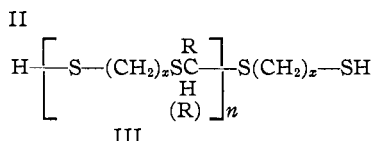
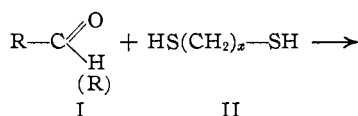
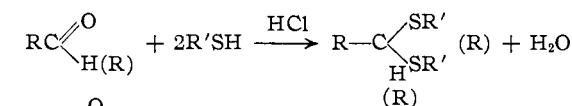


[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

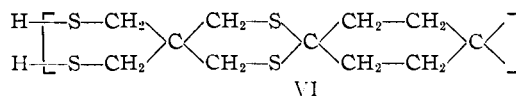
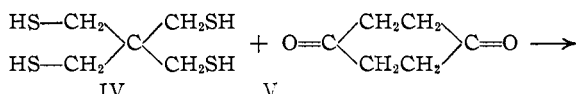
## Polymercaptals and Polymercaptols<sup>1</sup>

BY C. S. MARVEL, ELIZABETH HENG HUI SHEN AND R. R. CHAMBERS<sup>2</sup>

The reaction of a mercaptan with either an aldehyde or a ketone, which was first reported by Baumann,<sup>3</sup> is known to occur readily and to give a high yield of the corresponding mercaptal or mercaptol. The reaction is one that should lead to polymer formation (III) if a dimercaptan HS-(CH<sub>2</sub>)<sub>x</sub>SH (II) with *x* greater than three is used.



Autenrieth and Geyer<sup>4</sup> found that pentamethylenedithiol gave crystalline cyclic mercaptols with acetone and diethyl ketone. They stated that the same dithiol gave non-crystalline products with benzaldehyde, benzophenone and acetaldehyde. These were undoubtedly polymeric in character but they were not adequately described to establish this fact. Fisher and Wiley<sup>5</sup> have prepared a spiran type polymer (VI) of this general variety from the tetramercaptan derived from pentaerythritol (IV) and 1,4-cyclohexandione (V). Apparently, however, the simpler linear type polymer (III) has not been carefully investigated.



It has been found that mixing a wide variety of carbonyl compounds with dimercaptans such as hexamethylene dimercaptan and decamethylene dimercaptan, in dioxane solution and adding a small amount of dry hydrogen chloride, leads to a vigorous polymerization reaction. The reaction will also occur in the absence of a solvent. The polymers were usually solids but varied from white powders to sticky gums in their physical properties.

In order to gain some information on the best conditions for the reaction, benzaldehyde and decamethylenedithiol were allowed to react under a variety of conditions. In each case 1 cc. of benzaldehyde was treated with 1 cc. of decamethylenedithiol with or without a solvent, cooled to -10°, and dry hydrogen chloride was passed in rapidly for the time specified. The polymer was then isolated by adding methanol and filtering. The inherent viscosities were determined in chloroform or benzene solutions of approximately 0.5% concentration. These experiments are summarized in Table I.

TABLE I

BENZALDEHYDE-DECAMETHYLENEDITHIOL POLYMERCAPTALS

Run	Solvent	Time of adding dry HCl, minutes	Appearance of polymer	Inherent viscosity	M. P., °C.
1	None	2	Transparent gum	0.36	...
2	None	12 (hours) <sup>a</sup>	White powder	.43	135
3	None	0.5	Soft polymer	.44	98
4	Dioxane (10 cc.)	15 <sup>b</sup>	White powder	.45	125
5	Dioxane (10 cc.)	50	Soft jelly	.14	40
6	Dioxane (10 cc.)	10	Soft jelly	.29	93

<sup>a</sup> The dry hydrogen chloride was added very slowly in this run. <sup>b</sup> After the hydrogen chloride had been added, this mixture was allowed to stand for six hours at room temperature.

The results were slightly erratic but in general they indicate a rapid reaction with some tendency for reversal if continued too long. Considerable heat was developed during the addition of dry hydrogen chloride, and this may have been responsible for the apparent degradation of polymer at longer reaction times. Either benzene or cyclohexane seemed less satisfactory as a solvent than did dioxane.

For further reactions the solution of the carbonyl compound in dioxane was cooled to -10°, the dimercaptan was added, and dry hydrogen chloride introduced for fifteen to thirty minutes. The polymers were precipitated by adding cold methanol, filtered and washed free of acid with distilled water. In this manner decamethylenedithiol has given polymers with benzaldehyde, vanillin, *m*-nitrobenzaldehyde, acetaldehyde, and *n*-butyraldehyde; and hexamethylenedithiol has given polymers with benzaldehyde, vanillin, *m*-nitrobenzaldehyde, anisaldehyde, *p*-nitrobenzaldehyde, *p*-bromobenzaldehyde, acetaldehyde, *n*-butyraldehyde, ethyl methyl ketone, 3-methyl-2-pentanone, 4-methyl-2-pentanone, cyclohexanone and acetophenone.

The polymers have capillary melting points varying from 30 to 110° and inherent viscosities of

(1) This work was done under the sponsorship of the Office of Rubber Reserve, Reconstruction Finance Corporation, in connection with the Government Synthetic Rubber Program.

(2) Monsanto Chemical Company Fellow, 1946-1947.

(3) Baumann, *Ber.*, **18**, 258, 883 (1885).

(4) Autenrieth and Geyer, *ibid.*, **41**, 4249 (1908).

(5) Fisher and Wiley, U. S. Patent 2,389,662 (1945), *C. A.*, **40**, 1062 (1946).

0.042 to 1.37. In general the aliphatic aldehydes and ketones yield low melting products of low molecular weight and the aromatic aldehydes give higher melting polymers of high molecular weight. Some of these latter will cold draw to give fibers.

The lower molecular weight polymers were soluble in benzene and in chloroform. The products from hexamethylenedithiol with vanillin, and *p*-nitrobenzaldehyde, proved to be insoluble in benzene, chloroform, cyclohexane, *m*-cresol, pyridine, dioxane, ethylene glycol dimethyl ether, and dimethylformamide. In these cases some secondary reaction may have produced cross linking, but this has not been established by other means.

The X-ray diffraction patterns of the decamethylenedithiol polymers from benzaldehyde and vanillin and the hexamethylenedithiol polymer with vanillin indicate a fair order of regularity (see Figs. 1 and 2).<sup>6</sup>

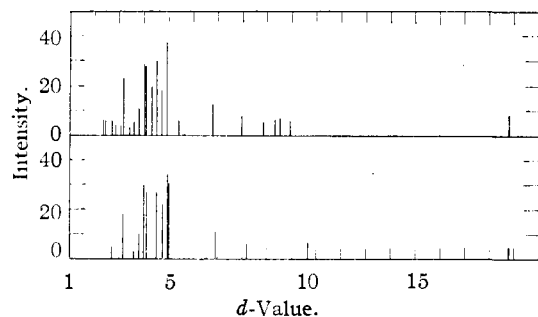


Fig. 1.—X-Ray diffraction patterns of benzaldehyde decamethylenedithiol polymercaptal: upper, polymer prepared in dioxane; lower, polymer prepared without solvent.

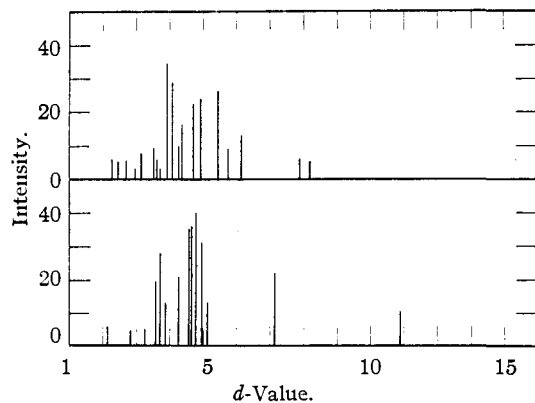


Fig. 2.—X-Ray diffraction patterns of polymercaptals: upper, vanillin hexamethylenedithiol polymer; lower, vanillin decamethylenedithiol polymer.

The infrared absorption of the benzaldehyde-hexamethylenedithiol polymer (Fig. 3) indicated the phenyl group ( $3000\text{--}3080\text{ cm.}^{-1}$ ) as would be expected. There was also evidence of hydroxyl group ( $3690\text{ cm.}^{-1}$ ) which may be an end group in

(6) We are indebted to Professor G. L. Clark, Mr. T. S. Yen, and Mr. R. S. Sprague for these X-ray diffraction data.

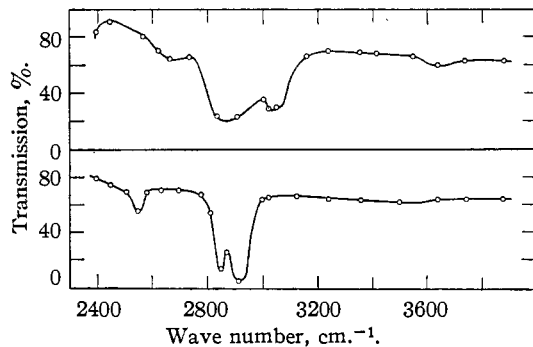


Fig. 3.—Infrared absorption curve: upper, benzaldehyde hexamethylenedithiol polymercaptal; lower, hexamethylenedithiol.

this type of polymer. Also in Fig. 3 is shown the infrared absorption of hexamethylenedithiol which has a marked  $\text{-SH}$  band at  $2550\text{ cm.}^{-1}$ . This band is barely visible in the polymer absorption.<sup>7</sup> In the case of polymers from most of the carbonyl compounds as shown by the infrared absorption of benzaldehyde-decamethylenedithiol polymer (Fig. 4) no hydroxyl bands were observed. Consequently these groups cannot be the end groups for most of our products.

Apparently the principal end group in these polymercaptals and polymercaptols is the  $\text{-SH}$  group. Mild oxidation of the polymers with alkaline iodine solution gave polymers of higher inherent viscosity and generally higher melting points. Amperometric titration<sup>8</sup> of dioxane solutions of the polymers again indicated mercaptan end groups and the molecular weights calculated from the titration data generally agreed with the inherent viscosity data.<sup>9</sup>

When comparisons were made between molecular weights calculated from amperometric end group titrations and those by the use of inherent viscosity data, it was found that some agreed and some needed to be multiplied by a factor of two to obtain agreement. This suggests that in some cases there is only one terminal  $\text{-SH}$  group and in other polymers there are two such groups.

Amperometric titrations of the unreacted mercaptan in the reaction mixtures were also found to be an excellent method of determining the extent of the reaction. When aldehydes were used in the polymerizations, the dimercaptan was used to the extent of 95–99%. With ketones the reaction was less complete and the variation in yield was from 45–90% depending on the substitution around the carbonyl group.

In general these polymers were stable on standing in the air. If placed in solution and warmed, a few showed an increase in inherent viscosity in

(7) We are indebted to Miss E. M. Petersen and Mrs. J. L. Johnson for the infrared absorption data and their interpretation.

(8) Kolthoff and Harris, *Ind. Eng. Chem., Anal. Ed.*, **18**, 161 (1946).

(9) We are indebted to Professor H. A. Laitinen and Dr. C. H. Shoemaker for aid in connection with the amperometric titration.

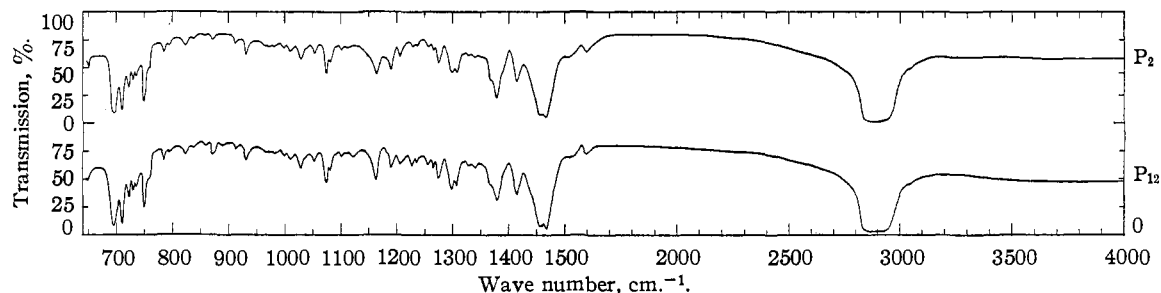


Fig. 4.—Infrared absorption of benzaldehyde decamethylenedithiol polymer: upper, polymer prepared in absence of solvent; lower, polymer prepared in solvent.

dicating oxidation to disulfide. If a solution of the polymer was treated with acid, the inherent viscosity dropped indicating degradation. Thus the polymer from cyclohexanone and hexamethylenedithiol in 50 cc. of benzene containing three drops of hydrochloric acid showed a decrease in inherent viscosity from 0.166 to 0.078 in twenty-four hours. Some decomposition appeared to occur on heating the polymers as the odor of dithiol usually became apparent at the melting point.

The polymercaptal from benzaldehyde and

decamethylenedithiol (m. p. 93°) was oxidized to an impure polysulfone (m. p. 180°) by the action of potassium permanganate. Because of the great insolubility of the polysulfone, it could not be purified to a high degree, and the analytical results were not as good as would be desired.

### Experimental

**Benzaldehyde-Decamethylenedithiol Polymercaptal.**—One cc. each of freshly distilled benzaldehyde and decamethylenedithiol were mixed in a small flask and dry hydrogen chloride was bubbled into the mixture at the rate

TABLE II  
PROPERTIES OF POLYMERCAPTALS AND POLYMERCAPTOLS

Dithiol	G.	Carbonyl compound	G.	Time, min., passing HCl	% Reaction detd. by un-used -SH	M. p., °C.	Inherent viscosity	Calcd. mol. wt.	Eqv. wt. by amperometric titration	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Sulfur, % Calcd.	Sulfur, % Found
Decamethylene	0.9444	Acetaldehyde	0.2078	30	95.39	35	0.042	1100	...	62.01	62.01	10.49	10.69	27.59	27.30
Hexamethylene	.9800	Acetaldehyde	.3685	11½	...	60	.146	5100	...	54.49	54.66	9.15	8.88	36.36	35.93
Decamethylene	.9370	Butyraldehyde	.4587	17	...	...	.102	3300	3930	64.64	64.43	10.83	10.65	24.62	24.62
Hexamethylene	.97	Butyraldehyde	.8170	15	...	40	.049	1400	...	58.76	58.89	9.86	10.01	31.37	31.19
Decamethylene	.98	Benzaldehyde	1.0504	12 (hr.) <sup>a</sup>	...	135	.428	18600	...	69.33	68.61	8.9	8.98	21.77	21.98
Decamethylene	.98	Benzaldehyde	1.0504	15 <sup>b</sup>	...	120	.452	19900	...	69.33	69.09	8.9	8.63	21.77	21.69
Hexamethylene	.97	Benzaldehyde	1.0504	7	...	115	1.374	76000	...	65.50	65.34	7.61	7.62	26.89	27.11
The above polymer after a month in corked tube										...	...	...	...	...	...
Hexamethylene	.97	Benzaldehyde	1.0504	10	...	110	.98	50000	...	...	...	...	...	...	...
The above polymer after a month in vacuum										...	...	...	...	...	...
Hexamethylene	1.5329	Vanillin	1.0178	25	...	40	.065	1900	528	59.15	55.49	7.08	7.67	22.56	25.75
Hexamethylene	0.9810	Vanillin	0.9950	10	...	150	Insoluble	...	...	59.15	58.26	7.08	6.97	22.56	20.39
Hexamethylene	0.9840	Anisaldehyde	0.9278	10	99.8	130	.44	19000	...	62.67	62.61	7.50	7.65	23.86	22.35
Decamethylene	1.8847	<i>m</i> -Nitrobenzaldehyde	1.3842	60	99.75	75	.16	5700	...	60.15	59.71	7.42	7.56	18.89	18.88
Hexamethylene	0.9872	<i>p</i> -Nitrobenzaldehyde	1.0005	22	99.71	80	Insoluble	...	...	55.09	55.06	6.04	6.06	22.62 <sup>d</sup>	21.61
Hexamethylene	.9818	<i>p</i> -Bromobenzaldehyde	1.2253	17	99.16	72	.067	2000	...	49.21	48.76	5.40	5.18	20.21	21.41
Hexamethylene	.9823	2-Butanone	0.5023	1¾ (hrs.)	70.87	Low	.088	2700	2380	58.76	57.61	9.86	9.69	31.37	32.11
Hexamethylene	.9886	3-Methyl-2-pentanone	.6653	60	45.83	Low	.048	1300	...	62.01	59.82	10.41	9.41	27.59	30.14
Hexamethylene	.9779	4-Methyl-2-pentanone	.6649	60	48.45	Low	.053	1500	1360	62.01	60.00	10.41	9.57	27.59	29.62
Hexamethylene	.9920	Acetophenone	.8013	12	71.40	30	.088	2700	...	66.64	64.61	7.97	7.66	25.37	26.82
Hexamethylene	.9797	Cyclohexanone	.7345	10	90.00	...	...	...	...	62.54	61.83	9.62	9.45	27.81	29.54
Hexamethylene	.9815	Cyclohexanone	.6662	10 <sup>c</sup>	95.93	75	.34	14300	...	62.54	61.53	9.62	9.69	27.81	25.94
Decamethylene	.9502	Vanillin	.7042	10	97.18	140	Insoluble	...	...	63.48	62.74	8.26	8.07	18.82	18.89

<sup>a</sup> Hydrogen chloride gas was passed very slowly. This reaction was done without solvent. <sup>b</sup> After passing hydrogen chloride into the mixture for fifteen minutes, the reaction mixture was left in contact with air for six hours. This reaction was carried out in dioxane solution (10 cc.). <sup>c</sup> The polymer solution was exposed to air for ten hours before precipitating by methanol. <sup>d</sup> Calcd.: N, 4.90. Found: N, 4.87.

of two to three bubbles per second for the times indicated in Table I. The polymers were treated with excess methanol, filtered, and dried in a desiccator.

*Anal.* Calcd. for  $C_{17}H_{16}S_2$ : C, 69.33; H, 8.9; S, 21.77. Found (Run 1, Table I): C, 66.12; H, 8.50; S, 21.88. Found (Run 2, Table I): C, 68.61; H, 8.98; S, 21.98. Found (Run 4, Table I): C, 69.09; H, 8.63; S, 21.69.

**General Procedure for Polymercaptals and Polymercaptols.**—In general the carbonyl compound and an equivalent amount of dithiol were placed in 10 cc. of freshly distilled dry dioxane. The solution was cooled in an ice-bath and dry hydrogen chloride was bubbled into the mixture for varying lengths of time in different experiments. In all cases the reaction developed heat and usually a pink color appeared. The mixture was cooled thoroughly and 20 cc. of cold methanol added to precipitate the polymer. The polymer was filtered and the unreacted dithiol titrated amperometrically. The polymer was dried in a desiccator first under water pump pressure (approximately 20–30 mm.) and finally at about 1 mm.

The results are summarized in Table II.

**Amperometric Titrations of -SH Groups.**—The method of Kolthoff and Harris<sup>8</sup> was used to determine unused dithiol. The sample solution was diluted with absolute methanol to 100 cc. for the titration.

To determine end-groups in the polymers it was necessary to adapt the method to use in a dioxane solution. A solution of 0.5 g. of polymer in 100 cc. of dioxane (dried and freed of peroxides) was used as the base solution. Aliquots (about 5 cc.) of this solution were added to 100 cc. of pure dioxane, 10 cc. of dilute ammonium hydroxide was added, and then 0.3 g. of ammonium nitrate was introduced. The solution was stirred until the salt was entirely dissolved. This solution was titrated with 0.005 *N* silver nitrate. A blank without polymer was run and the difference was used to calculate the -SH groups in the polymer.

**Oxidation of Polymercaptals to Give -S-S Links.**—To a solution of 0.1 g. of the benzaldehyde-hexamethylenedithiol polymer (inherent viscosity, 0.86) in 20 cc. of benzene was added 0.01 g. of iodine and small amounts of aqueous sodium hydroxide solution. The mixture was

shaken, the water layer removed, and the benzene evaporated. The polymer was precipitated with methanol and purified by solution in benzene and reprecipitation with methanol. The white polymer thus obtained had an inherent viscosity of 1.25.

A sample of butyraldehyde-hexamethylenedithiol polymer (inherent viscosity, 0.05, m. p. 40°) oxidized in the same way gave an oxidation product, m. p. 60–70°, inherent viscosity, 0.055.

A sample of *m*-nitrobenzaldehyde-decamethylenedithiol polymer (inherent viscosity, 0.16, m. p. 75°) on oxidation gave a polymer m. p. 90°, inherent viscosity 0.23.

**Oxidation of Benzaldehyde-Decamethylenedithiol Polymer.**—To a solution of 1.2 g. of benzaldehyde-decamethylenedithiol polymer (m. p. 93°) in 21 cc. of hot benzene was added 33 cc. of 10% sulfuric acid and then a solution of 4 g. of potassium permanganate in 40 cc. of water was introduced dropwise. The mixture was heated under a reflux condenser for an hour and filtered. The precipitate was suspended in 150 cc. of water and sulfur dioxide added to dissolve the manganese dioxide. The white powder remaining was collected on a filter and dried, m. p. 180° with decomposition.

*Anal.* Calcd. for  $C_{17}H_{26}S_2O_4$ : C, 56.95; H, 7.31; S, 17.88. Found: (corrected for ash) C, 54.33; H, 6.97; S, 18.99.

The sample contained 5.73% ash and its high degree of insolubility prevented recrystallization from solvents. The high sulfur content indicates that oxidation was incomplete.

### Summary

The reactions of hexamethylenedithiol and decamethylenedithiol with a variety of aldehydes and ketones have given a variety of new polymeric mercaptals and mercaptols. The polymers seem to have at least one and sometimes two terminal -SH groups. They have fair stability toward hydrolytic agents and heat.

URBANA, ILLINOIS

RECEIVED OCTOBER 11, 1949

[CONTRIBUTION FROM THE ANTIBIOTICS RESEARCH DEPARTMENT, THE UPJOHN COMPANY]

## 5-Substituted 2-Thiopheneacetic Acids and Amides as Penicillin Precursors

BY JARED H. FORD, GEORGE C. PRESCOTT AND DONALD R. COLINGSWORTH

A series of 5-substituted 2-thiopheneacetic acids was desired for evaluation as penicillin precursors<sup>1</sup> since it had been demonstrated that the parent compound, 2-thiopheneacetic acid, was readily utilized by penicillin-producing molds.<sup>2</sup> Furthermore, the resulting 2-thiophenemethylpenicillin<sup>3</sup> was found to be one of the most promising of a large number of new biosynthetic penicillins from the standpoint of blood level duration as tested in animals.<sup>4</sup>

2-Thiopheneacetic acid was prepared by the method of Blicke and Zienty<sup>5</sup> which involved

(1) Behrens, Corse, Huff, Jones, Soper and Whitehead, *J. Biol. Chem.*, **175**, 771 (1948).

(2) Jones, Soper, Behrens and Corse, *THIS JOURNAL*, **70**, 2843 (1948).

(3) Behrens, "The Chemistry of Penicillin," Princeton University Press, Princeton, N. J., 1949, p. 672.

(4) Personal communication, Anderson, Behrens and Chen, The Lilly Research Laboratories.

(5) Blicke and Zienty, *THIS JOURNAL*, **63**, 2945 (1941).

chloromethylation of thiophene, conversion of the 2-thiophenemethyl chloride to the nitrile and alkaline hydrolysis of the nitrile. When this method was applied to 2-chlorothiophene, the first two steps gave better yields than with thiophene, but attempts to hydrolyze the 5-chloro-2-thiopheneacetonitrile to the acid were unsuccessful. The nitrile was treated with dry hydrogen chloride in methanol and the resulting imino ether hydrochloride was converted to the methyl ester when it was refluxed with slightly more than the calculated amount of water.

An attempted chloromethylation of 2-methylthiophene yielded the corresponding diarylmethane as the principal product.

An effort to prepare 2-thiopheneacetic acid from 2-acetylthiophene by the Willgerodt-Kindler reaction<sup>6</sup> was unsuccessful, but this method was used

(6) Carmack and Spielman, "Organic Reactions," Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1946, p. 97.