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Thioureas and Thiouronium Salts. V. Some Reactions of 1,1,3-Trimethyl-2-thiourea

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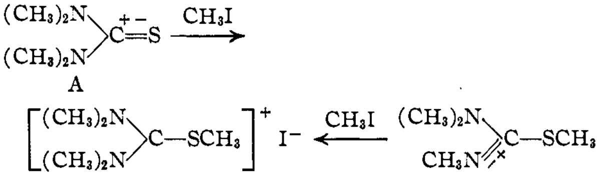
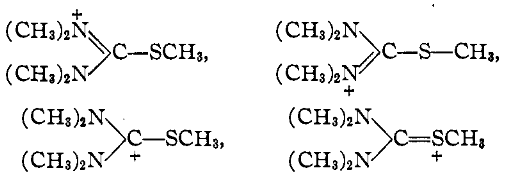
The structures of thioureas and thiouronium salts are discussed. The action of mercuric oxide on 1,1,3-trimethyl-2-thiourea in different reaction media and the products obtained have been studied. Related reactions of ethylenethiourea are referred to. Also the reactions of 1,1,3,3-tetramethyl-2-thiourea and of 1,3-di-*n*-propyl-2-thiourea with mercuric oxide have been investigated. 1,1,3-Trimethyl-2-thiourea has been oxidized to a salt of the corresponding diguanyldisulfide and the reactions of the latter have been studied.

The earlier papers of this series[3–6] elucidated the salt formation of thioureas and isothioureas with acids and alkyl halides. It was shown that a proton or an alkyl group attaches itself to the sulfur in thioureas and to the double bonded nitrogen in S-alkyl-isothioureas. In the resulting thiouronium salts the function of the two nitrogen atoms becomes indistinguishable



This fact was explained by an oscillation of the carbon–nitrogen double bond, a hypothesis which was a precursor to the modern resonance concept. Applying the latter it seems probable that two imonium, one carbonium and—to a minor extent—one sulfonium ion contribute to the resonance of thiouronium ions, *i.e.*



Thioureas are dipoles, but the polarity varies with the substituents. Solid thiourea itself may represent the extreme case of a zwitterion,[3] while, *e.g.*, 1,1,3,3-tetramethyl-2-thiourea with a m.p. 78° and a b.p. 245° certainly represents a lower degree of polarity.[7] For the understanding of this paper it is important to keep in mind that both thioureas and isothioureas have some polarity; that in the former the negative end of the molecule is the sulfur, in the latter the double bonded nitrogen (as indicated in the formulas A and B above).

Our former papers dealt with salts thioureas form with acids and alkyl halides. Thioureas, being zwitterions or dipoles, should also be capable of forming salts with metals, and we were particularly interested in obtaining a mercury salt because of the well-known affinity of mercury to sulfur. We regarded the preparation of a mercury salt derived from a thiourea containing more than one hydrogen attached to a nitrogen atom very difficult, because of the ready formation of cyanamides or carbodiimides. However, a trisubstituted thiourea such as 1,1,3-trimethyl-2-thiourea (I) seemed to offer some promise.

For the preparation of this mercury compound we used Lecher's[8] method for the preparation of mercury mercaptides. According to this method, a dry pyridine solution of the thiol is shaken with yellow mercuric oxide. The mercury mercaptides are very soluble in pyridine and form very easily in this medium from which they are precipitated by the aid of non-dissolving diluents. In the preparation of the mercury derivative of the 1,1,3-trimethyl-2-thiourea we found it very important to avoid the presence of any water which decomposes this very sensitive mercury derivative.

The analysis of this mercuric compound (II) showed that it was not a simple "mercury salt" of the thiourea, but contained in addition two coördinated molecules of the thiourea and one molecule of carbon tetrachloride "of crystallization." As far as the latter is concerned, it probably plays an important part in building up the crystal structure though it has been omitted from the formula (II) as sketched.

This mercury compound easily undergoes a thermic decomposition when heated in an inert anhydrous medium such as benzene. The two complex-bound molecules of thiourea and the molecule of carbon tetrachloride remain unchanged; the mercury salt itself decomposes into one molecule mercuric sulfide and one molecule of a strong base, which by analysis and its behavior is undoubtedly the 1-(trimethylguanyl)-1,3,3-trimethyl-2-thiourea (III). We found it expedient to isolate first the perchlorate from which the base could be obtained by treating with potassium carbonate and benzene and a little water.

The same 1-(trimethyl-guanyl)-1,3,3-trimethyl-2-thiourea (III) is also obtained when the 1,1,3-trimethyl-2-thiourea (I) is boiled with mercuric oxide

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(2) Most of the experimental work reported in this paper was done in 1921–1922 and was the subject of the unpublished thesis (University of Munich) of Dr. Gubernator.

(3) H. Z. Lecher, *et al.*, *Ann.*, **438**, 169 (1924).

(4) *Ibid.*, **445**, 35 (1925).

(5) *Ibid.*, **445**, 77 (1925).

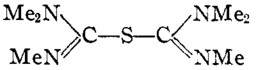
(6) *Ibid.*, **456**, 192 (1927).

(7) In the long interval since the publication of the earlier papers of this series the structure of thioureas has been discussed by several other authors: N. V. Sidgwick, "The Organic Chemistry of Nitrogen," 1937, pp. 281, 291; F. Arndt, *Ber.*, **63**, 2966 footnote (1930); A. Clow, *et al.*, *Trans. Faraday Soc.*, **33**, 381 (1937); **34**, 457 (1937); **36**, 685 (1940); H. Rivier and J. Borel, *Helv. Chim. Acta*, **11**, 1219 (1928); K. W. F. Kohlrausch and J. Wagner, *Z. physik. Chem.*, **B45**, 229 (1940).

(8) H. Z. Lecher, *Ber.*, **48**, 1429 (1915).

in benzene. In this reaction, however, some 1,1,3-trimethylurea (IV) is formed as a by-product due to the presence of the water formed in the reaction.

The 1-(trimethyl-guanyl)-1,3,3-trimethyl-2-thiourea (III) is a strong monoacid base and, therefore, the compound cannot have the formula (C) of a di-(trimethylguanyl)-monosulfide



C

which (like the corresponding disulfide VI) would be a diacid base. Furthermore, the structure of III has been proven by its conversion into the corresponding urea derivative, *i.e.*, by replacement of the sulfur by an oxygen atom. While this guanylthiourea does not appreciably react with mercuric oxide in an anhydrous inert solvent, it reacts easily with mercuric oxide in water and gives as the main product 1-(trimethylguanyl)-1,3,3-trimethylurea (V) with a little 1,1,3-trimethylurea (IV) as a by-product formed by simultaneously occurring hydrolysis. Also the 1-(trimethylguanyl)-1,3,3-trimethyl-2-urea (V) is a strong monoacid base.

Further proof of the structure of this guanylthiourea is its behavior toward hydrolysis by boiling water. This hydrolysis gives equivalent quantities of 1,1,3-trimethyl-2-thiourea (I) and 1,1,3-trimethyl-2-urea (IV).

When the 1,1,3-trimethyl-2-thiourea (I) is boiled with mercuric oxide in water it is converted into 1,1,3-trimethylurea (IV), *i.e.*, the sulfur atom is replaced by oxygen.

Thus we know at present three types of reactions of thioureas with mercuric oxide: There is the unique conversion of a 1,1,3-trisubstituted thiourea into a guanylthiourea which has been described above and has been shown to go probably through a mercury salt. Secondly, there is the conversion into ureas and, thirdly, the conversion into carbodiimides and cyanamides.

The conversion of thioureas into ureas by mercuric oxide requires the presence of water. This can be most conspicuously demonstrated with the example of 1,1,3,3-tetramethyl-2-thiourea which does not react with mercuric oxide in anhydrous medium at all but gives an excellent yield of the corresponding 1,1,3,3-tetramethylurea with mercuric oxide in a mixture of alcohol and water. This example also shows that the conversion of a thiourea into the corresponding urea by the aid of mercuric oxide does not, or at least not necessarily, go through the carbodiimide.

In order to investigate this latter point further we have prepared the known di-*n*-propylcarbodiimide[9] from 1,3-di-*n*-propyl-2-thiourea[10] and mercuric oxide under anhydrous conditions; under such conditions no 1,3-di-*n*-propylurea could be observed as a by-product. However, if the same thiourea was treated with mercuric oxide in a mixture of alcohol and water, only very little of the carbodiimide but a 70% of the theory yield of 1,3-di-*n*-propylurea was obtained. It could be argued that in the latter case the urea formation was due to a reaction of primarily formed carbodiimide with water. However, when the di-*n*-propylcarbodiimide was heated with a water–alcohol mixture under exactly the same conditions, a much smaller (only 28%) yield of the urea was obtained. The di-*n*-propylcarbodiimide is, as a matter of fact, quite unreactive against water and alcohol.

We have therefore reached the conclusion that the formation of carbodiimides and of ureas in the reaction of thioureas with mercuric oxide follow different routes. Probably the carbodiimide is formed by a thermal decomposition of a labile mercury salt while the urea is formed by hydrolysis of such a mercury compound. It should be borne in mind that as soon as thioureas are covalently substituted on the sulfur atom the resulting isothiourea type is a very strong base. As such, it will combine with a proton to a thiouronium cation. However, thiouronium cations are not stable in alkaline media and hydrolyze easily with the formation of ureas and thiols (in our case $Hg(SH)_2$).

It has already been shown in a previous paper[4] that the 1,1,3,3-tetramethylthiourea can be oxidized to salts of a completely methylated diguanyl disulfide in exactly the same fashion as the unsubstituted thiourea itself can be oxidized to salts of diguanyl disulfide (formamidine disulfide). We became interested in oxidizing also the 1,1,3-trimethyl-2-thiourea (I) to a salt of di-(trimethylguanyl) disulfide (VI) because we hoped that we would be able to isolate the corresponding base. So far, diguanyl disulfides are known only in the form of their salts and all attempts to isolate the corresponding bases have failed. We considered the possibility that the corresponding bases owe their instability to a radical dissociation at the sulfur–sulfur bridge. We had no difficulty in obtaining salts of the desired disulfide, but attempts to isolate the base failed. Aqueous alkali hydrolyzed the molecule with extreme ease,[11] probably in the same manner as other disulfides are hydrolyzed by aqueous alkali under more strenuous conditions, *i.e.*, one sulfur combines with hydrogen and the other with hydroxyl and the resulting sulfur-hydroxyl compound (which in other cases is called a sulfenic acid) disproportionates. In our case there are indications that half of the molecule is obtained as 1,1,3-trimethyl-2-thiourea (I) and two-thirds of the other half of the molecule are also obtained as the same thiourea. The remainder suffers a more complicated decomposition resulting in the formation of amines, sulfate, carbonate, thiosulfate, etc.

The disulfide is also not stable in acid aqueous medium and decomposes on boiling. In this case sulfur and 1-(trimethylguanyl)-1,3,3-trimethyl-2-thiourea (III) are formed in about equivalent amounts, but the yields are far from quantitative and also other decomposition products are formed.

The formation of the 1-(trimethylguanyl)-1,3,3-trimethyl-2-thiourea (III) from both the mercury compound (II) and the disulfide (VI) is not difficult to understand. In a space model the C and N

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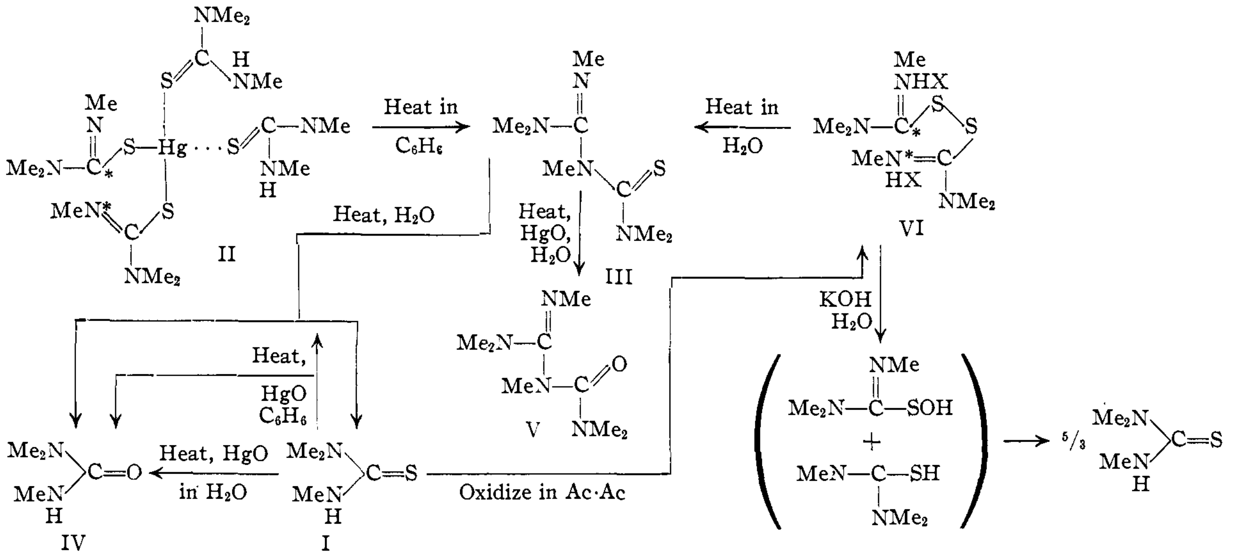
[9] F. Chancel, *Compt. rend.*, **116**, 330 (1893); *Bull. soc. chim. France*, [3] **9**, 239 (1893); A. Franssen, *ibid.*, [4] **43**, 180 (1928).

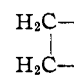
[10] O. Hecht, *Ber.*, **23**, 285 (1890); F. Chancel, *Compt. rend.*, **116**, 62 (1893).

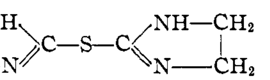
[11] Generally disulfides with "neighboring double bonds" are easily hydrolyzed; "Fromm's rule," *cf. Ann.*, **348**, 144 (1906).



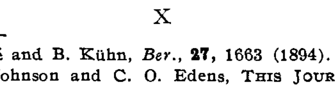
atoms marked with an asterisk are in close proximity and the intermediate formation of a six- and five-membered ring, respectively, seems easy. As pointed out above, the carbon–nitrogen bond in the isothiourea type compounds ought to be polarized. Thus the combination of the carbon* with the nitrogen* is facilitated by both the electronic and the steric arrangements.

Since the work reported in this paper was done about 30 years ago, we thought it desirable to scan the subsequent literature in order to determine whether analogous rearrangements leading to guanylthioureas have been described. In doing so we noticed a compound obtained from the so-called "ethylenethiourea" (2-tetrahydroimidazolethione (VII)). This derivative of ethylenethiourea was first obtained by Jaffé and Kühn[12] by action of thiophosgene on ethylenediamine. It was again obtained by Johnson and Edens[13] by oxidation of ethylenethiourea and the formula IX was assigned to it. Later[14] the same authors got the compound by boiling the periodide of the disulfide VIII with water, a mode of formation which is reminiscent of the decomposition of the salts of our disulfide VI by boiling in water; it will be recalled that this reaction did not give a substituted formamidine monosulfide but a guanylthiourea. The derivative of ethylenethiourea is a monoacid base[12] while the corresponding disulfide VIII is a diacid base.[15] It is quite clear that IX, being a bis-amidine, ought to be also a diacid base while X, being a guanylthiourea, ought to be a monoacid base. Therefore, Jaffé's and Johnson's compound has unquestionably not the formula IX but X (in analogy to our guanylthiourea III.


VII


VIII


IX


X

Acknowledgment.—The experiments on the reactions of 1,1,3,3-tetramethyl-2-thiourea and of 1,3-di-*n*-propyl-2-thiourea with mercuric oxide were carried out by my former assistant, the late Dr. Karl Köberle (H. Z. L.).

Experimental

1,1,3-Trimethyl-2-thiourea (I).—This thiourea is prepared by the convenient method described by H. Lecher and T. Weigel;[16] m.p. 86–87°; very soluble in water, alcohol, chloroform, pyridine; soluble in 10 parts benzene, precipitated by hexane; sparingly soluble in cold, easily in warm carbon tetrachloride.

Mercury Derivative of 1,1,3-Trimethyl-2-thiourea (II).—2.36 g. (0.02 mole) of 1,1,3-trimethyl-2-thiourea was dissolved in 12 cc. of pure dry pyridine. This solution was cooled and there was added first 1 g. of anhydrous sodium sulfate and then 1.08 g. (0.005 mole) of powdered yellow mercuric oxide. This mixture was shaken on the machine for 1.25 hours, light being excluded. The solution was filtered and 50 cc. of dry carbon tetrachloride was slowly added. (In a separate experiment it was determined that a solution of 2.36 g. of the thiourea in 12 cc. of pyridine was not precipitated by 50 cc. of carbon tetrachloride; therefore, no uncombined 1,1,3-trimethyl-2-thiourea could have been precipitated.) Colorless crystals precipitated and were filtered off, washed with 25 cc. of carbon tetrachloride and dried *in vacuo* over sulfuric acid and paraffin scraps to constant weight; the desiccator was kept in the refrigerator; yield between 2.3 and 2.8 g. The colorless crystals decompose on heating: around 60° the substance turns gray, at about 80° it is already black, and around 120° a black melt is formed. The analysis showed that the substance is a complex of the mercuric salt of the 1,1,3-trimethyl-2-thiourea with 2 molecules of 1,1,3-trimethyl-2-thiourea, containing 1 molecule of carbon tetrachloride of crystallization.

Anal. Calcd. for $C_8H_{18}HgN_4S_2 + 2C_4H_{10}N_2S + CCl_4$: C, 24.73; N, 13.58; Cl, 17.19; S, 15.54; Hg, 24.31. Found: C, 25.11; N, 13.42; Cl, 17.57; S, 15.78; Hg, 24.39.

If the substance is not pure it decomposes rather fast,

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[12] M. Jaffé and B. Kühn, *Ber.*, **27**, 1663 (1894).

[13] T. B. Johnson and C. O. Edens, THIS JOURNAL, **63**, 1058 (1941).

[14] T. B. Johnson and C. O. Edens, *ibid.*, **64**, 2706 (1942).

[15] L. D. Freedman and A. H. Corwin, *J. Biol. Chem.*, **181**, 616 (1949).

[16] German Patent 526,799, July 1, 1928, I. G. *Friedl.*, **18**, 363 (1933).

sometimes already within one day. The pure substance is more stable. A good preparation was unchanged after ten days but was decomposed after a quarter of a year. The decomposition is considerably accelerated by a rise in temperature.

This mercury compound is very soluble in pyridine; if the pyridine contains traces of water, mercuric sulfide is soon precipitated even at ordinary temperature. It is sparingly soluble in water and in benzene. It is easily soluble in hot benzene but decomposes quite fast; nevertheless, small amounts may be recrystallized from benzene if the hot benzene solution is poured into a chilled vessel. The substance is insoluble in carbon tetrachloride and in gasoline.

Decomposition of the Mercury Derivative in Boiling Benzene.—4.13 g. of the mercury compound were refluxed with 75 cc. of benzene for 0.75 hour. The mercuric sulfide was filtered off on a Gooch crucible and washed with benzene; calcd. 1.16 g., found 1.1 g. The filtrate was concentrated, water was added and the remainder of the benzene was stripped off; traces of mercuric sulfide precipitated and were removed by filtration. To the aqueous filtrate there was added the calculated amount (0.7 g.) of 70% perchloric acid. The solution was concentrated to a volume of 25 cc. and on cooling separated 0.6 g. of the perchlorate of 1-(trimethylguanyl)-1,3,3-trimethyl-2-thiourea (III), which was identified by melting point and mixed melting point. The mother liquor was evaporated and the oily residue dried *in vacuo;* 2.0 g. Benzene extracted from this oil 0.8 g. of 1,1,3-trimethyl-2-thiourea identified by mixed melting point.

Reaction of 1,1,3-Trimethyl-2-thiourea with Mercuric Oxide in Benzene.—A solution of 26.1 g. of this thiourea in 260 cc. of benzene was refluxed with 52 g. of powdered yellow mercuric oxide until a filtered sample did not blacken mercuric oxide any longer on boiling; this took 20 minutes. The reaction mixture was dried with potassium carbonate (to remove the water formed) and filtered, and the filtrate was evaporated under reduced pressure. The residue was dissolved in water and neutralized with 1 *N* perchloric acid, using methyl orange as indicator. After seeding and cooling to 4°, 15.0 g. of the sparingly soluble perchlorate of 1-(trimethylguanyl)-1,3,3-trimethyl-2-thiourea (III) crystallized out. The mother liquor was evaporated under reduced pressure and the residue was extracted with benzene. This procedure left an additional 3.2 g. of the perchlorate unextracted to the effect that its total yield amounted to 18.2 g. (calcd. 33.4 g.).

The benzene extract was dried with anhydrous sodium sulfate, filtered and evaporated under reduced pressure. The residue was distilled under 11 mm.; 4.2 g. came over between 120 and 132°, while 1.4 g. stayed behind. The partly oily, partly crystalline still residue contained some unchanged 1,1,3-trimethyl-2-thiourea. The distillate was for the main part crystalline; it showed a neutral reaction but contained sulfur and had a sharp odor. In order to remove the contamination it was boiled in water with mercuric oxide whereupon a repeated distillation yielded about 3 g. of pure 1,1,3-trimethylurea (IV), b.p. 126–128.5° (15.5 mm.). It should be noted that the separation of the 1,1,3-trimethylurea and the 1,1,3-trimethyl-2-thiourea by distillation does not work smoothly because the thiourea, which should stay behind, undergoes a partial decomposition.

1-(Trimethylguanyl)-1,3,3-trimethyl-2-thiourea (III).—Its perchlorate was purified by recrystallization from 10 parts of water and was thereby obtained in colorless, half an inch long crystals, m.p. 164–165°.

Anal. Calcd. for $C_8H_{19}ClN_4O_4S$: C, 31.72; H, 6.33; N, 18.51; Cl, 11.71; S, 10.59. Found: C, 32.01; H, 6.47; N, 18.45; Cl, 11.94; S, 10.66.

The perchlorate is sparingly soluble in cold, considerably in hot water. The aqueous solution shows a neutral reaction. When the perchlorate is heated in the free flame it puffs.

In order to prepare the free base, 12 g. of the pure perchlorate was ground in a mortar with 12 g. of potassium carbonate, 3 cc. of water and 80 cc. of benzene. The benzene solution was decanted and the stiff dough was ground twice more with 12 g. of potassium carbonate, 3 cc. of water and 80 cc. of benzene each time. The combined benzene extracts were dried with potassium carbonate and evaporated. An oil stayed behind which is very slow to crystallize and tends to be supercooled; however, by dissolving a sample in ether and evaporating seeds can be obtained; yield almost quantitative.

The 1-(trimethylguanyl)-1,3,3-trimethyl-2-thiourea forms colorless crystals, m.p. 53°.

Anal. Calcd. for $C_8H_{18}N_4S$: C, 47.48; H, 8.97; N, 27.70. Found: C, 47.62; H, 9.32; N, 27.61.

The base is exceedingly soluble in water, imparting a strong alkaline reaction. It is also very soluble in alcohol, ether, gasoline and in most other solvents. When boiled with mercuric oxide in water it gives mercuric sulfide but does not do so in boiling benzene, toluene, etc.

Reaction of 1-(Trimethylguanyl)-1,3,3-trimethyl-2-thiourea with Mercuric Oxide in Water.—The base prepared from 21 g. of its perchlorate was dissolved in 150 cc. of water and heated with excess mercuric oxide on the water-bath. Mercuric sulfide in the modification of Cinnabar was formed. The mercury compounds were removed by filtration, the aqueous filtrate was evaporated and the residue distilled under reduced pressure; 8.3 g. distilled between 118 and 128° (10 mm.). The distillate was a colorless, strongly basic oil which constituted a mixture of much 1-(trimethylguanyl)-1,3,3-trimethylurea (V) and a little 1,1,3-trimethylurea; this urea probably resulted from a simultaneous hydrolysis. The oily mixture was dissolved in 35 cc. of ethanol. A saturated solution of picric acid in ethanol was added until no more yellow crystals separated; yield of the picrate, about 15 g. and after recrystallization from 320 cc. alcohol, 13.2 g. The mother liquor of the sparingly soluble, just mentioned picrate was evaporated under reduced pressure, the residue was extracted with benzene, the extract was dried with potassium carbonate and then subjected to a vacuum distillation. A small amount of 1,1,3-trimethylurea boiling at 120° (12 mm.) was obtained.

The picrate of the 1-(trimethylguanyl)-1,3,3-trimethylurea crystallizes in yellow crystals which grow half an inch long and which, after drying on a porous plate, contain half a molecule of ethanol of crystallization. When heated in a capillary tube the picrate starts to shrink at 70°, starts to sinter at 120° and melts unsharp at 126–133° (dec.).

Anal. Calcd. for $2C_8H_{18}N_4O + 2C_6H_3N_3O_7 + 1C_2H_6O$: C, 41.08; H, 5.52; N, 22.37. Found: C, 41.20; H, 5.56; N, 22.40.

The alcohol of crystallization is removed only by long drying *in vacuo* at 60°. The alcohol free picrate starts to sinter at 123° and melts at 130–133° (dec.).

Anal. Calcd. for $C_8H_{18}N_4O + C_6H_3N_3O_7$: C, 40.47; H, 5.10; N, 23.61. Found: C, 40.87; H, 5.38; N, 23.66.

The picrate is insoluble in carbon tetrachloride and only sparingly soluble in benzene.

In order to convert the picrate into the base, 8 g. was ground in a mortar with 10 g. of potassium hydroxide powder and a small amount of water. Then 250 cc. of carbon tetrachloride was poured into the mortar and the grinding was continued. The carbon tetrachloride extract was dried over powdered potassium hydroxide and subjected to a fractional distillation under reduced pressure: 2.5 g. of the base distilled at 123° (10.5 mm.). It should be noted that the boiling point is almost the same as that of 1,1,3-trimethylurea, a fact which made the detection and isolation of the base difficult. The base was redistilled for analysis. The 1-(trimethylguanyl)-1,3,3-trimethylurea (V) is a colorless liquid easily miscible with most of the common solvents.

Anal. Calcd. for $C_8H_{18}N_4O$: C, 51.57; H, 9.74; N, 30.09. Found: C, 51.94; H, 9.74; N, 29.92.

The base forms salts with one equivalent of acid; 0.2920 g. was titrated with 0.1 *N* hydrochloric acid and methyl orange and consumed 15.85 cc. instead of 15.68 cc.

Hydrolysis of 1-(Trimethylguanyl)-1,3,3-trimethyl-2-thiourea (III).—A solution of 6.07 g. (0.03 mole) of the base in 60 cc. of water was refluxed for 2.25 hours. After cooling, the unreacted base was titrated with 1 *N* perchloric acid and phenolphthalein; 20.2 cc. was used which corresponds to about $^{2}/_{3}$ of the base started with, so that only about $^{1}/_{3}$ was hydrolyzed. On cooling to 0°, 3.7 g. of the perchlorate crystallized out. The mother liquor was evaporated under reduced pressure and the residue was extracted with benzene; 2.2 g. more of the perchlorate remained undissolved. Therefore, $^{2}/_{3}$ of the base was recovered in the form of the solid perchlorate (calcd. 6.08 g., found 5.9 g.).

The benzene extract was evaporated and then subjected to distillation under reduced pressure. About 1 g. (calcd. 1.02 g. from $^{1}/_{3}$ of the base used) of 1,1,3-trimethylurea distilled between 122–129° (12 mm.); the boiling point was not sharp and the product was not pure for reasons mentioned above. The residue was mainly 1,1,3-trimethyl-2-thiourea; 1.15 g. (calcd. 1.18 g. from $^{1}/_{3}$ of the base); after recrystallization from water, m.p. and mixed m.p. 87°.

When the aqueous solution of the 1-(trimethylguanyl)-1,3,3-trimethyl-2-thiourea is boiled for a longer period of time, such as 24 hours, all of the base disappears. However, in working up the reaction mixture the yields of the trimethylurea are only moderately greater than in the former experiment because of the formation of by-products. A formation of 1-(trimethylguanyl)-1,3,3-trimethylurea was not observed.

Reaction of 1,1,3-Trimethyl-2-thiourea with Mercuric Oxide in Water.—A solution of 7.09 g. (0.06 mole) of this thiourea in 120 cc. of water was treated at water-bath temperature with excess mercuric oxide; carbon dioxide was passed through the reaction mixture and the reaction was continued until a filtered sample did not blacken mercuric oxide on boiling. Mercuric sulfide and mercuric oxide were removed by filtration and the filtrate was evaporated under reduced pressure. The residue was dissolved in benzene, dried with potassium carbonate, and subjected to a fractional distillation under 10 mm. pressure. At 119°, 5 g. (calcd. 6.1 g.) pure 1,1,3-trimethylurea distilled over. (For purpose of comparison we prepared this urea also from methyl isocyanate and dimethylamine.[17] Solutions of dimethylamine and methyl isocyanate in ether were slowly mixed with cooling and with exclusion of moisture. Most of the urea crystallized immediately in form of hard crystals, the remainder on evaporation; yield quantitative.)

1,1,3-Trimethylurea (IV) forms rather hygroscopic, colorless crystals, m.p. 75–76°. It is already somewhat volatile on the water-bath; b.p. 127° (15.5 mm.). It is very soluble in water and alcohol, easily soluble in benzene and carbon tetrachloride, hardly in gasoline. There are no conspicuous basic properties. The aqueous solution shows a neutral reaction. Anhydrous hydrogen chloride precipitates a crystalline hydrochloride from a solution in anhydrous ether. Otherwise, we were unable to obtain a characteristic and difficultly soluble salt; neither nitric nor perchloric acid in water nor oxalic acid in ether nor picric acid in water, ether or benzene caused precipitation.[18]

Reaction of 1,1,3,3-Tetramethyl-2-thiourea[19] with Mercuric Oxide.—This thiourea remains unchanged when boiled with mercuric oxide in benzene under anhydrous conditions; no mercuric sulfide is formed. However, reaction does occur in aqueous alcohol.

A solution of 4 g. of this thiourea in 40 cc. of alcohol was mixed with a slurry of 20 g. freshly precipitated mercuric oxide in 40 cc. of water. This mixture was refluxed for 2 hours. Extraction with ether gave more than 90% of the calculated yield of 1,1,3,3-tetramethylurea, b.p. 174–177°.

Reaction of 1,3-Di-*n*-propyl-2-thiourea with Mercuric Oxide.—Chancel carried out this reaction in benzene and obtained di-*n*-propylcarbodiimide as the main product and 1,3-di-*n*-propylurea as a by-product. We refluxed a solution of 10 g. of the thiourea in 60 cc. of benzene with 40 g. of dry yellow mercuric oxide. The water formed during the reaction was removed by the aid of barium oxide which was placed in a filter-paper cup underneath the reflux condenser; thus the vapors and the condensed liquid were continuously dehydrated. Under such anhydrous conditions the reaction proceeds quite slowly and we found it advantageous not to complete it but to interrupt the experiment after six hours. Otherwise the yield suffers by polymerization of the diimide; yield of diimide about 60%, b.p. 53° (10 mm.).

In another experiment 20 g. of freshly precipitated mercuric oxide was slurried in 20 cc. of water and mixed with a solution of 4 g. of the thiourea in 20 cc. of ethanol. There was an immediate exothermic reaction which was completed by refluxing for half an hour. The mercuric compounds were filtered off and the filtrate was extracted with ether. The ether extract was evaporated and the residue was distilled under 10 mm. pressure. Only 0.3 g. of the diimide corresponding to 10% of the theoretical yield was obtained. The residue contained 2.5 g. of 1,3-di-*n*-propylurea corresponding to 70% of the theoretical yield.

In order to determine whether the urea formation in the last described experiment is due to reaction of diimide with water, a parallel experiment was carried out as follows. Again 20 g. of freshly precipitated mercuric oxide was slurried with 20 cc. of water and mixed with a solution of 3.1 g. of the diimide in 20 cc. of ethanol; it should be noted that the quantity of diimide used is equivalent to the quantity of the thiourea used in the former experiment. This mixture was again refluxed for half an hour and worked up as in the former experiment. This time 8 g. of unchanged diimide corresponding to 58% and only 1.0 g. of the urea corresponding to 28% of the theoretical yield were obtained.

Toward water alone the di-*n*-propylcarbodiimide is very unreactive, probably on account of its insolubility. 1.5 g. was refluxed with 25 cc. of water for 1.5 hours. The reaction product was extracted with ether and the ether extract gave on vacuum distillation 0.9 g. of unchanged diimide. The still residue was a thick sirup, evidently a polymer of the diimide. When this residue was extracted with hot water, only traces of the urea were obtained.

Also, toward alcohol the di-*n*-propylcarbodiimide is very unreactive. A solution of 1.2 g. in 20 cc. of absolute alcohol was refluxed for 1.5 hours. The reaction product was distilled under reduced pressure and gave 0.5 g. of unchanged diimide while the residue was again a viscous product, probably containing polymerized diimide.

However, the diimide reacts quite easily with amines as evidenced by the following experiment. 2.5 g. of di-*n*-propylcarbodiimide and 10 cc. of anhydrous diethylamine were refluxed for 2 hours and then kept for another 14 hours at room temperature. A fractional distillation gave no diimide; at 89–94° (10 mm.) 1.5 g. of a colorless oil went over which proved to be 1,1-diethyl-2,3-di-*n*-propylguanidine.

Anal. Calcd. for $C_{11}H_{25}N_3$: C, 66.26; H, 12.65. Found: C, 66.51; H, 12.73.

Di-(trimethylguanyl) Disulfide (VI).—The hydrobromide is prepared as follows. A solution of 2.4 g. (0.02 mole) of 1,1,3-trimethyl-2-thiourea in 48 cc. of chloroform was thoroughly cooled and agitated while a solution of 1.6 g. (0.01 mole) of bromine in 32 cc. of chloroform was slowly added. The bromine color disappeared immediately upon addition and an oil separated. By scratching with a glass rod this oil was gradually converted into a granular yellow product which was filtered by suction, washed with chloroform, and dried *in vacuo*; yield 3.6 g. (90%).

Since this hydrobromide proved to be very difficult to purify it was converted into a perchlorate. One gram of the hydrobromide was dissolved in a mixture of 5 cc. of glacial acetic acid and 1.5 cc. of 70% perchloric acid. Five cc. more glacial acetic acid was added to the yellow solution, and upon seeding and scratching, a few crystals made their appearance. Then 30 cc. of ether was added in small portions. The precipitated perchlorate was filtered off and washed with a mixture of 3 cc. of glacial acetic acid and 9 cc. of ether; yield 0.9 g. The perchlorate forms colorless crystals, m.p. 167° (decompn.). It detonates on heating but not on percussion. It dissolves in 10 parts of water with acid reaction.

Anal. Calcd. for $C_8H_{18}N_4S_2 + 2HClO_4$: C, 22.06; H, 4.63; N, 12.87; Cl, 16.29; S, 14.73. Found: C, 22.22; H, 4.74; N, 12.92; Cl, 16.65; S, 14.96.

This disulfide decomposes in acid medium on boiling and in alkaline medium even at room temperature. A solution of 4.35 g. (0.01 mole) of the perchlorate in 60 cc. of water was heated for 2 hours on the water-bath. 0.19 g. of sulfur separated (0.01 mole S would be 0.32 g.). The filtrate was concentrated to a volume of 25 cc. and cooled to 0°. 1.25 g. (0.01 mole equals 3.0 g.) of the perchlorate of 1-(trimethylguanyl)-1,3,3-trimethyl-2-thiourea (III) crystallized out and was identified by m.p. and mixed m.p. The mother liquor contained sulfuric acid and other products.

In order to investigate the hydrolysis in alkaline medium a solution of 13.05 g. (0.03 mole) of the perchlorate in 190 cc. of water was dropwise added to a solution of 5.05 g. (0.09 mole) of potassium hydroxide in 50 cc. of water with stirring and cooling. Potassium perchlorate crystallized out and was removed by filtration. The filtrate was concentrated on the water-bath to a volume of 20 cc.; there was an evolution of amines, the formation of which could already be noticed at low temperature. The concentrated solution was cooled in ice; it then precipitated a mixture of additional potassium perchlorate and 1.75 g. of 1,1,3-tri-

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[17] Franchimont, *Rec. trav. chim.*, **3**, 226 (1884).

[18] M. Schenck, *Z. physiol. Chem.*, **77**, 383 (1912), has described a chloroaurate.

[19] O. Billeter, *Ber.*, **43**, 1857 (1910), b.p. 123° (9 mm.).

methyl-2-thiourea which could be isolated by extraction of the dry mixture with warm benzene. The aqueous filtrate from the potassium perchlorate and the trimethylthiourea was now evaporated to dryness on the water-bath and left a solid residue which upon extraction with hot benzene gave an additional 4.15 g. of 1,1,3-trimethyl-2-thiourea. The total crude yield of this thiourea corresponded to 0.05 mole. The salt mixture which was left from the benzene extraction contained sulfate, thiosulfate, carbonate and a little perchlorate.

Bound Brook, N. J.

[Contribution from the Georgetown University Medical Center]

Hypotensive Agents. II.[1] Alicyclic Amino Alcohols[2a,b]

By Leonard M. Rice, Charles H. Grogan, C. F. Geschickter and E. Emmet Reid[3]

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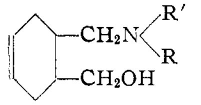
Nine new mono- and di-N-substituted aminomethyl-2-hydroxymethyl-*cis*-Δ^4-cyclohexenes have been prepared by the reduction of the corresponding tetrahydrophthalamic acids with excess lithium aluminum hydride. These compounds have been screened for hypotensive activity in dogs. Three new N-substituted-*cis*-Δ^4-tetrahydrophthalamic acids are reported.

Because of the widespread use of amino alcohol residues in many substances of high physiological activity, it was desirable to be able to obtain readily a series of these compounds in which the two carbon atoms holding the fixed and variable substituents are rigidly held in place. In the series of compounds prepared, two of the carbon atoms are part of an alicyclic ring system, *i.e.*, cyclohexene (I).



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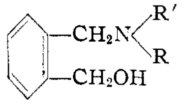
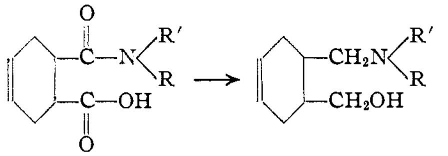


II

The substituent, R, in the compounds may represent hydrogen, an alkyl group or it may be a heterocyclic ring system. R′ may be the same as R, or it may represent a different, although similar type of group. It is of interest to note that these compounds may be considered the cyclic analogs of the dialkylaminobutyl alcohols.

By a rather involved sequence of reactions Funke and Rougeaux[4] have prepared a similar type of compound in which two of the carbon atoms are part of the benzene ring system (II).

We believe that the method used in our investigation offers a more direct synthesis for these types of compounds and is applicable to the phthalamic acids derived from other ring systems, such as phthalic, hexahydrophthalic and related compounds. We have prepared the alicyclic compounds in yields up to 92% by the reduction of 50 g. of the corresponding tetrahydrophthalamic acids with an excess of lithium aluminum hydride in anhydrous ether. Under the conditions in which we carried out our reactions all reductions were very smooth and when judged by the yields and the purity of materials obtained were relatively free of side reactions. The various hydroxymethyl-2-mono- or dialkylaminomethyl-*cis*-Δ^4-cyclohexenes prepared are shown in Table I. The several variations in R and R′ show the wide applicability and general nature of the reaction.



It may be noted that not only the amide group but, also, the carboxyl group is reduced. The structures of the reduction products were proven experimentally. From the compound in which R and R′ were ethyl, the *p*-nitrobenzoate ester was prepared. Subsequently, the formation of a methiodide and hydrochloride demonstrated the amine function. When this compound was hydrogenated at room temperature using platinum oxide catalyst one mole of hydrogen was absorbed. Ordinary tests for unsaturation, decolorization of aqueous permanganate and bromine in carbon tetrachloride, were also positive.

The tetrahydrophthalamic acids used in the present work, with the exception of those derived from diethylamine, isopropylamine and pyrrolidine, have been described in previous papers.[1,5] Three new tetrahydrophthalamic acids are listed in Table II.

Compound one, in Table I, on injection into dogs produced a moderate fall in blood pressure with a simultaneous increase in respiratory rate.

Experimental

N,N-Disubstituted-*cis*-Δ^4-tetrahydrophthalamic Acids.—The tetrahydrophthalamic acids were prepared by treating equimolecular quantities of the appropriate amine and tetrahydrophthalic anhydride. Benzene was used as a solvent to prevent loss of the low boiling amines, since the reaction is exothermic. When isopropylamine was used the reaction mixture was permitted to stand for several hours at room temperature with occasional stirring. When diethylamine and pyrrolidine were used the mixture was maintained at 100° for one hour after the benzene had boiled off. After cooling to room temperature, the products were recrystallized from suitable solvents.

Reductions: The Preparation of Diethylaminomethyl-2-hydroxymethyl-*cis*-Δ^4-cyclohexene.—The following general method was used for all of the lithium aluminum hydride

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[1] For the first paper in this series see L. M. Rice, A. Popovici, M. Rubin, C. F. Geschickter and E. E. Reid, This Journal, **74**, 3025 (1952).

[2] (a) Presented at the Meeting of the American Chemical Society, Medicinal Section, Atlantic City, N. J., September 15, 1952. (b) Supported in part by the Geschickter Fund for Medical Research, Inc.

[3] Professor Emeritus, Johns Hopkins University, Baltimore 18, Md.

[4] M. A. Funke and O. Rougeaux, *Bull. soc. chim.*, **12**, 1050 (1945).

[5] L. M. Rice, M. Rubin, J. Scholler and E. E. Reid, *J. Org. Chem.*, **16**, 501 (1951).