606. *Partition Coefficients of Some Amidines.*

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Partition coefficients between liquid paraffin and water at pH 7·2 have been measured for some twenty *N*-4-diphenylylamidines, *p*-phenylbenzamidines, and related compounds. Ionisation constants for ten *p*-phenylbenzamidines have been determined in 50% alcohol, and the results are discussed.

As part of an investigation of the effect of variation in lipoid solubility and basic strength on antituberculous activity, two series of compounds containing the diphenyl structure, *viz.*, *N*-4-diphenylylamidines (II) and *p*-phenylbenzamidines (I), were prepared (Bauer and Cymerman, *J.*, 1950, 1826, 2078). The ionisation constants of the former series have been reported by Carswell, Cymerman, and Lyons (*J.*, 1952, 430), and the determination of the basic strengths of the ten substances of the latter series, and the lipoid–water partition coefficients of sixteen bases belonging to both series, and of four related aromatic amines, are now described.

Method.—The partition coefficients between liquid paraffin (B.P. 1932) and aqueous phosphate buffer at pH 7·2 (the physiological pH) were determined at 20° ± 2° by the spectrophotometric method of Cymerman-Craig and Diamantis (*J.*, 1953, 1619), and the values of the apparent partition coefficient (k') are given in Tables 1 and 2, together with the wave-length of the absorption maximum.

For five amidines, water-solubility of the hydrochlorides was so low that a suitable aqueous solution (*i.e.*, one of optical density not less than 0·2) could not be obtained, and so measurement was impossible. In the twenty compounds measured, the partition coefficients range from 0·075 to 126 according to the nature of the lipophilic group.

In view of the unexpectedly low values of k' found for some compounds of type (I) (Table 1), their pK_a values were determined by potentiometric titration in 50% aqueous-alcoholic solution at 20° ± 1° by the method described by Carswell, Cymerman, and Lyons (*loc. cit.*), and the results are given in Table 1.

For the amidines, the hydrochlorides were titrated with 50% aqueous-alcoholic N/20-sodium hydroxide, and the base 2 : 4′-diphenylylbenziminazole was titrated with 50% aqueous-ethanolic N/20-hydrochloric acid. Results were corrected for hydrogen- and hydroxyl-ion concentration where necessary.

Owing to the low solubility of *N*-*p*-chlorophenyl-*p*-phenylbenzamidine in 50% ethanol, its potentiometric titration was carried out in 67% ethanol, and the pK_a in 50% aqueous-alcoholic solution was determined by measurement of the pH at the exact half-neutralisation point.

It has been shown (Hall and Sprinkle, *J. Amer. Chem. Soc.*, 1932, **54**, 3472; Albert and Goldacre, *J.*, 1946, 706) that the temperature coefficient of basic strength is of the order of −0·01 to −0·03 unit per degree; our results, although therefore mainly of qualitative interest, do provide an interpretation of the apparently anomalous partition coefficients (k') found for the compounds recorded in Table 1.

Discussion.—Benzamidine has pK_a 11·23 in 50% alcohol (Baxter and Cymerman-Craig, *J.*, 1953, 1490), and in *p*-phenylbenzamidine (Table 1) the $+E$ effect of the additional phenyl group is seen to reduce the basic strength by 0·14 unit. The introduction of an alkyl residue R on the amino-nitrogen atom of the amidine group [Table 1 (*a*)] has a base-weakening effect (ΔpK − 0·36 and −0·33 unit) when R is *n*-butyl and *cyclo*hexyl respectively. Clearly, the destruction of the equivalence of the two structures contributing to the amidinium ion has a base-weakening effect greater than the base-strengthening ($-I$) effect of the additional alkyl group. That the presence of two $-I$ groups is capable of offsetting this drop in pK_a is shown by *NN*-di-*n*-butylbenzamidine (Lorz and Baltzly, *J. Amer. Chem. Soc.*, 1949, **71**, 3992) which has pK_a 11·27 in 50% methanol and by the similar effect observed in the *N*-methyl-substituted guanidines (Angyal and Warburton, *J.*, 1951, 2492).

Series (*b*) (I; R = aryl) shows the $+E$ effect of the phenyl residue together with the effect of the *p*-substituent attached to the phenyl group. The pK_a (7·95) of the compound (I; R = Ph) is seen to be close to that (8·10) of the isomer (II; R = Ph) (Carswell, Cymerman, and Lyons, *loc. cit.*), as expected. The pK_a's of the *p*-alkoxy-substituted compounds are in accord with the $-E$ effect of these substituents, and the very small difference between the *p*-ethoxy- and *p*-*n*-butoxy-substituted compounds is in agreement with the close resemblance between the pK_a values of the corresponding *p*-alkoxybenzoic acids (Cavill, Gibson, and Nyholm, *J.*, 1949, 2466). The *p*-chloro-group shows the expected base-weakening effect.

TABLE 1. *Ionisation and partition coefficients of* p-*phenylbenzamidines*, *p*-Ph·C_6H_4·C(:NH)·NHR (I).

	R	pK_a[1] at 20° ± 1°	*k'* at 20° ± 2°	$\lambda_{max.}$, mμ
(*a*)	H	11·09	0·075	273
	n-C_4H_9	10·73	0·20	273
	*cyclo*Hexyl	10·76	0·21	269
	(2-4′-Diphenylyl-4 : 5-dihydroglyoxaline [4])	9·29	0·11	280
(*b*)	Ph [6]	7·95	6·4	278
	p-Ethoxyphenyl	8·12	6·7	278
	p-*n*-Butoxyphenyl [7]	8·10	— [5]	—
	p-Chlorophenyl [8]	7·65 [2]	— [5]	—
		7·74 [3]		
	p-*N*-Piperidinophenyl	8·00	7·5	278
	(2-4′-Diphenylylbenziminazole)	3·64	— [5]	—

[1] In 50% alcohol. [2] In 67% alcohol by potentiometric titration. [3] In 50% alcohol from half-neutralisation point. [4] The *hydrochloride* formed needles from methanol–ether, m. p. 318° (Found: N, 10·65. $C_{15}H_{14}N_2$,HCl requires N, 10·8%). [5] Measurement impossible owing to insolubility in water. [6] The *hydrochloride* formed plates, m. p. 210—211°, from alcohol–ether (Found: N, 9·45. $C_{19}H_{16}N_2$,HCl requires N, 9·1%). [7] The *hydrochloride* had m. p. 213° (Found: 7·4. $C_{23}H_{24}ON_2$,HCl requires N, 7·35%). [8] The *hydrochloride* had m. p. 224° (Found: N, 8·25. $C_{19}H_{15}N_2Cl$,HCl requires N, 8·15%).

TABLE 2. *Partition coefficients of* N-4-*diphenylylamidines*, *p*-Ph·C_6H_4·NH·CR(:NH) (II) *and aminodiphenyls at* 20° ± 2°.

	R	*k'*	$\lambda_{max.}$, mμ		R	*k'*	$\lambda_{max.}$, mμ
(*a*)	Me	0·18	259	(*b*)	Ph	7·0	263
	n-C_5H_{11}	1·9	259		*p*-Ethoxyphenyl	19·0	275
	n-C_7H_{15}	26·0	259		3 : 4-Dimethoxyphenyl	33·0	272
	n-$C_{16}H_{33}$ [1]	— [2]	—		*p*-Chlorophenyl	— [2]	—
	*cyclo*Pent-1-enyl	3·4	254		*p*-Ethoxycarbonylphenyl	— [2]	—
	*cyclo*Hex-1-enyl	7·5	259				
	*cyclo*Hexyl	7·6	260	(*c*)	4-Aminodiphenyl	55	272
					3-Aminodiphenyl	47	230
					2-Aminodiphenyl	126	221
					Aniline	0·75	230

[1] The *hydrochloride* formed waxy plates from benzene–ether, m. p. 167—168° (Found: C, 75·95; H, 9·5. $C_{29}H_{44}N_2$,HCl requires C, 76·2; H, 9·85%). [2] Measurement impossible owing to insolubility in water.

The cyclic analogue 2-4′-diphenylyl-4 : 5-dihydroglyoxaline is seen to be a strong base, although almost 1·5 pK units weaker than the open-chain *N*-alkyl-*p*-phenylbenzamidines. The high basic strength of glyoxaline (pK_a 7·03 at 20° in water: Albert, Goldacre, and Phillips, *J.*, 1948, 2240) compared with that of pyridine or pyrimidine is probably due to the symmetry of the glyoxalinium cation (cf. Schofield, *Quart. Reviews*, 1950, **4**, 382) in spite of the electron-withdrawing effect of the olefinic linkage in the ring. It can be presumed that dihydroglyoxaline (the pK_a of which has apparently not been measured) would be a still stronger base, since it could be regarded as a cyclised *NN*′-dimethylformamidine, and the high pK_a of the diphenylyl derivative is thus consistent with the expected results. Its lower homologue, 4 : 5-dihydro-2-phenylglyoxaline, is described as a " strong base " (Forssel, *Ber.*, 1892, **25**, 2135). In benziminazole the additional mesomeric effect of the benzo-group has reduced the pK_a to 5·53 in water at 20° (Albert, Goldacre, and Phillips, *loc. cit.*), and the further reduction to 3·64 in the case of the diphenylyl derivative is again in accord with the $+E$ effect of the aryl group.

The oil–water partition coefficients of the *N*-4-diphenylylamidines (II) (Table 2) follow the accepted order of lipophilic nature of the group R, whereas in the corresponding results for the *p*-phenylbenzamidines (I) (Table 1) the aliphatic group (*a*) is seen to have very much lower values for k' than their isomers (II; R = aliphatic) in Table 2 (*a*). This apparent anomaly is, however, accounted for by the higher pK_a (9·3—11) of the substances in section (*a*) of Table 1, whereas those in Table 2 (*a*) have pK_a 8·6—9·3. Since the measured partition coefficient (k') is related to the true partition coefficient (k, where $k = [B]_0/[B]_w$, $[B]_0$ and $[B]_w$ being the concentrations of the undissociated base in the two phases) as shown in the equation below (Cymerman-Craig and Diamantis, *loc. cit.*), it follows that at pH 7·2 the ratio k/k' for a base of pK_a 10·2 will be ten times as great as for a base of pK_a 9·2. This explanation is borne out by the similarity of the values of k' for compounds of comparable pK_a in section (*b*) of Tables 1 and 2. The high values of k' for the isomeric aminodiphenyls [Table 2 (*c*)] compared with that of aniline are in accord with the fact that here all four compounds have pK_a not exceeding 4·5, so that $k = k'$ in the equation $k/k' = 1 + \text{antilog}\ (pK_a - \text{pH})$.

This work was carried out under the auspices of the National Health and Medical Research Council, to whom we are indebted for financial support. We also thank Mrs. E. Bielski for microanalyses.

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[*Received, March 26th*, 1953.]