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Methylene-hydantoin and Related Compounds. III. Synthesis of 5-Ethylidene-hydantoin: Attempts to Synthesize 5-Vinyl-hydantoin

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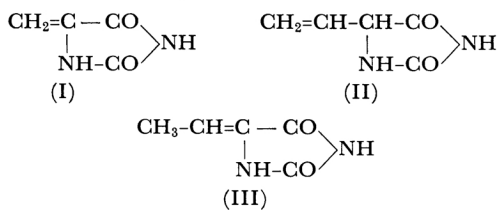
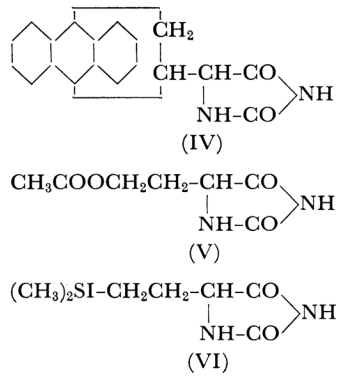
A number of methods of preparation were studied in an attempt to synthesize 5-vinyl-hydantoin using acrolein as a starting material. There were three possible routes: 1) the thermal decomposition of 5-(9, 10-dihydroanthracene-9, 10-*endo*-α, β-ethyl)-hydantoin at 400°C; 2) that of 5-(2-acetoxyethyl)-hydantoin and 3) the elimination reaction of dimethyl 2-(5-hydantoin)-ethyl sulfonium iodide in dimethyl sulfoxide by potassium *t*-butoxide. However, all the reactions gave 5-ethylidene-hydantoin as the product instead of 5-vinyl-hydantoin. An extreme ease of isomerization from 5-vinyl-hydantoin to 5-ethylidene-hydantoin was caused by the highly stable structure of the latter compound. The strong resonance stabilization of 5-ethylidene-hydantoin was observed in the ultraviolet spectrum. 5-Methyl-5-vinyl-hydantoin, which has no migrating hydrogen, could not be obtained from the 5-methyl derivatives of the above compounds.

In previous papers the present authors reported the synthesis of 5-methylene-hydantoin[1] (I) and its polymerization.[2] As an extension of these studies, the synthesis of 5-vinyl-hydantoin (II) was attempted. *C*-Vinyl-glycine and 5-vinyl-hydantoin are expected to form a new amino acid and new types of vinyl monomers, but these compounds have never been prepared, although their homologues, such as 5-allyl-hydantoin,[3] 5-(3-butenyl)-hydantoin,[4] and the corresponding amino acids derived from them, have been reported.

Among the several routes investigated, it seemed that three routes could give 5-vinyl-hydantoin. These are: (1) the retro Diels-Alder reaction of 5-(9, 10-dihydroanthracene-9, 10-*endo*-α, β-ethyl)-hydantoin (IV); (2) the elimination of acetic acid from 5-(2-acetoxyethyl)-hydantoin (V), and (3) the decomposition of dimethyl 2-(5-hydantoin)-ethyl sulfonium iodide (VI).





In the present work, however, 5-vinyl-hydantoin could not be obtained; therefore, its isomer, 5-ethylidene-hydantoin (III) was taken as the product. 5-Ethylidene-hydantoin had been known since 1887,[5] and recently Guyot has prepared it by the decarboxylation of 5-carboxyethylidene-hydantoin.[6] This paper will give information on new methods of preparing 5-ethylidene-hydantoin.

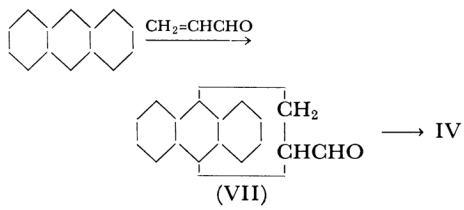
Results and Discussion

The Decomposition of 5-(9, 10-Dihydroanthracene-9, 10-*endo*-α, β-ethyl)-hydantoin (IV). —5-Vinyl-hydantoin might seem to be easily prepared from acrolein in one step by Bucherer's

1) S. Murahashi, H. Yuki, K. Kosai and F. Doura, This Bulletin, **39**, 1559 (1966).
2) S. Murahashi, H. Yuki, K. Kosai and F. Doura, ibid., **39**, 1563 (1966).
3) R. Gaudry, L. Berlinguet, A, Langis and G. Paris, *Can. J. Chem.*, **34**, 502 (1956).
4) F. J. Marshall, *J. Am. Chem. Soc.*, **78**, 3696 (1956).
5) A. Pinner and J. Lifshutz, *Chem. Ber.*, **20**, 2345 (1887).
6) A. Guyot, J. Chopin and C. Mentzer, *Bull. soc. chim. France*, **1960**, 1596.

method[7] if the method could be applied to it. However, the addition of hydrogen cyanide to the C=C, instead of the C=O double bond, in acrolein takes place by Bucherer's reaction in a methanol-water mixture. Küchlin[8] has reported that the cyanohydrin could be obtained from acrolein and hydrogen cyanide in anhydrous ether, but in the presence of water the cyanohydrin dissociates to acrolein and hydrogen cyanide and gives an addition compound of hydrogen cyanide to the C=C double bond.

The difficulty in preparing 5-vinyl-hydantoin by a straightforward method from acrolein suggested to us that we employ an indirect route, including the Diels-Alder addition of acrolein and retro-reaction after the conversion of the adduct to its hydantoin derivative. In the present study anthracene was used as the diene because of the moderate stability of its acrolein adduct. 9, 10-Dihydroanthracene-9, 10-*endo*-α, β-propionaldehyde (VII) was obtained by heating a mixture of the components at 150°C.



(VII)

This was then converted to 5-(9, 10-dihydroanthracene-9, 10-*endo*-α, β-ethyl)-hydantoin (IV) by Bucherer's reaction in a methanol-water mixture. The decomposition of IV was carried out above 250°C in a stream of nitrogen by dropping a solution of IV in glacial acetic acid through a packed quartz tube (Table I). It was found that copper pellets have a good catalytic action in the retro-reaction. The efficiency was improved by using a copper gauze; the decomposition product was then obtained in a 85% yield at 400°C. However, as has been described above, the product was not 5-vinyl-hydantoin, but its isomer, 5-ethylidene-hydantoin. This was confirmed by the absorption band at 826 cm^{-1} due to $R_2C{=}CHR$ in its infrared spectrum (Fig. 1). The reaction was carried out at a lower temperature to avoid isomerization, but this resulted only in a lower yield of 5-ethylidene-hydantoin. The use of a silver gauze as a packing did not improve the reaction. When silica gel or alumina was used as the packing material, the decomposition occurred at the hydantoin group.

The decomposition of IV could not take place in a solution, in such a solvent as benzene, *o*-dichlorobenzene, nitrobenzene, decalin or acetic acid, at the boiling point. The dienophile exchange reaction also did not proceed in these solvents. In the reaction, dimethyl acetylenedicarboxylate, maleic anhydride and dimethyl maleate were employed as dienophiles.

Table I. Pyrolysis of 5-(9, 10-dihydroanthracene-9, 10-*endo*-α, β-ethyl)-hydantoin

Packing material	Starting material g.	Temp. °C	Press. mmHg	Products, g.* A	B	C
Glass	1.0	400	760	carbonized		
Glass	1.0	500	760	carbonized		
Silica gel	1.0	400	760	unknown**		
Alumina	1.0	425	760	unknown**		
Cu-pellet	1.0	250	760	0.01	0.89	
Cu-pellet	1.0	300	760	0.05	0.72	
Cu-pellet	1.0	400	760	0.10	0.70	
Cu-pellet	1.0	550	760	0.01	0.43	
Cu-gauze	2.0	250	760	0.32	0.76	0.41
Cu-gauze	2.0	250	100	0.45	0.85	0.18
Cu-gauze	4.0	400	760	1.42	0.40	1.56
Cu-gauze	4.0	400	100	1.28	1.24	0.57
Cu-gauze	2.0	500	100	0.38	0.18	0.86
Ag-gauze	1.0	300	760	0.30	0.13	0.36
Ag-gauze	1.0	400	760	0.33	0.07	0.38
Cu-gauze	1.0***	400	760	0		

* A: 5-Ethylidene-hydantoin, B: Unreacted, C: Anthracene.
** IR spectra showed no hydantoin group in the product.
*** Solvent: Benzene.

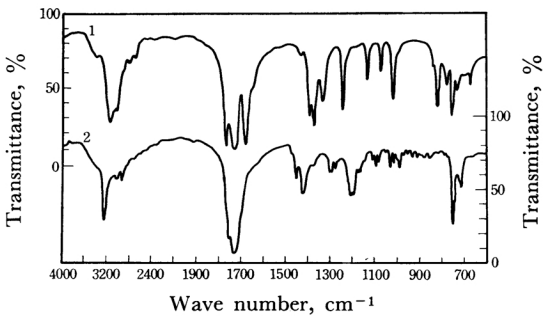
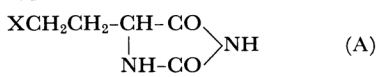


Fig. 1. Absorption spectra of: 1, 5-ethylidene-hydantoin; 2, 5-(9, 10-dihydroanthracene-9, 10-*endo*-α, β-ethyl)-hydantoin (in KBr disks).

The Elimination of Acetic Acid from 5-(2-Acetoxyethyl)-hydantoin (V).—The next route investigated to approach 5-vinyl-hydantoin was the elimination of HX from the compounds of the type A:



(A)

X: Br, I, OH or AcO

When 5-(2-halogenoethyl)-hydantoin was treated with strong bases, such as sodium methoxide and sodium hydroxide, in anhydrous alcohol, the decomposition took place at the hydantoin group.

7) H. Th. Bucherer, *J. prakt. Chem.*, **141**, 23 (1934).
8) A. T. Küchlin, Jr., *Rec. trav. chim.*, **49**, 705 (1930).

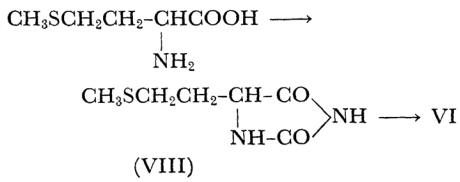
Silver oxide and morpholin did not react with the halogeno-compound. The compound gave only its pyridinium salt when heated in pyridine.

5-(2-Acetoxyethyl)-hydantoin was prepared from 5-(2-halogenoethyl)-hydantoin and potassium acetate. It was found that the elimination of acetic acid from 5-(2-acetoxyethyl)-hydantoin gave 5-ethylidene-hydantoin in a good yield. The elimination reaction was conducted with a procedure similar to that used in the retro-reaction of the anthracene adduct described above (Table II).

TABLE II. PYROLYSIS OF 5-(2-ACETOXYETHYL)-HYDANTOIN

Acetate g.	(Solvent)	ml.	Temp. °C	5-Et-Hyd. g.	Unreacted g.
1.0	AcOH	(100)	300	—	0.90
1.0	*t*-BuOH	(100)	300	0.40	0.37
1.0	*t*-BuOH	(100)	400	0.42	0.16
1.0	*t*-BuOH	(100)	500	0.39	0.07

The Decomposition of Dimethyl 2-(5-Hydantoin)-ethyl Sulfonium Iodide (VI).—The cause of the isomerization of 5-vinyl-hydantoin to 5-ethylidene-hydantoin during the reaction, described in the preceding sections, was supposed to be the high reaction temperature. As a third attempt, the decomposition of dimethyl 2-(5-hydantoin)-ethyl sulfonium iodide (VI) was investigated, as the reaction was expected to proceed under milder conditions. As the starting material, the sulfonium salt was prepared from *dl*-methionine:



(VIII)

The salt was decomposed into dimethyl sulfide and 5-(2-iodoethyl)-hydantoin by heating it in *n*-butanol. By a reaction with sodium ethoxide in absolute ethanol, it gave a small quantity of 5-(2-ethoxyethyl)-hydantoin, and the residual part of the iodide was decomposed at the hydantoin group. In dimethyl sulfoxide, the hydantoin group was decomposed by potassium *t*-butoxide at 80°C, and 5-ethylidene-hydantoin was obtained from the sulfonium salt in a good yield at 20°C. In this case, also, no 5-vinyl-hydantoin was obtained, and the isomerization proceeded very easily and completely at such a low reaction temperature, even if the isomerization could be catalyzed by the base in the polar solvent.

The Stability of 5-Ethylidene-hydantoin.—Vinylacetic acid exists with sufficient stability, as does its isomer, crotonic acid. On the other hand, 5-vinyl-hydantoin, the derivative of vinylacetic acid, could not be obtained. The extreme ease of the isomerization of 5-vinyl-hydantoin to 5-ethylidene-hydantoin suggests that the high stability of 5-ethylidene-hydantoin is due to the resonance between the C=C double bond and the hydantoin group. This was proved by the strong absorption band of 5-ethylidene-hydantoin at 270 mμ, which was absent in the spectra of acrylic acid and 5-methyl-hydantoin (Fig. 2). The same band was observed in the spectrum of 5-methylene-hydantoin, which showed a large *Q*-value, a factor correlated with the resonance stabilization, in Alfrey-Price's *Q-e* scheme.[2]

5-Ethylidene-hydantoin not only polymerized by itself with a radical initiator, but even inhibited the polymerization of styrene in the copolymerization reaction with the latter monomer.

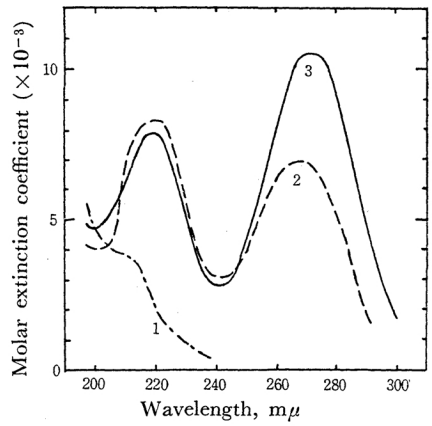
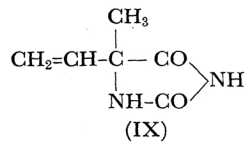
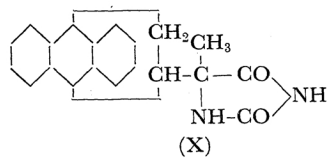


Fig. 2. Absorption spectra of: 1, 5-methyl-hydantoin in H_2O; 2, 5-methylene-hydantoin in H_2O (λ_{max} 268 mμ, ε_{max} 7×10^3); 3, 5-ethylidene-hydantoin in EtOH (λ_{max} 272 mμ, ε_{max} 10.5×10^3).

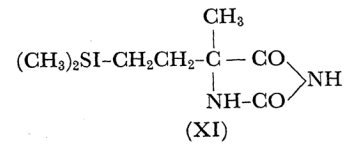
Furthermore, it was found that 5-vinyl-5-methyl-hydantoin (IX), which has no migrant hydrogen, could not be obtained from either 5-(9, 10-dihydroanthracene-9, 10-*endo*-α, β-ethyl)-5-methyl-hydantoin (X) or dimethyl 2-(5-(5-methyl)-hydantoin)-ethyl sulfonium iodide (XI) by the pro-



(IX)



(X)



(XI)

cedures described previously. That is, these compounds not only gave 5-vinyl-5-methyl-hydantoin, but showed no decomposition reaction which did not destroy the hydantoin group in the course of the treatment.

These facts seem to explain the stable conjugate structure of 5-ethylidene-hydantoin and the ease of the isomerization of 5-vinyl-hydantoin to it.

Experimental

9, 10-Dihydroanthracene-9, 10-*endo*-α, β-propionaldehyde (VII).—A mixture of anthracene (40 g., 0.23 mol.), freshly-distilled acrolein (12 g., 0.21 mol.), benzene (90 ml.) and a small amount of hydroquinone was heated in an autoclave at 140—150°C for 12 hr. The reaction mixture was then concentrated under reduced pressure. The residual syrup was dissolved in methanol (250 ml.), and a small amount of the unreacted anthracene was removed by filtration. An equal amount of water was then added to the filtrate, and the mixture was left to stand overnight. Fine crystals of the adduct monohydrate were thus obtained almost quantitatively. The hydrate was recrystallized from acetone; m. p. 100°C.

Found: C, 81.15; H, 6.28. Calcd. for $C_{17}H_{14}O \cdot H_2O$: C, 80.92; H, 6.37%.

The hydrate was soluble in acetone and benzene, but insoluble in water and methanol. Its infrared spectrum showed no absorption band resulting from the carbonyl group of the aldehyde, but it did show the absorption band at 3300 cm^{-1} resulting from the hydroxy group of $-CH(OH)_2$. It gave anhydrous aldehyde when heated at 80°C under reduced pressure. The anhydrous aldehyde was a crystalline compound which melted at 95°C (lit.,[9] 95°C) and which was soluble in methanol. It was gradually converted into the monohydrate in moist air.

5-(9, 10-Dihydroanthracene-9, 10-*endo*-α, β-ethyl)-hydantoin (IV).—Into a solution of ammonium carbonate (92 g.) and sodium cyanide (20 g.) in water (200 ml.), a solution of the anhydrous aldehyde (VII) (50 g.) in methanol (250 ml.) was stirred at 60°C; the reaction was then continued for 10 hr. After the solution had cooled, the precipitates produced were filtered, washed with water, and then suspended in 6 N hydrochloric acid. The suspension was heated at 90°C for 2 hr., and the solid was filtered, washed with water, and dried. The raw product was then extracted with three portions of hot acetone (500 ml.). The concentration of the acetone solution gave the hydantoin (51 g.), which was recrystallized from acetic acid (800 ml.). Yield, 46 g. (71%); m. p. 225°C; colorless crystals sublimed at 220°C/30 mmHg; soluble in hot acetone and hot acetic acid, and insoluble in water, benzene and petroleum ether.

Found: C, 74.86; H, 5.24; N, 9.12. Calcd. for $C_{19}H_{16}N_2O_2$: C, 74.98; H, 5.30; N, 9.20%.

The Decomposition of 5-(9, 10-Dihydroanthracene-9, 10-*endo*-α, β-ethyl)-hydantoin.—A quartz tube (60 cm. long and 5.2 cm. in diameter) packed with the material described in Table I was placed vertically in an electric furnace and heated. The solution of IV in 100 parts of acetic acid was then introduced drop by drop into the tube under a nitrogen stream at atmospheric pressure or at a pressure of about 100 mmHg. The products were collected in two traps connected in a series, one cooled with ice water and the other with dry ice - acetone. After the solution had been added, the inside of the tube was washed with acetic acid (50 ml.) drop by drop. The products and the washings were then combined and evaporated to dryness under a reduced pressure of nitrogen. The residues were extracted with hot water, and the aqueous solution was concentrated under reduced pressure to give 5-ethylidene-hydantoin. The water-insoluble part was fractionated by extraction with hot acetic acid into anthracene and unreacted hydantoin. 5-Ethylidene-hydantoin was recrystallized from water. Colorless crystals subliming at 200°C; m. p. 265°C (lit.,[6] 265°C). The infrared spectrum is shown in Fig. 1.

Found: C, 47.69; H, 4.87; N, 21.50. Calcd. for $C_5H_6N_2O_2$: C, 47.62; H, 4.80; N, 22.21%.

5-(2-Acetoxyethyl)-hydantoin (V).—According to the method of Nyberg,[10] 5-(2-hydroxyethyl)-hydantoin and its brom- and iodo-derivatives were prepared from γ-butyrolactone. A solution of freshly-fused potassium acetate (9.8 g., 0.1 mol.) and 5-(2-iodoethyl)-hydantoin (25.4 g., 0.1 mol.) in ethyl methyl ketone (400 ml.) was refluxed for 10 hr. After the solution had then cooled, the precipitates were filtered off, and the filtrate was evaporated under reduced pressure. By the recrystallization of the residue from a mixture of equal amounts of chloroform and benzene, 5-(2-acetoxyethyl)-hydantoin (12 g.) was obtained in a 65% yield; m. p. 122°C; soluble in water, alcohol, acetone and chloroform, and slightly soluble in ethyl ether and benzene.

Found: C, 44.96; H, 5.45; N, 14.47. Calcd. for $C_7H_{10}N_2O_4$: C, 45.16; H, 5.42; N, 15.05%.

The same product was also obtained from 5-(2-bromoethyl)-hydantoin.

The Decomposition of 5-(2-Acetoxyethyl)-hydantoin.—The same apparatus and procedures described in the pyrolysis of IV were used, employing a copper gauze as a packing material. A solution of 5-(2-acetoxyethyl)-hydantoin in *t*-butyl alcohol was added, drop by drop and under a stream of nitrogen at atmospheric pressure, over a 2 hr. period. The products were fractionated into water-soluble and water-insoluble parts. 5-Ethylidene-hydantoin was obtained from the water-insoluble fraction. When acetic acid was used as a solvent for pyrolysis, the acetate was recovered almost unchanged. The results of the reaction are shown in Table II.

5-(2-Methylmercaptoethyl) - hydantoin (VIII).—This compound was synthesized from commercial *dl*-methionine according to the method of Livak.[11] Yield, 85.5%; m. p. 107°C (lit.[11] 105—106°C).

Dimethyl 2 - (5 - Hydantoin) - ethyl Sulfonium Iodide (VI).—VIII (10 g., 0.06 mol.) was dissolved in acetonitrile, and then methyl iodide (10 ml., 0.16 mol.) was added. Colorless crystals of the sulfonium salt were obtained from the solution after it had stood in

9) B. A. Arbuzov and E. Kh. Isklakov, *Chem. Abstr.*, **52**, 339 (1958).

10) D. D. Nyberg and B. E. Christenson, *J. Am. Chem. Soc.*, **79**, 1222 (1957).

11) J. E. Livak, E. C. Britton, J. C. VanderWeele and M. F. Murray, ibid., **67**, 2218 (1945).

a refrigerator for several hours. A recrystallization of the raw product (18 g.) from water (70 ml.) gave pure crystals (14 g.) (m. p. 168°C (decomp.); soluble in water and methanol, and sparingly soluble in ether and acetone).

Found: C, 26.59; H, 4.14. Calcd. for $C_7H_{13}N_2O_2IS$: C, 26.67; H, 4.12%.

The Decomposition of Dimethyl 2-(5-Hydantoin)-ethyl Sulfonium Iodide.—To a solution of VI (5.4 g., 0.017 mol.) in purified dimethyl sulfoxide (170 ml.), a solution of potassium *t*-butoxide (6.5 g., 0.033 mol.) in the same solvent (80 ml.) was added. The reaction mixture was then stirred at 20°C under a stream of dry nitrogen, and the dimethyl sulfide evolved was introduced into a 1% solution of mercuric chloride in water through a drying tube containing 4A molecular sieves. The progress of the reaction was observed by the precipitation of the dimethyl sulfide-mercuric chloride complex. After 48 hr. the reaction mixture was neutralized with acetic acid and concentrated to a syrup under reduced pressure. The syrup gave crystals when 5 ml. of water was added. By recrystallization from water, pure 5-ethylidene-hydantoin (1.7 g., 81%) was obtained.

When VI was heated in morpholin or in *N*-methyl morpholin at 100°C, a vigorous evolution of dimethyl sulfide was observed. After the evolution had ended, the reaction mixture was concentrated to dryness under reduced pressure. The obtained residue was, however, found to be 5-(2-iodoethyl)-hydantoin.

9, 10 - Dihydroanthracene-9, 10 - *endo*-α, β - ethyl Methyl Ketone.—This compound was prepared from anthracene and methyl vinyl ketone by a method which has been described for VII. The reaction mixture was then concentrated to dryness, and the residue was recrystallized from acetone. The adduct was thus obtained; yield, 72%; colorless crystals subliming at 100°C; m. p. 150°C.

Found: C, 87.29; H, 6.38. Calcd. for $C_{18}H_{16}O$: C, 87.06; H, 6.49%.

5-(9, 10-Dihydroanthracene-9, 10-*endo*-α, β-ethyl)-5-methyl-hydantoin (X).—This hydantoin was prepared, in a 78% yield, from the ketone by the method which has been described for IV. It did not melt below 300°C, it sublimed at 130°C/10 mmHg, and it was soluble in acetone, slightly soluble in acetic acid and benzene, and insoluble in water and methanol.

Found: C, 75.36; H, 5.72; N, 8.63. Calcd. for $C_{20}H_{18}N_2O_2$: C, 75.44; H, 5.69; N, 8.80%.

This compound could not be decomposed, even at 500°C, by the procedure used for IV, but its hydantoin group was decomposed at higher temperatures.

Dimethyl 2-(5-(5-Methyl)-hydantoin)-ethyl Sulfonium Iodide (XI).—A concentrated solution of 5-(2-methylmercaptoethyl)-5-methyl-hydantoin[12] (17 g.) in dry methanol was mixed with methyl iodide (20 g.). The precipitates thus produced were then filtered and dried. Recrystallization from methanol gave pure crystals; yield, 21 g.; m. p. 169°C (decomp.); soluble in water, methanol and dimethyl sulfoxide, slightly soluble in acetone and ether, and insoluble in benzene.

Found: C, 29.29; H, 4.53. Calcd. for $C_9H_{15}N_2O_2IS$: C, 29.10; H, 4.58%.

This compound was treated with potassium *t*-butoxide in dimethyl sulfoxide by the procedure described for VI. Dimethyl sulfide was observed to evolve at a very slow rate, but there was also a simultaneous decomposition of the hydantoin group. The expected compound was not obtained.

12) K. Pfister, W. J. Leanza, J. P. Conbere, H. J. Becker, A. R. Matzuk and E. F. Rogers, ibid., **77**, 697 (1955).