

HYDANTOINS, THIOHYDANTOINS, GLYKOCYAMIDINES. XVII*

THE REACTION OF S,S'-DIMETHYL-5,5-DIPHENYL-DITHIOHYDANTOIN AND
S-METHYL-5,5-DIPHENYL-4-THIOHYDANTOIN WITH OXO REAGENTS AND
POTASSIUM HYDROGEN SULFIDE

By

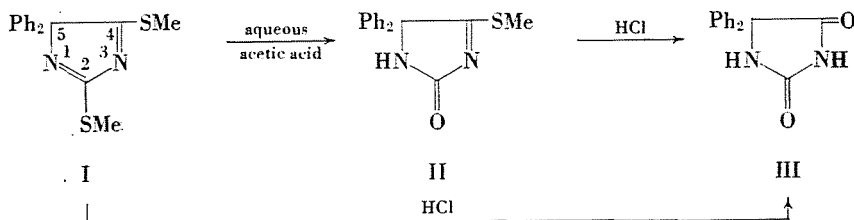
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S,S'-Dimethyl-5,5-diphenyl-dithiohydantoin [I] (I) is one of the few known compounds, which contain a 4H-imidazole ring. Therefore, a study of its reactions seemed to be of interest.

A search in the literature revealed, that only two reactions of I were as yet known, viz. its partial hydrolysis with aqueous acetic and its total hydrolysis with hydrochloric acid leading to S-methyl-5,5-diphenyl-4-thiohydantoin (II) and 5,5-diphenyl hydantoin (III), respectively [1].



First we investigated the reactions of I and, in addition, those of its partial hydrolysis product II, with different oxo reagents as hydroxylamine, phenyl-hydrazine, semicarbazide and hydrazine. Starting from I, with 1 mole of the first three reagents in hot alcoholic solution and in the presence of slight quantities of the hydrochloride of the particular reagent, a selective reaction took place, during which merely the methylmercapto group in position 2 was replaced and eliminated in the form of methanethiol.

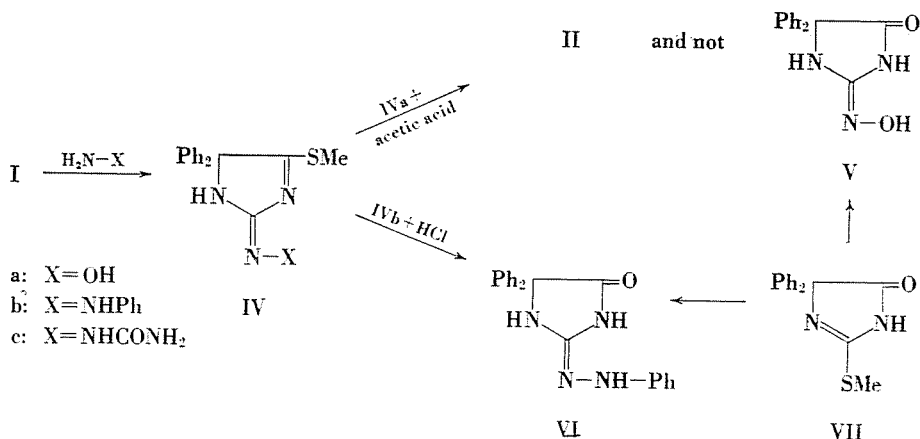
The structure of the products formed has been proved by hydrolysis. Thus, the condensation product of I with hydroxylamine which, by analysis, has to be one of the two isomeric S-methyl-5,5-diphenyl-thiohydantoin-oximes yields, on treatment with acetic acid, the already known S-methyl-5,5-diphenyl-4-thiohydantoin (II), proving thereby the structure IVa for the

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initial product. It is interesting to note that the alternate hydrolysis product of IVa, viz. 5,5-diphenyl-hydantoin-2-oxime (V) which may be prepared from the well-known S-methyl-5,5-diphenyl-2-thiohydantoin (VII) with hydroxylamine is, under the conditions applied, not formed at all.

On the other hand, structure IVb for the condensation product of I and phenylhydrazine is proved by the fact that its hydrolysis with hydrochloric acid* leads to 5,5-diphenyl-hydantoin-2-phenyl-hydrazone (VI), an authentic



sample of which can be prepared by condensation of VII with phenylhydrazine. The isomeric 4-phenylhydrazone of 5,5-diphenylhydantoin has been synthesized too (analogously from II and phenylhydrazine) and, of course, has been proved to be different from the hydrolysis product of IVb.

By analogy, the structure IVc for the condensation product from I and semicarbazide may be accepted. This structure could not directly be proved by hydrolysis. However, in the course of our attempts to prepare the expected hydrolysis product of IVc, viz. 5,5-diphenyl-hydantoin-2-semicarbazone (VIII) by condensation of VII and semicarbazide hydrochloride in pyridine** the formation of the 2,2'-azine of 5,5-diphenyl-hydantoin: N,N'-bis-(5,5-diphenyl-4-oxo-2-imidazolidinylidene)-hydrazine (IX) was observed. This could also be prepared by condensation of VII and hydrazine, and an analogous synthesis, starting from II led to the isomeric 4,4'-azine (X).

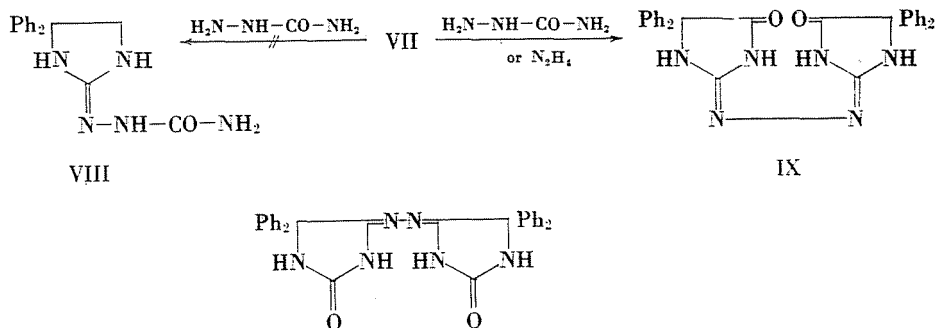
Thus, in the selective reactions of I with oxo reagents so far investigated, it was always the methylmercapto group at position 2 which was replaced, indicating that C—2 is more readily attacked by nucleophiles than C—4. This may be contrasted to the behaviour of the dithiohydantoin with the sulfur

* Acetic acid does not affect this compound.

** In alcoholic solution even in the presence of sodium hydroxide no reaction occurred.

atoms *not* alkylated which are known to react with nucleophyles predominantly at C-4 [1].

Here after the reaction of I and II with alcoholic potassium hydrogen sulfide has been investigated. This reagent is known in the S-methyl-2-thiohydantoin series to cleave the methylmercapto groups and to replace them by a thiol group [2]. The same reaction was also observed with I and II, leading smoothly to 5,5-diphenyl-dithiohydantoin and 5,5-diphenyl-4-thiohydantoin, respectively.



Experimental*

S,S'-Dimethyl-5,5-diphenyl-dithiohydantoin (I)**

To a filtered solution of 1.63 g (5.74 mmoles) of 5,5-diphenyl-dithiohydantoin [1] and 0.51 g (12.7 mmoles) of sodium hydroxide in 3.7 ccm of water and 16 ccm methanol 0.79 ccm (12.7 mmoles) of methyl iodide was added. The precipitated crystals were collected after standing a few hours and washed with methanol. Yield: 1.48 g (82.7%), mp.: 140—142°, lit.[1]: 140°

The product without further purification was pure enough for the subsequent preparations.

S-Methyl-5,5-diphenyl-4-thiohydantoin-2-oxime (IVa)

A mixture consisting of 1 g (3.2 mmoles) of I, 0.24 g (3.45 mmoles) of hydroxylamine hydrochloride, 0.18 g (3.2 mmoles) of potassium hydroxide and 15 ccm of alcohol was refluxed for 8 hours, the crystals (potassium chloride) thereby deposited were removed by filtration after cooling. The filtrate was evaporated to dryness and the residue crystallized first from aqueous alcohol and subsequently from benzene. Yield: 0.55 g (58%), mp.: 210—212°.

* All melting points uncorrected.

** cf.[1]

$C_{16}H_{15}N_3OS = 297.5$			
Calc'd:	C 64.70	H 5.08	N 14.10
Found:	C 64.45	H 4.82	N 13.77
	64.56	4.79	

S-Methyl-5,5-diphenyl-4-thiohydantoin (II)

0.65 g (2.19 mmoles) of IVa were refluxed for 5 hours with 5 ccm of acetic acid; after cooling and dilution with water 0.2 g (45.4%*) of an orange solid was precipitated, which, after crystallization from acetone melted at 245–248°

$C_{16}H_{14}N_2OS = 282.3$			
Calc'd:	C 68.07	H 5.00	N 9.92
Found:	C 68.17	H 5.25	N 9.97

By mixed mp. determination this substance proved to be identical with an authentic sample of II prepared by partial hydrolysis of I with aqueous acetic acid [1].

From the original mother liquor by further dilution with water 0.18 g (28%) of unreacted IVa was precipitated.

5,5-Diphenyl-hydantoin-2-oxime (V)

0.85 g (3 mmoles) of S-methyl-5,5-diphenyl-2-thiohydantoin (VII) were refluxed for 3 hours with a mixture consisting of 0.42 g (6 mmoles) of hydroxylamine hydrochloride, 0.34 g (6 mmoles) of potassium hydroxide, 20 ccm of alcohol and 1 ccm of water. Crystallization of the hot mixture started on scratching. After cooling and dilution with 20 ccm of water the crystals were separated by suction and washed with water. Yield: 0.73 g (91%) mp.: 271–272° (from alcohol, containing some dimethylformamide).

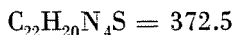
$C_{15}H_{13}N_3O_2 = 267.3$			
Calc'd:	C 67.40	H 4.90	N 15.72
Found:	C 67.26	H 4.92	N 15.76
	67.53	5.26	15.72

S-Methyl-5,5-diphenyl-4-thiohydantoin-2-phenylhydrazone (IVb)

A mixture consisting of 3.12 g (10 mmoles) of I, 1.59 g (11 mmoles) of phenylhydrazine-hydrochloride, 0.56 g (10 mmoles) of potassium hydroxide and 50 ccm alcohol was refluxed for 2 hours, concentrated to about 10 ccm, the yellow crystalline product separated by suction and washed successively

* Based on unrecovered IVa (see below)

with methanol and water. Yield: 2.8 g (75%), yellow crystals, mp.: 228–229° (from an alcohol benzene mixture), the mp. greatly depending on the rate of heating the capillary tube.



Calc'd: C 70.95 H 5.41 N 15.05 S 8.59

Found: C 70.76 H 5.54 N 15.00 S 8.32

70.71 5.50 15.05 8.72

UV spectrum in alcohol: $\lambda_{\max} = 256 \text{ m}\mu$ ($\log \epsilon = 4.06$) and
357 $\text{m}\mu$ ($\log \epsilon = 3.96$).

5,5-Diphenyl-hydantoin-2-phenylhydrazone (VI)

a) 2.0 g (5.37 mmoles) of IVb were refluxed for 6 hours with a mixture of 10 ml each of acetic and concentrated hydrochloric acid, whereby a white crystalline solid slowly deposited. The mixture was concentrated to about half of its original volume, diluted with 2 parts of water, whereby a creme coloured resinous substance was precipitated which, after neutralising with potassium carbonate to pH 5, slowly solidified.

The latter was collected by filtration with suction, washed thoroughly with water and recrystallised from aqueous alcohol. Yield: 1.17 gr (64%), mp.: 232–234°.



Calc'd: C 73.66 H 5.30 N 16.36

Found: C 73.58 H 5.10 N 17.08

73.75 5.20

b) 5.64 g (20 mmoles) of VII, 3.18 g (22 mmoles) of phenyl-hydrazine hydrochloride and 1.12 g (20 mmoles) of potassium hydroxide were refluxed for 9 hours in 60 ccm alcohol, the mixture concentrated to 10 ccm, diluted with 5 ccm of water and finally filtered by suction and the solid washed with 50% aqueous methanol and subsequently with water. Yield: 6.86 g (100%), mp.: 229–230° (from aqueous alcohol), mixed mp. with the above product: 231–232°.



Calc'd: C 73.66 H 5.30 N 16.36

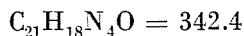
Found: C 73.42 H 5.43 N 16.75

73.54 5.27 16.78

The two products proved to be identical also by their UV spectra: $\lambda_{\max} = 231 \text{ m}\mu$, $\log \epsilon = 4.30$ (in alcohol).

5,5-Diphenyl-hydantoin-4-phenylhydrazone

A mixture consisting of 0.85 g (3 mmoles) of II, 0.52 g (3.6 mmoles) of phenylhydrazine hydrochloride and 10 ccm of pyridine was refluxed for 9 hours; after 1 hour a crystalline product began to deposit. After cooling and dilution with 40 ccm of water a brown oil was precipitated which slowly solidified. Yield: 0.97 g (95%), mp.: 234–235° (from alcohol).



Calc'd: C 73.66 H 5.30 N 16.36

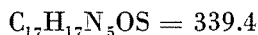
Found: C 73.74 H 5.40 N 16.46

73.63 5.26 16.55

$\lambda_{\max} = 240 \text{ m } \mu$, $\log \varepsilon = 4.15$ (in alcohol).

S-Methyl-5,5-diphenyl-4-thiohydantoin-2-semicarbazone (IVc)

A mixture consisting of 1.56 g (5 mmoles) of I, 0.56 g (5.05 mmoles) of semicarbazide hydrochloride, 0.28 g (5 mmoles) of potassium hydroxide, 25 ccm alcohol and 1 ccm of water was refluxed for 9 hours and subsequently evaporated in vacuo to dryness. The crystalline residue was digested with a mixture of 10 ccm each of methanol and water. The material remaining undissolved proved to be IVc. From its aqueous methanolic mother liquor by dilution with water a second crop was precipitated. Total yield: 1.35 (79.5%), white crystals, mp. 219–220° (from a chloroform alcohol mixture, 3 : 1 vol.)



Calc'd: C 60.17 H 5.05 N 20.64

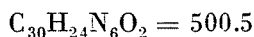
Found: C 59.85 H 5.20 N 20.50

59.70 5.03 20.84

UV spectrum (in alcohol): $\lambda_{\max} = 298 \text{ m } \mu$, $\log \varepsilon = 3.96$; shoulder: $\lambda = 233 \text{ m } \mu$, $\log \varepsilon = 3.98$.

N,N'-Bis-(5,5-diphenyl-4-oxo-2-imidazolidinylidene)-hydrazine (IX)

a) A solution consisting of 1.41 g (5 mmoles) of VII and 0.67 g (6 mmoles) of semicarbazide hydrochloride in 10 ccm dry pyridine was refluxed for 8 hours and subsequently diluted with 20 ccm of water; the creme coloured precipitate was separated and washed with water. For further purification it was dissolved in aqueous pyridine and reprecipitated by adding water. Yield: 0.66 g (52.7%), mp.: 338–339°, (dec., from aqueous pyridine)



Calc'd: C 71.98 H 4.83 N 16.79

Found: C 72.14 H 5.14 N 17.07

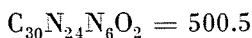
72.15 4.94 16.83

The product has been proved by mixed mp. and UV spectrum to be identical with the substance prepared according to *b*). UV spectrum in alcohol: $\lambda_{\max} = 268 \text{ m}\mu$, $\log \epsilon = 4.22$.

b) A solution consisting of 1.41 g (5 mmoles) of VII, 0.19 (2.77 mmoles) of hydrazine hydrochloride, 0.20 g (2.44 mmoles) of anhydric sodium acetate in 10 ccm dry pyridine was refluxed for 26 hours and subsequently diluted with 30 ccm of water, the creme coloured precipitate separated and washed with water. Yield: 1.03 g (82.5%), mp.: 338–339° (dec., from dimethyl-sulf-oxide).

N,N'-Bis-(5,5-diphenyl-2-oxo-4-imidazolidinylidene)-hydrazine (*X*)

A solution consisting of 1.41 g (5 mmoles) of II, 0.48 g (7 mmoles) of hydrazine hydrochloride and 0.49 g (6 mmoles) of anhydric sodium acetate in 10 ccm dry pyridine was refluxed for 24 hours subsequently diluted with 30 ccm of water, the creme coloured precipitate collected and washed with water. Yield: 0.62 g (49.5%), mp.: over 420° (dec., from dimethylformamide-methanol).



Calc'd: C 71.98 H 4.83 N 16.79

Found: C 71.72 H 5.15 N 16.70

71.64 4.98 16.57

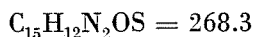
UV spectrum (in alcohol): $\lambda_{\max} = 273 \text{ m}\mu$.

5,5-Diphenyl-dithiohydantoin

A solution consisting of 3.8 g (67 mmoles) of potassium hydroxide, 4 ccm of water and 20 ccm alcohol was saturated with hydrogen sulfide under cooling and the aqueous alcoholic potassium hydrogen sulfide solution so prepared, heated in a bomb tube with 1.05 g (3.37 mmoles) of I for 6 hours to $115 \pm 2^\circ$. After cooling and filtration the solution was acidified with 5 ccm of acetic acid, subsequently diluted with 55 ccm of water and the yellow crystals thereby precipitated collected and washed with water. Yield: 0.90 g (93.7%), mp.: 267° (dec., from aqueous methanol); lit. [1]: 268°.

5,5-Diphenyl-4-thiohydantoin

An aqueous alcoholic solution of 67 mmoles of potassium hydrogen sulfide prepared as above was heated with 0.95 g (3.37 mmoles) of II for 19 hours to $117 \pm 2^\circ$ and then worked up as above. Yield: 0.88 g (99%), mp.: 272–273° (dec., from an aqueous methanol pyridine mixture); lit. [1]: 273–274°.



Calc'd: C 67.15 H 4.51 N 10.44 S 11.94

Found: C 67.08 H 4.63 N 10.65 S 12.19

Acknowledgment

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Summary

S,S'-Dimethyl-5,5-diphenyl-dithiohydantoin (I) reacts with 1 mole of different oxo reagents selectively at C—2, yielding thereby condensation products (IVa—c) of S-methyl-5,5-diphenyl-4-thiohydantoin (II). The latter compound reacts with the same reagents at C—4. Both II and the isomeric S-methyl-5,5-diphenyl-2-thiohydantoin (VII) react with semicarbazide in pyridine solution to yield, instead of the expected semicarbazones (eg. VIII), the azines IX and X, respectively. — I and II, upon heating with aqueous alcoholic potassium hydrogen sulfide, react to form 5,5-diphenyl-dithio- and 5,5-diphenyl-4-thiohydantoin, respectively.

References

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2. LEMPert, K.: Chem. Ber. **95**, 1066 (1962)

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