Internuclear Cyclisation. Part XI. The Synthesis of* ind-N-*Methyl-α-carbolines.*

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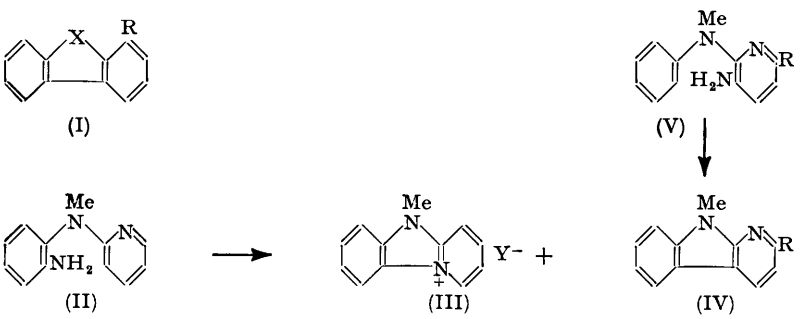
The formation of polycyclic systems containing a five-membered ring by means of the Pschorr reaction has been extended to include *ind*-*N*-methyl-α-carbolines. Whereas *N*-(3-amino-2-pyridyl)-*N*-methylanilines give good yields of α-carbolines, with 2-amino-*N*-methyl-*N*-2′-pyridylaniline the main product is a pyrido[1 : 2-*a*]benziminazolium salt.

In Part V (*J.*, 1952, 2276) the Pschorr phenanthrene synthetic method and its various modifications were applied to the synthesis of compounds of type (I), where X was CH_2, CO, or NMe, and R was H or NO_2, in which the new internuclear bond resulted in the formation of a five-membered ring. It is known that the pyridine ring is highly resistant to attack by electrophilic reagents but is attacked more readily by free radicals: Hey and Osbond (Part I, *J.*, 1949, 3164) were able to effect ring-closure on to a pyridine ring in the preparation of 7 : 8-dihydro-5 : 6-benzoquinoline from 2-(2-*o*-aminophenylethyl)pyridine. It was therefore of interest to attempt the conversion of 2-amino-*N*-methyl-*N*-2′-pyridylaniline (II) into *ind*-*N*-methyl-α-carboline (IV; R = H). The synthesis of the latter type of compound is also of interest because, whereas the chemistry of the β-carbolines has been extensively investigated mainly on account of their relation to the harmine and other groups of alkaloids, comparatively little work has been carried out with the α-isomers. Lawson, Perkin, and Robinson (*J.*, 1924, 626) prepared α-carboline itself by an extension of the Graebe–Ullmann carbazole synthesis from the triazole prepared from 2-amino-*N*-2′-pyridylaniline. Freak and Robinson (*J.*, 1938, 2013) later showed that methylation of α-carboline with methyl sulphate took place at the pyridine-nitrogen atom and that on treatment of the resulting methosulphate with alkali the 3-methyl*iso*-α-carboline resulted. On the other hand Eiter (*Monatsh.*, 1948, **79**, 17) showed that methylation of the sodium salt of α-carboline with methyl iodide resulted in the formation of the *ind*-*N*-methyl derivative. Smith and Boyer (*J. Amer. Chem. Soc.*, 1951, **73**, 2626) obtained a mixture of α- and γ-carboline by the thermal decomposition of *o*-3-pyridylphenyl azide.

2-Amino-*N*-methyl-*N*-2′-pyridylaniline (II) was prepared by condensation of 2-bromopyridine with *N*-methyl-*o*-nitroaniline, followed by reduction of the product with



stannous chloride. The aqueous diazonium sulphate of the amine was decomposed by the action of heat to give the required *ind*-*N*-methyl-α-carboline (IV; R = H) in 7% yield. A crude water-soluble product was also obtained in 84% yield. On the basis of the analysis of the derived picrate, this is considered to be 5-methylpyrido[1 : 2-*a*]benziminazolium chloride (III; Y = Cl), which can arise from the co-ordination of the diazonium cation with the pyridine-nitrogen atom followed by loss of a molecule of nitrogen. The chloride anion

* Part X, *J.*, 1954, 2481.

arises from the use of hydrochloric acid during the process of isolation. In support of the formulation of this compound as (III) are: (*a*) its high solubility in water, (*b*) its high melting point, and (*c*) the sharp melting point (without decomposition) of the picrate which thus behaves as a salt as distinct from most picrates which are addition complexes (cf. evidence for ionic structure of dehydroquinolizinium iodide; Boekelheide and Gall, *J. Amer. Chem. Soc.*, 1954, **76**, 1833).

The low yield of the α-carboline obtained in this reaction makes it unsuitable as a general method of synthesis. The method was therefore modified to avoid the formation of (III) by taking advantage of the fact that a 3-amino-group in pyridine is aromatic and therefore undergoes diazotisation normally. Thus, the decomposition of the aqueous diazonium sulphate of *N*-(3-amino-2-pyridyl)-*N*-methylaniline (V; R = H) with copper powder at room temperature gave *N*-methyl-α-carboline (IV; R = H) in 78% yield. The amine (V; R = H) was readily obtained by the condensation of 2-chloro-3-nitropyridine with *N*-methylaniline, followed by reduction of the *N*-methyl-*N*-(3-nitro-2-pyridyl)aniline with hydrogen and Raney nickel. This method allows a variety of α-carbolines to be prepared by the introduction of substituents in either the benzene or the pyridine ring. Thus, condensation of 6-chloro-5-nitro-2-picoline (Baumgarten and Su, *J. Amer. Chem. Soc.*, 1952, **74**, 3828) with *N*-methylaniline followed by reduction gave (V; R = Me), which on cyclisation gave *ind-N*: 2-dimethyl-α-carboline (IV; R = Me) in good yield.

The yields obtained in these cyclisations confirm the suggestion put forward by Hey and Mulley (Part V, *loc. cit.*) that the ease of formation of the five-membered ring is related to the distance in the unstrained molecule between which the new internuclear bond is to be formed. Thus, α-carboline and carbazole formation are somewhat easier than fluorenone formation, which in turn is easier than fluorene formation. With regard to the mechanism of the reactions which give rise to the simultaneous formation of the α-carboline and the pyridobenziminazolium cation, it is obvious that the latter must arise of necessity as a result of a heterolytic process. This is in agreement with the views put forward by DeTar and Relyea (*J. Amer. Chem. Soc.*, 1954, **76**, 1680) on the formation of fluorenones in the thermal decomposition of diazotised 2-aminobenzophenones. It is not possible to state whether the substituting agent is the substituted phenyl cation or the diazonium cation, but the latter appears the more probable. With regard to the formation of the α-carboline no positive evidence on mechanism is yet available.

It is of interest that whereas *N*-methyl-2-nitro-*N*-2′-pyridylaniline forms a picrate, yet when the nitro-group is in the pyridine ring, *i.e.*, in the ring probably involved in picrate formation as in *N*-methyl-*N*-(3-nitro-2-pyridyl)aniline, no picrate is formed.

Experimental

N-Methyl-2-nitro-N-2′-pyridylaniline (cf. Ullmann, *Annalen*, 1907, **355**, 327).—2-Bromopyridine (15 g.), *N*-methyl-*o*-nitroaniline (22 g.), dry potassium carbonate (11 g.), and a trace of cuprous chloride were heated at 190—200° for 6 hr. There was initially a fairly rapid evolution of carbon dioxide. The mixture was distilled with steam to remove unchanged starting material, and the residue was extracted with chloroform. The product obtained on evaporation of the dried chloroform extract was distilled, *N-methyl-2-nitro-N-2′-pyridylaniline* being obtained as a dark red oil (9·05 g., 42%), b. p. 126—130°/0·1 mm. (Found: C, 62·7; H, 4·4; N, 18·3. $C_{12}H_{11}O_2N_3$ requires C, 62·9; H, 4·8; N, 18·3%). The picrate crystallised from benzene in yellow needles, m. p. 177—179° (decomp.).

2-Amino-N-methyl-N-2′-pyridylaniline.—Stannous chloride (40 g.) was added to a solution of *N*-methyl-2-nitro-*N*-2′-pyridylaniline (11·04 g.) in concentrated hydrochloric acid (100 c.c.). The mixture was boiled under reflux for 45 min., the colour changing from deep red to light yellow after a few minutes. Whilst still hot the solution was poured into an excess of hot concentrated aqueous potassium hydroxide. The green oil which separated was extracted with ether, and the residue after evaporation of the solvent distilled at 104—108°/0·02 mm. to give *2-amino-N-methyl-N-2′-pyridylaniline* (8·8 g., 92%) as a viscous, slightly yellow oil which very slowly solidified and crystallised from light petroleum (b. p. 40—60°) in white prisms, m. p. 66—67° (Found: C, 72·2; H, 6·5; N, 21·7. $C_{12}H_{13}N_3$ requires C, 72·3; H, 6·6; N, 21·1%). The *acetyl* derivative was prepared by refluxing the amine with acetic anhydride

for 45 min. It crystallised from benzene–light petroleum (b. p. 60—80°) in prisms, m. p. 110—111° (Found: C, 70·1; H, 6·4. $C_{14}H_{15}ON_3$ requires C, 69·7; H, 6·3%).

Action of Heat on the Aqueous Diazonium Sulphate prepared from 2-*Amino*-N-*methyl*-N-2′-*pyridylaniline*.—A solution of the amine (4 g.) in concentrated sulphuric acid (6 c.c.) and water (100 c.c.) was diazotised at 5° with sodium nitrite (1·8 g.) in water (20 c.c.). After being stirred overnight at room temperature, the light red diazonium solution was boiled under reflux for 45 min. to complete the decomposition. The clear solution was made just alkaline with aqueous sodium hydroxide and extracted with chloroform. The neutral product, a dark brown oil (0·62 g.), in benzene was chromatographed on a column (30 × 2 cm.) of activated alumina. Elution with benzene gave a white solid which on crystallisation from light petroleum (b. p. 30—40°) deposited *ind*-*N*-methyl-α-carboline (0·25 g., 7%) in white plates, m. p. 51—53° (Found: C, 79·0; H, 5·5; N, 15·2. Calc. for $C_{12}H_{10}N_2$: C, 79·1; H, 5·5; N, 15·4%). The picrate (from alcohol) had m. p. 225° (decomp.). Eiter (*Monatsh.*, 1948, **79**, 18) gives m. p. 53° for the base and m. p. 225° (decomp.) for its picrate. Elution with ether–ethyl alcohol (9 : 1) gave a brown oil, which was distilled at 170°/25 mm. to give a pale mobile oil (0·2 g.). The aqueous solution from the chloroform extract was acidified with hydrochloric acid, and an excess of calcium carbonate was added to make the solution neutral. Chloroform extraction yielded no product, so the aqueous solution was evaporated to dryness and the residue extracted with ethyl alcohol. A light brown solid (3·6 g.) was obtained which, on crystallisation from dry ethyl alcohol, gave long white plates of crude 5-methylpyrido[1 : 2-*a*]benziminazolium chloride having no m. p. (Found: C, 59·2; H, 5·8; N, 10·6; Cl, 12·6. Calc. for $C_{12}H_{11}N_2Cl$: C, 65·9; H, 5·1; N, 12·8; Cl, 16·2%). A portion of this solid (0·25 g.) in ethyl alcohol was mixed with alcoholic picric acid (0·25 g.) to give *5-methylpyrido*[1 : 2-a]*benziminazolium picrate* (0·47 g.), m. p. 196—198° (without decomp.) (Found: C, 52·7; H, 3·6; N, 17·1. $C_{12}H_{11}N_2,C_6H_2O_7N_3$ requires C, 52·6; H, 3·2; N, 17·0%). The yield, calculated on the basis of picrate obtained, was 82%.

N-*Methyl*-N-(3-*nitro*-2-*pyridyl*)*aniline*.—2-Chloro-3-nitropyridine (5 g.) and *N*-methylaniline (10 c.c.) were heated together at 160—170° for 6 hr. The cooled mixture was then treated with dilute alkali and extracted repeatedly with carbon tetrachloride. The extract was passed through alumina (6″ × 1″), and the red eluate evaporated on the water-bath. The residue was fractionally distilled under a vacuum. The first fraction (up to 100°/0·4 mm.) consisted of unchanged *N*-methylaniline. N-*Methyl*-N-(3-*nitro*-2-*pyridyl*)*aniline* (5·6 g.) distilled at 108°/0·07 mm. as an orange-red oil, which solidified to orange-red needles, m. p. 73—74° (Found: C, 63·0; H, 4·8. $C_{12}H_{11}O_2N_3$ requires C, 62·9; H, 4·8%). This compound did not yield a picrate.

N-(3-*Amino*-2-*pyridyl*)-N-*methylaniline*.—*N*-Methyl-*N*-(3-nitro-2-pyridyl)aniline (0·5 g.) in methanol (25 c.c.) was shaken with hydrogen at room temperature and pressure in the presence of Raney nickel (0·5 g.). Reduction was complete in <1 hr. The catalyst was filtered off and the solvent evaporated. The residue was distilled in a vacuum, giving colourless N-(3-*amino*-2-*pyridyl*)-N-*methylaniline* (0·43 g.), b. p. 128°/0·4 mm., m. p. 80—81° (Found: C, 72·9; H, 6·6. $C_{12}H_{13}N_3$ requires C, 72·3; H, 6·6%). The *picrate*, which separated from benzene, crystallised from ethanol in yellow rosettes of needles, m. p. 170° (Found: C, 50·2; H, 3·7. $C_{12}H_{13}N_3,C_6H_3O_7N_3$ requires C, 50·5; H, 3·8%).

ind-N-*Methyl*-α-*carboline*.—*N*-(3-Amino-2-pyridyl)-*N*-methylaniline (2 g.) in concentrated sulphuric acid (4 c.c.) and water (50 c.c.) was diazotised at 0—5° with sodium nitrite (2 g.) in water (20 c.c.), stirring at 0—5° being continued for 0·5 hr. Urea (1·5 g.) was added to the clear solution, and then copper powder (2 g.), and stirring was continued overnight. The suspension was then boiled for 1 min., cooled, filtered, and made alkaline with an excess of concentrated aqueous ammonia. The oil which separated was extracted with chloroform (2 × 200 c.c.) and dried (Na_2SO_4) and the solvent evaporated. Vacuum-distillation of the residue gave *N*-methyl-α-carboline (1·42 g., 78%), b. p. 139—144°/1·7 mm., which solidified. Recrystallisation from light petroleum (b. p. 40—60°) gave colourless plates, m. p. 53° (Found: C, 79·1; H, 5·6. Calc. for $C_{12}H_{10}N_2$, C, 79·1; H, 5·5%). The m. p. was not depressed on admixture with the product obtained as above from 2-amino-*N*-methyl-*N*-2′-pyridylaniline. The picrate separated from alcohol in yellow needles, m. p. 225—226°.

N-*Methyl*-N-(6-*methyl*-3-*nitro*-2-*pyridyl*)*aniline*.—6-Chloro-5-nitro-2-picoline (5 g.; Baumgarten and Su, *J. Amer. Chem. Soc.*, 1952, **74**, 3828) and *N*-methylaniline (5·0 g., excess) were heated with potassium carbonate (1 g., anhyd.) and a trace of copper power for 6·5 hr. at 160—170° under an air-condenser. The cooled mixture was extracted repeatedly with boiling carbon tetrachloride, and the cold, black extract was passed through alumina (6″ × 1″). An orange product was eluted with the same solvent. Vacuum-distillation of the residue after removal of the solvent gave first a small amount of unchanged *N*-methylaniline (up to 80°/0·1 mm.)

and then N-*methyl*-N-(6-*methyl*-3-*nitro*-2-*pyridyl*)*aniline* (4·4 g.), b. p. 140—142°/0·4 mm., as a red oil which did not solidify (Found: C, 64·0; H, 5·4. $C_{13}H_{13}O_2N_3$ requires C, 64·2; H, 5·4%). This nitro-compound also did not give a picrate.

N-(3-*Amino*-6-*methyl*-2-*pyridyl*)-N-*methylaniline*.—The nitro-compound (1·3 g.) in methanol was hydrogenated as above with Raney nickel (1·5 g.). The residue left on evaporation crystallised. It was distilled, giving the colourless 3-*aminopyridyl* compound (1·2 g.), b. p. 130°/0·4 mm., m. p. 100° (Found: C, 73·0; H, 7·0. $C_{13}H_{15}N_3$ requires C, 73·2; H, 7·1%). The *picrate* separated from benzene and crystallised from ethanol in yellow globules, m. p. 186° (decomp.) (Found: C, 51·1; H, 4·2. $C_{13}H_{15}N_3,C_6H_3O_7N_3$ requires C, 51·6; H, 4·1%).

ind-N: 2-*Dimethyl*-α-*carboline*.—The above amine (3·1 g.) in concentrated sulphuric acid (8 c.c.) and water (50 c.c.) was diazotised at 0—5° with sodium nitrite (2·5 g.) in water (10 c.c.). After ½ hour's stirring at 0° the red solution was filtered from a small amount of insoluble yellow material, the residue being washed repeatedly with water, and the combined filtrates were treated with urea (2 g.). Copper powder (3 g.) was then added and the mixture was stirred at room temperature for 2 hr. It was then brought to the boil, cooled, filtered from copper, and made alkaline with an excess of aqueous ammonia. The oil which separated was extracted with chloroform (2 × 150 c.c.), dried (Na_2SO_4), and recovered. Distillation gave ind-N: 2-*dimethyl*-α-*carboline* (2·03 g.), b. p. 142—150°/1·5 mm., which solidified. It crystallised from light petroleum (b. p. 40—60°) in fine colourless needles, m. p. 71·5—72° (Found: C, 79·6; H, 6·2. $C_{13}H_{12}N_2$ requires C, 79·6; H, 6·2%). The *picrate* separated from alcohol and crystallised from dioxan in yellow prisms, m. p. 206—207° (decomp.) (Found: C, 53·8; H, 4·2. $C_{13}H_{12}N_2,C_6H_3O_7N_3$ requires C, 53·65; H, 3·55%).

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