4. The toxicities, as determined by intravenous injection to rabbits, show a regular increase as the length of the side chain increases.

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

THE ACTION OF THE HALOGEN HYDRINS AND OF ETHYLENE OXIDE ON THE THIOUREAS

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The basis of this investigation was the observation that thiocarbanilide could be desulfurized with ethylene chlorohydrin, as follows. The thiourea was boiled with the chlorohydrin, giving a partial yield of diphenylurea which could be increased to 60% by heating the reaction product with alcoholic potassium hydroxide, thus completing the hydrolysis of the intermediate thio ether, $C_6H_5NHC(NC_6H_5)SCH_2CH_2OH$.

In order to throw more light on these results, which are analogous to the desulfurizing effect of chloro-acetic acid, the action of the chlorohydrins on thioureas and mono- and disubstituted thioureas was studied.

The results show that the primary product is a thio ether which can be isolated in many cases as the halogen hydride salt. These thio ethers are hydrolyzed with great ease, yielding a mixture of decomposition products.

When the hydroxyl of the hydrin is replaced by an ether or ester grouping, the compound is more stable. In the unsubstituted γ-thio ethers the NH and NH_2 groups react readily with acyl chlorides, yielding diacyl derivatives of the type $RCONHC(NCOR)CH_2CH_2OH(R)$, and with phenyl isocyanate, ethers of thiocarbonyl-diurea, $(R)HOCH_2CH_2SCNHCONHC_6H_5(NCONHC_6H_5)$.

Ethylene oxide was found to add to the C–SH groups, giving ethers, $RNHC(NR)SCH_2CH_2OH$, which in the case of thiocarbanilide could be isolated; in other instances only the hydrolysis products were identified.

Experimental

Ethylene Chlorohydrin and Thiourea. Oxyethylthiourea Hydrochloride, $HOCH_2CH_2SC(NH)NH_2$.—When the molar mixture is heated for thirty minutes, allowing the temperature to rise slowly from 90 to 105° and no higher, no precipitation of ammonium chloride occurs. The resulting product is a heavy oil soluble in alcohol and acetone but not in other organic solvents. Cold dry ether precipitated the hydrochloride which crystallized from butyl alcohol in slender needles melting at 111° and which probably had been obtained by Schatzmann,[1] though no melting point was given

Anal. Calcd. for $C_3H_8N_2OSHCl$: N, 17.90. Found: N, 17.87.

All efforts to close the ring, thus forming the simple thiazolidine $\underline{SC(NH)NHCH_2CH_2}$

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[1] Schatzmann, *Ann.*, **261**, 1 (1891).

have thus far failed. In the case of the substituted amino-ethanol-thiourea, with the grouping N—CH_2CH_2OH, ring closure with the enol SH group is easily effected.[2]

Ethylene bromo- and iodohydrins show the same general behavior as the chlorohydrins, but give oily non-crystallizable products.

When the reaction temperature of the mixture is allowed to rise to 135–140°, precipitation of ammonium chloride occurs, the weight of which amounts to about one fourth of the total nitrogen, and the residue consists of a mixture of unidentified compounds consisting in part of polymers of thio-ethylene glycol.

Trimethylene Chlorohydrin and Thiourea. Oxypropylthiourea Hydrochloride, $H_2NC(NH)CH_2CH_2CH_2OH.HCl$.—When molar quantities of the two reagents are heated carefully at 120–125°, an oil is formed which solidifies when treated with dry ether. The crystals from butyl alcohol melt at 130°.

Anal. Calcd. for $C_4H_{10}N_2OS{\cdot}HCl$: N, 16.43. Found: N, 16.25.

Repeated evaporation of the thiourea with ammonium hydroxide gave guanidine, identified as its nitrate (m. p. 209°) and its dibenzoyl derivative (m. p. 214°).[3] Ethylamine yielded ethylguanidine, the dibenzoyl derivative of which melts at 87°.

Anal. Calcd. for $C_{17}H_{17}N_3O_2$: N, 14.24. Found: N, 14.19.

Methylguanidine was formed in like manner from the thio ether and methylamine.

β-Bromo-ethyl Ether and Thiourea. γ-Ethoxyethylthiourea Hydrobromide, $NH_2C(NH)SCH_2CH_2OC_2H_5{\cdot}HBr$.—The components diluted with a little alcohol were heated for thirty minutes at 100°. After removal of the excess bromo ether and alcohol by vacuum distillation, the hydrobromide salt melting at 28–29° was isolated. The oily free base is unstable.

Anal. Calcd. for $C_5H_{12}N_2OS{\cdot}HBr$: N, 12.23. Found: N, 12.33.

Heating the thiourea ether with potassium hydroxide gave the strong smelling ethoxyethyl mercaptan (b. p. 125–126° at 740 mm.).[4]

Thioncarbanilic β-Ethoxyethyl Ester, $C_6H_5NHCOSC_2H_4OC_2H_5$.—To further characterize the mercaptan, it was heated in a bomb tube for four hours at 150° with phenyl isocyanate. The resulting oily ester slowly crystallized in plates melting at 45°.

Anal. Calcd. for $C_{11}H_{15}NO_2S$: N, 6.22. Found: N, 6.17.

Its isomer, thiolcarbanilic β-ethoxyethyl ester, is formed when phenyl mustard oil is heated with the monoethyl ether of ethylene glycol at 150°.

Anal. Calcd. for $C_{11}H_{15}NO_2S$: N, 6.22. Found: N, 6.35.

It melts at 42–43°, but a mixture of the thiol and thion esters liquefies at room temperature. This ester was converted into its thiol isomer by heating with ethoxyethyl iodide at 130° for four hours.[5] The resulting product melted at 44°. Its constitution was proved by a mixed melting point with the thiol ester, by its dissociation into phenyl isocyanate and mercaptan at 150° and by the formation of carbanilide and mercaptan when heated with aniline.

Phenyl isocyanate adds to the NH and NH_2 groups giving with the above thiourea, the ethoxyethyl ether of thiocarbonyldiphenyl-diurea, $C_6H_5NHCONHC(NCONHC_6H_5)SC_2H_4OC_2H_5$. The hydrogen bromide salt of the thio ether (12 g.) in concentrated water solution was treated with phenyl isocyanate (12 g.) and potassium hydroxide (3 g.). The resulting heavy oil on crystallization from alcohol gave a solid melting at 132°.

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[2] Dains, Brewster, Blair and Thompson, THIS JOURNAL, **44**, 2639 (1922).

[3] Korndorfer, *Archiv. Phar.*, **241**, 478 (1903).

[4] Rojahn and Lemme, *ibid.*, **263**, 623 (1925). From potassium hydrosulfide and the bromo ether.

[5] Wheeler and Barnes, *Am. Chem. J.*, **24**, 71 (1902).

Anal. Calcd. for $C_{19}H_{22}N_4O_2S$: N, 14.52. Found: N, 14.39.

Its identity was proved by its conversion by means of alcoholic ammonia[6] into the diphenyl amide of guanidine dicarboxylic acid (m. p. 176°) and mercaptan. The corresponding methyl ether gives the same guanidine derivative.[7] Phenyl isothiocyanate yields only oily addition products with the thio ethers.

β-Ethyl Acetate Derivative of Isothiourea, $CH_3COOCH_2CH_2SC(NH)NH_2HBr$.—β-Bromo-ethyl acetate heated at 125° formed an oil which crystallized from acetone in needles melting at 99°.

Anal. Calcd. for $C_5H_{10}N_2O_2S \cdot HBr$: N, 11.53; Br, 32.28. Found: N, 11.64; Br, 32.04.

The ester heated with aniline gave phenylguanidine and with phenyl isocyanate a thiocarbonyl diurea derivative melting at 134°.

Anal. Calcd. for $C_{19}H_{20}N_4O_4S$: N, 14.01. Found: N, 13.80.

The acyl chlorides yield with the thiourea ethers α,β-diacyl derivatives of the type RCONHC(NCOR)S—R′. Thus acetyl oxyethyl isothiourea with benzoyl chloride gives a heavy oil, but with *p*-nitrobenzoyl chloride in pyridine solution, the di-*p*-nitrobenzoyl thiourea ether, melting at 189°, resulted.

Anal. Calcd. for $C_{19}H_{18}N_4O_8S$: N, 12.13. Found: N, 12.30.

The α,β-dibenzoyl-γ-methyl thiourea (m. p. 149°) is readily formed from benzoyl chloride and the methyl thiourea in alkaline solution.[8]

Anal. Calcd. for $C_{16}H_{14}O_2N_2S$: N, 9.40. Found: N, 9.53.

That it has the symmetrical constitution or rearranges easily to it is shown by the fact that on heating with aniline the known dibenzoyl-monophenylguanidine (m. p. 185°) was obtained and confirmed by a mixed melting point.[9]

Reactions with Monophenylthiourea. γ-Hydroxyethyl-phenylthiourea Hydroiodide, $C_6H_5NHC(NH)SC_2H_4OH$.—The iodohydrin and phenyl thiourea were heated in alcohol solution at water-bath temperature and the resulting heavy oil after washing with ether was dried at 100° *in vacuo*.

Anal. Calcd. for $C_9H_{13}N_2OS \cdot HI$: N, 8.62. Found: N, 8.49.

The free base is a heavy oil which rapidly decomposes, yielding mono-phenyl urea and mercaptan. Boiled with sodium hydrosulfide, the ether gives the phenyl thiourea. With ethylene chlorohydrin only decomposition products were obtained.

γ-Acetyl-oxyethyl-phenylthiourea, $C_6H_5NHC(NH)SCH_2CH_2OCOCH_3$, was isolated as the hydrogen bromide salt (m. p. 158°). The free is base fairly stable and melts at 69–70°.

Anal. Calcd. for $C_{11}H_{14}N_2O_2S$: N, 11.77. Found: N, 11.78.

Aniline at 150° gave diphenylguanidine (m. p. 146°).

Nitrobenzoyl chloride in pyridine solution formed an acyl derivative, crystallizing from alcohol in orange colored flakes melting at 132°.

Anal. Calcd. for $C_{18}H_{17}N_3O_5S$: N, 10.85. Found: N, 10.67.

Its stability would point to the symmetrical structure.[10] With phenyl isocyanate, it showed the usual behavior, yielding the thio ether of 1,5-diphenyl-4-monothiobiuret, $C_6H_5NHCONH(SC_2H_4OCOCH_3)NHC_6H_5$, m. p. 81–82°.

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[6] A convenient method for this type of reaction is to dissolve the substance in alcohol in a Dewar flask, add liquid ammonia and allow the solution to slowly evaporate.

[7] Lakra and Dains, THIS JOURNAL, **51**, 2223 (1929).

[8] The corresponding dibenzoyl-γ-ethyl thiourea melts at 112°.

[9] McKee, *Am. Chem. J.*, **26**, 222 (1901); Kampf, *Ber.*, **37**, 1683 (1904).

[10] Wheeler, *Am. Chem. J.*, **27**, 279 (1902).

Anal. Calcd. for $C_{18}H_{19}N_3O_3S$: N, 11.70. Found: N, 11.63.

Disubstituted Thioureas. Thiocarbanilide and β-Chloro-ethyl Benzoate.—Molar proportions were heated alone or in xylene solution at 130–150° for several hours. From the reaction mixture were isolated diphenylurea, phenyl mustard oil, benzanilide, benzoic acid, sulfur containing oils and 2,3-diphenylthiazolidine (m. p. 136°).

Two sets of reactions evidently occur; first, the formation of a thio ether which is then hydrolyzed to the urea, benzoic acid, and mercaptan; second, dissociation of the thiocarbanilide into phenyl isothiocyanate and aniline, which with the chloro-ethyl benzoate gives phenylamino-ethanol benzoate. The amino-ethanol adds the mustard oil, yielding the thiourea. The thiazolidine results from loss of benzoic acid, closing the ring.[11] The possibility of such a reaction is shown experimentally as follows.

β-Phenylamino-ethyl benzoate (m. p. 78°) gave with phenyl isothiocyanate in alcohol solution the benzoate of γ,β-diphenyl-γ-ethanol thiourea, $C_6H_5NHCSN(C_6H_5)CH_2CH_2O—COC_6H_5$, melting at 145°.

Anal. Calcd. for $C_{22}H_{20}N_2O_2S$: N, 7.45. Found: N, 7.61.

The ring is closed when the thiourea is heated with hydrochloric acid, yielding the 2,3-diphenylthiazolidine and benzoic acid. Since no evidence of ring formation has been obtained from the hydroxy-ethyl thio ethers, the above seems the most probable explanation of the reaction. Thiocarbanilide and mono-*m*-nitrodiphenylthiourea formed the usual γ-thio ethers with bromo and iodo ethyl ether.

The Action of Ethylene Oxide on the Thioureas.—Since ethylene oxide unites with primary and secondary amines to form a substituted amino-ethanol, it seemed possible that the thiourea might add the oxide either on the NH or the enol SH position. The experimental evidence indicates that the SH group alone is affected, yielding more or less stable thio ethers, $—N—C(=NR)S—CH_2CH_2OH$, or their hydrolysis products.

Ethylene oxide (35 g.) was added to a solution of the thiourea (38 g.) in acetone (200 cc.). The mixture was allowed to stand at room temperature for three weeks. On concentrating to half its volume and cooling, a yield of 25 g. of pure oxygen urea was obtained. The solution showed the presence of thioethylene glycol due to hydrolysis of the unstable thio ether. If the acetone solution of the oxide and thiourea was heated at 30–35° for forty-eight hours, there was found not only the oxygen urea but also an indefinite mixture of nitrogen and sulfur-containing products. With propylene oxide in acetone solution at room temperature the oxygen urea was formed. When heated at 60° there were isolated the urea and an oil (b. p. 128–135° at 11 mm.) whose sulfur content (21.7%) suggested that it might be an addition product of propylene-oxide and thiopropylene glycol, $HSCH(CH_3)CH_2OCH(CH_3)CH_2OH$. Phenyl oxygen urea (77% yield) and sulfur-containing oils were formed from ethylene oxide and phenylthiourea in acetone solution.

γ-Hydroxyethyl-diphenylthiourea.—A mixture of diphenylthiourea (100 g.), acetone (750 cc.) and ethylene oxide (50 g.) was heated at 50–55° for eighteen hours. On cooling, the ether crystallized out in transparent cubes which melted at 145°. The same compound had been isolated in small amount in the reaction product from ethylene iodohydrin and diphenylthiourea at 125°.

Anal. Calcd. for $C_{15}H_{16}N_2OS$: N, 10.30. Found: N, 10.32.

When heated the fused compound solidified at 148° and melted again at 220°; this latter compound proved to be impure diphenylurea.

That the compound (m. p. 145°) was a thio ether and not the isomeric α,β-diphenyl-α-ethanol-thiourea[12] was proved by its melting point, 145°, by the fact that hydrolysis

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[11] Dains, Brewster, Blair and Thompson, THIS JOURNAL, **44**, 2639 (1922).

[12] Dains, Brewster and others, *ibid.*, **47**, 1983 (1925).

with alkali gave diphenylurea and that heating with halogen acids yielded again the diphenylurea and not diphenylthiazolidine.

Warmed in benzene solution, phenyl isocyanate united with the hydroxyl group, yielding a phenyl urethan (m. p. 101°).

Anal. Calcd. for $C_{22}H_{21}N_3O_2S$: N, 10.75. Found: N, 10.96.

On hydrolysis with alcoholic potassium hydroxide, only diphenylurea was obtained and not a triphenylbiuret which might have formed had the isocyanate reacted with an NH group.

Thiohydrolysis by Means of Potassium or Sodium Hydrosulfide.[13]—One of the characteristic properties of the isothiourea ethers is the ease with which they are hydrolyzed with alkalies, yielding oxygen ureas. An interesting analogous reaction has been developed in this investigation, *viz.*, thiohydrolysis, whereby thioureas can be obtained from these thio ethers.

Method for the Conversion of the β-Ethoxyethyl Ether of Thiocarbonyl Diphenyldiurea to the Diphenyl Amide of Thiourea-α,β-dicarboxylic Acid, $(C_6H_5NHCONH)_2\cdot CS$.—The thio ether (8 g.) was dissolved in hot alcohol (50 cc.) together with 5 g. of potassium hydrosulfide in water (10 cc.). Hydrogen sulfide was passed into the boiling solution for an hour. The hot solution was filtered and acidified with acetic acid. On cooling, fine needles of the thiourea (m. p. 202°) separated.

Anal. Calcd. for $C_{15}H_{14}N_4O_2S$: N, 17.85. Found: N, 17.85.

Using this method, thioureas in good yield were obtained from the following thio ethers: γ-methylphenylthiourea, γ-methyldiphenylthiourea and the 4-methyl ether of 1-phenyldithiobiuret.[14]

1,5-Diphenyl-dithiobiuret, which melts at 149°, was obtained from its methyl ether.[15]

Anal. Calcd. for $C_{14}H_{13}N_3S_2$: N, 14.64. Found: N, 14.63.

The Hydrolysis of Diacyl Thiourea Ethers.—When the γ-methyl ethers of dibenzoyl- or diacetylthiourea were treated with potassium sulfhydrate, complete hydrolysis occurred.[16]

γ-Methyl Ether of Thiocarbonyl-di-urethan, $CH_3SC(NCOOC_2H_5)NHCOOC_2H_5$.—Methyl isothiourea sulfate (35 g.) was dissolved in water at 0°. To it was added slowly ethyl chlorocarbonate (60 g.) and potassium hydroxide (50 g.) in water solution with constant stirring. The resulting oil was extracted with ether. Upon evaporating the ether and cooling, the ether melting at 50–51° was obtained.

Anal. Calcd. for $C_8H_{14}N_2O_4S$: N, 11.97. Found: N, 12.14.

Its constitution was proved by conversion by means of liquid ammonia into symmetrical dicarbethoxyguanidine (m. p. 165°).

Thiocarbonyl-diurethan, $CS(NHCOOC_2H_5)_2$.—The greater stability of the carbethoxy over other acyl groups was indicated by the ready thiohydrolysis of the methyl ether (m. p. 51°). The carbethoxy thiourea melts at 111–112° and is soluble in alkalies, hot water and organic solvents. Previous efforts to synthesize the compound from thiophosgene and urethan had failed.

Anal. Calcd. for $C_7H_{12}N_2O_4S$: N, 12.73. Found: N, 12.75.

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[13] Lakra and Dains, THIS JOURNAL, **51**, 2224 (1929).

[14] Johnson, *Am. Chem. J.*, **30**, 174 (1903); Gentz, *Ann.*, **154**, 44 (1870); Fromm, *ibid.*, **275**, 34 (1893); Wunderlich, *Ber.*, **19**, 452 (1886); Hecht, *ibid.*, **25**, 756 (1892).

[15] Johnson, *Am. Chem. J.*, **30**, 174 (1903).

[16] The diacetyl-γ-methylthiourea from methyl-isothiourea sulfate and acetic anhydride melts at 107–108°. N, 16.10. Found: N, 15.97.

α-Phenyl-α-carbethoxy-γ-methyl Thiourea, $C_6H_5N(COOC_2H_5)C(SCH_3)NH$, is formed from the interaction of γ-methylphenylthiourea, ethyl chlorocarbonate and alkali. It melts at 128° and on thiohydrolysis breaks down into thiocyanic acid mercaptan and phenylurethan.

Anal. Calcd. for $C_{11}H_{14}N_2O_2S$: N, 11.76. Found: N, 11.57.

Summary

1. The chlorohydrins, their esters and ethers react with thiourea giving γ-thio ethers, which are easily hydrolyzed, the hydroxy derivatives being especially unstable. The thio ethers yield with amines guanidines, with acyl chlorides diacyl derivatives and with phenyl isocyanate the phenyl amide derivatives of α,β-thioureadicarboxylic acids.
2. A method has been described for the thiohydrolysis of the thio ether ethers.

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[CONTRIBUTION FROM THE FRICK CHEMICAL LABORATORY OF PRINCETON UNIVERSITY]

THE PARACHORS OF TWO ISOMERIC CHLORO-DINITROBENZENES

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It has been found by Sugden and his collaborators[1] that the parachors of isomerides which differ in structure only by the position of groups or linkages in the molecule are identical within the limits of experimental error. On examining the published data for surface tension, it was noticed that the values for the two isomers (A) 1-chloro-3,4-dinitrobenzene and (B) 1-chloro-2,4-dinitrobenzene differed very widely, the value for the latter being more than three times that for the former at like temperature. The reported densities differ by only a few per cent. As a consequence, the parachors of these two isomers, as computed from the available experimental data, show a wide divergence, namely, 258.7 for (A) and 346.4 for (B). The parachor computed from the atomic and structural parachors given by Sugden[2] is 358.3, and is, of course, identical for both substances.

Now the chloro-dinitrobenzenes differ considerably in reactivity, and they are known to exist in a number of different crystalline forms, so that a difference of parachor was not *a priori* unthinkable. Furthermore, it seemed hardly possible that experimental error could account for the enormous discrepancy found in surface tension. It therefore seemed worth while to redetermine the surface tensions and densities of the substance (A).

The existing values of surface tension and density for the two isomers (A)

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[1] (a) Sugden and Wilkins, *J. Chem. Soc.*, **127**, 2517 (1925); (b) Sugden, "The Parachor and Valency," **1930**, p. 33.

[2] Ref. 1b, pp. 38, 114.