DATA ON THE REDUCTION OF DIMETHYL ISONITROSO-MALONATE (DIMETHYL MESOXALIC OXIME)

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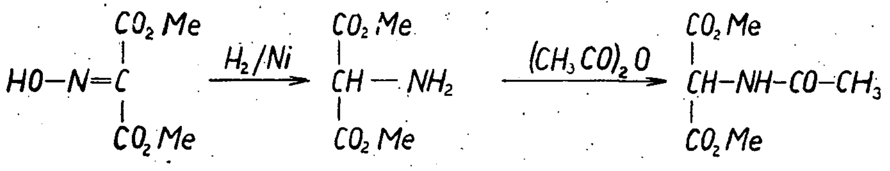
Acetamino malonates are important initial substances in the synthesis of α-amino-carboxylic acids occurring in nature. As dimethyl acetamino malonate proved to be the best suitable compound for this purpose, it seemed worth to examine and modify the synthesis of this substance.

Dialkyl acylamino-malonates are compounds of great importance when synthesizing aminocarboxylic acids. Numerous amino-carboxylic acids occurring in nature may be obtained by syntheses starting from the intermediate mentioned above [1]—[3]. Owing to the reactivity and easyness of preparation of dialkyl acylamino-malonates, aminoacid syntheses starting from these compounds lend themselves readily to the large scale industrial production of the corresponding aminoacids as well.

Diethyl acetamino-malonate is used, in general, most frequently. In syntheses of aminoacids evolved recently [4], [5] at modifications of earlier syntheses, however, dimethyl acetamino-malonate is preferred (III). Namely, according to reference [5] the acetamino compound (III) may be prepared



$$HO{-}N{=}\underset{CO_2Me}{\overset{CO_2Me}{C}} \xrightarrow{H_2/Ni} \underset{CO_2Me}{\overset{CO_2Me}{CH}}{-}NH_2 \xrightarrow{(CH_3CO)_2O} \underset{CO_2Me}{\overset{CO_2Me}{CH}}{-}NH{-}CO{-}CH_3$$

I. II. III.

Fig. 1

from dimethyl malonate in a yield of 96%, against the 75% yield of the synthesis starting from the diethyl derivative. While the isonitroso intermediate of the diethyl derivative is a not distillable oil, the isonitroso intermediate of the corresponding dimethyl compound presents a readily crystallizing substance which can readily be isolated and refined. Aminoacid intermediates obtained with the use of dimethyl acetamino-malonate (III) proved to be all compounds more readily processable and refinable than the derivatives of the corresponding diethyl compound [4].

The synthesis of dimethyl acetamino-malonate starts, similarly to the diethyl analogue, with treating by nitrous acid of the corresponding malonate [5], [6]. The process is ended by the reduction of the nitroso group and acylation of the amino group formed.

No difficulties were encountered when preparing the isonitroso derivative (I) [5] in a yield of 98%. Reduction of dimethyl isonitroso-malonate was carried out by pulverized zinc and glacial acetic acid in a yield of about 60% [3].

Owing to the fact that reduction by zinc in a glacial acetic medium is rather expensive and inconvenient, it seemed practical to attempt reduction by catalytically activated hydrogen since *e. g.*, the reduction of the corresponding diethyl derivative under similar conditions is known [3], although it does not appear to be a process easily controllable.

The catalytic reduction of the isonitroso intermediate of the diethyl derivative was carried out several times by the authors. However, values of yield were rather unreliable, due to the obstacles in refining the isonitroso derivative. Beside some experiments showing fair yields in accordance with reference [3], quite negative tests occurred as well, although the experimental conditions were kept strictly equal during isonitroso-treatment and reduction.

As the isonitroso derivative of dimethyl malonate (I) proved to be a crystalline substance readily refinable, in contrast to the corresponding diethyl derivative, the authors set the aim to conduct the reduction of (I) by catalytically activated hydrogen. Owing to the convenient purification process of the starting substance, it was expected to attain reliably higher yields than with the diethyl derivative.

Aminomalonates (*e. g.* II) contain an amino group of extreme reactivity. As the amino groups already reduced react with the carboxylate groups of other malonate molecules and become acylated, the yield is appreciably reduced. Thus, it seemed practical to conduct reduction in the presence of anhydrous acetic acid in a glacial acetic acid medium, over palladium catalyst on active carbon, at room temperature and at 60° C, respectively, under atmospheric pressure. It was expected that the formed amino-derivative will be acylated during reduction. The attempts were, however, unsuccessful since the hydrogen uptake stopped at about 30%. Tests carried out under systematically varied conditions similarly failed. As it was presumed that certain contaminations affecting the sensitive palladium catalyst were responsible for this failure, reductions were conducted in a methanolic medium over Raney nickel. It was expected that reduction at room temperature will not facilitate the course of the mentioned side reaction. According to expectations, the reaction system took up the calculated quantity of hydrogen in about 5 hours at room temperature under an initial pressure of 60 atm when the reduction was conducted over less sensitive Raney nickel. It is very important to process quickly the reduction product. Of numerous variations, the most suitable procedure was to remove catalyst by filtering, and then reflux the reaction mixture with anhydrous acetic acid. On evaporating the reaction mixture dimethyl acetamino-malonate was obtained.

A great number of tests confirmed that this type of reduction is, in contrast to the reduction of the diethyl derivative, reliably reproducible and can be carried out in satisfactory yields. Aminoacid synthesis starting from dimethyl acetamino-malonate presents thus the advantages mentioned above.

Experimental

Dimethyl acetamino-malonate (III). 1. The solution of 16,1 g (0,1 mole) of dimethyl isonitroso-malonate (I) in a mixture of 102 ml of anhydrous acetic acid and 60 ml of glacial acetic acid is reduced over 1 g of palladium on active carbon (16%) at room temperature under atmospheric pressure. Hydrogen consumption of the system in 48 hours 1080 ml (against calculated 4480 ml). On removing catalyst by filtration, the reaction mixture was evaporated *in vacuo,* the recrystallising oil rubbed with ether and filtered by suction. Yield 5,6 g (33,6%) of III, m. p. 120—124° C.

2. The solution of 32,6 g of I in 100 ml of glacial acetic acid was reduced over 2 g of palladium on active carbon (16%) at room temperature under atmospheric pressure. In 36 minutes the system consumed 300 ml of hydrogen (against 8960 ml calculated) and did not take up more, even when processed at 60—70° C. Attempts to isolate III from the reaction mixture failed.

3. The solution of 100 g of I in 150 ml of methanol was reduced over 40 g of Raney nickel at room temperature under a pressure of 60 atm for 5 hours. Consumed 27,6 l of hydrogen (against 27,8 l calculated). On removing catalyst by filtration and clarifying the liquid, the reaction mixture was distributed into 5 portions and processed by various methods.

a) On evaporating the reaction mixture under reduced pressure, 40 ml of anhydrous acetic acid was added under cooling, and the system allowed to stand for 24 hours. Then the excess of anhydrous acetic acid was removed by evaporation under reduced pressure. The residual oil quickly recrystallized, crystals were filtered by suction to afford 19 g of crude III, m. p. 115° C. On recrystallizing from 25 ml of ethanol, yield 8 g of pure III (34,1% referred to pure product), m. p. 127° C.

b) Another portion of the reaction mixture was allowed to stand at room temperature for a day with 40 ml of anhydrous acetic acid, evaporated under reduced pressure, and the obtained crystalline substance (19,4 g, m. p. 118° C) recrystallized from 25 ml of ethanol to give 9 g of III (yield 38,3% referred to pure product), m. p. 127° C.

c) The third portion of reaction mixture was refluxed for 30 minutes with 32 ml of anhydrous acetic acid (temperature of water bath 85—90° C). On allowing to stand at room temperature for 24 hours and evaporation, 25 g of crystalline substance, m. p. 117° C was obtained which afforded, on recrystallisation from 25 ml of ethanol, 9,5 g of III, m. p. 127° C (yield 40,4% referred to pure substance).

d) The fourth portion of reaction mixture was kept with 40 ml of anhydrous acetic acid at 2—3° C for 24 hours and evaporated as previously described, to afford 29,5 g of crude III, m. p. 119° C. On recrystallisation from 25 ml of ethanol, yield 9 g of III, m. p. 127° C (38,3% referred to pure product).

e) The fifth portion of reaction mixture was refluxed with 32 ml of anhydrous acetic acid for an hour in a bath of 80—90° C, allowed to stand for 24 hours and evaporated to give 23,5 g of crystalline substance, m. p. 119° C. Recrystallisation from 25 ml of ethanol afforded 15,8 g of III of unobjectionable purity, m. p. 127° C (yield 67%).

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