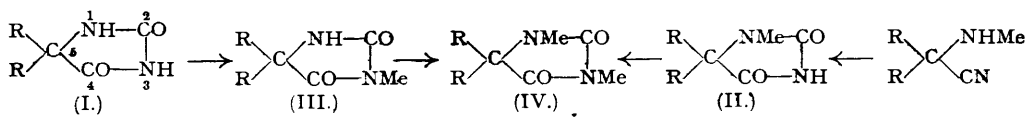
79. *Thiohydantoins. Part III. The* N- *and* S-*Methyl Derivatives of* 5 : 5-*Disubstituted Hydantoins and Their Mono- and Di-thio-analogues.*

By H. C. Carrington and W. S. Waring.

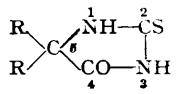
Examples have been provided of all the possible types of *N*- and *S*-methyl derivatives of 5 : 5-disubstituted hydantoins and their mono- and di-thio-analogues with the single exception of the 4-thio-2-methylthio-1-methyl derivatives. The experiments have been carried out in the 5 : 5-diphenyl and 5 : 5-pentamethylene series, and the results have been closely similar, but a few minor differences have been observed. The experimental methods used were simple, namely, methylation by methyl iodide, methyl sulphate, or diazomethane, replacement of oxygen by sulphur by the action of phosphorus pentasulphide, removal of methylthio-groups by acid hydrolysis, and replacement of sulphur by oxygen by the action of 2-aminoethanol followed by acid hydrolysis as described in Part II (Carrington, *J.*, 1947, 684).

Although a considerable amount of information on the alkylation of hydantoins is available, no systematic study of the various possible methyl derivatives of 5 : 5-disubstituted hydantoins and their thio-analogues has yet been made. It is well known that the alkali-soluble 5 : 5-disubstituted hydantoins (I) are readily methylated by the usual reagents to give the 3-methyl derivatives (III), which are converted by further, somewhat more drastic methylation into the 1 : 3-dimethyl derivatives (IV). The 1-methyl-5 : 5-disubstituted hydantoins (II) are not obtained by direct methylation, but are usually synthesised from the corresponding α-methylamino-nitriles by the action of cyanate, with subsequent hydrolysis. The 1-methyl derivatives, unlike the 3-methyl compounds, are soluble in alkali, and readily undergo further methylation to the 1 : 3-dimethyl derivatives. There appears to be no description of *O*-methylation occurring during the methylation of hydantoin derivatives.



When we consider the thiohydantoins, however, the formation of *S*-methyl derivatives must be taken into account, and the number of possible products is greatly increased. Thus with the 5 : 5-disubstituted-2-thiohydantoins (V) there are formally possible three monomethyl derivatives (VI—VIII) and three dimethyl derivatives (IX—XI). The corresponding 4-thiohydantoins (XXII) may lead to three possible monomethyl derivatives (XXIII—XXV) and two dimethyl derivatives (XXVI and XXVII), while the 2 : 4-dithiohydantoins (XII) may give rise to four monomethyl derivatives (XIII—XVI) and no less than five dimethyl derivatives (XVII—XXI).

The present experiments have set out to investigate how far these numerous possibilities can be realised in practice. They have been carried out, for the most part, with two series of compounds, the 5 : 5-diphenyl- and the 5 : 5-pentamethylene-hydantoins. In the first series the parent compound, 5 : 5-diphenylhydantoin itself, is well known, being widely used as a drug in the treatment of epilepsy. Several other members of this series are also known. Biltz, in his study of the reaction between benzil and urea and its derivatives, prepared 5 : 5-diphenyl-3-methylhydantoin (*Ber.*, 1908, **41**, 1386) and 5 : 5-diphenyl-1 : 3-dimethylhydantoin (*ibid.*, pp. 170, 1379). Similar experiments with thiourea and its derivatives led to 5 : 5-diphenyl-, 5 : 5-diphenyl-3-methyl-, and 5 : 5-diphenyl-1 : 3-dimethyl-2-thiohydantoin, and it was also shown that methylation of the corresponding thio-compounds with methyl sulphate could give rise to the methylthio-derivatives 2-methylthio-4-keto-5 : 5-diphenyl- and 2-methylthio-4-keto-5 : 5-diphenyl-3-methyl-4 : 5-dihydroglyoxaline (*idem*, *ibid.*, 1909, **42**, 1792). 5 : 5-Diphenyl-2 : 4-dithiohydantoin was prepared by Henze and Smith (*J. Amer. Chem. Soc.*, 1943, **65**, 1090) by the action of phosphorus trisulphide on the parent hydantoin. While the present work was in progress 5 : 5-diphenyl-1-methylhydantoin was prepared by Long, Miller, and Troutman (*ibid.*, 1948, **70**, 902) by a modification of the method usually used for 1-methylhydantoins.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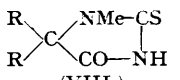
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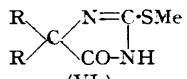
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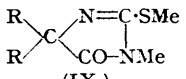
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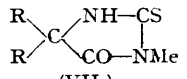
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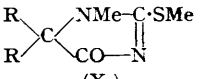
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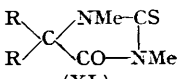
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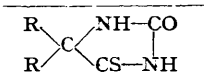
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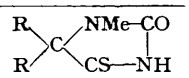
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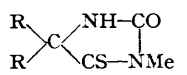
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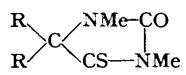
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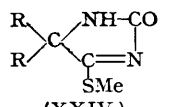
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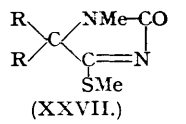
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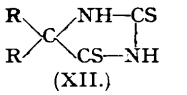
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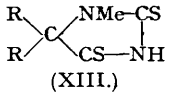
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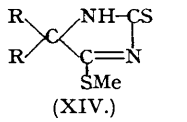
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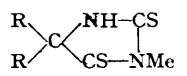
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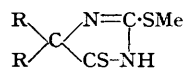
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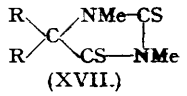
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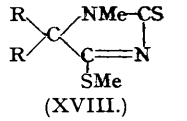
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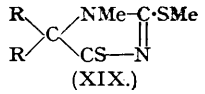
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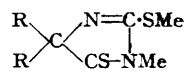
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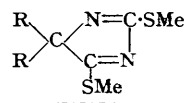

(XXI.)

In the 5 : 5-pentamethylenehydantoin series the parent compound was prepared by Bucherer and Lieb (*J. pr. Chem.*, 1934, **141**, 5) during their pioneer development of new hydantoin syntheses. The corresponding 2-thio-, 4-thio-, and 2 : 4-dithio-hydantoins were described in the earlier papers of this series (Carrington, *J.*, 1947, 681, 684).

Comparatively few experimental procedures have been employed in the present study.

Methylations have been carried out using methyl iodide, methyl sulphate, and diazomethane. Phosphorus pentasulphide has been used for the replacement of oxygen by sulphur, and the reverse replacement of sulphur by oxygen has been accomplished by the action of 2-aminoethanol and subsequent hydrolysis of the 2-hydroxyethylimino-derivatives as described in Part II (*loc. cit.*). Alternatively, sulphur, where present in the form of methylthio-groups, has been removed by direct acid hydrolysis. By applying various permutations and combinations of these procedures it has been possible to synthesise nearly all the possible methyl derivatives.

Most of the experiments have been carried out in both the 5 : 5-diphenyl- and the 5 : 5-pentamethylene hydantoin series, and the results have been closely parallel. Only in a few cases have minor differences in behaviour been observed, and attention will be drawn to these. It is proposed to describe first the synthesis of some key reference compounds and then to discuss the more complicated methylations.

5 : 5-Diphenyl-1-methylhydantoin (II; R = Ph) was prepared both by the method of Long, Miller, and Troutman (*loc. cit.*) and by an alternative method which will be described later. Several other routes to the 5 : 5-diphenyl-1-methylhydantoin series were also investigated. α-Chlorodiphenylacetamide (Steinkopf, *Ber.*, 1908, **41**, 3593) was converted by methylamine in benzene into *α-methylaminodiphenylacetamide*, but attempts to cause this to react with carbon disulphide to give 5 : 5-diphenyl-1-methyl-2-thiohydantoin failed. Again, 5 : 5-diphenylhydantoin with benzyl chloride in aqueous-alcoholic alkali gave 5 : 5-*diphenyl*-3-*benzylhydantoin*, which was further substituted by reaction with methyl sulphate to give 5 : 5-*diphenyl*-1-*methyl*-3-*benzylhydantoin*, but attempts to remove the benzyl group by catalytic hydrogenation were unsuccessful. Treatment of 5 : 5-diphenyl-1-methylhydantoin with phosphorus pentasulphide in boiling tetralin gave 5 : 5-*diphenyl*-1-*methyl*-2 : 4-*dithiohydantoin* (XIII; R = Ph). 5 : 5-Diphenyl-3-methylhydantoin (III; R = Ph) gave similarly 5 : 5-*diphenyl*-3-*methyl*-2 : 4-*dithiohydantoin* (XV; R = Ph). 5 : 5-*Diphenyl*-1 : 3-*dimethyl*-2 : 4-*dithiohydantoin* (XVII; R = Ph) was likewise prepared from 5 : 5-diphenyl-1 : 3-dimethylhydantoin (IV; R = Ph).

1-*Methyl*-5 : 5-*pentamethylenehydantoin* was prepared from α-methylaminohexahydrobenzonitrile in the usual way by treatment with cyanate followed by acid hydrolysis. 3-*Methyl*-5 : 5-*pentamethylenehydantoin* was prepared by methylation of 5 : 5-pentamethylenehydantoin in alkaline solution by methyl sulphate. Diazomethane may also be used. 1 : 3-*Dimethyl*-5 : 5-*pentamethylenehydantoin* was prepared from the 1-methyl-hydantoin in either of these ways. These three hydantoins were converted into the corresponding 2 : 4-*dithiohydantoins* (XIII, XV, and XVII; RR = $<[CH_2]_5$, respectively).

These compounds, synthesised by unequivocal routes, form the basis on which the identification of most of the other derivatives depends.

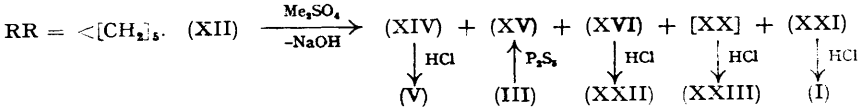
The first methylation of a thiohydantoin studied in detail was the reaction of 5 : 5-diphenyl-2 : 4-dithiohydantoin with methyl sulphate. There were obtained an alkali-insoluble substance, and an alkali-soluble fraction which was clearly a mixture. The alkali-insoluble product was a colourless crystalline dimethyl derivative. When acid hydrolysis resulted in elimination of all the sulphur as methanethiol and formation of 5 : 5-diphenylhydantoin, it was clear that this derivative was 2 : 4-*dimethylthio*-5 : 5-*diphenylglyoxaline* (XXI; R = Ph). The alkali-soluble fraction, on chromatographic separation, gave a pale yellow and a bright orange product; both were monomethyl derivatives and lost methanethiol on acid hydrolysis, giving monothiohydantoins. The pale yellow compound gave the known colourless 5 : 5-diphenyl-2-thiohydantoin (V; R = Ph), and was therefore identified as 2-*thio*-4-*methylthio*-5 : 5-*diphenyl*-2 : 5-*dihydroglyoxaline* (XIV; R = Ph). The isomeric bright orange derivative, by elimination, must therefore be the 4-*thio*-2-*methylthio*-compound (XVI; R = Ph), and the yellow monothiohydantoin obtained from it on hydrolysis must be 5 : 5-*diphenyl*-4-*thiohydantoin* (XXII; R = Ph). It is of interest that the dimethyl derivative is formed in this methylation when only one equivalent of methyl sulphate, or even less, is used, and there is a corresponding recovery of unchanged 5 : 5-diphenyl-2 : 4-dithiohydantoin. It would appear that the monomethyl derivatives formed are more susceptible to further methylation than the unmethylated substance itself.

$$\text{R = Ph. (XII)} \xrightarrow[\text{-NaOH}]{Me_2SO_4} \text{(XIV)} + \text{(XVI)} + \text{(XXI)}$$

$$\text{(XIV)} \xrightarrow{HCl} \text{(V)} \qquad \text{(XVI)} \xrightarrow{HCl} \text{(XXII)} \qquad \text{(XXI)} \xrightarrow{HCl} \text{(I)}$$

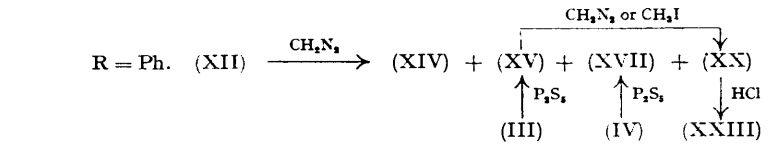
Some preliminary experiments on the methylation of 5 : 5-pentamethylene-2 : 4-dithiohydantoin were described in Part II. There the main product isolated after removal of alkali-

insoluble material and acidification of the remainder was identified as 5 : 5-pentamethylene-4-thiohydantoin. A more detailed study which has now been made showed that the alkali-insoluble product was mainly 2 : 4-*dimethylthio*-5 : 5-*pentamethyleneglyoxaline*, identified by acid hydrolysis to 5 : 5-pentamethylenehydantoin. This was probably accompanied by a little (XX; RR = $<[CH_2]_5$), for acid hydrolysis of the crude product gave also an alkali-insoluble substance later identified as 3-methyl-5 : 5-pentamethylene-4-thiohydantoin (XXIII; RR = $<[CH_2]_5$). The alkali-soluble fraction was isolated by careful acidification with phosphoric acid, and on chromatographic separation gave three products, first, 3-methyl-5 : 5-pentamethylene-2 : 4-dithiohydantoin, identical with that obtained by introduction of sulphur into the corresponding hydantoin, secondly, 4-*thio*-2-*methylthio*-5 : 5-*pentamethylene*-4 : 5-*dihydroglyoxaline* (XVI; RR = $<[CH_2]_5$), identified by acid hydrolysis to 5 : 5-pentamethylene-4-thiohydantoin (XXII), and thirdly, the 2-*thio*-4-*methylthio*-isomer (XIV), which was identified both by acid hydrolysis to 5 : 5-pentamethylene-2-thiohydantoin (V; RR = $<[CH_2]_5$), and by reaction with 2-aminoethanol to give 4-2′-hydroxyethylimino-5 : 5-pentamethylene-2-thiohydantoin, identical with that described in Part II (*loc. cit.*). As in the 5 : 5-diphenylhydantoin series, there was also some unchanged starting material.



The main differences between the two series were, first, the slight tendency to *N*-methylation in the 3-position in the 5 : 5-pentamethylene series, and secondly, the variation in the proportion of the two monomethylthio-derivatives produced. In the 5 : 5-diphenyl series, the 4-methylthio-compound predominated, while in the 5 : 5-pentamethylene series there was more of the 2-methylthio-derivative. In the 5 : 5-pentamethylene series, the 4-thiohydantoin was the main alkali-soluble product when the acidification took place under such conditions as would bring about the hydrolysis of the very labile 2-methylthio-group.

The methylation of 5 : 5-diphenyl-2 : 4-dithiohydantoin with diazomethane gave rather different results. There were obtained two monomethyl and two dimethyl derivatives. The former were the 2-thio-4-methylthio-compound (XIV; R = Ph), the only product common to the methyl sulphate and diazomethane methylations, and 5 : 5-diphenyl-3-methyl-2 : 4-dithiohydantoin (XV; R = Ph), identical with that obtained by introduction of sulphur into 5 : 5-diphenyl-3-methylhydantoin. The dimethyl derivatives were 5 : 5-diphenyl-1 : 3-dimethyl-2 : 4-dithiohydantoin (XVII; R = Ph), identical with that obtained from 5 : 5-diphenyl-1 : 3-dimethylhydantoin, and a new, pale yellow, crystalline compound, the structure of which was established as follows. It was identical with a dimethyl derivative obtained by the further methylation of 5 : 5-diphenyl-3-methyl-2 : 4-dithiohydantoin (XV; R = Ph) either by methyl iodide or by diazomethane. Only two dimethyl derivatives could be derived by the further methylation of this compound. One of these was the 1 : 3-dimethyl compound (XVII; R = Ph) already identified, and the new compound must therefore be the other, 4-*thio*-2-*methylthio*-5 : 5-*diphenyl*-3-*methyl*-4 : 5-*dihydroglyoxaline* (XX; R = Ph). Confirmation of this structure was obtained by acid hydrolysis, methanethiol being evolved and a monomethyl monothio-derivative of diphenylhydantoin obtained which must clearly be 5 : 5-*diphenyl*-3-*methyl*-4-*thiohydantoin* (XXIII; R = Ph).



Methylation of 5 : 5-pentamethylene-2 : 4-dithiohydantoin by diazomethane gave as the main products 3-methyl-5 : 5-pentamethylene-2 : 4-dithiohydantoin (XV; RR = $<[CH_2]_5$) and 2-thio-4-methylthio-5 : 5-pentamethylene-2 : 5 dihydroglyoxaline (XIV; RR = $<[CH_2]_5$). There was also an oily fraction of dimethyl derivatives which was not completely separated into its constituents, but which gave on acid hydrolysis 3-*methyl*-5 : 5-*pentamethylene*-4-*thiohydantoin* (XXIII; RR = $<[CH_2]_5$) thus indicating the presence of the 2-methylthio-3-methyl-4-thio-derivative, analogous to that obtained in the 5 : 5-diphenylhydantoin series.

The methylation of 5 : 5-diphenyl-2 : 4-dithiohydantoin in aqueous-alcoholic sodium hydroxide with one equivalent of methyl iodide gave a mixture of the 2-thio-4-methylthio-

(XIV; R = Ph) and the 2 : 4-dimethylthio-compound (XXI; R = Ph), with a recovery of some unchanged starting material. Methylation in alcoholic solution with an excess of methyl iodide and in the presence of sodium hydrogen carbonate gave the 2 : 4-dimethylthio-derivative, or, if the reaction was carried out at a higher temperature and without efficient stirring, *4-methylthio-2-keto-5 : 5-diphenyl-2 : 5-dihydroglyoxaline* (XXIV; R = Ph). The structure of this compound was proved by its reaction with aqueous 2-aminoethanol to give *4-2′-hydroxyethylimino-5 : 5-diphenylhydantoin* identical with that produced from 5 : 5-diphenyl-4-thiohydantoin by the same reagent. The formation of (XXIV) during this methylation clearly resulted from a partial hydrolysis of the preformed 2 : 4-dimethylthio-derivative, and this hydrolysis was, in fact, accomplished by careful treatment of 2 : 4-dimethylthio-5 : 5-diphenylglyoxaline with 80% acetic acid.

In the methyl iodide methylation of 5 : 5-pentamethylene-2 : 4-dithiohydantoin, loss of methanethiol occurred even more readily, and the only product isolated was *4-methylthio-2-keto-5 : 5-pentamethylene-2 : 5-dihydroglyoxaline* (XXIV; RR = $<[CH_2]_5$), identical with the product obtained by the action of methyl iodide on 5 : 5-pentamethylene-4-thiohydantoin. Its structure was confirmed (*a*) by conversion into 4-2′-hydroxyethylimino-5 : 5-pentamethylenehydantoin, identical with that obtained from the 4-thiohydantoin by the same method (Carrington, *J.*, 1947, 684), and (*b*) by acid hydrolysis to 5 : 5-pentamethylenehydantoin.

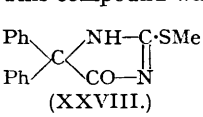
To complete the account of the methylation of the dithiohydantoin derivatives, it remains to describe experiments on the further methylation of various monomethyl derivatives. 5 : 5-Diphenyl-1-methyl-2 : 4-dithiohydantoin with methyl iodide or methyl sulphate gave mainly *4-methylthio-2-thio-5 : 5-diphenyl-1-methyl-2 : 5-dihydroglyoxaline* (XVIII; R = Ph) (evidence for this structure will be discussed later), accompanied by a little 5 : 5-diphenyl-1 : 3-dimethyl-2 : 4-dithiohydantoin. The methylation of 5 : 5-diphenyl-3-methyl-2 : 4-dithiohydantoin with methyl iodide or diazomethane to give the 4-thio-2-methylthio-derivative has already been mentioned. 2-Thio-4-methylthio-5 : 5-diphenyl-2 : 5-dihydroglyoxaline with diazomethane gave the 2 : 4-dimethylthio-derivative.

Methylation of 1-methyl-5 : 5-pentamethylene-2 : 4-dithiohydantoin has been studied using all three reagents, and in all cases the 1 : 3-dimethyl- and the *4-methylthio-1-methyl*-compound (XVIII; RR = $<[CH_2]_5$) were obtained. The proportions of the two products, however, varied with the methylation procedure adopted. Thus, with diazomethane the former predominated, and with methyl iodide the latter, while with methyl sulphate approximately equal amounts of each were produced. With methyl iodide there was also formed, however, a very small amount of a yellow alkali-soluble monomethyl-monothio-derivative, which it seems can, by elimination, only be *1-methyl-5 : 5-pentamethylene-4-thiohydantoin* (XXV; RR = $<[CH_2]_5$), produced by hydrolysis of preformed 4-thio-2-methylthio-1-methyl-5 : 5-pentamethylene-4 : 5-dihydroglyoxaline. This last type, the 4-thio-2-methylthio-1-methyl-derivative, remains the only class of methylated derivative which has not been exemplified in the present work.

3-Methyl-5 : 5-pentamethylene-2 : 4-dithiohydantoin gave *4-thio-2-methylthio-3-methyl-5 : 5-pentamethylene-4 : 5-dihydroglyoxaline* (XX; RR = $<[CH_2]_5$) on methylation either with methyl iodide or with diazomethane. The structure of this compound was proved in a similar way to that of the corresponding 5 : 5-diphenylhydantoin derivative, by the fact that acid hydrolysis liberated methanethiol, showing the second methyl group to be attached to sulphur, and gave as product 3-methyl-5 : 5-pentamethylene-4-thiohydantoin (XXIII; RR = $<[CH_2]_5$). The presence of this dimethyl derivative had been deduced in the product of the diazomethane methylation of 5 : 5-pentamethylene-2 : 4-dithiohydantoin by a similar hydrolysis, but its isolation in a state of purity was not accomplished in that case.

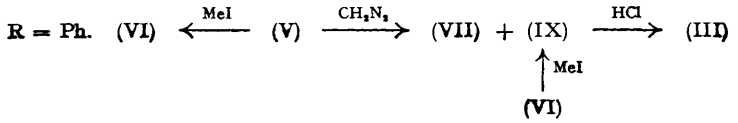
4-Thio-2-methylthio-5 : 5-pentamethylene-4 : 5-dihydroglyoxaline with methyl iodide gave the 2 : 4-dimethylthio-derivative.

We must consider next experiments on the methylation of the monothiohydantoins. 5 : 5-Diphenyl-2-thiohydantoin (V; R = Ph), with methyl iodide in the usual way, gave 4-keto-2-methylthio-5 : 5-diphenyl-4 : 5-dihydroglyoxaline (VI; R = Ph) (cf. Biltz, *loc. cit.*). This compound was also described by Cattelaine and Chabrier (*Bull. Soc. chim.*, 1947, 639) who gave it the formula (XXVIII), and stated that further methylation with methyl iodide gave 4-keto-2-methylthio-5 : 5-diphenyl-1-methyl-4 : 5-dihydroglyoxaline, which could then be hydrolysed to 5 : 5-diphenyl-1-methylhydantoin. The present work, however, was in agreement with the observation of Biltz, and confirmed that the product of further methylation was the 3-methyl compound (IX; R = Ph), for on hydrolysis it gave 5 : 5-diphenyl-3-methylhydantoin.

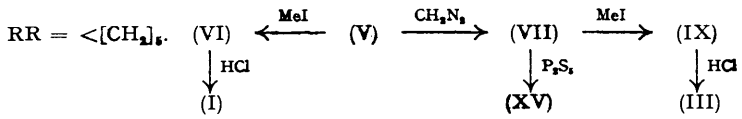


(XXVIII.)

Methylation of 5 : 5-diphenyl-2-thiohydantoin with diazomethane gave three products. In addition to 4-keto-2-methylthio-5 : 5-diphenyl- and 4-keto-2-methylthio-5 : 5-diphenyl-3-methyl-4 : 5-dihydroglyoxaline described above, there was also produced 5 : 5-diphenyl-3-methyl-2-thiohydantoin (VII; R = Ph). The other possible structure for this compound, namely 5 : 5-diphenyl-1-methyl-2-thiohydantoin, was excluded by the synthesis of this latter compound by another route which will be described later.



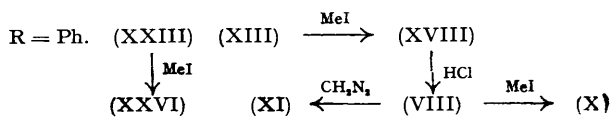
With methyl iodide 5 : 5-pentamethylene-2-thiohydantoin (V; RR = <[CH_2]$_5$) gave a result parallel to that just described for the 5 : 5-diphenyl series, *4-keto-2-methylthio-5 : 5-pentamethylene-4 : 5-dihydroglyoxaline* (VI; RR = <[CH_2]$_5$) being produced, the structure of which was proved by acid hydrolysis to methanethiol and 5 : 5-pentamethylenehydantoin. Diazomethane, however, gave only *3-methyl-5 : 5-pentamethylene-2-thiohydantoin* (VII; RR = <[CH_2]$_5$); the location of the methyl group in the 3-position was established, first, by conversion by phosphorus pentasulphide into 3-methyl-5 : 5-pentamethylene-2 : 4-dithiohydantoin, and secondly, by further methylation with methyl iodide to give *4-keto-2-methylthio-3-methyl-5 : 5-pentamethylene-4 : 5-dihydroglyoxaline* (IX; RR = <[CH_2]$_5$) which was hydrolysed by acid to 3-methyl-5 : 5-pentamethylenehydantoin.



Comparatively few experiments have been carried out in the 4-thiohydantoin series. 2-Keto-4-methylthio-5 : 5-diphenyl-2 : 5-dihydroglyoxaline (XXIV; R = Ph) with methyl iodide gave the *1-methyl* derivative (XXVII; R = Ph), which was readily hydrolysed to 5 : 5-diphenyl-1-methylhydantoin. This series of reactions was of interest in that it provided another means of entry into the series of 5 : 5-diphenyl-1-methyl derivatives, which is otherwise rather difficult of access.

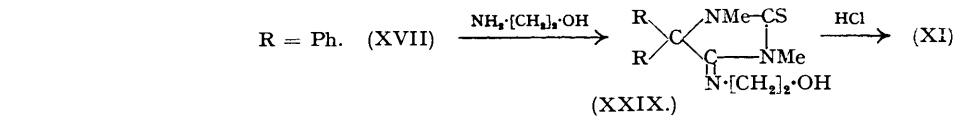
5 : 5-Pentamethylene-4-thiohydantoin, with methyl iodide, gave 2-keto-4-methylthio-5 : 5-pentamethylene-2 : 5-dihydroglyoxaline (XXIV; RR = <[CH_2]$_5$). When diazomethane was used, this product was accompanied by 3-methyl-5 : 5-pentamethylene-4-thiohydantoin, which had previously been obtained by the hydrolysis of the 2-methylthio-3-methyl-4-thio-derivative.

5 : 5-Diphenyl-3-methyl-4-thiohydantoin (XXIII; R = Ph), on treatment with methyl iodide, gave the 1 : 3-*dimethyl* derivative (XXVI; R = Ph). The establishment of the structure of this compound was of great value in settling the constitution of another derivative mentioned previously, the product obtained by the methylation of 5 : 5-diphenyl-1-methyl-2 : 4-dithiohydantoin (XIII; R = Ph). On acid hydrolysis, this last methylated product lost methanethiol and gave a 1-methyl-monothio-derivative, which could only be the 2- or 4-thio-compound. This was converted by diazomethane into a dimethyl-monothio-derivative, stable to acid and, therefore, with both methyl groups attached to nitrogen. As this substance was different from the 1 : 3-dimethyl-4-thiohydantoin described above, it clearly could only be 5 : 5-diphenyl-1 : 3-dimethyl-2-thiohydantoin (XI; R = Ph). The 1-methyl-monothio-derivative from which it was obtained must, therefore, be 5 : 5-*diphenyl-1-methyl-2-thiohydantoin* (VIII; R = Ph), and the product of methylation of the 1-methyl-2 : 4-dithiohydantoin was *2-thio-4-methylthio-5 : 5-diphenyl-1-methyl-2 : 5-dihydroglyoxaline* (XVIII; R = Ph). Methylation of 5 : 5-diphenyl-1-methyl-2-thiohydantoin with methyl iodide gave *4-keto-2-methylthio-5 : 5-diphenyl-1-methyl-4 : 5-dihydroglyoxaline* (X; R = Ph), a compound of considerable interest, since it was the only example of a dimethyl derivative substituted in both the 1- and the 2-positions.

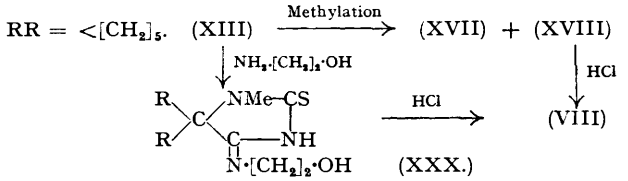


Further evidence of the structure of 5 : 5-diphenyl-1 : 3-dimethyl-2-thiohydantoin (XI;

R = Ph) has been obtained from its formation by another series of reactions. It was shown in Part II that when 2-aminoethanol reacted with a 5 : 5-disubstituted-2 : 4-dithiohydantoin the sulphur in the 4-position was preferentially replaced. It was further established that a 2-hydroxyethylimino-group was readily removed from the 4-position by acid hydrolysis, while in the 2-position it was unaffected by this treatment. The reaction of 2-aminoethanol with 5 : 5-diphenyl-1 : 3-dimethyl-2 : 4-dithiohydantoin (XVII; R = Ph) was therefore of considerable interest. First, it was not known whether reaction would occur at all, in view of the absence of a tautomerisable hydrogen atom : it was possible that the reaction would only take place with a $-C(SH)=N-$ grouping. Secondly, if reaction did take place, it was uncertain whether the preferential substitution in the 4-position would still occur, and whether the product would be hydrolysed by acid. In fact, the reaction followed the normal course, although it was slow, and the product, 4-2′-*hydroxyethylimino*-5 : 5-*diphenyl*-1 : 3-*dimethyl*-2-*thiohydantoin* (XXIX; R = Ph) was readily hydrolysed by acid, giving 5 : 5-diphenyl-1 : 3-dimethyl-2-thiohydantoin (XI; R = Ph).

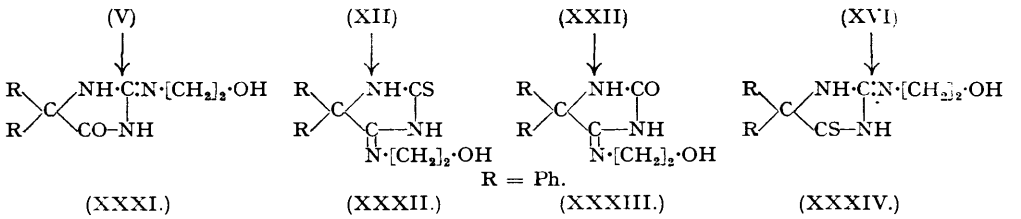


4-2′-*Hydroxyethylimino*-1-*methyl*-5 : 5-*pentamethylene*-2-*thiohydantoin* (XXX; RR = $<[CH_2]_5$) was obtained by the action of aqueous 2-aminoethanol on the 1-methyl-2 : 4-dithiohydantoin. On acid hydrolysis it gave 1-*methyl*-5 : 5-*pentamethylene*-2-*thiohydantoin* (VIII; RR = $<[CH_2]_5$), which was also produced by acid hydrolysis of 2-thio-4-methylthio-1-methyl-5 : 5-pentamethylene-2 : 5-dihydroglyoxaline (XVIII), one of the products of methylation of the 1-methyl-2 : 4-dithiohydantoin.



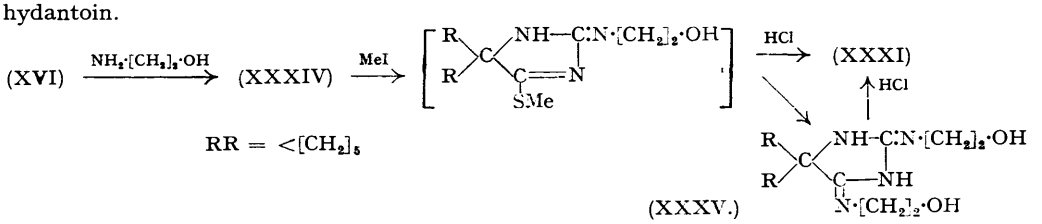
The action of diazomethane on 1-methyl-5 : 5-pentamethylene-2-thiohydantoin gave the 1 : 3-*dimethyl* derivative (XI). From its method of formation this could only be the 1 : 3-dimethyl or the 2-methylthio-1-methyl derivative. As it was stable to acids, and therefore contained no methylthio-group, the former structure was correct.

Methylthio-substituents in the hydantoin nucleus were replaced by 2-aminoethanol more readily than were the unmethylated thio-groups. Thus whereas 5 : 5-diphenyl-2 : 4-dithiohydantoin gave 4-2′-*hydroxyethylimino*-5 : 5-*diphenyl*-2-*thiohydantoin* (XXXII; R = Ph), 5 : 5-diphenyl-4-thiohydantoin gave 4-2′-*hydroxyethylimino*-5 : 5-*diphenylhydantoin* (XXXIII; R = Ph), and 5 : 5-diphenyl-2-thiohydantoin gave 2-2′-*hydroxyethylimino*-5 : 5-*diphenylhydantoin* (XXXI; R = Ph), it was found that with 4-thio-2-methylthio-5 : 5-diphenyl-4 : 5-dihydroglyoxaline reaction occurred preferentially in the 2-position, with formation of 2-2′-*hydroxyethylimino*-5 : 5-*diphenyl*-4-*thiohydantoin* (XXXIV; R = Ph).



It might therefore be expected that the 2 : 4-dimethylthioglyoxalines would react with 2-aminoethanol with great ease to give derivatives with two 2-hydroxyethylimino-substituents. This, however, was not the case. These compounds were inert towards 2-aminoethanol, and when, under drastic conditions, reaction did occur, no identifiable products could be isolated. A hydantoin derivative with basic substituents in both the 2- and 4-positions has, however, been obtained by an indirect route. 4-Thio-2-methylthio-5 : 5-pentamethylene-4 : 5-dihydro-

glyoxaline (XVI; RR = <[CH$_2$]$_5$) reacted readily with 2-aminoethanol to give 2-2′-*hydroxyethylimino*-5 : 5-*pentamethylene*-4-*thiohydantoin* (XXXIV; RR = <[CH$_2$)$_5$). This could be methylated with methyl iodide in the usual way to give 2-2′-hydroxyethylimino-4-methylthio-5 : 5-pentamethylene-2 : 5-dihydroglyoxaline, which was not obtained analytically pure but was characterised by acid hydrolysis with loss of methanethiol to give 2-2′-hydroxyethylimino-5 : 5-pentamethylenehydantoin (XXXI; RR = <[CH$_2$]$_5$), identical with that described in Part II. The 4-methylthio-compound now reacted readily with a second molecule of 2-aminoethanol to give 2 : 4-*di*-(2′-*hydroxyethylimino*)-5 : 5-*pentamethylenehydantoin* (XXXV; RR = <[CH$_2$]$_5$), which on acid hydrolysis was also converted into 2-2′-hydroxyethylimino-5 : 5-pentamethylenehydantoin.



Another interesting reaction was the removal of methylthio-groups in the reaction with phosphorus pentasulphide. Thus, an attempt was made to find a more convenient method for the preparation of 4-thio-2-methylthio-5 : 5-diphenyl-4 : 5-dihydroglyoxaline (XVI; R = Ph) by the action of this reagent on the 4-keto-2-methylthio-compound, but the product obtained was 5 : 5-diphenyl-2 : 4-dithiohydantoin. A similar case was the preparation of 5 : 5-diphenyl-1-methyl-2 : 4-dithiohydantoin directly from 2-keto-4-methylthio-5 : 5-diphenyl-1-methyl-2 : 5-dihydroglyoxaline. Such replacements have been described previously, for example, in the uracil series, by Elion and Hutchings (*J. Amer. Chem. Soc.*, 1947, **69**, 2138).

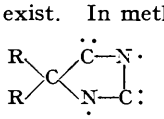
Of the twenty-seven possible types of 5 : 5-disubstituted hydantoins, their thio-analogues, and *N*- and *S*-methyl derivatives, we have thus been able to prepare representatives of all but one, namely, the 4-thio-2-methylthio-1-methyl compounds (XIX). The only case where it was possible to isolate a product with methyl groups in both the 1- and the 2-position was with 5 : 5-diphenyl-1-methyl-2-thiohydantoin, when methylation with methyl iodide occurred on the sulphur atom rather than at the 3- or 4-position.

It is not possible to formulate simple rules governing the methylation of these hydantoin derivatives, but a few general trends may be mentioned. Of the methylating agents used, methyl iodide tends to give most complete *S*-methylation. Diazomethane has the greatest tendency towards *N*-methylation, and methyl sulphate is intermediate. This is of course only to be expected, since diazomethane is used in ethereal solution, where the existence of –CS·NH– systems would be expected to be favoured. With the other methylating agents, the reaction was carried out in polar solvents in presence of sodium hydroxide, where –C(·SH)=N– systems should predominate.

There appears to be a general tendency for less *N*-methylation to occur in the 5 : 5-diphenyl series than in the 5 : 5-pentamethylene series.

An interesting contrast exists between the dithiohydantoins and the methylthio-derivatives in their behaviour towards acid. The 5 : 5-disubstituted 2 : 4-dithiohydantoins as a class are stable to acid hydrolysis, but, as described in Part II, 5 : 5-dimethyl-2 : 4-dithiohydantoin can be hydrolysed by acid to the corresponding 2-thio-derivative, the sulphur atom in position 4 being replaced by oxygen. When, however, 2 : 4-dimethylthio-5 : 5-diphenylglyoxaline was submitted to a careful partial hydrolysis the 2-methylthio-group was removed first, leaving the 4-methylthio-group intact.

The ultra-violet absorption of the available pentamethylene derivatives has been measured in methanol solution. The hydantoins themselves show no specific absorption, but the thio-derivatives in general have characteristic bands. The structure of the dimethyl derivatives is fixed, and from their absorption spectra some deductions can be made of the probable structure of some of the unmethylated and monomethylated derivatives, where possibilities of tautomerism exist. In methanol solutions the compounds appear to exist wherever possible in the annexed



form, with both the double bonds outside the ring. Thus in the dithio-series the compounds (XII), (XIII), and (XV) have spectra closely similar to that of (XVII) which must have a structure of the type indicated, and in the 2-thio-series the compounds (V), (VII), and (VIII) have spectra similar to that of (XI). In the 4-thiohydantoins there is no available compound in which this structure is obligatory,

but (XXII), (XXIII), and (XXV), with closely similar spectra, probably also exist in this form. No clear grounds appear to exist for the correlation of the structures of other members of the series with the fixed structures of (XVIII), (XX), and (XXI) on the basis of their absorption spectra in methanol solution.

Experimental.

In view of the large number of compounds involved and the fact that many of them are prepared by more than one experimental procedure, the table serves as an index to the Experimental section. References are there given for known compounds. Where alternative methods are described, the most favoured procedure is given first, followed by the others in order of preference. In the text below, cross-references given as " cf. A " etc. indicate identity established by mixed m. p. Absorption spectra were determined in methanol.

Formula no.	5 : 5-Diphenyl series.	5 : 5-Pentamethylene series.
I.	—	Bucherer and Lieb, *J. pr. Chem.*, 1934, **141**, 5.
II.	Long, Miller and Troutman, *J. Amer. Chem. Soc.*, 1948, **70**, 902; D.	G.
III.	Biltz, *Ber.*, 1908, **41**, 1386.	C, B.
IV.	Biltz, *Ber.*, 1908, **41**, 170, 1379.	C, B.
V.	Biltz, *Ber.*, 1909, **42**, 1792.	Carrington, *J.*, 1947, 684.
VI.	Biltz, *Ber.*, 1909, **42**, 1792; A, B.	A.
VII.	Biltz, *Ber.*, 1909, **42**, 1792; B.	B.
VIII.	D.	D.
IX.	Biltz, *Ber.*, 1909, **42**, 1792; A, B.	A.
X.	A.	—
XI.	Biltz, *Ber.*, 1909, **42**, 1792; F.	B.
XII.	Henze and Smith, *J. Amer. Chem. Soc.*, 1943, **65**, 1090.	Carrington, *J.*, 1947, 681.
XIII.	E.	E.
XIV.	A, B, C.	B, C.
XV.	E, B.	E, B, C.
XVI.	C.	C.
XVII.	E, B, A, C.	E, B, C, A.
XVIII.	A.	A, C.
XIX.	—	—
XX.	A, B.	A, B, (C).
XXI.	A, C, B.	C, A.
XXII.	D.	Carrington, *J.*, 1947, 684.
XXIII.	D.	D, B.
XXIV.	D, A.	A, B.
XXV.	—	A.
XXVI.	A.	—
XXVII.	A, C.	—

(A) *Methylations with Methyl Iodide.*—The hydantoin (1 mol.) was suspended in methanol (or ethanol) (about 10 c.c. per g.) and aqueous sodium hydroxide (1 mol.; 12% solution) was added, whereupon the hydantoin dissolved. Alternatively, the hydantoin was dissolved in 1 equivalent of methanolic sodium hydroxide. Methyl iodide (1·1 mols.) was added and the mixture was set aside. The product usually crystallised, sometimes in a few minutes, sometimes overnight. When this failed to occur the alcohol was removed *in vacuo*, and the residue was washed with water, to remove sodium iodide, and purified by crystallisation.

In this way 5 : 5-diphenyl-2-thiohydantoin (V) gave 4-keto-2-methylthio-5 : 5-diphenyl-4 : 5-dihydroglyoxaline (VI), colourless needles (from ethanol), m. p. 213° (90%) (Found : C, 67·75; H, 4·85; N, 10·1. Calc. for $C_{16}H_{14}ON_2S$: C, 68·1; H, 4·95; N, 9·95%). This (in ethanol) gave 4-keto-2-methylthio-5 : 5-diphenyl-3-methyl-4 : 5-dihydroglyoxaline (IX), colourless needles (from ethanol), m. p. 175° (81%) (Found : C, 69·2; H, 5·4; N, 9·15. Calc. for $C_{17}H_{16}ON_2S$: C, 68·9; H, 5·4; N, 9·5%). 2-Keto-4-methylthio-5 : 5-diphenyl-2 : 5-dihydroglyoxaline (XXIV) (in ethanol) gave 2-*keto*-4-*methylthio*-5 : 5-*diphenyl*-1-*methyl*-2 : 5-*dihydroglyoxaline* (XXVII), colourless needles (from ethanol), m. p. 229° (86%) (Found : C, 69·0; H, 5·65; N, 9·55. $C_{17}H_{16}ON_2S$ requires C, 68·9; H, 5·4; N, 9·5%). 5 : 5-Diphenyl-3-methyl-4-thiohydantoin (XXIII) (in ethanol) gave 5 : 5-*diphenyl*-1 : 3-*dimethyl*-4-*thiohydantoin* (XXVI), long cream-coloured prisms (from methanol), m. p. 211° (74%) (Found : C, 69·2; H, 5·4; N, 9·1. $C_{17}H_{16}ON_2S$ requires C, 68·9; H, 5·4; N, 9·5%). 5 : 5-Diphenyl-3-methyl-2 : 4-dithiohydantoin (XV) gave 4-*thio*-2-*methylthio*-5 : 5-*diphenyl*-3-*methyl*-4 : 5-*dihydroglyoxaline* (XX), pale yellow plates (from methanol), m. p. 148° (92%) (Found : C, 65·2; H, 5·2; N, 8·95. $C_{17}H_{16}N_2S_2$ requires C, 65·3; H, 5·15; N, 9·0%). 5 : 5-Diphenyl-1-methyl-2 : 4-dithiohydantoin (XIII) (in ethanol) gave 2-*thio*-4-*methylthio*-5 : 5-*diphenyl*-1-*methyl*-2 : 5-*dihydroglyoxaline* (XVIII), pale yellow needles (from methanol), m. p. 205° (82%) (Found : C, 65·3; H, 5·15; N, 9·1. $C_{17}H_{16}N_2S_2$ requires C, 65·3; H, 5·15; N, 9·0%), accompanied by a very small amount of 5 : 5-diphenyl-1 : 3-dimethyl-2 : 4-dithiohydantoin (XVII) (cf. E).

5 : 5-Diphenyl-2 : 4-dithiohydantoin (XII) gave a mixture, which on chromatographic analysis from chloroform solution on alumina gave 2 : 4-dimethylthio-5 : 5-diphenylglyoxaline (XXI), m. p. 140° (32%; see below), 2-*thio*-4-*methylthio*-5 : 5-*diphenyl*-2 : 5-*dihydroglyoxaline* (XIV), pale yellow plates (from ethanol), m. p. 256° (15%; this figure is probably low, owing to the difficulty of extracting this

very sparingly soluble substance from the alumina) (Found: C, 64·2; H, 4·5; N, 9·1. $C_{16}H_{14}N_2S_2$ requires C, 64·4; H, 4·7; N, 9·4%), and a small amount of unchanged starting material.

5 : 5-Diphenyl-1-methyl-2-thiohydantoin (VIII) gave a gummy product, which after chromatographic treatment on alumina from a solution in 1 : 1 ether–chloroform gave 4-*keto*-2-*methylthio*-5 : 5-*diphenyl*-1-*methyl*-4 : 5-*dihydroglyoxaline* (X), colourless needles (from methanol), m. p. 170° (20%) (Found: C, 68·7; H, 5·3; N, 9·7. $C_{17}H_{16}ON_2S$ requires C, 68·9; H, 5·4; N, 9·5%).

5 : 5-Pentamethylene-2-thiohydantoin (V) gave 4-*keto*-2-*methylthio*-5 : 5-*pentamethylene*-4 : 5-*dihydroglyoxaline* (VI), colourless needles (from aqueous methanol), m. p. 152—153° (70%) (Found: C, 54·3; H, 7·1; N, 13·8. $C_9H_{14}ON_2S$ requires C, 54·5; H, 7·1; N, 14·15%); light absorption: Maximum, 2370 A.; $\varepsilon = 11{,}100$. 3-Methyl-5 : 5-pentamethylene-2 : 4-dithiohydantoin (XV) gave 4-*thio*-2-*methylthio*-3-*methyl*-5 : 5-*pentamethylene*-4 : 5-*dihydroglyoxaline* (XX), colourless plates (from methanol), m. p. 63—64° (75%) (Found: C, 52·6; H, 6·8; N, 12·4. $C_{10}H_{16}N_2S_2$ requires C, 52·6; H, 7·0; N, 12·3%); light absorption: Maxima, 2500 and 2950 A.; $\varepsilon = 8{,}900$ and 11,800 respectively. 3-Methyl-5 : 5-pentamethylene-2-thiohydantoin (VII) gave 4-*keto*-2-*methylthio*-3-*methyl*-5 : 5-*pentamethylene*-4 : 5-*dihydroglyoxaline* (IX), colourless prisms (from aqueous methanol), m. p. 62—63° (80%) (Found: C, 56·8; H, 7·5; N, 13·1. $C_{10}H_{16}ON_2S$ requires C, 56·6; H, 7·55; N, 13·2%); light absorption showed end absorption only. 5 : 5-Pentamethylene-4-thiohydantoin (XXII) gave 2-*keto*-4-*methylthio*-5 : 5-*pentamethylene*-2 : 5-*dihydroglyoxaline* (XXIV), colourless prisms (from a small quantity of methanol), m. p. 236° (42%) (Found: C, 54·3; H, 7·2; N, 14·0. $C_9H_{14}ON_2S$ requires C, 54·5; H, 7·1; N, 14·15%); light absorption: Maximum, 2440 A.; $\varepsilon = 9{,}820$. 4-Thio-2-methylthio-5 : 5-pentamethylene-4 : 5-dihydroglyoxaline (XVI) gave 2 : 4-dimethylthio-5 : 5-pentamethyleneglyoxaline (XXI), m. p. 48—49° (84%) (cf. C). 1-Methyl-5 : 5-pentamethylene-2 : 4-dithiohydantoin (XIII) gave 2-*thio*-4-*methylthio*-1-*methyl*-5 : 5-*pentamethylene*-2 : 5-*dihydroglyoxaline* (XVIII), yellow prisms (from methanol), m. p. 148—149° (50%) (Found: C, 52·9; H, 7·0; N, 12·0. $C_{10}H_{16}N_2S_2$ requires C, 52·6; H, 7·0; N, 12·3%); light absorption: Maximum, 2880 A.; $\varepsilon = 17{,}400$. There was also found a small amount of 1 : 3-dimethyl-5 : 5-pentamethylene-2 : 4-dithiohydantoin (XVII), m. p. 126—127° (cf. E), and a few yellow needles of an alkali-soluble substance of m. p. 188—189°, which is believed to be 1-*methyl*-5 : 5-*pentamethylene*-4-*thiohydantoin* (XXV) (Found: C, 54·7; H, 7·1; N, 13·8. $C_9H_{14}ON_2S$ requires C, 54·5; H, 7·1; N, 14·15%) (light absorption: Maxima, 2360 and 2850 A.; $\varepsilon = 5{,}750$ and 11,400, respectively). When the sodium salt of 5 : 5-pentamethylene-2 : 4-dithiohydantoin (XII) was treated with methyl iodide in methanol solution at room temperature, methanethiol was evolved; after removal of the solvent *in vacuo* the residue was washed with ether and water, and extracted with chloroform. Evaporation of the chloroform solution gave 2-keto-4-methylthio-5 : 5-pentamethylene-2 : 5-dihydroglyoxaline (XXIV), m. p. 234° (from methanol) (cf. above).

Other methylations with methyl iodide were carried out in alcoholic solution in presence of sodium hydrogen carbonate. 5 : 5-Diphenyl-2 : 4-dithiohydantoin (XII) (7·1 g.) in methanol (100 c.c.) was heated under reflux to 50° with efficient stirring for 5 hours with methyl iodide (10 g.) and sodium hydrogen carbonate (6 g.). After the mixture had been kept overnight the product crystallised, and was filtered off, washed with water, and dried, giving 2 : 4-*dimethylthio*-5 : 5-*diphenylglyoxaline* (XXI), long colourless prisms (from methanol), m. p. 140° (88%) (Found: C, 65·3; H, 5·35; N, 8·6. $C_{17}H_{16}N_2S_2$ requires C, 65·3; H, 5·15; N, 9·0%) (cf. above). Under slightly more vigorous conditions and without efficient stirring, a different product was obtained. Thus, (XII) (7·1 g.) in methanol (100 c.c.) was heated under reflux at 60—70° with methyl iodide (8·5 g.) and sodium hydrogen carbonate (5 g.) for 6 hours without stirring. After cooling the crystalline product was filtered off to give 2-keto-4-methylthio-5 : 5-diphenyl-2 : 5-dihydroglyoxaline (XXIV), colourless prisms (from ethanol), m. p. 264° (32%) (cf. D).

(B) *Methylations with Diazomethane.*—The hydantoin was added to excess of an ethereal solution of diazomethane. In some cases a little methanol was added. The mixture was set aside overnight, and the product was isolated by removal of excess of diazomethane and ether by distillation.

5 : 5-Diphenyl-2 : 4-dithiohydantoin (XII) gave a complex mixture of products from which, by chromatographic separation of a chloroform solution on alumina, there were isolated: 4-thio-2-methylthio-5 : 5-diphenyl-3-methyl-4 : 5-dihydroglyoxaline (XX), m. p. 148° (42%) (cf. A), 5 : 5-diphenyl-3-methyl-2 : 4-dithiohydantoin (XV), m. p. 206° (20%) (cf. E), 2-thio-4-methylthio-5 : 5-diphenyl-2 : 5-dihydroglyoxaline (XIV), m. p. 256° (15%) (cf. A), and 5 : 5-diphenyl-1 : 3-dimethyl-2 : 4-dithiohydantoin (XVII), m. p. 167° (2%) (cf. E). The proportion of the mono- and di-methyl derivatives obtained probably depends upon the amount of diazomethane in excess. 2-Thio-4-methylthio-5 : 5-diphenyl-2 : 5-dihydroglyoxaline (XIV) gave 2 : 4-dimethylthio-5 : 5-diphenylglyoxaline (XXI), m. p. 140° (40%) (cf. A). 5 : 5-Diphenyl-3-methyl-2 : 4-dithiohydantoin (XV) gave 4-thio-2-methylthio-5 : 5-diphenyl-3-methyl-4 : 5-dihydroglyoxaline (XX), m. p. 148° (75%) (cf. A). 5 : 5-Diphenyl-2-thiohydantoin (V) gave a mixture, separated by passage of its ethereal solution through an alumina column, into 4-keto-2-methylthio-5 : 5-diphenyl-3-methyl-4 : 5-dihydroglyoxaline (IX), m. p. 175° (5%) (cf. A), 5 : 5-diphenyl-3-methyl-2-thiohydantoin (VII), colourless needles (from ethanol), m. p. 186° (25%) (Found: C, 68·1; H, 5·2; N, 10·0. Calc. for $C_{16}H_{14}ON_2S$: C, 68·1; H, 4·95; N, 9·95%), and 4-keto-2-methylthio-5 : 5-diphenyl-4 : 5-dihydroglyoxaline (VI), m. p. 212° (7%) (cf. A).

5 : 5-Pentamethylenehydantoin (I) gave 3-methyl-5 : 5-pentamethylenehydantoin (III), m. p. 213° (93%) (cf. C). 1-Methyl-5 : 5-pentamethylenehydantoin (II) gave 1 : 3-dimethyl-5 : 5-pentamethylenehydantoin (IV), m. p. 68—69° (cf. C). 5 : 5-Pentamethylene-2-thiohydantoin gave 3-*methyl*-5 : 5-*pentamethylene*-2-*thiohydantoin* (VII), colourless plates (from methanol), m. p. 174—175° (78%) (Found: C, 54·8; H, 7·1; N, 14·3. $C_9H_{14}ON_2S$ requires C, 54·5; H, 7·1; N, 14·15%); light absorption: Maxima, 2320 and 2670 A.; $\varepsilon = 9{,}360$ and 18,000 respectively. 5 : 5-Pentamethylene-4-thiohydantoin (XXII) gave a mixture of 2-keto-4-methylthio-5 : 5-pentamethylene-2 : 5-dihydroglyoxaline (XXIV), m. p. 234° (50%) (cf. A), and 3-methyl-5 : 5-pentamethylene-4-thiohydantoin (XXIII), m. p. 191° (25%) (cf. D). 1-Methyl-5 : 5-pentamethylene-2-thiohydantoin (VIII) gave 1 : 3-*dimethyl*-5 : 5-*pentamethylene*-2-*thiohydantoin* (XI), colourless jagged needles (from aqueous methanol), m. p. 118—119° (70%) (Found: C, 56·4; H, 7·5; N, 13·0. $C_{10}H_{16}ON_2S$ requires C, 56·6; H, 7·55; N, 13·2%); light

absorption: Maxima, 2380 and 2650 A., ε = 13,570 and 17,100 respectively. 5 : 5-Pentamethylene-2 : 4-dithiohydantoin (XII) gave a mixture of products. There separated from the reaction mixture *2-thio-4-methylthio-5 : 5-pentamethylene-2 : 5-dihydroglyoxaline* (XIV), colourless needles (from methanol), m. p. 217—218° (26%) (Found: C, 50·7; H, 6·6; N, 12·7. $C_9H_{14}N_2S_2$ requires C, 50·5; H, 6·5; N, 13·1%); light absorption: Maximum, 2820 A.; ε = 11,600. Inflexion, 3070 A., ε = 8,700. The residue, after removal of ether and excess of diazomethane, was triturated with light petroleum (b. p. 40—60°) to give 3-methyl-5 : 5-pentamethylene-2 : 4-dithiohydantoin (XV), m. p. 191—192° (46%) (cf. E). The light-petroleum washings, on evaporation, left an oil which was not purified but on acid hydrolysis lost methanethiol and gave 3-methyl-5 : 5-pentamethylene-4-thiohydantoin (XXIII), m. p. 191° (9%) (cf. D); this indicated the presence of 4-thio-2-methylthio-3-methyl-5 : 5-pentamethylene-4 : 5-dihydroglyoxaline (XX). Methylation of 1-methyl-5 : 5-pentamethylene-2 : 4-dithiohydantoin (XIII) with diazomethane gave 1 : 3-dimethyl-5 : 5-pentamethylene-2 : 4-dithiohydantoin (XVII), m. p. 126° (45%) (cf. E), and 2-thio-4-methylthio-1-methyl-5 : 5-pentamethylene-2 : 5-dihydroglyoxaline (XVIII), m. p. 148—149° (5%) (cf. A). 3-Methyl-5 : 5-pentamethylene-2 : 4-dithiohydantoin (XV) gave 4-thio-2-methylthio-3-methyl-5 : 5-pentamethylene-4 : 5-dihydroglyoxaline (XX), m. p. 63—64° (90%) (cf. A).

(C) *Methylations with Methyl Sulphate.*—5 : 5-Diphenyl-2 : 4-dithiohydantoin (XII) (15 g.) was dissolved in dilute aqueous sodium hydroxide (165 c.c.; 4%). To the stirred solution, methyl sulphate (9 g.) was added during 10 minutes, the temperature being kept below 20°. The mixture was stirred for a further 2 hours and was then filtered. The solid product, recrystallised from methanol, gave 2 : 4-dimethylthio-5 : 5-diphenylglyoxaline (XXI), m. p. 140° (25%) (cf. A). The alkaline filtrate was clarified with kieselguhr and then acidified with hydrochloric acid, and the product was extracted with chloroform. The dried chloroform solution was passed through an alumina column, affording 2-thio-4-methylthio-5 : 5-diphenyl-2 : 5-dihydroglyoxaline (XIV), m. p. 256° (19%) (cf. A), and *4-thio-2-methylthio-5 : 5-diphenyl-4 : 5-dihydroglyoxaline* (XVI), bright orange-yellow needles (from methanol), m. p. 211° (13%) (Found: C, 64·3; H, 4·65; N, 9·1. $C_{16}H_{14}N_2S_2$ requires C, 64·4; H, 4·7; N, 9·4%), which darkened on exposure to light.

In a similar manner 5 : 5-diphenyl-1-methyl-2 : 4-dithiohydantoin (XIII) gave a mixture from which there were obtained, by chromatographic separation from ether–chloroform (1 : 1) on alumina, 5 : 5-diphenyl-1 : 3-dimethyl-2 : 4-dithiohydantoin (XVII), m. p. 167° (12%) (cf. E), and 2-thio-4-methylthio-5 : 5-diphenyl-1-methyl-2 : 5-dihydroglyoxaline (XVIII), m. p. 205° (30%) (cf. A).

Methyl sulphate (32 g.) was added during 5 minutes to a stirred solution of 5 : 5-pentamethylenehydantoin (I) (34 g.) in aqueous sodium hydroxide (10 g. in 200 c.c.), the temperature being kept below 40°. After being stirred for a further 10 minutes the mixture was cooled and filtered, and the solid product was recrystallised from methanol, giving *3-methyl-5 : 5-pentamethylenehydantoin* (III), colourless needles, m. p. 212—213° (75%) (Found: C, 59·5; H, 7·8; N, 15·3. $C_9H_{14}O_2N_2$ requires C, 59·3; H, 7·7; N, 15·4%).

Similarly 1-methyl-5 : 5-pentamethylenehydantoin gave 1 : 3-*dimethyl-5 : 5-pentamethylenehydantoin*, colourless prisms (from aqueous methanol), m. p. 68—69° (74%) (Found: C, 60·8; H, 8·2; N, 14·4. $C_{10}H_{16}O_2N_2$ requires C, 61·2; H, 8·2; N, 14·3%).

5 : 5-Pentamethylene-2 : 4-dithiohydantoin (XII) (48 g.) in aqueous sodium hydroxide (360 c.c.; 8%) was methylated by addition of methyl sulphate (36 g.) with stirring, during 20 minutes, temperature being kept at 5—10°. The mixture was stirred for a further 3 hours, the temperature being allowed to rise to 20°. The insoluble solid was filtered off and recrystallised from aqueous methanol, to give 2 : 4-*dimethylthio-5 : 5-pentamethyleneglyoxaline* (XXI) as colourless needles, m. p. 48—49° (33%) (Found: C, 53·0; H, 7·1; N, 12·5. $C_{10}H_{16}N_2S_2$ requires C, 52·6; H, 7·0; N, 12·3%); light absorption: Maximum, 2570 A.; ε = 6,800. This substance was soluble in dilute hydrochloric acid and could be distilled *in vacuo* (b. p. 120°/0·3 mm.). The crude alkali-insoluble solid also appeared to contain some 4-thio-2-methylthio-3-methyl-5 : 5-pentamethylene-4 : 5-dihydroglyoxaline (XX), for acid hydrolysis gave, in addition to 5 : 5-pentamethylenehydantoin (I), an alkali-insoluble product identified as 3-methyl-5 : 5-pentamethylene-4-thiohydantoin (XXIII), m. p. 191° (cf. D). The alkaline filtrate from the methylation was acidified below 10° with phosphoric acid, and the solid was filtered off, washed with water, and dried. Chromatographic separation from chloroform solution on alumina gave as the main product *4-thio-2-methylthio-5 : 5-pentamethylene-4 : 5-dihydroglyoxaline* (XVI), bright yellow needles (from aqueous methanol), m. p. 161° (30%) (Found: C, 50·6; H, 6·6; N, 13·4. $C_9H_{14}N_2S_2$ requires C, 50·5; H, 6·5; N, 13·1%); light absorption: Maxima, 2550, 2970, and 3300 A.; ε = 7,880, 8,340, and 8,890 respectively. This compound darkened on exposure to light. It was accompanied by small quantities of 3-methyl-5 : 5-pentamethylene-2 : 4-dithiohydantoin (XV), m. p. 191—192° (cf. E), and 2-thio-4-methylthio-5 : 5-pentamethylene-2 : 5-dihydroglyoxaline (XIV), m. p. 217—218° (cf. B).

1-Methyl-5 : 5-pentamethylene-2 : 4-dithiohydantoin (XIII), methylated under similar conditions, gave a mixture which was separated chromatographically from chloroform solution on alumina into 1 : 3-dimethyl-5 : 5-pentamethylene-2 : 4-dithiohydantoin (XVII), m. p. 126° (29%) (cf. E), and 2-thio-4-methylthio-1-methyl-5 : 5-pentamethylene-2 : 5-dihydroglyoxaline (XVIII), m. p. 148—149° (23%) (cf. A).

(D) *Hydrolysis of Methylthio-compounds.*—The methylthio-compound (5 g.) in 20% hydrochloric acid (20 c.c.) was heated under reflux for ½—4 hours. Methanethiol was evolved, and on cooling the product separated. In the 5 : 5-diphenyl series, where the starting materials were sparingly soluble, the hydrolysis was usually carried out in a mixture of 36% hydrochloric acid (20 c.c.) and ethanol (50 c.c.).

In this way 2 : 4-dimethylthio-5 : 5-diphenylglyoxaline (XXI) gave 5 : 5-diphenylhydantoin (I), colourless crystals (from aqueous methanol), m. p. 300° (60%). The same product was obtained from 2-keto-4-methylthio-5 : 5-diphenyl-2 : 5-dihydroglyoxaline (XXIV) (65%). 2-Keto-4-methylthio-5 : 5-diphenyl-1-methyl-2 : 5-dihydroglyoxaline (XXVII) gave 5 : 5-diphenyl-1-methylhydantoin (II), long colourless prisms (from aqueous methanol), m. p. 225° (94%) (Found: C, 72·3; H, 5·3; N, 11·2. Calc. for $C_{16}H_{14}O_2N_2$: C, 72·2; H, 5·25; N, 11·5%). The same product was obtained in almost theoretical yield from 4-keto-2-methylthio-5 : 5-diphenyl-1-methyl-4 : 5-dihydroglyoxaline (X). 4-Keto-2-methylthio-5 : 5-diphenyl-3-methyl-4 : 5-dihydroglyoxaline (IX) gave 5 : 5-diphenyl-3-methylhydantoin (III)

in almost theoretical yield. 4-Thio-2-methylthio-5 : 5-diphenyl-4 : 5-dihydroglyoxaline (XVI) gave 5 : 5-*diphenyl*-4-*thiohydantoin* (XXII), bright yellow prisms (from methanol), m. p. 273—274° (80%) (Found : C, 66·8; H, 4·6; N, 10·4. $C_{15}H_{12}ON_2S$ requires C, 67·2; H, 4·5; N, 10·45%). 2-Thio-4-methylthio-5 : 5-diphenyl-1-methyl-2 : 5-dihydroglyoxaline (XVIII) gave 5 : 5-*diphenyl*-1-*methyl*-2-*thiohydantoin* (VIII), cream needles (from aqueous ethanol), m. p. 215° (83%) (Found : C, 68·2; H, 4·95; N, 10·0. $C_{16}H_{14}ON_2S$ requires C, 68·1; H, 4·95; N, 9·95%). 4-Thio-2-methylthio-5 : 5-diphenyl-3-methyl-4 : 5-dihydroglyoxaline (XX) gave 5 : 5-*diphenyl*-3-*methyl*-4-*thiohydantoin* (XXIII), pale yellow needles (from aqueous methanol), m. p. 202° (82%) (Found : C, 68·2; H, 5·1; N, 9·95. $C_{16}H_{14}ON_2S$ requires C, 68·1; H, 4·95; N, 9·95%).

2 : 4-Dimethylthio-5 : 5-pentamethyleneglyoxaline (XXI), 4-keto-2-methylthio-5 : 5-pentamethylene-4 : 5-dihydroglyoxaline (VI), or 2-keto-4-methylthio-5 : 5-pentamethylene-2 : 5-dihydroglyoxaline (XXIV) gave 5 : 5-pentamethylenehydantoin (I), m. p. 217—218°, on acid hydrolysis. 4-Keto-2-methylthio-3-methyl-5 : 5-pentamethylene-4 : 5-dihydroglyoxaline (IX) gave 3-methyl-5 : 5-pentamethylenehydantoin (III), m. p. 212° (47%). 2-Thio-4-methylthio-5 : 5-pentamethylene-2 : 5-dihydroglyoxaline (XIV) gave 5 : 5-pentamethylene-2-thiohydantoin (V), m. p. 190—191° (81%); light absorption : Maxima, 2240 and 2660 A.; ε = 9,910 and 20,300 respectively. 4-Thio-2-methylthio-5 : 5-pentamethylene-4 : 5-dihydroglyoxaline (XVI) gave 5 : 5-pentamethylene-4-thiohydantoin (XXII), m. p. 240°; light absorption : Maxima, 2300 and 2780 A.; ε = 4,360 and 15,500 respectively. 4-Thio-2-methylthio-3-methyl-5 : 5-pentamethylene-4 : 5-dihydroglyoxaline (XX) gave 3-*methyl*-5 : 5-*pentamethylene*-4-*thiohydantoin* (XXII), almost colourless plates (from methanol), m. p. 190—191° (71%) (Found : C, 54·8; H, 6·9; N, 14·1. $C_9H_{14}ON_2S$ requires C, 54·5; H, 7·1; N, 14·15%); light absorption : Maxima, 2290 and 2780 A.; ε = 5,300 and 15,100 respectively. 2-Thio-4-methylthio-1-methyl-5 : 5-pentamethylene-2 : 5-dihydroglyoxaline (XVIII) gave in almost quantitative yield 1-*methyl*-5 : 5-*pentamethylene*-2-*thiohydantoin* (VIII), colourless needles (from aqueous methanol), m. p. 153° (Found : C, 54·8; H, 7·2; N, 14·1. $C_9H_{14}ON_2S$ requires C, 54·5; H, 7·1; N, 14·15%); light absorption : Maxima, 2300 and 2650 A.; ε = 7,450 and 12,750 respectively.

2 : 4-Dimethylthio-5 : 5-diphenylglyoxaline (XXI) (8 g.) was heated under reflux for ½ hour with glacial acetic acid (80 c.c.) and water (20 c.c.). Methanethiol was evolved. Water (200 c.c.) was added, the mixture was cooled, and the product was filtered off, washed with water, and recrystallised from ethanol, to give 2-*keto*-4-*methylthio*-5 : 5-*diphenyl*-2 : 5-*dihydroglyoxaline* (XXIV), colourless prisms, m. p. 264° (64%) (Found : C, 67·7; H, 5·0; N, 9·5. $C_{16}H_{14}ON_2S$ requires C, 68·1; H, 4·95; N, 9·95%).

(E) *Introduction of Sulphur.*—The hydantoin (10 g.) and phosphorus pentasulphide (10 g.) were suspended in tetralin (60 c.c.; more was occasionally required with sparingly soluble compounds), and boiled under reflux with efficient stirring for 1—1½ hours. The mixture was filtered hot. The product separated from the solution on cooling. It was filtered off, and purified by recrystallisation.

5 : 5-Diphenyl-2-thiohydantoin (V) gave 5 : 5-diphenyl-2 : 4-dithiohydantoin (XII), bright yellow prisms (from methanol), m. p. 268° (70%), also produced similarly from 4-keto-2-methylthio-5 : 5-diphenyl-4 : 5-dihydroglyoxaline (VI). 5 : 5-Diphenyl-1-methylhydantoin (II) gave 5 : 5-*diphenyl*-1-*methyl*-2 : 4-*dithiohydantoin* (XIII), lemon-yellow prisms (from methanol), m. p. 217° (82%) (Found : C, 64·8; H, 4·85; N, 9·25. $C_{16}H_{14}N_2S_2$ requires C, 64·4; H, 4·7; N, 9·4%), also obtained from 2-keto-4-methylthio-5 : 5-diphenyl-1-methyl-2 : 5-dihydroglyoxaline (XXVII). 5 : 5-Diphenyl-3-methylhydantoin (III) gave 5 : 5-*diphenyl*-3-*methyl*-2 : 4-*dithiohydantoin* (XV), yellow prisms (from methanol), m. p. 206° (47%) (Found : C, 64·6; H, 4·75; N, 9·3. $C_{16}H_{14}N_2S_2$ requires C, 64·4; H, 4·7; N, 9·4%). 5 : 5-Diphenyl-1 : 3-dimethylhydantoin (IV) gave 5 : 5-*diphenyl*-1 : 3-*dimethyl*-2 : 4-*dithiohydantoin* (XVII), yellow needles (from methanol), m. p. 167° (60%) (Found : C, 65·5; H, 5·3; N, 8·8. $C_{17}H_{16}N_2S_2$ requires C, 65·3; H, 5·15; N, 9·0%).

1-Methyl-5 : 5-pentamethylenehydantoin (II) gave 1-*methyl*-5 : 5-*pentamethylene*-2 : 4-*dithiohydantoin* (XIII), yellow hexagonal plates (from aqueous methanol), m. p. 192—193° (60%) (Found : C, 50·2; H, 6·5; N, 13·25. $C_9H_{14}N_2S_2$ requires C, 50·5; H, 6·5; N, 13·1%); light absorption : Maxima, 2250 and 2980 A.; ε = 7,430 and 26,200. 3-Methyl-5 : 5-pentamethylenehydantoin (III) gave 3-*methyl*-5 : 5-*pentamethylene*-2 : 4-*dithiohydantoin* (XV), yellow prisms (from methanol), m. p. 191—192° (46%) (Found : C, 50·5; H, 6·8; N, 13·4. $C_{19}H_{14}N_2S_2$ requires C, 50·5; H, 6·5; N, 13·1%); light absorption : Maxima, 2250 and 2980 A.; ε = 6,690 and 29,100 respectively. This compound was also obtained similarly from 3-methyl-5 : 5-pentamethylene-2-thiohydantoin (VII). 1 : 3-Dimethyl-5 : 5-pentamethylenehydantoin (IV) gave 1 : 3-*dimethyl*-5 : 5-*pentamethylene*-2 : 4-*dithiohydantoin* (XVII), long yellow needles (from ethanol), m. p. 126° (26%) (Found : C, 52·5; H, 7·2; N, 12·0. $C_{10}H_{16}N_2S_2$ requires C, 52·6; H, 7·0; N, 12·3%); light absorption : Maxima, 2240 and 2980 A.; ε = 6,300 and 26,250 respectively.

(F) 2-*Aminoethanol Derivatives.*—5 : 5-Diphenyl-2 : 4-dithiohydantoin (XII) was boiled under reflux for ½ hour with 5 parts of 2-aminoethanol. Hydrogen sulphide was evolved, and after cooling the solid product was filtered off. Recrystallisation from ethanol gave 4-2′-*hydroxyethylimino*-5 : 5-*diphenyl*-2-*thiohydantoin*, colourless crystals, m. p. 218° (60%) (Found : C, 63·8; H, 5·6; N, 13·0. $C_{17}H_{17}ON_3S,\frac{1}{2}H_2O$ requires C, 63·8; H, 5·95; N, 13·1%), obtained also from 2-thio-4-methylthio-5 : 5-diphenyl-2 : 5-dihydroglyoxaline (XIV). In a similar manner 5 : 5-diphenyl-2-thiohydantoin (V), on refluxing for 3 hours with aqueous 2-aminoethanol, gave 2-2′-*hydroxyethylimino*-5 : 5-*diphenylhydantoin*, colourless prisms (from dimethylformamide), m. p. 298° (Found : C, 68·9; H, 5·9; N, 14·3. $C_{17}H_{17}O_2N_3$ requires C, 69·2; H, 5·75; N, 14·25%), also was obtained by the action of 2-aminoethanol on 4-keto-2-methylthio-5 : 5-diphenyl-4 : 5-dihydroglyoxaline (VI). 4-Thio-2-methylthio-5 : 5-diphenyl-4 : 5-dihydroglyoxaline (XVI) with aqueous 2-aminoethanol (15 minutes under reflux) gave 2-2′-*hydroxyethylimino*-5 : 5-*diphenyl*-4-*thiohydantoin*, colourless crystals (from aqueous ethanol), m. p. 239° (Found : C, 66·0; H, 5·0; N, 13·3. $C_{17}H_{17}ON_3S$ requires C, 65·6; H, 5·45; N, 13·5%). 2-Keto-4-methylthio-5 : 5-diphenyl-2 : 5-dihydroglyoxaline (XXIV), on heating under reflux with aqueous 2-aminoethanol for 15 minutes, gave an almost quantitative yield of 4-2′-*hydroxyethylimino*-5 : 5-*diphenylhydantoin*, colourless crystals (from ethanol), m. p. 249° (Found : C, 69·2; H, 5·7; N, 14·1. $C_{17}H_{17}O_2N_3$ requires C, 69·2; H, 5·75; N, 14·25%). 5 : 5-Diphenyl-1 : 3-dimethyl-2 : 4-dithiohydantoin (XVII), when

heated under reflux with aqueous 2-aminoethanol for 4 hours, gave 4-2′-*hydroxyethylimino*-5 : 5-*diphenyl*-1 : 3-*dimethyl*-2-*thiohydantoin*, colourless crystals (from aqueous ethanol), m. p. 158° (Found : C, 67·2; H, 6·2; N, 12·2. $C_{19}H_{21}ON_3S$ requires C, 67·2; H, 6·2; N, 12·4%). It was found difficult to complete this reaction, and in the isolation of the product it was best to extract it with excess of cold dilute hydrochloric acid, filter from unchanged starting material, and reprecipitate it with ammonia before crystallisation. This compound, on being heated under reflux for ½ hour with 50 parts of 20% hydrochloric acid, was hydrolysed to 5 : 5-diphenyl-1 : 3-dimethyl-2-thiohydantoin (XI), colourless needles (from aqueous methanol), m. p. 144° (Found : C, 68·8; H, 5·3; N, 9·7. Calc. for $C_{17}H_{16}ON_2S$: C, 68·9; H, 5·4; N, 9·5%).

4-2′-*Hydroxyethylimino*-1-*methyl*-5 : 5-*pentamethylene*-2-*thiohydantoin* was obtained in 55% yield by heating 1-methyl-5 : 5-pentamethylene-2 : 4-dithiohydantoin (XIII) with aqueous 2-aminoethanol. The oily product solidified on cooling and trituration with ether, and crystallised from methanol–ether in colourless prisms, melting incompletely at 158—159° and clearing at 174—175° (Found, on material dried *in vacuo* at 56° : N, 15·5; on material dried *in vacuo* at 140° for 4 hours : N, 17·8. $C_{11}H_{19}ON_3S,2H_2O$ requires N, 15·2%; $C_{11}H_{19}ON_3S$ requires N, 17·4%). The same compound was obtained in quantitative yield by heating 2-thio-4-methylthio-1-methyl-5 : 5-pentamethylene-2 : 5-dihydroglyoxaline (XVIII) (1·15 g.) with 2-aminoethanol (0·6 g.) at 110—120° for 15 minutes. Hydrolysis of this compound with boiling 20% hydrochloric acid gave, in 91% yield, 1-methyl-5 : 5-pentamethylene-2-thiohydantoin (VIII), colourless needles (from aqueous methanol), m. p. 153° (cf. D). 4-2′-Hydroxyethylimino-5 : 5-pentamethylene-2-thiohydantoin, m. p. 245°, 4-2′-hydroxyethylimino-5 : 5-pentamethylenehydantoin, m. p. 255° (decomp.), and 2-2′-hydroxyethylimino-5 : 5-pentamethylenehydantoin, m. p. 243°, were prepared by the action of 2-aminoethanol on the corresponding methylthio-derivatives, and were identical with the products described in Part II. 4-Thio-2-methylthio-5 : 5-pentamethylene-4 : 5-dihydroglyoxaline (XVI), with 2-aminoethanol at 110—120° for 10 minutes, gave 2-2′-*hydroxyethylimino*-5 : 5-*pentamethylene*-4-*thiohydantoin*, colourless prisms (from methanol), m. p. 193—194° (Found : C, 52·8; H, 7·3; N, 18·3. $C_{10}H_{17}ON_3S$ requires C, 52·9; H, 7·5; N, 18·5%). This compound, on treatment with methyl iodide and methanolic sodium hydroxide as described in A, gave an oil (91%), which was not analysed but apparently consisted in the main of 4-methylthio-2-2′-hydroxyethylimino-5 : 5-pentamethylene-2 : 5-dihydroglyoxaline, since on acid hydrolysis it lost methanethiol and gave 2-2′-hydroxyethylimino-5 : 5-pentamethylenehydantoin, m. p. 243°, identical with that described above and in Part II. The oily methylthio-derivative was heated with 2-aminoethanol at 130—140° for ½ hour. Methanethiol was evolved and the product was a water-soluble glass, which crystallised from methanol–ether to give 2 : 4-*di*-(2′-*hydroxyethylimino*)-5 : 5-*pentamethylenehydantoin*, small colourless prisms, m. p. 117—118° (Found : N, 21·5. $C_{12}H_{22}O_2N_4$ requires N, 22·0%). This product, too, was hydrolysed by acid to 2-2′-hydroxyethylimino-5 : 5-pentamethylenehydantoin, m. p. 243°.

(G) *Miscellaneous.*—α-*Methylaminodiphenylacetamide.* α-Chlorodiphenylacetamide (5 g.) (Steinkopf, *loc. cit.*) was heated in a sealed tube at 80—90° for 20 hours with a saturated solution of methylamine in benzene (50 c.c.). The contents of the tube were filtered from methylamine hydrochloride, evaporated to dryness, and recrystallised from methanol to give α-*methylaminodiphenylacetamide*, m. p. 191° (2·7 g., 55%) (Found : N, 11·3. $C_{15}H_{16}ON_2$ requires N, 11·65%). This was recovered unchanged after being heated with carbon disulphide in ethanol in a sealed tube at 80—90° for 20 hours.

5 : 5-*Diphenyl*-3-*benzylhydantoin*.—To a solution of 5 : 5-diphenylhydantoin (6 g.) in ethanol (50 c.c.) were added benzyl chloride (3 g.) and a solution of sodium hydroxide in the minimum of water. The mixture was heated under reflux for 17 hours and was poured into water. The solid product was filtered off and recrystallised from methanol to give 5 : 5-*diphenyl*-3-*benzylhydantoin*, m. p. 151° (5·7 g., 70%) (Found : N, 7·9. $C_{22}H_{18}O_2N_2$ requires N, 8·2%).

5 : 5-*Diphenyl*-3-*benzyl*-1-*methylhydantoin*.—To a solution of 5 : 5-diphenyl-3-benzylhydantoin (3·4 g.) in ethanol (50 c.c.) were added 20% aqueous sodium hydroxide (2 c.c.) and methyl sulphate (1·3 g.). The mixture was heated under reflux for 4 hours, cooled, and filtered. The filtrate was poured into water, and the oil which separated crystallised on storage. Recrystallisation from methanol gave 5 : 5-*diphenyl*-3-*benzyl*-1-*methylhydantoin*, m. p. 125° (1·5 g., 42%) (Found : N, 8·1. $C_{23}H_{20}O_2N_2$ requires N, 7·9%). Attempts to debenzylate this compound by hydrogenation in methanol solution using a palladium–charcoal catalyst at 100° were unsuccessful; the starting material was recovered unchanged.

1-*Methyl*-5 : 5-*pentamethylenehydantoin*.—α-Methylaminohexahydrobenzonitrile (42 g.) was suspended in water (100 c.c.) and neutralised by the addition of 36% hydrochloric acid. A solution of potassium cyanate (27 g. in 50 c.c. water) was added at 30—35° with stirring, and the mixture was stirred for a further ½ hour. The *ureide* separated as an oil which crystallised, and was filtered off. A sample, recrystallised from methanol in colourless needles, had m. p. 167—168° (Found : C, 59·9; H, 8·0; N, 23·0. $C_9H_{15}ON_3$ requires C, 59·7; H, 8·3; N, 23·2%). It was suspended in water (100 c.c.) with stirring, and 36% hydrochloric acid (40 c.c.) was added. The solid went into solution and the product separated. The mixture was heated to 80—90° on the steam-bath for 15 minutes to complete the reaction, and then cooled, and the *product* (II) filtered off, washed with cold water, and recrystallised from hot water as long needles, m. p. 174° (20 g., 36%) (Found : C, 59·5; H, 7·6; N, 15·0. $C_9H_{14}O_2N_2$ requires C, 59·3; H, 7·7; N, 15·4%).

5 : 5-*Pentamethylene*-2 : 4-*dithiohydantoin*.—The light absorption of this compound (XII) showed maxima at 2270 and 2970 A., and ε = 5,540 and 26,300 respectively.

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