42. *An Investigation of Wada's Method of Converting α-Amino-acids into 2-Substituted Ethylamines.*

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The reaction (Wada, *Biochem. Z.*, 1933, **260**, 47), whereby an α-amino-acid is converted into a 2-substituted ethylamine by hydrolytic decarboxylation of the corresponding hydantoin, could not be repeated: the amino-acid was regenerated in each case. Some observations on the Rimini reaction for primary amines are recorded.

Wada (*loc. cit.*) has reported that amino-acids (I) can be decarboxylated advantageously through the hydantoins (II) formed from (I) and urea, since he found that (II) were hydrolysed by acid or alkali to the 2-substituted ethylamines (III) in good yield:

$$\underset{\text{(I.)}}{CH_2R{\cdot}CH(NH_2){\cdot}CO_2H} \longrightarrow \underset{\text{(II.)}}{CH_2R{\cdot}CH\begin{cases}CO{-}NH\\ \\ NH{\cdot}CO\end{cases}} \longrightarrow \underset{\text{(III.)}}{CH_2R{\cdot}CH_2{\cdot}NH_2} + 2CO_2 + NH_3$$

Wada described the preparation of a large number of amines by this procedure: these were usually identified as picrates, and the formation of the amine was often deduced from the Rimini reaction.

We were rather surprised at the ease with which this conversion was stated to occur, since hydantoins have been used as intermediates for the preparation of α-amino-acids (cf. Harries and Weiss, *Ber.*, 1900, **33**, 3419, for glycine; Wheeler and Hoffman, *Amer. Chem. J.*, 1911, **45**, 368, for tyrosine). We have investigated this hydrolytic decarboxylation reaction, starting with representative amino-acids of the type *p*-R·SO_2·C_6H_4·CH_2·$CH(NH_2)$·CO_2H (R = NH_2, Me, Ph, or *p*-C_6H_4Cl) (Burton and Hu, preceding paper), and, as expected, found that hydrolysis of two of the corresponding *hydantoins* gave the original amino-acids.

In one experiment, 4-*p*-methylsulphonylbenzylhydantoin was refluxed with concentrated barium hydroxide solution for 16 hours, care being taken to prevent any absorption of carbon dioxide from the atmosphere. The barium carbonate formed during the hydrolysis was removed and the residual barium ion determined as sulphate. It was found that approximately 1 mol. of carbon dioxide was liberated during the hydrolysis. Actually, the hydantoins often showed a considerable resistance to cleavage by boiling dilute acid or alkali: they were hydrolysed, however, by the concentrated reagents.

We have repeated two of Wada's experiments, using glycine and tyrosine, and, as expected, the original amino-acids were again recovered. Wada claimed to have separated methylamine as the picrate from the resulting solution after hydantoin had been hydrolysed by boiling concentrated hydrochloric acid for a long time. No mention was made about the separation of ammonium chloride from the solution on cooling; we found that 4 g. (≡ 0·075 mol.) of ammonium chloride were thus obtained when 5 g. each of glycine (0·066 mol.) and urea (0·08 mol.) were originally used.

Mention should be made of the Rimini reaction which was also used by Wada to detect the presence—presumably after basification—of the primary amines in the reaction mixtures.

We have investigated this colour test with all the substances, except hydantoin, which could be present in the hydrolysis product from glycine, under the following conditions:

Aqueous solution ...	NH_4Cl	NH_3MeCl	Glycine	$NaHCO_3$	NH_3	NH_4Cl with $NaHCO_3$	NH_3MeCl with $NaHCO_3$	Glycine with $NaHCO_3$
Rimini test	−	−	−	−	+	+	+	+

We think that further comment is unnecessary.

Experimental.

4-p-*Sulphamylbenzylhydantoin.*—*p*-Sulphamylphenylalanine hydrochloride (2 g.) in water (20 c.c.) was made faintly alkaline with dilute sodium hydroxide, urea (1 g.) added, and the solution refluxed for 3 hours. The cooled solution was acidified with dilute hydrochloric acid and evaporated on the steam-bath. The crystalline *hydantoin* was collected, washed with a little cold water, and air dried; yield 1·4 g. (68%), m. p. 206—207° (decomp.) (Found: C, 41·6; H, 4·5; N, 14·3. $C_{10}H_{11}O_4N_3S,H_2O$ requires C, 41·8; H, 4·5; N, 14·6%).

4-p-*Methylsulphonylbenzylhydantoin.*—A mixture of *p*-methylsulphonylphenylalanine (1 g.), barium hydroxide octahydrate (0·4 g.), and urea (0·5 g.) in water (40 c.c.) was boiled gently for 3 hours, filtered whilst still hot, and the filtrate acidified with hydrochloric acid. Evaporation gave crystals of the *hydantoin* which separated from aqueous acetic acid (1 : 1 by volume) in colourless fine prisms, m. p. 214° (decomp.) (Found: C, 49·2; H, 4·5. $C_{11}H_{12}O_4N_2S$ requires C, 49·2; H, 4·5%); yield 0·9 g. (84%).

4-p-*Phenylsulphonylbenzylhydantoin*, m. p. 226—228° (decomp.) from aqueous acetic acid (Found: C, 57·7; H, 4·5. $C_{16}H_{14}O_4N_2S$ requires C, 58·1; H, 4·3%), was similarly prepared in 74% yield from *p*-phenylsulphonylphenylalanine.

4-4′-p-*Chlorophenylsulphonylbenzylhydantoin*, m. p. 228—229° (decomp.) from acetic acid (Found: C, 50·4; H, 3·9. $C_{16}H_{13}O_4N_2ClS,H_2O$ requires C, 50·2; H, 3·9%), was similarly obtained in 83% yield. It is possible that this compound and the sulphamyl analogue are the corresponding ureido-acids since the analytical data indicate 1 molecule of water of crystallisation in each case.

Hydrolysis of 4-p-*Methylsulphonylbenzylhydantoin.*—(*a*) The hydantoin (0·8 g.; 0·003 mol.) and barium hydroxide octahydrate A.R. (2·14 g.; 0·0068 mol.) in water (20 c.c.) were refluxed for 16 hours in a ground-glass apparatus with a soda-lime guard tube. The precipitate which separated was filtered off and washed repeatedly with boiling water, and the barium ion in the filtrate determined as sulphate (Found: 0·8 g.; 0·0034 mol.) by precipitation with dilute sulphuric acid. Concentration of the acidic filtrate and subsequent neutralisation with dilute aqueous ammonia gave a solid (0·6 g.), m. p. 266°, raised to 270° (decomp.) by crystallisation from water, and unaffected by admixture with the original amino-acid.

(*b*) The hydantoin (0·5 g.) was refluxed with concentrated hydrochloric acid (10 c.c.) for 16 hours, the resulting solution evaporated to dryness, and the residue dissolved in the minimum amount of water. Neutralisation with ammonia gave the original amino-acid, m. p. and mixed m. p. 270° (decomp.).

Hydrolysis of 4-4′-p-*Chlorophenylsulphonylbenzylhydantoin.*—(*a*) The hydantoin was recovered unchanged after 18 hours' treatment with boiling 30% sulphuric acid.

(*b*) Hydrolysis of the hydantoin (0·5 g.) with boiling 2% sodium hydroxide (10 c.c.) for 40 hours or 10% sodium hydroxide (10 c.c.) for 18 hours gave, on acidification with acetic acid, the original amino-acid, m. p. and mixed m. p. 258° (decomp.) after crystallisation from alcohol.

Attempted Preparation of Methylamine from Glycine.—Following Wada's method (*loc. cit.*), glycine (5 g.), urea (5 g.), and 0·4N-barium hydroxide (25 c.c.) were refluxed for 3 hours. The solution was then acidified with sulphuric acid, filtered, and the filtrate evaporated almost to dryness. The residue was refluxed with concentrated hydrochloric acid (25 c.c.) for 16 hours. The cooled solution deposited ammonium chloride (4 g.) which was identified by (i) liberation of ammonia, etc., (ii) analysis of the ammonium chloroplatinate. The filtrate was evaporated to dryness and the residue extracted with hot absolute alcohol. The cooled alcoholic extract deposited needles of impure glycine hydrochloride, m. p. 160—170° (which could not be improved, probably because of a trace of admixed ammonium chloride), which were acidic to methyl-orange and when made alkaline with sodium hydroxide gave only a faint ammoniacal odour. Methylamine could not be detected either as the hydrochloride (m. p. 226°) or picrate.

Attempted Decarboxylation of Tyrosine.—L-Tyrosine (decomp. 325—326°) (2 g.), urea (1 g.), and barium hydroxide octahydrate (0·2 g.) in water (100 c.c.) were refluxed for 2 hours, filtered hot, and the filtrate acidified with hydrochloric acid. Evaporation then gave the hydantoin, m. p. 264°. This was recovered unchanged after 3 hours' boiling with 2% sodium hydroxide, but 16 hours' boiling with concentrated hydrochloric acid regenerated tyrosine, decomp. 325—326°.

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