LXII. THE SYNTHESIS OF AMINO-ACIDS.

I. PIPERIDINE AND DIETHYLAMINE AS CATALYSTS IN THE CONDENSATION OF AROMATIC ALDEHYDES WITH HYDANTOINS.

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AN important method of synthesising aromatic α -amino-acids is that of Wheeler and Hoffman [1911] which involves in its first stage the condensation of the appropriate aldehyde with hydantoin, the reaction being carried out in hot glacial acetic acid containing anhydrous sodium acetate. The yield of the condensation product so obtained varies considerably according to the aldehyde used. For example benzalhydantoin may be prepared in a yield of 80 % of the theoretical whilst indolalhydantoin is only obtainable in a yield of 47 %. Majima and Kotake [1922], who first prepared the latter compound from indole-3-aldehyde and hydantoin, found that it was necessary to substitute acetic anhydride for acetic acid in the condensation. Besides indolalhydantoin they also obtained unspecified amounts of acetylated indolalhydantoin, unchanged indole-3-aldehyde and another unidentified substance. From a study of the same reaction in this laboratory it appears, however, that the low yield obtained is due not so much to incomplete reaction or to acetylation as to the formation of tarry products of complex character.

Whatever be the cause, such a loss of material becomes a matter of no small importance when the parent aldehyde, *e.g.* indole-3-aldehyde, is not easy of access. Since moreover a scheme of study in this laboratory involved the condensation of such aldehydes with hydantoin, it was decided, as a first measure, to investigate the possibility of carrying out the reaction in solvents other than glacial acetic acid and with catalysts other than anhydrous sodium acetate.

The reaction under study falls into the class of condensations between an aldehydic and a reactive methylene group with elimination of a molecule of water. From a consideration of the reaction in its various aspects there seemed to be no apparent reason why the organic bases, diethylamine, aniline, piperidine, nicotine *etc.*, used with such success by Knoevenagel [1894] for effecting similar condensations, should not be equally applicable in this case.

That these bases can be so used has now been proved experimentally. It soon became clear however that in specific cases individual catalysts are more effective than others. For example, in attempting the condensation of benzaldehyde, *p*-hydroxybenzaldehyde or *p*-methoxybenzaldehyde with hydantoin by means of piperidine, using pyridine as solvent, poor yields accompanied by much tar were obtained. On substituting 3-acetyl-2-thiohydantoin for ordinary hydantoin, there resulted practically quantitative yields of condensation products of a high degree of purity. Replacement of piperidine by diethylamine as the catalyst employed gave good yields in the case of ordinary hydantoin, and it is notable that the recrystallised product was not straw-coloured, as when

made by the Wheeler-Hoffman technique, but colourless. A series of experiments on the above lines with 1-phenylhydantoin gave results analogous to those obtained with ordinary hydantoin; owing to its high cost however 1-phenylhydantoin is of little importance in schemes of synthesis of α -amino-acids. The substitution of absolute alcohol for pyridine as the solvent, in conjunction with diethylamine as catalyst, gave only a 25 % yield of benzalhydantoin after heating for 24 hours; it is probable that a longer period of heating would improve the yield.

The results described in the experimental section may be briefly summarised thus:

Reactants	% yield of condensation product	
	Piperidine	Diethylamine
Benzaldehyde and hydantoin	33	76
„ acetylthiohydantoin	92.5	
Anisaldehyde and hydantoin	14	94
„ acetylthiohydantoin	95	
<i>p</i> -Hydroxybenzaldehyde and hydantoin	25	65
„ acetylthiohydantoin	95-100	

It will be clear that the work herein described is capable of extension in several directions. For example, whilst it will be noted that the condensations described have all been carried out at 100°, nevertheless evidence is not lacking that they may proceed at a very much lower temperature. Moreover, of the bases originally employed by Knoevenagel only diethylamine and piperidine have been used up to the present, and it is proposed to extend the study to include others of those mentioned above. Finally, reference may be made to one other important phase of this problem. Whilst the Wheeler-Hoffman process has been of considerable value in the synthesis of aromatic α -amino-acids the applicability of the method to the synthesis of aliphatic α -amino-acids has never been demonstrated. The introduction of new solvents and catalysts for promoting the reaction between aldehydes and hydantoin suggests new lines of attacking the problem of synthesising aliphatic α -amino-acids by way of the hydantoins. This aspect of the investigation is receiving attention.

EXPERIMENTAL.

Experiments involving piperidine as catalyst.

4-Benzalhydantoin. Pure benzaldehyde (2.2 g.), hydantoin (2.0 g.) and piperidine (2 ml.) were boiled together for 1 hour. The product was treated with 100 ml. of hot water and filtered, whereby some tarry material was removed. The filtrate was neutralised with dilute hydrochloric acid, whereupon benzalhydantoin separated in characteristic rhombic plates. It was recrystallised from dilute alcohol and had M.P. 220°; N 14.72 %. Wheeler and Hoffman [1911] give the same melting-point. $C_{10}H_8O_2N_2$ requires 14.90 % N. The yield was 1.6 g. or 33 % of the theoretical value.

Benzalthiohydantoin. The acetylthiohydantoin required in this experiment was prepared from glycine and ammonium thiocyanate as described by Johnson and Nicolet [1911]. Benzaldehyde (2.5 g.) and acetylthiohydantoin (3 g.) were dissolved in pyridine (5 ml.). On adding piperidine (3 ml.), the mixture became warm and deep yellow in colour. It was boiled for 2 minutes and then water (100 ml.) was added. The resulting aqueous solution was acidified by the addition

of acetic acid and warmed until the oily mass which separated had given place to a yellow crystalline deposit. The mixture was cooled and kept overnight. The yellow crystals which had then separated were collected, washed with cold water and recrystallised from dilute alcohol. They weighed only 2.4 g., but further crops were obtained after the mother-liquor had stood for some days. The total yield was 3.65 g. or about 92.5 % of the theoretical figure; m.p. 258° (Johnson and Nicolet give 258°). Found N 13.59 %. $C_{10}H_8ON_2S$ requires N 13.73 %.

Benzalhydantoin from the above benzalthiohydantoin. A portion of the benzalthiohydantoin (1.3 g.), synthesised according to the procedure detailed above, was boiled with 50 % chloroacetic acid (20 ml.) for 3 hours. The resulting clear solution was evaporated to small volume *in vacuo* and the residue diluted with water. A slightly yellow crystalline substance separated and after some time was filtered off and washed with cold water. Without recrystallisation, it weighed 0.92 g., melted at 220° and contained 14.8 % N. The yield, referred back to the original acetylhydantoin, was 77 % of the theoretical.

p-Methoxybenzalhydantoin. This experiment was carried out as described for benzalhydantoin. From 2.64 g. of anisaldehyde, 0.45 g. (14 %) of *p*-methoxybenzalhydantoin was obtained together with much tar. After recrystallisation from dilute alcohol the m.p. was 243° (Wheeler and Hoffman quote 243–244°). Found N 12.79 %. $C_{11}H_{10}O_3N_2$ requires N 12.85 %.

p-Methoxybenzalthiohydantoin. *p*-Methoxybenzalthiohydantoin was prepared from anisaldehyde (2.5 g.) and acetylthiohydantoin (3 g.) as described for benzalthiohydantoin. The yield of uncrystallised product was 4.33 g. or 95 % of the theoretical calculated on the acetylthiohydantoin taken. After crystallisation from alcohol, the product melted at 256° (Johnson and O'Brien [1912] give 257°). Found N 12.14 %. $C_{11}H_{10}O_2N_2S$ requires N 11.97 %.

p-Methoxybenzalhydantoin from the above p-methoxybenzalthiohydantoin. *p*-Methoxybenzalthiohydantoin (5 g.), obtained as in the preceding experiment but without recrystallisation, was boiled with a mixture of 50 % chloroacetic acid (50 ml.) and acetic acid (150 ml.) for 4 hours. The substance was very insoluble and only went into solution gradually. The resulting solution was evaporated to small volume *in vacuo* and the residual fluid was diluted with water. A yellow crystalline substance separated from the cold solution and was, after some time, collected and washed with cold water. The yield was 94 %. It melted at 247° before recrystallisation, and contained 12.79 % N. Referred back to the acetylthiohydantoin used for the preparation of the *p*-methoxybenzalthiohydantoin, the yield was equivalent to 85–90 %.

p-Hydroxybenzalhydantoin. This substance was prepared in the same manner as benzalhydantoin. From 2.4 g. of *p*-hydroxybenzaldehyde, 0.75 g. (25 %) of the desired product was obtained. The product separated from alcohol in needles which melted at 315°. Found N 13.62 %. $C_{10}H_8O_3N_2$ requires N 13.72 %.

p-Hydroxybenzalthiohydantoin. The compound was prepared from *p*-hydroxybenzaldehyde (2.5 g.) and acetylthiohydantoin (3 g.) as described for benzalthiohydantoin. The yield of recrystallised product was 4.2 g. which is practically theoretical. The purified product melted at 305° and contained 12.82 % N. $C_{10}H_8O_3N_2S$ requires N 12.73 %.

p-Hydroxybenzalhydantoin from p-hydroxybenzalthiohydantoin. *p*-Hydroxybenzalthiohydantoin (4.0 g.), obtained in the preceding experiment but not recrystallised, was boiled with 50 % chloroacetic acid (50 ml.) for 3 hours. The solution was evaporated to small bulk *in vacuo* and the residual liquor diluted with water. A yellow crystalline substance separated; this was collected after some time and washed with cold water. After crystallisation from alcohol it

weighed 2.9 g., melted at 314° and contained 13.84 % N. The yield of the desulphurised hydantoin was thus 85 % of the theoretical calculated on the weight of the acetylthiohydantoin used.

Experiments involving diethylamine as catalyst.

Benzalhydantoin. Benzaldehyde (5.5 g.), hydantoin (4.5 g.), pyridine (5 ml.) and diethylamine (6 drops) were heated together at 100° for 22 hours in a closed bottle. On cooling the mixture became solid. The contents of the bottle were dissolved in alcohol and evaporated to dryness. The product so obtained was crystallised from alcohol and it then melted at 220° and contained 14.95 % N. The yield of recrystallised material was 6.4 g. or 76 % of theory.

Another experiment, carried out under the same conditions but with the addition of 0.5 ml. of water, gave only 4.0 g. of product.

A third experiment carried out under the same conditions as the first, the temperature being raised to 120°, yielded a slightly sticky product which gave 70 % of the theoretical amount of recrystallised material.

p-Methoxybenzalhydantoin. Anisaldehyde (6.0 g.), hydantoin (4.5 g.), pyridine (5 ml.) and diethylamine (3 ml.) were heated together at 100° for 22 hours in a closed bottle. The product was worked up as in the preparation of benzalhydantoin by means of diethylamine. The *p*-methoxybenzalhydantoin was not recrystallised but was washed with a little cold benzene and dried. It then melted at 240–244° and contained 12.82 % N. The yield was 94 % of the theoretical calculated on the hydantoin used.

p-Hydroxybenzalhydantoin. A mixture of *p*-hydroxybenzaldehyde (6.0 g.), hydantoin (4.5 g.), pyridine (5 ml.) and diethylamine (3 ml.) was heated in a closed bottle at 100° for 22 hours. The product was worked up as in the analogous preparation of benzalhydantoin. It was recrystallised from alcohol after being washed with cold benzene. In this way 5.1 g. of *p*-hydroxybenzalhydantoin were obtained. It melted at 312°. The yield approximated to 65 % of the theoretical.

SUMMARY.

The original method of Wheeler and Hoffman of effecting the condensation of aromatic aldehydes with hydantoins by heating a mixture of these substances in glacial acetic acid containing anhydrous sodium acetate may be modified with advantage.

Instead of the mixture of acetic acid and sodium acetate, mixtures of pyridine and piperidine or of pyridine and diethylamine or even piperidine alone in some cases can be successfully substituted.

A table summarising the results is given. From this, it will be seen that the relative efficiencies of piperidine and diethylamine as catalysts vary according to the reactants involved.

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