[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, POLYTECHNIC INSTITUTE OF BROOKLYN AND THE RESEARCH LABORATORIES OF CHAS. PFIZER AND CO., INC.]

Esters of Pyrazinoic and Pyrazine-2,3-dicarboxylic Acids

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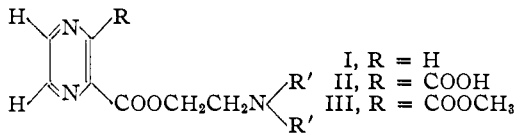
β-Dialkylaminoethyl esters of pyrazinoic and pyrazine-2,3-dicarboxylic acids have been prepared as possible local anesthetics.

Numerous compounds related to cocaine have been prepared and tested for local anesthetic action. Through these investigations it has been shown that the majority of the dialkylaminoethyl esters of aromatic and heterocyclic acids exhibit activity. As yet, however, to our knowledge, only one example of this type of compound containing the pyrazine nucleus has been described.[1] Consequently, it was the purpose of this study to prepare and evaluate as local anesthetics several β-dialkylaminoethyl esters of pyrazine.

Compounds of the type



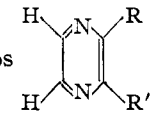
I, R = H
II, R = COOH
III, R = $COOCH_3$

where R′ = methyl, ethyl or *n*-butyl were prepared. The R′ groups were chosen as representative of that type of product in which the N-alkyl has been varied. It has been demonstrated previously that both local anesthetic activity and toxicity increase with increasing number of carbon atoms in these groups.[2] Since methyl β-diethylaminoethylphthalate has been described as a good local anesthetic,[3] analogous compounds (R = $COOCH_3$) and compounds containing a carboxyl (R = COOH) rather than a carbomethoxyl group were also investigated.

Hydrochlorides of type I compounds resulted from the reaction of pyrazinoyl chloride with the appropriate β-dialkylaminoethanol. Pyrazinoic acid was prepared by vacuum sublimation of the dicarboxylic acid or by saponification of methyl pyrazinoate, obtained by the series of reactions: pyrazine-2,3-dicarboxylic acid → pyrazine-2,3-dicarboxylic anhydride → methyl acid pyrazine-2,3-dicarboxylate → methyl pyrazinoate → pyrazinoic acid. Methyl acid pyrazine-2,3-dicarboxylate is decarboxylated smoothly above its melting point to afford methyl pyrazinoate in good yield. Though this latter series of reactions leading to pyrazinoic acid involves more steps, all are readily performed, and in high yield. Consequently, this route is preferred to vacuum sublimation for the preparation of large quantities of the acid. Type II and hydrochlorides of type III were obtained by treating the β-dialkylaminoethanol with pyrazine-2,3-dicarboxylic anhydride and the acid chloride of methyl pyrazine-2,3-dicarboxylate, respectively. Though the methyl acid chloride of pyrazine-2,3-dicarboxylic acid is more stable than pyrazinoyl chloride, as evidenced by little or no decomposition during vacuum distillation, it slowly decomposes over a period of several days at room temperature. Characterization data for the esters and ester hydrochlorides are presented in Table I.

TABLE I

β-DIALKYLAMINOETHYL ESTERS OF PYRAZINOIC AND PYRAZINE-2,3-DICARBOXYLIC ACIDS



	R	R′	Crystallization solvent	M.p., °C.	Calculated C	Calculated H	Calculated N	Calculated Cl	Found C	Found H	Found N	Found Cl
I	COOH	$COOCH_2CH_2N(CH_3)_2$	Dimethylformamide	186–187	50.20	5.48	17.56	...	50.04	5.63	17.49	...
II	COOH	$COOCH_2CH_2N(C_2H_5)_2$	Dimethylformamide	157–158	53.92	6.41	15.72	...	53.81	6.60	16.55[a]	...
III	COOH	$COOCH_2CH_2N(C_4H_9)_2$	*n*-Butanol–acetone	151–152	59.42	7.79	13.00	...	59.44	7.77	13.39[a]	...
IV	$COOCH_3$	$COOCH_2CH_2N(CH_3)_2$·HCl	*n*-Butanol	138–139	45.58	5.57	14.51	12.24	45.55	5.55	14.52	...
V	$COOCH_3$	$COOCH_2CH_2N(C_2H_5)_2$·HCl	Acetone	113–115	49.12	6.34	13.23	11.15	48.78	6.15	13.23	11.02
VI	$COOCH_3$	$COOCH_2CH_2N(C_4H_9)_2$·HCl	Ethyl acetate	101–103	54.61	7.54	11.24	9.48	54.77	7.71	11.53[a]	9.30
VII	H	$COOCH_2CH_2N(CH_3)_2$·HCl	*n*-Propanol–isopropyl alcohol	184–185	46.65	6.09	18.14	15.31	46.67	6.34	18.61[a]	15.21
VIII	H	$COOCH_2CH_2N(C_2H_5)_2$·HCl	*n*-Butanol	139–140	50.86	6.99	16.18	13.65	51.12	7.14	16.34	13.76
IX	H	$COOCH_2CH_2N(C_4H_9)_2$·HCl	Ethyl acetate	95–97	57.03	8.30	13.31	11.23	56.94	8.31	14.00[a]	11.27

[a] Average of six analyses, both Dumas and Kjeldahl.

Infrared absorption spectra of the esters and intermediates were obtained. Significant maxima in the 1500–2000 cm.$^{-1}$ region are listed in Table II. The spectra of both pyrazine-2,3-dicarboxylic acid and pyrazinoic acid in Nujol mull are somewhat anomalous. The former exhibits two definite maxima and a shoulder, one peak being quite high (1760 cm.$^{-1}$) for a conjugated acid. Pyrazinoic acid absorbs normally, with a broad band at 1700 cm.$^{-1}$, but unexpected absorption occurs also at 1880 cm.$^{-1}$. Though at first believed due to impurities, this latter band was present in the spectra of carefully purified samples prepared both by decarboxylation of the diacid and by saponification of methyl pyrazinoate. Possibly it is due to interaction of the ring nitrogen and carboxyl groups, though on this basis, absorption would also be ex-

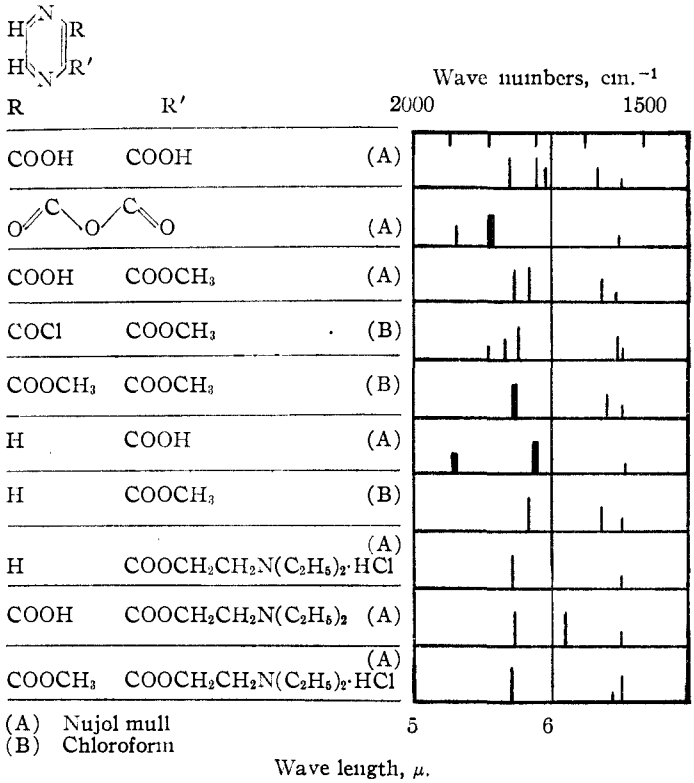
(1) E. Epstein, Thesis, Polytechnic Institute of Brooklyn, 1939.

(2) W. B. Burnett, R. L. Jenkins, C. H. Peet, E. E. Dreger and R. Adams, THIS JOURNAL, **59**, 2248 (1937).

(3) German Patent 371,046; *C. A.*, **18**, 1504 (1924).

TABLE II

INFRARED ABSORPTION MAXIMA IN THE 1500-2000 CM.$^{-1}$ REGION OF PYRAZINOIC ACIDS AND ESTERS



(A) Nujol mull
(B) Chloroform

pected in the other compounds containing the $\diagup\!\!N\!\!\diagdown$C—COOH moiety. Carbonyl absorption maxima in the spectra of the anhydride, esters, acid esters and ester hydrochlorides occur at the anticipated wave lengths. The spectra of all compounds in the series exhibited one or two weak bands in the 1530–1580 cm.$^{-1}$ region.

The compounds listed in Table I, methyl acid pyrazine-2,3-dicarboxylate and methyl pyrazinoate were tested for local anesthetic activity.[4] The *n*-dibutyl esters were the most active of those in Table I, and compound VI the best of this group. The latter was approximately half as active as procaine, but the duration of anesthesia was twice as long. Surprisingly, both of the methyl esters exhibited local anesthetic action; the methyl acid ester was comparable to or slightly better than compound I and the methyl ester not quite as good.

While this investigation was in progress, it was discovered that pyrazine carboxamide possesses tuberculostatic activity.[5] Consequently, all the pyrazine compounds herein described were screened for *in vitro* activity against *Mycobacterium tuberculosis* H37Rv by serial dilution methods under such conditions that streptomycin is inhibitory at 0.3 to 0.6 γ/ml. Pyrazine carboxamide, prepared by reaction of pyrazinoyl chloride with aqueous ammonia or methyl pyrazinoate with ammonia in methanol, was active at 250 γ/ml. Compounds VII and VIII (Table I) and pyrazinoic acid were also found to be active at this concentration, whereas the remainder were inactive at 1000 γ/ml.

(4) The authors wish to thank Dr. S. Y. P'an of Chas. Pfizer and Co., Inc., for performing these tests.

(5) S. Kushner, *et al.*, THIS JOURNAL, **74**, 3617 (1952).

Experimental

Pyrazine-2,3-dicarboxylic Acid.—Pyrazine-2,3-dicarboxylic acid was prepared by potassium permanganate oxidation of quinoxaline with modifications of a previously described procedure.[6] Quinoxaline (72 g., 0.56 mole) and potassium hydroxide (32 g., 0.57 mole) in 1600 ml. water was stirred and treated with 560 g. (3.55 moles) of potassium permanganate, added periodically in 3-g. portions, while the temperature was maintained between 25 and 30°. The reaction mixture was heated at 70° for two hours, the slight excess of permanganate was removed with methanol and the manganese dioxide was filtered and thoroughly repulped in hot water. The light yellow filtrate was concentrated to 2 l., acidified with acetic acid, and further concentrated to completely remove carbon dioxide. The resulting solution was then made alkaline with ammonium hydroxide, warmed and treated with 180 g. of barium chloride in a minimum amount of water. The precipitated barium pyrazine-2,3-dicarboxylate was filtered and dried; weight 148 g. The salt, suspended in 400 ml. of water, was treated with a slight excess (28.7 ml.) of sulfuric acid and the barium sulfate was filtered. The filtrate was evaporated to 50 ml. and the pyrazine-2,3-dicarboxylic acid was filtered and dried (65 g.). Further evaporation afforded a second crop, 11.1 g., total yield 82%. Recrystallization from water gave colorless needles, which after drying thoroughly *in vacuo* had m.p. 185° (dec.). This product was not as spectrally pure (infrared), probably due to small amounts of oxalic acid, as that obtained from the anhydride (see below).

Pyrazine-2,3-dicarboxylic Anhydride.—Pyrazine-2,3-dicarboxylic acid was converted to the anhydride by the method of Gabriel and Sonn.[6] Acetic anhydride, which was superior to thionyl chloride for the dehydration, gave 95% yield in two crops. For analysis samples were recrystallized from acetic anhydride; the compound darkens at about 175°, but does not melt.[6]

Anal. Calcd. for $C_6H_2O_3N_2$: C, 48.01; H, 1.34; N, 18.67. Found: C, 47.96; H, 1.45; N, 18.94.

Dissolving the anhydride in warm water gave pyrazine-2,3-dicarboxylic acid, m.p. 187° (dec.); reported m.p. 193°.[6]

Anal. Calcd. for $C_6H_4O_4N_2$: C, 42.86; H, 2.40; N, 16.67. Found: C, 42.82; H, 2.47; N, 16.80.

Methyl Acid Pyrazine-2,3-dicarboxylate.—Pyrazine-2,3-dicarboxylic anhydride (5 g.) was refluxed in 15 ml. of dry methanol for 15 minutes, and then the methanol was evaporated to leave a colorless crystalline product, weight 6.0 g., m.p. 115–116°. The methyl acid ester after recrystallization from benzene–methanol had m.p. 117–118°.

Anal. Calcd. for $C_7H_6O_4N_2$: C, 46.16; H, 3.32; N, 15.38; neut. equiv., 182.1. Found: C, 46.14; H, 3.46; N, 15.62; neut. equiv., 181.

Methyl Pyrazinoate.—Crude methyl acid pyrazine-2,3-dicarboxylate (3.0 g., 0.0165 mole) was decarboxylated by maintaining the molten product at 135–140° for one hour. The carbon dioxide was flushed with nitrogen into aqueous barium hydroxide and determined as barium carbonate (3.20 g., 0.016 mole). The residue, weight 2.32 g., was dissolved in ether, treated with carbon and the solution was filtered. Evaporation of the solvent afforded pale yellow crystals of methyl pyrazinoate, weight 2.0 g. (88% yield), m.p. 52–56°. Low temperature crystallization from ether raised the m.p. to 59–60°, reported 59°.[7]

The methyl ester in methanolic ammonia[8] afforded the amide, m.p. 185–187°. The m.p. was raised to 190–191° by recrystallization from water, reported m.p. 188°.[8]

Pyrazinoyl Chloride.—Pyrazinoic acid was prepared either by decarboxylation of pyrazine-2,3-dicarboxylic acid[6]

(6) S. Gabriel and A. Sonn, *Ber.*, **40**, 4851 (1907).

(7) S. A. Hall and P. E. Spoerri, THIS JOURNAL, **62**, 664 (1940).

(8) U. S. Patent 2,149,279 (Mar. 7, 1939).

or by saponification of the methyl ester. The acid (3 g.) suspended in 18 ml. of benzene and 12 ml. of purified thionyl chloride was refluxed for 1.5 hours. The solvent and excess thionyl chloride were removed *in vacuo* leaving a reddish crystalline solid. The crude pyrazinoyl chloride was purified by vacuum sublimation (2.0 mm.) at a bath temperature of 50–60° to give colorless crystals that weighed 2.9 g. (84% yield) and had m.p. 59–61°.[9] Attempts to distil the acid chloride as described by Dalmer and Walter[6] resulted in extensive decomposition.

When pyrazinoyl chloride is stored, it rapidly turns red with concurrent decomposition. Consequently, it was prepared and used immediately.

Acid Chloride of Methyl Pyrazine-2,3-dicarboxylate.—Methyl acid pyrazine-2,3-dicarboxylate (2.0 g.) was refluxed in 6 ml. of benzene and 3.3 ml. of thionyl chloride for one hour. The solvent and excess thionyl chloride were removed under vacuum and the amber residue (weight 2.2 g.) was fractionally distilled. The three fractions of methyl acid chloride all boiled at 94–96° (0.2 mm.); the center cut (1.4 g., $n^{25}D$ 1.5301) was analyzed.

Anal. Calcd. for $C_7H_5O_3N_2Cl$: C, 41.91; H, 2.51; N, 13.96. Found: C, 42.25; H, 2.41; N, 14.29.

A portion of the acid chloride (1.0 g.) reacted exothermally with 1 ml. of methanol. The methanol was evaporated and the residue in 15 ml. of ether was washed with excess sodium bicarbonate in 20% sodium chloride solution. The ether phase was dried over anhydrous sodium sulfate and evaporated to give the crystalline dimethyl ester, weight 0.95 g., m.p. 59–62°. The m.p. was raised to 62–63° by low temperature recrystallization from ether. The reported[6] m.p. is 47–50°.

(9) B. Meltsner, Thesis, Polytechnic Institute of Brooklyn, 1950.

Anal. Calcd. for $C_8H_8O_4N_2$: C, 48.91; H, 4.11; N, 14.28. Found: C, 49.07; H, 4.18; N, 14.33.

β-Dimethylaminoethyl Pyrazinoate Hydrochloride.—Freshly prepared pyrazinoyl chloride (2.7 g., 0.019 mole) dissolved in 25 ml. of dry benzene was treated with 1.7 g. (0.019 mole) of β-dimethylaminoethanol. The ester hydrochloride precipitated immediately as a semi-crystalline, colorless solid and after one hour at 5° was filtered; weight 3.7 g. Recrystallization from *n*-propanol–isopropyl alcohol gave needles, m.p. 184–185°. By comparable methods the β-diethylaminoethyl and β-dibutylaminoethyl ester hydrochlorides were prepared (see Table I).

Methyl β-Diethylaminoethyl Pyrazine-2,3-dicarboxylate Hydrochloride.—A solution of 6.4 g. of the acid chloride of methyl pyrazine-2,3-dicarboxylate in 8 ml. of benzene was treated with an equimolar quantity (3.42 g.) of β-diethylaminoethanol. The precipitated ester hydrochloride was filtered, washed with benzene and dried; weight 9.6 g., m.p. 98–110°. Two recrystallizations from acetone gave colorless crystals, m.p. 113–115°. Reaction of the acid chloride with β-dimethylaminoethanol or β-dibutylaminoethanol gave the respective ester hydrochlorides (see Table I).

β-Dibutylaminoethyl Acid Pyrazine-2,3-dicarboxylate.—To 10.9 g. (0.072 mole) of pyrazine-2,3-dicarboxylic anhydride in refluxing benzene, 12.5 g. (0.072 mole) of β-dibutylaminoethanol was added in small portions over a period of four hours. The mixture was heated for an additional hour and then the tan crystals were filtered and dried *in vacuo;* weight 22.2 g. Two recrystallizations from *n*-butanol–acetone afforded colorless crystals, m.p. 151–152°. In a similar manner the β-dimethylaminoethyl and β-diethylaminoethyl esters were prepared with the appropriate amino alcohol.

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[CONTRIBUTION FROM THE ORGANIC CHEMICALS DIVISION, NITRO RESEARCH DEPARTMENT, MONSANTO CHEMICAL COMPANY]

Chloro-substituted Unsaturated Alkylmercapto Thiazoles

BY JOHN J. D'AMICO

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The following nine compounds have been synthesized and characterized: 2-(3-chloro-2-butenylmercapto)-benzothiazole, 2-(2-chloroallylmercapto)-benzothiazole, 2-(*trans*-2,3-dichloro-2-butenylmercapto)-benzothiazole, 2-(3-chloroallylmercapto)-benzothiazole, 2-(2-chloroallylmercapto)-4-methylthiazole, 2-(3-chloro-2-butenylmercapto)-4-methylthiazole, 2,2′-bis-(2-butenylmercapto)-benzothiazole, 2-(4-chloro-2-butenylmercapto)-benzothiazole and 2-(2-butynylmercapto)-benzothiazole.

Thiazolethiols and some of their derivatives are known to be excellent accelerators for the vulcanization of rubber with sulfur. The purpose of this investigation was the synthesis of chloro-substituted unsaturated alkylmercapto thiazoles and determination of the effect of unsaturation and chloro-substituents on the properties of the rubber vulcanizates. The results and comparison of the activity of these compounds as accelerators for rubber will be reported in another paper.

The new compounds were prepared by treating the sodium salt of either 2-mercaptobenzothiazole or 4-methyl-2-thiazolethiol in an aqueous solution with the following unsaturated chloro compounds: *trans*-1,2,3-trichloro-2-butene, 1,3-dichloro-2-butene, 2,3-dichloro-1-propene, 1,4-dichloro-2-butene, 1,3-dichloropropene and 1-chloro-2-butyne. The reaction may be represented as follows: RSNa + R′Cl → RSR′ + NaCl where R is a thiazolyl group and R′ is either chloro-substituted alkenyl or alkinyl group. In the reaction of the sodium salt of 2-mercaptobenzothiazole with 1,4-dichloro-2-butene, two products were obtained and identified. Physical data are listed in Table I.

Experimental[1]

2-(3-Chloro-2-butenylmercapto)-benzothiazole (I).—A solution containing 1.5 moles of 2-mercaptobenzothiazole was prepared by dissolving 258 g. of 97% 2-mercaptobenzothiazole in 240 g. (1.5 moles) of 25% sodium hydroxide and 1500 g. of water. This solution was filtered and to the stirred filtrate was added 169 g. (1.35 moles) of 1,3-dichloro-2-butene.[2] An exothermic reaction set in, the temperature rising from 27 to 38° within 20 minutes. The reaction mixture was stirred for five hours and the organic layer separated. The unreacted sodium 2-mercaptobenzothiazole was recovered from the aqueous layer by acidification with concentrated hydrochloric acid. The amber oily organic layer was dissolved in 400 ml. of ethyl ether, washed repeatedly with 2% sodium hydroxide, then with water until the wash water was neutral to litmus, and the solvent was removed by distillation. The residue was dried over Attapulgus clay and a yield of 322 g. of an amber oily product was obtained.

2-(2-Chloroallylmercapto)-benzothiazole (II).—This procedure was similar to compound I except 190 g. (1.1 moles) of 97% 2-mercaptobenzothiazole, 176 g. (1.1 moles) of 25% aqueous sodium hydroxide, 1100 g. of water and 111 g.

(1) All melting points were taken upon a Fisher-Johns block and are uncorrected.

(2) Kindly supplied by E. I. du Pont de Nemours and Company, Wilmington, Delaware.