Synthesis of Some Hydroxymethyl- and Aminomethyl-indolizines

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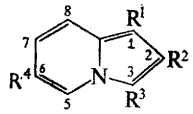
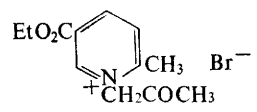
Syntheses are reported of 2-hydroxymethylindolizine (4), 3-hydroxymethylindolizine (5), and 2-methyl-6-hydroxymethylindolizine (6). Attempts to prepare 1-hydroxymethyl-2-methylindolizine by reduction of the corresponding ethoxycarbonyl derivative or by a Chichibabin synthesis from a 2-pyridylethanol derivative were unsuccessful, although 1-(2-hydroxyethyl)-2-methylindolizine (13) was so obtained. The very unstable 2-aminomethylindolizine (15) and 7-aminomethyl-2-methylindolizine (34) have been obtained by reduction of the corresponding nitriles; attempts to obtain 6-aminomethyl-2-methylindolizine are described.

For a study of the properties of indolizinyl carbonium ions (chemically generated and in the mass spectrometer) we required a range of hydroxymethyl- and aminomethylindolizines. Of these classes the only recorded example was 1-aminomethylindolizine prepared by Melton and Wibberley;[1] we record here our attempts to prepare a number of compounds of this type.



	R^1	R^2	R^3	R^4
(1)	H	CO_2Me	H	H
(2)	H	H	CO_2Me	H
(3)	H	Me	H	CO_2Et
(4)	H	CH_2·OH	H	H
(5)	H	H	CH_2·OH	H
(6)	H	Me	H	CH_2·OH
(7)	H	H	COCl	H
(8)	H	CD_2·OH	H	H
(9)	H	Me	H	CD_2·OH
(10)	CH_2·OH	Me	H	H
(11)	CO_2Et	Me	H	H
(12)	Me	Me	H	H
(13)	$[CH_2]_2$·OH	Me	H	H
(14)	H	$CONH_2$	H	H
(15)	H	CH_2NH_2	H	H
(16)	H	Me	H	$CONH_2$
(17)	H	Me	H	CN



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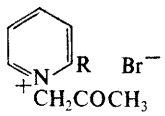
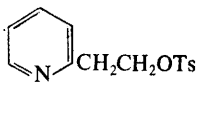


(19) R = CH_2CH_2OH
(20) R = $CH_2CH_2CH_2OH$



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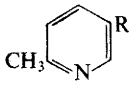
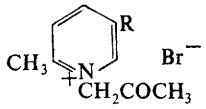
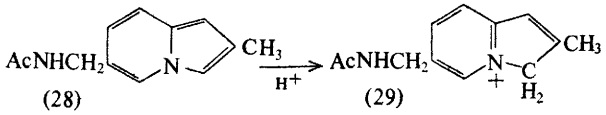


(22) R = $CONH_2$
(23) R = CN
(24) R = CH_2NHAc



(25) R = $CONH_2$
(26) R = CN
(27) R = CH_2NHAc



(28) (29)

The indolizine esters (1), (2), and (3) gave, on reduction with lithium aluminium hydride, 2-hydroxymethylindolizine (4), 3-hydroxymethylindolizine (5), and 2-methyl-6-hydroxymethylindolizine (6) respectively. Methyl indolizine-3-carboxylate was prepared from indolizine-3-carbonyl chloride (7) by treatment with boiling methanol. It is interesting to note that Scholz and Fraude[2] prepared the carbonyl chloride (7) and assigned the structure shown but the only evidence to date for this assignment was the analogy with the proved 2-methylindolizine-3-carboxylic acid[3] obtained by a similar route from 2-methylindolizine. We discuss below evidence based on the n.m.r. spectra of 3-substituted indolizines which appears to substantiate Scholtz and Fraude's formula. The 2-methyl-6-ethoxycarbonylindolizine (3) was prepared by a standard Chichibabin procedure from *N*-acetonyl-5-ethoxycarbonyl-2-methylpyridinium bromide (18). By reduction of the esters (1) and (3) with lithium aluminium deuteride the dideuterio-derivatives (8) and (9) were obtained.

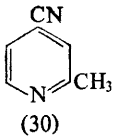
Attempts were also made to prepare the 1-hydroxymethylindolizine (10) by reduction of the known[4] ester (11). Reduction with lithium aluminium hydride in ether gave mixtures; reduction in tetrahydrofuran gave a single product identified as 1,2-dimethylindolizine (12). Attempted reduction with sodium or potassium borohydride was unusccessful. The complete reduction of the ester group by lithium aluminium hydride is not entirely unexpected in view of the similar reduction of 1- or 3-acylindolizines to the corresponding alkyl derivatives;[5] perhaps more surprising is the successful reduction of the ester (2) to give a good (68%) yield of the corresponding hydroxymethyl derivative (5). An alternative route to the hydroxymethyl derivative (10) was the Chichibabin cyclisation of the acetonylpicolinium salt (19) obtained in high yield from 2-pyridylethanol and bromoacetone in sulpholane. Attempts to cyclise the salt (19) with aqueous or nonaqueous base gave an uncharacterised yellow solid; it has been reported[6] that attempts to prepare 2-phenyl-1-(α-hydroxyethyl)indolizine by a similar route led to 2-phenylindolizine only, presumably *via* a retro-aldol reaction. We were unable to isolate 2-methylindolizine so that the reason for the failure of the cyclisation remains obscure. On the other hand, the homologous pyridylpropanol derivative (20) gave the hydroxyethylindolizine (13) which could be characterised although it rapidly decomposed on being kept. The toluene-*p*-sulphonate

[1] T. Melton and D. G. Wibberley, *J. Chem. Soc.* (*C*), 1967, 983.
[2] M. Scholtz and W. Fraude, *Ber.*, 1913, **46**, 1069.
[3] D. O. Holland and J. H. C. Nayler, *J. Chem. Soc.*, 1955, 1504.
[4] D. R. Bragg and D. G. Wibberley, *J. Chem. Soc.*, 1962, 2627.
[5] E. D. Rossiter and J. E. Saxton, *J. Chem. Soc.*, 1953, 3654.
[6] E. T. Borrows and D. O. Holland, *J. Chem. Soc.*, 1947, 670.

of 2-pyridylethanol (21) was prepared in good yield, but could not be quaternised with bromoacetone; attempts to prepare the toluene-*p*-sulphonate of the quaternary salt (19) gave the toluene-*p*-sulphonate (21).

Much more difficulty was experienced in attempts to prepare aminomethylindolizines. Melton and Wiberley [1] have noted the extreme instability of 1-aminomethylindolizine although they were able to stabilise and characterise the system by acetylation. We chose first to investigate routes from the readily available indolizine-2-carboxylic acid.[7] We were unable to obtain the amide (14) from the ammonium salt of the acid or *via* the acid chloride, but eventually the methyl ester (1) was converted into the amide (14) by treatment with methanolic ammonia at 155°. Reduction of the amide (14) with lithium aluminium hydride in tetrahydrofuran gave a solid, m.p. 77·5°, lacking carbonyl absorption in the i.r. region, and whose n.m.r. spectrum was in good accord with that expected for the 2-aminomethylindolizine (15): multiplets equivalent to a total of six indolizine aromatic protons between 6 and 8 p.p.m. (all shifts are in p.p.m. from internal tetramethylsilane standard), a sharp methylene singlet at 4 p.p.m. in good agreement with that expected for the 2-methylene group, and a broad two proton singlet near 2 p.p.m. (varying in chemical shift with dilution and vanishing on D_2O treatment) which is assigned to the primary amine protons. However, the instability of the amine (15) was such that inconsistent analyses were obtained and no stable derivatives could be prepared.

For the introduction of aminomethyl substituents in the six-membered ring two routes were considered; the first route was the modification of groups already present (*e.g.* conversion of an ester to a nitrile with subsequent reduction) and the second involved the application of the Chichibabin synthesis to a suitable aminomethyl- or acetamido-methylpicoline. The known 2-methyl-5-carbamoylpyridine (22) and 2-methyl-5-cyanopyridine (23) were quaternised with bromoacetone to give the corresponding acetonylpyridinium salts (25) and (26). The carbamoyl derivative (25) cyclised in high yield on treatment with di-n-butylamine in ethanol to give 2-methyl-6-carbamoylindolizine (16); attempts to convert the amide (16) into the nitrile (17) were only partly successful. Cyclisation of the pyridinium salt (26) was achieved under the usual Chichibabin conditions, again in high yield, to give 2-methyl-6-cyanoindolizine (17). Reduction of the cyanoindolizine (17) or of the amide (16) with lithium aluminium hydride gave an inseparable mixture, but the appearance of absorption in the aliphatic region of the n.m.r. indicated that reduction of the six-membered ring had taken place. We feel that this (the only case of reduction of the heterocyclic ring observed in all our hydride reductions) is due to the unique combination of a strongly electron-withdrawing group in a position *ortho* to the position calculated to be the most electron-deficient (position 5), giving sufficient activation to enable hydride attack. The alternative approach to the 6-acetamidomethyl derivative (28) has been performed only on a small scale [(24) ⟶ (28)] but the n.m.r. spectrum of the protonated acetamidomethylindolizine (29) obtained in tetrafluoroacetic acid leaves no doubt as to the structure. A broadened singlet at 9·15 p.p.m. (N*H*), a 2H signal at 8·65 p.p.m. (singlet 5-H overlying doublet 7-H), a doublet at 8·07 p.p.m. (8-H), a broadened singlet at 7 p.p.m. (H, 1 position), a broadened singlet at 5·55 p.p.m. ($CH_2\overset{+}{N}$, position 3), a 2H doublet at 4·85 p.p.m. (CH_2NHAc), and two methyl singlets at 2·38 (sharp), and 2·43 p.pm.(allylic broadening) are in full accord with structure (29).



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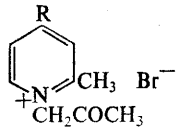
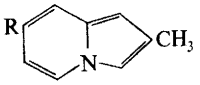


(31) R = CN
(32) R = CH_2NHAc



(33) R = CN
(34) R = CH_2NH_2
(35) R = CH_2NHAc

Interaction of 1-methoxy-2-methylpyridinium sulphate with aqueous cyanide gives a mixture of 6-cyano-2-methylpyridine and 4-cyano-2-methylpyridine (30). Quaternisation of the mixed cyanides with acetonyl bromide gave, exclusively, the *N*-acetonyl-4-cyano-2-methylpyridinium bromide (31). The Chichibabin cyclisation of the bromide (31) with aqueous hydrogen carbonate gave a product contaminated by amide; use of di-n-butylamine in ethanol gave a product which it was difficult to free completely from dibutylamine. The most satisfactory modification of the Chichibabin synthesis for the production of 7-cyano-2-methylindolizine (33) was the use of a weak-base resin on an ethanol solution of the salt (31); the yield was not high but the product was pure. Reduction of the nitrile (33) with lithium aluminium hydride proceeded smoothly with no apparent ring reduction, to give the 7-aminomethylindolizine (34); the n.m.r. spectrum showed, apart from five aromatic protons, only broadened singlets at 3·7 (2H), 2·3 (3H), and 1·2 p.p.m. (2H; disappears on treatment of the solution with D_2O). Again a small-scale preparation of 1-acetonyl-4-acetylaminomethyl-2-methylpyridinium bromide (32) was followed by cyclisation with aqueous hydrogen carbonate to give the 7-acetamidomethylindolizine (35) but the route showed no advantage over that *via* the 7-cyanoindolizine.

During the course of this work we have confirmed the observation by Acheson and Robinson [8] that a carbonyl substituent at position 1 or 3 in indolizine causes a marked downfield shift of the 8- or 5-proton signal

[7] E. T. Borrows and D. O. Holland, *J. Chem. Soc.*, 1947, 672.
[8] R. M. Acheson and D. A. Robinson, *J. Chem. Soc.* (*C*), 1968, 1633.

respectively (see Experimental section). These shifts combined with the different major coupling shown by the 5- and 8-protons ($J_{5,6}$ 6·4—7·5 Hz, $J_{7,8}$ 8—9·1 Hz [8]) enable a clear determination of the point of entry of an electrophile (the 1- and 3-positions being alternative sites for electrophilic substitution: notably formylation and acylation). The carbonyl stretching frequencies of 1- and 3-substituted indolizines are appreciably longer in wavelength than the corresponding 2-substituted derivatives (as has been noted particularly for the acetyl group by Hurst, Melton, and Wibberley [9]) but the difference between a given substituent in the 1- and in the 3-position is insufficient to enable the use of i.r. absorption alone to determine the position of a substituent.

EXPERIMENTAL

Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. I.r. spectra were determined on a Perkin-Elmer 257 instrument, and n.m.r. spectra on a 60 MHz Perkin-Elmer R10; chemical shifts are given in p.p.m. from TMS as internal standard. Mass spectral data were obtained on an A.E.I. MS9.

Methyl Indolizine-2-carboxylate (1).—This was prepared as described by Borrows and Holland,[7] m.p. 101° (lit.,[7] 97—99°) (83%); $\nu_{max.}$ (Nujol) 1720 cm.$^{-1}$.

2-*Hydroxymethylindolizine* (4).—A solution of the ester (1) (5·0 g.) in dry ether (400 ml.) was added slowly with stirring to a suspension of lithium aluminium hydride (1·1 g.) in dry ether (75 ml.). After being stirred at room temperature for 0·5 hr. the solution was briefly boiled. Ethyl acetate, water, and then dilute hydrochloric acid (5N; 50 ml.) were added. The pH was adjusted to a value in the range 5—6 (ammonia) and the ethereal layer was separated; the aqueous layer was further extracted with ether and then the extracts were combined, dried (Na_2SO_4), and evaporated to dryness. The residue was crystallised from light petroleum (b.p. 40—60°) to give plates of 2-*hydroxymethylindolizine* (4) (3·3 g., 79%), m.p. 105° (Found: C, 73·7; H, 6·2; N, 9·3%; M^+, 147. C_9H_9NO requires C, 73·5; H, 6·2; N, 9·5%; M^+, 147), $\nu_{max.}$ (CCl_4) 3590 cm.$^{-1}$: n.m.r. ($CDCl_3$) τ 7·85 (d, 5-H, $J_{5,6}$ 6 Hz), 7·3—6·3 (m, 5H), 4·78 (2H, s, CH_2OH), 1·85 (s, OH, exchanges with D_2O).

2-*Hydroxydideuteriomethylindolizine* (8).—This was prepared as above, with lithium aluminium deuteride; the deuteriated compound (8) had an n.m.r. spectrum identical with the above except for the absence of the signal at 4·78 p.p.m.; M^+, 149.

2-*Carbamoylindolizine* (14).—A solution of the methyl ester (1) (15 g.) in absolute methanol (500 ml.) was saturated with ammonia at −5° and the solution was heated at 155° for 65 hr. (22 atmos.). Evaporation under reduced pressure and crystallisation of the residue from water gave 2-*carbamoylindolizine* (14), m.p. 158° (softening and resolidifying at 133°) (6·0 g., 44%) (Found: C, 67·1; H, 4·8; N, 17·2. $C_9H_8N_2O$ requires C, 67·5; H, 5·0; N, 17·5%), $\nu_{max.}$ ($CHCl_3$) 3660, 3520, 3415, and 1665 cm.$^{-1}$.

2-*Aminomethylindolizine* (15).—A solution of the amide (14) (0·5 g.) in dry tetrahydrofuran (25 ml.) was added to a suspension of lithium aluminium hydride (0·3 g.) in dry tetrahydrofuran (20 ml.). The mixture was stirred (½ hr.) and then boiled (1—2 hr.). Water (0·6 g.) was added dropwise and the solids present were filtered off and extracted several times with boiling tetrahydrofuran. The combined extracts were dried (Na_2SO_4), filtered, and evaporated under reduced pressure. The aminomethylindolizine (15) (0·28 g.) was crystallised from light petroleum (b.p. 60—80°), m.p. 77·5°; $\nu_{max.}$ ($CHCl_3$) 3470 and 3380 (NH_2); the n.m.r. spectrum is described in the text. The aminomethyl derivative decomposed very rapidly and gave inconsistent analyses.

Indolizine-3-carbonyl Chloride (7).—A solution of indolizine (8·0 g.) in dry toluene was added dropwise to a cooled and stirred solution of phosgene in toluene [50 ml.; 12·5% (w/v)]. The solution was kept overnight and the precipitated indolizine hydrochloride was filtered off. The filtrate was evaporated under reduced pressure and the residual solid was crystallised from light petroleum (b.p. 60—80°) to give the *acyl chloride* (7), m.p. 82° (lit.,[2] 81°) (7·5 g., 61%) (Found: C, 60·7; H, 3·3; N, 8·0. Calc. for C_9H_6ClNO: C, 60·3; H, 3·3; N, 7·8%), $\nu_{max.}$ (CCl_4) 1720 cm.$^{-1}$; n.m.r. (CCl_4) δ 9·3 (d, 5-H, $J_{5,6}$ 6·5 Hz), 7·72 (d, 2-H, $J_{1,2}$ 4·5 Hz), 7·6—6·7 (m, 3H), and 6·55 (d, 1H, $J_{1,2}$ 4·5 Hz).

Methyl Indolizine-3-carboxylate (2).—The acyl chloride (7) (3·0 g.) was dissolved in methanol (30 ml.) and the solution was boiled (20 min.), to give a deep red solution. The solvent was removed under reduced pressure and the residue was treated with saturated sodium hydrogen carbonate. The aqueous mixture was extracted with ether, the ether was dried (Na_2SO_4) and then evaporated; the residue was distilled, b.p. 144—146°/14 mm., to give the *ester* (2) (2·5 g., 86%) (Found: C, 68·3; H, 5·0; N, 7·9. $C_{10}H_9NO_2$ requires C, 68·6; H, 5·2; N, 8·0%); $\nu_{max.}$ (CCl_4) 1695 cm.$^{-1}$; n.m.r. (CCl_4) δ 9·48 (d, 5-H, $J_{5,6}$ 6 Hz), 7·6—6·6 (4H, m), 6·4 (d, 1-H, $J_{1,2}$ 4 Hz), and 6·15 (s, CO_2CH_3).

3-*Hydroxymethylindolizine* (5).—A solution of the ester (2) (3·0 g.) in dry ether (100 ml.) was added dropwise to a stirred suspension of lithium aluminium hydride (0·7 g.) in dry ether (100 ml.). After 1 hr. at room temperature the mixture was boiled (15 min.), cooled, and treated with ethyl acetate (3 g.) and then water (0·7 g.). The mixture was filtered, the solid precipitate was extracted several times with ether, and the combined ether extracts were dried (Na_2SO_4) and distilled. The solid residue crystallised from light petroleum (b.p. 40—60°) to give needles of 3-*hydroxymethylindolizine*, m.p. 101° (Found: C, 73·8; H, 6·2; N, 9·5. C_9H_9NO requires C, 73·45; H, 6·2; N, 9·5%), $\nu_{max.}$ (CCl_4) 3610 cm.$^{-1}$; n.m.r. (CCl_4) δ 9·05—6·3 (6 ArH), 4·85 (2H, s, CH_2O), and 1·8 (1H, s, OH, exchanges with D_2O).

3-*Carbamoylindolizine*.—A mixture of the acyl chloride (7) (2 g.) and aqueous ammonia (30 ml.; *d* 0·88) was shaken for 24 hr. and then set aside for 24 hr. at room temperature. The yellow solid was filtered off, and crystallised from ethyl acetate to give the *amide*, m.p. 146—147° (0·5 g., 28%) (Found: C, 67·2; H, 5·0; N, 17·1. $C_9H_8N_2O$ requires C, 67·5; H, 5·0; N, 17·5%), $\nu_{max.}$ (Nujol) 3370, 3190, and 1640 cm.$^{-1}$.

Ethyl 2-*Methylindolizine-6-carboxylate* (3).—Ethyl 2-methylpyridine-5-carboxylate [10] (8·25 g.) was quaternised with bromoacetone (8·0 g.) in boiling absolute ethanol 30 ml., 6 hr.). Evaporation to dryness gave a gum which was dissolved in water; the aqueous solution was then ex-

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

[10] Pl. A. Plattner, W. Keller, and A. Boller, *Helv. Chim. Acta*, 1954, **37**, 1379.

tracted with chloroform several times. Evaporation of the aqueous solution under reduced pressure gave an uncrystallisable gum (13·7 g.) having $\nu_{max.}$ (film) 1700—1730br cm.$^{-1}$ and an n.m.r. spectrum consistent with structure (18).

The cyclisation was carried out by two methods. (*a*) The quaternary salt (18) (13·7 g.) was dissolved in 10% aqueous hydrogen carbonate solution (180 ml.) and the solution was heated on a steam-bath (2 hr.). The cooled mixture was extracted with ether and the ethereal extracts dried (Na_2SO_4) and evaporated to dryness; the residue crystallised from light petroleum (b.p. 40—60°) to give yellow crystals of the *indolizine ester* (3), m.p. 73·5° (3·5 g., 35%) (Found: C, 71·1; H, 6·1; N, 6·7. $C_{12}H_{13}NO_2$ requires C, 70·9; H, 6·5; N, 6·9%), $\nu_{max.}$ (Nujol) 1705 cm.$^{-1}$; n.m.r. (CCl_4) δ 8·6br (s, 5-H), 7·2—6·2 (4 ArH), 4·3 (2H q, OCH_2), 2·3 (3H, s), and 1·4 (3H, t, CH_3CH_2).

(*b*) The quaternary compound (18) (7·6 g.) was cyclised in boiling absolute ethanol (100 ml.) with di-n-butylamine (2·5 ml.) (2·5 hr.). Evaporation of the solution, treatment with water and ether, and evaporation of the ethereal extracts gave recrystallised ester (3) (1·9 g., 34%).

6-Hydroxymethyl-2-methylindolizine (6).—Reduction of the ester (3) (1·83 g.) with lithium aluminium hydride in ether as described above gave, after work-up the *6-hydroxymethyl-2-methylindolizine* (6), m.p. 96°, from light petroleum (b.p. 60—80°) (1·28 g., 88%) (Found: C, 74·2; H, 6·6; N, 8·3%; M^+, 161. $C_{10}H_{11}NO$ requires C, 74·5; H, 6·9; N, 8·7%; M^+, 161), $\nu_{max.}$ (Nujol) 3240br; n.m.r. ($CDCl_3$) δ 7·65br (s, 5-H), 7·25 (d, 8-H, $J_{7,8}$ 8 Hz), 7·0 (s, 3-H), 6·55 (d, 7-H), 6·3 (s, 1-H), 4·4 (s, CH_2–O), 2·85 (s, OH, exchangeable with D_2O), and 2·3 (3H, s).

6-Hydroxydideuteriomethyl-2-methylindolizine (9).—This was prepared as described for compound (6); the n.m.r. spectrum of dideuterio-derivative (9) was identical with that of compound (6) except for the absence of the 2H singlet at δ 4·4; M^+, 163.

Reduction of Ethyl 2-Methylindolizine-1-carboxylate.—(*a*) The ester (11) [4] (1·02 g.) was reduced with lithium aluminium hydride (1·0 g.) in tetrahydrofuran (35 ml.). Work-up as described above gave 1,2-dimethylindolizine (0·45 g., 62%), m.p. 61° (lit.,[11] 63°) identical in all spectra with an authentic sample.

(*b*) Reduction with lithium aluminium hydride in ether gave a mixture; the n.m.r. spectrum indicated the presence of starting material and 1,2-dimethylindolizine.

(*c*) A solution of the ester (11) (1·0 g.) in absolute ethanol (15 ml.) was treated with potassium borohydride (1·0 g.) and the mixture was boiled overnight. Treatment with water and benzene, and evaporation of the benzene solution gave unchanged ester (11).

1-Acetonyl-2-(2′-hydroxyethyl)pyridinium Bromide (19).—A solution of 2-pyridylethanol (6·2 g.) and bromoacetone (6·8 g.) in sulpholane (30 ml.) was kept at 35° for 3 days. The sulpholane solution was added dropwise to a large volume of acetone to give a thick oil. The acetone layer was removed and concentrated to give a small quantity of solid (A). The thick oil was dissolved in water, the aqueous solution was washed with ether and then with chloroform, and then evaporated under reduced pressure. The residual solid, plus the solid (A), were crystallised from acetone to give the *acetonylpyridinium bromide* (19), m.p. 144° (11·9 g., 92%) (Found: C, 46·1; H, 5·4; N, 5·4. $C_{10}H_{14}BrNO_2$ requires C, 46·2; H, 5·45; N, 5·3%), $\nu_{max.}$ (Nujol) 1725 cm.$^{-1}$; n.m.r. (D_2O) δ 8·8—7·8 (4H, m), 5·9 (2H, s, $\overset{+}{N}CH_2CO$, exchanges slowly), 4·05 (2H, OCH_2), 3·25 (2H, CH_2CH_2OH), and 2·5sh and 1·6sh (2s, 3H); n.m.r. (TFA, after 12 hr.): δ 9·1—8·6 (2H, m), 8·5—8·1 (2H, m), 7·2 (2H, s, $\overset{+}{N}CH_2CO$), 5·0 (2H, t), 3·7 (2H, t), and 2·7 (3H, s). The *toluene-p-sulphonate* (21) prepared in acetone and recrystallised from light petroleum (b.p. 60—80°) had m.p. 44° (60% yield) (Found: C, 57·1; H, 5·3; N, 4·8. $C_{14}H_{15}NO_3S,H_2O$ requires C, 56·9; H, 5·7; N, 4·7%). When the toluene-*p*-sulphonate (21) was treated with ethanol a white solid was obtained which crystallised from acetone and had m.p. 134°; this compound was shown by comparison with an authentic specimen to be the toluene-*p*-sulphonate salt of the toluene-*p*-sulphonate (21).

All attempts to quaternise the toluene-*p*-sulphonate (21) with bromoacetone gave complex mixtures.

Attempted Cyclisation of Acetonylpyridinium Salt (19).—The pyridinium salt (19) (4·0 g.) was added to a saturated solution of aqueous hydrogen carbonate (200 ml.) and the solution was heated on a steam-bath (2 hr.). A yellow solid (2·0 g.) was precipitated and was filtered off and dried. The solid showed no m.p. below 300° and had no characteristic peaks in the n.m.r. spectrum.

A similar result was obtained by using diethylamine in absolute ethanol as the cyclisation medium.

1-(2-Hydroxyethyl)-2-methylindolizine (13).—A solution of 3-(2-pyridyl)propan-1-ol (7·0 g.) and bromoacetone (7·0 g.) in acetone (20 ml.) was boiled for 1 hr. during which time a gummy quaternary salt separated. The acetone was decanted off and the residue was heated under reduced pressure to remove acetone. The yield of crude acetonylpyridinium bromide (20) was 12·1 g. (chloroplatinate, m.p. 168°). The crude bromide (20) was dissolved in aqueous hydrogen carbonate (50 ml.; 10%) and the solution was heated on a steam-bath for 40 min. The cooled mixture was extracted with ether and the ethereal extracts were dried. Evaporation of the ether left a residual oil which was extracted with light petroleum (b.p. 60—80°) to give the *hydroxy-ethylindolizine* (13), m.p. 53—55° (4·8 g., 54%) (Found: C, 57·7; H, 7·3; N, 8·0. $C_{11}H_{13}NO$ requires C, 75·4; H, 7·5; N, 8·0%), $\nu_{max.}$ (Nujol) 3330br; n.m.r. ($CDCl_3$) δ 7·7br (d, 5-H, $J_{5,6}$ 6 H), 7·25br (d, 8-H, $J_{7,8}$ 8 Hz), 7·05 (s, 3-H), 6·7—6·3 (m, 2H), 3·75 (t, CH_2O), 2·95 (t, CH_2CH_2O), 2·25 (3H, s), and 1·8 (1H, s, exchangeable with D_2O).

1-Acetonyl-5-carbamoyl-2-methylpyridinium Bromide (25).—This was prepared from 5-carbamoyl-2-methyl pyridine [10] (5·0 g.) and bromoacetone (6·0 g.) in boiling ethanol (50 ml., 7 hr.). Concentration of the solution gave a total of 7·4 g. (74%) of *pyridinium salt* (25) which crystallised from aqueous ethanol as flakes, m.p. 253° (Found: C, 44·4; H, 4·6; N, 10·1. $C_{10}H_{13}BrN_2O$ requires C, 44·0; H, 4·8; N, 10·3%), $\nu_{max.}$ (Nujol) 3270, 3120, 1735, and 1695 cm.$^{-1}$ (chloroplatinate, m.p. 212°); n.m.r. (TFA) δ 9·7 (s, 6-H), 9·3 (d, 4-H), 8·6—7·8 (3H, 3-H, and $CONH_2$), 7·2 (s, $\overset{+}{N}CH_2CO$), and 3·0 and 2·7 (2s, Me).

6-Carbamoyl-2-methylindolizine (16).—A solution of the pyridinium salt (25) (3·3 g.) and di-n-butylamine (5 ml.) in ethanol (95%) was boiled for 2·5 hr. When the solution was cooled a yellow solid separated; this was removed and further solid was obtained by concentration of the solution. The solid was crystallised from ethanol to give the *amide* (16), m.p. 205° (decomp.), (1·7 g., 81%) (Found: C, 68·8; H, 5·7; N, 15·9. $C_{10}H_{10}N_2O$ requires C, 69·0; H, 5·8;

[11] D. O. Holland and J. H. C. Nayler, *J. Chem. Soc.*, 1955, 1657.

N, 16·1%), $\nu_{max.}$ (Nujol) 3370, 3190, and 1655 cm.$^{-1}$; n.m.r. (TFA) δ 9·6br (s, 5-H), 9·0 (d, 7-H, $J_{7,8}$ 7·5 Hz), 8·4 (d, overlying broad signal, 8-H and $CONH_2$), 7·1br (s, 1-H), 5·6 (2H, s, $\overset{+}{N}CH_2$), and 2·5 (3H, s).

Attempted Dehydration of the Amide (16).—The amide (16) was heated with phosphoryl chloride at 130° for 4 hr. Work up gave a solid, with i.r. absorption characteristic of both the amide (16) and the nitrile (17).

1-*Acetonyl*-5-*cyano*-2-*methylpyridinium Bromide* (26).—(*a*) A solution of 2-methyl-5-cyanopyridine [10] (23) with bromoacetone in boiling absolute ethanol (16 hr.) gave the *pyridinium bromide* (26), m.p. 156° (from acetone) (46%) (Found: C, 47·1; H, 4·1; N, 10·6. $C_{10}H_{11}BrN_2O$ requires C, 47·1; H, 4·3; N, 11·0%), $\nu_{max.}$ (Nujol) 2250 and 1735 cm.$^{-1}$; n.m.r. (D_2O) δ 9·5 (s, 6-H), 9·1 (d, 4-H), 8·4 (d, 3-H), 7·1 (s, 2H, $COCH_2\overset{+}{N}$, exchanges slowly), and 2·9 and 2·6 (methyl, s).

(*b*) The nitrile (23) (10·1 g.) and bromoacetone (20·0 g.) were kept in sulpholane solution (50 ml.) for 3 days at 42°. The solution was poured into an excess of ethyl acetate and the solid quaternary salt was filtered off. To remove traces of sulpholane the crude quaternary salt was dissolved in water, extracted with chloroform and ether, and the solution was evaporated under reduced pressure to give a solid (23·3 g., 75%) sufficiently pure for use in cyclisation.

6-*Cyano*-2-*methylindolizine* (17).—The pyridinium salt (26) (5·46 g.) was cyclised in aqueous sodium hydrogen carbonate (10%; 100 ml.) for 1·5 hr. at steam-bath temperature. The cooled solution was extracted with chloroform, and the chloroform extracts were dried and evaporated to give a solid. Extraction with hot, light petroleum (b.p. 60—80°) and then cooling of the light petroleum solution gave the *nitrile* (17), m.p. 99° (2·44 g., 78%) (Found: C, 76·6; H, 4·8; N, 17·6. $C_{10}H_8N_2$ requires C, 76·9; H, 5·2; N, 17·9%), $\nu_{max.}$ (Nujol) 2225 cm.$^{-1}$; n.m.r. ($CDCl_3$) δ 8·3br (s, 5-H), 7·3 (2H, m), 6·7 (q, 7-H, $J_{7,8}$ 9, $J_{7,5}$ 2 c./sec.), 6·4 (s, 1-H), and 2·35 (3H, s).

Attempted Reduction of the Nitrile (17).—The nitrile (17) (0·5 g.) in dry ether (70 ml.) was added to a suspension of lithium aluminium hydride (0·5 g.) in ether (50 ml.) under nitrogen. The mixture was boiled (2·5 hr.) and worked up as described above to give a liquid (0·4 g.) showing $\nu_{max.}$ at 3490 and 3400 (benzene solution) which indicated the presence of NH_2, but n.m.r. spectra showed peaks at 1·7 and 3·3 p.p.m. indicative of ring reduction.

7-*Cyano*-2-*methylindolizine* (33).—4-Cyano-2-methylpyridine (30) [12] (7·0 g.) and bromoacetone (14·0 g.) in sulpholane (30 ml.) were allowed to react for 3 days at 35° and then worked up as described for compound (26), method (*b*). The crude bromide (31) (13·3 g., 88%) was crystallised from acetone, m.p. 152—155° (chloroplatinate, m.p. 186°). The bromide (31) (4·8 g.) was dissolved in ethanol (95%) and the solution was boiled with added Amberlite IR-4B (OH) ion-exchange resin (30 g.). The resin was filtered off and the filtrate was evaporated under reduced pressure. Extraction of the residual solid with light petroleum (b.p. 60—80°) gave 7-*cyano*-2-*methylindolizine* (33), m.p. 75·5° (0·75 g., 24%) (Found: C, 76·5; H, 5·1; N, 18·0. $C_{10}H_8N_2$ requires C, 76·9; H, 5·2; N, 17·9%), $\nu_{max.}$ (Nujol) 2235 cm.$^{-1}$.

7-*Aminomethyl*-2-*methylindolizine* (34).—The nitrile (33) (0·14 g.) was reduced by lithium aluminium hydride in boiling ether (15 min.) and worked up as described above to give the solid *aminomethylindolizine* (34) (0·1 g., 72%) m.p. 94° (from light petroleum) (Found: N, 17·3. $C_{10}H_{12}N_2$ requires N, 17·3%), $\nu_{max.}$ (Nujol) 3360 and 3280 cm.$^{-1}$; the n.m.r. spectrum is quoted in the text.

4-*Acetamidomethyl*-1-*acetonyl*-2-*methylpyridinium Bromide* (32).—The 4-cyano-2-methylpyridine [12] was reduced with lithium aluminium hydride in ether to give 4-aminomethyl-2-methylpyridine, b.p. 112—116°/15mm.; n.m.r. ($CDCl_3$) δ 8·6 (d, 6-H), 7·2 (2H, m), 3·9 (s, CH_2N), 2·6 (3H, s), and 1·55 (s, NH_2, exchanges with D_2O). The 4-aminomethylpyridine was heated with acetic anhydride and acetic acid at 100° for 0·5 hr., evaporated under reduced pressure, treated with an excess of aqueous saturated sodium carbonate and extracted with chloroform. From the dried chloroform solution 4-acetamidomethyl-2-methylpyridine was obtained; n.m.r. ($CDCl_3$) δ 8·5 (d, 6-H), 7·5br (s, NHCO), 2·9 (m, 3- and 5-H), 4·4 (d, CH_2NH), and 2·5 and 2·05 (2s, 6H). The acetamidomethyl pyridine (1·1 g.) was quaternised in 87% yield by bromoacetone (2·0 g.) in boiling acetone (25 ml., 3·5 hr.). Recrystallised from acetone–ethanol the 4-*acetamidomethyl*-1-*acetonylpicolinium bromide* (32) had m.p. 197° (Found: C, 47·4; H, 5·6; N, 8·9. $C_{17}H_{17}BrN_2O_2$ requires C, 47·8; H, 5·7; N, 9·3%), $\nu_{max.}$ (Nujol) 3280, 1730, and 1665 cm.$^{-1}$; n.m.r. (D_2O) δ 8·65 (d, 6-H), 7·9 (m, 3- and 5-H), 5·85 (2H, s, slowly exchanging, $\overset{+}{N}CH_2CO$), and 2·7, 2·5 and 2·15 (3s, 9H).

Cyclisation of 4-*Acetamidomethyl*-1-*acetonyl*-2-*methylpyridinium Bromide*.—The salt (32) (0·5 g.) was cyclised with aqueous sodium hydrogen carbonate (40 ml., 10%) for 0·5 hr. on a steam-bath. The cooled solution was extracted with ether and the extract was dried; evaporation of the ether solution gave 7-acetamidomethyl-2-methylindolizine (35) (0·1g., 57%); crystallised from light petroleum (b.p. 60—80°) it had m.p. 158°; $\nu_{max.}$ (Nujol) 3300 and 1650 cm.$^{-1}$.

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