less electron-withdrawing than the *p*-methylsulfonyl group,[20] but the introduction of a 4-nitro group causes a change in the electronic character which is entirely unexpected on the basis of additive inductive effects. Thus, while the 4-nitro group causes an increase in the σ-constants of the *p*-phenylmercapto and *p*-phenylsulfinyl groups, the opposite effect is observed in the *p*-phenylsulfonyl substituent. This phenomenon can be explained by the application of the hypothesis[4] that the presence of the 4-nitro group in the phenylsulfonyl substituent causes a greater double bond character in the sulfur–oxygen bonds; the consequently smaller positive charge at the sulfur atom exerts a smaller electron-withdrawing effect on the benzoic acid moiety. A similar but understandably smaller effect is caused by a 4-carboxy group. The relative acidity of the benzoic acid containing the *p*-(4-aminophenylsulfonyl) substituent indicates that, regardless of which electronic structure of the sulfone is preferred, the large +E effect of the amino group is the governing factor.

The value of the σ-constant of the *p*-methylsulfonyl group was shown by Bordwell and Andersen[26] to increase proportionally with the influence which resonance interactions exert on the species in a given equilibrium. Thus, the value increases sharply when one proceeds from the benzoic acid to the phenol series, and an additional rise is observed in the substituted anilines. The same trend is found in the case of the *p*-phenylsulfonyl group (Table III).

The results listed in Table II show that the variation in the relative acidities of *p*-arylsulfonylphenols is of the same magnitude as that found in the corresponding benzoic acids. The effect of the substituents seems to be in line with the recognized fact that the phenol equilibrium is governed by the resonance stabilization of the phenolate ion. Electron-releasing substituents are believed to favor sulfone structure I but, on the other hand, they compete with the resonance of the phenoxide portion. Contrary to its effect in the benzoic acid series, the *p*-nitro substituent causes an increase in the relative acidity of the phenol. This may be interpreted in terms of increased resonance possibilities in the anion of a phenolic sulfone of structure II. Such an interpretation is supported by the observation that of all the phenolic sulfones listed in Table II only the anion of the *p*-nitro compound is colored.[27]

The relative basicities of substituted phenylsulfonylanilines will be discussed in a future paper.[28]

TABLE III

THE σ-CONSTANTS OF *p*-R-SO_2 SUBSTITUENTS

R	Benzoic Acids	Phenols	Anilines
CH_3	0.72[a]	0.98[a]	1.13[a]
C_6H_5	.70	0.95	1.21[b]
4-$O_2NC_6H_4$	.54	1.09	1.06[b]
4-$H_2NC_6H_4$	.58	0.825	1.33[c]

[a] See reference 26 for a critical tabulation. [b] Tentative values (reference 5a) from potentiometric titrations using perchloric acid in glacial acetic acid. [c] Estimated value from data reported in reference 5b.

(26) F. G. Bordwell and H. M. Andersen, THIS JOURNAL, **75**, 6019 (1953).

(27) H. H. Szmant and J. Dixon, *ibid.*, in press.

(28) The data for anilines given in Table III can be reconciled with the hypothesis of variable sulfone structure if it is considered that resonance of anilines (unlike that of phenolate ions) causes charge separation.

PITTSBURGH 19, PENNA.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, LANGSTON UNIVERSITY]

Local Anesthetics. I. β-Diethylaminoethyl Esters of Alkoxybenzoic and Cinnamic Acids

BY R. P. PERRY, DORISTA C. JONES AND CHARLES PRATT

RECEIVED JANUARY 16, 1956

The β-diethylaminoethyl esters of some dialkoxybenzoic and cinnamic acids were prepared and tested for topical anesthesia. Some of these proved to be highly potent and non-irritating local anesthetics with minimum toxic action. The ethylenic linkage was a factor in the increased anesthetic duration of the compounds. The hydrochloride of β-diethylaminoethyl-3-methoxy-4-ethoxy cinnamate, when tested topically on the rabbit cornea, was shown to be 18.6 times as efficient as procaine.

Synthetic local anesthetics of the benzoic acid ester type have been studied extensively but the short duration of anesthetic action and the toxicity and irritation of most of them leave much to be desired. The majority of the compounds studied have been alkamine esters of the type $XC_6H_4CO_2(CH_2)_yNR_2$ in which X is a primary amino group, *y* is 2, 3 or 4, and R is an alkyl group. Some investigators,[1–5] however, have shown that in the above type formula, X can be an alkoxy group, giving compounds reported to exhibit minimum toxicity and high anesthetic potency. Thus Christiansen and Harris[4] have prepared a series of alkamine esters of both alkoxy benzoic acids and alkyl substituted alkoxybenzoic acids and found them to be effective as local anesthetics. Krayer and co-workers[5] prepared the β-dimethylaminoethyl ester of 3,4-dimethoxybenzoic acid and tested it for its action on the isolated mammalian heart. It was therefore of interest to prepare and evaluate a series of alkamine esters of dialkoxybenzoic acids to test further the effect of alkoxy groups on anesthetic activity.

Corresponding cinnamic acid esters were pre-

(1) Wildman and Thorp, U. S. Patent 1,193,650 (1916).

(2) C. Rohmann and B. Scheurle, *Arch. Pharm.*, **274**, 110 (1936).

(3) J. S. Pierce, J. M. Salsbury and J. M. Fredericksen, THIS JOURNAL, **64**, 1691 (1942).

(4) W. G. Christiansen and S. E. Harris, U. S. Patent 2,409,663 (1946); U. S. Patent 2,412,966 (1946).

(5) O. Krayer, A. Farah and F. C. Uhle, *J. Pharmacol. Exper. Therap.*, **88**, 277 (1946).

TABLE I

β-DIETHYLAMINOETHYL-X-ALKOXYBENZOATE HYDROCHLORIDES

Substituents	Yield, %	M.p., °C.	Formula	Nitrogen, % Calcd.	Found	Halogen, % Calcd.	Found	Local anesthetic activity, topical × procaine
2,3-Dimethoxy-	65	153–154	$C_{15}H_{23}O_4N\cdot HCl$	4.40	4.42	11.15	11.13	1.5
3,4-Methyleneoxy-	70	104–105	$C_{14}H_{19}O_4N\cdot HCl$	4.64	4.66	11.74	11.75	2.0
3,4-Dimethoxy-	70	145–146	$C_{15}H_{23}O_4N\cdot HCl$	4.40	4.43	11.15	11.17	2.0
3,4-Dimethoxy-6-bromo-	68	149–150	$C_{15}H_{22}O_4NBr\cdot HCl$	3.53	3.56	29.08	29.11	2.3
3,4-Dimethoxy-5-bromo-	70	164–165	$C_{15}H_{22}O_4NBr\cdot HCl$	3.53	3.51	29.08	29.10	6.5
3,4-Dimethoxy-5-chloro-	70	154–155	$C_{15}H_{22}O_4NCl\cdot HCl$	3.97	4.00	20.13	20.15	5.5
3-Methoxy-4-ethoxy-	75	158–159	$C_{16}H_{25}O_4N\cdot HCl$	4.22	4.21	10.68	10.65	8.0

TABLE II

β-DIETHYLAMINOETHYL-X-ALKOXYCINNAMATE HYDROCHLORIDES

Substituents	Yield, %	M.p., °C.	Formula	Nitrogen, % Calcd.	Found	Halogen, % Calcd.	Found	Local anesthetic activity, topical × procaine
2,3-Dimethoxy-	70	164–165	$C_{17}H_{25}O_4N\cdot HCl$	4.07	4.07	10.31	10.32	3.6
3.4-Methyleneoxy-	74	183–184	$C_{16}H_{21}O_4N\cdot HCl$	4.27	4.29	10.81	10.84	4.5
3,4-Dimethoxy-	78	138–139	$C_{17}H_{25}O_4N\cdot HCl$	4.07	4.07	01.31	10.29	4.9
3,4-Dimethoxy-6-bromo-	72	195–196	$C_{17}H_{24}O_4NBr\cdot HCl$	3.31	3.29	27.29	27.28	5.0
4-Methoxy-	79	175–176	$C_{16}H_{23}O_3N\cdot HCl$	4.46	4.44	11.29	11.31	2.0
3-Ethoxy-4-methoxy-	76	140–141	$C_{18}H_{27}O_4N\cdot HCl$	3.91	3.92	9.90	9.91	6.7
3-Methoxy-4-ethoxy-	78	160–161	$C_{16}H_{27}O_4N\cdot HCl$	3.91	3.90	9.90	9.89	18.6

pared to observe the effect of an ethylenic linkage on the anesthetic potency of the compounds.

In this work the esters were prepared by a modification of the Horenstein–Pählicke method,[6] by which the sodium salt of the required acid was refluxed with β-diethylaminoethyl chloride hydrochloride in sodium-dried toluene. The 3,4-dialkoxy acids used were prepared from the appropriate alkylvanillin by methods already described in the literature.[7] Thus the starting material for the 3,4-dialkoxybenzoic and cinnamic acids was the required alkylvanillin which was oxidized by potassium permanganate[7] to the corresponding benzoic acid or converted into the related cinnamic acid by the Doebner modification of the Perkin reaction.[8] Other acids used were obtained similarly from commercial stocks of the necessary aldehydes. The esters were isolated as water-soluble hydrochlorides and are listed in Tables I and II.

Pharmacology.—A preliminary pharmacological investigation of these compounds was carried out by noting the length of anesthetic duration produced by various concentrations of the individual compounds, on the rabbit cornea, and thus compared with equal concentrations of procaine. The compounds were all more potent than procaine and produced no degree of irritation. Dialkoxy groups increased anesthetic potency, which was further enhanced by the presence of an ethylenic linkage between the aryl and ester moieties of the compounds.

(6) H. Horenstein and H. Pählicke, *Ber.*, **71**, 1644 (1938).

(7) L. C. Raiford and R. P. Perry, *J. Org. Chem.*, **7**, 358 (1942).

(8) "Organic Reactions," Vol. I, edited by Adams, John Wiley and Sons, Inc., New York, N. Y., 1942, p. 249.

Experimental

β-Diethylaminoethyl Alkoxybenzoate and Cinnamate Hydrochlorides.—These esters were prepared by a modification of the Horenstein–Pählicke method[6] and the following procedure is representative. To 3.3 g. (0.15 mole) of clean, freshly cut sodium dissolved in 150 ml. of absolute ethanol was added, with stirring, 13 g. (0.05 mole) of 5-bromomethylvanillic acid. The mixture was then stirred and refluxed for 30 minutes. On cooling to room temperature, the salt was filtered off, washed with absolute ethanol and allowed to dry. The dried salt was then suspended in 200 ml. of sodium-dried toluene and treated with 8.5 g. (0.05 mole) of β-diethylaminoethyl chloride hydrochloride. The mixture was now stirred and refluxed for 18–20 hours. The hot mixture was then filtered. On cooling, the filtrate was washed twice with 75-ml. portions of 10% sodium hydroxide followed by washing with water. The toluene layer of the basic ester was then dried for several hours over anhydrous magnesium sulfate. Anhydrous hydrogen chloride was then bubbled through the toluene solution until salt formation was complete. The product was filtered, allowed to dry in a desiccator and then recrystallized from a mixture of absolute ethanol and anhydrous ether to give a water-soluble product which melted at 164–165°. The analyses and other data on the esters prepared in this work are given in Tables I and II.

Acknowledgment.—This work was made possible by a grant from Research Corporation, New York, for which the authors are grateful.

LANGSTON, OKLAHOMA