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BEHAVIOR OF SEMICARBAZONES UNDER THE CONDITIONS OF THE FISCHER REACTION

M. F. Marshalkin and L. N. Yakhontov

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Cyclohexanone semicarbazone and phenylsemicarbazone form 1,2,3,4-tetrahydro- and 1,2,3,4,5,6,7,8-octahydrocarbazoles under the conditions of the Fischer reaction. The reaction proceeds through a cyclohexanone azine intermediate. The product of oxidation of the azine is oxidized by air oxygen to 1,2,3,4-tetrahydrocarbazole. The investigated semicarbazones are stable with respect to the action of sodium ethoxide at up to 300°C.

In addition to the extensively studied Fischer indolization of arylhydrazones, various transformations of N-acylated hydrazines and hydrazones have been described in the literature: the cyclization of N-acyl-N'-arylhydrazines to hydroxyindoles by the Brunner method [1], the thermal cleavage of benzaldehyde benzoylhydrazone to benzamide and benzonitrile with cuprous chloride [2], and the cationotropic rearrangement of N-acyl-N'-arylhydrazines to 2-aminoindoles [3]. The behavior of semicarbazones, which are N-acylated hydrazones in which the acylating group is a carbamide residue, under the conditions of the Fischer reaction has not been previously investigated.

We have studied the behavior of cyclohexanone phenylsemicarbazone (I) under the conditions of the Fischer reaction. 1,2,3,4-Tetrahydrocarbazole (II), which was identical to the substance formed in the Fischer cyclization of cyclohexanone phenylhydrazone [4], was obtained in 10% yield when I was heated with zinc chloride to 240-250°C and the mixture was chromatographed on aluminum oxide. A subsequent study of the reaction products enabled us to isolate aniline (IV) in 47% yield and 1,2,3,4,5,6,7,8-octahydrocarbazole (III) in 24% yield. Analysis of the reaction mixture by gas—liquid chromatography (GLC) showed that the percentages of II, III, and IV prior to separation are 15, 35, and 50%, respectively. These results constitute evidence that the principal transformation of semicarbazone I is not indolization of the Fischer type but rather cleavage of the N—N bond with the subsequent formation of aniline and an intermediate containing two cyclohexane residues that is capable of undergoing cyclization to octahydrocarbazole III. Experiments with pure octahydrocarbazole III showed that III is capable upon heating of undergoing oxidation by air oxygen to tetrahydrocarbazole II; this oxidation process is virtually quantitative at 240°C after 6 h. Thus the formation of tetrahydrocarbazole II to a considerable extent may be due to secondary oxidation of octahydrocarbazole III. (See scheme at top of next page.)

In order to determine the role of the phenyl residue in the formation of the tetrahydrocarbazole system we carried out a similar reaction with cyclohexanone semicarbazone (V), which does not contain a phenyl group. The reaction was carried out under the same conditions as in the reaction with semicarbazone I and led to the formation of octahydrocarbazole III in ~90% yield and tetrahydrocarbazole II in ~3% yield (according to GLC data). We were

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S. Ordzhonikidze All-Union Scientific-Research Pharmaceutical-Chemistry Institute, Moscow 119021. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 11, pp. 1487-1489, November, 1978. Original article submitted July 7, 1977.

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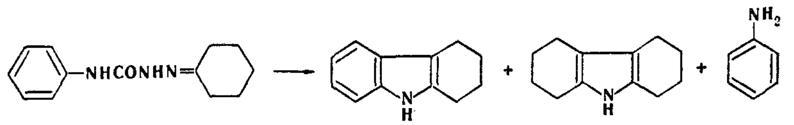
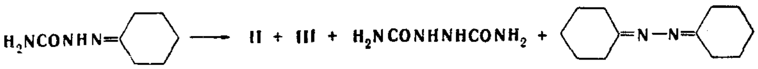


I II III IV



V VI VII

able to isolate octahydrocarbazole III preparatively in 54% yield. A decrease in the amount of zinc chloride to a catalytic quantity and heating semicarbazone V in the absence of Lewis acids made it possible to slow down the process and facilitated the isolation of the other reaction products. In the latter case hydrazodiformamide (VI) (84% yield) and cyclohexanone azine (VII) (in 68% yield) were isolated.

The results obtained in this research make it possible to represent the course of the reaction in the following manner. Homolytic cleavage of the N–N bond with subsequent recombination of the radicals to give VI and VII evidently occurs when semicarbazone V is heated. The formation of azine VII was also recently observed by Larsen and Jakobsen [5] in the thermal fragmentation of cyclohexanone semicarbazone in a mass spectrometer under the influence of electron impact. In conformity with the mechanism proposed by Kost and Grandberg [6], the resulting azine VII undergoes cyclization to octahydrocarbazole III. Partial oxidation of the latter with air oxygen is also responsible for the formation of tetrahydrocarbazole II. In the case of cyclohexanone phenylsemicarbazone (I) the process is evidently similar, with the difference that stabilization of the phenyl-containing radical leads to the formation of aniline (IV). The cyclohexylimine radical undergoes the same transformations as in the case of semicarbazone V.

EXPERIMENTAL

The IR spectra of mineral oil pastes of the crystalline compounds were recorded with a Perkin–Elmer 457 spectrometer. Gas-liquid chromatography (GLC) was carried out with a Pye–Unicam series 104 chromatograph with a catharometer and a 2.1 by 4 mm column filled with 10% SE-30 silicone elastomer on silanized diatomaceous earth (100-120 mesh); the helium flow rate was 30 ml/min, the column temperature was 200°C, and the retention times were 5 min for I, 9 min for II, 6.5 min for III, 4 min for V, and 5.5 min for VII. In the analysis of samples containing aniline (IV) determinations were also made with the same column at 100°C, and the retention time of IV was 4 min. Analytically pure samples of the individual compounds were used as the standards in the quantitative analysis by GLC.

Result of Heating Cyclohexanone Phenylsemicarbazone with Zinc Chloride. A mixture of 2.5 g (13 mmole) of I [7] and 3 g (21 mmole) of anhydrous zinc chloride was heated at 240-250°C for 15 min, after which it was cooled and dissolved in water. The aqueous solution was made alkaline to pH 9, and the reaction products were extracted with chloroform. The chloroform solution was dried with magnesium sulfate and evaporated, and the residue (1.54 g) was applied to a column (25 cm by 2 cm) filled with activity II aluminum oxide. Elution with ether (300 ml) gave a mixture of products, after which elution with 200 ml of ether–methanol (9:1) gave 0.1 g (10%) of pure 1,2,3,4-tetrahydrocarbazole (II) with mp 115-116°C [4]. No melting-point depression was observed for a mixture of this product with a genuine sample of II [4]. The IR spectra and GLC retention times of the two samples were identical. The first ether eluate was evaporated, and the residue was vacuum distilled. The first fraction [0.54 g (47%)] had bp 52-53°C (3 mm) and was identified as aniline (IV) from its IR spectrum and GLC retention time. The second fraction [0.28 g (24%)] had bp 143-145°C (3 mm) and was identified as 1,2,3,4,5,6,7,8-octahydrocarbazole (III) [6] from its IR and PMR spectra and GLC retention time.

Starting I was recovered when 0.6 g of semicarbazone I was heated with sodium ethoxide at 240-250°C for 10 min.

Thermal Transformations of Cyclohexanone Semicarbazone (V). A 2.5-g (16 mmole) sample of semicarbazone V [8] was heated at 210°C for 10 min, after which it was cooled and treated with 50 ml of chloroform. The precipitate was removed by filtration and washed with ether to give 0.8 g (84%) of hydrazodiformamide (VI) with mp 245-246°C. Found: C 20.4; H 5.4; N 47.5%. $C_2H_6N_4O_2$. Calculated: C 20.3; H 5.1; N 47.4%. The product was identified as VI from a mixed-melting point determination and IR spectra for a genuine sample of VI synthesized from semicarbazide by the method in [9].

The chloroform solution was evaporated, and the residue (1.48 g) was distilled to give 1.04 g (68%) of cyclohexanone azine (VII) with bp 97-98°C (2 mm) and mp 34-35°C. According to its IR spectrum, GLC retention time, and the results of a mixed-melting-point determination the product was identidal to a sample obtained by the method in [6].

Result of Cyclohexanone Semicarbazone (V) with Zinc Chloride. A) A mixture of 2.8 g (18 mmole) of semicarbazone V and 2 g (14 mmole) of anhydrous zinc chloride was heated at 240-250°C for 10 min, after which it was cooled and dissolved in water. The aqueous solution was made alkaline to pH 9 and extracted with chloroform. The chloroform extract was dried with magnesium sulfate, and the residue (1.68 g) was distilled with collection of the fraction with bp 140-141°C (3 mm) to give 0.85 g (54%) of 1,2,3,4,5,6,7,8-octahydrocarbazole (III). Found: C 81.8; H 9.7; N 8.2%. $C_{12}H_{17}N$. Calculated: C 82.3; H 9.7; N 8.0%. According to the IR and PMR spectra and GLC retention time, the product was identical to a sample of III obtained by the method in [6]. According to the GLC data, the percentage of III in the chloroform extract of this experiment was 90% of the theoretical value, and ~3% 1,2,3,4-tetrahydrocarbazole (II) was present.

B) A 2.8-g (18 mmole) sample of semicarbazone V was heated with 0.05 g (0.35 mmole) of anhydrous zinc chloride at 240-250°C for 10 min, after which the mixture was cooled and dissolved in water. The aqueous solution was made alkaline to pH 9 and extracted with chloroform. According to the GLC data, the chloroform extract contained 55% VII, 35% III, and 3% II.

Cyclization of Cyclohexanone Azine (VII). A 2-g (10 mmole) sample of azine VII was heated with 3 g (21 mmole) of anhydrous zinc chloride at 240°C for 10 min, after which the mixture was cooled and dissolved in water. The solution was made alkaline to pH 9 and extracted with chloroform. The chloroform extract was evaporated, and the residue (1.6 g) was distilled to give 1.05 g (51%) of octahydrocarbazole III with bp 140-141°C (3 mm). Analysis by GLC of the residue from the evaporization of the chloroform extract (1.6 g) showed that 74% octahydrocarbazole III and 12% tetrahydrocarbazole II were present.

In a similar reaction with 0.05 g (0.35 mmole) of zinc chloride the yields (from GLC data) were as follows: 55% III, 35% VII, and 3% II. An increase in the heating time to 4 h under these conditions led to the following yields (from GLC data): 80% III and 14% II. A further increase in the reaction time to 8 h made it possible to obtain tetrahydrocarbazole II in 90% yield.

Conversion of Octahydrocarbazole III to Tetrahydrocarbazole II. A 0.1-g (0.6 mmole) sample of octahydrocarbazole III was heated at 240°C for 6 h, after which it was cooled and treated with 10 ml of 30% aqueous methanol, and the precipitated tetrahydrocarbazole II was removed by filtration to give 0.07 g (71%) of a product with mp 115-116°C [4]. According to the data from GLC of the reaction mixture, quantitative conversion of III to II was realized.

When semicarbazones I and V were heated with sodium ethoxide at various temperatures ranging from 240-300°C, the cleavage of the N–N bond with simultaneous N-alkylation that was observed in similar reactions with hydrazones [10] did not occur. Only starting semicarbazones I and V were recovered in all cases.

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