529. *Indolizines. Part III* [1]

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1-Cyano- and 1-nitro-indolizines have been prepared. Indolizines have also been prepared by the cyclisation of intermediates formed from the reaction of 2-bromomethylpyridine with active methylene compounds. Pyrrolo-[1,2-*a*]quinolines have been obtained by a similar route from 2-bromomethylquinoline. The properties of some aminoindolizines are described.

Amino- and aminomethyl-indolizines were required for biological evaluation. Convenient routes to these compounds appeared to be the reduction of the corresponding nitro- and cyano-derivatives by an extension of the previously reported route [1,2] for the synthesis of indolizine-1-carboxylates. The preparation of 1-cyano-2-phenylindolizine by the reaction of 2-cyanomethylpyridine with phenacyl bromide has been described in Part II.[1] We have now extended this type of synthesis to the preparation of 1-cyanoindolizine itself and 1-cyanoindolizines containing 2-methyl, 3-phenyl, 3-methyl-2-phenyl, and 2-ethoxycarbonyl substituents by reaction of the appropriate α-bromocarbonyl compounds.

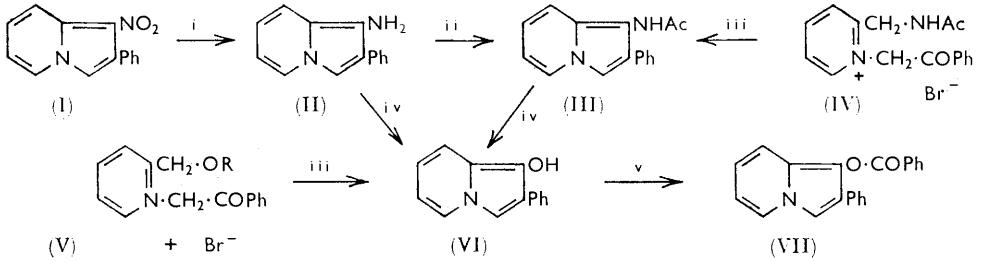
2-Nitromethylpyridine, a possible starting material for 1-nitroindolizines had been previously obtained [3] in unstated yield by the alkaline hydrolysis of 2-methyl-α-nitro-α-phthaloylpyridine. The product was a dark oil which decomposed on attempted distillation but which was characterised as its picrate. We have demonstrated that a chromatographic purification of this crude product gives a pale yellow oil, which forms the authentic picrate, and which slowly absorbs moisture from the air to form a stable, solid monohydrate. 2-Nitromethylpyridine, even in the form of its hydrate, rapidly yielded indolizines with the more reactive α-bromocarbonyl compounds. The less-reactive α-bromocarbonyl compounds, however, required a longer period of heating and the dark colour of the final reaction mixture suggested that side-reactions could be lowering the yields. The cause of such side-reactions is possibly the instability of the 2-nitromethylpyridine, a sample obtained directly from an alumina column decomposed with near-explosive violence when heated on a water-bath.

2-Methyl-1-nitroindolizine, prepared in the above manner from bromoacetone and 2-nitromethylpyridine was shown to be identical with the product obtained by nitration of 2-methylindolizine as described by Burrows *et al.*[4] Hydrogenation of 1-nitro-2-phenylindolizine (I) in the presence of palladium–charcoal and hydrochloric acid yielded the hydrochloride of 1-amino-2-phenylindolizine (II). This compound and the corresponding base were unstable, but the amine was characterised as its acetyl derivative (III), which was also prepared by treatment of 2-acetamido-1-phenacylpyridinium bromide (IV) with sodium hydrogen carbonate. The properties of the amine (II) were those expected of a compound containing an amino-group directly attached to a heteroaromatic ring of high π-electron density.[5] Thus, the infrared spectrum showed the typical double NH stretching vibrations of a primary amine, the amine diazotised normally and the diazonium salt coupled with β-naphthol. Boiling hydrochloric acid gave a rapid and quantitative conversion into the hydrochloride of 1-hydroxy-2-phenylindolizine (VI) and ammonium chloride. Previous authors [6] noted the formation of ammonium chloride, though with no other isolatable product, by the action of hydrochloric acid on 3-acetamido-1-acetyl-2-methylindolizine. The similar hydrolysis of indol- and benzo[*b*]thiophen-amines is

[1] Part II, D. R. Bragg and D. G. Wibberley, *J.*, 1963, 3277.
[2] D. R. Bragg and D. G. Wibberley, *J.*, 1962, 2627.
[3] L. Zalukajevs and E. Vanags, *Zhur. obshchei Khim.*, 1957, **27**, 3278.
[4] E. T. Burrows, D. O. Holland, and J. Kenyon, *J.*, 1946, 1077.
[5] A. R. Katritzky and J. M. Lagowski, "Heterocyclic Chemistry," Methuen, London, 1959, p. 199.
[6] D. O. Holland and J. H. C. Nayler, *J.*, 1955, 1504.

known and has been suggested [7] to be due to the easy hydrolysis of the protonated form of the imino-tautomer (=C=NH_2^+).

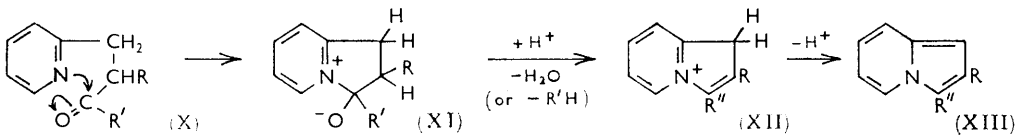
The free hydroxyindolizine (VI), which turned black on exposure to the air for a few hours, was characterised as its benzoyl derivative. 1-Hydroxyindolizines were hitherto unrecorded in the literature, but Boekelheide and Godfrey [8] reported some hydroxypyrrolo[1,2-*a*]isoquinolines of similar colour and stability. The same 1-hydroxy-2-phenylindolizine was additionally prepared by treatment of either 2-hydroxymethyl- (V; R = H), or 2-acetoxymethyl-1-phenacylpyridinium bromide (V; R = Ac) with sodium hydrogen carbonate. It gave an olive-green colour with ferric chloride and showed no carbonyl absorption in its infrared spectrum.



Reagents: i, H_2; ii, Ac_2O; iii, $NaHCO_3$; iv, HCl; v, Ph·COCl

1-Acetamido-2-phenylindolizine remained unchanged on boiling with aqueous alkali but with acid it was readily hydrolysed to the hydroxyindolizine (VI). Treatment of the acetamido-compound (III) with acetic anhydride yielded 3-acetyl-1-diacetylamino-2-phenylindolizine which lost one *N*-acetyl group on basic hydrolysis. 1-Amino-2-methylindolizine was less stable than the above 1-amino-2-phenylindolizine although 1-acetamido-2-methylindolizine, prepared by the action of sodium hydrogen carbonate on 2-acetamidomethyl-1-acetonylpyridinium bromide, was quite stable.

Our interest in 2-bromomethylpyridines [9] led us to investigate their use in an alternative type of indolizine synthesis. 2-Bromomethylpyridine was treated with the sodio-derivatives of methyl and ethyl acetoacetate, diethyl malonate, and acetylacetone, and the resulting 2-(2-oxoethyl)pyridines (X) were cyclised by a short period of reflux in acetic anhydride solution to give the indolizines (XIII; R = CO_2Me, R″ = Me), (XIII; R = CO_2Et, R″ = Me), (XIII; R = CO_2Et, R″ = OAc), and (XIII; R = Ac, R″ = Me), respectively. The reaction can be regarded as commencing with an intramolecular nucleophilic attack of the ring nitrogen atom on the side-chain carbonyl group. Of the several possible routes from the enolic betaine (XI) to the indolizine (XIII) the indicated route *via* the 1-protonated indolizinium cation (XII) presumes an initial acid-catalysed dehydration. From this



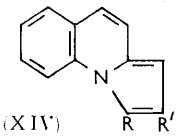
reaction mechanism it could be forecast that 2-(2,2-diacetylethyl)pyridine (X; R = Ac, R′ = Me) would give a better yield than 2-(2,2-diethoxycarbonylethyl) pyridine (X; R = CO_2Et, R′ = OEt) since it contains the more reactive carbonyl group. This was found to be true and, moreover, it was the ketonic carbonyl which was involved in the

[7] Ref. 5, p. 200.
[8] V. Boekelheide and J. C. Godfrey, *J. Amer. Chem. Soc.*, 1953, **75**, 3679.
[9] J. Hurst and D. G. Wibberley, *J.*, 1962, 1119.

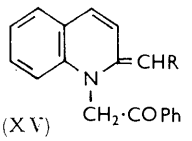
cyclisation of the acetoacetates (X; R′ = Me, R = CO_2Et or CO_2Me) with formation of 2-alkoxycarbonyl-3-methylindolizines. This type of cyclisation has been described by Boekelheide and Wingassen [10] in their preparation of indolizine itself by heating 3-(2-pyridyl)propanol with palladium–charcoal although the intermediate 3-(2-pyridyl)propan-1-one (X; R = R′ = H) was not isolated by these authors. It also strongly resembles the formation of 3-(2-pyridyl)indolizine by heating 1,1-diacetoxy-1,3-di-2-pyridylpropane *in vacuo*.[11]

Another example of intramolecular nucleophilic attack, on this occasion at a side-chain nitrile, was observed in the formation of 3-diacetylamino-2-phenylindolizine by the action of acetic anhydride on 2-β-cyanophenethylpyridine. As in the case of the 1-amino-indolizines, acid hydrolysis yielded ammonium chloride and, in this instance, 3-hydroxy-2-phenylindolizine hydrochloride. The expected 2-(2-cyano-2-ethoxycarbonylethyl)-pyridine was not isolated from the reaction of 2-bromomethylpyridine with ethyl cyano-acetate; instead, cyclisation occurred, without the addition of acetic anhydride, to yield ethyl 3-aminoindolizine-2-carboxylate. This was the most stable of the free amino-indolizines to be investigated, a sample recrystallised for analysis darkened only after exposure to the air for several weeks. Treatment with acetyl chloride yielded the 3-acetamido-, and acetic anhydride the 3-diacetylamino-2-ethoxycarbonylindolizines. Hydrolysis with hydrochloric acid gave ammonium chloride although the expected 2-ethoxycarbonyl-3-hydroxyindolizine could not be isolated from the reaction mixture.

An attempt to extend our first method for the synthesis of indolizine from ethyl 2-pyridylacetate to the synthesis of pyrrolo[1,2-*a*]quinolines (XIV) from ethyl 2-quinolylacetate was unsuccessful: 1,2-dihydro-2-ethoxycarbonylmethylene-1-phenacylquinoline



(XIV)



(XV)

(XV; R = CO_2Et) was the sole product from the action of phenacyl bromide on ethyl 2-quinolylacetate. Attempted cyclisation of this methine with sodium hydrogen carbonate yielded only unchanged starting material and, with sodium hydroxide, yielded 1,2-dihydro-2-methylene-1-phenacylquinoline (XV; R = H). The formation of nitrogen bridgehead compounds by the application of the Tschitschibabin synthesis to quinaldine has also not been substantiated, and it seems probable that the reason for the failure lies in the extra stability of exocyclic methine forms in the quinloine series over those in the pyridine series.[12] Two pyrrolo[1,2-*a*]quinolines were, however, successfully prepared by application of the second general method described above. In this instance, the treatment of 2-(2,2-diethoxycarbonylethyl)quinoline with acetic anhydride yielded ethyl 1-acetoxy-pyrrolo[1,2-*a*]quinoline-2-carboxylate (XIV; R = OAc, R′ = CO_2Et) and the treatment of 2-(2,2-diacetylethyl)quinoline yielded 2-acetyl-1-methylpyrrolo[1,2-*a*]quinoline (XIV; R = Me, R′ = Ac).

Experimental

Infrared spectra were, unless otherwise stated, taken in chloroform solution with a Unicam S.P. 200 spectrophotometer.

General Procedure for 1-*Cyano- and* 1-*Nitro-indolizines.*—Except where otherwise stated, the α-bromocarbonyl compound (0·01 mole), the picolyl derivative (0·02 mole), and acetone were refluxed together for the stated time and the indolizine was isolated by the method previously described.

1-*Cyanoindolizine.* 2-Cyanomethylpyridine and bromoacetaldehyde were heated together

[10] V. Boekelheide and R. J. Wingassen, *J. Amer. Chem. Soc.*, 1959, **81**, 1456.
[11] J. Michalshi, K. Wojaczynski, and H. Zajac, *Bull. Acad. polon. Sci., Ser. Sci. chim.*, 1960, **8**, 557.
[12] K. Winterfeld and K. Küllmar, *Arch. Pharm.*, 1958, **291**, 485.

without solvent on a water-bath for 22 hr. to yield the *nitrile* (45%). Sublimation at 50°/1·0 mm. followed by crystallisation from light petroleum gave needles, m. p. 52—53° (Found: C, 76·1; H, 4·4; N, 19·55. $C_9H_6N_2$ requires C, 76·0; H, 4·3; N, 19·7%), $\nu_{max.}$ 2205s cm.$^{-1}$ (C≡N).

1-*Cyano*-2-*methylindolizine*. 2-Cyanomethylpyridine and α-bromoacetone (17 hr., reflux) yielded 1-*cyano*-2-*methylindolizine* (69%). Sublimation at 90°/1·0 mm. followed by crystallisation from light petroleum gave leaflets, m. p. 100—101° (Found: C, 77·2; H, 5·4; N, 17·4. $C_{10}H_8N_2$ requires C, 76·9; H, 5·2; N, 17·95%), $\nu_{max.}$ 2200s cm.$^{-1}$ (C≡N).

1-*Cyano*-3-*phenylindolizine*. 2-Cyanomethylpyridine and α-bromo-α-phenylacetaldehyde (6 hr., reflux) yielded 1-*cyano*-3-*phenylindolizine* (50%). Sublimation at 90°/1·0 mm. followed by crystallisation from ethanol yielded green-tinted needles, m. p. 95—96° (Found: C, 82·5; H, 4·75; N, 12·7. $C_{15}H_{10}N_2$ requires C, 82·5; H, 4·6; N, 12·8%), $\nu_{max.}$ 2230s cm.$^{-1}$ (C≡N).

1-*Cyano*-3-*methyl*-2-*phenylindolizine*. 2-Cyanomethylpyridine and α-bromopropiophenone (17 hr.) yielded 1-*cyano*-3-*methyl*-2-*phenylindolizine* (2·0%). Sublimation at 160°/1·0 mm. followed by crystallisation from ethanol yielded pale green needles, m. p. 173—174° (Found: C, 82·9; H, 5·2; N, 12·2. $C_{16}H_{12}N_2$ requires C, 82·7; H, 5·2; N, 12·1%), $\nu_{max.}$ 2210s cm.$^{-1}$ (C≡N).

Ethyl 1-*cyanoindolizine*-2-*carboxylate*. 2-Cyanomethylpyridine and ethyl bromopyruvate (1 hr.) yielded the *ester* (77%), needles, m. p. 125—126° (from ethanol) (Found: C, 66·9; H, 4·6; N, 13·05. $C_{12}H_{10}N_2O_2$ requires C, 67·3; H, 4·7; N, 13·1%), $\nu_{max.}$ 2210s (C≡N), 1705s cm.$^{-1}$ (ester C=O).

2-*Nitromethylpyridine*.—A suspension of 2-[nitro(phthaloylmethyl]pyridine (100 g.) in 10% sodium hydroxide solution (400 ml.) was stirred vigorously at room temperature for 3 hr. The clear red solution was acidified and the precipitated phthalic acid (42 g.) collected. The filtrate was extracted with chloroform, the extract washed with sodium hydrogen carbonate solution, dried, and evaporated. The resulting brown oil was dissolved in benzene and run through an alumina column; the bright yellow band of product was eluted with more benzene. Evaporation of the eluate under reduced pressure yielded the nitro-compound as a pale yellow oil which absorbed water from the atmosphere to form a *monohydrate* (44 g., 76%). Crystallisation from ethanol gave yellow prisms, m. p. 48—49° (Found: C, 46·1; H, 5·0; N, 18·4; H_2O, 11·6%. $C_6H_6N_2O_2,H_2O$ requires C, 46·2; H, 5·2; N, 18·0; H_2O, 11·5%), $\nu_{max.}$ 1565 and 1365 cm.$^{-1}$ (NO_2). The picrate had m. p. 152—153° (Found: C, 39·4; H, 2·6; N, 18·8%. Calc. for $C_{12}H_5N_5O_9$: C, 39·3; H, 2·5; N, 19·0%). Zalukajevs and Vanags [3] describe 2-nitromethylpyridine as a dark oil (Found: N, 16·31%) which formed a picrate, m. p. 152—153° (Found: N, 18·7%).

1-*Nitroindolizine*.—2-Nitromethylpyridine hydrate and bromoacetaldehyde were heated together without solvent on a water-bath for 1 hr. to yield the *nitroindolizine* (47%). Sublimation at 130°/1·0 mm. followed by crystallisation from ethanol yielded yellow needles, m. p. 141—142° (Found: C, 59·3; H, 3·9; N, 17·1. $C_8H_6N_2O_2$ requires C, 59·2; H, 3·7; N, 17·3%), $\nu_{max.}$ 1520m and 1325s cm.$^{-1}$ (NO_2).

2-*Methyl*-1-*nitroindolizine*.—2-Nitromethylpyridine hydrate and bromoacetone (17 hr., reflux) yielded 2-methyl-1-nitroindolizine (70%) which was purified by chromatography on an alumina column.[4] The product (Found: C, 61·0; H, 4·8; N, 16·1%. Calc. for $C_9H_8N_2O_2$: C, 61·3; H, 4·6; N, 15·9%) separated from ethanol as pale yellow needles, m. p. 153—154° alone and with a sample prepared by the nitration of 2-methylindolizine. The infrared spectra of the two samples were also identical $\nu_{max.}$ 1520s and 1315s cm.$^{-1}$ (NO_2).

1-*Nitro*-2-*phenylindolizine* (I).—2-Nitromethylpyridine hydrate and phenacyl bromide (24 hr., reflux) yielded 1-*nitro*-2-*phenylindolizine* (52%), golden yellow plates (from ethanol), m. p. 151—152° (Found: C, 70·35; H, 4·5; N, 12·0. $C_{14}H_{10}N_2O_2$ requires C, 70·6; H, 4·2; N, 11·8%), $\nu_{max.}$ 1515s and 1315s cm.$^{-1}$ (NO_2).

1-*Nitro*-3-*phenylindolizine*.—2-Nitromethylpyridine hydrate and α-bromo-α-phenylacetaldehyde (17 hr., reflux) yielded 1-*nitro*-3-*phenylindolizine* (75%). Sublimation at 130°/1·0 mm. followed by crystallisation from ethanol gave yellow prisms, m. p. 137—138° (Found: C, 70·75; H, 4·3; N, 11·7. $C_{14}H_{10}N_2O_2$ requires C, 70·6; H, 4·2; N, 11·8%).

Ethyl 1-*Nitroindolizine*-2-*carboxylate*.—2-Nitromethylpyridine hydrate and ethyl bromopyruvate (1 hr., reflux) yielded the *ester* (78%), yellow prisms (from ethanol), m. p. 117—118° (Found: C, 56·6; H, 4·2; N, 12·1. $C_{11}H_{10}N_2O_4$ requires C, 56·4; H, 4·3; N, 12·0%), $\nu_{max.}$ 1710s (ester C=O), 1515m and 1320s cm.$^{-1}$ (NO_2).

2-*Acetamidomethyl*-1-*phenacylpyridinium Bromide* (IV).—2-Acetamidomethylpyridine (2·4 g.), phenacyl bromide (3·0 g.), and acetone (10 ml.) were refluxed for 4 hr. to yield the *quaternary salt* (3·52 g.), prisms (from ethanol), m. p. 181—182° (decomp.) (Found: C, 54·75; H, 5·1; Br, 23·2; N, 8·2. $C_{16}H_{17}BrN_2O_2$ requires C, 55·0; H, 4·9; Br, 22·9; N, 8·0%).

1-*Acetamido*-2-*phenylindolizine* (III).—A solution of 2-acetamidomethyl-1-phenacylpyridinium bromide (1·0 g.) in 10% sodium hydrogen carbonate (10·0 ml.) was heated at 100° for 20 min. The precipitated *indolizine* (0·7 g.) was collected, sublimed at 160°/1·0 mm., and crystallised from ethanol to give pale yellow prisms, m. p. 192—193° (decomp.) (Found: C, 76·4; H, 5·6; N, 11·0. $C_{16}H_{14}N_2O$ requires C, 76·8; H, 5·6; N, 11·2%), $\nu_{max.}$ (Nujol) 3240m (NH), 1665s cm.$^{-1}$ (amide C=O).

1-*Amino*-2-*phenylindolizine* (II).—1-Nitro-2-phenylindolizine (1·14 g.), palladium–charcoal (0·57 g.), ethanol (20 ml.), and concentrated hydrochloric acid (0·6 ml.) were shaken together in the presence of hydrogen at 4·0 atm. for 1 hr. The mixture was filtered through Celite and the filtrate concentrated to low volume when the amine hydrochloride (0·97 g.) separated as an orange-yellow solid, m. p. 115—116° (from ethanol). This darkened on heating or keeping for several days and gave unsatisfactory analysis figures (Found: C, 63·7; H, 5·5; Cl, 10·0, N, 9·7. Calc. for $C_{14}H_{13}ClN_2,H_2O$: C, 64·0; H, 5·8; Cl, 13·5; N, 10·7%). A solution of the hydrochloride (0·25 g.) in water was treated with 5% sodium hydrogen carbonate solution (5·0 ml.) followed by acetic anhydride (2·0 ml.). The mixture was shaken for 5 min. and the acetyl derivative collected. Crystallisation from ethanol gave yellow prisms, m. p. 193° (decomp.). The m. p. was undepressed with that of the above 1-acetamido-2-phenylindolizine and the two infrared spectra were identical. A freshly liberated sample of 1-amino-2-phenylindolizine showed $\nu_{max.}$ 3400m and 3320m cm.$^{-1}$ (NH) and gave a red dye after diazotisation and addition to alkaline β-naphthol. The amine was bright yellow but within a few hours turned green; the colour deepened even more rapidly in hot solvents.

2-*Hydroxymethyl*-1-*phenacylpyridinium Bromide* (V; R = H).—2-Hydroxymethylpyridine (2·18 g.), phenacyl bromide (4·0 g.), and acetone (20 ml.) were refluxed for 4 hr. to yield the *quaternary salt* (5·35 g.), prisms (from ethanol), m. p. 164—165° (Found: C, 54·6; H, 4·9; Br, 25·6; N, 4·6. $C_{14}H_{14}BrNO_2$ requires C, 54·6; H, 4·6; Br, 25·9; N, 4·5%).

2-*Acetoxymethyl*-1-*phenacylpyridinium Bromide* (V; R = Ac).—2-Acetoxymethylpyridine (2·2 g.), phenacyl bromide (2·93 g.), and acetone (15 ml.) were refluxed for 4 hr. to yield the *bromide* (3·5 g.), prisms (from ethanol), m. p. 183—184° (decomp.) (Found: C, 54·8; H, 4·5; Br, 22·8; N, 3·9. $C_{16}H_{16}BrNO_3$ requires C, 54·9; H, 4·6; Br, 22·8; N, 4·0%).

1-*Hydroxy*-2-*phenylindolizine Hydrochloride* (VI).—(*a*) 1-Acetamido-2-phenylindolizine (0·5 g.) and concentrated hydrochloric acid (5·0 ml.) were refluxed together for 30 min. The mixture was cooled and the *hydrochloride* (0·46 g.) collected. Crystallisation from ethanol gave yellow prisms of a hemihydrate, m. p. >360° (Found: C, 66·0; H, 5·3; Cl, 13·85; N, 5·35. $C_{14}H_{12}ClNO,0{\cdot}5H_2O$ requires C, 66·0; H, 5·1; Cl, 13·9; N, 5·5%), $\nu_{max.}$ (Nujol) 3500m (free OH) and 2500—2750w cm.$^{-1}$ (bonded OH). Evaporation of the filtrate yielded ammonium chloride (0·15 g.). The same hydroxyindolizine hydrochloride was formed from 1-amino-2-phenylindolizine hydrochloride after boiling with hydrochloric acid.

(*b*) 2-Hydroxymethyl-1-phenacylpyridinium bromide (V; R = H) (3·9 g.), sodium hydrogen carbonate (3·9 g.), and water (40 ml.) were heated together for 30 min. and the precipitated dark red hydroxyindolizine collected. Immediate crystallisation from concentrated hydrochloric acid (20 ml.) yielded the hydrochloride (2·3 g.), m. p. >360°, and of identical infrared spectrum with that obtained in (*a*). 2-Acetoxymethyl-1-phenacylpyridinium bromide under these conditions gave the same hydroxyindolizine.

1-*Benzoyloxy*-2-*phenylindolizine* (VII).—1-Hydroxy-2-phenylindolizine hydrochloride (0·4 g.), benzoyl chloride (0·4 ml.), and 5% sodium hydroxide solution (4·0 ml.) were shaken together for 30 min. The *benzoyl derivative* (0·3 g.) separated as an oil which solidified on trituration with ethanol. Sublimation at 180°/1·0 mm. followed by crystallisation from ethanol gave lime-green prisms, m. p. 196—197° (Found: C, 80·4; H, 4·6; N, 4·6. $C_{21}H_{15}NO_2$ requires C, 80·4; H, 4·8; N, 4·5%), $\nu_{max.}$ 1720s cm.$^{-1}$ (C=O).

3-*Acetyl*-1-*diacetylamino*-2-*phenylindolizine*.—1-Acetamido-2-phenylindolizine (1·0 g.) and acetic anhydride (10·0 ml.) were refluxed together for 2 hr. The solution was diluted with water to yield the *triacetyl derivative* (1·34 g.), needles (from ethanol), m. p. 162—163° (Found: C, 71·9; H, 5·4; N, 8·3. $C_{20}H_{18}N_2O_3$ requires C, 71·9; H, 5·4; N, 8·4%), $\nu_{max.}$ NH absent, 1710s (amide C=O), 1620s cm.$^{-1}$ (C=C–O$^-$). ("Carbonyl" bands have been noted previously,[10] in

the region 1613—1626 cm.$^{-1}$. We find that, in 3-acetyl-2-methylindolizine, this band was at 1605 cm.$^{-1}$.) The triacetyl derivative slowly formed a purple 2,4-dinitrophenylhydrazone, m. p. 250—252°. Hydrolysis of the triacetyl derivative with hydrochloric acid yielded 1-hydroxy-2-phenylindolizine hydrochloride. Alkaline hydrolysis with 10% sodium hydroxide solution (2 hr., reflux) yielded 1-*acetamido*-3-*acetyl*-2-*phenylindolizine* (80%), pale green prisms (from ethanol), m. p. 209—210° (Found: C, 74·1; H, 5·5; N, 9·8. $C_{18}H_{16}N_2O_2$ requires C, 74·0; H, 5·5; N, 9·6%), $\nu_{max.}$ (Nujol) 3290m (NH), 1660s (amide C=O), 1620s cm.$^{-1}$ (C=C–O$^-$).

1-*Acetamido*-2-*methylindolizine*.—2-Acetamidomethylpyridine (0·65 g.) and bromoacetone were refluxed together in acetone (7·0 ml.) for 6 hr. The acetone was removed and the crude oily quaternary salt (0·9 g.) boiled with 10% sodium hydrogen carbonate solution (9·0 ml.). The precipitated indolizine (0·4 g.) was sublimed at 120°/1·0 mm. and crystallised from ethanol to give pale green prisms, m. p. 135—136° (decomp.) (Found: C, 70·2; H, 6·5; N, 14·4. $C_{11}H_{12}N_2O$ requires C, 70·2; H, 6·4; N, 14·9%), $\nu_{max.}$ (Nujol) 3250m (NH), 1650s cm.$^{-1}$ (amide C=O).

General Procedure for the Preparation of Indolizines from 2-Bromomethylpyridine.—2-Bromomethylpyridine (0·02 mole) was added to a solution of the active methylene compound (0·022 mole) and sodium ethoxide (from 0·022 mole of sodium) in ethanol (20 ml.), and the solution stirred at room temperature for the stated time. Water was added, the liberated 2-(2-oxoethyl)pyridine extracted into ether, and the extract dried and distilled. The intermediates were refluxed in acetic anhydride (10·0 ml./g.) for the stated time and the indolizine (XIII) isolated by dilution with water.

Ethyl 3-*acetoxyindolizine*-2-*carboxylate* (XIII; R = CO_2Et, R″ = OAc). 2-Bromomethylpyridine and diethylmalonate (1 hr.) yielded 2-(2,2-diethoxycarbonylethyl)pyridine [12] (X; R = CO_2Et, R′ = OEt) (80·5%), as a pale yellow oil, b. p. 132—133°/2·5 mm. (Found: C, 62·2; H, 7·0; N, 5·9. Calc. for $C_{13}H_{17}NO_4$: C, 62·1; H, 6·8; N, 5·6%). The malonate and acetic anhydride (2 hr., reflux) yielded the *indolizine ester* (36%), cream needles (from ethanol), m. p. 73—74° (Found: C, 62·8; H, 5·8; N, 5·5. $C_{13}H_{13}NO_4$ requires C, 63·1; H, 5·3; N, 5·7%), $\nu_{max.}$ 1780s (acetoxyl C=O), 1700s cm.$^{-1}$ (ester C=O). Basification of the mother-liquors from the isolation gave unchanged starting material (50%).

2-*Acetyl*-3-*methylindolizine* (XIII; R = COMe, R″ = Me). 2-Bromomethylpyridine and acetylacetone (18 hr.) yielded 2-(2,2-*diacetylethyl*)*pyridine* (X; R = Ac, R′ = Me) (57·5%) as a colourless oil, b. p. 91—93°/0·2 mm. (Found: C, 69·5; H, 7·3; N, 6·7. $C_{11}H_{13}NO_2$ requires C, 69·1; H, 6·9; N, 7·3%). The diketone and acetic anhydride (2 hr., reflux) yielded the *keto-indolizine* (65%). Purification was effected by extraction into ether, washing with dilute hydrochloric acid, evaporation to dryness, and crystallisation from light petroleum to give pale yellow plates, m. p. 60—61° (Found: C, 76·0; H, 6·4; N, 8·4. $C_{11}H_{11}NO$ requires C, 76·3; H, 6·4; N, 8·0%), $\nu_{max.}$ 1655s cm.$^{-1}$ (C=O). The 2,4-*dinitrophenylhydrazone* separated from nitrobenzene as black prisms, m. p. 265—266° (Found: C, 57·8; H, 4·3; N, 20·0. $C_{17}H_{15}N_5O_4$ requires C, 57·8; H, 4·3; N, 19·8%).

Ethyl 3-*methylindolizine*-2-*carboxylate* (XIII; R = CO_2Et, R″ = Me). 2-Bromomethylpyridine and ethyl acetoacetate (1 hr.) yielded 2-(2-*acetyl*-2-*ethoxycarbonylethyl*)*pyridine* (X; R = Ac; R′ = OEt) (43·5%) as a pale red oil, b. p. 97—99°/0·2 mm. (Found: C, 64·9; H, 6·9; N, 6·4. $C_{12}H_{15}NO_3$ requires C, 65·1; H, 6·8; N, 6·3%). The acetoacetate and acetic anhydride (1 hr., reflux) yielded the *indolizine ester* (19%). The ester, purified by crystallisation from light petroleum then from ethanol, separated as pale fawn needles, m. p. 49—50° (Found: C, 70·95; H, 6·3; N, 6·8. $C_{12}H_{13}NO_2$ requires C, 70·9; H, 6·4; N, 6·9%). In a closely similar preparation, but without the purification of the intermediate 2-(2-acetyl-2-methoxycarbonylethyl)pyridine, 2-bromomethylpyridine and methyl acetoacetate yielded *methyl* 3-*methylindolizine*-2-*carboxylate* (XIII; R = CO_2Me, R″ = Me) (9·0%) which crystallised from ethanol as pale fawn prisms, m. p. 87—88° (Found: C, 70·0; H, 6·1; N, 7·5. $C_{11}H_{11}NO_2$ requires C, 69·8; H, 5·9; N, 7·4%). Hydrolysis of either ester with 20% sodium hydroxide solution (4 hr., reflux) yielded, on acidification, 3-*methylindolizine*-1-*carboxylic acid* which crystallised as needles (from ethanol), m. p. 77—78° (Found: C, 68·9; H, 5·3; N, 7·8. $C_{10}H_9NO_2$ requires C, 68·6; H, 5·2; N, 8·0%) $\nu_{max.}$ 1685s cm.$^{-1}$ (C=O).

2-β-*Cyanophenethylpyridine*.—No reaction occurred with 2-bromomethylpyridine and benzyl cyanide with sodium ethoxide as catalyst. Powdered sodamide (4·1 g.) was added gradually to a solution of 2-bromomethylpyridine (9 g.) and benzyl cyanide (6·12 g.) in dry toluene (60 ml.) and the mixture stirred at room temperature for 18 hr. The resulting suspension was

washed with water and extracted with 10% hydrochloric acid. Basification of the acid extract yielded an oil which was distilled at 170—200°/0·6 mm. The distillate (4·4 g.) solidified on cooling and the solid was crystallised from ethanol to yield 2-β-*cyanophenethylpyridine* as prisms, m. p. 53° (Found: C, 80·6; H, 5·8; N, 13·35. $C_{14}H_{12}N_2$ requires C, 80·7; H, 5·8; N, 13·5%). A fraction (1·3 g.) boiling at 220—230°/0·6 mm. was also collected. Crystallisation from ether gave 2-*cyano*-2-*phenyl*-1,3-*di*-(2-*pyridyl*)*propane* as blunt needles, m. p. 80—81° (Found: C, 80·2; H, 5·8; N, 13·95. $C_{20}H_{17}N_3$ requires C, 80·2; H, 5·7; N, 14·0%).

3-*Diacetylamino*-2-*phenylindolizine*.—2-β-Cyanophenethylpyridine and acetic anhydride (2 hr., reflux) yielded the *indolizine* (18%), prisms (from ethanol), m. p. 113—114° (Found: C, 73·7; H, 5·7; N, 9·6. $C_{18}H_{16}N_2O_2$ requires C, 74·0; H, 5·5; N, 9·6%), $\nu_{max.}$ 1720s cm.$^{-1}$ (C=O), NH absent. Basification of the aqueous filtrate yielded unchanged starting material (75%). A solution of the diacetylamine (0·34 g.) in concentrated hydrochloric acid (4·0 ml.) was boiled for 1 hr. and cooled to yield the hydrochloride, m. p. 197—198° (from ethanol), of 3-hydroxy-2-phenylindolizine. The hydrochloride was not obtained analytically pure; evaporation of the acid filtrate gave ammonium chloride.

Ethyl 3-*Aminoindolizine*-2-*carboxylate*.—A solution from sodium (0·8 g.) and ethanol (40 ml.) was treated with ethyl cyanoacetate (19·4 g.) followed by 2-bromomethylpyridine and the mixture stirred at room temperature for 1 hr. Water was added and the liberated oil extracted into ether. The ethereal solution was extracted with dilute hydrochloric acid and the acidic extract made alkaline. The liberated *aminoindolizine* was distilled and the fraction (3·4 g.) b. p. 170—200°/2·0 mm. collected. Crystallisation from ethanol gave yellow needles, m. p. 71—72° (Found: C, 64·6; H, 6·1; N, 13·7. $C_{11}H_{12}N_2O_2$ requires C, 64·7; H, 5·9; N, 13·7%), $\nu_{max.}$ 3400m and 3320m (NH), 1670s cm.$^{-1}$ (ester C=O). *Ethyl* 3-*acetamidoindolizine*-2-*carboxylate* was prepared by stirring the amine with acetyl chloride. It separated from benzene as needles, m. p. 137—138° (Found: C, 63·2; H, 5·7; N, 11·6. $C_{13}H_{14}N_2O_3$ requires C, 63·4; H, 5·7; N, 11·4%), $\nu_{max.}$ 3380m (NH), 1695s and 1680s cm.$^{-1}$ (C=O of ester and amide). *Ethyl* 3-*diacetylaminoindolizine*-2-*carboxylate* was prepared by refluxing the amine with acetic anhydride for 2 hr. It separated from ethanol as prisms, m. p. 154—155° (Found: C, 62·5; H, 5·8; N, 9·9. $C_{15}H_{16}N_2O_4$ requires C, 62·5; H, 5·6; N, 9·7%), $\nu_{max.}$ 1720s, 1715s cm.$^{-1}$ (C=O of ester and amide), NH absent. Ethyl 3-aminoindolizine-2-carboxylate was refluxed with concentrated hydrochloric acid for 30 min. Evaporation of the solution gave a mixture of ammonium chloride and an oil which could not be solidified.

1,2-*Dihydro*-2-*ethoxycarbonylmethylene*-1-*phenacylquinoline*.—Ethyl 2-quinolylacetate (2·15 g.), phenacyl bromide (1·0 g.), and acetone (5·0 ml.) were refluxed together for 17 hr. The solution was evaporated to dryness and the residue triturated with dilute hydrochloric acid (10 ml.) and ether (10 ml.) to precipitate the *methine hydrochloride* (1·39 g.), m. p. 181—182° (decomp.) (from ethanol) (Found: C, 68·2; H, 5·6; N, 3·7. $C_{21}H_{20}ClNO_3$ requires C, 68·2; H, 5·4; N, 3·8%). Basification of the acid layer yielded unchanged ethyl 2-quinolylacetate (1·1 g.). A solution of the hydrochloride (1·2 g.) in water was treated with alkali to yield the *ethoxycarbonylmethylenequinoline* (0·7 g.) needles (from ethanol), m. p. 64—65° (Found: C, 75·5; H, 5·7; N, 4·4%; Equiv., 327. $C_{21}H_{19}NO_3$ requires C, 75·7; H, 5·7; N, 4·2%; Equiv., 333), $\nu_{max.}$ 1725s (ester C=O), 1685s cm.$^{-1}$ (ketone C=O). The product was unchanged after boiling for 30 min. with aqueous sodium hydrogen carbonate.

1,2-*Dihydro*-2-*methylene*-1-*phenacylquinoline*.—1,2-Dihydro-2-ethoxycarbonylmethylene-1-phenacylquinoline (0·2 g.), 20% sodium hydroxide solution (1·0 ml.), and ethanol (10 ml.) were refluxed together for 1·5 hr. The solution was concentrated to low bulk, adjusted to pH 7·0 and extracted with ether. Evaporation of the ethereal extract yielded the *methylenequinoline* (0·14 g.), needles (from ethanol), m. p. 77—78° (Found: C, 82·3; H, 5·8; N, 5·6%; Equiv., 259. $C_{18}H_{15}NO$ requires C, 82·7; H, 5·8; N, 5·4%; Equiv., 261), $\nu_{max.}$ 1685s (aryl C=O).

Ethyl 1-*Acetoxypyrrolo*[1,2-a]*quinoline*-2-*carboxylate* (XIV; R = OAc, R′ = CO_2Et).—Under the conditions described above for the preparation of indolizines from 2-bromomethylpyridine, 2-bromomethylquinoline (1·3 g.) and diethylmalonate (0·94 g.) yield the intermediate 2-(2,2-diethoxycarbonylethyl)quinoline (2·0 g.) which was treated with acetic anhydride without further purification to yield the *pyrroloquinoline* (0·16 g.), needles (from methanol), m. p. 105—106° (Found: C, 68·3; H, 5·1; N, 4·7. $C_{17}H_{15}NO_4$ requires C, 68·6; H, 5·1; N, 4·7%), $\nu_{max.}$ 1790s (acetoxyl C=O), 1700s cm.$^{-1}$ (ester C=O).

2-*Acetyl*-1-*methylpyrrolo*[1,2-a]*quinoline* (XIV; R = Me, R′ = Ac). Acetylacetone (0·84 g.)

and 2-bromomethylquinoline (2·2 g.) under the conditions described above for the pyrroloquinoline ester yielded an intermediate diketone (1·93 g.) which was cyclised to the *acetylpyrroloquinoline* (0·35 g.), needles (from ethanol), m. p. 102—103° (Found: C, 80·4; H, 5·9; N, 6·6. $C_{15}H_{13}NO$ requires C, 80·7; H, 5·9; N, 6·3%), $\nu_{max.}$ 1650s cm.$^{-1}$ (ketone C=O).

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[*Received, November 2nd*, 1964.]