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Methyl-substituted Semicarbazides

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The entire series (17 compounds) of semicarbazides substituted with one or more methyl groups has been prepared. The 1-methylsemicarbazides unsubstituted in the 2-position were prepared from 1-*tert*-butoxycarbonyl-1-methylhydrazine. The 1-methylsemicarbazide prepared by this unambiguous method proved to be identical with a methylsemicarbazide obtained earlier from the methyl derivative of camphorquinone cyanohydrazone. In some attempts to prepare 1,4,4-trimethylsemicarbazide the main product was 1,5-dimethylcarbonohydrazide.

In connection with NMR and IR spectroscopic studies of semicarbazides, thiosemicarbazides and selenosemicarbazides [1] the complete series derived from semicarbazide (*1*) by substitution with one or more methyl groups has been prepared. Among the 17 possible compounds of this type only the following were known with certainty: 2-methylsemicarbazide,[2] 4-methylsemicarbazide,[3–5] 1,2-dimethylsemicarbazide,[6] 2,4-dimethylsemicarbazide,[7] and 4,4-dimethylsemicarbazide.[7] 1,1-Dimethylsemicarbazide has been described as an intermediate [8] but no melting point or other details were given. A compound alleged to be 1-methylsemicarbazide was obtained by Foster and Saville [9] in a complicated reaction from the methyl derivative of camphorquinone cyanohydrazone but there has been some doubt as to the identity of the product; the compound is marked with a question mark in Beilstein's handbook.

$$\overset{4}{H_2N}-CO-\overset{2}{NH}-\overset{1}{NH_2} \qquad 1$$

Some of the methods we have used for the preparation of hitherto inaccessible thiosemicarbazides [10] and selenosemicarbazides [11] have also been used for the preparation of the missing methyl-substituted semicarbazides. Thus, 1-methylsemicarbazide was prepared in an unambiguous way analogous to one of the methods used for the preparation of 1-methylthiosemicarbazide:[10]

$$H^2N-N(CH_3)CO_2Bu^t + Bu^tNCO \longrightarrow \underset{2}{}$$

$$Bu^tNH-CO-NH-N(CH_3)CO_2Bu^t \xrightarrow{HCl}$$

$$H_2N-CO-NH-NHCH_3$$

By means of mixed melting point, IR and NMR spectra the semicarbazide prepared in this way proved identical with the semicarbazide prepared from camphorquinone cyanohydrazone. Thus Foster and Saville's assignment of the structure of 1-methylsemicarbazide is confirmed.

1,4-Dimethylsemicarbazide and 1,4,4-trimethylsemicarbazide were prepared by reaction of 1-methyl-1-*tert*-butoxycarbonylhydrazine [10] (*2*) with methyl isocyanate and dimethylcarbamoyl chloride, respectively. The *tert*-butoxycarbonyl group was eliminated by treatment with concentrated hydrochloric acid.

The other methyl-substituted semicarbazides were prepared in more conventional ways by reaction of hydrazine or methylsubstituted hydrazines with cyanic acid, methyl isocyanate, or dimethylcarbamoyl chloride.

An attempt was made to prepare semicarbazides unsubstituted in the 4-position by elimination of the *tert*-butyl group from 4-*tert*-butylsemicarbazides. The latter are obtained in almost quantitative yields from hydrazines and *tert*-butyl isocyanate. However, with the exception of 1-methylsemicarbazide mentioned above, none of these semicarbazides could be obtained by this method. The corresponding selenosemi-

carbazides [11] and thiosemicarbazides [10] were obtained in good and low yields, respectively, by elimination of a *tert*-butyl group in the 4-position. This difference in behaviour is not unexpected because the higher basicity of the CO group as compared to the CSe and CS groups render the CO-NH group more susceptible to acid catalyzed cleavage.

1,1,2-Trimethylsemicarbazide, 1,1,2,4- and 1,2,4,4-tetramethylsemicarbazides, and pentamethylsemicarbazide form colourless liquids which were distilled *in vacuo*. The other methyl-substituted semicarbazides form colourless crystals. Great difficulties were, however, encountered in preparing 1,4,4-trimethylsemicarbazide. In our first attempts to prepare this semicarbazide it was only possible to isolate 1,5-dimethylcarbonohydrazide (*3*) together with tetramethylurea. These compounds originate in a disproportionation reaction of the *tert*-butoxycarbonyl derivative of 1,4,4-trimethylsemicarbazide:

$$2Me_2N-CO-NH-NMeCO_2Bu^t \longrightarrow$$

$$Me_2N-CO-NMe_2 + OC(NH-NMeCO_2Bu^t)_2$$

On addition of concentrated hydrochloric acid to the reaction product the dihydrochloride of the hitherto unknown carbonohydrazide (*3*) crystallized.

$$CH_3NH-NH-CO-NH-NHCH_3 \qquad 3$$

All the methyl-substituted semicarbazides are readily soluble in alcohols and in water (some of them are very hygroscopic). They all form blue Cu(II) complexes with aqueous copper(II) salts but differ when the solution is made alkaline: 1-methyl-, 1,4-dimethyl-, and 1,4,4-trimethylsemicarbazide reduce Cu(II) (yellow precipitate of Cu_2O, aq); those disubstituted in the 4-position (or monosubstituted with *tert*-butyl) do not form complexes in alkaline solution [precipitate of $Cu(OH)_2$]; the others give a violet solution (biuret reaction). Unlike 1-methylsemicarbazide, 1,5-dimethylcarbonohydrazide forms a Cu(II) complex with a very intense purple colour in alkaline solution.

The 1-methylsemicarbazides unsubstituted in the 2-position become faintly yellow when exposed to air, possibly because of oxidation to the corresponding azo compounds. The 1,4,4-derivative decomposes rapidly, even when kept in a refrigerator.

EXPERIMENTAL

Satisfactory C, H, N, and Cl analyses have been obtained for all compounds described. The melting points are corrected.

1-Methylsemicarbazide, $C_2H_7N_3O$. A solution of *tert*-butyl isocyanate (4.0 g) and *2* [10] (7.3 g) in ether (50 ml) was kept at room temperature overnight. On addition of light petroleum and cooling 6.5 g of colourless crystals of 1-*tert*-bytoxycarbonyl-4-*tert*-butylmethylsemicarbazide, $C_{11}H_{23}N_3O_3$, separated. M.p. 130 °C after recrystallization from ether/light petroleum.

On addition of 3 ml of conc. hydrochloric acid to 3.0 g of this product it dissolved with the evolution of CO_2. When the effervescence had stopped 1 ml of conc. hydrochloric acid was added and the solution heated to boiling for 2 min. The solution was cooled in ice and made alkaline with solid Na_2CO_3. Ethanol (10 ml) was added and the mixture was heated to boiling and filtered. The filtrate was evaporated to dryness *in vacuo*, the residue was extracted with abs. ethanol, and the ethanol solution was evaporated to dryness and the residue extracted with boiling benzene. On cooling the benzene solution yielded 0.20 g (20 %) of colourless crystals of the title compound, m.p. 94 – 95 °C (chloroform). This semicarbazide was also prepared from camphorquinone cyanohydrazone following the procedure described by Foster and Saville.[9]

The other 4-unsubstituted semicarbazides were prepared by the following general procedure: The appropriate hydrazine was dissolved in the equivalent amount of 4 M hydrochloric acid and the equivalent amount of aqueous NaOCN or KOCN was added. The solution was heated to boiling for 15 min, maintaining a pH value of 8 – 9, and then evaporated to dryness. The residue was carefully dried *in vacuo* and extracted with abs. ethanol. The solvent was evaporated and the residue was recrystallized from the solvents indicated below.

1,1-Dimethylsemicarbazide, $C_3H_9N_3O$, yield 62 %, m.p. 141 – 142 °C (benzene).

1,1,2-Trimethylsemicarbazide, $C_4H_{11}N_3O$, yield 74 %, m.p. 50 – 51 °C (ether/light petroleum).

1,4-Dimethylsemicarbazide, $C_3H_9N_3O$. Methyl isocyanate (3.5 ml) and *2* (9.0 g) in ether/light petroleum yielded 10.6 g of 1-*tert*-butoxycarbonyl-1,4-dimethylsemicarbazide, $C_8H_{17}N_3O_3$ (m.p. 114 – 115 °C, recryst. ether/pentane). The hydrochloride of 1,4-dimethylsemicarbazide, $C_3H_{10}ClN_3O$ (m.p. 125 °C) crystallized by addition of ethanol and ether to a solution of the *tert*-butoxycarbonyl derivative (10.0 g) in conc. hydrochloric acid (10 ml). An additional crop was obtained by evaporating the mother liquor to dryness and recrystallizing the residue from ethanol/ether. Total yield 86 %. The free base was prepared by adding the equivalent amount of aqueous KOH to the hydrochloride, evaporating to dryness and extracting the residue with ether, yield 60 %, m.p. 83 – 84 °C (ether). In

our first preparation of this semicarbazide it could not be obtained crystalline in this way. It was distilled *in vacuo* (b.p. 130 – 131 °C/0.35 mmHg) but still formed a glass on cooling. However, when the latter was heated at 50 °C *in vacuo* for 1 h it was transformed into a crystalline mass.

The other 4-monosubstituted semicarbazides were prepared from the appropriate hydrazine and methyl isocyanate. For the preparation of 2,4-dimethylsemicarbazide and 1,1,4-trimethylsemicarbazide a solution of methyl isocyanate (0.05 mol) in ether was added slowly with stirring to a solution of the hydrazine (0.05 mol) in ether. The reaction was instantaneous and exothermic, the semicarbazides separating as crystalline compounds in almost quantitative yields when light petroleum was added. For the preparation of 1,2,4-trimethylsemicarbazide and 1,1,2,4-tetramethylsemicarbazide it was found advantageous to use benzene as solvent. After evaporation of the benzene these semicarbazides were isolated by distillation *in vacuo*. For the preparation of 4-methylsemicarbazide a solution of methyl isocyanate in benzene was added to a solution of anhydrous hydrazine in ethanol. An insoluble precipitate of 1,2-bis(methylcarbamoyl)hydrazine [7] (m.p. 260 °C) separated. The semicarbazide was isolated from the filtrate by evaporation of the solvent.

1,1,4-Trimethylsemicarbazide, $C_4H_{11}N_3O$, yield 95 %, m.p. 118 – 119 °C (benzene). *1,2,4-Trimethylsemicarbazide*, $C_4H_{11}N_3O$, yield 75 %, b.p. 100 – 101 °C/0.3 mmHg. *1,1,2,4-Tetramethylsemicarbazide*, $C_5H_{13}N_3O$, yield 80 %, b.p. 68 – 69 °C/1 mmHg.

The following 4-*tert*-butylsemicarbazides were prepared from the appropriate hydrazine and *tert*-butyl isocyanate in ether. The reaction is slower than with methyl isocyanate and the solutions were kept for 24 h at room temperature. The residues obtained by evaporation of the ether were recrystallized from pentane.

4-tert-*Butyl-2-methylsemicarbazide*, $C_6G_{15}N_3O$, m.p. 92 – 93 °C. 4-tert-*Butyl-1,2-dimethylsemicarbazide*, $C_7H_{17}N_3O$, m.p. 60 – 61 °C. 4-tert-*Butyl-1,1,2-trimethylsemicarbazide*, $C_8H_{19}N_3O$, m.p. 36 – 37 °C. The *tert*-butyl group was eliminated as *tert*-butyl chloride when these compounds were heated with conc. hydrochloric acid but the expected semicarbazide unsubstituted in the 4-position could not be isolated.

1,4,4-Trimethylsemicarbazide, $C_4H_{11}N_3O$. After some unsuccessful attempts (see below) this semicarbazide was obtained in the following way: Dimethylcarbamoyl chloride (2.2 g; 23 mmol) was added to a solution of *2* (6.0 g; 44 mmol) in ether (50 ml). On standing a precipitate of the hydrochloride of the hydrazine, $C_6H_{15}ClN_2O_2$ (m.p. *ca* 130 °C, decomp.) slowly separated. After 1 month (shorter reaction time resulted in correspondingly lower yields) the filtered solution was purified by column chromatography (Aluminium Oxide W 200 neutral). The main fraction yielded 1.2 g (24 %) of colourless crystals of 1-*tert*-butoxycarbonyl-1,4,4-trimethylsemicarbazide, $C_9H_{19}N_3O_3$, with m.p. 107 – 108 °C (ether/pentane). Treatment of 500 mg of this compound with 0.5 ml conc. hydrochloric acid, addition of ethanol and benzene, filtration and evaporation yielded 300 mg (85 %) of the hydrochloride of 1,4,4-trimethylsemicarbazide, $C_4H_{12}ClN_3O$. M.p. 154 – 157 °C (ethanol/ether). To obtain the free base the equivalent amount of methanolic KOH was added to the hydrochloride, the filtered solution was evaporated to dryness and the residue extracted with ether. Concentration of the ether solution to initiate crystallization followed by the addition of pentane gave a 62 % yield of the semicarbazide. M.p. 79 – 81 °C.

In the first attempts to prepare this semicarbazide equivalent amounts of *2* and dimethylcarbamoyl chloride were used together with an excess of triethylamine in ether. In this case the reaction was much faster. After 3 – 4 days the calculated amount of triethylammonium chloride had separated. The oily product, remaining after removal of ether and excess triethylamine, could not be induced to crystallize and was therefore treated with conc. hydrochloric acid in the usual way. On evaporation of an ethanol/benzene solution to remove water, followed by addition of ethanol/ether a colourless crystalline compound was obtained. This was identified by analysis and its NMR spectrum (D_2O, δ 3.0, s) as the dihydrochloride of 1,5-dimethylcarbonohydrazide, $C_3H_{12}Cl_2N_4O$ (m.p. 154 – 156 °C). Yields corresponded to up to 50 % conversion of dimethylcarbamoyl chloride. The same compound was formed from *2* and carbonyl chloride. The mother liquor from the hydrochloride was neutralized and distilled with ethanol/benzene until water had been removed and the filtered solution was then distilled *in vacuo*. A fraction boiling at 46 – 47 °C/0.35 mmHg was identified as tetramethylurea. A fraction boiling at 110 – 120 °C/0.25 mmHg contained a significant amount of 1,4,4-trimethylsemicarbazide, according to its NMR spectrum.[1] However, attempts to purify it to give a crystalline semicarbazide failed.

The free *1,5-dimethylcarbonohydrazide*, $C_3H_{10}N_4O$, was prepared by addition of the equivalent amount of ethanolic KOH to the hydrochloride, evaporation of the filtered solution and recrystallization of the residue from benzene. Yield 80 %. M.p. 100 – 101 °C. NMR spectrum ($CDCl_3$): δ 2.60 (s, CH_3); 3.84 (s, N^1-H); 7.00 (s, N^2-H).

The other 4,4-dimethylsemicarbazides – except 4,4-dimethylsemicarbazides which was prepared according to Vogelesang [7] – were prepared by the following procedure: A solution of dimethylcarbamoyl chloride (0.05 mol) in ether (50 ml) was added with cooling and stirring to a solution of the hydrazine (0.05 mol) and triethylamine (20 ml) in ether (50 ml). The mixture was kept for 2 h at room temperature or, for the preparation of pentamethylsemi-

carbazide, heated at reflux for 2 h. The solutions were filtered from Et_3NHCl; ether and excess triethylamine were removed *in vacuo*. The residue was recrystallized, or when liquid, distilled *in vacuo*.

2,4,4-Trimethylsemicarbazide, $C_4H_{11}N_3O$, yield 80 %, m.p. 47–48 °C (ether). *1,1,4,4-Tetramethylsemicarbazide*, $C_5H_{13}N_3O$, yield 62 %, m.p. 81–82 °C (ether). *1,2,4,4-Tetramethylsemicarbazide*, $C_5H_{13}N_3O$, yield 60 %, b.p. 48–50 °C/1 mmHg. *1,1,2,4,4-Pentamethylsemicarbazide*, $C_6H_{15}N_3O$, yield 40 %, b.p. 80–82 °C/12 mmHg.

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