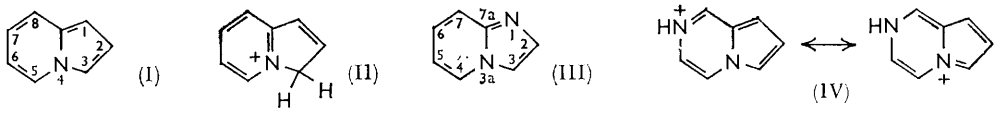
500. *Triazaindenes (Diazaindolizines). The Site of Protonation*

By W. L. F. Armarego

The syntheses of 1,3a,4-, 1,3a,5-, 1,3a,6-, and 1,3a,7-triazaindenes and their 2,3-dihydro-derivatives are described. Ionisation and ultraviolet spectra measurements indicate that in each case protonation occurs on N-1. Evidence is given that 1,2,3a- and 2-methyl-1,3,3a-triazaindene cations are also protonated on N-1, but 1,2,7a-triazaindene cation is protonated on N-2.

Protonation of indolizine (I) was shown by nuclear magnetic resonance spectroscopy to take place on C-3 with the formation of the cation (II).[1] Alkylindolizines also gave a cation similar to (II) when the alkyl groups were in positions other than on C-3.[1,2] However, protonation occurred on C-1 when C-3 was substituted with a methyl group (*e.g.*, in 3-methyl-, 2,3-, and 3,7-dimethyl-indolizines).[2] It was also shown that in three monoazaindolizines (*i.e.*, 1,3a-, 2,3a-, and 1,7a-diazaindenes) protonation took place on the non-bridgehead nitrogen atom irrespective of its position in the molecule.[2] In each



diazaindene a resonance-stabilised cation was formed which accounted for its high basic strength.[2] This investigation has now been extended to include the six triazaindenes (diazaindolizines) which have in common the structure (III) and in which the carbon atoms (excluding only C-7a) are in turn replaced by the third nitrogen atom. Four of these are new. It will be shown that in all cases protonation occurs predominantly on N-1. The 2,3-dihydro-derivatives of 1,3a,4-, 1,3a,5-, 1,3a,6-, and 1,3a,7-triazaindenes were also prepared and it was shown that their cations are protonated on the imino-nitrogen atom N-1.

Ionisation Measurements.—The pK_a values of fifteen azaindenes were measured and they are given in Table 1. The neutral species of indolizine and its aza-derivatives are planar molecules and protonation takes place on C-3 and on the non-bridgehead nitrogen atoms respectively, otherwise if protonation occurs on the bridgehead nitrogen atom it would result in considerable distortion of the molecules. Resonance structures can be written for all the seven possible monoazaindolizine (diazaindene) cations. The above three diazaindene cations are stabilised by resonance.[2] The cation of the fourth example, 3a,6-diazaindene, studied in this work, has the structure (IV) in agreement with its basic strength (pK_a, 6·28; compare indolizine pK_a 3·94 [2]). By analogy similar resonance structures should be possible for the remaining three diazaindene cations. In all such structures

[1] M. Frazer, A. Melera, B. B. Molloy, and D. H. Reid, *J.*, 1962, 3288.
[2] W. L. F. Armarego, *J.*, 1964, 4226.

TABLE 1

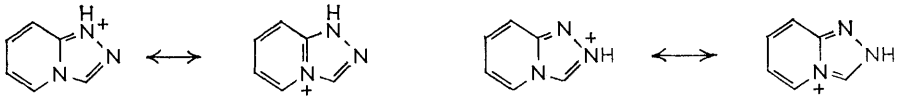
Ionisation [a] and ultraviolet spectra [b] of azaindenes (in water at 20°)

Indenes	pK_a	Spread (±)	Concn. 10^4M	λ [c] mμ	$\lambda_{max.}$ (mμ)	log ε	Species [d]	pH
3a,6-Diaza-	6·28	0·03	1·0	300	224·5 + *235*; *274* + 283 + 292·5; 338·5	4·39 + *4·30*; *3·33* + 3·49 + 3·48; 3·43	0	10
					217 + 222 + 242 + *249*; 296 + 302; 358	4·42 + 4·36 + 4·15 + *4·02*; 3·61 + 3·62; 3·54	+	2·0
1,2,3a-Triaza-	3·18	0·03	0·4	300	*255·5* + *259* + 266 + 278 + *287*	*3·49* + *3·53* + 3·60 + 3·62 + *3·57*	0	7·0
					266 + 274·5 + *286*	*3·74* + 3·80 + *3·57*	+	1·0
2-Methyl-1,3,3a-triaza-	2·96	0·06	0·4	284	*238* + 260 + *273* + *283*	*3·45* + 3·56 + *3·53* + *3·34*	0	7·0
					237 + *246* + 264 + 268·5 + 275 + 291	3·67 + *3·62* + 3·49 + 3·52 + 3·48 + 3·10	+	0·0
1,2,7a-Triaza-	0·42	0·03	60·0	310	*217* + 222·5; 278	*4·05* + 3·72; 3·81	0	4·0
					223 + *230*; 271 + *288* + 299	*3·72* + *3·47*; 3·78 + *3·67* + 3·36	+	−2·0 [e]
1,3a,4-Triaza-	4·57	0·03	1·0	330	*223* + 225·5 + 230; *250* + *268* + 278; *322* + *326* + *329* + 333 + 337 + 346 + 350 + *355* + 366	*4·26* + 4·28 + 4·38; *3·15* + *3·08* + 3·02; *3·46* + *3·48* + *3·50* + 3·54 + 3·55 + 3·49 + 3·48 + *3·35* + 3·32	0	— [f]
					221; *254* + *260* + *271*; 325	4·20; *3·24* + *3·20* + *3·10*; 3·59	0	7·0
					211; *244* + 251 + *261*; 291	4·20; *3·40* + 3·42 + *3·73*; 3·66	+	2·0
1,3a,5-Triaza-	4·41	0·03	0·24	264	<225; 251 + 256 + 260 + *264* + 270; 300 + 309 + 321·5 + 339	—; 3·52 + 3·55 + 3·63 + *3·54* + 3·64; 3·31 + 3·31 + 3·20 + 2·83	0	— [f]
					214·5; 259·5 + 269·5; 294 + 298	4·29; 3·73 + 3·73; 3·39 + 3·39	0	7·0
					261	3·93	+	1·7
1,3a,6-Triaza-	3·59	0·05	0·36	290	211 + *227* + 231·5; 276 + 284; 300 + 312 + 326·5	4·26 + *4·22* + 4·08; 3·54 + 3·58; 3·46 + 3·39 + 3·07	0	— [f]
					221·5; *276* + 282; 302	4·21; *3·61* + 3·67; 3·69	0	7·0
					212 + *221*; 289 + *305*	4·17 + *3·99*; 3·82 + 3·63	+	1·0
1,3a,7-Triaza-	4·81	0·02	0·8	330	*224* + 227·5 + 232; 277 + 287; 326 + 333 + *340* + 349 + *356* + 369	*4·26* + 4·30 + 4·28; 3·30 + 3·29; 3·41 + 3·42 + *3·38* + 3·30 + *3·08* + 2·91	0	— [f]
					211 + 223; 275 + 283; 317	4·15 + 4·30; 3·45 + 3·47; 3·46	0	7·0
					214; 276 + *290*	4·29; 3·66 + *3·61*	+	2·0
4,6-Dimethyl-1,3a,7-triaza-	5·76	0·01	0·3	320	223·5 + *230*; 272 + 280·5; 305·5	4·43 + *4·27*; 3·57 + 3·58; 3·53	0	8·0
					214·5; 274 + *290*	4·44; 3·83 + *3·65*	+	3·0
1,2-Dihydro-3*H*-3a-aza-	>14		—	—	*258* + 264 + 271	*3·61* + 3·70 + 3·57	+	7·0
2,3-Dihydro-1,3a-diaza-	12·51	0·03	1·0	325	260·5; 368	4·08; 3·37	0	14·5
					238·5; 324	4·01; 3·58	+	7·0
2,3-Dihydro-1,3a,4-triaza-	9·97	0·03	0·26	260	218; 258 + *264* + *273*; 381	4·09; 3·90 + *3·87* + *3·59*; 3·06	0	12·4
					209 + *215*; 241·5; 326	4·18 + *4·05*; 3·85; 3·24	+	7·0
2,3-Dihydro-1,3a,5-triaza-	8·83	0·01	0·36	256	251 + *258*; 329	4·11 + *4·04*; 3·16	0	11·0
					238; 300·5	4·04; 3·45	+	5·0
2,3-Dihydro-1,3a,6-triaza-	9·32	0·03	0·33	260	258 + *264*; 394	4·09 + *4·05*; 3·94	0	11·5
					239·5; 354	4·09; 3·62	+	7·0
2,3-Dihydro-1,3a,7-triaza-	10·15	0·02	0·4	250	249; 390	4·14; 3·24	0	12·3
					233; 333	4·13; 3·42	+	7·0
2-2′-Hydroxyethylamino-pyrazine (for comparison)	3·08	0·03	0·4	250	242·5; *286* + 330	4·17; *3·09* + 3·69	0	7·0
					238; 332	4·07; 3·70	+	1·0

[a] Measured spectrophotometrically as described in A. Albert and E. P. Serjeant, "Ionization Constants of Acids and Bases," Methuen, London 1962; the buffers used had ionic strength 0·01, see D. D. Perrin, *Austral. J. Chem.*, 1963, *16*, 572. [b] Inflexions are in italics. [c] Analytical wavelength. [d] 0 = Neutral species, + = cation. [e] H_0 value in hydrochloric acid. [f] In cyclohexane.

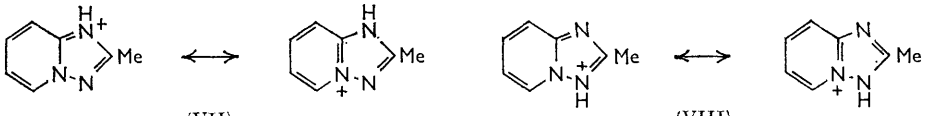
the bridgehead nitrogen atom shares some of the positive charge given to the molecule by protonation.

In the triazaindenes protonation can take place on either of the two non-bridgehead nitrogen atoms. 1,2,3a-Triazaindene can form the two cations, (V) or (VI). It cannot readily be said which cation is formed, although from theoretical considerations (V) is preferred because a fully conjugated pyridine ring (Vb) is present in one of the forms contributing to the resonance. The difference in pK_a values between 1,3a-diaza- (6·79) and



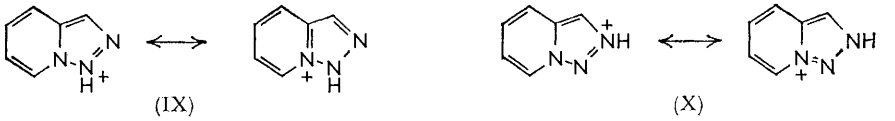
(Va) (Vb) (VIa) (VIb)

1,2,3a-triaza-indenes (3·18) is 3·61, whereas the difference between 2,3a-diaza- (5·54) and 1,2,3a-triaza-indene, 2·36, is somewhat less. Imidazole (pK_a 6·95) [3] is a stronger base than 1,2,4-triazole (pK_a 2·30) [4] by 4·65 pH units indicating a large base-weakening effect due to the third ring nitrogen atom. Although this favours the larger difference, *i.e.*, the cation (V), and also in this molecule N-1 would be more basic than N-2, a small quantity of the cation (VI) cannot be excluded. In 2-methyl-1,3,3a-triazaindene, the two possible cations (VII) and (VIII) each have one fully conjugated pyridine canonical form. The effect of



(VII) (VIII)

the methyl group in this compound cannot be very large (compare 1,2,4-triazole pK_a 2·30 and 3,5-dimethyl-1,2,4-triazole pK_a 3·79).[4] 2-Methyl-1,3,3a-triazaindene cation which has a pK_a value of 2·96 has most probably the structure (VII). It is a stronger base then 1,7a-diazaindene (pK_a 1·43) [2] and the pK_a lowering effect of N-1 (estimated as >3) would prevent a value above zero being obtained, even when allowing as much as 1 pH unit for the base-strengthening effect of the methyl group. The methyltriazaindene is a weaker base than 1,3a-diazaindene by (6·79—2·96) 3·83 pH units and is compatible with the added effects of the methyl group and N-3 on the latter. The 1,2,7a-triazaindene cation can be either (IX) or (X). Although structure (IX) has a resonance form with a fully conjugated pyridine ring, structure (X) is favoured. Its pK_a value of 0·42 is 1 and 5 pH



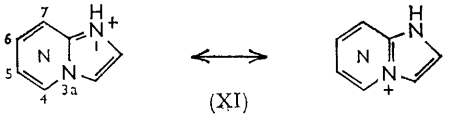
(IX) (X)

units weaker than 1,7a- and 2,3a-diazaindene, respectively. Hence the cation of 1,2,7a-triazaindene must have a structure similar to 2,3a-diazaindene cation because a large base-weakening effect is observed by inserting the third nitrogen atom (compare imidazole, 6·95 and 1,2,3-triazole, 1·17; [5] also benzimidazole, 5·53, and benzotriazole, 1·6).[6]

1,3a,4-, 1,3a,5-, 1,3a,6-, and 1,3a,7-Triazaindenes have pK_a values which are closely

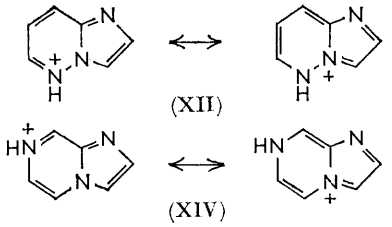
[3] A. H. M. Kirby and A. Neuberger, *Biochem. J.*, 1938, **32**, 1146; H. Walba and R. Isensee, *J. Amer. Chem. Soc.*, 1955, **77**, 5488.
[4] G. Dedichen, *Ber.*, 1906, **39**, 1831.
[5] A. Albert and C. Pedersen, personal communication.
[6] A. Albert, R. Goldacre, and J. N. Phillips, *J.*, 1948, 2240.

similar (see Table 1). This suggests that the resonance stabilisations in the cations are to a large extent similar to each other, there being little stabilisation of this type in the neutral species. The structure (XI) is common to all the cations of the triazaindenes in which



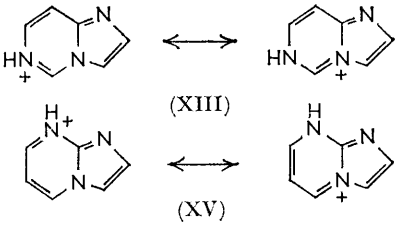
(XI)

the nitrogen atom in the pyridine ring of (XI) replaces the carbon atoms C-4, C-5, C-6, or C-7. The only contribution of the extra nitrogen atom in the pyridine ring is to lower the basic strength. The largest effect is observed in 1,3a,6-triazaindene and it is not surprising because of the three bases pyridazine, pyrimidine, and pyrazine (pK_a values: 2·33, 1·30,[6] and 0·65,[7] respectively), the second nitrogen atom in pyrazine has the largest base-weakening effect on the pyridine ring. On the other hand, if protonation occurs on the nitrogen atom in the pyridine ring, the cations would have resonance stabilisations of two general types involving, (*a*) an *ortho*-quinonoid structure, *e.g.*, (XII) and (XV), and (*b*) a *para*-quinonoid structure, *e.g.*, (XIII) and (XIV). It was shown in the cations of amino-derivatives of *N*-heterocycles (*e.g.*, pyridines, quinolines, isoquinolines, acridines, and cinnolines), that where *para*-quinonoid structures were possible a large base-strengthening effect was observed, but where only *ortho*-quinonoid structures were possible the effects were comparatively small.[6,8] This property was attributed to the higher stability of the *para*-quinonoid over the *ortho*-quinonoid structures. The pK_a value differences between the four triazaindenes are not large enough to account for these structures and the pK_a values do not follow the order: (XIII) and (XIV) > (XII) and (XV). Therefore protonation in all cases must be on N-1 to give the common structure (XI) in which, unlike the quinonoid structures, one canonical form has a fully conjugated pyridine ring.



(XII)

(XIV)



(XIII)

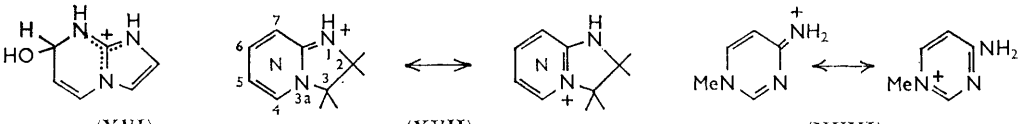
(XV)

The possibility that the cations of these four triazaindenes are hydrated (covalent) across a C=N bond was not overlooked because the number of nitrogen atoms in indolizine was increased and because in each case considerable resonance stabilisation would be present in the hydrated cation [*e.g.*, in (XVI) by guanidinium resonance]. These are two essential properties of heterocyclic compounds that undergo reversible covalent hydration.[9] However, there was no hydration in 1,3a,7-triazaindene because no unstable hydrated species was detected by rapid reaction methods,[10] and also by comparison with its 4,6-dimethyl derivative (the methyl groups being in positions where hydration was most likely to occur), its pK_a value was not abnormally high (cf. ref. 10). Similarities with this isomer in pK_a values and ultraviolet spectra (see below) excluded the possibility of covalent hydration in the other three triazaindenes.

2,3-Dihydro-1,3a-diaza-, and 1,3a,4-, 1,3a,5-, 1,3a,6-, and 1,3a,7-triaza-indenes are all

[7] A. S. Chia and R. F. Trimble, *J. Phys. Chem.*, 1961, **65**, 863.
[8] A. Albert and R. Goldacre, *J.*, 1943, 454; P. H. Gore, and J. N. Phillips, *Nature*, 1949, **163**, 690; see also A. R. Osborn, K. Schofield, and L. N. Short, *J.*, 1956, 4191.
[9] A. Albert and W. L. F. Armarego, *J.*, 1963, 4237.
[10] A. Albert and W. L. F. Armarego, *Adv. Heterocyclic Chem.*, 1965, in the press.

strong bases with pK_a values >8·8 (see Table 1) and are to be considered as imino-compounds. They are all protonated on N-1 to give the cation (XVII).



(XVI) (XVII) (XVIII)

The following pairs have similar pK_a values: 2,3-dihydro-1,3a-diazaindene (12·51) and 1,2-dihydro-2-imino-1-methylpyridine (12·2),[11] and 2,3-dihydro-1,3a-7-triazaindene (10·15) and 1,2-dihydro-2-imino-1-methylpyrimidine (10·75) [12] (because their cations have similar structures) but not 2,3-dihydro-1,3a,5-triazaindene (8·83) and 1,4-dihydro-4-imino-1-methylpyrimidine (12·2) [12] (because the cation of the latter (XVIII) is different). The true analogue is the unknown 1,6-dihydro-6-imino-1-methylpyrimidine. The base-weakening effect of the nitrogen atom in positions 4, 5, 6, and 7 of 2,3-dihydro-1,3a-diazaindene, *viz.*, 2·5, 3·7, 3·2, and 2·3 pH units, is comparable with the base-weakening caused by substituting a nitrogen atom in the positions 6, 5, 4, and 3 of 2-aminopyridine (cf. ref. 13), *viz.*, 1·7, 3·2, 3·8, and 3·4. but the respective order is not the same and can be attributed to protonation on the same site (N-1) in the dihydroindenes, but not in the aminodiazines.[13]

1,2-Dihydro-3*H*-indolizinium perchlorate has no pK_a value below 14. This is consistent with the difficulty in removing a proton from C-1 or C-3 to give the neutral species.

The ionisation constants of all the above triazaindenes cannot be discussed in more detail because even though protonation gives predominantly one cation, as in any polyaza-heterocyclic system, the small amount of cationic species protonated on the less basic nitrogen atoms is not known, and yet must have some small effect on the overall ionisation constants.

Ultraviolet Spectra.—The spectra of fifteen azaindenes were measured and are given in Table 1. The spectra of 1,2,3a-, 2-methyl-1,3,3a-, and 1,2,7a-triazaindenes cannot be used to confirm the site of protonation because their cations have spectra that are all quite similar to each other and to 1,3a-, 2,3a-, and 1,7a-diazaindene cations (see ref. 2). Unlike the spectra of these azaindenes, the spectrum of the neutral species of 3a,6-diazaindene in water is similar to that of the neutral species of indolizine and its alkyl derivatives, and is typical, *i.e.*, it consists generally of three main bands, the second of which is made up of one or two peaks.[2] The spectrum of 3a,6-diazaindene cation is similar to that of its neutral species but is wholly displaced to longer wavelengths. It differs from that of 3-methylindolizinium cation which has only two main bands,[2] and is supporting evidence that protonation does not occur on C-1 and must therefore occur on N-6.

The spectra of the neutral species of 1,3a,4-, 1,3a,5-, 1,3a,6-, and 1,3a,7-triazaindene are very similar to that of indolizine. As is typical of nonpolar solvents, the spectra in cyclohexane reveal more fine structure than those observed in water. Here it must be pointed out that the typical spectrum of the neutral species of indolizine is considerably altered when C-1 and/or C-3 is replaced by a ring nitrogen atom (*i.e.*, in 1,3a- and 1,7a-diazaindene) [14] but not when C-6 is replaced by a nitrogen atom (*i.e.*, 3a,6-diazaindene) (see ref. 14 for a discussion of these effects). However, when a carbon atom in the pyridine ring of 1,3a-diazaindene is replaced by a third nitrogen atom to give the above triazaindenes, the typical indolizine spectrum is restored. The spectra of 1,3a,5-, 1,3a,6-, 1,3a,7-, and 4,6-dimethyl-1,3a,7-triaza-indene cations are also similar to that of 3-methylindolizine cation, *i.e.*, a

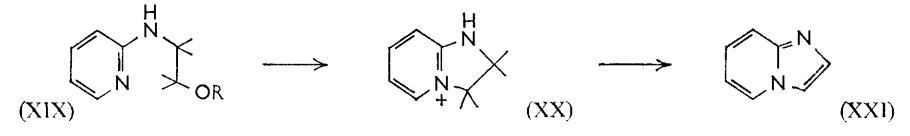
[11] S. J. Angyal and C. L. Angyal, *J.*, 1952, 1461.
[12] D. J. Brown, E. Hoerger, and S. F. Mason, *J.*, 1955, 4035.
[13] A. Albert, " Physical Methods in Heterocyclic Chemistry," Academic Press, ed. A. R. Katritzky, **1963**, **1**, 1.
[14] S. F. Mason, " Physical Methods in Heterocyclic Chemistry," Academic Press, ed. A. R. Katritzky, **1963**, **2**, 61.

large hypsochromic shift is observed on passing from the neutral species to the cation. This confirms the ionisation data and that they are all protonated on the same site—namely N-1. The spectral changes from neutral species to cation in 1,3a,4-triazaindene are smaller than the above and less typical. Nevertheless, unlike the protonation of 3a,6-diazaindene which produces a bathochromic shift, protonation of 1,3a,4-triazaindene causes a hypsochromic shift in the spectrum.

The large hypsochromic shifts observed above in the triazaindenes on protonation are due to the change in the electronic structure of the chromophore to (XI) and not to the formation of a hydrated cation, *e.g.*, (XVI). This is because the spectral changes on protonation of 4,6-dimethyl-1,3a,7-triazaindene (where the methyl groups are expected to decrease hydration to a considerable extent) [10] are almost identical with those observed in 1,3a,7-triazaindene.

The spectra of the 2,3-dihydrotriazaindenes and their respective cations had two bands, and the long wavelength band in some cases moved into the visible spectrum. In all cases protonation caused a large hypsochromic shift of both bands. These spectral changes are consistent with the protonation of imino-structures because 1,2-dihydro-2-imino-1-methylpyridine and pyrimidine, and 1,6-dihydro-6-imino-1,3-dimethylpyridazine [15] show similar large hypsochromic shifts on protonation. In contrast 2-aminopyridine, 2-aminopyrimidine, 2-aminopyrazine, 3-aminopyridazine, and 4-aminopyrimidine all show bathochromic shifts on protonation.[15] These spectral changes are in agreement with the ionisation measurements which indicate that protonation of the 2,3-dihydroazaindenes is on N-1 in each case. 1,2-Dihydro-3*H*-indolizinium cation had the typical α-picoline absorption band at ~264 mμ.

Syntheses of Triazaindenes.—Two routes were attempted for the preparation of the triazaindenes with two nitrogen atoms in the six-membered ring. The first was unambiguous and modelled on the synthesis of 1,3a-diazaindene,[16] *viz.*, (XIX) ⟶ (XX) ⟶ (XXI). The reaction (XIX; R = OH) to (XX) with thionyl chloride proceeded without the separation of (XIX; R = Cl) and the oxidation with alkaline potassium ferricyanide gave (XXI) in 56% yield. The starting material used for the preparation of 1,3a,4-triazaindene was 3-methylthiopyridazine because it was more stable than 3-chloropyridazine. It gave a good yield of the required 3-2′-hydroxyethylaminopyridazine with ethanolamine. With thionyl chloride the corresponding β-chloro-compound was obtained and cyclised to 2,3-dihydro-1,3a,4-triazaindenium chloride in boiling ethanol. Oxidation as described above gave a 5% yield of 1,3a,4-triazaindene. 2,3-Dihydro-1,3a,5-triazaindene was prepared in a similar way starting from 4-methylthiopyrimidine. The latter was prepared



(XIX) (XX) (XXI)

by methylation of 4-mercaptopyrimidine which was in turn obtained in 58% yield by thiation of 4-hydroxypyrimidine. Previously [17] 4-mercaptopyrimidine was prepared in 18% overall yield from 4-hydroxypyrimidine *via* 4-chloropyrimidine hydrochloride followed by reaction with thiourea. Oxidation of 2,3-dihydro-1,3a,5-triazaindenium chloride as above failed to give any triazaindene. 2-Chloropyrazine and ethanolamine gave only a 33% yield of 2-2′-hydroxyethylaminopyrazine and reflects on the sluggish reactivity of this chloro-compound. The reaction with thionyl chloride, unlike those described above, gave a considerable amount of tar and finally only a 6·5% yield of 2,3-dihydro-1,3a,6-triazaindenium chloride was obtained. An ethanolic solution of this salt darkened after

[15] S. F. Mason, *J.*, 1960, 219.
[16] D. J. Bower, *J.*, 1957, 4510.
[17] (*a*) M. P. V. Boarland and J. F. W. McOmie, *J.*, 1951, 1218; (*b*) A. Albert and G. B. Barlin, *J.*, 1962, 3129.

standing at 20° for 4 hr. and more rapidly on warming. This dihydro-compound analysed for a monohydrate and was thought to be 2-2′-hydroxyethylaminopyrazine hydrochloride. However, it is undoubtedly the dihydroindenium chloride hydrate because its pK_a value was 9·32 as compared with 3·08 for the 2-β-hydroxy-compound and the ultraviolet spectra of the neutral species and cation, although different from those of the latter, were like those of the other 2,3-dihydrotriazaindenes examined (see above).

Starting from 2-chloropyrimidine, 2,3-dihydro-1,3a,7-triazaindenium chloride was obtained in high overall yield. In this series 2-2′-chloroethylaminopyrimidine was isolated and, in contrast with the direct methylation of 2-aminopyrimidine with boiling methyl iodide in ethanol which gave only a 33% yield of methiodide after one hour, this chloro-

(XXII) (XXIII)

compound cyclised in >90% yield after being boiled for 30 min. in ethanol. Attempted oxidation of this dihydrotriazaindene to 1,3a,7-triazaindene (XXIII) with ethanolic ferric chloride (2·2 mol.), triphenylmethyl perchlorate (1 mol.), or lead tetra-acetate (1·1 mol.) in acetic acid failed. Alkaline ferricyanide under a variety of conditions destroyed some of the material but the rest was recovered unchanged. Silver oxide (8 mol.) in ethanol, mercuric acetate (3 mol.) in 5% aqueous acetic acid, and alkaline potassium permanganate (1 mol.) destroyed all the compound, whereas bromine (2 mol.) in acetic acid gave a poor yield of a high-melting solid.

The second route involved the preparation of the ββ-diethoxyethylamino-heterocycle [*e.g.*, (XXII)] followed by ring closure to the triazaindene [*e.g.*, (XXIII)]. 4-Methylthiopyrimidine with aminoacetaldehyde diethylacetal under reflux for 18 hr. was recovered unchanged, but 4-chloropyrimidine hydrochloride and the aminoacetal in boiling ethanol gave high yields of 4-ββ-diethoxyethylaminopyrimidine contaminated with a little 1,3a,5-triazaindene. The crude mixture was cyclised with phosphorus oxychloride or concentrated sulphuric acid as described below. 1,3a,6-Triazaindene, isolated as its perchlorate salt, was also obtained by this method in poor yield. Although in the above examples there is the possibility that ring closure may lead to a diazaindole instead of a diazaindolizine, *i.e.*, cyclisation on to a carbon atom, the similarity of the ultraviolet spectra with that of indolizine and compound (XXIII) (see above), and of the ionisation constants, clearly exclude this possibility. This alternative ring closure was not possible with compound (XXII). Cyclisation of this compound with concentrated sulphuric acid gave the highest yield (50%) and the cleanest product. On the other hand, phosphorus oxychloride in boiling benzene for 15 min. to 3 hr., polyphosphoric acid at 100° for 1 hr., and boiling concentrated hydrochloric acid for 30 min. gave 17—21, 5, and 24% yields, respectively, of 1,3a,7-triazaindene. 4,6-Dimethyl-1,3a,7-triazaindene was prepared similarly.

The following hygroscopic indenes were isolated and stored as their less hygroscopic and more stable perchlorate salts: 3a,6-diaza-, 1,2,3a-, 2-methyl-1,3-3a-triazaindenes, and 1,2-dihydro-3*H*-inolizinium bromide. These salts melted with slight (or even without) decomposition but 1,2,7a-triazaindene perchlorate exploded violently on being warmed to 70°.

2-Aminopyridine was formylated with anhydrous formic acid in 10—15% yields (see ref. 18), but with acetic formic anhydride 2-formamidopyridine was obtained in high yield. With phosphorus pentasulphide it gave 2-thioformamidopyridine. An attempt to prepare *N*-2-pyridylformamidine, and from this 1,3,3a-triazaindene, by reaction of the thio-compound with ammonia at 120° for 2 hr., gave 2-aminopyridine. At room temperature the

[18] A. E. Tschitschibabin and I. L. Knunjanz, *Ber.*, 1931, **64**, 2839.

reaction was slow but after 48 hr. 2-aminopyridine was isolated and identified by its infrared spectrum.

Experimental

Microanalyses were made by Dr. J. E. Fildes and her staff. Evaporations were carried out in a rotary evaporator at 30—40°/15 mm., and the purity of materials was examined as before.[19] All extracts were dried over anhydrous sodium sulphate, and light petroleum (b. p. 40—60°) was used unless otherwise stated. 3a,6-Diazaindene,[20] 1,2,7a-triazaindene, 2-methyl-1,3,3a-triazaindene,[21] 1,2,3a-triazaindene,[16] 2,3-dihydro-1,3a-diazaindene,[22] and 1,2-dihydro-3*H*-indolizinium bromide [23] were prepared as in the references cited.

Analyses are given in Table 2.

Table 2

	Found (%)				Requires (%)		
Pyrimidine	C	H	N	Formula	C	H	N
2-2′-Hydroxyethylamino-	51·4	6·5	30·1	$C_6H_9N_3O$	51·8	6·5	30·2
2-2′-Chloroethylamino-[a]	45·8	5·2	26·7	$C_6H_8ClN_3$	45·7	5·1	26·7
2-(2,2-Diethoxyethylamino)-	57·2	8·3	19·8	$C_{10}H_{17}N_3O_2$	56·9	8·1	19·9
4,6-Dimethyl-2-2′-hydroxyethylamino-	57·4	7·9	25·0	$C_8H_{13}N_3O$	57·5	7·8	25·1
2-(2,2-Diethoxyethylamino)-4,6-dimethyl[b]	60·2	8·65	—	$C_{12}H_{21}N_3O_2$	60·2	8·85	—
4-2-Hydroxyethylamino-	52·1	6·5	30·4	$C_6H_9N_3O$	51·8	6·5	30·2
Pyrazine							
2-2′-Hydroxyethylamino-	52·0	6·6	29·9	$C_6H_9N_3O$	51·8	6·5	30·2
2-(2′,2′-Diethoxyethylamino)-[b]	54·1	7·6	19·2	$C_{10}H_{17}N_3O_2,\frac{1}{2}H_2O$	54·5	8·2	19·1
2,3-*Dihydroindene*							
1,3a-Diaza- (perchlorate) [c]	—	—	12·4	$C_9H_9ClN_2O_4$	—	—	12·7
1,3a,4-Triaza (hydrochloride) [d]	45·7	5·1	—	$C_6H_8ClN_3$	45·7	5·1	—
1,3a,5-Triaza- (hydrochloride) [e]	45·5	5·1	—	$C_6H_8ClN_3$	45·7	5·1	—
1,3a,6-Triaza- (hydrochloride)	41·4	5·7	23·9	$C_6H_8ClN_3,H_2O$	41·0	5·7	23·9
1,3a,7-Triaza- (hydrochloride) [f]	45·9	5·1	—	$C_6H_8ClN_3$	45·7	5·1	—
1,2-Dihydro-3*H*-indolizinium perchlorate	43·4	4·5	6·3	$C_8H_{10}ClNO_4$	43·7	4·6	6·4
Triazaindene							
1,2,3a- (perchlorate) [g]	33·1	2·8	—	$C_6H_6ClN_3O_4$	32·8	2·75	—
2-Methyl-1,3,3a (perchlorate)	35·8	3·55	18·0	$C_7H_8ClN_3O_4$	36·0	3·45	18·0
1,3a,4-[b]	54·0	5·1	32·1	$C_6H_5N_3,\frac{1}{4}H_2O$	54·3	4·9	31·7
1,3a,4- (perchlorate) [b]	32·4	2·8	18·4	$C_6H_6ClN_3O_4,\frac{1}{4}H_2O$	32·2	2·9	18·7
1,3a,5-	60·5	4·11	34·6	$C_6H_5N_3$	60·5	4·2	35·3
1,3a,6- (perchlorate)	32·5	2·9	18·7	$C_6H_6ClN_3O_4$	32·8	2·8	19·1
1,3a,7-	60·5	4·3	35·3	$C_6H_5N_3$	60·5	4·2	35·3
4,6-Dimethyl-1,3a,7-	65·6	6·2	28·6	$C_8H_9N_3$	65·3	6·2	28·55
2-Thioformamidopyridine [h]	52·1	4·2	—	$C_6H_6N_2S$	52·1	4·4	—

[a] Picrate found: Cl, 9·1; requires Cl, 9·2%. [b] Hygroscopic. [c] Exploded during C and H analysis. [d] Found: Cl, 22·7; requires Cl, 22·5%. [e] Found: Cl, 22·4; requires Cl, 22·5%. [f] Found: Cl, 22·7; requires Cl, 22·5%. [g] Found: Cl, 16·2; requires Cl, 16·15. [h] Found: S, 23·4; requires S, 23·2%.

4-Mercaptopyrimidine.—4-Hydroxypyrimidine (10 g.) and phosphorus pentasulphide (10 g.) in dry pyridine (50 ml.) were refluxed for 1 hr., diluted with water (100 ml.), and evaporated. The residue was washed with water, dried, and crystallised from ethanol to give 4-mercaptopyrimidine (6·8 g., 58%) m. p. 186—188° (lit.,[17a] 188°). With methyl iodide in N-sodium hydroxide it gave a 90% yield of 4-methylthiopyrimidine, b. p. 68°/0·9 mm. (lit.,[17b] 65% yield, b. p. 86—87°/12 mm.).

2-2′-Hydroxyethylaminopyridazine.—3-Methylthiopyridazine [24] (3·78 g., 1 mol.) and ethanolamine (1·83 ml., 2 mol.) were heated at 180° under reflux for 18 hr. (68% of starting material

[19] W. L. F. Armarego, *J.*, 1962, 561.
[20] W. Herz and S. Tocker, *J. Amer. Chem. Soc.*, 1955, **77**, 6355.
[21] D. J. Bower and G. R. Ramage, *J.*, 1957, 4506.
[22] O. Bremer, *Annalen*, 1935, **521**, 286.
[23] O. G. Lowe and L. C. King, *J. Org. Chem.*, 1959, **24**, 1200.
[24] G. F. Duffin and J. D. Kendall, *J.*, 1959, 3789.

was recovered after 2 hr.) and distilled to give 2,2′-*hydroxyethylaminopyridazine* (3·9 g., 94%), b. p. 204—205°/0·2 mm., as a thick oil.

2-2′-*Hydroxyethylaminopyrimidine.*—2-Chloropyrimidine [25] (26 g., 1 mol.) and ethanolamine (34·5 g., 2·5 mol.) in ethanol (150 ml.) were refluxed for 1 hr., the solvent evaporated, the residue poured into cold water (100 ml.) saturated with sodium chloride, the pH adjusted to 11 with 5N-sodium hydroxide, and the whole extracted with chloroform (12 × 75 ml.). The dried extract was evaporated and the residue crystallised from benzene–light petroleum to give 2-2′-*hydroxyethylaminopyrimidine* (21·8 g., 70%), m. p. 77—78°.

4-2′-*Hydroxyethylaminopyrimidine.*—4-Methylthiopyrimidine (4·5 g., 1 mol.) and ethanolamine (4·8 ml., 2·2 mol.) were heated at 180° for 3 hr., worked up as above, and the residue was recrystallised from ethanol–light petroleum to give 4-2′-*hydroxyethylaminopyrimidine* (2·3 g., 46%), m. p. 119—120°.

4,6-*Dimethyl*-2-2′-*hydroxyethylaminopyrimidine.*—This compound, m. p. 82—83°, was prepared in 94% yield from 2-chloro-4,6-dimethylpyrimidine [26] and ethanolamine at 180° for 30 min. It was worked up as described above then sublimed at 70°/0·3 mm. and crystallised from light petroleum (b. p. 60—80°).

2-2′-*Hydroxyethylaminopyrazine.*—2-Chloropyrazine [27] (2·8 g., 1 mol.) and ethanolamine (3·0 ml., 3 mol.) were heated at 160—180° under reflux for 2½ hr., worked up as described above and the residue distilled at 145°/0·5 mm. to give 2-2′-*hydroxyethylaminopyrazine* (32%), m. p. 68—69°, from benzene.

2-2′-*Chloroethylaminopyrimidine.*—2-2′-Hydroxyethylaminopyrimidine (21·8 g.) and chloroform (150 ml.) were treated dropwise with redistilled thionyl chloride (17·6 ml.). After the vigorous reaction subsided the solution was refluxed for 15 min. and evaporated. The residue in water (300 ml.) was shaken for 5 min. with charcoal, the mixture filtered, and the filtrate stirred with benzene (70 ml.) while sodium carbonate was added to give a pH of 10. The benzene layer was separated and the aqueous solution extracted with benzene (6 × 70 ml.). The dried extracts were evaporated and 2-2′-*chloroethylaminopyrimidine* (19 g., 77%), m. p. 65—66° after crystallisation from light petroleum (b. p. 60—80°), was obtained.

When this chloro-compound (18 g.) in ethanol (100 ml.) was refluxed for 30 min. (separation of solid appeared complete after 10 min.) 2,3-*dihydro*-1,3a,7-*triazaindenium chloride* (92%) (decomp. >280°) was obtained and crystallised from ethanol.

Similarly, 2,3-*dihydro*-1,3a,4-, -1,3a,5-, and -1,3a,6-*triazaindenium chlorides* with m. p.s 225—226° (decomp.), 283—284° (decomp.), and 207—208° (decomp.) were prepared in 43, 21, 6·5% overall yields, respectively, from the corresponding 2-2′-hydroxyethylamino-compound without isolation of the intermediate chloro-compound, and were crystallised from ethanol–light petroleum.

2-(2,2-*Diethoxyethylamino*)*pyrimidine.*—2-Chloropyrimidine [25] (6·0 g., 1 mol.), aminoacetaldehyde diethylacetal (15·3 g., 2·2 mol.), and sodium iodide (0·78 g., 0·1 mole) in ethanol (100 ml.) were refluxed for 3 hr., and evaporated. The residue was treated with water (10 ml.), extracted with chloroform, dried, the extract evaporated, and the residue distilled to give 2-(2,2-*diethoxyethylamino*)*pyrimidine* (10 g., 99%), b. p. 134°/1 mm., 120°/0·3 mm., m. p. 51—52°, which solidified and was crystallised from light petroleum.

Similarly, 4-(2,2-*diethoxyethylamino*)*pyrimidine* (72% yield), b. p. 120—122°/0·3 mm., was prepared from 4-chloropyrimidine hydrochloride [17a] and aminoacetal (3·2 moles).

2-(2,2-*Diethoxyethylamino*)*pyrazine.*—2-Chloropyrazine [27] (5·2 g., 1 mol.) and aminoacetaldehyde diethylacetal (17·2 ml., 3 mol.) were heated at 140—150° under reflux for 2½ hr., cooled, treated with water, and extracted with chloroform in the manner described above. The residue was distilled to give 2-(2,2-*diethoxyethylamino*)*pyrazine* (3·9 g., 40%), b. p. 109—111°/0·2 mm.

Similarly, 2-(2,2-*diethoxyethylamino*)-4,6-*dimethylpyrimidine* (57% yield), b. p. 116—117°/0·3 mm., m. p. 53—55°, was obtained after 30 min. heating and was crystallised from light petroleum below 0°.

1,3a,4-*Triazaindene.*—2,3-Dihydro-1,3a,4-triazaindenium chloride (1·11 g.) and potassium ferricyanide (6·7 g.) in water (50 ml.) containing sodium hydrogen carbonate (3·7 g.) were heated

[25] K. L. Howard, U.S.P. 2,477,409/1949 (*Chem. Abs.*, 1949, **43**, 8105); I. C. Kogon, R. Minin, and C. G. Overberger, *Org. Synth.*, 1955, **35**, 34.
[26] T. Matsukawa and B. Ohta, *J. Pharm. Soc. Japan*, 1949, **69**, 491 (*Chem. Abs.*, 1950, **44**, 3456).
[27] A. E. Erickson and P. E. Spoerri, *J. Amer. Chem. Soc.*, 1946, **68**, 400.

at 100° for 1 hr., cooled, and extracted with chloroform. The dried extract was evaporated and the residue in benzene was purified through an alumina column (1 × 5 in., B.D.H.) and the benzene eluates (white fluorescence under a mercury lamp, 254 mμ) were evaporated and the residue sublimed at 30—35°/0·1 mm. to give 1,3a,4-*triazaindene* (43 mg., 4·9%), m. p. 54—55°, as a white hygroscopic solid with violet fluorescence. The yield was unaltered after heating for 3 hr. and no starting material was recovered. The *perchlorate* had m. p. 199—200° (decomp.).

1,3a,7-*Triazaindene*.—(*a*) *With phosphorus oxychloride*. 2-(2,2-Diethoxyethylamino)-pyrimidine (0·5 g.) in benzene (4 ml.) and phosphorus oxychloride (1 ml.) were refluxed for 1¾ hr., evaporated, treated with cold water and then saturated aqueous sodium carbonate to give pH 11, and extracted with chloroform (6 × 50 ml.). The extract was evaporated and the residue in benzene was purified through an alumina column (½ × 4 in., B.D.H.) and eluted first with benzene to remove a small amount of oil, then with 3% ethanol in benzene. The eluates which gave the higher melting solids were combined, sublimed at 130—140°/0·4 mm., and crystallised once from benzene–light petroleum, then three times from light petroleum (b. p. 80—100°) to give 1,3a,7-*triazaindene* (68 mg., 21%), m. p. 129—130°.

(*b*) *With concentrated sulphuric acid*. The aminoacetal (250 mg.) in concentrated sulphuric acid (2·5 ml.) was heated at 100° for 30 min., poured on to ice, basified with cold 5N-sodium hydroxide, and extracted with chloroform. The residue obtained from the dried extract was sublimed and crystallised from light petroleum (b. p. 80—100°) to give 1,3a,7-*triazaindene* (71 mg., 50%), m. p. 129—130°. 1,3*a*,5-*Triazaindene* (24% yield), m. p. 102—103°, was prepared from the corresponding aminoacetal by method (*b*) but required the purification used for method (*a*). 1,3*a*,6-*Triazaindene* was prepared by method (*b*) (see above) and was converted into the *perchlorate*, m. p. 157—158° (decomp.), in 7% overall yield by the general method described below. 2,3-*Dihydro*-1,3*a*-*diazaindenium perchlorate*, (m. p. 82—84°), 1,2,3*a*- (m. p. 174·5—175·5°), and 2-*methyl*-1,3,3a- (m. p. 167—169°) *triazaindenium perchlorates*, and 1,2-*dihydro*-3H-*indolizinium perchlorate* (m. p. 111—112°) were prepared by adding 70% w/w perchloric acid (1 ml.) to a cool solution of the base or its salt (100 mg.) in ethanol (5 ml.), and the crystalline solid collected. When no solid separated, dry ether was added until crystallisation was complete. The solid was washed with ether containing 5% ethanol and dried in a vacuum desiccator over phosphorus pentoxide for 24 hr. and analysed. The yields were almost quantitative. The salt could be crystallised by dissolution in the least volume of ethanol containing a drop of perchloric acid followed by the slow addition of ether.

2-*Formamidopyridine*.—Anhydrous formic acid (12·6 ml., 1 mole) and acetic acid (32·8 ml., 0·96 mole) were heated at 50° for 2 hr. To this cooled solution was added slowly with stirring a solution of 2-aminopyridine (32·8 g., 0·88 mole) in dry benzene (150 ml.); the mixture was allowed to stand at 20° for 48 hr. then distilled. 2-Formamidopyridine (34·5 g., 84%) which distilled at 154—156°/12 mm., solidified and had m. p. 69—70° (lit.,[18] b. p. 161—162°/15 mm., m. p. 71°).

2-*Thioformamidopyridine*.—2-Formamidopyridine (13 g.) and phosphorus pentasulphide (13 g.) in xylene (50 ml.) were refluxed for 2 hr. and the xylene decanted from the tar, cooled, and the yellow needles collected and washed with light petroleum. Very little product could be extracted by boiling the tar with more xylene. 2-*Thioformamidopyridine* (2·5 g., 17%), m. p. 164—165°, was recrystallised from ethanol.

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Department of Medical Chemistry, Institute of Advanced Studies,
Australian National University,
Canberra, A.C.T., Australia. [*Received, September 29th*, 1964.]