{13}NO$: C, 77.0; H, 7.0.

Found: C, 76.9; H, 6.9.

Ethyl 3-isoquinolyl ketone (X). To a solution of 5 g. (0.027 mole) of ethyl-3-isoquinolylcarbinol in 25 ml. of sulfuric acid (*sp. gr.* 1.84) and 150 ml. of water was added in small por-

[3] All melting points are corrected for stem exposure. Boiling points are uncorrected.

[4] Microanalyses were done by Clark Microanalytical Laboratory, Urbana, Illinois; Schwarzkopf Microanalytical Laboratory, Middle Village, New York; and Mr. Goji Kodama of the University of Michigan laboratories.

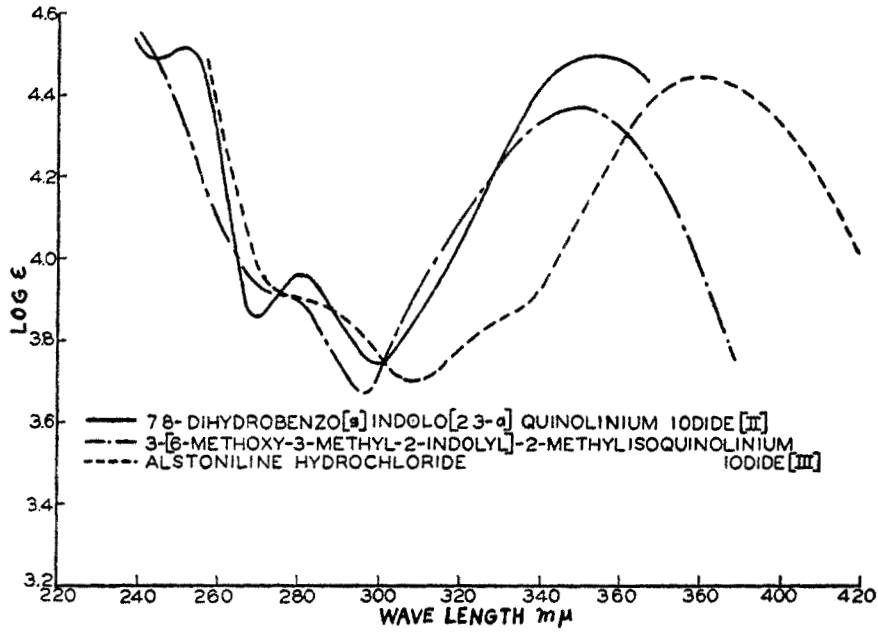


FIG. 1

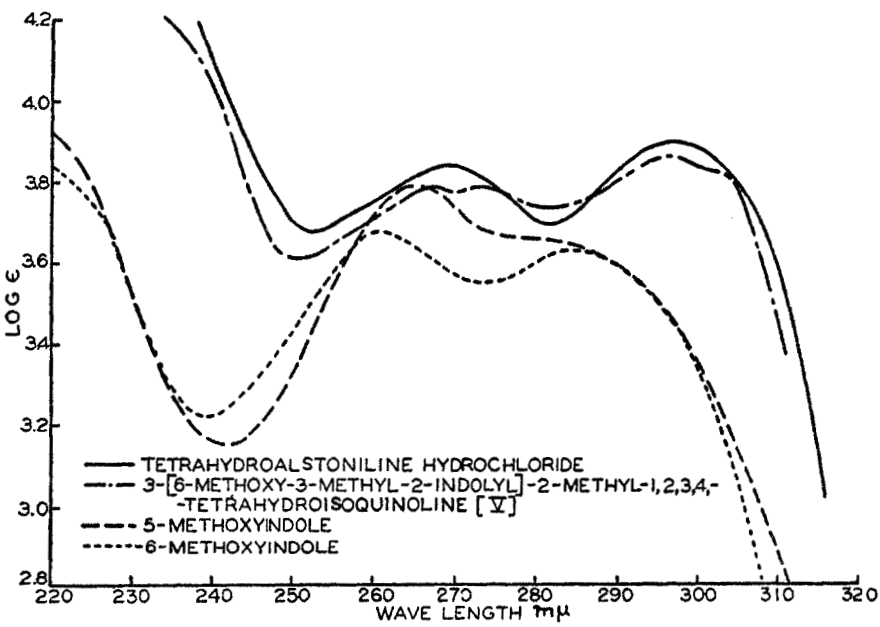


FIG. 2

tions over 15 minutes a solution of 5 g. (0.017 mole) of sodium dichromate heptahydrate in 25 ml. of water. The mixture was allowed to stand at room temperature for 18 hours. The solution was made strongly basic with sodium hydroxide and was extracted exhaustively with ether. After drying the combined ether extracts over sodium sulfate and removal of

the solvent an oil which solidified on standing remained. Recrystallization from petroleum ether (b.p. 30–60°) gave 2.2 g. (45%) of the ketone, m.p. 63–64°.

Anal. Calc'd for $C_{12}H_{11}NO$: C, 77.8; H, 6.0.
Found: C, 77.7; H, 6.0.

3-(6-Methoxy-3-methyl-2-indolyl)isoquinoline (XI). A solution of 1 g. (0.0055 mole) of ethyl 3-isoquinolyl ketone and 0.8 g. (0.0058 mole) of *m*-methoxyphenylhydrazine (8) in 15 ml. of absolute ethanol was refluxed for 15 minutes. A stream of dry hydrogen chloride was then passed through the cooled solution as rapidly as possible during which the alcohol boiled. In a few minutes a copious red precipitate separated. Passage of hydrogen chloride was continued for an additional 20 minutes. The suspension was cooled, diluted with 15 ml. of water and the red solid [0.7 g., m.p. 270–272° (dec.)] was filtered. When the red hydrochloride was refluxed with 25 ml. of ethanol to which 5 drops of 10% aqueous sodium hydroxide solution had been added the red color was discharged and the resulting yellow solution deposited 0.5 g. (35%) of 3-(6-methoxy-3-methyl-2-indolyl)isoquinoline on cooling. After recrystallization from ethanol the substance formed fine yellow needles, m.p. 195–197°.

Anal. Calc'd for $C_{19}H_{16}N_2O$: C, 79.1; H, 5.6.
Found: C, 79.0; H, 5.6.

3-(6-Methoxy-3-methyl-2-indolyl)-2-methylisoquinolinium iodide (III). When a solution of 0.45 g. (0.0016 mole) of the above substance was refluxed with 10 ml. of methyl iodide in 10 ml. of ethanol and 20 ml. of benzene for 12 hours a red solid deposited. After chilling the solid was collected and recrystallized from benzene-ethanol. The yield was 0.35 g. (53%) of fine red needles, m.p. 250–251° (dec.).

Anal. Calc'd for $C_{20}H_{19}IN_2O$: C, 55.8; H, 4.4.
Found: C, 55.7; H, 4.3.

3-(6-Methoxy-3-methyl-2-indolyl)-2-methyl-1,2,3,4-tetrahydroisoquinoline. A suspension of the above methiodide (0.152 g., 0.353 millimole) in 100 ml. of methanol was shaken with 22 mg. of Adams' platinum oxide catalyst with hydrogen at atmospheric pressure and room temperature. After five hours the hydrogen uptake was 26.5 ml. (theoretical for 2 moles). After filtration from the catalyst the filtrate was made basic with a few drops of 10% sodium hydroxide solution and concentrated under reduced pressure to 15 ml. After addition of 30 ml. of hot water, the solution was boiled a few minutes, filtered, and chilled yielding 100 mg. of light yellow platelets, m.p. 134–136°.

Anal. Calc'd for $C_{20}H_{22}N_2O$: C, 78.4; H, 7.2.
Found: C, 78.6; H, 7.0.

SUMMARY

1. Synthesis of an analog of the structure proposed for alstoniline in which Ring C is open is described.

2. Spectrographic properties of this analog and its reduction product support the structure assigned to alstoniline.

ANN ARBOR, MICHIGAN

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