CCCXXXVII.—*Reactions of Thiosemicarbazones. Part III.*

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It has been found that the sodium derivative of acetonethiosemicarbazone reacts with ethyl, propyl, allyl, and butyl halides, also with ethyl ω-bromo-*o*-toluate, to give *S*-alkyl compounds of the type $CMe_2{:}N{\cdot}N{:}C(SR){\cdot}NH_2$. Whilst *S*-benzylthiosemicarbazide (J., 1922, **121**, 870) gave a monohydrochloride only and the benzylidene derivative was non-basic, the *S*-alkylthiosemicarbazides described in this paper are diacid bases giving dihydrochlorides of the type $NH_2{\cdot}N{:}C(SR){\cdot}NH_2,2HCl$, which were obtained from the parent compounds by hydrolysis with acid. The benzylidene derivatives are monoacid bases and were obtained as monohydrochlorides, $CHPh{:}N{\cdot}N{:}C(SR){\cdot}NH_2,HCl$. These acetone- and benzaldehyde-*S*-alkylthiosemicarbazones melt at much lower temperatures than the thiosemicarbazones themselves and it therefore appears probable that the thiosemicarbazones contain the group $-C{:}S$ and not $-C{\cdot}SH$.

Whilst the sodium derivative of acetonethiosemicarbazone reacts with esters of α-halogenated monobasic acids to produce cyclic compounds (J., 1923, **123**, 799), esters of β- and γ-halogenated monobasic acids behave quite differently. With ethyl β-chloro-*n*-butyrate and ethyl β-bromo-β-phenylpropionate, elimination of hydrogen halide as sodium halide occurred with formation of acetonethiosemicarbazone and the unsaturated ester, ethyl crotonate and ethyl cinnamate, respectively: ethyl γ-chloro-*n*-butyrate, ethyl γ-chloro-*n*-valerate, and ethyl γ-chloro*iso*hexoate reacted in a similar way. These reactions were carried out in alcoholic solution; in benzene suspension, no reaction took place even after several hours' boiling.

The interaction of thiosemicarbazones and primary amines, when hot, takes place according to the scheme $CRR'{:}N{\cdot}NH{\cdot}CS{\cdot}NH_2 + R''NH_2 = CRR'{:}N{\cdot}NH{\cdot}CS{\cdot}NHR'' + NH_3$, yielding δ-substituted thiosemicarbazones with the alkyl or aryl group attached, not to sulphur as in the preceding cases, but to nitrogen. The reaction is similar to that between semicarbazones and primary amines investigated by Borsche and others (*Ber.*, 1901, **34**, 4299; 1904, **37**, 3177; 1905, **38**, 83) and by workers in these laboratories; thiosemicarbazones, however, react much more slowly. Acetonethiosemicarbazone was chiefly employed, the amines being benzylamine, α-phenylethylamine, aniline, β-naphthylamine, and *n*-heptylamine. These δ-substituted thiosemicarbazones on hydrolysis with dilute hydrochloric acid yielded the corresponding thiosemicarbazide hydrochlorides, $NH_2{\cdot}NH{\cdot}CS{\cdot}NHR'',HCl$, with the exception of the β-naphthyl derivative, which suffered further decomposition; from these hydrochlorides the thiosemicarbazides were obtained. That these compounds contain the substituent in the δ-position is evident from the fact that acetonethiosemicarbazone and aniline yielded a product identical with a specimen of acetone-δ-phenylthiosemicarbazone prepared in the usual way; also δ-benzylthiosemicarbazide, synthesised from benzylthiocarbimide and hydrazine hydrate, $CH_2Ph{\cdot}NCS + NH_2{\cdot}NH_2 = CH_2Ph{\cdot}NH{\cdot}CS{\cdot}NH{\cdot}NH_2$ (a general reaction for the preparation of such substances), was identical with the compound obtained by us.

It is hoped to prepare the optically active δ-α-phenylethylthiosemicarbazides and to investigate possible applications of these compounds.

EXPERIMENTAL.

The Reaction between the Sodium Derivative of Acetonethiosemicarbazone and Alkyl Halides.—Procedure. Alcoholic solutions of acetonethiosemicarbazone and sodium ethoxide (equimolecular quantities) were mixed, boiled for 10 minutes, and cooled, the alkyl halide (1 mol.) was then added, and after 12 hours the mixture was heated under reflux for 15 minutes. The solution was then evaporated to dryness under reduced pressure and the acetone-*S*-alkylthiosemicarbazone was separated from the sodium halide and acetonethiosemicarbazone by dissolving it in ether; after evaporation of the ether, it was recrystallised from light petroleum. These compounds were readily soluble in the usual organic solvents.

Hydrolysis was effected by boiling under reflux for 15 minutes with 0·5*N*-hydrochloric acid; unchanged substance and any mercaptan formed were then removed by extraction with ether, the acid solution was concentrated under reduced pressure, and the *S*-alkylthiosemicarbazide dihydrochloride obtained in the solid form by keeping the residual syrup over sulphuric acid or phosphorus pentoxide in an evacuated desiccator. These dihydrochlorides were very hygroscopic and very soluble in water.

The benzylidene monohydrochloride was obtained by shaking an aqueous solution of the dihydrochloride with a little benzaldehyde, washing the product with a little ether, and then precipitating it from alcoholic solution by addition of ether. These compounds were readily soluble in alcohol and sparingly soluble or insoluble in benzene, ether, and water. The benzylidene derivative itself was obtained by treating the monohydrochloride with the necessary quantity of sodium carbonate in aqueous-alcoholic solution, evaporating the solution to dryness under reduced pressure, extracting the residue with ether, and, after evaporation of the ether, recrystallising the product from light petroleum. These derivatives were soluble in the usual organic solvents.

With ethyl bromide. Acetone-S-*ethylthiosemicarbazone* formed flat, transparent prisms, m. p. 55°, having a slight, unpleasant odour (yield, 65—70%) (Found: N, 26·4. $C_6H_{13}N_3S$ requires N, 26·4%). S-*Ethylthiosemicarbazide dihydrochloride* was obtained as a white powder after being kept for several weeks over phosphorus pentoxide; it melted indefinitely at about 60° (Found: HCl, 37·7. $C_3H_9N_3S,2HCl$ requires HCl, 38·0%). *Benzaldehyde*-S-*ethylthiosemicarbazone hydrochloride* formed fine, colourless needles, m. p. 195° (Found: N, 17·2. $C_{10}H_{13}N_3S,HCl$ requires N, 17·2%); *benzaldehyde*-S-*ethylthiosemicarbazone* formed flat prisms, m. p. 66° (Found: N, 20·2. $C_{10}H_{13}N_3S$ requires N, 20·3%).

With propyl bromide. Acetone-S-*propylthiosemicarbazone* distilled at 121°/7 mm.; the distillate solidified on cooling in carbon dioxide and ether and then melted at 26—27° (Found: N, 24·2. $C_7H_{15}N_3S$ requires N, 24·3%). S-*Propylthiosemicarbazide dihydrochloride* was a thick syrup which would not solidify (Found: HCl, 35·3. $C_4H_{11}N_3S,2HCl$ requires HCl, 35·4%). *Benzaldehyde*-S-*propylthiosemicarbazone hydrochloride* formed lustrous needles, m. p. 209° (Found: N, 16·3. $C_{11}H_{15}N_3S,HCl$ requires N, 16·3%); *benzaldehyde*-S-*propylthiosemicarbazone* formed short prisms, m. p. 54° (Found: N, 18·9. $C_{11}H_{15}N_3S$ requires N, 19·0%).

With allyl iodide. Acetone-S-*allylthiosemicarbazone* crystallised in flat, transparent prisms (yield, 75%), m. p. 51° (Found: N, 24·5. $C_7H_{13}N_3S$ requires N, 24·6%). S-*Allylthiosemicarbazide di-*

hydrochloride, a crystalline mass, melted at 75° (Found : HCl, 35·4. $C_4H_9N_3S,2HCl$ requires HCl, 35·9%). *Benzaldehyde*-S-*allylthiosemicarbazone hydrochloride* formed lustrous plates, m. p. 190° (Found : HCl, 14·2; N, 16·2. $C_{11}H_{13}N_3S,HCl$ requires HCl, 14·3; N, 16·4%); *benzaldehyde*-S-*allylthiosemicarbazone* formed transparent, rhombic prisms, m. p. 42° (Found : N, 19·0. $C_{11}H_{13}N_3S$ requires N, 19·2%).

With n-*butyl bromide. Acetone*-S-*butylthiosemicarbazone*, a colourless oil of b. p. 146°/16 mm., did not solidify when strongly cooled and became slightly coloured on standing (Found: N, 22·4. $C_8H_{17}N_3S$ requires N, 22·5%). S-*Butylthiosemicarbazide dihydrochloride* formed a crystalline mass, m. p. 100—101° (decomp.) (Found: HCl, 33·1; N, 19·1. $C_5H_{13}N_3S,2HCl$ requires HCl, 33·2; N, 19·1%). *Benzaldehyde*-S-*butylthiosemicarbazone* was obtained as a viscid oil which solidified on cooling in ether and carbon dioxide; the solid, after being pressed on porous tile, crystallised from light petroleum in transparent prisms, m. p. 50° (Found: N, 17·8. $C_{12}H_{17}N_3S$ requires N, 17·9%).

*With ethyl ω-bromo-*o-*toluate. Acetone*-S-o-*carbethoxybenzylthiosemicarbazone*, $CMe_2{:}N{\cdot}N{:}C(S{\cdot}CH_2{\cdot}C_6H_4{\cdot}CO_2Et){\cdot}NH_2$, formed pale yellow, transparent prisms, m. p. 66°, from light petroleum containing a little benzene; yield, 70% (Found: N, 14·3. $C_{14}H_{19}O_2N_3S$ requires N, 14·3%). S-o-*Carbethoxybenzylthiosemicarbazide dihydrochloride*, $NH_2{\cdot}N{:}C(S{\cdot}CH_2{\cdot}C_6H_4{\cdot}CO_2Et){\cdot}NH_2,2HCl$, a crystalline mass, melted at 125—130° (decomp.) (Found: HCl, 22·2; N, 12·7. $C_{11}H_{15}O_2N_3S,2HCl$ requires HCl, 22·4; N, 12·9%). *Benzaldehyde*-S-o-*carbethoxybenzylthiosemicarbazone hydrochloride* formed lustrous, white plates, m. p. 115°, containing $1H_2O$ (Found: HCl, 8·7; N, 10·5. $C_{18}H_{19}O_2N_3S,HCl,H_2O$ requires HCl, 9·2; N, 10·6%); *benzaldehyde*-S-o-*carbethoxybenzylthiosemicarbazone* crystallised from light petroleum, containing a little benzene, in short, transparent prisms, m. p. 74° (Found: N, 12·2. $C_{18}H_{19}O_2N_3S$ requires N, 12·3%).

Interaction of Thiosemicarbazones and Primary Amines when Hot.—Procedure. With one exception (acetophenonethiosemicarbazone, as noted below), acetonethiosemicarbazone was used throughout. Equimolecular quantities of the reactants were heated under reflux in toluene solution or suspension at 125—130° until evolution of ammonia ceased; if necessary, the solution was then evaporated under reduced pressure. Hydrolysis was effected by refluxing with 6% hydrochloric acid, followed, if necessary, by evaporation under reduced pressure.

With benzylamine (20 hours). On cooling, *acetone-δ-benzylthiosemicarbazone* and a little unchanged substance separated. The product was crystallised from alcohol (prismatic needles) and then from benzene (plates); it melted at 147—148°, had a slightly creamy tint, and was insoluble in ether and light petroleum (yield, 65%) (Found: N, 18·9; S, 14·4. $C_{11}H_{15}N_3S$ requires N, 19·0; S, 14·5%). After hydrolysis (1 g.; 20 c.c. of acid; 20 minutes) the solution, which contained acetone as shown by distillation, was filtered from a small amount of insoluble matter and evaporated after removal of the crystals which separated on cooling. The residue and the crystals were united and extracted with absolute alcohol to remove hydrazine hydrochloride; the alcoholic extract on cooling deposited *δ-benzylthiosemicarbazide hydrochloride* in colourless plates, of m. p. 189° (decomp.) after recrystallisation (yield, 87%). It was insoluble in ether and benzene, but soluble in warm water (Found: Cl, 16·2. $C_8H_{11}N_3S,HCl$ requires Cl, 16·3%). The formation of hydrazine hydrochloride and an odour of cress (due probably to thiocarbimide) after the hydrolysis showed that some decomposition had occurred. *δ-Benzylthiosemicarbazide* was obtained by boiling 0·8 g. of the hydrochloride with 20 c.c. of water for 5 minutes (an odour of thiocarbimide was apparent); the base deposited on cooling was recrystallised from absolute alcohol and then from benzene. It formed glistening leaves (yield, 76%), m. p. 130°, insoluble in light petroleum and slightly soluble in ether and water. The aqueous solution gave a white precipitate with silver nitrate (Found: N, 23·2. $C_8H_{11}N_3S$ requires N, 23·2%). The *benzylidene* derivative, prepared from benzaldehyde and the base or the hydrochloride in aqueous-alcoholic solution, crystallised from light petroleum–alcohol in long, matted needles, m. p. 133—134° (Found: N, 15·7. $C_{15}H_{15}N_3S$ requires N, 15·6%). δ-Benzylthiosemicarbazide, identical with the specimen just described (mixed m. p. test), was prepared in good yield by mixing equimolecular quantities of benzylthiocarbimide and hydrazine hydrate in ice-cold alcoholic solution. Heat was developed and the substance, which soon separated, was recrystallised from alcohol (tabular prisms) and then from benzene (leaves); both forms melted at 130°.

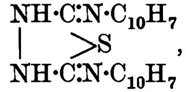
Acetophenonethiosemicarbazone and benzylamine reacted much more slowly (42 hours). *Acetophenone-δ-benzylthiosemicarbazone*, which separated on cooling (a little more was obtained by evaporation), crystallised from benzene as a mass of fine, colourless needles, m. p. 157—159°, and from alcohol in colourless plates, m. p. 160—161° (yield, 85%) (Found: N, 14·9; S, 11·2. $C_{16}H_{17}N_3S$ requires N, 14·8; S, 11·3%). The hydrolysis (1 g.; 20 c.c. of acid; 4½ hours), which was slow and incomplete, gave acetophenone and δ-benzylthiosemicarbazide hydrochloride besides hydrazine hydrochloride and benzylthiocarbimide.

With α-phenylethylamine (35½ hours). The solution after filtration from a small quantity of insoluble matter and evaporation left a viscid oil which set to a transparent resin on cooling. The solution of this in a little hot absolute alcohol deposited crystals of *acetone-δ-α-phenylethylthiosemicarbazone* after cooling and scratching; recrystallisation from alcohol gave colourless, tabular prisms, m. p. 89—90° (yield, 66%) (Found: N, 18·0; S, 13·8. $C_{12}H_{17}N_3S$ requires N, 17·9; S, 13·6%). The substance was fairly soluble in benzene, sparingly soluble in light petroleum, and could be crystallised from a mixture of these solvents. The solution obtained by hydrolysis (1 g.; 20 c.c. of acid; 17 minutes) contained acetone and had an odour of thiocarbimide; a small quantity of an oil which was deposited on cooling was removed. The residue obtained by evaporation of the solution was dissolved in hot alcohol–benzene, and concentration in a vacuum then gave small, colourless plates of *δ-α-phenylethylthiosemicarbazide hydrochloride*, m. p. 157—158° (yield, 80%) (Found: Cl, 15·5. $C_9H_{13}N_3S,HCl$ requires Cl, 15·3%). The *benzylidene* derivative, prepared in the usual way, tended to separate as an oil but formed colourless plates, m. p. 128—129°, from light petroleum (Found: N, 15·0. $C_{16}H_{17}N_3S$ requires N, 14·8%). An aqueous solution of the hydrochloride was boiled with barium carbonate, and the residue obtained by evaporation of the filtrate under reduced pressure was extracted with benzene. This extract, after drying and spontaneous evaporation in a vacuum, gave an oil which solidified on standing; recrystallisation from alcohol–light petroleum gave a crystalline mass of *δ-α-phenylethylthiosemicarbazide*, m. p. 84°, which was extremely soluble in alcohol and sparingly soluble in light petroleum (Found: N, 21·6. $C_9H_{13}N_3S$ requires N, 21·5%).

With aniline (20 hours at 120—125° and 17 hours at 130—135°). Some hydrogen sulphide was evolved and a small amount of insoluble matter separated. After cooling and filtration, the toluene was evaporated, leaving a viscid oil which solidified on cooling and scratching. Recrystallisation from alcohol gave plates (yield, only 30%) of acetone-δ-phenylthiosemicarbazone, which was identified by comparison with an authentic specimen. The insoluble matter after recrystallisation from alcohol gave glistening leaves, softening at about 235° and melting at 245°. The quantity obtained was too small for identification.

With β-naphthylamine (18 hours). An appreciable quantity of an insoluble substance was formed, and hydrogen sulphide and ammonia were evolved. The substance was collected and after extraction with boiling absolute alcohol was crystallised from alcohol–pyridine. The colourless crystals softened and darkened at about 266° and melted at about 275° (Found: N, 15·5%).

This substance may be *di-β-naphthyliminotetrahydrothiodiazole* ($C_{22}H_{16}N_4S$ requires N, 15·2%) produced from acetone-δ-β-naphthylthiosemicarbazone by the reaction $2CMe_2{:}N{\cdot}NH{\cdot}CS{\cdot}NH{\cdot}C_{10}H_7 = CMe_2{:}N{\cdot}N{:}CMe_2 + C_{10}H_7{\cdot}NH{\cdot}CS{\cdot}NH{\cdot}NH{\cdot}CS{\cdot}NH{\cdot}C_{10}H_7$, the hydrazinedithiocarbo-β-naphthylamide then giving di-β-naphthyliminotetrahydrothiodiazole,



$$\begin{matrix} NH{\cdot}C{:}N{\cdot}C_{10}H_7 \\ | \quad >S \\ NH{\cdot}C{:}N{\cdot}C_{10}H_7 \end{matrix}$$

, and hydrogen sulphide (compare Busch and Schmidt, *Ber.*, 1913, **46**, 2241, on the corresponding phenyl derivatives; also Pulvermacher, *Ber.*, 1894, **27**, 616). The toluene solution on cooling in ice deposited a substance which, after repeated recrystallisation from alcohol, benzene, and finally from alcohol to remove a little insoluble matter, gave yellow plates (yield, 60%) of *acetone-δ-β-naphthylthiosemicarbazone*, m. p. 150—151°; from benzene it separated apparently amorphous, m. p. 137—138° (Found: N, 16·4. $C_{14}H_{15}N_3S$ requires N, 16·3%). The substance was easily soluble in hot alcohol and hot benzene. Hydrolysis with acid gave acetone, hydrazine hydrochloride, a small amount of an unidentified hydrochloride which softened at 175° and decomposed at 190°, and also a substance insoluble in water and alcohol. The last substance separated from alcohol–pyridine as a white, apparently amorphous powder, which began to decompose at about 220° and finally melted at 252°; it became slightly pink on standing (Found: N, 13·7. $C_{22}H_{18}N_4S_2$ requires N, 13·9%). It is believed to be *hydrazinedithiocarbo-β-naphthylamide*, formed by decomposition of δ-β-naphthylthiosemicarbazide hydrochloride: $2(NH_2{\cdot}NH{\cdot}CS{\cdot}NH{\cdot}C_{10}H_7,HCl) =$

$$C_{10}H_7{\cdot}NH{\cdot}CS{\cdot}NH{\cdot}NH{\cdot}CS{\cdot}NH{\cdot}C_{10}H_7 + N_2H_4,2HCl.$$

With n-*heptylamine* (21¼ hours). The toluene solution on evaporation left a viscid oil which crystallised on cooling. On dissolving this in hot absolute alcohol and cooling the solution in ice, *acetone-δ-heptylthiosemicarbazone* separated, and recrystallisation from light petroleum gave silvery, glistening plates (yield, 65%), m. p. 75° (Found: N, 18·4. $C_{11}H_{23}N_3S$ requires N, 18·3%). The substance was easily soluble in benzene, ether, and carbon tetrachloride, and moderately or slightly soluble in other organic solvents. The solution obtained by hydrolysis (1 g.; 20 c.c. of acid; 10 minutes) contained acetone, and on cooling, *δ-heptylthiosemicarbazide hydrochloride* separated. This, on recrystallisation from light petroleum containing a little alcohol, formed silvery, glistening leaves, m. p. 135—136°, which were easily soluble in hot water, very soluble in alcohol, and insoluble in other common solvents (Found: N, 18·5. $C_8H_{19}N_3S,HCl$ requires N, 18·6%). The *benzylidene* derivative formed matted needles, m. p. 73°, from light petroleum (Found:

N, 15·3. $C_{15}H_{23}N_3S$ requires N, 15·2%). *δ-Heptylthiosemicarbazide*, which formed silky, glistening, acicular plates, m. p. 54—55°, was prepared by boiling the hydrochloride with sodium carbonate in aqueous-alcoholic solution; the solution was filtered from the excess of sodium carbonate and allowed to evaporate spontaneously in a vacuum; extraction of the residue with hot light petroleum and recrystallisation from the same solvent gave the desired product (Found : N, 22·3. $C_8H_{19}N_3S$ requires N, 22·2%).

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