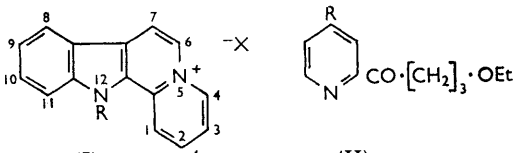
638. *The Constitution of Yohimbine and Related Alkaloids. Part XIII.*[1] *The Synthesis of Some* 12H-*indolo*[2,3-a]*pyridocolinium Salts Substituted at the 2-Position.*

By G. A. Swan and P. R. Thomas.

Syntheses are described of 12*H*-indolo[2,3-*a*]pyridocolinium salts (I) containing a methyl or formyl group at the 2-position and of 6,7-dihydro-12*H*-indolo[2,3-*a*]pyridocolinium salts (IV) containing a methyl, bromomethyl, or 2-bromoethyl group at the 2-position.

This paper describes the extension of Prasad and Swan's [2] synthesis of 12*H*-indolo[2,3-*a*]-pyridocolinium salts (cf. also Glover and Jones [3] and Kaneko [4]) to yield products containing in the 2-position reactive groups which might be used to build side chains or rings such as occur in certain alkaloids of the indole group.

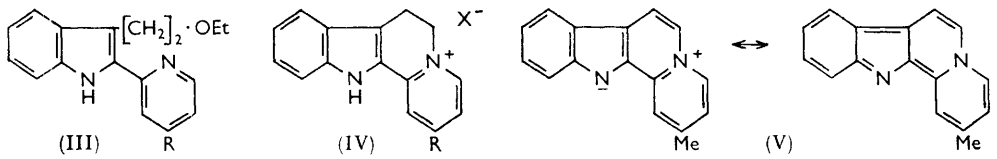
As the methyl group of 2-methyl-12*H*-indolo[2,3-*a*]pyridocolinium chloride (I; R = H, R′ = Me, X = Cl) might be expected to be reactive, we first synthesised this compound by the general method of Prasad and Swan,[2] starting with 2-cyano-4-methylpyridine which was conveniently obtained by Feely and Beaver's method.[5] When we treated the intermediate 2-γ-ethoxybutyryl-4-methylpyridine (II; R = Me) with hydrobromic acid in



acetic acid we obtained a mixture of crystalline 2-γ-bromobutyryl-4-methylpyridinium bromide and a gum containing 1,2,3,4-tetrahydro-8-methyl-1-oxopyridocolinium bromide, both of which, on treatment with phenylhydrazine, yielded the phenylhydrazone of 1,2,3,4-tetrahydro-8-methyl-1-oxopyridocolinium bromide. After we had completed this synthesis other workers [6] described a similar synthesis up to the stage of 1,2,3,4-tetrahydro-8-methyl-1-oxopyridocolinium bromide.

[1] Part XII, Prasad and Swan, *J.*, 1958, 2045.
[2] Prasad and Swan, *J.*, 1958, 2024.
[3] Glover and Jones, *J.*, 1958, 1750.
[4] Kaneko, *Yakugaku Zasshi*, 1960, **80**, 1374.
[5] Feely and Beavers, *J. Amer. Chem. Soc.*, 1959, **81**, 4004.
[6] Moynehan, Schofield, Jones, and Katritzky, *J.*, 1962, 2637.

We also prepared the intermediate dihydro-derivative (IV; R = Me, X = Cl) by a modification of Prasad and Swan's method. The phenylhydrazone of 2-γ-ethoxybutyryl-4-methylpyridine, when treated with ethanolic hydrogen chloride, underwent a Fischer indole reaction to give 3-2′-ethoxyethyl-2-(4-methyl-2-pyridyl)indole (III; R = Me), isolated as the perchlorate. Treatment of the latter with hydrobromic acid in acetic acid afforded 6,7-dihydro-2-methyl-12*H*-indolo[2,3-*a*]pyridocolinium salts (IV; R = Me). Attempts to effect these two steps in a single process (treatment with hydrobromic acid) were unsuccessful, although ammonium bromide was formed.



The action of sodium hydroxide on 2-methyl-12*H*-indolo[2,3-*a*]pyridocolinium chloride yielded 2-methylindolo[2,3-*a*]pyridocoline (V). n-Butyl-lithium in ether reacted with this base to give a deep red solution, but subsequent treatment with carbon dioxide failed to yield a carboxylic acid derived from the base. Probably the butyl-lithium brought about nucleophilic attack in the pyridocoline nucleus. 2-Methylindolo[2,3-*a*]pyridocoline reacted with methyl iodide, to give 2,12-dimethyl-12*H*-indolo[2,3-*a*]pyridocolinium iodide (I; R = R′ = Me, X = I); but reaction of the latter with butyl-lithium, followed by carbon dioxide again failed to yield an acid.

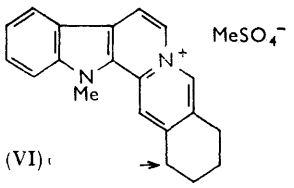
Attempts to condense 2-methyl-12*H*-indolo[2,3-*a*]pyridocolinium chloride or 2,12-dimethyl-12*H*-indolo[2,3-*a*]pyridocolinium iodide with benzaldehyde in ethanol in the presence of catalytic amounts of piperidine failed. As, however, 1-ethyl-4-methylpyridinium iodide is known to condense with benzaldehyde in the presence of catalytic amounts of piperidine to form 1-ethyl-4-styrylpyridinium iodide,[7] we investigated the reaction between 6,7-dihydro-2-methyl-12*H*-indolo[2,3-*a*]pyridocolinium chloride and benzaldehyde in methanol. In the presence of piperidine or cyclohexylamine (approximately 1 mole per mole of chloride) condensation occurred to give 6,7-dihydro-2-styryl-12*H*-indolo[2,3-*a*]-pyridocolinium chloride (IV; R = ·CH:CHPh, X = Cl). That condensation had indeed occurred at the methyl group, rather than at the reactive methylene group adjacent to the quaternary nitrogen atom or at position 7, was shown by the failure of 6,7-dihydro-12*H*-indolo[2,3-*a*]pyridocolinium chloride (IV; R = H, X = Cl) to react with benzaldehyde under similar conditions. Dehydrogenation of 6,7-dihydro-2-styryl-12*H*-indolo[2,3-*a*]-pyridocolinium chloride with tetrachloro-*o*-benzoquinone yielded a product formulated as 2-styryl-12*H*-indolo[2,3-*a*]pyridocolinium chloride (I; R = H, R′ = ·CH:CHPh, X = Cl). Oxidation of either of these styryl compounds with potassium permanganate yielded an unidentified compound and attempts to hydroxylate the styryl double-bond of the second compound with performic acid failed.

Attempts to oxidise the 2-methyl group of 2-methylindolo[2,3-*a*]pyridocoline or 2,12-dimethyl-12*H*-indolo[2,3-*a*]pyridocolinium chloride directly to a carboxyl group by potassium permanganate, by selenium dioxide, or by chromium trioxide in acetic acid were unsuccessful.

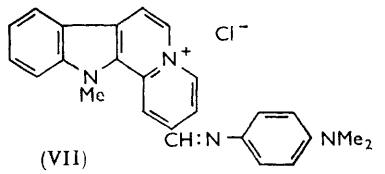
Bentley and Stevens[8] found that *NN*-dimethyl-*p*-nitrosoaniline condensed with sempervirine methosulphate (VI), supposedly at the position indicated by the arrow, to give a deep purple product. We failed to isolate a condensation product of 2,12-dimethyl-12*H*-indolo[2,3-*a*]pyridocolinium iodide, 6,7-dihydro-2-methyl-12*H*-indolo[2,3-*a*]pyridocolinium chloride, or 6,7-dihydro-12*H*-indolo[2,3-*a*]pyridocolinium chloride with *NN*-dimethyl-*p*-nitrosoaniline in the presence of catalytic amounts of piperidine, although the production

[7] Takahashi and Sato, *Yakugaku Zasshi*, 1958, **78**, 467.
[8] Bentley and Stevens, *Nature*, 1949, **164**, 141.

of colour in the two former cases indicated that reaction had occurred to a minor extent. However, the condensation of 2,12-dimethyl-12*H*-indolo[2,3-*a*]pyridocolinium iodide with *NN*-dimethyl-*p*-nitrosoaniline was successful when the amount of piperidine used was

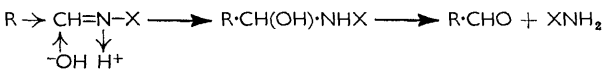


(VI)



(VII)

equimolecular to the chloride. The resulting purple-red 2-*N*-(*p*-dimethylaminophenyl)-formimidoyl-12-methyl-12*H*-indolo[2,3-*a*]pyridocolinium chloride (VII) was very readily hydrolysed by cold, dilute hydrochloric acid to give 2-formyl-12-methyl-12*H*-indolo-[2,3-*a*]pyridocolinium chloride (I; R = Me, R′ = ·CHO, X = Cl). In contrast to our experiences, Richards and Stevens [9] found that 2-methylpyridocolinium iodide condensed with *NN*-dimethyl-*p*-nitrosoaniline apparently using only catalytic quantities of piperidine to give an anil which was decolorised reversibly by dilute acids, *i.e.*, the anil was much more stable to hydrolysis than was our anil (VII). The difference may be due to electron release from the indolopyridocolinium nucleus to its 2-position, thus facilitating hydrolysis:



Following the general method of Feely and Beavers,[5] we converted 4-methoxymethylpyridine *via* its *N*-oxide into 2-cyano-4-methoxymethylpyridine, which reacted with 3-ethoxypropylmagnesium bromide to give 2-γ-ethoxybutyryl-4-methoxymethylpyridine (II; R = ·CH_2·OMe). We were unable to cyclise the latter by treatment with hydrogen bromide, presumably because the 4-methoxymethyl group was converted into the bromomethyl group, which then quaternised the nitrogen atom of another similar molecule, leading to polymerisation. However, the phenylhydrazone of the ketone (II; R = ·CH_2·OMe) was isolated as a perchlorate and this, when treated with ethanolic hydrogen chloride yielded 3-2′-ethoxyethyl-2-(4-methoxymethyl-2-pyridyl)indole (III; R = ·CH_2·OMe), isolated as the perchlorate. The latter, when treated with hydrogen bromide, afforded 2-bromomethyl-6,7-dihydro-12*H*-indolo[2,3-*a*]pyridocolinium perchlorate (IV; R = ·CH_2Br, X = ClO_4).

We prepared 4-2′-ethoxyethylpyridine by addition of ethanol to 4-vinylpyridine in an analogous way to that used by Doering and Weil [10] to prepare the 2-isomer. This was converted in the above manner into 2-cyano-4-2′-ethoxyethylpyridine, which reacted with 3-ethoxypropylmagnesium bromide to give 2-γ-ethoxybutyryl-4-2′-ethoxyethylpyridine (II; R = ·$[CH_2]_2$·OEt). The latter was similar to the corresponding 4-methoxymethyl compound (II; R = ·CH_2·OMe) in that cyclisation by hydrobromic acid failed, but that the ketone yielded a phenylhydrazone which underwent a Fischer indole reaction to give 3-2′-ethoxyethyl-2-(4-2′-ethoxyethyl-2-pyridyl)indole (III; R = ·$[CH_2]_2$OEt). The latter, when treated with hydrobromic acid yielded 2-2′-bromoethyl-6,7-dihydro-12*H*-indolo-[2,3-*a*]pyridocolinium perchlorate (IV; R = ·$[CH_2]_2Br$, X = ClO_4).

Attempts to prepare 2-cyano-4-2′-diethylaminoethylpyridine, with a view to use in a similar type of synthesis, were unsuccessful, as we were unable to isolate either a mono- or a di-*N*-oxide from 4-2′-diethylaminoethylpyridine. The latter compound reacted with peracetic acid to yield an oil which gave a 2,4-dinitrophenylhydrazone (analysis of which

[9] Richards and Stevens, *J.*, 1958, 3067; cf. Kröhnke, Leister, and Vogt, *Chem. Ber.*, 1957, **90**, 2792.
[10] Doering and Weil, *J. Amer. Chem. Soc.*, 1947, **69**, 2461.

suggested that it might be that of 4-pyridylacetaldehyde *N*-oxide) and a picrate which showed no carbonyl absorption in the infrared region. It is probable that the di-*N*-oxide was formed and underwent thermal rearrangement in the manner observed in the case of the *N*-oxides of tertiary allyl- or benzyl-amines.[11] In other cases thermal elimination is known [12] and indeed we found that the action of perbenzoic acid on 4-2′-diethylaminoethylpyridine yields 4-vinylpyridine *N*-oxide.

The convenient preparation of 4-acetoxymethylpyridine by the action of acetic anhydride on 4-picoline 1-oxide [13] led us to investigate the use of the former compound as starting material for our synthesis. We found that it reacted with peracetic acid to yield 4-hydroxymethylpyridine 1-oxide, identical with that prepared by Hata's method [14] and readily hydrogenated over palladium to 4-hydroxymethylpyridine. While our work was in progress Oae, Kitao, and Kitaoka [15] showed that the 4-acetoxymethylpyridine prepared as above is contaminated with 3-acetoxy-4-methylpyridine. In confirmation of this, we found that the action of perbenzoic acid on this material yielded a compound which we believe to be 3-hydroxy-4-methylpyridine 1-oxide, in addition to 4-acetoxymethylpyridine 1-oxide. The sample of the latter isolated was not quite pure and when treated with methyl sulphate, followed by potassium cyanide, it yielded 4-acetoxymethyl-2-cyanopyridine, together with a smaller amount of a compound thought to be either 2-cyano-3- or 2-cyano-5-methoxy-4-methylpyridine.

The action of 3-ethoxypropylmagnesium bromide on 4-acetoxymethyl-2-cyanopyridine yielded 2-cyano-4-hydroxymethylpyridine in addition to 2-γ-ethoxybutyryl-4-hydroxymethylpyridine (II; R = $\cdot CH_2 \cdot OH$). Further transformations of the latter were not attempted, as the above synthesis of 2-bromomethyl-6,7-dihydro-12*H*-indolo[2,3-*a*]-pyridocolinium perchlorate seemed more useful.

The use of 3-ethoxypropylmagnesium bromide in our general synthetic route involves heating with hydrobromic acid, at a later stage, to effect dealkylation of an ethoxy-compound before closure of the pyridocoline ring can be achieved and this treatment may result in attack of other groups present in the molecule in certain cases. We therefore investigated the possibility of using a Grignard reagent prepared from 2-3′-bromopropoxytetrahydropyran, in which case the protective group might be removed by very mild treatment with acid. However, although we obtained the required bromo-compound, we were unable to prepare a Grignard reagent from it and its reaction with lithium in ether resulted in conversion into an alkyl-lithium only to the extent of 25%. In the latter reaction lithium bromide was precipitated and an oil, thought from its infrared spectrum and high boiling point to be the bisdihydropyranyl derivative of hexamethyleneglycol, was formed. Parham and Anderson [16] found that 2-2′-bromoethoxytetrahydropyran reacted with magnesium only under forcing conditions, ethylene being formed. On the other hand, Cuvigny and Normant [17] reported the preparation of a Grignard reagent from 2-4′-chlorobutoxytetrahydropyran.

Experimental

Ultraviolet absorption measurements referred to as " alkaline " were made in 0·015N-ethanolic potassium hydroxide and those referred to as " acid " were in ethanolic hydrogen chloride. M. p.s were measured in open capillaries. Evaporation of aqueous, ethanolic, or acetic acid solutions was carried out under reduced pressure on a water-bath.

Many of the salts described in this paper appeared to be hydrates and difficulty was

[11] Cope and Towle, *J. Amer. Chem. Soc.*, 1949, **71**, 3423.
[12] Cope, Foster, and Towle, *J. Amer. Chem. Soc.*, 1949, **71**, 3929.
[13] Boekelheide and Linn, *J. Amer. Chem. Soc.*, 1954, **76**, 1286.
[14] Hata, *Bull. Chem. Soc. Japan*, 1958, **31**, 224.
[15] Oae, Kitao, and Kitaoka, *J. Amer. Chem. Soc.*, 1962, **84**, 3362.
[16] Parham and Anderson, *J. Amer. Chem. Soc.*, 1948, **70**, 4187.
[17] Cuvigny and Normant, *Compt. rend.*, 1962, **254**, 316.

experienced in obtaining them anhydrous, as has been noticed earlier for other pyridocolinium salts, particularly those carrying fused benzene [18] or indole [2,3,19] rings.

2-*γ*-*Ethoxybutyryl*-4-*methylpyridine* (II; R = Me).—2-Cyano-4-methylpyridine [5] (17 g.) was treated with a Grignard reagent prepared from 1-bromo-3-ethoxypropane (48 g.) as described for the preparation of 2-*γ*-ethoxybutyrylpyridine [2] except that hydrolysis was effected by 5N-hydrochloric acid (420 ml.) instead of sulphuric acid and subsequent extraction was by 2N-hydrochloric acid (2 × 420 ml.). The resulting ketone, which probably contained a small amount of the corresponding imine, had b. p. 118—120°/1 mm. (18·5 g.) (Found: C, 70·15; H, 9·35; N, 7·9. Calc. for $C_{12}H_{17}NO_2$: C, 69·5; H, 8·25; N, 6·75%).

1,2,3,4-*Tetrahydro*-8-*methyl*-1-*phenylhydrazonopyridocolinium Bromide*.—The above ketone (8 g.) was refluxed for 12 hr. with acetic acid (48 ml.) and constant-boiling hydrobromic acid (24 ml.), and the solution was then evaporated to dryness. Crystallisation of the residue from methanol–acetone afforded 2-*γ*-*bromobutyryl*-4-*methylpyridinium bromide* (3·8 g.), which after recrystallisation from the same mixture formed colourless needles, m. p. 147—148° (Found: C, 37·3; H, 4·4. $C_{10}H_{12}BrNO,HBr$ requires C, 37·15; H, 4·1%). This compound (3·7 g.), when heated with phenylhydrazine hydrochloride (2·25 g.) and crystalline sodium acetate (7·5 g.) in aqueous solution for 3 hr. on a water-bath and then cooled, yielded 1,2,3,4-*tetrahydro*-8-*methyl*-1-*phenylhydrazonopyridocolinium bromide* (4·37 g.) which crystallised from ethanol–ether as orange-yellow needles, m. p. 274° (3·9 g.) (Found: C, 56·7; H, 5·6. $C_{16}H_{18}BrN_3,0·5H_2O$ requires C, 56·3; H, 5·6%). The mother-liquor from which the 2-*γ*-bromobutyryl-4-methylpyridinium bromide had been obtained was evaporated to dryness, and the resulting gum (5·9 g.) when treated with phenylhydrazine in the same way yielded the identical phenylhydrazone bromide (5·9 g.).

6,7-*Dihydro*-2-*methyl*-12H-*indolo*[2,3-a]*pyridocolinium Chloride* (IV; R = Me, X = Cl).—The above phenylhydrazone bromide (0·5 g.) in ethanol (30 ml.), when treated as for the preparation of 6,7-dihydro-12*H*-indolo[2,3-*a*]pyridocolinium chloride [2] except that the solution was refluxed for 7 hr., yielded the *chloride* (0·35 g.) as yellow needles, decomp. >380° (Found: C, 69·65; H, 5·4. $C_{16}H_{15}ClN_2,0·25H_2O$ requires C, 69·75; H, 5·7%), $\lambda_{max.}$ (acid) 2200, 3135, and 3870 Å (log ε 4·44, 4·15, and 4·23), with a shoulder at 2450 Å, $\lambda_{min.}$ 2745 and 3380 Å (log ε 3·27 and 3·94), $\lambda_{max.}$ (alkaline) 2225, 2635, 3650, and 4150 Å (log ε 4·53, 4·10, 4·21, and 4·33), $\lambda_{min.}$ 2495, 2940, and 3700 Å (log ε 3·98, 3·44, and 4·20). The yellow neutral or acidic ethanolic solution of the chloride was yellow-green-fluorescent under ultraviolet irradiation; the alkaline solution was brown and showed no fluorescence. The corresponding *picrate* separated from dimethylformamide–light petroleum as needles, m. p. 256° (decomp.) (Found: C, 57·35; H, 3·7. $C_{22}H_{17}N_5O_7$ requires C, 57·0; H, 3·7%). The *nitrate* separated from ethanol as yellow needles, decomp. >250° (Found: C, 64·5; H, 5·4. $C_{16}H_{15}N_3O_3$ requires C, 64·65; H, 5·1%). The *perchlorate* separated from acetone–methanol as pale yellowish-green needles, m. p. 286—287° (decomp.) (Found: C, 57·85; H, 4·9. $C_{16}H_{15}ClN_2O_4$ requires C, 57·4; H, 4·5%).

2-*Methyl*-12H-*indolo*[2,3-a]*pyridocolinium Chloride* (I; R = H, R′ = Me, X = Cl).—The above chloride (IV; R = Me, X = Cl) (114 mg.), when dehydrogenated as for the preparation of 12*H*-indolo[2,3-*a*]pyridocolinium chloride [2] except that refluxing was for only 11 hr., yielded the *product* as very pale yellow needles (90 mg.), decomp. >300° (Found: C, 68·95; H, 5·9. $C_{16}H_{13}ClN_2,0·5H_2O$ requires C, 69·2; H, 5·45%), $\lambda_{max.}$ (acid) 2240, 2465, 2930, 3425, and 3845 Å (log ε 4·54, 4·61, 4·09, 4·33, and 4·24), $\lambda_{min.}$ 2300, 2755, 3020, and 3725 Å (log ε 4·44, 3·96, 3·94, and 4·16), $\lambda_{max.}$ (alkaline) 2280, 2420, 2895, 3600, and 4460 Å (log ε 4·39, 4·33, 4·38, 4·34, and 3·72) with a shoulder at 2550 Å, $\lambda_{min.}$ 2370, 2645, 3105, and 4200 Å (log ε 4·31, 4·12, 3·95, and 3·67). The pale yellow neutral or acidic ethanolic solution of the chloride was violet-fluorescent under ultraviolet irradiation; the alkaline solution was deeper yellow and was yellow-fluorescent. The corresponding *picrate* separated from dimethylformamide–methanol as needles, m. p. 291° decomp.) (Found: C, 56·9; H, 3·8. $C_{22}H_{15}N_5O_7$ requires C, 57·25; H, 3·45%). The *perchlorate* separated from acetone–methanol as very pale yellowish-green needles, m. p. 299° (decomp.) (Found: C, 57·65; H, 4·25. $C_{16}H_{13}ClN_2O_4$ requires C, 57·75; H, 3·95%).

2-*Methylindolo*[2,3-a]*pyridocoline* (V).—An aqueous solution of the above chloride, when treated with 40% sodium hydroxide solution, gave a yellow precipitate of the *base*, which

[18] Buck, Perkin, and Stevens, *J.*, 1925, **127**, 1462.
[19] Forsyth, Marrian, and Stevens, *J.*, 1945, 579; Swan, *J.*, 1958, 2038; Ban and Seo, *Tetrahedron*, 1961, **16**, 11.

separated from aqueous propan-2-ol as dark yellowish-brown needles, decomp. >350° (Found: C, 82·5; H, 5·2. $C_{16}H_{12}N_2$ requires C, 82·75; H, 5·2%).

2-*γ*-*Ethoxybutyryl*-4-*methylpyridine Phenylhydrazone Perchlorate*.—A mixture of 2-*γ*-ethoxybutyryl-4-methylpyridine (4 g.), phenylhydrazine (2 ml.), and ethanol (10 ml.) was refluxed for 3 hr. on a water-bath, concentrated, then treated with ethanolic perchloric acid. On cooling, the *perchlorate* (6·9 g.) separated and after recrystallisation from ethanol formed orange rhombs, m. p. 163—164° (Found: C, 54·0; H, 6·3. $C_{18}H_{24}ClN_3O_5$ requires C, 54·35; H, 6·05%). The corresponding *picrate* separated from ethanol as needles, m. p. 202° (Found: C, 54·85; H, 5·3. $C_{24}H_{26}N_6O_8$ requires C, 54·75; H, 4·95%).

3-2′-*Ethoxyethyl*-2-(4-*methyl*-2-*pyridyl*)*indole* (III; R = Me).—A solution of the above phenylhydrazone perchlorate (3·1 g.) in absolute ethanol (75 ml.) was cooled in ice and saturated with dry hydrogen chloride, then kept at room temperature for 1 hr., refluxed for 5 hr. on a water-bath, and then allowed to cool. The resulting crystals were collected and recrystallised from ethanol, affording the *perchlorate* of the indole as yellow, diamond-shaped plates, m. p. 232° (1·62 g.) (Found: C, 56·9; H, 5·5; N, 7·25. $C_{18}H_{21}ClN_2O_5$ requires C, 56·8; H, 5·5; N, 7·35%), $\lambda_{max.}$ (acid) 2180, 2500, and 3660 Å (log ε 4·45, 3·86, and 4·18), with a shoulder at 3160 Å, $\lambda_{min.}$ 2405 and 2740 Å (log ε 3·85 and 3·39), $\lambda_{max.}$ (alkaline) 2190 and 3240 Å (log ε 4·28 and 4·29) with a slight shoulder at 2400 Å, $\lambda_{min.}$ 2730 Å (log ε 3·56). The pale yellow neutral or acidic ethanolic solution of the perchlorate was pale green-fluorescent under ultraviolet irradiation: the alkaline solution was yellow-brown and non-fluorescent.

The mother-liquor from which the above perchlorate had been filtered was evaporated to dryness and a solution of the residue in a minimum of water was basified with saturated sodium carbonate solution and extracted with ether. Removal of the ether from the dried (Na_2SO_4) extract gave the indole as a gum (1·1 g.), which yielded a *picrate* separating from dimethylformamide–ethanol as dark yellow needles, m. p. 210°, after sintering at 200° (Found: C, 56·45; H, 4·85; N, 13·9. $C_{24}H_{23}N_5O_8$ requires C, 56·6; H, 4·5; N, 13·75%). The base, liberated from this picrate by Nicolaus and Testa's method,[20] formed a colourless gum.

6,7-*Dihydro*-2-*methyl*-12H-*indolo*[2,3-a]*pyridocolinium Perchlorate* (IV; R = Me, X = ClO_4).—The above pyridylindole perchlorate (1 g.) was refluxed for 12 hr. with acetic acid (6 ml.) and constant-boiling hydrobromic acid (3 ml.). The yellow needles, m. p. 272° (decomp.) (0·39 g.), which were deposited on cooling were recrystallised from acetic acid–ethanol, after which they had m. p. 275° (decomp.) but consisted of a mixture of the perchlorate with a little of the bromide (Found: C, 57·5; H, 4·6; N, 8·15; Br, 4·05. Calc. for $C_{16}H_{15}ClN_2O_4$: C, 57·4; H, 4·5; N, 8·35; Br, 0; Cl, 10·6. Calc. for $C_{16}H_{15}BrN_2$: C, 61·0; H, 4·75; N, 8·9; Br, 32·0%). The mixture was recrystallised from ethanolic perchloric acid, affording the perchlorate (IV; R = Me, X = ClO_4) (see above) as yellowish-green needles, m. p. 286° (decomp.) (Found: C, 57·35; H, 4·1; N, 8·2; Cl, 10·9%), $\lambda_{max.}$ (acid) 2200, 3140, and 3835 Å (log ε 4·55, 4·26, and 4·34), with a shoulder at 2500 Å, $\lambda_{min.}$ 2750 and 3395 Å (log ε 3·65 and 4·08), $\lambda_{max.}$ (alkaline) 2240, 2645, 3650, and 4130 Å (log ε 4·53, 4·11, 4·23, and 4·36), $\lambda_{min.}$ 2480, 2950, and 3760 Å (log ε 3·95, 3·49, and 4·22).

The mother-liquor from which the yellow needles (0·39 g.) had been filtered was evaporated to a small volume and allowed to cool. The resulting yellow needles (0·29 g.) were recrystallised from acetic acid–ethanol, affording the corresponding *bromide*, decomp. >305° (Found: C, 61·3; H, 4·85%).

The above mixture of perchlorate and bromide (100 mg.) was shaken with a mixture of saturated sodium carbonate solution and chloroform. The red chloroform layer was treated with dry hydrogen chloride; the resulting precipitate (69 mg.) when recrystallised from methanol–ether afforded the chloride as yellow needles, identical with the same compound described above.

2,12-*Dimethyl*-12H-*indolo*[2,3-a]*pyridocolinium Iodide* (I; R = R′ = Me, X = I).—A mixture of 2-methylindolo[2,3-*a*]pyridocoline and an excess of methyl iodide was kept overnight at room temperature, then refluxed for 1 hr. and evaporated to dryness. The residue, when twice recrystallised from methanol–ether, afforded the *iodide* as yellow needles, sintering at 270° and decomposing above 350° (Found: C, 54·6; H, 4·4. $C_{17}H_{15}IN_2$ requires C, 54·5; H, 4·0%), $\lambda_{max.}$ (acid) 2210, 2510, 2915, 3360, and 3950 Å (log ε 4·49, 4·28, 3·95, 4·23, and 4·07), $\lambda_{min.}$ 2460, 2815, 3015, and 3660 Å (log ε 4·26, 3·90, 3·88, and 3·91), $\lambda_{max.}$ (alkaline) 2235, 2500,

[20] Nicolaus and Testa, *Angew. Chem.*, 1961, **73**, 655.

2915, 3375, and 3950 Å (log ε 4·47, 4·37, 4·07, 4·31, and 4·18), $\lambda_{min.}$ 2465, 2810, 3015, and 3660 Å (log ε 4·36, 4·02, 4·00, and 4·01). The solution of the iodide in acidic, neutral, or alkaline ethanol was yellow with blue fluorescence under ultraviolet irradiation. The corresponding *picrate* separated from dimethylformamide as needles, m. p. 252° (decomp.) (Found: C, 57·2; H, 4·05; N, 14·7. $C_{23}H_{17}N_5O_7,0{\cdot}5H_2O$ requires C, 57·1; H, 3·7; N, 14·45%). A solution of the iodide (39 mg.) in methanol (20 ml.) was refluxed for 4 hr. with freshly prepared silver chloride (15 mg.), then filtered and evaporated to give the *chloride* (26 mg.) which separated from water as pale yellow needles, decomp. >280° (Found: C, 68·3; H, 6·2; N, 9·4. $C_{17}H_{15}ClN_2,H_2O$ requires C, 67·9; H, 5·7; N, 9·3%).

6,7-*Dihydro*-2-*styryl*-12H-*indolo*[2,3-a]*pyridocolinium Chloride* (IV; R = ·CH:CHPh, X = Cl).—(*a*) A solution of 6,7-dihydro-2-methyl-12*H*-indolo[2,3-*a*]pyridocolinium chloride (2·8 g., 0·01 mole) in absolute methanol (30 ml.) was refluxed for 4 hr. with benzaldehyde (2·1 g., 0·02 mole) and cyclohexylamine (1 ml., 0·008 mole). On cooling, orange needles (1·2 g.) were deposited and concentration of the mother-liquor gave a further crop (1·6 g.). After recrystallisation from methanol this *chloride* had m. p. 328° (decomp.) (Found: C, 76·9; H, 5·8; N, 7·4. $C_{23}H_{19}ClN_2$ requires C, 77·0; H, 5·3; N, 7·8%), $\lambda_{max.}$ (acid) 2130, 2520, and 3540 Å (log ε 4·26, 4·13, and 4·5), with a shoulder at 4150 Å, $\lambda_{min.}$ 2360 and 2760 Å (log ε 4·09 and 3·66), $\lambda_{max.}$ (alkaline) 2170, 3450, and 4520 Å (log ε 4·39, 4·51, and 4·10), with a shoulder at 2500 Å, $\lambda_{min.}$ 2880 and 4080 Å (log ε 3·85 and 3·95). The orange-yellow neutral or acidic ethanolic solution of the chloride was pale green-fluorescent under ultraviolet irradiation; the alkaline solution was brown and pale yellow-fluorescent. The chloride was sparingly soluble in water, ethanol, acetone, and benzene and insoluble in ether. The corresponding *picrate* separated from dimethylformamide–ethanol as needles, m. p. 250° (decomp.), after sintering at 243° (Found: C, 62·3; H, 4·05. $C_{29}H_{21}N_5O_7,0{\cdot}5H_2O$ requires C, 62·15; H, 3·9%).

(*b*) The pyridocolinium chloride (8·4 g., 0·03 mole) in methanol (100 ml.), refluxed for 18 hr. with benzaldehyde (6·3 g., 0·06 mole) and piperidine (3 ml., 0·037 mole) gave the recrystallised styryl compound (7·1 g.), identical with that obtained by method (*a*).

2-*Styryl*-12H-*indolo*[2,3-a]*pyridocolinium Chloride* (I; R = H, R′ = ·CH:CHPh, X = Cl).—A solution of the last-mentioned chloride (0·2 g.) in ethanol (50 ml.) was refluxed for 11 hr. with tetrachloro-*o*-benzoquinone (1 g.), then concentrated to 20 ml. and diluted with ether. The precipitated *chloride* separated from ethanol as dark yellow needles which darkened at 200°, m. p. 303—307° (decomp.) (Found: C, 75·85; H, 5·25. $C_{23}H_{17}ClN_2,0{\cdot}5H_2O$ requires C, 75·5; H, 4·95%), $\lambda_{max.}$ (acid) 2210, 2510, 2910, 3360, 4170, and 4340 Å (log ε 4·63, 4·61, 4·44, 4·62, 4·70, and 4·71), $\lambda_{min.}$ 2360, 2790, 3040, 3720, and 4250 Å (log ε 4·51, 4·33, 4·40, 4·41, and 4·68), $\lambda_{max.}$ (alkaline) 2270, 2730, 3270, 4080, and 5120 Å (log ε 4·38, 4·52, 4·49, 4·38, and 4·03), $\lambda_{min.}$ 2500, 3000, 3660, and 4600 Å (log ε 4·27, 4·33, 4·28, and 3·91). The neutral or acidic ethanolic solution of the chloride was yellow and strongly green-fluorescent in daylight or under ultraviolet irradiation; the alkaline solution was red and slightly yellow-fluorescent under ultraviolet irradiation. The corresponding *picrate* separated from dimethylformamide as needles, m. p. 278° (decomp.) after sintering at 257° (Found: C, 62·55; H, 3·75. $C_{29}H_{19}N_5O_7,0{\cdot}5H_2O$ requires C, 62·4; H, 3·6%).

Oxidation of 6,7-*Dihydro*-2-*styryl*-12H-*indolo*[2,3-a]*pyridocolinium Chloride*.—Finely powdered potassium permanganate (2·6 g.) was added during 5 hr. to a stirred mixture of the styryl compound (IV; R = ·CH:CHPh, X = Cl) (1 g.) and acetone (200 ml.) at room temperature. The excess of permanganate was destroyed by sulphur dioxide and the mixture filtered. The precipitate was repeatedly extracted with hot water; the extracts, on cooling, deposited yellow needles, decomp. >350° (0·17 g.). Concentration of the aqueous extract yielded a further crop (0·31 g.). This substance separated from acetic acid as yellow needles, decomp. >330° (Found: C, 63·8; H, 5·3; N, 6·75%), $\lambda_{max.}$ (acid) 2110, 2225, 3260, and 4140 Å, with a shoulder at 2450 Å, $\lambda_{min.}$ 2150, 2720, and 3575 Å; $\lambda_{max.}$ (alkaline) 2230, 2950, 3220, and 3750 Å, $\lambda_{min.}$ 2800, 3120, and 3350 Å. The neutral or acidic ethanolic solution of the compound was yellow and strongly green-fluorescent under ultraviolet irradiation; the alkaline solution was yellowish-brown with a slight yellow fluorescence. The same substance was obtained by oxidation of 2-styryl-12*H*-indolo[2,3-*a*]pyridocolinium chloride (I; R = H, R′ = ·CH:CHPh, X = Cl) with aqueous potassium permanganate at room temperature.

2-N-(p-*Dimethylaminophenyl*)*formimidoyl*-12-*methyl*-12H-*indolo*[2,3-a]*pyridocolinium Chloride* (VII).—A solution of *NN*-dimethyl-*p*-nitrosoaniline hydrochloride (0·46 g., 0·0025 mole) in 95% ethanol (6 ml.) was refluxed for 30 min. with anhydrous sodium carbonate

(0·14 g.). The filtered solution was then refluxed with stirring for 9 hr. with 2,12-dimethyl-12*H*-indolo[2,3-*a*]pyridocolinium chloride (0·63 g., 0·0022 mole), ethanol (6 ml.), and piperidine (0·2 g., 0·0024 mole); on cooling, it deposited purple-red needles with a green iridescence (0·275 g.). Concentration of the filtered solution yielded a further crop of these needles (0·285 g.) Recrystallisation from ethanol afforded the *chloride* (VII), m. p. 337° (decomp.) (Found: C, 65·95; H, 6·3; N, 11·8. $C_{25}H_{23}ClN_4,2H_2O$ requires C, 66·4; H, 6·0; N, 12·3%), $\lambda_{max.}$ (acid) 2100, 2500, 2945, 3460, 4020, and 5200 Å (log ε 4·30, 4·36, 4·17, 4·12, 4·00, and 4·24), with a shoulder at 2300 Å, $\lambda_{min.}$ 2150, 2780, 3160, 3900, and 4300 Å (log ε 4·23, 4·13, 4·04, 3·97, and 3·91), $\lambda_{max.}$ (alkaline) 2190, 2505, 2905, and 4600 Å (log ε 4·35, 4·35, 4·19, and 3·85), with slight shoulders at 3300 and 5200 Å, $\lambda_{min.}$ 2350, 2740, and 4120 Å (log ε 4·33, 4·18, and 3·82), $\lambda_{max.}$ (neutral) 2110, 2340, 2485, 2930, 3510, and 5190 Å (log ε 4·33, 4·31, 4·33, 4·26, 4·12, and 4·46), $\lambda_{min.}$ 2190, 2390, 2775, 3200, and 4040 Å (log ε 4·29, 4·30, 4·23, 4·05, and 3·92). The neutral ethanolic solution of the chloride was vivid red, without fluorescence, but the colour disappeared rapidly in the presence of either acid or alkali.

2-*Formyl*-12-*methyl*-12H-*indolo*[2,3-a]*pyridocolinium Chloride* (I; R = Me, R′ = ·CHO, X = Cl).—The chloride (VII) (0·3 g.) was heated for 2 min. at 100° with 2N-hydrochloric acid (4 ml.). The crystals (0·18 g.) which separated on cooling were collected and recrystallised from water, affording the *aldehyde chloride* as dark yellow needles, decomp. >350° (Found: C, 57·85; H, 5·7; N, 8·65. $C_{17}H_{13}ClN_2,0·3H_2O$ requires C, 58·1; H, 5·4; N, 8·0%). The infrared spectrum of this compound showed a carbonyl vibration frequency of medium strength at 1695 $cm.^{-1}$; $\lambda_{max.}$ (acid) 2250, 2385, 2495, 2760, 2935, 3385, and 4000 Å (log ε 4·37, 4·33, 4·31, 4·02, 4·05, 4·23, and 4·11), $\lambda_{min.}$ 2340, 2450, 2700, 2830, 3050, and 3740 Å (log ε 4·32, 4·31, 4·02, 4·01, 3·97, and 3·97), $\lambda_{max.}$ (alkaline) 2240, 2525, 2910, 3420, and 3950 Å (log ε 4·33, 4·31, 4·08, 4·15, and 4·10), with a shoulder at 2340 Å, $\lambda_{min.}$ 2440, 2820, 3040, and 3700 Å (log ε 4·28, 4·06, 4·00, and 3·99). The neutral or acidic ethanolic solution of the chloride was pale yellow, with a sea-green fluorescence; the alkaline solution was yellowish-brown and pale green-fluorescent under ultraviolet irradiation.

A solution of this chloride (33 mg.) in ethanol (10 ml.) was added to one of phenylhydrazine hydrochloride (17 mg.) and crystalline sodium acetate (55 mg.) in 50% aqueous ethanol (15 ml.). The resulting precipitate (45 mg.) when crystallised from acetic acid afforded the *phenylhydrazone* of the aldehyde chloride as red needles, decomp. >205° (Found: C, 62·6; H, 6·05; N, 12·7. $C_{23}H_{19}ClN_4,3H_2O$ requires C, 62·7; H, 5·7; N, 12·45%). The 2,4-*dinitrophenylhydrazone* of the aldehyde hydrogen sulphate, formed in ethanol in the presence of sulphuric acid, was orange and too insoluble to be recrystallised; it was therefore purified by repeated extractions with hot ethanol, after which it decomposed above 300° (Found: C, 49·45; H, 3·5; N, 15·1. $C_{23}H_{18}N_6O_8S,1·5H_2O$ requires C, 49·0; H, 3·7; N, 14·9%).

4-*Methoxymethylpyridine* 1-*Oxide*.—Thionyl chloride (40 g.) was added during 30 min. to 4-hydroxymethylpyridine (32·7 g.) in chloroform (105 ml.) with stirring and cooling. The mixture was refluxed for 1 hr., cooled, and diluted with benzene (400 ml.), and the resulting 4-chloromethylpyridinium chloride (49·1 g.) was collected and, after being washed with benzene, followed by ether, had m. p. 171° (cf. ref. 21).

This chloride was converted into 4-methoxymethylpyridine.[22] To the latter (12·3 g.) in acetic acid (60 ml.), 35% hydrogen peroxide solution (10 ml.) was added and the mixture was heated at 70—80°. After 3 hr. further hydrogen peroxide (7 ml.) was added and the mixture kept at 70—80° for a further 9 hr. The bulk of the solvent was removed and the residue basified with hot, saturated sodium carbonate solution and extracted with chloroform. Distillation of the dried (Na_2SO_4) extract in an atmosphere of nitrogen afforded the N-*oxide* (13·4 g.), b. p. 141·5°/1·2 mm. (Found: C, 60·05; H, 6·6; N, 9·8. $C_7H_9NO_2$ requires C, 60·45; H, 6·45; N, 10·05%). The *picrate* separated from ethanol as needles, m. p. 117° (Found: C, 42·55; H, 3·15; N, 15·55. $C_{13}H_{12}N_4O_9$ requires C, 42·4; H, 3·25; N, 15·2%).

2-*Cyano*-4-*methoxymethylpyridine*.—The above *N*-oxide (10·8 g.) was treated with methyl sulphate (7·45 ml.), and the resulting salt (20·6 g.) was washed thoroughly with ether, then dissolved in water and added with stirring during 2 hr. to a solution of potassium cyanide (15·2 g.) in water (40 ml.) at −5° in an atmosphere of nitrogen. The mixture was kept for a further 1 hr. at −5°, then allowed to come to room temperature, kept there for 2 hr., and extracted with chloroform. The aqueous layer was kept overnight at room temperature and

[21] Mosher and Tessieri, *J. Amer. Chem. Soc.*, 1951, **73**, 4925.
[22] Suzuki, *Pharm. Bull.* (*Japan*), 1956, **4**, 211.

again extracted with chloroform. The combined extracts were dried (Na_2SO_4), boiled with charcoal, filtered, and distilled, affording the *nitrile* (6·4 g.), b. p. 96—97·5°/0·4 mm., which solidified. After recrystallisation from ethanol it formed needles, m. p. 38° (Found: C, 64·75; H, 5·2; N, 18·9. $C_8H_8N_2O$ requires C, 64·85; H, 5·4; N, 19·0%). The *perchlorate* separated from ethanol as plates, m. p. 137—138° (Found: C, 38·85; H, 3·65; N, 11·05. $C_8H_9ClN_2O_5$ requires C, 38·65; H, 3·6; N, 11·25%).

2-*γ*-*Ethoxybutyryl*-4-*methoxypyridine* (II; R = ·CH_2·OMe).—The above nitrile (4·6 g.) in ether (86 ml.) was treated in the usual way with a Grignard reagent prepared from 1-bromo-3-ethoxypropane (10·6 g.) and magnesium (1·6 g.) in ether (43 ml.), and the complex was hydrolysed with hydrochloric acid. However, the acid extracts were not heated, but merely kept for 10 min. at room temperature before being basified with saturated potassium carbonate solution and extracted with chloroform. Distillation of the dried (K_2CO_3) extract afforded the *ketone* (5·8 g.), b. p. 138—139°/0·95 mm. (Found: C, 65·8; H, 7·7; N, 5·85. $C_{13}H_{19}NO_3$ requires C, 65·85; H, 8·0; N, 5·9%). The 2,4-*dinitrophenylhydrazone hydrochloride* separated from ethanol as yellow needles, m. p. 164° (Found: C, 50·7; H, 5·25; N, 15·25. $C_{19}H_{24}ClN_5O_6$ requires C, 50·25; H, 5·3; N, 15·45%).

2-*γ*-*Ethoxybutyryl*-4-*methoxymethylpyridine Phenylhydrazone Perchlorate*.—The above ketone (2 g.) was refluxed for 4 hr. in aqueous ethanol containing phenylhydrazine hydrochloride (1·23 g.) and crystalline sodium acetate (4·1 g.). The ethanol was removed and the residual liquid basified with sodium carbonate and extracted with ether. The solvent was removed from the dried (Na_2SO_4) extract, and the residue was treated with ethanolic perchloric acid, affording the *phenylhydrazone perchlorate*, which separated from ethanol as orange plates, m. p. 155—156° (Found: C, 53·6; H, 6·2; N, 9·7. $C_{19}H_{26}ClN_3O_6$ requires C, 53·35; H, 6·1; N, 9·8%).

3-2′-*Ethoxyethyl*-2-(4-*methoxymethyl*-2-*pyridyl*)*indole* (III; R = ·CH_2·OMe).—A solution of the above perchlorate (2·1 g.) in ethanol (50 ml.) was saturated with hydrogen chloride at 0°, kept for 1 hr. at room temperature, then refluxed for 3 hr. and evaporated to dryness. The residue was shaken with sodium carbonate solution and ether, the dried (Na_2SO_4) extract was evaporated to dryness, and a solution of the residual gum in ethanol was treated with perchloric acid. Fractional crystallisation of the resulting product from ethanol yielded the starting material (0·29 g., m. p. 154°) and the less soluble *pyridylindole perchlorate* (1·27 g.), which formed yellow rhombs, m. p. 203° (Found: C, 55·5; H, 5·6; N, 7·1. $C_{19}H_{23}ClN_2O_6$ requires C, 55·55; H, 5·6; N, 6·8%), $\lambda_{max.}$ (acid) 2150, 2425, 3185, and 3695 Å (log ε 4·47, 4·09, 4·03, and 4·18), $\lambda_{min.}$ 2365, 2750, and 3250 Å (log ε 4·08, 3·69, and 4·03), $\lambda_{max.}$ (alkaline) 2185 and 3270 Å (log ε 4·37 and 4·31), $\lambda_{min.}$ 2735 Å (log ε 3·75). The neutral or acidic ethanolic solution of the perchlorate was pale yellow and pale green-fluorescent under ultraviolet irradiation; the alkaline solution was yellowish-brown and non-fluorescent.

2-*Bromomethyl*-6,7-*dihydro*-12H-*indolo*[2,3-a]*pyridocolinium Perchlorate* (IV; R = ·CH_2Br, X = ClO_4).—The last-mentioned perchlorate (0·83 g.) was refluxed for 12 hr. with acetic acid (5 ml.) and constant-boiling hydrobromic acid (2·5 ml.). On cooling, yellow needles (0·63 g.) separated and concentration of the filtrate from these yielded a further crop (0·19 g.). When recrystallised from acetic acid this material yielded yellowish-brown needles, m. p. 246° (decomp.), apparently a mixture of the perchlorate and bromide (Found: C, 47·9; H, 3·75; N, 5·85; Br, 31·0. Calc. for $C_{16}H_{14}BrClN_2O_4$: C, 46·45; H, 3·4; N, 6·75; Br, 19·35; Cl, 8·6. Calc. for $C_{16}H_{14}Br_2N_2$: C, 48·7; H, 3·55; N, 7·1; Br, 40·6%). Recrystallisation of this mixture from ethanolic perchloric acid afforded the *perchlorate* as orange-brown needles, m. p. 242° (decomp.) (Found: C, 47·0; H, 3·55; N, 7·1; Cl, 8·2%), $\lambda_{max.}$ (acid) 2190, 3215, and 3915 Å (log ε 4·42, 4·18, and 4·15) with a shoulder at 2470 Å, $\lambda_{min.}$ 2800 and 3510 Å (log ε 3·68 and 4·00), $\lambda_{max.}$ (alkaline) 2275, 3700, and 4300 Å (log ε 4·40, 4·13, and 4·16), $\lambda_{min.}$ 3010 and 3900 Å (log ε 3·71 and 4·10). The acidic ethanolic solution of the perchlorate was pale yellow and pale green-fluorescent under ultraviolet irradiation; the alkaline solution was light brown, with slight yellow fluorescence under irradiation.

4-2′-*Ethoxyethylpyridine*.—Freshly distilled 4-vinylpyridine (20 g.) was added to a solution of sodium (3 g.) in absolute ethanol (250 ml.), and the mixture was refluxed for 15 hr., acidified with hydrochloric acid, and evaporated to dryness. The residue was shaken with ether and an excess of sodium hydroxide solution, and the dried (Na_2SO_4) extract was distilled. The fraction of b. p. 112—115°/21 mm. (15·6 g.) was shaken in ethereal solution with sodium hydrogen sulphite solution, again dried (Na_2SO_4) and distilled, affording the *base* (14·6 g.) b. p.

110°/19 mm. (Found: C, 71·8; H, 9·05. $C_9H_{13}NO$ requires C, 71·5; H, 8·6%). The *picrate* separated from methanol as needles, m. p. 90° (85° after resolidification) (Found: C, 47·3; H, 4·3. $C_{15}H_{16}N_4O_8$ requires C, 47·4; H, 4·2%).

4-2′-*Ethoxyethylpyridine* 1-*Oxide*.—The above base (13·1 g.) was treated as for the preparation of 4-methoxymethylpyridine 1-oxide, affording the N-*oxide* (12·1 g.), b. p. 159°/0·75 mm. (Found: C, 64·95; H, 8·15. $C_9H_{13}NO_2$ requires C, 64·7; H, 7·8%). The *picrate* separated from ethanol as needles, m. p. 161° (Found: C, 45·45; H, 3·75. $C_{15}H_{16}N_4O_9$ requires C, 45·45; H, 4·05%).

2-*Cyano*-4-2′-*ethoxyethylpyridine*.—The above *N*-oxide (10·9 g.) was treated with methyl sulphate (6·2 ml.) with stirring during 30 min., then heated for 2 hr. on a water-bath. The resulting salt (19 g.) was washed with ether and dissolved in water (22 ml.). The resulting solution was added during 1 hr. to a stirred solution of potassium cyanide (14·3 g.) in water (44 ml.) at −5° in an atmosphere of nitrogen. The mixture was kept at −5° for a further 1·5 hr., then at room temperature for 1·5 hr., extracted with chloroform, kept overnight, and again extracted with chloroform. Distillation of the combined and dried ($MgSO_4$) extracts in an atmosphere of nitrogen afforded the *nitrile* (4·3 g.) as a very pale yellow liquid, b. p. 118—122°/0·5 mm., which darkened even when kept in a sealed tube. The *picrolonate* separated from water as crystals, m. p. 251° (Found: C, 52·7; H, 4·75. $C_{20}H_{20}N_6O_6,H_2O$ requires C, 52·4; H, 4·8%).

2-γ-*Ethoxybutyryl*-4-2′-*ethoxyethylpyridine* (II; R = ·$[CH_2]_2$·OEt).—The preceding nitrile (5·2 g.) in ether (20 ml.) was treated with a Grignard reagent prepared from 1-bromo-3-ethoxypropane (10·5 g.) and magnesium (1·8 g.) in ether (50 ml.) as for the preparation of 2-γ-ethoxybutyryl-4-methylpyridine, yielding the ketone (5·7 g.), probably containing a little of the corresponding imine, as a colourless liquid, b. p. 150—154°/0·35 mm. (Found: C, 67·8; H, 8·7; N, 6·45. Calc. for $C_{15}H_{23}NO_3$: C, 68·0; H, 8·7; N, 5·3. Calc. for $C_{15}H_{24}N_2O_2$: C, 68·2; H, 9·1; N, 10·6%). The 2,4-*dinitrophenylhydrazone hydrochloride* separated from ethanol as yellow needles, m. p. 112° (Found: C, 56·35; H, 6·5. $C_{21}H_{28}ClN_5O_6$ requires C, 56·6; H, 6·1%).

An ethanolic solution of the ketone was refluxed for 4·5 hr. with a slight excess of phenylhydrazine, then treated with perchloric acid, affording the *phenylhydrazone perchlorate*, which separated from ethanol as orange-brown needles, m. p. 143—144° (Found: C, 55·45; H, 6·85. $C_{21}H_{30}ClN_3O_6$ requires C, 55·35; H, 6·6%). The *phenylhydrazone picrate* separated from ethanol as light orange needles, m. p. 124° (Found: C, 55·55; H, 5·7. $C_{27}H_{32}N_6O_9$ requires C, 55·5; H, 5·5%).

3-2′-*Ethoxyethyl*-2-(4-2′-*ethoxyethyl*-2-*pyridyl*)*indole* (III; R = ·$[CH_2]_2$·OEt).—A solution of the above phenylhydrazone perchlorate (3·2 g.) in ethanol (75 ml.) was saturated with hydrogen chloride at 0°, kept at room temperature for 1·5 hr., refluxed for 5 hr., then evaporated to dryness. The residue was shaken with ether and sodium carbonate solution. Evaporation of the dried (Na_2SO_4) ethereal extract yielded the pyridylindole as a gum, which afforded a *picrate*, separating from methanol as crystals, m. p. 151° (Found: C, 57·7; H, 5·15; N, 12·65. $C_{27}H_{29}N_5O_9$ requires C, 57·2; H, 5·1; N, 12·4%), $\lambda_{max.}$ (acid) 2190 and 3650 Å (log ε 4·73 and 4·46) with shoulders at 2420 and 3150 Å, $\lambda_{min.}$ 2750 Å (log ε 4·04), $\lambda_{max.}$ (alkaline) 2250 and 3300 Å (log ε 4·57 and 4·56), $\lambda_{min.}$ 2750 Å (log ε 3·87).

2-2′-*Bromoethyl*-6,7-*dihydro*-12H-*indolo*[2,3-a]*pyridocolinium Perchlorate* (IV; R = ·$[CH_2]_2$·Br, X = ClO_4).—The above gummy pyridylindole (2·1 g.) was refluxed for 12 hr. with acetic acid (12·5 ml.) and constant-boiling hydrobromic acid (6·25 ml.). The resulting solution was evaporated to a small volume, diluted with absolute ethanol (5 ml.), and allowed to cool, whereupon yellow needles (1·0 g.) were deposited. Dilution of the filtrate from the latter with ether yielded a further crop (0·81 g.). This combined material was recrystallised from ethanolic perchloric acid, affording a *perchlorate* as orange-brown needles, m. p. 201—202° (Found: C, 49·95; H, 4·35; N, 6·25; Cl, 7·8. $C_{17}H_{16}BrClN_2O_4$ requires C, 50·25; H, 4·85; N, 6·2; Cl, 7·85%), $\lambda_{max.}$ (acid) 2120, 2460, 3215, and 4000 Å (log ε 4·40, 4·11 4·17, and 4·15), $\lambda_{min.}$ 2380, 2800, and 3530 Å (log ε 4·10, 3·55, and 3·91) $\lambda_{max.}$ (alkaline) 2300, 2650, and 4240 Å (log ε 4·39, 4·10, and 4·14), with a shoulder at 3700 Å, $\lambda_{min.}$ 2550 and 3000 Å (log ε 3·81 and 3·70). The acidic ethanolic solution of the perchlorate was pale yellow and pale green-fluorescent under ultraviolet irradiation; the alkaline solution was light brown and slightly yellow-fluorescent under irradiation.

Action of Peracetic Acid on 4-2′-*Diethylaminoethylpyridine*.—A solution of 4-2′-diethylaminoethylpyridine [23] (8·9 g.) in acetic acid (120 ml.) was heated for 3 hr. at 70—80° with 30%

[23] Matuszko and Taurins, *Canad. J. Chem.*, 1954, **32**, 538.

hydrogen peroxide solution (20 ml.). Additional hydrogen peroxide (14 ml.) was then added and the mixture kept at 70—80° for 9 hr. The solvent was removed at 80°, and the residue basified with hot saturated sodium carbonate solution and extracted with chloroform. Removal of the chloroform at 80° from the dried (Na_2SO_4) extract yielded an oil (7·1 g.) which on distillation gave a colourless liquid, b. p. 56—57°/0·4 mm. (3·7 g.) (Found: C, 50·05; H, 9·6; N, 8·8%). This afforded a 2,4-*dinitrophenylhydrazone* which separated from methanol–ethanol as yellow needles, m. p. 237° (Found: C, 47·1; H, 3·8. $C_{13}H_{11}N_5O_5,H_2O$ requires C, 46·6; H, 3·9%). It also afforded a picrate which separated from dimethylformamide–ether as needles, m. p. 144° (Found: C, 43·35; H, 4·55%).

Action of Perbenzoic Acid on 4-2′-Diethylaminoethylpyridine.—A solution of perbenzoic acid (21·3 g., 0·14 mole) in dry chloroform (410 ml.) was added to one of the base (9 g., 0·05 mole) in chloroform (45 ml.) at 0°. The mixture was kept at 0° with frequent shaking for 12 hr., then stirred with anhydrous potassium carbonate for 12 hr. and filtered. The filtrate was evaporated at 40° under reduced pressure. The residue when crystallised from benzene afforded 4-vinylpyridine 1-oxide (4·1 g.) as unstable, colourless crystals, m. p. 127°; for analysis it was dried for 2 hr. at room temperature over phosphoric oxide (Found: C, 68·65; H, 6·1. Calc. for C_7H_7NO: C, 69·4; H, 5·8. Calc. for $C_7H_7NO,0{\cdot}1H_2O$: C, 68·4; H, 5·85%). The *picrate* separated from ethanol as needles, m. p. 163° (decomp.) (Found: C, 44·55; H, 3·05. $C_{13}H_{10}N_4O_8$ requires C, 44·55; H, 2·85%).

4-*Hydroxymethylpyridine* 1-*Oxide.*—A solution of 4-acetoxymethylpyridine [13] (0·53 g.) in acetic acid (2 ml.) was heated for 3 hr. at 70—80° with 30% hydrogen peroxide solution (0·33 ml.). Further hydrogen peroxide (0·22 ml.) was added and the mixture kept at 70—80° for 9 hr. When worked up in the usual way, this solution yielded a gum which after trituration with ether yielded the *N*-oxide (0·5 g.), which separated from ethanol–benzene as colourless plates, m. p. 122° (Found: C, 57·7; H, 5·65. Calc. for $C_6H_7NO_2$: C, 57·6; H, 5·6%), $\lambda_{max.}$ (in EtOH) 2140 and 2680 Å (log ε 4·24 and 4·42), $\lambda_{min.}$ 2300 Å (log ε 2·53).

4-*Acetoxymethylpyridine* 1-*Oxide.*—A solution of perbenzoic acid (87·3 g.) in dry chloroform (1700 ml.) was added to (impure) 4-acetoxymethylpyridine [13] (82 g.) at 0° and the mixture was kept at 0° with frequent shaking for 18 hr., then stirred for 12 hr. with anhydrous potassium carbonate (100 g.) and filtered. The resulting solution apparently contained benzoyl peroxide. It liberated iodine only slowly from acidified potassium iodide solution, but if first treated with sodium methoxide it liberated it immediately. The peroxide was not removed by stirring the solution with ferrous sulphate, sodium sulphite, or active charcoal; and stirring it with solid potassium hydroxide resulted in a violent reaction and tar-formation. Attempts to isolate the *N*-oxide without removal of this peroxide led to explosions. The greater part of the chloroform was therefore removed at 50° under reduced pressure and the residue was extracted with water (3 × 250 ml.). The aqueous extract (which did not liberate iodine from acidified iodide) was evaporated, yielding 3-*hydroxy*-4-*methylpyridine* 1-*oxide* (3·7 g.), which separated from ethanol as colourless needles, m. p. 192° (Found: C, 57·9; H, 5·8; N, 10·95. $C_6H_7NO_2$ requires C, 57·6; H, 5·6; N, 11·2%), $\lambda_{max.}$ (acid) 2130, 2360, and 2855 Å (log ε 4·21, 3·79, and 3·79), $\lambda_{min.}$ 2245 and 2540 Å (log ε 3·71 and 3·24), $\lambda_{max.}$ (neutral) 2230, 2625, and 3000 Å (log ε 4·21, 4·10, and 3·65), $\lambda_{min.}$ 2375 and 2840 Å (log ε 3·54 and 3·51), $\lambda_{max.}$ (alkaline) 2390 and 3225 Å (log ε 4·36 and 3·75) with a shoulder at 2580 Å (log ε 3·94), $\lambda_{min.}$ 2820 Å (log ε 3·05). The filtrate, from the hydroxymethylpyridine 1-oxide was dissolved in chloroform (100 ml.), dried (Na_2SO_4), and distilled, affording 4-*acetoxymethylpyridine* 1-*oxide* (29 g.) as an almost colourless liquid, b. p. 155—162°/0·8 mm. (Found: C, 57·7; H, 5·65; N, 8·15. $C_8H_9NO_3$ requires C, 57·5; H, 5·4; N, 8·4%); the *picrate* separated from ethanol as needles, m. p. 125° (Found: C, 42·65; H, 3·0. $C_{14}H_{12}N_4O_{10}$ requires C, 42·4; H, 3·0%).

In another experiment 4-acetoxymethylpyridine (70 g.) yielded the *N*-oxide (31 g.) when treated with *m*-chloroperbenzoic acid (84 g.), without trouble due to peroxide contamination.

4-*Acetoxymethyl*-2-*cyanopyridine.*—4-Acetoxymethylpyridine 1-oxide (22·3 g.) was treated with methyl sulphate (12·7 ml.), the resulting salt washed with ether, and a solution of it (37·9 g.) in water (40 ml.) was added during 2 hr. to one of potassium cyanide (26 g.) in water (72 ml.) at −5° in an atmosphere of nitrogen. The mixture was kept for a further 1 hr. at −5°, then allowed to come to room temperature. After 1 hr. a solid (2·4 g.) was collected; this separated from ethanol as colourless needles, m. p. 138°, and was thought to be either 2-cyano-3- or 2-cyano-5-methoxy-4-methylpyridine (Found: C, 64·95; H, 5·65. $C_8H_8N_2O$ requires C, 64·8; H, 5·4%). It had light absorption: (*a*) neutral or acid, $\lambda_{max.}$ 2200 and 2690 Å (log

ε 3·83 and 3·41) with a shoulder at 2750 Å (log ε 3·32), $\lambda_{min.}$ 2450 Å (log ε 3·15); (*b*) alkaline, $\lambda_{max.}$ 2220 and 2690 Å (log ε 3·83 and 3·40) with a shoulder at 2750 Å (log ε 3·34), $\lambda_{min.}$ 2450 Å (log ε 3·17). The infrared spectrum of this compound contained bands at 1260 and 1125 $cm.^{-1}$ associated with the ether linkage. The aqueous filtrate from which the above compound had been obtained was kept for 1 hr. at room temperature, then extracted with chloroform. It was then kept overnight and again extracted with chloroform. The combined and dried (Na_2SO_4) extracts were distilled and the fraction of b. p. 120—125°/0·35 mm., which solidified on cooling, was fractionally crystallised from ethanol, affording the less soluble nitrile, m. p. 138°, obtained above (0·5 g.) and the more soluble 4-*acetoxymethyl*-2-*cyanopyridine* (5·6 g.), colourless needles, m. p. 58° (Found: C, 61·8; H, 4·8; N, 15·7. $C_9H_8N_2O_2$ requires C, 61·35; H, 4·55; N, 15·9%). This had light absorption: (*a*) neutral or acid, $\lambda_{max.}$ 2200 and 2650 Å (log ε 3·99 and 3·62) with a shoulder at 2700 Å, $\lambda_{min.}$ (log ε 3·18); (*b*) alkaline, $\lambda_{max.}$ 2230 and 2630 Å (log ε 3·96 and 3·58) with a shoulder at 2700 Å, $\lambda_{min.}$ 2420 Å (log ε 3·34).

2-*γ*-*Ethoxybutyryl*- *and* 2-*Cyano*-4-*hydroxymethylpyridine*.—4-Acetoxymethyl-2-cyanopyridine (5·7 g.) in ether (100 ml.) was treated with a Grignard reagent from 1-bromo-3-ethoxypropane (12·9 g.) and magnesium (1·95 g.) in ether (52 ml.) and worked up in the usual way, affording 2-*cyano*-4-*hydroxymethylpyridine* (1·3 g.), b. p. 140—150°/0·25 mm., colourless needles (from ethanol), m. p. 110° (Found: C, 62·6; H, 4·95; N, 20·8. $C_7H_6N_2O$ requires C, 62·6; H, 4·5; N, 20·9%), and a liquid (2·4 g.), b. p. 150—156°/0·25 mm. The latter when redistilled afforded 2-*γ*-*ethoxybutyryl*-4-*hydroxymethylpyridine*, b. p. 153—158°/0·3 mm. (Found: C, 64·5; H, 7·6; N, 6·35. $C_{12}H_{17}NO_3$ requires C, 64·6; H, 7·6; N, 6·25%).

2-3′-*Bromopropoxytetrahydropyran*.—3-Bromopropan-1-ol was prepared from β-bromopropionyl chloride [24] by Nystrom's method.[25] It (3·9 g.) was heated at 100° for 3 hr. with dihydropyran (2·36 g.) and ammonium chloride (0·024 g.). The cooled mixture was diluted with ether, washed with sodium hydrogen carbonate solution, dried (K_2CO_3), and distilled, affording the *product* (5·2 g.) as a colourless liquid with a pleasant smell, b. p. 64—65°/0·8 mm. (Found: C, 43·35; H, 7·05; Br, 35·45. $C_8H_{15}BrO_2$ requires C, 43·05; H, 6·75; Br, 35·9%).

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Department of Chemistry, King's College (University of Durham),
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[24] Hamilton and Simpson, *J. Amer. Chem. Soc.*, 1929, **51**, 3158.
[25] Nystrom, *J. Amer. Chem. Soc.*, 1955, **77**, 2544.