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Reactions of Semicarbazones

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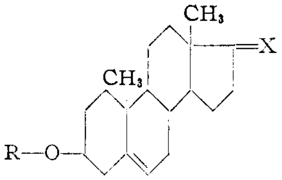
Introduction

Reactions of semicarbazones may be divided into two classes, of which one includes those reactions concerned with the carbon-to-nitrogen double bond, such as hydrolysis and the Wolff–Kishner reduction, while the second includes reactions concerned with other linkages of the semicarbazide moiety. This paper deals with reactions of the latter class, and a new reaction of this class is reported, *viz.*, the conversion of a semicarbazone into an acetylhydrazone or a diacetylhydrazone

$$\mathrm{RR'C{=}NNHCONH_2 + Ac_2O \longrightarrow RR'C{=}NNH_2 \longrightarrow RR'C{=}NNHAc \longrightarrow RR'C{=}NNAc_2} \quad (A)$$

This reaction was first noticed in the case of 3(β)-acetoxy-Δ^5-androsten-17-one semicarbazone (I). When this semicarbazone was heated with acetic anhydride, II was formed in the presence of pyridine, and V was formed in the presence of acetic acid. When the hydrazone IV or the acetylhydrazone V were heated with acetic anhydride in the presence of pyridine, II was again formed. Thus, the conversion of I into II doubtless proceeded according to the process (A).

The conversion of a semicarbazone into the corresponding monoacetyl- and diacetyl-hydrazones has been found to occur in the cases of other steroid semicarbazones, of acetone, and of acetophenone. However, in these cases the selectivity of action found in the case of I was lacking, for the diacetylhydrazone tended to be formed even when pyridine was absent. This tendency was only partially diminished by limiting the amount of acetic anhydride and indicates that the acetylation steps in the process (A) are much more rapid than the formation of the hydrazone.



Compound	R—	=X
I	CH_3CO—	$=NNHCONH_2$
II	CH_3CO—	$=NN(COCH_3)_2$
III	H—	=O
IIIa	CH_3CO—	=O
IV	H—	$=NNH_2$
V	CH_3CO—	$=NNHCOCH_3$

Acetone diacetylhydrazone was hydrolyzed in an attempt to prepare N,N-diacetylhydrazine, which had been once prepared from hydrazine mercurichloride. The latter compound proved to be a detonant, so that the preparation of N,N-diacetylhydrazine from the acetone derivative seemed more attractive. However, acetone diacetylhydrazone was hydrolyzed to hydrazine in alcoholic hydrochloric acid, and to N,N'-diacetylhydrazine in aqueous acetic acid. Apparently, N,N-diacetylhydrazine isomerizes very easily.

Discussion

Reactions of semicarbazones similar to the one described here have appeared from time to time in the chemical literature, and although they have not been correlated, it appeared to the author that they all have a common basis, *viz.*, the decomposition (B).

$$\mathrm{RR'C{=}NNHCONH_2 \longrightarrow RR'C{=}NNH_2 + HNCO} \quad (B)$$

This decomposition may be effected by high temperature, but occurs at lower temperatures when acids or bases are present. After this initial step any among several steps may occur. Some of these are

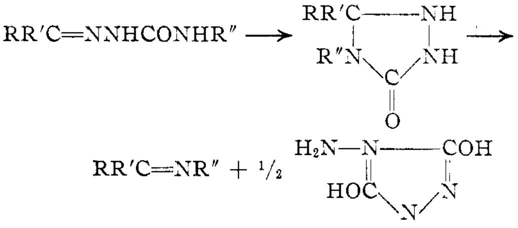
$$\mathrm{2RR'C{=}NNH_2 \longrightarrow RR'C{=}NN{=}CRR' + H_2NNH_2} \quad (C)$$

$$\mathrm{H_2NNH_2 + 2HNCO \longrightarrow H_2NCONHNHCONH_2} \quad (D)$$

$$\mathrm{R''NH_2 + HNCO \longrightarrow R''NHCONH_2 \longrightarrow R''NCO + NH_3} \quad (E)$$

$$\mathrm{R''NCO + R''NH_2 \longrightarrow R''NHCONHR''} \quad (F)$$

$$\mathrm{RR'C{=}NNH_2 + R''NCO \longrightarrow RR'C{=}NNHCONHR''} \quad (G)$$



(H)

These steps account for many, if not all, of the reactions of semicarbazones in which the semicarbazide moiety is involved. Among these reactions are the following:

Steps (B), (C) and (D) provide a mechanism for the process which occurs when semicarbazones are submitted to dry distillation.[1] The formation of a δ-arylsemicarbazone and a diarylurea by heating a semicarbazone with an arylamine[2] is accounted for by steps (B), (E), (F) and (G). Similarly, these steps account for the formation of a δ-anilinosemicarbazone[3] (R'' is C_6H_5NH—). Step (H) accounts for the formation of 4-amino-urazole when a δ-substituted semicarbazone is unstable[3,4a] or when it is decomposed thermally.[4a,4b] Other

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[1] Scholtz, *Ber.*, **29**, 610 (1896).

[2] (a) Borsche, *Ber.*, **34**, 4297 (1901); (b) Borsche and Merkwitz, *ibid.*, **37**, 3177 (1904).

[3] Sutherland and Wilson, *J. Chem. Soc.*, **125**, 2145 (1924).

[4] (a) Baird and Wilson, *ibid.*, 2367 (1926); (b) 2114 (1927).

reactions of semicarbazones[5,6,7,8] may also be explained on the basis of the steps (B) to (H).

Among the above reactions, steps (C), (D), (E) and (F) are well established, while (G) resembles (E). Reaction (H) seems plausible in view of the decomposition of acetophenone δ-anilinosemicarbazone.[4a] All these steps necessarily depend on the occurrence of the initial step (B), which is established in the case of a β-phenylsemicarbazone.[5] The reaction with acetic anhydride reported here establishes (B) for simple semicarbazones.

These mechanisms differ from those previously proposed. Wilson and his collaborators[4] considered the conversion of a semicarbazone into the corresponding phenylhydrazone in the presence of phenylhydrazine to be a simple displacement reaction. Similarly, Minunni, D'urso, *et al.*,[9] believed that when the β,δ-diphenylsemicarbazone of benzaldehyde was converted into the phenylhydrazone by heating with phenylhydrazine, a displacement had occurred. In view of what is now known of reaction mechanisms a simple displacement is impossible.

Experimental[10]

3(β)-Acetoxy-Δ⁵-androsten-17-one Diacetylhydrazone (II).—Five grams (12.9 millimoles) of 3(β)-acetoxy-Δ⁵-androsten-17-one semicarbazone (I) was heated under reflux with 10 cc. of acetic anhydride and 20 cc. of pyridine for five hours. The cooled solution was added to 200 cc. of water. One hour later the precipitate which had formed was filtered and washed with water, then dissolved in a mixture of 80 cc. of acetone and 80 cc. of methanol and decolorized with charcoal. The solution was concentrated until crystallization could be induced. After several days in the cold, the crystallizate was filtered; weight, 3.86 g. (70%); m. p. 184–187°. After two similar recrystallizations the melting point became constant at 188–189°.

Anal. Calcd. for $C_{25}H_{36}O_4N_2$: C, 70.06; H, 8.47; N, 6.54. Found: C, 70.01; H, 8.80; N, 6.52.

A qualitative test for nitrogen was positive only after several trials in which the substance and sodium were heated slowly together. The filtrate from the 3.86 g. of II yielded a small quantity of V.

One gram of II was hydrolyzed by boiling under reflux for six hours in a mixture of 30 cc. of alcohol and 3 cc. of concd. hydrochloric acid. After the addition of 10 cc. of water the mixture was concentrated. This process was repeated, then 30 cc. of water was added, and the mixture was allowed to stand overnight. The filtered precipitate weighed 0.63 g. and melted at 138–148°. Since 3(β)-hydroxy-Δ⁵-androsten-17-one (III) is polymorphous, the product was acetylated. The resulting compound melted at 165–167°, undepressed on admixture with a specimen of 3(β)-acetoxy-Δ⁵-androsten-17-one (IIIa).

3(β)-Hydroxy-Δ⁵-androsten-17-one Hydrazone (IV).—This compound, prepared in alcohol from 1.00 g. of III and 0.60 cc. of hydrazine hydrate, melted at 213–215°.

Anal. Calcd. for $C_{19}H_{30}ON_2$: C, 75.45; H, 9.99; N, 9.26. Found: C, 75.14; H, 9.85; N, 9.59.

Nineteen-hundredths gram of IV was boiled under reflux for two hours with 1 cc. of acetic anhydride and 1 cc. of pyridine. The product was precipitated with water, and the mixture was shaken with chloroform. The chloroform extract, washed with dilute hydrochloric acid, sodium bicarbonate solution, and water, and dried over magnesium sulfate, was evaporated. The residue after two recrystallizations from ethanol melted at 186–187.5°, undepressed on admixture with II.

When 0.30 g. of IV was dissolved in 2 cc. of pyridine and 1 cc. of acetic anhydride and allowed to stand overnight, a crystallizate formed. It was filtered and washed copiously with water. The dry product weighed 0.35 g. and melted at 225–226°, undepressed on admixture with a specimen of V.

3(β)-Acetoxy-Δ⁶-androsten-17-one Acetylhydrazone (V).—One gram (2.6 millimoles) of I was heated under reflux for five hours with 4 cc. of acetic acid and 2 cc. of acetic anhydride. The product was precipitated with water and washed into a separatory funnel with ether. The ether extract was washed to neutrality with sodium bicarbonate solution, then with water, dried over magnesium sulfate, and evaporated. The dry residue, 0.88 g. (88%), was recrystallized from 4 cc. of alcohol. After another recrystallization the melting point was 227–228.5°, unchanged by further purification, and undepressed on admixture with a specimen whose preparation is described below.

Anal. Calcd. for $C_{23}H_{34}O_3N_2$: C, 71.47; H, 8.87; N, 7.25. Found: C, 71.23; H, 9.34; N, 7.42.

Seventy-seven hundredths of a gram (2.3 millimoles) of IIIa, dissolved in 4 cc. of ethanol, was treated with 0.34 g. (4.6 millimoles) of acetohydrazide dissolved in 1 cc. of ethanol and allowed to stand sixty hours. The crystallizate, 0.72 g. (80%), was filtered; m. p. 224–226°.

After 0.40 g. of IV had been boiled under reflux in 2 cc. of acetic anhydride and 2 cc. of pyridine for three hours, the solution was treated with water and extracted with chloroform. After the usual washings, described above, the chloroform solution was dried and evaporated. The residue, after one recrystallization from ethanol, weighed 0.28 g. (63%) and melted at 188–189°, undepressed on admixture with II.

3(β)-Acetoxy-Δ⁵-pregnen-20-one Diacetylhydrazone.—3(β)-Hydroxy-Δ⁵-pregnen-20-one semicarbazone was converted into the diacetylhydrazone in the manner described for I and isolated by the procedure described for V. The pure diacetylhydrazone melted at 122–123°.

Anal. Calcd. for $C_{27}H_{40}O_4N_2$: C, 71.02; H, 8.83. Found: C, 70.68; H, 8.78.

3(β)-Acetoxy-Δ⁵-pregnen-20-one Acetylhydrazone.—One and forty-five one-hundredths grams of 3(β)-hydroxy-Δ⁵-pregnen-20-one semicarbazone was boiled under reflux for five hours with 4 cc. of acetic anhydride and 2 cc. of acetic acid. The product was isolated by extraction with ether in the manner described for the isolation of V. After evaporation of the solvent the oily residue was crystallized from ethanol–water. The crystallizate, 0.73 g., melted at 113–114.5°, and proved to be chiefly the diacetylhydrazone. By fractional crystallization a small quantity of the monoacetylhydrazone was isolated; m. p. 177–185°. It was identified by the melting point of a mixture with a specimen whose preparation is described below.

Both of the acetylhydrazones of pregnenolone were difficult to purify because, like many other derivatives of pregnenolone, they formed gels in several solvents.

From experiments in which less acetic anhydride was used much unreacted semicarbazone was recovered, and very little acetylhydrazone was obtained.

The acetylhydrazone was also prepared from 3(β)-acetoxy-Δ⁵-pregnen-20-one and acetohydrazide in ethanol. After recrystallization from absolute ethanol the acetylhydrazone melted at 204–206°.

Anal. Calcd. for $C_{25}H_{38}O_3N_2$: C, 72.42; H, 9.24. Found: C, 72.92; H, 9.39.

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[5] Chapman and Wilson, *J. Chem. Soc.*, 507 (1931).

[6] Stratton and Wilson, *ibid.*, 1154 (1931).

[7] Wilson, Hopper and Crawford, *ibid.*, **121**, 866 (1922).

[8] Wilson and Crawford, *ibid.*, **127**, 103 (1925).

[9] Minunni, D'urso, *et al.*, *Gazz. chim. ital.*, **58**, 808 (1928); *C. A.*, **23**, 3681 (1929).

[10] Analyses were performed by Mr. Joseph F. Alicino of Metuchen, N. J. The hydrazones reported here were difficult to analyze and several analyses had to be repeated before satisfactory values were obtained.

$3(\beta)$-Acetoxy-Δ^5-norcholesten-25-one Diacetylhydrazone.—This compound was prepared from $3(\beta)$-acetoxy-Δ^5-norcholesten-25-one semicarbazone in the manner described for the preparation of II and was isolated by extraction with ether according to the procedure for the isolation of V. The pure product melted at 121–122°.

Anal. Calcd. for $C_{32}H_{50}O_4N_2$: C, 72.96; H, 9.57. Found: C, 73.51; H, 9.63.

Acetophenone Acetylhydrazone.—Six grams of acetophenone semicarbazone, 6 cc. of acetic acid, and 3.9 cc. of acetic anhydride were boiled under reflux for five hours. All substances which were volatile at 150° were distilled, and the residue was treated with water. The crystallizate which formed was filtered and washed with water. It weighed 2.60 g. and melted at 98–110°. On recrystallization from methanol, 0.85 g. of yellow prisms of m. p. 121–122° was obtained. The melting point of a mixture of this substance and of methyl phenyl ketazine was unchanged.

The filtrate yielded 0.55 g. of substance; m. p. 113–119°. After recrystallization from methanol the almost white crystallizate melted at 126°, undepressed on admixture with acetophenone acetylhydrazone. The latter compound was also prepared from acetophenone and 1.6 equivalents of acetohydrazide in ethanol; yield of pure substance, 75%; m. p. 131–132°.

Anal. Calcd. for $C_{10}H_{12}ON_2$: C, 68.15; H, 6.87; N, 15.90. Found: C, 68.19; H, 6.67; N, 15.78.

Methyl Phenyl Ketazine.—This compound was prepared by heating acetophenone semicarbazone.[2a] After one recrystallization from methanol, yellow prisms of m. p. 121.5–122° were obtained; reported,[2a] 121°.

Acetone Diacetylhydrazone.—Thirty-four grams (0.30 mole) of acetone semicarbazone was boiled under reflux for five hours with 108 cc. (1.90 moles) of acetic anhydride and 200 cc. of pyridine. The mixture was then distilled through a column at 20 mm. pressure. Most of the solution distilled below 60°. That which distilled at 85–92°, 23 g. (50%), was retained and redistilled. The fraction which distilled at 84–85° and 20 mm. was analyzed.

Anal. Calcd. for $C_7H_{12}O_2N_2$: N, 17.94. Found: N, 18.14.

When the distillation of the hydrazone was attempted at atmospheric pressure, it decomposed with evolution of a gas at about 170° When the hydrazone was heated with concentrated hydrochloric acid in ethanol, hydrazine dihydrochloride was formed.

N,N'-Diacetylhydrazine.—A mixture of 1.56 g. of acetone diacetylhydrazone, 0.18 g. of water, and 2 cc. of acetic acid was boiled under reflux for one-half hour and evaporated *in vacuo*. When benzene was added to the residue, a crystallizate formed at once. After having stood one hour in the cold it was filtered; weight, 0.84 g. (72%); m. p. 122–129°, softening at 103°. Although the compound appeared to be dry, it melted at 138–139° after drying *in vacuo* at 78°. On recrystallization from ethanol it melted at 139.0–139.5°, and the melting point of a mixture of the compound with N,N'-diacetylhydrazine was unchanged.

Anal. Calcd. for $C_4H_8O_2N_2$: C, 41.37; H, 6.94. Found: C, 41.21; H, 6.96.

A sample of N,N'-diacetylhydrazine was prepared by boiling 5.00 g. (0.10 mole) of hydrazine hydrate with 30.0 cc. (0.30 mole) of acetic anhydride under reflux for ninety minutes. After distillation of the volatile substances *in vacuo*, the residue was recrystallized from methanol. The colorless crystals weighed 10.4 g. (90%); m. p. 139–139.5°; reported[11] 138°.

Acetone Acetylhydrazone.—Attempts to prepare this compound from acetone semicarbazone and the calculated quantity of acetic anhydride in acetic acid led only to small quantities of the diacetylhydrazone.

The monoacetylhydrazone was prepared when 0.74 g. (0.01 mole) of acetohydrazide and 2.35 g. (0.04 mole) of acetone were boiled under reflux for thirty minutes. The cooled mixture gave 0.96 g. of white needles (84%); m. p. 138–139.5°. On recrystallization from methanol the substance melted at 139.5–140°.

Anal. Calcd. for $C_5H_{10}ON_2$: N, 24.55. Found: N, 24.54.

Summary

Semicarbazones of ketones may be converted into the corresponding acetylhydrazones and diacetylhydrazones by heating with acetic anhydride. A mechanism for this reaction and for similar reactions is advanced.

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[11] Stollé, *Ber.*, **32**, 796 (1899).

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF IOWA STATE COLLEGE]

The Reaction of Aryllithium Compounds with 2-Arylquinolines

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Incidental to the preparation of 2-(*p*-aminophenyl)-quinoline from quinoline and the lithium salt of *p*-aminophenyllithium, a secondary product was isolated. This was considered to be a 2,4-disubstituted quinoline which may have formed as a consequence of 1,4-addition to the previously formed 2-substituted quinoline. In order to throw light on the structure of the compound, as well as to examine the generality of the reaction, 2-phenylquinoline was brought into reaction with phenyllithium.

Ziegler and Zeiser[1] obtained from a reaction between quinoline and *n*-butyllithium not only the expected 2-*n*-butylquinoline but an isomeric by-product (isolated as the picrate) which they considered to be 4-*n*-butylquinoline. However, the quantity of this product was insufficient to make identification decisive. Also, from a reaction between quinoline and phenyllithium they isolated in addition to 2-phenylquinoline a small quantity of a lower melting product which they suggested might be 4-phenylquinoline. Then Bergmann and Rosenthal[2] reported that reaction of quinoline and benzylmagnesium chloride gave 2-benzylquinoline and small quantities of 4-benzylquinoline and 2,4-dibenzylquinoline. The picrate of their 4-benzylquinoline had a melting point in agreement with that reported for 4-benzylquinoline prepared by another method.

From our reaction of 2-phenylquinoline with phenyllithium there was obtained a compound melting at 86–87°. This compound was not 2,4-

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[1] Ziegler and Zeiser, *Ann.*, **485**, 174 (1931).

[2] Bergmann and Rosenthal, *J. prakt. Chem.*, [2] **135**, 274 (1932).