

131. *Thiohydantoins. Part I. Preparation of 5 : 5-Disubstituted 2 : 4-Dithiohydantoins from the Corresponding Ketones.*

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Ketones are converted into 5 : 5-disubstituted 2 : 4-dithiohydantoins by reaction with carbon disulphide and ammonium cyanide (or a mixture of salts capable of reacting as such) in aqueous methyl-alcoholic solution.

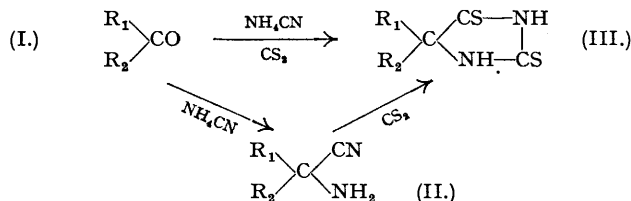
THE replacement of the oxygen atom in the 2-position of the 5 : 5-dialkylbarbituric acids by sulphur has a marked effect on their hypnotic action. For instance, the duration of action of 5-ethyl-5- α -methylbutylbarbituric acid is greatly diminished on passing to the corresponding 2-thio-derivative, and the increased control over the depth of hypnosis given by this rapid detoxication or elimination has made possible the widespread use of 5-ethyl-5- α -methylbutyl-2-thiobarbituric acid as an intravenous anæsthetic.

The 5 : 5-disubstituted hydantoin is much less powerful hypnotic than the corresponding barbituric acid, but nevertheless it appeared possible that the replacement of the oxygen atoms by sulphur in this series, too, might lead to hypnotics of value. This paper is the first of a short series in which the chemical work involved in the preparation of a large number of thiohydantoin derivatives will be described. The results of their pharmacological examination will be reported elsewhere.

The conversion of aldehydes and ketones into 5-substituted hydantoin by the action of sodium cyanide and ammonium carbonate (Bucherer and Steiner, *J. pr. Chem.*, 1934, **140**, 291) is well-known. During the development of this method, Bucherer and Lieb (*ibid.*, **141**, 5) made some attempts to extend the procedure to the preparation of 5-substituted 2 : 4-dithiohydantoin. They studied the reaction of the cyanohydrins from acetone and cyclohexanone with ammonia and carbon disulphide under various conditions, and also the action of carbon disulphide on α -aminoisobutyronitrile (II; $R_1 = R_2 = \text{Me}$). In no case did they identify the expected 2 : 4-dithiohydantoin among the products of the reactions.

Later, it was claimed by Jacobson (U.S.P., 2,143,816, 1939) that despite the failure of Bucherer and Lieb 2 : 4-dithiohydantoin could be obtained by the action of carbon disulphide on α -amino-nitriles, and his examples included the preparation of 5 : 5-dimethyl-2 : 4-dithiohydantoin (III; $R_1 = R_2 = \text{Me}$) from α -aminoisobutyronitrile. Henze and Smith (*J. Amer. Chem. Soc.*, 1943, **65**, 1090) treated several 5 : 5-disubstituted hydantoin with phosphorus trisulphide in a hydrocarbon solvent to give the corresponding 2 : 4-dithio-derivatives.

In a reinvestigation of the application of the Bucherer reaction to the preparation of dithiohydantoin it has been found that when ketones (I) react with carbon disulphide and ammonium cyanide (or, in practice, a mixture of salts capable of reacting as ammonium cyanide) the corresponding 2 : 4-dithiohydantoin (III) can readily be isolated.



It is clearly possible that the α -amino-nitriles (II) are intermediates in this reaction. Of a wide variety of ketones employed, only diisopropyl ketone and camphor have failed to give the corresponding 2 : 4-dithiohydantoin. The reaction can be carried out in a variety of ways. For example, in the preparation of 5 : 5-cyclopentamethylene-2 : 4-dithiohydantoin (III, $R_1R_2 = [\text{CH}_2]_5$) from cyclohexanone, solvents such as aqueous methyl alcohol, ethyl alcohol, and benzene have been used. The best yields may be obtained by conducting the experiments under pressure at about 80°, but, in general, boiling under reflux in aqueous methyl alcohol is the most convenient procedure.

The failure of Bucherer and Lieb to obtain or identify the 2 : 4-dithiohydantoin in their experiments is difficult to understand. In studies of the action of ammonia and carbon disulphide on cyclohexanone cyanohydrin they described a number of products, among which, in one experiment, was a yellow crystalline substance of m. p. 265°, which was not further investigated. This may well have been the dithiohydantoin which they were seeking. In experiments with acetone cyanohydrin, ammonia, and carbon disulphide, or α -aminoisobutyronitrile and carbon disulphide they described one product of m. p. 155°, which has not been encountered in the present studies, and one of m. p. 297°, which was probably identical with that obtained as a by-product in the procedure now given. The structure of this compound will be discussed in the next paper.

EXPERIMENTAL.

Conversion of Ketones into Dithiohydantoin.—The early experiments were carried out under pressure the following being a typical procedure.

5 : 5-Dimethyl-2 : 4-dithiohydantoin. Acetone (58 g.), sodium cyanide (51 g.), ammonium chloride (55 g.), carbon disulphide (76 g.), and industrial ethyl alcohol (100 c.c.) were heated together in an autoclave at 80—85° for 8 hours. After collection of the solid residue, and washing it with ethyl alcohol, the united filtrate and washings were treated with carbon, and evaporated to a syrup, which crystallised on standing. It was purified by dissolving it in sodium hydroxide solution, treating the solution with carbon, filtering it, and reprecipitating the hydantoin with hydrochloric acid. It recrystallised from benzene in long, pale yellow needles, m. p. 144° (50 g., 31%) (Found: C, 37.8; H, 5.2; N, 17.45; S, 40.1. Calc. for $C_8H_8N_2S_2$: C, 37.5; H, 5.0; N, 17.45; S, 40.0%).

In a similar way, equivalent amounts of the corresponding ketones being used, there were obtained: 5 : 5-diethyl-2 : 4-dithiohydantoin, bright yellow needles, m. p. 155°, from aqueous methyl alcohol (yield, 37%) (Found: N, 15.0; S, 33.8. $C_7H_{12}N_2S_2$ requires N, 14.9; S, 34.0%); 5 : 5-di-n-propyl-2 : 4-dithiohydantoin, pale yellow needles, m. p. 111—112°, from light petroleum (b. p. 100—120°) (yield, 16%) (Found: N, 13.2; S, 29.2. $C_{13}H_{16}N_2S_2$ requires N, 13.0; S, 29.6%); 5-phenyl-5-methyl-2 : 4-dithiohydantoin, bright yellow needles, m. p. 173—174°, from aqueous methyl alcohol (yield, 2%; 55% of the acetophenone was recovered unchanged) (Found: N, 12.6; S, 29.1. Calc. for $C_{10}H_{10}N_2S_2$: N, 12.5; S, 28.9%).

In later experiments, a standard procedure was adopted of heating the ketone under reflux at 50—55° for 20—24 hours with equivalent amounts of ammonium chloride, sodium cyanide, and carbon disulphide, the whole being maintained in solution in aqueous alcohol. The solvents, any unchanged ketone, and carbon disulphide were removed by steam-distillation, and the product, which separated either as a solid or as an oil which solidified on cooling, was purified by recrystallisation, usually from aqueous methyl alcohol. With some of the cyclic ketones, the product crystallised directly from the reaction mixture either during the reaction or on cooling. The results of these experiments are summarised in the table.

	Formula.	M. p.	Yield, %.	Analysis.	
				Found, N %.	Required, N %.
2 : 4-Dithiohydantoin.					
5 : 5-Substituents.					
5 : 5-Dimethyl	$C_8H_8N_2S_2$	144°	27	—	—
5-Methyl-5-ethyl	$C_9H_{10}N_2S_2$	147—148	15	16.1	16.1
5 : 5-Diethyl	$C_7H_{12}N_2S_2$	155	10	—	—
5-Methyl-5-n-propyl	$C_7H_{12}N_2S_2$	123—124	10	14.55	14.9
5-Methyl-5-isopropyl	$C_7H_{12}N_2S_2$	225—226	7.5	15.15	14.9
5-Methyl-5-isobutyl	$C_8H_{14}N_2S_2$	91—92	10	13.65	13.85
5-Methyl-5-tert.-butyl	$C_8H_{14}N_2S_2$	235—236	5	13.7	13.85
5-Methyl-5-n-amyl	$C_9H_{16}N_2S_2$	117—118	14	12.4	13.0
5-Methyl-5-isohexenyl	$C_{10}H_{16}N_2S_2$	99	13	12.3	12.3
5-Methyl-5-cyclohexyl	$C_{10}H_{16}N_2S_2$	190	7	12.1	12.3
5-Benzyl-5-methyl	$C_{11}H_{12}N_2S_2$	156	9	11.7	11.8
5-β-Phenylethyl-5-methyl	$C_{12}H_{14}N_2S_2$	180	22	10.9	11.2
5 : 5-cycloTetramethylene (a)	$C_7H_{10}N_2S_2$	242—243	27	15.2	15.0
5 : 5-2'-MethylcycloTetramethylene (b)	$C_8H_{12}N_2S_2$	232	25	13.5	14.0
5 : 5-cycloPentamethylene (c)	$C_8H_{12}N_2S_2$	267	36	13.7	14.0
5 : 5-1'-Methylcyclopentamethylene (d)	$C_9H_{14}N_2S_2$	184	10	12.8	13.1
5 : 5-2'-Methylcyclopentamethylene (e)	$C_9H_{14}N_2S_2$	203	32	12.65	13.1
5 : 5-3'-Methylcyclopentamethylene (f)	$C_9H_{14}N_2S_2$	255	38	13.0	13.1
5 : 5-cycloHexamethylene (g)	$C_9H_{14}N_2S_2$	242	21	13.1	13.1
5 : 5-1' : 3'-Dimethylcyclopentamethylene (h) ...	$C_{10}H_{16}N_2S_2$	172	13	12.0	12.3
5 : 5-1' : 4'-Dimethylcyclopentamethylene (i) ...	$C_{10}H_{16}N_2S_2$	197	14	12.35	12.3
5 : 5-2' : 4'-Dimethylcyclopentamethylene (j) ...	$C_{10}H_{16}N_2S_2$	230	20	11.75	12.3
5 : 5-4'-Methylisopropylcyclopentamethylene (k)	$C_{12}H_{20}N_2S_2$	209	5	10.5	10.9

(a) From cyclopentanone. (b) From 3-methylcyclopentanone. (c) From cyclohexanone. (d) From 2-methylcyclohexanone. (e) From 3-methylcyclohexanone. (f) From 4-methylcyclohexanone. (g) From cycloheptanone. (h) From 2 : 4-dimethylcyclohexanone. (i) From 2 : 5-dimethylcyclohexanone. (j) From 3 : 5-dimethylcyclohexanone. (k) From menthone.

Attempts to prepare the dithiohydantoin from diisopropyl ketone and camphor by this method were unsuccessful, the ketone being recovered unchanged. Except 5 : 5-dimethyl- and 5-phenyl-5-methyl-2 : 4-dithiohydantoin, all the dithiohydantoin described above are new.

When 5 : 5-dimethyl-2 : 4-dithiohydantoin was prepared by this method, there was also obtained a by-product, very sparingly soluble in methanol, crystallising from water as small colourless prisms, m. p. 300° (decomp.).

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