1770, 1739, 1709 cm.$^{-1}$, no color with tetranitromethane. Treatment of an ether solution of IX with an ethereal diazomethane solution gave the dimethyl ester, m.p. 218–219° (reported[6]: m.p. 218–220°), ν_{max}^{KBr} 1779, 1739, 1709 cm.$^{-1}$.

Oxidation of Lactone V with Alkaline Permanganate. Preparation of VIII. Procedure A.—The conditions used by Ruzicka and Lalande[5] were followed exactly in this procedure and VIII was isolated as previously reported in very low yield. The product VIII, m.p. 310° (reported[5]: 307–308°) was found to have ν_{max}^{KBr} 3450, 1775, 1720, 1150 cm.$^{-1}$.

Anal. Calcd. for $C_{24}H_{34}O_8$: C, 63.98; H, 7.61. Found: C, 64.29; H, 7.24.

Procedure B.—In this procedure maleopimaric acid was oxidized directly with five equivalents of permanganate under the conditions described for the preparation of V. The product isolated was identical in infrared and melting point with that isolated by procedure A and was obtained again in very low yield.

Equivalent weight calcd: monobasic, 450; dibasic, 225; tribasic, 149. Found on titration in the cold: 237, 241. Found at room temperature: 178, 173. Titrations were run with 0.0982 *N* and 0.0098 *N* sodium hydroxide, respectively.

Reduction of V with Lithium Aluminum Hydride. Preparation of VI.—Three grams of dry lactone V in ether was added slowly to an ether solution containing 6 g. of lithium aluminum hydride. After refluxing overnight, ethyl acetate was added to destroy the excess lithium aluminum hydride and the solution was acidified with dilute sulfuric acid. The ether layer was separated, dried over sodium sulfate, and concentrated to a small volume, which on cooling gave 0.66 g. of white needles, m.p. 200–205°. Recrystallization from methanol–water gave the analytical sample of B, m.p. 207–209°, positive tetranitromethane test, negative test with bromine in carbon tetrachloride, ν_{max}^{KBr} 3425 (O—H), 1665 (C=C) cm.$^{-1}$; $[\alpha]D$ −57.2° (*c*, 3.00 in methanol), single peak in gas chromatography with retention time of 12.5 min.

Anal. Calcd. for $C_{24}H_{40}O_4$: C, 73.43; H, 10.27; O, 16.30; active hydrogen (4), 1.02; mol. wt. 393. Found: C, 73.78; H, 10.16; active hydrogen, 0.90; mol. wt. (Rast), 371.

B did not give a 2,4-dinitrophenylhydrazone with a methanolic–hydrogen chloride solution of the test reagent and aqueous hydrochloric acid and *p*-toluenesulfonic acid in benzene gave only negligible amounts of carbonyl-containing products.

Attempts to show that B was an allylic alcohol by oxidation to an α,β-unsaturated ketone with manganese dioxide and chromic anhydride failed to give any products that showed absorption in the ultraviolet region.

Reaction of I with Bromine in Alkaline Solution. Preparation of XI.—This bromolactone was prepared by a procedure recently reported by Grovenstein,[18] *et al.* The bromolactone (m.p. 225–228°) was found to decompose readily.

Anal. Calcd. for $C_{24}H_{33}O_6Br$: C, 57.95; H, 6.69. Found: C, 57.54; H, 6.70.

It was found more convenient to convert the crude bromolactone directly to its dimethyl ester with diazomethane. In a typical run 2 g. of I gave 1.5 g. of the dimethyl ester, m.p. 233–236°, ν_{max}^{KBr} 1783, 1736, 1727 cm.$^{-1}$.

Anal. Calcd. for $C_{26}H_{37}O_6Br$: C, 59.42; H, 7.09; Br, 15.20. Found: C, 59.03; H, 6.93; Br, 15.24.

Acknowledgment.—The authors are grateful to Dr. D. McGreer for running some of the n.m.r. spectra and for numerous valuable discussions.

(18) E. Grovenstein, Jr., D. V. Rao, and J. W. Taylor, *J. Am. Chem. Soc.*, **83**, 1705 (1961).

Oxidation of Monomeric and Polymeric Sulfhydryl Compounds[1]

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Using a spectrophotometric procedure, the relative rates of oxidation of a series of thiols were determined based on the observed rate of reduction of a dye, sodium 2,6-dichlorobenzeneoneindophenol. In aqueous pH 10 buffered solution, 2,2-dimethyl-4-(*p*-mercaptophenyl)valeric acid and a saponified copolymer of vinyl thiolacetate and methyl methacrylate were oxidized at approximately the same rate while 2,2-dimethyl-4-mercaptovaleric acid was oxidized about two times as fast. In dimethylformamide solution, 2,3-butanedithiol was oxidized approximately 61 times as fast as 2,6-heptanedithiol. These results have been compared to previous work reported and are discussed in terms of the ease of sulfur participation and disulfide formation.

From our previous work and that of Barron,[4] it is clear that a neighboring mercaptan group will influence the rate of oxidation of a polymercaptan in a very specific way. Thus, it was found that 2,4-di(*p*-mercaptophenyl)pentane was oxidized more than six times as fast as *p*-thiocresol.[5] It was suggested that two thiol groups existing as parts of the same molecule in juxtaposition may give rise to some type of participation. Likewise a polymer of *p*-mercaptostyrene gave an increased oxidation rate slightly higher than the model dimercapto system, 2,4-di(*p*-mercaptophenyl)pentane.

In confirmation of Barron's[4] earlier findings, it was found that 2,4-pentanedithiol was oxidized faster than 2,5-hexanedithiol, both of which were oxidized faster than the monothiol 2-mercaptoethanol.[1] It was suggested that facile ring forma-

(1) This is the 23rd in a series of papers on new monomers and polymers. For the previous paper in this series, see C. G. Overberger, J. J. Ferraro, and F. W. Orttung, *J. Org. Chem.*, **26**, 3458 (1961).

(2) Present address: St. John's University, Jamaica 32, New York.

(3) This paper comprises a portion of a dissertation submitted by J. J. Ferraro in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the Graduate School of the Polytechnic Institute of Brooklyn.

(4) E. S. G. Barron, Z. B. Miller, and G. Kalnitsky, *Biochem. J.*, **41**, 62 (1947).

(5) C. G. Overberger and P. V. Bonsignore, *J. Am. Chem. Soc.*, **80**, 5431 (1958).

tion was the result of sulfur participation and that the ease of formation of cyclic disulfide, unstable or stable, might be correlated with oxidation rate.

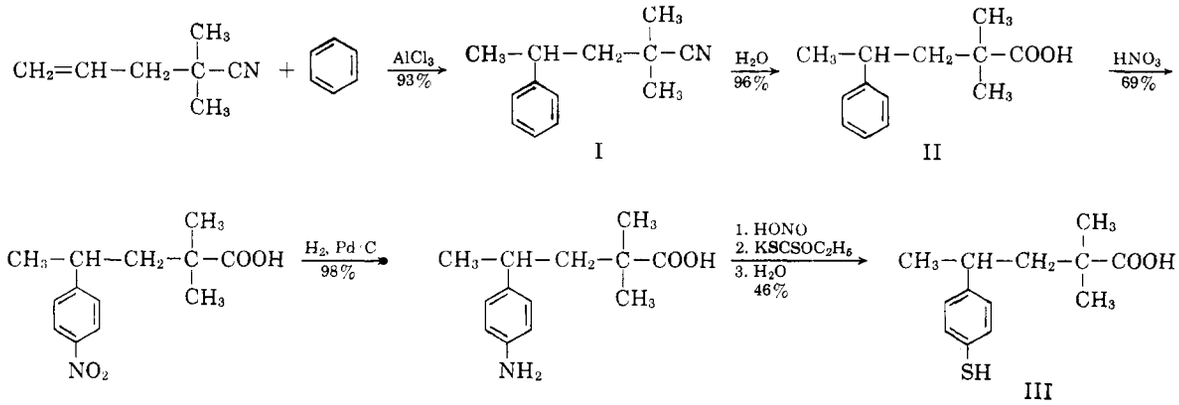
It was also reported[1] that poly(vinyl mercaptan) was oxidized fifty times as fast as 2-mercaptoethanol and ten times as fast as its model, 2,4-pentanedithiol, in a system studied spectrophotometrically in dimethylformamide (DMF) solution. The relatively fast rate of the polymer was partly attributed to the fact that a single mercaptan group of the polymer has two nearest neighbors while in the model, 2,4-pentanedithiol, a single mercaptan has only one nearest neighbor, although this may not be a complete explanation.

It was of interest to continue these oxidation studies on polymercaptans to obtan further information about the effect of structure on rates of oxidation. We had previously reported[5,6] the copolymerization of *p*-vinylphenyl thiolacetate and methyl methacrylate followed by subsequent hydrolysis. This hydrolyzed copolymer gave only a slight increase in rate (2.5 times) when compared with *p*-thiocresol.[5] In this paper we describe the preparation and oxidation of 2,3-butanedithiol and 2,6-heptanedithiol to compare these oxidation rates with the previously described model systems. In addition, we report the preparation, hydrolysis, and oxidation of a copolymer of vinyl thiolacetate and methyl methacrylate. The synthesis and oxidation of an alternating sequence of this copolymer, 2,2-dimethyl-4-mercaptovaleric acid is described. The synthesis and oxidation of 2,2-dimethyl-4-(*p*-mercaptophenyl)valeric acid, a model of an alternating sequence of the hydrolyzed copolymer of *p*-vinylphenyl thiolacetate and methyl methacrylate, is also reported. Our current investigations are germane to the question of the effect of the detailed stereochemistry of di- and polymercaptans on oxidation rate.

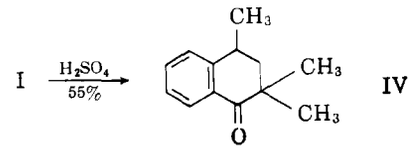
These mercaptan polymers and copolymers are also of interest as possible semipermanent protective agents against ionizing radiation,[7-10] although this topic will not be discussed here.

(6) C. G. Overberger and A. Lebovits, *J. Am. Chem. Soc.*, **78**, 4792 (1956).

Preparation of Sulfhydryl Compounds.—The scheme adopted for the preparation of 2,2-dimethyl-4-(*p*-mercaptophenyl)valeric acid (III) is outlined below:



An attempt to hydrolyze 2,2-dimethyl-4-phenylvaleronitrile (I) to the corresponding carboxylic acid (II) with sulfuric acid gave instead a 55% yield of 2,2,4-trimethyltetralone-1 (IV) identified by infrared analysis, elemental analysis, and derivatization. Compound II was finally obtained by basic hydrolysis in ethylene glycol. Attempts



to introduce the sulfhydryl group in the *para* position of compound II by chlorosulfonation[11] or thiocyanation[12] proved fruitless.

Prior to the adaption of the successful scheme depicted above it was decided to prepare the model compound III by a series of reactions in which the phenyl group containing the sulfhydryl moiety, protected by an easily removable blocking group, would be introduced onto an aliphatic chain. For this purpose, 4-nitrobenzylthiobenzene (V) was chosen. Friedel-Crafts acylation with 2,2-dimethylsuccinic anhydride gave 2,2-dimethyl-*p*-(4′-nitrobenzylthio)phenyl-4-ketobutyric acid (VI). However, attempts to introduce the methylene group in the 4-position of VII by treatment with triphenylmethylphosphonium iodide and n-butyllithium gave only starting material.

The following scheme was adopted for the prep-

(7) E. S. G. Barron and S. Dickman, *J. Gen. Physiol.*, **32**, 595 (1949).

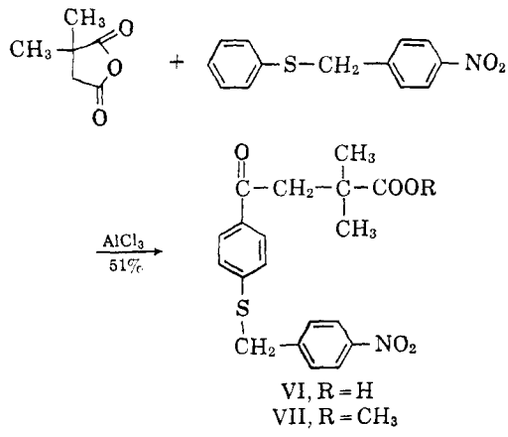
(8) E. S. G. Barron, S. Dickman, J. Muntz, and T. P. Singer, *ibid.*, **32**, 537 (1949).

(9) H. M. Pott, E. B. Tyree, R. L. Straube, and D. E. Smith, *Science*, **110**, 213 (1949).

(10) W. H. Chapman, C. R. Sipe, D. C. Elizholt, E. P. Cronkite, and F. W. Charbers, Project *NM* **006012.08.05**, Naval Medical Institute, Bethesda, Maryland, September 1949.

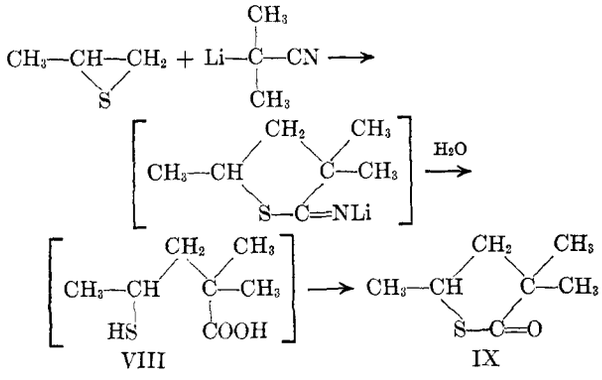
(11) A. Burger and S. Avakian, *J. Org. Chem.*, **5**, 606 (1940).

(12) E. Soderbock, *Acta Chem. Scand.*, **8**, 1851 (1954).



VI, R = H
VII, R = CH_3

paration of 2,2-dimethyl-4-mercaptovaleric acid (VIII):

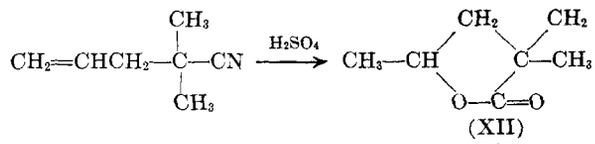


VIII IX

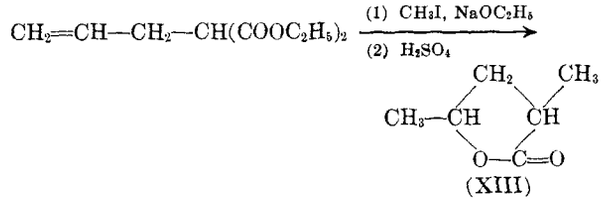
The free 4-mercaptocarboxylic acid (VIII) was not isolated as such but as the thiolactone (IX), since it was felt that this would offer protection against air oxidation while being handled and that hydrolysis *in situ* would generate the free thiol.

2,3-Butanedithiol (X) was prepared from 2,3-epoxybutane by treatment first with ammonium thiocyanate and then with potassium hydrogen sulfide. 2,6-Heptanedithiol (XI) was prepared from 2,6-dibromoheptane by treatment with thiourea and then hydrolysis.

Since 4-mercaptocarboxylic acids may be prepared from γ-lactones by reaction with thiourea and aqueous hydrobromic acid,[13] it was decided that an attempt should be made to prepare compound VIII and 2-methyl-4-mercaptovaleric acid, a model compound of the hydrolyzed copolymer of vinyl thiolacetate and methyl acrylate which was to be studied at some future date, from their respective lactones (XII and XIII). These lactones were prepared as follows:



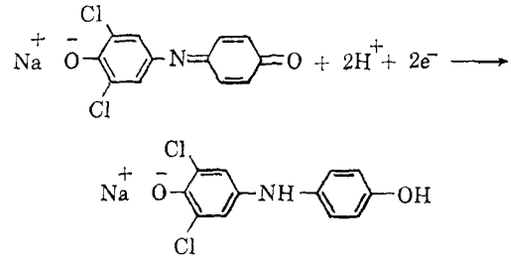
(XII)



(XIII)

Reactions of these lactones with thiourea and aqueous hydrobromic acid gave unchanged starting material.

Reaction Velocity of Thiols at pH 10.—Sodium 2,6-dichlorobenzeneoneindophenol, in neutral or basic solution, possesses an absorption maximum in the visible range of the spectrum at 600 to 605 mμ. When placed in contact with an easily oxidized molecule, it will undergo reduction to its leuco form.



Since the rate of reduction of the dye is related to the rate of oxidation of the other molecular species, following spectrophotometrically the rate of disappearance of the peak at 605 mμ, the rate of oxidation of the other species is automatically known.

This method has been worked out in detail for water soluble thiols by Huennekens[14] and was used to great advantage previously[5] at pH 10.

In this work, the rates were measured in pH 10 aqueous buffered solution in order to compare our results with previous work.[5] The results are shown in Table I, entries 2, 3, and 4. These values are the average of results obtained by measuring the rates at several concentrations (two- to threefold in —SH). These have been compared to other thiols in Table I.

As Table I shows, 2,2-dimethyl-4-mercaptovaleric acid, entry 4, is about two times as fast as 2,2-dimethyl-4-(*p*-mercaptophenyl)valeric acid, entry 2.

The fact that the hydrolyzed copolymer of *p*-vinylphenyl thiolacetate and methyl methacrylate, entry 5, is almost three times faster than its model, entry 2, can be explained by the observation that in the copolymer, *p*-vinylphenyl thiolacetate entered the polymer faster than methyl methacrylate.[5] This would indicate that there are undoubtedly some blocks of *p*-mercaptostyrene in the hydrolyzed copolymer. Since this is known to enhance oxidizability (entries 7 and 8, Table I),

(13) L. Scotte, *Arkiv, Kemi*, **8**, 457 (1956).

(14) R. E. Basford and F. M. Huennekens, *J. Am. Chem. Soc.*, **77**, 3873 (1955).

TABLE I
RELATIVE OXIDIZABILITIES OF THIOLS AT pH 10

Thiol	Observed oxidation rates, μm/ml./min./—SH × 10^3	$k \times 10^{3d}$	Relative oxidizabilities
1. *p*-Thiocresol	1.17[a]	1.9 ± 0.10	1.00
2. 2,2-Dimethyl-4-(*p*-mercaptophenyl)-valeric acid	1.04[b]	1.73 ± 0.10	0.89
3. Hydrolyzed copolymer of vinyl thiolacetate and methyl methacrylate	1.21[b]	2.08 ± 0.10	1.04
4. 2,2-Dimethyl-4-mercaptovaleric acid	2.16[b]	3.60 ± 0.20	1.85
5. Hydrolyzed copolymer of *p*-vinylphenyl thiolacetate and methyl methacrylate	3.29[a]	5.48 ± 0.20	2.81
6. Thioglycolic acid	4.26[a]	7.10 ± 0.30	3.64
7. 2,4-Di(*p*-mercaptophenyl)pentane	7.51[a]	8.00 ± 0.30	6.43
8. Hydrolyzed homopolymer of *p*-vinylphenyl thiolacetate	8.88[a]	15.0 ± 0.60	7.58
9. 2,4-Pentanedithiol[c]	23.0[e]	38.4 ± 1.80	19.7

[a] Ref. 5. [b] This work. [c] Ref. 1. [d] Second order rate constant, l. m^{-1} $sec.^{-1}$. [e] Aqueous ethanol pH 10 borate buffer.

We are now studying the effect of pH on the oxidation rates.

Reaction Velocities in Dimethylformamide (DMF).—The use of the dye was previously extended to the nonaqueous systems of dimethylformamide and acetonitrile for use with water insoluble mercaptans.[1] In air-free DMF, the spectrum of the dye showed a single peak at 643 mμ.

Table II, entries 1 and 5, shows the results of this part of the present work. These results are averages of rates run at several concentrations (two- to threefold in —SH) and are compared to results of previous work.

The obvious conclusion to be made from the results listed in Table II is that the ease of oxidation of dithiols increases as the distance between the thiol groups decreases, thus confirming Barron's[4] earlier results. Thus as the distance between thiols decrease from five carbons in entry 1, to two carbons in entry 5, the rate increases 61.2 times. Furthermore, the stability of the resultant cyclic disulfide does not appear to influence its ease of formation. Entries 1 and 3, Table II, should form seven- and six-membered rings, respectively, which are more stabe than those formed from entries 4 and 5, five- and four-membered rings, respectively. However, as can be seen,

TABLE II
RELATIVE OXIDIZABILITIES OF THIOLS IN DMF

Thiol	Observed oxidation rate, μm/ml./min./—SH × 10^5	$k \times 10^{3c}$	Rel. rate
1. CH_3—CH(SH)—$(CH_2)_3$—CH(SH)—CH_3 (XI)	0.328[a]	0.0547 ± 0.002	1.0
2. HO—CH_2—CH_2—SH	1.70[b]	0.233 ± 0.010	5.2
3. CH_3—CH(SH)—$(CH_2)_2$—CH(SH)—CH_3	3.90[b]	0.650 ± 0.030	11.9
4. CH_3—CH(SH)—CH_2—CH(SH)—CH_3	9.70[b]	1.62 ± 0.10	28.7
5. CH_3—CH(SH)—CH(SH)—CH_3 (X)	20.1[a]	3.35 ± 0.20	61.2
6. —(CH_2—CH(SH)—CH_2—CH(SH)—CH_2)—$_{n/2}$	91.4[a]	15.2 ± 0.60	280

[a] This work. [b] Ref. 1. [c] Second-order rate constant, l. $mole^{-1}$ $sec.^{-1}$.

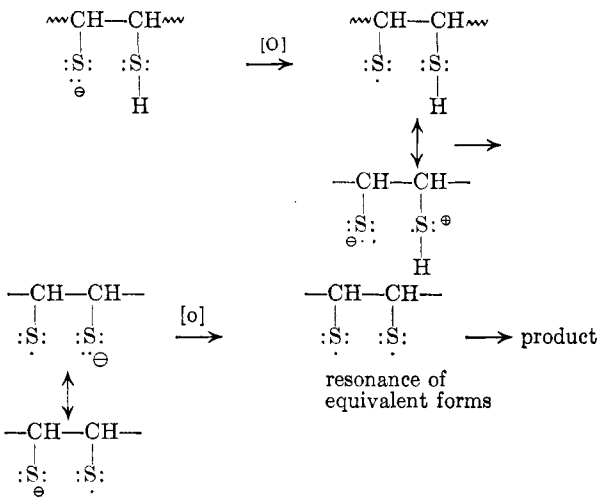
this would explain the increased rate of the polymer over its model.

Comparison of the relative rates of *p*-thiocresol, entry 1, and the model thiol, entry 2, indicates that the carboxyl group of entry 2 has no important effects on the rate. At this pH it is undoubtedly present as a carboxylate ion.

Although the differences are small, it is difficult to understand why the hydrolyzed copolymer of vinyl thiolacetate and methyl methacrylate, entry 3, is slower than its model, entry 4. Explanation of this result must be postponed at the present. the reverse order of ease of formation is operating.

An interesting observation is the relative rate of the hydrolyzed homopolymer of vinyl thiolacetate. As expected, its ease of oxidation is greatly enhanced compared to 2,6-heptanedithiol, entry 1. However, the polymer also oxidizes over four times faster than 2,3-butanedithiol, entry 5. This appears to indicate that although thiol groups in 2,3-butanedithiol are closer together than any two thiols in the polymer, there is greater enhancement of rate when a thiol has more than one nearest neighbor as in entry 6.

There are a number of other questions to consider here. Are the dimercaptans in the form of their mono or dianions in these nonaqueous solutions? How much influence does one mercaptan group have on the other's salt formation? We are attempting to answer these questions experimentally. Tentatively, we suggest neighboring sulfur participation in the following way. This would help to explain the faster rates obtained with the 1,2- and 1,3-dimercaptan structures.



Entry 2, Table II, 2-mercaptoethanol, appears to be anomalous. One might expect it to be slower if not equal to the rate exhibited by 2,6-heptanedithiol, entry 1. Apparently, an hydroxyl group in a beta position to a thiol introduces an enhancement in rate as was shown by Barron.[15]

Experimental[16]

Kinetic Procedure.—The procedure has been described previously.[1,5] Water and organic solvents used for the kinetic procedure were deaerated and stored under nitrogen. All transfers were accomplished by hypodermic syringes. A pH of 10 was maintained by borate buffered solutions.

The mercaptan titer of stock solutions used in the kinetic runs was determined either by spectrophotometric titration with *p*-chloromercuribenzoic acid[17] or by iodine titration.

Copolymerization and Saponification of a Copolymer of Vinyl Thiolacetate and Methyl Methacrylate.—Vinyl thiolacetate, prepared according to Overberger, Biletch and Nickerson[18] was copolymerized with methyl methacrylate with 0.5% azobisisobutyronitrile at a feed ratio of 1:1 at 79° for 0.5 hr. to give a conversion of 26.5%. Sulfur analysis indicated a copolymer composition of 1.90:1, methyl methacrylate–vinyl thiolacetate. $[\eta]_{30}$° 0.200 in benzene.

The copolymer, 1.0 g., was added to 100 ml. of an ethanol–water solution of 4 g. of sodium hydroxide and heated at reflux under a nitrogen atmosphere for 24 hr. An aliquot of this solution was diluted with pH 10 buffer solution and titrated with *p*-chloromercuribenzoic acid indicating 63.5% hydrolysis of —*S*-acetyl.

2,2-Dimethyl-4-phenylvaleronitrile (I).—Allylisobutyronitrile, prepared according to the method of Wittig,[19] 85.0 g. (0.777 mole), was added to a stirred suspension of 133 g. (1.00 mole) of aluminum chloride in 500 ml. of anhydrous benzene at such a rate so as to maintain gentle reflux. The green solution was maintained at reflux for an additional hour and then cooled. After decomposition with crushed ice and hydrochloric acid, the organic layer was washed with aqueous sodium bicarbonate and dried with anhydrous magnesium sulfate. Fractional distillation through an 8-inch helices packed column afforded 135 g. (93%) of colorless oil, b.p. 157° (21 mm.), n^{25}°D 1.4979.

Infrared analysis revealed the presence of nitrile absorption at 4.45 μ and phenyl absorption at 13.1 and 14.3 μ.

Anal. Calcd. for $C_{13}H_{17}N$: C, 83.37; H, 9.15; N, 7.48. Found: C, 83.01; H, 9.21; N, 7.81.

2,2-Dimethyl-4-phenylvaleric Acid (II).—2,2-Dimethyl-4-phenylvaleronitrile, 33.0 g. (0.176 mole), was dissolved in a mixture of 45 g. of potassium hydroxide, 250 ml. of ethylene glycol, and 15 ml. of water. The mixture was heated at reflux under an atmosphere of nitrogen until ammonia evolution stopped (36 hr). After cooling and dilution with a large amount of water, the solution was acidified. An oil was separated with methylene chloride and dried over anhydrous magnesium sulfate. Distillation gave 35 g. (96%) of a viscous oil, b.p. 113° (0.06 mm.), m.p. 46.8–47.5°.

Anal. Calcd. for $C_{13}H_{18}O_2$: C, 75.69; H, 8.86; neut. equiv., 206.3. Found: C, 76.02; H, 9.10. neut. equiv., 205.4.

2,2-Dimethyl-4-(*p*-nitrophenyl)valeric Acid.—A slightly modified procedure of Reppe[20] was used. To a stirred ice-cold solution of 155 g. (0.750 mole) of 2,2-dimethyl-4-phenylvaleric acid in 900 ml. of acetic anhydride was added 450 ml. of fuming nitric acid (*d*, 1.50) at a rate so as to keep the reaction temperature below 15°. After addition, the mixture was stirred for 15 min. at 15° and for 15 min. at room temperature. The solution was then poured onto crushed ice with vigorous stirring. The almost white precipitate was filtered and washed thoroughly with water until the washings were neutral to litmus. The solid was then dried in a vacuum oven to give 178 g. (95%) of cream-colored material, m.p. 120–140°. Recrystallization from cyclohexane gave 130 g. (69%), m.p. 151.0–152.0.

Anal. Calcd. for $C_{13}H_{17}NO_4$: C, 62.14; H, 6.28; N, 5.58; neut. equiv., 251.3. Found: C, 62.09; H, 7.04; N, 5.85; neut. equiv. 250.4.

2,2-Dimethyl-4-(*p*-aminophenyl)valeric Acid.—2,2-Dimethyl-4-(*p*-nitrophenyl)valeric acid, 15.1 g. (0.060 mole), was dissolved in 150 ml. of ethanol and hydrogenated with 1 g. of 10% palladium on charcoal in a Parr hydrogenator. In 30 min., the theoretical quantity of hydrogen was absorbed. After filtration and removal of solvent, 13.0 g. (98%) of tan solid was obtained, m.p. 137.0–141.0°. Two recrystallizations from benzene afforded analytically pure crystals, m.p. 141.0–142.0°.

Anal. Calcd. for $C_{13}H_{19}NO_2$: C, 70.55; H, 8.66; N, 6.33. Found: C, 70.89; H, 8.83; N, 6.16.

2,2-Dimethyl-4-(*p*-mercaptophenyl)valeric Acid.—An aqueous solution (60 ml.) 11.1 g. (0.050 mole) of 2,2-dimethyl-4-(*p*-aminophenyl)valeric acid (as its sodium salt) containing 3.5 g. (0.05 mole) of sodium nitrite was added to a solution of 10 ml. of concentrated sulfuric acid and 50 ml. of water maintained at 0–5°. After addition was completed the solution was stirred at 5° for 15 min. The solution was then adjusted to a pH of 4 and added (Caution) dropwise to 10 g. of potassium ethyl xanthate in 20 ml. of water maintained at 65°. After addition, the temperature was maintained for 0.5 hr. at 65°, and 100 ml. of 10% aqueous sodium

(15) E. S. G. Barron, "Advances in Enzymology," Vol. II, Interscience Publishers, Inc., New York, N. Y., 1951, p. 219.

(16) Melting points and boiling points are uncorrected. Analysis performed by Schwarzkopf Microanalysis Laboratory, Woodside, New York.

(17) F. D. Boyer, *J. Am. Chem. Soc.*, **76**, 4331 (1954).

(18) C. G. Overberger, H. Biletch, and R. G. Nickerson, *J. Polymer Sci.*, **27**, 381 (1958).

(19) G. Wittig, *Angew. Chem.*, **53**, 241 (1940).

(20) W. Reppe, *Ann.*, **596**, 80 (1955).

hydroxide was then added. After 5 hr. of heating at reflux, the cooled solution was acidified to Congo Red with 6 *N* hydrochloric acid and the yellow solid filtered. A 10.0-g., sample (91%) of crude material was obtained. One recrystallization from hexane gave 5.4 g. (46%) of golden-yellow needles, m.p. 100.0–103.0°. Repeated recrystallization from hexane afforded an analytical sample m.p. 104.0–104.9°. Infrared analysis revealed mercaptan absorption at 3.90 μ and phenyl absorption at 12.2 μ.

Anal. Calcd. for $C_{13}H_{18}O_2S$: C, 65.51; H, 7.61; S, 13.45. Found: C, 65.66; H, 7.79; S, 13.16.

2,2,4-Trimethyltetralone-1 (IV).—To 100 ml. of 50% aqueous sulfuric acid was added 18.7 g. (0.100 mole) of 2,2-dimethyl-4-phenylvaleronitrile. The mixture was heated to reflux and maintained at this temperature for 6 hr. The cooled mixture was poured into water and extracted with several portions of ether. After drying over anhydrous magnesium sulfate and filtration the residue was fractionally distilled. The first fraction distilled at b.p. 79° (0.01 mm.), $n^{25}D$ 1.5380, λ_{max}, 5.91 μ and weighed 10.3 g. (55% based on tetralone). Redistillation provided an analytical fraction, b.p. 152° (12 mm.), $n^{25}D$ 1.5391.

Anal. Calcd. for $C_{13}H_{16}O$: C, 82.93; H, 8.57. Found: C, 82.97; H, 8.66.

The 2,4-dinitrophenylhydrazone was prepared,[21] m.p. 245.0–245.9°.

Anal. Calcd. for $C_{19}H_{20}N_2O_4$: C, 61.94; H, 5.47; N, 5.21. Found: C, 61.97; H, 5.51; N, 5.49.

Two higher boiling fractions were obtained, total weight 7.8 g. Infrared analysis showed the mixture to be largely a carboxylic acid.

2,2-Dimethyl-4-*p*-(4-nitrobenzylthio)phenyl-4-ketobutryric Acid (VI).—*as*-Dimethylsuccinic anhydride was prepared according to Bone and Sprankling.[22]

***p*-(4-Nitrobenzylthio)benzene Was Prepared According to Reid.**[23]—To 25.6 g. (0.200 mole) of *as*-dimethylsuccinic anhydride in 200 ml. of 80:20 v./v. mixture of 1,1,2,2-tetrachloroethane and nitrobenzene was added 53.2 g. (0.400 mole) of aluminum chloride. *p*-(4-Nitrobenzylthio)benzene, 49.0 g. (0.200 mole), was then added in portions. The green solution was allowed to stand at room temperature for 2 days and was then poured into ice water containing hydrochloric acid. The organic layer was separated, dried, filtered, and chilled, whereupon 32 g., m.p. 159–160°, of yellow crystals were obtained. From the supernatant, 6 g. were isolated by concentration, m.p. 158–160°, for a total yield of 51%. Recrystallization from ethanol afforded an analytical sample, m.p. 159.4–160.0°.

Anal. Calcd. for $C_{19}H_{19}NO_5S$: C, 61.10; H, 5.13; N, 3.75; S, 8.59. Found: C, 61.24; H, 5.34; N, 3.76; S, 8.72.

The 2,4-dinitrophenylhydrazone was prepared[21] m.p. 178.0–178.6°.

Anal. Calcd. for $C_{25}H_{23}N_5O_8S$: C, 54.24; H, 4.19; N, 12.70; S, 5.79. Found: C, 54.32; H, 4.24; N, 12.75; S, 5.66.

The methyl ester (VII) was prepared[24] with diazomethane to give an 87% yield of a solid, m.p. 99.5–100.4°. Recrystallization from ethanol afforded an analytical sample, m.p. 100.1–100.8°.

Anal. Calcd. for $C_{20}H_{21}NO_5S$: C, 62.00; H, 5.46; N, 3.62; S, 8.28. Found: C, 61.98; H, 5.69; N, 3.73; S, 8.52.

2,2-Dimethyl-4-thiovalerolactone (IX).—To a suspension of 7.00 g. (1.00 g.-atom) of finely cut lithium ribbon in 250 ml. of anhydrous ether was added 78.5 g. (0.500 mole) of bromobenzene in 125 ml. of ether. Anhydrous diethylamine, 36.5 g. (0.500 mole), in 100 ml. ether was then added rapidly and maintained at reflux for 0.5 hr. The suspension was then cooled with an ice water bath and maintained at 10° while 37.1 g. (0.500 mole) of propylene sulfide in 100 ml. of ether was added dropwise. The entire mixture was then heated to reflux and maintained at this temperature for 1 hr. The suspension was concentrated and 100 g. of potassium hydroxide in 1 l. of ethylene glycol and 50 ml. of water was added. Heat was applied and the mixture maintained at reflux temperature 15 hr. at which time the evolution of ammonia ceased. Hydrochloric acid, 750 ml. of 6 *N*, was then added and the mixture extracted with several portions of methylene chloride. The organic layer was dried, filtered, and then distilled. At a pot temperature of 120° and a pressure of 21 mm., the first fraction of distillate contained large amounts of water, apparently from lactonization of the mercapto acid. A final distillation through an 8-in. Widmer column gave 30 g., (41%) of a water-white liquid, b.p. 102° (23 mm.) $n^{25}D$ 1.4825, d^{25}_4 1.0363. Infrared snalysis showed carbonyl absorption at 5.87 μ.

Anal. Calcd. for $C_7H_{12}OS$: C, 58.31; H, 8.39; S, 22.23. Found: C, 58.21; H, 8.59; S, 22.19.

2,2-Dimethyl-4-valerolactone (XII).—Allylisobutyronitrile, 84.4 g. (0 755 mole) was heated at reflux with 200 ml. of 50% aqueous sulfuric acid for 24 hr. The dark colored mixture was then cooled and poured into 1 l. of ice-water, filtered, and the solid dried to give 70 g. (72.3%) of cream colored crystals, m.p. 50.5–51.9°, lit.[25] 52°. Infrared analysis showed carbonyl absorption at 5.65 μ.

2-Methyl-4-valerolactone (XIII).—Diethyl allylmalonate, 200 g. (1.00 mole), was alkylated with methyl iodide (200 g., 1.40 moles) in 1 l. of an ethanol solution of sodium ethoxide (from 23 g. of sodium). After acidification of the reaction mixture, a large quantity of water was added and the mixture extracted with benzene. The benzene solution was dried, filtered, and concentrated under vacuum. To the residue was added 400 ml. of water and 150 ml. of concentrated sulfuric acid. The suspension was heated at reflux until carbon dioxide evolution ceased (3 days). The mixture was poured into water, extracted with methylene chloride, dried, and distilled through an 8-in. helices packed column to give 84.5 g. (74%) of water-white liquid, b.p. 96° (13 mm.), $n^{25}D$ 1.1470, d^{25}_4 1.0018, lit.[26] b.p. 206° (atm.)

2,3-Butanedithiol.—Into 50 ml. of an aqueous solution of 23.0 g. (0.300 mole) of ammonium thiocyanate was added 19.0 g. (0.260 mole) of 2,3-epoxybutane, the reaction being carried out in a closed vessel. After standing at room temperature for 2 days, the organic layer was isolated, dried, and added dropwise to an alcoholic solution of potassium hydrogen sulfide (prepared from alcoholic potassium hydroxide and hydrogen sulfide.) After standing for 1 day, the mixture was acidified and a large volume of dearated water was added. Extraction with ether followed by distillation afforded 6.0 g. (20%) of a colorless liquid, b.p. 67° (29 mm.), $n^{25}D$ 1.5173, lit.[27] 50–51° (20 mm.), $n^{21}D$ 1.5315.

Anal. Calcd. for $C_4H_{10}S_2$: C, 39.12; H, 8.25; S, 52.46. Found: C, 38.83; H, 8.14; S, 52.46.

2,6-Heptanedithiol (XI).—2,6-Dibromoheptane was prepared by the method of Fargher and Perkin.[28] The dibromide, 42.0 g. (0.160 mole), was added to 32.0 g. (0.410

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(23) E. Reid, *J. Am. Chem. Soc.*, **45**, 2407 (1923).

(24) Ref. 21, p. 312.

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mole) of thiourea in 30 ml. of water and the mixture heated at reflux 6 hr. at which time one layer formed. Aqueous sodium hydroxide was added and heated at reflux an additional 6 hr. under nitrogen. Acidification and separation of the oily layer and distillation afforded 20.8 g. (79.5%) of a colorless liquid, b.p. 120° (26 mm.), $n^{25}D$ 1.4978.

Anal. Calcd. for $C_7H_{16}S_2$: C, 51.16; H, 9.82; S, 39.03. Found: C, 51.26; H, 10.10; S, 38.70.

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The Preparation and Properties of 6-Halomethylpurines[1]

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6-Methylpurine (I) was converted by sulfuryl chloride or N-chlorosuccinimide into 6-trichloromethylpurine in trifluoroacetic acid solution. Stepwise or partial chlorination of the methyl group was not achieved. N-Bromosuccinimide converted I into the 6-dibromo- and, by further substitution, 6-tribromomethylpurine. Stepwise catalytic reduction of the trihalomethylpurines afforded dihalo- and monohalomethylpurines. The chemical and physical properties of the new compounds are described.

6-Methylpurine (I), an analog of adenine, is highly toxic to mammals and human tumor cells.[3,4] This outstanding biological potency made I an attractive model for the synthesis of potential anticancer agents through minor alterations in its structure.[5-9] Accordingly, studies of the preparation and properties of compounds derived from I by direct halogenation of the methyl group were undertaken.

A number of examples of the exhaustive halogenation of methyl groups in heterocyclic compounds have been published.[10-12] These procedures require the use of elemental chlorine or bromine in the presence of sodium acetate and may involve a polar reaction mechanism. In the present investigation, we have used sulfuryl chloride, N-chloro-, and N-bromosuccinimide in trifluoroacetic acid solution. The action of these agents on organic compounds is known to be more selective than that of elemental halogen.[13]

When an equimolar mixture of I and sulfuryl chloride was refluxed in trifluoroacetic acid, hydrogen chloride was evolved, but the only products isolated were the trifluoroacetic acid salt (Ia) of I and its hydrochloride (Ib). The same reaction in cold acetic acid gave Ib which could be readily converted into Ia by evaporating its solution in trifluoroacetic acid to dryness. It was assumed, therefore, that the chlorinating agent had been consumed although the expected halogenated product could not be isolated. Indeed, the use of two moles of sulfuryl chloride per mole of I afforded 6-trichloromethylpurine (II), in low yield. Subsequently, II was prepared in 70–80% yield by use of excess sulfuryl chloride in trifluoroacetic acid. The reaction was exothermic and proceeded to completion within a short time.

The use of N-chlorosuccinimide in the same solvent did not prove more advantageous for the purpose of controlling the extent of chlorination. When used in equimolar ratio, this reagent afforded the trichloro product (II) only. Under similar conditions, an equimolar mixture of N-bromosuccinimide and I gave 6-dibromomethylpurine (VII), but use of excess brominating agent resulted in an excellent yield of 6-tribromomethylpurine (VI). Under the mild conditions used, the failure to achieve stepwise halogenation is unusual. At a carbon atom bearing a halogen, the tendency for further halogenation is in harmony with the known effect of halogen atoms in decreasing the carbon–hydrogen bond dissociation energy. But this tendency is usually diminished by the electron-withdrawing inductive effect of the same halogen.

A few correlations of reactions in related systems are informative: Toluene or nuclear-substituted toluenes and sulfuryl chloride yield benzyl chlorides.[14] With N-bromosuccinimide, nuclear bromination of methylpyridines takes precedence over

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