8-1947

# Alkylaminoalkyl esters of 2-thiophene carboxylic and furoic acids

Henry Alouis Rutter Jr.

# ALKYLAMINOALKYL ESTERS OF 2-THIOPHENE CARBOXYLIC AND FUROIC ACIDS

---

THESIS

Presented in Partial Fulfillment of the Requirements for the Degree of Master of Science in the Graduate Department of the University of Richmond.

by

Henry Alouis Rutter Jr., B. S.

---

The University of Richmond

August 1947

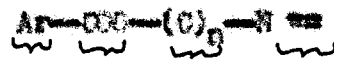
Approved by

J. Stanton Bruce

TABLE OF CONTENTS

# INTRODUCTION

The association of local anesthetic activity with alkaminoalkyl esters of aromatic carboxylic acids has been well substantiated. Compounds obtained as variations of the "anesthesiophoric" group,



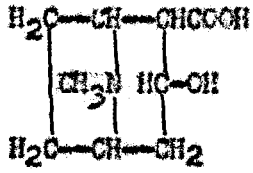

are usually capable of some degree of local anesthetic activity.

The structural unit, A, is usually an aromatic ring, B is usually an ester linkage although in certain compounds it is an amide linkage, C is a straight chain or branched chain hydrocarbon and D is a secondary or tertiary amine group.

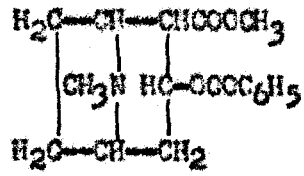
The purpose of this investigation is the preparation of compounds demonstrating the effect of variation of the aromatic group when A is thiophene and furan respectively.

# HISTORY

Wohler (1862)[1] found that on heating cocaine, the active principle from the leaves of Erythroxylon coca, with hydrochloric acid it split giving benzoic acid and ecgonine (I). Loosen (1865) split off $CH_3OH$ and concluded that cocaine is methyl benzoylecgonine (II).

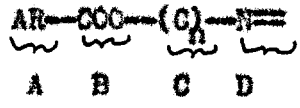


I



II

Later studies showed ecgonine itself is a piperidine derivative. Ehrlich (1890) established the "anesthesiophoric" action of the benzoyl group, and thereafter many synthetic local anesthetics have been variations of the fundamental structure (III).



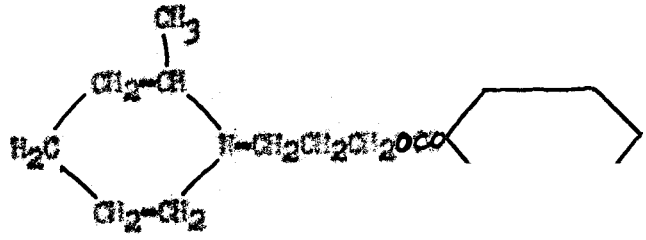
III

The early synthesis of local anesthetics involved variations in the group D. McElwain[2] produced "neothesine" (IV), a cyclic compound

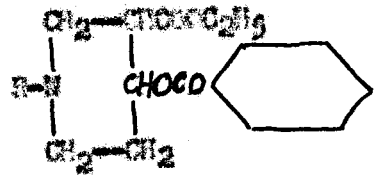
(1) Physiol. Rev. 12, 190 (1932).

(2) McElwain, J. Am. Chem. Soc. 46, 1721 (1924).

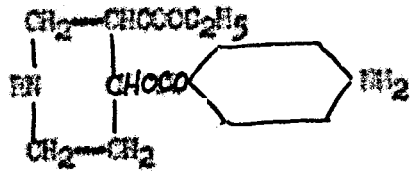
related in structure to cocaine, and a series of 1-alkyl-3-carbethoxy-4-piperidyl benzoates (V)[3], 1-alkyl-3-carbethoxy-4-piperidyl-p-amino benzoates (VI)[4] and substituted piperidyl alkyl benzoates and p-amino benzoates[5].



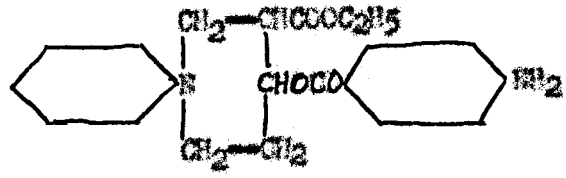
IV



V



VI



VII

Also Thayer and McElwain[6] prepared a series from phenyl substituted 3-carbethoxy-4-piperidones (VII). Barnes and Adams[7],

(3) McElwain, J. Am. Chem. Soc. 48, 2179 (1926).

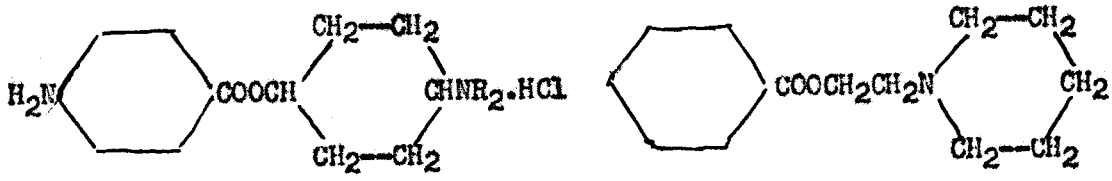
(4) McElwain, ibid., 49, 2239 (1926).

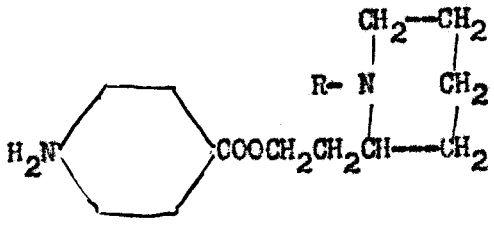
(5) McElwain, ibid., 49, 2835 (1927).

(6) Thayer and McElwain, ibid., 49, 2862 (1927).

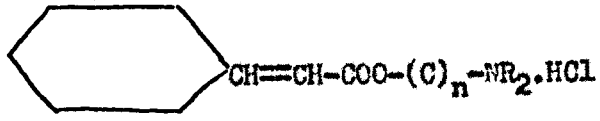
(7) Barnes and Adams, J. Am. Chem. Soc. 47, 1307 (1927).

Heckel and Adams[8], Sandborn and Marvel[9] and Marvel and Shelton[10] have also prepared series of piperidyl esters of benzoic and p-amino-benzoic acids;





Variations of the aromatic group A in the "anesthesiophoric" structure include the investigations of Schmitz and Loevenhart[11] who prepared basic esters of cinnamic acid (VIII) and found that anesthetic activity and toxicity increase with lengthening of the side chain as n varies from 2 to 4.



VIII

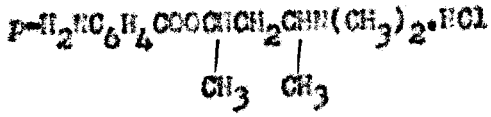
(8) Heckel and Adams, ibid., 49, 1303 (1927).

(9) Sandborn and Marvel, ibid., 50, 563 (1928).

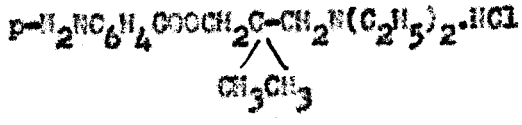
(10) Marvel and Shelton, ibid., 51, 914 (1929).

(11) Schmitz and Loevenhart, J. Pharm. Exper. Therap. 24, 159 (1924).

Vliet and Adams[12] found in the basic esters of cinnamic acid that when R is lengthened in $NR_2$ the basicity decreases progressively. This corresponds to an increased hydrolysis of the anesthetic salt and a corresponding increase in potency. Increase of the chain length between the p-aminobenzoyl group and the $NR_2$ group has an opposite effect on basicity. Branching of this part of the side chain causes basicity again to decrease and is again accompanied by increase in anesthetic potency and toxicity in tutocaine and larocaine (IX and X).

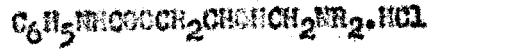


IX

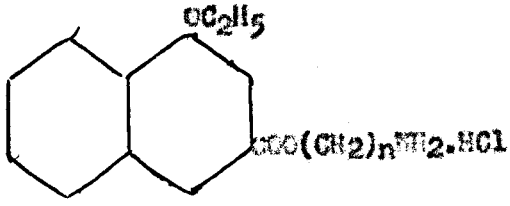


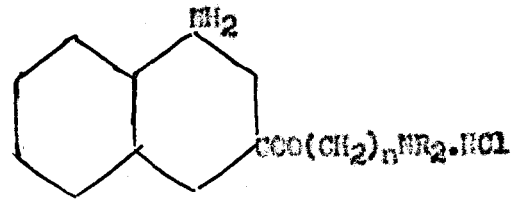
X

Phenyl urethans were prepared by Rider[13] which are very effective local anesthetics.



Hill and Smith[14] prepared a series with definite activity;



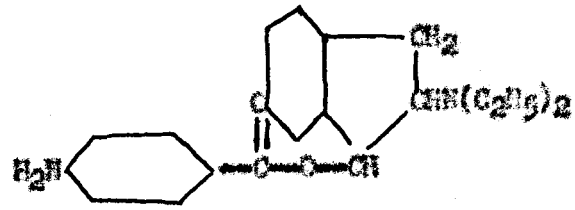


(12) Vliet and Adams, J. Am. Chem. Soc. 48, 2158 (1926).

(13) Rider, ibid., 52, 2115 (1930).

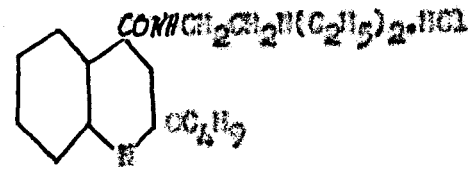
(14) Hill and Smith, Am. Chem. Soc. Div. Med. Chem. (1929)

Marvel and du Vigneaud[15] combined p-aminobenzoic acid with substances having a hydrindene nucleus, homologues of



in hope of obtaining local anesthetics with a vasoconstrictor or pressor action. These substances have some local anesthetic activity, but pressor action was not obtained.

Quinoline anesthetics such as Nupercaine (XI) were synthesized by Ullman[16].



XI

Since Goldberg and Whitmore[17] have demonstrated that the group O may be that of a secondary amine, Pierce, Salsbury, and Fredericksen[18] have prepared beta-monoalkylamino ethanol esters of alkoxybenzoic acids (XIII) and Pierce, Salsbury, Haden and Willis[19] prepared alkoxybenzoates

(15) Marvel and du Vigneaud, J. Am. Chem. Soc. 46, 2003 (1924).

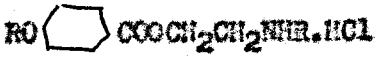
(16) Ullman, J. Am. Pat. Assoc. 26, 943 (1931).

(17) Goldberg and Whitmore, J. Am. Chem. Soc. 57, 2280 (1937).

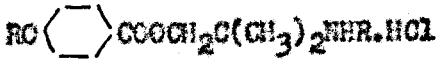
(18) Pierce, Salsbury and Fredericksen, Ibid., 64, 1691 (1942).

(19) Pierce, Salsbury, Haden, and Willis, Ibid., 64, 2024 (1942).

of 2-monoalkylamino-2-methyl-1-propanols (XIII) and 2-monoalkylamino-1-butanols (XIV).



XII

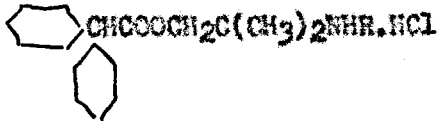


XIII

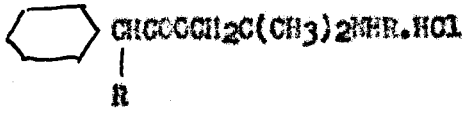
XIV

Also Pierce, Haden, and Cano[20] prepared phenylacetates, diphenylacetates, and phenylalkylacetates of beta-methyl-beta-monoalkylamino-propanols (XV a, b, c) in a search for antispasmodics.

XV a



XV b



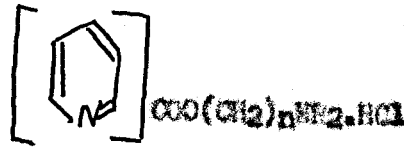
XV c

Blicke and Jenner[21] have prepared esters of pyridine carboxylic

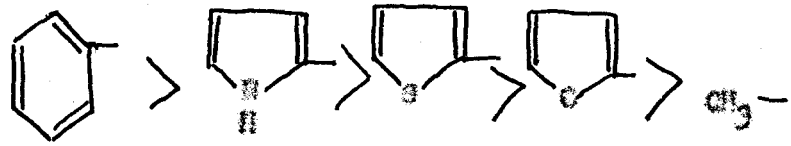
(20)Pierce, Haden, and Cano, J. Am. Chem. Soc. 67, 408 (1945).

(21)Blicke and Jenner, ibid., 64, 1721 (1942).

acids showing slight anesthetic activity;



Gilman and Fleikema[22] prepared a series of aromatic esters of tertiary aminoalkanols and showed that local anesthetic activity ran parallel with aromaticity;



An unusual series of local anesthetics having the ketone group between the aromatic ring and $NR_2$ group were prepared by Levvy and Nisbet[23];

Of particular value to the present investigation is the synthesis of the thiophene isolog of cocaine (XVI) by Steinkopf and Chao[24], the thiophene isologs of atropine (XVII) by Steinkopf and Wolfram[25],

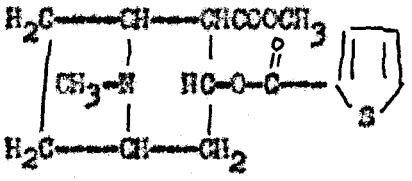
(22) Gilman and Fleikema, J. Am. Chem. Soc. 47, 245 (1925).

(23) Levvy and Nisbet, J. Chem. Soc. 1053 (1938).

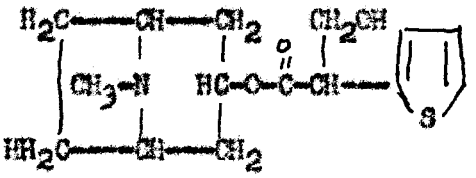
(24) Steinkopf and Chao, Ann. 437, 14; C. A. 18, 2158 (1924).

(25) Steinkopf and Wolfram, Ann. 437, 22; C. A. 18, 2158 (1924)

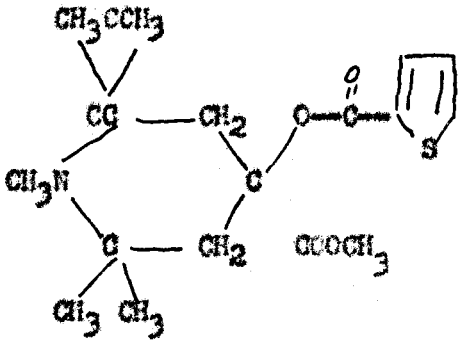
and of eucaine-A (XVIII) by Steinkopf and Chse[26], and the furan isolog of cocaine by Menshakov[27] (XIX).



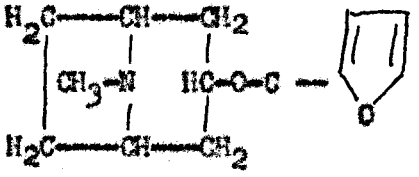
XVI



XVII



XVIII



XIX

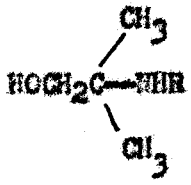
(26)Steinkopf and Chse, Ann.,448,205; C. A. 20, 2854 (1926).

(27)Menshakov, Bull. biol. med. exptl. U.S.S.R. 4, 269 (1937); C. A. 33, 6442 (1939).

## DISCUSSION OF RESULTS

The 2-monoalkylamino-2-methyl-1-propanol and 2-monoalkylamino-1-butanol esters of 2-thiophene carboxylic acid were prepared by condensing the acid chloride with the alkylaminoalkanol hydrochloride. Of the two series only the alkylaminopropanol ester hydrochlorides were obtained as crystalline products, the others being obtained as impure oils having the formula $(C_4H_3S)$ $COOCH_2CH(C_2H_5)$ NHR.HCl, where R is ethyl, n-propyl, n-butyl and n-amyl.

The 2-monoalkylamino-2-methyl-1-propanol and 2-mono-alkylamino-1-butanol esters of furoic acid were prepared by condensing the acid chloride with the alkylamino-alkanol free base to avoid decomposing the furan ring. The secondary amino group apparently was sufficiently protected by the 2-methyl groups to avoid amide formation as shown in the structural formula;



Of the two series only the alkylaminopropanol ester hydrochlorides were obtained as crystalline products, the others being obtained as impure oils having the formula $(C_4H_3O)$ $COOCH_2CH(C_2H_5)$ NHR.HCl, where R is ethyl, n-propyl, n-butyl and n-amyl.

## EXPERIMENTAL

2-Thienyl chloride:- To 15.7 g. (0.12 mole) of 2-thiophene carboxylic acid[28] was added 25 g. (.12 mole) of phosphorus pentachloride and the mixture heated to drive off phosphorus oxychloride. The product was vacuum distilled, the fraction coming over at 102°-105° (23 mm.) was collected.

Alkaminoalkyl ester hydrochlorides of 2-thiophene carboxylic acid:- In a typical run 13.1 g. (0.1 mole) of2-n-propyl-amino-2-methyl-1-propanol was treated with 1.5 equivalents of concentrated hydrochloric acid and the solution was evaporated to dryness in a vacuum. To the solution 14.6 g. (0.1 mole) of 2-thienyl chloride was added, and the mixture was heated on an oil bath at 100° for 15 minutes, at 130° for 15 minutes, and at 150° for 15 minutes. The product was taken up in 50 ml. of 95 per cent ethanol, poured into 100 ml. of N sodium hydroxide solution, the free base separated and dissolved in 25 ml. of isopropyl ether. The isopropyl ether solution was saturated with dry hydrogen chloride and the crystalline product separated and washed with isopropyl ether on a Buchner funnel. The product was recrystallized twice by dissolving in the minimal amount of 95 per cent ethanol, adding isopropyl ether until just cloudy, and stirring vigorously. After constant melting point was attained, the per cent chlorine was determined

[28] Supplied through the courtesy of Socony-Vacuum Oil Company.

by titration of the hydrochloride, dissolved in 25 ml. of 95 per cent ethanol, with standard 0.05 N silver nitrate using potassium chromate as indicator.

Alkylaminoalkyl ester hydrochlorides of furoic acid:- In a typical run 14.5 g. (0.1 mole) of 2-n-butyl-amino-2-methyl-1-propanol was treated with 13.0 g. (0.1 mole) of furoyl chloride and the mixture was heated on an oil bath at 100° for 15 minutes, 130° for 15 minutes, and 150° for 15 minutes. The product was taken up in 50 ml. of 95 per cent ethanol, poured into 100 ml. of N sodium hydroxide solution, the free base was separated and dissolved in 25 ml. of isopropyl ether. The isopropyl ether solution was saturated with dry hydrogen chloride and the crystalline product separated and washed with isopropyl ether on a Buchner funnel, recrystallized to constant melting point from minimal amount of 95 per cent ethanol and isopropyl ether and per cent chlorine determined by titration with standard silver nitrate.

# TABLE OF PHYSICAL CONSTANTS

## TABLE I

(a) 2-methyl-2-monoalkylaminopropyl thiophene carboxylate hydrochloride:

$(C_4H_3S)COOCH_2C(CH_3)_2NHR.HCl$

| R | M.P.,°C (uncor.) | Yield % | Formula | Chlorine,% Calcd. | Found | |
|---|---|---|---|---|---|---|
| n-Propyl | 165-166 | 7 | $C_{12}H_{20}O_2NSCl$ | 12.64 | 12.87 | 12.81 |
| n-Butyl | 175-176 | 24 | $C_{13}H_{22}O_2NSCl$ | 12.03 | 12.25 | 12.30 |
| n-Amyl | 130-131 | 16 | $C_{14}H_{24}O_2NSCl$ | 11.44 | 11.56 | 11.79 |

(b) 2-methyl-2-monoalkylaminopropyl furoate hydrochloride:

$(C_4H_3O)COOCH_2C(CH_3)_2NHR.HCl$

| R | M.P.,°C (uncor.) | Yield % | Formula | Chlorine,% Calcd. | Found | |
|---|---|---|---|---|---|---|
| n-Propyl | 184-185 | 6 | $C_{12}H_{20}O_3NCl$ | 13.41 | 13.47 | 13.75 |
| n-Butyl | 146-147 | 23 | $C_{13}H_{22}O_3NCl$ | 12.73 | 13.00 | 13.75 |
| n-Amyl | 144-145 | 17 | $C_{14}H_{24}O_3NCl$ | 12.11 | 12.13 | 12.35 |

## SUMMARY

Some 2-monoalkylamino-2-methyl-1-propanol ester hydrochlorides of 2-thiophene carboxylic and furoic acids have been prepared and characterised and will be submitted for pharmacological testing elsewhere.

ACKNOWLEDGEMENT

Very grateful acknowledgement is made to Dr. J. Stanton Pierce for his helpful criticism, advice and encouragement during the course of this investigation.

# AUTOBIOGRAPHY

I, Henry Alouis Rutter Jr., was born on March 22, 1922 in Richmond, Virginia. I received my pre-science diploma from John Marshall High School in Richmond in 1939 and entered the Virginia Polytechnic Institute, Blacksburg, Virginia that same year. Received the B. S. Degree in Chemistry in 1943 and was employed as Chemist with the Standard Oil Company of Louisianna, Baton Rouge, Louisianna until I accepted the position of Chemist P-1 Naval Ordnance, U. S. Naval Powder Factory, Indian Head, Maryland in 1944. In 1945-1946 I matriculated as a graduate student in Biochemistry at the Virginia Polytechnic Institute, and in 1946-1947 I matriculated as candidate for the M. S. Degree in Chemistry at the University of Richmond, Richmond, Virginia.

## BIBLIOGRAPHY


Barnes and Adams, J. Am. Chem. Soc. 47, 1307 (1927).

Blick and Jenner, J. Am. Chem. Soc. 64, 192 (1942).

Gilman and Pickens, J. Am. Chem. Soc. 47, 245 (1925).

Goldberg and Whitmore, J. Am. Chem. Soc. 52, 2220 (1937).

Heckel and Adams, J. Am. Chem. Soc., 49, 1303 (1927).

Hill and Smith, Am. Chem. Soc. Div. Med. Chem. (1929).

Levvy and Nisbet, J. Am. Chem. Soc. 51, 914 (1929).

McElwain, J. Am. Chem. Soc. 46, 1721 (1924).

ibid., 48, 2179 (1926).

ibid., 48, 2239 (1926).

ibid., 49, 2335 (1927).

Menshakov, Bull. Biol. med. exptl. U. S. S. R. 4, 269 (1937); C.A. 33, 6442[8] (1939).

Physiol. Rs. 12, 190 (1932).

Pierce, Salsbury and Frederickson, J. Am. Chem. Soc. 64, 169 (1942).

Pierce, Salsbury, Haden and Willis 64, 2334 (1942).

Pierce, Haden and Cano, J. Am. Chem. Soc. 67, 408 (1945).

Rider, J. Am. Chem. Soc. 52, 2115 (1930).

Sandborna nd Marvel, J. Am. Chem. Soc. 50, 563 (1928).

Schmitz and Loevenhart, J. Pharm. Exper. Therap. 24, 159 (1924).

Steinkopf and Ohse, Ann. 437,14; C.A. 18, 2158 (1924): 448

Ibid., 448,205; C.A. 20.

Steinkopf and Wolfram, Ann. 437,22; C.A. 18, 2158 (1924).

Thayer and McElwain, J. Am. Chem. Soc. 49, 2862 (1927).

Uhlman, J. Am. Med. Assoc. 96, 943 (1931).

Vliet and Adams, J. Am. Chem. Soc. 48, 2158 (1926).