[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF MISSOURI]

β-DIETHYLAMINOETHYL ESTERS OF STERICALLY HINDERED ALKYL SUBSTITUTED BENZOIC ACIDS

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Although the local anesthetic procaine is employed widely in medicine, its relatively short duration of action leaves much to be desired in many cases. Since it is well known that procaine suffers hydrolysis at the ester linkage in an organism, any factors which could influence this reaction might be expected to change the length of action of the drug.

Dvoretsky and Richter (1) have prepared the ethyl and *n*-propyl esters of 2,6-dimethyl-4-aminobenzoic acid and reported that they appeared to show a more prolonged anesthetic effect than does benzocaine, the related unhindered ester. On the other hand, Lespagnol and Bar (2) synthesized 2,6-dibromoamylocaine [1-(dimethylaminomethyl)-1-methylpropyl 2,6-dibromobenzoate] and claimed that it was hydrolyzed more readily than the corresponding unsubstituted benzoate. Recently Childress, Cordasco, Plekss, and Reiner (3) reported that β-diethylaminoethyl 2,6-dichloro-4-aminobenzoate has an intradermal local anesthetic activity of 3.5 times that of procaine.

In the course of a study of the effect of substituents in local anesthetics of the procaine type, we made the hindered ester, β-diethylaminoethyl 2,3,5,6-tetramethylbenzoate. A preliminary pharmacological investigation[1] showed that this compound is twice as potent in producing minimal infiltration anesthesia in guinea pigs, and has a very prolonged anesthetic effect when compared in equipotent concentrations with procaine. It is of interest that the increased activity was obtained without the presence of a *para* amino group, for the introduction of this into the above type of molecule would be laborious and would limit greatly the practicality of such materials.

Accordingly, the present investigation was undertaken to synthesize a number of β-diethylaminoethyl esters of sterically hindered benzoic acids which contained only alkyl substituents. They were obtained by conventional procedures from the appropriate alkyl substituted benzenes, with the exception of the 2,6-dimethyl derivative. The hydrocarbons were brominated in the ring, and the bromo compounds were converted to the substituted benzoic acids by carbonation of the corresponding Grignard reagents. The potassium salts of these acids then were caused to react with β-diethylaminoethyl chloride by a modification of the Horenstein-Pählicke method (4) to give the esters, as hydrochloride salts, which are recorded in Table I.

From the pharmacological data available, it appears that none of the other compounds in Table I is superior to the 2,3,5,6-tetramethyl derivative in

[1] The authors are indebted to Dr. D. F. Marsh of the McNeil Laboratories for the pharmacological tests and statements. The pharmacological data will be published elsewhere by Dr. Marsh.

TABLE I

β-DIETHYLAMINOETHYL SUBSTITUTED BENZOATE HYDROCHLORIDES

Substituents	M.P., °C.	Formula	Analyses			
			Carbon		Hydrogen	
			Calc'd	Found	Calc'd	Found
2,6-Dimethyl-	161–164	$C_{15}H_{24}ClNO_2$	63.03	62.91	8.46	8.34
2,4,6-Trimethyl-	182–184	$C_{16}H_{26}ClNO_2$	64.09	64.14	8.74	8.99
2,3,5,6-Tetramethyl-	192–194	$C_{17}H_{28}ClNO_2$	65.05	64.80	8.99	9.14
2,3,4,5,6-Pentamethyl-	204–206	$C_{18}H_{30}ClNO_2$	65.93	66.04	9.22	9.36
2,4,6-Triethyl-	145–146	$C_{19}H_{32}ClNO_2$	66.74	66.41	9.43	9.56
2,6-Dimethyl-4-*tert*-butyl	158–159	$C_{19}H_{32}ClNO_2$	66.74	66.62	9.43	9.66
2,3,5,6-Tetraethyl-	151–152	$C_{21}H_{36}ClNO_2$	68.17	67.84	9.80	9.92
2,4,6-Triisopropyl-	195–197	$C_{22}H_{38}ClNO_2$	68.81	68.96	9.98	10.21

potency or duration either by topical application or by injection. This compound also shows a lower order of toxicity than does procaine when administered to dogs and mice by various routes.

EXPERIMENTAL[2]

Starting materials. Mesitylene, triethylbenzene, pentamethylbenzene, and 2,6-dimethylaniline were purchased from the Eastman Kodak Co. The durene was supplied generously by the Chemical Division of Esso Laboratories. The triisopropylbenzene (Alkazene-13) was obtained as a sample from the Dow Chemical Co. 1,3-Dimethyl-5-*tert*-butylbenzene was prepared according to the procedure of Buu-Höi and Cagniant (5).

1,2,4,5-Tetraethylbenzene. This was synthesized by a modification of the procedure of Smith and Guss (6). A mixture of 649 g. (4 moles) of technical triethylbenzene and 67 g. (0.5 mole) of anhydrous aluminum chloride was heated and stirred on a steam-bath while 436 g. (4 moles) of ethyl bromide was added over a period of 3½ hours. Stirring and heating were continued for an additional 27 hours, the mixture was allowed to cool, and then was poured onto 1000 g. of crushed ice. The hydrocarbon layer was separated, washed well with water, and dried over calcium chloride. It was distilled through a Todd Precise Fractionation Assembly. There was obtained 237 g. of a mixed tetraethylbenzene fraction which boiled at 62–64°/1 mm.; n_D^{20} 1.5055; d_4^{25} 0.8773.

The tetraethylbenzene fraction (237 g., 1.25 moles) was treated with 215 g. (1.83 moles) of chlorosulfonic acid at 0–10°. The reaction mixture was poured onto 300 g. of crushed ice and the resulting mixture was extracted twice with 300-ml. portions of ether. The ether was evaporated and 500 ml. of 25% sodium hydroxide solution was added cautiously to the residue. The mixture was heated to 95°, 500 ml. of water was added and the solution was allowed to cool slowly to room temperature. The precipitate of sodium 1,2,4,5-tetraethylbenzenesulfonate was removed by filtration, sucked as dry as possible, and washed well with ether. It was recrystallized from water, and the crystalline material was transferred to a 3-l., 3-necked flask which contained 1000 ml. of 50% sulfuric acid. Superheated steam was passed through the mixture while the temperature was increased gradually to 140° at which point hydrolysis occurred readily. The hydrocarbon layer of the distillate was separated, washed with water, and dried over calcium chloride. There was obtained 99 g. of 1,2,4,5-tetraethylbenzene which distilled at 63–65°/1 mm.; m.p. 9–10°.

[2] All melting points are uncorrected. The semi-micro analyses were performed by R. E. Bolin and R. L. Elliott.

Alkyl substituted bromobenzenes. 2,6-Dimethylbromobenzene (b.p. 101–103°/22 mm.) was prepared from 2,6-dimethylaniline by the method of Brown and Grayson (7). The following bromo compounds were obtained by direct bromination of the corresponding hydrocarbons essentially according to the directions of Smith (8): bromomesitylene, b.p. 110–112°/18 mm.; bromodurene, b.p. 111–113°/6 mm.; bromopentamethylbenzene, m.p. 157–159°; 2,4,6-triethylbromobenzene, b.p. 92–94°/4 mm.; 2,6-dimethyl-4-*tert*-butylbromobenzene, m.p. 48–50°; 2,4,6-triisopropylbromobenzene, b.p. 110–112°/4 mm.; and 2,3,5,6-tetraethylbromobenzene, b.p. 97–99°/1 mm.

Alkyl substituted benzoic acids. From 72 g. (0.27 mole) of 2,3,5,6-tetraethylbromobenzene, 54.5 g. (0.5 mole) of ethyl bromide and 18.9 g. (0.79 g.-atom) of magnesium, followed by carbonation of the mixture of Grignard reagents, there was obtained in the usual fashion 35 g. (56%) of 2,3,5,6-tetraethylbenzoic acid which melted at 106–107.5°, after recrystallization from dilute ethanol.

Anal. Calc'd for $C_{15}H_{22}O_2$: C, 76.88; H, 9.46; N.E., 234.

Found: C, 76.89; H, 9.70; N.E., 233.

The following known acids were synthesized by the same general procedure: 2,6-dimethylbenzoic, m.p. 114–116°; 2,4,6-trimethylbenzoic, m.p. 151–154°; 2,3,5,6-tetramethylbenzoic, m.p. 176–179°; 2,3,4,5,6-pentamethylbenzoic, m.p. 204–207°; 2,4,6-triethylbenzoic, m.p. 113–114°; 2,6-dimethyl-4-*tert*-butylbenzoic, m.p. 164–165°; and 2,4,6-triisopropylbenzoic, m.p. 183–184°.

β-Diethylaminoethyl substituted benzoate hydrochlorides. These esters were prepared by a modification of the method of Horenstein and Pählicke (4), and the following directions are representative. In a 500-ml., 3-necked flask fitted with a mechanical stirrer, a Stark and Dean water separator, and a reflux condenser were placed 17.8 g. (0.1 mole) of 2,3,5,6-tetramethylbenzoic acid, 20 g. (0.2 mole) of potassium bicarbonate, and 250 ml. of anhydrous toluene. The mixture was stirred and refluxed for about six hours, or until water no longer collected in the trap. The reaction mixture was allowed to cool and 17.2 g. (0.1 mole) of β-diethylaminoethyl chloride hydrochloride was added. Stirring and refluxing were continued for an additional 25–30 hours, at which time the formation of water had ceased. After cooling, the reaction mixture was shaken once with a 100-ml. and twice with 50-ml. portions of 10% sodium hydroxide solution. The toluene solution of the basic ester was washed once with 50 ml. of water and dried over magnesium sulfate. Anhydrous hydrogen chloride was bubbled into the toluene solution until salt formation was complete. After recrystallization of the product from a mixture of absolute alcohol and anhydrous ether, there was obtained 17.3 g. (55%) of the ester hydrochloride which melted at 192–194°. The analyses and properties of the ester hydrochlorides prepared are recorded in Table I.

SUMMARY

A number of β-diethylaminoethyl esters of sterically hindered alkyl substituted benzoic acids have been synthesized. They show a considerably longer period of anesthetic action than does procaine.

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