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

β-Diethylaminoethyl Esters of the Trimethoxybenzoic Acids

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Received October 31, 1955

The β-diethylaminoethyl esters of all of the isomeric trimethoxybenzoic acids have been synthesized.

A number of mono- and di-alkylaminoalkyl esters of monoalkoxybenzoic acids have been prepared and tested as local anesthetics.[2–6] It appears that only one dialkylaminoalkyl dialkoxybenzoate, β-diethylaminoethyl 3-methoxy-4-ethoxybenzoate, has been prepared and is claimed to have local anesthetic properties.[5] Likewise, β-diethylaminoethyl 3,4,5-trimethoxybenzoate[7] seems to be the lone such trialkoxybenzoate listed in the literature, and apparently no dialkylaminoalkyl tetra- or penta-alkoxybenzoates have been reported.

Since alkoxyl groups appear to improve the anesthetic properties of aminobenzoates,[8] and since the β-diethylaminoethyl esters of certain polyalkyl substituted benzoic acids are more potent than procaine in producing anesthesia,[9] it was thought that the β-diethylaminoethyl esters of the trimethoxybenzoic acids might conceivably possess interesting pharmacological properties. The present investigation reports the methods of synthesis of these six isomeric compounds.

All of the trimethoxybenzoic acids are known and can be obtained fairly conveniently by published procedures, with the exception of the 2,3,5-isomer. The latter acid, or related hydroxy acids, have been prepared by a variety of methods,[10–13] which give poor yields.

Several unsuccessful attempts were made to develop improved directions for the preparation of 2,3,5-trimethoxybenzoic acid. 2,3-Dimethoxybenzoic acid was nitrated[14] to a mixture of the 5- and 6-nitro derivatives which was separated readily. The 5-nitro-2,3-dimethoxybenzoic acid was reduced satisfactorily to the corresponding amino compound[15] which in turn was diazotized. Repeated trials at hydrolysis of the diazonium salt led only to tarry reaction products.

Since 2,3,5-trihydroxyacetophenone can be obtained readily from hydroxyhydroquinone triacetate by a Fries rearrangement and the trihydroxy compound can be methylated easily, it appeared that a haloform reaction on the ketone might lead to the desired acid. Treatment of the 2,3,5-trimethoxyacetophenone with sodium hypobromite resulted in a neutral product which was shown to be 2,4,5-trimethoxybromobenzene. Apparently bromination, as well as oxidation occurred during the haloform reaction, and the intermediate 2,3,5-trimethoxy-6-bromobenzoic acid suffered decarboxylation during the working up of the reaction mixture.

The synthesis of 2,3,5-trimethoxybenzoic acid was accomplished, although in poor yields, by the carbonation of 2,3,5-trimethoxyphenylmagnesium bromide. The required bromide was obtained by the methylation of 1-bromo-2,5-dihydroxy-3-methoxybenzene which was prepared by a Dakin oxidation on 5-bromovanillin.

The β-diethylaminoethyl benzoate hydrochlorides recorded in Table I were obtained from the trimethoxybenzoic acids and β-diethylaminoethyl chloride hydrochloride by a modification of the Horenstein and Pählicke[16] procedure.

The pharmacological tests on these compounds are being carried out by Dr. D. F. Marsh of the McNeil Laboratories and will be reported elsewhere.

EXPERIMENTAL[17]

Materials. 2,3,4-Trimethoxybenzoic acid (m.p. 95–97°; lit.[18] m.p. 99°) was obtained by the reaction of methyl sulfate on 2,3,4-trihydroxybenzoic acid. The latter was prepared by the carbonation of pyrogallol, by means of potassium bicarbonate, according to the method of Kostanecki.[19] *2,3,6-Trimethoxybenzoic acid* (m.p. 148–149°) resulted from

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[1] Abstracted in part from the M.A. thesis of Arthur Mendel, 1955.

[2] Rohmann, *et al., Arch. Pharm.*, **274**, 110 (1936); **278**, 425 (1940); and **280**, 76 (1942).

[3] Pierce, Salsbury, and Fredericksen, *J. Am. Chem. Soc.*, **64**, 1691 (1942).

[4] Lott, Harris, and Christiansen, *J. Am. Pharm. Assoc.*, **27**, 661 (1938).

[5] Christiansen and Harris, U. S. Patent 2,404,691 [*Chem. Abstr.*, **41**, 155 (1947)].

[6] Sauter, German Patent 805,670 [*Chem. Abstr.*, **46**, 5792 (1952)].

[7] Löfgren and Lundqvist, *Svensk. Kem. Tid.*, **58**, 206 (1946) [Chem. Abstr., **43**, 1022 (1949)].

[8] Epstein and Meyer, *J. Am. Chem. Soc.*, **77**, 4059 (1955).

[9] Rabjohn, Fronabarger, and Linstromberg, *J. Org. Chem.*, **20**, 271 (1955).

[10] Baker, Brown, and Scott, *J. Chem. Soc.*, 1922 (1939).

[11] Corbett, Hassall, Johnson, and Todd, *J. Chem. Soc.*, 1 (1950).

[12] Schock and Tabern, *J. Org. Chem.*, **16**, 1772 (1951). U. S. Patent 2,641,609 [*Chem. Abstr.*, **48**, 6468 (1954)].

[13] Smith and LaForge, *J. Am. Chem. Soc.*, **53**, 3072 (1931).

[14] Cain and Simonsen, *J. Chem. Soc.*, **105**, 156 (1914).

[15] Rubenstein, *J. Chem. Soc.*, 648 (1926).

[16] Horenstein and Pählicke, *Ber.*, **71**, 1644 (1938).

[17] All melting points are uncorrected. The authors are indebted to R. E. Elliott for the analytical data.

[18] Will, *Ber.*, **21**, 2020 (1888).

[19] Kostanecki, *Ber.*, **18**, 3202 (1885).

the carbonation of 2,3,6-trimethoxyphenyllithium, in the manner described by Gilman and Thirtle.[20] The required 1,2,4-trimethoxybenzene was obtained by converting quinone to 1,2,4-triacetoxybenzene[21] which in turn was hydrolyzed and methylated in one step[22] to the triether. *2,4,5-Trimethoxybenzoic acid* (m.p. 143–144°) was synthesized by methylation of the corresponding trihydroxy acid. The hydroxy acid was made by the carbonation of 1,2,4-trihydroxybenzene by means of potassium bicarbonate and carbon dioxide.[23] The trihydroxybenzene was obtained from 1,2,4-triacetoxybenzene by transesterification with methanol.[24] *2,4,6-Trimethoxybenzoic acid* (m.p. 140–142°) was prepared by the metallation of phloroglucinol trimethyl ether with *n*-butyllithium, followed by carbonation, after the directions of Gilman, Arntzen, and Webb.[25] *3,4,5-Trimethoxybenzoic acid* was purchased from the Eastman Kodak Company.

TABLE I

β-DIETHYLAMINOETHYL TRIMETHOXYBENZOATE HYDROCHLORIDES

Isomer	M.p., °C.	Analyses Carbon Calc'd	Carbon Found	Hydrogen Calc'd	Hydrogen Found
2,3,4-	150–153	55.24	55.00	7.54	7.72
2,3,5-	124–128[a]	55.24	55.23	7.54	7.93
2,3,6-	110–114[a]	55.24	55.22	7.54	7.68
2,4,5-	164–167	55.24	55.33	7.54	7.77
2,4,6-	171–174	55.24	55.22	7.54	7.54
3,4,5-	152–155[b]	—	—	—	—

[a] Hygroscopic. [b] Löfgren and Lundqvist[7] have reported the melting point to be 159°.

Haloform reaction on 2,3,5-trimethoxyacetophenone. 1,2,4-Triacetoxybenzene was converted to 2,3,5-trihydroxyacetophenone in 30% yield by treatment with aluminum chloride according to the procedure of Mauthner.[26] The trihydroxyacetophenone then was methylated with methyl sulfate to the corresponding trimethoxy ketone (m.p. 99–100°; lit.[26] m.p. 102–103°).

A solution of 8 g. (0.038 mole) of 2,3,5-trimethoxyacetophenone in 130 ml. of methanol was stirred rapidly while an ice-cold solution of sodium hypobromite, which had been prepared by dissolving 18 g. (0.11 mole) of bromine in a solution of 12.8 g. (0.32 mole) of sodium hydroxide in 100 ml. of water, was added dropwise. The reaction mixture was stirred for 2 hours after all of the hypobromite solution had been added, and then the methanol was removed by distillation on a steam-bath. The residue was extracted with ether, heated to remove dissolved ether, decolorized, filtered, and acidified with hydrochloric acid. The solution was cooled and the resulting oily crystals were collected by filtration and purified by recrystallization from dilute methanol. There was obtained 2 g. of a white crystalline solid, m.p. 51–53°, which was insoluble in alkali and which gave a positive test for halogen upon fusion with sodium.

Anal. Calc'd for $C_9H_{11}BrO_3$: C, 43.78; H, 4.49. Found: C, 43.90; H, 4.61.

These data suggested that the compound was 2,4,5-trimethoxybromobenzene. An authentic sample of this material was prepared (m.p. 52–54°) according to the procedure of Fabinyi and Széki[27] and the mixture melting point of this with the unknown reaction product was not depressed.

Preparation of 2,3,5-trimethoxybenzoic acid. 5-Bromovanillin was synthesized by the method of Torrey and Clarke[28] and was converted to 2,5-dihydroxy-3-methoxybromobenzene by a Dakin oxidation.[29] The dihydroxy compound (40 g.) was methylated with methyl sulfate, the reaction product was extracted with ether, and one-half of the dried ethereal solution (100 ml.) was added to 3 g. of magnesium in 100 ml. of absolute ether. The resulting reaction mixture was poured onto Dry Ice, and after the usual manipulations there was obtained 0.78 g. of the desired acid which melted at 99–101°; lit.[30] m.p. 104°.

β-Diethylaminoethyl 2,3,4-trimethoxybenzoate hydrochloride. The following procedure is representative of the method which was employed for preparing the ester hydrochlorides. A mixture of 5.0 g. (0.024 mole) of 2,3,4-trimethoxybenzoic acid, 4.2 g. (0.024 mole) of β-diethylaminoethyl chloride hydrochloride, 5 g. (0.05 mole) of potassium bicarbonate, and 150 ml. of dry isopropyl alcohol was stirred and refluxed for 27 hours. The solvent was removed by distillation under diminished pressure on a steam-bath and 100 ml. of water was added to the residue. The mixture was made alkaline with 10% sodium hydroxide solution and extracted several times with ether. The combined extracts were dried over magnesium sulfate and filtered. The filtrate was saturated with anhydrous hydrogen chloride and the precipitate was collected by filtration. After recrystallization from a mixture of absolute alcohol and absolute ether, there was obtained 3.6 g. (44%) of the ester hydrochloride; m.p. 150–153°.

Anal. Calc'd for $C_{16}H_{26}ClNO_5$: C, 55.24; H, 7.54. Found: C, 55.00; H, 7.72.

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(20) Gilman and Thirtle, *J. Am. Chem. Soc.*, **66**, 858 (1945).

(21) Vliet, *Org. Syntheses*, Coll. Vol. I, 2nd Ed., 317 (1941).

(22) Bargellini and Martegiani, *Gazz. chim. ital.*, **41**, **II**, 445 (1911).

(23) Thiele and Jaeger, *Ber.*, **34**, 2837 (1901).

(24) Thiele, *Ber.*, **31**, 1247 (1898).

(25) Gilman, Arntzen, and Webb, *J. Org. Chem.*, **10**, 374 (1945).

(26) Mauthner, *J. prakt. Chem.*, **136**, 213 (1933).

(27) Fabinyi and Széki, *Ber.*, **43**, 2676 (1910).

(28) Torey and Clark, *J. Am. Chem. Soc.*, **31**, 583 (1909).

(29) Dakin, *Am. Chem. J.*, **42**, 477 (1909).

(30) Baker, Brown, and Scott, *J. Chem. Soc.*, 1922 (1939).