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Synthesis of Dialkylaminoalkyl Esters of Sterically Hindered 4-Alkoxybenzoic Acids

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A series of dialkylaminoalkyl esters of 2,6-dimethyl-4-alkoxybenzoic acids was prepared for pharmacologic evaluation.

A number of dialkylaminoalkyl esters of *p*-alkoxybenzoic acids have been prepared previously [1,2]. They were found to have a greater local anesthetic activity than procaine, β-diethylaminoethyl *p*-aminobenzoate. These esters, however, hydrolyze in an organism more easily than the corresponding *p*-aminoesters, and this shortens the length of the anesthetic action.

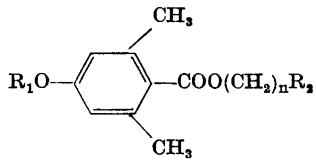
Rabjohn *et al.*[3] have synthesized some β-dialkylaminoethyl esters of sterically hindered benzoic acids which contained only alkyl substituents and reported that β-diethylaminoethyl 2,3,5,6-tetramethylbenzoate is twice as potent as procaine in infiltration anesthesia.

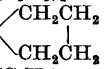
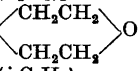
The Upjohn Co [4,5] has prepared dialkylamino alkyl esters of 2,6-dimethyl-4-aminobenzoic acid and reported that the *ortho* dialkyl substitution has an advantageous effect on the local anesthetic activity and that these esters do not hydrolyze readily. However, Lespagnol and Bar [6] claimed that that 1-(dimethylaminomethyl)-1-methylpropyl 2,6-dibromobenzoate hydrolyzes more readily than the unsubstituted benzoate. Childress *et al.*[7] reported that β-diethylaminoethyl 2,6-dichloro-4-aminobenzoate has an intradermal local anesthetic activity 3.5 times that of procaine.

As can be seen from the foregoing, the *ortho* dialkyl substitution not only increases the stability of the ester but also its local anesthetic activity. It was therefore also of interest to investigate the effect of the *ortho* dialkyl substitution on the esters of 4-alkoxybenzoic acids.

During the course of the present investigation two publications have appeared. In one, Reid [8] reported the synthesis of some pyrrolidylalkyl esters of 2,6-dimethyl-4-propoxybenzoic acid, and in the other Bernstein *et al.*[9] that of alkylaminoalkyl esters of 2,6-dimethyl-4-methoxy- and 4-ethoxybenzoic acids.

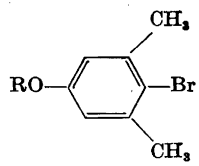
Table 1. Dialkylaminoalkyl esters of 2,6-dimethyl-4-alkoxybenzoic acids.



R_1	n	R_2	B.p., °C	M.p., °C	Analyses		
					Formula	Calc. N	Found N
C_2H_5	2	$N(C_2H_5)_2$	120—123/0.01	·HCl 149—150*	$C_{17}H_{27}NO_3$.HCl	4.24	4.36
C_2H_5	2		120—122/0.05	—	$C_{17}H_{25}NO_3$	4.81	4.94
n-C_3H_7	2	$N(C_2H_5)_2$	124—125/0.01	·$(COOH)_2$, 125—126	$C_{18}H_{29}NO_3$.$(COOH)_2$	3.52	3.58
i-C_3H_7	2	$N(C_2H_5)_2$	116—117/0.005	—	$C_{18}H_{29}NO_3$	4.56	4.43
n-C_4H_9	2	$N(CH_3)_2$	116—117/0.005	—	$C_{17}H_{27}NO_3$	4.77	4.53
n-C_4H_9	2	$N(C_2H_5)_2$	136—137/0.01	·$(COOH)_2$ 113—115	$C_{19}H_{31}NO_3$.$(COOH)_2$	3.40	3.59
n-C_4H_9	2		145—147/0.003	—	$C_{19}H_{29}NO_4$	4.18	4.10
n-C_4H_9	2	$N(i\text{-}C_3H_7)_2$	130—132/0.009	—	$C_{21}H_{35}NO_3$	4.01	4.05
n-C_4H_9	2	$N(n\text{-}C_3H_9)_2$	146—148/0.002	—	$C_{23}H_{39}NO_3$	3.71	3.58
n-C_4H_9	3	$N(n\text{-}C_3H_9)_2$	153—154/0.005	—	$C_{24}H_{41}NO_3$	3.58	3.34
i-C_4H_9	2	$N(C_2H_5)_2$	117—118/0.008	—	$C_{19}H_{31}NO_3$	4.36	4.17
n-C_5H_{11}	2	$N(C_2H_5)_2$	128—129/0.003	—	$C_{20}H_{33}NO_3$	4.18	4.12
i-C_5H_{11}	2	$N(C_2H_5)_2$	122—123/0.004	—	$C_{20}H_{33}NO_3$	4.18	4.03

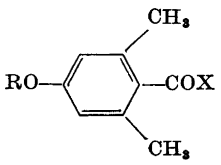
* Bernstein *et al.*[9] also reported the m. p. 149—150°.

Table 2. 2,6-Dimethyl-4-alkoxybromobenzenes.



R	B.p., °C	Yield %
C_2H_5	133—134/14	86
n-C_3H_7	145—146/15	90
i-C_3H_7	146—147/24	83
n-C_4H_9	156—157/15	94
i-C_4H_9	163—164/25	50
n-C_5H_{11}	182—184/24	90
i-C_5H_{11}	179—181/24	75

Table 3. 2,6-Dimethyl-4-alkoxybenzoic acids and 2,6-dimethyl-4-alkoxybenzoyl chlorides.



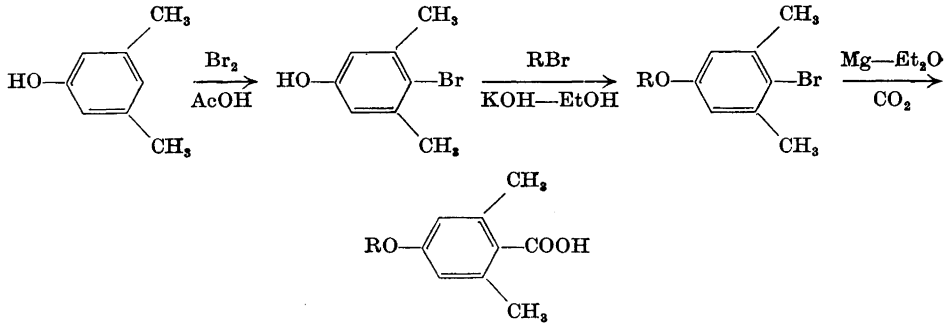
Acids X=OH								Acid chlorides X = Cl	
R	M.p., °C	Analyses					Yield %	B.p., °C	Yield %
		Formula	Carbon		Hydrogen				
			Calc.	Found	Calc.	Found			
C_2H_5	122—124	$C_{11}H_{14}O_3$	68.02	68.23	7.27	7.36	60	138—140/ 9	93
n-C_3H_7	88— 90 *	$C_{12}H_{16}O_3$	69.21	69.63	7.74	7.73	48	150—151/10	92
i-C_3H_7	123—124 *	$C_{12}H_{16}O_3$	69.21	69.37	7.74	7.51	54	158—160/26	85
n-C_4H_9	97— 98	$C_{13}H_{18}O_3$	70.24	70.43	8.16	8.02	57	163—165/13	92
i-C_4H_9	116—117	$C_{13}H_{18}O_3$	70.24	69.88	8.16	7.97	49	172—175/25	60
n-C_5H_{11}	93— 95	$C_{14}H_{20}O_3$	71.16	71.04	8.53	8.25	43	109—110/0.2	73
i-C_5H_{11}	104—105	$C_{14}H_{20}O_3$	71.16	71.01	8.53	8.22	40	99—100/0.07	79

* Reid [8] reported the melting points 90—91° and 121—122° for the *n*- and *i*-propoxy-2,6-dimethylbenzoic acids, respectively.

In the present paper the synthesis of a number of dialkylaminoalkyl esters of 2,6-dimethyl-4-alkoxybenzoic acids is described. These esters have a high local anesthetic activity. In addition they are very resistant to hydrolysis. With the exception of β-diethylaminoethyl 2,6-dimethyl-4-ethoxybenzoate, which Bernstein *et al.*[9] have prepared, all the esters here described are new.

The esters of 2,6-dimethyl-4-alkoxybenzoic acids, which were prepared by allowing the corresponding 2,6-dimethyl-4-alkoxybenzoyl chlorides to react with a dialkylaminoalkanol in boiling benzene solution, are recorded in Table 1.

The 2,6-dimethyl-4-alkoxybenzoic acids were synthesized from 3,5-dimethylphenol by a series of reactions, first described by Fuson *et al.*[10] in the case of 2,6-dimethyl-4-methoxybenzoic acid.



The acid chlorides were prepared in the usual way with thionyl chloride. The 2,6-dimethyl-4-alkoxybromobenzenes from which the 2,6-dimethyl-4-alkoxybenzoic acids were prepared by carbonation of the magnesium compounds are presented in Table 2, the corresponding benzoic acids and acid chlorides in Table 3.

EXPERIMENTAL

The melting points were determined on a Kofler microscope. All boiling points are uncorrected. Microanalyses were performed by the Microanalytisches Laboratorium in Max-Planck-Institut für Kohlenforschung, Mülheim, Germany.

Synthesis of dialkylaminoalkyl esters of 2,6-dimethyl-4-alkoxybenzoic acids. 0.01 Mole of the required 2,6-dimethyl-4-alkoxybenzoyl chloride was dissolved in 50 ml of dry benzene. To this solution was added with stirring 0.02 mole of dialkylaminoalkanol dissolved in 20 ml of benzene. The mixture was refluxed and stirred for 24 h. The benzene solution was washed, first with 2 N aqueous sodium hydroxide, then with water, and dried over anhydrous sodium sulfate. The solvent was evaporated and the residue distilled in a high vacuum. The yield varied from 70 to 95 %.

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