71. *Thiohydantoins. Part V.* A New Synthesis of 5 : 5-Disubstituted 4-Thiohydantoins.*

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

5 : 5-Disubstituted 4-thiohydantions are formed by the reaction of ketones with ammonium monothiocarbamate and sodium cyanide.

Ketones react with sodium cyanide and ammonium carbonate in the well-known Bucherer reaction to give 5 : 5-disubstituted hydantoins,[1] and replacement of the ammonium carbonate by carbon disulphide and an ammonium salt leads to the formation of the corresponding 2 : 4-dithiohydantoins.[2] The behaviour of carbon oxysulphide or ammonium monothiocarbamate in this reaction is therefore of interest, as in this case it is possible that either the 2- or the 4-monothiohydantoin might be formed. The 2-thiohydantoins are readily available by other methods,[3] but very few members of the 4-thiohydantoin series have been described, and the methods for their preparation are far from satisfactory. 5 : 5-Pentamethylene-4-thiohydantoin,[3] 5 : 5-diphenyl-4-thiohydantoin,[4] and 5-methyl-5-phenyl-4-thiohydantoin [5] have been prepared by methylation of the 2 : 4-dithiohydantoins and hydrolysis of the 2-methylthio-derivatives, but the methylations lead to mixtures of products, the separation of which is tedious, and the yields of the 4-thiohydantoins are low and variable. 5 : 5-Dimethyl-4-thiohydantoin has also been prepared by Hazard *et al.*[6] by a similar method.

Ketones on treatment with ammonium monothiocarbamate and sodium cyanide gave the corresponding 4-thiohydantoins, often in quite good yield.

Aliphatic, *cyclo*alkyl, and alkyl–aralkyl ketones have been used. The 5 : 5-pentamethylene-4-thiohydantoin obtained from *cyclo*hexanone by this method had a melting point slightly higher than that previously described. Further evidence of structure has been obtained in the case of 5-*iso*butyl-5-methyl-4-thiohydantoin by its conversion by phosphorus pentasulphide in boiling tetralin into the known 2 : 4-dithiohydantoin,[2] and by its non-identity with the 2-thio-compound, which has been prepared from the 2 : 4-dithiohydantoin by the action of 2-aminoethanol followed by acid hydrolysis. The ready

* Part IV, *J.*, 1953, 3105.

[1] Bucherer and Steiner, *J. prakt. Chem.*, 1934, **140**, 291; Bucherer and Lieb, *ibid.*, 1934, **141**, 5.
[2] Carrington, *J.*, 1947, 681.
[3] *Idem*, *J.*, 1947, 684.
[4] Carrington and Waring, *J.*, 1950, 354.
[5] Carrington, Vasey, and Waring, *J.*, 1953, 3105.
[6] Hazard, Cheymol, Chabrier, and Smarzewska, *Bull. Soc. chim. France*, 1949, 228.

desulphurisation of the 4-thio-compound by a similar process to give the known 5-*iso*butyl-5-methylhydantoin [7] is additional evidence of the position of the sulphur atom, since it has already been shown [3] that the intermediate 2-hydroxyethylimino-compounds are readily hydrolysed when this substituent is in the 4-position but are very resistant to hydrolysis when it is in position 2. The 4-thiohydantoins are all yellow crystalline solids, in contrast to the 2-thio-compounds which are colourless.

Experimental.—5 : 5-*Disubstituted* 4-*thiohydantoins*. The ketone (0·1 mole), sodium cyanide (0·2 mole), and ammonium monothiocarbamate (0·2 mole; prepared from carbon oxysulphide and ethanolic ammonia) were stirred in aqueous ethanol (150 c.c.; equal parts by volume) at 50—55° under reflux for 4 hr. The cooled mixture was acidified with hydrochloric acid, and the pale yellow solid was collected and crystallized from ethanol or aqueous ethanol. In some cases it was convenient to purify the product through its colourless sodium salt which was often sparingly soluble and readily crystallized from hot water or methanol.

The 4-thiohydantoins which have been prepared by this method are shown in the Table.

Some transformations of 5-iso*butyl-5-methyl-4-thiohydantoin*. 5-*iso*Butyl-5-methyl-4-thiohydantoin (0·5 g.) and phosphorus pentasulphide (1·0 g.) were suspended in tetralin (10 c.c.) and boiled under reflux for 45 min. The mixture was filtered hot, light petroleum (b. p. 40—60°; 50 c.c.) was added to the cooled solution and the supernatant liquid was decanted from the gum.

5 : 5-*Disubstituted* 4-*thiohydantoins*.

5 : 5-Substituents	M. p.	Yield (%)	Formula	Required (%) C	H	N	Found (%) C	H	N
R, R = Me, Et	232—233°	46	$C_6H_{10}ON_2S$	45·6	6·3	17·7	45·6	6·2	18·0
R, R = Me, Bu^i	198—199	51	$C_8H_{14}ON_2S$	51·6	7·5	15·05	51·5	7·2	14·8
R, R = Me, Me·$[CH_2]_5$	155—156	62	$C_{10}H_{18}ON_2S$	56·1	8·4	13·1	56·2	8·3	13·5
R, R = Me, $PhCH_2$	216—217	67	$C_{11}H_{12}ON_2S$	60·0	5·45	12·7	60·0	5·8	12·7
RR = ·$[CH_2]_4$·	205—206	14	$C_7H_{10}ON_2S$	49·4	5·9	16·5	49·1	5·7	16·4
RR = ·$[CH_2]_5$·	242—243	49	$C_8H_{12}ON_2S$	(ref. 3)					
RR = ·$[CH_2]_4$·CHMe·	252	22	$C_8H_{14}ON_2S$	54·5	7·1	14·1	54·2	7·2	14·3
RR = ·$[CH_2]_3$·CHMe·CH_2·	279	47	$C_9H_{14}ON_2S$	54·5	7·1	14·1	54·5	6·8	14·1
RR = ·$[CH_2]_2$·CHMe·$[CH_2]_2$·	262	17	$C_8H_{14}ON_2S$	54·5	7·1	14·1	54·4	7·0	14·7
RR = ·$[CH_2]_3$·CH[$CHMe_2$]·CH_2·	262	14	$C_{11}H_{18}ON_2S$	58·4	8·0	12·4	58·5	8·2	11·9
RR = ·CH_2·CHMe·CH_2·CHMe·CH_2·	sublimes at 330	69	$C_{10}H_{16}ON_2S$	56·6	7·55	13·2	56·9	7·6	13·2
RR = ·CH_2·CHMe·CH_2·CMe_2·CH_2·	224—225	57	$C_{11}H_{18}ON_2S$	58·4	8·0	12·4	58·3	8·0	12·2
RR = ·$[CH_2]_2$·$[CHMe]_2$·CH_2·	274—275	—	$C_{10}H_{16}ON_2S$	—	—	13·2	—	—	13·7
RR = ·$[CH_2]_6$·	177—178	51	$C_8H_{14}ON_2S$	54·5	7·1	14·15	54·7	7·2	14·1
RR = ·CHMe·$[CH_2]_5$·	248—249	45	$C_{10}H_{16}ON_2S$	—	—	13·2	—	—	13·3

Further dilution with light petroleum (b. p. 40—60°) precipitated a sticky solid which after trituration with light petroleum (b. p. 100—120°) was readily crystallized from benzene, yielding very pale yellow prisms, m. p. 89—90° undepressed on admixture with an authentic specimen of 5-*iso*butyl-5-methyl-2 : 4-dithiohydantoin.[2]

5-*iso*Butyl-5-methyl-4-thiohydantoin (0·5 g.), 2-aminoethanol (0·5 c.c.), and water (0·5 c.c.) were heated under reflux for 30 min. Hydrogen sulphide was evolved. Hydrochloric acid (20%; 5 c.c.) was added and refluxing was continued for 45 min. The solution was cooled, and the crystals were filtered off and washed with water. The product had m. p. 142—143° undepressed on admixture with an authentic specimen of 5-*iso*butyl-5-methylhydantoin.[7]

5-*iso*Butyl-5-methyl-2 : 4-dithiohydantoin (1 g.), 2-aminoethanol (1 c.c.), and water (5 c.c) were heated under reflux for 30 min. Hydrochloric acid (20%; 25 c.c.) was added, and refluxing was continued for a further 30 min. The solution was cooled, the crystals were filtered off, washed with water, and recrystallized from aqueous methanol, giving 5-iso*butyl-5-methyl-2-thiohydantoin* as crystals, m. p. 152° (Found: C, 51·8; H, 7·6; N, 14·7. $C_8H_{14}ON_2S$ requires C, 51·6; H, 7·5; N, 15·0%). A mixture with the isomeric 4-thiohydantoin (m. p. 198—199°) had m. p. 130—134°.

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[7] Henze, Thompson, and Speer, *J. Org. Chem.*, 1943, **8**, 17.