View Article Online / Journal Homepage / Table of Contents for this issue

Synthesis of some Substituted α-Carbolines

By **L. Stephenson** and **W. K. Warburton,*** Chemistry Research Department, Glaxo Research Ltd., Greenford, Middlesex

α-Carboline-1-oxide (I) with acetic anhydride gives 2-acetoxy-9-acetyl-α-carboline; with dimethyl sulphate it gives the salt (II; R = H). The latter salt is converted by alkali into the anhydronium base (III; R = OMe). The salt (II; R = H) and the base (III; R = OMe) are converted by sufficiently basic nucleophilic reagents into 2-substituted α-carbolines; the salt (II; R = Me) reacts even more readily with basic nucleophilic compounds.

Diethyl malonate and ethyl acetoacetate with (III; R = OMe) give the ester (V; R = CH_2CO_2Et). The acid (V; R = CH_2CO_2H) is readily decarboxylated to 2-methyl-α-carboline.

The benzotriazole (IV; $R^1 = NO_2$, $R^2 = H$) in hot phosphoric acid does not give 3-nitro-α-carboline, but gives instead 2-nitropyrido[1,2-*a*]benzimidazole (VIII); the latter compound is also obtained by treating the amine (VII) with hydrochloric acid. However the benzotriazole (IV; $R^1 = NH_2$, $R^2 = H$) is converted by phosphoric acid into 3-amino-α-carboline; the benzotriazole (IV; $R^1 = H$, $R^2 = CO_2H$) is similarly converted into α-carboline-4-carboxylic acid. The preparation and proof of orientation of some 6-substituted α-carbolines are described.

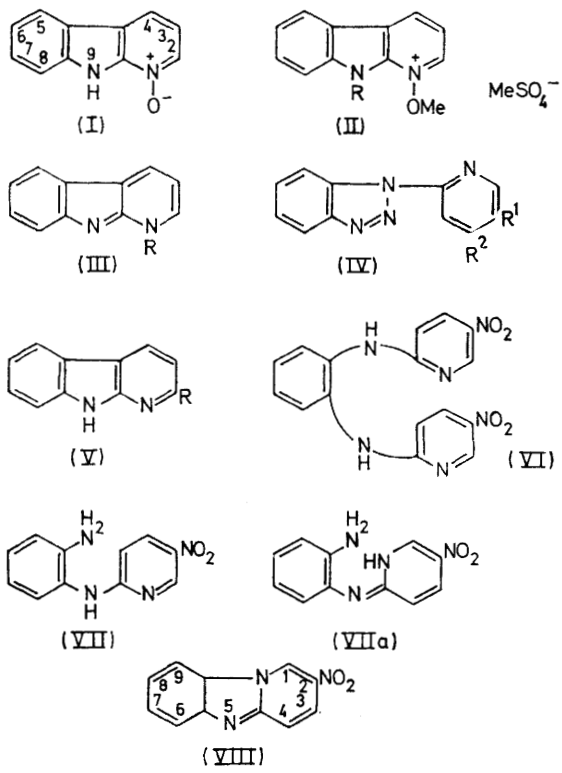
The ^1H n.m.r. spectra of 2-, 3-, and 4-substituted α-carbolines are discussed.

Published on 01 January 1970. Downloaded by University of Idaho Library on 31/10/2014 11:45:59.

We required substituted α-carbolines for pharmacological testing. Lawson, Perkin, and Robinson,[1a] and later Freak and Robinson,[1b] prepared α-carboline from *o*-phenylenediamine and 2-chloropyridine by a modification of the Graebe–Ullmann synthesis.

This method can be used to prepare, *e.g.*, 2- and 4-methyl-α-carboline,[2] but it has not been widely used,[3] and many apparently suitable 2-halogeno-pyridines are not readily available or do not react as chloropyridine does (we were unable, for example, to condense *o*-phenylenediamine with 2-chloro-6-hydroxypyridine or 2-chloro-6-ethoxypyridine).

By modifying the method[1] of Robinson *et al.* in several minor respects (see Experimental section) we raised the reproducible overall yield of α-carboline to 21% (from *o*-phenylenediamine). Peracetic acid converted α-carboline almost quantitatively into the *N*-oxide (I). When (I) was heated under reflux with acetic anhydride, 2-acetoxy-9-acetyl-α-carboline was isolated in 65% yield. 2-Hydroxy-α-carboline was obtained from the product by hydrolysis; it was acetylated to give 2-acetoxy-α-carboline. However the *N*-oxide (I) was not attacked by boiling aqueous or ethanolic potassium cyanide or sodium hydroxide. We therefore prepared the salt (II; R = H) by heating the *N*-oxide (I) with dimethyl sulphate. We treated (II; R = H) with cold aqueous potassium cyanide, expecting to obtain a cyano-α-carboline (when similarly treated the salt obtained by the action of dimethyl sulphate on pyridine 1-oxide or quinoline 1-oxide[4,5] gives 2-cyanopyridine or 2-cyanoquinoline), but obtained instead a yellow oil that was not a nitrile. The same product was obtained when (II; R = H) was treated with aqueous sodium hydroxide. We next treated 1-methyl-α-carbolinium methyl sulphate with aqueous potassium cyanide and obtained the anhydronium base (III; R = Me), identical with that obtained[1b] by treating the same methyl sulphate with sodium hydroxide. These observations suggested that the product from (II; R = H) was the new anhydronium base (III; R = OMe). This suggestion was confirmed by the similarity of the i.r. and the u.v. spectra of the two bases, and by the ^1H n.m.r. spectrum of (III; R = OMe).



The base (III; R = OMe) and the salt (II; R = H), unlike the *N*-oxide (I), were attacked by many nucleophilic reagents. Thus, when (III; R = OMe) was boiled for 4 hr. with sodium methoxide in methanol, 2-methoxy-α-carboline was obtained in 21% yield; the same ether was obtained in 38% yield by heating the salt (II; R = H) with refluxing methanolic sodium

[1] (*a*) W. Lawson, W. H. Perkin, and R. Robinson, *J. Chem. Soc.*, 1924, 626; (*b*) R. H. Freak and R. Robinson, *J. Chem. Soc.*, 1938, 2013.

[2] U.S.P. 2,690,441.

[3] W. O. Kermack and J. E. McKail, 'Heterocyclic Compounds,' John Wiley, New York, 1961, vol. 7, p. 237.

[4] W. E. Feely and E. M. Beavers, *J. Amer. Chem. Soc.*, 1959, **81**, 4004.

[5] T. Okamoto and H. Tani, *Chem. Pharm. Bull. Japan*, 1959, **7**, 130, 925, 930.

View Article Online

Published on 01 January 1970. Downloaded by University of Idaho Library on 31/10/2014 11:45:59.

methoxide. By similar methods we obtained the compounds enumerated in the Table.

TABLE

2-Substituted α-carbolines obtained from (II; R = H) by nucleophilic displacement

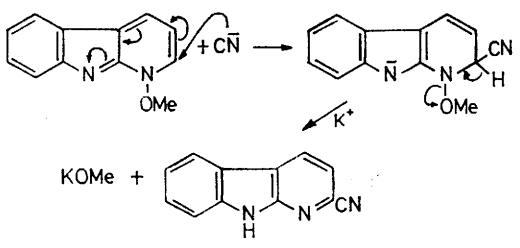
Nucleophilic reagent	Substituent	Nucleophilic reagent	Substituent
NaOH	OH	$CH_3COCHNaCOCH_3$	CH_2Ac
NaOMe	OMe	$CHNa(CN)_2$	$CH(CN)_2$
NH_3	NH_2	$NaS(CH_2)_3CH_3$	$S[CH_2]_3Me$
$MeNH_2$	MeNH	$NaSCH_2Ph$	SCH_2Ph
$H_2N{\cdot}NH_2$	$HN{\cdot}NH_2$	$NaO[CH_2]_2NEt_2$	$O[CH_2]_2NEt_2$
KCN	CN	$H_2N[CH_2]_2NEt_2$	$HN[CH_2]_2NEt_2$
$NaCH(CO_2Et)_2$	CH_2CO_2Et	$NaS[CH_2]_2NEt_2$	$S[CH_2]_2NEt_2$
$AcCHNa{\cdot}CO_2Et$	CH_2CO_2Et		

1-Ethoxy-α-carbolinium tetrafluoroborate was prepared by treating α-carboline 1-oxide with triethyloxonium tetrafluoroborate. With 3-aminopropanol it gave 2-(3-hydroxypropylamino)-α-carboline.

When the base (III; R = OMe) was treated with methylmagnesium iodide in ether or tetrahydrofuran it gave no methyl-α-carboline, but only some α-carboline 1-oxide. However, 1-methoxy-9-methyl-α-carbolinium methyl sulphate (II; R = Me) reacted rapidly at room temperature with potassium cyanide and with sodium hydroxide to give 2-cyano- and 2-hydroxy-9-methyl-α-carboline respectively. With boiling aqueous potassium iodide it gave only 9-methyl-α-carboline and 9-methyl-α-carboline 1-oxide.

The reactivity of the salt (II; R = Me) is thus similar to that of 1-methoxypyridinium and 1-methoxyquinolinium salts;[4,5] compounds that, like (II; R = Me), but, unlike (II; R = H), cannot form anhydronium bases. The much lower reactivity of the base (III; R = OMe) suggests that the principal reaction path of the salt (II; R = H) with basic nucleophilic compounds is through the anhydronium base (III; R = OMe). Two by-products from the direct nucleophilic attack on the base (III; R = OMe), α-carboline and α-carboline 1-oxide, are usually formed. The mechanism of formation of such by-products has been reviewed by Eisenthal and Katritzky.[6]

The anhydronium base (III; R = Me), unlike (III; R = OMe), is unaffected by boiling aqueous cyanide, presumably because the group R must leave as an anion. The base (III; R = OMe) probably reacts with nucleophilic compounds (*e.g.* potassium cyanide) as shown below, or by a similar concerted mechanism:



The orientation of the respective products obtained by treating (II; R = H) or (III; R = OMe) with potassium cyanide, ammonia, ethyl acetoacetate, and diethyl malonate has been established by chemical methods; the orientation of the other substituted α-carbolines obtained from the same intermediates and from (II; R = Me) has been deduced by analogy. It is, however, strongly supported by ^1H n.m.r. spectroscopy (see below).

We obtained 2- and 4-methyl-α-carboline [2] from *o*-phenylenediamine and the appropriate chloropicoline, but we were not able to convert either methylcarboline into a carboxylic acid. We therefore prepared 4-carboxy-α-carboline by condensing *o*-phenylenediamine with 2-chloro-4-cyanopyridine, converting the resultant amine into the benzotriazole (IV; R^1 = H, R^2 = CN), hydrolysing off the cyano-group, and finally heating the acid so obtained in phosphoric acid. 4-Carboxy-α-carboline was isomeric with, but different from, the acid obtained by hydrolysis of the nitrile produced by treating (III; R = OMe) with potassium cyanide. This comparison strongly suggested that the nitrile just mentioned was 2-cyano-α-carboline. Final proof came from another source.

Alkaline hydrolysis of the ester obtained from the salt (II; R = H) and either ethyl acetoacetate or diethyl malonate gave an acid that was readily decarboxylated to 2-methyl-α-carboline, identical with the 2-methyl compound mentioned above. The ester must therefore have been (V; $R = CH_2CO_2Et$).

The ester (V; $R = CH_2CO_2Et$) was converted by peracetic acid into 2-carboxy-α-carboline 1-oxide. The same *N*-oxide was obtained by peracetic acid oxidation of the acid derived from the product of the reaction between potassium cyanide and (II; R = H) or (III; R = OMe). The amine obtained from this acid by Curtius degradation was the same as that obtained by amination of (III; R = OMe). The compounds obtained by treating (II; R = H) or (III; R = OMe) with potassium cyanide or ammonia are therefore 2-substituted α-carbolines.

^1H N.m.r. spectroscopy provides evidence that the compounds enumerated in the Table are also 2-substituted α-carbolines. For all these compounds, in the aromatic region, $J_{3,4} = 8{\cdot}5 \pm 0{\cdot}5$ Hz in dimethyl sulphoxide, deuteriochloroform, or trifluoroacetic acid. The spectra of the 2-substituted compounds (V; R = CO_2H, CO_2Et, and Me), measured in dimethyl sulphoxide or deuteriochloroform solution, all exhibit strong coupling (J = 8 Hz) between the 3- and the 4-proton. For the corresponding 4-substituted compounds $J_{2,3} = 5{\cdot}5 \pm 0{\cdot}5$ Hz. The same respective coupling constants are observed in deuteriochloroform solution for 2- and 4-methyl-9-acetyl-α-carboline. In trifluoroacetic solution, for (V; R = Me) J = 8 Hz and for 4-methyl-α-carboline J = 6 Hz. Our results thus agree with the general principle [7] that $J_{3,4} > J_{2,3}$.

[6] R. Eisenthal and A. R. Katritzky, *Tetrahedron*, 1965, **21**, 2205.

[7] M. H. Palmer and B. Semple, *Chem. and Ind.*, 1965, 1766.

View Article Online

Published on 01 January 1970. Downloaded by University of Idaho Library on 31/10/2014 11:45:59.

The ^{1}H n.m.r. spectrum of 3-amino-α-carboline, prepared as indicated below, exhibits weak coupling between the 2- and the 4-proton (J = 2·5 Hz).

We attempted to make 3-nitro-α-carboline by a modification of Freak and Robinson's method,[1b] but obtained from *o*-phenylenediamine and 2-chloro-5-nitropyridine, under acid conditions, a small amount of the diamine (VI) and, in 58% yield, a yellow compound ($C_{11}H_7N_3O_2$); none of the expected condensation product (VII) was formed. However, compound (VII) was obtained by heating the same starting materials in refluxing aqueous potassium carbonate. When (VII) was treated with hydrochloric acid it gave the same compound $C_{11}H_7N_3O_2$ in 65% yield. The amine (VII) also reacted with nitrous acid to give the benzotriazole (IV; $R^1 = NO_2$, $R^2 = H$) which, in hot phosphoric acid, gave not the expected 3-nitro-α-carboline but again the same compound $C_{11}H_7N_3O_2$.

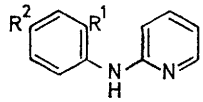
In order to discover whether this compound contained the pyrido[1,2-*a*]benzimidazole ring system we dehydrogenated the known 3-nitro-6,7,8,9-tetrahydropyrido[1,2-*a*]benzimidazole (prepared by the method of Campbell and McCall[8] from 2-chlorocyclohexanone and 2-amino-5-nitropyridine) and obtained a product identical with our compound $C_{11}H_7N_3O_2$. The latter must have therefore have been 2-nitropyrido[1,2-*a*]-benzimidazole (VIII).

The fully aromatic[9] pyrido[1,2-*a*]benzimidazole system is formed with remarkable ease, as are also the 1,2,3,4,-tetrahydropyrido[1,2-*a*]-benzimidazole[10–12] and the 6,7,8,9-tetrahydropyrido[1,2-*a*]benzimidazole[8] system. The formation of 2-nitropyrido[1,2-*a*]benzimidazole (VIII) from the amine (VII) under acid conditions requires simply the elimination of ammonia from the tautomeric form (VIIa). The nitro-group evidently favours the formation of (VIII) from the benzotriazole (IV; $R^1 = NO_2$, $R^2 = H$), for the benzotriazoles (IV; $R^1 = NH_2$, $R^2 = H$), (IV; $R^1 = NHAc$, $R^2 = H$), and (IV; $R^1 = H$, $R^2 = CO_2H$) all give α-carbolines when treated with phosphoric acid.

After we had completed this work, it was reported[13] that the benzotriazole (IV; $R^1 = NO_2$, $R^2 = H$) when heated with phosphoric acid gave 3-nitro-α-carboline (m.p. 239·5—240·5°); this nitro-compound on reduction gave an amine reported to be 3-amino-α-carboline (m.p. 216—217°). These compounds are undoubtedly 2-nitropyrido[1,2-*a*]benzimidazole (m.p. 240—241°) and 2-aminopyrido[1,2-*a*]benzimidazole (m.p. 220°) respectively; the m.p. of 3-amino-α-carboline is 271—273°.

Burtner[2] nitrated α-carboline and obtained in unspecified yield a compound described as 6-nitro-α-carboline, but gave no proof of orientation. We have supplied this proof (see below). Burtner reduced the nitro-group to an amino-group and obtained a series of 6-substituted α-carbolines. From Burtner's amine we have prepared 6-chloro-, 6-bromo-, 6-iodo, and 6-cyano-α-carboline by the Sandmeyer reaction, as well as 6-acetamido-α-carboline and 6-acetamido-9-acetyl-α-carboline. We also obtained 6-iodo-α-carboline by direct iodination of α-carboline.

We did not succeed in obtaining 6-nitro-α-carboline by an unambiguous synthesis. 2-Chloro-5-nitroaniline did not react with 2-aminopyridine even at 200°; 1,2-diamino-4-nitrobenzene similarly failed to react with 2-chloropyridine. 2,4-Dinitrochlorobenzene condensed readily with 2-aminopyridine to give the amine (IX; $R^1 = R^2 = NO_2$), but we were unable to prepare (IX; $R^1 = NH_2$, $R^2 = NO_2$) by selective reduction. We therefore reduced both nitro-groups to obtain the diamine[10] (IX; $R^1 = R^2 = NH_2$), but then failed to obtain the monoacetyl compound (IX; $R^1 = NH_2$, $R^2 = NHAc$).



(IX)

We did, however, prove that the chloro-compound that we obtained by nitration of α-carboline, with subsequent reduction, diazotisation, and chlorination, was 6-chloro-α-carboline. Ashton and Suschitzky[14] prepared 6-chloro-α-carboline probably not quite pure, m.p. 229—230°, in 3·3% overall yield by an unambiguous synthesis from 2,5-dichloronitrobenzene and 2-aminopyridine. The chloro-α-carboline that we obtained from the nitration product of α-carboline had m.p. 266—268°. To prove the orientation of our chloro-compound we condensed 1,2-diamino-4-chlorobenzene with 2-chloropyridine and treated the product with nitrous acid to obtain a chloro-1-α-pyridylbenzotriazole (this had the m.p. reported by Ashton and Suschitzky[14] for 5-chloro-1-α-pyridylbenzotriazole), and finally cyclised the benzotriazole. The chloro-α-carboline was identical with that obtained from the nitro-compound.

The product from 1,2-diamino-4-chlorobenzene and 2-chloropyridine must be 6- or 7-chloro-α-carboline, whereas that derived from the nitro-compound must be 6- or 8-chloro-α-carboline, for nitration must proceed *o*- or *p*- to the 9-nitrogen atom. The products are identical, and must therefore both be 6-chloro-α-carboline.

EXPERIMENTAL

U.v. spectra were measured in ethanol. The internal reference standard for ^{1}H n.m.r. spectra was tetramethylsilane. T.l.c. was carried out as described earlier.[15] M.p.s are corrected. Coupling-constants are expressed in Hz.

[8] N. Campbell and E. B. McCall, *J. Chem. Soc.*, 1951, 2411.
[9] G. Morgan and J. Stewart, (*a*) *J. Chem. Soc.*, 1938, 1292; (*b*) 1939, 1057.
[10] K. H. Saunders, *J. Chem. Soc.*, 1955, 3275.
[11] W. L. Mosby, *J. Org. Chem.*, 1959, **24**, 419.
[12] R. Huisgen and H. Rist, *Annalen*, 1959, **594**, 159.
[13] Pawel Nantka-Namirski, *Acta Polon. Pharm.*, 1966, **23**, 331 (*Chem. Abs.*, 1967, **66**, 28,714).
[14] B. W. Ashton and H. Suschitzky, *J. Chem. Soc.*, 1957, 4559.
[15] W. K. Warburton, *J. Chem. Soc.* (*C*), 1966 1522.

View Article Online

Published on 01 January 1970. Downloaded by University of Idaho Library on 31/10/2014 11:45:59.

N-o-*Anilino*-N-2-*pyridylamine*.—2-Chloropyridine (10·0 g.) and *o*-phenylenediamine (8·0 g.) were heated together under nitrogen at 135° for 6 hr. The product in hot ethanol was treated with 5N-hydrochloric acid (50 ml.); the solution was concentrated under reduced pressure and then made basic with ammonia. The solid that separated was recrystallised (charcoal) from water to give the *amine* (3·91 g., 24%), m.p. 133·5—137° (Found: C, 71·4; H, 6·2; N, 22·7. $C_{11}H_{11}N_3$ requires C, 71·3; H, 6·0; N, 22·7%).

1-1-*Pyridylbenzotriazole* (IV; $R^1 = R^2 = H$).—2-Chloropyridine (112 g.) and *o*-phenylenediamine (108 g.) were heated at 140° for 5·5 hr. and the product in hot ethanol (600 ml.) was treated with 5N-hydrochloric acid (1·7 l.). The cooled solution was added slowly with stirring at 0° to sodium nitrite (120 g.) in water (1200 ml.). The suspension was kept overnight and the solid was crystallised from methanol to give 1-1-pyridylbenzotriazole (118·4 g., 61%), m.p. 111·5—113° (lit.,[1a] m.p. 110—111°).

α-*Carboline* (V; R = H).—1-1-Pyridylbenzotriazole (100 g.) in orthophosphoric acid (88%; 520 ml.) was heated at 150° for 30 min.; the temperature was then raised to 200° during 20 min. No more nitrogen was then being evolved. The cooled mixture was dissolved in hot ethanol (1 l.) and heated with picric acid (120 g.) in hot ethanol (2 l.), and then with hot water (1 l.); the mixture was then cooled again. The picrate was washed with water and heated with 8% (w/v) aqueous sodium hydroxide (5 l.) for 20 min. on a steam-bath. The solid was dissolved in 5N-hydrochloric acid (310 ml.) and the solution was refrigerated overnight. The precipitated hydrochloride was dissolved in water and the filtered solution was made basic with ammonia to give α-carboline (30·4 g., 35%), m.p. 217—219°. A sample (3·0 g.) recrystallised from ethanol (charcoal) gave α-carboline (2·9 g.), m.p. 219—220° (lit.,[1b] m.p. 211°); $\lambda_{max.}$ 232—233, 259, 297—298 nm. (ε 21,700, 14,000, 18,100); τ(Me_2SO) — 1·79 (NH), 1·32—1·92 (Ar), 2·38—2·92 (Ar). Acetylation of α-carboline with acetic anhydride in acetic acid at 100° gave 9-acetyl-α-carboline, m.p. 99—99·5° (lit.,[16] m.p. 98°); $\lambda_{max.}$ 228, 258, 289 nm. (ε 35,800, 13,800, 15,500) (Found: C, 74·3; H, 4·8; N, 13·3. Calc. for $C_{13}H_{10}N_2O$: C, 74·3; H, 4·7; N, 13·4%).

2-o-*Hydroxyanilinopyridine*.— 1-1-Pyridylbenzotriazole (2·5 g.) was heated in orthophosphoric acid (13 ml.) as in the preceding experiment, after which the mixture was cooled and poured into water (100 ml.). The pH was adjusted to 8, when a solid (2·06 g.) separated. Part of this (0·7 g.) was crystallised (charcoal) from ethanol to give α-carboline (0·235 g., 32%), m.p. 217—220°. The solid from the evaporated mother-liquors was chromatographed in benzene–ethanol on alumina (Grade I; 25 g.). The eluate containing the less-polar component was evaporated to dryness and the residue (0·23 g.), in ether, was treated with dry hydrogen chloride. 2-*o*-Hydroxyanilinopyridine hydrochloride separated; it had m.p. 158—158·5° (lit.,[17] m.p. 153—154°) and was identical (i.r. spectrum) with the compound described below (Found: C, 61·5; H, 5·1; Cl, 15·9; N, 12·0. Calc. for $C_{11}H_{11}ClN_2O$: C, 59·4; H, 4·95; Cl, 15·9; N, 12·5%). The base, obtained from the hydrochloride by treatment with aqueous ammonia until the pH was 7·5, had m.p. and mixed m.p. 89—91° (from benzene) (lit.,[18] m.p. 87—89°); $\lambda_{max.}$ 267—268 nm. (ε 11,250) (Found: C, 70·0; H, 5·1; N, 15·0. Calc. for $C_{11}H_{10}N_2O$: C, 70·9; H, 5·4; N, 15·0%); it was identical (i.r. spectrum) with the base described below.

2-*o*-Hydroxyanilinopyridine was also prepared[17] from *o*-aminophenol and 2-chloropyridine; it had m.p. 90·5—91·5°; the hydrochloride had m.p. 155—157°.

1-(6-*Methyl*-2-*pyridyl*)*benzotriazole*.—This *compound* was prepared in 40% yield from *o*-phenylenediamine and 2-bromo-6-methylpyridine[19] by the method described for 1-1-pyridylbenzotriazole; it had m.p. 84—85° (lit.,[2] m.p. 84—85°) (Found: C, 68·6; H, 4·5; N, 26·8. $C_{12}H_{10}N_4$ requires C, 68·55; H, 4·8; N, 26·65%).

2-*Methyl*-α-*carboline*.—Treatment of the preceding compound with phosphoric acid as described for α-carboline gave 2-*methyl*-α-*carboline* in 46% yield, m.p. 252—254° (lit.,[2] m.p. 255°); $\lambda_{max.}$ 259, 302 nm. (ε 16,000, 22,250); τ(Me_2SO) — 1·63 (NH), 1·66, 2·91 (d, *J* 8); τ(CF_3CO_2H) 1·20, 2·57 (d, *J* 8) (Found: C, 79·5; H, 5·6; N, 15·5. $C_{12}H_{10}N_2$ requires C, 79·1; H, 5·5; N, 15·4%).

9-*Acetyl*-2-*methyl*-α-*carboline* was obtained in 76% yield by treatment of 2-methyl-α-carboline with acetic anhydride in acetic acid, it had m.p. 112—113°; τ($CDCl_3$) 1·93, 2·88 (d, *J* 8), 2·31 (Ar), 6·88 (NAc), 7·38 (Me) (Found: C, 75·25; H, 5·6; N, 12·4. $C_{14}H_{12}N_2O$ requires C, 75·0; H, 5·4; N, 12·5%).

1,2-*Dimethyl*-α-*carbolinium Methyl Sulphate*.—To 2-Methyl-α-carboline (1·26 g.) in refluxing toluene (54 ml.) was added dimethyl sulphate (1·5 ml.) in toluene (10 ml.). The mixture was heated under reflux for 30 min. after which it was cooled; the resulting solid was recrystallised from acetone–methanol to give 1,2-*dimethyl*-α-*carbolinium methyl sulphate* (1·29 g., 60%), m.p. 282·5—284° (Found: C, 54·3; H, 5·2; N, 8·9; S, 10·1. $C_{14}H_{16}N_2O_4S$ requires C, 54·5; H, 5·2; N, 9·1; S, 10·4%).

1-(4-*Methyl*-2-*pyridyl*)*benzotriazole* (IV; R^1 = H, R^2 = Me).—Treatment of *o*-phenylenediamine with 2-bromo-4-methylpyridine[19] as described for 1-1-pyridylbenzotriazole gave the *benzotriazole* in 55% yield; it had m.p. 118—119·5° (from methanol) (lit.,[2] m.p. 118°) (Found: C, 68·3; H, 4·75; N, 26·25. $C_{12}H_{10}N_4$ requires C, 68·55; H, 4·8; N, 26·65%.

4-*Methyl*-α-*carboline*.—Treatment of the preceding compound with phosphoric acid as described above gave 4-methyl-α-carboline in 29% yield; it had m.p. 217—219° (lit.,[2] m.p. 212—213°); $\lambda_{max.}$ 233, 260, 293, 325 nm. (ε 24,400, 14,700, 17,600, 3640); τ(CF_3CO_2H) 1·73, 2·53 (d, *J* 6); τ(Me_2SO) 1·65, 2·94 (d, *J* 5) (Found: C, 78·9; H, 5·6; N, 15·6. $C_{12}H_{10}N_2$ requires C, 79·1; H, 5·5; N, 15·4%).

9-*Acetyl*-4-*methyl*-α-*carboline*, prepared in 86% yield as described above, had m.p. 137—138°; $\lambda_{max.}$ 230, 285 nm. (ε 36,700, 17,500); τ($CDCl_3$) 8·86 (NAc), 7·21 (CMe), 1·68, 2·95 (d, *J* 5) (Found: C, 75·2; H, 4·5; N, 12·1. $C_{14}H_{12}N_2O$ requires C, 75·0; H, 5·4; N, 12·5%).

1-(4-*Cyano*-2-*pyridyl*)*benzotriazole* (IV; R^1 = H, R^2 = CN).—2-Chloro-4-cyanopyridine[20] (12·0 g.) and *o*-phenylenediamine (9·4 g.) were heated together under nitrogen at 130° for 7 hr. The product was dissolved in hot ethanol (80 ml.) and 5N-hydrochloric acid (350 ml.) was added to it; the solution was cooled, filtered, and added at 0° with stirring to sodium nitrite (26·0 g.) in water (250 ml.).

[16] O. Kruber and R. Oberkobusch, *Chem. Ber.*, 1953, **86**, 309.
[17] E. Deuerlein and E. Diepolder, *J. prakt. Chem.*, 1923, **106**, 46.
[18] E. Steinhäuser and E. Diepolder, *J. prakt. Chem.*, 1916, [2], **93**, 396.
[19] F. H. Case, *J. Amer. Chem. Soc.*, 1946, **68**, 2574.
[20] B. Prijs, A. H. Lutz, and H. Erlenmeyer, *Helv. Chim. Acta*, 1948, **31**, 571; D. Libermann, N. Rist, F. Grumbach, S. Cals, M. Moyeux, and A. Rouaix, *Bull. Soc. chim. France*, 1958, 694.

View Article Online

Published on 01 January 1970. Downloaded by University of Idaho Library on 31/10/2014 11:45:59.

Next day the solid was extracted into hot chloroform. The extract was filtered, dried ($MgSO_4$), and evaporated to dryness under reduced pressure. The residue was recrystallised from ethanol to give the *triazole* (5·69 g. (30%), m.p. 188—190·5° (Found: C, 65·1; H, 3·2; N, 31·4. $C_{12}H_7N_5$ requires C, 65·15; H, 3·2; N, 31·7%).

1-(4-*Carboxy*-2-*pyridyl*)*benzotriazole* (IV; R^1 = H, R^2 = CO_2H).—The preceding compound (1·0 g.) was stirred and heated under reflux in aqueous sodium hydroxide (40% w/v; 8 ml.) for 2·5 hr. The cooled mixture was diluted with water and filtered. The filtrate was acidified and the resulting precipitate was recrystallised from ethanol (charcoal) to give the *acid* (0·65 g., 60%), m.p. 257—259°; $\lambda_{max.}$ 235, 262, 310 nm. (ε 14,150, 8500, 10,800) (Found: C, 60·1; H, 3·4; N, 23·5. $C_{12}H_8N_4O_2$ requires C, 60·0; H, 3·4; N, 23·3%).

α-*Carboline*-4-*carboxylic Acid*.—The preceding compound (2·0 g.) was heated in orthophosphoric acid (*d* 1·75) (10 ml.) at 140°; the temperature was then gradually increased to 180° during 30 min. The mixture was cooled and poured into water (100 ml.); the resulting solid (A) was filtered off. The pH of the filtrate was adjusted to 6·0 with aqueous sodium hydroxide and the solid (B) (0·52 g.) was collected. The solid (A) was dissolved in 2N-sodium hydroxide and reprecipitated with 2N-hydrochloric acid. Recrystallisation of the product from glacial acetic acid (charcoal) gave α-*carboline*-4-*carboxylic acid* (0·23 g., 13%), m.p. 359° (decomp.); $\lambda_{max.}$ 248, 262, 320 nm. (ε 13,900, 12,600, 10,900); τ(Me_2SO) — 2·3 (CO_2H,NH), 1·38, 2·30 (d, *J* 5) (Found: C, 67·7; H, 3·9; N, 13·2. $C_{12}H_8N_2O_2$ requires C, 67·9; H, 3·8; N, 13·2%). The *ethyl ester* had m.p. 195—197° (from ethanol), $\lambda_{max.}$ 249·5, 264, 323 nm. (ε 13,500, 12,800, 11,050); τ(Me_2SO) — 2·14 (NH), 5·43, 8·60 (Et), 1·24, 2·37 (d, *J* 5) (Found: C, 70·0; H, 5·3; N, 11·5. $C_{14}H_{12}N_2O_2$ requires C, 70·0; H, 5·0; N, 11·7%). Solid (B) was recrystallised from glacial acetic acid (charcoal) to give 2-*o*-hydroxyanilopyridine-4-carboxylic acid (0·34 g., 18%), m.p. 332° (decomp.), $\lambda_{max.}$ 259—260, 355—360 nm. (ε 15,100, 4210) (Found: C, 62·2; H, 4·5; N, 12·2. $C_{12}H_{10}N_2O_3$ requires C, 62·6; H, 4·4; N, 12·2%).

1-(5-*Amino*-2-*pyridyl*)*benzotriazole* (IV; R^1 = NH_2, R^2 = H).—The preceding nitro-compound (12·0 g.) was hydrogenated in ethanol (600 ml.) at room temperature and pressure in the presence of 5% palladium–charcoal (5 g.) until no more hydrogen was taken up. The mixture was filtered and the filtrate on evaporation to dryness gave the *amine* (8·52 g., 81%), m.p. 162—163°. A sample recrystallised from ethanol (charcoal) in 71% yield had m.p. 163·5—165° (Found: C, 62·4; H, 4·6; N, 32·8. $C_{11}H_9N_5$ requires C, 62·55; H, 4·3; N, 33·2%). The *acetyl derivative*, prepared in 80% yield by brief treatment of the amine with acetic anhydride in acetic acid on a steam-bath, had m.p. 257—258° (Found: C, 61·4; H, 4·3; N, 27·9. $C_{13}H_{11}N_5O$ requires C, 61·65; H, 4·4; N, 27·7%).

3-*Acetamido*-9-*acetyl*-α-*carboline*.—The preceding acetyl compound (9·4 g.) in orthophosphoric acid (98%, 50 ml.) was heated to 180° for 45 min. after which the solution was cooled and diluted with water. The pH was adjusted to 5·0 with ammonium hydroxide and some tar was filtered off. The pH was raised to 9·0, when a solid (2·26 g.) separated. This was re-acetylated and recrystallised from ethanol to give 3-*acetamido*-9-*acetyl*-α-*carboline* (1·0 g., 10%), m.p. 250—251° (Found: C, 67·6; H, 4·75; N, 15·7. $C_{15}H_{13}N_3O_2$ requires C, 67·4; H, 4·9; N, 15·7%).

3-*Amino*-α-*carboline*.—The preceding compound (400 mg.) in ethanol (4 ml.) and aqueous sodium hydroxide solution (40% w/v) (3 ml.) was heated under reflux for 1·5 hr. The mixture was cooled and diluted with water to give 3-*amino*-α-*carboline* (190 mg., 70%), m.p. 271—273°; $\lambda_{max.}$ 309—310, 372 nm (ε 14,200, 4700); τ(Me_2SO) — 1·20 (NH), 5·22 (NH_2), 2·00, 2·30 (d, *J* 2·5) (Found: C, 72·2; H, 5·3; N, 22·6. $C_{11}H_9N_3$ requires C, 72·1; H, 5·0; N, 22·9%).

α-*Carboline* 1-*Oxide* (I).—α-Carboline (10·0 g.) was heated in glacial acetic acid (40 ml.) and hydrogen peroxide (30%; 7·5 ml.) at 80° for 4 hr. More hydrogen peroxide (3 ml.) was added, and the heating was continued for a further 2 hr. Removal of solvent from the mixture and addition of water to the residue gave the *N*-oxide (10·0 g., 92%), m.p. 237—239°; $\lambda_{max.}$ 253 nm (ε 33,000). Recrystallisation from ethanol (charcoal) gave α-*carboline* 1-*oxide*, m.p. 236—238°, $\lambda_{max.}$ 253—254 nm (ε 34,200) (Found: C, 72·0; H, 4·6; N, 14·95. $C_{11}H_8N_2O$ requires C, 71·7; H, 4·4; N, 15·2%).

2-*Methyl*-α-*carboline* 1-*Oxide*.—Treatment of 2-methyl-α-carboline [2] with peracetic acid as described above gave 2-*methyl*-α-*carboline* 1-*oxide* (55%), m.p. 259—262·5°; $\lambda_{max.}$ 249—250 nm. (ε 35,800) (Found: C, 72·9; H, 5·2; N, 13·9. $C_{12}H_{10}N_2$ requires C, 72·7; H, 5·1; N, 14·1%).

9-*Methyl*-α-*carboline* 1-*Oxide*.—9-Methyl-α-carboline [21] (5·46 g.) in chloroform (20 ml.) was treated with *m*-chloroperbenzoic acid (6·75 g.) in chloroform (20 ml.). After 30 min., more *m*-chloroperbenzoic acid (3·4 g.) was added. After 24 hr. the mixture was washed with sodium carbonate solution and evaporated to dryness. The residue was chromatographed on six 20 × 20 cm. silica-coated plates in chloroform containing 5% of methanol. Elution of the slow-running band with chloroform containing 10% of methanol gave 9-methyl-α-carboline 1-oxide (3·3 g., 55%), m.p. 77—85°; $\lambda_{max.}$ 224, 259, 276, 300, 368 nm. (ε 20,800, 28,100, 16,100, 10,000, 5150). The *hydrochloride* had m.p. 219° (from 2-methoxyethanol) (Found: C, 61·3; H, 5·0; Cl, 15·2; N, 11·8. $C_{12}H_{11}ClN_2O$ requires C, 61·4; H, 4·8; Cl, 15·1; N, 11·9%).

2-*Acetoxy*-9-*acetyl*-α-*carboline*.—α-Carboline 1-oxide (4·0 g.) was heated under reflux in acetic anhydride (40 ml.) for 0·5 hr. The solvent was removed under reduced pressure and the residue was recrystallised from ethanol (charcoal) to give the acetoxy-compound (2·75 g., 47%), m.p. 153—154°. A second crystallisation from ethanol (charcoal) gave 2-*acetoxy*-9-*acetyl*-α-*carboline*, m.p. 155—157·5°; $\lambda_{max.}$ 229, 262, 292 nm. (ε 35,200, 13,700, 15,500); τ($CDCl_3$) 7·61 (OAc), 6·95 (NAc), 1·73, 1·96 (d, *J* 8) (Found: C, 67·1; H, 4·4; N, 10·2. $C_{15}H_{12}N_2O_3$ requires C, 67·15; H, 4·5; N, 10·4%).

2-*Hydroxy*-α-*carboline* (V; R = OH).—2-Acetoxy-9-acetyl-α-carboline (7·0 g.) was heated under reflux in aqueous sodium hydroxide (20% w/v; 210 ml.) and ethanol (140 ml.) for 2 hr. The ethanol was removed under reduced pressure and water was added to the residue; a little solid was filtered off. The filtrate was neutralised with hydrochloric acid and the precipitate (4·56 g.) was crystallised from ethanol to give the hydroxy-compound (3·81 g., 65%), m.p. 293° (decomp.). Recrystallisation from ethyl acetate gave 2-*hydroxy*-α-*carboline*, m.p. 294° (decomp.); $\lambda_{max.}$ 226, 261—262, 333 nm. (ε 40,000, 12,100, 13,900); τ(Me_2SO) — 2·48 (OH), —1·02 (NH), 1·90, 3·00 (d, *J* 8) (Found: C, 72·0; H, 4·1; N, 14·9. $C_{11}H_8N_2O$ requires C, 71·7; H, 4·4; N, 15·2%).

[21] K. Eiter, *Monatsh.*, 1948, **79**, 17.

View Article Online

Published on 01 January 1970. Downloaded by University of Idaho Library on 31/10/2014 11:45:59.

2-Acetoxy-α-carboline (V; R = OAc).—Acetylation of the hydroxy-compound (0·70 g.) with acetic anhydride (15 ml.) at 100° for 0·5 hr. gave *2-acetoxy-α-carboline* (0·60 g., 70%), m.p. 210°; $\lambda_{max.}$ 259, 298 nm. (ε 14,900, 17,300) (Found: C, 69·2; H, 4·6; N, 12·4. $C_{13}H_{10}N_2O_2$ requires C, 69·0; H, 4·5; N, 12·4%).

1-Methoxy-α-carbolinium Methyl Sulphate (II; R = H).—α-Carboline-1-oxide (3·0 g.) and dimethyl sulphate (2·0 ml.) were heated in dry toluene (60 ml.) on a steam-bath for 0·5 hr. The solvent was decanted off and the residue was recrystallised from acetone to give *1-methoxy-α-carbolinium methyl sulphate* (3·68 g., 73%), m.p. 133—136°; $\lambda_{max.}$ 245, 260, 268, 298 nm. (ε 14,400, 15,150, 13,150, 11,500) (Found: C, 50·3; H, 4·7; N, 9·0; S, 10·0. $C_{13}H_{14}N_2O_5S$ requires C, 50·3; H, 4·55; N, 9·0; S, 10·3%).

Hydrogen 1-Methoxy-α-carbolinium Sulphate.—Finely ground α-carboline 1-oxide (2·0 g.) was heated under reflux in dry toluene (30 ml.); to this stirred solution was added dimethyl sulphate (1·4 ml.) in toluene (10 ml.) during 15 min. The mixture was heated under reflux for a further 0·5 hr. after which it was cooled; the solvent was decanted off, and the residual oil was crystallised from acetone (charcoal) to give *hydrogen 1-methoxy-α-carbolinium sulphate* (0·74 g., 23%), m.p. 164—165°; $\lambda_{max.}$ 245, 262, 269, 301 nm. (ε 14,950, 13,700, 13,600, 11,650) (Found: C, 48·8; H, 4·2; N, 9·3; S, 10·65. $C_{12}H_{12}N_2O_5S$ requires C, 48·65; H, 4·1; N, 9·5; S, 10·8%).

1-Ethoxy-α-carbolinium Hydrogen Sulphate.—This *compound* was prepared in 43% yield in a similar way to the methoxy-compound described above; it had m.p. 209—210°; $\lambda_{max.}$ 262, 268, 278, 300, 318 nm. (ε 17,700, 16,400, 15,500, 9400, 9250) (Found: C, 50·6; H, 4·6; N, 8·8; S, 9·95. $C_{13}H_{14}N_2O_5S$ requires C, 50·3; H, 4·55; N, 9·0; S, 10·3%).

1-Methoxy-9-methyl-α-carbolinium Methyl Sulphate (II; R = Me).—9-Methyl-α-carboline 1-oxide (0·96 g.) was heated at 60° in dimethyl sulphate (2 ml.) for 10 min. The mixture was cooled and diluted with dry ether to give the salt, (1·26 g., 80%), m.p. 170°. Recrystallisation from acetone gave the *methyl sulphate*, m.p. 184—185°; $\lambda_{max.}$ 251, 273, 302 nm. (ε 14,300, 16,200, 10,600) (Found: C, 51·5; H, 4·8; N, 8·7; S, 10·2. $C_{14}H_{16}N_2O_5S$ requires C, 51·85; H, 5·0; N, 8·6; S, 9·9%).

1-Ethoxy-α-carbolinium Tetrafluoroborate.—Triethyloxonium tetrafluoroborate (4·5 g.) in dry chloroform (20 ml.) was added, with stirring, to α-carboline 1-oxide (3·68 g.) in chloroform (30 ml.). The mixture was stirred for 1·5 hr. at room temperature and then for 1·5 hr. at 4°. The solid was filtered off, washed with chloroform, dried, and recrystallised from ethanol to give the salt (3·3 g., 55%), m.p. 179—181°. A sample recrystallised again from ethanol had m.p. 181—183°; $\lambda_{max.}$ 237, 260, 267, 297 nm. (ε 17,070, 13,860, 11,790, 13,560) (Found: C, 51·9; H, 4·5; N, 9·4. $C_{13}H_{13}BF_4N_2O$ requires C, 52·0; H, 4·35; N, 9·35%).

1-Methoxy-α-isocarboline (III; R = OMe).—Sodium hydroxide solution (40% w/v; 3 ml.) was added to an ice-cold aqueous solution of 1-methoxy-α-carbolinium methyl sulphate (1·0 g.). The yellow oil was extracted with ether to give 1-methoxy-α-isocarboline, (0·58 g., 91%); $\lambda_{max.}$ 277, 319 nm. (ε 16,300, 8400); τ($CDCl_3$) 1·70—3·00 (Ar), 5·59 (OMe). The same compound (i.r. spectrum) was obtained in quantitative yield by treatment of the methyl sulphate with cold 30% (w/v) potassium cyanide solution.

1-Methyl-α-isocarboline (III; R = Me).—Sodium hydroxide solution (40% w/v; 1 ml.) was added to 1-methyl-α-carbolinium methyl sulphate (0·30 g.) in water (1 ml.). The yellow isocarboline (0·10 g., 54%) was extracted with ether; it had m.p. 130—132°, raised to 132—133° by recrystallisation from acetone (lit.,[1b] m.p. 138—139°); $\lambda_{max.}$ 278, 319 nm. (ε 30,000, 13,350). The same compound (i.r. spectrum) was obtained in 44% yield on treatment of the methyl sulphate with cold 30% (w/v) potassium cyanide; it had m.p. 129—130°.

Reaction of 1-Ethoxy-α-carbolinium Tetrafluoroborate with 3-Aminopropanol.—1-Ethoxy-α-carbolinium tetrafluoroborate (3·0 g.) and 3-aminopropanol (5·0 g.) were heated under reflux in dry toluene (50 ml.) for 7·5 hr. The toluene was evaporated off and the residue was washed with chloroform and with water. Recrystallisation of the residue from isopropyl alcohol gave *2-(3-hydroxypropylamino)-α-carboline* (0·29 g., 12%), m.p. 163—166°; $\lambda_{max.}$ 236, 264, 343 nm. (ε 40,800, 12,900, 23,100) (Found: C, 68·3; H, 6·1; N, 16·9. $C_{14}H_{15}N_3O,1/3H_2O$ requires C, 68·0; H, 6·4; N, 17·0%).

Reaction of 1-Methoxy-α-carbolinium Methyl Sulphate with Hot Sodium Hydroxide.—The methyl sulphate (II; R = H) (0·30 g.) was heated under reflux, with stirring, in 27% (w/v) sodium hydroxide solution (6 ml.) for 3 hr. The mixture was cooled and filtered and the filtrate was neutralised with hydrochloric acid. The resulting precipitate (0·18 g.) was recrystallised from ethanol (charcoal) to give 2-hydroxy-α-carboline (0·09 g., 30%), m.p. 295° (decomp.), identical (i.r. spectrum) with the hydroxy-compound described above.

2-Methoxy-α-carboline (V; R = OMe).—1-Methoxy-α-carbolinium methyl sulphate (4·0 g.) was added to a solution of sodium (6·5 g.) in methanol (100 ml.) and the mixture was heated under reflux for 4·5 hr. The solvent was removed, water was added to the residue, and the solid was extracted with ether and washed with 2N-hydrochloric acid. The residue (1·78 g.) was recrystallised from methanol (charcoal) to give *2-methoxy-α-carboline* (0·96 g., 38%), m.p. 167—169°; τ($CDCl_3$) 0·68 (NH), 5·98 (OMe), 1·83, 2·38 (d, *J* 8); $\lambda_{max.}$ 224—225, 259—260, 302 nm. (ε 47,700, 14,600, 15,200) (Found: C, 72·5; H, 4·8; N, 14·0. $C_{12}H_{10}N_2O$ requires C, 72·7; H, 5·1; N, 14·1%). When 1-methoxy-α-isocarboline (640 mg.) was heated with a solution of sodium (1·0 g.) in methanol (10 ml.) on a steam-bath for 1 hr. and the reaction was worked up as described above, 2-methoxy-α-isocarboline, m.p. 166—169° (150 mg., 23%) was obtained.

2-(2-Diethylaminoethoxy)-α-carboline (V; R = $OCH_2CH_2NEt_2$).—1-Methoxy-α-carbolinium methyl sulphate (7·0 g.) was added to a solution of sodium (3·5 g.) in diethylaminoethanol (70 ml.) and the mixture was heated on a steam-bath for 1·75 hr. Most of the solvent was removed and water was added to the residue; the resulting solid (4·56 g.) was chromatographed in benzene on silica (200 g.). Elution with benzene containing up to 50% of ethyl acetate removed some impurities after which ethyl acetate eluted a product (1·18 g.) which was recrystallised from light petroleum (b.p. 60—80°) to give *2-(2-diethylaminoethoxy)-α-carboline* (0·64 g., 10%), m.p. 117—119°; $\lambda_{max.}$ 224, 259, 302 nm. (ε 46,500, 14,550, 15,200); τ($CDCl_3$) 0·58 (NH), 5·46, 7·02 (CH_2CH_2), 7·30, 8·92 (Et), 1·90, 3·42 (d, *J* 8) (Found: C, 72·1; H, 7·3; N, 14·7. $C_{17}H_{21}N_3O$ requires C, 72·05; H, 7·5; N, 14·8%).

2-Amino-α-carboline (V; R = NH_2).—1-Methoxy-α-carb-

View Article Online

Published on 01 January 1970. Downloaded by University of Idaho Library on 31/10/2014 11:45:59.

olinium methyl sulphate (2·0 g.) was heated with aqueous ammonia (*d* 0·88) (35 ml.) in a sealed tube at 110° for 4 hr. The resulting solid (1·03 g.) was chromatographed in benzene on silica (100 g.). Benzene which contained 5—25% of ethyl acetate removed an unidentified compound, m.p. 162—163° (0·27 g.). Benzene which contained 50% of ethyl acetate gave the crude amine (0·76 g.). Recrystallisation from ethanol gave 2-*amino-α-carboline* (0·45 g., 38%), m.p. 202—203°; $\lambda_{max.}$ 231, 262, 336 nm. (ε 42,000, 13,850, 19,500); τ(Me_2SO) — 1·10 (NH), 3·94 (NH_2), 1·91, 3·60 (d, *J* 8) (Found: C, 72·2; H, 5·1; N, 23·0. $C_{11}H_9N_3$ requires C, 72·1; H, 4·95; N, 22·9%). Treatment of the amine with acetic anhydride in acetic acid at 100° for 1 hr. gave 2-*acetamido*-9-*acetyl-α-carboline*, m.p. 239—240°; $\lambda_{max.}$ 235, 314, 320 nm. (ε 30,800, 25,000, 24,400); τ(CF_3CO_2H) 6·83, 7·42 (NAc), 1·10, 2·50 (d, *J* 8) (Found: C, 67·3; H, 5·0; N, 15·9. $C_{15}H_{13}N_3O_2$ requires C, 67·4; H, 4·9; N, 15·7%).

2-*Methylamino-α-carboline* (V; R = NHMe).—1-Methoxy-α-carbolinium methyl sulphate (2·0 g.) and aqueous methylamine solution (25% w/v) (45 ml.) were heated in a sealed tube at 105° for 4·5 hr. Water was added to the cooled mixture and the solid (1·1 g.) was recrystallised from benzene–light petroleum (b.p. 80—100°) (charcoal) to give 2-*methylamino-α-carboline* (0·72 g., 57%), m.p. 156—157°), $\lambda_{max.}$ 236, 263, 344 nm. (ε 40,800, 13,300, 21,500); τ($CDCl_3$) 0·00 (NH), 5·28 (NH), 6·99 (NMe), 1·98, 3·73 (d, *J* 8·5) (Found: C, 72·85; H, 5·5; N, 20·9. $C_{12}H_{11}N_3$ requires C, 73·1; H, 5·6; N, 21·3%).

2-*Hydrazino-α-carboline* (V; R = NH·NH_2).—1-Methoxy-α-carbolinium methyl sulphate (1·0 g.) was heated under reflux for 3 hr. in 98% hydrazine hydrate (10 ml.). Water was added to the cooled mixture and the solid (0·47 g.) was recrystallised from ethanol to give 2-*hydrazino-α-carboline* (0·29 g., 45%), m.p. 185—187°; $\lambda_{max.}$ 233—234, 263, 342 nm. (ε 35,800, 13,900, 19,700); τ(CF_3CO_2H) —0·06, —1·12 (NH), 1·25, 2·89 (d, *J* 8) (Found: C, 66·5; H, 5·1; N, 28·2. $C_{11}H_{10}N_4$ requires C, 66·65; H, 5·1; N, 28·3%). The same compound (i.r. spectrum) was obtained in 50% yield from 1-ethoxy-α-carbolinium hydrogen sulphate.

2-(2-*Diethylaminoethylamino*)-α-*carboline* [V; R = $NH(CH_2)_2NEt_2$].—1-Methoxy-α-carbolinium methyl sulphate (4·0 g.) was heated under reflux in *NN*-diethylethylenediamine (50 ml.) for 2 hr. Water was added to the cooled mixture and the solid was extracted with chloroform. The chloroform was evaporated off and the residue (3·35 g.) was chromatographed in benzene on silica (100 g.). Elution with benzene which contained 5% of ethyl acetate and further chromatography of the earlier fractions gave a product (1·26 g.) which was recrystallised from light petroleum (b.p. 60—80°) to give 2-β-*diethylaminoethylamino-α-carboline* (0·61 g., 17%), m.p. 102—103°; $\lambda_{max.}$ 235—236, 263—264, 342 nm. (ε 42,000, 13,600, 24,000); τ(CF_3CO_2H) 5·80—6·83 (CH_2), 8·50 (Et), 1·40—3·26 (d, *J* 9) (Found: C, 72·6; H, 7·65; N, 20·25. $C_{17}H_{22}N_4$ requires C, 72·3; H, 7·85; N, 19·8%).

2-*Cyano-α-carboline* (V; R = CN).—1-Methoxy-α-carbolinium methyl sulphate (1·0 g.) was stirred and heated under reflux for 1·5 hr. in a solution of potassium cyanide (0·5 g.) in water (5 ml.). The solid (0·52 g.) that separated from the cooled solution was recrystallised from ethanol (charcoal) to give the crude nitrile (0·24 g., 39%). Further recrystallisation from ethanol gave 2-*cyano-α-carboline*, m.p. 289—291°; $\lambda_{max.}$ 245, 312 nm. (ε 27,200, 24,300); τ(Me_2SO) — 2·28 (NH), 1·24, 2·19 (d, *J* 8) (Found: C, 74·7; H, 3·8; N, 21·55. $C_{12}H_7N_3$ requires C, 74·6; H, 3·65; N, 21·75%).

2-*Ethoxycarbonylmethyl-α-carboline* (V; R = CH_2CO_2Et). —(*a*) Diethyl malonate (18·4 ml.), and then 1-methoxy-α-carbolinium methyl sulphate (8·0 g.) were added to a solution of sodium (2·8 g.) in ethanol (80 ml.); the mixture was then heated under reflux for 1·5 hr. The solvent was removed from the mixture and water (800 ml.) was added to the residue. The residual solid (6·33 g.) was recrystallised from ethanol (charcoal) to give the ester (2·93 g., 45%), m.p. 206—209°. A sample further recrystallised from ethanol gave 2-*ethoxycarbonylmethyl-α-carboline*, m.p. 208—210°; $\lambda_{max.}$ 233, 260, 300, 330 nm. (ε 22,000, 14,300, 19,700, 5430); τ(CF_3CO_2H) 5·60 (CH_2), 5·52, 8·60 (Et), 1·14, 2·50 (d, *J* 8) (Found: C, 71·1; H, 5·5; N, 10·7. $C_{15}H_{14}N_2O_2$ requires C, 70·85; H, 5·5; N, 11·0%).

(*b*) Ethyl acetoacetate (24 ml.) and then 1-methoxy-α-carbolinium methyl sulphate (8·0 g.) were added to a solution of sodium (4·0 g.) in ethanol (120 ml.); the mixture was then heated under reflux for 2·5 hr. The solvent was evaporated off and water was added to the residue. The resulting solid was crystallised twice from ethanol (charcoal) to give 2-ethoxycarbonylmethyl-α-carboline (2·13 g., 32·5%), m.p. 207—210°, identical (i.r. spectrum) with the compound described above. The same ester (18·5%) was obtained when 1-methoxy-α-isocarboline was heated in an excess of ethyl acetoacetate on a steam-bath for 2·5 hr.

2-*Acetonyl-α-carboline* (V; R = CH_2Ac).—The 1-methoxy-α-isocarboline prepared from 1-methoxy-α-carbolinium methyl sulphate (6·0 g.) as described above was heated on a steam-bath in acetylacetone (15 ml.) for 1 hr. The solvent was removed under reduced pressure and the residue, in benzene, was chromatographed on silica (200 g.). Elution of the most polar component with benzene which contained 10—50% of ethyl acetate, removal of the solvent from the fraction, and recrystallisation of the residue (1·68 g.) from ethanol gave 2-*acetonyl-α-carboline* (1·03 g., 24%), m.p. 205—207°; $\lambda_{max.}$ 230, 260, 301 nm. (ε 21,700, 14,700, 19,400); τ(Me_2SO) 7·62 (Me), 1·54, 2·86 (d, *J* 8) (Found: C, 74·8; H, 5·4; N, 12·3. $C_{14}H_{12}N_2O$ requires C, 75·0; H, 5·4; N, 12·5%).

2-*Dicyanomethyl-α-carboline* [V; R = $CH(CN)_2$].—The 1-methoxy-α-isocarboline prepared from 1-methoxy-α-carbolinium methyl sulphate (2·0 g.) was heated in malononitrile (5 ml.) on a steam-bath for 1 hr. Water was added to the cooled reaction mixture and the resulting precipitate (1·44 g.) was recrystallised from pyridine–benzene (charcoal) to give 2-*dicyanomethyl-α-carboline* (0·17 g., 12%), m.p. 296—297°; $\lambda_{max.}$ 230, 250, 291 nm. (ε 26,000, 16,600, 12,200); τ(Me_2SO) — 1·26 (NH), 1·60, 3·16 (d, *J* 9) (Found: C, 72·6; H, 3·8; N, 23·95. $C_{14}H_8N_4$ requires C, 72·4; H, 3·5; N, 24·1%).

2-*n-Butylthio-α-carboline* (V; R = SBu).—1-Methoxy-α-carbolinium methyl sulphate (3·0 g.) was added to a solution of sodium (1·0 g.) in n-butanethiol (50 ml.) and the mixture was heated on a steam-bath for 2 hr. The mixture was then cooled and 2N-sodium hydroxide solution was added to it. The remaining solid (2·0 g.) was chromatographed in benzene on silica (100 g.). Elution with benzene gave a solid (1·61 g.) which was recrystallised from ethanol to give the butylthio-compound (1·04 g., 42%), m.p. 176—178°. A second recrystallisation from ethanol gave 2-*n-butylthio-α-carboline*, m.p. 179—180·5°; $\lambda_{max.}$ 237, 260,

View Article Online

Published on 01 January 1970. Downloaded by University of Idaho Library on 31/10/2014 11:45:59.

334 nm. (ε 29,000, 18,600, 21,300); τ(CF_3CO_2H) 8·26 (CH_2CH_2), 6·68, 8·99 (t, *J* 6) (Et), 1·34, 2·58 (d, *J* 8) (Found: C, 70·2; H, 6·0; N, 10·7; S, 12·4. $C_{15}H_{16}N_2S$ requires C, 70·3; H, 6·3; N, 10·9; S, 12·5%).

2-Benzylthio-α-carboline (V; R = SCH_2Ph).—1-Methoxy-α-carbolinium methyl sulphate (1·0 g.) was added to a solution of sodium (0·5 g.) in toluene-α-thiol (20 ml.) and the mixture was heated on a steam-bath for 2 hr.; the mixture was then cooled and added to 2N-sodium hydroxide. The resulting solid was washed with 2N-hydrochloric acid and with water and then recrystallised from ethanol (charcoal) to give the benzylthio-compound (0·30 g., 32%), m.p. 180—182°. Further crystallisation from ethanol gave *2-benzylthio-α-carboline*, m.p. 182·5—183°; $\lambda_{max.}$ 238, 260, 335 nm. (ε 31,200, 19,500, 21,700); τ(Me_2SO) −0·90 (NH), 5·40 (CH_2), 1·65, 2·84 (d, *J* 8) (Found: C, 74·7; H, 4·8; N, 9·5; S, 10·8. $C_{18}H_{14}N_2S$ requires C, 74·4; H, 4·9; N, 9·65; S, 11·0%).

2-(*2-Diethylaminoethylthio*)-α-*carboline* [V; R = $S(CH_2)_2NEt_2$]. Diethylaminoethanethiol hydrochloride (10 g.) and then 1-methoxy-α-carbolinium methyl sulphate (5·0 g.) were added to a solution of sodium (2·7 g.) in dry ethanol (35 ml.); the mixture was then heated under reflux for 2 hr. The solvent was evaporated off, water was added to the residue, and the solid (4·7 g.) was chromatographed in benzene on silica (200 g.). Several impurities were eluted with benzene which contained up to 50% of ethyl acetate. Further elution with ethyl acetate gave a solid (1·82 g.) which was recrystallised from benzene–light petroleum (m.p. 80—100°) to give 2-(*2-diethylaminoethylthio*)-α-*carboline* (1·12 g., 23·5%), m.p. 137—139°; $\lambda_{max.}$ 235—236, 259—260, 334 nm. (ε 28,500, 17,800, 20,300); τ($CDCl_3$) −0·46 (NH), 6·68, 7·13 (CH_2CH_2), 7·38, 8·98 (Et), 1·91, 2·92 (d, *J* 8·5) (Found: C, 68·4; H, 7·0; N, 14·1; S, 10·55. $C_{17}H_{21}N_3S$ requires C, 68·2; H, 7·1; N, 14·0; S, 10·7%).

2-Hydroxy-9-methyl-α-carboline. Sodium hydroxide solution (40% w/v; 2 ml.) was added at room temperature to a stirred solution of 1-methoxy-9-methyl-α-carbolinium methyl sulphate (0·40 g.) in water (2 ml.). After 2 hr. the mixture was filtered and the solid was washed with 2N-sodium hydroxide and with water. The filtrate and washings were neutralised with 2N-hydrochloric acid to give the hydroxy-compound (0·11 g., 45%). Recrystallisation of a 40-mg. sample gave *2-hydroxy-9-methyl-α-carboline* (30 mg.), m.p. 266—268°; $\lambda_{max.}$ 227, 264, 304 nm. (ε 42,200, 13,300, 12,300); τ(Me_2SO) — 0·94 (OH), 1·68, 3·50 (d, *J* 8) (Found: C, 72·7; H, 5·2; N, 13·8. $C_{12}H_{10}N_2O$ requires C, 72·7; H, 5·1; N, 14·1%).

2-Cyano-9-methyl-α-carboline. Potassium cyanide (0·50 g.) in water (2 ml.) was added at room temperature, with stirring, to 1-methoxy-9-methyl-α-carbolinium methyl sulphate (0·90 g.) in water (5 ml.). The solid that separated at once was collected after 1 hr. and recrystallised from ethanol (charcoal) to give *2-cyano-9-methyl-α-carboline* (0·36 g., 63%), m.p. 152—153°; $\lambda_{max.}$ 249, 263, 314 nm. (ε 29,100, 22,500, 25,600); τ($CDCl_3$) 6·12 (Me), 1·73, 2·54 (d, *J* 8) (Found: C, 75·5; H, 4·6; N, 20·5. $C_{13}H_9N_3$ requires C, 75·3; H, 4·4; N, 20·3%).

Hydrolysis of 2-Ethoxycarbonylmethyl-α-carboline.—The ester (1·70 g.) was heated under reflux for 3 hr. in ethanol (50 ml.) and sodium hydroxide solution (40% w/v; 30 ml.). Most of the solvent was removed, water was added to the residue, and the solid was filtered off and washed with water. The filtrate and washings were neutralised to pH 6 with hydrochloric acid to give *2-carboxymethyl-α-carboline* (1·07 g., 71%), m.p. 252—254°; $\lambda_{max.}$ 232—233, 260, 300 nm. (ε 21,700, 13,800, 19,300); τ(Me_2SO) — 1·66 (CO_2H), 1·60, 2·83 (d, *J* 8) (Found: C, 68·7; H, 4·5; N, 12·45. $C_{13}H_{10}N_2O_2$ requires C, 69·0; H, 4·5; N, 12·4%).

Decarboxylation of 2-Carboxymethyl-α-carboline.—The acid (0·40 g.) was added to glacial acetic acid (12 ml.) and the mixture heated to its b.p. Water was added to the mixture until it became cloudy after which it was heated under reflux for 1·75 hr. The mixture cooled and 2N-sodium hydroxide solution was added to it; the resulting solid (0·27 g.) was recrystallised from toluene (charcoal) to give 2-methyl-α-carboline (0·18 g., 56%), m.p. 255—257°; $\lambda_{max.}$ 258, 300, 326 nm. (ε 13,500, 18,300, 6200) identical (i.r. and ^1H n.m.r. spectra and t.l.c.) with the compound described above.

Oxidation of 2-Ethoxycarbonylmethyl-α-carboline.—The ester (0·50 g.) in glacial acetic acid (4 ml.) and hydrogen peroxide (30%, 0·75 ml.) was heated for 6·5 hr. at *ca.* 85°, further portions (0·75 ml.) of hydrogen peroxide being added after 1·5 and 4 hr. The solvent was removed, water was added to the residue, and the resulting solid (0·43 g.) was recrystallised from ethanol (charcoal) to give 2-carboxy-α-carboline 1-oxide (0·08 g., 14·5%), m.p. 229—230° (decomp.); τ(Me_2SO) — 3·16 (NH), 1·60, 1·92 (d, *J* 8) (Found: C, 63·3; H, 3·9; N, 11·8. $C_{12}H_8N_2O_3$ requires C, 63·2; H, 3·5; N, 12·3%).

Oxidation of α-Carboline-2-carboxylic Acid.—α-Carboline-2-carboxylic acid (see next experiment) (0·50 g.) was oxidised as in the preceding experiment to give 2-carboxy-α-carboline 1-oxide, (0·03 g., 5·5%), m.p. 235—236° (decomp.), identical (i.r. and ^1H n.m.r. spectra) with the compound described above.

Hydrolysis of 2-Cyano-α-carboline.—2-Cyano-α-carboline (0·90 g.) was stirred and heated under reflux in sodium hydroxide solution (40% w/v; 15 ml.) for 4 hr. Water (750 ml.) was added to the mixture which was then filtered. The pH of the filtrate was adjusted to 5 and the solid was recrystallised from acetic acid to give *α-carboline-2-carboxylic acid* (V; R = CO_2H) (0·73 g., 74%), m.p. 298° (decomp.); $\lambda_{max.}$ 245—246, 312 nm. (ε 27,200, 24,100); τ(Me_2SO) — 2·05 (NH), 1·28, 1·96 (d, *J* 8) (Found: C, 68·1; H, 3·7; N, 12·9. $C_{12}H_8N_2O_2$ requires C, 67·9; H, 3·8; N, 13·2%). The *ethyl ester*, (V; R = CO_2Et) obtained in 70% yield, had m.p. 250—251·5°; $\lambda_{max.}$ 246, 314 nm. (ε 27,800, 25,000); τ($CDCl_3$) 5·49, 8·53 (Et), 1·50, 2·80 (d, *J* 8) (Found: C, 70·2; H, 5·1; N, 11·8. $C_{14}H_{12}N_2O_2$ requires C, 70·0; H, 5·0; N, 11·7%).

2-Hydrazinocarbonyl-α-carboline V; R = $CONH{\cdot}NH_2$).—2-Ethoxycarbonyl-α-carboline (0·20 g.) was heated under reflux in hydrazine hydrate (98%; 5 ml.) for 1·5 hr. The mixture was cooled and diluted with water. The solid that separated was crystallised from ethanol to give *2-hydrazinocarbonyl-α-carboline* (0·14 g., 75%) m.p. 308—310° (decomp.); $\lambda_{max.}$ 245—246; 314 nm. (ε 29,100, 25,300); τ(CF_3CO_2H) 0·91, 1·63 (d, *J* 8) (Found: C, 63·8; H, 4·6; N, 24·8. $C_{12}H_{10}N_4O$ requires C, 63·7; H, 4·5; N, 24·8%).

2-Azidocarbonyl-α-carboline (V; R = CON_3).—Sodium nitrite (0·40 g.) in water (3 ml.) was added to a stirred solution of 2-hydrazinocarbonyl-α-carboline (1·2 g.) in 2N-hydrochloric acid (26 ml.), glacial acetic acid (45 ml.), and water (5 ml.) at 5°. *2-Azidocarbonyl-α-carboline*, (1·08 g., 85%), separated at once; it had $\lambda_{max.}$ 227—228, 250, 313 nm. (ε 28,200, 20,700, 21,000); τ(Me_2SO) 1·28,

View Article Online

Published on 01 January 1970. Downloaded by University of Idaho Library on 31/10/2014 11:45:59.

2·00 (d, *J* 8) (Found: C, 60·6; H, 3·1; N, 29·65. $C_{12}H_7N_5O$ requires C, 60·75; H, 3·0; N, 29·5%).

2-*Amino*-α-*carboline from* 2-*Azidocarbonyl*-α-*carboline*.—The azide (0·10 g.) was heated under reflux for 2·5 hr. in diphenyl ether (5 ml.) after which the solution was cooled and filtered. The filtrate was stirred and heated on a steam-bath for 10 min. with 10N-hydrochloric acid (4 ml.) after which the acid solution was cooled and extracted with ether. It was then basified to give 2-amino-α-carboline (0·30 g., 39%), m.p. 199—200°, identical (i.r. spectrum) with the amine described above.

6-*Nitro*-α-*carboline*.—α-Carboline (1·0 g.) was added in portions with stirring to nitric acid (*d* 1·42) (10 ml.) at <30°. The mixture was stirred for a further 30 min. after which it was set aside overnight at 0°. The resulting solid was filtered off and stirred with dilute ammonium hydroxide solution (30 ml.); it was then filtered off and washed with water to leave the crude nitro-compound (1·0 g.). Recrystallisation from pyridine gave 6-*nitro*-α-*carboline* (0·86 g., 68%), m.p. >320° (lit.,[2] m.p. >315°) (Found: C, 61·8; H, 3·5; N, 19·9. $C_{11}H_7N_3O_2$ requires C, 62·0; H, 3·3; N, 19·7%).

6-*Amino*-α-*carboline*.—6-Nitro-α-carboline (5·0 g.), stannous chloride dihydrate (22 g.), water (100 ml.), and hydrochloric acid (*d* 1·18) (30 ml.) were stirred and heated under reflux for 2 hr. The mixture was left at room temperature overnight after which the solid was filtered off and stirred with aqueous sodium hydroxide solution (10%, 100 ml.) to give 6-amino-α-carboline (4·04 g., 93%), m.p. 262—264° (lit., m.p. 263—264°). The same product was obtained in 65% yield by catalytic reduction (5% palladium charcoal) in ethanol.

6-*Acetamido*-α-*carboline*.—A solution of 6-amino-α-carboline (1·0 g.) in glacial acetic acid (15 ml.) was treated at 10° with acetic anhydride (3 ml.). After 2 hr. at room temperature the solution was poured into water, when 6-acetamido-9-acetyl-α-carboline (0·14 g.), m.p. 240—242°, separated and was filtered off. The filtrate was basified with ammonia and the resulting precipitate (1·03 g.) was recrystallised (charcoal) from ethanol to give 6-*acetamido*-α-*carboline* (0·75 g., 61%), m.p. 313—315° (Found: C, 69·2; H, 5·3; N, 18·7. $C_{13}H_{11}N_3O$ requires C, 69·3; H, 4·9; N, 18·7%).

6-*Acetamido*-9-*acetyl*-α-*carboline*.—Acetylation of 6-amino-α-carboline (1·0 g.) in glacial acetic acid (5 ml.) and acetic anhydride (5 ml.) at 100° for 1 hr. gave 6-*acetamido*-9-*acetyl*-α-*carboline* (1·21 g., 83%), m.p. 253—254° (from ethanol) (Found: C, 67·4; H, 5·2; N, 15·7. $C_{15}H_{13}N_2O_3$ requires C, 67·4; H, 4·9; N, 15·7%).

6-*Chloro*-α-*carboline*.—(*a*) The diazonium solution prepared in 10N-hydrochloric acid (4·5 ml.) and water (3 ml.) from 6-amino-α-carboline (3·0 g.) was added to cuprous chloride (1·02 g.) in 10N-hydrochloric acid (3 ml.); the mixture was heated to 60—70° for 15 min. and then cooled and filtered. The solid was dried and extracted several times with hot ethanol. The combined extracts were evaporated to dryness and the residue was recrystallised from ethanol (charcoal) to give 6-chloro-α-carboline (0·86 g., 26%), m.p. 265—269° (lit.,[14] m.p. 229—230°); $\tau(CF_3CO_2H)$ 1·86 (5-H); AB quartet, 2 centre-peaks at 2·32 and 2·35 (7- and 8-H) (Found: C, 65·2; H, 3·7; Cl, 17·4; N, 13·45. Calc. for $C_{11}H_7ClN_2$: C, 65·2; H, 3·5; Cl, 17·5; N, 13·8%).

(*b*) 5-Chloro-1-(1-pyridyl)benzotriazole (see later) (2·5 g.) was heated in 88% orthophosphoric acid (13 ml.) at 140° for 20 min. after which the temperature was gradually raised to 200° during 25 min. Picric acid (5 g.) in hot ethanol (75 ml.) was added to the cooled reaction mixture followed by hot water (25 ml.). The solid that separated was added to aqueous sodium hydroxide solution (8% w/v) and the suspension was heated on a steam-bath for 30 min. and then cooled. The residual solid was dissolved in 5N-hydrochloric acid (20 ml.) and the solution was filtered. The filtrate, left overnight at 0°, deposited a hydrochloride, which was dissolved in N-hydrochloric acid. The filtered solution was made basic with ammonia and the precipitated solid (0·52 g.) was collected and recrystallised from ethanol to give 6-chloro-α-carboline (0·32 g., 14·5%), m.p. 266—268°, identical (i.r. spectrum and mixed m.p.) with the compound described above.

6-*Bromo*-α-*carboline*.—The *bromo-compound*, prepared from 6-amino-α-carboline similarly to the chloro-compound in 40% yield had m.p. 266—270° (Found: C, 53·5; H, 3·0; Br, 32·4; N, 11·2. $C_{11}H_7BrN_2$ requires C, 53·5; H, 2·9; Br, 32·3; N, 11·3%).

6-*Iodo*-α-*carboline*.—α-Carboline (2·0 g.) and potassium iodide (1·32 g.) were stirred and heated to b.p. in glacial acetic acid (32 ml.); powdered potassium iodate (1·92 g.) was then added to the solution. The mixture was heated under reflux until a colourless suspension was obtained (*ca.* 25 min.). The mixture was filtered at its b.p. and the filtrate was concentrated and poured into water, when the *iodo-compound* (1·94 g., 55%), separated; it had m.p. 280—283°, unchanged by recrystallisation from ethanol (Found: C, 44·7; H, 2·5; I, 42·8; N, 9·3. $C_{11}H_7N_2I$ requires C, 44·9; H, 2·4; I, 43·2; N, 9·5%). The same compound (i.r. spectrum), m.p. 280—283°, was prepared in 29% yield from 6-amino-α-carboline by treating the derived diazonium salt with iodine.

6-*Cyano*-α-*carboline*.—6-Amino-α-carboline (2·0 g.) was diazotised in water (10 ml.) and 10N-hydrochloric acid (3 ml.) and the diazonium solution was added to cuprous cyanide (1·3 g.) in aqueous potassium cyanide (1·7 g.). The suspension was heated on a steam-bath for 20 min. and was then cooled; the resulting solid was collected and washed with dilute aqueous ammonium hydroxide and then extracted several times with hot ethanol. The ethanol was evaporated off and the residue was recrystallised from ethanol (charcoal) to give the cyano-compound (0·48 g., 23%), m.p. 319° (decomp.). Recrystallisation from ethyl acetate (charcoal) gave the *cyano-compound*, m.p. 322—326° (Found: C, 74·8; H, 4·0; N, 21·8. $C_{12}H_7N_3$ requires C, 74·6; H, 3·65; N, 21·75%).

2-*Methyl*-6-*nitro*-α-*carboline*.—Nitration of 2-methyl-α-carboline as described for 6-nitro-α-carboline gave 2-*methyl*-6-*nitro*-α-*carboline* (55%), m.p. 362—366° (lit.,[2] m.p. >350°) (Found: C, 63·65; H, 4·3; N, 18·3. $C_{12}H_9N_3O_2$ requires C, 63·4; H, 4·0; N, 18·5%).

6-*Amino*-2-*methyl*-α-*carboline*.—Reduction of the preceding compound as described for 6-amino-α-carboline gave 6-*amino*-2-*methyl*-α-*carboline* (78%), m.p. 282—285° (lit.,[2] m.p. 290°) (Found: C, 73·4; H, 5·5; N, 21·5. $C_{12}H_{11}N_3$ requires C, 73·1; H, 5·6; N, 21·3%). Acetylation on a steam-bath for 30 min. with a large excess of acetic anhydride in acetic acid gave 6-*acetamido*-9-*acetyl*-2-*methyl*-α-*carboline* (82%), m.p. 303—304° (Found: C, 68·1; H, 5·3; N, 15·2. $C_{16}H_{15}N_3O_2$ requires C, 68·3; H, 5·4; N, 14·9%).

4-*Methyl*-6-*nitro*-α-*carboline*.—Nitration of 4-methyl-α-carboline as described for 6-nitro-α-carboline gave 4-*methyl*-6-*nitro*-α-*carboline* (48%), m.p. 355—360° (from pyridine)

View Article Online

Published on 01 January 1970. Downloaded by University of Idaho Library on 31/10/2014 11:45:59.

(lit.,[2] m.p. >315°) (Found: C, 63·5; H, 4·0; N, 18·6. $C_{12}H_9N_3O_2$ requires C, 63·4; H, 4·0; N, 18·5%).

6-*Amino*-4-*methyl*-α-*carboline*.—Reduction of the preceding compound as described for 6-amino-α-carboline gave 6-*amino*-4-*methyl*-α-*carboline* (83%), m.p. 252—253° (lit.,[2] m.p. 245—247°) (Found: C, 72·9; H, 5·8; N, 21·0. $C_{12}H_{11}N_3$ requires C, 73·1; H, 5·6; N, 21·3%). Acetylation as described above gave 6-*acetamido*-4-*methyl*-α-*carboline* (56%), m.p. 326—329° (from ethanol) (Found: C, 70·5; H, 5·4; N, 17·6. $C_{14}H_{13}N_3O$ requires C, 70·3; H, 5·5; N, 17·6%). Acetylation of the amine for 30 min. on a steam-bath with a large excess of acetic anhydride in acetic acid gave 6-*acetamido*-9-*acetyl*-4-*methyl*-α-*carboline* (65%), m.p. 277—279° (from ethanol) (Found: C, 68·3; H, 5·1; N, 14·7. $C_{16}H_{15}N_3O_2$ requires C, 68·3; H, 5·4; N, 14·9%).

5-*Chloro*-1-α-*pyridylbenzotriazole*.— 2-Chloropyridine (16·0 g.) and 1,2-diamino-4-chlorobenzene [22] (20·0 g.) were heated together under nitrogen at 150° for 6 hr. The cooled reaction mixture was dissolved in hot ethanol (charcoal) and filtered; the filtrate was concentrated and treated with 5N-hydrochloric acid (300 ml.). The solution was added slowly with stirring at 0—5° to a cooled solution of sodium nitrite (20·0 g.) in water (200 ml.). The resultant solid was crystallised from methanol (charcoal) to give 5-*chloro*-1-1-*pyridylbenzotriazole* (7·35 g., 23%), m.p. 147—148·5°. A sample further recrystallised from methanol had m.p. 153·5—154° (lit.,[14] m.p. 152°) (Found: C, 57·1; H, 3·2; Cl, 15·5; N, 24·0. Calc. for $C_{11}H_7ClN_4$: C, 57·3; H, 3·1; Cl, 15·4; N, 24·3%).

2-o-*Aminoanilino*-5-*nitropyridine* (VII).—o-Phenylenediamine (1·0 g.), 2-chloro-5-nitropyridine (1·5 g.), and potassium carbonate (1·5 g.) were heated under reflux in water (20 ml.) and ethanol (4 ml.) for 4·5 hr. The solid that separated from the cooled solution was recrystallised from ethanol (charcoal) to give 2-o-*aminoanilino*-5-*nitropyridine* as red needles, (0·74 g., 35%), m.p. 182—183·5°; $\lambda_{max.}$ 352 nm. (ε 15,500) (Found: C, 57·4; H, 4·3; N, 23·9. $C_{11}H_{10}N_4O_2$ requires C, 57·4; H, 4·4; N, 24·3%).

1-(5-*Nitro*-2-*pyridyl*)*benzotriazole* (IV; $R^1 = NO_2$, $R^2 = H$).—Sodium nitrite (10·0 g.) in water (50 ml.) was added slowly at 0° to a stirred solution of 2-o-aminoanilino-5-nitropyridine (13·4 g.) in 5N-hydrochloric acid; the mixture was left overnight at room temperature. The resulting solid (14·5 g.), m.p. 238—242° was recrystallised from ethyl acetate (charcoal) to give the nitro-compound (9·14 g., 65%), m.p. 242·5—246°. A second recrystallisation from ethyl acetate gave 1-(5-*nitro*-2-*pyridyl*)*benzotriazole*, m.p. 244—247°; $\lambda_{max.}$ 319 nm. (ε 20,200) (Found: C, 54·7; H, 2·85; N, 29·0. Calc. for $C_{11}H_7N_5O_2$: C, 54·8; H, 2·9; N, 29·0%).

2-*Nitropyrido*[1,2-a]*benzimidazole* (VIII).—The preceding triazole (2·5 g.) and orthophosphoric acid (98%, 14 ml.) were heated under nitrogen for 30 min. at 160°. The reaction mixture was added to hot water and the cooled solution was filtered. The filtrate was neutralised with ammonia and the precipitated solid (0·51 g.) was recrystallised from ethanol (charcoal) to give 2-nitropyrido-[1,2-*a*]benzimidazole (0·26 g., 12%), m.p. 237—239°, identical (t.l.c., mixed m.p., and i.r. spectrum) with the compound described in the next two experiments.

Reaction of o-*Phenylenediamine with* 2-*Chloro*-5-*nitropyridine in Acid Solution*.—o-Phenylenediamine (4·0 g.) and 2-chloro-5-nitropyridine (6·0 g.) were heated in 2N-hydrochloric acid (25 ml.), water (56 ml.), and ethanol (16 ml.) on a steam-bath for 22 hr. The mixture was cooled and basified, and the precipitated solid was treated with 2N-hydrochloric acid. The suspension was filtered to leave a residual solid (A). Addition of ammonia to the filtrate gave a solid (B) which, on crystallisation from ethanol (charcoal) gave 2-*nitropyrido*[1,2-a]*benzimidazole* as yellow needles (4·55 g., 58%), m.p. 240—241°; $\lambda_{max.}$ 297—299 nm. (ε 28,000), τ(Me_2SO) — 0·38, 1·75, 2·35 (d, *J* 10) (pyridine ring), 1·20—2·60 (benzene ring) (Found: C, 62·1; H, 3·3; N, 19·5. Calc. for $C_{11}H_7N_3O_2$: C, 62·0; H, 3·3; N, 19·7%). The solid (A) was washed with aqueous sodium carbonate solution and with water and was then recrystallised from ethanol to give NN′-*bis*-(5-*nitro*-2-*pyridyl*)-o-*phenylenediamine* (VI) (0·60 g., 5%), m.p. 238·5—240°; $\lambda_{max.}$ 353 nm. (ε 34,600) (Found: C, 54·3; H, 3·7; N, 24·2. $C_{16}H_{12}N_6O_4$ requires C, 54·5; H, 3·4; N, 23·9%).

Reaction of 2-o-*Aminoanilinopyridine in Acid Solution*.—2-o-Aminoanilinopyridine (0·50 g.) was heated under reflux in 0·67N-hydrochloric acid (9 ml.) and ethanol (2 ml.) for 18 hr. Tne cooled mixture was basified with ammonia to give a precipitate (0·42 g.) which was recrystallised from ethanol to give 2-nitropyrido[1,2-*a*]benzimidazole as yellow needles (0·23 g., 50%), m.p. 240—243·5°; $\lambda_{max.}$ 297—299 nm. (ε 27,400).

Dehydrogenation of 2-*Nitro*-6,7,8,9-*tetrahydropyrido*[1,2-a]-*benzimidazole*.— 2-Nitro-6,7,8,9-tetrahydropyrido[1,2-*a*]-benzimidazole was prepared by the method of Campbell and McCall; [8] it had m.p. 218·5—220° (lit.,[8] m.p. 214—215°); $\lambda_{max.}$ 281—283 nm. (ε 22,800). The nitro-compound (1·5 g.) and chloranil (3·5 g.) were stirred and heated under reflux in xylene (60 ml.) for 24 hr. More chloranil (1·75 g.) was added, and the heating was continued for a further 20 hr. The mixture was cooled and filtered, and the filtrate was chromatographed in benzene on alumina (grade H; 150 g.). The fractions that were free of starting material and chloranil were evaporated to dryness and the residues (0·1 g.) were recrystallised from ethanol (charcoal) to give 2-nitropyrido[1,2-*a*]benzimidazole as yellow needles (0·06 g., 4%), m.p. 239—241°; $\lambda_{max.}$ 297—300 nm. (ε 28,200).

2-*Aminopyrido*[1,2-a]*benzimidazole*.— 2-Nitropyrido-[1,2-*a*]benzimidazlle (2·5 g.) in ethanol (250 ml.) was hydrogenated in the presence of 5% palladium charcoal at room temperature and pressure until the uptake of hydrogen ceased. The mixture was filtered and the solvent was evaporated off under reduced pressure; the residue in 2N-hydrochloric acid was treated with charcoal. The mixture was filtered and the filtrate was treated with ammonia to give 2-*aminopyrido*[1,2-a]*benzimidazole* (1·27 g., 60%), m.p. 220° (decomp.); $\lambda_{max.}$ 249, 315, 328 nm. (ε 35,600, 6600, 7100); $\nu_{max.}$ (Nujol) 3430, 3180 (NH_2); τ(Me_2SO) 4·92 (NH_2), 1·7, 2·8 (d, *J* 2·5) (Found: C, 71·9; H, 5·2; N, 22·6. Calc. for $C_{11}H_9N_3$: C, 72·1; H, 5·0; N, 22·9%). Acetylation at 40° with acetic anhydride gave 2-*acetamidopyrido*[1,2-a]*benzimidazole*, m.p. 230·5—231° (Found: C, 69·1; H, 4·8; N, 18·65. $C_{13}H_{11}N_3O$ requires C, 69·3; H, 4·9; N, 18·7%).

[9/1419 *Received, August 19th*, 1969]

[22] F. Ullmann and F. Mauthner, *Ber.*, 1903, **36**, 4027.