# Studies on Amino-Acids and Related Compounds. XV.* The Formation of Isovaleronitrile from Leucine by Electrolysis.

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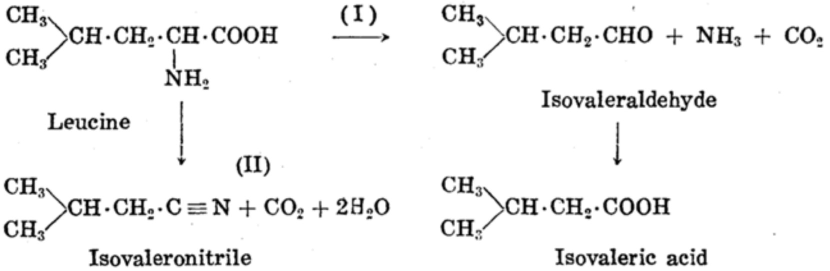
In Part XI⁽¹⁾ it was described that the electrolysis of leucine in dilute sulphuric acid at 100°, gave isovaleraldehyde as a main product and a little of isovaleric acid as well as a little of a neutral substance which had comparatively high boiling point. The present communication deals with the confirmation of the above-mentioned neutral substance as isovaleronitrile, and the conditions of its formation.

The neutral substance distilling over at 125–130° (as described in Part XI) was fractionated three times and the fraction, boiling at 128–129°, was collected. This fraction contained nitrogen on being hydrolised with sulphuric acid, and it gave isovaleric acid as well as ammonia and on being reducted with sodium and alcohol in toluene it gave isoamylamine.

From these facts the neutral substance was identified as isovaleronitrile, and the yield of the nitrile was only about 5% to isovaleralsdehyde. Attempts were made to find the conditions which gave good yields of nitrile, and it was found that on the electrolysis of leucine in dilute sulphuric acid, mainly aldehyde was formed and the yield of the nitrile was small, while it was also found that the amount of the nitrile formed greatly increased, and gave the yield of about 30% of the nitrile to leucine(2), when the acidity was kept as low as possible in the presence of sodium or ammonium sulphate.

It is known that amino-acids when oxidised by chloramine-T(3) or sodium hypobromite(4) give the corresponding nitriles. From the present experiments, it was found that also on electrolysis, leucine yielded isovaleronitrile and moreover gave good yields of nitrile under suitable conditions.

From these facts, it is quite probable that the electrolysis of leucine in dilute sulphuric acid proceeds in the following scheme (I and II).



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* Translated by the authors from *J. Chem. Soc. Japan*, **62** (1941), 252.

(1) Part XI, this Bulletin, **12** (1937). 342.

(2) Japanese patent 134719.

(3) H. D. Dakin, *Biochem. J.*, **10** (1916), 319.

(4) A. H. Friedman and S. Morgulis, *J. Am. Chem. Soc.*, **58** (1936), 909. See also Japanese patent 98556 (S. Komatsu).

In the electrolysis of leucine in dilute sulphuric acid, the aldehyde-formation (I) is the main reaction, but the electrolysis at an acidity as low as possible in the presence of sodium or ammonium sulphate is rather favourable to the nitrile-formation (II). These facts may be attributed to the amphoteric properties of the amino-acids. The formation of nitriles from other amino-acids by electrolysis will be reported in near future.

**Experimental.** It was already described in Part XI that when leucine was electrolysed in dilute sulphuric acid at 100°, yielded an oily substance. When this oil was extracted with alkali to remove isovaleric acid there remained a neutral part which consisted of mainly isovaleraldehyde and a little neutral substance boiling at 125–130°.

In the present experiments, the neutral substance (125–130°) was submitted to fractional distillation three times as shown in Table 1.

Table 1.

| Fractions | Temperature (°C) | Distillate (g.) | Index of refraction $n_D^{25}$ |
|---|---|---|---|
| 1 .... | 125–127 | 2.1 | |
| 2 .... | 127–128 | 2.9 | |
| 3 .... | 128–128.2 | 8.0 | |
| 4 .... | 128.2–129 | 10.5 | 1.3904 |
| 5 .... | 129–130 | 5.1 | 1.3906 |

The fraction 3 had a sp. gravity $d_4^{19.5} = 0.79321$.(5)

1. **Isovaleronitrile.** *Hydrolysis.*—Formation of isovaleric acid and ammonia. The fraction 4 (0.2505 g.) boiling at 128.2–129, was refluxed in 20 c.c. of sulphuric acid (1:1) for 17 hours and distilled with addition of an excess of alkali to estimate nitrogen by Kjeldahl method (Found: N, 16.58%. Calc. for isovaleronitrile $C_5H_9N$: N, 16.80%).

The volatile base in the above distillate was identified as ammonia by the analysis of chloroplatinate (Found: Pt, 43.65%. Calc. for $(NH_4)_2PtCl_6$: Pt, 43.96%.)

After the removal of the volatile base ($NH_3$) as described above, the residue was acidified with sulphuric acid and submitted to steam distillation to separate volatile acid. From the distillate silver salt was obtained as usual (Found: Ag, 51.87%. Silver isovalerate $C_5H_9O_2Ag$: Ag, 51.63%). Its anilide was also prepared, m.p. 111–112°. No lowering of melting point was observed when mixed with a pure specimen of the anilide of isovaleric acid.

*Reduction.*(6)—Formation of isoamylamine. Metallic sodium (10 g.) was melted in toluene (50 g.) on heating and a solution of the fraction 3 (6.1 g., b.p. 128–128.2) in absolute alcohol (12 g.) was added to it drop by drop with continual stirring. After 1 hour, absolute alcohol (12 g.) was added in the same way as above and then 97% alcohol (8 g.) was added to dissolve the excess of sodium. After adding water (7 g.), it was submitted to steam distillation. When concentrated hydrochloric acid (7 g.) was added to the distillate, an aqueous layer separated out. After distilling off the alcohol from the aqueous solution, the residue was evaporated up and hydrochloride (7.7 g.) was obtained. By the addition

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(5) A. E. Arbusow, *Ber.*, **43** (1910), 2298 ($d_0^{20}=0.7884$, b.p. 128.5).

(6) R. Adams and C. S. Marvel, *J. Am. Chem. Soc.*, **42** (1920), 314.

of alkali to the hydrochloride, free amine was obtained and fractionated as shown in Table 2.

Table 2.

| Fraction | Temperature (°C) | Distillate (g.) |
|---|---|---|
| 1 ..... | 42–92 | 0.2 |
| 2 ..... | 92–95 | 0.6 |
| 3 ..... | 95–97 | 2.5 |
| 4 ..... | 97 | 0.5 |
| Total .. | | 3.8 |

The fraction 3 had a sp. gravity $d_4^{21.5} = 0.7483$.(7)

*Isoamylamine-chloroplatinate and its oxalate.* — Isoamylamine-chloroplatinate was prepared as usual. It decomposed at 215°. (Found: Pt, 33.20%. Calc. for $(C_5H_{13}N)_2H_2PtCl_6$: Pt, 33.41%). When the solution of anhydrous oxalic acid (0.35 g.) in ether (25 g.) was added to the ethereal solution of the amine (0.3 g.), white precipitate separated out. The precipitate was filtered, washed twice with ether, and recrystallised from 97% alcohol into plates, m.p. 178°. (Found: N, 7.76%. Calc. for isoamylamine monooxalate $C_5H_{13}N \cdot C_2H_2O_4$: N, 7.90%).

From the facts described above, the neutal substance, boiling at 128–130°, was identified as isovaleronitrile. Its yield was about 5% to isovaleraldehyde.

**2. Electrolysis of leucine under various conditions.** To improve the yield of the nitrile, several attempts were made. For instance:

Leucine (25 g.) was dissolved in the mixture of N-$H_2SO_4$ (105 c.c., equivalent to leucine) and N-$Na_2SO_4$ (105 c.c.) and electrolysed at above 100°. The volatile oxidation products were collected in the distillate during the electrolysis as described in Part XI. The conditions of the electrolysis were as follows: Electrodes: lead peroxide anode (6.5× 18.5 cm.), lead cathode (6.5×5 cm.). C. D.: 2 amps/dm.$^2$ Electric quantity: 4.7 F/mol. The voltage between electrodes: 3.1–3.3 volts.

The distillate consisted of an oily (10.3 g.)-and an aqueous (89 c.c.)-layers. The acidity of the electrolysed solution was 0.322N and its *p*H, 1.4. The content of the nitrile in oil (calculated from its nitrogen) was 28.5%. The oil (20 g.) of the distillate obtained by the same way as described above, was dissolved in ether and the corresponding aqueous layer was extracted with ether. The combined ethereal solution was treated with N-NaOH to remove isovaleric acid and shaked with 30%-$NaHSO_3$ to remove isovaleraldehyde and then treated with 1% sodium carbonate. The ethereal solution thus obtained was dried over anhydrous sodium sulphate and submitted to fractional distillation as shown in Table 3.

The fraction 3 and 4 were combined and the nitrile was reduced to the isoamylamine by the same way as described above, and submitted to fractional distillation as shown in Table 4.

Isoamylamine oxalate was also prepared. It melted at 178°. The results of the electrolysis of leucine under various conditions are shown in Table 5.

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(7) W. E. S. Turner and E. W. Merry, *J. Chem. Soc.*, **97** (1910), 2073 ($d_4^{20}$= 0.7505).

### Table 3.

| Fraction | Temperatnre (°C) | Distillate (g.) |
|---|---|---|
| 1 ..... | 44–110 | 0.4 |
| 2 ..... | 110–126 | 1.0 |
| 3 ..... | 126–128 | 3.9 |
| 4 ..... | 128–128.3 | 0.5 |
| 5 ..... | residue | 0.7 |
| Total .. | | 6.5 |

The fraction 3 had sp. gravity $d_4^{30} = 0.7855$.(5)

### Table 4.

| Fraction | Temperature (°C) | Distillate (g.) |
|---|---|---|
| 1 ...... | 45–95.5 | 0.55 |
| 2 ...... | 95.5–97 | 2.17 |
| 3 ...... | 97 | 0.41 |
| 4 ...... | Residue | 0.40 |
| Total ... | | 3.50 |

The fraction 3 had sp. gravity $d_4^{30.5} = 0.7409$.(7)

### Table 5.

| No. of expt. | 1 | 2 | 3 | 4 | 5 | 6 |
|---|---|---|---|---|---|---|
| Electrolysate. (c.c.) | Sol. A. (200) + 2N-NaOH (15) | Sol. A. (133) + 2N-NaOH (20) | Sol. B. (220) | Sol. C. (220) | Sol. D. (210) | Sol. E. (210) |
| Leucine in the electrolysate. (g.) | 19.19 | 11.24 | 24.6 | 26·7 | 24 9 | 22.45 |
| Water added (c.c.) | 91 | 100 | 100 | 85 | 91 | — |
| C. D. (amps / dm$^2$) | 2 | 2 | 2 | 2 | 2 | 2 |
| F / mol. | 3.67 | 6.25 | 2.86 | 2.63 | 4.70 | 5.28 |
| Amp. × hours. | 2.4×6 | 2.4×6 | 2.4×6 | 2.4×6 | 2.4×10 | 2.4×10 |
| Volts. | 4.0–4.5 | 4.7–5.0 | 33–3.4 | 4.1–4.0 | 3.1–3.5 | 3.4–3.8 |
| $p$H (After electr.) | 2.4 | 3.5 | $<1.0$ | 2.0 | 1.4 | — |
| $H_2SO_4$(N) | 0.585 | 0.239 | 1.163 | 0.185 | 0.1675 | — |
| (c.c.) | (210) | (215) | (215) | (197) | (235) | (206) |
| $NH_3$ / T.N. (%) | 95.5 | 98.0 | 82.2 | 83.6 | 100 | — |
| Distillate oil (g.) | 8.1 | 5.6 | 7.3 | 8.9 | 10.6 | 9.12 |
| Percent to leucine. (%) | 42.2 | 49.5 | 29.6 | 33.3 | 42.4 | 40.7 |
| aq. layer (c.c.) | 92 | 79 | 86 | 106 | 41 | 86 |
| Nitrile (g.) | 1.8 | 2.13 | 1.10 | 1.28 | 3.28<br>(3.60)* | 2.96<br>(3.60)* |
| Percent to leucine. (%) | 14.8 | 29.9 | 7.06 | 7.60 | 20.8<br>(24.0)* | 20.8<br>(25.8)* |

* and ** The quantity of isovaleronitrile or isovaleric acid in aqueous solution was combined.

Table 5.—(*Concluded*)

| No. of expt. | 1 | 2 | 3 | 4 | 5 | 6 |
|---|---|---|---|---|---|---|
| Aldehyde (g.) | 5.47 | 3.34 | 5.42 | 6.90 | 6.10 | 4.98 |
| Percent to leucine. (%) | 43.5 | 45.2 | 33.3 | 39.2 | 37.1 | 34.0 |
| Isovaler. acid in oil. (g.) | 0.83 | 0.125 | 0.785 | 0.725 | 0.24 | 1.18 |
| Percent to leucine. (%) | 5.57 | 1.40 | 4.08 | 3.95 | 5.95<br>(7.80)** | 6.30<br>(10.5)** |

Electrolysates:

Solution A.—To a solution of leucine (90 g.) in 2N-$H_2SO_4$ (305 c.c.) 2N-$Na_2SO_4$ (305 c.c.) was added.

Solution B.—Leucine (30 g.) was dissolved in 2N-$H_2SO_4$ (200 c.c.) and water (20 c.c.) was added to it.

Solution C.—Leucine (30 g.) was dissolved in N-$H_2SO_4$ (220 c.c.)

Solution D.—Leucine (60 g.) was added to 2N-$H_2SO_4$ (200 c.c.) and $(NH_4)_2SO_4$ (26.4 g., 0.2 mol) in water (200 c.c.) were mixed thoroughly and insoluble leucine (about 9 g.) was filtered off, then water (10 c.c.) was added. Thus, 444 c.c. of the solution was obtained. 210 c.c. of the solution contained 24.9 g. (0.19 mol) of leucine and the concentration of sulphuric acid was 0.922 N.

Solution E.—Leucine (52 g.) was dissolved in 2N-$H_2SO_4$ (200 c.c.) and $Na_2SO_4$ (32 g., 0.2 mol) in water (200 c.c.), was added and filtered. 210 c.c. of this solution contained 22.45 g. (0.17 mol) of leucine and the concentration of sulphuric acid was 0.913 N.

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As it is shown in Table 5, the yields of the nitrile in the experiments, 1, 2, 3, 4, 5 and 6 were 14.8, 29.9, 7.06, 7.60, 20.8 and 20.8 respectively. The yields to 1 faraday per mol were 4.04, 4.78, 2.47, 3.05, 4.43 and 3.93% respectively. Thus, it was found that in the case of the higher acidity as in expt. 3, the yield was small, and in the case of the lower acidity, by the presence of $Na_2SO_4$ or $(NH_4)_2SO_4$ the yields were better. From the above experiments, it was found that the yields of isovaleronitrile could be increased if the electrolysis was carried out under suitable conditions.

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