CL.—*The Action of Piperidine on Acetonesemicarbazone.*

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THE interaction of semicarbazones and primary aliphatic and aromatic amines and amino-esters has been very fully studied (Borsche and his collaborators, *Ber.*, 1901, **34**, 4297; 1904, **37**, 3177; 1905, **38**, 831; Wilson, Hopper, and Crawford, J., 1922, **121**, 866; Heilbron and Wilson, J., 1913, **103**, 1504; Wilson and Crawford, J., 1925, **127**, 103; Hopper and Wilson, J., 1928, 2483), but no work has hitherto been carried out on the interaction of semicarbazones and secondary amines. We have now investigated the reaction between acetonesemicarbazone and piperidine.

It was expected that the reaction would take the normal course $CMe_2{:}N{\cdot}NH{\cdot}CO{\cdot}NH_2 + NHC_5H_{10} =$ (I) $CMe_2{:}N{\cdot}NH{\cdot}CO{\cdot}NC_5H_{10} + NH_3$, giving *acetonepiperidinoformylhydrazone*. Equimolecular quantities of the reactants were refluxed in toluene solution. In the first experiments no special precautions were taken to dry the materials or solvents used, or to exclude moisture while the reaction was proceeding: as will be seen, this profoundly affected the course of the reaction. Ammonia was evolved and a substance, $C_{10}H_{21}O_3N_5$ (II), m. p. 145°, was obtained. This reacted with benzaldehyde in aqueous-alcoholic solution, giving a *substance*, $C_{14}H_{19}O_2N_5$ (III), m. p. 211°; with acetophenone it gave a *substance*, $C_{15}H_{21}O_2N_5$ (IV), m. p. 204°.

When boiled for 2 hours with 20—25% hydrochloric acid, (II) was completely hydrolysed, yielding acetone, hydrazine hydrochloride, and piperidine hydrochloride in the molecular ratios 1 : 1·9 : 1·025. Since the method of analysis adopted tended to give a low result for hydrazine and a high one for piperidine, it was concluded that (II) contained one acetone residue, two hydrazine residues, and one piperidine residue, and therefore had the structure,

$$CMe_2{:}N{\cdot}NH{\cdot}CO{\cdot}NH{\cdot}NH{\cdot}CO{\cdot}NC_5H_{10},H_2O,$$

of *acetone-ε-piperidinoformylcarbohydrazone hydrate*. Substance (III) would then be *benzaldehyde-ε-piperidinoformylcarbohydrazone*, $CHPh{:}N{\cdot}NH{\cdot}CO{\cdot}NH{\cdot}NH{\cdot}CO{\cdot}NC_5H_{10}$, and (IV) would be *acetophenone-ε-piperidinoformylcarbohydrazone*,

$$CPhMe{:}N{\cdot}NH{\cdot}CO{\cdot}NH{\cdot}NH{\cdot}CO{\cdot}NC_5H_{10}.$$

It was not possible to remove water from (II) even by heating it at just below the melting point in a high vacuum; when heated a little above the melting point, it lost water but decomposition ensued. We therefore prefer to reformulate (II) as

$$CMe_2(OH)\cdot NH\cdot NH\cdot CO\cdot NH\cdot NH\cdot CO\cdot NC_5H_{10}.$$

A somewhat similar case has been reported by Read and Smith (J., 1922, **121**, 1869). It is rather remarkable that (III) and (IV) are anhydrous.

Substances (II) and (III), when boiled with 1% hydrochloric acid, gave ε-*piperidinoformylcarbohydrazide hydrochloride* (V),

$$NH_2\cdot NH\cdot CO\cdot NH\cdot NH\cdot CO\cdot NC_5H_{10},HCl,H_2O,$$

which exhibited dimorphism. Treatment of the hydrochloride with acetone, benzaldehyde, and acetophenone yielded the substances (II), (III), and (IV) respectively. With picric acid, (II) gave ε-*piperidinoformylcarbohydrazide picrate*, obtainable also from the hydrochloride and picric acid.

Benzaldehydesemicarbazone and piperidine failed to react at 130°; at 165°, decomposition products only were obtained. When heated at 130—135° in solvent naphtha, acetophenonesemicarbazone and piperidine reacted in the normal manner, giving *acetophenonepiperidinoformylhydrazone*, $CPhMe{:}N\cdot NH\cdot CO\cdot NC_5H_{10}$ (VI), m. p. 168°. Hydrolysis of this with boiling 1% hydrochloric acid gave acetophenone and *piperidinoformylhydrazide hydrochloride* (VII), $NH_2\cdot NH\cdot CO\cdot NC_5H_{10},HCl$, which with benzaldehyde gave *benzaldehydepiperidinoformylhydrazone* (VIII), $CHPh{:}N\cdot NH\cdot CO\cdot NC_5H_{10}$. The structure of the last compound was confirmed by its synthesis from piperidinoformylhydrazide and benzaldehyde: when, however, acetone was substituted for benzaldehyde, the reaction proceeded abnormally and (II) was produced: $2C_5H_{10}N\cdot CO\cdot NH\cdot NH_2 \longrightarrow C_5H_{10}N\cdot CO\cdot NH\cdot NH\cdot CO\cdot NH\cdot NH_2 \xrightarrow{CMe_2O}$ (II).

The reaction between acetonesemicarbazone and piperidine was then repeated, all the materials and solvents being carefully dried and access of moisture from the air being excluded. The reaction proceeded normally, $CMe_2{:}N\cdot NH\cdot CO\cdot NH_2 + NHC_5H_{10} = NH_3 + CMe_2{:}N\cdot NH\cdot CO\cdot NC_5H_{10}$, giving (I), m. p. 101°, which yielded acetone on hydrolysis and (VIII) with benzaldehyde. The substance was deliquescent and slowly decomposed when moist, giving an alkaline reaction.

When the substance (II) was boiled with water, it gave acetone and ε-*piperidinoformylcarbohydrazide* (IX),

$$C_5H_{10}N\cdot CO\cdot NH\cdot NH\cdot CO\cdot NH\cdot NH_2,$$

the latter being obtained as a monohydrate which became anhydrous in a vacuum over sulphuric acid. When boiled with water, (I) also gave (IX) together with acetone and piperidine: the alkaline reaction which (I) develops when moist is evidently due to this hydrolysis. With acetone and benzaldehyde in aqueous alcoholic solutions, (IX) yielded (II) and (III) respectively.

The formation of (II) from acetonesemicarbazone and piperidine appears, therefore, to proceed through the following stages:

$$2CMe_2{:}N{\cdot}NH{\cdot}CO{\cdot}NH_2 + 2C_5H_{10}NH \xrightarrow{-2NH_3}$$
$$2CMe_2{:}N{\cdot}NH{\cdot}CO{\cdot}NC_5H_{10}\ (I) \xrightarrow[-2CMe_2O]{+2H_2O} 2C_5H_{10}N{\cdot}CO{\cdot}NH{\cdot}NH_2$$
$$\xrightarrow{-C_5H_{10}NH} C_5H_{10}N{\cdot}CO{\cdot}NH{\cdot}NH{\cdot}CO{\cdot}NH{\cdot}NH_2\ (IX) \xrightarrow{+CMe_2O}$$
$$C_5H_{10}N{\cdot}CO{\cdot}NH{\cdot}NH{\cdot}CO{\cdot}NH{\cdot}NH{\cdot}CMe_2{\cdot}OH\ (II).$$

Heating for 6 hours at 190—200° effected a smooth decomposition of (VII) into piperidine hydrochloride and 4-aminourazole: $2(VII) = 2C_5H_{10}NH,HCl + CO\langle^{NH\cdot NH}_{N(NH_2)}\rangle CO$. Attempts were made to obtain the base corresponding to the hydrochloride (VII), but it was too unstable to permit of purification.

EXPERIMENTAL.

Piperidine and Acetonesemicarbazone (non-anhydrous conditions).—Equimolecular quantities were refluxed in toluene at 130° for 9 hours, ammonia being evolved. The solution was evaporated under reduced pressure, and the residue dissolved in a little alcohol. Addition of much ether and a small quantity of water precipitated a colourless crystalline solid, which, after being washed with ether and recrystallised by addition of ether to a concentrated alcoholic solution, or of light petroleum to a chloroform solution, or from acetone, water or benzene, gave *acetone-ε-piperidinoformylcarbohydrazone hydrate* (II) in prismatic needles, m. p. 145° (Found: C, 46·6; H, 7·9; N, 27·2, 26·9 *; *M*, cryoscopic in nitrobenzene, 311. $C_{10}H_{21}O_3N_5$ requires C, 46·3; H, 8·1; N, 27·0%; *M*, 259). To a solution of the substance in a little hot water, benzaldehyde and a little alcohol were added: the precipitated *benzaldehyde-ε-piperidinoformylcarbohydrazone* (III) crystallised, on addition of water to an alcoholic solution, in long, felted, thread-like prisms, m. p. 211° after repeated crystallisation, soluble in alcohol and ether (Found: C, 57·8; H, 6·6; N, 24·4, 24·5. $C_{14}H_{19}O_2N_5$ requires C, 58·1; H, 6·6; N, 24·2%). When treated with acetophenone in a similar manner, (II) gave *acetophenone-ε-piperidinoformylcarbohydrazone* (IV), which separated from an alcoholic solution on addition of water in needle-like prisms, m. p. 204° (Found: C, 59·3; H, 6·7; N, 23·1. $C_{15}H_{21}O_2N_5$ requires C, 59·4; H, 6·9; N, 23·1%).

A known weight of (II) was distilled with 1% sulphuric acid. The acetone in the distillate was estimated by the method of Denigès

* In all nitrogen estimations copper oxide–cobalt oxide mixture was used (Campbell and Gray, *J. Soc. Chem. Ind.*, 1930, **49**, 450), as otherwise irregular results were obtained.

(*Compt. rend.*, 1898, **127**, 963). The solution in the distilling flask was then boiled for 3 hours with 20% hydrochloric acid : in one half of it, cooled and made alkaline, hydrazine was estimated by measuring the nitrogen evolved on heating with Fehling's solution ; the other half, cooled and made alkaline, was distilled with Fehling's solution (to destroy hydrazine), and the piperidine was collected in standard acid and estimated by titration. The results (molecular ratios) were : acetone 1·0, hydrazine 1·9, piperidine 1·025.

The substance (II) was boiled for ½ hour with 1% hydrochloric acid, and the solution evaporated to dryness under reduced pressure (acetone was detected in the distillate). The residue crystallised from water or alcohol–ether containing a little hydrochloric acid in plates, m. p. 144°, but slow crystallisation from absolute alcohol with addition of ether or light petroleum yielded long prisms, m. p. 185—186° (decomp.) : a mixture of the two forms melted at the higher temperature. The substance was *ε-piperidinoformylcarbohydrazide hydrochloride* (V) (Found in substance of m. p. 144° : C, 32·6; H, 7·0; N, 27·5; Cl, 13·8. Found in substance of m. p. 185—186° : C, 33·1; H, 6·9; N, 27·5; Cl, 14·0. $C_7H_{15}O_2N_5,HCl,H_2O$ requires C, 32·9; H, 7·1; N, 27·4; Cl, 13·9%). Hydrolysis of (III) gave a similar result, the same hydrochloride being obtained. Substance (II) in water was distilled with aqueous picric acid : acetone was present in the distillate, and the residual, fairly concentrated solution on cooling deposited *ε-piperidinoformylcarbohydrazide picrate*, which formed long, bright yellow prisms, m. p. 204° (decomp.), from alcohol (Found : C, 35·8; H, 4·2; N, 25·9. $C_7H_{15}O_2N_5,C_6H_3O_7N_3$ requires C, 36·3; H, 4·2; N, 26·0%. The substance for analysis was mixed with silica). The same picrate was obtained by addition of picric acid to a solution of (V) in water.

When shaken with benzaldehyde and acetophenone in aqueous alcohol, (V) gave precipitates of (III) and (IV) respectively. The substance (V) was mixed with potassium acetate in absolute alcohol, and the solution was filtered from potassium chloride, treated with acetone, and allowed to evaporate in a desiccator. A trace of solid separated, ether was added, and the slight precipitate was removed (potassium acetate). On addition of a very little water and shaking, the ethereal solution deposited a crystalline solid which on recrystallisation from alcohol–ether proved to be (II).

Piperidine and Acetophenonesemicarbazone (*equimolecular quantities*).—These substances were heated in high-boiling solvent naphtha at 130—135° for 30—35 hours until all solid had dissolved. The solid which separated on cooling was pressed free from oil and recrystallised from alcohol or ether, or from chloroform with addition of light petroleum, *acetophenonepiperidinoformylhydrazone* (VI) being

obtained in needles, m. p. 168° (Found : N, 17·1. $C_{14}H_{19}ON_3$ requires N, 17·1%). This substance was quickly hydrolysed by boiling 1% hydrochloric acid; the liquid was evaporated under reduced pressure (acetophenone was present in the distillate), and the residue dissolved in absolute alcohol. Addition of ether precipitated *piperidinoformylhydrazide hydrochloride* (VII) in needles, m. p. 189° (Found : N, 23·6. $C_6H_{13}ON_3,HCl$ requires N, 23·5%). To a filtered solution of this hydrochloride and potassium acetate in aqueous alcohol, benzaldehyde and water were added; the precipitated *benzaldehydepiperidinoformylhydrazone* (VIII) crystallised in very fine, long prisms, m. p. 179°, from aqueous alcohol, acetone, or ether or on addition of light petroleum to a chloroform or ethylene dichloride solution (Found : N, 18·2. $C_{13}H_{17}ON_3$ requires N, 18·2%).

A solution of the hydrochloride (VII) in absolute alcohol was treated with sodium ethoxide in alcohol until it was almost neutral; it was then filtered from sodium chloride and concentrated, acetone and a few drops of water were added, and the whole was refluxed for 6 hours. The solution was then distilled under slightly reduced pressure into dilute hydrochloric acid, the heating being carried out in a glycerol bath up to 120° in a current of air free from carbon dioxide. The presence of piperidine in the distillate was proved by conversion into the benzenesulphonyl derivative. The yellow oil in the distilling flask was dissolved in chloroform and cleaned with charcoal, a few drops of acetone were added and then light petroleum until the solution became turbid. Crystals gradually separated; after being washed with ether and recrystallised from benzene, the substance was identical with (II).

To an absolute alcoholic solution of hydrazine hydrate (slightly more than 2 mols.) piperidinoformyl chloride (Wallach and Lehmann, *Annalen*, 1887, **237**, 249) was added drop by drop. After the vigorous action was over, hydrazine monohydrochloride was filtered off. To a portion of the filtrate, acetone was added, and the solution was evaporated to small bulk under reduced pressure; the solid which separated on addition of ether was shown to consist of (II) and piperidine hydrochloride. The other portion of the filtrate on dilution with water and shaking with benzaldehyde gave a precipitate, from which benzalazine was removed by light petroleum; the residue after recrystallisation from benzene–light petroleum was found to be identical with (VIII).

Thermal Decomposition of Piperidinoformylhydrazide Hydrochloride (VII) (190—200°, 6 hours).—The cold melt was extracted with boiling absolute alcohol; the residue on recrystallisation from water gave crystals, m. p. 273°, recognised as 4-aminourazole by

its characteristic reactions. Addition of dry ether to the alcoholic extract precipitated a crystalline hydrochloride, identified as piperidine hydrochloride by conversion into benzenesulphonpiperidide.

Piperidine and Acetonesemicarbazone (anhydrous conditions).—The piperidine was dried over potassium hydroxide and distilled, acetonesemicarbazone was dried in a vacuum over sulphuric acid, dry solvents were employed, and during the reaction moisture was excluded by means of a calcium chloride tube. The reactants (equimolecular quantities) were refluxed in toluene (dried over sodium) for 25 hours at 110°, ammonia being evolved. The hot solution was filtered, evaporated to dryness under reduced pressure, and the residue extracted with hot light petroleum.

Acetonepiperidinoformylhydrazone (I), which separated on cooling, was repeatedly crystallised from light petroleum (Found : C, 59·1; H, 9·1; N, 22·9. $C_9H_{17}ON_3$ requires C, 59·0; H, 9·3; N, 22·9%). It formed rosettes of prisms, m. p. 101°, extremely soluble in water, methyl and ethyl alcohols, benzene, ether and light petroleum; the high solubility made purification troublesome.

Production of ε-Piperidinoformylcarbohydrazide (IX) *from Acetonepiperidinoformylhydrazone* (I) *and Acetone-ε-piperidinoformylcarbohydrazone Hydrate* (II) *by Hydrolysis with Water.*—Acetone-ε-piperidinoformylcarbohydrazone (II) was boiled with water, and the product distilled; acetone was present in the distillate. The crystalline residue obtained by evaporation of the solution was dissolved in hot absolute alcohol and precipitated by addition of light petroleum; repetition of this treatment gave plates, m. p. 106—108°, of *ε-piperidinoformylcarbohydrazide* (IX), containing one molecule of water [Found (air-dried) : N, 32·6, 32·8. $C_7H_{15}O_2N_5,H_2O$ requires N, 32·0%]. This was dried in a high vacuum over sulphuric acid until constant in weight, and the product crystallised in the cold from absolute alcohol–ether or –light petroleum, the anhydrous substance being obtained in plates, m. p. 106—107° (Found : N, 34·9. $C_7H_{15}O_2N_5$ requires N, 34·8%). The anhydrous substance appeared to decompose on keeping and for this reason was difficult to purify : the hydrate was more stable. The hydrolysis of (I) proceeded in the same manner, piperidine as well as acetone being present in the distillate.

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