537. *Thiohydantoins. Part VI.* Stereospecific Syntheses of Spirohydantoins and Spirothiohydantoins.*

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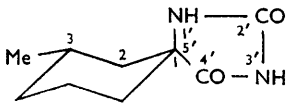
Synthesis of spiro-5-hydantoins by the Bucherer hydantoin reaction applied to monosubstituted or unsymmetrically polysubstituted cyclic ketones gives predominantly one of the two expected stereoisomers. Other methods of synthesis give predominantly the other isomer.

Application of the Bucherer hydantoin synthesis to monosubstituted or unsymmetrically polysubstituted cyclic ketones can theoretically give rise to two stereoisomeric hydantoins. In practice, however, it has been found that such cyclic ketones give almost entirely one form of the hydantoin in this reaction, and that other methods give almost entirely the other isomer. The stereospecific syntheses which are described here were first observed in reactions starting from 3-methylcyclohexanone, and the following account deals for simplicity mainly with hydantoins made from this ketone. The syntheses, however, appear to be general, and similar results have been obtained in most cases where unsymmetrically substituted cyclic ketones have been used.

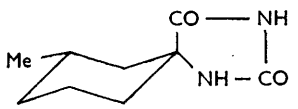
When 3-methylcyclohexanone was subjected to the Bucherer reaction [1] a good yield of 3-methylcyclohexanespiro-5′-hydantoin (Ia or b), m. p. 268°, was obtained.[2] Examination of the mother-liquors from the crystallisation of the crude product showed the presence of an isomeric hydantoin, m. p. 238°, present to the extent of about 7% of the first isomer. We term the former the α- and the latter the β-form.

* Part V, *J.*, 1959, 396.

[1] Bucherer and Steiner, *J. prakt. Chem.*, 1934, **140**, 291; Bucherer and Lieb, *ibid.*, 1934, **141**, 5.
[2] Henze and Speer, *J. Amer. Chem. Soc.*, 1942, **64**, 522.



(Ia)



(Ib)

An alternative synthesis in which 3-methylcyclohexanone was converted into the corresponding amino-nitrile, and this by cyanate into the ureido-derivative which was cyclised by acid, gave exclusively the β-form of the hydantoin (m. p. 238°). In a similar way methyl isothiocyanate reacted with the same amino-nitrile to give on ring closure with acid the β-form of 3,3′-dimethylcyclohexanespiro-5′-(2′-thiohydantoin) which was also synthesised by standard methods from the β-form of 3-methylcyclohexanespiro-5′-hydantoin, m. p. 238°.

Isomeric hydantoins have previously been isolated from a Bucherer hydantoin reaction with (+)-[but not (±)-]camphor.[3] Recently it has been shown that from 2-, 3-, and 4-alkylcyclohexanones the Bucherer hydantoin reaction and the Strecker synthesis lead to geometrically isomeric 1-amino-alkylcyclohexanecarboxylic acids. The amino-acids prepared from 3- and 4-methylcyclohexanone by the Strecker synthesis have been converted *via* the ureido-acids into the corresponding hydantoins, which were shown to be different from the hydantoins prepared by the Bucherer synthesis. The 1-amino-2-methylcyclohexanecarboxylic acid produced by the Strecker synthesis could not, however, be converted into a hydantoin by this method.[4]

The α- and the β-form of 3-methylcyclohexanespiro-5′-hydantoin gave separate series of derivatives by the standard methods [5,6] of methylation, sulphurisation, and partial desulphurisation. In this way the α- and β-forms of the 3′-methyl-, 2′,4′-dithio-, and 2′-thio-derivative were obtained. Hydrolysis of the parent hydantoins gave isomeric amino-acids which could be converted back into the hydantoins by standard methods. It therefore became possible to identify the 3′-methyl-2′-thiohydantoin referred to above which was obtained from 1-amino-1-cyano-3-methylcyclohexane and methyl isothiocyanate, as belonging to the β-series. Methylation of the β-form of 3-methylcyclohexanespiro-5′-(2′-thiohydantoin) with diazomethane gave the β-form of the 3,3′-dimethyl-2′-thio-compound that was identical with the product of the methyl isothiocyanate reaction.

A modification of the Bucherer hydantoin synthesis in which a ketone, carbon disulphide, and ammonium cyanide are used to prepare 2,4-dithiohydantoins has been described.[7]

When 3-methylcyclohexanone was used in this reaction the product was found to be almost entirely the β-form of the spiro-2′,4′-dithiohydantoin. The β-relation of this product was proved by total desulphurisation with hot chloroacetic acid to give the β-form of the hydantoin of m. p. 238°. Only a trace (<1%) of the α-form of the dithiohydantoin could be isolated from the mother-liquors of the crude product. Another modification of the Bucherer hydantoin reaction, in which ammonium monothiocarbamate is used to prepare 4-thiohydantoins,[8] when applied to 3-methylcyclohexanone, gave a good yield of the spiro-4′-thiohydantoin, almost entirely in the β-form, the structure being proved by desulphurisation in the same way.

Both α- and β-forms of the spiro-2′,4′-dithiohydantoins thus became readily available, the β-form directly by the carbon disulphide modification of the Bucherer reaction, and the α-form by sulphurisation of the α-form of the hydantoin which was the main product

[3] Hoyer, *Chem. Ber.*, 1950, **83**, 491.
[4] Munday, *J.*, 1961, 4372.
[5] Carrington, *J.*, 1947, 684.
[6] Carrington and Waring, *J.*, 1950, 354.
[7] Carrington, *J.*, 1947, 681.
[8] Carrington, Vasey, and Waring, *J.*, 1959, 396.

of the normal Bucherer reaction. The β-forms of the hydantoins were available from the amino-nitriles by the cyanate method, or by desulphurisation of the β-thiohydantoins with chloroacetic acid.

Although this work has been exemplified only with hydantoins derived from 3-methylcyclohexanone, a similar highly selective formation of α- and β-forms of hydantoins and thiohydantoins has been demonstrated starting from 2- and 4-methyl-, 3,4- and *cis*-3,5-dimethyl-, 3-ethyl-5-methyl-, 3-ethyl-, 3-n-propyl-, 3-isopropyl-, and 3-phenyl-cyclohexanone, tetrahydrocarvone, 2-methylcycloheptanone, and *cis*- and *trans*-forms of 2-decalone. In almost all these cases two forms of hydantoin, dithiohydantoin, and 2-thiohydantoin were obtained. For hydantoins from 3,4-dimethylcyclohexanone the stereospecificity was less marked than in the other cases, *e.g.*, the carbon disulphide modification of the Bucherer reaction afforded as much as 10% of the α-dithiohydantoin and only 90% of the β-isomer.

As would be expected, only one isomer was obtained from unsubstituted cyclic ketones, such as the series from cyclopentanone to cyclodecanone, and also from the symmetrically disubstituted ketones 2,2- and 3,3-dimethylcyclopentanone, and 3,3-dimethylcyclohexanone.

The reactions of spirohydantoins prepared from 2-substituted cycloalkanones were strongly hindered sterically. Spiro-5′-(2′,4′-dithiohydantoins) are normally readily attacked by hot 2-aminoethanol, giving 4-2′-hydroxyethylimino-derivatives. This reaction was completely inhibited when there was a substituent on the alicyclic ring adjacent to the spiro-atom, *e.g.*, 2,4-dithiohydantoins (α- and β-forms alike) derived from 2-methylcyclohexanone, tetrahydrocarvone, 2-methylcycloheptanone, and 2,5-dimethylcyclopentanone did not react with 2-aminoethanol. Unexpectedly the 4-thiohydantoin derived from 2-methylcyclohexanone was cleanly and readily attacked by 2-aminoethanol, giving the 4-2′-hydroxyethylimino-derivative, a behaviour which was in complete contrast to the stability of the corresponding 2,4-dithiohydantoin. A similar example of apparent steric hindrance was the complete failure to effect sulphurisation of the hydantoin derived from 2,2-dimethylcyclopentanone by phosphorus pentasulphide in boiling tetralin. All other hydantoins prepared in this work were sulphurised without difficulty in 70—80% yields by this treatment. Finally, steric hindrance was clearly implicated in the rate of formation of hydantoins, and particularly of dithiohydantoins prepared by the carbon disulphide modification of the Bucherer reaction. The yields from such α-substituted ketones as 2,2-dimethyl- and 2,5-dimethyl-cyclopentanone, 2-methyl- and 2-methyl-5-isopropyl-cyclohexanone, and 2-methylcycloheptanone were less than 30% for hydantoins and less than 10% for dithiohydantoins (β forms), in place of ~90% and 30%, respectively, from unhindered cyclic ketones such as 3-methylcyclohexanone.

Experimental

The procedures used may be exemplified by the preparations given below for the hydantoins, dithiohydantoins, monothiohydantoins, and *N*-methyl derivatives obtained by starting from 3-methylcyclohexanone.

3-Methylcyclohexanespiro-5′-hydantoin (I) (*α-Form*).—*Normal Bucherer hydantoin synthesis.* 3-Methylcyclohexanone (107 g.), sodium cyanide (92 g.), ammonium carbonate (355 g.), ethanol (740 c.c.), and water (740 c.c.) were mixed and stirred under reflux at 50—55° for 6 hr., then diluted with water (740 c.c.), acidified with hydrochloric acid, and cooled. The product was filtered off and washed with water. The crude mixture of hydantoins (104 g.), m. p. 257°, was extracted with boiling methanol, leaving a residue (68 g.), m. p. 264°, from which the pure α-form, m. p. 268°, was obtained by further crystallisation. The methanolic extract, on cooling, deposited a further 6 g. of the α-form, m. p. 263°. Concentration of the filtrate gave further crops as follows: 3rd crop, 22 g., m. p. 250—260°; 4th crop, 5 g., m. p. 210—217°; 5th crop, 2 g., m. p. 208—211°. Crops 4 and 5 were combined and recrystallised twice from methanol, giving the β-hydantoin, m. p. 238°.

TABLE 1.

Substituted cyclohexanespiro-5′-hydantoins (cf. I) and other spirohydantoins.

No.	Spiran ring	Note	Isomer *	M. p.	Yield (%)	Formula	Required (%) C	Required (%) H	Required (%) N	Found (%) C	Found (%) H	Found (%) N
	Cyclopentane											
1	2,2-Me_2	(*a*)	—	233°	29	$C_9H_{14}N_2O_2$	59·3	7·7	15·4	59·1	7·7	15·1
2	2,5-Me_2	(*b*)	α	178	15	$C_9H_{14}N_2O_2$	59·3	7·7		59·2	7·7	
	Cyclohexane											
3	2-Me	(*c*) (*d*)	α	217	55	$C_9H_{14}N_2O_2$	59·3	7·7	15·4	Ref. 2		
			β	187	—					59·7	7·6	15·9
4	3-Me	(*d*) (*e*)	α	268	72	$C_9H_{14}N_2O_2$	59·3	7·7	15·4	Ref. 2		
			β	238	—					59·4	7·7	15·7
5	4-Me	(*d*) (*f*)	α	276	—	$C_9H_{14}N_2O_2$	59·3	7·7	15·4	Ref. 2		
			β	206	—					59·2	7·4	15·0
6	3,4-Me_2	(*d*) (*g*)	α	268	33	$C_{10}H_{16}N_2O_2$	61·2	8·2		61·3	8·1	
			β	240	—					61·2	8·2	
7	3,5-Me_2	(*h*)	α	334	66	$C_{10}H_{16}N_2O_2$	61·2	8·2		Ref. 9		
			β	250	—					61·4	8·3	
8	3-Et-5-Me	(*d*) (*i*)	α	274	64	$C_{11}H_{18}N_2O_2$	62·8	8·6		Ref. 9		
			β	222	—					63·0	8·4	
9	3-Et	(*d*) (*j*)	α	221	70	$C_{10}H_{16}N_2O_2$	61·2	8·2		60·9	8·3	
			β	201	—					61·5	8·5	
10	3-Pr^n	(*k*)	α	216	90	$C_{11}H_{18}N_2O_2$	62·8	8·6	13·3	63·1	8·3	12·9
			β	184	65					62·6	8·4	13·7
11	3-Pr^i	(*l*)	α	242	95	$C_{11}H_{18}N_2O_2$	62·8	8·6	13·3	62·5	8·7	13·3
			β	226	—					63·3	8·8	13·5
12	3,3-Me_2	(*m*)	—	248	97	$C_{10}H_{16}N_2O_2$	61·2	8·2	14·3	61·1	8·2	14·0
13	3,3,5-Me_3	(*n*)	α	270	—	$C_{11}H_{18}N_2O_2$	62·8	8·6	13·3	Ref. 10		
			β	256	—					62·5	8·8	13·4
14	3-Ph	(*o*)	α	295	80	$C_{14}H_{16}N_2O_2$	68·8	6·6	11·5	68·5	6·6	11·6
			β	290	75					68·6	6·7	11·4
15	2-Me-5-Pr^i	(*p*)	α	231	29	$C_{12}H_{20}N_2O_2$	64·25	9·0	12·5	64·2	8·9	12·6
	Other rings											
16	2-Methylcycloheptane	(*q*)	α	221	58	$C_{10}H_{16}N_2O_2$	61·2	8·2	14·3	61·4	8·3	14·7
17	Cyclononane	(*r*)	—	269	43	$C_{11}H_{18}N_2O_2$	62·8	8·6	13·3	63·2	8·2	13·1
18	Cyclodecane	(*s*)	—	275	56	$C_{12}H_{20}N_2O_2$	64·25	9·0	12·5	63·9	9·0	12·7
19	Decalin-2-	(*d*) (*t*)	α	308	58	$C_{12}H_{18}N_2O_2$	64·8	8·2	12·6	65·0	8·0	12·7
			β	269	75					65·0	8·0	12·4
20	Decalin-2-	(*d*) (*u*)	α	291	47	$C_{12}H_{18}N_2O_2$	64·8	8·2	12·6	65·0	8·0	
			β	288	80					65·1	8·1	12·7

* The α-forms were prepared by the normal Bucherer reaction on the appropriate ketones. The β-forms were prepared by the action of chloroacetic acid on the β-forms of the corresponding 2-thiohydantoins, except where otherwise stated.

(*a*) From 2,2,-dimethylcyclopentanone.[11] The ketone was purified by recrystallisation of the semicarbazone. (*b*) From 2,5-dimethylcyclopentanone.[12] (*c*) From 2-methylcyclohexanone; ref. 2 gives m. p. 216° for the α-form. (*d*) The required ketone was obtained by hydrogenation of the phenol over Raney nickel followed by oxidation by Beckmann's chromic acid mixture. (*e*) From 3-methylcyclohexanone; ref. 2 gives m. p. 269° for the α-form; ref. 4 gives m. p. 238° for the β-form. (*f*) From 4-methylcyclohexanone; ref. 2 gives m. p. 279° for the α-form; ref. 4 gives m. p. 215° for the β-form. (*g*) From 3,4-dimethylcyclohexanone, presumed *cis* from the method of preparation. (*h*) From *cis*-3,5-dimethylcyclohexanone, obtained by catalytic reduction of the cyclohexenone derivative;[13] no trace of *trans*-3,5-dimethylcyclohexanone was obtained; ref. 9 gives m. p. 335° for the α-form. (*i*) From 3-ethyl-5-methylcyclohexanone, presumed *cis* from the method of preparation; ref. 9 gives m. p. 282° for the α-form. (*j*) From 3-ethylcyclohexanone. (*k*) From 3-n-propylcyclohexanone, prepared by the method of Crossley and Renouf;[14] the intermediate 3-substituted 5-chlorocyclohexenone was, however, reduced directly to the substituted cyclohexanone by hydrogen at 1 atm. over palladium–strontium carbonate and magnesium oxide in ethanol. (*l*) From 3-isopropylcyclohexanone, prepared by the method given in (*k*). (*m*) From 3,3-dimethylcyclohexanone, prepared by method given in (*k*). (*n*) From dihydroisophorone; ref. 10 gives m. p. 281° for the α-form. (*o*) From 3-phenylcyclohexanone, prepared by method given in (*k*). (*p*) From tetrahydrocarvone. (*q*) From 2-methylcycloheptanone, obtained by diazoethane ring-expansion of cyclohexanone.[15] (*r*) From cyclononanone.[16] (*s*) From cyclodecanone.[16] (*t*) From *cis*-2-decalone;[17] the *cis*-2-decalol, m. p. 105°, was isolated by crystallisation from light petroleum before oxidation. (*u*) From *trans*-2-decalone;[17] for characterisation pure *trans*-2-decalone was prepared by the method of van Tamelen and Proost.[18]

TABLE 2.

Substituted cyclohexanespiro-5′-(2′,4′-dithiohydantoins) and other spiro-2′,4′-dithiohydantoins.

					Required (%)			Found (%)		
No.*	Isomer †	M. p.	Yield (%)	Formula	C	H	N	C	H	N
i	—	233°	75	$C_9H_{14}N_2S_2$	50·5	6·6	13·1	50·4	6·7	13·3
2 (*a*)	α	274	25	$C_9H_{14}N_2S_2$	50·5	6·6	13·1	50·7	6·8	
	β	217	4					50·7	6·9	13·3
3	α	257	—	$C_9H_{14}N_2S_2$	50·5	6·6	13·1	50·6	6·5	12·8
	β	194 (*b*)	10					50·3	6·5	Ref. 7
4	α	274	65	$C_9H_{14}N_2S_2$	50·5	6·6		50·7	6·5	
	β	204 (*c*)	34					Ref. 7		
5	α	232	—	$C_9H_{14}N_2S_2$	50·5	6·6	13·1	50·9	6·8	13·1
	β	253 (*d*)	38					Ref. 7		
6	α	287	—	$C_{10}H_{16}N_2S_2$	52·6	7·1		53·0	7·4	
	β	205	50					52·6	7·2	
7	α	290	90	$C_{10}H_{16}N_2S_2$	52·6	7·1		52·5	7·1	
	β	233 (*e*)	20					Ref. 7		
8	α	208	45	$C_{11}H_{18}N_2S_2$	54·5	7·5		54·6	7·3	
	β	184	70					54·6	7·4	
9	α	220	90	$C_{10}H_{16}N_2S_2$	52·6	7·1		52·5	7·0	
	β	177	44					52·7	7·1	
10	α	198	83	$C_{11}H_{18}N_2S_2$	54·5	7·5	11·6	54·4	7·4	
	β	147	50					54·5	7·6	11·3
11	α	228	90	$C_{11}H_{18}N_2S_2$	54·5	7·5	11·6	54·3	7·1	11·8
	β	202	36					54·1	7·4	12·0
12	—	223	22	$C_{10}H_{16}N_2S_2$	52·6	7·1	12·3	52·6	6·7	12·3
13	α	232	56	$C_{11}H_{18}N_2S_2$	54·5	7·5	11·6	54·4	7·4	11·8
	β	218	25					54·7	7·5	
14	α	268	64	$C_{14}H_{16}N_2S_2$	60·9	5·8	10·1	60·5	5·6	10·4
	β	247	65					60·9	5·8	10·3
15	α	206	60	$C_{12}H_{20}N_2S_2$	56·2	7·9		56·2	7·8	
	β	215	8					56·2	7·5	
16	α	214	—	$C_{10}H_{16}N_2S_2$	52·6	7·1	12·3	52·3	6·7	12·0
	β	222	2					52·8	7·1	12·0
(*f*)	—	261	6	$C_{10}H_{16}N_2S_2$	52·6	7·1	12·3	52·6	7·0	11·9
18	—	239	1	$C_{12}H_{20}N_2S_2$	56·3	7·9		56·5	7·8	
19 (*g*)	α	287	81	$C_{12}H_{18}N_2S_2$	56·7	7·1	11·0	57·0	6·9	11·2
	β	242	30					57·0	7·0	11·2
20 (*h*)	α	267	76	$C_{12}H_{18}N_2S_2$	56·7	7·1	11·0	56·7	6·8	10·8
	β	260	16					57·0	7·1	11·2

* This number denotes the spiran ring shown under the same number in Table 1.

† The α-forms were prepared from the α-forms of the hydantoins by the action of phosphorus pentasulphide. The β-forms were prepared from the appropriate ketones by the carbon disulphide modification of the Bucherer hydantoin reaction. The ketones were prepared as described in Table 1.

(*a*) From *cis*-2,5-dimethylcyclopentanone; *trans*-2,5-dimethylcyclopentanone would be expected to give only one series of hydantoins. As two forms of the dithiohydantoin were obtained the ketone evidently reacted in the *cis*-form. Ref. 7 gives (*b*) m. p. 184°, (*c*) m. p. 203°, (*d*) m. p. 255°, and (*e*) m. p. 230°. (*f*) Cyclo-octanespiro-compound; from cyclo-octanone.[19] (*g*) From *cis*-2-decalone. (*h*) From *trans*-2-decalone. (*i*) 3,3-Dimethylcyclopentanespiro.

A preparation in which carbon dioxide was passed during 4 hr. into a solution of 3-methylcyclohexanone (21 g.), sodium cyanide (9·2 g.), and ammonium chloride (10·2 g.) in methanol (113 c.c.) and water (75 c.c.) stirred at 50—55°, yielded the α-form of the hydantoin, m. p. 268°.

3-Methylcyclohexanespiro-5′-hydantoin (I) (*β-Form*).—*Amino-nitrile–cyanate synthesis.* 3-Methylcyclohexanone (50 g.) was stirred with a solution of potassium cyanide (32·5 g.) and ammonium chloride (27·5 g.) in water (100 c.c.) for 5 hr. with water-cooling. The solution

[9] Henze, Wilson, and Townley, *J. Amer. Chem. Soc.*, 1943, **65**, 963.
[10] Tiffeneau, Tchoubar, and Saias-Lambert, *Bull. Soc. chim. France*, 1947, 445.
[11] Haller and Cornubert, *Compt. rend.*, 1924, **179**, 315, 320.
[12] Noyes and Kyriakides, *J. Amer. Chem. Soc.*, 1910, **32**, 1057, 1065.
[13] Wallach, *Annalen*, 1913, **397**, 199.
[14] Crossley and Renouf, *J.*, 1907, **91**, 70, 82.
[15] Adamson and Kenner, *J.*, 1939, 185.
[16] Prelog, Frenkiel, Kobelt, and Barman, *Helv. Chim. Acta*, 1947, **30**, 1741.
[17] Huckel, *Annalen*, 1925, **441**, 1.
[18] van Tamelen and Proost, *J. Amer. Chem. Soc.*, 1954, **76**, 3632.
[19] Kohler, Tishler, Potter, and Thompson, *J. Amer. Chem. Soc.*, 1939, **61**, 1057.

TABLE 3.

Substituted cyclohexanespiro-5′-(2′-thiohydantoins) and other spiro-5′-(2′-thiohydantoins).

No.*	Isomer †	M. p.	Yield (%)	Formula	Required (%) C	Required (%) H	Required (%) N	Found (%) C	Found (%) H	Found (%) N
e	—	192°	55	$C_9H_{14}N_2OS$	54·5	7·1	14·1	54·5	7·1	14·2
4	α	211	66	$C_9H_{14}N_2OS$	54·5	7·1	14·1	54·8	7·0	14·1
	β	216	60					54·4	7·4	
5	α	248	—	$C_9H_{14}N_2OS$	54·5	7·1	14·1	54·8	6·9	13·8
	β	220 (*a*)	—					Ref. 5		
6	α	233	—	$C_{10}H_{16}N_2OS$	56·6	7·6		56·5	7·6	
	β	256	27					56·4	7·2	
7	α	241	59	$C_{10}H_{16}N_2OS$	56·6	7·6		57·0	7·3	
	β	213	64					56·8	7·5	
8	α	241	—	$C_{11}H_{18}N_2OS$	58·4	8·0		58·1	7·7	
	β	156	33					58·8	8·2	
9	α	158	26	$C_{10}H_{16}N_2OS$	56·6	7·6		56·3	7·7	
	β	145	46					56·7	7·7	
10	α	189	80	$C_{11}H_{18}N_2OS$	58·4	8·0	12·4	58·7	7·9	12·1
	β	170	64					58·1	7·9	12·4
11	α	189	89	$C_{11}H_{18}N_2OS$	58·4	8·0	12·4	58·4	7·8	12·9
	β	199	47					58·3	7·7	12·9
12	—	200	74	$C_{10}H_{16}N_2OS$	56·6	7·6	13·2	57·0	7·8	13·5
13	α	239	—	$C_{11}H_{18}N_2OS$	58·4	8·0	12·4	58·4	8·4	12·1
	β	231	88					58·5	7·8	12·2
(*c*)	—	210	72	$C_9H_{14}N_2OS$	54·5	7·1	14·1	54·7	7·0	14·6
(*d*)	—	204	69	$C_{10}H_{16}N_2OS$	56·6	7·6	13·2	56·6	7·3	13·0
20 (*b*)	α	288	31	$C_{12}H_{18}N_2OS$	60·5	7·6	11·8	60·3	8·0	11·9
	β	212	34					60·8	7·6	12·1

* This number denotes the spiran ring shown under that number in Table 1.

† All the 2-thiohydantoins were obtained from the corresponding dithiohydantoins (α- or β-forms) by heating them with 2-aminoethanol, then hydrolysing the intermediate 4-2′-hydroxyethyliminoderivative by acid without isolating it.

(*a*) Ref. 5 gives m. p. 219°. (*b*) From *trans*-2-decalone. (*c*) Cycloheptanespiro. (*d*) Cyclooctanespiro. (*e*) 3,3-Dimethylcyclopentanespiro.

was extracted with ether, and the ether solution was dried ($MgSO_4$) and then saturated with dry hydrogen chloride. The precipitate crystallised from methanol–ether, giving 1-*amino*-3-*methylcyclohexanecarboxynitrile hydrochloride* (22 g.), m. p. 172° (decomp.) (Found: C, 55·1; H, 8·6; N, 15·8. $C_8H_{15}ClN_2$ requires C, 55·0; H, 8·6; N, 16·05%).

1-Amino-3-methylcyclohexanecarboxynitrile hydrochloride (4·4 g.) and sodium cyanate (2 g.) in acetic acid (20 c.c.) and water (3 c.c.) were heated at 95—100° for 1 hr. Concentrated hydrochloric acid (10 c.c.) was added and heating at 95—100° continued for 15 min. longer. The mixture was diluted with water and cooled. The crystalline product was filtered off and had m. p. 230°, raised to m. p. 238° by recrystallisation from methanol. This was the β-form of the spiran (I).

Hydrolytic desulphurisation of thiohydantoins. 3-Methylcyclohexanespiro-5′-(2′-thiohydantoin) (β-form; m. p. 216°) (2 g.) and 20% aqueous chloroacetic acid (100 c.c.) were heated under reflux for 4 hr. After cooling, crystals of the β-form of the spiran (I) were collected; recrystallised from methanol, they had m. p. 238°. The same hydantoin was also obtained by similar treatment of the β-form of the dithiohydantoin.

3-*Methylcyclohexanespiro*-5′-(2′,4′-*dithiohydantoin*) (α-*Form*).—A mixture of 3-methylcyclohexanespiro-5′-hydantoin (α-form; m. p. 268°) (10 g.), phosphorus pentasulphide (10 g.), and tetralin (100 c.c.) was heated under reflux for 1·25 hr. The hot solution was decanted from some tar and allowed to cool. The product was filtered off, washed with a little cold benzene, and crystallised from methanol, giving 10 g. of the α-form, m. p. 274°, of 3-methylcyclohexanespiro-5′-(2′,4′-dithiohydantoin).

Monothiohydantoins were also sulphurised to dithiohydantoins by this method when required.

3-*Methylcyclohexanespiro*-5′-(2′,4′-*dithiohydantoin*) (β-*Form*).—*Carbon disulphide modification of the Bucherer hydantoin synthesis.* A mixture of 3-methylcyclohexanone (20 g.), sodium cyanide (8·8 g.), ammonium chloride (9·6 g.), carbon disulphide (15·4 g.), methanol (108 c.c.),

and water (71 c.c.) was stirred and heated under reflux at 50—55° for 24 hr. Unchanged ketone was removed by steam-distillation, the residue cooled, and the crude product filtered off (19·5 g.; m. p. 183—200°). Crystallisation from methanol yielded the β-form of the dithiohydantoin having m. p. 204° (8·6 g.), $\lambda_{max.}$ (in MeOH) 2300 and 2980 Å (*E* 6750 and 31,200, respectively).

Concentration of the methanolic mother-liquor yielded 5 g. of less pure β-dithiohydantoin m. p. 190—200°, and then 0·15 g.) of material, m. p. 250—260°, which after recrystallisation had m. p. 274° and was shown by mixed m. p. to be the α-form of the dithiohydantoin. It had $\lambda_{max.}$ (in MeOH) 2300 and 3000 Å (*E* 5700 and 28,000, respectively).

3-*Methylcyclohexanespiro*-5′-(2′-*thiohydantoin*) (α-*Form*).—3-Methylcyclohexanespiro-5′-(2′,4′-dithiohydantoin) (α-form; m. p. 274°) (14 g.), 2-aminoethanol (14 c.c.), and water (14 c.c.) were heated under reflux for 30 min., cooled, diluted with water, and filtered. A sample of the precipitated 4-2′-hydroxyethylimino-derivative, crystallised from ethanol, had m. p. 250°. The crude product was heated under reflux with concentrated hydrochloric acid (120 c.c.) and water (60 c.c.) for 30 min., then cooled, filtered, and washed with water. Recrystallisation from aqueous ethanol yielded the 2-thiohydantoin, α-form, m. p. 211°.

3-*Methylcyclohexanespiro*-5′-(2′-*thiohydantoin*) (β-*Form*).—The spirodithiohydantoin (β-form; m. p. 204°) (10 g.), 2-aminoethanol (10 c.c.), and water (20 c.c.) were heated under reflux for 1 hr. The 4-2′-hydroxyethylimino-derivative was not isolated, but was heated directly with an excess of concentrated hydrochloric acid under reflux for a further 15 min. After cooling, the crude product was filtered off and crystallised from aqueous methanol, giving the spiro-2-thiohydantoin, β-form, m. p. 216° (4 g.).

3,3′-*Dimethylcyclohexanespiro*-5′-*hydantoin*.—(i) α-*Form*. The 3-methyl-spiran (α-form, m. p. 268°) (91 g.) and sodium hydroxide (20 g.) in water (300 c.c.) were stirred, and to the suspension of sodium salt was added dimethyl sulphate (60 g.), the temperature being kept below 40°. The thick paste was filtered, and the solid washed with water, and crystallised from aqueous methanol, giving the 3,3′-*dimethyl derivative* (α-*form*), m. p. 171° (Found: C, 61·3; H, 8·2; N, 14·3. $C_{10}H_{16}N_2O_2$ requires C, 61·2; H, 8·2; N, 14·3%).

(ii) β-*Form*. Methylation of the β-form, m. p. 238°, as for the α-form, and crystallisation from aqueous methanol gave the 3,3′-*dimethyl compound*, β-*form*, m. p. 150°, depressed on admixture with the α-form (Found: C, 61·3; H, 7·9. $C_{10}H_{16}N_2O_2$ requires C, 61·2; H, 8·2%).

3,3′-*Dimethylcyclohexanespiro*-5′-(2′-*thiohydantoin*) (β-*Form*).—(*a*) *From amino-nitrile and methyl isothiocyanate*. 1-Amino-3-methylcyclohexanecarboxynitrile (7 g.) and methyl isothiocyanate (3 g.) in ether (10 c.c.) were left at room temperature for 3 days, and the crystals of the thioureido-compound filtered off and recrystallised from aqueous methanol (3 g.; m. p. 131—132°). This compound (2 g.) was heated in concentrated hydrochloric acid (3 c.c.) and water (10 c.c.) on the steam-bath for 30 min. The product was filtered off and recrystallised from aqueous methanol, giving 3,3′-*dimethylcyclohexanespiro*-5′-(2′-*thiohydantoin*) (β-*form*) (1·5g.), m. p. 182° (Found: S, 15·1. $C_{10}H_{16}N_2OS$ requires S, 15·1%). The m. p. was undepressed with an authentic sample prepared as below.

(*b*) *By methylation of* 3-*methylcyclohexanespiro*-5′-(2′-*thiohydantoin*) (β-*form*). A solution of this compound (m. p. 216°; 5 g.) in ether containing methanol (1 c.c.) was treated with an excess of ethereal diazomethane and left overnight at room temperature. The solvent was removed and the residue washed with sodium hydroxide solution and extracted with ether. Evaporation of the ether left a solid residue which after crystallisation from methanol yielded prisms, m. p. 182° (Found: C, 56·5; H, 7·4. $C_{10}H_{16}N_2OS$ requires C, 56·6; H, 7·5%).

2-*Methylcyclohexanespiro*-5′-*hydantoin* (β-*Form*).—2-Methylcyclohexanespiro-5′-(4′-thiohydantoin) (0·8 g.), 2-aminoethanol (1 c.c.), and water (1 c.c.) were heated under reflux for 1 hr.; an excess of concentrated hydrochloride acid was then added and heating continued for 30 min. longer. The mixture was cooled; the crystalline product, filtered off and recrystallised from aqueous methanol, had m. p. 187° (depressed on admixture with the α-form, m. p. 215°).

1-*Amino*-3-*methylcyclohexanecarboxylic Acid*.—α-*Form*. 3-Methylcyclohexanespiro-5′-hydantoin (α-form; m. p. 268°) (20 g.), sodium hydroxide (24 g.), and water (200 c.c.) were heated under reflux in a steel vessel for 48 hr. The solution was acidified to pH 2 with concentrated hydrochloric acid and filtered while still hot with the aid of charcoal. The filtrate was acidified strongly with concentrated hydrochloric acid, then cooled, and the precipitated hydrochloride was collected, suspended in water, and brought to pH 8 by addition of ammonia. The mixture was cooled in ice, and the solid filtered off and washed with cold water. The product (8·5 g.), m. p. 300° (sublimes), crystallised from water or 90% ethanol, giving the

α-form of 1-amino-3-methylcyclohexanecarboxylic acid as prisms, m. p. 316—317° (sublimes). A sample was dried at 130°/12 mm. for 12 hr. for analysis (Found: C, 57·7; H, 9·7; N, 8·2. Calc. for $C_8H_{15}NO_2,\frac{1}{2}H_2O$: C, 57·8; H, 9·7; N, 8·4%). Munday [4] gives m. p. 312—315° (sublimes).

When the α-form of the amino-acid had been heated in aqueous solution with potassium cyanate for 1 hr. acidification precipitated the ureido-compound, m. p. 184—185° (decomp.), which was then heated with 20% hydrochloric acid for 15 min. It was converted into the α-form of the hydantoin, m. p. and mixed m. p. 268°.

β-*Form of the acid.* The spirohydantoin (β-form; m. p. 238°) (60 g.), sodium hydroxide (70 g.), and water (600 c.c.) were heated under reflux for 50 hr. The solution was diluted with water (300 c.c.) and neutralised to pH 6·5—7·0 with hydrochloric acid. The cooled mixture was filtered, and the product (52 g.) recrystallised from water, giving the β-form of 1-amino-3-methylcyclohexanecarboxylic acid as prisms, m. p. 344—346° (sublimes) (Found: C, 60·8; H, 9·6; N, 8·9. Calc. for $C_8H_{15}NO_2$: C, 61·1; H, 9·6; N, 8·9%). Munday [4] gives m. p. 360—365° (sublimes).

The same acid was obtained by boiling 1-amino-3-methylcyclohexanenitrile hydrochloride (7 g.) with concentrated hydrochloric acid (100 c.c.) under reflux for 24 hr. The crystalline hydrochloride (10 g.), obtained on cooling, was filtered off, its solution in water adjusted to pH 8 by addition of ammonia, and the precipitated amino-acid was recrystallised from water. The product (4·2 g.) sublimed at 344—346° and had an infrared spectrum identical with that of the amino-acid obtained from the β-hydantoin.

The β-form of the amino-acid, when treated with potassium cyanate and acid as above, gave a ureido-compound, m. p. 188—190° (decomp.) which was converted by hot 20% hydrochloric acid into the β-form of the hydantoin m. p. 238°, undepressed on admixture with an authentic specimen, and depressed to 210—214° on admixture with the α-form of the hydantoin.

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