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New Antibacterial Agents. 2-Acylamino-1-(4-hydrocarbonylsulfonylphenyl)-1,3-propanediols and Related Compounds

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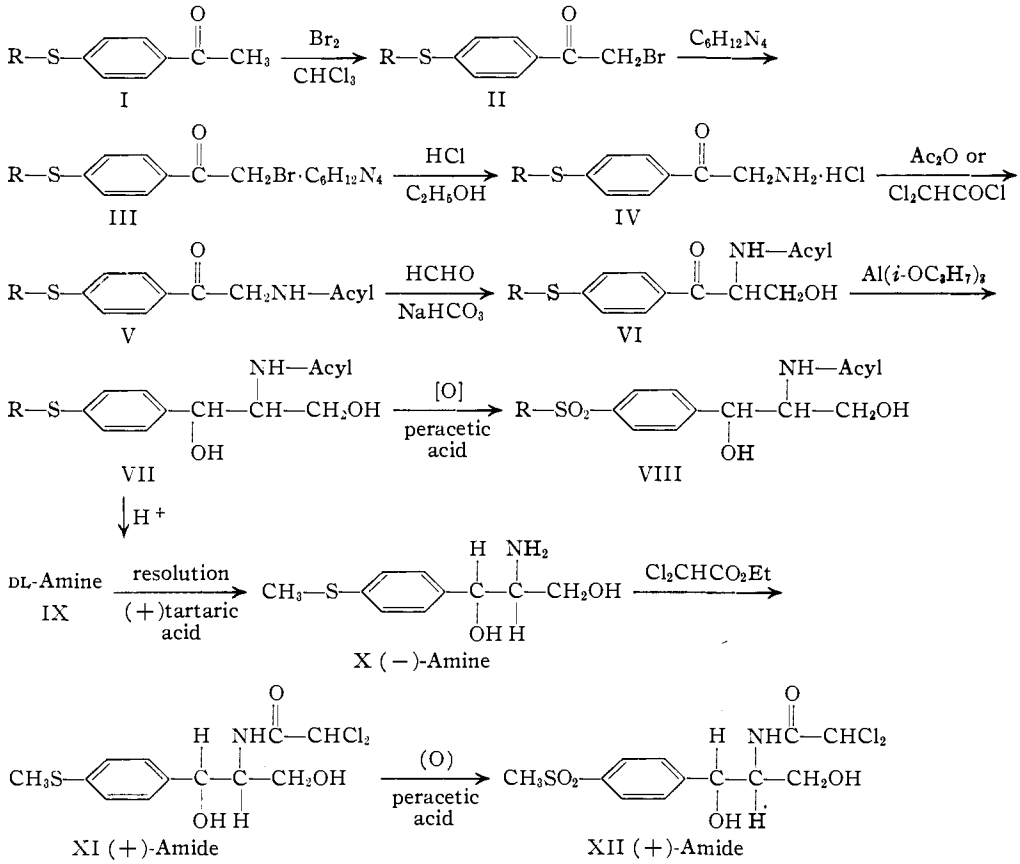
A number of racemic *threo*-2-dichloroacetamido-1-(4-hydrocarbonylmercaptophenyl)-1,3-propanediols (VII) and the corresponding sulfones (VIII) have been prepared and tested as antibacterial agents. Of these, the methyl analogs in both the sulfide (VIIa) and sulfone (VIIIa) series exhibited outstanding antibacterial action against a number of pathogenic organisms. These same two compounds have also been prepared in their optically active forms (XI and XII; see Chart I). A preliminary report of the bacteriostatic activity of a number of the compounds prepared in this series has been included (Table I).

In the search for superior antibacterial agents, a number of racemic *threo*-2-dichloroacetamido-1-(4-hydrocarbonylmercaptophenyl)-1,3-propanediols (VII, Table III) and the corresponding sulfones (VIII) have been synthesized. These compounds were prepared according to the scheme outlined in Chart I. The desired sulfones (VIII) were readily prepared from the corresponding racemic *threo*-2-dichloroacetamido-1-(4-hydrocarbonylmercaptophenyl)-1,3-propanediols (VII) by oxidation with peracetic acid.

The hydrocarbonylmercaptoacetophenones (I) were prepared by a Friedel–Crafts reaction between the corresponding phenyl sulfides and acetyl chloride. The preparation of 4-methylmercaptoacetophenone[1] (Ia) was studied in some detail in an effort to improve the yield and quality of product obtained.

As a starting point, the two literature methods[1b,e] which were reported as giving the best yields were selected for trial. The method of Burton and Hu,[1b] whereby the reaction was carried out in re-

CHART I



R = (a), CH_3–; (b), C_2H_5–; (c), *n*-C_3H_7–; (d), *n*-C_4H_9–; (e), C_6H_5–; (f), $C_6H_5CH_2$–.

Acyl = $Cl_2CHC(=O)$– when the letter is unprimed and $CH_3C(=O)$– when the letter is primed: *e.g.*, Va′ refers to α-acetamido-4-methylmercaptoacetophenone.

(1) Reported as a new compound by five independent investigators; (a) L. C. King, M. McWhirter and R. L. Rowland, THIS JOURNAL, **70**, 239 (1948); (b) H. Burton and P. F. Hu, *J. Chem. Soc.*, 601 (1948); (c) J. W. Corse, R. G. Jones, Q. F. Soper, C. W. Whitehead and O. K. Behrens, THIS JOURNAL, **70**, 2837 (1948); (d) P. Cagniant, *Compt. rend.*, **226**, 1133 (1948); (e) F. Krollpfeiffer, H. Hartmann and F. Schmidt, *Ann.*, **563**, 15 (1949).

fluxing carbon disulfide, proved to be the better of the two, giving the theoretical weight of the crude ketone (Ia). However, the quality of the latter was such that purification losses amounted to 15–20%. In the second method,[1e] in which no solvent was used, stirring became increasingly difficult and less effective as the reaction proceeded. This resulted in local overheating due to the exothermic reaction which occurred on the dropwise addition of thioanisole to the aluminum chloride–acetyl chloride mixture. The purity of the resulting crude ketone was inferior to that obtained above.

It was thus concluded that the application of heat led to excessive decomposition and should be avoided.[2]

Further experiments conducted at temperatures of 0–10° not only gave good yields of satisfactory product but also indicated that the reaction is practically instantaneous even at these lower temperatures. With chloroform[3] as the reaction solvent, the yield of ketone (Ia) was 98%. In addition, the product as isolated directly from the reaction mixture was colorless and substantially pure; m.p. 80–82° (uncor.).

Bromination of the acetophenone (I) in chloroform[4] solution yielded the α-bromo-4-hydrocarbonylmercaptoacetophenones (II). Treatment of the latter, dissolved in acetonitrile,[5] with hexamethylenetetramine gave the adducts (III) in uniformly good yields.

Certain of the adducts (IIIa, b, f) were readily converted to the corresponding α-aminoketone hydrochlorides (IVa, b, f) by hydrolysis at room temperature with a mixture of alcohol and concentrated hydrochloric acid. Those remaining, (IIIc, d, e) and especially the propyl analog (IIIc), gave very poor yields by this method. It appeared that these adducts were quite unstable in the hydrolysis medium and that decomposition was occurring more rapidly than hydrolysis. The difficulty was largely avoided by hydrolyzing at reflux temperature, the higher temperature causing a greater increase in the hydrolysis rate than in the rate of decomposition. An additional modification was also required in the isolation of the propyl, butyl and phenyl analogs (IVc, d, e) due to the appreciable solubility of these aminoketone hydrochlorides in the reaction medium (see Experimental).

From the amine hydrochlorides (IV), two alternate routes were employed for the synthesis of the propanediols (VII).

The methylmercapto and benzylmercapto analogs (IVa and f) were converted to the α-acetamidoacetophenones (Va′ and f′), which were in turn hydroxymethylated and the resulting products (VIa′ and f′) reduced with aluminum isopropoxide to give the racemic *threo*-2-acetamido-1-(4-hydrocarbonylmercaptophenyl)-1,3-propanediols (VIIa′ and f′). In the second method the α-aminoketone hydrochlorides (IV) were treated with dichloroacetyl chloride in refluxing benzene to yield the dichloroacetamides (V). Of several other solvents tried, in the preparation of Va, toluene seemed to be most advantageous (see Experimental).

Hydroxymethylation of the dichloroacetamidoacetophenones (V), with formaldehyde and catalytic amounts of sodium bicarbonate in ethanol, gave the desired propiophenones (VI) in good yield. Aluminum isopropoxide reduction of the latter yielded the racemic *threo*-2-dichloroacetamido-1-(4-hydrocarbonylmercaptophenyl)-1,3-propanediols (VII).

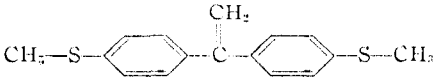
Initially the reductions were carried out by the slow distillation of 2-propanol for several hours until the test for acetone in the distillate was negative. In later experiments a shortened reaction time proved to be advantageous.[6] Thus, after a 35–40-minute period of heating, a 60% yield of VIIa of excellent purity was obtained. This compares with a 51% yield obtained by the longer heating period originally employed (see Table II). In the phenylmercapto series an even shorter reaction time (15 minutes) was used, thus indicating that the reaction is very rapid indeed.

Oxidation with 40% peracetic acid proved to be the method of choice for the conversion of the sulfides (VII) to the sulfones (VIII). The yields were excellent and the products usually separated in analytically pure form. Though acetone proved to be a very useful solvent for this reaction on a small scale, the formation of acetone peroxide as a by-product would constitute a potential hazard in larger operations.

Hydrolysis of either VIIa′ or VIIa with dilute hydrochloric acid gave the free racemic amine (IX, see Chart I). Partial resolution of the latter was achieved through the (+)-tartrates, the resolution being completed by reconversion to the free amines followed by recrystallization of each form from methanol to give the two optical isomeric amines.

Treatment of the (−)-amine (X) with ethyl dichloroacetate gave a (+)-amide (XI) which proved to be a potent antibacterial agent. On the other hand the (±)-dichloroacetamido derivative of the (+)-amine was virtually devoid of antibacterial

(2) The effect of heat was further illustrated in an experiment carried out in hot chlorobenzene (see Experimental). One of the products isolated was 1,1-bis-(4-methylmercaptophenyl)-ethylene. Similar



compounds have been isolated from Friedel–Crafts reactions of (a) thioanisole with phenylacetyl chloride, D. Xuong, P. Cagniant and C. Mentzner, *Compt. rend.*, **226**, 1453 (1948); (b) anisole with acetyl chloride, L. Gattermann, R. Ehrhardt and H. Maisch, *Ber.*, **23**, 1199 (1890); (c) anisole and phenetole with propionyl chloride, L. Gattermann, *ibid.*, **22**, 1129 (1889); (d) anisole and butyryl chloride, S. Skraup and F. Nieten, *Ber.*, **57**, 1294 (1924); (e) *n*-butyl phenyl ether and acetyl chloride, R. E. Lutz, *et al.*, *J. Org. Chem.*, **12**, 617 (1947).

(3) The insoluble nature of the orange-colored aluminum chloride complex of the ketone (1a), which separated during the reaction, made stirring rather ineffective when solvents such as carbon disulfide, chlorobenzene and carbon tetrachloride were used. As a consequence lowered yields resulted from incomplete reaction. However, solvents such as chloroform or nitromethane, in which the complex is more soluble, gave practically quantitative yields of product (1a) of excellent purity. Insoluble aluminum chloride complexes were not noted in the preparation of the other ketones in this series (1b,c,d,e,f).

(4) The choice of solvent was made on the basis of studies by F. Krōhnke, *Ber.*, **69B**, 921 (1936), on the bromination of a number of acetophenones in various solvents.

(5) Whereas chloroform functioned well as a solvent in the formation of some of the adducts (IIIa,b,f), its use in the preparation of the others (IIIc,d,e) led to considerable decomposition with a consequent lowering of yields.

(6) C. W. L. Trieti and W. N. Moulton, THIS JOURNAL, **73**, 5013 (1951).

properties. This relationship between the optical rotation of the antibacterially active (+)-amide (XI) and that of the corresponding free (−)-base (X) parallels that between (+)-chloramphenicol and the (−)-base[7] derived from it by hydrolysis. We have therefore designated the antibacterially active (+)-amide (XI) as D-*threo*-2-dichloroacetamido-1-(4-methylmercaptophenyl)-1,3-propanediol. Oxidation of the latter with peracetic acid gives the corresponding (+)-sulfone (XII) which is likewise a potent antibacterial agent (see Table I). Hydrolysis of the (+)-sulfone (XII) with dilute hydrochloric acid gives the free (−)-amine (XIII) which is very soluble in water.

Biological Results.—The preliminary bacteriological assays reported in this paper were carried out by Mr. W. F. Warner. More complete and detailed accounts of the antibacterial,[8] experimental chemotherapeutic and pharmacological properties[9] of the two most active compounds of this series (XI and XII) are published elsewhere by members of the Chemotherapy Section of these laboratories.

The results of preliminary *in vitro* antibacterial screening tests are shown in Table I. It will be noted that lengthening of the chain attached to the sulfur atom results in a marked decrease in activity in both the sulfide (VII) and sulfone (VIII) series. It is also evident that replacement of the dichloroacetyl group by acetyl leads to a very great diminution in activity (compare VIIa with VIIa′ and VIIIa with VIIIa′). With the exception of D-*threo*-2-dichloroacetamido-1-(4-methylmercaptophenyl)-1,3-propanediol (XI) and the corresponding D-sulfone (XII) all of the compounds listed in Table I are the racemic forms, hence their reported activities are less than would be the case for their resolved forms.

TABLE I

PRELIMINARY *in vitro* BACTERIOSTATIC ACTIVITY OF COMPOUNDS XI, XII AND THOSE IN GROUPS VII AND VIII

Compound	Minimum effective concentration (mcg./ml.) *Staph. aureus* (209)	*Strep. hemolyticus* (C203)	*E. typhi* (Hopkins)	*Br. abortus*
XI[a]	25	1.0	2.5	1.0
VIIa	40	2.5	8	2.5
VIIa′	1,000	250	250	
VIIIb	77	8	50	
VIIc	250	50	500	
VIId	250	50	250	
VIIe	250	500	80	
XII[a]	25	2.5	30	0.75
VIIIa	40	5.0	50	2.0
VIIIa′	500	25	>1,000	
VIIIb	250	10	80	
VIIIc	800	100	500	
VIIId	250	25	250	
VIIIe	1,000	500	800	

[a] The L-isomer is devoid of antibacterial activity.

(7) (a) The designation of this base as D(−)-*threo*-2-amino-1-(4-nitrophenyl)-1,3-propanediol was based on the parallel existing between its optical properties (and those of its derivatives) and those of D(−)-nor-*pseudo*-ephedrine (and its derivatives); M. C. Rebstock, H. M. Crooks, Jr., J. Controulis and Q. R. Bartz, *ibid.*, **71**, 2458 (1949); (b) the direct correlation of the DL-form of chloramphenicol with DL-nor-*pseudo*-ephedrine by chemical means has firmly established that chloramphenicol exists in the *threo*-form; G. Fodor, J. Kiss and I. Sallay, *Nature*, **167**, 690 (1951); *J. Chem. Soc.*, 1858 (1951).

(8) E. W. Dennis, W. F. Warner and J. H. Bailey, *Antibiotics and Chemotherapy*, in press.

(9) E. W. Dennis, E. J. Froelich and D. A. Berberian, *ibid.*, in press.

Acknowledgment.—The authors are grateful for the assistance of Mr. Samuel Schalit who was responsible for the preparation and purification of a number of the compounds in the phenylmercaptophenyl series.

Experimental[10]

Preparation of Sulfides.—The methyl and ethyl phenyl sulfides were prepared from the corresponding sulfates and thiophenol in aqueous alkali. Diphenyl sulfide was purchased from the Eastman Organic Chemicals Department of Distillation Products.

The *n*-propyl, *n*-butyl and benzyl phenyl sulfides were prepared by a simple modification of known methods.[11] Yields of purified sulfide were better than 90% in each case and represent improvements of 10–30% over the methods originally employed.[11]

A mixture of 110 g. (1 mole) of thiophenol, 900 ml. of 5% aqueous sodium hydroxide solution and 1.1 moles of halide (*n*-propyl iodide, *n*-butyl iodide or benzyl chloride) was stirred and heated on a steam-bath under reflux until the the reaction was complete.[12] After cooling the reaction mixture the upper oily layer[13] was separated, washed once with 10% caustic, and distilled at the water-pump to give in each case a colorless oil whose physical properties agreed with those previously reported.[11a,b]

4-Hydrocarbonylmercaptoacetophenones (I, Table II).—The alkylmercaptoacetophenones (Ia–d) were each prepared according to the following general procedure.

To a well stirred slurry of 160 g. (1.2 moles) of anhydrous aluminum chloride and 650 ml. of dry chloroform was added 102 g. (1.3 moles) of acetyl chloride. During this addition the temperature of the reaction mixture was maintained at 0–10° by means of strong external cooling with an ice–methanol mixture. To the resulting gray suspension was added dropwise 1 mole of the alkyl phenyl sulfide at a temperature of 0–5°. When the addition was complete,[14] the cooling bath was removed, stirring continued and the reaction mixture allowed to warm to 20°. After hydrolysis the chloroform layer was separated, dried over Drierite and the solvent removed by distillation. Analytical samples were prepared by recrystallization of the residue from ethanol (Ia) or Skellysolve B (Ib) or by distillation *in vacuo* (Ic and d) followed by crystallization from Skellysolve A.

The phenyl (Ie) and benzyl (If) analogs were prepared similarly with the exception that equimolecular quantities of sulfide, aluminum chloride and acetyl chloride were used

(10) The analyses, melting points and optical rotations were performed by the staffs of M. E. Auerbach and K. D. Fleischer of these laboratories. All melting points, unless otherwise specified, are corrected and were determined with an electrically heated, mechanically stirred, Thiele type apparatus. Thermometers used were calibrated Anschütz internal thermometers. Samples were placed in 1-mm. capillary tubing and the latter immersed when the temperature of the melting point bath was about 20° below the approximate melting point of the sample and the rate of temperature rise of the bath was approximately 3° per minute. Nitrogen, unless otherwise specified, was determined by a modified Kjeldahl procedure. Chlorine and sulfur, exceptions noted, were determined by the Parr bomb method.

(11) (a) F. G. Mann and D. Purdie, *J. Chem. Soc.*, 1549 (1935) (*n*-butyl phenyl sulfide); (b) V. N. Ipatieff, H. Pines and B. S. Friedman, THIS JOURNAL, **60**, 2731 (1938); see also A. I. Vogel, *J. Chem. Soc.*, 1820 (1948) (*n*-propyl and *n*-butyl phenyl sulfides); (c) R. L. Shriner, H. C. Struck and W. J. Jorison, THIS JOURNAL, **52**, 2060 (1930) (benzyl phenyl sulfide).

(12) The reaction was considered complete when a sample of the aqueous layer failed to show any turbidity on acidification with concd. hydrochloric acid. Under these conditions the reaction with benzyl chloride and *n*-propyl iodide was complete in less than 30 minutes. The reaction with *n*-butyl iodide was allowed to run for four hours to ensure completion.

(13) Benzyl phenyl sulfide solidified on cooling and was removed by filtration to give 94% of crystalline product.

(14) In the case of Ia, the aluminum chloride complex of the product separated as an orange solid which necessitated the addition of more dry chloroform to facilitate stirring.

TABLE II

INTERMEDIATE 4-HYDROCARBONYLACETOPHENONES R—S—C$_6$H$_3$(—C(=O)—CH(X)—Y)

No.	R	X	Y	Yield, %	M.p., °C.	Empirical formula	Analyses, % Calcd.	Found
Ia	CH_3–[a]	–H	–H	98	80.6–81.4	$C_9H_{10}OS$	C, 65.03[b]	65.33
Ib	C_2H_5–[c]	–H	–H	88	44.6–45.7	$C_{10}H_{12}OS$	S, 17.78	18.01
Ic	n-C_3H_7–	–H	–H	85	37.7–39.1[d]	$C_{11}H_{14}OS$	S, 16.50	16.49
Id	n-C_4H_9–	–H	–H	66	24–25[e]	$C_{12}H_{16}OS$	S, 15.39	16.09
Ie	C_6H_5–[f]	–H	–H	65	65.8–66.8	$C_{14}H_{12}OS$	C, 73.65[g]	73.56
If	$C_6H_5CH_2$–	–H	–H	26[h]	113.9–115.3	$C_{15}H_{14}OS$	S, 13.23	13.39
IIa	CH_3–	–Br	–H	52[h]	65.5–66.5	C_9H_9BrOS	Br,[i] 32.60	32.72
IIb	C_2H_5–	–Br	–H	49[h]	74.4–75.4	$C_{10}H_{11}BrOS$	Br,[i] 30.84	31.12
IIc	n-C_3H_7–	–Br	–H	51[h]	40.9–41.6	$C_{11}H_{13}BrOS$	Br,[i] 29.25	28.85
IId	n-C_4H_9–	–Br	–H	50[h]	61.5–63	$C_{12}H_{15}BrOS$	Br,[i] 27.82	27.38
IIe	C_6H_5–	–Br	–H	[j]	63.0–64.0	$C_{14}H_{11}BrOS$	Br,[i] 26.01	26.11
IIf	$C_6H_5CH_2$–	–Br	–H	27[h]	76.9–77.5	$C_{15}H_{13}BrOS$	Br,[i] 24.88	26.78
IIIa	CH_3–	–Br·$C_6H_{12}N_4$	–H	93	144.2–145.0 dec.	$C_{15}H_{21}BrN_4OS$	N, 14.54	14.40
IIIb	C_2H_5–	–Br·$C_6H_{12}N_4$	–H	75	141.3–143.0 dec.	$C_{16}H_{23}BrN_4OS$	N, 14.03	13.96
IIIc	n-C_3H_7–	–Br·$C_6H_{12}N_4$	–H	70	134–138 dec.	$C_{17}H_{25}BrN_4OS$	S, 7.76	7.66
IIId	n-C_4H_9–	–Br·$C_6H_{12}N_4$	–H	67	105–108 dec.	$C_{18}H_{27}BrN_4OS$	N, 13.11	12.76
IIIe	C_6H_5–	–Br·$C_6H_{12}N_4$	–H	95	120.1–121.8 dec.	$C_{20}H_{23}BrN_4OS$	Br,[k] 17.86	17.70
IIIf	$C_6H_5CH_2$–	–Br·$C_6H_{12}N_4$	–H	81	145–170 dec.	$C_{21}H_{25}BrN_4OS$	N, 12.14	11.93
IVa	CH_3–	–NH_2·HCl	–H	95	234.5–235.0 dec.	$C_9H_{12}ClNOS$	Cl,[k] 16.28	15.99
IVb	C_2H_5–	–NH_2·HCl	–H	90	186.5 dec.	$C_{10}H_{14}ClNOS$	Cl,[k] 15.30	14.93
IVc	n-C_3H_7–	–NH_2·HCl	–H	50	158 dec.	$C_{11}H_{16}ClNOS$	Cl,[k] 14.43	13.94
IVd	n-C_4H_9–	–NH_2·HCl	–H	64	175.5–179.3 dec.	$C_{12}H_{18}ClNOS$	N, 5.39	5.28
IVe	C_6H_5–	–NH_2·HCl	–H	61	216.7–217 dec.	$C_{14}H_{14}ClNOS$	Cl,[k] 12.69	12.97
IVf	$C_6H_5CH_2$–	–NH_2·HCl	–H	80	214.5–216.5 dec.	$C_{15}H_{16}ClNOS$	S,[l] 10.92	10.87
Va'	CH_3–	CH_3CONH–	–H	90	133.2–134.6	$C_{11}H_{13}NO_2S$	N, 6.27	6.30
Va	CH_3–	$Cl_2CHCONH$–	–H	86	151.7–152.9	$C_{11}H_{11}Cl_2NO_2S$	Cl,[l] 24.27	24.41
Vb	C_2H_5–	$Cl_2CHCONH$–	–H	77	127.6–128.8	$C_{12}H_{13}Cl_2NO_2S$	Cl, 23.16	23.04
Vc	n-C_3H_7–	$Cl_2CHCONH$–	–H	47	123.2–123.8	$C_{13}H_{15}NO_2S$	Cl, 22.10	21.80
Vd	n-C_4H_9–	$Cl_2CHCONH$–	–H	91	127.4–128[m]	$C_{14}H_{17}Cl_2NO_2S$	Cl, 21.21	21.12
Ve	C_6H_5–	$Cl_2CHCONH$–	–H	65	139.0–141.4	$C_{16}H_{13}Cl_2NO_2S$	Cl,[l] 20.02	19.82
Vf	$C_6H_5CH_2$–	$Cl_2CHCONH$–	–H	87	185.6–186.4	$C_{17}H_{15}Cl_2NO_2S$	Cl, 19.25	19.44
Vf'	$C_6H_5CH_2$–	CH_3CONH–	–H	85	162.6–163.8	$C_{17}H_{17}NO_2S$	C, 68.19[n]	68.28
VIa'	CH_3–	CH_3CONH–	$-CH_2OH$	62	125.6–127.8	$C_{12}H_{15}NO_3S$	S, 12.61	12.71
VIa	CH_3–	$Cl_2CHCONH$–	$-CH_2OH$	72	147.7–148.5	$C_{12}H_{13}Cl_2NO_3S$	Cl,[l] 22.01	22.15
VIb	C_2H_5–	$Cl_2CHCONH$–	$-CH_2OH$	93	153.2–154.3	$C_{13}H_{15}Cl_2NO_3S$	Cl, 21.09	21.00
VIc	n-C_3H_7–	$Cl_2CHCONH$–	$-CH_2OH$	89	133.4–136.8	$C_{14}H_{17}Cl_2NO_3S$	Cl, 20.23	20.29
VId	n-C_4H_9–	$Cl_2CHCONH$–	$-CH_2OH$	79	123.0–123.8	$C_{15}H_{19}Cl_2NO_3S$	Cl, 19.46	19.16
VIe	C_6H_5–	$Cl_2CHCONH$–	$-CH_2OH$	78	128.5–129.5	$C_{17}H_{15}Cl_2NO_3S$	Cl,[k] 18.45	18.68
VIf'	$C_6H_5CH_2$–	CH_3CONH–	$-CH_2OH$	62[h]	165.9–167.0	$C_{18}H_{19}NO_3S$	S,[l] 9.73	9.87

[a] See ref. 1. [b] Calcd.: H, 6.06. Found: H, 6.31. [c] K. Auwers and C. Berger, *Ber.*, **27**, 1733 (1894); m.p. 43.5°. [d] B.p. 188–192° at 29 mm. [e] Uncorrected melting point; b.p. 112–114° at 0.2 mm.; $n^{25}D$ 1.5788. [f] W. Dilthey, L. Neuhaus, E. Reis and W. Schommer, *J. prakt. Chem.*, **124**, 81 (1930); see also H. H. Szmant and F. P. Palpoli, THIS JOURNAL, **72**, 1757 (1950). [g] Calcd.: H, 5.30. Found: H, 5.50. [h] Yield of purified compound. [i] Halogen by hydrolytic method; KOH–methanol hydrolysis medium. [j] Yield of purified product not determined. [k] Ionic halogen. [l] Determined by Pregl combustion method. [m] Sinters at 120°. [n] Calcd.: H, 5.72. Found: H, 5.51.

in order to minimize diacetylation. For the same reason the order of reactants was also reversed; *i.e.*, the acetyl chloride was added to the chloroform slurry of the sulfide and aluminum chloride. In the case of If, hydrolysis of the aluminum chloride complex yielded an almost quantitative amount of a dark red, evil smelling oil. This oily mixture was dissolved in 700 ml. of boiling Skellysolve C, filtered with charcoal and the yellow filtrate cooled to give 93 g. of yellow solid still having a strong odor. The odor and color were eliminated by two recrystallizations from ethanol and an additional one from a large volume of Skellysolve B.

α-Bromo-4-hydrocarbonylmercaptoacetophenones (II).—One mole of the 4-hydrocarbonylmercaptoacetophenone (I), dissolved in 10 volumes of chloroform, was treated with one mole of bromine at room temperature. Initially, about one-fifth of the bromine was run into the reaction mixture, the solution stirred briefly and allowed to stand until reaction was initiated. Immediately vigorous stirring was instituted and the remainder of the bromine dropped in as rapidly as practicable (3–5 minutes). When all had been added, the solution was allowed to stir for about a minute and an excess of 10% sodium bicarbonate solution added. Separation of the chloroform layer, followed by drying over Drierite, filtration with charcoal and evaporation of the solvent from the filtrate yielded the crude product.

Analytical samples were prepared by recrystallization of the crude mixture from benzene–Skellysolve A mixture followed by recrystallization from methanol (IIa and b); crystallization from Skellysolve A (IIc and e); crystallization from Skellysolve B followed by recrystallization from methanol (IId and f).

Hexamethylenetetramine Salt of α-Bromo-4-hydrocarbonylmercaptoacetophenone (III).—One mole of the α-bromoketone (II) was dissolved in 1500 ml. of chloroform (IIIa,b,f) or acetonitrile (IIIc,d,e) and treated with 140 g. (1 mole) of hexamethylenetetramine. The mixture was stirred for two hours at room temperature. The solid adduct which separated was collected on a suction filter,

washed with water (to remove excess hexamethylenetetramine) and finally with acetone. The adducts were white to pinkish solids with the exception of the ethyl analog (IIIb) which was a bright canary yellow. On washing with water the yellow color disappeared leaving a white product. The bright yellow color reappeared, however, on washing again with acetone.

α-Amino-4-hydrocarbonylmercaptoacetophenone Hydrochlorides (IV).—The procedure for the preparation of IVa, b and f was essentially the same in each case.

One mole of the crude adduct (III) was stirred overnight at room temperature with 450 ml. of concentrated hydrochloric acid and 900 ml. of ethanol. After cooling to 5°, the separated solid was collected on a suction funnel and washed once with ethanol. The ammonium chloride was removed by suspending the dried solid in a stirred solution of 700 ml. of water containing 15 ml. of concentrated hydrochloric acid at 50°. The resulting slurry was cooled to 5°, the solid collected on a filter and the filter cake washed once with ice-water. Analytical samples were prepared by recrystallization from dilute acid (IVa,f) or from dilute acid followed by an additional recrystallization from ethanol (IVb).

Because of decreased stability of the adducts (IIIc,d,e) and increased alcohol solubility of the amine hydrochlorides, IVc, d and e were prepared by modified versions of the above.

In the case of the propyl analog (IVc), 92 g. of the adduct (IIIc) was mixed with 90 ml. of concentrated hydrochloric acid and 225 ml. of methanol and the mixture stirred and refluxed for 30 minutes. Initially, the mixture became dark red in color and after about 10 minutes ammonium chloride separated from the solution. The ammonium chloride was removed by filtration and the filtrate cooled to −5°. The solid which separated was collected on a filter and dissolved in 125 ml. of water acidulated with hydrochloric acid. After filtering with charcoal, the aqueous solution was cooled to 0° and the pure aminoketone hydrochloride (IVc), which separated in the form of white leaflets, was filtered off, washed with ice-water and dried.

The *n*-butyl analog (IVd) was prepared by the hydrolysis of 86 g. of the adduct (IIId) with 85 ml. of concentrated hydrochloric acid and 170 ml. of ethanol over a period of 10 hours at room temperature. The ammonium chloride was removed by filtration and discarded. The filtrate was evaporated *in vacuo* to a small volume whereupon 48.5 g. of a brown gummy solid was obtained. This was slurried with 60 ml. of acetone, cooled to −5° and the yellowish tan solid was collected on a filter and washed with additional portions of cold acetone. The crude product was recrystallized from 100 ml. of water, to which 3 ml. of concentrated hydrochloric acid had been added, to give 32.5 g. of the aminoketone hydrochloride (IVd) as white flaky crystals. Water solutions of this substance and also of IVc suds strongly when shaken.

An analytical sample of IVd was prepared by further recrystallization from ethanol followed by an additional recrystallization from dilute acid solution.

The phenyl analog (IVe) was prepared by a procedure similar to that described for the propyl analog (IVc) above.

α-Dichloroacetamido-4-hydrocarbonylmercaptoacetophenones (V).—One mole of powdered, dry aminoketone hydrochloride (IV) was stirred and heated under reflux with 1.1 moles of dichloroacetyl chloride and varying amounts of dry benzene until the solid phase had disappeared.[15] The hot solution was filtered with charcoal and the filtrate allowed to cool, whereupon an initial crop of white crystals separated which were generally practically pure. A second crop could usually be obtained by evaporation of the benzene filtrate to a small volume followed by cooling.

Ideally, the amount of benzene used in each case should be determined by the solubility of the final product (V) in the boiling solvent. The volumes which were actually used do not always represent optimum amounts, inasmuch as several of the experiments were run but once.

The volumes of dry benzene and reflux times used in the preparation of the compounds V are as follows; also included are the solvents used for recrystallization in the preparation of analytical samples: Va, 20 vol., 18 hr., benzene followed by acetone; b, 22 vol., overnight, ethylene chloride; c, 18 vol., 30 min., benzene; d, 5 vol., 15 min., benzene; e, 7 vol., 30 min., benzene; f, 50 vol., 7 hr., ethylene chloride.

In the last case, solution was not achieved even after seven hours refluxing. However, the insoluble material proved to be the desired product (Vf) in about 40% yield. An additional 47% was obtained from the filtrate on cooling.

In order to decrease the amount of solvent and reaction time necessary for the preparation of Va, a set of experiments was performed in which 10.9 g. (0.05 mole) of the amine hydrochloride (IVa) and 0.056 mole of dichloroacetyl chloride were heated at reflux with various solvents. The amount of solvent in each case was in slight excess over that required to dissolve the product (Va) at the reflux point. The solvent (and amount), period of reflux and yield of Va obtained in each case is as follows: toluene (80 ml.), 3 hr., 82%; chlorobenzene (55 ml.), 1.5 hr., 70%; ethylene chloride (60 ml.), 6 hr., 65%; dioxane (55 ml.), 1 hr., 57%.

On the basis of these experiments it was concluded that toluene afforded a convenient solvent for the preparation of this compound.

α-Acetamido-4-hydrocarbonylmercaptoacetophenones (Va′ and f′).—To a vigorously stirred slurry of 1 mole of the aminoketone hydrochloride (IVa and f), 1 liter of water and 2 kg. of ice there was added 200 ml. of acetic anhydride followed by the immediate addition of a solution of 290 g. of sodium acetate trihydrate in 1200 ml. of water. The temperature of the reaction mixture, which did not rise during the addition of the acetic anhydride and sodium acetate, was allowed to warm to room temperature and stirring continued for two hours. Sufficient acid was then added to make the reaction mixture acid to congo red paper, the white solid in the mixture was collected on a filter and the filter cake was washed with water and dried. Analytical samples were prepared in each case by recrystallization from acetone.

Racemic α-Dichloroacetamido-β-hydroxy-4-hydrocarbonylmercaptopropiophenones (VI).[16]—One mole of the α-dichloroacetamidoacetophenone (V) was stirred and warmed at 40–45°, for varying lengths of time,[17] with 2.5 liters[18] of 95% ethanol to which had been added a solution of 15 g. of sodium bicarbonate dissolved in 150 ml. of a 37% aqueous solution of formaldehyde. When the reaction was complete,[17] the solid sodium bicarbonate was removed from the warm solution by filtration and the filtrate chilled to 0–10°. After standing overnight at this temperature, the product was collected on a filter, washed with a little cold alcohol and dried. The product at this point was usually of sufficient purity for direct use in the next step.

Analytical samples were prepared by recrystallization from ethylene chloride (VIa, b, c and d) or benzene (VIe).

Racemic α-Acetamido-β-hydroxy-4-hydrocarbonylmercaptopropiophenone (VIa′ and f′).[16]—The preparation of VIa′ was accomplished by stirring a mixture of 15 g. (0.067 mole) of the acetamidoketone (Va′), 70 ml. of ethanol, 25 ml. of water, 10 ml. of 37% aqueous formaldehyde solution and a solution of 0.3 g. of sodium bicarbonate in 10 ml. of water at 35° for two hours. At the end of the two-hour period, the solution was filtered, the filtrate refrigerated for 10 hours and the crystalline solid which separated was collected on a filter and washed with water. Recrystallization from ethyl acetate gave fluffy white needles.

Because of the lesser solubility of the acetamidoketone (Vf′), the preparation of VIf′ was modified as follows.

(15) The reaction of dichloroacetyl chloride directly on the appropriate aminoketone hydrochloride was used by F. Sörm, J. Gut, M. Suchý and D. Reichl, *Collection Czechoslov. Chem. Communs.*, **16**, 501 (1950), for the preparation of α-dichloroacetamido-4-nitroacetophenone and related compounds.

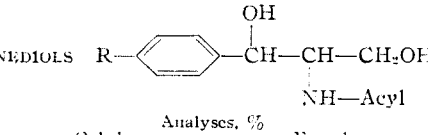
(16) *Cf.* the preparation of racemic α-acetamido-β-hydroxypropiophenone and the corresponding 4-nitro derivative, (a) L. M. Long and H. D. Troutman, THIS JOURNAL, **71**, 2469 (1949); (b) *ibid.*, **71**, 2473 (1949).

(17) Inasmuch as solution of the reactants (V) in the reaction medium was not always a reliable guide as to completeness of reaction, small samples of the reaction mixture were withdrawn from time to time, filtered, the filtrate chilled and the melting point of the separated solid determined. When this material melted sharply, yet depressed the melting point of the starting material, the reaction was considered complete. The heating times are as follows: VIa, 8 hr.; b, 10 hr.; c, d and e, 4 hr.

(18) In the preparation of VIa, 14.5 liters of 95% ethanol was used. After the reaction was complete the sodium bicarbonate was removed by filtration and the filtrate evaporated *in vacuo*, while maintaining the temperature of the solution below 40°, to a volume of 2.5 liters. On chilling to 10° the desired product separated.

TABLE III

RACEMIC *threo*-2-ACYLAMINO-1-[4-HYDROCARBONYLMERCAPTO- (AND SULFONYL)-PHENYL]-1,3-PROPANEDIOLS



No.	R	Acyl	Yield,[a] %	M.p., °C.	Empirical formula	Analyses, % Calcd.		Found	
VIIa′	CH_3S–	–$COCH_3$	50	172.1–173.5	$C_{12}H_{17}NO_5S$	C, 56.45	H, 6.71	C, 56.77	H, 6.67
VIIa	CH_3S–	–$COCHCl_2$	51	101.2–102.4	$C_{12}H_{15}Cl_2NO_5S$	C, 44.45	H, 4.66	C, 44.49	H, 4.96
VIIb	C_2H_5S–	–$COCHCl_2$	51.5	92.4–93.4	$C_{13}H_{17}Cl_2NO_5S$	Cl, 20.97	N, 4.14	Cl, 20.90	N, 4.05
VIIc	*n*-C_3H_7S–	–$COCHCl_2$	45	91.8–94.8	$C_{14}H_{19}Cl_2NO_5S$	Cl, 20.13	S, 9.10	Cl,[b] 20.23	S, 9.02
VIId	*n*-C_4H_9S–	–$COCHCl_2$	40	85.5–87.0	$C_{15}H_{21}Cl_2NO_5S$	Cl, 19.36	N, 3.82	Cl,[b] 19.70	N, 3.82
VIIe	C_6H_5S–	–$COCHCl_2$	46	90.6–97.4	$C_{17}H_{17}Cl_2NO_5S$	Cl, 18.36	N, 3.63	Cl,[b] 18.67	N, 3.71
VIIf′	$C_6H_5CH_2S$–	–$COCH_3$	47	157.0–158.0	$C_{18}H_{21}NO_5S$	S, 9.67	N, 4.23	S,[b] 9.69	N, 4.22
VIIIa′	CH_3SO_2–	–$COCH_3$	60	172.7–173.7	$C_{12}H_{17}NO_5S$	S, 11.16	N, 4.88	S, 11.12	N, 4.93
VIIIa	CH_3SO_2–	–$COCHCl_2$	90	179.6–181.0	$C_{12}H_{15}Cl_2NO_5S$	C, 40.46[c]	H, 4.25	C, 40.33	H, 4.45
VIIIb	$C_2H_5SO_2$–	–$COCHCl_2$	94	184.0–185.0	$C_{13}H_{17}Cl_2NO_5S$	Cl, 19.16	N, 3.78	Cl, 18.96	N, 3.71
VIIIc	*n*-$C_3H_7SO_2$–	–$COCHCl_2$	55	182.9–184.5	$C_{14}H_{19}Cl_2NO_5S$	Cl, 18.45		Cl, 18.73	
VIIId	*n*-$C_4H_9SO_2$–	–$COCHCl_2$	92	131.6–132.8	$C_{15}H_{21}Cl_2NO_5S$	Cl, 17.81	N, 3.52	Cl,[b] 17.75	N, 3.46
VIIIe	$C_6H_5SO_2$–	–$COCHCl_2$	87	124.9–127.3	$C_{17}H_{17}Cl_2NO_5S$	Cl, 16.95	N, 3.35	Cl,[b] 16.93	N, 3.52
VIIIf′	$C_6H_5CH_2SO_2$	–$COCH_3$	91	222.9–223.9	$C_{18}H_{21}NO_5S$	S, 8.83		S, 8.53	

[a] Yields based on purified product. [b] Determined by Pregl combustion method. [c] Calcd.: Cl, 19.91. Found: Cl,[b] 20.05.

A mixture of 50 g. (0.167 mole) of Vf′, 3.5 liters of ethanol, 45 ml. of 37% aqueous formaldehyde solution and 4 g. of sodium bicarbonate was stirred and warmed at 40° for 24 hours. The suspended sodium bicarbonate was removed from the solution by filtration and the filtrate evaporated to a volume of about 100 ml. Dilution of the concentrate with water gave 49 g. of pale yellow product. Recrystallization from ethylene chloride followed by an additional recrystallization from nitroethane gave the pure product (VIf′).

Racemic *threo*-2-Dichloroacetamido-1-(4-hydrocarbonylmercaptophenyl)-1,3-propanediols (VII, Table III).—The propiophenones (VI) were reduced, in most cases, according to standard procedures with aluminum isopropoxide in boiling isopropyl alcohol. The yields obtained in the preparation of VIIa, b, c and d by this method are shown in Table III. For comparative purposes we reprepared VIIa using a shorter reflux time.[6] The following procedure for the preparation of VIIa not only illustrates this modification but also indicates the general method of isolation used with all the compounds in this group.

A mixture of 9.6 g. (0.03 mole) of the ketone (VIa), 7 g. (0.034 mole) of aluminum isopropoxide and 90 ml. of isopropyl alcohol (dried over Drierite) was heated at reflux on a steam-bath for 35–40 minutes. The excess isopropyl alcohol was removed by distillation *in vacuo* and the red gummy residue heated on a steam-bath for 15 minutes with 60 ml. of 10% aqueous sodium chloride solution.[19] The precipitated aluminum hydroxide was removed from the hot solution by filtration and the filter cake washed thoroughly with several portions of ether. The combined ether filtrates and ether extracts of the original aqueous filtrate were combined and dried over Drierite. Filtration of the ether solution with charcoal and removal of the solvent by distillation yielded 8.5 g. of pale orange oil. Crystallization from 50 ml. of ethylene chloride gave 5.8 g. (60%) of VIIa as white crystals, m.p. 99.5–100.5° (uncor.).

The phenyl analog (VIIe) was prepared by adding the ketone (VIe) to the boiling isopropyl alcohol and aluminum isopropoxide solution followed by a reflux period of only 15 minutes.

Analytically pure samples of the compounds in Group VII were obtained by recrystallization from the following solvents: a, ethylene chloride then nitroethane; b, ethylene chloride; c, benzene–Skellysolve B mixture then benzene; d and e, benzene then ethylene chloride.

Racemic *threo*-2-Acetamido-1-(4-hydrocarbonylmercaptophenyl)-propanediols (VIIa′ and f′, Table III).—These compounds were prepared according to the usual conditions of the Meerwein–Ponndorf–Verley reduction. When the test for acetone was negative, the excess isopropyl alcohol was removed by distillation *in vacuo* and the residue treated with 10% sodium chloride solution as described in VII above. The aluminum hydroxide was removed by filtration and, because the reduction products were largely insoluble in ether, the aluminum hydroxide cake was extracted with boiling ethylene chloride. The products were isolated from the ethylene chloride extracts and also from the aqueous ether filtrate (VIIa′). Further purification was achieved by recrystallization first from water and then nitroethane (VIIa′) or nitroethane and then isopropyl alcohol (VIIf′).

Racemic *threo*-2-Dichloroacetamido-1-(4-hydrocarbonylsulfonylphenyl)-1,3-propanediols (VIII, Table III).—To a stirred solution of 0.1 mole of the sulfide (VII) dissolved in 100 ml. of acetone was added, in dropwise fashion, 40 ml. of 40% peracetic acid. External cooling was applied and the rate of addition adjusted so that the internal temperature was maintained at 35–40°. After the addition was complete, the cooling bath was removed and the stirring continued for an hour. The reaction mixture was cooled to −5°, the white crystalline product collected on a filter and washed with two portions of chilled acetone. After drying, these preparations were analytically pure. VIIIa was recrystallized once from water but no change in melting point was noted.

Racemic *threo*-2-Acetamido-1-(4-hydrocarbonylsulfonylphenyl)-propanediols (VIIIa′ and f′, Table III).—These compounds were prepared by a procedure similar to that described for the preparation of the racemic *threo*-2-dichloroacetamido-1-(4-hydrocarbonylsulfonylphenyl)-propanediols (see VIII above). The products were each recrystallized from nitroethane in order to achieve further purification.

DL-*threo*-2-Amino-1-(4-methylmercaptophenyl)-1,3-propanediol (IX).—Hydrolysis of 9 g. (0.0277 mole) of DL-*threo*-2-dichloroacetamido-1-(4-methylmercaptophenyl)-1,3-propanediol (VIIa) was achieved by heating on a steam-bath with 100 ml. of 8% aqueous hydrochloric acid for 30 minutes. The resulting clear solution was cooled, made strongly alkaline with 35% aqueous sodium hydroxide and allowed to stand overnight at 5°. The separated white crystalline solid was collected on a filter and washed twice with water to give 5 g. (0.0234 mole) (85%) of the free amine, m.p. 126–128° (uncor.). Recrystallization from six volumes of methanol gave white needles, m.p. 129.9–132.3°.

Anal. Calcd. for $C_{10}H_{15}NO_2S$: N, 6.57; S, 15.03. Found: N, 6.55; S, 15.16.

Hydrolysis of DL-*threo*-2-acetamido-1-(4-methylmercaptophenyl)-1,3-propanediol (VIIa′) under similar conditions gave the same amine.

Resolution of DL-*threo*-2-Amino-1-(4-methylmercaptophenyl)-1,3-propanediol into Its Optical Isomers (X).—A solution of 17.5 g. of DL-*threo*-2-amino-1-(4-methylmercaptophenyl)-1,3-propanediol (IX) in 100 ml. of methanol was

(19) The presence of the salt favors the precipitation of the aluminum hydroxide in a form which greatly facilitates its removal by filtration.

mixed with a solution which contained 13 g. of (+)-tartaric acid dissolved in 100 ml. of methanol and the resulting solution was allowed to stand at 15–20° for about six hours. The solid which separated was collected on a filter, the methanolic filtrate being retained for treatment as described below. There was thus obtained 18 g. of solid which melted at 190–196°. The solid was suspended in 150 ml. of water and sufficient dilute hydrochloric acid added to effect solution. On rendering strongly alkaline with 50 ml. of 35% aqueous sodium hydroxide solution, 11.7 g. of a yellowish solid separated which melted at 127–135° (uncor.). Two recrystallizations from methanol yielded 1.5 g. of coarse white needles, m.p. 151.9–152.9°, $[\alpha]^{25}D$ −21° (1% in ethanol). This is D-*threo*-2-amino-1-(4-methylmercaptophenyl)-1,3-propanediol (X).

Anal. Calcd. for $C_{10}H_{15}NO_2S$: N, 6.57. Found: N, 6.48.

The dextrorotatory form of the above amine was isolated as follows. The methanolic filtrate retained above was concentrated *in vacuo* on a steam-bath. The residue obtained was dissolved in 50 ml. of water and the resulting solution treated with 15 ml. of 35% caustic solution. This caused the separation of 3.0 g. of white solid, m.p. 141–150° (uncor.), which was recrystallized twice from methanol to give 1.0 g. of white crystals, m.p. 151.9–152.9°, $[\alpha]^{25}D$ +21° (1% in ethanol). This is the L-isomer.

Anal. Calcd. for $C_{10}H_{15}NO_2S$: N, 6.57. Found: N, 6.36.

D-*threo*-2-**Dichloroacetamido**-1-(4-**methylmercaptophenyl**)-1,**3-propanediol** (**XI**).—A mixture of 1.1 g. of D(−)-*threo*-2-amino-1-(4-methylmercaptophenyl)-1,3-propanediol (X) and 1.6 ml. of ethyl dichloroacetate was heated on a steam-bath for three hours. The resulting viscous yellow oil was dissolved in 25 ml. of ethylene chloride, the solution filtered hot with charcoal and the filtrate cooled. From the filtrate there separated 0.92 g. of product which was further recrystallized from nitroethane to give white leaflets, m.p. 111.6–112.6°, $[\alpha]^{25}D$ +12° (1% in ethanol).

Anal. Calcd. for $C_{12}H_{15}Cl_2NO_3S$: Cl, 21.87; N, 4.32. Found: Cl, 21.80; N, 4.16.

This isomer has marked antibacterial action against a wide variety of organisms (see Table I).

The other optical isomer, L-*threo*-2-dichloroacetamido-1-(4-methylmercaptophenyl)-1,3-propanediol, was prepared in similar fashion, from L(+)-*threo*-2-amino-1-(4-methylmercaptophenyl)-1,3-propanediol, m.p. 112.0–113.0°, $[\alpha]^{25}D$ −12° (1% in ethanol).

Anal. Calcd. for $C_{12}H_{15}Cl_2NO_3S$: C, 44.45; H, 4.66; Cl, 21.87. Found: C, 44.37; H, 4.83; Cl, 22.04.

This isomer is practically devoid of antibacterial action.

D-*threo*-**2-Dichloroacetamido**-1-(4-**methylsulfonylphenyl**)-1,**3-propanediol** (**XII**).—Seven grams of D-*threo*-2-dichloroacetamido-1-(4-methylmercaptophenyl)-1,3-propanediol (XI) was dissolved in 30 ml. of acetone and treated with 10 ml. of 40% peracetic acid according to the procedure described in the preparation of VIII. After stirring for two hours the reaction mixture was diluted with 100 ml. of water and the solution allowed to stand three days in the refrigerator to give 6.2 g. of pure product; m.p. 164.3–166.3°, $[\alpha]^{25}D$ +12.9° (1% in ethanol).

Anal. Calcd. for $C_{12}H_{15}Cl_2NO_5S$: Cl, 19.91; N, 3.93. Found: Cl, 19.95; N, 3.87.

This isomer has marked antibacterial action against a wide variety of organisms (see Table I). Its solubility in water is about four times that of the DL-compound (XIIa).

Hydrolysis of the above amide (XII) with dilute hydrochloric acid gave the amine, D-*threo*-2-amino-1-(4-methylsulfonylphenyl)-1,3-propanediol, m.p. 141.4–142.6° (from *n*-butanol), $[\alpha]^{25}D$ −19.8° (1% in U.S.P. alcohol).

Anal. Calcd. for $C_{10}H_{15}NO_4S$: N, 5.71. Found: N, 5.64.

This amine is very soluble in water. In order to achieve its isolation, the acid hydrolysis mixture was rendered strongly alkaline with sodium hydroxide, saturated with sodium chloride and extracted with warm *n*-butanol (50–70°). The free amine separated as a crystalline solid from the cooled butanol extracts.

The L-*threo*-2-dichloroacetamido-1-(4-methylsulfonylphenyl)-1,3-propanediol isomer was prepared from the corresponding L-sulfide above by peracetic acid oxidation; m.p. 164.3–166.3°, $[\alpha]^{25}D$ −12.6° (1% in ethanol). This isomer has negligible antibacterial activity.

Anal. Calcd. for $C_{12}H_{15}Cl_2NO_5S$: Cl, 19.91; N, 3.93. Found: Cl, 19.80; N, 3.87.

1,1-**Bis**-(4-**methylmercaptophenyl**)-**ethylene** (**See Ref. 2**).—This compound was formed as a by-product in the preparation of Ia using chlorobenzene as a solvent.

To a stirred solution of 124 g. of thioanisole and 78.5 g. of acetyl chloride, dissolved in 400 ml. of chlorobenzene, was added 133 g. of aluminum chloride in four equal portions. The temperature of the reaction mixture was maintained at 20–25° by means of external cooling during these additions. The resulting dark green solution was stirred for 3 hours at room temperature and then heated for ½ hour on a steam-bath. After pouring into ice, the chlorobenzene solution was separated, dried over Drierite, filtered with charcoal and the chlorobenzene removed by distillation *in vacuo*. The residual dark brown oil was dissolved in 500 ml. of ethanol, filtered hot with charcoal and the filtrate cooled to give 110 g. of tan solid, m.p. 75–78°. Recrystallization from 800 ml. of Skellysolve B, including treatment with charcoal, gave 66 g. of a dense white solid which stuck to the bottom of the flask and consisted largely of the desired product, Ia. Also deposited in the flask was 23 g. of pale greenish leaflets (m.p. 78–96° (uncor.)) which crystallized later and were easily separated from the denser material at the bottom of the flask. Recrystallization of the leaflets from ethanol yielded 4 g. of fluffy white leaflets, m.p. 129–132° (uncor.). An additional recrystallization from 60 ml. of *n*-propyl alcohol gave 3.5 g. of flaky white platelets, m.p. 129.4–130.0°. Analysis indicated that this material was 1,1-bis-(4-methylmercaptophenyl)-ethylene.[2]

Anal. Calcd. for $C_{16}H_{16}S_2$: C, 70.55; H, 5.92; S, 23.54; mol. wt., 272.4. Found: C, 70.64; H, 5.69; S, 23.82; mol. wt. (cryoscopic in dioxane), 266.

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