MODIFIED SYNTHESIS OF DL-ORNITHINE

By Ö. KOVÁCS and I. VINCZE

Institute of Organic Chemistry, The University, Szeged

(Received September 18, 1957)

A convenient modified synthesis was evolved for the synthesis of DL-ornithine, applying dimethyl acetaminomalonate as an intermediate.

Numerous syntheses are described in recent literature [1]—[10] suitable for the preparation of the important aminoacid DL-ornithine. On subjecting these methods to a critical examination, three of them [8]—[10] which appeared to be promising, were tested in detail. The ALBERTSON and ARCHER method [10] was found to be most reliable and conductable economically also in large scale. The original yield of this method was raised by some per cents through certain modification [11]. However, in the second step of this otherwise excellent process β-acetamino-β-carbethoxy-α-piperidone forms which, as a poorly crystallising compound, cannot usually be converted into the end product without further refining. Its recrystallisation requires a long time and is connected with serious losses of material.

In order to overcome this difficulty, we made use of an observation of HELLMANN and LINGENS [12] according to which it is more practical to prepare and apply dimethyl acetamino malonate (III a) in place of the corresponding diethyl derivate. Namely, when at the preparation of the acetamino malonate derivative generally used as one of the reactants in aminoacid syntheses, dimethyl malonate is applied instead of diethyl malonate, the end product is obtained in higher yields and in an easier processable and refinable form. By the best evolved method available in literature [13], starting from malonate and preparing acetamino malonate by reducing iso-nitrosomalonate in anhydrous acetic acid by reduction with acetic acid and pulverized zinc, diethyl acetamino malonate can be produced in an overall yield of only 75 %. On starting from dimethyl malonate, in turn, the corresponding end product is obtained in an overall yield of 96 % [12]. Practical experiences gathered during the careful reproduction of both methods [12], [13] about 25—30-times proved yields of only 56—60 % with diethyl malonate, against 63—65 % with dimethyl malonate.

Dimethyl malonate required for preparing the starting material was produced by the modified method of REIMER and DOWNES [14], through the esterification of diethyl malonate with potassium methoxide as catalyst. This method proved more suitable than the LEUCHS and THEODORESCU [15] reaction catalysed by ammonia. Dimethyl malonate obtained in this way was treated with nitrous acid by the known method [12] and converted into the acetamino derivative in fair yields by the catalytic process evolved in this Institute [16].

Later on, the ALBERTSON and ARCHER method [10] was followed, affording, as expected, β-acetamino-β-carbomethoxy-α-piperidone of more favourable physical and chemical properties. Hydrolysis by hydrochloric acid of the latter compound gave DL-ornithine in fair yield.

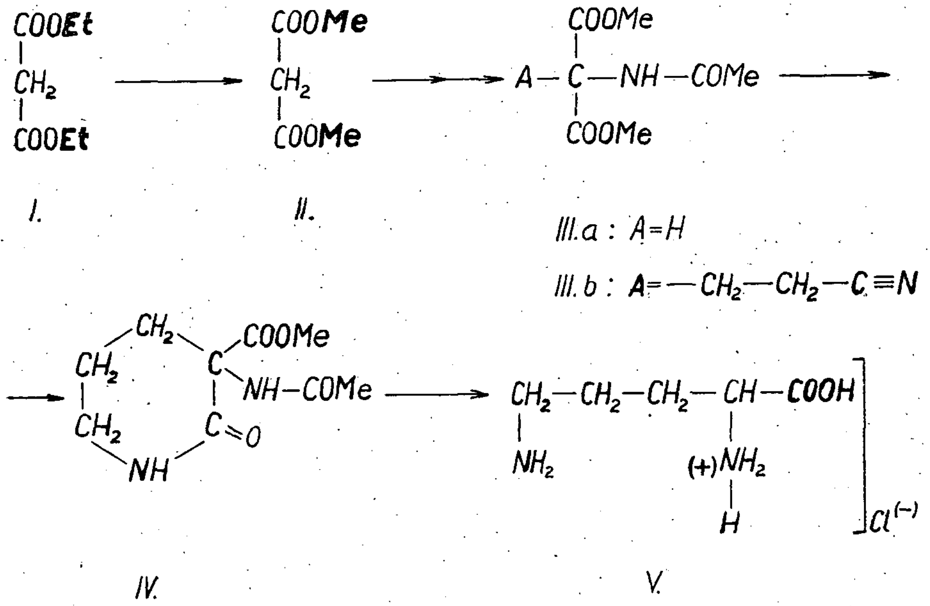

Fig. 1

Although there is no appreciable difference between the overall yields of both methods (68,0 and 73,5 %, respectively) referred to the partial process III a → V of the preparation of ornithine, the present method may be considered more economical and reliable, due to the easier way of preparing dimethyl acetamino malonate and to the more favourable properties of piperidone derivative, obtained as an intermediate.

Experimental

Dimethyl malonate (II). Small particles of refined metallic potassium (25 g) were, under stirring, slowly added within an hour to a solution of 2 000 g of diethyl malonate (I) in 15 000 ml of methanol. On stirring further for an hour, the mixture was neutralized with 108 ml of 6,05 N methanolic hydrochloric acid, methanol removed by distillation under reduced pressure and the residual oil distilled *in vacuo*. B. p. 67° C (at 11 mm Hg). Yield 1741 g (89 %) [14], [15].

Dimethyl acetamino malonate (III a). Dimethyl isonitroso-malonate was obtained in 96 % yield by the HELLMANN and LINGENS method [12], and converted into III a in a 67 % yield by the TÓTH and JANZSÓ method [16]. M. p. 127° C.

Dimethyl β-cyano ethylacetamino-malonate (III b). On dissolving 0,14 g of metallic sodium in 68 ml of waterfree methanol, 30 g of finely pulverized dimethyl acetamino-malonic acid (III a) was added, then 9,65 g of acrylonitrile dropwise added in 30 minutes under vigorous stirring at a temperature between 0 and —5° C. On stirring further for an hour at room temperature, the precipitated crystals were filtered by suction at —10° C, washed with some waterfree methanol at 0°. M. p. 124—125° C. Yield 35 g (86,5 %). Analysis: $C_{10}H_{14}O_5N_2$. Calcd. C 49,59; H 5,83; N 11,57; found C 50,01; H 6.22; N 11,68 %.

β-Carbomethoxy-β-acetamino-α-piperidone (IV). 30 g of dimethyl-cyano ethylacetamino-malonate (III b) was reduced in 130 ml of methanol over 7 g of Raney-nickel at 65—75° C under an initial pressure of 50 atm. The theoretical amount of hydrogen was consumed in 45 minutes. On distilling the filtrate *in vacuo,* 25 g of crude product was obtained. Recrystallising from methanol afforded 23,6 g substance of m. p. 185—187° C (90 %). Analysis: $C_9H_{14}O_4N_2$. Calcd. C 50,47; H 6,59; N 13,18. Found: C 50,95; H 7,03; N 13,44 %.

DL-ornithine monohydrochloride (V). On refluxing 5,86 g of β-carbomethoxy-β-acetamino-α-piperidone (IV) for 4 hours in 25 ml of concentrated hydrochloric acid, the solution was evaporated to dryness *in vacuo,* the residue taken up with 12 ml of hot ethanol, 3.5 ml of concentrated ammonia added, the precipitated crystals filtered by suction, boiled with 2 x 10 ml of ethanol. Yield: 4,39 g of DL-ornithine monohydrochloride (95 %), m. p. 232° C [8]-[10].

This work was supported by the „Factory of Fine Chemicals", Budapest. The authors wish to express their thanks to Miss C. LÁNG for the microanalyses.

References

[1] *Gagnon, P. E., J. L. Boivin:* Canad. J. Research **26 B**, 503 (1948).
[2] *Fischer, E., K. Raske:* Chem. Ber. **38**, 3607 (1905).
[3] *Adamson, D. W.:* J. Chem. Soc. 1564 (1939).
[4] *Gaudry, R.:* Canad. J. Research **27 B**, 21 (1949).
[5] *Fischer, E.:* Chem. Ber. **34**, 454 (1901).
[6] *Sörensen, S. P. L.:* Chem. Zbl. **II**, 33 (1903).
[7] *Fischer, E., G. Zemplén:* Chem. Ber. **42**, 1022 (1909).
[8] *Clutton, R. F., R. Schoenheimer, D. Rittenberg:* J. Biol. Chem. **132**, 227 (1940).
[9] *Tox, S. W., W. S. Dunn, H. P. Stoddard:* J. Org. Chem. **6**, 410 (1941).
[10] *Albertson, N. F., S. Archer:* J. Amer. Chem. Soc. **67**, 2043 (1945).
[11] *Vincze, I. W., P. Dobó, J. Tóth:* communications not published.
[12] *Hellmann, H., F. Lingens:* Z. physiol. Chem. **297**, 283 (1954).
[13] *Sorm, F.:* Laboratorni chemické predpisy (Prirodovedecké vydavatelstvi, Praha, 1952), p. 29—33.
[14] *Reimer, M., H. R. Downes:* J. Amer. Soc. **43**, 945 (1921).
[15] *Leuchs, H., G. Theodorescu:* Chem. Ber. **43**, 1251 (1910).
[16] *Tóth, J., G. Janzsó:* Acta Phys. et Chem. Szeged. **3**, 125 (1957).