THE SYNTHESIS OF SOME POTENTIAL ANTIMETABOLITES OF PHENYLALANINE

PART II. THE SYNTHESIS OF SOME ββ-DIALKYL-α-AMINOPROPIONIC ACIDS

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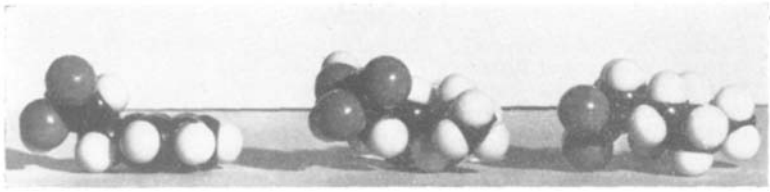
Seven ββ-dialkyl-α-aminopropionic acids, including five new compounds, have been synthesised as potential antiviral and antibacterial agents. None showed any significant activity against the Newcastle Disease virus *in vitro*. Several methods of preparation of the compounds have been investigated, and theories are advanced to explain the failure of some of these methods.

PHENYLALANINE is an essential metabolite for the Influenza A and Newcastle Disease viruses[1] (Dickinson, personal communication), and in Part I[2] we reported the synthesis of some γγ-dialkyl-α-aminobutyric acids as possible but unsuccessful antagonists of phenylalanine in the Newcastle Disease virus- Chick chorio-allantoic membrane system.

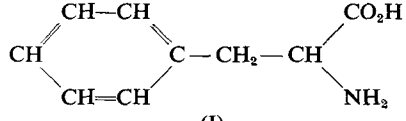
Continuing this work, in which we are trying to formulate and synthesise possible theoretical antagonists of phenylalanine, we have now prepared a similar series of ββ-dialkyl-α-aminopropionic acids.



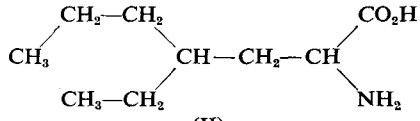
1 2 3

FIG. 1. Catalin models of β-phenylalanine (1), α-amino-γ-ethyl-γ-propylbutyric acid (2) and α-amino-β-ethyl-β-propylpropionic acid (3).

Catalin models of these compounds (Fig. 1) indicate that their bulk more nearly approaches that of phenylalanine (I) than does that of the γγ-dialkyl-α-aminobutyric acids from which they differ only in the length of the main carbon chain, which is reduced from three to two carbon atoms.

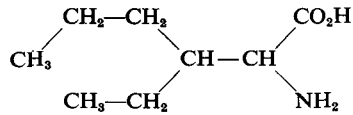


(I)



(II)

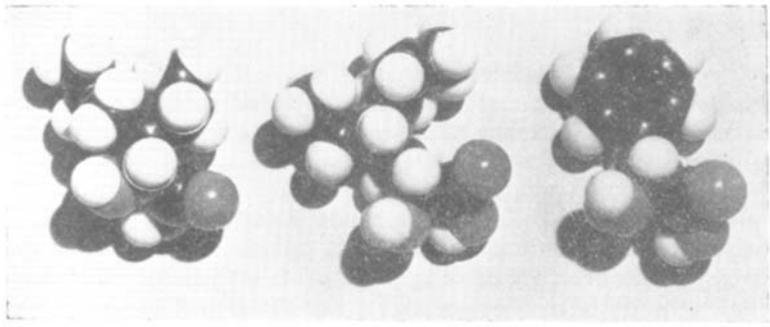
α-Amino-γ-ethyl-γ-propylbutyric acid



(III))

α-Amino-β-ethyl-β-propylpropionic acid

However, the absence of the methylene group between the two carbon atoms carrying the polar and non-polar residues results in an appreciable change in the spatial configuration of the molecule compared to that of phenylalanine (Fig. 2*a* and *b*).



1 2 3

FIG. 2A. Catalin models of α-amino-β-ethyl-β-propylpropionic acid (1), α-amino-γ-ethyl-γ-propylbutyric acid (2) and β-phenylalanine (3).

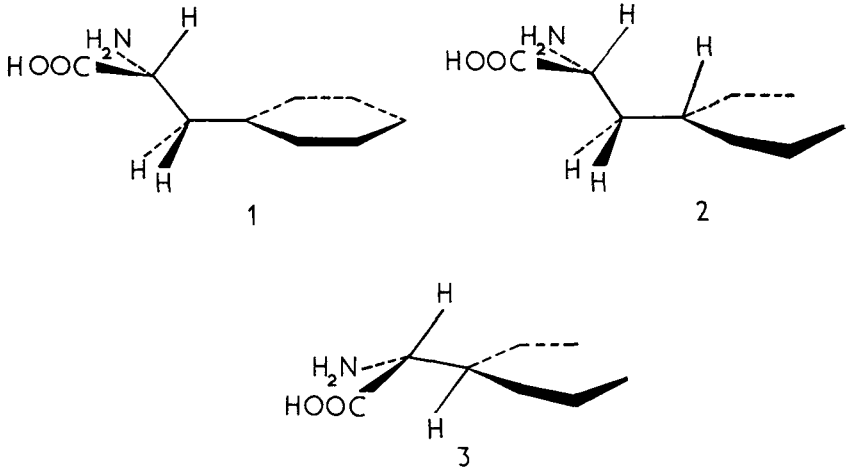


FIG. 2B. Steric conformations of phenylalanine (1), α-amino-γ-ethyl-γ-propylbutyric acid (2), and α-amino-β-ethyl-β-propylpropionic acid (3).

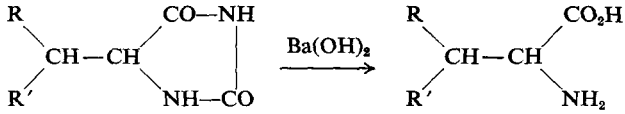
The model of phenylalanine shows that the amino-acid moiety is above the plane of the aromatic ring and a similar structure can be attained by the γγ-dialkyl-α-aminobutyric acids where the amino-acid moiety is above the plane of the alkyl groups, which themselves may approach a

ring structure. But in the case of the $\beta\beta$-dialkyl-α-aminopropionic acids, the absence of the methylene group ensures that the carbon atom carrying the two polar groups is in a very similar plane to that of the non-polar residue, and the polar groups themselves are directed slightly below this plane (Fig. 2*a* and *b*). Therefore, from a theoretical chemotherapeutic viewpoint, it is possible that this series of amino-acids may be utilised in the virus protein synthesis instead of phenylalanine, because of the similarity in the bulk and the chemical nature of the compounds. Thus antagonism may be effected by virtue of the difference in the spatial relationship of the polar and non-polar residues, which may result in the formation of a foreign protein and therefore interfere with virus protein synthesis.

Preparation of the Compounds

The parent of the $\beta\beta$-dialkyl-α-aminopropionic acids is the naturally occurring amino-acid valine, for which many syntheses are available. Several of these appear to be readily applicable to the synthesis of the higher homologues and consequently no difficulty was envisaged in the preparation of this series of compounds. However, we found that the higher $\beta\beta$-dialkyl-α-aminopropionic acids cannot be synthesised by the following procedures: (i) the alkylation of diethyl acetamidomalonate; (ii) the α-carbon nitrosation of alkylmalonates and alkylacetoacetates; (iii) hydrolysis and subsequent reduction of the α-hydroxyamino-nitriles; (iv) Schmidt's reaction with alkylmalonic esters; (v) Curtius' degradation of alkylcyanacetic esters.

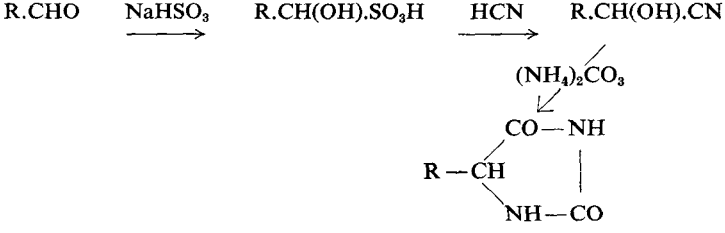
The compounds were eventually prepared by the hydrolysis of the 5-(dialkylmethyl)hydantoins (IV).



(IV)

The various methods available for the synthesis of the 5-alkylhydantoins have been reviewed by Ware[3] and of these, two are seemingly easily applicable to the preparation of the 5-(dialkylmethyl)hydantoins, namely the Bucherer-Bergs' synthesis from carbonyl compounds and the condensation of hydantoin with carbonyl compounds and subsequent reactions.

The Bucherer-Bergs' synthesis is outlined by the following reaction sequence.



The appropriate 2,2-dialkylacetaldehydes are the desired starting materials for the preparation of the 5-(dialkylmethyl)hydantoins, but of those required, only 2-ethylhexanal is commercially available. Others, as indicated in the relevant literature, have often been obtained as by-products in other investigations, for instance, Sutter and Wijkmann[4] isolated 2-ethylvaleraldehyde from the degradation of glauconic acid, while investigating the chemistry of moulds and Bunner and Farmer[5] obtained 2-isopropyl-2-methylacetaldehyde from the ozonolysis of olefin condensation products. Two apparently general methods for the synthesis of 2,2-dialkylacetaldehydes appear in the literature, but in each, the starting materials are difficult to obtain. Sommelet and his colleagues[6–8] prepared 2-methylvaleraldehyde and 2-propylvaleraldehyde by heating the appropriate 2,2-dialkylethylene glycols or their 1-ethyl ethers and Sou[9] reported a new aldehyde synthesis involving the distillation of the hydrobromides of 2,2-dialkyl-2-dialkylaminoethanols, from which he obtained some of the corresponding 2,2-dialkylacetaldehydes.

Of the standard methods for the preparation of aldehydes, only the Rosenmund reduction appears to have been applied to these compounds (excluding isobutyraldehyde), and although Cason and Reinhart[10] reported a 71 per cent yield of 2-methyldodecanal from the corresponding acid chloride, Discherl and Nahm[11] obtained only 7 per cent of 2-ethylisovaleraldehyde by this procedure. We failed to obtain either of the corresponding aldehydes from 2-butylhexanoylchloride and 2-ethylvalerylchloride by the Rosenmund method.

Furthermore, we were also unable to prepare the compounds by the Stephen procedure, the reaction of the appropriate Grignard compounds with ethyl orthoformate or by the reduction of acid halide derivatives with aluminium lithium hydride according to Weygand and his colleagues[12–14].

As a result of these unsuccessful attempts to synthesis the necessary 2,2-dialkylacetaldehydes, only 5-(3-heptyl)hydantoin was prepared by the Bucherer-Bergs' method, being obtained in 65 per cent yield from 2-ethylhexanal. The hydantoin was successfully hydrolysed with barium hydroxide octahydrate at 160° for 30 minutes to give α-amino-β-butyl-β-ethylpropionic acid (2-amino-3-ethylheptanoic acid) in 85 per cent yield.

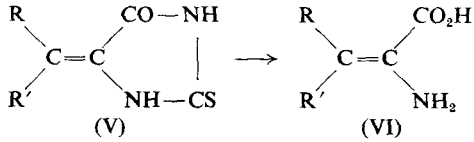
Consequently recourse had to be made to the second method available for the preparation of the required hydantoins.

Hydantoin has a reactive methylene group in the 5 position and therefore, might be expected to condense with carbonyl compounds which are reactive to such groups. Most of the past work in this field has been carried out with aldehydes, Wheeler and Hoffmann[15] first showing that hydantoin would condense with benzaldehyde in the presence of glacial acetic acid and sodium acetate to yield the 5-arylidene derivative, and soon afterwards, Wheeler and Brauchtlecht[16] and Johnson and Scott[17] showed that 2-thiohydantoin would condense similarly and often more readily than the oxygen analogue. Boyd and Robinson[18] introduced the use of a basic condensing agent instead of the acid medium used previously, finding that 1-acetyl-2-thiohydantoin would condense with

benzaldehyde in the presence of piperidine and pyridine or diethylamine and pyridine. Morpholine has also been used in similar condensations[19]. It has been shown that the nature of the secondary base is sometimes important, for Boyd and Robinson[18] obtained only 14 per cent of anisylidenehydantoin in the presence of piperidine–pyridine, whereas a diethylamine–pyridine medium gave 94 per cent of the same compound. 1-acetyl-2-thiohydantoin condensed with anisaldehyde equally well in either medium. The indifference of 2-thiohydantoin to the nature of the basic condensing agent was also demonstrated by Beer and his colleagues[20] who observed that piperidine–pyridine and morpholine–pyridine gave equally good yields of 5-isopropylidene-2-thiohydantoin from 1-acetyl-2-thiohydantoin and acetone. Our work on 5-(2-pentylidene)-2-thiohydantoin has shown that it is immaterial whether piperidine or diethylamine is used with pyridine for the condensation.

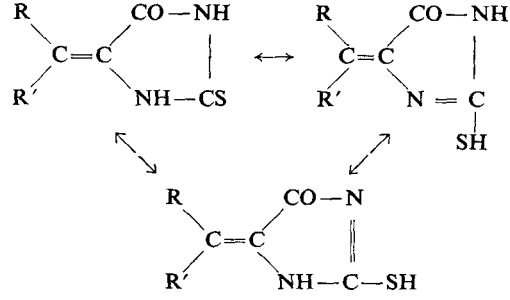
A few reports of the condensation of aliphatic ketones with 2-thiohydantoin have been made[20,21] and Yale[22] successfully condensed seven ketones with 2-thiohydantoin in good yields, although unlike Beer[20] and Dupré[21] he could not condense the ketones with 1-acetyl-2-thiohydantoin.

We have successfully condensed a further six aliphatic ketones with 2-thiohydantoin by refluxing the reactants for 1 hour in a mixture of piperidine and pyridine, followed by standing overnight. It was hoped that the hydrolysis of the condensates (V) would lead to the formation of the unsaturated amino-acids (VI).



(V) (VI)

Hydrolysis however, merely produced a cleavage at the double bond in an analagous manner to that described by Doyle, Holland and Naylor[23] who obtained thiohydantoic acid by the loss of the alkylidene group from 5-isopropylidene-2-thiohydantoin, on treatment with dilute alkali. In our case, glycine, identified by paper chromatography, was isolated.



Reduction to the saturated hydantoin before hydrolysis avoids this cleavage, and Ware[3] lists several methods for the reduction of the 5-alkylidenehydantoins to their corresponding saturated derivatives. As

the ease of reduction depends to some extent on the nature of the 5-alkyl group, it was felt, that in this instance, catalytic reduction would be the most suitable. However, the reduction of 5-(2-pentylidene)-2-thiohydantoin failed with both palladised charcoal and Raney nickel. This was attributed to the possibility of tautomerism in the molecule leading to thiol group formation, which probably leads to poisoning of the catalyst.

This problem was easily overcome by the conversion of the thiohydantoins to their oxygen analogues. Of the many reagents which have been used for this desulphurisation, aqueous chloracetic acid, introduced by Johnson, Pfau and Hodge[24] seemed the most satisfactory as it does not interfere with the alkylidene double bond as do the oxidising agents hydrogen peroxide and bromine water, which have also been used for this purpose. Refluxing the 5-alkylidene-2-thiohydantoins with 50 per cent aqueous chloracetic acid gave excellent yields of the oxygen derivatives, 5-(2-hexylidene)-2-thiohydantoin in particular giving a quantitative yield of 5-(2-hexylidene)hydantoin.

The 5-alkylidenehydantoins were readily reduced at room temperature and normal pressure using Raney nickel prepared by the method of Tucker[25], hydrogen uptake being completed after about 12 hours. This compared favourably with the results of Beer[20], who hydrogenated 5-isopropylidenehydantoin at 50 atmospheres pressure at 60° and Doyle[23], whose hydrogenation of the same compound at atmospheric pressure took 40 hours.

The saturated hydantoins were hydrolysed to the corresponding amino-acids by autoclaving with aqueous barium hydroxide at 160° for 30 minutes.

Examination of the results indicates that the inability to obtain some of the amino-acid intermediates was due to steric factors.

In the case of the alkylation of acetamidodiethylmalonate, Snyder, Shekelton and Lewis[26] found that they could not obtain the alkylated derivative from either isopropyl or secondary butyl bromide. Atkinson and Scott[27] obtained valine by this route, by using a prolonged reacton period, albeit in low yield, but they were unable to synthesis isoleucine by this route. Construction of models indicates the likelihood of steric hindrance, which increases with the molecular weight of the substituting secondary alkyl group.

Similar factors operate during the Curtius degradation of the secondary alkyl substituted malonic esters. Russel[28] found, that while he could ammonate monoethylmalonic ester to give 80 to 90 per cent of the amide, he could only obtain 3·7 per cent of diethylmalonamide and he attributed this to the steric nature of the diethylmalonic ester. The secondary alkyl malonic esters are very similar in structure to the dialkylmalonic esters and the reaction of the former with hydrazine is analogous to the reaction of the latter with ammonia.

Again, in the *C*-nitrosation of the alkylmalonic esters and alkylacetoacetates, the size of the substituting alkyl group appears to determine whether or no the reaction takes place. In the case of the compounds

with a primary alkyl group, nitrosation occurs readily, but although we successfully prepared the ethyl ester of 2-methyl-1-oximinobutyric acid by the method of Shivers and Hauser[29], which was then reduced to valine with palladised charcoal, the application of the method to the higher members of the series was completely unsuccessful.

In the case of the hydantoins, however, the precursors of the polar residues of the amino-acid are held in the rigid structure of the heterocyclic ring while the alkyl group is introduced. Similarly, in the preparation of α-amino-β-ethyl-β-propylpropionic acid by Gol'dfarb, Fabrichnyi

TABLE I

DIALKYLMETHANOLS, R.CH(OH).R′

R	R′	Yield per cent	B.p. found	B.p. lit.	n_D^{20}	Reference
CH_3	C_4H_9	72	139°	137–138°	1·4135	31
C_2H_5	C_3H_7	75	132–134°	134–136°	1·4140	32
C_3H_7	C_3H_7	76	151–152°	154°	1·4200	33
C_3H_7	C_4H_9	71	169–171°	71° 10mm.	1·4250	34
C_4H_9	C_4H_9	70	193–194°	194°	1·4290	35

and Shalovina[30], where the compound is synthesised by the desulphurisation of (1,5-dimethylthienyl-3)aminoacetic acid, the non-polar part of the molecule is held in the ring whilst the amino-acid moiety is added.

These results therefore suggest, that the higher homologues of valine can only be synthesised when the free movement of the polar and non-polar residues of the intermediates is reduced by clamping one end of the amino-acid precursor in a rigid ring structure.

TABLE II

ALIPHATIC KETONES, R.CO.R′

R	R′	Yield per cent	B.p. found	B.p. lit.	n_D^{20}	Reference
CH_3	C_4H_9	71	124–125°	127°	1·4005	36
C_2H_5	C_3H_7	64	123°	123°	1·4010	32
C_3H_7	C_3H_7	76	144°	144°	1·4080	37
C_3H_7	C_4H_9	75	166–168°	165–168°	1·4160	38
C_4H_9	C_4H_9	83	186–188°	187–188°	1·4198	35

Biological Results

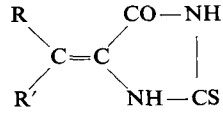
The 7 amino-acids were tested against Newcastle Disease virus in tissue culture using monolayers of chick embryo. None of the compounds showed any significant activity. BM 21 and 31 were inactive at a concentration of 1·7 mg./ml. BM 27, 38, 39 and 43 gave varying results at 1·7 mg./ml. but were all inactive at one fifth of this dose. BM 47 was toxic at 1·7 and 0·34 mg./ml. and inactive at 0·07 mg./ml.

EXPERIMENTAL

Typical syntheses are described. Details for the individual compounds are given in Tables I to VI.

TABLE III

5-ALKYLIDENE-2-THIOHYDANTOINS

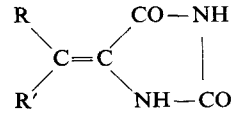


R	R′	Yield per cent	M.p.	Analysis					
				Found			Required		
				C	H	N	C	H	N
CH_3	C_3H_7	87	157°*a*	52·3	6·8	15·4	52·2	6·5	15·2
CH_3	C_4H_9	72	130°*b*	54·0	7·3	14·1	54·5	7·1	14·1
C_2H_5	C_3H_7	50	148–149°	54·7	7·2	14·3	54·5	7·1	14·1
C_3H_7	C_3H_7	35	147–150°	57·0	7·9	13·3	56·6	7·6	13·2
C_3H_7	C_4H_9	28	118–119°	58·6	7·8	12·4	58·4	8·0	12·4
C_4H_9	C_4H_9	25	126°	59·9	8·4	12·2	60·0	8·3	11·7

All recrystallisations were carried out from 50 per cent aqueous ethanol.
[a]Yale[22], gives m.p. 152° from toluene. Recrystallisation of our sample from toluene gave m.p. 157°.
[b]Yale[22], gives m.p. 112–114° from toluene. Recrystallisation of our sample from toluene gave m.p. 130°.

TABLE IV

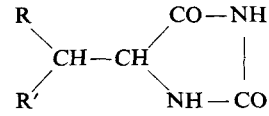
5-ALKYLIDENEHYDANTOINS



R	R′	Yield per cent	M.p.	Analysis					
				Found			Required		
				C	H	N	C	H	N
CH_3	C_3H_7	84	170°	57·0	7·5	16·7	57·2	7·1	16·7
CH_3	C_4H_9	100	150°	59·0	7·8	15·6	59·3	7·7	15·4
C_2H_5	C_3H_7	78	155°	59·2	7·9	15·2	59·3	7·7	15·4
C_3H_7	C_3H_7	85	158°	61·6	8·2	14·5	61·2	8·2	14·3
C_3H_7	C_4H_9	94	134°	63·4	8·8	13·1	62·9	8·6	13·3
C_4H_9	C_4H_9	88	155°	64·5	8·7	12·5	64·3	8·9	12·5

TABLE V

5-ALKYLHYDANTOINS



R	R′	Yield per cent	M.p.	Method of preparation	Analysis					
					Found			Requierd		
					C	H	N	C	H	N
CH_3	C_3H_7	90	119–120°	*b*	56·3	8·0	16·8	56·5	8·2	16·5
CH_3	C_4H_9	97	98–100°	*b*	59·1	8·5	15·3	58·7	8·7	15·2
C_2H_5	C_3H_7	94	170°	*b*	59·0	8·5	15·1	58·7	8·7	15·2
C_2H_5	C_4H_9	65	125–126°	*a*	61·1	9·4	14·0	60·6	9·1	14·2
C_3H_7	C_3H_7	94	160°	*b*	60·5	8·8	14·5	60·6	9·1	14·2
C_3H_7	C_4H_9	94	134°	*b*	62·3	9·5	13·3	62·3	9·4	13·2
C_4H_9	C_4H_9	75	99°	*b*	64·4	9·6	12·4	63·8	9·7	12·4

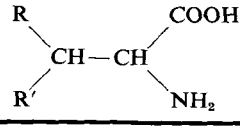
Method of Preparation. *a* from the aldehyde via the cyanhydrin.
b from the reduction of the 5-alkylidene.

Method A

5-(3-*Heptyl*)*hydantoin.* 2-Ethylhexanal (11·5 g.) was shaken with a solution of sodium metabisulphite (11 g.) in water (30 ml.). The resulting bisulphite compound was filtered off, sucked dry, and then treated with sodium cyanide (5 g.) in water (15 ml.) in three portions, cooling after each addition. The 3-butyl-3-ethyl-2-hydroxyacetonitrile which separated as an oil was removed and the aqueous residue extracted with benzene (20 ml.). The organic liquors were combined and extracted with 10 per cent aqueous sodium metabisulphite (25 ml.), and the benzene removed

TABLE VI

ββ DIALKYL-α-AMINOPROPIONIC ACIDS



Code No.	R	R′	Yield per cent	M.p.*	Analysis					
					Found			Required		
					C	H	N	C	H	N
BM 27	CH_3	C_3H_7	76	230–233°	57·5	10·5	10·1	57·9	10·5	9·7**
BM 31	CH_3	C_4H_9	91	235–239°	60·1	10·5	8·9	60·4	10·7	8·8
BM 38	C_2H_5	C_3H_7	76	248–249°	59·7	10·6	8·8	60·4	10·7	8·8***
BM 21	C_2H_5	C_4H_9	85	238–240°	62·8	10·7	7·9	62·4	11·0	8·1
BM 39	C_3H_7	C_3H_7	73	248–252°	61·9	10·8	8·1	62·4	11·0	8·1
BM 43	C_3H_7	C_4H_9	64	236–238°	64·2	11·5	7·6	64·2	11·3	7·5
BM 47	C_4H_9	C_4H_9	82	240–243°	65·1	11·4	6·7	65·7	11·4	6·9

* Melting points all occurred with decomposition
** Reported by Gagnon and others[89]
*** Reported by Gol'dfarb and others[80]

over a water bath. To the residual oil ammonium carbonate (40 g.) in 50 per cent aqueous ethanol (300 ml.) was added and the mixture heated at 55° for 3 hours, followed by heating to reflux for 5 minutes. The solvent was removed under reduced pressure, leaving a white solid which crystallised from 50 per cent aqueous ethanol to yield 5-(3-*heptyl*)-*hydantoin* (11·6 g., 65 per cent), m.p. 125–126°.

Method B

Hexan-2-ol. To magnesium (26 g.), in ether (300 ml.), was added butyl bromide (5 g.), and the mixture vigorously stirred until the formation of the Grignard complex commenced. The remainder of the butyl bromide (132 g.) was then added over 1½ hours and the mixture gently refluxed for 30 minutes. Acetaldehyde (44 g.) was added at a rate which just maintained reflux, and then the mixture was refluxed for 3 hours. The complex was decomposed by iced dilute hydrochloric acid, the ether layer separated and the aqueous residue extracted with ether (50 ml.). The ethereal liquors were combined and washed with 50-ml. portions of water, 10 per cent aqueous sodium carbonate and water. After drying over anhydrous sodium sulphate the ether was removed, and the residue fractionally distilled to yield hexan-2-ol (78 g., 72 per cent), b.p. 139°.

Butyl methyl ketone. Hexan-2-ol (76 g.) was added slowly to a mixture of sodium dichromate (180 g.) in concentrated sulphuric acid (150 g.)

and water (900 ml.), with vigorous stirring. After cooling, the upper layer was separated and the aqueous layer extracted twice with ether (50 ml.). The ethereal liquors were combined, dried over anhydrous sodium sulphate, the ether removed and the residue distilled to yield butyl methyl ketone (53·5 g., 71 per cent., b.p. 124–125°.

5-(2-*Hexylidene*)-2-*thiohydantoin.* 2-Thiohydantoin (10 g.), in a mixture of pyridine (30 ml.), and piperidine, (30 ml.) was refluxed with butyl methyl ketone (20 g.) for 1 hour. After standing overnight, the solvents and excess ketone were removed under reduced pressure, the residue dissolved in water (50 ml.), cooled in ice, and acidified with concentrated hydrochloric acid. The oil which separated solidified after standing overnight at 0°, and the resultant solid was filtered off and recrystallised from 50 per cent aqueous ethanol-charcoal to yield 5-(2-hexylidene)-2-thiohydantoin (12·2 g., 72 per cent), m.p. 130°.

5-(2-*Hexylidene*)*hydantoin.* 5-(2-Hexylidene)-2-thiohydantoin (10 g.) was refluxed with 50 per cent aqueous chloracetic acid (50 ml.) for 1 hour. After cooling, the white crystals were filtered off, and recrystallised from 50 per cent aqueous ethanol to yield 5-(2-*hexylidene*)*hydantoin* (10 g., 99 per cent), m.p. 150°.

5-(2-*Hexyl*)*hydantoin.* 5-(2-Hexylidene)hydantoin (8 g.) was hydrogenated in the presence of Raney nickel (8 g.) in ethanol (50 ml.) at atmospheric pressure and room temperature until the theoretical amount of hydrogen had been taken up (about 12 hours). The catalyst was filtered off, the solvent removed, and the resulting solid recrystallised from 50 per cent aqueous ethanol to yield 5-(2-*hexyl*)*hydantoin* (7·8 g., 97 per cent), m.p. 98°–100°.

α-*Amino*-β-*butyl*-β-*methylpropionic acid* (2-*amino*-3-*methylheptanoic acid*). 5-(2-Hexyl)hydantoin (5 g.) was autoclaved at 160° for 30 minutes with barium hydroxide octahydrate (12 g.) suspended in water (70 ml.). After filtration, carbon dioxide was passed into the mixture until precipitation of barium carbonate was complete. The solution was filtered, evaporated to dryness under reduced pressure, and the residue recrystallised from 50 per cent aqueous ethanol to yield α-*amino*-β-*butyl*-β-*methylpropionic acid* (3·4 g., 78 per cent., m.p. 243–248° with decomposition.

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