356. *Diazaindenes ("Azaindoles"). Part I. Ionization Constants and Spectra.*

By TERRINE K. ADLER and ADRIEN ALBERT.

Ionization constants and ultraviolet spectra have been determined for 1,4-, 1,5-, 1,6-, and 1,7-diazaindene. They are discussed with particular reference to the remaining isomers. 1,5- and 1,6-Diazaindene are stronger bases than other heteroaromatic parent substances yet measured.

DIAZAINDENES ("azaindoles") are of interest as possible metabolite antagonists of the purines (3,5,7-triazaindoles) and of physiologically active indoles such as serotonin, tryptophan, and *NN*-diethyl-lysergamide. Competition has recently been demonstrated between 1,7-diazaindenes and indoles in bacteria, viruses, fungi, and protozoa. Thus 7-azatryptophan is incorporated into bacterial protein in the place of tryptophan by a tryptophan-requiring mutant of *E. coli*, but growth soon ceases.[1] T2 bacteriophage behaves somewhat similarly,[1] 1,7-Diazaindene inhibits the conversion of indole into tryptophan in the mould *Neurospora crassa*,[2] and 7-azatryptophan prevents the uptake of tryptophan by the protozoon *Tetrahymena pyriformis*.[3]

Whereas much has been written about indazole and benzimidazole, indoles containing an additional nitrogen derivative incorporated in the *Bz*-ring have been little studied and few of the physical properties of the parent substances are known. Hence, the ionization constants and ultraviolet spectra of these substances have now been investigated. These compounds are stable, colourless, almost odourless solids, more soluble than indole in water, and with higher melting points.

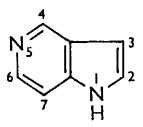
		Ionization in H_2O at 20°			Ultraviolet spectra in H_2O (shoulders in italics)		
Substance	M. p.	pK_a (basic)	spread	Concn. (M)	$\lambda_{max.}$ (mμ)	log ε	pH
1,4-Diazaindene	127°				292 [b]	3·92	9·2
Cation		6·94	±0·01	0·005	284, 327	3·85, 3·70	4·7
1,5-Diazaindene	112				265, *273*	3·59, *3·50*	10·5
Cation		8·26	±0·06	0·005	268, 293	3·46, 3·29	6·0
1,6-Diazaindene	137				260, 291	3·59, 3·68	10·0
Cation		7·95	±0·06	0·005	261, 319	3·70, 3·73	6·0
1,7-Diazaindene	105				290	3·91	7·0
Cation		4·59	±0·01	0·005	293	3·94	2·1
Indole	52				273 + 278, 288	3·79 + 3·78, 3·69 [d]	
Cation		<1					
Quinoline					275, 299, 312	3·51, 3·46, 3·52 [e]	
Cation		4·94 [a]			313	3·80 [d]	
Indazole	146				250, 284, 296	3·65, 3·63, 3·52	4·0
Cation		1·22	0·04	0·00003 [c]	253, 291, *302*	3·75, 3·67, *3·53* [f]	−1·2
Benzimidazole ...	170				242, 265, 271, 277	3·72, 3·58, 3·70, 3·69 [f, g]	9·1
Cation		5·53 [a]			240, 267, 273	3·61, 3·81, 3·89 [f]	2·0

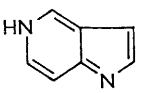
[a] Ref. 4. [b] The first four compounds (and their cations), like indole, have a peak below 220 mμ. [c] Determined spectroscopically at 302 mμ. [d] In EtOH (Edwards, *Arch. Biochem.*, 1949, **21**, 105; Karrer and Schmid, *Helv. Chim. Acta*, 1946, **29**, 1853; the spectrum in water, in which indole is insoluble, should resemble that in alcohol because the spectrum of tryptophan, which resembles that of indole, is virtually identical in the two solvents (Edwards, *loc. cit.*). In cyclohexane, the peaks are at 262, 266, 280, and 288 mμ (Friedel and Orchin, "Ultraviolet Spectra of Aromatic Compounds," New York, Wiley, 1951. [e] Albert, Brown, and Cheeseman, *J.*, 1951, 474. [f] Present work. [g] No extra resolution in cyclohexane.

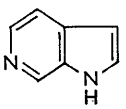
Ionization.—Indole, unlike quinoline, has practically no basic properties because the lone pair of electrons on the nitrogen atom are incorporated into the mobile π-electron system. Thus, as expected, the compounds now studied are stronger bases than indole. However, three of them are very much stronger than quinoline (see Table).

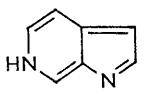
[1] Pardee, Shore, and Prestidge, *Biochem. Biophys. Acta*, 1956, **21**, 406.
[2] Sundaram and Sarma, *Current Sci.*, 1957, **26**, 13.
[3] Kidder and Dewey, *Biochim. Biophys. Acta*, 1955, **17**, 288.
[4] Albert, Goldacre, and Phillips, *J.*, 1948, 2240.

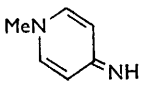
The most potent influence on the ionization constants of these compounds arises from possible tautomerisms of the type (I) ⇌ (II) and (III) ⇌ (IV), which permit additional resonance in the cations. The neutral molecules can take part in resonance also, *e.g.*, with forms of (I) and (III) where $N_{(1)}$ carries a positive and the other nitrogen atom carries a negative charge. However, separations of charge in a neutral molecule contribute little to its stability. On the other hand, a large stabilization of the cations by resonance is to be expected from such pairs of canonical forms as (I) protonated on $N_{(5)}$ and (II) protonated


(I)


(II)


(III)


(IV)


(V)

on $N_{(1)}$. These are the lines along which the high basic strength of many α- and γ-amino-aza-aromatic compounds have been explained.[4] Indeed, compound (I) may be regarded as 4-aminopyridine (pK_a 9·2) with a vinyl substituent, and (III) as a 4-aminovinyl-pyridine. Resonances involving *ortho*-quinonoid forms commonly produce weaker baser than those where *para*-quinonoid forms take part,[4,5] and hence the comparative weakness of the 4- and the 7-isomer is explained.

The 7-isomer is further weakened by the inductive effect of $N_{(1)}$ because of the nearness of the two nitrogen atoms (the Table shows that, as would be expected, indazole has this inductive effect in a heightened degree, and benzimidazole to about the same extent as 1,7-diazaindene). Steric hindrance to protonation of 1,7-diazaindene should be no greater than in quinoline, but the fractional positive charge on $N_{(1)}$ may exert a coulombic repulsion on an approaching proton.

1,5- and 1,6-Diazaindene are stronger bases than any other hetero-aromatic parent substance measured hitherto, the strongest of which is imidazole (pK 7·2), followed by acridine (5·6). Substances in the pK range 6—8·5 often show diversified physiological properties because they are distributed both as ions and as neutral molecules at pH 7·3.

No acidic function could be elicited in aqueous solutions of these diazaindenes, and this is consonant with the weakness as acids of benzimidazole (pK 13·2) [6] and indazole (14, present work).

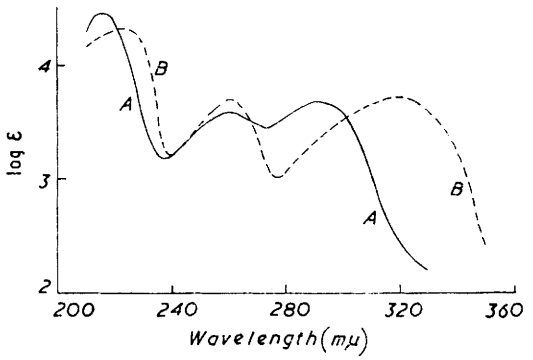
Spectra.—It is often found that the insertion of a doubly bound nitrogen atom into a heterocyclic nucleus makes little difference to the spectrum.[7] Thus 1,9- and 2,9-diaza-fluorene (which are 2,3-benzologues of 1,7- and 1,6-diazaindene) have almost identical spectra, which differ little from that of carbazole. The difference is mainly in the III band (about 320 mμ) which is less resolved, has twice the extinction coefficient, and is shifted 5 mμ towards the visible region.[8] However our diazaindenes differ more from one another, and from indole.

The spectrum of indole is related to that of naphthalene [9] in that the 219, 273~278, and 288 mμ bands of the former correspond to the I, II, and III bands of the latter which are respectively at 220, 275, and 312 mμ. 1,4-, 1,5-, and 1,7-Diazaindene have a III band at 290—292 mμ, and two of them have a band at 260—265 mμ. Only 1,6-diazaindene (see Figure) has both bands. The resolution of the diazaindene spectra is poorer than is that of indole, and is little improved in dichloromethane (the diazaindenes are not soluble in cyclohexane). Hence it seems that in 1,4-, 1,5-, and 1,7-diazaindene, some telescoping of bands has occurred, as with the II and III bands in anthracene. 1,5-Diazaindene in

[5] Gore and Phillips, *Nature*, 1949, **163**, 690.
[6] Brown, *J.*, 1958, 1974.
[7] Albert, "Heterocyclic Chemistry," The Athlone Press, London, 1959.
[8] Horner, *Annalen*, 1939, **540**, 73; cf. Pruckner and Witkop, *Annalen*, 1943, **554**, 135.
[9] Badger and Christie, *J.*, 1956, 3438.

dichloromethane absorbs at lower wavelengths than 1,4-dihydro-4-imino-1-methylpyridine (V) which has $\lambda_{max.}$ 326 mμ. This suggests that very little of the tautomer (II) is present in the neutral molecule.

In the *cations* of 1,4-, 1,5-, and 1,6-diazaindene, the band of longest wavelength is displaced 20—35 mμ to longer wavelengths than for the neutral molecules. Similar displacements are found in many heterocyclic bases (*e.g.*, isoquinoline, quinoxaline, acridine, and 2- and 3-aminopyridine) but are absent in others (*e.g.*, quinoline, pyridine, and 4-aminopyridine).[7] 1,7-Diazaindene, indazole, and benzimidazole show the latter type of behaviour.



Ultraviolet absorption of 1,6-*diazaindene*: (*A*) *neutral molecule*, (*B*) *cation*.

Improvements have been made in yields and reproducibility of synthesis of three of the diazaindenes.

Experimental

Analyses by Dr. J. E. Fildes and her staff. Ionization constants and spectra were determined as before.[10]

1,4-Diazaindene was obtained by the ring-closure of 3-formamido-2-methylpyridine (Madelung reaction), but with sodium anilide at 300° (as used by Robison and Robison for 1,7-diazaindene [11]) instead of the usual potassium ethoxide.[12] The necessary 6-amino- and 6-chloro-2-methyl-3-nitropyridine were obtained by methods [13] more efficient than used by Clemo and Swan [12] (Found: C, 71·0; H, 5·4; N, 23·5. Calc. for $C_7H_6N_2$: C, 71·2; H, 5·1; N, 23·7%).

1,5-Diazaindene was prepared by irradiating diazotized 3-amino-4-hydroxy-1,6-naphthyridine and decarboxylating the 1,5-diazaindene-3-carboxylic acid so formed,[14] a method which we prefer to the Madelung ring-closure of 4-formamido-3-methylpyridine.[15] 4-Hydroxy-1,6-naphthyridine [16] was nitrated [14] to 4-hydroxy-3-nitro-1,6-naphthyridine which was reduced at 20° and atmospheric pressure (lit.,[14] 80 atm.) in methanolic suspension over Raney nickel (30 min.). The filtrate and washings (boiling water) were taken to dryness. The residue was dissolved in N-hydrochloric acid (12 parts) and precipitated with ethanol (40 parts), giving 3-*amino*-4-*hydroxy*-1,6-*naphthyridine dihydrochloride* (Found: C, 40·9; H, 4·0; N, 17·5; Cl, 28·9. $C_8H_9ON_3Cl_2$ requires C, 41·0; H, 3·9; N, 17·95; Cl, 30·3%). After diazotization of this amine, the solution must be taken to dryness within 2 hr. at <25°/0·1 mm. 1,5-Diazaindene was sublimed at 80°/0·001 mm. (Found: C, 71·0; H, 4·9; N, 23·5%). It was stable in 0·01M-sodium hydroxide at 20°.

1,6-Diazaindene was similarly made by irradiating diazotized 3-amino-4-hydroxy-1,7-naphthyridine and decarboxylating the product.[17] To prevent the formation of 1,5-naphthyridines (and hence of 1,4-diazaindene) this preparation started from 3-aminopyridine 1-oxide

[10] Albert and Phillips, *J.*, 1956, 1294.
[11] Robison and Robison, *J. Amer. Chem. Soc.*, 1955, **77**, 457.
[12] Clemo and Swan, *J.*, 1948, 198.
[13] Clemo and Holt, *J.*, 1953, 1313; Baumgarten and Su, *J. Amer. Chem. Soc.*, 1952, **74**, 3828.
[14] Möller and Süs, *Annalen*, 1958, **612**, 153.
[15] Okuda and Robison, *J. Org. Chem.*, 1959, **24**, 1008.
[16] Albert, preceding paper.
[17] Süs and Möller, *Annalen*, 1956, **599**, 233.

and not from 3-aminopyridine.[18] 4-Hydroxy-1,7-naphthyridine [16] (1·1 g.) was refluxed with nitric acid (*d* 1·5; 15 ml.) for 1 hr. The excess of acid was distilled off, the residue stirred with water (20 ml.), and the pH adjusted to 3·5. The 3-nitro-derivative was obtained in 74% yield (lit.,[17] 21%), had m. p. 309—310° (decomp.), and was chromatographically homogeneous. It was converted into 3-amino-4-hydroxy-1,7-naphthyridine dihydrochloride (75% yield) as was the 1,6-isomer (above). Diazotization with sodium nitrite in N-hydrochloric acid at 0° gave more reproducible yields (80%) than did pentyl nitrite.[17] Irradiation in 0·1N-acetic acid at 20° until coupling with β-naphthol ceased (3 hr.) gave a 90% yield (lit.,[17] 57%) of 1,6-diazaindene-3-carboxylic acid, m. p. 196°. Decarboxylation at 200° gave 1,6-diazaindene, m. p. 137° (Found: C, 71·1; H, 5·2; N, 23·6%). Preparation [19] of 1,6-diazaindene, m. p. 129·5°, from 2-formylpyrrole and 2-aminoacetaldehyde diethyl acetal gave a product that had only 22% of the required absorption at 260 mμ.

1,7-Diazaindene was prepared by the Madelung ring-closure of 3-formamido-2-methylpyridine [11] (Found: C, 71·3; H, 5·1; N, 23·7%).

We thank Drs. D. J. Brown, D. D. Perrin, and E. Spinner for helpful discussions, also Messrs. K. Tratt, D. Light, and F. Robinson for technical assistance. One of us (T. K. A.) is indebted to the U.S. Public Health Service for a Research Fellowship (National Institute of Mental Health).

Department of Medical Chemistry, Australian National University,
Canberra, Australia. [*Received, November 23rd,* 1959.]

[18] Murray and Hauser, *J. Org. Chem.*, 1954, **19**, 2008.
[19] Herz and Tocker, *J. Amer. Chem. Soc.*, 1955, **77**, 6357.