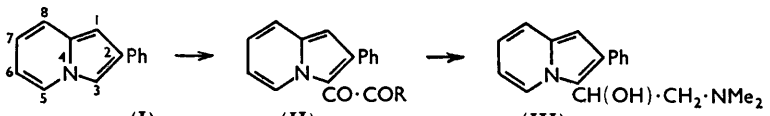
124. *The Preparation of Aminoalkylpyrrocolines.*

By D. E. Ames, T. F. Grey, and W. A. Jones.

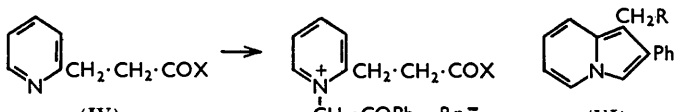
Oxalyl chloride condenses readily with 2-phenylpyrrocoline to give 2-phenylpyrrocoline-3-glyoxylyl chloride which on treatment with dimethylamine followed by lithium aluminium hydride affords 3-(2-dimethylamino-1-hydroxyethyl)-2-phenylpyrrocoline. An aminoethylpyrrocoline was, however, obtained by an alternative route.

The pharmacological properties of serotonin and other tryptamine derivatives suggested that the synthesis of analogous aminoethylpyrrocoline derivatives would be of interest. The readily-available 2-phenylpyrrocoline was used as starting material. In view of the rapidity with which oxalyl chloride condenses with indoles in the absence of catalyst,[1] the condensation of oxalyl chloride with 2-phenylpyrrocoline in ether was examined. The resulting crystalline acid chloride (II; R = Cl) was readily converted into amides (II; R = NH_2 and NMe_2). The acyl group is presumed to have entered the 3-position by analogy with the uncatalysed benzoylation of pyrrocoline [2] and 2-phenylpyrrocoline [3] in the 3-position.



(I) (II) (III)

Reduction of the amide (II; R = NMe_2) with lithium aluminium hydride gave the hydroxyamine (III) in small yield. It is of interest that the hydroxyl group was not lost by hydrogenolysis, as occurs in the corresponding reduction of 3-indolylglyoxyl amides other than the 1-alkyl compounds.[4]

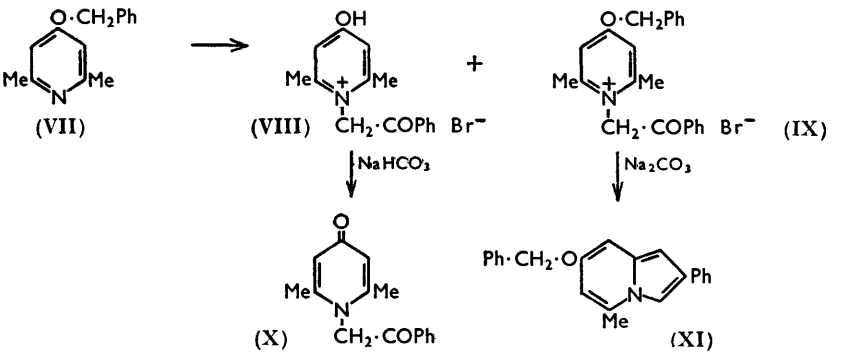


An alternative approach was therefore required for the synthesis of a pyrrocoline bearing an aminoethyl group. Condensation of the ester (IV; X = OEt) with phenacyl bromide gave the quaternary salt (V; X = OEt) but this could not be cyclised to a pyrrocoline. The corresponding amide (IV; X = NH_2) did, however, yield the pyrrocoline (VI; R = $CO{\cdot}NH_2$), which was reduced with lithium aluminium hydride to 1-aminoethyl-2-phenylpyrrocoline (VI; R = $CH_2{\cdot}NH_2$), isolated as the dipicrate.

Although it appears that no hydroxypyrrocolines have been described, some preliminary experiments were made to examine the possibility of preparing an aminoalkyl-hydroxy-

[1] Speeter and Anthony, *J. Amer. Chem. Soc.*, 1954, **76**, 6208 and references cited therein.
[2] Scholtz and Fraude, *Ber.*, 1913, **46**, 1069.
[3] Borrows, Holland, and Kenyon, *J.*, 1946, 1069; Borrows and Holland, *Chem. Rev.*, 1948, **42**, 611.
[4] Clemo, Morgan, and Raper, *J.*, 1935, 1744.

pyrrocoline. 4-Chloro-2 : 6-dimethylpyridine was converted into the 4-benzyloxy-compound (VII) by the action of potassium benzyl oxide. Quaternisation with phenacyl bromide then yielded a mixture from which the salt (VIII), formed by debenzylation, was isolated. Treatment of this with sodium hydrogen carbonate solution yielded 2 : 6-dimethyl-1-phenacylpyrid-4-one (X) and not a pyrrocoline. However, when the non-crystalline part of the quaternisation products, presumably containing the benzyloxy-compound (IX), was



treated with sodium carbonate solution, crystalline 7-benzyloxy-5-methyl-2-phenylpyrrocoline (XI) was obtained in very small yield. An attempt to remove the benzyl group by catalytic hydrogenation in the presence of palladised strontium carbonate was unsuccessful. The low yield of benzyloxy-compound (XI) prevented its use in further synthesis.

Experimental

2-Phenyl-3-pyrrocolinylglyoxylyl Chloride.—Oxalyl chloride (25 g.) was added gradually to a suspension of 2-phenylpyrrocoline [3] (30 g.) in ether (50 c.c.) and benzene (300 c.c.), and the mixture was left at room temperature for 4 hr. The crude *product* was filtered off and recrystallised from benzene–light petroleum (b. p. 60—80°) to give green material [75%; m. p. 110—114° (decomp.)]. Further recrystallisation furnished yellow prisms, m. p. 114—115° (decomp.) (Found: C, H, 3·4; Cl, 12·3. $C_{16}H_{10}O_2NCl$ requires C, 67·6; H, 3·4; Cl, 11·9%).

NN-Dimethyl-2-phenyl-3-pyrrocolinylglyoxylamide.—A stirred solution of the acid chloride (15 g.) in benzene (250 c.c.) was cooled while excess of dimethylamine was passed in. The mixture was left at room temperature for 2 hr., then filtered; the solid was taken up in chloroform (100 c.c.) and washed with 2N-sodium hydroxide and water, dried (Na_2SO_4), and evaporated. Recrystallisation from 2-methoxyethanol furnished the *amide* (11 g.), yellow needles, m. p. 198—200° (Found: C, 73·9; H, 5·4; N, 9·6. $C_{18}H_{16}O_2N_2$ requires C, 74·0; H, 5·5; N, 9·6%), $\lambda_{max.}$ 2350 (ε 22,600), 2650 (ε 16,900) and 3810 Å (ε 17,400) in ethanol.

2-Phenyl-3-pyrrocolinylglyoxylamide, prepared similarly, formed yellow needles, m. p. 178—181°, from ethyl acetate (Found: C, 72·8; H, 4·5; N, 11·0. $C_{16}H_{12}O_2N_2$ requires C, 72·7; H, 4·6; N, 10·6%).

3-(2-Dimethylamino-1-hydroxyethyl)-2-phenylpyrrocoline.—A solution of the foregoing dimethylamide (4·6 g.) in tetrahydrofuran (100 c.c., dried over CaH_2) was added gradually to lithium aluminium hydride (2 g.) in tetrahydrofuran (100 c.c.) at room temperature. The mixture was refluxed for 1 hr. and left overnight. After addition of ethyl acetate (25 c.c.) and then water (5 c.c.), the mixture was refluxed for 15 min. and filtered, the solid being washed with ethyl acetate. Evaporation *in vacuo* (bath 30°) gave a gum which crystallised on trituration with methanol. Fractional crystallisation from methanol yielded 0·25 g. of material, m. p. 99—103°, from which the *hydroxy-amine* was obtained as prisms, m. p. 112—115°, by further crystallisation (Found: C, 77·1; H, 7·2; N, 9·9. $C_{18}H_{20}ON_2$ requires C, 77·1; H, 7·2; N, 10·0%).

2-2′-Ethoxycarbonylethyl-1-phenacylpyridinium Bromide.—A solution of ethyl 3-2′-pyridylpropionate [4] (10 g.) and phenacyl bromide (11·1 g.) in acetone (25 c.c.) was set aside for 1 hr., then refluxed for 3·5 hr. The *salt*, which separated on cooling, formed needles, m. p. 154—155°,

from butan-2-one–ethanol (Found: C, 57·4; H, 5·2; Br, 21·1. $C_{18}H_{20}O_3NBr$ requires C, 57·2; H, 5·3; Br, 21·1%). Attempts to cyclise the compound by treatment with sodium hydrogen carbonate solution were unsuccessful.

2-Phenyl-1-pyrrocolinylacetamide.—β-2-Pyridylpropionamide [5] (8·2 g.) and phenacyl bromide (11 g.) in butan-2-one (150 c.c.) were refluxed for 8·5 hr. The supernatant liquid was decanted from gummy residue which was then boiled with water (100 c.c.). The hot aqueous solution was filtered (charcoal) and sodium hydrogen carbonate (40 g.) added. On cooling, crude product separated (3·8 g.; m. p. 165—169°). Recrystallisation from butan-2-one furnished the *pyrrocoline* as needles, m. p. 168—170° (Found: C, 76·6; H, 5·6; N, 11·3. $C_{16}H_{14}ON_2$ requires C, 76·8; H, 5·6; N, 11·2%).

1-2′-Aminoethyl-2-phenylpyrrocoline.—The amide (2·8 g.) was reduced with lithium aluminium hydride (1·0 g.) in ether (100 c.c.) (Soxhlet extraction for 6 hr.). After addition of ethyl acetate (10 c.c.) and 5N-sodium hydroxide (3 c.c.) the mixture was filtered and the filtrate evaporated *in vacuo*. The residue was treated with methanolic picric acid, to give the *dipicrate*, m. p. 135—136°, of the amine as prisms from aqueous ethanol (Found: C, 47·9; H, 3·9; N, 15·7. $C_{28}H_{22}O_{14}N_8$ requires C, 48·4; H, 3·2; N, 16·1%). Starting material (2·1 g.) was recovered from the Soxhlet thimble. No product was isolated on reduction in tetrahydrofuran.

4-Benzyloxy-2 : 6-dimethylpyridine.—A solution of potassium hydroxide (48 g.) in benzyl alcohol (630 c.c.) and xylene (130 c.c.) was refluxed through a phase-separator (Dean and Stark) until all the water had been removed. 4-Chloro-2 : 6-dimethylpyridine [6] (48 g.) was then added and the mixture was heated at 210° (bath) for 2 hr. The cooled solution was poured into water, and the product isolated with ethyl acetate. Fractional distillation through a short Fenske column yielded the *benzyloxypyridine*, b. p. 130°/0·8 mm., n_D^{20} 1·5653 (Found: C, 78·8; H, 6·9. $C_{14}H_{15}ON$ requires C, 78·8; H, 7·1%).

Quaternisation of 4-Benzyloxy-2 : 6-dimethylpyridine with Phenacyl Bromide.—The benzyloxypyridine (15 g.) and phenacyl bromide (14·5 g.) in butanol (75 c.c.) were left at room temperature overnight and then heated on a steam-bath for 5 hr. The gum obtained by evaporation *in vacuo* partially crystallised on trituration with acetone. *4-Hydroxy-2 : 6-dimethyl-1-phenacylpyridinium bromide* [2·7 g.; m. p. 207—210° (decomp.)] was collected and recrystallised from ethanol; it formed plates, m. p. 214—215° (Found: C, 55·8; H, 5·0; N, 4·2; Br, 24·2. $C_{15}H_{16}O_2NBr$ requires C, 55·9; H, 5·0; N, 4·3; Br, 24·8%). Evaporation of the acetone filtrate gave a gum from which the benzyloxy-compound could not be isolated.

2 : 6-Dimethyl-1-phenacylpyrid-4-one.—The foregoing quaternary salt was warmed with sodium hydrogen carbonate solution and the cooled mixture was filtered. Recrystallisation from benzene–light petroleum (b. p. 60—80°) afforded plates of the *pyridone*, m. p. 103—104° (Found: C, 74·3; H, 6·2. $C_{15}H_{15}O_2N$ requires C, 74·7; H, 6·3%), $\lambda_{max.}$ 2450 Å (ε 14,200) in ethanol.

7-Benzyloxy-5-methyl-2-phenylpyrrocoline.—The residual gum from the above quaternisation was boiled with water (300 c.c.) while sodium carbonate (35 g.) was added in portions. The cooled liquid was extracted with ether, and the extracts were washed with water, dried (K_2CO_3), and evaporated. On trituration with benzene–light petroleum (b. p. 40—60°), some solid (0·4 g.), m. p. 145—151°, was obtained. The *pyrrocoline* recrystallised from the same solvents as needles, m. p. 152—153° (Found: C, 84·2; H, 6·1; N, 5·0. $C_{22}H_{19}ON$ requires C, 84·3; H, 6·1; N, 4·5%), $\lambda_{max.}$ 2600 Å (ε 27,100) in ethanol.

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[5] Walter, Hunt, and Fosbinder, *J. Amer. Chem. Soc.*, 1941, **63**, 2771.
[6] Kato and Ohta, *J. Pharm. Soc. Japan*, 1952, **71**, 217; *Chem. Abs.*, 1952, **46**, 4541.