411. *The Constitution of Yohimbine and Related Alkaloids. Part X.* The Synthesis of Some* 12H-*Indolo*[2 : 3-a]*pyridocolinium Salts, including Flavocoryline and Flavopereirine.*

By K. B. Prasad and G. A. Swan.

A synthesis is described of 12*H*-indolo[2 : 3-*a*]pyridocolinium salts (II), the chromophore of sempervirine. As well as the parent compound, derivatives (XI) have been prepared in which R = H, Et, and Pr^{i}. Of these, the first two were identical with flavopereirine and flavocoryline respectively, but it was not possible to establish the identity of the third with flavocorynanthyrine. 3-Ethyl-2-(5-ethyl-4-*iso*propyl-2-pyridyl)indole (XV; R = Pr^{i}), a homologue of alstyrine, has also been synthesised.

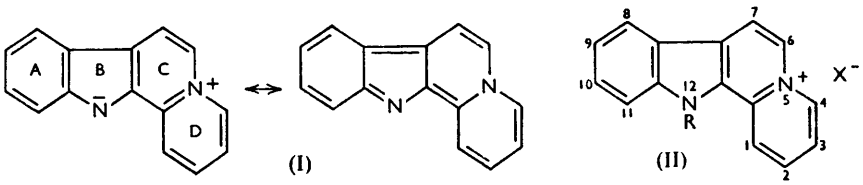
This and the following paper are concerned with a new synthetic route to rings A, B, C, and D of the yohimbine skeleton, with or without ring E. First, we synthesised the parent compound in the lowest possible state of hydrogenation and without substituents, *i.e.*, indolo[2 : 3-*a*]pyridocoline (I) [the salts being 12*H*-indolo[2 : 3-*a*]pyridocolinium salts (II; R = H)], the chromophore of sempervirine. This is here represented as a resonance hybrid of the covalent and the dipolar form, although Paolini and Marini-Bettolo [1] have

* Part IX, Lee and Swan, *J.*, 1956, 771.

[1] Paolini and Marini-Bettolo, *Nature*, 1957, **179**, 41.

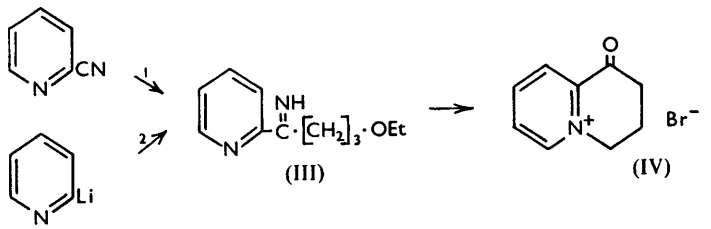
recently suggested that such anhydronium bases can be adequately represented by a purely covalent structure.

An earlier attempt by Bentley, Stevens, and Thompson (see Stevens [2]) to synthesise compound (I) failed, although the method used succeeded when a protective benzyl group



was present, giving the derivative (II; R = CH_2Ph). The latter compound has, however, apparently not been debenzylated.

Craig,[3] describing the preparation of 2-γ-ethoxybutyrylpyridine by the action of 3-ethoxypropylmagnesium bromide on 2-cyanopyridine, stated that the product was hydrolysed by 17% hydrochloric acid and ammonium chloride solution, apparently in the cold. We carried out a similar reaction except that we used excess of the Grignard reagent (thus obtaining a somewhat higher yield) and heated the product for 20 min. with



1, Br·Mg·$[CH_2]_3$·OEt. 2, NC·$[CH_2]_3$·OEt.

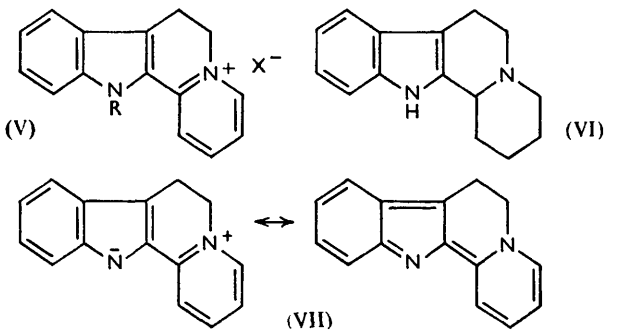
2N-sulphuric acid at 100°. Our product was, however, the imine (III) rather than the ketone, as shown by analysis and a strong absorption band at 3376 cm.$^{-1}$ (N–H). A band was also present at 1681 cm.$^{-1}$, but we were unable to decide whether this would be due to C=O or C=N. The use of hydrochloric acid gave a product which was essentially the same. For both our purposes and those of Craig it would be immaterial whether the ketone or imine was obtained. Craig converted his material into an oxime and our product gave the 2 : 4-dinitrophenylhydrazone of the expected ketone. The next step in our synthesis involved refluxing the ketone or imine with hydrobromic acid in acetic acid, after which there was no doubt that the imine had been hydrolysed. From this reaction we had expected to obtain the hydrobromide of 2-γ-bromobutyrylpyridine; but evaporation of the solution yielded a crystalline product, m. p. 205° (decomp.), which was clearly a quaternary salt and proved to be 1 : 2 : 3 : 4-tetrahydro-1-oxopyridocolinium bromide (IV). As cyclisation could scarcely occur in the strongly acidic reaction mixture, it seems that it must have happened during evaporation of the solution.[4] More than a year after we had prepared this compound, Glover and Jones [5] described the preparation of the same compound (for which they give m. p. 197°) in a similar way, except that they carried out the final cyclisation in chloroform and do not comment on Craig's alleged ketone.

We also investigated certain variants on the first stage of the synthesis. Attempts to use 3-phenoxypropyl bromide for the preparation of a Grignard reagent were unsuccessful, magnesium bromide being precipitated.[6] Use of 3-ethoxypropyl-lithium was also examined, but this reagent was obtained in only low yield by the action of lithium on the bromide in

[2] Stevens, *Chem. Soc. Special Publ.*, No. 3, 1955, p. 19.
[3] Craig, *J. Amer. Chem. Soc.*, 1934, **56**, 1144.
[4] Cf. Wieland and Neeb, *Annalen*, 1956, **600**, 161.
[5] Glover and Jones, *Chem. and Ind.*, 1956, 1456.
[6] Cf. Winterfeld and Holschneider, *Ber.*, 1933, **66**, 1751.

ether. The action of 2-pyridyl-lithium on γ-ethoxybutyronitrile however provided an alternative route, although the yield was somewhat lower than that from the method first described, and the use of γ-phenoxybutyronitrile was even less successful.

Ethanolic hydrogen chloride cyclised the phenylhydrazone of 1 : 2 : 3 : 4-tetrahydro-1-oxopyridocolinium bromide with formation of 6 : 7-dihydro-12*H*-indolo[2 : 3-*a*]pyridocolinium chloride (V; R = H, X = Cl), the structure of which was confirmed by absorption



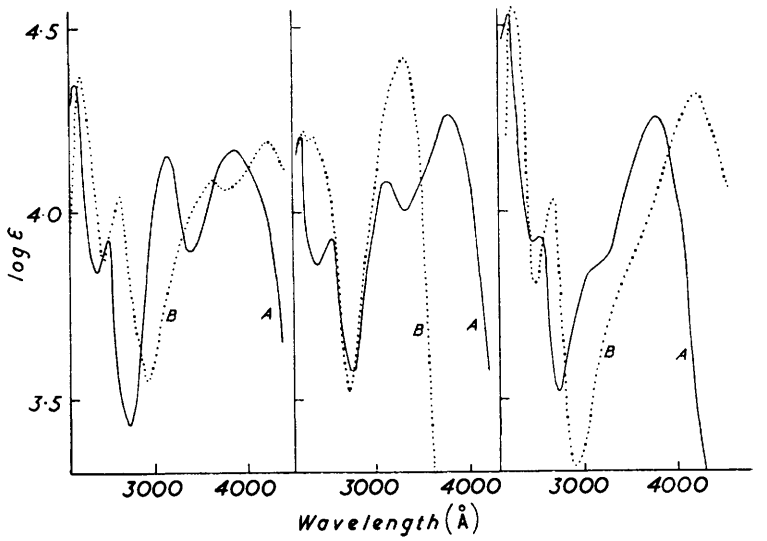
of three mols. of hydrogen in the presence of Adams catalyst, giving the octahydro-compound (VI), identical with a sample previously synthesised by Groves and Swan [7] by a different method (this compound has also been prepared by Keufer [8]). The ultraviolet absorption spectra in acid and alkaline solutions are shown in Fig. 1 and correspond with a change in structure from (V) to (VII).

For comparison the spectra of 2-2′- and 2-4′-pyridylindole and their respective methiodides are shown in Figs. 2—5. The spectrum of 2-2′-pyridylindole was identical in alkaline and in neutral solution and that of the corresponding methiodide was identical in acid and in neutral solution. The same applies to the 4′-pyridyl compounds. The alkaline spectra of the two bases resembled that of 2-phenylindole.[9] In acid solution the possibility of resonance involving structures (VIII and VIIIa; R = H or Me) is introduced and the spectrum of 6 : 7-dihydro-12*H*-indolo[2 : 3-*a*]pyridocolinium chloride is then rather similar to that of 2-2′-pyridylindole and of the methiodide of the latter, although the intensity of the band at 3140 Å diminishes in the order in which these three compounds are mentioned, probably owing to diminishing coplanarity. (For alstyrine, in acid solution, this band is represented by only a shoulder.) The spectra of 6 : 7-dihydro-12*H*-indolo[2 : 3-*a*]pyridocolinium chloride and 2-2′- and 2-4′-pyridylindole methiodide in alkaline solution suggest that all three compounds may yield anhydronium bases, although Gray and Archer [10] did not consider that their electrometric titrations pointed to this in the last case. The possibility, however, that this compound may exist in alkaline solution as a pseudo-base rather than an anhydronium base (IX) is not excluded.

That the change in structure which compound (V) undergoes in alkaline solution depends on the hydrogen atom attached to the indole-nitrogen atom was shown as follows. Addition of concentrated aqueous sodium hydroxide to a solution of the chloride gave a bright red solid, which, when treated with methyl iodide, yielded 6 : 7-dihydro-12-methyl-12*H*-indolo[2 : 3-*a*]pyridocolinium iodide (V; R = Me, X = I), identical with that obtained by a Fischer indole reaction on the 1-methyl-1-phenylhydrazone of 1 : 2 : 3 : 4-tetrahydro-1-oxopyridocolinium bromide. The spectrum of this compound was almost identical with that of the chloride (V; R = H, X = Cl) in acid solution, and did not change on addition of alkali.

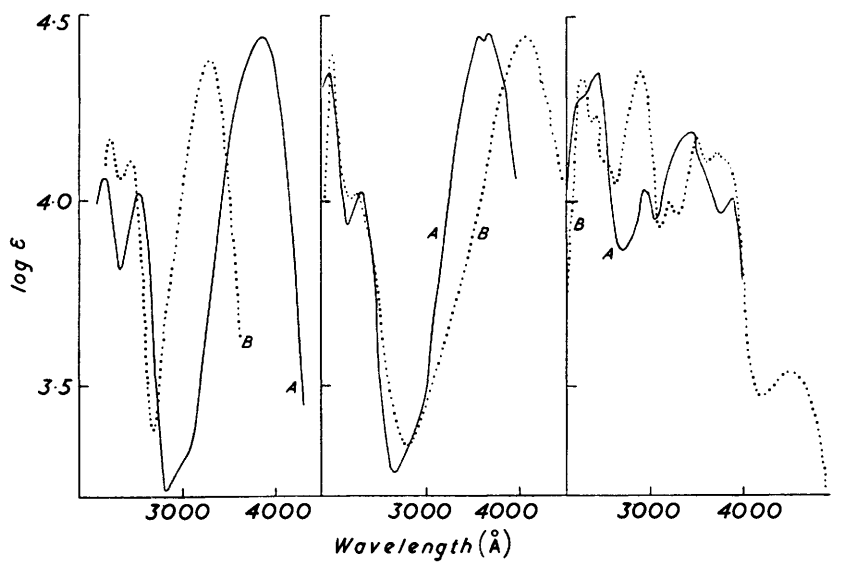
[7] Groves and Swan, *J.*, 1952, 650.
[8] Keufer, *Ann. pharm. franç.*, 1950, **8**, 816.
[9] Carlin, Wallace, and Fisher, *J. Amer. Chem. Soc.*, 1952, **74**, 990.
[10] Gray and Archer, *ibid.*, 1957, **79**, 3554.

FIG. 1. FIG. 2. FIG. 3.



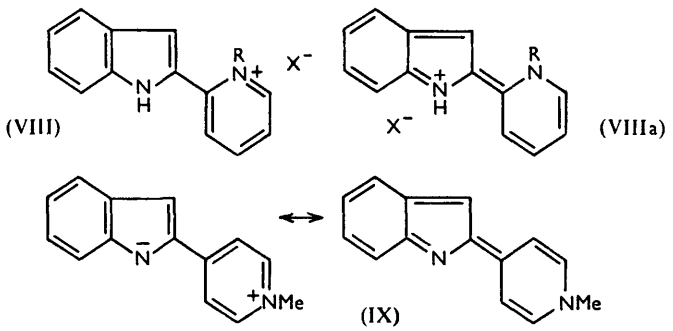
Absorption spectra of: FIG. 1, 6 : 7-*dihydro*-12H-*indolo*[2 : 3-a]*pyridocolinium chloride* (*A, acid or neutral; B, alkaline*); FIG. 2, 2-2′-*pyridylindole* (*A, acid; B, neutral or alkaline*); FIG. 3, 2-2′-*pyridylindole methiodide* (*A, acid or neutral; B, alkaline*).

FIG. 4. FIG. 5. FIG. 6.

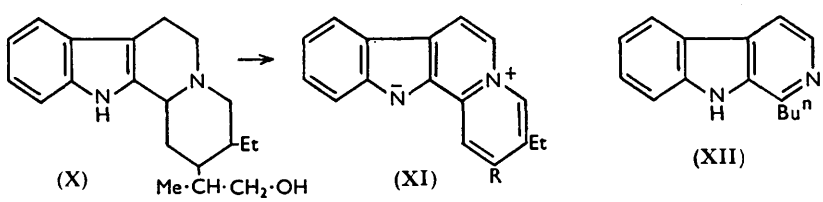


Absorption spectra of: FIG. 4, 2-4′-*pyridylindole* (*A, acid; B, alkaline or neutral*); FIG. 5, 2-4′-*pyridylindole methiodide* (*A, acid or neutral; B, alkaline*); FIG. 6, 12H-*indolo*[2 : 3-a]*pyridocolinium chloride* (*A, acid or neutral; B, alkaline*).

We had thought that dehydrogenation of 6 : 7-dihydro-12*H*-indolo[2 : 3-*a*]pyridocolinium chloride would be effected readily since Schwyzer [11] had shown that a compound of structure (X) (obtained by degradation of corynantheine), when heated with acidic palladium–charcoal, was dehydrogenated to flavocorynanthyrine to which he attributed



structure (XI; R = Et or, less probably, Pr^i). However, in the case of our compound, a similar dehydrogenation failed. Moreover, the chloride was recovered unchanged after being refluxed with chloranil in butanol solution or shaken in acetic acid with oxygen in the presence of freshly reduced Adams catalyst (no absorption). Also, heating 1 : 2 : 3 : 4 : 6 : 7 : 12 : 12b-octahydroindolo[2 : 3-*a*]pyridocoline with acidic palladium–charcoal yielded a product thought to be 1-butyl-β-carboline (XII) as its solution in acids showed a blue-violet fluorescence at great dilution and its ultraviolet spectrum closely resembled that recorded for β-carboline by Spenser.[12]



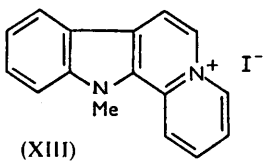
Braude, Brook, and Linstead's [13] systematic study of the use of high-potential quinones for dehydrogenation has not previously been extended to heterocyclic compounds. However, we found tetrachloro-*o*-benzoquinone to be very effective and this enabled us to prepare 12*H*-indolo[2 : 3-*a*]pyridocolinium chloride from its 6 : 7-dihydro-derivative by reaction at 100° in acetic acid or in refluxing ethanol (in the latter case excess of the quinone was used, as part was probably used up in reaction with the solvent). The absorption spectra of the product in neutral and alkaline solution (Fig. 6) correspond to structures (II) and (I) respectively, and resemble very closely those of sempervirine under corresponding conditions. The fully dehydrogenated chloride and its dihydro-derivative show a striking difference in dilute solution under ultraviolet irradiation, the former being brilliantly blue-fluorescent and the latter greenish-yellow (this applies also to the homologues described below).

Basification of an aqueous solution of the dehydrogenated chloride yielded a product which with methyl iodide gave 12-methylindolo-12*H*-[2 : 3-*a*]pyridocolinium iodide (XIII), the spectrum of which was rather similar to that of the original salt (II) in neutral solution, but was little changed in the presence of alkali, except that the band at 2930 Å slowly disappeared on storage. This was thought to indicate the slow formation of a pseudo-base

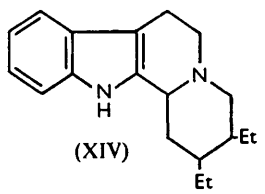
[11] Schwyzer, *Helv. Chim. Acta*, 1952, **35**, 867.
[12] Spenser, *J.*, 1956, 3659.
[13] Braude, Brook, and Linstead, *J.*, 1954, 3569.

in alkaline solution (compare the case of 7 : 8-dihydro-13*H*-benz[*g*]indolo[2 : 3-*a*]pyridocolinium chloride in the following paper, where a band at 2810 Å disappears in alkaline solution).

We also synthesised 2 : 3-diethylindolo[2 : 3-*a*]pyridocoline (XI; R = Et) by a similar route to the above from 2-cyano-4 : 5-diethylpyridine. This was of interest because it had the structure suggested for flavocoryline by Goutarel, Janot, and Perezamador y Barron [14] and for flavocorynanthyrine by Schwyzer,[11] although the last author admitted that his compound might be 3-ethyl-2-*iso*propylindolo[2 : 3-*a*]pyridocoline (XI; R = Pr^i). Moreover, a compound believed to have structure (XIV) has been obtained by Janot and



(XIII)



(XIV)

Goutarel [15] by degradation of corynantheine and we hoped it might be possible to cast light on the stereochemistry of the alkaloid by studying the stereospecific hydrogenation of our synthetic compound, but unsuccessfully. In surprising contrast to the lower homologue, both 2 : 3-diethyl-12*H*-indolo[2 : 3-*a*]pyridocolinium chloride and its 6 : 7-dihydro-derivative failed to absorb hydrogen in acetic acid solution in the presence of Adams catalyst at 20°/760 mm.

The final dehydrogenation step of the synthesis was again carried out by tetrachloro-*o*-benzoquinone. Attempts to dehydrogenate the free base by heating it with palladium–charcoal at 290° gave a product, the light absorption of which ($\lambda_{max.}$ 3200 Å, $\lambda_{min.}$ ~2800 Å) corresponded to that of alstyrine, so that evidently fission of ring c had occurred. A similar attempt using the chloride led to the recovery of part of it unchanged.

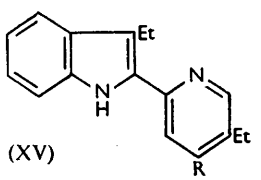
The ultraviolet spectra of the synthetic 2 : 3-diethylindolo[2 : 3-*a*]pyridocoline in neutral and alkaline solutions resembled those recorded by Schwyzer [11] for flavocorynanthyrine, and for flavocoryline by Goutarel *et al.*[14] The melting point of the base was 150—151°, while those recorded for flavocorynanthyrine and flavocoryline are 110—112° and 161—162°, respectively. We were, however, able to establish the identity of the perchlorate of the synthetic base with a sample of flavocoryline perchlorate, kindly supplied by Professor Janot, by mixed melting point and infrared spectra.

We also synthesised 3-ethyl-2-*iso*propylindolo[2 : 3-*a*]pyridocoline (XI; R = Pr^i). The required 2-cyano-5-ethyl-4-*iso*propylpyridine was synthesised from 4-acetyl-5-ethyl-4-methylpyridine by reaction with methylmagnesium iodide, followed by treatment of the resulting tertiary alcohol with hydrogen iodide to give 5-ethyl-2-methyl-4-*iso*propylpyridine. The infrared spectrum of this was almost indistinguishable from that of 4 : 5-diethyl-2-methylpyridine, but a band at 1365 cm.$^{-1}$ in the former was absent in the latter. The base was converted into the nitrile by standard methods, *via* 5-ethyl-4-*iso*propylpyridine-2-carboxylic acid, decarboxylation of which yielded 3-ethyl-4-*iso*propylpyridine, the picrate of which was identical with a sample synthesised by Karrer and Mainoni.[16] The yellow synthetic base (XI; R = Pr^i) was initially crystallised from aqueous ethanol and had m. p. 117—118°, softening at 113°. Schwyzer gave m. p. 110—112° for flavocorynanthyrine and it seemed that the synthetic compound might be identical with that of natural origin, although unfortunately it was not possible to obtain a sample of the latter. Later, however we recrystallised our base from methanol and obtained crystals melting at 204°, which, when recrystallised from the same solvent, gave a product of apparently the same composition but of m. p. 149°.

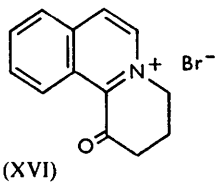
[14] Goutarel, Janot, and Perezamador y Barron, *Bull. Soc. chim. France*, 1954, 863.
[15] Janot and Goutarel, *ibid.*, 1951, 588.
[16] Karrer and Mainoni, *Helv. Chim. Acta*, 1953, **36**, 127.

Bejar, Goutarel, Janot, and Le Hir [17] have deduced structure (XI; R = H) for the alkaloid flavopereirine and we have synthesised a compound of this structure from 2-cyano-5-ethylpyridine. The perchlorate of our base was shown to be identical with a sample of the alkaloid perchlorate, kindly supplied by Professor Janot, by mixed melting point and infrared spectra.

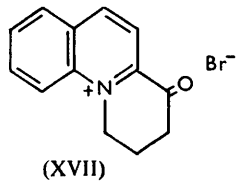
As we had prepared 2-cyano-5-ethyl-4-*iso*propylpyridine, we took the opportunity of synthesising 3-ethyl-2-(5-ethyl-4-*iso*propyl-2-pyridyl)indole (XV; R = Pr^i), a homologue of alstyrine (XV; R = Et). The melting point of this base (103—104°) is rather close to that of alstyrine (110—111°) and scarcely any depression occurs on mixing them. It is thus possible that the presence of the *iso*propyl compound in the alstyrine obtained by dehydrogenation of alkaloids might escape notice and it should be mentioned that Karrer, Schwyzer, and Flam [18] were able to detect its presence in the dehydrogenation product of demethoxytetrahydrocorynantheine alcohol only by further degradation.



(XV)



(XVI)



(XVII)

Speculation that certain highly potent calabash-curare alkaloids might contain a hexahydrobenzindolopyridocoline nucleus led Boekelheide *et al.* [19,20] to synthesise 5 : 6 : 8 : 9 : 14 : 14a-hexahydrobenz[*e*]indolo[2 : 3-*a*]pyridocoline. However, the methochloride of this base displayed only low curariform activity. We also prepared 5 : 7 : 8 : 13 : 13b : 14-hexahydrobenz[*g*]indolo[2 : 3-*a*]pyridocoline methochloride and Dr. W. D. M. Paton kindly carried out tests on this compound; but it proved to have less than one-tenth of the activity of (+)-tubocurarine. We also attempted to synthesise 8 : 9-dihydro-14*H*-benz[*h*]- and 6 : 7-dihydro-12*H*-benz[*f*]-indolo[2 : 3-*a*]pyridocolinium chloride from 1-cyano*iso*quinoline and 2-cyanoquinoline, respectively, following our general synthetic method. Although we thus succeeded in preparing the bromides (XVI) and (XVII), the phenylhydrazones were recovered unchanged from an attempted Fischer indole reaction.

Experimental

Ultraviolet absorption measurements were made with a Hilger " Uvispec " spectrophotometer. Those referred to as " alkaline " were made in 0·015N-ethanolic potassium hydroxide and those referred to as " acid " were in ethanolic hydrogen chloride. Difficulty was experienced in obtaining satisfactory analytical results on some of the salts described in this paper, probably owing to solvation. Unless otherwise stated, analytical samples were dried in a vacuum-desiccator at room temperature. M.p.s were measured in open capillaries.

2-*γ-Ethoxybutyrylpyridine*.—(*a*) 2-Cyanopyridine (2·5 g.) in ether (50 ml.) was added during 10 min. to an ice-cooled and stirred Grignard reagent, prepared from magnesium (1·2 g.), 1-bromo-3-ethoxypropane [21] (8 g.), and ether (30 ml.). The mixture was then refluxed for 3 hr., cooled in ice, and treated gradually, with stirring, with water (20 ml.) and 5N-sulphuric acid (70 ml.). The ethereal layer was extracted with 2N-sulphuric acid (2 × 70 ml.). The acid extracts were heated on a water-bath for 20 min., cooled, basified with saturated potassium carbonate solution, and extracted with chloroform. Distillation of the dried (K_2CO_3) extract gave a colourless liquid (3·2 g.), b. p. 90—98°/0·6 mm., 145°/11 mm., apparently consisting mainly of the *imine* (III), corresponding to the above ketone (Found: C, 68·7; H, 8·55; N, 15·8. $C_{11}H_{16}ON_2$ requires C, 68·75; H, 8·35; N, 14·6%).

[17] Bejar, Goutarel, Janot, and Le Hir, *Compt. rend.*, 1957, **244**, 2066.
[18] Karrer, Schwyzer, and Flam, *Helv. Chim. Acta*, 1952, **35**, 851.
[19] Boekelheide and Ainsworth, *J. Amer. Chem. Soc.*, 1950, **72**, 2134.
[20] Boekelheide and Liu, *ibid.*, 1952, **74**, 4920.
[21] Smith and Sprung, *ibid.*, 1943, **65**, 1276.

(*b*) When the Grignard complex was decomposed by hydrochloric acid (concentrated acid, 15 ml.; water, 15 ml.) and the subsequent heating was omitted, the product (2·25 g.), b. p. 160°/20 mm., again appeared to be mainly the imine, as a strong band was present at 3357 $cm.^{-1}$ (Found: C, 69·25; H, 8·4%).

(*c*) A fresh solution of *n*-butyl-lithium in ether (the double titration method of Gilman and Haubein [22] showed that 1 ml. of this solution was equivalent to 1·44 ml. of N-hydrochloric acid) (8 ml.) was stirred at −50° in nitrogen while 2-bromopyridine (2 g.) in ether was added. After the mixture had been stirred for a further 15 min., a solution of γ-ethoxybutyronitrile [23] (2 g.) in ether was added. After 15 min. at −50°, the mixture was allowed to come to room temperature and stirred for a further 1 hr. Water (15 ml.) and 2N-sulphuric acid (8 ml.) were added and the product (0·75 g.), b. p. 150°/15 mm., was worked up as in (*a*).

Treatment of the above products with warm, ethanolic 2 : 4-dinitrophenylhydrazine containing a few drops of hydrobromic acid yielded the 2 : 4-dinitrophenylhydrazone hydrobromide of the ketone, as orange-yellow needles, m. p. 197°. When this was shaken with chloroform and dilute sodium carbonate solution, the dried (Na_2SO_4) chloroform layer yielded the free 2 : 4-*dinitrophenylhydrazone*, which separated from benzene–light petroleum as yellow prisms, m. p. 137° (Found: C, 55·1; H, 5·2. $C_{17}H_{19}O_5N_5$ requires C, 54·70; H, 5·1%).

1 : 2 : 3 : 4-*Tetrahydro*-1-*oxopyridocolinium Bromide* (IV).—The above imine (3 g.) was refluxed for 15 hr. in a current of nitrogen with acetic acid (18 ml.) and constant-boiling hydrobromic acid (9 ml.). The solution was evaporated to dryness (water-bath/reduced pressure) and the residue was dissolved in a small volume of methanol and diluted with acetone. On cooling, the *bromide* (2·75 g.) separated as colourless needles, m. p. 205° (decomp.) (Found: C, 46·2; H, 5·7. $C_9H_{10}ONBr,CH_4O$ requires C, 46·15; H, 5·4%). The corresponding *picrate* separated from ethanol as needles, m. p. 147—148° (Found: C, 47·7; H, 3·2. $C_{15}H_{12}O_8N_4$ requires C, 47·85; H, 3·2%). The 2 : 4-*dinitrophenylhydrazone* of the bromide separated from ethanol as orange-yellow needles, m. p. 192° (decomp.), darkening at 183° (Found: C, 44·95; H, 4·55. $C_{15}H_{14}O_4N_5Br,C_2H_6O$ requires C, 44·9; H, 4·4%), and from acetic acid as pale yellow prisms, m. p. 249—250° (decomp.), becoming red at 220° (Found: C, 42·7; H, 4·3. $C_{15}H_{14}O_4N_5Br,3C_2H_4O_2$ requires C, 42·85; H, 4·4%). With dilute sodium hydroxide solution this yielded a deep blue-violet colour, soluble in chloroform.

The bromide (1·5 g.), phenylhydrazine hydrochloride (0·9 g.), and crystalline sodium acetate (3 g.) were dissolved separately each in a minimum volume of water, mixed, and heated for 3 hr. on a water-bath. On cooling, the resulting solid (2·1 g.) was collected and washed with water; a little more of it was obtained on addition of saturated sodium bromide solution to the filtrate. This *phenylhydrazone* of the bromide separated from ethanol–ether as orange-brown prisms, m. p. 271° (decomp.) (for analysis dried for 24 hr. at 105°/1 mm.) (Found: C, 55·1; H, 5·2. $C_{15}H_{16}N_3Br,0{\cdot}5H_2O$ requires C, 55·05; H, 5·2%). The corresponding *phenylhydrazone picrate* separated from dimethylformamide–ethanol as orange-red crystals, m. p. 225° (decomp.) (Found: C, 54·7; H, 3·95. $C_{21}H_{18}O_7N_6$ requires C, 54·1; H, 3·9%).

6 : 7-*Dihydro*-12H-*indolo*[2 : 3-a]*pyridocolinium Chloride* (V; R = H, X = Cl).—A solution of the phenylhydrazone of 1 : 2 : 3 : 4-tetrahydro-1-oxopyridocolinium bromide (1·5 g.) in absolute ethanol (45 ml.) was cooled in ice, saturated with dry hydrogen chloride, kept at room temperature for 1 hr., and then refluxed for 5 hr. The mixture was kept overnight at 0° and the product was collected, washed with ice-cold ethanol, and recrystallised from methanol–ethanol, giving the *chloride* (1·2 g.) as bright yellow needles, m. p. 340° (decomp.) (Found: C, 65·2; H, 5·8. $C_{15}H_{13}N_2Cl,H_2O$ requires C, 65·55; H, 5·45%). Light absorption: (*a*) acid, $\lambda_{max.}$ 2170, 2520, 3140, and 3850 Å (log ε 4·35, 3·93, 4·15, and 4·16), $\lambda_{min.}$ 2390, 2745, and 3410 Å (log ε 3·83, 3·42, and 3·89); (*b*) alkaline, $\lambda_{max.}$ 2230, 2645, 3630, and 4200 Å (log ε 4·37, 4·04, 4·09, and 4·19), $\lambda_{min.}$ 2490, 2940, and 3780 Å (log ε 3·87, 3·55, and 4·06).

The corresponding *picrate* separated from dimethylformamide–methanol as needles, m. p. 249° (decomp.) (Found: C, 55·9; H, 3·45. $C_{21}H_{15}O_7N_5$ requires C, 56·1; H, 3·35%). Addition of saturated sodium nitrate solution to an aqueous solution of the chloride precipitated the *nitrate*, which separated from ethanol as orange-yellow needles, m. p. 259° (decomp.) (Found: C, 63·65; H, 4·8. $C_{15}H_{13}O_3N_3$ requires C, 63·6; H, 4·6%).

2-2′-*Pyridylindole Methiodide* (VIII; R = Me, X = I).—2-Acetylpyridine phenylhydrazone was recovered unchanged after an attempt to effect a Fischer indole reaction in refluxing

[22] Gilman and Haubein, *J. Amer. Chem. Soc.*, 1944, **66**, 1515.
[23] Wertheim, *ibid.*, 1934, **56**, 735.

ethanolic hydrogen chloride. However, the reaction succeeded by the use of polyphosphoric acid, as described by Sugasawa, Terashima, and Kanaoka.[24] The resulting 2-2′-pyridylindole was largely unchanged when refluxed for 7 hr. with excess of methyl iodide, and the *methiodide* was therefore prepared by 20 hours' heating at 100°. It was isolated by dilution with ether and separated from methanol as yellow needles, m. p. 238° (Found: C, 47·4; H, 4·2. $C_{14}H_{13}N_2I,H_2O$ requires C, 47·45; H, 4·25%). Light absorption: (*a*) acid, $\lambda_{max.}$ 2180, 2520, and 3730 Å (log ε 4·53, 3·93, and 4·25), $\lambda_{min.}$ 2450 and 2750 Å (log ε 3·93 and 3·51); (*b*) alkaline, $\lambda_{max.}$ 2200, 2640, and 4150 Å (log ε 4·56, 4·03, and 4·31), $\lambda_{min.}$ 2470 and 2900 Å (log ε 3·80 and 3·32). Light absorption of 2-2′-pyridylindole: (*a*) acid, $\lambda_{max.}$ 2170, 2510, 3090, and 3760 Å (log ε 4·21, 3·94, 4·09, and 4·27), $\lambda_{min.}$ 2350, 2730, and 3290 Å (log ε 3·86, 3·57, and 4·00); (*b*) neutral, $\lambda_{max.}$ 2200, 2290, and 3250 Å (log ε 4·22, 4·21, and 4·42), $\lambda_{min.}$ 2250 and 2710 Å (log ε 4·19 and 3·52). Light absorption of 2-(4 : 5-diethyl-2-pyridyl)-3-ethylindole: (*a*) acid, $\lambda_{max.}$ 2230 and 3710 Å (log ε 4·53 and 4·19), $\lambda_{min.}$ 2750 Å (log ε 3·55); (*b*) neutral, $\lambda_{max.}$ 3250 Å (log ε 4·39), $\lambda_{min.}$ 2740 Å (log ε 3·71). Light absorption of 2-4′-pyridylindole: (*a*) acid, $\lambda_{max.}$ 2170, 2530, and 3850 Å (log ε 4·06, 4·02, and 4·44), $\lambda_{min.}$ 2340 and 2830 Å (log ε 3·82 and 3·21); (*b*) neutral, $\lambda_{max.}$ 2240, 2450, and 3300 Å (log ε 4·17, 4·11, and 4·38), $\lambda_{min.}$ 2350 and 2690 Å (log ε 4·06 and 3·37). Light absorption of 2-4′-pyridylindole methiodide: (*a*) acid, $\lambda_{max.}$ 2200, 2550, 3800, and 3900 Å (log ε 4·34, 4·02, 4·44, and 4·44), $\lambda_{min.}$ 2500, 2900, and 3840 Å (log ε 3·93, 3·26, and 4·42); (*b*) alkaline, $\lambda_{max.}$ 2220, 2500, and 4300 Å (log ε 4·40, 4·02, and 4·43), $\lambda_{min.}$ 2450 and 3020 Å (log ε 4·00 and 3·33).

1 : 2 : 3 : 4 : 6 : 7 : 12 : 12*b*-*Octahydro*-12H-*indolo*[2 : 3-a]*pyridocoline* (VI).—The above chloride (V; R = H, X = Cl) (80·6 mg.) in acetic acid (10 ml.) absorbed 20·5 ml. of hydrogen at 18°/760 mm. during 4 hr. in the presence of freshly reduced Adams catalyst. Towards the end of the hydrogenation the sparingly soluble colourless hydrochloride of the product separated and the yellow colour of the solution disappeared. Before filtration, the solution was heated to dissolve this salt, and the filtrate was evaporated to dryness (water-bath; reduced pressure). The residue was recrystallised twice from ethanol, giving the hydrochloride, m. p. 302° (decomp.). An aqueous solution of this was basified with sodium hydroxide; the resulting base (VI) separated from light petroleum (b. p. 60—80°) as colourless prisms, m. p. 150° (Found: C, 79·55; H, 8·3. Calc. for $C_{15}H_{18}N_2$: C, 79·65; H, 8·0%). When mixed with a sample (m. p. 147—148°) synthesised by Groves and Swan,[7] it had m. p. 149°.

6 : 7-*Dihydro*-12-*methylindolo*-12H-[2 : 3-a]*pyridocolinium Iodide* (V; R = Me, X = I).—(*a*) 1 : 2 : 3 : 4-Tetrahydro-1-oxopyridocolinium bromide (0·25 g.) was treated with 1-methyl-1-phenylhydrazine (0·17 g.) in the presence of N-hydrochloric acid (1·5 ml.) and crystalline sodium acetate (0·75 g.) as described above for the corresponding phenylhydrazone. The resulting 1 : 2 : 3 : 4-*tetrahydro*-1-*oxopyridocolinium* 1-*methyl*-1-*phenylhydrazone* was, however, isolated as the *iodide* (0·37 g.), the bromide being too soluble in water, by addition of saturated potassium iodide solution to the reaction mixture. This separated from ethanol as orange needles, m. p. 203° (for analysis dried for 2·5 hr. at 95°/0·5 mm.) (Found: C, 50·5; H, 4·85. $C_{16}H_{18}N_3I$ requires C, 50·65; H, 4·75%). This was subjected to a Fischer indole reaction, as above, and the resulting solution was concentrated to one-third of its volume and kept at 0°; then ammonium chloride and a small amount of brown solid were removed by filtration. The filtrate was evaporated to dryness (water-bath; reduced pressure), the residue was dissolved in water, and the solution filtered and treated with saturated potassium iodide solution. The precipitated *iodide* (V; R = Me, X = I) was collected, washed with water, and recrystallised from methanol, affording deep yellow needles, m. p. 295° (decomp.) (Found: C, 50·45; H, 4·4. $C_{16}H_{15}N_2I,H_2O$ requires C, 50·55; H, 4·45%). Light absorption: (*a*) acid, $\lambda_{max.}$ 2120, 2510, 3150, and 3780 Å (log ε 4·60, 4·07, 4·10, and 4·21), $\lambda_{min.}$ 2400, 2760, and 3370 Å (log ε 3·99, 3·38, and 3·95); (*b*) alkaline, $\lambda_{max.}$ 2530, 3150, and 3770 Å (log ε 4·06, 4·09, and 4·19), $\lambda_{min.}$ 2400, 2750, and 3380 Å (log ε 3·97, 3·34, and 3·92).

(*b*) A solution of 6 : 7-dihydro-12*H*-indolo[2 : 3-*a*]pyridocolinium chloride in a small volume of water was treated with 40% sodium hydroxide solution; a bright red precipitate was collected, washed with a little cold water, and dried for 2 days in a vacuum-desiccator. It was then mixed with excess of methyl iodide, kept overnight at room temperature, then refluxed for 1 hr. The residue left on evaporation was recrystallised twice from methanol, affording the *iodide* (V; R = Me, X = I) as deep yellow needles, m. p. 292° (decomp.); when mixed with a specimen prepared according to (*a*) it had m. p. 295° (decomp.).

[24] Sugasawa, Terashima, and Kanaoka, *Pharm. Bull.* (*Japan*), 1956, **4**, 16.

Dehydrogenation of 1 : 2 : 3 : 4 : 6 : 7 : 12 : 12*b*-*Octahydro*-12H-*indolo*[2 : 3-a]*pyridocoline*.—The temperature of a mixture of the base (VI) (50 mg.) and acidic palladium–charcoal [11] (100 mg.) was gradually raised to 260° during 20 min. Hydrogen evolution began at 200° and ceased at 260°. After cooling, the mixture was extracted with methanol. The residue left on evaporation of the extract was dissolved in warm, dilute hydrochloric acid, and the solution was basified with aqueous ammonia, and extracted with ether. The solvent was removed from the dried (K_2CO_3) extract, leaving an oil which rapidly crystallised, giving 1-*butyl*-β-*carboline* (XII), which separated from benzene–light petroleum (charcoal) as cream-coloured prisms (20 mg.), m. p. 166° Found: C, 79·75; H, 7·25. $C_{15}H_{16}N_2$ requires C, 80·35; H, 7·15%). Light absorption in EtOH: $\lambda_{max.}$ 2350, 2900, 3340, and 3500 Å (log ε 4·61, 4·24, 3·73, and 3·75), $\lambda_{min.}$ 2680, 3000, and 3450 Å (log ε 3·73, 3·10, and 3·68).

12H-*Indolo*[2 : 3-a]*pyridocolinium Chloride* (II; R = H, X = Cl).—The 6 : 7-dihydro-compound (V; R = H, X = Cl) (80 mg.) in ethanol (10 ml.) was refluxed for 15 hr. with tetrachloro-*o*-benzoquinone (0·4 g.), the solvent was removed, and the residue crystallised from methanol–ether, giving the *chloride* (35 mg.) as pale yellow needles, decomp. 295° (Found: C, 65·6; H, 4·9. $C_{15}H_{11}N_2Cl,H_2O$ requires C, 66·05; H, 4·8%). Light absorption: (*a*) acid, $\lambda_{max.}$ 2440, 2940, 3450, and 3880 Å (log ε 4·43, 4·12, 4·27, and 4·10), $\lambda_{min.}$ 2680, 3050, and 3770 Å (log ε 3·96, 4·03, and 4·05); (*b*) alkaline, $\lambda_{max.}$ 2270, 2410, 2890, 3200, 3490, 3700, and 4490 Å (log ε 4·42, 4·32, 4·43, 4·09, 4·26, 4·22, and 3·63), $\lambda_{min.}$ 2370, 2620, 3100, 3280, 3600, and 4180 Å (log ε 4·30, 4·13, 4·02, 4·05, 4·19, and 3·57). The corresponding picrate separated from dimethylformamide–ethanol as needles, m. p. 252—253° (decomp.).

12-*Methylindolo*-12H-[2 : 3-a]*pyridocolinium Iodide* (XIII).—This *iodide* was prepared from the above chloride in essentially the manner described under (*b*) for 6 : 7-dihydro-12-methyl-12*H*-indolo[2 : 3-*a*]pyridocolinium iodide and, after being recrystallised four times from methanol, formed yellow crystals, m. p. 360° (decomp.) (Found: C, 53·6; H, 3·9. $C_{16}H_{13}N_2I$ requires C, 53·35; H, 3·6%). Light absorption: (*a*) neutral, $\lambda_{max.}$ 2240, 2480, 2930, 3360, and 3990 Å (log ε, 4·52, 4·31, 4·08, 4·27, and 4·07), $\lambda_{min.}$ 2450, 2830, 3050, and 3760 Å (log ε 4·30, 4·01, 3·98, and 3·96); (*b*) alkaline, $\lambda_{max.}$ 2250, 2530, 3300, and 4000 Å (log ε 4·51, 4·33, 4·27, and 4·08), $\lambda_{min.}$ 2460, 2830, and 3780 Å (log ε 4·30, 4·05, and 4·00).

2-*Cyano*-4 : 5-*diethylpyridine*.—This was prepared by Lee and Swan's [25] route; but modifications led to the yields of many stages being improved. In the formation of the *N*-oxide of 5-ethyl-2-methylpyridine, increasing the time of heating to 26 hr. afforded a yield of 89·5% and on a 227 g. scale this was nitrated in 72% yield. The nitro-compound (60 g.) in benzene (300 ml.) when refluxed with phosphorus tribromide (250 ml.) for 12 hr. afforded 4-bromo-5-ethyl-2-methylpyridine in 72% yield. This, when heated with cyanide for only 12 hr. at 180—200° in the autoclave yielded ethyl 5-ethyl-2-methylpyridine-4-carboxylate in 79% yield. Clemmensen reduction of 36·5 g. of 4-acetyl-5-ethyl-2-methypyridine (12 hours' reflux) and treatment of the alcoholic by-product with hydriodic acid afforded 4 : 5-diethyl-2-methypyridine in almost theoretical yield. Oxidation of the styryl compound (16 g.), followed by esterification of the crude product, after removal of benzoic acid, afforded ethyl 4 : 5-diethylpyridine-2-carboxylate in 56·5% yield. The corresponding amide (7·7 g.) was converted into 2-cyano-4 : 5-diethylpyridine in 69·5% yield.

2-γ-*Ethoxybutyryl*-4 : 5-*diethylpyridine*.—When 2-cyano-4 : 5-diethylpyridine (3 g.) was treated with a Grignard reagent prepared from magnesium (1·5 g.) and 1-bromo-3-ethoxypropane (10 g.) as described under (*a*) for 2-γ-ethoxybutyrylpyridine; the product (2·8 g.), b. p. 132—140°/0·2 mm., had a strong absorption band at 3354 cm.$^{-1}$ and appeared to be the *imine* corresponding to this ketone (Found: C, 72·7; H, 9·95; N, 10·8. $C_{15}H_{24}ON_2$ requires C, 72·75; H, 9·7; N, 11·3%). The 2 : 4-*dinitrophenylhydrazone* of 2-γ-ethoxybutyryl-4 : 5-diethylpyridine hydrobromide separated from ethanol as yellow needles, m. p. 202° (decomp.) (Found: C, 49·2; H, 5·85. $C_{21}H_{27}O_5N_5,HBr$ requires C, 49·4; H, 5·5%). The corresponding *base*, recrystallised from benzene–light petroleum (b. p. 60—80°), had m. p. 109—110° (Found: C, 58·85; H, 6·6. $C_{21}H_{27}O_5N_5$ requires C, 55·75; H, 6·3%).

Action of Hydrobromic Acid on 2-γ-*Ethoxybutyrimidoyl*-4 : 5-*diethylpyridine*.—The product obtained by refluxing the above imine (1 g.) with acetic–hydrobromic acid for 21 hr., as for the preparation of 1 : 2 : 3 : 4-tetrahydro-1-oxopyridocolinium bromide, failed to crystallise. It was dissolved in a small volume of water, basified with sodium carbonate, and extracted with chloroform, as it was thought that perhaps cyclisation had not occurred. However, evaporation

[25] Lee and Swan, *J.*, 1956, 771.

of the dried (Na_2SO_4) extract yielded only an oil (0·8 g.), but this was converted into the 7 : 8-*diethyl*-1 : 2 : 3 : 4-*tetrahydro*-1-*phenylhydrazonopyridocolinium bromide* (0·5 g.), separating from ethanol–ether as yellow cubes, m. p. 255° (Found: C, 60·75; H, 6·7. $C_{19}H_{24}N_3Br$ requires C, 60·95; H, 6·4%). On two occasions, when the imine was treated with hydrobromic acid, a small amount of 2-*γ-bromobutyryl*-4 : 5-*diethylpyridine hydrobromide* was isolated; it separated from methanol–acetone as colourless plates, m. p. 155—156° (Found: C, 43·1; H, 5·7. $C_{13}H_{18}ONBr,HBr$ requires C, 42·75; H, 5·2%). Basification of this salt yielded an oil.

2 : 3-*Diethyl*-6 : 7-*dihydro*-12H-*indolo*[2 : 3-a]*pyridocolinium Chloride*.—This *chloride* (35 mg.) was obtained from the above phenylhydrazone bromide (55 mg.) by the Fischer indole reaction, as before and separated from ethanol as bright yellow needles, decomposing at 273° (Found: C, 67·05; H, 7·2. $C_{19}H_{21}N_2Cl,1·5H_2O$ requires C, 67·15; H, 7·05%). Light absorption: (*a*) acid, $\lambda_{max.}$ 2220, 3120, and 3880 Å (log ε 4·41, 4·19, and 4·20), $\lambda_{min.}$ 2760, and 3390 Å (log ε 3·51 and 3·94); (*b*) alkaline, $\lambda_{max.}$ 2300, 2630, 3610, and 4110 Å (log ε 4·44, 4·01, 4·13, and 4·23), $\lambda_{min.}$ 2520, 2920, and 3740 Å (log ε 3·95, 3·50, and 4·12). The corresponding *picrate* separated from ethanol–acetone as needles, decomp. 253° (Found: C, 59·15; H, 4·65. $C_{25}H_{23}O_7N_5$ requires C, 59·4; H, 4·55%). The corresponding *nitrate* separated from ethanol as yellow needles, m. p. 262—263° (Found: C, 68·05; H, 7·1. $C_{19}H_{21}O_3N_3$ requires C, 67·25; H, 6·2%).

2 : 3-*Diethyl*-12H-*indolo*[2 : 3-a]*pyridocolinium Chloride*.—Dehydrogenation of the above 6 : 7-dihydro-chloride with tetrachloro-*o*-benzoquinone, as before, yielded the pale yellow *chloride*, which crystallised from ethanol–ether and decomposed at 258° (Found: C, 67·8; H, 6·3. $C_{19}H_{19}N_2Cl,1·5H_2O$ requires C, 67·55; H, 6·5%). Light absorption: (*a*) acid, $\lambda_{max.}$ 2380, 2910, 3460, and 3850 Å (log ε 4·52, 4·15, 4·30, and 4·24), $\lambda_{min.}$ 2750, 3050, and 3740 Å (log ε 4·04, 4·05, and 4·16); (*b*) alkaline, $\lambda_{max.}$ 2310, 2410, 2880, 3180, 3640, and 4400 Å (log ε 4·43, 4·42, 4·44, 4·07, 4·31, and 3·74), $\lambda_{min.}$ 2370, 2650, 3090, 3260, and 4190 Å (log ε 4·41, 4·14, 4·03, 4·05, and 3·72). Basification of an aqueous solution of the chloride yielded 2 : 3-*diethylindolo*[2 : 3-a]-*pyridocoline*, which was purified by chromatography in chloroform on alumina and then separated from methanol as deep yellow needles, m. p. 150—151° (Found: C, 75·25; H, 7·25. $C_{19}H_{18}N_2,1·5H_2O$ requires C, 75·55; H, 7·0%). This base, in methanol solution, yielded a perchlorate as pale yellow needles, m. p. 301° (decomp.). The sample of flavocoryline perchlorate supplied by Professor Janot, under the same conditions, had m. p. and mixed m. p. 304° (decomp.).

5-*Ethyl*-2-*methyl*-4-iso*propylpyridine*.—A solution of 4-acetyl-5-ethyl-2-methylpyridine (10·8 g.) in ether (100 ml.) was added during 10 min. with stirring at room temperature to a Grignard reagent, prepared from magnesium (4·1 g.), methyl iodide (24·3 g.), and ether (125 ml.), and the mixture was stirred and refluxed for 3 hr., then cooled in ice, decomposed by saturated ammonium chloride solution (210 ml.) and concentrated hydrochloric acid (35 ml.), basified with 10% aqueous sodium hydroxide, and extracted with chloroform. The crude tertiary alcohol (11·8 g.), a very viscous, pale yellow liquid, obtained by evaporation of the solvent from the dried (Na_2SO_4) extract, was refluxed with freshly distilled constant-boiling hydriodic acid (86 ml.) and red phosphorus (4·5 g.) for 6 hr. The mixture was diluted with water, filtered, basified with 20% aqueous sodium hydroxide, and extracted with chloroform. Distillation of the dried (Na_2SO_4) extract gave the *base* (9·2 g., 85%), b. p. 105—106°/20 mm. (Found: C, 80·7; H, 10·55. $C_{11}H_{17}N$ requires C, 81·0; H, 10·4%). The *picrate* separated from ethanol as prisms, m. p. 179—180° (Found: C, 51·8; H, 5·2. $C_{11}H_{17}N,C_6H_3O_7N_3$ requires C, 52·05; H, 5·1%).

5-*Ethyl*-4-iso*propyl*-2-*styrylpyridine*.—When the above base (10·5 g.) was condensed with benzaldehyde as described [25] for 4 : 5-diethyl-2-methylpyridine except that the mixture was refluxed for 96 hr., the *product* (10·5 g.) was obtained as a pale yellow liquid, b. p. 188—194°/2 mm. (Found: C, 86·15; H, 8·8. $C_{18}H_{21}N$ requires C, 86·05; H, 8·35%), together with unchanged base (3 g.). The *picrate* separated from dimethylformamide–ethanol as needles, m. p. 235—236° (decomp.), softening at 213° (Found: C, 60·25; H, 5·25. $C_{18}H_{21}N,C_6H_3O_7N_3$ requires C, 60·0; H, 5·0%).

Ethyl 5-*Ethyl*-4-iso*propylpyridine*-2-*carboxylate*.—The above styryl compound (10·5 g.) was oxidised as described [25] for 4 : 5-diethyl-2-styrylpyridine, except that, after removal of the benzoic acid, the solution was evaporated to dryness (water-bath/reduced pressure). The residue was treated with absolute ethanol, which was then evaporated, and the residue was again mixed with ethanol (150 ml.), saturated with hydrogen chloride at 0°, kept at room temperature overnight, and refluxed for 4 hr. The mixture was evaporated to dryness (water-bath/reduced pressure), the residue was cooled, diluted with water, basified with saturated aqueous sodium

carbonate, and extracted with chloroform. Distillation of the dried (K_2CO_3) extract gave the *ester* (5·2 g.), b. p. 125—129°/0·5 mm. (Found: C, 70·85; H, 8·9. $C_{13}H_{19}O_2N$ requires C, 70·6; H, 8·6%). The *picrate* separated from ethanol as prisms, m. p. 111°, softening at 106° (Found: C, 50·45; H, 5·3. $C_{13}H_{19}O_2N,C_6H_3O_7N_3$ requires C, 50·75; H, 5·3%).

5-*Ethyl*-4-iso*propylpyridine*-2-*carboxylic Acid*.—The ester (0·45 g.) was refluxed with ethanol (10 ml.) and 40% aqueous potassium hydroxide solution (2·5 ml.) for 5 hr., the ethanol was removed, and the residue was extracted with ether. The solution was then adjusted to pH 4 and extracted continuously with ether for 30 hr. The *acid* left on evaporation of the latter, dried (Na_2SO_4) extract separated from methanol–ether as colourless crystals (0·23 g.), m. p. 147°, unchanged by sublimation at 60—80°/0·01 mm. (Found: C, 68·65; H, 8·25. $C_{11}H_{15}O_2N$ requires C, 68·4; H, 7·75%). In air this absorbed moisture (Found: C, 63·0; H, 8·1. $C_{11}H_{15}O_2N,H_2O$ requires C, 62·55; H, 8·05%). Light absorption in EtOH: $\lambda_{max.}$ 2670 and 2340 Å (log ε 3·64 and 3·78), $\lambda_{min.}$ 2525 Å (log ε 3·48).

When heated with copper powder the acid yielded a distillate which gave a picrate, separating from ethanol as needles, m. p. 136—137°, softening at 123°, not depressed on admixture with 3-ethyl-4-*iso*propylpyridine picrate supplied by Professor Karrer (Found: C, 50·6; H, 4·75. Calc. for $C_{10}H_{15}N,C_6H_3O_7N_3$: C, 50·8; H, 4·75%).

2-*Carbamoyl*-5-*ethyl*-4-iso*propylpyridine*.—The above ester (4·9 g.) when shaken for 72 hr. with aqueous ammonia (*d* 0·88; 49 ml.) yielded the *amide* (3·8 g.) which, when sublimed at 60—80°/0·01 mm., had m. p. 164—165° (Found: C, 68·75; H, 8·7. $C_{11}H_{16}ON_2$ requires C, 68·75; H, 8·3%).

2-*Cyano*-5-*ethyl*-4-iso*propylpyridine*.—Dehydration of the amide (3·8 g.) in the way described [25] for the 4 : 5-diethyl compound, but with a reaction time of 3·5 hr., gave the *cyanopyridine* (2·75 g.), b. p. 113—117°/0·2 mm. (Found: C, 75·45; H, 8·2; N, 15·5. $C_{11}H_{14}N_2$ requires C, 75·85; H, 8·05; N, 16·1%).

2-γ-*Ethoxybutyryl*-5-*ethyl*-4-iso*propylpyridine*.—Treatment of the preceding nitrile with 3-ethoxypropylmagnesium bromide as described under (*a*) for 2-γ-ethoxybutyrylpyridine gave the ketone, b. p. 165°/2 mm. (Found: C, 72·85; H, 10·35; N, 6·0. $C_{16}H_{25}O_2N$ requires C, 73·0; H, 9·5; N, 5·3%). The 2 : 4-*dinitrophenylhydrazone* separated from light petroleum (b. p. 60—80°) as orange plates, m. p. 94° (Found: C, 59·6; H, 6·8. $C_{22}H_{29}O_5N_5$ requires C, 59·6; H, 6·55%).

Action of Hydrobromic Acid on 2-γ-*Ethoxybutyryl*-5-*ethyl*-4-iso*propylpyridine*.—When the above ketone (1·15 g.) was treated with hydrobromic acid as before, the residue left on evaporation of the solution yielded colourless crystals (0·34 g.), m. p. 145—147° (from methanol–acetone). Recrystallisation from the same solvent gave colourless plates, m. p. 150—151°, of 2-γ-*bromobutyryl*-5-*ethyl*-4-iso*propylpyridine hydrobromide* (for analysis dried for 4 hr. at 50°/0·1 mm.) (Found: C, 44·4; H, 5·75. $C_{14}H_{21}ONBr_2$ requires C, 44·35; H, 5·55%). An aqueous solution of this salt was basified with sodium carbonate and extracted with ether and the dried (K_2CO_3) extract yielded a gum. This readily afforded 7-*ethyl*-1 : 2 : 3 : 4-*tetrahydro*-1-*phenylhydrazono*-8-iso*propylpyridocolinium bromide*, which separated from ethanol–ether as yellow crystals, m. p. 256—257°, although melting at a much lower temperature if heated rapidly, apparently owing to hydration (Found: C, 59·85; H, 7·1. $C_{20}H_{26}N_3Br,0{\cdot}5H_2O$ requires C, 60·5; H, 6·8%). A further quantity of this compound was obtained by the action of phenylhydrazine on the residue left on evaporation of the methanol–acetone mother-liquor from which the 2-γ-bromobutyryl-5-ethyl-4-*iso*propylpyridine hydrobromide had been obtained.

3-*Ethyl*-6 : 7-*dihydro*-2-iso*propyl*-12H-*indolo*[2 : 3-a]*pyridocolinium Chloride*.—This *salt*, obtained by the Fischer indole reaction on the above phenylhydrazone, separated from ethanol–ether as bright yellow crystals, decomp. 260° (Found: C, 72·05; H, 7·35. $C_{20}H_{23}N_2Cl,0{\cdot}5H_2O$ requires C, 71·55; H, 7·15%). Light absorption: (*a*) acid, $\lambda_{max.}$ 2220, 3140, and 3880 Å (log ε 4·44, 4·25, and 4·22), $\lambda_{min.}$ 2750 and 3410 Å (log ε 3·58, 3·97); (*b*) alkaline, $\lambda_{max.}$ 2310, 2660, 3600, and 4110 Å (log ε 4·45, 4·04, 4·16, and 4·23), $\lambda_{min.}$ 2520, 2910, and 3770 Å (log ε 3·95, 3·41, and 4·13).

3-*Ethyl*-2-iso*propyl*-12H-*indolo*[2 : 3-a]*pyridocolinium Chloride*.—(*a*) Dehydrogenation of the above 6 : 7-dihydro-chloride with tetrachloro-*o*-benzoquinone, as before, yielded the pale yellow *chloride* which, when crystallised from ethanol–ether, decomposed at 270° (Found: C, 70·6; H, 6·3. $C_{20}H_{21}N_2Cl,H_2O$ requires C, 70·05; H, 6·7%). Light absorption: (*a*) acid, $\lambda_{max.}$ 2400, 2920, 3460, and 3860 Å (log ε 4·55, 4·15, 4·29, and 4·25), $\lambda_{min.}$ 2760, 3050, and 3750 Å (log ε 3·99, 4·02, and 4·16); (*b*) alkaline, $\lambda_{max.}$ 2310, 2890, 3180, 3610, and 4420 Å (log ε 4·43, 4·43, 4·07, 4·30, and

3·71), $\lambda_{min.}$ 2620, 3090, 3280, and 4180 Å (log ε 4·12, 4·01, 4·03, and 3·67). Basification of an aqueous solution of this chloride yielded 3-*ethyl*-2-iso*propylindolo*[2 : 3-a]*pyridocoline* (XI; R = Pr^i) which, when recrystallised from dilute ethanol, had m. p. 117—119° after softening at 113° (Found: C, 76·15; H, 7·55. $C_{20}H_{21}N_2Cl,H_2O$ requires C, 76·2; H, 7·3%).

(*b*) The 6 : 7-dihydro-chloride (0·2 g.) and tetrachloro-*o*-benzoquinone (0·35 g.) were heated together in acetic acid (2·5 ml.) for 8 hr. on a water-bath. The mixture was cooled and diluted with ether, and the solid was collected, washed with ether, and shaken with chloroform and sodium hydroxide solution until it passed into solution. The chloroform extract was dried (K_2CO_3), the solvent removed, the residue was dissolved in ethanol containing a little hydrochloric acid, and ether added to the solution. The resulting precipitate was dissolved in water and basified with ammonia. The resulting bright yellow solid was chromatographed in chloroform on alumina. The product formed deep yellow crystals (50 mg.; m. p. 204°) from methanol; but when recrystallised from the same solvent, the *base* had m. p. 149° (Found: C, 77·5; H, 7·1. $C_{20}H_{20}N_2,1·25H_2O$ requires C, 77·55; H, 6·95%). The *perchlorate* formed pale yellow needles, m. p. 312° (decomp.), from methanol (Found: C, 61·55; H, 5·75. $C_{20}H_{21}O_4N_2Cl$ requires C, 61·75; H, 5·4%).

2-*γ-Ethoxybutyryl*-5-*ethylpyridine*.—2-Cyano-5-ethylpyridine [25] (1·77 g.) when treated with 3-ethoxypropylmagnesium bromide as under (*b*) for 2-*γ*-ethoxybutyrylpyridine gave the *ketone* (1·77 g.), b. p. 150—160°/3 mm. (Found: C, 70·1; H, 9·3. $C_{13}H_{19}O_2N$ requires C, 70·6; H, 8·6%). Only a trace of an absorption band in the 3360 cm.$^{-1}$ region was present.

7-*Ethyl*-1 : 2 : 3 : 4-*tetrahydro*-1-*oxopyridocolinium Bromide*.—When the above ketone (1·65 g.) was treated with hydrobromic acid in the usual way, the resulting pyridocolinium bromide failed to crystallise and was therefore converted directly into the *phenylhydrazone* which, when recrystallised from ethanol–ether, weighed 1·22 g. and had m. p. 279°.

3-*Ethyl*-6 : 7-*dihydro*-12H-*indolo*[2 : 3-a]*pyridocolinium Nitrate*.—The above phenylhydrazone (0·5 g.) in a Fischer indole reaction yielded the chloride (0·33 g.), which was converted into the *nitrate*, separating from ethanol as yellow needles, m. p. 267° (decomp.) (Found: C, 65·25; H, 5·4. $C_{17}H_{17}O_3N_3$ requires C, 65·6; H, 5·45%). Light absorption: (*a*) acid, $\lambda_{max.}$ 2130, 2520, 3160, and 3950 Å (log ε 4·41, 3·95, 4·21, and 4·16), $\lambda_{min.}$ 2430, 2750, and 3450 Å (log ε 3·88, 3·55, and 3·92); (*b*) alkaline, $\lambda_{max.}$ 2220, 2670, 3600, and 4230 Å (log ε 4·40, 4·01, 4·09, and 4·21), $\lambda_{min.}$ 2490, 2950, and 3830 Å (log ε 3·83, 3·32, and 4·05).

3-*Ethyl*-12H-*indolo*[2 : 3-a]*pyridocolinium Perchlorate*.—The above 6 : 7-dihydro-chloride (0·13 g.) was heated with tetrachloro-*o*-benzoquinone (0·23 g.) in acetic acid (2 ml.) for 9 hr. on a water-bath and worked up as under (*b*) for the 3-ethyl-2-*iso*propyl compound, except that the dehydrogenated chloride was dissolved in methanol and treated with perchloric acid. The resulting *perchlorate* separated from methanol as pale yellow needles (38 mg.), m. p. 331° (decomp.) (Found: C, 56·7; H, 5·05. $C_{17}H_{15}O_4N_2Cl,CH_4O$ requires C, 57·05; H, 5·0%). Light absorption: (*a*) acid, $\lambda_{max.}$ 2350, 2950, 3500, and 3900 Å (log ε 4·52, 4·21, 4·32, and 4·20), $\lambda_{min.}$ 2730, 3090, and 3820 Å (log ε 4·03, 4·07, and 4·16); (*b*) alkaline, $\lambda_{max.}$ 2300, 2350, 2890, 3200, 3660, and 4500 Å (log ε 4·46, 4·45, 4·49, 4·10, 4·33, and 3·68), $\lambda_{min.}$ 2320, 2670, 3100, 3300, and 4200 Å (log ε 4·44, 4·14, 4·08, 4·05, and 3·62). The sample of flavopereirine perchlorate supplied by Professor Janot melted at 330° (decomp.) under the same conditions, and had mixed m. p. 330° (decomp.).

2-*Butyryl*-5-*ethyl*-4-iso*propylpyridine*.—2-Cyano-5-ethyl-4-*iso*propylpyridine (0·81 g.) when treated with *n*-propylmagnesium bromide as described for the preparation of 2-butyryl-4 : 5-diethylpyridine [25] gave the *ketone* (0·3 g.), b. p. 80—90°/1 mm. (Found: C, 76·6; H, 9·95. $C_{14}H_{21}ON$ requires C, 76·7; H, 9·6%).

3-*Ethyl*-2-(5-*ethyl*-4-iso*propyl*-2-*pyridyl*)*indole* (XV; R = Pr^i).—When the preceding ketone (0·3 g.) was subjected to a Fischer indole reaction as for the synthesis of 2-(4 : 5-diethyl-2-pyridyl)-3-ethylindole [25] it yielded the *base*, b. p. 184—195°/0·3 mm. (bath-temp.), which solidified on trituration with light petroleum and recrystallised first from methanol, then from light petroleum (b. p. 40—60°), as colourless prisms, m. p. 103—104° (Found: C, 82·3; H, 8·65. $C_{20}H_{24}N_2$ requires C, 82·2; H, 8·2%). The yellow *hydrochloride*, crystallised from methanol–ethyl acetate, softened at 190°, and had m. p. 221—223° (decomp.) (Found: C, 71·6; H, 7·8. $C_{20}H_{25}N_2Cl,0·5H_2O$ requires C, 71·1; H, 7·7%). Light absorption in EtOH: $\lambda_{max.}$ 3260 Å (log ε 4·30), $\lambda_{min.}$ 2730 Å (log ε 3·61). The *picrate* separated from dimethylformamide–ethanol as needles, m. p. 211—213° (decomp.) (Found: C, 59·35; H, 5·15. $C_{20}H_{24}N_2,C_6H_3O_7N_3,0·5C_2H_6O$ requires C, 59·55; H, 5·5%).

4-Chloro-5-ethyl-2-methylpyridine 1-Oxide.—Acetyl chloride (5 ml.) was added to 5-ethyl-2-methyl-4-nitropyridine 1-oxide [25] (2 g.) with ice-cooling and after 1 hr. at room temperature the mixture was heated for 2 hr. at 55—60°, cooled in ice, treated with water, basified with sodium carbonate, and extracted with ether. The dried (K_2CO_3) extract on distillation yielded the *product* (1·5 g.), b. p. 140°/3 mm., which crystallised (Found: C, 55·8; H, 6·15. $C_8H_{10}ONCl$ requires C, 56·0; H, 5·85%). This was recovered unchanged after being refluxed for 48 hr. with aqueous-ethanolic potassium cyanide containing a little potassium iodide. The action of acetyl bromide on 5-ethyl-2-methyl-4-nitropyridine 1-oxide gave a product which became tarry on distillation. When the last-named compound (1 g.) was refluxed for 4 hr. with 48% hydrobromic acid (4 ml.), and the resulting solution kept at room temperature, dark red crystals (0·87 g.) separated. These were recrystallised from benzene, giving orange-yellow plates, m. p. 118—119° (Found: C, 32·05; H, 3·6. $2C_8H_{10}O_3N_2,Br_3$ requires C, 31·8; H, 3·3%). Treatment of the latter, in chloroform solution, with aqueous sodium carbonate gave back 5-ethyl-2-methyl-4-nitropyridine 1-oxide, m. p. 80° (Found: C, 52·85; H, 5·5. Calc. for $C_8H_{10}O_3N_2$: C, 52·75; H, 5·5%).

5 : 7 : 8 : 13 : 13b : 14-Hexahydrobenz[g]*indolo*[2 : 3-a]*pyridocoline Methiodide.*—A solution of the base [Swan,[26] previously referred to as 3 : 4 : 6 : 9-tetrahydro-7 : 8-benzindolo(2′ : 3′-1 : 2)-pyridocoline] in benzene was kept overnight at room temperature with excess of methyl iodide. The resulting precipitate of the *methiodide* separated from methanol as yellow prisms, m. p. 279° (decomp.) (Found: C, 57·35; H, 5·45. $C_{19}H_{18}N_2,CH_3I$ requires C, 57·65; H, 5·05%). When this was refluxed with excess of silver chloride in aqueous methanol it yielded the methochloride, which recrystallised from methanol–acetone. With concentrated nitric acid this gave a bright orange-yellow colour. In concentrated sulphuric acid it gave a yellow solution, changed to red on the addition of 1 drop of water and to intense blue-purple on the addition of potassium dichromate. The methopicrate formed orange-yellow prisms, m. p. 199°, from methanol.

*1-γ-Ethoxybutyryl*iso*quinoline.*—When 1-cyano*iso*quinoline [27] (2·7 g.) was treated with 3-ethoxypropylmagnesium bromide, as under (*b*) for the preparation of 2-γ-ethoxybutyrylpyridine, it afforded the *ketone* (2·2 g.), b. p. 170—175°/2 mm. (Found: C, 74·15; H, 7·4; N, 5·9. $C_{15}H_{17}O_2N$ requires C, 74·05; H, 7·0; N, 5·75%). This showed a scarcely detectable peak at 3341 $cm.^{-1}$, whereas when method (*a*) was used a large peak was observed, indicating the presence of the imine. The 2 : 4-*dinitrophenylhydrazone* separated from ethanol as yellow needles, m. p. 163° (for analysis dried for 10 hr. at 120°/0·1 mm.) (Found: C, 59·4; H, 4·9. $C_{21}H_{21}O_5N_5$ requires C, 59·55; H, 4·95%).

1 : 2 : 3 : 4-Tetrahydro-1-oxobenzo[a]*pyridocolinium Bromide* (XVI).—Treatment of the ketone (1·09 g.) with hydrobromic acid yielded the *bromide* (0·8 g.) as a brown solid which when recrystallised from ethanol–acetone had m. p. 223—224° (Found: C, 55·95; H, 4·3. $C_{13}H_{12}ONBr$ requires C, 56·1; H, 4·3%). When this was reduced under Clemmensen conditions it gave a base, whose picrate had m. p. 184° (decomp.) (Found: C, 54·65; H, 4·9. $C_{13}H_{17}N,C_6H_3O_7N_3$ requires C, 54·8; H, 4·8%). The phenylhydrazone (0·7 g.) formed from the ketone (0·8 g.) separated from ethanol–ether as reddish-brown crystals, m. p. 279° (Found: C, 62·05; H, 5·05. $C_{19}H_{18}N_3Br$ requires C, 61·95; H, 4·9%). The corresponding *phenylhydrazone chloride* separated from ethanol–ether as brown prisms, m. p. 243—246° (Found: C, 63·1; H, 5·8. $C_{19}H_{18}N_3Cl,2H_2O$ requires C, 63·4; H, 6·1%). Light absorption of this chloride: (*a*) acid, $\lambda_{max.}$ 2430, 2650, and 4490 Å (log ε 4·65, 4·06, and 4·41), $\lambda_{min.}$ 2600 and 3600 Å (log ε 4·04 and 3·0); (*b*) alkaline, $\lambda_{max.}$ 2300, 2440, 3300, and 5120 Å (log ε 4·38, 4·38, 3·78, and 4·44), $\lambda_{min.}$ 2380, 3020, and 3760 Å (log ε 4·36, 3·60, and 3·22). The corresponding *phenylhydrazone nitrate* separated from ethanol as yellow needles, m. p. 237° (Found: C, 65·5; H, 5·55. $C_{19}H_{18}O_3N_4$ requires C, 65·15; H, 5·15%). The *phenylhydrazone picrate* separated from dimethylformamide–ethanol as orange needles, m. p. 200° (Found: C, 58·3; H, 4·45. $C_{25}H_{20}O_7N_6$ requires C, 58·15; H, 3·90%).

2-γ-Ethoxybutyrylquinoline.—For the preparation of 2-cyanoquinoline Henze's [28] method was found to be preferable to that of Kaufmann and Dändliker.[27] When this nitrile (2·6 g.) was treated with 3-ethoxypropylmagnesium bromide as under (*a*) for the preparation of 2-(γ-ethoxybutyryl)pyridine, the product (2·2 g.) appeared to consist mainly of the *imine*, b. p. 165°/0·5 mm.

[26] Swan, *J.*, 1949, 1720.
[27] Kaufmann and Dändliker, *Ber.*, 1913, **46**, 2924.
[28] Henze, *ibid.*, 1936, **69**, 1566.

(Found: C, 74·15; H, 7·5. $C_{15}H_{18}ON_2$ requires C, 74·4; H, 7·45%), and showed a strong band at 3343 cm.$^{-1}$. Method (*b*), however, gave the *ketone* (2 g.), b. p. 190°/2 mm., in which this band was virtually absent (Found: N, 6·75. $C_{15}H_{17}O_2N$ requires N, 5·75%). The 2 : 4-*dinitrophenylhydrazone* melted at 148°, after softening at 138° (Found: C, 59·5; H, 5·0. $C_{21}H_{21}O_5N_5$ requires C, 59·55; H, 4·95%).

1 : 2 : 3 : 4-*Tetrahydro*-4-*oxobenzo*[c]*pyridocolinium Bromide* (XVII).—The above imine or ketone (1·9 g.) when refluxed for 21 hr. with acetic–hydrobromic acid yielded the *bromide* (1·6 g.) as brown cubes, m. p. 116—118° (from methanol–acetone) (Found: C, 47·05; H, 5·65. $C_{13}H_{12}ONBr,3H_2O$ requires C, 47·0; H, 5·4%). The *phenylhydrazone* separated from ethanol–ether as deep red crystals, m. p. 251—252° (Found: C, 59·0; H, 5·65. $C_{19}H_{18}N_3Br,H_2O$ requires C, 59·05; H, 5·2%); when dried for 16 hr. at 150°/0·1 mm. this melted at 260° (Found: C, 60·5; H, 4·9. $C_{19}H_{18}N_3Br,0{\cdot}5H_2O$ requires C, 60·45; H, 5·05%). The *phenylhydrazone chloride* separated from ethanol–ether as dark, brick-red needles, m. p. 257—258° (Found: C, 62·85; H, 6·45. $C_{19}H_{18}N_3Cl,2H_2O$ requires C, 63·4; H, 6·1%). Light absorption: (*a*) acid, $\lambda_{max.}$ 2280, 2680, 3270, and 4570 Å (log ε 4·13, 3·96, 3·62, and 4·35), $\lambda_{min.}$ 2500, 2900, and 3670 Å (log ε 3·86, 3·43, and 3·24); (*b*) alkaline, $\lambda_{max.}$ 2290 and 4890 Å (log ε 4·14 and 4·27), $\lambda_{min.}$ 3390 Å (log ε 2·97). The phenylhydrazone nitrate separated from ethanol as red needles, m. p. 257—258° and the *phenylhydrazone picrate* from ethanol–acetone as yellow, silky needles, m. p. 245° (decomp.) (Found: C, 58·1; H, 4·05. $C_{25}H_{20}O_7N_6$ requires C, 58·15; H, 3·90%).

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