quickly as possible at 49–50 mm. to prevent polymerization in the still-pot. After removal of the monochloroamines from the product of run 10A, the pressure was reduced to 5–7 mm. and two fractions were removed. The first fraction (yield 2.0 g.) boiling 35–36° gave a picrate which melted at 132.0–133.2° (cor.). The second fraction (yield 0.9 g.) boiling at 44° gave a picrate which melted at 104.5–105.1° (cor.).

Chlorination of N,N-Dimethylpropylamine Hydrochloride in Absence of Phosphorus Pentoxide.—(Runs B1–B3) These chlorinations were carried out following the procedure used for Runs A1–A10 except that no phosphorus pentoxide was added.

Chlorination of N,N-Dimethylpropylamine Hydrochloride in Water.—(Runs C1–C3) One-third mole of amine (29 g.) was placed in an ampule and cooled to −75°. Thirty cubic centimeters of concentrated hydrochloric acid was added slowly with alternate shaking and cooling until one liquid phase was obtained. Dry chlorine gas was then passed into the ampule at −75° until the gain in weight was 24 g. The ampule was sealed and placed two inches from a 200-watt incandescent lamp to react. Additional chlorine was added to runs C2 and C3 when the reaction mixture became colorless. After the desired amount of chlorine had reacted, the solution of hydrochlorides was removed from the ampule and diluted with 250 cc. of water. This solution was treated in a manner similar to the solution of hydrochlorides in runs A1–A10.

Chlorination of *n*-Propylamine Hydrochloride and N,N-Dimethyl-*n*-butylamine Hydrochloride.—These amines were chlorinated using a procedure similar to that in runs A1–A10 for N,N-dimethylpropylamine hydrochloride. The following proportions of reagents were used. *n*-Propylamine: 250 cc. of chloroform, 0.25 mole of amine, 0.66 mole of chlorine. N,N-Dimethyl-*n*-butylamine: 100 cc. of chloroform, 0.25 mole of amine, 0.75 mole of chlorine. The products of these reactions could not be rectified because of the ease with which they formed quaternary salts. The dried chlorinated amines were refluxed for 1 hour in a sodium ethoxide solution prepared by adding 23 g. of sodium to 300 cc. of absolute ethanol. The precipitated sodium chloride was filtered, washed with absolute ethanol, dried and weighed. The *n*-propylamine reaction yielded 8.7 g. of sodium chloride (equivalent to 60% remote monochlorination). The N,N-dimethyl-*n*-butylamine reaction yielded 9.5 g. of sodium chloride (equivalent to 66% remote monochlorination).

Proof of Structure of Dichloro-N,N-dimethylpropylamine Isomers.—A sample of 120 g. of the combined monochloramines obtained from runs A1–A10 was carefully rectified through the 50-cm. Vigreux column at 48 mm. The following fractions were obtained: 2-chloro-N,N-dimethylpropylamine; 50.0 g. b.p. 43–43.5° (48 mm.); $n^{20}D$ 1.4250, d^{20}_{20} 0.9093; picrate, m.p. 100.5° (cor.). The reported melting point of this picrate is 101–103°.[6a] 3-Chloro-N,N-dimethylpropylamine; 28.7 g., b.p. 53–53.5° (48 mm.); $n^{20}D$ 1.4313; d^{20}_{20} 0.9287; picrate, m.p. 109.8–110.1° (cor.). The reported melting point of the picrate is 110°.[6b]

One-third of a mole of purified 2-chloro-N,N-dimethylpropylamine was chlorinated using the procedure developed for N,N-dimethylpropylamine. The dried chlorinated product from this reaction was rectified through the semimicro Vigreux column at 48–49 mm. to remove unreacted 2-chloro-N,N-dimethylpropylamine. The pressure was reduced to 19–20 mm. and 2,2-dichloro-N,N-dimethylpropylamine was collected at 42–42.5°, $n^{20}D$ 1.4372. A picrate prepared from ethanol came down as an oil. An analysis was therefore run on the free amine. *Anal.* Calcd. for $C_5H_{11}NCl_2$: Cl, 45.44. Found: Cl, 45.45, 44.87. 2,3-Dichloro-N,N-dimethylpropylamine was collected at 66.5–67°, $n^{20}D$ 1.4586. Picrate: m.p. 106.8–107.5° (cor.). *Anal.* Calcd. for $C_{11}H_{14}O_7N_4Cl_2$: Cl, 18.41. Found: Cl, 18.60, 18.70.

One-quarter mole of 3-chloro-N,N-dimethylpropylamine was chlorinated similarly to 2-chloro-N,N-dimethylpropylamine. Rectification of the dichloroisomers at 19–20 mm. gave 3,3-dichloro-N,N-dimethylpropylamine, b.p. 55–56°, $n^{20}D$ 1.4492. Picrate: m.p. 133.2–133.5°. *Anal.* Calcd. for $C_{11}H_{14}O_7N_4Cl_2$: Cl, 18.41. Found: Cl, 18.56, 18.70. 2,3-Dichloro-N,N-dimethylpropylamine, b.p. 64–65.5°, $n^{20}D$ 1.4588. The picrate could not be purified.

Synthesis of 2,3-Dichloro-N,N-dimethylpropylamine.—A mixture of 27.6 g. (0.25 mole) of 3-chloro-1,2-propanediol and 25 g. (0.55 mole) of liquefied dimethylamine was prepared at −75° and sealed in a glass tube and placed in a steel bomb. The sealed bomb was maintained at 190° for 5 hours. The bomb was then cooled and opened. The semi-solid crystalline mass in the tube was filtered and washed with 50 cc. of chloroform. The filtrate was placed in a 500-cc. flask equipped with a dropping funnel and a reflux condenser and a solution of 120 g. of thionyl chloride in 50 cc. of chloroform was added slowly while cooling the reaction mixture in an ice-bath. After addition of the thionyl chloride solution, the unreacted thionyl chloride was distilled off with the chloroform and 50 cc. of water was added to the still-pot. The distillation was continued until the temperature of the vapors reached 100°. The sirup of hydrochlorides was then cooled and the amine freed using 75 cc. of saturated sodium hydroxide solution. The dried amine (7 g.) was distilled at 19–20 mm. and the fraction boiling at 66–68° collected, $n^{20}D$ 1.4582. A picrate crystallized from *n*-propyl alcohol melted at 104.0–104.7° (cor.). *Anal.* Calcd. for $C_{11}H_{14}O_7N_4Cl_2$: Cl, 18.41. Found: Cl, 18.04, 18.18.

STORRS, CONNECTICUT RECEIVED MAY 8, 1950

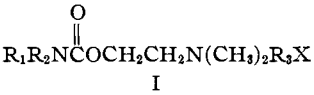
[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF MERCK & CO., INC.]

Some New Choline Type Thiols

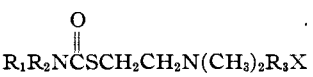
BY JOHN WEIJLARD AND MAX TISHLER

Twenty-five new thiols of the choline type have been prepared, and several of these compounds are effective antispasmodics of low toxicity.

A class of urethan derivatives of choline type compounds, having the general formula of I, were found to be effective as antispasmodics.[1]



I



II

One compound of this class, Dibutoline, where R_1 and R_2 are *n*-butyl, R_3 is ethyl and X sulfate, has been subjected to considerable clinical study.[2] Since a major defect of Dibutoline is its low activity when administered orally, we undertook the preparation of a number of related compounds of the general formula II, containing a sulfur atom in place of an oxygen atom in the ester linkage. The new class of compounds were prepared by quater-

(1) Swan and White, *J. Pharmacol. Exper. Therapy*, **80**, 285 (1944).

(2) Featherstone and White, *ibid.*, **84**, 105 (1945); Peterson and Peterson, *ibid.*, **84**, 236 (1945), and *Gastroenterology*, **5**, 169 (1945); Cummins, Marquardt and Grossman, *ibid.*, **8**, 205 (1947); and others.

TABLE I

$RCOSCH_2CH_2N(CH_3)_2$ = THIOURETHANS

Compd.	R =	Name	Yield, %	Formula	Physical state[a]
1	$(CH_3CH_2CH_2CH_2)_2N$	2-Dimethylaminoethyl dibutylthiolcarbamate	97	$C_{13}H_{28}ON_2S$	Semicrystalline mass
2	$[CH_3(CH_2)_4CH_2]_2N$	2-Dimethylaminoethyl diamylthiolcarbamate	94	$C_{15}H_{32}ON_2S$	Liquid
3		2-Dimethylaminoethyl dicyclohexylthiolcarbamate	95	$C_{17}H_{32}ON_2S$	Crystals, m.p. 48–50°
4		2-Dimethylaminoethyl 4-morpholine carbothiolate	78	$C_9H_{18}O_2N_2S$	Liquid
5		2-Dimethylaminoethyl 1-piperidine carbothiolate	98	$C_{10}H_{20}ON_2S$	Liquid

[a] These compounds were difficult to prepare for analyses since they resisted crystallization and decomposed on attempted distillation.

nizing the thiourethans, $RCOSCH_2CH_2N(CH_3)_2$. Five compounds of the latter general formula were prepared by the reaction of dimethylamino ethyl thiol and the requisite carbamyl chlorides. The intermediate thiourethans (Table I) were obtained in high yields but, with the exception of one, they were not obtained in crystalline forms.

The thiourethans listed in Table I reacted readily with alkyl iodides from which the sulfates were prepared by treatment with silver sulfate. The thiourethans were also converted to the ethosulfate salts by reaction with diethyl sulfate in ether. The properties of these quaternary salts are compiled in Table II. The sulfates and ethosulfates have been tested for antispasmodic activity by Dr. Charles A. Winter of the Merck Institute for Therapeutic Research, and, of those listed, Compounds 12, 13, 15, 17 and 19 were found to have low toxicities and outstanding antispasmodic activities.[3]

(3) C. A. Winter, to be published elsewhere.

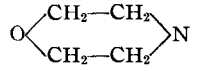
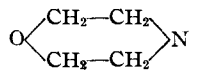
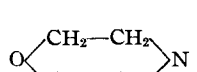
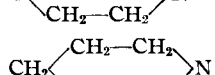
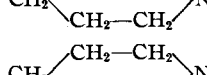
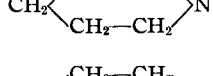
TABLE II

$RCOSCH_2CH_2N(CH_3)_2R_3X$

Compd.	R	R_3	X	Name	Yield, %	M.p., °C., (cor.)[a]	Formula	Analyses, % Calcd. C	H	N	H_2O	Found C	H	N	H_2O
6	$(C_4H_9)_2N$	C_2H_5	I	[2-(Dibutylcarbamyl-mercapto)-ethyl]-ethyldimethylammonium iodide	97	56	$C_{15}H_{35}ON_2SI$[b]			6.73				6.85	
7	$(C_4H_9)_2N$	C_2H_5	SO_4	[2-(Dibutylcarbamyl-mercapto)-ethyl] ethyldimethylammonium sulfate	89	127–128	$C_{30}H_{66}O_6N_2S_2{\cdot}H_2O$	51.99	9.89	8.08	2.60	51.78	10.09	7.80	2.45[c]
8	$(C_5H_{11})_2N$	C_2H_5	I	[2-(Diamylcarbamyl-mercapto)-ethyl]-ethyldimethylammonium iodide	97	[d]	$C_{17}H_{37}ON_2SI$	45.94	8.39	6.30		45.89	8.02	6.38	
9	$(C_5H_{11})_2N$	C_2H_5	SO_4	[2-(Diamylcarbamyl-mercapto)-ethyl] ethyldimethylammonium sulfate	91	124–125	$C_{34}H_{74}O_6N_2S_2{\cdot}1^1/_2H_2O$ $C_{34}H_{74}O_6N_2S_2$			7.67	3.56			8.09	3.85
10	$(C_5H_{11})_2N$	$SO_4C_2H_5$		[2-(Diamylcarbamyl-mercapto)-ethyl]-ethyldimethylammonium ethosulfate	55[e]	55–56	$C_{19}H_{42}O_6N_2S_2{\cdot}1^1/_2H_2O$	50.51	9.59	6.19	1.99	50.20	9.08	6.36	1.85
11	$(C_6H_{11})_2N$	C_2H_5	I	[2-(Dicyclohexylcarb-amylmercapto)-ethyl]-ethyldimethylammonium iodide	98	190–191	$C_{19}H_{37}ON_2SI{\cdot}^1/_2H_2O$	47.79	8.02	5.87	1.88	47.90	7.78	5.63	2.00
12	$(C_6H_{11})_2N$	C_2H_5	SO_4	[2-(Dicyclohexylcarb-amylmercapto)-ethyl]-ethyldimethylammonium sulfate	97	143–144	$C_{38}H_{74}O_6N_4S_3{\cdot}5^1/_2H_2O$	51.96	9.75	6.37	11.27	51.73	9.60	6.41	11.17
13	$(C_6H_{11})_2N$	C_2H_5	$SO_4C_2H_5$	[2-(Dicyclohexylcarb-amylmercapto)-ethyl]-ethyldimethylammonium ethosulfate	62	178–179	$C_{21}H_{42}O_6N_2S_2$	54.04	9.07	6.00		53.88	8.87	5.93	

TABLE II (*Continued*)

$RCOSCH_2CH_2N(CH_3)_2R_3X$

Compd.	R	R_3	X	Name	Yield, %	M.p., °C., (cor.)[a]	Formula	Analyses, % Calcd. C	H	N	H_2O	Found C	H	N	H_2O
14	$(C_6H_{11})_2N$	C_3H_7	I	[2-(Dicyclohexylcarbamylmercapto)-ethyl]-propyldimethylammonium iodide	42[f]	149–151	$C_{29}H_{59}ON_2SI$	49.78	8.15	5.80		49.63	7.99	5.82	
15	$(C_6H_{11})_2N$	C_3H_7	SO_4	[2-(Dicyclohexylcarbamylmercapto)-ethyl]-propyldimethylammonium sulfate	85	137–139	$C_{40}H_{78}O_6N_4S_3\cdot 6H_2O$	52.48	9.91	6.12	11.80	52.61	9.60	6.37	11.44
16	$(C_6H_{11})_2N$	C_4H_9	I	[2-(Dicyclohexylcarbamylmercapto)-ethyl]-butyldimethylammonium iodide	58[f]	161.5–162.5	$C_{21}H_{41}ON_2SI$	50.80	8.32	5.64		51.10	8.15	5.63	
17	$(C_6H_{11})_2N$	C_4H_9	SO_4	[2-(Dicyclohexylcarbamylmercapto)-ethyl]-butyldimethylammonium sulfate	87	99–99.5	$C_{42}H_{82}O_6N_4S_3\cdot 6H_2O$	53.47	10.04	5.94	11.45	53.47	9.90	5.94	11.12
18	$(C_6H_{11})_2N$	C_5H_{11}	I	[2-(Dicyclohexylcarbamylmercapto)-ethyl]-amyldimethylammonium iodide	71[f]	179–180	$C_{22}H_{43}ON_2SI$	51.75	8.49	5.48		51.96	8.38	5.64	
19	$(C_6H_{11})_2N$	C_5H_{11}	SO_4	[2-(Dicyclohexylcarbamylmercapto)-ethyl]-amyldimethylammonium sulfate	92	99–105	$C_{44}H_{86}O_6N_4S_3\cdot 3H_2O$			6.10	5.88			6.03	5.50
20		C_2H_5	I	[2-(4-Morpholinecarbonylmercapto)-ethyl]-ethyldimethylammonium iodide	100	123–124	$C_{11}H_{23}O_2N_2SI$	35.29	6.19	7.48		35.36	6.13	7.43	
21		C_2H_5	SO_4	[2-(4-Morpholinecarbonylmercapto)-ethyl]-ethyldimethylammonium sulfate	97	115–117	$C_{22}H_{46}O_8N_4S_3\cdot 2^1/_2H_2O$[b] $C_{22}H_{46}O_8N_4S_3$	44.72	7.85	9.48	7.07	44.89	7.66	9.80	7.10
22		C_2H_5	$SO_4C_2H_5$	[2-(4-Morpholinecarbonylmercapto)-ethyl]-ethyldimethylammonium ethosulfate	72	66.5–68	$C_{13}H_{28}O_6N_2S_2$	41.91	7.58	7.52		42.22	7.42	7.42	
23		C_2H_5	I	[2-(1-Piperidinecarbonylmercapto)-ethyl]-ethyldimethylammonium iodide	92	140–140.5	$C_{12}H_{25}ON_2SI$	38.71	6.77	7.52		38.70	6.75	7.56	
24		C_2H_5	SO_4	[2-(1-Piperidinecarbonylmercapto)-ethyl]-ethyldimethylammonium sulfate	94	116–117	$C_{24}H_{50}O_6N_4S_3\cdot 2^1/_2H_2O$[b] $C_{24}H_{50}O_6N_4S_3$			9.55	7.13			9.90	7.04
25		C_2H_5	$SO_4C_2H_5$	[2-(1-Piperidinecarbonylmercapto)-ethyl]-ethyldimethylammonium ethosulfate	100	74–76	$C_{14}H_{30}O_5N_2S_2$	44.94	8.13	7.48		44.65	7.86	7.03	

[a] The melting points recorded were taken on the original products because of the difficulty of recrystallizing these compounds in organic solvents. [b] Very hygroscopic and difficult to handle for the analysts; dehydrated at 80° (1 mm.). [c] All water determinations by the Karl Fischer method. [d] Soapy mass with no definite melting point. [e] The low yield was due to the difficulties in handling this soapy substance; the foaming was excessive on concentration. [f] The yield increased with increased reaction time, the propyl compound stood 4 hours at room temperature, the butyl compound 6 hours, and the amyl compound 18 hours.

Experimental

General Method for the Preparation of the Thiolurethans (Compound 3 as Example).—Three hundred fifty grams of analytically pure dimethylaminoethylthiol[4] (3.3 moles) was dissolved in 2000 cc. of anhydrous pyridine, 781 g. of dicyclohexylcarbamyl chloride,[5] (3.2 moles) was added and the mixture was heated and stirred at 100–105° for 3 hours. The batch was cooled to room temperature, the nearly solid mass was dissolved in 1000 cc. of water and distilled *in vacuo* below 50° to a mush to remove most of the pyridine. The residue was dissolved in 2000 cc. of water, the solution acidified to congo red with concentrated hydrochloric acid and extracted with three 1500-cc. portions of ether which were discarded. The acid solution was made strongly alkaline by adding sodium carbonate and extracted with four 1000-cc. portions of chloroform. The combined chloroform extracts were dried over Drierite, the chloroform was distilled *in vacuo* and the residue held for several hours at 100° (1 mm.) to remove all pyridine; yield, etc. (see Table I).

The Preparation of the Ammonium Iodides.—The urethans were dissolved in 3 to 4 moles of the requisite alkyl iodides, the mixtures were held at 25–35° for 4 hours or longer, cooling in ice as needed. Anhydrous ether was added in excess and the mixtures were allowed to stand overnight at room temperature. The iodides were filtered, washed with anhydrous ether and dried; yields see Table II.

The Ethosulfate Salts.—The urethans (1, 3, 4, 5) were dissolved in ether, 2 moles of ethyl sulfate was added, and on standing one to two days at room temperature the products crystallized out and were filtered and washed with ether. As the ethosulfate of urethan 2, however, did not crystallize, compound 10 of Table II [2-(diamylcarbamylmercapto)-ethyl]-ethyldimethylammonium ethosulfate was obtained as follows:

Fifteen grams of dimethylaminoethylthioldiamylurethan (0.052 mole) was dissolved in 100 cc. of anhydrous ether, 15.4 g. of diethyl sulfate (0.1 mole) was added, and the solution was refluxed for 24 hours. The reaction mixture was extracted with two 25-cc. portions of water and the aqueous extracts were adjusted to a *p*H of 6.5 by adding a little barium hydroxide solution. The turbid solution was clarified by treating with charcoal and filtering through a layer of Supercel. A faint trace of Ba^{++} in the solution was removed by adding a minute amount of ammonium sulfate and filtering. The solution was reduced to a sirup which was air-dried; a sluggish crystallization gradually took place. The soapy masses were frequently broken up, and drying in the air was continued until the weight was constant; yield, etc., see Table II.

Conversion of the Iodides to Sulfates.—As an example, the conversion of iodide 8 to [2-(diamylcarbamylmercapto)-ethyl]-ethyldimethylammonium sulfate (9) was carried out as follows:

Ninety grams of the iodide (0.20 mole) was dissolved in 500 cc. of 50% alcohol, 41 g. of powdered silver sulfate (0.13 mole) was added and the mixture was stirred rapidly until the reaction was completed. The silver salts were filtered and washed with 50% alcohol. The solution was treated with slight excess of hydrogen sulfide to remove a trace of silver, adjusted to *p*H 6.5 by adding barium hydroxide solution, decolorized by treatment with carbon and filtered through a bed of Super-cel. The clear and colorless filtrate was concentrated to a sirup *in vacuo* and the residue was dehydrated by distillation under reduced pressure with ethanol.

Some of the sulfates crystallized in the air and were air-dried to constant weight; others were hygroscopic and were dried *in vacuo* over sulfuric acid to constant weight. For yields, etc., see Table II.

Acknowledgment.—We are indebted to Mr. R. N. Boos and associates for the analyses, and to Mr. E. van Gilder for technical assistance.

RAHWAY, N. J. RECEIVED AUGUST 28, 1950

(4) Gilman, THIS JOURNAL, **67**, 1845 (1945).

(5) The carbamyl chlorides were prepared from the corresponding amines with excess phosgene in xylene at 0°, in about 90% yields; see Boon, *J. Chem. Soc.*, 313 (1947).

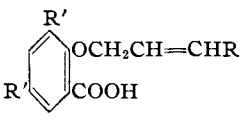
[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF ROCHESTER]

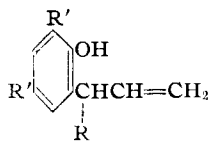
The Effect of Changes in the Allyl Group on the Rearrangement of Allyl Ethers of Salicylic Acids

BY WILLIAM R. NUMMY[1] AND D. STANLEY TARBELL

The synthesis of ethers prepared from 3,5-dichlorosalicylic acid and 3,5-dimethylsalicylic acid, with 3-bromomethylcoumarin and 3-bromomethyl-2,2-dimethylbenzopyran, has been investigated. 2-(3-Coumarinylmethoxy)-3,5-dichlorobenzoic acid yields carbon dioxide, but no crystalline product, upon pyrolysis. An unsaturated phenolic carbinol, 1-*o*-hydroxyphenyl-2,3-dimethylbutene-1-ol-3, has been shown to be an intermediate in the formation of 2,2,3-trimethylbenzopyran from 3-methylcoumarin and methylmagnesium iodide. Measurements of the rate of rearrangement of the allyl and crotyl ethers of 3,5-dimethyl- and 3,5-dichlorosalicylic acid show that the change in nuclear substitution does not affect the rate; the crotyl ethers, however, rearrange several times as rapidly as the allyl ethers in both series, an effect attributed to the inductive effect of the methyl group.

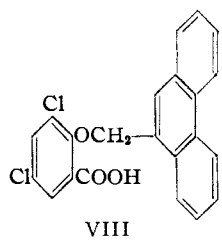
It has been shown that rearrangement of O-crotyl-3,5-dichlorosalicylic acid[2] I takes place with inversion to yield II in which the γ-carbon atom of the crotyl group is attached to the ring.



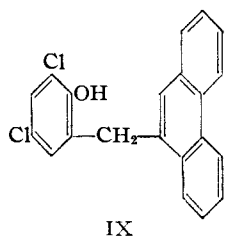


I, R = CH_3, R′ = Cl
II, R = CH_3, R′ = Cl
III, R = H, R′ = CH_3
IV, R = H, R′ = CH_3
V, R = R′ = CH_3
VI, R = R′ = CH_3
VII, R = H, R′ = Cl

The corresponding 9-phenanthrylmethyl ether VIII likewise undergoes rearrangement with loss of carbon dioxide,[3] but the product has been proved by synthesis[4] to be IX; the shift therefore occurs *without* inversion.



VIII



IX

Inversion and other characteristics of the

(1) Sherman Clarke Fellow, 1949–1950.

(2) Tarbell and Wilson, THIS JOURNAL, **64**, 607 (1942).

(3) Tarbell and Wystrach, *ibid.*, **65**, 2149 (1943).

(4) Tarbell and Sato, *ibid.*, **68**, 1091 (1946).