Indolizines. Part IV.[1] Syntheses from 2-Acylmethylene-1-benzyl-1,2-dihydropyridine, Phenyl-2-picolyl Sulphone, and Related Compounds

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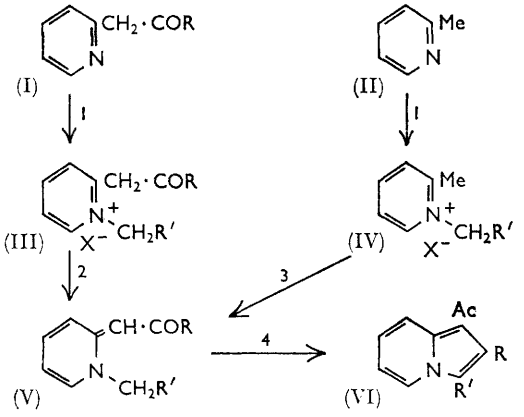
The scope of a new route to indolizines, which involves ring-closure at the 2-3 positions, has been investigated. In this method suitable 2-acyl- and 2-ethoxycarbonylmethylene-1-benzyl-1,2-dihydropyridines are cyclised to 2-acetoxy-3-aryl-, 2,3-diaryl-, and 2-alkyl-3-aryl-1-acetylindolizines by the action of acetic anhydride. Preparations of 1-amino- and 1-aminomethyl-indolizines have been continued. Indolizinyl sulphones have been synthesised from phenyl 2-picolyl sulphone.

In a preliminary Communication [2] we reported that indolizines could be prepared by a method of ring-closure at the 2—3 positions in the indolizine ring. The cyclisation involved an intramolecular aldol-type condensation of a suitable acyl- or ethoxycarbonyl-methine (V), and was best accomplished by heating under reflux with acetic anhydride. In successful cases excellent yields of the expected 1-acetylindolizines (VI) were obtained within 1 hr.

We have now investigated the scope of this reaction and find it particularly useful for the synthesis of 2,3-diaryl-, 2-alkyl-3-aryl-, and 2-acetoxy-3-aryl-indolizines. Where the required methine (V) can be prepared [3] by simultaneous acylation and dehydrohalogenation of a suitable 2-methylpyridinium bromide (IV) the overall route gives a cheap and rapid synthesis from α-picoline (II).



Reagents: 1, $R'CH_2X$; 2, NaOH; 3, RCOCl + NaOH; 4, Ac_2O

This route to the methines was not applicable, however, in the majority of cases necessitating an approach [3] *via* the quaternisation of the less readily accessible substituted picolines (I). 2-Benzoylmethylene-1-benzyl-1,2-dihydropyridine (V; R = R′ = Ph) which may be prepared by either of the above routes gave a 90% yield of 1-acetyl-2,3-diphenylindolizine (VI; R = R′ = Ph) by heating with acetic anhydride for 1 hr. The use of propionic anhydride yielded an analogous 1-propionylindolizine (VI; R = R′ = Ph; C_2H_5·CO for Ac) but sodium hydrogen carbonate, piperidine, and hydrochloric acid all failed to catalyse the cyclisation. The introduction of substituents into the 1-benzyl group had the expected effect, the yields obtained of 1-acetyl-3-aryl-2-phenylindolizines were in the order *p*-nitrophenyl > phenyl > *p*-methoxyphenyl. 2-Benzoylmethylene-1-benzyl-1,2-dihydro-5-methylpyridine, which was obtained from 2,5-lutidine, gave an excellent yield of a 6-methylindolizine.

With those methines in which either the *N*-methylene or the side-chain carbonyl group were not appreciably activated, the expected indolizines were not obtained. Thus, whereas 2-acetonylidene-1-benzyl-1,2-dihydropyridine (V; R = Me, R′ = Ph) had given an excellent yield of 1-acetyl-2-methyl-3-phenylindolizine (VI; R = Me, R′ = Ph) and 1-benzyl-2-ethoxycarbonylmethylene-1,2-dihydropyridine (V; R = OEt, R′ = Ph), under slightly stronger conditions, had yielded 2-acetoxy-1-acetyl-3-phenylindolizine (VI; R = OAc, R′ = Ph) the closely related 1-ethylmethines (V; R = Ph, R′ = Me and R = OEt, R′ = Me) both yielded 1-acetyl-2,3-dimethylindolizine (VI; R = R′ = Me). Similarly 2-cyanomethyl- (V; R′ = Ph, CN for COR), 2-carbamoylmethylene- (V; R = NH_2, R′ = Ph) and 2-phenylcarbamoylmethylene-1-benzyl-1,2-dihydropyridine (V; R = PhNH, R′ = Ph) all gave 1-acetyl-2-methyl-3-phenylindolizine (VI; R = Me, R′ = Ph); in the latter

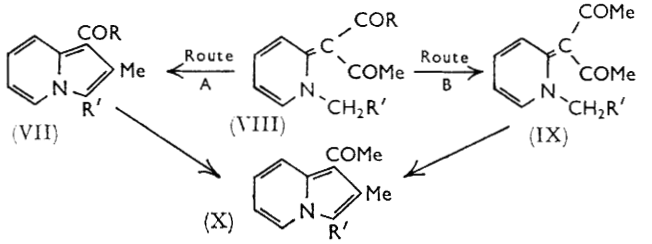
[1] Part III, J. Hurst, T. Melton, and D. G. Wibberley, *J. Chem. Soc.*, 1965, 2948.

[2] T. Melton, J. Taylor, and D. G. Wibberley, *Chem. Comm.*, 1965, 151.

[3] B. R. Baker and F. J. McEvoy, *J. Org. Chem.*, 1955, **20**, 118.

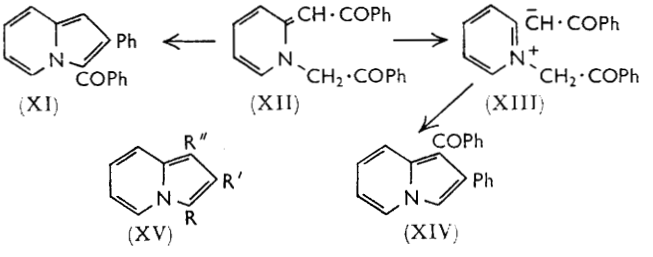
two cases ammonia and acetanilide, respectively, were isolated.

The starting materials (V) are keto-enamines and such compounds have been shown [4] to undergo C-acetylation when heated with acetic anhydride. With the above methines which gave unexpected compounds, the product of this type of C-acetylation, the diacylmethine (VIII) could form an indolizine by one of two alternative routes.



Either cyclisation can occur at this stage (route A), through the acetyl group, with subsequent transacylation of the indolizine (VII) to the 1-acetylindolizine (X), or the transacylation stage could occur initially (route B). No positive evidence was found for the formation of the diacetylmethine (IX) but the stability of 1-ethoxycarbonyl- and 1-cyanoindolizines towards acetic ahydride is strong evidence that route B is more likely in these examples.

2-Benzoylmethylene-1,2-dihydro-1-phenacylpyridine (XII) is theoretically capable of cyclisation to yield two different products. Closure of the indolizine ring at the 2—3 positions under the above conditions would yield 3-benzoyl-2-phenylindolizine (XI) (or its 1-acetyl derivative). But ring-closure to the indolizines at the 1–2 positions which has been suggested by us [5] to occur *via* carbanionbetaines (XIII) would yield the isomeric 1-benzoyl-2-phenylindolizine (XIV) (or its 3-acetyl derivative).



The product was shown, by comparison of the thin-layer chromatogram with that of authentic 3-benzoyl-2-phenylindolizine,[6] to be a mixture of the 3-benzoyl- (*ca.* 85%) and 1-benzoyl- (*ca.* 15%) 2-phenylindolizines. By a similar technique a sample of 1-benzoyl-2-phenylindolizine prepared by our previously described route [5] was shown to contain *ca.* 5% of the 3-isomer.

The infrared spectra of the benzoylmethines (V) all showed carbonyl absorption at the unusually low wavenumber (1510 cm.$^{-1}$) reported by other workers.[7] The 1-acylindolizines (VI) also showed a strong peak around 1495—1510 cm.$^{-1}$ together with the absorptions in the 1600—1620 cm.$^{-1}$ region about which we have previously commented.[1]

We have prepared further aminoindolizines for their biological evaluation by the methods recorded in Part III of this Series. Thus, the hydrogenation of the corresponding 1-nitroindolizines yielded 2,3-diphenyl-, 2-ethoxycarbonyl-, and 3-phenyl-1-aminoindolizines, all of which were more stable as their *N*-acetyl derivatives (XV; R'' = NHAc). Two other 1-acetamidoindolizines with 2,3-dimethyl- and 2-*p*-methylsulphonylphenyl substituents were prepared by the alternative Chichibabin route from 2-acetamidomethylpyridine. The hydrochloride of 1-hydroxy-2,3-diphenylindolizine, prepared by hydrolysis of the 1-acetamidoindolizine with hydrochloric acid, darkened to green on storage for 2 weeks, and to black after several months.

The n.m.r. spectra in trifluoroacetic acid of both the hydrochloride of 1-amino-2-ethoxycarbonylindolizine and the perchlorate of 1-hydroxy-2-phenylindolizine [1] showed signals (2H) at τ 4·33 and 4·4 indicating protonation at C-3.[8]

The formation of indolizines in one stage by the reaction of suitable side-chain substituted picolines has been extended to the sulphones (XV; R'' = SO_2Ph) and amides (XV; R'' = $CONH_2$). Three other indolizine-1-amides, the 2-methyl-, 2-ethoxycarbonyl-, and 2-phenyl- were prepared by reaction of the appropriate α-bromocarbonyl-compounds with 2-pyridylacetamide. 1-Carbamoyl-2-methylindolizine was alternatively prepared by alkaline hydrolysis of the corresponding nitrile. Similar hydrolysis of 1-cyano- and 1-cyano-3-phenylindolizines gave the corresponding amides together with small amounts of the 1-acid.

Neither the 1-nitriles nor the 1-amides proved suitable intermediates for the preparation of 1-aminomethylindolizines. Difficulty was experienced in reductions using lithium aluminium hydride because of the low solubility of these compounds in suitable solvents. 1-Cyanoindolizine, however, was soluble in ether and reduction with lithium aluminium hydride gave 1-aminomethylindolizine which was characterised as its triacetyl derivative. An alternative synthesis of these side chain amines is the cyclisation of *N*-carbonylmethylquaternary salts of 2-acetamidoethylpyridines and this proved to be a successful route for the synthesis of 1-acetamidomethyl-2-phenylindolizine.

Few sulphur-containing indolizines are known [9] and the publication [10] of the pharmacological properties

[4] G. H. Alt and A. J. Speziale, *J. Org. Chem.*, 1964, **29**, 798.
[5] D. R. Bragg and D. G. Wibberley, *J. Chem. Soc.*, 1963, 3277.
[6] E. T. Borrows, D. V. Holland, and J. Kenyon, *J. Chem. Soc.*, 1946, 1069.
[7] A. R. Katritzky and J. D. Rowe, *Spectrochim. Acta*, 1966, **22**, 381.
[8] M. Fraser, S. McKenzie, and D. H. Reid, *J. Chem. Soc.* (*B*), 1966, 44; W. L. F. Armarego, *ibid.*, p. 191.
[9] W. L. Mosby, "Heterocyclic Systems with Bridgehead Nitrogen Atoms," Interscience, New York, 1961, Part I, p. 265.
[10] L. Almirante, L. Polo, A. Magnaini, E. Provinciali, P. Rugarli, A. Biancotti, A. Gamba, and W. Murmann, *J. Medicin. Chem.*, 1965, **8**, 305.

of 2-*p*-methylsulphonylphenylimidazo[1,2-*a*]pyridine led us to synthesise the closely related 2-*p*-methylsulphonylphenylindolizines (XV; R = R'' = H, R' = $MeSO_2Ph$ and R = H, R' = $MeSO_2Ph$, R'' = NHAc) from α-picoline and 2-acetamidomethylpyridine, respectively. A series of indolizin-1-yl phenyl sulphones was also prepared from phenyl 2-picolyl sulphone. The latter is a much weaker base [11] (pK_a 2·54) than, for example, 2-phenacylpyridine (pK_a 5·03) so the isolation of some unchanged starting material, together with the expected indolizines, in reactions with α-bromocarbonyl compounds, was not surprising. Once formed, however, the quaternary salts of phenyl 2-picolyl sulphone, by virtue of their acidity located on the α-methylene group, would be expected to undergo the intramolecular aldol-type condensation and dehydrobromination more readily than related carbonyl-substituted picolines. This was difficult to prove since, although most α-bromocarbonyl compounds yielded the expected indolizin-1-yl sulphones with no isolated quaternary salt, phenacyl bromide did yield the intermediate salt, 1-phenacyl-2-phenylsulphonylmethylpyridinium bromide. The low solubility in the reaction solvent might well be the reason for the reluctance of this salt to cyclise since simply boiling a dilute aqueous solution, without the addition of any basic catalyst, caused quantitative conversion to phenyl 2-phenylindolizin-1-yl sulphone (XV; R = H, R'' = Ph, R'' = SO_2Ph).

Low solubility again, but on this occasion in an indolizine, necessitated a modification of the general conditions for the preparation of 1-morpholinothiocarbonyl-2-phenyl-1-indolizine (XV; R = H, R' = Ph, R'' = $C_4H_8NO{\cdot}CS$).

EXPERIMENTAL

Infrared spectra were determined, unless otherwise stated, in chloroform solution on a Unicam SP 200 spectrophotometer. Major peaks only are recorded except where assignment of a minor peak was obvious. Compounds obtained by more than one route were deemed identical when their mixed m. p.s were undepressed and their i.r. spectra were superimposable.

General Procedure for the Preparation of Methines (V).—The alkyl halide (0·01 mole) and the picolyl derivative (0·01 mole) were heated together on the water-bath for the stated time. The viscous residue was triturated with acetone to yield the quaternary salt. Basification of an aqueous solution of this salt with 5N-sodium hydroxide precipitated the methine. Stable crystalline methines were analysed at this stage; the less stable products were analysed at the quaternary salt stage and used immediately for the synthesis of the indolizines.

In this manner *p*-nitrobenzyl bromide and 2-phenacylpyridine (4 hr.) yielded the quaternary salt (25%) in plates, m. p. 190—191° (from ethanol). Basification of a solution of the salt gave 2-*benzoylmethylene*-1,2-*dihydro*-1-p-*nitrobenzylpyridine* (V; R = Ph, R' = p-$NO_2{\cdot}C_6H_4$) (94%), yellow needles, m. p. 203—204° (from ethanol) (Found: C, 72·4; H, 4·8; N, 8·6. $C_{20}H_{16}N_2O_3$ requires C, 72·3; H, (4·8; N, 8·4%), $\nu_{max.}$ 1635, 1530, and 1350 (NO_2), 1505 C=O), 1150 cm.$^{-1}$.

p-Methoxybenzyl bromide and 2-phenacylpyridine (4 hr.) yielded the quaternary salt (31%). Basification gave 2-*benzoylmethylene*-1,2-*dihydro*-1-p-*methoxybenzylpyridine* (V; R = Ph, R' = p-$CH_3OC_6H_4$) (95%), yellow needles, m. p. 142—143° (from light petroleum) (Found: C, 79·2; H, 5·8; N, 4·6. $C_{21}H_{19}NO_2$ requires C, 79·5; H, 6·0; N, 4·4%), $\nu_{max.}$ 1640, 1510 (C=O), 1480, 1260, 1150 cm.$^{-1}$.

Benzyl bromide and ethyl 2-pyridylacetate (3 hr.) yielded 1-*benzyl*-2-*ethoxycarbonylmethylpyridinium bromide* (III; R = OEt, R' = Ph, X = Br) (73%), prisms, m. p. 174—175° (from ethanol) (Found: C, 57·2; H, 5·5; Br, 23·4; N, 4·3. $C_{16}H_{18}BrNO_2$ requires C, 57·15; H, 5·4; Br, 23·8; N, 4·2%). Basification of a solution of this salt gave 1-benzyl-2-ethoxycarbonylmethylene-1,2-dihydropyridine (V; R = OEt, R' = Ph) (100%), yellow needles, m. p. 94—95° (from light petroleum) (Found: C, 75·05; H, 6·6; N, 5·8. $C_{16}H_{17}NO_2$ requires C, 75·25; H, 6·7; N, 5·6%), $\nu_{max.}$ 1655, 1630, 1540, 1270, 1140 cm.$^{-1}$.

Benzyl bromide and 2-pyridylacetone (12 hr.) gave a syrupy quaternary salt (52%) which was shaken with water and chloroform, and the cold aqueous layer basified to yield 2-*acetonylidene*-1-*benzyl*-1,2-*dihydropyridine* (V; R = Me, R' = Ph) (98%), yellow needles, m. p. 124—125° (from ethanol–light petroleum) (Found: C, 79·8; H, 6·7; N, 6·4. $C_{15}H_{15}NO$ requires C, 80·0; H, 6·7; N, 6·2%), $\nu_{max.}$ 1640, 1600, 1505 (C=O), 1470, 1310, 1145 cm.$^{-1}$.

Benzyl bromide and 2-cyanomethylpyridine (1 hr.) yielded the quaternary salt (76%). Basification gave 1-*benzyl*-2-*cyanomethylene*-1,2-*dihydropyridine* (V; R' = Ph, CN for COR) (94%), yellow prisms, m. p. 128—129° (from light petroleum) (Found: C, 81·2; H, 5·5; N, 13·45. $C_{14}H_{12}N_2$ requires C, 80·7; H, 5·8; N, 13·45%), $\nu_{max.}$ 2180 (CN), 1640, 1560, 1520, 1170 cm.$^{-1}$.

Benzyl bromide and 2-pyridylacetamide (6 hr.) gave the quaternary salt (95%). Basification gave 1-*benzyl*-2-*carbamoylmethylene*-1,2-*dihydropyridine* (V; R = NH_2, R' = Ph) (90%), yellow prisms, m. p. 153—154° (decomp.) (from ethanol) (Found: C, 73·9; H, 6·1; N, 12·1. $C_{14}H_{14}N_2O$ requires C, 74·3; H, 6·2; N, 12·4%), $\nu_{max.}$ 3450 and 3350 (N–H), 1645, 1620, 1540, 1300, 1150 cm.$^{-1}$.

Ethyl iodide and 2-phenacylpyridine (12 hr.) yielded 1-*ethyl*-2-*phenacylpyridinium bromide* (75%), prisms, m. p. 155—156° (from ethanol) (Found: C, 50·8; H, 4·4; N, 4·3. $C_{15}H_{16}INO$ requires C, 51·0; H, 4·6; N, 4·0%). An aqueous solution of the salt was basified in the presence of methylene chloride, the extract dried and evaporated to yield crude 2-benzoylmethylene-1-ethyl-1,2-dihydropyridine (96%) as a pale brown oil.

Ethyl iodide and ethyl 2-pyridylacetate (6 hr.) yielded 2-*ethoxycarbonylmethyl*-1-*ethylpyridinium iodide* (75%), prisms, m. p. 129—130° (from ethanol) (Found: C, 40·8; H, 5·2; N, 4·55. $C_{11}H_{16}INO_2$ requires C, 41·1; H, 5·0; N, 4·4%). 2-Ethoxycarbonyl-1-ethyl-1,2-dihydropyridine (100%) was isolated as a yellow oil in the manner described above for the 2-benzoylmethine.

2-*Benzoylmethylene*-1-*benzyl*-1,2-*dihydro*-5-*methylpyridine*.—2,5-Lutidine (4·3 g.) and benzyl bromide (6·8 g.) were heated together without solvent on the water-bath for 2 hr. to yield the quaternary salt (10·3 g., 92%). Benzoyl chloride (4·7 ml.) was added to a solution of the salt (6·0 g.) in water (25 ml.), and methylene chloride (50 ml.) under an atmosphere of nitrogen, followed immediately by 6N-sodium hydroxide (35 ml.) added over 5 min. with vigorous

[11] A. R. Katritzky, H. Z. Kucharska, and J. D. Rowe, *J. Chem. Soc.*, 1965, 3092.

stirring. The colour deepened rapidly from yellow through green to deep blue. After a further 30 min. the methylene chloride layer was separated, dried, and evaporated. The crude methine was dissolved in dilute hydrochloric acid (charcoal) and basified with sodium hydrogen carbonate to yield the methine (3·0 g., 46%), yellow prisms, m. p. 143—144° (from ethanol) (Found: C, 83·5; H, 6·1; N, 4·85. $C_{21}H_{18}NO$ requires C, 83·7; H, 6·3; N, 4·65%), $\nu_{max.}$ 1650, 1595, 1510 (C=O), 1300, 1140 cm.$^{-1}$.

2-*Benzoylmethylene*-1,2-*dihydro*-1-*phenacylpyridine* (V; R = Ph, R′ = PhCO).—α-Picoline (2·9 ml.), phenacyl bromide (5·8 g.), and dry ethanol (6·0 ml.) were heated under reflux for 2 hr. The mixture was cooled to yield 1-phenacyl-2-picolinium bromide (6·6 g.). Benzoyl chloride (4·5 ml.) was added to a solution of the salt (6·0 g.) in methylene chloride (50 ml.) and water (25 ml.) under an atmosphere of nitrogen, followed immediately by 6N-sodium hydroxide (36 ml.) added over 5 min. After a further 5 min. the mixture was cooled and filtered to yield a hydrate which was crystallised from ethanol and dried at 110° to give the anhydrous yellow *methine* (50%), m. p. 196—197° (Found: C, 79·7; H, 5·5; N, 4·6. $C_{21}H_{17}NO_2$ requires C, 79·95; H, 5·4; N, 4·4%), $\nu_{max.}$ 3400—3200 (O–H), 1625, 1505 (C=O), 1390 cm.$^{-1}$.

2-*Benzoylmethylene*-1-*benzyl*-1,2-*dihydropyridine* was prepared in 30% yield by the method of Baker and McEvoy.[3] It separated from benzene as plates, m. p. 161—162°, $\nu_{max.}$ 1640, 1570, 1510 (C=O), 1300, 1140 cm.$^{-1}$.

General Procedure for the Formation of Indolizines from the Methines.—The methine (1·0 g.) and acetic anhydride (10·0 ml.) were heated together under reflux for the stated time. The dark solution was stirred with water (100 ml.) for 10 min. and the precipitated indolizine collected.

1-*Acetyl*-2,3-*diphenylindolizine* (VI; R = R′ = Ph). 2-Benzoylmethylene-1-benzyl-1,2-dihydropyridine (1 hr. reflux) yielded the *acetylindolizine* (87%), plates, m. p. 175—176° (from ethanol) (Found: C, 84·7; H, 5·65; N, 4·3. $C_{22}H_{17}NO$ requires C, 84·85; H, 5·5; N, 4·5%), $\nu_{max.}$ 1645, 1620, 1505 cm.$^{-1}$.

1-Acetyl-2,3-diphenylindolizine (0·5 g.) and conc. hydrochloric acid (5·0 ml.) were heated together under reflux for 10 min. The mixture was diluted with water, made alkaline with 5N-sodium hydroxide and extracted with ether. Evaporation of the extract yielded 2,3-diphenylindolizine (0·39 g.). A suspension of 1-acetyl-2,3-diphenylindolizine (0·4 g.) in water (4·0 ml.) was stirred during the addition of conc. nitric acid until a clear solution was obtained. After a further 5 min. the solution was diluted with water to yield 1-*nitro*-2,3-*diphenylindolizine* (0·37 g.), yellow prisms, m. p. 229—230° (from ethanol–benzene) (Found: C, 76·4; H, 4·45; N, 8·9. $C_{20}H_{14}N_2O_2$ requires C, 76·4; H, 4·5; N, 8·9%), $\nu_{max.}$ 1630, 1520 and 1350 (NO_2), 1500, 1300 cm.$^{-1}$.

2-Benzoylmethylene-1,2-dihydro-1-*p*-nitrobenzylpyridine (1 hr. reflux) yielded 1-*acetyl*-3-p-*nitrophenyl*-2-*phenylindolizine* (VI; R = Ph, R′ = *p*-NO_2·C_6H_4 (93%), orange needles, m. p. 192—193° (from ethanol) (Found: C, 74·15; H, 4·4; N, 7·9. $C_{22}H_{16}N_2O_3$ requires C, 74·15; H, 4·5; N, 7·9%), $\nu_{max.}$ 1635, 1620, 1600, 1520 and 1350 (NO_2), 1495 cm.$^{-1}$.

2-Benzoylmethylene-1,2-dihydro-1-*p*-methoxybenzylpyridine (1 hr. reflux) yielded 1-*acetyl*-3-p-*methoxyphenyl*-2-*phenylindolizine* (VI; R = Ph, R′ = *p*-$CH_3OC_6H_4$) (27%). Sublimation at 160°/1 mm. followed by crystallisation from ethanol gave pale green prisms, m. p. 173—174° (Found: C, 80·7; H, 5·6; N, 4·0. $C_{23}H_{19}NO_2$ requires C, 80·9; H, 5·6; N, 4·1%), $\nu_{max.}$ 2750 (C–H), 1630, 1615, 1500, 1390, 1260 cm.$^{-1}$.

1-Benzyl-2-ethoxycarbonylmethylene-1,2-dihydropyridine (2 hr. reflux) yielded 2-*acetoxy*-1-*acetyl*-3-*phenylindolizine* (VI; R = OAc, R′ = Ph) (83%), plates, m. p. 104—105° (from ethanol) (Found: C, 73·8; H, 5·3; N, 4·6. $C_{18}H_{15}NO_3$ requires C, 73·7; H, 5·15; N, 4·8%), $\nu_{max.}$ 1765 (acetoxy C=O), 1640, 1630, 1605, 1510, 1400 cm.$^{-1}$.

2-Benzoylmethylene-1-benzyl-1,2-dihydro-5-methylpyridine (1 hr. reflux) yielded 1-*acetyl*-6-*methyl*-2,3-*diphenylindolizine* (87%). Sublimation at 160°/1mm. followed by crystallisation from ethanol gave prisms, m. p. 199—200° (Found: C, 85·1; H, 6·1; N, 4·4. $C_{23}H_{19}NO$ requires C, 84·9; H, 5·9; N, 4·3%), $\nu_{max.}$ 1615, 1505, 1430 cm.$^{-1}$.

2-Benzoylmethylene-1-benzyl-1,2-dihydropyridine (0·5 g.) and propionic anhydride (5·0 ml.) in a similar manner yielded 2,3-*diphenyl*-1-*propionylindolizine* (0·2 g., 35%), pale green needles, m. p. 177—178° (from ethanol) (Found: C, 84·9; H, 5·7; N, 4·5. $C_{23}H_{19}NO$ requires C, 84·9; H, 5·9; N, 4·3%), $\nu_{max.}$ 1640, 1625, 1600, 1510, 1400, 1150 cm.$^{-1}$.

1-*Acetyl*-2-*methyl*-3-*phenylindolizine* (VI; R = Me, R′ = Ph). (a) 2-Acetonylidene-1-benzyl-1,2-dihydropyridine (1 hr. reflux) yielded the *indolizine* (90%). Sublimation at 90°/1 mm. followed by crystallisation from light petroleum gave needles, m. p. 111—112° (Found: C, 81·5; H, 6·3; N, 5·5. $C_{17}H_{15}NO$ requires C, 81·9; H, 6·1; N, 5·6%), $\nu_{max.}$ 1640, 1615, 1505, 1400, 1145 cm.$^{-1}$.

(b) 1-Benzyl-2-cyanomethylene-1,2-dihydropyridine (12 hr. reflux) yielded the same indolizine (11%).

(c) 1-Benzyl-2-carbamoylmethylene-1,2-dihydropyridine (1 hr. reflux) yielded the same indolizine (59%) and ammonia was liberated on basification of the aqueous mother-liquors.

(d) 1-Benzyl-1,2-dihydro-2-phenylcarbamoylmethylenepyridine (1 hr. reflux) yielded the same indolizine (96%). Concentration and cooling of the aqueous mother-liquors gave acetanilide, m. p. 114°.

1-*Acetyl*-2,3-*dimethylindolizine*.—(a) 2-Benzoylmethylene-1-ethyl-1,2-dihydropyridine and acetic anhydride were heated together under reflux (12 hr.) and the mixture diluted with water. The brown emulsion was extracted with ether and the ethereal extract washed with 2N-sodium hydroxide. Acidification of the alkaline layer yielded benzoic acid (12%). Evaporation of the ethereal extract gave an oil which solidified on trituration with light petroleum. Crystallisation from the same solvent gave needles (9%), m. p. 81—82°, identical with a sample prepared[11] by acetylation of 2,3-dimethylindolizine; $\nu_{max.}$ 1635, 1615, 1500, 1430, 1315 cm.$^{-1}$.

(b) 2-Ethoxycarbonylmethylene-1-ethyl-1,2-dihydropyridine by similar treatment (4 hr. reflux) yielded the same 1-acetylindolizine (25%).

3- *and* 1-*Benzoyl*-2-*phenylindolizine*.—2-Benzoylmethylene-1,2-dihydro-1-phenacylpyridine (1 hr. reflux) gave a yellow crystalline solid, m. p. 137—137·5° (Found: C, 84·9; H, 5·3; N, 4·6. $C_{21}H_{15}NO$ requires C, 84·8; H, 5·1; N, 4·7%). A thin-layer chromatogram on silica (solvent, benzene–5% methanol) showed the product to be a mixture of 3-benzoyl- (*ca.* 85%) and 1-benzoyl-2-phenylindolizine (*ca.* 15%). A sample of 1-benzoyl-2-phenylindolizine prepared by our earlier method[8] was shown to contain *ca.* 5% of the 3-benzoyl-isomer.

1-*Carbamoylindolizines*.— *Method A*. 2-Pyridylacetamide[10] (0·02 mole), the α-bromocarbonyl compound (0·01 mole), and acetone were heated together under reflux

with stirring for the stated time. The hydrobromide of 2-pyridylacetamide which had separated, was filtered off and the filtrate concentrated to low bulk to yield the indolizinyl amide.

Method B. The corresponding nitrile (0·5 g.), potassium hydroxide (1·0 g.), and aqueous ethanol (75%; 4·0 ml.) were heated together under reflux for 6 hr. to yield the indolizinyl amide.

1-*Carbamoylindolizine* (XV; R = R′ = H, R″ = $CONH_2$). This was prepared in 82% yield by method B. Sublimation at 130°/0·5 mm. followed by crystallisation from benzene–ethanol gave needles, m. p. 148—149° (Found: C, 67·5; H, 4·9; N, 17·7. $C_9H_9N_2O$ requires C, 67·5; H, 5·0; N, 17·5%), $\nu_{max.}$ (Nujol) 3380 and 3180 (N–H), 1640, 1600, 1520, 1315 $cm.^{-1}$. Indolizine-1-carboxylic acid was obtained in 11% yield by acidification of the alkaline filtrate.

1-*Carbamoyl*-2-*methylindolizine* (XV; R = H, R′ = Me, R″ = $CONH_2$). This was prepared in 59% yield by method A (17 hr. reflux) and in 88% yield by method B. Sublimation at 160°/0·5 mm. followed by crystallisation from ethanol gave needles, m. p. 196—197° (decomp.) (Found: C, 68·9; H, 6·0; N, 15·85. $C_{10}H_{10}N_2O$ requires C, 68·95; H, 5·8; N, 16·1%), $\nu_{max.}$ (Nujol) 3350 and 3150 (N–H), 1640, 1595, 1520, 1250 $cm.^{-1}$.

1-*Carbamoyl*-3-*phenylindolizine* (XV; R = Ph, R′ = H, R″ = $CONH_2$). This was prepared in 89% yield by method B. Sublimation at 160°/0·5 mm. followed by crystallisation from ethanol gave needles, m. p. 191—192° (Found: C, 76·1; H, 5·3; N, 11·8. $C_{15}H_{12}N_2O$ requires C, 76·25; H, 5·1; N, 11·9%), $\nu_{max.}$ (Nujol) 3370 and 3170 (N–H), 1640, 1600, 1520, 1310 $cm.^{-1}$. Acidification of the filtrate yielded 3-phenylindolizine-1-carboxylic acid (4%).

1-*Carbamoyl*-2-*phenylindolizine* (XV; R = H, R′ = Ph, R″ = $CONH_2$). This was prepared in 52% yield by method A (17 hr. reflux). Sublimation at 140°/0·5 mm. followed by crystallisation from ethanol gave plates, m. p. 169—170° (Found: C, 76·5; H, 5·2; N, 12·1. $C_{15}H_{12}N_2O$ requires C, 76·3; H, 5·1; N, 11·9%), $\nu_{max.}$ (Nujol) 3400 and 3100 (N–H), 1640, 1600, 1510 $cm.^{-1}$.

Ethyl 1-*carbamoylindolizine*-2-*carboxylate* (XV; R = H, R′ = CO_2Et, R″ = $CONH_2$). This was prepared in 52% yield by method A (1 hr. reflux). Sublimation at 160°/0·1 mm. followed by crystallisation from ethanol gave prisms, m. p. 213—214° (Found: C, 62·0; H, 5·4; N, 12·1. $C_{12}H_{12}N_2O_3$ requires C, 62·05; H, 5·2; N, 12·1%), $\nu_{max.}$ (Nujol) 3310 and 3150 (N–H), 1690 (ester C=O), 1665 $cm.^{-1}$ (amide C=O), 1605, 1230 $cm.^{-1}$.

Indolizin-1-*yl Phenyl Sulphones*.—Phenyl 2-picolyl sulphone (0·02 mole), the α-bromocarbonyl compound (0·01 mole), and acetone were heated together under reflux with stirring for the stated time. The hydrobromide of phenyl 2-picolyl sulphone, which had separated, was filtered off and the filtrate concentrated to low bulk, and triturated with dilute hydrochloric acid (5·0 ml.) to givetheindolizinyl sulphone. Basification of the acid filtrate gave unchanged starting material.

2-*Ethoxycarbonylindolizin*-1-*yl phenyl sulphone* (XV; R = H, R′ = CO_2Et, R″ = $PhSO_2$) (1 hr. reflux) (62%). This was purified by sublimation at 160°/0·5 mm. followed by crystallisation from ethanol to give needles, m. p. 178—179° (Found: C, 62·1; H, 4·5; N, 4·6; S, 10·1. $C_{17}H_{15}NO_4S$ requires C, 62·0; H, 4·6; N, 4·25; S, 9·7%), $\nu_{max.}$ (Nujol) 1715 (C=O), 1635, 1305, 1150 $cm.^{-1}$ (SO_2). The total recovery of phenyl 2-picolyl sulphone was 53%.

2-*Methylindolizin*-1-*yl phenyl sulphone* (XV; R = H, R′ = Me, R″ = $PhSO_2$) (17 hr. reflux) (46%). This was crystallised from ethanol as prisms, m. p. 139—140° (Found: C, 66·2; H, 4·95; N, 4·8. $C_{15}H_{13}NO_2S$ requires C, 66·4; H, 4·8; N, 5·2%), $\nu_{max.}$ (Nujol) 1595, 1305 and 1155 (SO_2), 1130 $cm.^{-1}$. The recovery of starting material was 63%.

Phenyl 3-*phenylindolizin*-1-*yl sulphone* (XV; R = Ph, R′ = H, R″ = $PhSO_2$) (6 hr. reflux (28%). This was crystallised from ethanol as prisms, m. p. 143—144° (Found: C, 72·3; H, 4·5; N, 4·0; S, 9·8. $C_{20}H_{15}NO_2S$ requires C, 72·1; H, 4·5; N, 4·2; S, 9·6%), $\nu_{max.}$ (Nujol) 1630, 1505, 1305, 1150 (SO_2), 1300 $cm.^{-1}$. The total recovery of starting material was 70%.

Phenyl 2-*phenylidolizin*-1-*yl sulphone*. Phenyl 2-picolyl sulphone and phenacyl bromide under the above conditions (17 hr. reflux) yielded 1-*phenacyl*-2-*phenylsulphonylmethylpyridinium bromide* (66%) plates, m. p. 195—196° (decomp.) (from ethanol) (Found: C, 55·4; H, 4·2; Br, 18·75; N, 3·4. $C_{20}H_{18}BrNO_3S$ requires C, 55·55; H, 4·2; Br, 18·5; N, 3·2%), $\nu_{max.}$ (Nujol) 1700 (C=O), 1625, 1320, 1145 (SO_2), 1175 $cm.^{-1}$. A solution of the quaternary salt (0·1 g.) in water (10 ml.) was heated at 100° for 10 min. and cooled to yield the *indolizinyl sulphone* (XV; R = H, R′ = Ph, R″ = $PhSO_2$) (0·072 g., 94%), prisms, m. p. 131—132° (from light petroleum) (Found: C, 72·2; H, 4·75; N, 4·1; S, 9·6. $C_{20}H_{15}NO_2S$ requires C, 72·1; H, 4·5; N, 4·2; S, 9·6%), $\nu_{max.}$ (Nujol) 1630, 1500, 1295, 1145 (SO_2), 1280 $cm.^{-1}$.

2-p-*Methylsulphonylphenylindolizine* (XV; R = R″ = H, R′ = $MeSO_2C_6H_4$).—α-Picoline (0·93 g.), ω-bromo-*p*-methylsulphonylacetophenone (2·72 g.) and acetone (10 ml.) were heated together under reflux for 3 hr. and the solution cooled to yield 1-*p*-methylsulphonylphenacyl-2-picolinium bromide (3·1 g., 85%), prisms, m. p. 209—210° (decomp.) (from ethanol) (Found: C, 48·6; H, 4·45; Br, 21·8; N, 3·9. $C_{15}H_{16}BrNO_3S$ requires C, 48·65; H, 4·4; Br, 21·6; N, 3·8%). The quaternary salt (2·0 g.), sodium hydrogen carbonate (2·0 g.), and water (20 ml.) were boiled together for 30 min. and the precipitated *indolizine* (1·26 g., 85%) collected. Sublimation at 200°/0·5 mm. followed by crystallisation from ethanol–benzene gave prisms, m. p. 249—250° (decomp.) (Found: C, 66·3; H, 4·8; N, 5·3. $C_{15}H_{13}NO_2S$ requires C, 66·4; H, 4·8; N, 5·2%), $\nu_{max.}$ (Nujol) 1600, 1300 and 1140 (SO_2), 780 $cm.^{-1}$.

1-*Morpholinothiocarbonyl*-2-*phenyl-indolizine* (XV; R = H, R′ = Ph, R″ = $C_4H_8NO{\cdot}CS$).—2-Morpholinothiocarbonylmethylpyridine (4·4 g.), phenacyl bromide (2·0 g.), and acetone (10 ml.) were stirred and heated together under reflux for 1 hr. The mixture was filtered to remove the hydrobromide of the product (1·35 g.), the filtrate heated under reflux for a further 10 min., filtered to remove the hydrobromide of 2-morpholinothiocarbonylmethylpyridine (1·3 g.) and finally heated under reflux for a further 16 hr. to yield a further crop (0·65 g.) of the *indolizine*. The base liberated from the hydrobromide was combined with this final crop and the total material (1·7 g., 53%) sublimed at 160°/0·5 mm. and crystallised from ethanol to give plates, m. p. 177—178° (Found: C, 70·65; H, 5·7; N, 8·4; S, 10·2. $C_{19}H_{18}N_2OS$ requires C, 70·8; H, 5·6; N, 8·7; S, 9·9%).

1-*Acetamidoindolizines*.—These compounds were prepared as described for 1-acetamido-2-phenylindolizine in Part III,[1] either from the corresponding 1-nitroindolizines (Method A) or from 2-acetamidomethylpyridine (Method B).

1-*Acetamido*-3-*phenylindolizine* (XV; R = Ph, R′ = H,

R'' = AcNH). This was obtained in 62% yield by Method A. Crystallisation from ethanol gave lime green prisms, m. p. 170—171° (Found: C, 76·5; H, 5·4; N, 11·1. $C_{16}H_{14}N_2O$ requires C, 76·8; H, 5·6; N, 11·2%), $\nu_{max.}$ 3260 (N–H), 1650 (amide C=O), 1640, 1600, 1360 cm.$^{-1}$.

1-*Acetamido*-2-*ethoxycarbonylindolizine* (XV; R = H, R' = CO_2Et, R'' = AcNH). Reduction of the corresponding 1-nitroindolizine by Method A yielded the amine hydrochloride, basification of which with sodium carbonate gave the 1-*aminoindolizine* (0·53 g., 61%), yellow prisms, m. p. 203—204° (decomp.) (from ethanol) (Found: C, 64·4; H, 6·2; N, 14·0. $C_{11}H_{12}N_2O_2$ requires C, 64·7; H, 5·9; N, 13·7%), $\nu_{max.}$ 3380 and 3300 (NH), 1675 (C=O), 1600, 1270s cm.$^{-1}$; n.m.r. of the amine hydrochloride: triplet at τ 8·5 (J = 7·0 c./sec., 3H, $CO_2CH_2CH_3$), quartet at 5·45 (J = 7·0 c./sec., 2H, $CO_2CH_2CH_3$), singlet at 4·33 ($-CH_2-$ at C-3), multiplet at 0·9—1·84 (4H, aromatic protons). The *acetyl derivative* was sublimed at 130°/0·5 mm. and crystallised from ethanol as needles, m. p. 147—148° (Found: C, 63·4; H, 5·9; N, 11·3. $C_{13}H_{14}N_2O_3$ requires C, 63·4; H, 5·7; N, 11·4%), $\nu_{max.}$ (Nujol) 3280 (NH), 1700 (ester C=O), 1660 (amide C=O), 1230 cm.$^{-1}$.

1-*Acetamido*-2,3-*diphenylindolizine* (XV; R = R' = Ph, R'' = AcNH). This was obtained in 42% yield by Method A. Sublimation at 200°/1·0 mm. followed by crystallisation from ethanol gave cream coloured prisms, m. p. 237—238° (Found: C, 81·0; H, 5·8; N, 8·4. $C_{22}H_{18}N_2O$ requires C, 80·95; H, 5·6; N, 8·6%), $\nu_{max.}$ (Nujol) 3240 (N–H), 1655 cm.$^{-1}$ (amide C=O).

1-*Acetamido*-2,3-*dimethylindolizine* (XV; R = R' = Me, R'' = AcNH). This was obtained in 27% yield by Method B. Sublimation at 150°/0·5 mm. followed by crystallisation from ethanol gave pale yellow prisms, m. p. 190—191° (Found: C, 71·2; H, 7·1; N, 13·6. $C_{12}H_{14}N_2O$ requires C, 71·3; H, 7·0; N, 13·9%), $\nu_{max.}$ 3380 (N–H), 1665, 1660 (amide C=O), 1500, 1385, 1360 cm.$^{-1}$.

1-*Acetamido*-2-p-*methylsulphonylphenylindolizine* (XV; R = H, R' = $CH_3SO_2C_6H_4$, R'' = AcNH). This was obtained in 44% yield by Method B. Crystallisation from ethanol gave green–yellow prisms, m. p. 230—231° (decomp.) (Found: C, 62·35; H, 5·1; N, 8·55; S, 9·75. $C_{17}H_{16}N_2O_3S$ requires C, 62·2; H, 4·9; N, 8·5; S, 9·8%), $\nu_{max.}$ (Nujol) 3250 (N–H), 1645 (amide C=O), 1290, 1140 (SO_2) 980 cm.$^{-1}$.

1-*Acetamidomethyl*-2-*phenylindolizine* (XV; R = H, R' = Ph, R'' = $AcNHCH_2$). (a) 2-Acetamidoethylpyridine (0·82 g.), phenacyl bromide (1·0 g.), and acetone (5·0 ml.) were heated together under reflux for 4 hr. The acetone was evaporated off and the crude quaternary salt (1·8 g.) boiled with 10% sodium hydrogen carbonate solution (20 ml.). The precipitated *indolizine* (1·17 g., 88%) was sublimed at 160°/0·5 mm. and crystallised from ethanol as plates, m. p. 188—189° (decomp.) (Found: C, 76·9; H, 5·9; N, 10·35. $C_{17}H_{16}N_2O$ requires C, 77·25; H, 6·1; N, 10·6%), $\nu_{max.}$ (Nujol) 3300 (NH), 1635 (amide C=O), 1540 cm.$^{-1}$.

(b) A suspension of 1-cyano-2-phenylindolizine (1·09 g.) in dry ether (5·0 ml.) was slowly added to a stirred suspension of lithium aluminium hydride (0·38 g.) in dry ether (5·0 ml.). The mixture was stirred for 30 min. and then treated with water (5·0 ml.) and 2N-sodium hydroxide. The alkaline solution was extracted with ether, the extract evaporated, and the resulting oil triturated with dilute hydrochloric acid to give unchanged starting material (32%). Basification of the filtrate yielded the crude amine (53%) as a grey solid. Acetylation gave a product identical to that obtained in (a) above.

3-*Acetyl*-1-*diacetylaminomethylindolizine* (XV; R = Ac, R' = H, R'' = Ac_2NCH_2). A similar reduction of 1-cyanoindolizine (0·75 g.) in solution in ether (5·0 ml.) gave the crude aminomethylindolizine (0·65 g., 84%) as a pale yellow oil. Immediate acetylation with acetic anhydride in the presence of sodium acetate (2 hr. reflux) yielded the *triacetyl derivative*. Sublimation at 100°/0·5 mm. followed by crystallisation from ethanol as needles, m. p. 117—118° (Found: C, 65·9; H, 6·0; N, 10·05. $C_{15}H_{16}N_2O_3$ requires C, 66·2; H, 5·9; N, 10·3%), $\nu_{max.}$ (Nujol) 1700 and 1695 (amide C=O), 1605 (acetyl C=O) 1340, 1220 cm.$^{-1}$.

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