at the higher temperatures where the least accuracy might be expected. The procedure employed was similar to that described previously.[2] Four thermoregulators, each set at a different temperature, facilitated rechecking of data. The exact temperatures were read from NBS certified thermometers. The densities are shown in Table I.

Determination of Interfacial Tension.—For measuring the interfacial tensions, a modification of the drop-weight method of Harkins and Brown was used.[5] The method involved drop volumes rather than weights because of the greater experimental convenience of the former. The apparatus consisted essentially of a glass spring, a series of glass tips upon which the drops formed, a series of measuring pipettes, a receiving tube, and a device for actuating the spring–pipet system. The experimental procedure was exactly the same as previously described.[3] To test for possible decomposition of the esters, measurements were repeated with the same identical mutually saturated liquids over the same temperature range for three consecutive days. The results were constant.

Results and Discussion

The tables contain the data for the four bromoesters. The empirical temperature–interfacial tension equations were formulated by using the method of least squares. The observed values, from which the empirical equations were determined, were averages of at least five independent measurements for each temperature in the range employed. The interfacial tension values of the esters against water, together with the empirical temperature equations for the temperature range 26.8 to 70.4°, are shown in Table II.

TABLE II

INTERFACIAL TENSIONS OF THE ORGANIC LIQUIDS AGAINST WATER (ERGS./CM.²)

Bromoacetate	Temperature 26.8°	42.6°	55.2°	70.4°
Methyl	13.3 ± 0.28	13.0 ± 0.28	12.3 ± 0.26	11.2 ± 0.26
Ethyl	17.6 ± 0.23	16.7 ± 0.22	16.0 ± 0.22	15.0 ± 0.21
n-Propyl	21.9 ± 0.20	21.3 ± 0.19	20.6 ± 0.16	19.6 ± 0.17
n-Butyl	23.8 ± 0.17	23.3 ± 0.16	22.8 ± 0.16	22.0 ± 0.15

Methyl bromoacetate: $\gamma_i = 13.15 + 0.0249t - 7.63 \times 10^{-4}t^2$

Ethyl bromoacetate: $\gamma_i = 18.72 - 0.0375t - 2.18 \times 10^{-4}t^2$

n-Propyl bromoacetate: $\gamma_i = 22.28 - 1.85 \times 10^{-3}t - 5.10 \times 10^{-4}t^2$

n-Butyl bromoacetate: $\gamma_i = 24.13 - 4.8 \times 10^{-4}t - 4.3 \times 10^{-4}t^2$

From reference to these equations, it is clear that the decrease in the interfacial tensions with temperature is not linear. Since the interfacial tension is influenced by mutual solubility of the respective liquid compounds, and the solubility, in turn, increases with the temperature, departure from linearity is due, at least in part, to the solubility factor.

With the aid of the empirical equations, it was possible to calculate the entropy ($d\gamma/dt$), latent heat (L), and the enthalpy (H) attending the formation of each sq. cm. of interfacial surface over the temperature range employed. The last two of these are shown in Table III.

TABLE III

VALUES OF SOME THERMODYNAMIC PROPERTIES OF THE ESTER–WATER INTERFACES (ERGS./SQ. CM.)

Temp., °C.	Methyl bromoacetate *L*	*H*	Ethyl bromoacetate *L*	*H*	*n*-Propyl bromoacetate *L*	*H*	*n*-Butyl bromoacetate *L*	*H*
26.8	4.8	18.1	14.8	32.4	8.8	30.7	7.1	30.9
42.6	12.7	25.6	17.7	34.4	14.3	35.6	11.8	35.1
55.2	19.5	31.8	20.2	36.2	19.1	39.7	15.8	38.6
70.4	28.4	39.7	23.4	38.4	25.4	45.0	21.0	43.0

For a saturated surface the latent heat L is related to the temperature coefficient by the equation, $L = -T(d\gamma/dt)$. Thus, L may have either a positive or a negative value. Since the interfacial tensions of the bromoesters have negative temperature coefficients, the corresponding values of L are positive, indicating that energy is utilized in the formation of the interface. The entropy, and also the temperature derivative of the latent heat, is positive.

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(5) A. Weissberger, ref. 4, p. 172.

[CONTRIBUTION FROM THE COBB CHEMICAL LABORATORY OF THE UNIVERSITY OF VIRGINIA]

Dissociation Constants of Adrenergic Amines[1]

BY ESTHER B. LEFFLER,[2] HUGH M. SPENCER AND ALFRED BURGER

Basic dissociation constants of a representative group of twenty-seven adrenergic amines have been determined. No obvious correlation between pressor activity and basicity has been found.

An attempt to correlate pharmacodynamic and electropolar properties might shed some light on the mode of action of adrenergic amines. We are reporting basic dissociation constants for twenty-seven adrenergic amines as a contribution to this question.

Experimental

Most of the compounds used in this study were kindly supplied by Smith, Kline and French Laboratories, Philadelphia, Pa.; six were obtained from Sterling-Winthrop Research Institute, Rensselaer, N. Y. Most of them were in the form of salts. Free bases were converted into the hydrochlorides by neutralization of an ethereal solution of the amine. The salts were recrystallized from absolute ethanol, precipitating with absolute ether, unless otherwise noted. The compounds were considered to be sufficiently pure when they had been recrystallized to constant melting point, and their analyses agreed with the calculated values.

The apparent dissociation constants of the amines were determined by measuring the *p*H of a solution containing equivalent concentrations of the amine and its salt. These solutions were obtained by adding to a solution of the salt the calculated amount of sodium hydroxide solution required for half-neutralization. The concentrations ranged from 0.0003–0.001 molal in salt and free base at the half-neutralization point. The *p*H values were measured with a hydrogen electrode or a *p*H meter. With the several com-

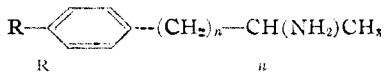
(1) Part of a dissertation presented to the Graduate Faculty of the University of Virginia by Esther B. Leffler in partial fulfillment of the requirements for the degree of Doctor of Philosophy, May, 1950.

(2) Philip Francis du Pont Senior Fellow, 1947–1948. Department of Chemistry, Randolph-Macon Women's College, Lynchburg, Virginia.

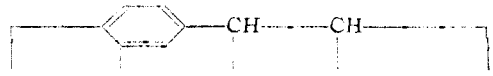
TABLE I

DISSOCIATION CONSTANTS AND PRESSOR ACTIVITIES

No.	Structure	Salt and name	pK_b	Pressor activity[a]
1[b,c]	$C_6H_{11}CH_2CH(NHCH_3)CH_3$	HCl	3.48	333,[d] 500[e]
2[b]	$(CH_3)_2CH(CH_2)_3CH(NH_2)CH_3$	HCl	3.72	500–1000[d]
3[b]	$C_6H_{11}CH_2CH(NH_2)CH_3$	HCl	3.86	200[f]
4	$C_5H_{11}CH(OH)C(NH_2)(CH_3)_2$	HCl	4.15	No data



R	n						
5[g]	H	3				HCl	4.01	No data
6	H	2				Sulfate	4.21	1500[d,h]
7[g]	OH	3				HBr	4.60	No data
8	OH	2				HBr	4.86	No data



9	H	H	CH_2	$NHCH_3$	H	Vonedrine·HCl	4.12	620,[i] 250[j]
10	H	H	H	$NHCH_3$	CH_3	HCl	4.13	500–1000[k]
11	H	H	H	NH_2	H	Phenethylamine·HCl	4.17[l]	80–250[k] 115,[d] 183[m]
12	OCH_3	OCH_3	H	$NHCH_3$	CH_3	HBr	4.19	No data
13[g]	H	H	H	NH_2	CH_3	Amphetamine sulfate	4.23	200–250[k] 100–200[m] 325,[d] 425[n] 420°
14	O–CH_2–O		H	NH_2	CH_3	HCl	4.33	100[n]
15[g]	OCH_3	OCH_3	H	NH_2	CH_3	HCl	4.40	No data
16	H	H	OH	$NHCH_3$	CH_3	Ephedrine·HCl	4.42	143–133[k] 250[n]
17[g]	OCH_3	H	H	NH_2	CH_3	HCl	4.47	3000[q]
18[g]	H	H	H	$N(CH_3)_2$	CH_3	HCl	4.60	1000[r]
19[s]	OH	H	H	NH_2	CH_3	Paredrine·HBr	4.69	50–100[d]
20	H	H	NH_2	H	H	Sulfate	4.92	1000[d]
21[t]	OH	H	OH	$NHCH_3$	H	Sympatol tartrate	5.10	25–100[k] 94[d],118[n]
22	H	OH	OH	$NHCH_3$	H	Neosynephrine·HCl	5.14	5–10[k] 4[d]
23	OH	H	OH	NH_2	CH_3	HCl	5.30	50[u], 100[v]
24[w]	OH	OH	OH	NHC_3H_7	H	Isuprel·HCl	5.43	No data
25[w]	OH	OH	OH	$NHCH_3$	H	Epinephrine·HCl	5.50	1[k] Depressor
26[w]	OH	OH	OH	NH_2	CH_3	Cobefrin·HCl	5.55	4[k], 5[d] 12[n]
27[w]	OH	OH	OH	NH_2	CH_2CH_3	Butanephrine·HCl	5.58	Depressor[d]

[a] Amount equivalent to unit dose of epinephrine. [b] Accuracy ±0.1 pK unit. [c] Alcohol solutions. [d] Smith, Kline and French Laboratories, Philadelphia, Pa., unpublished data. [e] D. F. Marsh, unpublished ms., 1948. [f] E. Rohrmann and H. A. Shonle, THIS JOURNAL, **66**, 1516 (1944). [g] Accuracy ±0.05 pK unit. [h] V. Larsen, *Skand. Arch. Physiol.*, **79**, 282 (1938). [i] M. R. Warren, *J. Pharmacol. Exptl. Therap.*, **79**, 187 (1943). [j] B. E. Graham and G. F. Cartland, *ibid.*, **81**, 360 (1944). [k] Eli Lilly Co., *Research Today*, **4** (1), 71 (1947). [l] *Cf.* W. H. Carothers, C. F. Bickford and G. J. Hurwitz, THIS JOURNAL, **49**, 2908 (1927). [m] G. A. Alles, *J. Pharmacol. Exptl. Therap.*, **47**, 339 (1933); **48**, 161 (1933). [n] W. H. Hartung, *Ind. Eng. Chem.*, **37**, 126 (1945). [o] J. M. Crisman and M. L. Tainter, *J. Pharmacol. Exptl. Therap.*, **64**, 190 (1938). [p] J. A. Gunn, M. R. Gurd and I. Sachs, *J. Physiol.*, **95**, 485 (1939). [q] B. E. Graham, G. F. Cartland and E. H. Woodruff, *Ind. Eng. Chem.*, **37**, 149 (1945). [r] A. N. Novelli and M. L. Tainter, *J. Pharmacol. Exptl. Therap.*, **77**, 324 (1943). [s] Recrystallized from ethanol–methyl ethyl ketone. [t] Recrystallized from 75% ethanol. [u] K. K. Chen, C.-K. Wu and E. Henriksen. *J. Pharmacol. Exptl. Therap.*, **36**, 363 (1929). [v] W. H. Hartung, J. C. Munch, E. Miller and F. Crossley, THIS JOURNAL, **53**, 4154 (1931). [w] Decomposes in aqueous solution.

pounds which were determined in both ways, good agreement was found between the two methods.[3]

The hydrogen electrode was used with a saturated calomel electrode. The latter was contained in a six-ounce wide-mouth bottle and was connected by agar–KCl bridges through a reservoir of saturated KCl solution to another six-ounce bottle. This latter bottle contained the base-salt solution and was fitted with a buret and a Hildebrand-type hydrogen electrode. Commercial tank hydrogen was purified in the standard way by passing it through potassium permanganate solution, alkaline pyrogallol and sulfuric acid.[4] The whole cell was immersed in a water-bath at 25 ± 0.2°. The calomel electrode was checked every day on which the apparatus was used with a saturated solution of potassium hydrogen tartrate which has a pH of 3.57 ± 0.02 at 25°.[5]

(3) N. F. Hall and M. R. Sprinkle, THIS JOURNAL, **54**, 3469 (1932).

(4) I. M. Kolthoff and H. A. Laitinen, "pH and Electrotitrations," 2nd ed., John Wiley and Sons, Inc., New York, N. Y., 1944, p. 90.

(5) J. J. Lingane, *Ind. Eng. Chem., Anal. Ed.*, **19**, 810 (1947).

Results were rejected if E_0 varied more than ±0.002 from the theoretical value of 0.2441 volt.[6]

The *p*H meter was a Beckman model G used with external electrodes. The solutions were not thermostated; instead, the temperature was measured and corrected to 25° according to Hall and Sprinkle[3] who found that for amines of the strength pK_b 6–4, the *p*H decreases linearly with increasing temperature and that the decrement is 0.02 *p*H unit per degree. The results are presented in Table I.

For one compound (no. 1), which was insufficiently soluble in water, ethanol–water solutions of the amine salt were made up to contain various percentages of ethanol at half-neutralization. The *p*H in water alone was obtained by extrapolation.[3]

Four of the compounds studied (no. 24, 25, 26 and 27) decompose in aqueous solution, so that it was necessary to measure the *p*H with the meter as soon as possible. Solutions of these compounds had already become discolored by the time the measurements were finished. The *p*H decreased on standing.

The results are estimated to be accurate to ±0.02 pK unit, except for (a) no. 5, 7, 13, 15, 17 and 18 which are estimated to be accurate to ±0.05 pK unit, and (b) no. 1, 2 and 3 for which an accuracy of no greater than ±0.1 pK unit is claimed because of insufficient solubility of the free base.

Discussion

Basicity and Structure.—In all three cases where a direct comparison is possible, secondary amines are more basic than primary (no. 1 and 3, 10 and 13 and 12 and 15). The magnitudes of the negative inductive effect caused by N-methyl substitution are roughly the same: the ΔpK values are 0.4, 0.1 and 0.2, respectively. These results are in agreement with studies on aliphatic amines[3] in which the order is $(CH_3)_2NH > CH_3NH_2 > (CH_3)_3N > NH_3$. This order is also followed by the one tertiary amine, no. 18.

Replacement of N-methyl by N-isopropyl (no. 24 and 25) results in a slight increase in basicity, as would be expected if alkyl groups exert a negative inductive effect which increases with branching, but steric hindrance probably also plays a part.

The introduction of a hydroxyl group in the beta position lowers the basicity because of its negativity. In the one available series (no. 3, 17 and 19) the hydroxyl group is more negative than the methoxyl. This would be expected, but such is not the case with the corresponding benzoic acids.[7]

The effect of the phenyl group on basicity may be shown in two ways: First, in two cases where a direct comparison has been possible in this investigation, substitution of the phenyl group on the carbon beta to the amino group lowers the basicity by the same amount. The results for no. 11 and 13 show that such substitutions in ethylamine and in isopropylamine increase pK_b by 0.84 and 0.86, respectively (pK_b = 3.33 and 3.37 for ethylamine and isopropylamine, respectively[3]). Second, replacement of cyclohexyl by phenyl (no. 3 and 13 and 1 and 10) brings about decreases in basicity of 0.37 and 0.65 pK unit.

Basicity and Adrenergic Activity.—It is of interest to compare basicity values with current conclusions about relations between structure and physiological activity in the adrenergic amines.[8] First, optimum pressor activity is found when the phenyl group is beta to the amino group; the basicity data indicate that the phenyl group seems to exert the least effect at this position. Second, alcoholic hydroxyl groups often lengthen activity, and they also lower the basicity. Two examples of correspondence between high activity and low basicity are shown in the primary amines as opposed to secondary amines, and in the effect of phenolic hydroxyl groups. On the other hand, tertiary amines are less basic than primary amines and are also less active.

In at least four other series of compounds, no correlation between activity and basicity has been found: the bacteriostatic activity of sulfanilamide type compounds[9] and of long-chain aliphatic amines,[10] the analgesic properties of morphine derivatives[11] and the histamine activity of beta-aminoethyl heterocyclic nitrogen compounds.[12] It might be concluded that basicity *per se* is not a criterion of physiological activity in certain groups of compounds. On the other hand, a correlation has been found between bacteriostatic activity and basicity of aminoacridines.[13]

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(6) D. I. Hitchcock, "Physical Chemistry," 3rd ed., Charles C Thomas, Baltimore, Md., 1940, p. 123.

(7) J. F. J. Dippy, *Chem. Rev.*, **25**, 151 (1939).

(8) G. L. Jenkins and W. H. Hartung, "Chemistry of Organic Medicinal Products," 2nd ed., John Wiley and Sons, Inc., New York, N. Y., 1943, p. 274.

(9) P. H. Bell and R. O. Roblin, THIS JOURNAL, **64**, 2914 (1942).

(10) E. T. Borrows, B. M. C. Hargreaves, J. B. Page, J. C. L. Resuggan and F. A. Robinson, *J. Chem. Soc.*, 197 (1947).

(11) F. W. Oberst and H. L. Andrews, *J. Pharmacol.*, **71**, 38 (1941).

(12) H. M. Lee and R. G. Jones, *J. Pharmacol. Exptl. Therap.*, **95**, 71 (1949).

(13) A. Albert, R. J. Goldacre and S. D. Rubbo, *Nature*, **147**, 332, 709 (1941); **161**, 95 (1948).