Heterocyclic Compounds with Bridgehead Nitrogen Atoms. Part 7.[1,2] The Synthesis of Pyrrolo[2,1,5-*cd*]indolizines ([2,2,3]Cyclazines) and Pyrazino[2,1,6-*cd*]pyrrolizines (6-Aza[2,2,3]cyclazines) from 3*H*-Pyrrolizine

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3*H*-Pyrrolizine reacts with *NN*-dimethylformamide and phosphoryl chloride to give a 3-(*NN*-dimethylaminomethylene)-3*H*,5*H*-pyrrolizinium salt (2), isolated as the perchlorate, which can be further converted, with *NN*-dimethylthioformamide and acetic anhydride, into 3,5-bis-(*NN*-dimethylaminomethylene)-3*H*,5*H*-pyrrolizinium perchlorate (8). The conjugate base of the salt (2) reacts with dimethyl but-2-yne-1,4-dioate to give dimethyl pyrrolo[2,1,5-*cd*]indolizine-5,6-dicarboxylate. The salt (8) reacts with nitromethane, in the presence of base, to give 6-nitropyrrolo[2,1,5-*cd*]indolizine (9a) and with ammonia to give pyrazino[2,1,6-*cd*]pyrrolizine (10a). Electrophilic substitution reactions of (9a) and (10a), and a nucleophilic substitution of (10a), are described.

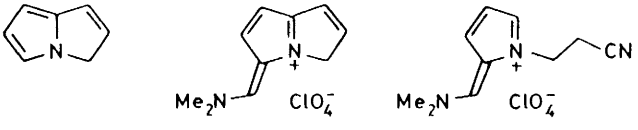
THE discovery, by Schweizer and Light,[3] of an efficient route to 3*H*-pyrrolizine (1) opened the way to the use of this compound in the synthesis of cyclazines. A preliminary account of our work in this field has already appeared [2] and in the present paper we give full details of that part of the work which is concerned with [2,2,3]-cyclazines † and their 6-aza-derivatives.

RESULTS AND DISCUSSION

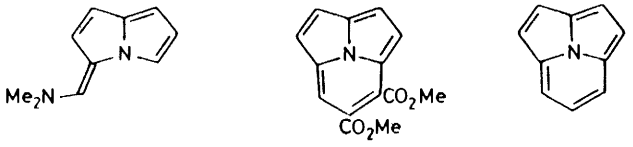
The reaction of 3*H*-pyrrolizine with *NN*-dimethylformamide (DMF) and phosphoryl chloride, at −65 °C in tetrahydrofuran, gave a Vilsmeier salt, isolated as the perchlorate. Subsequent reactions showed that the Vilsmeier reaction had taken place at the 5-position, and the salt is formulated as the 3*H*-isomer (2) on the basis of the CH_2 chemical shift (δ 4.90) which is close to that of the N-CH_2 protons (δ 4.74) in the pyrrolenium salt (3).

The conjugate base (4) of the cation of (2) was not sufficiently stable to be isolated but it reacted *in situ* with dimethyl but-2-yne-1,4-dioate to give dimethyl [2,2,3]cyclazine-5,6-dicarboxylate (5), the best yield being obtained by adding sodium hydride to a solution of the salt (2) and the acetylenic ester in DMF. The structure of compound (5) was confirmed by hydrolysis and decarboxylation to give the parent [2,2,3]cyclazine (6). The ^{1}H n.m.r. spectrum (Table) of the diester (5) was unique among those of the cyclazines described here in showing long-range coupling of H-1 to H-3 and of H-2 to H-4. In other respects, the spectrum agreed well with previously reported [4] spectra of [2,2,3]cyclazines.

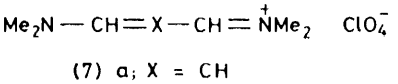
Jutz and his co-workers [7] have reported the synthesis of pyrenes from phenalene by reaction with iminium salts [*e.g.* (7a)], in the presence of sodium methoxide, followed by thermal cyclisation of the resulting ' phenafulvenes '. A similar reaction of 3*H*-pyrrolizine would, it was hoped, provide a direct route to [2,2,3]cyclazine (6), though it was expected that a stronger base would



(1) (2) (3)



(4) (5) (6)



(7) a; X = CH
b; X = N

be necessary since the acidity of pyrrolizine (pK_a 29) [8] is less than that of phenalene (pK_a 19.5).[9] [2,2,3]-Cyclazine was, in fact, obtained by this method, using sodium hydride as the base, but the yield (2.8%) was too low for the reaction to be of any real value. A similar reaction of 3*H*-pyrrolizine with the iminium salt (7b) failed completely, 6-aza[2,2,3]cyclazine being undetectable even by mass spectrometry.

Various attempts were made to carry out a second Vilsmeier reaction by treating solutions of the unstable pyrrolizine derivative (4) with DMF–phosphoryl chloride or DMF–thionyl chloride, or by treating the perchlorate (2) with diethoxy-*NN*-dimethylaminomethane.[10] None

† The widely accepted [4] cyclazine nomenclature [5] is used here in order to be able to use the same numbering system for the pyrrolo[2,1,5-*cd*]indolizines and their aza-derivatives, the pyrazino[2,1,6-*cd*]pyrrolizines. These two closely related classes of cyclazines can thus be discussed concurrently. Minor modifications of Boekelheide's original proposals [5] for nomenclature are introduced: (*a*) citing the bracketed numerals in increasing order, so that their sequence is correctly related to the numbering sequence in the peripheral cycle; and (*b*) placing the bracket before the word cyclazine rather than in the middle of it. The second modification removes certain difficulties in pronunciation and brings cyclazine nomenclature into line with the systems used for annulenes and cyclophanes. We do not believe that the more far-reaching proposals of Ceder and Beijer [6] for modification of cyclazine nomenclature would facilitate comparisons in the present series. In the interests of completeness, and for reference purposes, cyclazines described in the experimental section are named according to both the cyclazine and the IUPAC nomenclature systems.

of these reactions gave more than a trace of disubstituted product, but treatment of the perchlorate (2), with *NN*-dimethylthioformamide in acetic anhydride,[11] gave a *good* yield of a bis-(*NN*-dimethylaminomethylene)-pyrrolizinium salt. The ^{1}H n.m.r. spectrum of this product was complex and suggested the presence of more than one isomer but the success of subsequent reactions showed that a high proportion of the 3,5-isomer (8) was present.

The perchlorate (8) reacted with nitromethane, in the presence of potassium t-butoxide, to give 6-nitro-[2,2,3]cyclazine (9a) and with ammonia to give 6-aza[2,2,3]cyclazine (10a), both products, though previously unknown, being readily identified by their ^{1}H n.m.r. spectra (Table). The assignment of the low- and high-field components of the AB multiplets in these spectra to H-2,3 and H-1,4, respectively, is in line with the order of chemical shifts previously established [12] for the parent cyclazine (6). It is unlikely that these assignments ought to be interchanged, since this would place the H-2,3-resonance of the 6-azacyclazine at higher field than the corresponding resonance of the parent compound. Nevertheless, there is a selective deshielding of H-1 and H-4 (due to conjugative electron-withdrawal by the 6-nitro- or 6-aza-substituent) which decreases the A–B separation (by 0.1 p.p.m.) relative to that for the parent compound.

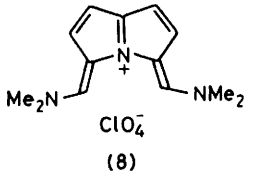
Despite the presence of an electron-withdrawing substituent, mild conditions were sufficient to cause electrophilic substitution in the 6-nitrocyclazine (9a). The Vilsmeier reaction with DMF–phosphoryl chloride gave the 1-formyl derivative (9b), in low yield, and nitration with copper(II) nitrate–acetic anhydride gave the 1,6-dinitrocyclazine (9c). The ^{1}H n.m.r. spectra of these two products were very similar to each other but differed from that of the starting material (9a) in showing marked deshielding (0.43—0.64 p.p.m.) of H-2 and H-7 due to the magnetic anisotropies of the 1-formyl- and 1-nitro-substituents. Smaller downfield shifts (0.07—0.21 p.p.m.) of the remaining proton signals were also observed. Reaction of the 6-nitrocyclazine with bromine at room temperature gave the 1-bromo- and 1,4-dibromo-derivatives, (9d) and (9e), identified by their ^{1}H n.m.r. spectra (Table) which showed very small effects (0.00—0.08 p.p.m.) of the bromine substituents on the chemical shifts of the remaining protons.

Electrophilic substitution in the 6-azacyclazine (10a) was, in general, much more difficult, probably because the initial attack occurred at N-6, creating a positively charged species. Bromination gave the 1-bromo- and 1,4-dibromo-derivatives, (10b) and (10c), identified by their ^{1}H n.m.r. spectra (Table), but formylation (DMF–$POCl_3$) and acetylation (MeCOCl–$SnCl_4$) failed completely. Treatment with copper(II) nitrate–acetic anhydride gave a very small yield (2%) of a dinitro-derivative, the ^{1}H n.m.r. spectrum of which showed two one-proton singlets (δ 8.44 and 9.15) and an AB multiplet (δ_A 8.05, δ_B 7.78). This product was identified as 1,7-dinitro-6-aza[2,2,3]cyclazine (10d) on the basis of the following reasoning: (*a*) the lower-field singlet shows that only one proton remains in the six-membered ring and that this is not *peri* to a nitro-group since it is not deshielded with respect to the corresponding proton(s) in

^{1}H N.m.r. data [a] of [2,2,3]cyclazines [b] and 6-aza[2,2,3]cyclazines [c]

Compound	H-1	H-2	H-3	H-4	H-5	H-6	H-7	*J*/Hz
(6) [d]	7.20	7.51	7.51	7.20	7.86	7.59	7.86	
(9a)	7.55	7.75	7.75	7.55	8.86		8.86	$J_{1,2} = J_{3,4} = 4.5$
(10a) [e]	7.44	7.64	7.64	7.44	9.21		9.21	$J_{1,2} = J_{3,4} = 4.5$
(5)	7.29	7.62	7.62	7.47	(4.08 and 3.98)		8.34	$J_{1,2}$ 4.2, $J_{3,4}$ 4.5, $J_{1,3} = J_{2,4} = 0.8$
(9b)	(10.35)	8.18	7.88	7.67	8.93		9.35	$J_{3,4}$ 4.7, $J_{5,7}$ 1.8
(9c)		8.39	7.94	7.76	8.99		9.49	$J_{3,4}$ 4.5
(9d)		7.78	7.75	7.59	8.92		8.92	$J_{3,4}$ 4.5
(9e)		7.77	7.77		8.94		8.94	
(10b) [e]		7.63	7.60	7.45	9.21		9.21	$J_{3,4}$ 4.5
(10c) [e]		7.62	7.62		9.18		9.18	
(10d) [e]		8.44	8.05	7.78	9.15			$J_{3,4}$ 4.5
(10e) [e]	7.37	◄———	7.53—7.66 [e]	———►	(8.28) [f]		9.21	$J_{1,2}$ 4.5
(10a-H$^+$) [e,g]	8.18	8.20	8.20	8.18	9.24		9.24	
(10a-MeI) [e,g]	8.10	8.20	8.20	8.10	9.13	(4.83)	9.13	$J_{1,2} = J_{3,4} = 4.5$

[a] In $CDCl_3$ unless otherwise stated, δ/p.p.m. from $SiMe_4$; values in parentheses refer to protons in substituent groups. [b] Pyrrolo-[2,1,5-*cd*]indolines. [c] Pyrazino[2,1,6-*cd*]pyrrolizines; the cyclazine numbering system is used (*i.e.* 1,2,3,4,5,6,7 correspond, respectively, to 4,5,6,7,1,2,3 in the IUPAC numbering system). [d] Ref. 12*a*. [e] Multiplet includes *m*- and *p*-Ph protons. [f] *o*-Ph protons. [g] In CF_3CO_2H.



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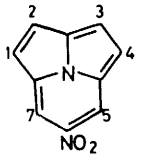
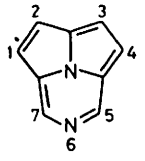


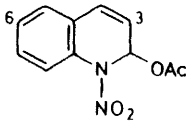
(9) a; parent
b; 1—CHO
c; 1—NO_2
d; 1—Br
e; 1 4—Br_2



(10) a; parent
b; 1—Br
c; 1,4—Br_2
d; 1,7—$(NO_2)_2$
e; 5—Ph
f; 5,7—Ph_2

the parent azacyclazine; (*b*) the higher-field singlet is attributed to H-2 since it has a chemical shift (δ 8.44) very close to that (δ 8.39) of H-2 in the 1,6-dinitrocyclazine (9c); (*c*) neither of the AB protons is strongly deshielded with respect to the corresponding proton (H-3 or -4) in the 1,6-dinitrocyclazine (9c), thus confirming the absence of a 2- or a 5-nitro-group.

This substitution pattern was quite unexpected since the 7(5)-position of the 6-azacyclazine is expected to be the least susceptible to electrophilic attack. It seems possible, however, that the behaviour of the cyclazine is related to that of quinoline, which also gives unusual (3- and 6-nitro) substitution products when treated with nitric acid (or metal nitrates) in acetic anhydride. Dewar and Maitlis [13] attributed the behaviour of quinoline to the initial attack of nitronium ion (or its equivalent) at the nitrogen atom and the subsequent formation of an adduct [*e.g.* (11)] which is then nitrated at carbon. A similar adduct (12), formed from the azacyclazine, might well be nitrated in the observed positions before being rearomatised by elimination of acetyl nitrate.



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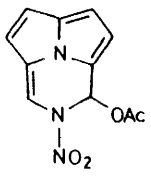

(12)

Attempts to nitrate the azacyclazine with nitric acid in acetic anhydride, or with tetranitromethane in pyridine, led only to recovery of starting material in 60% and 30% yield, respectively.

The chemical shift (δ 9.21) of H-5 and -7 in the 6-azacyclazine (10a) is very close to that (δ 9.26) of H-1 in isoquinoline and this suggested that nucleophilic substitution might be possible at these positions. Accordingly, the cyclazine was treated with phenyl-lithium under the conditions used [14] for nucleophilic phenylation of pyridine. 5-Phenyl-6-aza[2,2,3]cyclazine (10e), showing only one remaining ^{1}H resonance at low field, was obtained as the main product, together with the 5,7-diphenyl compound (10f) which, though not quite pure, was identifiable by the absence of a low-field resonance and by an accurate mass measurement of its molecular ion.

EXPERIMENTAL

^{1}H N.m.r. data were obtained at 100 MHz and, unless otherwise stated, refer to solutions in deuteriochloroform with tetramethylsilane as internal standard. I.r. data refer to Nujol mulls. Alumina for chromatography (Laporte type H) was deactivated, where specified, by treatment with 10% aqueous acetic acid (0.05—0.1 cm^3 per g alumina). For drying, ether, tetrahydrofuran, and toluene were kept over sodium; dichloromethane and t-butyl alcohol were kept over Linde molecular sieve (type 4A); and DMF, after being kept over molecular sieve, was distilled from calcium hydride. Light petroleum refers to the fraction of b.p. 60—80 °C. Extracts were dried over magnesium sulphate and evaporated under reduced pressure.

5-(NN-*Dimethylaminomethylene*)-3H,5H-*pyrrolizinium Perchlorate* (2).—A Vilsmeier reagent prepared by adding phosphoryl chloride (8.76 g) to ice-cold DMF (4.24 g) was dissolved in dry tetrahydrofuran (25 cm^3) and the solution was added, during 30 min, under dry nitrogen, to a stirred solution of freshly distilled 3*H*-pyrrolizine (5.92 g) in dry tetrahydrofuran kept at −65 °C. After a further 30 min at −65 °C, the temperature was allowed to rise to −35 °C and a little dry methanol was added, followed, dropwise by a saturated solution of sodium perchlorate (8.02 g) in dry methanol. The resulting suspension was stirred for 15 min (keeping the temperature below −30 °C), cooled to −65 °C, and diluted slowly with dry ether (250 cm^3). After a further 5 min at −60 °C, the product was rapidly filtered off and washed with dry ether (500 cm^3) to yield a pink powder (15.74 g), sufficiently pure for further reactions. Recrystallisation of a portion from ethanol containing a trace of perchloric acid gave the analytically pure, colourless *perchlorate*, m.p. 158—159 °C (Found: C, 46.0; H, 4.8; N, 10.5. $C_{10}H_{13}ClN_2O_4$ requires C, 46.2; H, 5.0; N, 10.8%); δ(CF_3CO_2H) 3.60 (3 H, s, NMe), 3.75 (3 H, s, NMe), 4.90 (2 H, br s, 5-CH_2), 6.65 (1 H, d, H-1), 6.75—7.05 (2 H, m, H-6 and -7), 7.50 (1 H, d, H-2), and 8.30 (1 H, s, NCH=).

Darker and less stable products were obtained if (*a*) the solvents were not carefully dried, (*b*) the stated temperatures were not carefully maintained, or (*c*) an inexact quantity of the Vilsmeier reagent was used.

1-(2-*Cyanoethyl*)-2-(NN-*dimethylaminomethylene*)-2H-*pyrroleninium Perchlorate* (3).—Phosphoryl chloride (1 cm^3) was added to a stirred solution of 1-(2-cyanoethyl)pyrrole [15] (1.1 g) and DMF (2.3 cm^3) in sodium-dried benzene (50 cm^3) at 70 °C. After being stirred at 70 °C for 15 min, the solution was cooled and diluted with dry ether to precipitate a dark red oil. The supernatant solution was decanted and the oil was dissolved in dry methanol (8 cm^3) and treated with a saturated solution of sodium perchlorate (1.23 g) in dry methanol. The resulting precipitate was filtered off, washed with dry methanol and dry ether, and recrystallised from ethanol to give the *pyrroleninium salt* (2.6 g) as needles, m.p. 133—134 °C (Found: C, 43.9; H, 4.8; N, 15.1. $C_{10}H_{14}ClN_3O_4$ requires C, 43.6; H, 5.1; N, 15.3%); δ(CF_3CO_2H) 3.14 (2 H, t, CH_2CN), 3.70 (3 H, s, NMe), 3.84 (3 H, s, NMe), 4.74 (2 H, t, CH_2N^+), 6.76 (1 H, dd, H-4), 7.54 (1 H, d, H-3), 7.72 (1 H, br s, H-5), and 8.53 (1 H, s, NCH=).

Reaction of 5-(NN-*Dimethylaminomethylene*)-3H,5H-*pyrrolizinium Perchlorate with* NN-*Dimethylthioformamide and Acetic Anhydride*.—*NN*-Dimethylthioformamide (10 cm^3) was added to the pyrrolizinium perchlorate (2.02 g) in acetic anhydride (250 cm^3) and the suspension was gradually brought to reflux, with vigorous stirring, under nitrogen. After 10 min, the solution, which had become brick-red, was cooled and poured into dry ether (600 cm^3). The precipitate, which was filtered off and washed with dry ether, was a bis-(*NN*-dimethylaminomethylene)pyrrolizinium perchlorate (2.17 g, 86%), brick-red solid, m.p. 218—222 °C (from ethanol containing a trace of perchloric acid) (Found: C, 49.2; H, 5.5; N, 13.0. $C_{13}H_{18}ClN_3O_4$ requires C, 49.4; H, 5.7; N, 13.3%); δ(NMe) 3.77 and

3.90 (major peaks), 4.10 4.15, and 4.25 (minor peaks); δ(CH) 6.9, 7.7, and 8.5 (major peaks), 6.7, 7.25, and 9.4 (minor peaks), ratio NMe : CH 2 : 1, all peaks broad. Subsequent reactions showed that this was mainly the *3,5-bis-(NN*-dimethylaminomethylene)-compound, but the ^{1}H n.m.r. spectrum suggested that other isomers (1,3- and/or 1,5-) were present.

Dimethyl Pyrrolo[2,1,5-cd]*indolizine-5,6-dicarboxylate* (*Dimethyl* [2,2,3]*Cyclazine-5,6-dicarboxylate*) (5).—A solution of the pyrrolizinium perchlorate (2) (5.54 g) and dimethyl but-2-yne-1,4-dioate (2.94 g) in dry DMF (120 cm^3) was stirred under nitrogen and treated with sodium hydride (1.05 g of 50% oil dispersion), in small portions, during 15 min. Stirring was continued for 1 h at room temperature and for 1 under reflux, and the solution was then cooled and filtered. The filtrate was evaporated and the residue was chromatographed on deactivated alumina, in benzene, to give the *diester* (3.8 g, 68%) as orange prisms, m.p. 88—89 °C (from ethanol) (Found: C, 65.1; H, 4.3; N, 5.1. $C_{14}H_{11}NO_4$ requires C, 65.4; H, 4.3; N, 5.4%); $\lambda_{max.}$ (EtOH) 269.5, 317, and 422 nm (log ε 4.57, 3.63, and 3.28).

Hydrolysis of Dimethyl Pyrrolo[2,1,5-cd]*indolizine-5,6-dicarboxylate*.—The diester (0.54 g) was heated under reflux with 5% methanolic potassium hydroxide (60 cm^3) for 30 min and the solution was then kept at room temperature for 5 d. The pale yellow potassium salt (0.72 g) that deposited was filtered off, dissolved in water, and treated with hydrochloric acid to give the dicarboxylic acid (0.40 g; 83%) as a yellow powder; $\nu_{max.}$ 1 680 (C=O) and 2 800—3 200 cm^{-1} (OH). An intimate mixture of the acid (0.10 g) and soda-lime (0.10 g) was heated at 200 °C in an evacuated (0.01 mmHg) sublimation apparatus to yield *pyrrolo*-[2,1,5-cd]*indolizine-5,6-dicarboxylic anhydride* (0.08 g) as an orange powder, m.p. 242—244 °C (Found: C, 67.9; H, 2.3; N, 6.3%; M^+, 211. $C_{12}H_5NO_3$ requires C, 68.25; H, 2.4; N, 6.6%; *M*, 211); $\nu_{max.}$ 1 760 and 1 830 cm^{-1}; δ 7.64 (1 H, d, H-1), 7.68 (1 H, d, H-4), 7.94 (2 H, d, H-2 and -3), and 8.46 (1 H, s, H-7).

Pyrrolo[2,1,5-cd]*indolizine* ([2,2,3]*Cyclazine*) (6).—(*a*) The foregoing dicarboxylic acid (0.21 g), in purified [12b] quinoline (60 cm^3) containing copper chromite catalyst [16] (0.30 g), was heated at 230 °C for 5 h, while dry nitrogen was passed through the solution. After being cooled under nitrogen, the solution was filtered and treated with an excess of aqueous hydrochloric acid. Extraction with ether and evaporation of the extract gave a yellow oil which was sublimed under reduced pressure to give the pyrroloindolizine (0.065 g, 50%), pale yellow plates, m.p. 62—63 °C (after re-sublimation) (lit.[5] m.p. 63.5—64.5 °C); ^{1}H n.m.r. spectrum as reported.[12]

(*b*) A solution of freshly distilled 3*H*-pyrrolizine (0.4 g) in dry DMF (40 cm^3) was stirred under dry nitrogen and 3-(*NN*-dimethylamino)propenylidenedimethylammonium perchlorate (7a) (0.88 g) was added, in one portion, followed by sodium hydride (0.4 g of 50% oil dispersion), in small portions, during 1 h. The deep red solution was stirred for a further 30 min at room temperature and then heated under reflux for 5.5 h. After being allowed to cool under nitrogen, the solution was filtered and evaporated under reduced pressure to give residue (A). The distillate, which was pale yellow and fluorescent owing to co-distillation of part of the cylazine, was diluted with water and extracted with ether. The extract was dried and evaporated to give residue (B). The combined residues (A) and (B) were dissolved in the minimum volume of benzene and chromatographed on alumina. Elution with light petroleum gave a pale yellow, fluorescent oil which contained the cyclazine, probably contaminated with DMF. A solution of the oil, in light petroleum, was washed several times with water (2.5 dm^3 total), dried, and evaporated. Chromatography of the residue and sublimation of the first material eluted with pentane gave the pyrroloindolizine (0.015 g, 2.8%), m.p. 60—61 °C, ^{1}H n.m.r. spectrum identical with that of the specimen obtained by method (*a*).

6-*Nitropyrrolo*[2,1,5-cd]*indolizine* (6-*Nitro*[2,2,3]*cyclazine*) (9a).—A stirred solution of the pyrrolizinium perchlorate (8) (2.0 g) and nitromethane (6 cm^3) in t-butyl alcohol (250 cm^3) was heated at 40 °C, under nitrogen, and a solution of potassium t-butoxide (5 g) in t-butyl alcohol (25 cm^3) was added, dropwise, during 15 min. The solution was then heated to reflux, more potassium t-butoxide (3 g) in t-butyl alcohol (20 cm^3) was added, and heating was continued for 12 h. After being allowed to cool, the solution was filtered and the filtrate was diluted with water and extracted with ether. The extract was dried and evaporated and the residue was chromatographed on deactivated alumina. Elution with ether yielded the *nitro-compound* (0.65 g; 55%) as a yellow powder, m.p. 147—148 °C (from benzene) (Found: C, 64.3; H, 3.1; N, 15.0. $C_{10}H_6N_2O_2$ requires C, 64.5; H, 3.25; N, 15.05%); $\lambda_{max.}$ (EtOH) 224, 265, 275sh, 312, and 392 nm (log ε 4.26, 4.43, 4.37, 3.53, and 3.89).

6-*Nitropyrrolo*[2,1,5-cd]*indolizine-1-carbaldehyde* (6-*Nitro*[2,2,3]*cyclazine-1-carbaldehyde*) (9b).—A solution of the 6-nitrocyclazine (0.085 g) in dry DMF (3 cm^3) was cooled in ice and stirred while phosphoryl chloride (0.075 g) was added dropwise. After 1 h at 0 °C and 1 h at 70 °C, the solution was diluted with saturated aqueous sodium carbonate, whereupon a yellow solid precipitated. The suspension was heated for 10 min, diluted further with 2M aqueous sodium hydroxide, and extracted with chloroform. The extract was dried and evaporated, and the residue was chromatographed on deactivated alumina. Elution with benzene yielded (*i*) starting material (0.040 g) and (*ii*) the *nitroaldehyde* (0.014 g, 15%) as yellow needles, m.p. 188—189 °C (from ethanol) (Found: C, 61.9; H, 3.0; N, 12.9. $C_{11}H_6N_2O_3$ requires C, 61.7; H, 2.8; N, 13.1%); $\nu_{max.}$ 1 660 cm^{-1} (C=O); $\lambda_{max.}$ (EtOH) 263, 309, 380sh, 414, and 423 nm (log ε 4.41, 3.86, 3.79, 3.97, and 3.97).

1,6-*Dinitropyrrolo*[2,1,5-cd]*indolizine* (1,6-*Dinitro*[2,2,3]-*cyclazine*) (9c).—The 6-nitrocyclazine (0.078 g) was stirred with copper(II) nitrate trihydrate (0.129 g) in acetic anhydride (4.5 cm^3) for 1.5 h at room temperature. The solution was diluted with water (50 cm^3), basified with sodium carbonate, and extracted with dichloromethane. The extract was dried and evaporated, and the residue was chromatographed on deactivated alumina. Elution with ether yielded the deep yellow *dinitro-compound* (0.030 g, 31%), m.p. 240—241 °C (from ethanol–chloroform) (Found: C, 51.9; H, 2.1; N, 17.95. $C_{10}H_5N_3O_4$ requires C, 52.0; H, 2.2; N, 18.2%); $\lambda_{max.}$ (EtOH) 248, 297, 365, 425sh, and 434 nm (log ε 4.30, 3.95, 3.66, 3.93, and 3.99).

Bromination of 6-*Nitropyrrolo*[2,1,5-cd]*indolizine*.—Bromine (0.140 g), in dichloromethane (14 cm^3) was added dropwise to a stirred solution of the nitrocyclazine (0.081 g) in dichloromethane (15 cm^3), which was then kept for 24 h at room temperature. The solution (containing a yellow precipitate) was evaporated and the residual solid was chromatographed on deactivated alumina. Elution with chloroform gave (*i*) 1-*bromo-6-nitropyrrolo*[2,1,5-cd]*indol-*

izine (1-*bromo*-6-*nitro*[2,2,3]*cyclazine*) (0.020 g, 17%) as a yellow powder, m.p. 284—288 °C (decomp.) (from ethanol–chloroform) (Found: C, 45.2; H, 1.6; N, 9.9%; M^+, 264 and 266. $C_{10}H_5BrN_2O_2$ requires C, 45.3; H, 1.9; N, 10.6%; *M*, 264 and 266) and (*ii*) 1,4-*dibromo*-6-*nitropyrrolo*[2,1,5-cd]*indolizine* (1,4-*dibromo*-6-*nitro*[2,2,3]*cyclazine*) (0.067 g, 45%) as an orange-yellow powder, sublimes 259—262 °C (from ethanol–chloroform) (Found: C, 37.2; H, 1.0; N, 8.05%; M^+, 342, 344, and 346. $C_{10}H_4Br_2N_2O_2$ requires C, 36.9; H, 1.2; N, 8.15%; *M*, 342, 344, and 346).

Pyrazino[2,1,6-cd]*pyrrolizine* (6-*Aza*[2,2,3]*cyclazine*) (10a).—A solution of the pyrrolizinium perchlorate (8) (2.0 g), in the minimum volume of hot water, was added dropwise with stirring to 9M aqueous ammonia (200 cm³). After 2 h at 60 °C, the solution was cooled and extracted with ether. The ethereal solution was extracted with 2M aqueous hydrochloric acid (3 × 150 cm³) which was then neutralised (Na_2CO_3) and re-extracted with ether. The final ether extract was dried and evaporated and the residue was chromatographed on alumina. Elution with ether gave a pale yellow, purple-fluorescent band which yielded the *pyrazinopyrrolizine* (0.342 g, 39%) as pale yellow plates, m.p. 52—53 °C (from ether) (Found: C, 76.4; H, 4.1; N, 19.4. $C_9H_6N_2$ requires C, 76.0; H, 4.25; N, 19.7%); $\lambda_{max.}$ (EtOH) 247, 290, 380sh, 388, 400sh, and 410 nm (log ε 4.56, 3.61, 3.26, 3.29, 3.22, and 2.99); $\lambda_{max.}$ (EtOH–HCl) 232, 256, 278sh, 304, and 370 nm (log ε 4.74, 4.41, 3.96, 3.50, and 3.11). Treatment of the pyrazinopyrrolizine with picric acid in ethanol gave a *picrate*, m.p. 248—250 °C (Found: C, 48.3; H, 2.4; N, 18.7. $C_{15}H_9N_5O_7$ requires C, 48.5; H, 2.4; N, 18.9%).

2-*Methylpyrazino*[2,1,6-cd]*pyrrolizinium iodide* (6-*Methyl*-6-*azonia*[2,2,3]*cyclazine iodide*).—Pyrazino[2,1,6-*cd*]pyrrolizine (0.046 g) was kept overnight with an excess of methyl iodide in dichloromethane (5 cm³). Evaporation of the solution and trituration of the residue with ether yielded the *methiodide* (0.078 g, 84%), m.p. 197—198 °C (from ethanol) (Found: C, 42.4; H, 2.9; N, 9.7. $C_9H_9IN_2$ requires C, 42.3; H, 3.2; N, 9.9%); $\lambda_{max.}$ (EtOH) 237, 260, 280sh, 288, 320, and 375 nm (log ε 4.60, 4.25, 3.73, 3.70, 3.38, and 2.90).

Bromination of Pyrazino[2,1,6-cd]*pyrrolizine*.—Bromine (0.125 g), in dichloromethane (12.5 cm³), was added dropwise, with stirring. to the pyrazinopyrrolizine (0.055 g) in dichloromethane (12.5 cm³) and the solution was kept overnight at room temperature. The solution (containing a precipitate) was evaporated and the residual yellow solid (probably a mixture of hydrobromides) was extracted with ether in the presence of 2M aqueous sodium hydroxide. The extract was dried and evaporated, and the residue was chromatographed on deactivated alumina, in benzene, to yield (*i*) 4,7-*dibromopyrazino*[2,1,6-cd]*pyrrolizine* (1,4-*dibromo*-6-*aza*[2,2,3]*cyclazine*) (0.045 g, 39%) as a yellow powder, m.p. 119—121 °C (from light petroleum–benzene) (Found: C, 36.3; H, 1.4; N, 9.55%; M^+, 298, 300, and 302. $C_9H_4Br_2N_2$ requires C, 36.0; H, 1.3; N, 9.3%; *M*, 298, 300, and 302) and (*ii*) 4-*bromopyrazino*[2,1,6-cd]*pyrrolizine* (1-*bromo*-6-*aza*[2,2,3]*cyclazine*) (0.037 g, 43%) as a pale yellow powder, m.p. 54—55 °C (from light petroleum–benzene) (Found: C, 48.9; H, 2.0; N, 12.75%; M^+, 220 and 222. $C_9H_5BrN_2$ requires C, 48.9; H, 2.3; N, 12.7%; *M*, 220 and 222).

Nitration of Pyrazino[2,1,6-cd]*pyrrolizine*.—The pyrazinopyrrolizine (0.063 g) was added to acetic anhydride (5 cm³) containing copper(II) nitrate trihydrate (0.136 g). After 30 min at 50 °C and *ca.* 16 h at room temperature, t.l.c. showed starting material and only a trace of an orange product. The solution was therefore heated for a further 2.5 h at 50 °C before being cooled, poured into water, and neutralised with sodium carbonate. Extraction with dichloromethane, evaporation of the dried extract, and chromatography of the residue on deactivated alumina, in ether, gave (*i*) impure starting material and (*ii*) an orange powder (0.0021 g, 2%) (Found: M^+, 232.022 9. $C_9H_4N_4O_4$ requires *M*, 232.023 2) which was probably 3,4-dinitropyrazino[2,1,6-*cd*]pyrrolizine (1,7-dinitro-6-aza[2 2,3]cyclazine). A quantity of immobile material remained on the alumina column.

Phenylation of Pyrazino[2,1,6-cd]*pyrrolizine*.—A solution of phenyl-lithium was prepared from lithium (0.5 g) and bromobenzene (5.7 g) in ether (27.5 cm³) and a portion (0.8 cm³) of this was added, under nitrogen, to a stirred solution of the pyrazinopyrrolizine (0.103 g) in dry toluene (20 cm³). The solution was boiled under nitrogen for 7 h and then treated with water. The toluene layer was separated and combined with a benzene extract of the aqueous layer, and the combined solution was dried and evaporated, keeping the temperature as low as possible to avoid loss of product. Chromatography of the residue on alumina, in benzene, gave (*i*) 1,3-diphenylpyrazino[2,1,6-*cd*]pyrrolizine (5,7-diphenyl-6-aza[2,2,3]cyclazine) (0.022 g, 10%) (Found: M^+, 294.115 0. $C_{21}H_{14}N_2$ requires *M*, 294.115 7), which was not obtained pure; (*ii*) 1-*phenylpyrazino*[2,1,6-cd]*pyrrolizine* (5-*phenyl*-6-*aza*[2,2,3]*cyclazine*) (0.049 g, 31%) as buff needles, m.p. 84—85 °C (from light petroleum) (Found: C, 82.8; H, 4.7; N, 12.9. $C_{15}H_{10}N_2$ requires C, 82.65; H, 4.6; N, 12.8%); $\lambda_{max.}$ (EtOH) 220, 250sh, 276, 319, and 394 nm (log ε 4.32, 4.19, 4.55, 4.13, and 3.13); (*iii*) an unidentified yellow oil (0.008 g); and (*iv*) starting material (0.031 g).

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