[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT OF NORTHWESTERN UNIVERSITY DENTAL SCHOOL]

Some Alkyl and Alkamine Esters of *p*-Aminothiobenzoic Acid and Related Compounds

BY HAROLD L. HANSEN AND LEONARD S. FOSDICK

Since Einhorn and Uhlfelder[1] published their report on novocaine and related substances, many compounds possessing local anesthetic properties have been prepared. In view of the growing interest in organic sulfur compounds and because of the similarities between sulfur and oxygen it was considered interesting to prepare and to study various alkyl and alkamine esters of *p*-aminothiobenzoic acid. It was anticipated that the presence of the sulfur atom in such compounds would not alter greatly the anesthetic properties and that the toxic properties might be less than those of the corresponding oxygen esters.

Synthetic studies of thio esters in the aromatic series are quite limited, especially when compared with the amount of work done on the oxygen esters. Kim[2] prepared both *p*-nitrothiobenzoic acid and thiobenzoic acid. More recently Pratt and Reid[3] prepared various alkyl esters of thiobenzoic acid. In the present study the alkyl esters were prepared by alkylation of *p*-nitrothiobenzoic acid, followed by reduction with iron powder and hydrochloric acid. Tin and hydrochloric acid gave uniformly low yields. The thio derivative of novocaine, or thiocaine, was prepared according to the scheme: $p\text{-}NO_2C_6H_4COCl \longrightarrow NO_2C_6H_4COSH \longrightarrow p\text{-}NO_2C_6H_4COSCH_2CH_2Cl \longrightarrow p\text{-}NH_2C_6H_4COSCH_2CH_2Cl \longrightarrow p\text{-}NH_2C_6H_4COSCH_2CH_2N(C_2H_5)_2$.

The alkyl esters prepared in this study produce intense anesthesia when applied to mucous membrane, as does also thiocaine. Preliminary experiments by the goldfish method of Adams and co-workers[4] indicate that thiocaine is several times as rapid an anesthetic as novocaine and its toxicity does not appear to be high. Preliminary determinations by subcutaneous injection of white mice indicate that the toxicity of thiocaine is about one-half that of cocaine. A detailed pharmacological investigation by us will be presented elsewhere.

The study of various types of thio esters of the anesthetic type is being continued in this Laboratory.

Experimental Part

p-Nitrothiobenzoic Acid.—This substance was prepared according to a procedure based upon that of Kim.[2] In a five-liter flask equipped with a mechanical stirrer and dropping funnel was placed a solution of 162 g. of potassium hydroxide in about 3

(1) Einhorn and Uhlfelder, *Ann.*, **371**, 131 (1909).
(2) Kim, *Ber.*, **32**, 3533 (1899).
(3) Pratt and Reid, THIS JOURNAL, **37**, 1934 (1915).
(4) Adams and co-workers, *ibid.*, **48**, 1758 (1926).

liters of ethanol. The solution was then saturated with hydrogen sulfide. To the solution cooled in an ice–salt bath was added slowly with rapid stirring 265 g. of *p*-nitrobenzoyl chloride in dry benzene. The yellow precipitate was removed and the filtrate evaporated slowly under reduced pressure. The combined precipitates were dissolved in cold water and the free acid was liberated with hydrochloric acid. The yellow solid was purified by solution in dilute alkali, followed by liberation with hydrochloric acid. The yield was 262 g. or 94% of the calculated amount, m. p. 96–98° corr.

***n*-Alkyl *p*-Nitrothiobenzoates.**—These compounds were prepared by the alkylation of potassium *p*-nitrothiobenzoate with the corresponding alkyl bromides except in the case of the methyl ester, where methyl iodide was used. The following experiment is typical.

Ethyl *p*-Nitrothiobenzoate.—In a round-bottomed flask equipped with mechanical stirrer, dropping funnel, and condenser was placed 18.3 g. of *p*-nitrothiobenzoic acid. To this was added 5.6 g. of potassium hydroxide in ethanol. The alkyl bromide was added dropwise with stirring and the flask was gently warmed to start the reaction. The mixture was heated on the water-bath for one hour to complete the reaction. The excess alcohol was removed by distillation and the residue poured into cold dilute alkali. The pale yellow precipitate was recrystallized from a mixture of ethanol and water.

***n*-Alkyl *p*-Aminothiobenzoates.**—The nitro esters were reduced with iron powder and hydrochloric acid. The hydrochloride of *n*-butyl *p*-aminothiobenzoate is sparingly soluble in water and is best purified by precipitation from dry ether or benzene. The following experiment is typical.

Methyl *p*-Aminothiobenzoate.—To a mixture of 3 g. of methyl *p*-nitrothiobenzoate, 75 cc. of 95% ethanol and 20 cc. of concentrated hydrochloric acid cooled in ice water was added in small portions and with rapid stirring one gram of iron powder. Stirring was continued for four to six hours after all the iron had been added. The reaction mixture was then filtered and the filtrate poured into four times its volume of ice water. The amino compound was precipitated by careful addition of ammonium hydroxide. The crude product was dissolved in absolute ethanol and precipitated with cold water. Recrystallization from a mixture of ethanol and water gave a very pale yellow flaky precipitate.

β-Chloroethyl *p*-Nitrothiobenzoate.—This substance was prepared from 183 g. of *p*-nitrothiobenzoate and 183 g. of 1-chloro-2-bromoethane according to the method previously described. The yellow compound was recrystallized from 98% ethanol.

β-Chloroethyl *p*-Aminothiobenzoate.—This compound was prepared from the nitro compound according to the method previously described with the exception that the reaction was allowed to run for about twenty hours. The product was purified by precipitation as the hydrochloride from dry ether. The hydrochloride was then suspended in water and treated with ammonium hydroxide.

β-Diethylaminoethyl *p*-Aminothiobenzoate.—A mixture of 30 g. of β-chloroethyl *p*-aminothiobenzoate and 30 g. of diethylamine was heated in a sealed tube at 100–110° for six hours. The contents of the tube were washed into an excess of cold dilute hydrochloric acid. The filtered acidic solution was neutralized with sodium hydroxide solution with strong cooling. The yellow precipitate was dissolved in dilute hydrochloric acid and warmed on the steam-bath with decolorizing carbon. The free base was precipitated by the addition of ammonium hydroxide in the cold. From dilute solutions it forms grayish-white needles. It was further purified by recrystallization from a mixture of ethanol and water. Occasionally a product of pronounced yellow color is obtained. This may be purified by treatment with decolorizing carbon, followed by recrystallization. The hydrochloride was obtained by treating the free base in dry ether with dry hydrogen chloride. Recrystallization from 98% ethanol gave a fine yellow powder, freely soluble in water and fairly stable to boiling.

Table I gives the yields, melting points and analytical data obtained for the compounds prepared in this study.

TABLE I

Compound	Yield, %	M. p., °C. corr.	Sulfur, % Calcd.	Sulfur, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
p-$NO_2C_6H_4COSCH_3$	66	96–97	16.26	16.47	7.11	7.17
p-$NO_2C_6H_4COSC_2H_5$	57	67–68	15.15	14.80	6.64	6.79
p-$NO_2C_6H_4COSC_3H_7$	50	30–31	14.24	14.00	6.36	6.32
p-$NO_2C_6H_4COSC_4H_9$	63	13–15	13.35	13.28	5.83	5.89
p-$NH_2C_6H_4COSCH_3$	98	113–114	19.18	18.92	8.39	8.45
p-$NH_2C_6H_4COSC_2H_5$	84	79–79.5	17.60	17.34	7.73	7.72
p-$NH_2C_6H_4COSC_3H_7$	78	60–61	16.25	16.46	7.02	7.25
p-$NH_2C_6H_4COSC_4H_9$	76	37–38	15.10	15.29	6.69	6.50
p-$NO_2C_6H_4COSCH_2CH_2Cl$	70	91–92	13.05	13.31	5.68	5.59
p-$NH_2C_6H_4COSCH_2CH_2Cl$	85	99–101	14.87	14.88	6.46	6.25
p-$NH_2C_6H_4COSC_2H_4N(C_2H_5)_2$	80	52–52.5	12.71	12.98	11.10	11.00
p-$NH_2C_6H_4COSC_2H_4N(C_2H_5)_2 \cdot HCl$	100	177.6–178	...	...	9.70	9.64

Summary

Several alkyl esters have been prepared from p-nitrothiobenzoic acid. The amino compounds obtained from them are topical anesthetics.

The thio derivative of novocaine has been prepared and found to have anesthetic properties.

CHICAGO, ILLINOIS RECEIVED JANUARY 30, 1933
PUBLISHED JULY 6, 1933

[CONTRIBUTION NO. 110 FROM THE COBB CHEMICAL LABORATORY, UNIVERSITY OF VIRGINIA]

The Desoxymorphines[1]

BY LYNDON F. SMALL AND DAVID E. MORRIS

Pharmacological studies which have been carried out on the series of desoxycodeines and their hydrogenated derivatives described in previous papers from this Laboratory[1a] make it seem probable that the action of codeine and its isomers in depressing the respiratory reflex may depend to a considerable degree upon the presence of the secondary alcoholic group located in ring III. In view of this hypothesis, an examination of the corresponding series of desoxymorphine derivatives seemed desirable. The desoxymorphines are, however, exceedingly sensitive substances, and the preparation of a complete series has not been possible.

Treatment of α-chloromorphide (I) with zinc dust in boiling alcohol yields only resinous products and unchanged α-chloromorphide instead of

(1) This investigation was supported by a grant from the Committee on Drug Addiction of the National Research Council from funds provided by the Bureau of Social Hygiene, Inc. Presented in part at the New Orleans Meeting of the American Chemical Society, March 30, 1932.

(1a) Small and Cohen, THIS JOURNAL, **53**, 2214, 2227 (1931); Mosettig, Cohen and Small, *ibid.*, **54**, 793 (1932); Small and Cohen, *ibid.*, **54**, 802 (1932).