HETEROCYCLIC COMPOUNDS, PART XV*

Synthesis of α-Pyridylindoles

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Alstyrine,[1] an important degradation product of a number of indole alkaloids, is characterised by the presence of α-pyridylindole ring system. Ever since the total synthesis of alstyrine was accomplished by Swan,[2] the chemistry and synthesis of substituted, as well as unsubstituted, α-pyridylindoles has engaged the attention of a number of workers. The present investigation had as its objective the synthesis of some of the methyl-substituted α-pyridylindoles by the obvious application of the Fischer indole reaction, with methyl groups in the various positions of the benzene ring.

This work also records the comparative efficacy of the following reagents to effect the Fischer ring closure, in the present work.

(1) Orthophosphoric acid (Sp. Gr. 1·75).

(2) Ethanolic hydrogen chloride.

(3) Polyphosphoric acid.

The indoles prepared in the present investigation can be conveniently classified as follows:—

(1) Indoles from 4-acetyl pyridine-tolylhydrazones.

(2) Indoles from 2-acetyl pyridine-tolylhydrazones.

1. *Indoles from 4-acetyl pyridine-tolylhydrazones*

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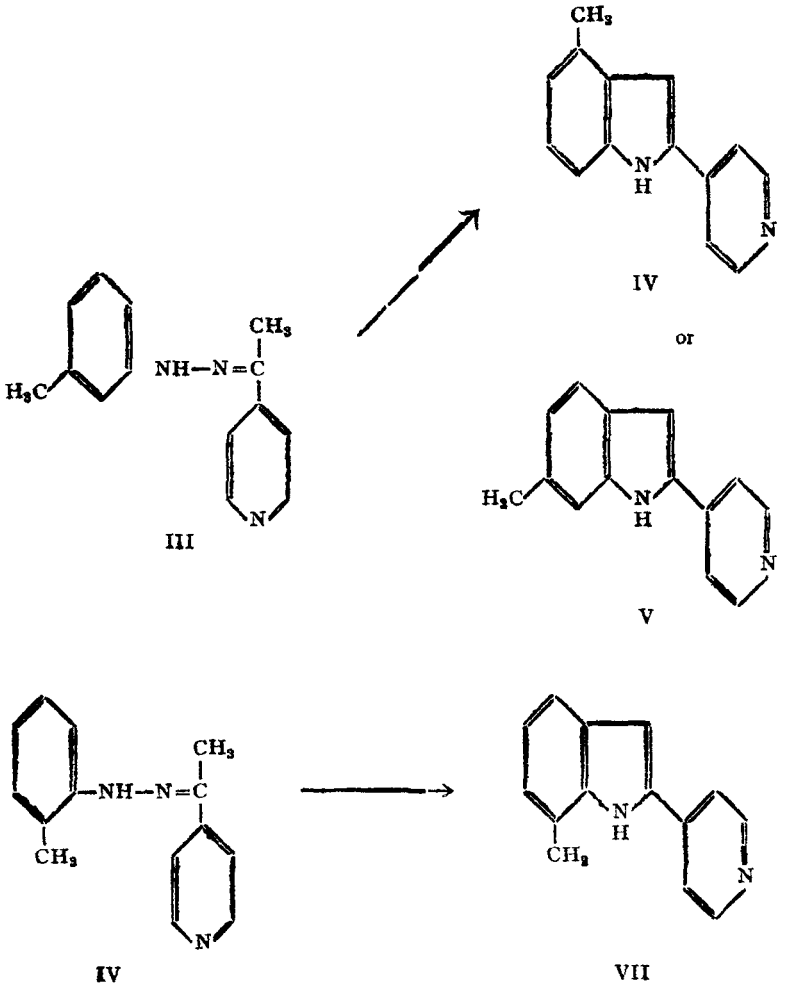
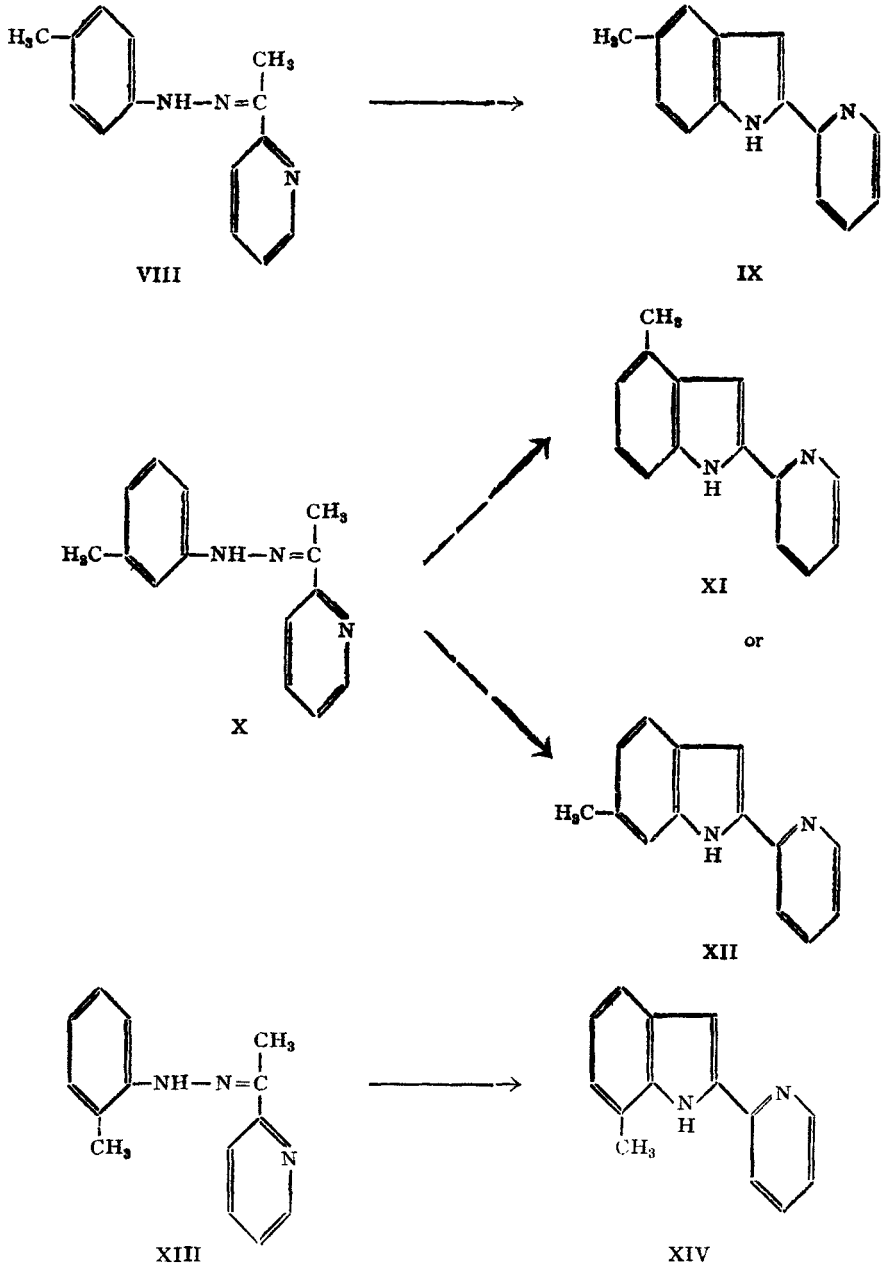


4-Acetyl pyridine-*p*-tolylhydrazone (I), from 4-acetyl pyridine,[3] on treatment with orthophosphoric acid, cyclized to give 2-(4′-pyridyl)-5-methyl indole (II). The ring closure of 4-acetyl pyridine-*m*-tolylhydrazone (III) was also effected with polyphosphoric acid. In this case the indole obtained may be either 2-(4′-pyridyl)-4-methyl indole (IV) or 2-(4′-pyridyl)-6-methyl indole (V). The proof of rigid structure has not been attempted in the present work. When an attempt was made to cyclize 4-acetyl pyridine-O-tolylhydrazone (VI) in the presence of ethanolic hydrogen chloride, the hydrazone was recovered unchanged. However it was successfully ring-closed to 2-(4′-pyridyl)-7-methyl indole (VII), with ploy phosphoric acid.

2. *Indoles from 2-acetyl pyridine tolylhydrazones*



2-(2′-pyridyl)-5-methylindole (**IX**).

2-(2′-pyridyl)-4-or-6-methyl indole (**XI** or **XII**).

2-(2′-pyridyl)-7-methyl indole (XIV).

The above three indoles were obtained by cyclizing respectively, *p*-, *m*-, and O-tolylhydrazones of 2-acetyl pyridine.

Of all three reagents employed for Fischer ring closure in the present investigation, polyphosphoric acid was found to be the most effective one. The superiority of polyphosphoric acid consists in that it produces much purer products in better yield and in lesser reaction period.

EXPERIMENTAL

*4-Acetyl pyridine-*p*-tolylhydrazone (I)*

4-Acetyl pyridine[3] (3 g.) in alcohol (15 ml.) was added to *p*-tolylhydrazine (3 g.), dissolved in alcohol (15 ml.), the mixture was allowed to stand overnight and then refluxed on a water-bath for an hour and a half. The hot solution was diluted with water and cooled in the refrigerator. The hydrazone separated as yellow needles, m.p. 140°; yield 5 g. The hydrazone could not be obtained in analytical purity and it was used in the next step without purification.

2-(4′-pyridyl)-5-methyl indole (II)

4-Acetyl pyridine-*p*-tolylhydrazone (4 g.) was added to orthophosphoric acid (40 ml.; sp. gr. 1·75) contained in a 100 ml. round-bottomed flask. The contents were heated on a water-bath for two hours with exclusion of moisture. The flask was cooled and the solution was poured over cracked ice. It was basified with solid sodium bicarbonate and left overnight in the ice-chest. The indole, which separated as an yellow solid, was collected and crystallised from methanol, m.p. 239°; yield 2 g. Found: N = 13·74. $C_{14}H_{12}N_2$ requires N = 13·46.

The picrate, crystallised from acetic acid in the form of red needles, m.p. 256° (decomp.). Found: N = 15·82. $C_{14}H_{12}N_2 \cdot C_6H_3N_3O_7$ requires N = 16·01.

*4-Acetyl pyridine-*m*-tolylhydrazone (III)*

This hydrazone was prepared from *m*-tolylhydrazine (3 g.) and 4-acetyl pyridine (3 g.) had m.p. 165°; yield 3·4 g.

2-(4′-pyridyl)-4-or-6-methyl indole (IV or V)

The crude hydrazone (3·4 g.) was added to polyphosphoric acid prepared from orthophosphoric acid (6 g.) and phosphorus pentoxide (10 g.).

The mixture was stirred with a thermometer by hand and gradually heated in an oil-bath until the internal temperature reached 120°. It was left at this temperature for 3 minutes. Then the flask was cooled and the contents diluted with water. The difficultly soluble phosphate was washed with concentrated hydrochloric acid to facilitate solubility. The clear solution was treated with charcoal, filtered and basified with 20% sodium hydroxide solution. The base, which separated immediately, was collected and dried. It crystallised from methanol in colourless needles, m.p. 280°, yield 2·5 g. Found: N = 13·26. $C_{14}H_{12}N_2$ requires N = 13·46.

The picrate crystallised from methanol in red plates, m.p. 270° (decomp.). Found: N = 15·88. $C_{14}H_{12}N_2 \cdot C_6H_3N_3O_7$ requires N = 16·01.

4-Acetyl pyridine O-tolylhydrazone (VI)

O-tolylhydrazine (3 g.) and 4-acetyl pyridine (3 g.) gave the hydrazone, m.p. 95°; yield 3·3 g.

2-(4'-pyridyl)-7-methyl indole (VII)

The following three methods have been attempted for the synthesis of this indole.

1. The hydrazone VI was cyclized in the presence of orthophosphoric acid to give the indole. But, it was obtained in a highly impure condition and could not be crystallised from any common organic solvent.

2. An unsuccessful attempt made to ring-close the hydrazone by the influence of ethanolic hydrogen chloride resulted only in the production of the hydrochloride of the hydrazone.

3. 4-Acetyl pyridine-O-tolylhydrazone (VI) (3 g.) was added to polyphosphoric acid. The mixture was gradually heated in an oil-bath until the internal temperature reached 140°. It was kept at this temperature for 2–3 minutes and then cooled and diluted with water. When concentrated hydrochloric acid was added to dissolve the difficultly soluble phosphate, the beautiful yellow hydrochloride of the indole separated instantaneously. The hydrochloride was collected and dissolved in hot water. The yellow solution was cooled and basified to give the corresponding indole. It crystallised from dilute methanol in colourless needles, m.p. 187°; yield 1·5 g. Found: N = 13·31. $C_{14}H_{12}N_2$ requires N = 13·46.

The picrate crystallised from alcohol in red plates, m.p. 284° (decomp.). Found: N = 15·76. $C_{14}H_{12}N_2 \cdot C_6H_3N_3O_7$ requires N = 16·01.

2-Acetyl pyridine-tolylhydrazone (VIII)

This hydrazone was obtained as a brown viscous liquid when 2-acetyl pyridine[4] (3 g.) was reacted with *p*-tolylhydrazine (3 g.). The crude compound weighed 4 g.

2-(2'-pyridyl)-5-methylindole (IX)

The above crude hydrazone (4 g.) underwent a Fischer ring closure when it was treated with orthophosphoric acid (40 ml.). The indole obtained was crystallised from methanol, m.p. 131°; yield 1 g. Found: N = 13·04. $C_{14}H_{12}N_2$ requires N = 13·46.

The picrate crystallised from acetic acid in the form of yellow needles, m.p. 229° (decomp.). Found: N = 16·00. $C_{14}H_{12}N_2 \cdot C_6H_3N_3O_7$ requires N = 16·01.

2-Acetyl pyridine-O-tolylhydrazone (XIII)

The above hydrazone was obtained when 2-acetyl pyridine (3 g.) was condensed with O-tolylhydrazine (3 g.), m.p. 65°; yield 4 g.

2-(2'-pyridyl)-7-methyl indole (XIV)

This indole was obtained when the hydrazone XIII (4 g.) was treated with polyphosphoric acid. The indole crystallised from dilute methanol in colourless needles, m.p. 110°; yield 1·5 g. Found: N = 13·62. $C_{14}H_{12}N_2$ requires N = 13·46.

The picrate crystallised from alcohol in red needles, m.p. 260° (decomp.). Found: N = 16·35. $C_{14}H_{12}N_2 \cdot C_6H_3N_3O_7$ requires N = 16·01.

2-Acetyl pyridine-m-tolylhydrazone (X)

This hydrazone was obtained from 2-acetyl pyridine (3 g.) and *m*-tolylhydrazone (3 g.), m.p. 105; yield 3 g.

2-(2'-Pyridyl)-6-or-4-methyl indole (XI or XII)

The above hydrazone was ring-closed with polyphosphoric acid. The indole (XI or XII) crystallised from methanol in colourless needles, m.p. 147°; yield 1·5 g. Found: N = 13·52. $C_{14}H_{12}N_2$ requires N = 13·46.

The picrate crystallised from acetic acid in yellow needles, m.p. 244° (decomp.). Found: N = 15·97. $C_{14}H_{12}N_2 \cdot C_6H_3N_3O_7$ requires N = 16·01.

SUMMARY

Synthesis of six α-pyridylindoles is reported.

ACKNOWLEDGEMENT

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