Indolizines. Part V.[1] The Synthesis of 3-Amino- and 3-Acetamido-indolizines and their Precursors, the 3-Azo-, -Nitroso-, -Nitro-, and -Acetyl-indolizines

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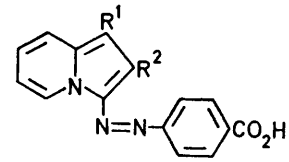
The most convenient method for the preparation of 3-aminoindolizines has been shown to be the rapid reduction of 3-nitrosoindolizines by means of hydrazine hydrate in the presence of palladium–charcoal. The amines have also been prepared by similar reduction of 3-nitro- and 3-azoindolizines, and, as their acetyl derivatives, by the Schmidt reaction from 3-acetylindolizines. Indolizine and 2-methylindolizine have, for the first time, been nitrated in the 3-position by the use of acetic anhydride and nitric acid: the implications of this reaction are discussed.

We were interested in the preparation of 3-aminoindolizines for an investigation of their chemical and pharmacological properties (see following paper). The few known 3-amino- and 3-acetamido-indolizines have been prepared by the cyclisation of 3-(2-pyridyl)propionitriles,[2] the reduction of a 3-azo-[3] or a 3-nitrosoindolizine,[4] and the Schmidt reaction of a 3-acetylindolizine.[3]

Previous work has shown[1,2] that, in common with other π-excessive amines such as the pyrrole[5] and indole[6] amines, the aminoindolizines are unstable. This was also true of the amines which we have now prepared, and influenced our choice of a synthetic route. The rapid reduction of a suitable N-containing 3-substituted indolizine appeared to offer the best opportunity of a general reaction, and 3-azo-, 3-nitroso-, and 3-nitroindolizines were prepared for the investigation of a number of methods of reduction to the amines.

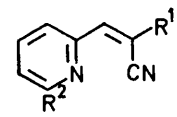
Two 3-(4-carboxyphenylazo)indolizines [(1) and (2)] were synthesised by the reactions of the corresponding indolizines with a neutral diazonium salt derived from 4-aminobenzoic acid. Nitrosation of six indolizines was accomplished by treatment with a mixture of sodium nitrite and hydrochloric acid and generally gave high yields of the required 3-nitrosoindolizines (3)—(9). These were bright green crystalline solids which turned red on treatment with acid and, with the exception of 3-nitrosoindolizine (3), were stable in air at room temperature. No crystalline product was isolated from the nitrosation of 1,2-dimethylindolizine although the reaction appeared to proceed normally. Concentration of the dark green chloroform extract of the reaction mixture gave an intractable tar. On occasion similar difficulty was experienced in the isolation of 2-methyl-3-nitrosoindolizine (4), prepared according to the known method.[7] In the latter case concentration of the chloroform extract gave a tar from which a small quantity of a ring-opened product, the acrylonitrile (10), was isolated. A similar product (11) separated in high yield in an attempted recrystallisation of 5-methyl-3-nitroso-2-phenylindolizine (9); the mechanisms of these ring-opening reactions are discussed in the following paper.

A diagnostic feature in the ^{1}H n.m.r. spectra of the 3-nitrosoindolizines was the pronounced deshielding of the 5-H [τ *ca.* 2·0 in the starting materials; τ *ca.* 0·0 ($J_{5,6}$ 6·5 Hz) in the 3-nitroso-compounds].

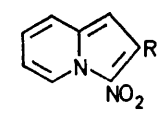


(1) R^1 = H, R^2 = Ph
(2) R^1 = CO_2Et, R^2 = Ph

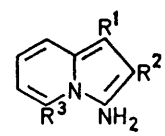
(3) R^1 = R^2 = R^3 = H
(4) R^1 = R^3 = H, R^2 = Me
(5) R^1 = R^2 = Ph, R^3 = H
(6) R^1 = CO_2Et, R^2 = Me, R^3 = H
(7) R^1 = CO_2Et, R^2 = Ph, R^3 = H
(8) R^1 = R^2 = CO_2Et, R^3 = H
(9) R^1 = H, R^2 = Ph, R^3 = Me



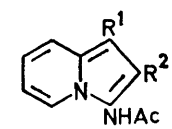
(10) R^1 = Me, R^2 = H
(11) R^1 = Ph, R^2 = CH_2OH



(12) R = H
(13) R = Me



(14) R^1 = R^2 = R^3 = H
(15) R^1 = R^3 = H, R^2 = Me
(16) R^1 = R^2 = Ph, R^3 = H
(17) R^1 = CO_2Et, R^2 = Me, R^3 = H
(18) R^1 = CO_2Et, R^2 = Ph, R^3 = H
(19) R^1 = R^2 = CO_2Et, R^3 = H
(20) R^1 = H, R^2 = Ph, R^3 = Me
(21) R^1 = R^3 = H, R^2 = Ph



(22) R^1 = H, R^2 = Ph
(23) R^1 = R^2 = Me
(24) R^1 = R^2 = Ph

Electrophilic substitution in N-bridgehead compounds generally occurs in the position adjacent to the bridgehead nitrogen atom. In the case of the indolizines this is the 3-position and usually only when this position is blocked does the attacking electrophile enter the 1-

[1] Part IV, T. Melton and D. G. Wibberley, *J. Chem. Soc.* (*C*), 1967, 983.
[2] J. Hurst, T. Melton, and D. G. Wibberley, *J. Chem. Soc.*, 1965, 2948.
[3] D. O. Holland and J. H. C. Naylor, *J. Chem. Soc.*, 1955, 1504.
[4] W. J. Irwin and D. G. Wibberley, *Chem. Comm.*, 1968, 878.
[5] K. Schofield, 'Heteroaromatic Nitrogen Compounds: Pyrroles and Pyridines,' Butterworths, London, 1967.
[6] R. J. Sundberg, 'The Chemistry of the Indoles,' Academic Press, New York, 1970.
[7] E. T. Borrows, D. O. Holland, and J. Kenyon, *J. Chem. Soc.*, 1946, 1075.

position.[8] The only apparent exception to this is seen in the nitration of indolizines with nitric acid and with nitric and sulphuric acids,[9] when mixtures are obtained with 1-nitro-derivatives as the major products. Borrows, Holland, and Kenyon [9] have also studied the effect of acetic anhydride and nitric acid on 2-methylindolizine but were unable to isolate any solid product, and Scholtz [10] has reported that indolizine cannot be nitrated because of its sensitivity to oxidising agents. In view of the strongly protic conditions used in those nitrations in which 1-substitution predominates, it was decided to reinvestigate this use of acetic anhydride and nitric acid as the nitrating agent. Indolizine and 2-methylindolizine when treated with nitric acid (*d* 1·5) in an excess of acetic anhydride at −70° gave moderate yields of the corresponding 3-nitroindolizines, (12) and (13), and no other isomers were detected. 1,2-Dimethyl-3-nitroindolizine was also prepared under similar conditions from 1,2-dimethylindolizine.

Thus indolizine and 2-methylindolizine fall into the category of aromatic substrates which show a large variation in the proportion of isomers according to conditions of nitration. Firm mechanistic proposals for this significant change in orientation must await kinetic measurements. By analogy with the present detailed investigations of other reactive aromatic species,[11] however, it appears possible that the nitronium ion is the effective electrophile in both instances, whereas the substrate varies with the solvent. Thus with acetic anhydride it is presumably the free indolizine which is nitrated at the position commonly susceptible to electrophilic attack (the 3-position). With nitric or sulphuric acid as solvent, however, where 1-nitration predominates the attacked species is either a 3-protonated indolizine (n.m.r. evidence for exclusive 3-protonation is available [12]) or, more likely, an intermediate which has a strong interaction (hydrogen-bonded) [11] between the nitric or sulphuric acid and the indolizine *via* the 3-position.

Methods of reduction of the 3-nitroso-, -nitro-, and -azo-indolizines to the corresponding amines included catalytic hydrogenation in the presence of palladium–charcoal, and transfer hydrogenations with palladium–charcoal and cyclohexene, sodium borohydride, or hydrazine hydrate. Complex mixtures of ring-opened products (*cf.* following paper), unchanged starting materials, and the required amines were commonly obtained but the use of hydrazine hydrate in the presence of palladium–charcoal gave high yields of the required amines in most cases. The nitroso-compounds were the most suitable precursors; eight new 3-aminoindolizines (14)—(21) were obtained in a high degree of purity within 10 min of the commencement of reduction.

The 3-aminoindolizines were all bright yellow crystalline solids when freshly prepared. On contact with the atmosphere or hot solvents they decomposed at a rate dependent on the nature of the other substituent groups. Thus 3-amino- (14) and 3-amino-2-methylindolizine (15) darkened to black tars on exposure to the air within 1 h whereas ethyl 3-amino-2-phenylindolizine-1-carboxylate (18) was stable for several months in air. In the n.m.r. spectra all the aromatic proton signals occurred to higher field than in the corresponding indolizines (*e.g.* for 1-H *ca.* τ 4·0, *cf.* τ 3·72 in indolizine). A spectrum of 3-amino-2-phenylindolizine in trifluoroacetic acid showed that protonation had occurred to the extent of *ca.* 25% at the 1-position.

All the 3-aminoindolizines with the exception of 3-aminoindolizine itself were converted into more stable monoacetamido-derivatives on treatment with acetyl chloride in pyridine or, preferably, acetic anhydride in ether at room temperature. Three 3-acetamidoindolizines (22)—(24) were obtained in high yield by treatment of the corresponding 3-acetylindolizines with hydrazoic acid under the conditions of a Schmidt rearrangement reaction, but 3-acetylindolizine did not undergo the reaction. The n.m.r. spectra of the 3-acetamidoindolizines showed their existence in two stereoisomeric forms within the n.m.r. time scale at room temperature in non-polar solvents. In the spectrum of 3-acetamido-2-methyl-indolizine in deuteriochloroform, for example, the methyl groups absorbed as four singlets at τ 8·32, 8·04, 7·98, and 7·80, but in pyridine the *N*-acetyl and 2-methyl groups absorbed coincidentally as singlets at τ 7·76. A similar merging of the methyl group absorptions on heating was expected but, as reported in the Experimental section, complete coalescence was not obtained.

More stringent conditions are required for further acetylation than had been recognised by earlier workers and the position of acetylation varied according to the 2-substituent. Thus 3-acetamido-2-methylindolizine was heated under reflux for 6 h with acetic anhydride and sodium acetate to give a 63% yield of 3-acetamido-1-acetyl-2-methylindolizine, whereas 3-acetamido-2-phenylindolizine in 4 h gave a 74% yield of 3-diacetylamino-2-phenylindolizine. The latter compound had previously been prepared by cyclisation of 2-phenyl-3-(2-pyridyl)propionitrile with acetic anhydride.[2]

EXPERIMENTAL

N.m.r. spectra were measured for solutions in deuteriochloroform with a Varian A60-A spectrometer (tetramethylsilane as internal standard). I.r. spectra were recorded with a Unicam SP 200 spectrophotometer. Mass spectra were obtained with an A.E.I. MS9 instrument; samples were introduced directly into the heated inlet system.

3-(4-*Carboxyphenylazo*)-2-*phenylindolizine* (1).—A neutral diazonium salt derived from 4-aminobenzoic acid (2·8 g) was added to 2-phenylindolizine (3·8 g) in dimethylformamide

[8] W. L. Mosby, 'Heterocyclic Systems with Bridgehead Nitrogen Atoms,' Interscience, London, Part I, 1961.
[9] E. T. Borrows, D. O. Holland, and J. Kenyon, *J. Chem. Soc.*, 1946, 1077.
[10] M. Scholtz, *Ber.*, 1912, **45**, 1718.
[11] S. R. Hartshorn, R. B. Moodie, and K. Schofield, *J. Chem. Soc.* (*B*), 1971, 2454 and references therein.
[12] M. Fraser, A. Melera, B. B. Molloy, and D. H. Reid, *J. Chem. Soc.*, 1962, 3288; W. L. F. Armarego, *J. Chem. Soc.* (*B*), 1966, 191.

(200 cm³) and the mixture was stirred at 20° for 4 h. Acetic acid (10%) was added to yield the *azo-compound* (5·1 g, 76%), dark red prisms, m.p. 246° (decomp.) (from 2-ethoxyethanol) (Found: C, 74·0; H, 4·5; N, 12·3%; M^+, 341. $C_{21}H_{15}N_3O_2$ requires C, 74·0; H, 4·4; N, 12·0%; *M*, 341), $\nu_{max.}$ ($CHCl_3$) 1690 (C=O) cm^{-1}. Similar treatment of ethyl 2-phenylindolizine-1-carboxylate, with ethanol as solvent, yielded the *azo-ester* (2) (98%) as orange prisms, m.p. 278—279° (decomp.) (from 2-ethoxyethanol) (Found: C, 69·5; H, 4·7; N, 10·4%; M^+, 413. $C_{24}H_{19}N_3O_4$ requires C, 69·7; H,4·6; N, 10·2%; *M*, 413), $\nu_{max.}$ 1690 (C=O) cm^{-1}.

3-*Nitrosoindolizines*.—A solution of sodium nitrite (0·041 mol) in water was added during 0·25—0·5 h to the indolizine (0·04 mol) in 8N-hydrochloric acid (or, where stated, in acetic acid). The mixture was stirred for 1 h in all and then neutralised with aqueous sodium hydrogen carbonate or ammonia. The following nitroso-compounds were variously isolated, according to their purity at this stage, by direct filtration, by extraction with chloroform and evaporation to dryness, or by chromatography on neutral alumina of the residue obtained by the latter procedure: 3-*nitrosoindolizine* (3) (14·5%), green needles, m.p. 39·5—41° (from light petroleum), isolated by chromatography with benzene–ethyl acetate (1 : 2) as eluant (Found: M^+, 146·04801. $C_8H_6N_2O$ requires *M*, 146·04813), τ ($CDCl_3$) −0·21 (1H, d, *J* 6·5 Hz, 5-H), 1·94 (1H, d, *J* 5 Hz, 2-H), 2·4 (2H, m, 7- and 8-H), 2·9 (1H, m, 6-H), and 3·21 (1H, d, *J* 5 Hz, 1-H); 2-methyl-3-nitrosoindolizine (4) (82%), m.p. 104—105° (lit.,[7] 106—107°), τ ($CDCl_3$) −0·25 (1H, d, *J* 7 Hz, 5-H), 2·6 (2H, m, 7- and 8-H), 2·9 (1H, m, 6-H), 3·51 (1H, s, 1-H), and 7·14 (3H, s, 2-Me); 3-nitroso-2-phenylindolizine (85%), m.p. 97—98° (lit.,[7] 97·5—98°), τ ($CDCl_3$) −0·50 (1H, d, *J* 7 Hz, 5-H), 1·85 (2H, m, 7- and 8-H), 2·45 (5H, m, 2-Ph), 2·85 (1H, m, 6-H), and 3·07 (1H, s, 1-H); 3-*nitroso*-1,2-*diphenylindolizine* (5) (96%) (acetic acid), dark green needles, m.p. 176·5—178° (from aqueous ethanol), isolated by evaporation of the chloroform extract (Found: C, 80·4; H, 4·8; N, 9·2%; M^+, 298. $C_{20}H_{10}N_2O$ requires C, 80·6; H, 4·7; N, 9·4%; *M*, 298), τ ($CDCl_3$) −0·18 (1H, d, *J* 7 Hz, 5-H) and 2·4—3·2 (13H, m, 1- and 2-Ph, 6-, 7-, and 8-H); *ethyl* 2-*methyl*-3-*nitrosoindolizine*-1-*carboxylate* (6) (80%), green prisms, m.p. 129—130° (decomp.) [from light petroleum (b.p. 40—60°)], isolated by direct filtration (Found: C, 61·8; H, 5·3; N, 12·2%; M^+, 232. $C_{12}H_{12}N_2O_3$ requires C, 62·0; H, 5·2; N, 12·0%; *M*, 232), $\nu_{max.}$ ($CHCl_3$) 1690 (C=O) cm^{-1}, τ ($CDCl_3$) −0·22 (1H, d, *J* 7 Hz, 5-H), 1·54 (1H, d, *J* 9 Hz, 8-H), 2·26 (1H, m, 7-H), 2·8 (1H, m, 6-H), 5·54 (2H, q, *J* 7 Hz, 1-CO_2CH_2Me), 6·96 (3H, s, 2-Me), and 8·55 (3H, t, *J* 7 Hz, 1-CO_2CH_2·CH_3); *ethyl* 2-*phenyl*-3-*nitrosoindolizine*-1-*carboxylate* (7) (92%), green needles, m.p. 158—159° (from ethanol), isolated by direct filtration (Found: C, 69·1; H, 5·0; N, 9·1%; M^+, 294. $C_{17}H_{14}N_2O_3$ requires C, 69·3; H, 4·8; N, 9·5%; *M*, 294), $\nu_{max.}$ ($CHCl_3$) 1690 (C=O) cm^{-1}, τ ($CDCl_3$) −0·19 (1H, d, *J* 7 Hz, 5-H), 1·5 (1H, d, *J* 8 Hz, 8-H), 2·1—2·9 (7H, m, 2-Ph, 6- and 7-H), 5·76 (2H, q, *J* 7 Hz, 1-CO_2CH_2Me), and 8·91 (3H, t, *J* 7 Hz, 1-CO_2CH_2·CH_3); *diethyl* 3-*nitrosoindolizine*-1,2-*dicarboxylate* (8) (83%), bright green needles, m.p. 109—111° (from aqueous ethanol), isolated by direct filtration (Found: C, 57·9; H, 5·0; N, 9·9%; M^+, 290. $C_{14}H_{14}N_2O_4$ requires C, 57·9; H, 4·9; N, 9·7%; *M*, 290), $\nu_{max.}$ ($CHCl_3$) 1700 (C=O) cm^{-1}, τ ($CDCl_3$) 0·11 (1H, d, *J* 6 Hz, 5-H), 1·56 (1H, d, *J* 9 Hz, 8-H), 2·23 (1H, m, 7-H), 2·68 (1H, m, 6-H), 5·5 (4H, q, *J* 7 Hz, 1- and 2-CO_2CH_2Me), and 8·6 (6H, t, *J* 7 Hz, 1- and 2-CO_2CH_2·CH_3).

3-*Nitroindolizine* (12).—A mixture of fuming nitric acid (*d* 1·5; 2·0 g, 1·5 equiv.) and acetic anhydride (5·0 cm³) was added dropwise to a stirred solution of indolizine (2·4 g) in acetic anhydride (20 cm³) cooled in an acetone–solid carbon dioxide bath. The mixture was stirred for a further 0·5 h poured on crushed ice, and neutralised with aqueous 40% potassium hydroxide. The neutral solution was extracted with ether and the extract dried ($MgSO_4$) and distilled to yield a dark tar, which was chromatographed on a column of basic alumina with benzene as eluant. Material from the broad yellow band which developed gave the *nitroindolizine* (0·92 g, 28%), yellow needles, m.p. 93—94° [from light petroleum (b.p. 60—80°)] (Found: C, 59·5; H, 3·9; N, 17·1%; M^+, 162. $C_8H_6N_2O_2$ requires C, 59·3; H, 3·7; N, 17·3%; *M*, 162), $\nu_{max.}$ 1510 and 1350 (NO_2) cm^{-1}, τ ($CDCl_3$) 0·4 (1H, d, *J* 7 Hz, 5-H), 2·19 (1H, d, *J* 5 Hz, 2-H), 2·6 (3H, m, 6-, 7-, and 8-H), and 3·39 (1H, d, *J* 5 Hz, 1-H). 2-Methyl-3-nitroindolizine (13) (40%) was similarly obtained from 2-methylindolizine. It separated as yellow needles, m.p. 103—104° (from aqueous ethanol), identical (mixed m.p.) with an authentic sample,[9] $\nu_{max.}$ 1520 and 1345 (NO_2) cm^{-1}, τ ($CDCl_3$) 0·34 (1H, d, *J* 6·5 Hz, 5-H), 2·3—3·2 (3H, m, 6-, 7-, and 8-H), 3·56 (1H, s, 1-H), and 7·35 (3H, s, 2-Me). 1,2-*Dimethyl*-3-*nitroindolizine* (50%) was similarly prepared as yellow prisms, m.p. 148—149° (from light petroleum) (Found: C, 62·9; H, 5·3; N, 14·7%; M^+, 190. $C_{10}H_{10}N_2O_2$ requires C, 63·2; H, 5·3; N, 14·5%; *M*, 190), $\nu_{max.}$ 1520 and 1350 (NO_2) cm^{-1}, τ 0·44 (1H, d, *J* 7 Hz, 5-H), 2·4—3·2 (3H, m, 6-, 7-, and 8-H), 7·51 (3H, s, 2-Me), and 7·83 (3H, s, 1-Me).

3-*Aminoindolizines* (14)—(21).—Hydrazine hydrate (1·0 cm³) was added dropwise to a vigorously stirred solution of the 3-nitrosoindolizine (1·0 g) under reflux in ethanol (20 cm³) and containing 10% palladium–charcoal (0·2 g). After the evolution of gas had ceased (*ca.* 10 min), the mixture was filtered rapidly through Celite and evaporated under reduced pressure at a bath temperature not exceeding 50°. The crude products were rapidly recrystallised from the appropriate solvent to yield the following aminoindolizines: 3-*aminoindolizine* (14) (89·5%) as a viscous yellow oil which decomposed rapidly on exposure to the air or on contact with hot solvents, $\nu_{max.}$ (film) 3350 and 3300 (NH_2) cm^{-1} (Found: M^+, 132·06874. $C_8H_8N_2$ requires *M*, 132·06850), *m/e* 133 (13%), 132 (M^+, 99), 130 (72), 129 (18), 116 (8), 105 (27), 104 (28), 100 (11), 80 (10), 79 (100), 78 (37), 77 (13), 76 (10), 58 (30), 52 (25), 51 (28), 50 (18), 41 (13), and 39 (14) (a sufficiently resolved n.m.r. spectrum was unobtainable); 3-*amino*-2-*methylindolizine* (15) (94%), yellow plates, m.p. 39—41°, decomposing rapidly on contact with the air or hot solvents (Found: M^+, 146·08512. $C_9H_{10}N_2$ requires *M*, 146·08439), $\nu_{max.}$ ($CHCl_3$) 3350 and 3290 (NH_2) cm^{-1}, τ ($CDCl_3$) 2·4 (1H, m, 5-H), 2·8 (1H, m, 7-H), 3·5 (2H, m, 6- and 7-H), 3·92 (1H, s, 1-H), 7·16br (2H, s, 3-NH_2, exchangeable), and 7·96 (3H, s, 2-Me) [the amine (15) was synthesised in 87% yield, by a similar procedure from 2-methyl-3-nitroindolizine]; 3-*amino*-2-*phenylindolizine* (21) (98%), yellow plates, m.p. 107—108° (from ethanol), darkening on exposure to the air or prolonged contact with hot solvents (Found: M^+, 208·10002. $C_{14}H_{12}N_2$ requires *M*, 208·10004), $\nu_{max.}$ ($CHCl_3$) 3400 and 3350 (NH_2) cm^{-1}, τ ($CDCl_3$) 2·3—2·8 (8H, m, 2-Ph, 5-, 7-, and 8-H), 3·54 (1H, m, 1-H), 3·60 (1H, m, 6-H), 6·60br (2H, s, 3-NH_2, exchangeable), τ (CF_3·CO_2H) 2·1—2·8 (9H, m, 2-Ph, 5-, 6-, 7-, and 8-H), 5·95 (*ca.* 0·5H, s, indolizinium 1-H_2); *ethyl* 3-*amino*-2-*methylindolizine*-1-

carboxylate (17) (68%), yellow plates, m.p. 85—86°, darkening on contact with the air or hot solvents (Found: M^+, 218·10552. $C_{11}H_{14}N_2O_2$ requires M, 218·10556), $\nu_{max.}$ ($CHCl_3$) 3400 and 3350 (NH_2), and 1685 (C=O) cm^{-1}, τ ($CDCl_3$) 1·9 (2H, m, 5- and 8-H), 3·15 (2H, m, 6- and 7-H), 5·62 (2H, q, J 7 Hz, 1-CO_2CH_2Me), 7·6 (3H, s, 2-Me), and 8·6 (3H, q, J 7 Hz, 1-CO_2CH_2·CH_3); *ethyl* 3-*amino*-2-*phenylindolizine*-1-*carboxylate* (18) (58%), yellow prisms, m.p. 90—92°, showing no darkening on exposure to the air for several months (Found: M^+, 280·12132. $C_{17}H_{16}N_2O_2$ requires M, 280·12120), $\nu_{max.}$ ($CHCl_3$) 3400 and 3300 (NH_2), and 1690 (C=O) cm^{-1}, τ ($CDCl_3$) 1·80 (1H, d, J 8 Hz, 8-H), 2·15 (1H, d, J 7 Hz, 5-H), 2·7 (5H, m, 2-Ph), 3·2 (2H, m, 6- and 7-H), 5·85 (2H, q, J 7 Hz, 1-CO_2CH_2·CH_3) 7·73 (2H, s, 3-NH_2) (removed on deuteriation), 8·89 (3H, t, J 7 Hz, 1-CO_2CH_2·CH_3) [the amine (18) was also synthesised in 52% yield by a similar procedure from the azo-derivative (1)]; *diethyl* 3-*aminoindolizine*-1,2-*dicarboxylate* (19) (82%), yellow plates, m.p. 94—96° (from methanol), a rapid reaction was essential to avoid the separation of tarry solids presumably contaminated with hydrazides (Found: M^+, 276·11100. $C_{14}H_{16}N_2O_4$ requires M, 276·11018), $\nu_{max.}$ ($CHCl_3$) 3400 and 3300 (NH_2) and 1680 (C=O) cm^{-1}, τ ($CDCl_3$) 2·2 (2H, m, 5- and 8-H), 3·3 (2H, m, 6- and 7-H), 4·8br (2H, s, 3-NH_2, exchangeable), 5·62 (4H, q, J 7 Hz, 1- and 2-CO_2CH_2Me), and 8·75 (6H, t, J 7 Hz, 1- and 2-CO_2CH_2·CH_3); 3-*amino*-5-*methyl*-2-*phenylindolizine* (20) (88%), yellow plates, m.p. 99—101°, darkening on exposure to the air or prolonged contact with hot solvents (Found: M^+, 222·11569. $C_{15}H_{14}N_2$ requires M, 222·11536), $\nu_{max.}$ ($CHCl_3$) 3400 and 3300 (NH_2) cm^{-1}, τ ($CDCl_3$) 2·2—2·85 (7H, m, 1-H, 2-Ph, and 8-H), 3·25—3·80 (2H, m, 6- and 7-H), 6·8br (2H, s, 3-NH_2, exchangeable), and 7·61 (3H, 5-Me) [in preparations where the addition of the hydrazine hydrate was delayed for a few minutes the product was contaminated with the nitrile (11)]; 3-*amino*-1,2-*diphenylindolizine* (16) (91%), yellow prisms, m.p. 94—96° (from methanol), showing no darkening on exposure to the air for several months (Found: M^+, 284·13134. $C_{20}H_{16}N_2$ requires M, 284·12958), $\nu_{max.}$ ($CHCl_3$) 3400 and 3300 (NH_2) cm^{-1}, τ ($CDCl_3$) 2·1—3·2 (13H, m, 1- and 2-Ph, 5-, 7-, and 8-H), 3·36 (1H, m, 6-H), and 6·7br (2H, s, 3-NH_2, exchangeable).

3-*Acetamidoindolizines*.—(*a*) A solution of the 3-aminoindolizine (0·5 g) in ether (20 cm^3) was stirred at room temperature, for the stated time, with acetic anhydride (1·0 cm^3). The solvent and excess of acetic anhydride were distilled off and the amide was isolated by trituration with light petroleum followed by crystallisation from an appropriate solvent.

(*b*) A solution of the 3-acetylindolizine (0·01 mol) in an 8% solution of hydrazoic acid (0·012 mol) in chloroform was added dropwise to a stirred mixture of chloroform (20 cm^3) and concentrated sulphuric acid (0·2 mol) at −5°. The mixture was stirred for the stated total time, poured on ice, and neutralised with 40% sodium hydroxide solution; the chloroform layer was separated, dried, and distilled to yield the amide, which was crystallised from a suitable solvent.

By one or both of the above methods the following amides were prepared: 3-acetamido-2-methylindolizine (*a*) (6 h) (51%), needles, m.p. 147—148° (from benzene), identical (mixed m.p.) with an authentic sample,[3] $\nu_{max.}$ ($CHCl_3$) 3250 (NH) and 1680 (C=O) cm^{-1}, τ ($CDCl_3$) 2·1—2·8 (3H, m, 3-N*H*Ac, 5- and 8-H), 3·1—3·8 (3H, m, 1-, 6-, and 7-H), 7·80, 7·98, 8·04, and 8·32 (6H, singlets 2-Me and 3-NH·CO*Me*), τ (pyridine) 7·76 (6H, 2-Me and 3-NH·CO*Me*), τ [$(CD_3)_2SO$] 7·91 (6H, s, 2-Me and 3NH·CO*Me*) (attempts to coalesce the methyl singlets in the former spectrum were unsuccessful); 3-*acetamido*-2-*phenylindolizine* (22) (*a*) (64%) (12 h) or (*b*) (78%) (0·75 h), pale yellow prisms, m.p. 196—197° (from aqueous ethanol) (Found: C, 76·7; H, 5·6; N, 10·9%; M^+, 250. $C_{16}H_{14}N_2O$ requires C, 76·7; H, 5·6; N, 11·2%; M, 250), $\nu_{max.}$ (Nujol) 3250 (N−H) and 1670 (C=O) cm^{-1}, τ ($CDCl_3$) 2·26—2·82 (8H, m, 2-Ph, 5- and 8-H, 3-N*H*Ac), 3·25—3·50 (3H, m, 1-, 6-, and 7-H), and 7·86 and 8·42 (3H, singlets, 3-NH·CO*Me*), τ (pyridine) 7·72 (3H, s, 3-NH·CO*Me*); 3-*acetamido*-1,2-*dimethylindolizine* (23) (*b*) (86%) (0·75 h), buff needles, m.p. 188—190° (from ethyl acetate) (Found: C, 71·2; H, 6·8; N, 14·0%; M^+, 202. $C_{12}H_{14}N_2O$ requires C, 71·3; H, 7·0; N, 13·9%; M, 202), $\nu_{max.}$ ($CHCl_3$) 3450 (N−H) and 1700 (C=O) cm^{-1}, τ ($CDCl_3$) 2·3—3·1 (3H, m, 5- and 8-H, 3-N*H*Ac), 3·2—3·65 (2H, m, 6- and 7-H), and 7·78, 7·80, 7·87, 7·96, and 8·3 (9H, singlets, 1- and 2-Me, 3-NH·CO*Me*); 3-*acetamido*-1,2-*diphenylindolizine* (24) (*a*) (82%) (12 h) or (*b*) (86%) (1·0 h), prisms, m.p. 271—273° (from benzene) (Found: C, 80·7; H, 5·5; N, 8·8%; M^+, 326. $C_{22}H_{18}N_2O$ requires C, 80·9; H, 5·6; N, 8·6%; M, 326), $\nu_{max.}$ (Nujol) 3300 (NH) and 1670 (C=O) cm^{-1}, τ ($CDCl_3$) 2·35—3·2 (14H, m, 1- and 2-Ph, 5-, 6-, 7-, and 8-H), and 7·89 and 8·02 (3H, singlets, 3-NH·CO*Me*); *ethyl* 3-*acetamido*-2-*methylindolizine*-1-*carboxylate* (*a*) (69%) (17 h) with ether and pyridine as solvent, buff prisms, m.p. 153—154° (from ethyl acetate) (Found: C, 64·4; H, 6·1; N, 10·8%; M^+, 260. $C_{14}H_{16}N_2O_3$ requires C, 64·6; H, 6·2; N, 10·8%; M, 260), $\nu_{max.}$ (Nujol) 3400 (NH) and 1665 (C=O) cm^{-1}, τ ($CDCl_3$) 2·02 (1H, d, J 9 Hz, 8-H), 2·50 (1H, d, J 6·5 Hz, 5-H), 3·0—3·45 (2H, m, 6- and 7-H), 5·77 (2H, q, J 7 Hz, 1-CO_2CH_2Me) 7·84, 7·95, 8·14, and 8·38 (6H, singlets, 2-Me and 3-NH·CO*Me*), and 8·71 (3H, t, J 7 Hz 1-CO_2CH_2·CH_3); *ethyl* 3-*acetamido*-2-*phenylindolizine*-1-*carboxylate* (*a*) (78%) (17 h) with pyridine as solvent, pale yellow prisms, m.p. 167·5—169° (from ethanol) (Found: C, 70·7; H, 5·7; N, 8·5%; M^+, 322. $C_{19}H_{18}N_2O_3$ requires C, 70·8; H, 5·6; N, 8·7%; M, 322), $\nu_{max.}$ ($CHCl_3$) 3350 (NH) and 1680 (C=O) cm^{-1}, τ ($CDCl_3$) 2·32 (1H, d, J 6·5 Hz, 5-H), 2·70 (5H, s, 2-Ph), 2·76 (1H, d, J 9 Hz, 8-H), 2·85—3·04 (2H, m, 6- and 7-H), 5·92 (2H, q, CO_2CH_2Me), 8·06 and 8·44 (3H, singlets, 3-NH·CO*Me*), and 8·90 (3H, t, J 7 Hz, 1-CO_2CH_2·CH_3); 3-*acetamido*-5-*methyl*-2-*phenylindolizine* (*a*) (83%) (17 h), pale cream prisms, m.p. 150—152° (from aqueous ethanol) (Found: M^+, 264·12626. $C_{17}H_{16}N_2O$ requires M, 264·12675), $\nu_{max.}$ (Nujol) 3250 (NH) and 1650 (C=O) cm^{-1}, τ ($CDCl_3$) 2·35—2·90 (8H, 2-Ph, 1- and 8-H, 3-N*H*Ac), 3·10—3·74 (2H, m, 6- and 7-H), and 7·54, 7·60, 7·91, and 8·37 (6H, singlets, 5-Me and 3-NH·CO*Me*); the attempted Schmidt reaction on 1-acetylindolizine (0·75 h) gave unchanged starting material (90%) and attempted acetylation of 3-aminoindolizine gave intractable tars.

3-*Acetamido*-1-*acetyl*-2-*methylindolizine*.— 3-Acetamido-2-methylindolizine (0·94 g), acetic anhydride (7·5 cm^3) and sodium acetate (1·5 g) were refluxed together for 6 h. The excess of acetic anhydride was removed and the residue extracted with ethyl acetate to yield the acetamido-acetylindolizine (0·72 g, 63%), needles, m.p. 187—188° (from ethanol) (lit.,[3] 190°), $\nu_{max.}$ ($CHCl_3$) 3300 (NH), 1660 (amide C=O), and 1610 (acetyl C=O) cm^{-1}, τ [$(CD_3)_2SO$] 1·80 (1H, d, J 9 Hz, 8-H), 2·09 (1H, d, J 6·5 Hz, 5-H), 2·5—3·1 (2H, m, 6- and 7-H), and 7·57, 7·73, and 7·86 (9H, singlets, 3-NH·CO*Me*, 2-Me, and 1-COMe).

3-*Diacetylamino*-2-*phenylindolizine*.— 3-Acetamido-2-phenylindolizine (0·5 g) was similarly treated with acetic anhydride and sodium acetate (4 h) to yield the 3-diacetylaminoindolizine (74%), m.p. 113—114° (lit.,[2] 113—114°) (Found: 73·7; H, 5·6; N, 9·4%; M^+, 292. Calc. for $C_{18}H_{16}N_2O_2$: C, 73·9; H, 5·5; N, 9·6%; M, 292), $\nu_{max.}$ (Nujol) 1720 (C=O) cm^{-1}, τ ($CDCl_3$) 2·5—2·8 (7H, m, 2-Ph, 5- and 8-H), 3·23 (1H, s, 1-H), 3·28—3·5 (2H, m, 6- and 7-H), and 7·91 (6H, s, 3-NAc_2).

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