[CONTRIBUTION FROM THE STERLING CHEMISTRY LABORATORY, YALE UNIVERSITY]

Some Alkamine Esters of Alkylthio-substituted Phenylcarbamic Acids

BY JOHN J. DONLEAVY AND JAMES ENGLISH, JR.[1]

It has been known for some time that certain types of carbamates are active local anesthetics. The phenylcarbamates of some amino alcohols have been investigated[2] and found to produce anesthesia of longer duration than that of the corresponding *p*-aminobenzoic acid esters. An investigation of the phenylcarbamates of some dioxy amino alcohols[3] has indicated that these are effective local anesthetics and also certain alkamine esters of diaryl substituted carbamates have been prepared.[4]

As yet, however, little effort has been devoted to the investigation of the effect of substituents in the benzene nucleus on the pharmacological activity of this class of compounds. It has been reported that the introduction of a methoxyl group in the para position of compounds of the type $C_6H_5NHCOOCH_2CH_2(C_2H_5)_2$ acts to decrease, while an amino group in this position increases, the local anesthetic activity of the product.[5]

In view of the recent work by the authors on the introduction of the alkylthio group in local anesthetics of the novocaine type,[6] it seemed desirable to discover whether this grouping would be effective in alkamine esters of phenylcarbamic acid also. The present paper describes the preparation of a series of such compounds. The alkylthio groups were introduced in the meta position since preliminary tests on alkylthiobenzoic esters indicated this to be the most favorable one. The method for the introduction of alkylthio groups into the aromatic nucleus is the same as that used in the previous investigation.[6]

The pharmacological data will be reported elsewhere[7] and it must suffice to say here that the compounds are of approximately the same toxicity as cocaine and are somewhat irritating. A 0.5% solution of compound 2 (Table I) gave anesthesia of duration equal to that of 2% cocaine; the other compounds were found less active than this.

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

(2) T. H. Rider, THIS JOURNAL, **52**, 2583 (1930); E. S. Cook and T. H. Rider, *ibid.*, **58**, 1079 (1936).

(3) T. H. Rider, *J. Pharmacol.*, **47**, 255 (1933); E. W. Scott and T. H. Rider, THIS JOURNAL, **55**, 804 (1933).

(4) A. D. Boese and R. T. Major, *ibid.*, **57**, 175 (1935); J. J. Donleavy and J. English, *ibid.*, **62**, 218 (1940).

(5) S. Frankel, "Arzneimittelsynthese," Berlin, 1927, p. 396.

(6) J. J. Donleavy and J. English, Jr., THIS JOURNAL, **62**, 2220 (1940).

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

Experimental

***m*-Nitrophenylalkyl Sulfides.**—A cold, filtered solution of diazotized *m*-nitroaniline (one mole) was poured into a solution of 1.25 moles of potassium ethyl xanthate in hot water (70°) with stirring. A vigorous evolution of gases took place and a dark oil separated from the solution on cooling. This oil, *m*-nitrophenylethylxanthate, was separated from the solution and used directly without further purification. The product was hydrolyzed by refluxing for two hours with a 20% solution of potassium hydroxide in 70% alcohol. The resulting solution was alkylated directly by the gradual addition of diethyl sulfate (one mole) or *n*-butyl bromide (two moles) and further refluxing for four hours more. The phenylalkyl sulfides were isolated by diluting the reaction mixture and extracting with ether; they were purified by distillation. The yields were 40 to 50% of the theoretical.

m-Nitrophenylethyl sulfide, b. p. 117° (3 mm.). *Anal.* Calcd. for $C_8H_9O_2NS$: N, 7.64. Found: N, 7.33.

m-Nitrophenylbutyl sulfide, b. p. 135° (3 mm.). *Anal.* Calcd. for $C_{10}H_{13}O_2NS$: N, 6.63. Found: N, 6.23.

***m*-Aminophenylalkyl Sulfides.**—The nitrophenylalkyl sulfides were reduced with tin and hydrochloric acid in the usual manner. The products were isolated by ether extraction and distillation under reduced pressure. The yields were about 80% of the theoretical.

m-Aminophenylethyl sulfide, b. p. 103° (3 mm.). *Anal.* Calcd. for $C_8H_{11}NS$: N, 9.15. Found: N, 8.82.

m-Aminophenylbutyl sulfide, b. p. 131° (3 mm.). *Anal.* Calcd. for $C_{10}H_{15}NS$: N, 7.73. Found: N, 7.52.

***m*-Alkylthiophenylurethans.**—A dry ether solution of the *m*-aminophenylalkyl sulfide was treated with two molecular quantities of pyridine and one molecular quantity of chloroethylcarbonate. A vigorous reaction took place with the formation of a precipitate of pyridine hydrochloride. The solution was refluxed for one-half hour to complete the reaction. Cold water was added to the cooled solution, the mixture made acid with hydrochloric acid and extracted with ether. The products were purified by distillation. The yields were 90% of the theoretical.

m-Ethylthiophenylurethan, b. p. 165° (4 mm.). *Anal.* Calcd. for $C_{11}H_{15}O_2NS$: N, 6.23. Found: N, 5.99.

m-Butylthiophenylurethan, b. p. 176° (3 mm.). *Anal.* Calcd. for $C_{13}H_{19}O_2NS$: N, 5.53. Found, N, 5.35.

***m*-Alkylthiophenylisocyanates.**—These compounds were prepared from the corresponding urethans by distillation under reduced pressure mixed with twice their weight of phosphorus pentoxide. The yield was about 50% of the theoretical. *m*-Ethylthiophenylisocyanate, b. p. 127° (10 mm.); *m*-butylthiophenylisocyanate, b. p. 129–134° (3 mm.).

TABLE I

	M. p., °C.	Nitrogen, % Calcd.	Found
m-$C_2H_5SC_6H_5NHCOOCH_2$-$CH_2N(C_2H_5)_2$·HCl	148	8.43	8.31
m-$C_2H_5SC_6H_5NHCOOCH_2CH_2$-$CH_2N(C_2H_5)_2$·HCl	113	8.09	7.90
m-$C_4H_9SC_6H_5NHCOOCH_2$-$CH_2N(C_2H_5)_2$·HCl	94	7.78	7.77
m-$C_4H_9SC_6H_5NHCOOCH_2CH_2$-$CH_2N(C_2H_5)_2$·HCl	158	7.48	7.35

Alkamine Esters of Alkylthiophenylcarbamic Acids.—These compounds were prepared from the above isocyanates by mixing them in dry ether solution with the desired amino alcohol and refluxing the solutions to complete the reaction. The free bases were not isolated but the hydrochlorides were precipitated by passing a stream of dry hydrogen chloride into the reaction mixture. These hydrochlorides were purified by recrystallization from dry acetone. The compounds prepared are listed in Table I.

Summary

Four alkamine esters of *m*-alkylthiophenyl carbamic acids have been prepared and found to be active local anesthetics.

NEW HAVEN, CONN. RECEIVED JULY 20, 1940

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

Quinonyl Derivatives of Fatty Acids

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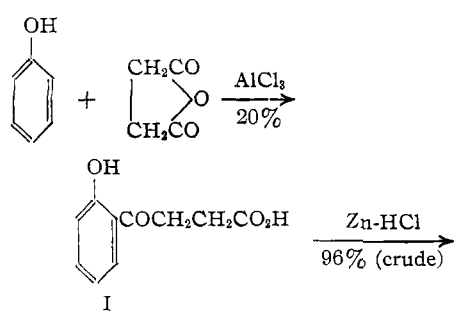
Various considerations suggest that, in the series of compounds characterized by having a quinone nucleus in combination with a fatty acid side chain, substances may be encountered possessing interesting biological actions. The association of a biological function with the isolated quinone structure itself is illustrated by the pronounced bactericidal[2] and spermicidal[3] potency of quinone and toluquinone, and by the antihemorrhagic activity of certain naphthoquinones possessing a long, branched-chain hydrocarbon residue (vitamin K type). The importance of the second structural feature mentioned is well set forth in Robinson's stimulating survey[4] of the role of branched-chain fatty acids associated with leprosy and with tuberculosis. Certain acids meeting this general specification exert a leprocidal action and are at least weakly germicidal to the similarly acid-fast bacteria of tuberculosis, while others, isolated from the tubercle bacillus, are capable of causing the formation of typical tubercular lesions at the point of injection. A fatty acid having an attached group capable of functioning as an oxido-reduction catalyst might possess enhanced or significantly modified actions. Furthermore, if such an acid were to occur as a constituent of a natural fat, the quinone group would almost certainly be destroyed in the saponification step of the usual isolation procedure. Thus the quinone group of vitamin K_1 is severed from the hydrocarbon chain by gentle treatment with alkali.[5] Another point of interest is that the simplest member of the quinone-fatty acid series is excreted in the reduced form (homogentisic acid) in huge amounts in the urine of persons suffering from alkaptonuria.

As a first step in a study of quinone-acids, we have synthesized for exploratory tests four acids of the general type indicated. Attempts to obtain the butyric acid derivative of quinone starting with the succinoylation of hydroquinone or its dimethyl ether appeared unpromising. The known β-(2,5-dimethoxybenzoyl)-propionic acid[6] was reduced successfully, if in poor yield, but the demethylation presented difficulties. A better route was found starting with the succinoylation of phenol at a high temperature as described in the literature,[7,8] although under the conditions employed by us the reaction afforded the desired ortho isomer (I) in only about 20% yield.



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(1) Du Pont Research Fellow.

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