Anal. Calcd. for $C_{15}H_{21}O_5Br$: C, 49.87; H, 5.86. Found: C, 49.75; H, 5.57. Calcd. for $C_{18}H_{19}OBr(COOH)_2$: neut. eq., 181. Found: neut. eq., 179.

Summary

It is shown that in the addition of maleic anhydride to 6,6-pentamethylenefulvene, a dissociable *endo* product and a stable *exo* isomer are obtained. The relation of the properties of these isomers and the conditions under which they are formed to the mechanism of diene-addition reactions is discussed.

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[CONTRIBUTION FROM THE RESEARCH LABORATORIES, S. M. A. CORPORATION]

Hydantoins of Some Sulfur Containing Amino Acids

BY JOSEPH V. KARABINOS[1] AND J. LESTER SZABO

Introduction

The preparation of a number of hydantoins from amino acids has been described by Boyd.[1a] The hydantoins of the sulfur containing amino acids, cystine[2] and methionine,[1a] have been cited previously. The preparation of a thiol hydantoin in crystalline form, however, has not been described in the literature although Boyd[1a] did mention a non-crystalline cysteine hydantoin which was very soluble in water and alcohol but only slightly soluble in ether, chloroform and benzene.

In this communication we describe the preparation of the crystalline hydantoins of *l*-cysteine, *dl*-homocysteine, homocysteine and S-benzylhomocysteine. *l*-Cysteine hydantoin was obtained in good yield by treating *l*-cystine hydantoin with sodium in liquid ammonia. In like manner we have prepared *dl*-homocysteine hydantoin from the hydantoins of both homocystine and S-benzylhomocysteine. It is interesting to note that under the conditions used in this work, the hydantoin ring is stable to the reduction of sodium in liquid ammonia. The hydantoins of homocystine and S-benzylhomocysteine were obtained by the action of potassium cyanate and hydrochloric acid on the corresponding amino acid. Following the isolation of *l*-cysteine and *dl*-homocysteine hydantoins each was oxidized quantitatively with iodine to yield *l*-cystine- and *dl*-homocystine hydantoins, respectively.

In addition to the many sulfur compounds which have gained attention in therapeutic research certain hydantoins have likewise commanded interest, *e. g.*, in alleviating the symptoms of epilepsy. The fact that the hydantoins of *l*-cysteine and *dl*-homocysteine proved to be water soluble suggested possible practical applications.

Experimental Part

***l*-Cysteine Hydantoin.**—Cystine hydantoin (29 g.) which was prepared according to the directions of Hess[2] was dissolved in 200 cc. of liquid ammonia to which sufficient sodium was added to maintain a blue color for ten minutes. The greater part of the ammonia was allowed to evaporate at room temperature and the last traces were removed in a vacuum. Ten per cent. hydrochloric acid (200 cc.) was added and the acid solution was extracted four times with 200-cc. portions of ethyl acetate. The extracts were combined, dried over sodium sulfate and the solvent was removed *in vacuo*. The white crystalline residue (15 g.) was easily recrystallized from water to give platelets melting at 144–145°.[3]

Anal. Calcd. for $C_4H_6O_2N_2S$: C, 32.87; H, 4.14. Found: C, 33.21; H, 4.14.

S-Benzylhomocysteine Hydantoin.—A mixture of 50 g. of S-benzylhomocysteine[4] and 22 g. of potassium cyanate was heated in 250 cc. of water for thirty minutes until a clear solution was obtained. When 10% hydrochloric acid (620 cc.) was added slowly, a solid precipitated which liquefied on heating. The mixture was heated on the steam-bath for several hours. After cooling the mixture, the crystals were collected on a filter. Following recrystallization from ethanol the material melted at 103–104° and weighed 45 g. (81%).

Anal. Calcd. for $C_{12}H_{14}O_2N_2S$: N, 11.19. Found: N, 11.43.

Homocystine Hydantoin.—Homocystine (10 g.) was suspended in 57 cc. of boiling water with 7.4 g. of potassium cyanate until complete solution was obtained. Ten per cent. hydrochloric acid (110 cc.) was added and the mixture evaporated on the steam-bath to about one-half the original volume. The homocystine hydantoin which crystallized from the cooled solution was collected by filtration, washed with water until chloride free and dried. The yield was 10 g. (82%); the compound melted at 204–205°.

Anal. Calcd. for $C_{10}H_{14}O_4N_4S_2$: N, 17.60. Found: N, 17.70.

***dl*-Homocysteine Hydantoin: (a) From Homocystine Hydantoin.**—To 5.2 g. of homocystine hydantoin in 50 cc. of liquid ammonia was added 1.8 g. of sodium. The ammonia was allowed to evaporate spontaneously. The residue was taken up in water and neutralized to a *p*H of 4 and extracted four times with 50-cc. portions of ethyl acetate. The extracts were combined, dried with sodium sulfate and the solvent removed *in vacuo*. The yield was 3.5 g. (67%) of a product melting at 120°.

(b) From S-Benzylhomocysteine Hydantoin.—To 6 g. of S-benzylhomocysteine hydantoin in 100 cc. of liquid ammonia was added 1 g. of sodium. The residue remaining after the evaporation of the ammonia was evacuated thoroughly, treated with 50 cc. of ice water, acidified with 12 cc. of concentrated hydrochloric acid and filtered. The solution was extracted twice with 10-cc. portions of benzene to remove toluene and dibenzyl and then with four 15-cc. portions of ethyl acetate. The ethyl acetate extracts were combined, dried and evaporated *in vacuo*. The residue weighed 3.5 g. (92%) and melted at 121–122°. Recrystallization from ethyl acetate did not raise the melting point.

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(1a) Boyd, *Biochem. J.*, **27**, 1838 (1933).

(2) Hess, THIS JOURNAL, **56**, 1421 (1934).

(3) All melting points were recorded on a microstage and are uncorrected.

(4) Patterson and du Vigneaud, *J. Biol. Chem.*, **111**, 393 (1935).

Anal. Calcd. for $C_5H_8O_2N_2S$: C, 37.50; H, 5.03. Found: C, 37.83; H, 5.05.

Oxidation of Homocysteine Hydantoin.—Fifty mg. of homocysteine hydantoin was titrated with 2.9 cc. of 0.1 *N* iodine solution which is 93% of the theoretical. The crystals which precipitated were collected by filtration, dried and gave a m. p. of 201–203°. A mixed m. p. with homocystine hydantoin gave no depression.

Oxidation of Cysteine Hydantoin.—Sixty-four and a half mg. of cysteine hydantoin consumed 4.4 cc. of 0.1 *N* iodine solution which is the theoretical quantity. The crystals were collected on a filter and dried. The compound decomposed above 300° and gave a positive disulfide test.

Summary

1. The preparation of the hydantoins of *l*-cysteine, *dl*-homocysteine, S-benzylhomocysteine, and *dl*-homocystine has been described.

2. The hydantoin ring is stable to the reduction of sodium in liquid ammonia.

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[CONTRIBUTION FROM THE RESEARCH LABORATORIES, S. M. A. CORPORATION]

The Dehydration of Hydantoin-5-propionic Acid

BY J. LESTER SZABO AND JOSEPH V. KARABINOS

Introduction

If it is assumed that hydantoins may enolize, three possible structures (II, IV and VI) may be postulated for the compound obtained by the dehydration of hydantoin-5-propionic acid. Dakin[1] has stated that such an enolization (III ⇄ I) is possible since racemization of optically active hydantoins probably occurs through this mechanism.

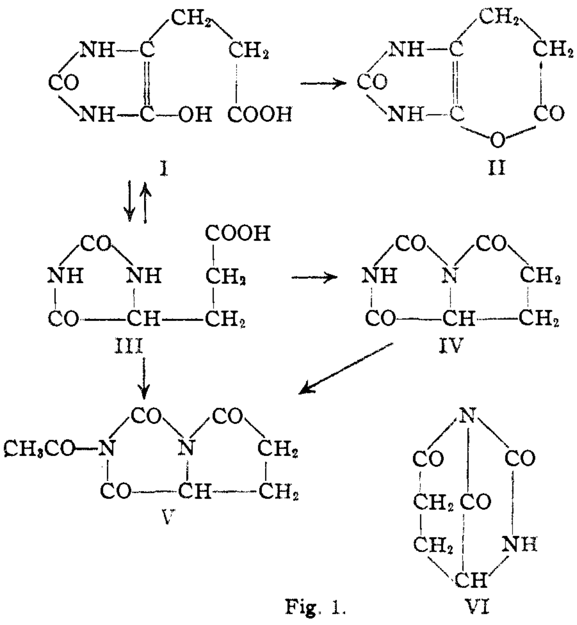

Fig. 1.

By the action of phosphoric anhydride on hydantoin-5-propionic acid (III) a molecule of water was split out and the resulting product obtained in good yield. Theoretically this could be either II, IV or VI. Acetylation of the acid as well as the lactam yielded the same mono-acetyl derivative (V). Neither the dehydration product nor the acetyl derivative reacted with aqueous potassium permanganate or bromine in carbon tetrachloride. The mono-acetyl derivative could not be acetylated further under conditions which yielded diacetyl hydantoin. These facts tend to indicate one of the lactam formulas (IV or VI).

However, the structure of the dehydration product was shown by the following experiment. 2-Thiohydantoin-5-propiolactam-1 (VIII) had been synthesized previously from pyrrolidone carboxylic acid and ammonium or potassium thiocyanate by Johnson and Guest[2] and also by Nicolet and Johnson.[3] By desulfurization of the thiohydantoin with chloroacetic acid they obtained hydantoin-5-propionic acid instead of hydantoin-5-propiolactam-1. Hydrolysis with dilute hydrochloric acid gave 2-thiohydantoin-5-propionic acid (IX). It was obvious, therefore, that if the acid (IX) could be converted back to the lactam (VIII) by dehydration with phosphoric anhydride, we could assume that hydantoin-5-propionic acid undergoes a similar reaction and that our dehydration product is the oxygen analog of VIII, *i. e.*, hydantoin-5-propiolactam-1 (IV). 2-Thiohydantoin-5-propionic acid (IX) was obtained by the hydrolysis of VIII and converted back to VIII by dehydration with phosphoric anhydride. We may assume, therefore, that the dehydration of hydantoin-5-propionic acid yields hydantoin-5-propiolactam-1 (IV) and not hydantoin-5-propiolactam-3 (VI) or the lactone (II).

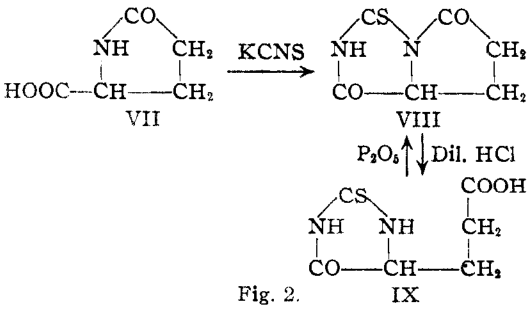

Fig. 2.

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[1] Dakin, *Am. Chem. J.*, **44**, 48 (1910).

[2] Johnson and Guest, *ibid.*, **47**, 242 (1912).

[3] Nicolet and Johnson, *ibid.*, **49**, 204 (1913).