673. *Further Syntheses and Properties of Pyrrolo*[1,2-a]*quinoxalines*

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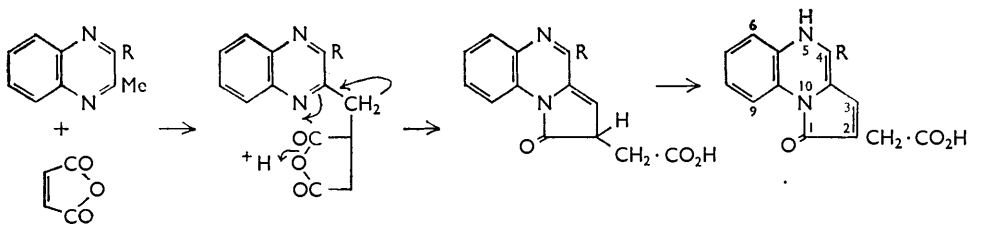
The relative merits of three general methods for the conversion of quinoxalines to pyrrolo[1,2-*a*]quinoxalines have been examined. The spectroscopic and ionisation properties of pyrrolo[1,2-*a*]quinoxalines suggest that the 5-nitrogen is the basic centre.

We have explored three main routes for pyrrolo[1,2-*a*]quinoxaline synthesis. The tricyclic ring system may be formed by a process which involves the addition of a two-carbon unit to a 2-methylquinoxaline. This may be achieved either by the Michael addition of the active methyl group to a maleic anhydride, or by the quaternisation of the 1-nitrogen with an α-halogeno-ketone. The third general route involves the intramolecular cyclisation of a quinoxaline substituted with a suitable three-carbon side chain at position 2.

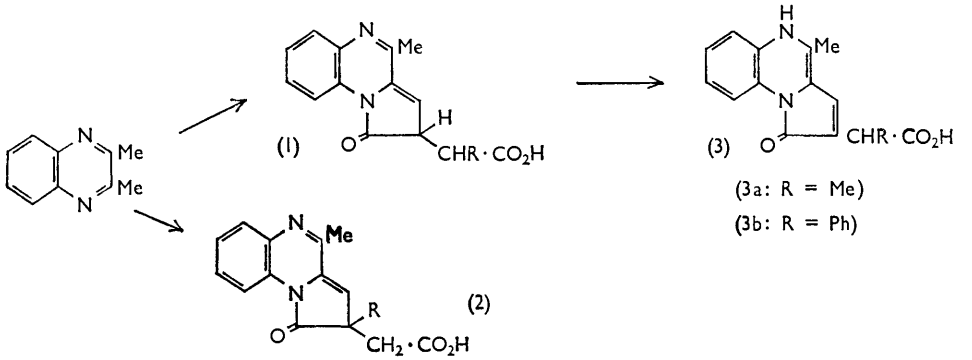
Pyrrolo[1,2-*a*]quinoxalines are formed by the reaction of 2-methylquinoxalines with maleic anhydride,[1,2] and Taylor and Hand have suggested the following mechanism for their formation:



We have attempted to extend this reaction by the use of mono- and di-substituted maleic anhydrides. The addition of 2,3,-dimethylquinoxaline to a monosubstituted maleic anhydride could give two possible disubstituted succinic anhydrides and these by a process

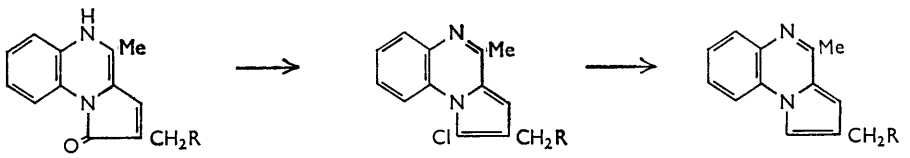
[1] E. C. Taylor and E. S. Hand, *J. Amer. Chem. Soc.*, 1963, **85**, 770.
[2] E. C. Taylor and G. W. H. Cheeseman, *J. Amer. Chem. Soc.*, 1964, **86**, 1830.

of ring opening and closing, the 1,2-dihydro-1-oxopyrrolo[1,2-*a*]quinoxalines (1) and (2). Only compounds of the former type could then isomerise to a 1,5-dihydro-1-oxopyrrolo-[1,2-*a*]quinoxaline (3).



We have treated 2,3-dimethylquinoxaline with both citraconic and phenylmaleic anhydride and the only products we were able to isolate from these reactions were the 1,5-dihydro-1-oxopyrrolo[1,2-*a*]quinoxalines (3a) and (3b). There is a marked difference in the reactivity of the two anhydrides; with citraconic anhydride, the product (3a) was formed comparatively slowly and in poor yield, whereas with phenylmaleic anhydride a highly exothermic reaction took place and the product (3b) was formed in high yield. On steric grounds a reverse order of reactivity might be anticipated. Citraconic anhydride is, however, in tautomeric equilibrium with itaconic anhydride and so there is the possible complication of initial addition to the exocyclic carbon–carbon double bond. We were unable to obtain any experimental evidence for this mode of addition.

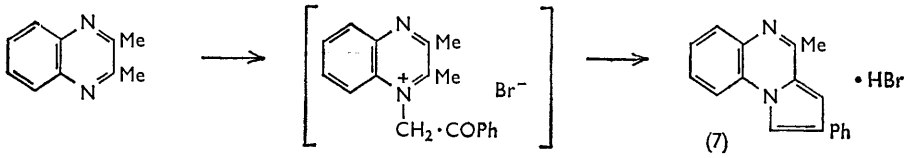
In the reaction of a 2-methylquinoxaline with a symmetrically disubstituted maleic anhydride, only one trisubstituted succinic anhydride can be formed and this by a process of ring opening and closing can only yield a 1,2-dihydro-1-oxopyrrolo[1,2-*a*]quinoxaline. In the hope of realising these possibilities we attempted to make 2,3-dimethylquinoxaline react with diphenylmaleic anhydride. The anhydride was recovered in 90% yield even after reaction with 2,3-dimethylquinoxaline in boiling xylene for 46 hr.



Various pyrrolo[1,2-*a*]quinoxalines were prepared from the carboxylic acids (3a) and (3b). These lost carbon dioxide on heating in a vacuum to give the amides (4a) and (4b), respectively. The decarboxylation of (3b) was carried out most conveniently by heating under reflux in quinoline. Treatment of (4a) and (4b) with phosphoryl chloride gave the 1-chloropyrrolo[1,2-*a*]quinoxalines (5a) and (5b) and these, on reduction with hydrogen gas in the presence of a platinum catalyst, furnished the pyrrolo[1,2-*a*]quinoxalines (6a) and (6b). Similar reductive de-chlorination of 1-chloro-4-methyl- and 1-chloro-2,4-dimethyl-pyrrolo[1,2-*a*]quinoxaline [2] was achieved in high yields.

A second general route for pyrrolo[1,2-*a*]quinoxaline synthesis was suggested by the observation that the reaction of 2-methyl-4-phenylquinoxaline with chloroacetone gives the hydrochloride of 2-methyl-4-phenylpyrrolo[1,2-*a*]quinoxaline.[2] The tricyclic ring system is presumably formed by dehydrative ring closure of the intermediate quaternary

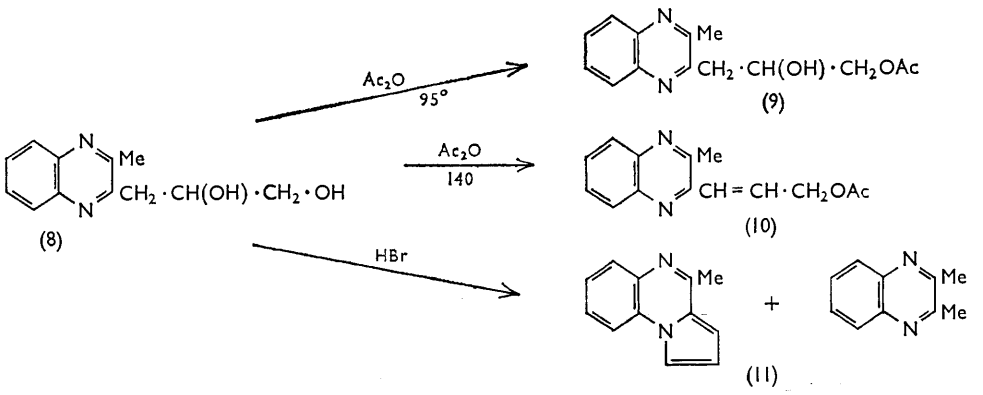
salt. It was therefore decided to re-investigate the report that anomalous products were formed by the reaction of 2,3-dimethylquinoxaline with various phenacyl bromides.[3] The reaction of 2,3-dimethylquinoxaline with phenacyl bromide is now shown to yield the hydrobromide of 2-phenyl-4-methylpyrrolo[1,2-*a*]quinoxaline (7). Only low yields of



(7)

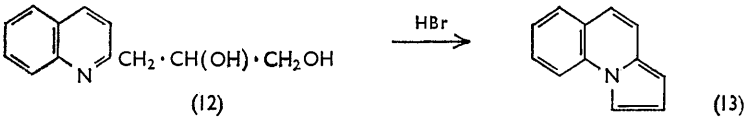
hydrobromide were obtained even after heating the reactants in boiling acetonitrile for many hours. The free base was readily obtained from the hydrobromide and it had the expected ionisation and spectral properties (see Tables 1, 3, and 4). The quaternisation of quinoxalines is generally difficult to achieve, so this route does not appear to have much potential value for the synthesis of pyrrolo[1,2-*a*]quinoxalines.

Several satisfactory syntheses of pyrrolo[1,2-*a*]quinoxalines have been effected by intramolecular cyclisation of 2-quinoxalinyl-β-propionic acids.[1,2] Cyclisation may be carried out by treatment with a mixture of acetic anhydride and sulphuric acid, with polyphosphoric acid or with phosphoryl chloride. We were prompted to investigate the cyclisation of the readily accessible quinoxalinyl propane-1,2-diol (8). Treatment of the diol with acetic anhydride at 95° produced a monohydroxyacetate, presumably (9), and when the reactants were heated under reflux, the propenyl acetate (10) was formed. Reaction of the diol with hydrobromic acid gave 4-methylpyrrolo[1,2-*a*]quinoxaline (11)



(8) (9) (10) (11)

in poor yield together with 2,3-dimethylquinoxaline. It is noteworthy that the quinolinylpropanediol (12) may be cyclised in excellent yield to the benzoindolizine (13) by treatment with hydrobromic acid.[4] The poor yield of tricyclic product from the quinoxalinyldiol (8) may be a further reflection of the difficulty in achieving the quaternisation, in this case an intramolecular quaternisation, of a quinoxaline ring nitrogen atom.



(12) (13)

The ultraviolet spectra of nine pyrrolo[1,2-*a*]quinoxalines are recorded in Table 1. The spectra of the neutral molecules, both in 96% ethanol or aqueous buffer are closely similar and show two principal bands. The band at 220—250 mμ in general has two

[3] W. K. Easley and C. J. Bahner, *J. Amer. Chem. Soc.*, 1950, **72**, 3803.
[4] E. M. Roberts, M. Gates, and V. Boekelheide, *J. Org. Chem.*, 1955, **20**, 1443.

subsidiary maxima; these appear at shortest wavelength in the case of the 1-chloro-compounds. The long-wavelength maximum is in the region 330—340 mμ, and substitution of phenyl at position 2 has the most pronounced bathochromic effect on this maximum. A well defined change in spectrum occurs on protonation. In the majority of the monocation spectra, the short-wavelength band shows a single maximum close to 240 mμ. In all cases the intensity of the long-wavelength absorption increases and a bathochromic shift in the position of the maximum from *ca.* 10—30 mμ is observed. This is most pronounced in the case of the 1-chloro-compounds. The ultraviolet spectra of five 1,5-dihydro-1-oxopyrrolo[1,2-*a*]quinoxalines are recorded in Table 2. These spectra show a characteristic three-banded pattern, the long-wavelength maxima in all cases being in the region 420—430 mμ.

The proton magnetic resonance spectra of the 4-methylpyrrolo[1,2-*a*]quinoxalines were measured on a Perkin-Elmer R.10 spectrometer operating at 60 megacycles per sec. and are summarised in Table 3. The values quoted are for chemical shift in c./sec. relative to tetramethylsilane which was used as an internal standard. The unsplit signals from the

TABLE 1

Ultraviolet spectra and ionisation constants of 4-methylpyrrolo[1,2-*a*]quinoxalines [a]

1-Subst.	2-Subst.	pK_a	Solvent	$\lambda_{max.}$ mμ ($\log_{10}$ ε)	
H	H	4·58 ± 0·03	96% EtOH	224(4·42); 242 [b] (4·35); 246(4·37); 259 [b] (4·08)	315 [b] (3·79); 329(3·92); 340(3·93); 352 [b] (3·74)
			H_2O, pH 7·8	224(4·44); 242(4·38); 245(4·38); 259 [b] (4·08)	333(3·94)
			H_2O, pH 1·5 [c]	224(4·48); 239(4·44); 246 [b] (4·39); 260 [b] (4·12); 280 [b] (3·83)	345(4·13); 360 [b] (4·09)
Cl	H	3·83 ± 0·04	96% EtOH	215(4·40); 227(4·48); 258 [b] (4·17)	329(3·98); 347 [b] (3·83)
			H_2O	214(4·36); 227(4·44); 258 [b] (4·12)	329(3·96)
			H_2O	223(4·43); 233 [b] (4·39); 240 [b] (4·36); 249 [b] (4·27); 265(4·07)	360(4·08)
H	Me	4·89 ± 0·01	96% EtOH	228(4·45); 244 [b] (4·43); 250(4·46); 262 [b] (4·07)	332 [b] (3·98); 340(4·01); 358 [b] (3·79)
			H_2O, pH 8·0	228(4·43); 245 [b] (4·43); 248(4·44); 259 [b] (4·03)	336(3·98)
			H_2O, pH 2·0 [c]	235 [b] (4·44); 242(4·48); 248 [b] (4·43); 263 [b] (3·88)	356(4·14)
Cl	Me	4·07 ± 0·04	96% EtOH [d]	216(4·29); 232(4·49); 240 [b] (4·47); 260 [b] (4·12)	326 [b] (4·01); 333(4·02); 350 [b] (3·88)
			H_2O, pH 7·1	216(4·27); 236(4·48); 260 [b] (4·07)	337(4·01)
			H_2O, pH 1·15 [c]	234 [b] (4·49); 240(4·50); 267(3·97)	364(4·17)
H	Et	4·86 ± 0·06 [e]	H_2O, pH 7·9	229(4·43); 245 [b] (4·44); 249(4·46); 262 [b] (4·01)	338(4·00)
			H_2O, pH 2·0 [c]	236 [b] (4·46); 243(4·49); 249 [b] (4·43); 263 [b] (3·87)	357(4·13)
Cl	Et	4·00 ± 0·03	96% EtOH	216(4·28); 233(4·50); 239 [b] (4·48); 260 [b] (4·11)	329 [b] (4·02); 337(4·04); 352 [b] (3·89)
			H_2O, pH 7·0	216(4·26); 239(4·47); 261 [b] (4·05)	337(4·00)
			H_2O, pH 1·1 [c]	234 [b] (4·50); 240(4·52); 267(3·94)	364(4·17)
H	CH_2Ph	4·48 ± 0·03	96% EtOH	230(4·47); 246 [b] (4·46); 251(4·51); 260 [b] (4·12)	334 [b] (3·98); 340(3·99); 357 [b] (3·78)
			H_2O, pH 7·5	231(4·48); 245 [b] (4·48); 249(4·50)	337(4·03)
			H_2O, pH 1·5 [c]	233 [b] (4·47); 244(4·54); 249 [b] (4·50); 265 [b] (3·87)	355(4·13)
Cl	CH_2Ph		96% EtOH	233(4·56); 240 [b] (4·53); 246 [b] (4·52); 259 [b] (4·17)	327 [b] (4·03); 337(4·05); 351 [b] (3·91)
H	Ph	4·22 ± 0·02	96% EtOH	265 [b] (4·56); 273(4·58); 281 [b] (4·51)	331 [b] (4·00); 342(4·05); 356 [b] (3·95)
			H_2O, pH 7·3	267 [b] (4·53); 273(4·54); 279 [b] (4·49)	342(4·01)
			H_2O, pH 1·4 [c]	265(4·59); 282 [b] (4·39)	368(4·18)

[a] pK_a values were determined potentiometrically in 50% aqueous ethanol at 25° and *ca.* 0·01M concentration. Buffers of pH 7·0—8·0 were prepared from solutions of K_2HPO_4 and $Na_2B_4O_7$; buffers of pH 1·1—2·0 from solutions of $NH_2{\cdot}CH_2{\cdot}CO_2H$ and HCl containing NaCl; solutions of pH < 1 with standard HCl. [b] Shoulder or inflexion. [c] Monocation. [d] A closely similar spectrum for this compound in absolute ethanol is reported in ref 2. [e] Determined by back titration of the hydrochloride.

TABLE 2

Ultraviolet spectra of 1,5-dihydro-4-methyl-1-oxopyrrolo[1,2-*a*]quinoxalines in 96% ethanol

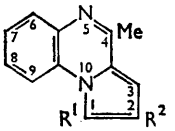
2-Subst.	$\lambda_{max.}$ mμ ($\log_{10}\varepsilon$)					
MeCH(CO_2H) ...	234(4·44);	256[a] (3·93)	289[a] (3·97);	298(4·00);	322[a] (3·52)	420(4·10)
Et	234(4·46);	256[a] (3·87)	291[a] (4·01);	298(4·02);	321[a] (3·42)	417(4·15)
PhCH(CO_2H) ...	236(4·32);	255[a] (4·07)	291[a] (3·92);	300(3·94);	328[a] (3·73)	429(3·80)
PhCH(CO_2Me) ...	235(4·44);	259[a] (3·81)	292[a] (3·92);	300(3·96);	329[a] (3·40)	427(4·12)
$PhCH_2$	236(4·52);	259[a] (3·88)	294[a] (4·02);	300(4·04);	328[a] (3·48)	424(4·20)

[a] Shoulder or inflexion.

TABLE 3

Chemical shifts [a] in the proton magnetic resonance spectra of 4-methylpyrrolo-[1,2-*a*]quinoxalines

(d = doublet; t = triplet; q = quartet; m = multiplet)



No.	1-Subst.	2-Subst.	Solvent	H-1	H-2
1	H	H	CCl_4	*b*	*c*
2	Cl	H [e]	CCl_4	—	410d (J = 5 c./sec.)
3	H	Me	CCl_4	450 [g]	—
4	H	Me hydrochloride	CF_3CO_2H	506	—
5	Cl	Me [e]	CCl_4	—	—
6	H	Et	CCl_4	458 [g]	—
7	H	Et hydrochloride	CF_3CO_2H	513	—
8	Cl	Et	CCl_4	—	—
9	H	CH_2Ph	CCl_4	450 [g]	—
10	Cl	CH_2Ph	CCl_4	—	—
11	Cl	CH_2Ph hydrochloride	CF_3CO_2H	—	—
12	H	Ph	CCl_4	469d (J_{13} = 2 c./sec.)	—

No.	H-3	H-6	H-7	H-8	H-9	2-Substituent	4-Me
1	*c*	*b*	*ca.* 438—460m		*b*	—	162
2	400d (J = 5 c./sec.)	475q [f]	*ca.* 438—456m		542q [f]	—	158
3	389 [g]	468q [f]	*ca.* 428—455m		455q [f]	136t	154
4	460	←	*ca.* 460—495m		→	150	183
5	397	471q [f]	*ca.* 438—450m		539q [f]	133	152
6	397 [g]	473q [f]	*ca.* 433—450m		467q [f]	77t(Me); 163q(CH_2); J = 8 c./sec.	157
7	467	←	*ca.* 465—510m		→	88t(Me); 180q(CH_2); J = 8 c./sec.	187
8	400	473q [f]	*ca.* 433—453m		541q [f]	76t(Me); 160q(CH_2); J = 8 c./sec.	156
9	392 [g]	469q [f]	*ca.* 423—447m		455q [f]	238(CH_2); 432(Ph)	154
10	389	467q [f]	*ca.* 425—447m		535q [f]	235(CH_2); 429(Ph)	151
11	459	←	*ca.* 460—490m	→	567q [f]	252(CH_2); 443(Ph)	179
12	409d (J_{13} = 2 c./sec.)	←	*ca.* 426—471m [h]	→			152

[a] In c./sec. relative to tetramethylsilane as internal standard. [b] Signals from the 1-, 6-, and 9-protons appear as multiplet at *ca.* 464—486 c./sec. [c] Signals from the 2- and 3-protons appear as a doublet in the range 408—412 c./sec. with slight splitting of the peak at 408 c./sec. [e] Closely similar p.m.r. data for this compound reported in ref. 2. [f] Intense quartet with weak side bands, $J_{AX} + J_{BX}$ = *ca.* 10 c./sec. [g] Signals showing *meta* spin–spin coupling, J = 0·5—1·0 c./sec. [h] Integrated intensity of this band shows that this multiplet includes signals from the 2-phenyl protons.

4-methyl group of each compound fall within the range 151—162 c./sec. The signals arising from the various substituents (Me, Et, or CH_2Ph) in position 2 are readily distinguishable and have the expected multiplicity. An analysis of the proton magnetic spectra of various 1-chloropyrrolo[1,2-*a*]quinoxalines was available [5] and this was used in the interpretation of the spectra of the new 1-chloro-derivatives prepared in this investigation and also of the more complex spectra of the de-chlorinated bases of corresponding structure. In the spectra of the three 1-chloro-2-substituted derivatives recorded in Table 3, the

[5] R. C. Fort, jun., G. W. H. Cheeseman, and E. C. Taylor, *J. Org. Chem.*, 1964, **29**, 2440.

unsplit signal from the 3-proton appears in the range 389—400 c./sec. A quartet with associated side bands and in the region 535—541 c./sec. is assigned to the deshielded aromatic proton at position 9. This proton is deshielded by the chlorine atom at position 1 and is the X proton of an ABX system.* Proton-6 is also the X portion of an ABX system; it gives rise to a quartet with associated side bands in the region 467—473 c./sec. The proximity of nitrogen-5 causes these signals to be deshielded relative to signals from the 7- and 8-aromatic protons. In the spectra of the dechlorinated bases, the signals from the 3, 6, 7,and 8 protons appear at closely similar chemical shifts to those of the corresponding protons of the 1-chloro compounds. The signal from the additional 1-proton appears downfield from the signal from the 3-proton, presumably because it is deshielded by the adjacent 10-nitrogen atom. Only slight spin–spin coupling (*J ca.* 0·5—1·0 c./sec.) is observed between the 1- and 3-protons.

In the spectrum of 1-chloro-4-methylpyrrolo[1,2-*a*]quinoxaline, coupling between the 2- and 3-protons gives rise to the usual double-doublet signals associated with an AB system. Comparison of this spectrum with that of 4-methylpyrrolo[1,2-*a*]quinoxaline enables the signals from the 7- and 8-protons in each compound to be assigned. The absorptions from the 1-, 6-, and 9-protons in the dechlorinated base merge into a complex multiplet, those from the 2- and 3-protons appear as a doublet with slight splitting of one of the peaks. Although the integrated intensities of these bands support these assignments, the signals from the 2- and 3-protons clearly do not have the expected multiplicity. In the spectrum of 4-methyl-2-phenylpyrrolo[1,2-*a*]quinoxaline signals from the 1- and 3-protons appear as well-defined doublets with *meta* spin–spin coupling of 2 c./sec.

The proton magnetic resonance spectra of solutions of three pyrrolo[1,2-*a*]quinoxaline hydrochlorides in trifluoroacetic acid were measured. Pronounced downfield shifts of all the proton signals of the protonated bases were observed. No new methylene or methine signals appeared, indicating that protonation did not occur on carbon. However, no signals arising from protonation on nitrogen could be detected. Evidence that protonation did, in fact, occur on nitrogen may be adduced from the infrared data presented in Table 4. The hydrochlorides of 2,4-dimethyl, 2-ethyl-4-methyl-, and 2-benzyl-1-chloro-4-methylpyrrolo[1,2-*a*]quinoxalines show strong bands in the 2510—2310 and 1910—

TABLE 4

Infrared spectra of 4-methylpyrrolo[1,2-*a*]quinoxalines in the region 3000—1500 cm.$^{-1}$

1-Subst.	2-Subst.	ν_{max} (cm.$^{-1}$)									
H	H [a]						1610m	1585w		1530m	1480s
Cl	H [a,b]						1600m	1580w		1530m	
H	Me [a]						1615m	1590w	1560m		1495s
H	Me hydrochloride [a]	2720m	2510s	1990w	1870s	1825w	1630s	1595m	1560m	1540m	1500s
Cl	Me [a]						1610m		1550m	1540m	1485s
H	Et [a]						1610m	1580w	1550m		1495s
H	Et hydrochloride [a]	2710m	2500s	1990w	1870s	1825w	1630s	1595m	1560m	1535m	1495s
Cl	Et [a]						1615m	1590w	1550m	1525w	1485s
H	CH_2Ph [c]						1600m	1580w	1550m		1490s
Cl	CH_2Ph [c]						1600m	1575w	1545m		1485s
Cl	CH_2Ph hydrochloride [a]	2500m	2310s	2030w	1950w	1910s	1625s	1590m	1560m	1520w	1490s
H	Ph [c]						1610m	1580w	1545w	1510s	1490s
H	Ph hydrobromide [c,d]	2840s					1620m	1590m	1540s	1505s	1490s

[a] Spectrum in a Nujol mull. [b] Spectrum showed a weak absorption at 1680 cm.$^{-1}$. [c] Spectrum in a KBr disc. [d] Spectrum showed a strong absorption at 3400 cm.$^{-1}$, both in a KBr disc and in a Nujol mull.

* A recent Paper (W. K. Gibson and D. Leaver, *Proc. Chem. Soc.*, 1964, 330) has drawn attention to the deshielding of the 9-proton in some structurally related cyclopenta[*c*]quinolizine derivatives by a 1-methoxycarbonyl group.

1870 cm.$^{-1}$ regions of the spectrum, not present in spectra of the parent bases. The hydrochloride spectra show a medium-strong band in the region 1630—1625 cm.$^{-1}$, whereas the corresponding bands in the spectra of the parent bases are in the region 1615—1600 cm.$^{-1}$. These observations are consistent with the formation of imonium ($>C=\overset{+}{N}H-$) rather than ammonium ions [6] and therefore point to protonation at the 5- rather than the 10-nitrogen atom.

The infrared spectrum of the hydrobromide of 4-methyl-2-phenylpyrrolo[1,2-*a*]quinoxaline does not show the expected additional strong band in the region 1910—1870 cm.$^{-1}$ However, the basic strength of this compound and the change in ultraviolet absorption observed on protonation (Table 1) suggest that the basic centre of the 4-methyl-2-phenyl compound is also the 5-nitrogen.* If it is assumed that pyrrolo[1,2-*a*]quinoxalines have an aromatic 14π electron system, then the 10-nitrogen is required to make a 2π electron contribution. This would account for basic function of the 5-nitrogen atom.

The basic strengths of eight 4-methylpyrrolo[1,2-*a*]quinoxalines are recorded in Table 1. Ionisation constants were determined by potentiometric titration in 50% ethanol, so that all titrations could be carried out in a common solvent. The pK_a values fall within the range 3·8—4·9 pK_a units, indicating that the pyrrolo[1,2-*a*]quinoxalines are appreciably stronger bases than either typical pyrroles or quinoxalines. The pK_a values reported for the structurally related mono- and di-methylindolizines are within the range 3·9—5·4 pK_a units [7] but recent p.m.r. studies have shown that these compounds protonate on carbon, and usually at position 3.[8,9] The pK_a data in Table 1 fall into an internally consistent pattern; substitution of chlorine in position 1 or phenyl in position 2 has a base-weakening effect and substitution of methyl or ethyl in position 2 is base-strengthening. The magnitude of the base-weakening effect of chlorine is about 0·8 pK_a unit; phenyl is base-weakening by about 0·35 pK_a unit and methyl or ethyl base-strengthening by about 0·2—0·3 pK_a unit.

Experimental

Infrared spectra were measured on a Perkin-Elmer model 137 instrument in Nujol mulls or potassium bromide discs. Ultraviolet spectra were measured on a Unicam S.P. 700 recording spectrophotometer. The integrated intensities of the p.m.r. bands were measured and are consistent with the assignments given below, and in Table 3.

(±)-2-1′-*Carboxyethyl*-1,5-*dihydro*-4-*methyl*-1-*oxopyrrolo*[1,2,-a]*quinoxaline*.—A mixture of 2,3-dimethylquinoxaline (15·8 g.) and citraconic anhydride (19·0 g.) was heated at 135° for 19 hr. After cooling and trituration with glacial acetic acid, the *adduct* (6·2 g.) was filtered off and washed with 96% ethanol. A further 1·14 g. was obtained by evaporation of the filtrate in a vacuum and addition of acetone to the residue (total yield: 27%).† A sample crystallised from glacial acetic acid and carefully dried *in vacuo*, decomposed indefinitely on heating above 200° (Found: C, 66·1; H, 5·2; N, 10·5. $C_{15}H_{14}N_2O_3$ requires C, 66·7; H, 5·2; N, 10·4%), $\nu_{max.}$ 3250(NH), 1700 and 1660 cm.$^{-1}$ (C=O).

2-*Ethyl*-1,5-*dihydro*-4-*methyl*-1-*oxopyrrolo*[1,2-a]*quinoxaline*.—(±)-2-1′-Carboxyethyl-1,5-dihydro-4-methyl-1-oxopyrrolo[1,2-a]quinoxline (6·2 g.) was decarboxylated by heating at 200°/0·05 mm. for *ca.* 15 hr. Crystallisation of the sublimate from methanol gave 2-*ethyl*-1,5-*dihydro*-4-*methyl*-1-*oxopyrrolo*[1,2-a]*quinoxaline* (1·45 g., 28%) as orange plates, m. p. 315° (with previous darkening) (Found: N, 12·4. $C_{14}H_{14}N_2O$ requires N, 12·4%), $\nu_{max.}$ 3200(NH) and 1770 cm.$^{-1}$ (C=O).

* The possibility that the site of protonation is different in solution and in the solid state has been ignored throughout this discussion.

† In one experiment the precipitated adduct was collected after 3 hr., and then at 3-hourly intervals. The product obtained by heating the reaction mixture for longer periods was very impure.

[6] B. Witkop, *Experientia*, 1954, **10**, 420.

[7] F. M. Miller and R. E. Brown, American Chemical Society, 130th National Meeting, 1956, Abstract, p. 49.

[8] M. Frazer, A. Melera, B. B. Molloy, and D. H. Reid, *J.*, 1962, 3288.

[9] M. Frazer and D. H. Reid, *J.*, 1963, 1421.

1-*Chloro*-2-*ethyl*-4-*methylpyrrolo*[1,2-a]*quinoxaline*.—A mixture of 2-ethyl-1,5-dihydro-4-methyl-1-oxopyrrolo[1,2-*a*]quinoxaline (1·9 g.) and phosphoryl chloride (15 ml.) was heated under reflux for 15 min., then evaporated in a vacuum. The residue was dissolved in chloroform and ice–water and excess of sodium carbonate added. The organic layer was separated, washed successively with 2N-sodium carbonate and water, and then dried (Na_2SO_4) and evaporated. The crude product was extracted with light petroleum (b. p. 40—60°), insoluble material removed by filtration, and the filtrate concentrated to *ca.* 10 ml. After cooling to 0°, the crystalline precipitate of 1-*chloro*-2-*ethyl*-4-*methylpyrrolo*[1,2-a]*quinoxaline* (0·93 g., 45%) was collected. An analytical specimen of m. p. 85·5—86° was obtained by crystallisation from light petroleum (b. p. 30—40°, 20 parts) (Found: C, 68·5; H, 5·3; N, 11·1. $C_{14}H_{13}ClN_2$ requires C, 68·7; H, 5·4; N, 11·45%).

Hydrochloride of 2-*Ethyl*-4-*methylpyrrolo*[1,2-a]*quinoxaline*.—A solution of 1-chloro-2-ethyl-4-methylpyrrolo[1,2-*a*]quinoxaline (1·75 g.) in methanol (25 ml.) was added to a suspension of platinum catalyst (prepared by pre-reducing 0·2 g. of platinum oxide in 10 ml. of methanol). The mixture was stirred in an atmosphere of hydrogen until 1 mol. of hydrogen had been absorbed. After removal of catalyst and solvent, ether and excess of sodium hydrogen carbonate solution were added. The ethereal layer was separated, dried (Na_2SO_4), and treated with dry hydrogen chloride. The precipitated *hydrochloride* (1·2 g., 68%) was crystallised from a mixture of methanolic hydrogen chloride (5 ml.) and ether (10 ml.) (Found: C, 68·5; H, 6·2; N, 11·0. $C_{14}H_{15}ClN_2$ requires C, 68·2; H, 6·1; N, 11·4%).

(±)-2-1′-*Carboxybenzyl*-1,5-*dihydro*-4-*methyl*-1-*oxopyrrolo*[1,2-a]*quinoxaline*.—A well-stirred melt of 2,3-dimethylquinoxaline (4·0 g.) and phenylmaleic anhydride [10] (4·4 g.) was heated cautiously in an oil-bath at 120° until reaction commenced. After the initial reaction had subsided, heating was continued at 140° for 1 hr. The resulting solid was thoroughly extracted with hot chloroform and the *adduct* (6·13 g., 73%) filtered off and dried. A sample crystallised from aqueous dimethylformamide melted with decomposition above 300° (Found: N, 8·65. $C_{20}H_{16}N_2O_3$ requires N, 8·4%), $\nu_{max.}$ 3280(NH), 1700, and 1665 cm.$^{-1}$ (C=O). The adduct was converted into its methyl ester by heating under reflux with methanolic hydrogen chloride for 1 hr. The *ester* crystallised from methanol in yellow needles, m. p. above 250° (Found: N, 8·0. $C_{21}H_{18}N_2O_3$ requires N, 8·1%), $\nu_{max.}$ 3190(NH), 1730, and 1665 cm.$^{-1}$ (C=O).

2-*Benzyl*-1,5-*dihydro*-4-*methyl*-1-*oxopyrrolo*[1,2-a]*quinoxaline*.—On heating a mixture of (±)-2-1′-carboxybenzyl-1,5-dihydro-4-methyl-1-oxopyrrolo[1,2-*a*]quinoxaline (13·0 g.) and quinoline (50 ml.) under reflux for 1 hr., the solid dissolved and carbon dioxide was evolved. The precipitate of 2-*benzyl*-1,5-*dihydro*-4-*methyl*-1-*oxopyrrolo*[1,2-a]*quinoxaline* (9·0 g., 80%) which separated from the cooled solution, was filtered off and washed well with benzene. A sample crystallised from methanol (14 parts) had m. p. above 250° (Found: C, 79·0; H, 5·6; N, 9·8. $C_{19}H_{16}N_2O$ requires C, 79·1; H, 5·6; N, 9·7%), $\nu_{max.}$ 3190(NH) and 1675 cm.$^{-1}$ (C=O).

2-*Benzyl*-1-*chloro*-4-*methylpyrrolo*[1,2-a]*quinoxaline*.—A mixture of 2-benzyl-1,5-dihydro-4-methyl-1-oxopyrrolo[1,2-*a*]quinoxaline (9·0 g.) and phosphoryl chloride (10 ml.) was heated under reflux for 1 hr. After cooling, the mixture was poured on ice with continuous stirring, the pH adjusted to 8 with sodium hydrogen carbonate, and the product extracted into chloroform. Evaporation of the dried (Na_2SO_4) extracts, and crystallisation of the resulting oil from light petroleum (b. p. 60—80°) gave 2-*benzyl*-1-*chloro*-4-*methylpyrrolo*[1,2-a]*quinoxaline* (7·4 g., 77%). Pale yellow needles of m. p. 111—112·5° were obtained after two crystallisations from methanol (12 parts) (Found: C, 74·0; H, 5·05; Cl, 11·8; N, 9·0. $C_{19}H_{15}ClN_2$ requires C, 74·4; H, 4·9; Cl, 11·55; N, 9·1%). The *hydrochloride* was prepared in methanolic hydrogen chloride; it crystallised from this solvent as pale yellow needles, m. p. 248—249° (decomp.) (Found: C, 66·3; H, 4·5; Cl, 20·65; N, 8·1. $C_{19}H_{16}Cl_2N_2$ requires C, 66·5; H, 4·7; Cl, 20·65; N, 8·2%).

2-*Benzyl*-4-*methylpyrrolo*[1,2-a]*quinoxaline*.—2-Benzyl-1-chloro-4-methylpyrrolo[1,2-*a*]-quinoxaline (2·31 g.) was added to a suspension of platinum catalyst (prepared by the pre-reduction of 0·2 g. of platinum oxide in 65 ml. of methanol). The mixture was stirred in an atmosphere of hydrogen until 1 mol. of gas had been absorbed. After removal of catalyst and solvent, chloroform and excess of sodium hydrogen carbonate solution were added to the residue. The chloroform layer was separated, dried (Na_2SO_4), and evaporated in a vacuum. Crystallisation of the residual 2-*benzyl*-4-*methylpyrrolo*[1-2-a]*quinoxaline* from light petroleum (b. p. 40—60°) gave pale yellow needles (1·44 g., 69%), m. p. 83—84°. The m. p. was raised to 85—86° by further crystallisation from light petroleum (b. p. 40—60°, 50 parts) (Found:

[10] R. K. Hill, *J. Org. Chem.*, 1961, **26**, 4745.

C, 83·7; H, 5·9; N, 10·4. $C_{19}H_{16}N_2$ requires C, 83·8; H, 5·9; N, 10·3%). The *picrate*, prepared in methanol and crystallised from acetone, had m. p. 196—198° (decomp.) (Found: C, 59·7; H, 3·9; N, 14·2. $C_{25}H_{19}N_5O_7$ requires C, 59·9; H, 3·8; N, 14·0%).

4-*Methylpyrrolo*[1,2-a]*quinoxaline*.—This was prepared from 1-chloro-4-methylpyrrolo-[1,2-*a*]quinoxaline [2] similarly to the 2-benzyl-4-methyl compound above and in 86% yield. 4-*Methylpyrrolo*[1,2-a]*quinoxaline* crystallised in colourless needles from light petroleum (b. p. 60—80°, 40 parts) and had m. p. 137°.(Found: C, 78·8; H, 5·7; N, 15·7. $C_{12}H_{10}N_2$ requires C, 79·1; H, 5·5; N, 15·4%).

2,4-*Dimethylpyrrolo*[1,2-a]*quinoxaline*.—This was prepared from 1-chloro-2,4-dimethyl-pyrrolo[1,2-*a*]quinoxaline [2] similarly to the 2-benzyl-4-methyl compound above, except that 2,4-*dimethylpyrrolo*[1,2-a]*quinoxaline hydrochloride* separated in 77% yield on concentration of methanolic solution from the reduction. The hydrochloride crystallised as yellow needles from methanol (25 parts) acidified with a little hydrochloric acid (Found: C, 67·15; H, 5·75; N, 11·95. $C_{13}H_{13}ClN_2$ requires C, 67·1; H, 5·6; N, 12·0%). The free *base* crystallised from light petroleum (b. p. 60—80°, 10 parts) and had m. p. 86—87° (Found: C, 79·4; H, 6·0; N, 14·7. $C_{13}H_{12}N_2$ requires C, 79·6; H, 6·2; N, 14·3%).

4-*Methyl-2-phenylpyrrolo*[1,2-a]*quinoxaline*.—A mixture of 2,3-dimethylquinoxaline (7·9 g., 0·05 mole) and phenacyl bromide (9·95 g., 0·05 mole) in methyl cyanide (50 ml.) was stirred and heated under reflux for 16 hr. After cooling, the precipitate of hydrobromide (0·89 g.) was filtered off. The filtrate was then stirred and heated under reflux for a further 14 hr. In this period 0·69 g. of product separated and after a further 20 hr. an additional 0·76 g. was formed (total yield, 2·34 g., 14%). The *hydrobromide* crystallised from methanol containing a few drops of hydrobromic acid (Found: Br, 23·9; N, 8·0. $C_{18}H_{15}BrN_2$ requires Br, 23·6; N, 8·3%). Excess of methanolic sodium methoxide was added to a suspension of the hydro-bromide (0·89 g.) in methanol (5 ml.). The resulting solution was diluted with water and the precipitate of 4-*methyl-2-phenylpyrrolo*[1,2-a]*quinoxaline* filtered off, washed with water, and dried. Crystallisation from light petroleum (b. p. 60—80°, 50 parts) gave pale yellow needles, m. p. 100—102° (Found: C, 83·6; H, 5·7; N, 10·8. $C_{18}H_{14}N_2$ requires C, 83·7; H, 5·5; N, 10·85%).

Reaction of 2-*Methyl*-3-2′,3′-*dihydroxypropylquinoxaline with Acetic Anhydride*.—(a) *At* 95°. A solution of the diol (3·18 g.) in acetic anhydride (50 ml.) was heated at 95° for 1 hr. Excess of acetic anhydride was then removed in a vacuum and the residue triturated with ether. Crystallisation of the resulting solid first from a little ethyl acetate and then from carbon tetra-chloride, gave 2-*methyl*-3-3′-*acetoxy*-2′-*hydroxypropylquinoxaline* (1·26 g.) m. p. 118—120°. An analytical specimen crystallised from benzene had m. p. 119—121° (Found: C, 65·0; H, 6·3; N, 10·7. $C_{14}H_{16}N_2O_3$ requires C, 64·6; H, 6·2; N, 10·8%), $\lambda_{max.}$ 236 ($\log_{10}\varepsilon$ 4·45), 240 (inflexion) ($\log_{10}\varepsilon$ 4·40), 318 mμ ($\log_{10}\varepsilon$ 3·19); $\nu_{max.}$ 3220(OH) and 1735 cm.$^{-1}$ (C=O). The p.m.r. spectrum ($CDCl_3$) showed two methyl groups as unsplit peaks at 126 and 162 c./sec. relative to tetramethylsilane, two methylene groups as doublets centred at 186 c./sec. (J = 6 c./sec.) and 256 c./sec. (J = 5 c./sec.) and four aromatic protons as a multiplet at 339—388 c./sec. The hydroxyl and methine proton absorptions overlapped and appeared as a multiplet at *ca.* 248—305 c./sec.

(b) *At* 140°. A solution of the diol (2·0 g.) in acetic anhydride (20 ml.) was heated under reflux for 1 hr., then evaporated in a vacuum. The residue was dissolved in ether and the ethereal solution washed with aqueous sodium carbonate and water and then dried (Na_2SO_4). After removal of ether, the residual 2-*methyl*-3-3′-*acetoxyprop*-1-*enylquinoxaline* was crystallised from light petroleum (b. p. 60—80°) and treated with carbon, to give colourless needles (0·85 g.) m. p. 81—84°. An analytical specimen of m. p. 85—85·5° was obtained by further crystallisation from light petroleum (b. p. 60—80°, 20 parts) (Found: C, 69·6; H, 5·9; N, 11·7. $C_{14}H_{14}N_2O_2$ requires 69·4; H, 5·8; N, 11·6%), $\lambda_{max.}$ 253 ($\log_{10}\varepsilon$ 4·47), 331 (inflexion) ($\log_{10}\varepsilon$ 3·99), 338 mμ ($\log_{10}\varepsilon$ 4·01); $\nu_{max.}$ 1730 (C=O), 974 cm.$^{-1}$ (*trans*-disubstituted C=C). The p.m.r. spectrum (CCl_4) showed two methyl groups as unsplit peaks at 124 and 162 c./sec. relative to tetramethylsilane, a methylene group as a doublet centred at 287 c./sec. (J = 5 c./sec.), two ethylenic protons as a multiplet at 420—438 c./sec. and four aromatic protons as a multiplet at *ca.* 440—485 c./sec.

Reaction of 2-*Methyl*-3-2′,3′-*dihydroxypropylquinoxaline with Hydrobromic Acid*.—A solution of the diol (3·06 g.) in concentrated hydrobromic acid (50 ml.) was heated under reflux for 6 hr., then evaporated to dryness in a vacuum. Excess of saturated sodium carbonate solution was

added to the residue, and the mixture distilled in steam until *ca.* 2·5 l. of distillate had been collected. Chloroform extraction of the distillate, followed by evaporation of the extracts gave a solid (0·62 g.), m. p. *ca.* 77—81°. This was separated by sublimation at 0·9 mm. into two main fractions. The more volatile fraction (0·34 g.) was re-sublimed at 60—65°/10 mm. to give 2,3-dimethylquinoxaline, m. p. (mainly) 97—102°, identified by mixed m. p. and ultraviolet and infrared spectra. Resublimation of the less volatile fraction (0·10 g.) at 95°/0·9 mm. gave 4-methylpyrrolo[1,2-*a*]quinoxaline, m. p. 135—136°, identical to a sample prepared as described above.

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