hexanol have been characterized by the preparation of various new derivatives and by X-ray powder spectra.

4. The chloro-amine obtained by phosphorus pentachloride treatment of *d,l-trans*-2-aminocyclohexanol hydrochloride has a very inert halogen characteristic of its *cis* structure.

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[CONTRIBUTION FROM THE STERLING-WINTHROP RESEARCH INSTITUTE]

Sulfur-containing Amines. VI.[1] Antispasmodics

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In previous communications[4,5] from these laboratories there have been described a number of sulfur-containing amines, which are of pharmacological interest as ester and amide precursors in local anesthetic types[1] and as side chains in antimalarial types.[6] In the present work we have extended the investigation to include derivatives of the sulfur-containing amines with a number of disubstituted acetic acid types, with the expectation that the sulfide linkage might provide favorable toxicity indices.[1]

The acids used were of the type which previous investigators have shown to form spasmolytically active esters, *viz.*: diphenylacetic, benzilic, fluorene-9-carboxylic, dibenzylacetic, α-cyclohexylphenylacetic and 9,10-dihydroanthracene-9-carboxylic acids.

The esters were prepared by either of two general methods. The first of these, reaction of an acid chloride with the alcohol or amine in cold benzene, is the preferable method. As has been previously indicated,[1] the reaction of the sulfur-containing amines with an acid chloride must be carefully controlled to avoid decomposition of the heat-labile sulfur compound. Only in two cases were satisfactorily stable hydrochlorides isolated; in general it was found preferable to isolate the free bases and convert them to the citrate salts.

The second method of preparing the basic esters utilized transesterification, in the presence of sodium alkoxide as catalyst. This method gave excellent results with both methyl benzilate[7] and methyl fluorene-9-carboxylate.

In Table I there are listed the esters prepared from straight and branched chain sulfur-containing amino alcohols. In addition, there was prepared one ester of an alcohol containing two sulfide linkages and a single example of an amide. These compounds, with other examples, are described in the experimental section.

(1) Paper V: Clinton, Salvador, Laskowski and Suter, THIS JOURNAL, **70**, 950 (1948).

(2) Present address: Barrett Division, Allied Chemical and Dye Corp., Philadelphia 6, Pennsylvania.

(3) Present address: Electronized Chemicals Corporation, New York, N. Y.

(4) Clinton, Suter, Laskowski, Jackman and Huber, THIS JOURNAL, **67**, 594 (1945).

(5) Laskowski and Clinton, *ibid.*, **69**, 519 (1947).

(6) Huber, Bair, Boehme, Laskowski, Jackman and Clinton, *ibid.*, **67**, 1849 (1945); **68**, 322 (1946).

(7) *Cf.* Holmes, U. S. Patent 2,399,736.

This series of compounds has been tested for antispasmodic activity *in vitro* against barium chloride and acetylcholine-induced spasms on rabbit intestinal strips and against histamine-induced spasms on strips of guinea pig ileum.[8] None of the compounds exhibited a high degree of activity against the acetylcholine-induced spasms. The activity against histamine-induced spasms was considerably less than that of papaverine, with the exception of 3-(3-(1-piperidyl)propylmercapto)-2-propyl fluorene-9-carboxylate citrate which was of the same order of magnitude. The compounds did not differ greatly in their musculotropic activity, *i. e.*, against barium chloride-induced spasms, all being equal to or slightly more active than papaverine.

Experimental[9]

The following examples will serve to illustrate the various procedures used. The yields of the compounds varied from 24 to 87%, the lower yields being chiefly ascribable to isolation difficulties.

2-(2-Diethylaminoethylmercapto)-ethyl Diphenylacetate Hydrochloride.—To an ice-cooled solution of 13.0 g. of diphenylacetyl chloride in 100 ml. of dry benzene was added during a five-minute period, with shaking, a cold solution of 10.0 g. of 2-(2-diethylaminoethylmercapto)-ethanol[4] in 50 ml. of dry benzene. The clear solution was warmed for fifteen minutes on the steam-bath and then cooled. Five hundred milliliters of Skellysolve A was then added; the precipitated oil crystallized on cooling and scratching. After three recrystallizations from ethyl acetate there was obtained 15.8 g. (67%) of large white prisms.

With the other sulfur-containing amines it was necessary to convert the oily or low-melting hydrochlorides to the free bases by means of ethyl acetate–ammonia, and thence to the citrate through the use of citric acid monohydrate in acetone or absolute alcohol solution.

3-(2-Diethylaminoethylmercapto)-propyl Benzilate Citrate.—A mixture of 5 g. of methyl benzilate, 4 g. of 3-(2-diethylaminoethylmercapto)-propanol,[4] and 0.15 g. of sodium metal in 50 ml. of Skellysolve E was refluxed under a pressure of about 30 mm. for four hours. An equal volume of benzene was then added and the mixture was washed several times with water and dried. The oily residue remaining after removal of the solvents *in vacuo* was taken up in dry acetone and treated with a solution of 4.2 g. of citric acid monohydrate in acetone. The white crystalline product was then repeatedly recrystallized from acetone.

(8) We are indebted to Dr. T. J. Becker (deceased) and his staff for the pharmacological testing of these compounds. A more detailed report of these tests will be published elsewhere.

(9) All melting points are uncorrected. We are indebted to Mr. Morris E. Auerbach and his staff for the analyses.

TABLE I

BASIC ESTERS OF DISUBSTITUTED ACETIC ACIDS[a]

Acid, RCOO-	m	n	R′	Yield, %	M. p., °C.[b]	Formula	Analyses, % Nitrogen Calcd.	Nitrogen Found	Sulfur Calcd.	Sulfur Found
					$RCOO(CH_2)_mS(CH_2)_nNR'_2$					
Diphenylacetic	2	2	$(CH_3)_2$	45	73–75	$C_{26}H_{33}NO_2S$	2.62	2.64	5.98	5.96
Diphenylacetic	2	2	$(C_2H_5)_2$	69	94–95[c]	$C_{22}H_{30}ClNO_2S$	3.43	3.37	[d]	[d]
Diphenylacetic	3	2	$(C_2H_5)_2$	87	112.5–113.0	$C_{29}H_{39}NO_2S$	2.42	2.39	[e]	[e]
Benzilic	3	2	$(C_2H_5)_2$	51	69–74	$C_{29}H_{39}NO_{10}S$	2.36	2.44	[f]	[f]
Fluorene-9-carboxylic	2	2	$(C_2H_5)_2$	54	95–97	$C_{28}H_{35}NO_2S$	2.49	2.50	5.69	5.62
Fluorene-9-carboxylic	3	2	$(CH_3)_2$	61	78–80	$C_{27}H_{33}NO_2S$	2.48	2.60	5.86	5.56
Dibenzylacetic	2	2	$(C_2H_5)_2$	71	95–101	$C_{30}H_{41}NO_2S$	2.38	2.59	[g]	[g]
Dibenzylacetic	2	3	C_5H_{10}[h]	51	67–70	$C_{32}H_{43}NO_2S$	2.28	2.24	5.20	5.11
Dibenzylacetic	2	3	$(C_2H_5)_2$	40	94–97	$C_{31}H_{43}NO_2S$	2.32	2.40	5.29	5.46
α-Cyclohexylphenylacetic	2	2	$(C_2H_5)_2$	85	102–106	$C_{28}H_{43}NO_2S$	2.46	2.63	5.63	5.30
α-Cyclohexylphenylacetic	3	2	$(C_2H_5)_2$	64	105–109	$C_{29}H_{45}NO_2S$	2.40	2.58	5.49	5.49
9,10-Dihydroanthracene-9-carboxylic	2	2	$(C_2H_5)_2$	33	137.0–137.5[c]	$C_{23}H_{30}ClNO_2S$	3.35	3.36	7.64	7.67
					$RCOOCH(CH_3)CH_2S(CH_2)_nNR'_2$					
Diphenylacetic	..	2	$(CH_3)_2$	30	65–70	$C_{27}H_{35}NO_2S$	2.56	2.58	5.84	6.02
Fluorene-9-carboxylic	..	3	C_5H_{10}[h]	41	71–73	$C_{31}H_{39}NO_2S$	2.33	2.37	5.32	5.15
α-Cyclohexylphenylacetic	..	3	$(C_2H_5)_2$	24	110–114	$C_{30}H_{47}NO_2S$	2.40	2.47	5.49	5.40

[a] The esters are listed as the citrate salts, unless otherwise specified. [b] The melting points are uncorrected. The citrate salts melted in all cases with effervescence. [c] Hydrochloride. [d] Calcd.: C, 64.76; H, 7.41. Found: C, 64.55; H, 7.73. [e] Calcd.: C, 60.29; H, 6.80. Found: C, 60.22; H, 6.93. [f] Calcd.: C, 58.67; H, 6.62. Found: C, 58.62; H, 7.19. [g] Calcd.: C, 60.89; H, 6.98. Found: C, 60.84; H, 6.59. [h] 1-Piperidyl.

2-(2-(2-Diethylaminoethylmercapto)-ethylmercapto)-ethyl Diphenylacetate Citrate.—The condensation of 2-(2-(2-diethylaminoethylmercapto)-ethylmercapto)-ethanol[4] with diphenylacetyl chloride, and conversion of the isolated free base to the citrate was carried out as described previously. The **citrate monohydrate** formed waxy white crystals from acetone, m.p. 87–89°.

Anal. Calcd. for $C_{24}H_{33}NO_2S_2.C_6H_8O_7.H_2O$: C, 56.13; H, 6.75; N, 2.19. Found: C, 55.80; H, 6.46; N, 2.30.

N-(2-(2-Diethylaminoethylmercapto)-ethyl) Diphenylacetamide.—To a mixture of 17.6 g. of 2-(2-diethylaminoethylmercapto)-ethylamine,[4] 12.6 g. of sodium bicarbonate, and 80 ml. of water was added a solution of 27.6 g. of diphenylacetyl chloride in 100 ml. of chloroform, with vigorous stirring, during a period of forty-five minutes. The mixture was stirred for an additional hour; the chloroform layer was separated, washed with dilute sodium hydroxide solution and water and dried over anhydrous potassium carbonate. Concentration of the chloroform solution *in vacuo* yielded a viscous colorless oil which readily crystallized. Two recrystallizations from ethyl acetate–Skellysolve A gave 24.5 g. (62%) of product as white leaflets, m.p. 55.8–57.0°.

Anal. Calcd. for $C_{22}H_{30}N_2OS$: C, 71.31; H, 8.16. Found: C, 71.55; H, 7.64.

The **citrate** was prepared in absolute alcohol–ethyl acetate mixture: white rosettes, m.p. 80°.

Anal. Calcd. for $C_{22}H_{30}N_2OS.C_6H_8O_7$: citric acid, 34. Found: citric acid, 33.

Summary

Fifteen esters of certain sulfur-containing amines with disubstituted acetic acids have been prepared for testing as antispasmodics. One related amide and an ester of a basic alcohol containing two sulfide linkages have also been prepared. No high degree of spasmolytic activity has been found in this series.

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