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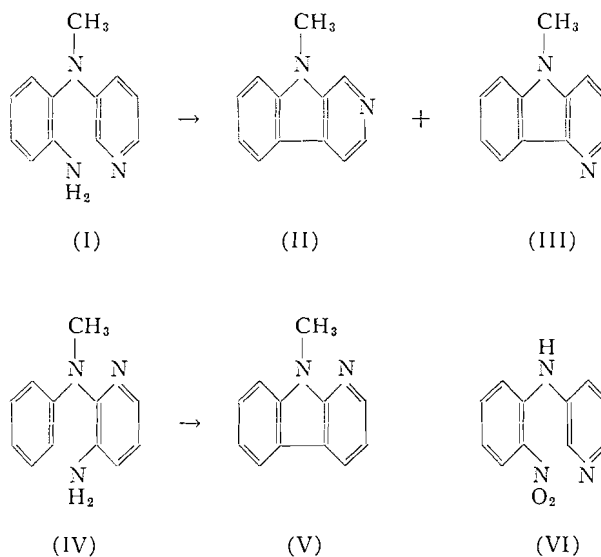
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TRYPTAMINES, CARBOLINES, AND RELATED COMPOUNDS PART VII. INTERNUCLEAR CYCLIZATION ONTO A PYRIDINE RING*†

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On the basis of two examples of internuclear cyclization of the Pschorr type onto a pyridine ring (1, 2) (one involving predominant electrophilic attack at the ring nitrogen) it was suggested (3) that the pyridine ring is more difficult to attack than a benzene ring in such reactions. The cyclization of 2-amino-*N*-methyl-*N*-3'-pyridylaniline (I) was studied to examine whether this was indeed so, as well as to provide a route to the δ -carboline ring system. Also, some evidence might thus be obtained to suggest a mechanism for the Pschorr reaction when carried out under such conditions, for the pyridine ring is known to be deactivated towards electrophilic substitution under mild conditions, but not towards homolytic attack. Should cyclization occur readily it was of interest to determine the orientation of the products since the isomer ratios for free radical phenylation of pyridine are in the order $\alpha > \beta > \gamma$ (4).



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Decomposition of the aqueous diazonium sulphate of 2-amino-*N*-methyl-*N*-3'-pyridyl-aniline (I) with copper powder at room temperature resulted in a good yield of a mixture of cyclized products which was separated into *ind-N*-methyl- δ -carboline (III) (47.5% yield) and *ind-N*-methyl- β -carboline (II) (25.5% yield) by chromatography on a column of alumina. The structure of (III) was confirmed by the analytical results and by its infrared spectrum, which showed no monosubstituted phenyl bands, thus eliminating the possibility that the substance isolated was the deaminated product. Its ultraviolet absorption spectrum was very similar to that of an authentic specimen of δ -carboline obtained by an unambiguous synthesis (5). The structure was finally proved by comparison with an authentic specimen whose preparation from δ -carboline is described in the next part of this series (5). The total yield of cyclized product (73%) is comparable with that obtained (78%) when *N*-(3-amino-2-pyridyl)-*N*-methylaniline (IV) is ring-closed to *ind-N*-methyl- α -carboline (V) (2), i.e. a similar cyclization, with similar inter-nuclear separation (6), onto a benzene ring. This clearly indicates that in the present case the pyridine ring is not deactivated towards nuclear attack and that under these very mild reaction conditions free radical intermediates (perhaps bound in some way with the copper catalyst) may be involved. An amino substituent in the pyridine is known to facilitate electrophilic attack of the ring due to the mesomeric effect of the electron pair of the amino nitrogen atom. Phenyl substitution at the 3-amino group is expected, however, to decrease the activating effect of this group and *o*-diazotization to decrease it still further. An attempt to eliminate this possible source of ambiguity by replacing the *N*-methyl group in (I) by an acyl grouping was made. 2-Nitro-*N*-3'-pyridyl-aniline (VI), however, resisted all attempts at acetylation, tosylation, or mesylation, so that the required starting material could not be obtained.

It is very likely (7) that in the absence of copper powder and at the boiling point of the aqueous acid the cyclization involves cationic intermediates so that in such a case, though the reaction conditions are more severe than in the one where copper powder is used, the yield of cyclized product would be expected to fall due to the resistance of the pyridine ring to electrophilic substitution. This was indeed found to be the case, the over-all yield of carboline being 47.2%: *ind-N*-methyl- δ -carboline (33%), *ind-N*-methyl- β -carboline (14.2%). A product, whose picrate analyzed for that of the deaminated product, was also obtained under these conditions. It is to be noted, however, that in contrast to the above results ring closure of 2-amino-*N*-methyldiphenylamine under both sets of conditions gave comparable yields of *N*-methylcarbazole (6). Thus, by the action of copper powder on the cold solution of the diazonium sulphate a 66% yield of cyclized product was obtained; the action of heat upon the aqueous diazonium sulphate solution in the absence of copper resulted in a 60% yield of *N*-methylcarbazole. Here there is no decrease in yield on passing from a heterolytic to a presumably homolytic process since the benzene, unlike the pyridine ring, is not deactivated towards electrophilic attack. These observations also support the suggestion that the side-chain tertiary amino group is probably not activating the ring towards electrophilic attack in such aqueous acid solutions.

EXPERIMENTAL

Melting points and boiling points are uncorrected. Ultraviolet absorption spectra were measured on a Beckman DK 2 recording spectrophotometer. For the chromatographic separations alumina supplied by Peter Spence and Sons, Ltd., as activated alumina type H, 100/200 mesh, was used.

N-Methyl-2-nitro-N-3'-pyridylaniline

A mixture of 3-bromopyridine (3.2 g), *N*-methyl-*o*-nitraniline (2.3 g), anhydrous potassium carbonate (2 g), and copper bronze (100 mg) in nitrobenzene (12 ml) was boiled under reflux for 24 hours. The suspension was steam-distilled and the residue extracted with chloroform, the extract dried (MgSO_4) and evaporated. The residue was distilled *in vacuo* giving a red viscous oil (1.4 g), b.p. $140\text{--}150^\circ/2 \times 10^{-2}$ mm, which formed a glass on cooling. The product was analyzed as the *picrate* which crystallized from ethanol as yellow needles, m.p. 168° . Found: C, 46.90; H, 2.99. Calc. for $\text{C}_{12}\text{H}_{11}\text{O}_2\text{N}_3$, $\text{C}_6\text{H}_3\text{O}_7\text{N}_3$: C, 47.17; H, 3.06.

2-Amino-N-methyl-N-3'-pyridylaniline

The above nitro compound (2.7 g), Raney nickel (1 g), and 100% hydrazine hydrate (10 ml) in alcohol (50 ml) were boiled under reflux for 15 minutes, the suspension filtered, and the filtrate evaporated to dryness leaving an oil (1.77 g) which slowly solidified. Vacuum distillation gave the *amine* as a colorless oil, b.p. $140\text{--}143^\circ/0.4$ mm, which solidified to a colorless solid. This was recrystallized from benzene - light petroleum (b.p. $60\text{--}80^\circ$) giving colorless needles, m.p. $93\text{--}94^\circ$. Found: C, 71.98; H, 6.24; N, 20.60. Calc. for $\text{C}_{12}\text{H}_{13}\text{N}_3$: C, 72.33; H, 6.57; N, 21.10.

*Decomposition of the Aqueous Diazonium Sulphate of 2-Amino-N-methyl-N-3'-pyridylaniline**(i) With Copper Powder at Room Temperature*

The *amine* (1.9 g) in concentrated sulphuric acid (4 ml) and water (50 ml) was diazotized at $0\text{--}5^\circ$ with sodium nitrite (2 g) in water (20 ml), stirring at $0\text{--}5^\circ$ being continued for $\frac{1}{2}$ hour. Urea (1.5 g) was added to the clear solution to decompose the excess nitrous acid, and then copper powder (2 g) was gradually stirred in. The decomposition was complete in $\frac{1}{2}$ hour as indicated by the cessation of effervescence and a negative alkaline β -naphthol test. The suspension was stirred at room temperature for a further $\frac{1}{2}$ hour and then it was filtered from the copper, made alkaline with an excess of concentrated ammonia, and extracted with chloroform (2×200 ml). The dried (MgSO_4) extract was evaporated and the tarry black residue was taken up in benzene and chromatographed on a column of alumina (70 g). Elution with benzene first gave a colorless oil (0.82 g, 47%) which soon solidified, and had a melting point of $73\text{--}74^\circ$. Recrystallization from light petroleum (b.p. $60\text{--}80^\circ$) gave *ind-N-methyl- δ -carboline* as colorless plates, m.p. 74° . Found: C, 78.75; H, 5.72. Calc. for $\text{C}_{12}\text{H}_{10}\text{N}_2$: C, 79.09; H, 5.53. λ_{max} 263, 267, 306 $\text{m}\mu$; λ_{inf} 235, 249 $\text{m}\mu$; $\epsilon \times 10^{-3}$ 18.92, 18.80, 11.83, 13.35, 10.62 (in ethanol). Infrared spectrum (Nujol mull) (main peaks only): 1628 (m), 1595 (m), 774 (m), 750 (m), 727 (s). The *picrate* separated from alcohol and was recrystallized from dioxane giving fine yellow needles, m.p. $229\text{--}230^\circ$. Found: C, 52.60; H, 3.0. Calc. for $\text{C}_{12}\text{H}_{10}\text{N}_2$, $\text{C}_6\text{H}_3\text{O}_7\text{N}_3$: C, 52.56; H, 3.19.

Further elution with benzene gave a brown oil which solidified very slowly. The solid was recrystallized from light petroleum (b.p. $60\text{--}80^\circ$) giving *ind-N-methyl- β -carboline* as colorless plates, m.p. 97° (0.45 g, 25%), undepressed on admixture with an authentic sample (8). Further recrystallization from light petroleum raised the melting point to $106\text{--}107^\circ$. Found: C, 79.03; H, 5.4. Calc. for $\text{C}_{12}\text{H}_{10}\text{N}_2$: C, 79.09; H, 5.53. The *picrate* separated from alcohol and was recrystallized from acetone giving fluffy yellow needles, m.p. 258° . Found: C, 52.31; H, 3.20. Calc. for $\text{C}_{12}\text{H}_{10}\text{N}_2$, $\text{C}_6\text{H}_3\text{O}_7\text{N}_3$: C, 52.56; H, 3.19. (Lit. (8) gives a melting point of 258° .)

(ii) *By Boiling Without Copper Powder*

The amine (2.0 g) was diazotized as before and the filtered diazonium solution was boiled under reflux for 10 hours. The cold solution was made just alkaline with aqueous sodium hydroxide and extracted with chloroform. The dried (MgSO_4) chloroform extract was evaporated, the residue taken up in benzene, and chromatographed on alumina as before. Elution with benzene gave first *ind-N*-methyl- δ -carboline (0.60 g, 33%), m.p. 73° , and then *ind-N*-methyl- β -carboline (0.26 g, 14.2%) as a very crude oil characterized as the picrate, m.p. and mixed m.p. 258° . Elution with ether gave a brown oil (0.10 g) which formed a picrate from alcohol. This picrate was recrystallized from acetone giving small yellow needles, m.p. $202\text{--}203^\circ$ (decomp.), which analyzed for the picrate of *N*-methyl-*N*-3'-pyridylaniline. Found: C, 52.09; H, 3.14; N, 17.30. Calc. for $\text{C}_{12}\text{H}_{12}\text{N}_2$, $\text{C}_6\text{H}_3\text{O}_7\text{N}_3$: C, 52.21; H, 3.32; N, 16.94.

2-Nitro-N-3'-pyridylaniline

3-Aminopyridine (0.94 g), *o*-bromonitrobenzene (2.02 g), anhydrous potassium carbonate (2 g), and copper bronze (0.05 g) in xylene (20 ml) were boiled under reflux for 6 hours. The solvent was decanted off and the residue extracted repeatedly with boiling benzene, the combined extracts were treated with dilute hydrochloric acid, the acid solution made alkaline, saturated with sodium chloride, and extracted with benzene. The benzene solution was chromatographed on a short column of alumina. Elution with ether gave *2-nitro-N-3'-pyridylaniline* (0.62 g) as a dark red solid, m.p. 90° , which crystallized from water containing a little ethanol in slender orange-red needles, m.p. $95\text{--}96^\circ$. Found: C, 61.50; H, 4.51. Calc. for $\text{C}_{11}\text{H}_9\text{O}_2\text{N}_3$: C, 61.39; H, 4.42.

Attempted Tosylation of 2-Nitro-N-3'-pyridylaniline

The nitro compound (60 mg) and tosyl chloride (60 mg) in 2 ml of redistilled pyridine were boiled under reflux for 24 hours. Addition of water and recovery of the solid which precipitated gave unchanged starting material, m.p. $95\text{--}96^\circ$.

Similar results were obtained on attempted mesylation and acetylation (even in the presence of perchloric acid).

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