[CONTRIBUTION FROM THE STERLING CHEMISTRY LABORATORY, YALE UNIVERSITY]

The Synthesis of Some Alkamine Esters of Alkylthiobenzoic Acids

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Among the numerous synthetic local anesthetics that have been prepared, those which are found most effective from a practical point of view are the *p*-aminobenzoic acid alkamine esters of the procaine type. Much experimental work has been carried out in an effort to improve the characteristics of these compounds and to correlate structure and physiological activity in this series. A considerable portion of this work has been directed toward modification of the amino alcohol portion of the molecule.[2]

It has been found, however, that the introduction of groups other than the amino group into the benzene ring of this class of compounds may increase their efficiency as local anesthetics. Alkoxy groups, for example, when introduced into the novocaine molecule are reported to increase the activity of this compound as a local anesthetic.[3] Indeed, investigation has shown that the alkoxy group may replace the nuclear amino group in aminobenzoic acid alkamine esters, in some cases increasing the activity of the resulting compound beyond that of the corresponding amino derivative.[4]

There are very few data in the literature on the effect of sulfur-containing groups on the pharmacological properties of local anesthetics and no data on the effect of alkylthio groups in this connection have appeared. In a few instances local anesthetics have been prepared which contain sulfur groupings[5] and these have been found superior to the oxygen analogs in these cases.

In view of the above facts it seemed worth while to prepare a series of alkylthio-substituted benzoic acid alkamine esters in order to determine whether such compounds possess local anesthetic activity and thus to establish the value of the alkylthio grouping in this series. By utilizing several different alkylthio groups as well as several amino alcohols it was hoped that some connection between structure and physiological action could be established in this series of compounds.

The method found most practical for the introduction of the alkylthio group into the benzoic acid nucleus is a modification of that of Leuckart[6] involving the reaction of a diazonium salt with potassium ethyl xanthate and direct alkylation of the reaction mixture. The alkylthiobenzoic acids prepared in this way from the corresponding aminobenzoic acids were converted to the acid chlorides and these were treated with the desired amino alcohol to give the alkamine ester. The basic esters were converted to the hydrochlorides for pharmacological testing.

The detailed report of the local anesthetic behavior of these compounds will be presented elsewhere.[7] It may be said that the compounds reported here are all less toxic than procaine. Furthermore, many of them surpass this local anesthetic in duration of anesthesia when tested on the rabbit cornea. The *o*- and *m*-ethylthio and methylthio compounds are more active than the corresponding *p*-derivatives.

Experimental

Alkylthiobenzoic Acids.—The aminobenzoic acid (ortho, meta, para) was diazotized in the usual manner with sodium nitrite and hydrochloric acid and the resulting diazonium salt solution poured into a hot (70°), freshly prepared solution of one mole of potassium ethyl xanthate containing sufficient sodium carbonate to neutralize the acid in the diazonium salt solution. After the reaction was over, as indicated by the cessation of the evolution of gases, the mixture was cooled. It was then treated with 1.1 moles of sodium hydroxide and one mole of diethyl or dimethyl sulfate. In the case of the higher members of the series two moles of the alkyl halide and an equivalent amount of sodium hydroxide in five times its weight of 70% alcohol was used. The mixture was then refluxed for five hours to complete the alkylation. On acidifying with hydrochloric acid, the crude alkylthiobenzoic acid was obtained in a form pure enough for use in subsequent operations. The yields ranged from 80 to 100% of the theoretical quantity. The pure alkylthiobenzoic acids are best prepared by recrystallization from dilute acetic acid. The compounds are white or slightly yellow crystalline solids, practically insoluble in water and soluble in organic solvents.

(1) This communication describes work done by James English, Jr., in partial fulfilment of the requirements for the degree of Doctor of Philosophy in Chemistry.

(2) S. Fränkel, "Arzneimittelsynthese," Berlin, 1927, p. 387.

(3) German Patents 512,723, 511,467 (1930).

(4) E. A. Wildman and L. Thorpe, U. S. Patent 1,193,650 (1915); C. Rohman and B. Scheurle, *Arch. Pharm.*, **274**, 110 (1936); A. R. McIntyre and R. F. Sievers, *J. Pharmacol.*, **61**, 107 (1937).

(5) H. L. Hansen and L. S. Fosdick, THIS JOURNAL, **55**, 2872 (1933); German Patent 239,310; C. F. Lischer and C. N. Jordan, *ibid.*, **59**, 1623 (1937); S. A. Karjala and S. M. McElvain, *ibid.*, **55**, 2966 (1933).

(6) R. Leuckart, *J. prakt. Chem.*, [2], **41**, 179 (1890).

(7) The authors are indebted to J. H. Weatherby, H. R. Hulpieu and the Pitman-Moore Company for carrying out the pharmacological testing.

TABLE I

ALKYLTHIOBENZOIC ACIDS AND CHLORIDES

	Methyl		Ethyl		*n*-Propyl		*n*-Butyl	
	m-	*o*-	*m*-	*p*-	*o*-	*m*-	*o*-	*m*-
Acids								
M. p., °C.	129	134	98	145	121	104	98	103
S, Calcd.	[b]	[a]	16.00[c]	[d]	16.32	16.32	15.24	15.24
% Found			16.06		16.14	16.19	14.98	14.97
Chlorides								
B. p., °C.	123	133	127	118	145	138	151	147
Press., mm.	8	3	3	3	3	3	3	3

[a] Previously reported m. p. 134°, German Patent 203,388 (1908). [b] Th. Zincke and J. Müller, *Ber.*, **46**, 775 (1913). [c] Monohydrate. [d] K. Auwers and C. Beger, *ibid.*, **27**, 1739 (1894).

Acid Chlorides.—To the dried alkylthiobenzoic acid prepared as above, there was added the calculated quantity of phosphorus pentachloride. A vigorous reaction ensued, and after this subsided the mixture was refluxed for one-half hour to complete the reaction. The phosphorus oxychloride was removed by distillation under reduced pressure and the product distilled. The alkylthiobenzoyl chlorides distill without decomposition at pressures below 5 mm. but on standing for some days they decompose slowly. They are light yellow, viscous oils which turn darker on standing.

Alkamine Esters.—A dry ether solution of the acid chloride prepared as above was treated with a mixture of one molecular quantity of the desired amino alcohol and an excess of pyridine (about 2 moles). After refluxing for three hours the mixture was poured into a cold dilute solution of sodium carbonate and the basic ester extracted with ether. The ether was then dried over sodium sulfate and removed in the usual manner. The products were distilled under reduced pressure. Hydrochlorides of these esters were prepared by passing dry hydrogen chloride into a dry ether solution of the free base. The precipitated salt was filtered and recrystallized from dry acetone. The pure salts are white crystalline compounds, somewhat hygroscopic, especially if not quite pure. The lower members of the series are readily soluble in water; the solubility diminishes with increase in the size of the alkyl groups on sulfur and in the amino alcohol portion of the molecule.

TABLE II

ALKAMINE ESTERS

	B. p. °C.	Mm.	Hydrochloride m. p., °C.	Nitrogen, % Calcd.	Found
***o*-Ethylthiobenzoates**					
β-Diethylaminoethyl	158	3	128	4.42	4.46
γ-Diethylaminopropyl	184	3	121	4.24	4.23
β-Piperidinoethyl	197	3	134	Cl, 10.54	10.55
β-Dibutylaminoethyl	187	3	116	3.75	3.83
***o*-*n*-Propylthiobenzoates**					
β-Diethylaminoethyl	176	3	123	4.24	4.22
γ-Diethylaminopropyl	182	3	87	4.02	4.03
β-Piperidinoethyl	190	3	128	Cl, 10.12	10.31
β-Dibutylaminoethyl	208	3	93	3.62	3.57
***o*-*n*-Butylthiobenzoates**					
β-Diethylaminoethyl	180	2	117	4.06	4.00
γ-Diethylaminopropyl	193	2	96	3.90	3.81
β-Piperidinoethyl	198	2	120	Cl, 9.72	9.85
β-Dibutylaminoethyl	193	3	107	3.49	3.37
***m*-Methylthiobenzoates**					
β-Diethylaminoethyl	185	5	153	4.63	4.62
γ-Diethylaminopropyl	190	4	149	4.42	4.38
***m*-Ethylthiobenzoates**					
β-Diethylaminoethyl	163	2	135	4.42	4.34
γ-Diethylaminopropyl	170	3	125	4.24	4.13
β-Piperidinoethyl	173	3	139	Cl, 10.54	10.65
***m*-*n*-Propylthiobenzoates**					
β-Diethylaminoethyl	172	2	110	4.24	4.32
γ-Diethylaminopropyl	183	3	94	4.06	3.98
β-Piperidinoethyl	182	3	116	Cl, 10.12	10.24
***m*-*n*-Butylthiobenzoates**					
β-Diethylaminoethyl	200	4	110	4.06	3.97
γ-Diethylaminopropyl	194	3	96	3.90	3.97
β-Piperidinoethyl	198	3	114	Cl, 9.72	9.95
***p*-Ethylthiobenzoates**					
β-Diethylaminoethyl	160	3	166	4.42	4.54
γ-Diethylaminopropyl	185	3	138	4.24	4.20

All nitrogen analyses in Table II were done by the Kjeldahl method on a semimicro scale. Chlorine analyses are reported for those compounds not suited to this method.

Summary

1. A general method of preparation of a series of alkylthiobenzoic acids has been described.

2. A series of alkamine esters of these acids has been prepared by action of their acid chlorides on a series of amino alcohols.

3. Preliminary pharmacological investigation has shown these compounds to possess marked local anesthetic activity and low toxicity.

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