

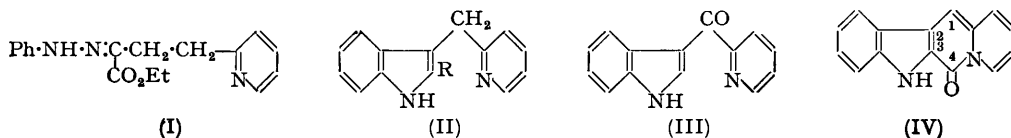
Syntheses in the Indole Series.

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[Reprint Order No. 5279.]

3-(2-Pyridylmethyl)indole (II; R = H) and 3-indolyl 2-pyridyl ketone (III) have been prepared, and an attempt made to cyclise them by the Scholl and other methods to give the tetracyclic system of lysergic acid. A rearrangement of some 3-substituted indoles to the corresponding 2-substituted compounds has been noted.

3-(2-PYRIDYLMETHYL)INDOLE (II) was prepared by condensing benzenediazonium chloride with ethyl β -(2-pyridylethyl)acetoacetate (cf. Doering and Weil, *J. Amer. Chem. Soc.*, 1947, **69**, 2461) in alkaline solution to give the hydrazone (I), cyclisation by alcoholic hydrogen chloride, and hydrolysis and decarboxylation of the resulting ester (II; R = CO₂Et). When 3-(2-pyridylmethyl)indole-2-carboxylic acid (II; R = CO₂H) was heated, water was eliminated and 4-oxoindolo(3' : 2'-2 : 3)pyridocoline (IV) was obtained.



Attempts to cyclise the base (II; R = H) by hot aluminium chloride-sodium chloride, however, isomerised it. In order to elucidate this, 3-benzylindole was prepared (cf. Robinson, Cornforth, and West, U.S.P. 2,407,452/1946) and heated with aluminium chloride-sodium chloride; it gave 2-benzylindole (Julian and Pikel, *J. Amer. Chem. Soc.*, 1933, **55**, 2105). Similarly skatole rearranged to 2-methylindole and it was therefore concluded that the pyridyl isomer was 2-(2-pyridylmethyl)indole. This appears to be the first record of such isomerisation in the indole series.

When however 3-benzylindole and 3-(2-pyridylmethyl)indole were *N*-acetylated by means of the indole Grignard reagent no such rearrangement occurred on fusion with aluminium chloride-sodium chloride. The former gave a product from which a small amount of anthracene was isolated.

With selenium dioxide the base (II; R = H) gave 3-indolyl 2-pyridyl ketone (III), but when this was heated with aluminium chloride and sodium chloride only the starting material was recovered.

2 : 5-Dichlorobenzenediazonium chloride coupled with ethyl β -(2-pyridylethyl)acetoacetate to give the 2 : 5-dichlorophenylhydrazone corresponding to (I). When this was regenerated from acid solution the product had a different melting point and it is suggested that this hydrazone can exist in stable *syn*- and *anti*-forms. The hydrazone did not cyclise when heated in alcohol and sulphuric acid at 180° or in alcohol with zinc chloride at 125°, but at 150° 4' : 7'-dichloro-4-oxoindolo(3' : 2'-2 : 3)pyridocoline was formed.

EXPERIMENTAL

Ethyl α -Phenylhydrazone- γ -2-pyridylbutyrate Hydrochloride (as I).—Ethyl β -(2-pyridylethyl)acetoacetate (36 g.) in ethanol (100 ml.) was cooled in ice, while a solution of sodium hydroxide (30 g.) in water (80 ml.) was added, followed at once by one of benzenediazonium chloride prepared from aniline (16 g.) in concentrated hydrochloric acid (80 ml.). A dark reddish-brown oil was liberated. After several minutes water was added and the oil extracted with ether. After removal of the solvent, hydrochloric acid was added to the residue, and the whole again evaporated to dryness; the crystalline *hydrochloride* remained. Crystallisation twice from alcohol gave straw-coloured plates (32 g.), m. p. 195° (Found : C, 61.2; H, 6.2, C₁₇H₁₉O₂N₃.HCl requires C, 61.2; H, 6.0%).

Ethyl 3-(2-Pyridylmethyl)indole-2-carboxylate (II; R = CO₂Et).—A solution of the above hydrazone (20 g.) in absolute ethanol (200 ml.) was saturated with dry hydrogen chloride and refluxed for 3 hr. The alcohol was removed, and the residue was dissolved in water and basified

with sodium carbonate. The ester that separated soon solidified and was filtered off and recrystallised from benzene to give buff-coloured needles (9.6 g.), m. p. 129° (Found : C, 72.8; H, 6.0. $C_{17}H_{16}O_2N_2$ requires C, 72.85; H, 5.7%).

3-(2-Pyridylmethyl)indole-2-carboxylic Acid (II; R = CO₂H).—The ester was refluxed with sodium hydroxide (5 g.) in methanol (30 ml.) for 6 hr. Water was added and the methanol removed. The pH was adjusted to 7 with dilute hydrochloric acid, and the solution extracted with ether. The extract was dried (Na₂SO₄) and the solvent removed, leaving a white acid which, recrystallised from benzene (6 g.), had m. p. 135° (Found : C, 71.4; H, 4.9. $C_{15}H_{12}O_2N_2$ requires C, 71.4; H, 4.8%).

3-(2-Pyridylmethyl)indole (II; R = H).—The acid (6 g.) was boiled with concentrated hydrochloric acid for 1 hr. The solution was basified with sodium carbonate and extracted with ether. The extract was dried (Na₂SO₄) and the solvent removed, leaving the base as a brown gum, which separated from light petroleum (b. p. 60–80°) (charcoal) in colourless prisms (4.1 g.), m. p. 104° (Found : C, 80.9; H, 6.0; N, 13.4. $C_{14}H_{12}N_2$ requires C, 80.8; H, 5.8; N, 13.4%). A pink colour was obtained with Ehrlich's reagent on heating. The *monopicrate* crystallised from ethanol in fine yellow needles, m. p. 121° (Found : C, 54.55; H, 4.1. $C_{14}H_{12}N_2 \cdot C_6H_5O_7N_3 \cdot C_2H_5 \cdot OH$ requires C, 54.65; H, 4.35%).

4-Oxoindolo(3':2'-2:3)pyridocoline (IV).—The carboxylic acid (0.5 g.) was heated at 200°/0.1 mm. Yellow crystals of the *indolopyridocoline* sublimed. Recrystallisation from benzene gave yellow needles, m. p. 308° (Found : C, 76.4; H, 4.6. $C_{16}H_{10}ON_2$ requires C, 76.9; H, 4.3%).

2-(2-Pyridylmethyl)indole.—The base (II; R = H) (0.6 g.) was heated with anhydrous aluminium chloride (0.6 g.) and sodium chloride (0.05 g.) at 250° for 30 min. The melt was decomposed with ice and hydrochloric acid, basified, and extracted with ether. The extract was dried (Na₂SO₄) and the ether removed giving a brown gum, which was extracted with boiling light petroleum (b. p. 60–80°). The concentrated extract was treated with charcoal and on cooling, fine colourless needles of the *isomer* were obtained (0.2 g.), having m. p. 96° (Found : C, 80.8; H, 5.6%). A transient pink colour was obtained with Ehrlich's reagent. The *monopicrate* crystallised from ethanol in stout yellow solvated prisms, m. p. 183° (Found : C, 54.55; H, 4.4%).

2-Benzylindole.—3-Benzylindole (1 g.) was heated with anhydrous aluminium chloride (1 g.) and sodium chloride (0.1 g.) at 240° for 20 min. The melt was treated as above. The dark oil from the ether extract was distilled (air-bath temp., 150°/0.1 mm.). The colourless distillate solidified and, crystallised from light petroleum (b. p. 60–80°) (0.63 g.), had m. p. 84°, not depressed on admixture with an authentic specimen (Julian and Pikel, *loc. cit.*) (Found : C, 87.0; H, 6.4. Calc. for $C_{18}H_{13}N$: C, 86.95; H, 6.3%). The picrate crystallised from light petroleum (b. p. 60–80°) in red needles, m. p. 115°.

2-Methylindole.—3-Methylindole (1 g.) was heated with anhydrous aluminium chloride (1 g.) and sodium chloride (0.1 g.) at 250° for 20 min. The melt was treated as above. The residue from the ether was distilled (b. p. 120°/3 mm.) and, crystallised from light petroleum (b. p. 60–80°) (0.36 g.), 2-methylindole had m. p. and mixed m. p. 59°.

1-Acetyl-3-benzylindole.—A Grignard reagent prepared from magnesium (0.25 g.) and methyl iodide (2.7 g.) in dry ether (10 ml.) was cooled in ice, and a solution of 3-benzylindole (2 g.) in dry ether (20 ml.) was added slowly. The mixture was kept for 1 hr. and then refluxed for 30 min. A solution of acetyl chloride (0.5 g.) in ether (10 ml.) was added slowly to the cooled mixture which was set aside and then refluxed for 30 min. It was cooled, aqueous ammonium chloride was added, and the ether layer was separated, dried (Na₂SO₄), and evaporated. The residual acetyl derivative crystallised from light petroleum (b. p. 60–80°) in large colourless prisms (1.7 g.), m. p. 71° (Found : C, 81.9; H, 6.4. $C_{17}H_{15}ON$ requires C, 81.9; H, 6.0%).

1-Acetyl-3-(2-pyridylmethyl)indole.—A Grignard reagent was prepared by warming magnesium (0.5 g.) and ethyl iodide (2.2 g.) in dry benzene (15 ml.) and ether (1 ml.) at 70° for 3 hr. Dry benzene (50 ml.) and then a solution of 3-(2-pyridylmethyl)indole (1 g.) in benzene (20 ml.) were added in 30 min. to the boiling mixture. After 1 hour's refluxing ethyl acetate (2 g.) was added and heating continued for 3 hr. The solution was cooled and aqueous ammonium chloride added. The benzene layer was evaporated, leaving a brown oil, which was separated in benzene solution on an alumina column into 1-acetyl-3-(2-pyridylmethyl)indole, crystallising from light petroleum (b. p. 60–80°) in colourless prisms (0.3 g.), m. p. 52° (Found : C, 76.6; H, 5.9. $C_{16}H_{14}ON_2$ requires C, 76.8; H, 5.6%), and 3-(2-pyridylmethyl)indole (0.5 g.), m. p. 104°. The yellow *methiodide* of the acetylindole had m. p. 263° (Found : C, 51.8; H, 4.5. $C_{16}H_{14}ON_2 \cdot CH_3I$ requires C, 51.8; H, 4.3%).

Action of Aluminium Chloride-Sodium Chloride on 1-Acetyl-3-benzylindole.—The acetylindole (1 g.) was heated with anhydrous aluminium chloride (1 g.) and sodium chloride at 150° for 45 min. The melt was decomposed, and evaporation of its ether extract gave a brown oil, which when passed down an alumina column in benzene yielded a band from which plates crystallising from ethanol were obtained (1 mg.), m. p. 204—208° not depressed on admixture with anthracene. The ultra-violet absorption spectrum was also identical with that of anthracene. Nothing further was eluted with benzene, but chloroform eluted a thick brown gum (0.05 g.) which did not crystallise.

Action of Aluminium Chloride-Sodium Chloride on 1-Acetyl-3-(2-pyridylmethyl)indole.—The acetylindole (1 g.), when heated as above with aluminium chloride (1 g.) and sodium chloride (0.1 g.) at 150° for 30 min., yielded 1-acetyl-3-(2-pyridylmethyl)indole (0.2 g.) and the base (II; R = H) (0.2 g.).

3-Indolyl 2-Pyridyl Ketone (III).—The base (II; R = H) (2 g.) was refluxed with selenium dioxide (2 g.) in dioxan (30 ml.) for 1½ hr. The dark solution was filtered and the dioxan removed, giving a dark red residue which was extracted several times with boiling benzene. The extracts were treated with charcoal and concentrated, to give the crystalline *ketone*, which crystallised from benzene in cream-coloured prisms (0.5 g.), m. p. 191° (Found: C, 75.8; H, 4.7. C₁₄H₁₀ON₂ requires C, 75.65; H, 4.5%). The 2:4-dinitrophenylhydrazone crystallised from ethanol in deep red prisms, m. p. 293—295° (Found: C, 59.4; H, 3.5. C₂₀H₁₄O₄N₆ requires C, 59.7; H, 3.5%).

When the ketone (0.5 g.) was heated with anhydrous aluminium chloride (0.5 g.) and sodium chloride (0.05 g.) at 250° for 1 hr., and the melt was decomposed and extracted as above, only unchanged ketone (4 mg.) was recovered.

Ethyl α-2:5-Dichlorophenylhydrazono-γ-2'-pyridylbutyrate.—Ethyl β-(2-pyridylethyl)acetate (4 g.) in ethanol (20 ml.) was cooled in ice while a solution of sodium hydroxide (4 g.) in water (10 ml.) was added, followed by one of 2:5-dichlorobenzenediazonium chloride prepared from 2:5-dichloroaniline (3 g.) and hydrochloric acid (90 ml.; 1:5). After a few minutes water was added and the dark oil extracted with ether. The extract was dried (Na₂SO₄) and the ether removed, giving the *hydrazone* which crystallised from ethanol in straw-coloured needles (3.3 g.), m. p. 101° (Found: C, 55.8; H, 4.8; N, 11.8. C₁₇H₁₇O₂N₃Cl₂ requires C, 55.7; H, 4.65; N, 11.5%). The *hydrochloride* crystallised from ethanol in straw-coloured prisms, m. p. 178—180° (Found: C, 50.65; H, 4.7. C₁₇H₁₇O₂N₃Cl₂.HCl requires C, 50.7; H, 4.5%). Regeneration of the hydrazone gave pale yellow prisms (m. p. 62°) crystallising from ethanol (Found: C, 56.1; H, 4.8; N, 11.3%).

4':7'-Dichloro-4-oxoindolo(3':2'-2:3)pyridocoline.—The dichlorohydrazone (0.5 g.) was heated with zinc chloride (2.5 g.) in dry ethanol (5 ml.) at 150° for 8 hr.; the mixture was evaporated to small bulk, basified, and extracted with chloroform. From the extract yellow needles (0.1 g.), m. p. 327° (from benzene or ethanol), of the *indolopyridocoline* were obtained (Found: C, 59.0; H, 2.7. C₁₆H₈ON₂Cl₂ requires C, 59.4; H, 2.6%).

One of us (J. C. S.) thanks the D.S.I.R. for a maintenance grant.

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[Received, April 3rd, 1954.]