

Synthesis of Alkyl Amino Alkanol Esters of *p*-Ethoxy Benzoic Acid

By F. F. MILLIKAN and A. E. WADE

A series of eight alkyl amino alkanol esters of *p*-ethoxy benzoic acid were prepared having hydrogen, methyl, ethyl, isopropyl, butyl, *t*-butyl, benzyl, and benzylmethyl groups so attached to give a secondary nitrogen in five of the compounds. Some physical properties were determined for comparative purposes in connection with the pharmacological studies.

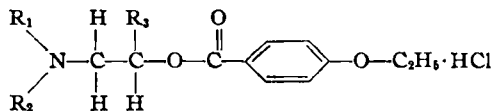
EARLY WORK in the field of local anesthetics established that these compounds were composed of three parts: (a) an acid portion, generally a derivative of benzoic acid, (b) an alkyl chain, and (c) a basic nitrogen group. This combination is achieved by the esterification of the appropriate acid with an amino alcohol, usually a dialkyl alcohol. Of the various acids employed for the acid portion (a) of the local anesthetic molecule, derivatives of *p*-ethoxy benzoic acid have exhibited satisfactory pharmacological activity. Some of these derivatives have been patented and are currently being used clinically (1). With this data in mind, the synthesis of some derivatives of *p*-ethoxy benzoic acid have been prepared for pharmacological studies. The compounds and their physical properties (given in Table I) were prepared

amine (VII); and benzylmethylethanolamine (VIII).

Esters.—A slight modification of the method described in Mannich's patent (2) was used to prepare the esters. In this work the alcohols (0.05 *M*) were dissolved in a volume of chloroform that equaled the weight of the particular alcohol; this cooled solution was added slowly dropwise to a solution of the acid chloride (0.05 *M* + 10% excess) in a volume of chloroform equal to its weight. The mixture was maintained at 0° throughout the reaction.

After all alcohol was added, the reaction mixture was allowed to stand for about 15 hours. This mixture was then heated for 2 hours at 45–50°, after which the solvent was removed under reduced pressure without heat. The residue in the flask was treated with dry ether and those which were

TABLE I.—DATA FOR THE ESTERS PREPARED



Ester	Substituent Groups			M. p., °C. ^a	pH ^b 1% Solution	0.03 <i>M</i> , pH	Surface ^c Tension, 1% Dynes/cm.	Yield
	R ₁	R ₂	R ₃					
I	CH ₃	H	H	165.0	5.65	5.6	61.7	50.0
II	CH ₃	CH ₃	CH ₃	170.0	4.50	5.4	59.2	91.0
III	C ₂ H ₅	H	H	157.0	5.80	5.5	59.6	19.9
IV	iso C ₃ H ₇	H	H	212.0	6.65	5.6	60.18	31.0
V	<i>n</i> -C ₄ H ₉ ^d	H	H	140 to 141.0	4.80	5.3	48.4	23.1
VI	<i>t</i> -C ₄ H ₉	H	H	222.0	4.80 ^e	^e	^c	29.0
VII	Benzyl	H	H	178 to 177.0	5.05	5.05	60.9	23.0
VIII	Benzyl	CH ₃	H	168.5 to 170.0	4.40	4.40	53.1	70.0

^a Fisher-Johns uncorrected. ^b Beckman pH meter model G. ^c Solubility did not permit 1% solution. ^d Prepared originally, U. S. pat. 2,372,116(1945). ^e Fisher model 20 DuNouy tensiometer.

from secondary and tertiary amino alcohols by esterification with *p*-ethoxy benzoyl chloride.

EXPERIMENTAL

Acid Chloride.—*p*-Ethoxy benzoic acid and excess thionyl chloride were refluxed for 3 hours. The residue remaining after removal of last traces of sulfur dioxide, hydrogen chloride gas, and excess thionyl chloride, was distilled. The portion boiling at 128–130°/6 mm. was collected.

Alkyl Amino Alkanols.—The following alcohols¹ were used: methylethanolamine (I); 1-dimethylamino-2-propanol (II); ethylethanolamine (III); isopropylethanolamine (IV); *n*-butylethanolamine (V); *t*-butylethanolamine (VI); benzylethanol-

oily to semisolid solidified with stirring. This solid material was collected, washed with dry ether, dissolved in isopropyl alcohol, and heated (not boiled) with Darco. The crystals forming after removal of carbon were then further purified by recrystallization from isopropyl alcohol.

DISCUSSION

The first pH values using a 1% w/v solution showed little relationship to each other when plotted against molecular weight. However, a 0.03-*M* solution of those compounds having a secondary nitrogen, except for Compound IV, gave a straight line when the pH was plotted against milligrams of chemical per 100 ml. (Fig. 1). The graph showed that the pH decreased in value as the molecular weight increased.

The ultraviolet absorption maximum of the esters as hydrochlorides (5 × 10⁻⁵ *M*) in water using a Beckman DU spectrophotometer occurred at 260 mμ (Fig. 2). The absorption peak of *p*-

Received May 9, 1963, from the School of Pharmacy, University of Georgia, Athens.

Accepted for publication July 29, 1963.

The authors acknowledge the financial support from the University of Georgia Research budget.

¹ The authors thank the following companies for the alcohols: I, II, III, IV, and V, Fensselt Chemical Corp.; VI, Rohm and Haas, VII and VIII, Sumner Chemical Co.

TABLE II.—ANALYTICAL DATA FOR ESTERS

Compd.	C		H		N		HCl		
	Found	Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.	
I	55.75	55.46	6.91	6.98	5.44	5.39	13.77	14.07	C ₁₂ H ₁₇ NO ₃ ·HCl
	55.68		6.71		5.38		13.79		
II	58.45	58.40	7.53	7.71	4.97	4.86	12.68	12.67	C ₁₄ H ₂₁ NO ₃ ·HCl
	58.55		7.47		4.81				
III	57.12	57.01	7.29	7.36	5.19	5.11	13.21	13.33	C ₁₃ H ₁₉ NO ₃ ·HCl
	57.17		7.27		5.02				
IV	58.31	58.40	7.95	7.71	4.81	4.86	12.66	12.67	C ₁₄ H ₂₁ NO ₃ ·HCl
	58.26		7.62		5.09				
V	59.59	59.66	7.76	8.01	4.73	4.64	11.82	12.08	C ₁₅ H ₂₃ NO ₃ ·HCl
	59.73		8.01		4.58				
VI ^a	59.98	59.66	7.85	8.01	4.68	4.64	11.82	12.08	C ₁₆ H ₂₂ NO ₃ ·HCl
VII	64.22	64.35	6.67	6.60	4.38	4.17	10.46	10.85	C ₁₃ H ₂₁ NO ₃ ·HCl
	64.18		6.39		4.12				
VIII	65.03	65.21	6.75	6.91	3.89	4.00	10.42	10.42	C ₁₉ H ₂₉ NO ₃ ·HCl
	64.88		6.64		4.04				

^a Insufficient sample for check analysis.

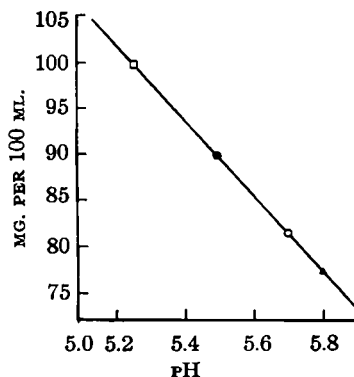


Fig. 1.—Plot of pH values vs. 0.03 *M* solution milligrams per 100 ml. Key: Δ , β -methylaminoethyl-*p*-ethoxybenzoate HCl (I); \circ , β -ethylaminoethyl-*p*-ethoxybenzoate HCl (III); \bullet , β -*n*-butylaminoethyl-*p*-ethoxybenzoate HCl (V); and \square , β -benzylaminoethyl-*p*-ethoxybenzoate HCl (VII).

ethoxy benzoic acid (5×10^{-5} *M*) in isopropyl alcohol came at 255 $m\mu$. The alcohol of Compound VII (5×10^{-5} *M*) in isopropyl alcohol gave an absorbance reading of 0.40 at 205 $m\mu$; the absorbance dropped rapidly before reaching 220 $m\mu$, and at 230 $m\mu$ approached zero and remained there. The alcohol in Compound VII contained a benzyl group; since it did not change the general curve, it may be assumed that the alcohols just shift the maximum peak toward the longer wavelength. The shoulder or irregularity in the curve between

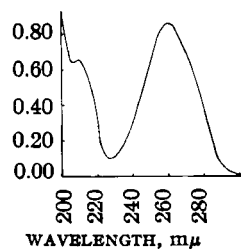


Fig. 2.—General curve which all compounds followed.

200 and 215 $m\mu$ may be due in part to the alcohol portion of ester. Six of the compounds had a molecular extension coefficient of 17,200, and Compounds V and IV had values of 17,100 and 17,800, respectively.

The surface tension results seem to follow the observations of Weiser (3) that the surface tension of water is lowered most strongly by organic compounds with a long chain of carbon atoms or with one or more benzene rings. The values obtained indicate that the substituent groups on the nitrogen influence the surface tension more than the benzoic acid group does.

REFERENCES

- (1) Christiansen, W. G., and Harris, S. E., U. S. pat. 2,404,691(1946); 2,412,966(1946); 2,415,235(1947). Christiansen, W. G., and Chase, G. O., U. S. pat. 2,444,395(1948). Pierce, J. S., Salsbury, J. M., and Fredericksen, J. M., U. S. pat. 2,372,116(1945).
- (2) Mannich, C., U. S. pat. 1,889,678(1932).
- (3) Weiser, H. B., "Colloid Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1939, p. 15.

Modified U.S.P. Tablet Disintegration Apparatus

By LEONARD L. KAPLAN

IN AN EARLIER REPORT (1) a modification of the U.S.P. tablet disintegration apparatus was described which creates more uniform attrition on all sides of the test tablet surfaces and serves to obviate the need for the disks in tablet disintegration testing.

Received June 3, 1963, from Walker Laboratories, Mount Vernon, N. Y.
Accepted for publication July 17, 1963.

The modification consists of a thin flexible insert placed inside the glass tubes of the apparatus at the lower end in contact with the bottom stainless steel wire cloth. The dimensions of this insert are external diameter 21.5 mm., internal diameter 15 mm., wall thickness 3.25 mm., and insert thickness 3.5 mm. The U.S.P. XVI specifies a basket rack assembly consisting of six open glass tubes,