

132. Thiohydantoin. Part II. Conversion of 5 : 5-Disubstituted 2 : 4-Dithiohydantoin into the Corresponding Monothiohydantoin.

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5 : 5-Disubstituted 2 : 4-dithiohydantoin reacts with ammonia or primary amino-compounds to give 5 : 5-disubstituted 4-imino(or substituted imino)-2-thiohydantoin, which are readily hydrolysed by acid to the corresponding 2-thiohydantoin. In one case studied, methylation of a 5 : 5-disubstituted 2 : 4-dithiohydantoin in alkaline solution with methyl sulphate led to the formation of the corresponding 4-thiohydantoin, methylthiol being liberated.

Two series of monothiohydantoin derivatives are possible, with CS replacing the CO groups in either the 2- or the 4-position, and members of both series are known. A well-established route to the 2-thiohydantoin is that of Johnson and Scott (*J. Amer. Chem. Soc.*, 1913, **35**, 1130) wherein α -amino-acids or their acyl derivatives are caused to react with ammonium thiocyanate and acetic anhydride to give the acyl derivatives of 2-thiohydantoin, which are then deacylated by acid hydrolysis. The 4-thiohydantoin are less well known, but the parent substance was prepared by Johnson and Chernoff (*J. Amer. Chem. Soc.*, 1912, **34**, 1208) by addition of hydrogen sulphide to carbethoxyaminoacetonitrile and conversion of the resulting carbethoxyaminothionacetamide into 4-thiohydantoin by the action of alkali.

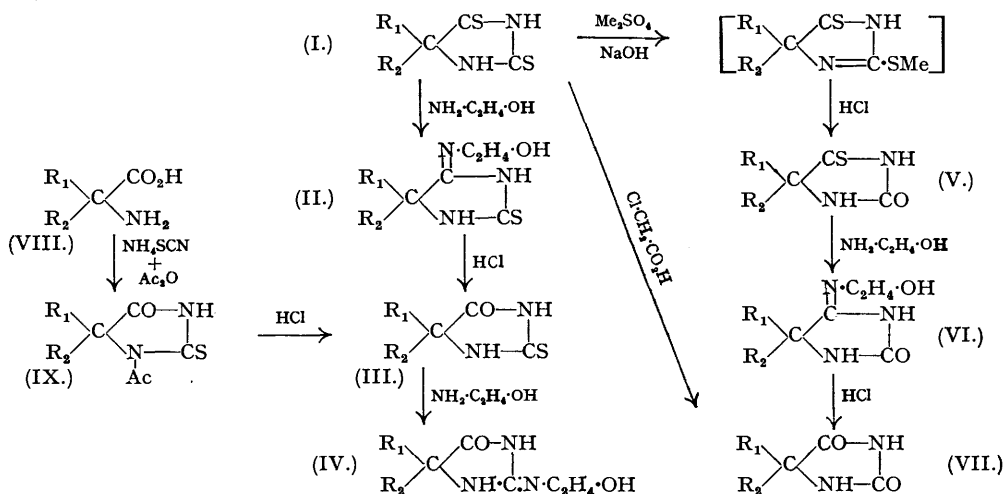
It seemed possible that easier routes to the 5 : 5-disubstituted monothiohydantoin might be achieved by partial hydrolysis of the now readily available 2 : 4-dithiohydantoin (see preceding paper). Johnson, Pfau, and Hodge (*J. Amer. Chem. Soc.*, 1912, **34**, 1041) showed that many 2-thiohydantoin could be desulphurised by heating with aqueous chloroacetic acid, and 4-thiohydantoin is converted into hydantoin by the action of hydrochloric acid (Johnson and Chernoff, *loc. cit.*). In preliminary experiments it was found that 5 : 5-dimethyl-2 : 4-dithiohydantoin (I, $R_1 = R_2 = \text{Me}$) was converted into the corresponding 2-thio-compound (III, $R_1 = R_2 = \text{Me}$) by heating with 20% hydrochloric acid, but higher members of the series, such as the 5 : 5-diethyl and the 5 : 5-cyclopentamethylene derivative were unchanged by this treatment. Boiling 20% aqueous chloroacetic acid completely removed the sulphur from 5 : 5-cyclopentamethylene-2 : 4-dithiohydantoin (I, $R_1R_2 = [\text{CH}_2]_5$), but intermediate compounds were not readily isolated. It therefore appeared that some other general method was desirable.

When 5 : 5-dimethyl-2 : 4-dithiohydantoin was treated with warm aqueous ammonia, hydrogen sulphide was evolved, and a sparingly soluble white crystalline product separated, which was identical with the by-product obtained in the preparation of the dithiohydantoin by the method described in Part I. This substance has now been shown to be 4-imino-5 : 5-dimethyl-2-thiohydantoin. Its empirical formula, $\text{C}_5\text{H}_9\text{N}_3\text{S}$, showed that $> \text{S}$ in the dithiohydantoin had been replaced by $> \text{NH}$, and on hydrolysis with hot hydrochloric acid it gave 5 : 5-dimethyl-2-thiohydantoin, m. p. 179° , identical with the product obtained by the action of hydrochloric acid on the dithiohydantoin, and also with that synthesised from α -aminoisobutyric acid (VIII, $R_1 = R_2 = \text{Me}$) by the method of Johnson and Scott (*loc. cit.*). Komatsu (*Mem. Coll. Sci. Kyoto Imp. Univ.*, 1914, **1**, 69; *A.*, 1915, **108**, i, 168) had already described a synthesis of 5 : 5-dimethyl-2-thiohydantoin by a method similar to that of Johnson and Scott, but his product had m. p. $163\text{--}164^\circ$, and the identity of the compound now under investigation was uncertain until a repetition of Komatsu's synthesis led to the isolation by an unequivocal route of 5 : 5-dimethyl-2-thiohydantoin in a pure condition, m. p. 179° .

The preferential attack of ammonia on the 4-thio-group of the dithiohydantoin corresponds with results previously described in the closely similar 5 : 5-diethyl-2 : 4-dithio- and -2 : 4 : 6-trithio-barbituric acids (Carrington, *J.*, 1944, 124). There, too, it was shown that the sulphur atoms of "thioamide" type in the 4- and 6-positions were replaced by ammonia in preference to the 2-thio-atoms of "thiourea" type.

Other primary amino-compounds reacted with 5 : 5-dimethyl-2 : 4-dithiohydantoin in a similar way. Thus, with hydrazine hydrate, 4-hydrazino-5 : 5-dimethyl-2-thiohydantoin was produced, and aqueous 2-aminoethyl alcohol gave 4-2'-hydroxyethylimino-5 : 5-dimethyl-2-thiohydantoin (II, $R_1 = R_2 = \text{Me}$), both of which were readily hydrolysed by hot hydrochloric acid to 5 : 5-dimethyl-2-thiohydantoin. The reaction with 2-aminoethyl alcohol, and subsequent hydrolysis of the 2-hydroxyethyl-imino compounds has been used as a general method for the conversion of the 5 : 5-disubstituted 2 : 4-dithiohydantoin into the corresponding 2-thio-compounds. 2-Aminoethyl alcohol is a convenient amine on account of its low volatility. 5 : 5-cyclopentamethylene-2 : 4-dithiohydantoin gave 4-2'-hydroxyethylimino-5 : 5-

cyclopentamethylene-2-thiohydantoin (II, $R_1R_2 = [CH_2]_5$), hydrolysing to 5:5-cyclopentamethylene-2-thiohydantoin (III, $R_1R_2 = [CH_2]_5$), which was also synthesised from 1-amino-hexahydrobenzoic acid (VIII, $R_1R_2 = [CH_2]_5$) by the method of Johnson and Scott (*loc. cit.*). This monothiohydantoin again reacted with 2-aminoethyl alcohol to give 2-2'-hydroxyethylimino-5:5-cyclopentamethylenehydantoin (IV, $R_1R_2 = [CH_2]_5$), which was much more stable to hydrolysis, being recovered unchanged after boiling with 20% hydrochloric acid. 5:5-(3'-Methylcyclopentamethylene)-2:4-dithiohydantoin with 2-aminoethyl alcohol similarly gave 4-2'-hydroxyethylimino-5:5-(3'-methylcyclopentamethylene)-2-thiohydantoin, which was readily hydrolysed to 5:5-(3'-methylcyclopentamethylene)-2-thiohydantoin.



When 5:5-cyclopentamethylene-2:4-dithiohydantoin, dissolved in aqueous sodium hydroxide, reacted with methyl sulphate, and the product was acidified, methylthiol was evolved, and a second monothio-compound obtained. It differed from the 2-thio-compound in several respects. It was much higher melting, 240° compared with 191°, and was bright yellow, whereas the 2-thio-compound was colourless. It was shown to be 5:5-cyclopentamethylene-4-thiohydantoin (V, $R_1R_2 = [CH_2]_5$) by reaction with 2-aminoethyl alcohol, whereby it gave 4-2'-hydroxyethylimino-5:5-cyclopentamethylenehydantoin (VI, $R_1R_2 = [CH_2]_5$), which, in contrast to the isomeric 2-2'-hydroxyethylimino-compound described above, was readily hydrolysed by dilute hydrochloric acid to 5:5-cyclopentamethylenehydantoin, identical with that obtained from cyclohexanone by Bucherer and Steiner's method (*J. pr. Chem.*, 1934, 140, 291).

The reaction of the dithiohydantoin with methyl sulphate would appear to proceed through an unstable intermediate 2-methylthio-derivative. This is in contrast with the results of an experiment in the barbituric acid series, where 5:5-diethyl-2:4:6-trithiobarbituric acid was found to be methylated in one of the "thioamide" positions, giving 6-methylthio-5:5-diethyl-2:4-dithiobarbituric acid (Carrington, *loc. cit.*).

EXPERIMENTAL.

1-Acetyl-5:5-dimethyl-2-thiohydantoin.— α -Aminoisobutyric acid (20 g.), ammonium thiocyanate (25 g.), and acetic anhydride (70 c.c.) were warmed gently until reaction commenced, and when the initial vigorous reaction had subsided the mixture was boiled under reflux for $\frac{1}{2}$ hour. It was cooled, poured into ice-water, and the solid product filtered off and crystallised from aqueous methyl alcohol; m. p. 186—187° (7 g.) (Found: N, 14.85; S, 17.6. Calc. for $C_7H_{10}O_2N_2S$: N, 15.05; S, 17.2%).

5:5-Dimethyl-2-thiohydantoin.—The acetyl derivative (1 g.) was heated under reflux for 1 hour with 20% hydrochloric acid (2 c.c.) and methyl alcohol (4 c.c.). The methyl alcohol was evaporated, and on cooling, 5:5-dimethyl-2-thiohydantoin crystallised in theoretical yield. Recrystallised from water, it had m. p. 178—179° (Found: C, 41.8; H, 5.6; N, 19.4; S, 22.3. Calc. for $C_5H_8ON_2S$: C, 41.7; H, 5.55; N, 19.45; S, 22.2%). The same product was obtained when 5:5-dimethyl-2:4-dithiohydantoin (2 g.) was heated under reflux for 4 hours with 20% hydrochloric acid (30 c.c.).

4-Imino-5:5-dimethyl-2-thiohydantoin.—5:5-Dimethyl-2:4-dithiohydantoin (2 g.) was warmed gently with aqueous ammonia (d 0.88, 6 c.c.). Hydrogen sulphide was evolved, and a white crystalline solid separated. After cooling, the product was filtered off and recrystallised from water; m. p. 300—302° (decomp.) (1.3 g.) (Found: C, 42.2; H, 6.1; N, 29.2; S, 22.4. $C_5H_8N_3S$ requires C, 41.85; H, 6.3; N, 29.4; S, 22.4%). It was identical with the by-product obtained in the preparation of 5:5-dimethyl-2:4-dithiohydantoin (see Part I), and on being heated under reflux for 1 hour with 20%

hydrochloric acid it was hydrolysed quantitatively to 5 : 5-dimethyl-2-thiohydantoin, m. p. 178—179°, identical with that described above.

4-Hydrazino-5 : 5-dimethyl-2-thiohydantoin.—5 : 5-Dimethyl-2 : 4-dithiohydantoin (2 g.) was dissolved in 50% hydrazine hydrate (5 c.c.). On warming, hydrogen sulphide was evolved and a white solid separated. After being cooled and collected, the product was recrystallised from ethyl alcohol; m. p. 188° (decomp.) (1.0 g.) (Found : N, 35.0; S, 19.8. $C_9H_{16}N_4S$ requires N, 35.4; S, 20.2%).

4-2'-Hydroxyethylimino-5 : 5-dimethyl-2-thiohydantoin.—5 : 5-Dimethyl-2 : 4-dithiohydantoin (5 g.) was heated to 100° for $\frac{1}{2}$ hour with 50% aqueous 2-aminoethyl alcohol (20 c.c.). Hydrogen sulphide was evolved, and on cooling, the product crystallised. After recrystallising from ethyl alcohol, it had m. p. 223—224° (3 g.) (Found : N, 22.5; S, 17.55. $C_7H_{13}ON_3S$ requires N, 22.5; S, 17.1%).

Both the 4-hydrazino- and the 4-2'-hydroxyethylimino-compound were hydrolysed quantitatively to 5 : 5-dimethyl-2-thiohydantoin when heated under reflux for 1 hour with ten parts of 20% hydrochloric acid.

1-Acetyl-5 : 5-cyclopentamethylene-2-thiohydantoin was obtained from 1-aminohexahydrobenzoic acid (35 g.), ammonium thiocyanate (50 g.), and acetic anhydride (140 c.c.) by the method described above. The product, after several crystallisations from aqueous methyl alcohol, had m. p. 165—167° (5 g.) (Found : N, 12.4. $C_{10}H_{14}O_2N_2S$ requires N, 12.4%).

5 : 5-cycloPentamethylene-2-thiohydantoin was obtained in 85% yield by hydrolysis of the acetyl derivative in a similar manner to that described above. Crystallised from aqueous methyl alcohol, it had m. p. 192° (Found : N, 15.05; S, 17.3. $C_8H_{12}ON_2S$ requires N, 15.2; S, 17.4%).

4-2'-Hydroxyethylimino-5 : 5-cyclopentamethylene-2-thiohydantoin, m. p. 245° (from ethyl alcohol), was obtained in 62% yield from 5 : 5-cyclopentamethylene-2 : 4-dithiohydantoin and aqueous 2-aminoethyl alcohol, by the method described above (Found : N, 18.2; S, 14.4. $C_{10}H_{17}ON_2S$ requires N, 18.5; S, 14.1%). It was readily hydrolysed in theoretical yield by boiling 20% hydrochloric acid to 5 : 5-cyclopentamethylene-2-thiohydantoin, m. p. 192°, identical with that described above.

2-2'-Hydroxyethylimino-5 : 5-cyclopentamethylenehydantoin, m. p. 243° (0.8 g. from ethyl alcohol), was obtained when 5 : 5-cyclopentamethylene-2-thiohydantoin (2 g.) was heated under reflux for 2 hours with 50% aqueous 2-aminoethyl alcohol (8 c.c.) (Found : C, 56.7; H, 8.1. $C_{10}H_{17}O_2N_2S$ requires C, 56.9; H, 8.1%). This compound was much more resistant to acid hydrolysis than the 4-2'-hydroxyethylimino-isomer (see below) and was recovered unchanged after boiling under reflux with 20% hydrochloric acid for 5 hours.

4-2'-Hydroxyethylimino-5 : 5-(3'-methylcyclopentamethylene)-2-thiohydantoin, m. p. 234°, was obtained in 65% yield from the corresponding dithiohydantoin and aqueous 2-aminoethyl alcohol as described above (Found : N, 17.35; S, 13.3. $C_{11}H_{19}ON_2S$ requires N, 17.45; S, 13.3%). It was readily hydrolysed by boiling 20% hydrochloric acid to 5 : 5-(3'-methylcyclopentamethylene)-2-thiohydantoin, m. p. 219° (Found : N, 14.0; S, 16.4. $C_9H_{14}ON_2S$ requires N, 14.15; S, 16.2%).

5 : 5-cycloPentamethylene-4-thiohydantoin.—5 : 5-cycloPentamethylene-2 : 4-dithiohydantoin (8 g.) in 8% sodium hydroxide solution (60 c.c.) was treated at 10° with methyl sulphate (6 g.), added during 15 minutes with stirring. The mixture was stirred for 3 hours and a small quantity of low-melting solid was separated. (This had m. p. 42—45°, was not readily purified, and was not investigated further.) The aqueous solution was acidified, whereupon methylthiol was evolved, and a pale yellow solid separated. It was filtered off, and purified first through the sparingly soluble sodium salt, and then by crystallisation from aqueous methyl alcohol, to give the 4-thio-compound as shining yellow plates, m. p. 240° (2.0 g.) (Found : C, 52.4; H, 6.7; N, 14.85; S, 17.7. $C_8H_{12}ON_2S$ requires C, 52.2; H, 6.5; N, 15.2; S, 17.4%).

4-2'-Hydroxyethylimino-5 : 5-cyclopentamethylenehydantoin, m. p. 255° (decomp.) (from methyl alcohol), was obtained in 40% yield by the action of aqueous 2-aminoethyl alcohol on the 4-thiohydantoin (Found : C, 56.6; H, 8.0; N, 19.75. $C_{10}H_{17}O_2N_2S$ requires C, 56.9; H, 8.1; N, 19.9%). A mixed m. p. with the 2-2'-hydroxyethylimino-isomer (m. p. 243°, above) was 220—225°. The 4-2'-hydroxyethylimino-compound was readily hydrolysed by heating at 100° for $\frac{1}{2}$ hour with 10% hydrochloric acid, to give 5 : 5-cyclopentamethylenehydantoin, m. p. 217°, identical with material prepared from cyclohexanone by Bucherer and Steiner's method (*loc. cit.*).

5 : 5-cycloPentamethylenehydantoin was also produced in almost quantitative yield when the corresponding dithio-derivative was heated under reflux with 20% aqueous chloroacetic acid for 5 hours.

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