LXVIII.—*The Action of Amines on 2-Substituted Semicarbazones.*

By JAMES CHAPMAN and FORSYTH JAMES WILSON.

THE action of primary amines and amino-esters on semicarbazones has been very fully investigated (Borsche and his collaborators, *Ber.*, 1901, **34**, 4297; 1904, **37**, 3177; 1905, **38**, 831; Heilbron and Wilson, J., 1913, **103**, 1504; Wilson, Hopper, and Crawford, J., 1922, **121**, 866; Wilson and Crawford, J., 1925, **127**, 103; Hopper and Wilson, J., 1928, 2483), the normal reaction being

$$CRR'{:}N{\cdot}NH{\cdot}CO{\cdot}NH_2 + R''NH_2 = CRR'{:}N{\cdot}NH{\cdot}CO{\cdot}NHR'' + NH_3.$$

It became of interest to investigate the behaviour of 2(or β)-substituted semicarbazones in this connexion to see if the reaction $CRR'{:}N{\cdot}NR''{\cdot}CO{\cdot}NH_2 + R'''NH_2 = CRR'{:}N{\cdot}NR''{\cdot}CO{\cdot}NHR''' + NH_3$ occurred. We have found that the reaction is in general not so simple as this.

Acetone-2-phenylsemicarbazone appeared to react equally readily with benzylamine, aniline, *p*-toluidine, β-phenylethylamine, and *n*-heptylamine, giving ammonia, acetonephenylhydrazone, and a symmetrical disubstituted urea: in no case was the expected 2:4-

disubstituted semicarbazone produced, $CMe_2{:}N{\cdot}NPh{\cdot}CO{\cdot}NH_2 + 2RNH_2 = CMe_2{:}N{\cdot}NHPh + (NHR)_2CO + NH_3$. In the case of benzylamine a small quantity of monobenzylurea was formed; this can be provisionally represented thus, $CMe_2{:}N{\cdot}NPh{\cdot}CO{\cdot}NH_2 + CH_2Ph{\cdot}NH_2 = CMe_2{:}N{\cdot}NHPh + CH_2Ph{\cdot}NH{\cdot}CO{\cdot}NH_2$. The intermediate stages in these reactions have been elucidated.

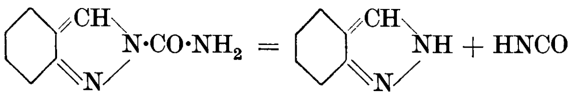
The reaction between semicarbazones and amines with formation of substituted ureas had been observed by Borsche (*Ber.*, 1901, **34**, 4297; 1904, **37**, 3177), who found that certain semicarbazones reacted primarily in the normal way but that the 4-substituted semicarbazone produced might react with another molecule of amine to give a disubstituted urea: thus with salicylaldehydesemicarbazone and aniline, $C_6H_4(OH){\cdot}CH{:}N{\cdot}NH{\cdot}CO{\cdot}NH_2 + PhNH_2 = NH_3 + C_6H_4(OH){\cdot}CH{:}N{\cdot}NH{\cdot}CO{\cdot}NHPh \xrightarrow{+PhNH_2} C_6H_4(OH){\cdot}CH{:}N{\cdot}NH_2 + (PhNH)_2CO$. Borsche employed a large excess of amine, in the case quoted 10 mols., and in most cases the 4-substituted semicarbazone was the main product. In the reactions carried out by us the quantity of amine was never more than 20% over one molecular proportion and in no case was the intermediate stage $CMe_2{:}N{\cdot}NPh{\cdot}CO{\cdot}NHR$ observed.

If Borsche's explanation is applicable to the present case, the stages would be, $CMe_2{:}N{\cdot}NPh{\cdot}CO{\cdot}NH_2 + RNH_2 = NH_3 + CMe_2{:}N{\cdot}NPh{\cdot}CO{\cdot}NHR \xrightarrow{+RNH_2} CMe_2{:}N{\cdot}NHPh + (NHR)_2CO$, and under the conditions employed by us considerable quantities of the 2 : 4-disubstituted semicarbazone would have been expected.

The explanation was afforded by an investigation of the thermal decomposition of acetone-2-phenylsemicarbazone. It is well known that semicarbazones in general undergo the thermal decomposition, $2CRR'{:}N{\cdot}NH{\cdot}CO{\cdot}NH_2 = (CRR')_2N_2 + NH_2{\cdot}CO{\cdot}NH{\cdot}NH{\cdot}CO{\cdot}NH_2$, giving azine and hydrazodicarbonamide, and presumably acetone-2-phenylsemicarbazone would undergo a similar decomposition. It was found, however, that this substance at 140—145° decomposed into acetonephenylhydrazone and cyanic acid (isolated as cyanuric acid), $CMe_2{:}N{\cdot}NPh{\cdot}CO{\cdot}NH_2 = CMe_2{:}N{\cdot}NHPh + HNCO$, a reversal of its method of formation.

Since the reactions between this semicarbazone and the amines employed usually required a temperature of about 160° (the lowest being 145—150° in the case of *p*-toluidine), the course of the reaction was obviously $CMe_2{:}N{\cdot}NPh{\cdot}CO{\cdot}NH_2 = CMe_2{:}N{\cdot}NHPh + HNCO \xrightarrow{+2RNH_2} (RNH)_2CO + NH_3$ (also, in the case of benzylamine, $\xrightarrow{+CH_2Ph{\cdot}NH_2} CH_2Ph{\cdot}NH{\cdot}CO{\cdot}NH_2$ to some extent). Hence none of the 2 : 4-disubstituted semicarbazone would be produced.

Such a thermal decomposition of a semicarbazone does not seem to have been recorded. A closely analogous case is tetrahydroindazole-2-carboxyamide, which at about 200° decomposes thus :



(Auwers, Buschmann, and Heidenreich, *Annalen*, 1924, **435**, 300).

Acetophenone-2-phenylsemicarbazone has a comparatively low melting point (126°) and would presumably have a low thermal decomposition temperature. It should therefore react with amines in the same manner as the acetone derivative : this was found to be the case, with aniline, the products being acetophenonephenylhydrazone and *s*-diphenylurea.

Benzaldehyde-2-benzylsemicarbazone is far more stable to heat than acetone-2-phenylsemicarbazone : even after $1\frac{1}{2}$ hours' heating at 200° most of the substance was recovered unchanged. If, then, it reacted with amines below this temperature, a 2 : 4-disubstituted semicarbazone might be expected. With aniline and *p*-toluidine the reaction occurred at 165—170°, $\mathrm{CHPh{:}N{\cdot}N(CH_2Ph){\cdot}CO{\cdot}NH_2 + RNH_2 = CHPh{:}N{\cdot}N(CH_2Ph){\cdot}CO{\cdot}NHR + NH_3}$ ($\mathrm{R = Ph}$ or $\mathrm{C_6H_4Me}$), giving benzaldehyde-2-benzyl-4-phenyl(or *p*-tolyl)semicarbazone. With benzylamine (minimum reaction temperature 175°) *benzaldehyde*-2 : 4-*dibenzylsemicarbazone* was produced but in addition some *s*-dibenzylurea. The formation of the latter substance was somewhat surprising in view of the thermal stability of benzaldehyde-2-benzylsemicarbazone : it probably originated in a reaction between benzaldehyde-2 : 4-dibenzylsemicarbazone and benzylamine, (A) $\mathrm{CHPh{:}N{\cdot}N(CH_2Ph){\cdot}CO{\cdot}NH{\cdot}CH_2Ph + CH_2Ph{\cdot}NH_2 = CHPh{:}N{\cdot}NH{\cdot}CH_2Ph + (CH_2Ph{\cdot}NH)_2CO}$ (compare Borsche, *loc. cit.*, first two references). No benzaldehyde-2-benzylhydrazone was obtained, and this was only to be expected in view of its instability even at the ordinary temperature.

Benzaldehyde-2-methylsemicarbazone gave with aniline at 180° benzaldehyde-4-phenyl-2-methylsemicarbazone, (B) $\mathrm{CHPh{:}N{\cdot}NMe{\cdot}CO{\cdot}NH_2 + PhNH_2 = NH_3 + CHPh{:}N{\cdot}NMe{\cdot}CO{\cdot}NHPh}$, no *s*-diphenylurea being formed : apparently the decomposition temperature of the 2-methylsemicarbazone was above 180°. With benzylamine, however, at 170° the main product was *s*-dibenzylurea, only a small quantity of *benzaldehyde*-4-*benzyl*-2-*methylsemicarbazone* being produced. Since the production of *s*-dibenzylurea from cyanic acid would imply a thermal pre-decomposition of the 2-methylsemicarbazone, the obvious explanation is that benzaldehyde-4-benzyl-2-methylsemicarbazone had reacted for the most part with benzylamine, (A) CHPh:N·NMe·CO·NH·CH_2Ph + CH_2Ph·NH_2 = CHPh:N·NHMe + $(CH_2Ph·NH)_2CO$. Benzaldehydemethylhydrazone was not isolated, however. In addition to the products mentioned, two substances were isolated, one, m. p. 63°, having the empirical formula $C_{17}H_{20}O_2N_2$, and the other, m. p. 207°, $C_{11}H_{12}O_3N_2$; the amounts were too small to permit of investigation. The only other products were oily or resinous.

As these two substances might possibly be decomposition products of benzaldehydemethylhydrazone, the preparation of this was attempted. Information regarding this substance is very meagre. It is described by Harries and Haga (*Ber.*, 1898, **31**, 62) as a crystalline solid of m. p. 179° obtained, with tribenzalmethylhydrazone, from equimolecular quantities of benzaldehyde and methylhydrazine. Attempts to prepare it by this method or by variations of the method gave tribenzalmethylhydrazone only.

The explanations expressed in equations (A) and (B) were confirmed by investigating the action of amines on 2 : 4-disubstituted semicarbazones. Benzaldehyde-4-phenyl-2-methylsemicarbazone did not react with aniline in 4 hours at 180°, this being in agreement with the fact that benzaldehyde-2-methylsemicarbazone with aniline at 180° gave benzaldehyde-4-phenyl-2-methylsemicarbazone and no *s*-diphenylurea, the action proceeding as far as the first stage only. Benzaldehyde-4-benzyl-2-methylsemicarbazone, reacting with benzylamine at 170° for 1½ hours, gave *s*-dibenzylurea, a small quantity of unaltered substance being recovered. This conforms with the observation that benzaldehyde-2-methylsemicarbazone and benzylamine at 170° gave mainly *s*-dibenzylurea and a small amount of benzaldehyde-4-benzyl-2-methylsemicarbazone, the second stage being nearly complete: (1) CHPh:N·NMe·CO·NH_2 + RNH_2 = NH_3 + CHPh:N·NMe·CO·NHR; (2) $\xrightarrow{+RNH_2}$ CHPh:N·NHMe + $(RNH)_2CO$.

It is evident that the introduction of a substituent in the 2-position in a semicarbazone effects a considerable change in its behaviour, as is seen, for example, in the thermal decomposition of acetone-2-phenylsemicarbazone. Further, the reactions of a 2-substituted semicarbazone with amines depend on the decomposition temperature: if this is low, the reaction is one between the amine and cyanic acid. If the 2-substituted semicarbazone is thermally stable, a 2 : 4-disubstituted semicarbazone may result, although this may react further with the amine. Apparently, 2 : 4-disubstituted semicarbazones react more readily than 4-substituted semicarbazones with amines.

EXPERIMENTAL.

Acetone-2-phenylsemicarbazone (Goodwin and Bailey, *J. Amer. Chem. Soc.*, 1924, **46**, 2829).—In the reactions with amines this substance was heated with the amine (1—1$\frac{1}{5}$ mols.) until the evolution of ammonia had abated. The acetonephenylhydrazone was isolated by distillation under reduced pressure and identified in various ways. The residue was recrystallised, usually from alcohol.

With benzylamine (160°, 1 hour). The residue was recrystallised several times from alcohol and from chloroform, colourless needles of *s*-dibenzylurea, m. p. 171°, being obtained (Found: N, 11·6, 11·7. Calc.: N, 11·7%). The mother-liquors were evaporated; the residue after several recrystallisations from ethyl acetate yielded colourless needles, m. p. 149°, shown to be monobenzylurea by comparison with a known specimen (Found: C, 63·8; H, 7·1; N, 18·5. Calc.: C, 64·0; H, 6·7; N, 18·7%). No other product except tar was obtained.

The melting point of *s*-dibenzylurea is variously given in the literature as 167° or 169°: a specimen prepared by the method of Davis and Blanchard (*J. Amer. Chem. Soc.*, 1923, **45**, 1819) melted at 171° after several recrystallisations and was identical with ours.

With aniline (155—160°, 40 minutes). The residue gave *s*-diphenylurea, identified as such by comparison with a stock sample. The mother-liquors on evaporation gave tar, from which a small quantity of a solid, m. p. 133°, was obtained by recrystallisation from benzene.

With p-*toluidine* (145°, 150° towards the end, 40 minutes). From the residue, di-*p*-tolylurea, m. p. 260°, identified by comparison with an authentic specimen, was obtained. The mother-liquors on evaporation gave tar, from which, by recrystallisation from chloroform, a small quantity of a solid, m. p. 162° (not sharp), was obtained.

With β-phenylethylamine (150—160°). The dark-coloured residue was recrystallised first from alcohol–light petroleum and then from ethyl acetate, from which *s*-di-(β-phenylethyl)urea, identified as such, separated in clusters of colourless needles, m. p. 136—137°. The only other product was tar.

With n-*heptylamine* (160°, $\frac{3}{4}$ hour). The residue yielded *s*-di-*n*-heptylurea, m. p. 91° (Found: N, 11·0. Calc.: N, 10·9%). Evaporation of the mother-liquors gave tar.

Thermal decomposition. The semicarbazone was heated at 140—145° for 1 hour: no gas was evolved. The somewhat dark-coloured liquid on distillation under reduced pressure yielded acetonephenylhydrazone, which was identified. The pasty residue was extracted with hot alcohol, then with benzene, and again with alcohol to remove colouring matter, and finally recrystallised from water. This gave a colourless substance which did not melt at 350° and was identified as cyanuric acid by the characteristic reaction with ammonia and copper sulphate (Found in anhydrous substance : N, 32·5, 32·5. Calc. : N, 32·5%).

Acetophenone-2-phenylsemicarbazone (Rolla, *Gazzetta*, 1908, **38**, i, 327).—The melting point was found to be 126°, not 122° as stated in the literature (Found : N, 16·7. Calc. : N, 16·6%).

With aniline (145—155°, 1¼ hours). Except for the distillation the usual procedure was followed. The product was recrystallised from alcohol, and the crystalline deposit extracted with ether. The residue after several recrystallisations from alcohol proved to be *s*-diphenylurea, m. p. 238°. The ethereal extract on evaporation left a solid which after several recrystallisations from alcohol was shown to be acetophenonephenylhydrazone, m. p. 104°, by comparison with a known specimen. No other products were obtained.

Benzaldehyde-2-benzylsemicarbazone (Bougault and Leboucq, *Compt. rend.*, 1928, **186**, 957).—The usual procedure was adopted.

With aniline (165—170°, 65 minutes). A few drops of aniline distilled over under reduced pressure. Repeated recrystallisation from alcohol gave benzaldehyde-4-phenyl-2-benzylsemicarbazone, m. p. 152° (Busch, Opfermann, and Walther, *Ber.*, 1904, **37**, 2327) (Found : N, 12·8. Calc. : N, 12·8%). The only other product was tar.

With p-*toluidine* (165—170°, 2 hours). A little *p*-toluidine distilled over under reduced pressure. After several recrystallisations from alcohol the residue gave *benzaldehyde*-4-p-*tolyl*-2-*benzylsemicarbazone* (Found : N, 12·0, 12·1. $C_{22}H_{21}ON_3$ requires N, 12·2%), which formed colourless felted prisms, m. p. 172°, soluble in hot alcohol and benzene, slightly soluble in hot ether, insoluble in light petroleum.

With benzylamine (175°, 1¼ hours). There was no volatile product. The residue was repeatedly crystallised from alcohol, from which *s*-dibenzylurea separated (Found : N, 11·6. Calc. : N, 11·7%). From the mother-liquors, on concentration, a mixture of *s*-dibenzylurea and another substance was deposited. Separation was effected by means of chloroform and then benzene, in both of which the second substance was the more soluble. Several recrystallisations from alcohol gave felted prisms, m. p. 124°, of *benzaldehyde*-2 : 4-*dibenzylsemicarbazone* (Found : N, 12·2. $C_{22}H_{21}ON_3$ requires N, 12·2%), soluble in chloroform, ether and acetone in the cold and in hot alcohol and benzene. The only other product was tar smelling strongly of benzaldehyde.

Benzaldehyde-2-methylsemicarbazone (Young and Oates, J., 1901, **79**, 662).—The usual procedure was followed.

With aniline (180°, 3 hours). Some aniline distilled. The residue was recrystallised several times from alcohol and then from benzene–light petroleum, which deposited benzaldehyde-4-phenyl-2-methylsemicarbazone (Busch, Opfermann, and Walther, *loc. cit.*, p. 2324) in clusters of small needles, m. p. 108° (Found : N, 16·7, 16·8. Calc. : N, 16·6%).

With benzylamine (165—170°, 3 hours). There was no distillate. Recrystallisation of the residue from alcohol gave *s*-dibenzylurea. The mother-liquors on evaporation under reduced pressure left a red oil which, after removal of more of the urea deposited on standing, was distilled at a pressure of less than 1 mm. (bath temperature up to 185°). The distillate soon solidified and after being pressed on tile the solid was recrystallised several times by solution in ether and precipitation with light petroleum. Long colourless needles, m. p. 63°, were obtained, easily soluble in alcohol, ether, benzene and chloroform in the cold, insoluble in light petroleum (Found : C, 71·9; H, 7·1; N, 9·6%). The quantity was too small for investigation; the empirical formula corresponded to $C_{17}H_{20}O_2N_2$ (requires C, 71·8; H, 7·0; N, 9·8%). The residue left from the distillation could not be worked up.

The experiment was repeated (170° for 1 hour). On distillation a liquid, b. p. 90°/6 mm., which soon solidified, was obtained. It was hygroscopic and its aqueous solution was alkaline to litmus. After being pressed on tile and kept in a vacuum over sulphuric acid for several days, it melted at 88—89°. Recrystallisation of this from benzene gave a minute amount of a solid, m. p. 207° (Found : C, 59·7; H, 5·4; N, 12·7%), of the empirical formula $C_{11}H_{12}O_3N_2$ (requires C, 60·0; H, 5·5; N, 12·7%). The benzene mother-liquors on evaporation left a thick oil smelling of benzaldehyde. The residue from which the liquid of b. p. 90°/6 mm. had distilled, on recrystallisation from alcohol, yielded *s*-dibenzylurea. On concentration the mother-liquors deposited a solid, which was extracted with boiling ether, from which plates, m. p. 106° after recrystallisation from ether or alcohol, were obtained. The residue insoluble in ether was recrystallised from alcohol, which deposited needles of *s*-dibenzylurea and large plates, m. p. 106°; these could easily be separated mechanically. This substance, m. p. 106°, was *benzaldehyde-4-benzyl-2-methylsemicarbazone* (Found : C, 71·9; H, 6·1; N, 16·0. $C_{16}H_{17}ON_3$ requires C, 71·9; H, 6·4; N, 15·7%). The only other product was a thick brown oil which would not solidify and decomposed on distillation under highly reduced pressure.

Evidently the benzaldehyde-4-benzyl-2-methylsemicarbazone formed by the second experiment had been destroyed by the prolonged reaction of the first.

Benzaldehyde-4-phenyl-2-methylsemicarbazone and Aniline (180°, 4 hours).—Aniline collected on distillation. The resinous mass on recrystallisation from alcohol gave unaltered semicarbazone; the mother-liquors on evaporation in a vacuum over sulphuric acid left a semi-solid mass which after pressure on tile and recrystallisation proved to be also unaltered substance.

Benzaldehyde-4-benzyl-2-methylsemicarbazone and Benzylamine (170°, 1½ hours).—There was no distillate. Recrystallisation from alcohol gave *s*-dibenzylurea. The mother-liquors on concentration yielded a trace of unaltered semicarbazone and oil.

We desire to convey our thanks to Imperial Chemical Industries, Ltd., for grants which have been of great assistance in this work. We wish also to thank the Department of Scientific and Industrial Research for a maintenance grant to one of us (J. C.).

THE ROYAL TECHNICAL COLLEGE,
GLASGOW.

[*Received, January 23rd*, 1931.]