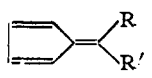
[CONTRIBUTION FROM THE CONVERSE MEMORIAL LABORATORY OF HARVARD UNIVERSITY]

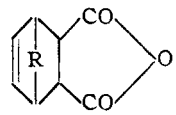
Studies on Diene-addition Reactions. II.[1] The Reaction of 6,6-Pentamethylenefulvene with Maleic Anhydride

BY R. B. WOODWARD AND HAROLD BAER

The capacity of fulvenes to participate in normal diene-addition reactions with maleic anhydride was first observed in the cases of 6,6-diphenylfulvene (I, R = R′ = C_6H_5), 6,6-dimethylfulvene (I, R = R′ = CH_3—), and 6-styrylfulvene (I, R = C_6H_5CH=CH—, R′ = H), by Diels and Alder,[2] who assigned the structures (II, R = $(C_6H_5)_2C<$ *or* $(CH_3)_2C<$ *or* C_6H_5CH=CH—CH<) to their products. Some years later,

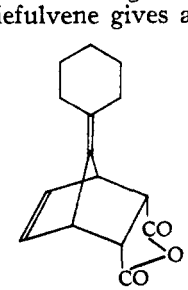


I

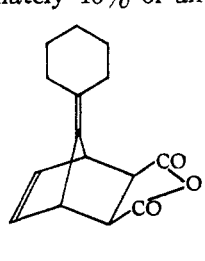


II

Kohler and Kable[3] obtained addition products from 6,6-tetramethylenefulvene (I, R,R′ = —$(CH_2)_4$—) and 6,6-pentamethylenefulvene (I, R,R′ = —$(CH_2)_5$—) with maleic anhydride. These adducts were hydrogenated to dihydroderivatives, from which cyclopentanone and cyclohexanone, respectively, were obtained on ozonization; these facts are in accordance with the formulations (II, R = $(CH_2)_4C$=C< *or* $(CH_2)_5C$=C<). These investigators made the further striking observation that their adducts, as well as those obtained earlier by Diels and Alder, had the remarkable property of dissociating readily into their components, even on solution in the cold in a variety of solvents. Subsequently, Alder and Stein[4] called attention to the fact that the reaction of fulvenes with maleic anhydride is not stereochemically homogeneous, but leads in many cases to a mixture of products having different configurations. Thus, according to these workers, 6,6-pentamethylenefulvene gives approximately 40% of an adduct having the *endo*- (III) and 60% of a product with the *exo*- configuration (IV). No experimental evidence in support of these statements has been forthcoming in the intervening six years.[4] In the course of a related investigation, we have had occasion to make a careful study of the reaction between 6,6-pentamethylenefulvene and maleic anhydride. As will appear in the sequel, our work provides *experimental proof of the formation of the stereoisomers III and IV:* beyond this, our picture differs very considerably in detail from that of Alder and Stein.



III



IV

When 6,6-pentamethylenefulvene and maleic anhydride are allowed to react in benzene solution, at room temperature, an *α-adduct*, $C_{15}H_{16}O_3$, m. p. 132°, is obtained.[3] If, however, the mother liquor from the recovery of this product is allowed to stand for several weeks, very large beautiful crystals of a new, *β-adduct*, $C_{15}H_{16}O_3$, m. p. 93°, gradually separate. *Further, as the initial condensation is carried out at higher temperatures, the formation of the β-adduct takes place more rapidly, and less of the α-adduct is obtained.* These isomeric substances exhibit strikingly different behavior on solution in organic solvents. Solutions of the α-adduct, *e. g.*, in ethyl acetate or benzene, develop a deep yellow color, slowly in the cold, and very rapidly if warmed, as a result of partial dissociation into the (colored) fulvene and maleic anhydride. The β-adduct, on the other hand, is stable for relatively long periods, even in boiling solution. Only on heating for long periods above its melting point does the material gradually turn yellow.

Each of the adducts is reduced on shaking in ethyl acetate solution with hydrogen over reduced platinum oxide to a dihydro compound; the α-dihydro adduct melts at 146°, while the corresponding β-derivative has m. p. 104°. Kohler[3] has shown that in the case of the α-adduct, addition of hydrogen takes place exclusively on the ethene bridge, and further addition of hydrogen with saturation of the cyclohexylidene double bond is not possible. Similar phenomena are observed in the case of the new β-adduct. It is worthy of note that these results are concordant with the theory of catalyst hindrance developed *inter alia* by Linstead and his associates,[5] *viz.*, approach of a hydrogen-laden catalyst surface to the ethene bridge (arrows) of the model skeleton (V) would be relatively unhindered, while on the other hand approach to the other double bond would be difficult, if not impossible.

Both dihydro derivatives were stable, and therefore were used to determine the relationships be-

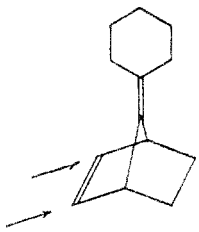
(1) *Cf.* Woodward, THIS JOURNAL, **64**, 3058 (1942).

(2) Diels and Alder, *Ber.*, **62**, 2081 (1929).

(3) Kohler and Kable, THIS JOURNAL, **57**, 917 (1935).

(4) This first suggestion of stereochemical complications in the reaction of fulvenes with maleic anhydride was made briefly by the German authors in a review article on their elegant work on the steric course of diene-addition reactions in general [*Angew. Chem.*, **50**, 514 (1937)]. However, in spite of intimations there and elsewhere [*cf.* Alder and Backendorf, *Ann.*, **535**, 102 (1938), Note 1] that experimental support for the ideas advanced would appear shortly, none has appeared in the considerable interval since 1937.

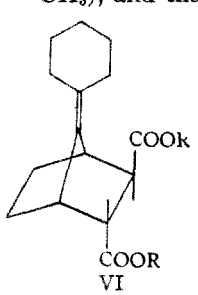
(5) Linstead, Doering, Davis, Levine and Whetstone, THIS JOURNAL, **64**, 1985 (1942).



V

tween the isomeric initial adducts, since the dissociation of the latter themselves, at least in the case of the α-adduct, would have precluded their survival in the reactions necessary for configurational determination.

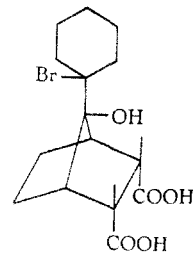
On catalytic esterification with methanol, the α-dihydro adduct was converted to an *oily* α-dihydrodimethyl ester, while the β-dihydro adduct gave a *crystalline* β-dihydrodimethyl ester, m. p. 65°. *Either dimethyl ester on boiling with sodium methoxide in methanol solution was inverted with the formation of the same trans-dihydrodimethyl ester, m. p. 75°.*[6] These facts demonstrate clearly that the latter compound has the structure (VI, R = CH_3), and that the difference



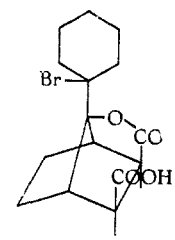
VI

between the initial α- and β-adducts is one of *endo-exo* isomerism. As a further check on the identity of the dimethyl esters, m. p. 75°, from the two sources, hydrolysis by acetic and hydrochloric acids of material prepared in either way gave the same *trans*-dihydrodicarboxylic acid (VI, R = H), m. p. 230–232° (dec.).

We are now in a position to determine which is the *endo*- and which the *exo*-series. On bromination of the α-dihydroanhydride (m. p. 146°) after long boiling in dilute acetic acid solution (to ensure opening of the anhydride ring), *a bromohydroxydicarboxylic acid* (VII), $C_{15}H_{21}O_5Br$, m. p. 153°, neutral equivalent, 179, was obtained. Similar treatment of the β-dihydroanhydride (m. p. 104°) gave a *bromolactone monocarboxylic acid* (VIII), $C_{15}H_{19}O_4Br$, m. p. 147°, neutral equivalent, 332. Since only *exo*-carboxyls are suitably placed for lactonization involving the cyclohexylidene double bond, it is evident that the bromination products have the structures (VII) and (VIII),[7] re-

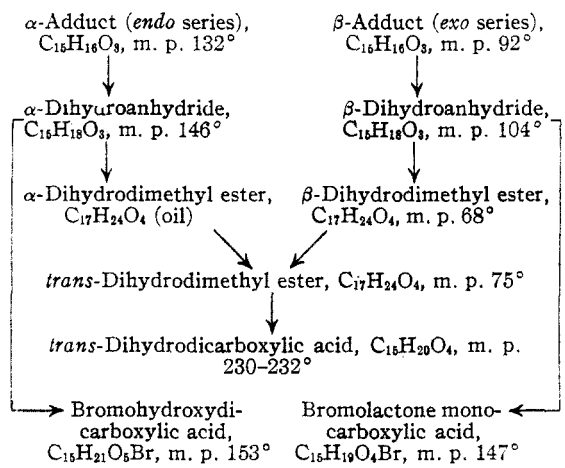


VII



VIII

spectively, and, consequently, *that the α-series has the endo-configuration, while the β-series are exo-derivatives, i. e., the α-adduct (m. p. 132°) has the structure (III), while the β-adduct (m. p. 93°) is to be formulated as (IV).* The accompanying chart will clarify the somewhat involved series of reactions of the configurational proof. A number of incidental products in each series, not further detailed here, are described in the experimental section.



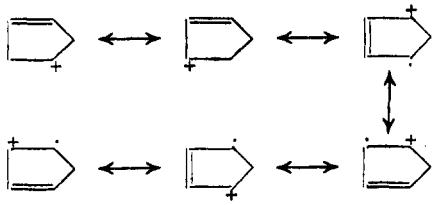
We turn now to a more detailed discussion of the phenomena observed in connection with the formation and stability of the two addition products. We have demonstrated clearly that while the *endo* isomer is formed more rapidly, longer reaction times, as well as relatively elevated temperatures, result in higher *exo*/*endo* ratios. These facts must be considered in the light of the remarkable stability of the *exo*-compound on the one hand, and the very facile dissociation of the *endo* isomer on the other. Since it is highly unlikely that there is a great difference in the energy content of the two stereoisomers we are justified in assuming that the intermediate, or activated complex for the formation of the *endo* isomer is of lower energy than that involved in the *exo* addition. On this basis, the *endo* addition, having the lower energy barrier, will proceed more rapidly, but will compete less favorably as the reaction is carried out at higher temperatures, and the true equilibrium ratio, c_{exo}/c_{endo} will be more rapidly approached. Further, considering the reverse process, the *endo* isomer will pass relatively easily over the same (low) barrier, while the *exo* compound is stabilized by the higher barrier over

(6) For similar inversions, *cf.*, Hückel and Goth, *Ber.*, **58**, 447 (1925); Cook and Linstead, *J. Chem. Soc.*, 946 (1934); Linstead and Doering, THIS JOURNAL, **64**, 1991 (1942).

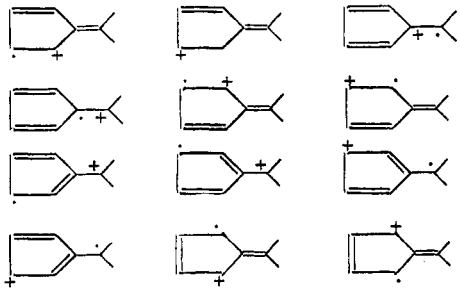
(7) There is some uncertainty in these formulations, in that the relative positions of the bromine and of the hydroxyl (or lactonic) substituents may be reversed. The point, of course, has no bearing on the configurational argument.

which it must pass during the dissociation process. The situation is symbolized in Fig. 1, and is not an unfamiliar one in organic chemistry.[8] (In the diagram E_{ABexo} is assumed to be somewhat lower than E_{ABendo} since the *exo* isomer apparently preponderates under those conditions under which it is likely that true *exo-endo* equilibrium is most nearly approached.)

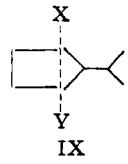
In mechanistic terms we are now faced with the problem of explaining the lower energy of the intermediate for *endo* addition. This may be interpreted in terms of the flat dipolar aggregate, $[A][B] \longleftrightarrow [A.]^+[B.]^- \longleftrightarrow [A]^+:[B]^-$, suggested by one of us as an intermediate in diene-addition reactions of this type.[1] The situation with regard to the distribution of charge over the diene moiety [A] of the intermediates is as follows; in the case of cyclopentadiene the charge will be distributed over the four carbon atoms of the unsaturated system:



In the case of the fulvenes, similar hybridization will likewise result in distribution of charge throughout the (now greater) conjugated system, *viz.*



It is clear that in the fulvene case, loss of charge will be distributed over the molecule (IX) on both sides of the line XY



IX

Now when a maleic anhydride molecule adds to a fulvene. the addition takes place at the carbon atoms intersected by the line XY. Further, depending on whether the adding molecule lies to the left or right of the line XY, the *endo* or *exo*

(8) Strictly speaking of course these considerations apply rigidly only to the *free* energies of the various processes. Since, however, the two isomers are both relatively rigid structures of equivalent symmetry, their entropies will be comparable, and we are justified in dealing with the absolute heat content of the various species.

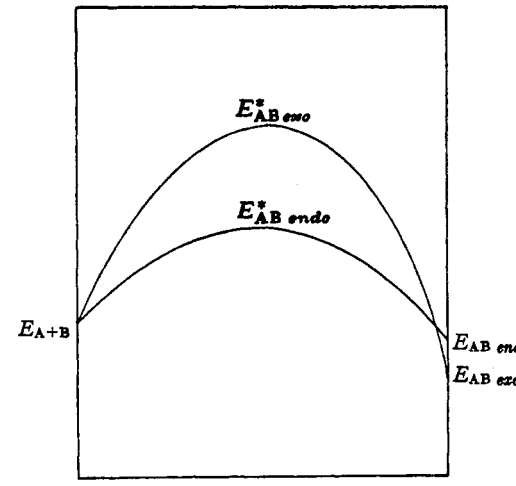
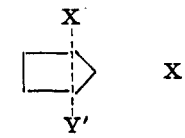


Fig. 1.

isomer will be obtained. It is now evident that in the fulvene case, attractive forces, arising both from exchange and charge overlapping, will be operative between the reacting fragments, whether the maleic anhydride molecule takes one position or the other and, further, that these attractive forces should be greater in the case of the intermediate for *endo* addition, in view of the somewhat greater concentration of charge within the pentacyclic ring. In the cyclopentadiene case it is clear that attractive forces will be operative only in the event that the molecule approaches from the left side of X'Y' (*cf.* X). These relations will



be apparent from inspection of the space models of Fig. 2. (In these models, the opposite charges on each template, A [or A'] and B, are small, and equal to one another. The signs are intended to represent approximate *distribution*, rather than magnitude of charge.)

It is very likely that similar energetic conditions obtain in the diene-addition reactions of the simple dienes, in which only *endo* products are normally obtained. In this case, E^*_{ABexo} (*cf.* Fig. 1) is so high that none of the *exo* product is obtained under attainable conditions. In this connection it is worthy of note that in one case, that of the dimerization of cyclopentadiene,[9] the observed phemomena are similar to those noted in the case of the fulvenes: *i. e.*, at moderate temperatures, only the *endo* isomer is formed, while heating for long periods at elevated temperatures gives a mixture of *exo* and *endo* products. It is not unlikely that further cases will be found where variation of the experimental conditions will permit isolation of both steroisomers.

(9) Alder and Stein, *Ann.*, **504**, 219 (1933).

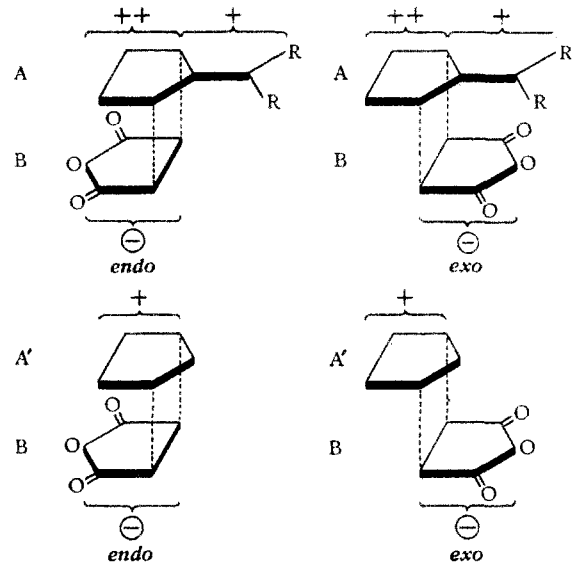


Fig. 2.—Models of intermediate complexes in the addition of maleic anhydride [B] to a fulvene [A] and to a simple diene [A']. Dotted lines indicate points of union in the final products.

Experimental

6,6-Pentamethylenefulvene was prepared according to Kohler's method.[3]

Condensation of 6,6-Pentamethylenefulvene and Maleic Anhydride.—All condensations were carried out with equimolar quantities of the reactants in concentrated benzene solution (fulvene/benzene = 1, by volume.) After standing (with or without heating) for specified times, the reaction mixture was placed in the cold room (5°), where the **α-adduct** (III) crystallized, and was collected and recrystallized from ether-petroleum ether, m. p. 132°. The mother liquors from this product, on standing for periods up to two weeks (or less if the initial reaction was carried out at higher temperatures) gradually deposited the **β-adduct** (IV) in very large beautiful plates, m. p. 87–90°, which on recrystallization from ligroin (b. p. 80–120°) had m. p. 92–93°. A sample recrystallized four times for analysis had m. p. 93.0–93.5°.

Anal. Calcd. for $C_{15}H_{18}O_3$: C, 73.9; H, 6.58. Found: C, 74.07; H, 6.75.

The following figures illustrate the effect of conditions on the yield of the α-adduct: ten minutes at 50°—20.8, 20.5%; 30 minutes at 60°—13.6, 14.5%; 60 minutes at 50°—3.1%.

The α-adduct, on solution in benzene or ethyl acetate, developed a yellow color, slowly in the cold, and rapidly on warming, while the β-adduct was apparently perfectly stable under these conditions.

β-Dihydroadduct.—On shaking with hydrogen over reduced platinum oxide, the β-adduct (3.2 g.) in 30 cc. purified[10] ethyl acetate consumed 315 cc. hydrogen (1 mole = 315 cc.) in *ca.* one-half hour at 26.5°, 776 mm., and the hydrogenation stopped. The residue after removal of solvent was thrice crystallized from ligroin (b. p. 90–120°), and dried *in vacuo* for three hours; needles, m. p. 103–104°.

Anal. Calcd. for $C_{15}H_{18}O_3$: C, 73.1; H, 7.37. Found: C, 73.3; H, 7.73.

Hydrogenation of the α-adduct under similar conditions gave the **α-dihydroadduct,**[3] m. p. 146°. Both dihydro adducts were readily converted into half-methyl esters by dissolving in methanol containing a drop of phenolphthalein solution, and adding 10% aqueous sodium hydroxide until the color persisted after boiling for a few minutes. After adding water to the cooled solution and acidifying with 10% hydrochloric acid, the substances were collected and recrystallized from ligroin. The **α-dihydromonomethyl ester** had m. p. 114°.

Anal. Calcd. for $C_{16}H_{22}O_4$: C, 69.05; H, 7.97. Found: C, 69.17; H, 8.39.

The **β-dihydromonomethyl ester had m. p. 118°.**

Anal. Calcd. for $C_{15}H_{22}O_4$: C, 69.05; H, 7.97. Found: C, 68.60; H, 7.92.

That these half-esters are different is evidenced by the mixed m. p., 89–92°.

In similar manner, using ethanol, certain half ethyl esters were prepared, *e. g.*, directly from the β-adduct, the **β-monoethyl ester, m. p. 137–137.5°, was obtained.**

Anal. Calcd. for $C_{17}H_{22}O_4$: C, 70.5; H, 7.6. Found: C, 70.57; H, 7.72.

From the α-dihydroadduct, an **α-dihydromonoethyl ester,** m. p. 104.5–105°, was prepared.

α-Dihydrodimethyl Ester.—One-half gram of the α-dihydroanhydride (m. p. 146°) was heated fifteen hours under reflux in 10 cc. of absolute methanol containing 0.2 cc. of 30% fuming sulfuric acid. After removal of solvent, neutralization with aqueous soda and extraction with ether, the crude ester recovered from the ether extract was purified by sublimation *in vacuo* (cold finger, dry ice), yield, 330 mg. This ester could not be induced to crystallize even on standing for long periods of time.

Anal. Calcd. for $C_{17}H_{24}O_4$: C, 69.82; H, 8.27. Found: C, 69.96; H, 8.31.

β-Dihydrodimethyl Ester.—Two hundred milligrams of the β-dihydroadduct (m. p. 104°) treated in the same way, gave 180 mg. of *crystalline* ester, recrystallized from methanol–water, m. p. 65°.

Anal. Calcd. for $C_{17}H_{24}O_4$: C, 69.82; H, 8.27. Found: C, 69.50; H, 8.59.

***trans*-Dihydrodimethyl Ester** (VI, R = CH_3).—The β-dihydrodimethyl ester (100 mg.) was heated under reflux for one hour in 10 cc. of methanol (very carefully dried over magnesium) in which 100 mg. of sodium had been dissolved. After dilution with water and acidification to litmus, the crystalline *trans*-ester separated during several hours, m. p. 68°. On recrystallization from methanol-water, the melting point was raised to 75°.

On similar treatment, the liquid α-dihydrodimethyl ester gave the same *trans* dimethyl ester, m. p. 75°, mixed m. p. 75°.

Anal. Calcd. for $C_{17}H_{24}O_4$: C, 69.82; H, 8.27. Found: C, 69.43; H, 8.36.

On saponification by heating with acetic and hydrochloric acids, the *trans* ester from either source gave the *trans*-dihydrodicarboxylic acid (VI, R = H), m. p. 230–232° (*dec.*).

Anal. Calcd. for $C_{13}H_{18}(COOH)_2$: neut. eq., 132. Found: neut. eq., 130.

Bromolactone Monocarboxylic Acid (VIII).—The β-dihydro adduct (m. p. 104°) was dissolved in glacial acetic acid, and water was added until the solution became cloudy. After boiling for five to six hours, the solution was rediluted with water until a slight cloudiness appeared. Bromine was then added dropwise until a slight yellow color persisted. After evaporation to very small volume (steam-bath), incipient precipitation was completed by immersion in ice. The collected solid was recrystallized from aqueous acetic acid, m. p. 146.5–147.5° (dec.).

Anal. Calcd. for $C_{15}H_{19}O_4Br$: C, 52.48; H, 5.58. Found: C, 52.41; H, 5.62. Calcd. for $C_{14}H_{18}O_2Br(COOH)$: neut. eq., 343. Found: neut. eq., 332.

Bromohydroxydicarboxylic Acid (VII).—Similar treatment of the α-dihydro adduct (m. p. 146°) gave the dibasic acid, recrystallized from aqueous acetic acid, m. p. 152–153° (dec.).

(10) Fieser, "Experiments in Organic Chemistry," 2nd ed., 1941, p. 364.

Anal. Calcd. for $C_{15}H_{21}O_5Br$: C, 49.87; H, 5.86. Found: C, 49.75; H, 5.57. Calcd. for $C_{13}H_{19}OBr(COOH)_2$: 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).