45. *The Action of Phosphorus Pentasulphide on Barbituric Acids.*

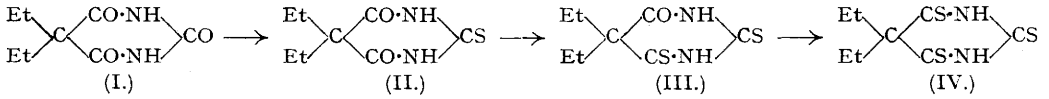
By H. C. Carrington.

When barbituric acids containing two hydrocarbon residues in the 5-position react with phosphorus pentasulphide, one, two or three of the oxygen atoms of the barbituric acid ring may be replaced by sulphur according to the conditions of the reaction and the nature of the substituents.

Thiobarbituric acids are generally prepared by condensation of substituted malonic esters with thiourea, leading to 5-substituted 2-thiobarbituric acids. Until recently, no substituted barbituric acids were known in which more than one of the oxygen atoms were replaced by sulphur, although the preparation of 2 : 4 : 6-trithiobarbituric acid by the action of potassium hydrosulphide on 2 : 4 : 6-trichloropyrimidine had been described (Büttner, *Ber.*, 1903, **36**, 2234). The conversion of amides into thioamides by heating with phosphorus pentasulphide is well known, and Kindler (*Annalen*, 1923, **431**, 187) has described an improved technique for this reaction. A study of the direct sulphurisation of substituted barbituric acids by the action of phosphorus pentasulphide has now been made. While the results of this work were being prepared for publication, an account appeared (Henze and Smith, *J. Amer. Chem. Soc.*, 1943, **65**, 1090) of the conversion of two substituted barbituric acids into the corresponding trithio-compounds by heating under reflux with phosphorus trisulphide in tetralin solution. This method is closely related to that here described, and the two products, 5-phenyl-5-ethyl-2 : 4 : 6-trithiobarbituric acid and 5 : 5-diethyl-2 : 4 : 6-trithiobarbituric acid, are among the compounds described in the present communication.

A series of barbituric acids, mostly well known hypnotics, carrying hydrocarbon substituents in the 5-position, has been used, and according to the nature of the substituents and the conditions of the reaction, one, two or three oxygen atoms may be replaced by sulphur. Simple fusion of the barbituric acid with phosphorus pentasulphide may lead to the formation of thiobarbituric acids, but the yields are extremely low, and the conditions used by Kindler in the preparation of thioamides give much better results. He carried out the reaction in the presence of an alkali polysulphide, and in an indifferent liquid medium. In the case of the barbituric acids this medium may be varied considerably; hydrocarbons and chlorohydrocarbons of different types, and also ethers, have been used.

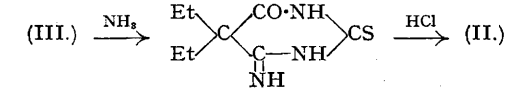
The sulphurisation of 5 : 5-diethylbarbituric acid (I) has been studied in some detail. In boiling toluene the product is a mixture of a 5 : 5-diethyldithiobarbituric acid and 5 : 5-diethyl-2-thiobarbituric acid (II), identical with that synthesised from ethyl diethylmalonate and thiourea. In boiling xylene a mixture of the same 5 : 5-diethyldithiobarbituric acid with 5 : 5-*diethyl*-2 : 4 : 6-*trithiobarbituric acid* (IV) is obtained. This suggests that the sulphurisation proceeds by stages, the " urea " oxygen atom being replaced first :



(I.) (II.) (III.) (IV.)

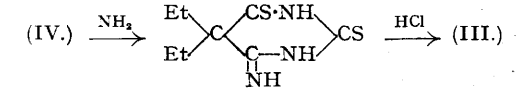
The formulation of the dithio-compound as 5 : 5-*diethyl*-2 : 4-*dithiobarbituric acid* (III) is supported by the following evidence. 5 : 5-Diethyl-2 : 4-dithiobarbituric acid can be converted into 5 : 5-diethyl-2-thiobarbituric

acid by reaction with ammonia to give 4-imino-5 : 5-diethyl-2-thiobarbituric acid, followed by hydrolysis with dilute acid :



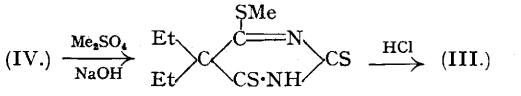
Furthermore, the sulphurisation of 5 : 5-diethyl-2-thiobarbituric acid synthesised from ethyl diethylmalonate and thiourea gives a mixture of the same 5 : 5-diethyl-2 : 4-dithiobarbituric acid and 5 : 5-diethyl-2 : 4 : 6-trithiobarbituric acid as that obtained from 5 : 5-diethylbarbituric acid itself.

5 : 5-Diethyl-2 : 4 : 6-trithiobarbituric acid with aqueous ammonia affords *6-imino-5 : 5-diethyl-2 : 4-dithiobarbituric acid,* which is readily converted by acid hydrolysis into 5 : 5-diethyl-2 : 4-dithiobarbituric acid :



The insolubility of the imino-compound in aqueous ammonia may account for the fact that only one of the two thioamide sulphur atoms in the trithio-compound is replaced by an imino-group.

Treatment of 5 : 5-diethyl-2 : 4 : 6-trithiobarbituric acid in aqueous sodium hydroxide with methyl sulphate affords the *6-methylthio*-derivative, which is readily hydrolysed by dilute acid to 5 : 5-diethyl-2 : 4-dithiobarbituric acid :



Barbituric acids with two primary alkyl groups in the 5-position sulphurise readily, and both di- and tri-thio-compounds can usually be obtained. The same holds true with a phenyl group in the 5-position. If, however, one of the substituents is a secondary alkyl group, the barbituric acid is more resistant to sulphurisation, and under the usual reaction conditions only monothio-compounds are generally formed. As would be expected, these are the 2-thio-compounds.

Experimental.

Preparation of the Substituted Barbituric Acids.—All the acids used have been previously described. Many of them are well-known hypnotics and are readily available. The others were synthesised from the corresponding substituted malonic or cyanoacetic esters by methods described in the literature.

Sulphurisation of 5 : 5-Diethylbarbituric Acid.—(a) *Action of phosphorus pentasulphide and liver of sulphur in boiling xylene.* A mixture of 5 : 5-diethylbarbituric acid (20 g.), phosphorus pentasulphide (20 g.), and liver of sulphur (30 g.) was stirred with xylene (350 c.c.) and refluxed for 16 hours. The hot liquid was filtered and, after cooling, the orange crystalline precipitate was separated. Fractional crystallisation from methyl alcohol or benzene gave 5 : 5-*diethyl*-2 : 4-*dithiobarbituric acid* (5 g.), bright yellow plates, m. p. 205—206°, readily soluble in methyl alcohol, sparingly soluble in benzene (Found : C, 44·7; H, 5·9; N, 12·9; S, 29·7. $C_8H_{12}ON_2S_2$ requires C, 44·5; H, 5·6; N, 13·0; S, 29·6%), and 5 : 5-*diethyl*-2 : 4 : 6-*trithiobarbituric acid* (10 g.), deep orange-red needles, m. p. 192—193°, sparingly soluble in methyl alcohol, fairly readily soluble in benzene (Found : C, 41·75; H, 5·25; N, 12·15; S, 40·9. $C_8H_{12}N_2S_3$ requires C, 41·4; H, 5·2; N, 12·1; S, 41·4%). Both compounds darken with rise of temperature, and revert to their original light colour on cooling, without apparent change in crystalline state. They are very sparingly soluble in water, readily soluble in alkali, and reprecipitated by acid.

(b) *Variation in the conditions of sulphurisation.* In boiling benzene no reaction took place. In boiling toluene a mixture was obtained of 5 : 5-diethyl-2-thiobarbituric acid (m. p. 173°, identical with material synthesised from ethyl diethylmalonate and thiourea) and the 5 : 5-diethyl-2 : 4-dithiobarbituric acid described above. When 5 : 5-diethylbarbituric acid was fused with phosphorus pentasulphide at 200°, there was a small yield of a crystalline sublimate which was a mixture of the di- and the tri-thio-compound, but no identifiable compound could be isolated from the main mass of the melt.

Sulphurisation of 5 : 5-Diethyl-2-thiobarbituric Acid.—5 : 5-Diethyl-2-thiobarbituric acid (5 g.) was stirred and refluxed for 16 hours with phosphorus pentasulphide (5 g.), liver of sulphur (8 g.), and xylene (70 c.c.). After filtration and cooling, the product which crystallised was a mixture of 5 : 5-diethyl-2 : 4-dithiobarbituric acid (m. p. 205—206°) and 5 : 5-diethyl-2 : 4 : 6-trithiobarbituric acid (m. p. 192—193°).

6-Imino-5 : 5-diethyl-2 : 4-dithiobarbituric Acid.—A solution of 5 : 5-diethyl-2 : 4 : 6-trithiobarbituric acid (4 g.) in aqueous ammonia (*d* 0·88, 40 c.c.) was warmed on the steam-bath for ½ hour; hydrogen sulphide was evolved and a bright yellow solid separated. After cooling, this was collected and recrystallised from methyl alcohol. It decomposed at about 230° (2·3 g.) (Found : N, 19·4; S, 29·5. $C_8H_{13}N_3S_2$ requires N, 19·55; S, 29·8%). The *imino*-compound was hydrolysed quantitatively to 5 : 5-diethyl-2 : 4-dithiobarbituric acid by warming for 20 minutes with 4% hydrochloric acid.

6-Methylthio-5 : 5-diethyl-2 : 4-dithiobarbituric Acid.—To a solution of 5 : 5-diethyl-2 : 4 : 6-trithiobarbituric acid (10 g.) in 4% aqueous sodium hydroxide (200 c.c.), methyl sulphate (6 g.) was added during 15 minutes. The mixture was stirred at 20° for 2 hours. A small quantity of dark insoluble matter was separated, and hydrochloric acid (36%) added with cooling until the mixture was just acid to Congo-red. A dark red oil separated, which rapidly solidified. After being stirred with 5% aqueous sodium carbonate at 45° to remove unchanged 5 : 5-diethyl-2 : 4 : 6-trithiobarbituric acid, the product was recrystallised from aqueous methyl alcohol, forming a dark red solid (3·5 g.), m. p. 130° (Found : N, 11·9; S, 39·2. $C_9H_{14}N_2S_3$ requires N, 11·4; S, 39·0%). The S-*methyl* derivative was hydrolysed to 5 : 5-diethyl-2 : 4-dithiobarbituric acid by heating on the steam-bath for ½ hour with 8% hydrochloric acid, methylthiol being evolved.

4-Imino-5 : 5-diethylthiobarbituric Acid.—A solution of 5 : 5-diethyl-2 : 4-dithiobarbituric acid (2 g.) in aqueous ammonia (*d* 0·88, 20 c.c.) was warmed on the steam-bath for ½ hour; hydrogen sulphide was evolved and a yellow solid separated After cooling, this was collected and recrystallised from methyl alcohol. It decomposed at about 220° (1·25 g.). This imino-compound was hydrolysed quantitatively to 5 : 5-diethyl-2-thiobarbituric acid (m. p. 173°) by warming for 20 minutes on the steam-bath with 4% hydrochloric acid.

Sulphurisation of Various Barbituric Acids.—A standard procedure was adopted based on that described for 5 : 5-diethylbarbituric acid. The reaction was carried out with phosphorus pentasulphide and liver of sulphur in boiling xylene, with a reaction time of 16 hours. Where mixtures of products were obtained, the separation was carried out by fractional crystallation from methyl alcohol or aqueous methyl alcohol. The results are summarised in the table. The yields recorded are only approximate, being largely dependent upon the ease of purification. In some cases, which are indicated, the higher sulphurisation products were only obtained in appreciable quantities after retreatment of the products of lower sulphur content with the sulphurising agents.

Attempts to sulphurise barbituric acids with unsaturated substituents in the 5-position were generally unsuccessful. Thus neither 5 : 5-diallylbarbituric acid nor 5-Δ²-*cyclo*hexenyl-5-ethylbarbituric acid gave identifiable products when treated in the standard way.

Barbituric acid substituents.	Thio-derivative formed.	Formula.	M. p.	Yield, %.	Analysis (%). Found. N.	Found. S.	Required. N.	Required. S.
5 : 5-Diethyl	Di	$C_8H_{12}ON_2S_2$	205—206°	20	12·9	29·7	13·0	29·6
,,	Tri	$C_8H_{12}N_2S_3$	192—193	30	12·15	40·9	12·1	41·4
5-Ethyl-5-*n*-propyl	Di	$C_9H_{14}ON_2S_2$	180	15	12·15	27·7	12·2	27·8
,,	Tri(*a*)	$C_9H_{14}N_2S_3$	177	10	11·3	38·8	11·4	39·0
5-Ethyl-5-*iso*propyl	Mono	$C_9H_{14}O_2N_2S$	189 (192)	50	13·3	15·3	13·1	15·0
,,	Di(*b*)	$C_9H_{14}ON_2S_2$	173	20	—	26·9	—	27·8
5 : 5-Di-*n*-propyl	Di	$C_{10}H_{16}ON_2S_2$	189	30	11·4	26·2	11·5	26·3
,,	Tri(*a*)	$C_{10}H_{16}N_2S_3$	205—206	20	10·7	37·2	10·75	36·9
5-Ethyl-5-*n*-butyl	Di	$C_{10}H_{16}ON_2S_2$	127	20	11·0	25·6	11·5	26·3
5-Ethyl-5-*iso*butyl	Di	$C_{10}H_{16}ON_2S_2$	190	25	11·55	25·4	11·5	26·3
,,	Tri(*a*)	$C_{10}H_{16}N_2S_3$	143	5	—	36·6	—	36·9
5-Ethyl-5-α-methylbutyl	Mono	$C_{11}H_{18}O_2N_2S$	156 (157)	30	—	13·5	—	13·8
5-Ethyl-5-β-methylbutyl	Di	$C_{11}H_{18}ON_2S_2$	158	40	10·75	24·4	10·85	24·8
5 : 5-Di-*n*-butyl	Di	$C_{12}H_{20}ON_2S_2$	125	10	10·7	22·5	10·3	23·5
,,	Tri(*a*)	$C_{12}H_{20}N_2S_3$	164	5	9·6	33·6	9·7	33·3
5-Ethyl-5-*cyclo*hexyl	Mono	$C_{12}H_{18}O_2N_2S$	203 (205)	40	12·9	10·65	12·6	11·0
5-Phenyl-5-ethyl	Di	$C_{12}H_{12}ON_2S_2$	246	10	10·8	24·8	10·6	24·3
,,	Tri	$C_{12}H_{12}N_2S_3$	162—164	20	9·9	34·3	10·0	34·3
5-Benzyl-5-ethyl	Mono	$C_{13}H_{14}O_2N_2S$	180	30	10·3	12·4	10·7	12·2
,,	Di	$C_{13}H_{14}ON_2S_2$	160	15	9·9	22·9	10·05	23·0

(*a*) Obtained by resulphurising the residues from the purification of the dithio-derivative.
(*b*) Obtained by resulphurising the residues from the purification of the monothio-derivative.

The figures in parentheses in the melting-point column are the melting points given in the literature for the monothio-compounds where these are known.

The author wishes to thank I.C.I. (Dyestuffs), Ltd., for permission to publish this paper.

Research Laboratories, I.C.I. (Dyestuffs), Ltd., Blackley, Manchester. [*Received, October 19th*, 1943.]