Apparent Dissociation Constants of Haloaralkylamines

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Introduction of halogen on the phenyl ring of primary aralkylamines lowers basicity relative to the unsubstituted amine. With the benzylamines this trend increases with the atomic weight of the halogen, with substitution in the *ortho* position and with the presence of more than one halogen substituent. Distinctions dependent on halogen and ring position are not as subtle with the phenethylamines. Tertiary amines, particularly those with two halobenzyl groups, show surprisingly low basicity.

While correlation between p*K*a values and pharmacological activity is infrequently obtained,[1-3] this constant is a measure of the ratios of ionized to non-ionized drugs[4] and is an aid to structural insight[5-8] into the molecule.

Detailed inspection of the p*K*a values of aralkylamines has reflected fundamental objectives[9,10] as well as distinctions within the sympathomimetic aralkylamines.[11,12] However, the influence of halogen on the basicity of the pharmacologically important aralkylamine derivatives [13-17] has received little attention. Since these laboratories

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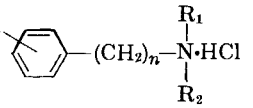
TABLE I

pK_a' VALUES OF ARALKYLAMINES



No.[a]	X	R_2	M.p., °C.[b](S)[c]	Formula	Analyses, %[d] Carbon Calcd.	Carbon Found	Hydrogen[e] Calcd.	Hydrogen Found	pK_a'[f]	pK_a'[g] Aniline
1[h]	H	H	228–230(A)	..	..	..	..	..	9.03	4.58
HP[i]	H	H	203(B)	..	..	..	..	..	..	..
2	H	CH_3	178–180(A)	$C_8H_{12}ClN$	61.0	60.8	7.7	7.8	9.29	..
3	H	$C_6H_5CH_2$	246–248(A)	$C_{14}H_{16}ClN$	..	..	6.0	5.8	8.34	..
4	*o*-F	H	174(A)	C_7H_9ClFN	..	..	8.7	8.6	8.93	2.96
HP	*o*-F	H	211(A)	$C_{13}H_{11}FN_4O_7$	44.1	44.3	3.1	2.9	..	..
5	*m*-F	H	260(A)	C_7H_9ClFN	52.0	52.2	5.6	5.9	8.87	3.32
6[j]	*p*-F	H	295(A)	C_7H_9ClFN	52.0	52.3	5.6	5.6	9.17	4.52
HP[k]	*p*-F	H	206(A)	$C_{13}H_{11}FN_4O_7$	..	..	15.8	16.0	..	..
7	*o*-Cl	H	226–227(A)	$C_7H_9Cl_2N$	..	..	7.9	8.2	8.73	2.62
HP	*o*-Cl	H	233(A)	$C_{13}H_{11}ClN_4O_7$	42.1	42.3	3.0	3.1	..	..
8	*o*-Cl	CH_3	139(A)	$C_8H_{11}Cl_2N$	50.0	49.7	5.8	5.6	8.99	..
HP	*o*-Cl	CH_3	111–112(A)	$C_{14}H_{13}ClN_4O_7$	..	..	14.6	14.7	..	..
9[l]	*m*-Cl	H	236(A)	$C_7H_9Cl_2N$	47.2	47.4	5.1	5.0	8.88	3.32
HP[m]	*m*-Cl	H	222(A)	$C_{13}H_{11}ClN_4O_7$	42.1	42.0	3.0	2.9	..	..
10[n]	*p*-Cl	H	270(A)	$C_7H_9Cl_2N$	47.2	47.2	5.1	4.9	9.01	3.81
11[o]	*p*-Cl	CH_3	205(A)	$C_8H_{11}Cl_2N$	50.0	50.2	5.8	5.8	9.21	..
12[p]	2,4-Cl_2	H	275–276	$C_7H_8Cl_3N$	..	..	6.6	6.9	8.38	..
HP	2,4-Cl_2	H	238	$C_{13}H_{10}Cl_2N_4O_7$	..	..	13.8	13.7	..	..
13[q]	2,4-Cl_2	C_2H_5	182–183(A)	..	..	..	..	..	8.42	..
14[q]	2,4-Cl_2	$CH_2{=}CHCH_2$	148–149(A)	..	..	..	..	..	7.42	..
15[q]	2,4-Cl_2	*i*-C_3H_7	188–189(A)	..	..	..	..	..	8.55	..

HP	2,4-Cl_2	*i*-C_3H_7	149(B)	$C_{16}H_{16}Cl_2N_4O_7$	43.0	43.4	3.6	3.6	..	..
16[r]	3,4-Cl_2	H	252(A)	$C_7H_8Cl_3N$	..	..	6.6	6.8	8.67	..
HP	3,4-Cl_2	H	227(A)	$C_{13}H_{10}Cl_2N_4O_7$	..	..	13.8	13.7	..	..
17[s]	3,4-Cl_2	C_2H_5	237–239(A)	$C_9H_{12}Cl_3N$	44.9	45.1	5.0	5.1	8.61	..
HP	3,4-Cl_2	C_2H_5	173(B)	$C_{15}H_{14}Cl_2N_4O_7$	41.6	42.1	3.3	3.2	..	..
18[t]	3,4-Cl_2	*n*-C_3H_7	240–242(A)	$C_{10}H_{14}Cl_3N$	47.2	47.5	5.5	6.0	8.59	..
19[u]	3,4-Cl_2	*i*-C_3H_7	207–208(A)	$C_{10}H_{14}Cl_3N$	47.2	47.2	5.5	5.9	8.60	..
20[v]	*o*-Br	H	228(A)	C_7H_9BrClN	..	..	6.3	6.3	8.55	2.60
21[w]	*m*-Br	H	221(A)	C_7H_9BrClN	..	..	6.3	5.8	8.82	3.51
HP[x]	*m*-Br	H	223(A)	$C_{13}H_{11}BrN_4O_7$	..	..	13.5	13.3	..	..
22[y]	*o*-I	H	257(A)	C_7H_9ClIN	..	..	5.2	5.0	8.45	2.24
HP	*o*-I	H	241(A)	$C_{13}H_{11}IN_4O_7$	..	..	12.1	12.3	..	..
23	*m*-I	H	193–195(A)	C_7H_9ClIN	31.2	31.1	3.4	3.6	8.66	3.5
HP	*m*-I	H	222(A)	$C_{13}H_{11}IN_4O_7$	33.8	34.1	2.4	2.4	..	..
24[z]	*p*-I	H	290(A)	C_7H_9ClIN	..	..	5.2	5.0	8.99	3.75
HP[aa]	*p*-I	H	247–248(A)	$C_{13}H_{11}IN_4O_7$	..	..	12.1	12.0	..	..
			n = 1, R_1 = 3,4-dichlorobenzyl[ab]							
25[ac]	H	C_2H_5	260–265(C)	$C_{16}H_{20}ClN$	..	..	5.4	5.2	8.02	..
26[ac]	2,4-Cl_2	H	198–199(C)	$C_{14}H_{14}Cl_3N$	..	..	4.6	4.9	7.01	..
27[ad]	2,4-Cl_2	CH_3	161–163(C)	$C_{15}H_{14}Cl_5N$	..	..	3.6	4.2	4.33	..
28	H	H	247–251(C)	$C_{14}H_{14}Cl_3N$	..	..	4.6	4.5	7.16	..
29[ae]	H	C_2H_5	245–246(C)	..	..	..	..	..	6.66	..
30	3,4-Cl_2	CH_3	233–235(C)	$C_{15}H_{14}Cl_6N$	46.7	46.7	3.7	3.8	5.30	..
31	3,4-Cl_2	C_2H_5	198–200(C)	$C_{16}H_{16}Cl_5N$	48.1	48.1	4.0	4.3	4.56	..
32	3,4-Cl_2	CH_2=$CHCH_2$	172–175(C)	$C_{17}H_{16}Cl_5N$	..	..	3.4	3.4	3.82	..
33	3,4-Cl_2	*n*-C_3H_7	205–208(D)	$C_{17}H_{18}Cl_6N$	..	..	3.4	3.2	4.32	..
34	3,4-Cl_2	*i*-C_3H_7	222–224(C)	$C_{17}H_{18}Cl_5N$	49.4	49.3	4.4	4.4	4.32	..

No.[a]	X	R₁	M.p., °C.[b](S)[c]	Formula	Analyses, %[d] Carbon Calcd.	Carbon Found	Hydrogen[e] Calcd.	Hydrogen[e] Found	p*Ka*′[f]	p*Ka*′[g] Aniline
				$n = 2$, $R_1 = H$						
35[a,j]	H	H	216–218(A)	..	..	..	..	..	9.38	..
36[a,g]	*o*-Cl	H	141–142(A)	$C_8H_{11}Cl_2N$	..	..	7.3	7.3	9.13	..
HP	*o*-Cl	H	191–192(A)	$C_{14}H_{13}ClN_4O_7$	..	..	14.6	15.0	..	..
37	*m*-Cl	H	170–171(A)	$C_8H_{11}Cl_2N$	50.0	50.3	5.8	5.5	9.13	..
HP	*m*-Cl	H	163(A)	$C_{14}H_{13}ClN_4O_7$	..	..	14.7	14.9	..	..
38[a,h]	*p*-Cl	H	220(A)	$C_8H_{11}Cl_2N$	..	..	7.3	7.2	9.18	..
39	*p*-Br	H	242–243(A)	$C_8H_{11}BrClN$	..	..	5.9	6.4	9.20	..
HP	*p*-Br	H	200–201(A)	$C_{14}H_{13}BrN_4O_7$	..	..	13.1	12.9	..	..
40	*o*-I	H	230–231(A)	$C_8H_{11}ClIN$	..	..	4.9	4.5	9.10	..
HP	*o*-I	H	204–205(A)	$C_{14}H_{13}IN_4O_7$	..	..	11.8	12.1	..	..
41	*m*-I	H	204(A)	$C_8H_{11}ClIN$	..	..	4.9	5.2	9.11	..
HP	*m*-I	H	177–179(A)	$C_{14}H_{13}IN_4O_7$	35.3	35.4	2.8	2.8	..	..
42	*p*-I	H	270(A)	$C_8H_{11}ClIN$	..	..	4.9	5.4	9.19	..
HP	*p*-I	H	189–190(A)	$C_{14}H_{13}IN_4O_7$	35.3	35.5	2.8	2.9	..	..

[a] HP is the picrate of the preceding compound. [b] Melting points (except compounds 30-35) were established on a Fisher–Johns melting point block. The block procedure gave a number of melting points which were not comparable to those cited in the literature. [c] S is recrystallizing solvent: A is propanol-hexane; B, propanol; C, ethanol; D, acetonitrile. [d] Analyses by Weiler and Strauss, Oxford, England. [e] Analytical figures are for nitrogen when shown without corresponding carbon analyses. [f] Established at 0.02 *M* concentration in 50% methanol at 25°. Compounds 26, 28 and 30 were run in 80% methanol. [g] p*Ka*′ values for the corresponding X-substituted aniline from D. H. McDaniel and H. C. Brown, *J. Am. Chem. Soc.*, **77**, 3756 (1955); the p*Ka* values for the aniline analogs of compounds 23 and 24 are from J. M. Vandenbelt, C. Henrich and S. G. Vanderberg, *Anal. Chem.*, **26**, 726 (1954). On p*Ka* values for the anilines, see also A. I. Biggs, *J. Chem. Soc.*, 2572 (1961). [h] A. E. Martell and R. M. Herbst, *J. Org. Chem.*, **6**, 878 (1941), report m.p. 260°. [i] "Handbook of Chemistry and Physics," Chemical Rubber Publishing Co., 1960, p. 158, repor tm.p. 194°. [j] S. Saijo, *J. Pharm. Soc. Japan*, **72**, 1009 (1952), m.p. 265–268°. [k] F. C. Brown, C. K. Bradsher, E. C. Morgan, M. Tetenbaum and P. Wilder, Jr., *J. Am. Chem. Soc.*, **78**, 384 (1956), m.p. 203°. [l] J. v. Braun, M. Kühn and J. Weismantel, *Ann.*, **449**, 249 (1926), m.p. 225°. [m] Ref. 1, m.p. 203°. [n] N. K.

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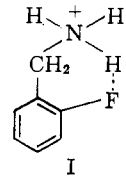
have been interested in work involving such groups,[18] we have determined the p*K*a′ values of a series of such amines. These are set forth in Table I.

In the monohalogenated benzylamines (other than fluoro), the trend relative to benzylamine follows the pattern noted with anilines although no direct resonance interaction between the ring and the functional group can occur because of the insulation provided by the intervening methylene group.[19] The *ortho* substituent has the greatest base weakening effect, the *meta* an intermediate effect, while the *p*-halobenzylamine has virtually the same basicity as the parent amine. It would appear that the predominant influence is an inductive one with a negative field effect[20] prevailing and falling off with distance. The greatest influence is exerted by the iodo group, followed by the bromo and chloro groups.

These trends are somewhat modified with the fluoro substituents and the relatively high basicity of *o*-fluorobenzylamine suggests stabilization of the cation by forms such as I. Unlike the other halogens, *p*-fluorobenzylamine is a somewhat stronger base than the parent amine.



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Introduction of more than one halogen is more base weakening than would be expected from the p*K*a values of the corresponding monosubstituted amines.[21]

N-Methylation of the haloaralkylamine has the anticipated base enhancing effect (about 0.2 p*K*a unit) as the secondary amine is formed. However, with 3,4-dichlorobenzylamine, conversion to the secondary amine with the larger ethyl or propyl groups is associated with a reduction in basicity. For the isomeric 2,4-dichlorobenzylamine, conversion to the secondary N-ethyl-2,4-dichlorobenzylamine gives virtually no enhancement. The corresponding N-isopropyl compound shows the expected increase in basicity over the primary amine while the N-allyl-2,4-dichlorobenzylamine is, as anticipated, a weaker base.[9] The depression in the basicity, noted as the amine becomes increasingly lipophilic[22] with the multiplicity of chlorine atoms, may result from inhibition of the stabilizing influence[23] of solvation.

With the halogenated β-phenethylamines, the critical distinctions between the halogens are lost. Substituents in the *ortho* and *meta* positions afford the same basicity and are 0.1 p*K*a unit less basic than the *para* derivatives which, in turn, are about 0.2 p*K*a unit less basic than the parent amine. This latter observation is probably best rationalized as due to a transannular field effect[22] in the halogenated β-phenethylamine (we are indebted to the referee for this suggestion).

As amines containing two benzyl groups were evaluated, dibenzylamine showed the additive lowering of basicity[6] anticipated from the two benzyl groups. Conversion to the tertiary amine, N-ethyldibenzylamine (25), had the expected base weakening influence. Introduction of halogen to give N-benzyl-2,4-dichlorobenzylamine (26) or N-benzyl-3,4-dichlorobenzylamine (28) decreases basicity by a full p*K*a unit. Conversion of the latter to the N-ethyl tertiary amine has an unexpectedly large effect, decreasing the basicity by another 0.5 p*K*a unit.

The striking influence of dihalobenzyl groups is evidenced by the low basicity (p*K*a′, 4.33) of N-methylbis-(2,4-dichlorobenzyl)-amine. The somewhat less hindered N-methylbis-(3,4-dichlorobenzyl)-amine (30) is more basic by a full p*K*a unit but, as the larger alkyl groups (31–34) are added, the tertiary amines show orders of basicity characteristic of aromatic amines. Also noteworthy is the effect (2 p*K*a

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units) as a benzyl group (29) is replaced to give the compound with two 3,4-dichlorobenzyl groups (31).

The high lipophilic[24] character of the free bases and the noted hydrophobic effect of the salts (many of the hydrochlorides of these weak bases are soluble to the extent of less than 1% in water) would suggest that inhibition of solvation, purportedly a minor factor for tertiary amines,[25] may exist. These properties should significantly alter the physiological penetration of these amines.[26]

With the longer chain aliphatic amines, anomalous pKa values have been ascribed to micelle formation.[27] Aqueous solutions of amines here studied showed no Tyndall effect.

A variety of other tertiary amines in which each substituent is electron-withdrawing gave very low pKa values.[28-30]

Experimental

Materials.—The primary haloaralkylamines and N-methylhaloaralkylamines were obtained through Sapon Laboratories, Lynbrook, N. Y., and Ames Laboratories, South Norwalk, Conn. The amines 13–19 and 25–34 were prepared from the haloaralkyl halide and the R_2 substituted amines in aqueous alkaline acetonitrile.[31]

Methods.—The simplified potentiometric procedure of Grantham[5] was adapted for use in the determination of pKa′ values.[32] Solutions of the hydrochlorides (0.02 molar) were half-neutralized with standard sodium hydroxide in 50% (by volume) of methanol,[5,33] and the pH established at 25°, using a Beckman Model G Glass Electrode pH Meter. The use of 50% methanol as the solvent would provide lower pKa values (lower apparent basicity) than use of water.[33]

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