[CONTRIBUTION FROM THE CHEMISTRY LABORATORY OF INDIANA UNIVERSITY]

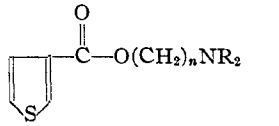
3-Substituted Thiophenes. II. Dialkylaminoalkyl Esters of 3-Thenoic Acid[1]

BY E. CAMPAIGNE AND WILLIAM M. LESUER[2]

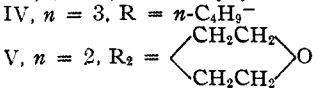
In a previous communication,[3] a method for readily preparing 3-substituted thiophenes was reported. Possibilities of different pharmacological action and, particularly, of differences in toxicity between the 2-substituted thiophene derivatives, make comparisons between analogous series of these two compounds interesting. For the first investigation, a relatively simple series of dialkylaminoalkyl esters of 3-thenoic acid was prepared for testing as local anesthetics.

This series was chosen for two reasons. First, the compounds were easy to prepare and, second, they could be compared to a number of 2-thenoate esters which have been reported as local anesthetics in the literature. Steinkopf and Ohse[4] prepared the cocaine analog, 2-thenoyl ecogonine methyl ester, which proved to be an effective local anesthetic slightly less toxic than cocaine. These same workers[5] found that the 2-thiophene analogs of eucaine and stovaine were active and less toxic. Gilman and Pickens[6] prepared β-diethylaminoethyl 2-thenoate, and reported it to be one-fourth as active as the corresponding benzoate and one-sixth as active as procaine. No mention was made of toxicity. Recently Dann[7] reported that β-diethylaminoethyl 5-amino-2-thenoate was as active as procaine. The anesthesin analog, ethyl 5-amino-2-thenoate, was also equal in activity. No specific toxicity data on these compounds was reported, but they were said to be less toxic than the benzene analogs. The reported activity of these compounds is particularly interesting in view of the instability of aminothiophenes.[8]

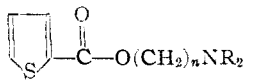
In addition to the 3-thenoates, one 2-thenoate was prepared for purposes of direct comparison in the pharmacological tests. This was γ-di-*n*-butylaminopropyl 2-thenoate, which had not previously been reported. β-Diethylaminoethyl 2-thenoate[9] was also tested for comparison.



I, n = 2, R = CH_3–
II, n = 2, R = C_2H_5–
III, n = 2, R = n-C_4H_9–
IV, n = 3, R = n-C_4H_9–



V, n = 2, R_2 =



VI, n = 2, R = C_2H_5–
VII, n = 3, R = n-C_4H_9–

TABLE I

PROPERTIES OF DIALKYLAMINOALKYL THENOATES

Compd.	M. p. of HCl salt, °C.	Yield, %	Formula	Analyses, % Calcd.	Found	B. p. of free base at 1 mm., °C.	Refractive index $n^{20}D$ free base
I	193–195	91	$C_9H_{14}O_2NSCl$	15.04	15.07	106–108	1.5200
II	100–101	80	$C_{11}H_{18}O_2NSCl$	13.44	13.60	113–114	1.5131
III	74–76	86	$C_{15}H_{26}O_2NSCl$	11.08	11.04	137–139	1.4981
IV	109–111	83	$C_{16}H_{28}O_2NSCl$	10.62	10.67	152–153	1.4965
V	210	77	$C_{11}H_{15}O_3NSCl$	12.77	12.79	140–142[a]	1.5380
VII	83–87	74	$C_{16}H_{28}O_2NSCl$	10.62	10.42	151–152	1.4946

[a] β-Morpholinoethyl 3-thenoate is a solid, m. p. 44°.

Pharmacological Data[10]

These compounds were tested in rabbits by the external canthus and the corneal irrigation tests. Only compounds IV and VII showed local anesthetic activity (Table II). These compounds have

TABLE II

ANESTHETIC ACTIVITY OF γ-DI-*n*-BUTYLAMINOPROPYL THENOATES

Compd.	Test no.	Rabbits no. +/ no. −	Av. duration of anesthesia, min.	Range, min.	Irritation	ALD-50[b] (i. v. in mice)
External Canthus Test[a]						
IV	1	0/3	..	..	0	11.3 mg./kg.
	2	3/3	17	17	0	
VII	1	3/3	25	20–30	0	12 mg./kg.
	2	3/3	23	15–30	0	
Corneal Irrigation Test[c]						
IV	1	3/3	22	20–25	+	(Moderate irritation)
VII	1	3/3	20	20	+	

[a] 0.5 cc. of 1% soln. injected around external canthus of the eye. [b] Average lethal dose, determined by D. K. Seppelin. [c] 0.5 cc. of 1% soln. instilled on the cornea.

(1) Taken from part of the thesis submitted by William M. LeSuer in partial fulfillment of the requirements for the degree of Doctor of Philosophy at Indiana University, June, 1948. Presented before the Medicinal Division, American Chemical Society, Chicago, April 21, 1948.

(2) Sterling-Winthrop Fellow in Chemistry, 1947. Present address, Lubrizol Corporation, Cleveland, Ohio.

(3) Campaigne and LeSuer, THIS JOURNAL, **70**, 1555 (1948).

(4) Steinkopf and Ohse, *Ann.*, **437**, 14 (1924).

(5) Steinkopf and Ohse, *ibid.*, **448**, 205 (1926).

(6) Gilman and Pickens, THIS JOURNAL, **47**, 252 (1925).

(7) Dann, *Ber.*, **76B**, 419 (1943).

(8) Steinkopf, *Ann.*, **403**, 17 (1914).

(9) Supplied by Frederick Stearns and Company.

(10) Testing by F. P. Ludena and Jaquelin Sherndal, Pharmacology Laboratory, Sterling-Winthrop Research Institute, to whom we are deeply indebted for support and coöperation in this research

weak local anesthetic action, are moderately irritating, and much more toxic than procaine (LD-50 of Procaine HCl = 57 mg./kg. i. v. in mice). The toxicity is equal that of Butyn (LD-50 = 12 mg./kg.).

These results are interesting in view of the previous report by Gilman and Pickens[6] that VI was one-sixth as active as procaine. It is also curious that γ-di-*n*-butylaminopropyl 3-thenoate (IV) is slightly less active than the corresponding 2-thenoate.

Experimental

Acid Chlorides.—The 3-thenoyl chloride was prepared from 3-methylthiophene by bromination with N-bromosuccinimide, conversion to the aldehyde by the Sommelet reaction, oxidation of the aldehyde with silver oxide, and conversion to the acid chloride with thionyl chloride, as previously described.[3] 2-Thenoic acid,[11] prepared by hypochlorite oxidation of 2-acetothienone, was also converted to the acid chloride satisfactorily with thionyl chloride.

(11) We are indebted to H. Grose, of this Laboratory, for a supply of 2-thenoic acid.

Ester Hydrochlorides.—The acid chlorides were allowed to react with the appropriate dialkylaminoalkanol in refluxing benzene, and after cooling the ester hydrochlorides were precipitated with dry ether. Samples of each of the six ester hydrochlorides were converted to the free bases by treating their water solutions with sodium carbonate and extracting the bases with ether. The physical constants of the salts and free bases are reported in Table I.

Summary

The β-dimethylaminoethyl, β-diethylaminoethyl, β-di-*n*-butylaminoethyl, γ-di-*n*-butylaminopropyl and β-morpholinoethyl esters of 3-thenoic acid have been prepared and characterized. The γ-di-*n*-butylaminopropyl ester of 2-thenoic acid was also prepared and characterized.

Of these, only γ-di-*n*-butylaminopropyl 2-thenoate and γ-di-*n*-butylaminopropyl 3-thenoate showed any activity as topical anesthetics on the rabbit cornea. The toxicities of the thiophene analogs are in the same order as the *p*-aminobenzoates.

BLOOMINGTON, INDIANA RECEIVED APRIL 30, 1948

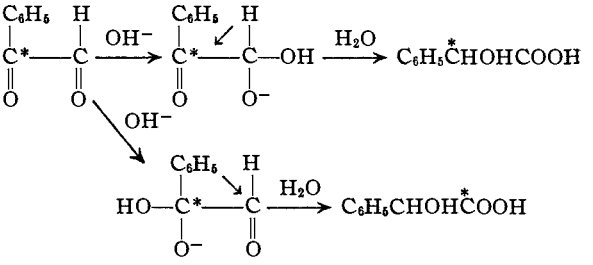
[CONTRIBUTION FROM OAK RIDGE NATIONAL LABORATORY AND THE UNIVERSITY OF TENNESSEE]

C¹⁴ Tracer Studies in the Rearrangements of Unsymmetrical α-Diketones: Phenylglyoxal to Mandelic Acid[1]

BY O. KENTON NEVILLE

The reaction of phenylglyoxal with aqueous alkali to form mandelic acid has been shown to follow the same second-order kinetics[2] as the benzilic acid rearrangement. The latter reaction is known from the work of Westheimer[3] and of Roberts and Urey[4] to involve the reversible addition of hydroxyl ion at one of the carbonyl groups, followed by a group migration. A similar mechanism in the case of phenylglyoxal allows two possible modes of reaction: one in which the aldehydic hydrogen shifts following hydroxyl ion addition at the aldehyde group, and a second in which a phenyl group migrates as the result of hydroxyl ion addition at the keto group. The former appears to be more probable since Gray and Fuson[5] have found that mesitylglyoxal, in which the keto group is shielded from hydroxyl ion attack, reacts smoothly to give mesitylglycolic acid.

A decision between the two possible mechanisms is possible by the device of labelling one of the carbonyl groups with isotopic carbon, since the two modes of reaction will lead to isotopically distinguishable products.



Accordingly, phenylglyoxal, labelled in the keto carbonyl group with C¹⁴ has been studied in its reaction with aqueous alkali, and is shown to be converted to mandelic acid without rearrangement of the carbon skeleton.[6]

Very recently, Doering, Taylor and Schoenewaldt[7] have reported that mandelic acid containing no deuterium was obtained from the reaction of phenylglyoxal in basic deuterium water, thus showing that, if hydrogen migrates, it must do so intramolecularly. In addition, they have shown, with the aid of C¹³, that when carbonyl-labelled α,α-dibromoacetophenone is allowed to react with aqueous base, similarly labelled mandelic acid is obtained. Previous to their publication, we had obtained, with the aid of C¹⁴-labelled α,α-dibromoacetophenone, results which are in agree-

(1) This document is based on work performed under Contract No. W-7405 eng 26 for the Atomic Energy Project at Oak Ridge National Laboratory. A part of the work herein described has been submitted, under the graduate study program of the Oak Ridge Institute of Nuclear Studies, to the University of Tennessee in partial fulfillment of the requirements for the Ph.D. degree.

(2) Alexander, THIS JOURNAL, **69**, 289 (1947).

(3) Westheimer, *ibid.*, **58**, 2209 (1936).

(4) Roberts and Urey, *ibid.*, 60, 880 (1938).

(5) Gray and Fuson, *ibid.*, **56**, 739 (1934).

(6) The results of this work were reported before the Division of Organic Chemistry of the American Chemical Society at the New York Meeting, September 19, 1947.

(7) Doering, Taylor and Schoenewaldt, THIS JOURNAL, **70**, 455 (1948).