mides cannot be ascribed to reaction of bromine with impurities.

This method of detecting and identifying free rad cals should be widely applicable in both liquid and gaseous systems. Iodine and bromine have their respective advantages, both chemically and radiochemically. The interpretation of the results of these experiments must await the accumulation of further data.

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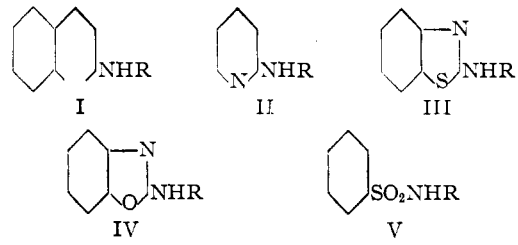
Certain Heterocyclic and Benzenesulfonyl Derivatives of γ-Diethylaminopropylamine[1]

BY MARTIN J. WEISS[2] AND CHARLES R. HAUSER

Various 2-methoxy-6-chloro-9-alkylaminoacridine derivatives having variations in the side chain[3] have been found to exhibit antitubercular activity. Since the derivative having the γ-diethylaminopropylamine side chain was one of the most active,[4] we have attached this side chain to several other heterocyclic nuclei and to the benzenesulfonyl group to form compounds I–V, R = $-(CH_2)_3N(C_2H_5)_2$. Although none of these compounds showed antitubercular activity under the conditions employed with the acridine,[4] their syntheses seemed worthy of reporting.



Compounds I to IV inclusive were prepared by heating halogen derivatives of the appropriate heterocyclic compounds with two molecular equivalents of γ-diethylaminopropylamine in the absence of a solvent. The extra equivalent of the diamine served to neutralize the hydrogen halide formed in the coupling reaction. The results are summarized in Table I. An attempt to couple 2-bromothiophene with the diamine was unsuccessful. Compound (V) was prepared from benzenesulfonyl chloride and the diamine in pyridine.

Compound (II) was prepared by Whitmore and co-workers[5] by heating a pyridine solution of 2-bromopyridine and the diamine in a sealed tube. Compound (III) has also been reported previously but no yield was given.[6]

TABLE I

COUPLING OF γ-DIETHYLAMINOPROPYLAMINE WITH HALOGEN COMPOUNDS

Halogen compound	Time, hr.	Product	B. p.[a] °C.	Mm.	Yield, %	Picrate M. p., °C.
2-Chloroquinoline	8[b]	2-(γ-Diethylaminopropylamino)-quinoline (I)	181–185	2	49	*ca.* 280[c] dec.
2-Bromopyridine[d]	6[b]	2-(γ-Diethylaminopropylamino)-pyridine (II)	136–138[e]	3.5	68	165–166[f]
2-Chlorobenzothiazole	4[g]	2-(γ-Diethylaminopropylamino)-benzothiazole (III)	216–218	6.5	85	195–196[h]
2-Chlorobenzoxazole	3.5[g]	2-(γ-Diethylaminopropylamino)-benzoxazole (IV)	170	1.5	71	168–169[i]

[a] The boiling points listed were obtained on redistillation of the product; the yield is based on the product obtained after the initial distillation. [b] At refluxing temperature. [c] After six recrystallizations from a mixture of methyl cellosolve and isopropyl ether, followed by several washings with ethyl ether. *Anal.* Calcd. for $C_{22}H_{26}N_6O_7$: C, 54.31; H, 5.39. Found: C, 54.55; H, 4.96. [d] Only 0.063 mole of 2-bromopyridine and 0.127 mole of diamine were used. [e] Reported b. p. 105–107° at 0.8 mm.[5] [f] After five recrystallizations from a mixture of methyl cellosolve and isopropyl ether; reported m. p. 163.5–164°.[5] [g] This reaction was carried out in a bath maintained at about 120°. [h] After one recrystallization from dioxane; reported m. p. 195–197°.[6] [i] After four recrystallizations from a mixture of acetone and isopropyl ether. The substance analyzed correctly for the dipicrate. *Anal.* Calcd. for $C_{26}H_{27}N_9O_{15}$: C, 44.26; H, 3.86. Found: C, 43.94; H, 3.64.

Experimental[7]

Compounds I–IV (Table I).—The halogen compound (0.10 mole) and γ-diethylaminopropylamine (0.20 mole) were mixed in the absence of a solvent and heated. With the highly reactive 2-chlorobenzoxazole, the diamine was added dropwise to the halogen compound. After the reaction had been allowed to cool to room temperature, it was poured into a potassium carbonate solution. The mixture was extracted several times with ether and the combined ether extracts were dried over Drierite. The solvent was removed and the residue was distilled *in vacuo* through an 11-cm. Vigreux column and then redistilled. Since 2-(γ-diethylaminopropylamino)-quinoline is not very soluble in ether, extraction with ether gave three layers. The aqueous layer was separated from the two organic layers, which were made homogeneous by the addition of commercial absolute ethanol. The ether–ethanol solution was then treated as above.

N-(γ-Diethylaminopropyl)-benzenesulfonamide (V).—To a solution of 13.0 g. (0.10 mole) of γ-diethylaminopropylamine in 50 ml. of anhydrous pyridine was slowly

(1) Paper II on antitubercular drugs; paper I, THIS JOURNAL, **70**, 4020 (1948).

(2) Eli Lilly Fellow, 1947–1948; present address: Hickrill Chemical Research Foundation, Katonah, New York.

(3) These compounds were prepared as potential antimalarial drugs; see Breslow, Walker, Yost, Shivers and Hauser, THIS JOURNAL, **68**, 100 (1946), and earlier papers.

(4) This compound showed antitubercular activity at a minimum dosage of 0.02 mg. per 10 ml. of culture, when tested by an *in vitro* method carried out at the laboratories of Eli Lilly and Company, Indianapolis, Indiana, using avirulent human strain no. 599 organism.

(5) Whitmore, Mosher, Goldsmith and Rytina, THIS JOURNAL, **67**, 393 (1945).

(6) Tsuda, Sakamoto, Mutsuda and Kanno, *J. Pharm. Soc. Japan*, **462** (1940); German abstract, p. 184.

(7) Analyses by the Clark Microanalytical Laboratories, Urbana, Illinois.

added 17.6 g. (0.10 mole) of benzenesulfonyl chloride. The solution was refluxed six hours and poured into ice-water. The precipitated white solid was filtered, washed with water and recrystallized from ethanol–water to give 17.2 g. (64%) of N-(γ-diethylaminopropyl)-benzenesulfonamide, melting at 75–77°. Additional recrystallizations from ethanol–water gave fine white crystals melting at 77–78°.

Anal. Calcd. for $C_{13}H_{32}N_2O_2S$: C, 57.74; H, 8.20; N, 10.36. Found: C, 57.43; H, 7.72; N, 10.49.

DEPARTMENT OF CHEMISTRY
DUKE UNIVERSITY
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Dissociation Constants of Higher Alkyl Phosphate Esters, Phosphonic Acids, Phosphonous Acids, Phosphinic Acids and Carboxylic Acids

BY J. R. WHITE

The dissociation constants in 50% by weight ethanol in water at 25° have been determined for the acids: benzoic, palmitic, oleic; mono-*n*-dodecyl ester of cyclohexene-3-1,6-dicarboxylic, 2-ethylhexanoic, di-*n*-decylphosphoric, di-*n*-dodecylphosphoric, mono-*n*-decylphosphoric, dodecanephosphonic, dodecanephosphonous and di-2-ethylhexylphosphinic. Measurements were made with a non-thermodynamic cell of the type

Glass electrode Beckman 1190E	KA HA ethanol (50% by wt.), H_2O (50% by wt.)	‖	Satd., KCl	Hg, Hg_2Cl_2

and employing a Beckman model G potentiometer. An e. m. f.–p_aH function in water solutions was established experimentally for each of several electrode systems by measuring the buffer solutions to which the p_aH values recommended by Bates, Hamer, Manov and Acree were assigned.[1]

$HKC_8H_4O_4$ (acid potassium phthalate) (0.05 molal)	$p_aH = 4.008$
KH_2PO_4 (0.02877*m*), Na_2HPO_4 (0.01834 *m*), NaCl (0.02877*m*)	$p_aH = 6.640$
$Na_2B_4O_7$ (0.006045*m*), NaCl (0.01210*m*)	$p_aH = 9.165$

The electrode systems were then regarded as establishing a similar e. m. f.–p_aH function in the aqueous ethanol solutions. Hydrogen ion activities in the aqueous ethanol solvent have thus been referred experimentally to a standard activity scale in water. Other ion and undissociated acid activities have been referred to a standard state of unit molarity with unit molar activity coefficients in the aqueous ethanol solvent. The resulting dissociation constants are essentially the "reduced" constants of Michaelis and Mizutani,[2] differing in the electrode system chosen to secure experimental reference with the hydrogen ion activity scale in water. pK' values computed on the molar scale have been converted to the molal scale by adding log $d(= -0.04)$, where d is the density of the aqueous ethanol solvent.

(1) Bates, Hamer, Manov and Acree, *J. Research Natl. Bur. Standards*, **29**, 183 (1942).

(2) Michaelis and Mizutani, *Z. physik. Chem.*, **116**, 135 (1925).

Uncertainties in the use of glass electrode liquid junction cells particularly when one electrode is responding to activity changes in the solvent[3] have been frequently discussed[4] and need not here be repeated. Justification for such a cell may derive from ready convenience and comparison of pK' values obtained with those from other cells. The pK' values for the series of acids here reported showed no systematic variance with particular electrode pairs; the pK' value obtained for benzoic acid is in excellent accord with the value Speakman[5] reported with a similar glass electrode cell and in good accord with the pK' value Michaelis and Mizutani obtained with a hydrogen electrode; Speakman found a pK value only 0.2 unit lower with a thermodynamic cell.

For the monobasic acids, pK' values were computed from the relation

$$pK' = p_aH + \log \frac{C_{HA}}{C_{A^-}} + \log \frac{y_{HA}}{y_{A^-}} \qquad (1)$$

where the C's refer to molar concentrations and the y's to molar activity coefficients. y_{HA} has been taken as unity and y_{A^-} has been evaluated from the limiting law expression

$$-\log y_{\pm} = S\,\Gamma^{1/2} \qquad (2)$$

where Γ is the ional concentration and S has the value of 0.71 for uni-univalent electrolytes in a solvent of dielectric constant 50. While (2) cannot with full justification be applied to a single ionic species, its application results in correction terms, log y_{HA}/y_{A^-}, not greater than 0.05.

TABLE I

DISSOCIATION CONSTANTS IN 50% (BY WT.) AQUEOUS ETHANOL 25° (MOLAL SCALE)

Acid	No.[a]	pK'_1[b]	Concn., mM.
Benzoic	8	5.87 ± 0.02[c]	0.7–2
Palmitic	8	6.46 ± 0.06	0.8–1.5
Oleic	5	6.42 ± 0.05	1–2
Monododecyl ester of cyclohexene-3-1,6-dicarboxylic	6	6.53 ± 0.08	0.7–1.5
2-Ethylhexanoic	5	6.74 ± 0.01	1–2
Di-*n*-decyl ester of orthophosphoric	7	3.28 ± 0.08	0.4–3
Di-*n*-dodecyl ester of orthophosphoric	7	3.40 ± 0.07	0.5–1
Mono-*n*-decyl ester of orthophosphoric	5	3.59 ± 0.13[d]	1.5–6
Dodecanephosphonic	6	4.22 ± 0.04[e]	1.7–4
Dodecanephosphonous	3	3.58 ± 0.06	1–4
Di-2-ethylhexylphosphinic	6	5.51 ± 0.03	0.9–4

[a] No. of determinations. [b] Average deviation. [c] Ref. 5, 5.87, glass electrode cell, 20°; 5.65, silver, silver chloride quinhydrone cell, 20°. Ref. 2, 5.78, H_2-electrode (interpolated value), 19°. [d] $pK'_2 = 8.75 \pm 0.16$. [e] $pK'_2 = 9.81 \pm 0.12$.

(3) Dole, "The Glass Electrode," John Wiley and Sons, Inc., New York, N. Y., 1941, p. 141.

(4) Dole, *ibid.*, p. 105; Manov, De Lollis and Acree, *J. Research Natl. Bur. Standards*, **34**, 115 (1945); Bates, *Chem. Revs.*, **42**, 1 (1948).

(5) Speakman, *J. Chem. Soc.*, 270 (1943).