327. *Compounds related to Thiosemicarbazide. Part VII. Benzylthiosemicarbazides.*

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Examples of 1-, 2-, and 4-benzylthiosemicarbazides have been prepared. These compounds were distinguished by their behaviour towards ferric chloride: 1-benzylthiosemicarbazides gave benzaldehyde thiosemicarbazones, 2-benzylthiosemicarbazide gave benzaldehyde 2-benzylthiosemicarbazone, and 4-benzylthiosemicarbazide gave benzyl *iso*thiocyanate. The last reaction was general for a number of 4- and 2 : 4-substituted thiosemicarbazides.

It is known that benzaldehyde semicarbazones are reduced by mild reducing agents to 1-benzylsemicarbazides (Kessler and Rupe, *Ber.*, 1912, **45**, 26), and a number of benzaldehyde thiosemicarbazones (I; R = H, *p*-OH, *p*-OMe, *p*-NMe_2 or *p*-SO_2Et) was readily reduced by sodium amalgam to give the corresponding 1-*benzylthiosemicarbazides* (II). The same reaction also proceeded smoothly with the thiosemicarbazones of acetophenone and *p*-methoxyacetophenone, giving the corresponding 1-1′-*phenylethylthiosemicarbazides*. It was noted that the melting point of 1-benzylthiosemicarbazide itself (155°) was the same as that which has been recorded by Cattelain (*Compt. rend.*, 1939, **207**, 799; *Bull. Soc. chim.*, 1940, **7**, 791) for the 2-isomer (III; R = H), and as the method used by this author (isomerisation of the thiocyanate salt of benzylhydrazine by heat) is not unambiguous, attempts were made to repeat this preparation in order to compare the product with that obtained by reduction of the thiosemi-

carbazone. The product obtained by heating the thiocyanate of benzylhydrazine as described in the papers cited was difficult to purify and it was found preferable to heat benzylhydrazine hydrochloride with dry ammonium thiocyanate in absolute alcohol. (Heating under aqueous conditions also gave a product which was difficult to purify.) The melting point of the compound obtained when using alcohol was raised by crystallisation to 171°, but this compound must be the same as that isolated by Cattelain as its benzylidene and *p*-methoxybenzylidene derivatives had the m. p.s recorded by him. By reaction of *p*-methoxybenzylhydrazine with ammonium thiocyanate under similar conditions, the *compound* (III; R = *p*-OMe) was obtained; this was also distinct from the isomer obtained by reduction of *p*-methoxybenzaldehyde thiosemicarbazone. 4-Benzyl- and 4-p-*methoxybenzyl-thiosemicarbazide* (IV; R = H or *p*-OMe) were prepared by a route which has been used for the first of these by Baird, Burns, and Wilson (*J.*, 1927, 2531). When (III; R = H) or (IV; R = H) in dilute acids was shaken with a solution of benzaldehyde in alcohol, the corresponding thiosemicarbazone was at once precipitated. Nothing separated when (II; R = H) was treated in the same way.

$R{\cdot}C_6H_4{\cdot}CH{:}N{\cdot}NH{\cdot}CS{\cdot}NH_2$ (I.)

$R{\cdot}C_6H_4{\cdot}CH_2{\cdot}NH{\cdot}NH{\cdot}CS{\cdot}NH_2$ (II.)

$R{\cdot}C_6H_4{\cdot}CH_2{\cdot}\overset{\displaystyle NH_2}{\underset{|}{N}}{\cdot}CS{\cdot}NH_2$ (III.)

$NH_2{\cdot}NH{\cdot}CS{\cdot}NH{\cdot}CH_2{\cdot}C_6H_4R$ (IV.)

Oxidation of 1-benzylthiosemicarbazides (II; R = H, *p*-OMe, or *p*-SO_2Et) in dilute acetic acid with ferric chloride gave the corresponding thiosemicarbazones. With the first compound, 2-amino-5-phenyl-1 : 3 : 4-thiadiazole (which is known to be formed by the action of mild oxidising agents on benzaldehyde thiosemicarbazone) was also isolated. Oxidation of 2-benzylthiosemicarbazide under the same conditions gave as the main product the benzaldehyde 2-benzylthiosemicarbazone. Presumably this is formed by oxidative breakdown of part of the thiosemicarbazide to benzaldehyde and condensation of this with unchanged thiosemicarbazide, giving the insoluble thiosemicarbazone, which is precipitated. Oxidation of 4-benzylthiosemicarbazide under the same conditions gave benzyl *iso*thiocyanate and this reaction proved to be general for the following 4-substituted thiosemicarbazides (prepared by condensation of appropriate *iso*thiocyanates and hydrazines): 4-ethyl-, 4-iso*propyl*-, 4-iso*butyl*-, 2-*methyl*-4-iso*propyl*- and 4-phenyl-thiosemicarbazide.

Experimental.

1-*Benzylthiosemicarbazide* (II; R = H).—Benzaldehyde thiosemicarbazone (9·0 g.) and alcohol (80%; 400 c.c.) were heated under reflux with good stirring whilst sodium amalgam (11·0 g. of sodium in 20 c.c. of mercury) was added in small pieces during 2 hours. After a further hour the solution was decanted from the residual amalgam which was washed with a little alcohol, and the united alcoholic liquors were diluted with ice and water (300 g.). Acetic acid was added to exact neutrality and the solution set aside at 0° overnight. The crystals (8·5 g.) were collected, washed with water, and crystallised from alcohol, giving 1-*benzylthiosemicarbazide* as colourless needles (6·0 g.), m. p. 154—155° (Found: C, 52·8; H, 6·2; S, 17·4. $C_8H_{11}N_3S$ requires C, 53·0; H, 6·1; S, 17·7%).

The following compounds were obtained in similar experiments: 1-p-*hydroxybenzyl*- (II; R = *p*-OH), large colourless needles, m. p. 180°, from alcohol (Found: C, 49·0; H, 5·5; S, 16·0. $C_8H_{11}ON_3S$ requires C, 48·7; H, 5·6; S, 16·2%), 1-p-*methoxybenzyl*- (II; R = *p*-OMe), large colourless prisms, m. p. 142—143°, from alcohol (Found: C, 51·4; H, 6·4; S, 15·2. $C_9H_{13}ON_3S$ requires C, 51·2; H, 6·2; S, 15·2%), 1-p-*dimethylaminobenzyl*- (II; R = *p*-NMe_2), colourless needles, m. p. 147°, from alcohol (Found: C, 53·5; H, 7·1; S, 14·3. $C_{10}H_{16}N_4S$ requires C, 53·6; H, 7·1; S, 14·3%), 1-p-*ethylsulphonylbenzyl*- (II; R = *p*-SO_2Et), colourless small needles, m. p. 155°, from alcohol (Found: C, 44·3; H, 5·3; S, 23·7. $C_{10}H_{15}O_2N_3S_2$ requires C, 44·0; H, 5·5; S, 23·4%), 1-1′-*phenylethyl*-, colourless leaflets, m. p. 156°, from alcohol (Found: C, 55·3; H, 6·3; S, 16·6. $C_9H_{13}N_3S$ requires C, 55·4; H, 6·7; S, 16·4%), and 1-(1-p-*methoxyphenylethyl*)-*thiosemicarbazide*, colourless glistening leaflets, m. p. 150°, from alcohol (Found: C, 53·4; H, 6·5; S, 14·2. $C_{10}H_{15}ON_3S$ requires C, 53·3; H, 6·7; S, 14·2%).

2-*Benzylthiosemicarbazide* (III; R = H).—(*a*) Freshly distilled benzylhydrazine was dissolved in dry ether, the solution saturated with dry hydrogen chloride, and the dihydrochloride collected, washed with ether, and dried in a vacuum. This dihydrochloride (9·8 g.), dry ammonium thiocyanate (3·8 g.), and absolute alcohol (100 c.c.) were refluxed for 24 hours and then cooled, and the crystals (1·4 g.; m. p. 170°) collected and crystallised from alcohol, giving colourless needles (1·1 g.), m. p. 171° (Found: C, 52·8; H, 6·0; N, 23·0; S, 17·6. Calc. for $C_8H_{11}N_3S$: C, 53·0; H, 6·1; N, 23·2; S, 17·7%).

(*b*) Benzylhydrazine dihydrochloride (19·5 g.) and ammonium thiocyanate (11·2 g.) were dissolved in water (200 c.c.), and the solution was slowly evaporated in a dish during 24 hours. The residue was digested on the steam-bath with water (200 c.c.) for a further 4 hours and then allowed to cool, and the solid collected (6·0 g.; m. p. 150—160°). Several crystallisations from alcohol gave colourless needles (1·0 g.), m. p. 166° not depressed by the compound prepared as in (*a*) (Found: S, 17·8%).

2-Benzylthiosemicarbazide (0·9 g.) in N-hydrochloric acid (5·0 c.c.) and alcohol (50 c.c.) was shaken with benzaldehyde (0·6 g.) in a little alcohol. Crystals (0·9 g.; m. p. 210°) separated in a few seconds,

were collected, and crystallised from 2-ethoxyethanol, giving colourless needles, m. p. 213—214° (Found : C, 67·0; H, 5·6; S, 11·8. Calc. for $C_{15}H_{15}N_3S$: C, 66·9; H, 5·6; S, 11·9%). The thiosemicarbazone from *p*-anisaldehyde obtained in the same way formed colourless fibrous needles, m. p. 178°, from alcohol (Found : C, 63·9; H, 5·6; S, 11·0. Calc. for $C_{16}H_{17}ON_3S$: C, 64·2; H, 5·7; S, 10·7%). Cattelain (*loc. cit.*) gives for these thiosemicarbazones, m. p. 214·5° and 175° respectively.

2-p-*Methoxybenzylthiosemicarbazide* (III ; R = OMe).—This *compound*, prepared as above, crystallised from alcohol in colourless needles, m. p. 193° (Found : C, 51·1; H, 6·5; N, 20·1; S, 14·8. $C_9H_{13}ON_3S$ requires C, 51·2; H, 6·2; N, 19·9; S, 15·2%).

The following thiosemicarbazides were prepared by the method of Baird *et al.* (*loc. cit.*) : 4-benzyl- (IV; R = H), colourless needles, m. p. 128°, from alcohol [benzylidene derivative (prepared as for the 2-isomer) crystallised from alcohol in colourless needles, m. p. 134°], 4-p-*methoxybenzyl-* (IV ; R = *p*-OMe), colourless needles, m. p. 130°, from alcohol (Found : C, 51·5; H, 6·4; S, 15·1. $C_9H_{13}ON_3S$ requires C, 51·2; H, 6·2; S, 15·2%), 4-iso*propyl-*, colourless prisms, m. p. 96°, from benzene (Found : C, 36·1; H, 8·2; S, 24·4. $C_4H_{11}N_3S$ requires C, 36·1; H, 8·3; S, 24·1%) [p-*dimethylaminobenzylidene* derivative, sulphur-yellow plates, m. p. 202°, from alcohol (Found : C, 59·3; H, 7·8. $C_{13}H_{20}N_4S$ requires C, 59·1; H, 7·6%)], 4-n-*butyl-*, colourless leaflets, m. p. 70°, from benzene–light petroleum (b. p. 60—80°) (Found : S, 21·7. $C_5H_{13}N_3S$ requires S, 21·8%) [p-*dimethylaminobenzylidene* derivative, pale yellow leaflets, m. p. 186°, from alcohol (Found : C, 60·8; H, 8·0. $C_{14}H_{22}N_4S$ requires C, 60·4; H, 7·9%)], 4-iso*butyl-*, colourless leaflets, m. p. 68°, from light petroleum (b. p. 60—80°) (Found : S, 22·2. $C_5H_{13}N_3S$ requires S, 21·8%) [p-*dimethylaminobenzylidene* derivative, pale yellow flat needles, m. p. 174°, from alcohol (Found : C, 60·5; H, 7·9. $C_{14}H_{22}N_4S$ requires C, 60·4; H, 7·9%)], and 4-sec.-*butyl-thiosemicarbazide*, colourless prisms, m. p. 52°, from benzene (Found : S, 22·2. $C_5H_{13}N_3S$ requires S, 21·8%) [p-*dimethylaminobenzylidene* derivative, greenish-yellow needles, m. p. 161—162°, from alcohol (Found : C, 60·5; H, 7·8. $C_{14}H_{22}N_4S$ requires C, 60·4; H, 7·9%)].

The following thiosemicarbazides were prepared by the method of Busche, Opfermann, and Walther (*Ber.*, 1904, **37**, 2318) : 2-*methyl*-4-iso*propyl-*, fine colourless needles, m. p. 107°, from benzene–light petroleum (b. p. 60—80°) (Found : C, 41·1; H, 9·0. $C_5H_{13}N_3S$ requires C, 40·8; H, 8·8%) [p-*dimethylaminobenzylidene* derivative, yellow plates, m. p. 150°, from alcohol (Found : C, 60·1; H, 7·9. $C_{14}H_{22}N_4S$ requires C, 60·4; H, 7·9%)], and 2-*methyl*-4-n-*butyl-thiosemicarbazide*, glistening plates, m. p. 50°, from light petroleum (b. p. 60—80°) (Found : C, 45·0; H, 9·1. $C_6H_{15}N_3S$ requires C, 44·7; H, 9·3%) [p-*dimethylaminobenzylidene* derivative, almost colourless needles, m. p. 118°, from alcohol (Found : C, 61·6; H, 8·1. $C_{15}H_{24}N_4S$ requires C, 61·6; H, 8·2%)].

Oxidation of 1-*Benzylthiosemicarbazide.*—1-Benzylthiosemicarbazide (1·8 g.) in 10% acetic acid (50 c.c.) was heated at 50° and stirred vigorously, and ferric chloride (anhydrous ; 6·4 g.) in water (30 c.c.) added during a few minutes. A solid which separated was collected after cooling (0·9 g. ; m. p. 154°), and crystallised from aqueous alcohol, giving colourless needles (0·7 g.) of benzaldehyde thiosemicarbazone, m. p. 162° not depressed by admixture with an authentic specimen (Found : S, 18·0. Calc. for $C_8H_9N_3S$: S, 17·9%). Using twice as much ferric chloride, the thiosemicarbazone (0·2 g.), m. p. 162—163°, was isolated as previously. The original filtrates were made alkaline with ammonia, boiled to coagulate the iron oxides, and filtered. The gelatinous solid was dried in a vacuum, powdered, and extracted with ether in a Soxhlet apparatus. The solvent was evaporated and the residue crystallised from aqueous alcohol, giving colourless glistening prisms (0·4 g.), of 2-amino-5-phenyl-1 : 3 : 4-thiadiazole, m. p. 226° not depressed by an authentic sample (Part I, *J.*, 1949, 1163) (Found : C, 54·0; H, 4·1. Calc. for $C_8H_7N_3S$: C, 54·2; H, 3·9%).

In similar experiments, 1-*p*-methoxybenzylthiosemicarbazide (2·2 g.) gave *p*-anisaldehyde thiosemicarbazone (1·0 g.), m. p. 169° (Found : S, 15·5. Calc. for $C_9H_{11}ON_3S$: S, 15·3%), and 1-*p*-ethylsulphonylbenzylthiosemicarbazide (2·7 g.) gave the corresponding thiosemicarbazone (2·0 g.), m. p. 226° (Found : S, 23·5. Calc. for $C_{10}H_{13}O_2N_3S_2$: S, 23·6%).

Oxidation of 2-*Benzylthiosemicarbazide.*—2-Benzylthiosemicarbazide (1·8 g.) was oxidised as described for the 1-isomer. Bleaching of the ferric chloride solution ceased after the addition of 18 c.c. and, after 10 minutes' stirring, the solid was collected and crystallised from alcohol, giving colourless needles (0·5 g.) of the 2-benzyl-1-benzylidenethiosemicarbazide, m. p. 212° not depressed by the compound prepared as above (Found : C, 67·1; H, 5·7; S, 12·0%).

Oxidation of 4-*Benzylthiosemicarbazide.*—4-Benzylthiosemicarbazide (1·8 g.) was oxidised as described for the 1-isomer. An intense purple colour was produced by the first few drops of ferric chloride solution, followed by the separation of a black oil. The oil was extracted with ether and distilled, giving benzyl *iso*thiocyanate (1·0 g.), b. p. 138—140°/20 mm. (Found : S, 21·8. Calc. for C_8H_7NS : S, 21·5%). Identification was confirmed by shaking this oil (0·5 g.) with alcohol (1·0 c.c.) and 50% hydrazine hydrate (2·0 c.c.), whereafter, on removal of the solvent, 4-benzylthiosemicarbazide, colourless needles (0·25 g.), m. p. 130° (from alcohol), was obtained (Found : S, 17·5. Calc. for $C_8H_{11}N_3S$: S, 17·7%).

Similar reactions were carried out with 4-ethylthiosemicarbazide, which gave ethyl *iso*thiocyanate, b. p. 128—129°/760 mm., 4-*iso*propylthiosemicarbazide, which gave *iso*propyl *iso*thiocyanate, b. p. 134—135°/760 mm., 4-*iso*butylthiosemicarbazide, which gave *iso*butyl *iso*thiocyanate, b. p. 164—168°/760 mm., 2-methyl-4-*iso*propylthiosemicarbazide, which gave *iso*propyl *iso*thiocyanate, b. p. 134—135°/760 mm., and 4-phenylthiosemicarbazide, which gave phenyl *iso*thiocyanate, b. p. 106—107°/20 mm. In each case the identity of the *iso*thiocyanate was checked by reaction with hydrazine and observation of the mixed melting point of the crystallised product with the corresponding thiosemicarbazide.

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