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SYNTHESIS OF 1-AMINOCYCLOPROPANE-1-CARBOXYLIC ACID

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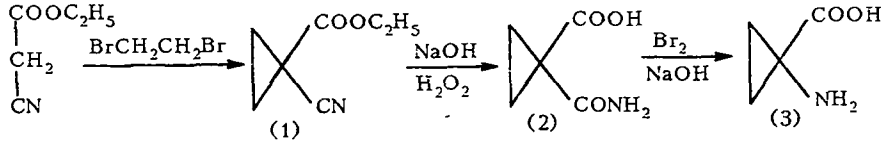
A three-stage method of synthesizing the natural plant growth regulator 1-aminocyclopropane-1-carboxylic acid by the interaction of cyanoacetic ester with 1,2-dibromoethane has been studied.

1-Aminocyclopropane-1-carboxylic acid (ACC), detected in and isolated from plant material [1], is a direct precursor of the biosynthesis of ethylene [2]. At the present time, ACC is regarded as a promising regulator of the growth and development of plants that is distinguished by ecological harmlessness [3-5]. Ever more practical importance is being acquired by the development of accessible methods of synthesizing this biologically active compound and various derivatives of it.

Thus, Kornakov et al. [6] have considered obtaining ACC by two routes: the most frequently used of the possible approaches to the synthesis of this compound through the cyclization of a quaternary derivative of methionine, and through the C-alkylation of malonuic ester with 1,2-dibromoethane. The yields of ACC were 30 and 33%, respectively, calculated on the initial methionine and malonic ester. It is considered that one of the disadvantages of these methods is their multistage nature [3].

We have undertaken a three-stage synthesis of ACC from cyanoacetic ester and 1,2-dibromoethane by the following scheme, given by Liu et al. [7]:



Liu et al. [7] used this scheme to synthesize labeled ACC, which was used for studying an enzymatic reaction.

Trials of their scheme showed that the proposed synthetic procedures were inadequately developed, since the yields of products in the first and the final stages were low, while in the second stage, because of total hydrolysis, it was frequently impossible to isolate the desired monoamide (**2**). The first and second stages of this scheme were therefore modified. Because of the low yield of ethyl 1-cyanocyclopropane-1-carboxylate (**1**) in the first stage, we undertook a search for the best conditions for the alkylation of cyanoacetic ester. Of the various systems catalyzing the process that were tested (we used deprotonating agents — Na_2CO_3, K_2CO_3, NaOH — in a liquid–solid phase system in the presence or in the absence of a phase-transfer catalyst — triethylbenzylammonium chloride), the simplest and most effective proved to be the K_2CO_3–DMSO system, the employment of which in place of sodium ethanolate (inconvenient in use, incidentally) enabled the yield of ester (**1**) to be raised from 24 to 90%.

In the second stage of the scheme, under the conditions given in [7] (temperature 70-90°C, time 2 h) the hydrolysis of the ethyl 1-cyanocyclopropane-1-carboxylate could not be stopped at the intermediate stage of the formation of the amide (**2**), and cyclopropane-1,1-dicarboxylic acid (**4**) was the main product isolated. Thus, when the reaction mixture was acidified

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to pH 2 the expected white crystals of the monoamide did not precipitate. After extraction with ether, the extract was dried and the ether was driven off, giving a crystalline residue with mp 141°C, which corresponds to the acid (**4**). According to the literature [8]: mp 140°C.

By varying the conditions of hydrolysis it was shown that lowering the temperature to 50°C and shortening the process to 1 h permitted the hydrolysis of the cyano group to be stopped at the first stage and ensured the predominant conversion of the nitrile (**1**) into the amide (**2**).

The desired acid (**3**) was obtained from the monoamide (**2**) by the Hofmann rearrangement under the action of bromine in caustic soda. In contrast to the procedure proposed in [7], the isolation of ACC from the reaction mixture was achieved on a column with the ion-exchange resin KU-2 (in place of the scarce Dowex-50). The modification of the intermediate stages of the synthesis has made the scheme reliable and reproducible and has enabled the yield of ACC to be raised to 20%, calculated on the initial cyanoacetic ester (in the procedure described in [7] it was only 5.2%).

EXPERIMENTAL

Ethyl 1-Cyanocyclopropane-1-carboxylate (1). With cooling (10°C) 22.6 g (0.2 mole) of cyanoacetic ester and 58 g (0.31 mole) of 1,2-dibromoethane in 160 ml of DMSO were added to 80 g of freshly calcined potash. The reaction mixture was stirred at 20°C for 8 h. Then it was treated with cold water (250 ml) and was extracted three times with ether (50 ml each time). The ethereal extract was dried over sodium sulfate, the ether was eliminated, and the residue, after analysis by GLC, was distilled in vacuum. The yield of the nitrile (**1**) was 24.9 g (90%), bp 122-124°C (6 mm Hg), n_D^{20} 1.4351 [9], PMR spectrum ($CDCl_3$, ppm): 1.30 (t, J = 7 Hz, 3 H, CH_3), 1.52 (s, 4 H, ring CH_2), 4.20 (q, J = 7 Hz, 2 H, CH_2). IR spectrum (cm^{-1}): 2240 (C≡O), 1735 (C=O). Mass spectrum, *m/z*: M^+ 139.

1-Carboxycyclopropane-1-carboxamide (2). A mixture of 7 g (0.058 mole) of ethyl 1-cyanocyclopropane-1-carboxylate and 30 ml of 20% aqueous NaOH (heterogeneous mixture) was stirred at 50°C for 30 min (the mixture became homogeneous). The resulting solution was cooled to room temperature, and 20 ml of 30% aqueous H_2O_2 was added in small portions. Then the reaction mixture was stirred at 50°C for 20 min, and, after cooling, it was acidified with concentrated HCl and glacial acetic acid (1:1) to pH 2. The white crystals that deposited were filtered off and recrystallized from hot water. Yield 5.87 g (79%). mp 195°C. Found, %: C 46.47; H 5.51; N 10.64. $C_5H_7NO_3$. Calculation, %: C 46.51; H 5.43; N 10.58. Mass spectrum, *m/z*: M^+ 129.

1-Aminocyclopropane-1-carboxylic Acid (3). A suspension of 6 g (46.2 mmole) of 1-carboxycyclopropane-1-carboxamide (**2**) in 24 ml of water was cooled to 0°C and was treated successively with 7.8 g (48.8 mmole) of bromine and a solution of 9 g of NaOH in 36 ml of water cooled with ice. The reddish-yellow reaction mixture became homogeneous. It was stirred for another 5 min (at 0°C), and a solution of 3.6 g of NaOH in 30 ml of water was added. Then the reaction mixture was kept at 70°C for 14 h and was neutralized with oxalic acid to pH 7. The white precipitate was filtered off and the filtrate was passed through a column (2.5 liters, 20 cm) with the ion-exchange resin KU-20 (H^+). The initial aqueous eluate was discarded, and the following NH_4OH (2-3 N) eluate was collected and concentrated in vacuum. The solid residue was crystallized from aqueous ethanol. Yield 1.3 g (28%). mp 254-255°C. Literature: 257-258°C [7]. Found, %: C 47.44; H 6.85; N 13.71. $C_4H_7NO_2$. Calculation, %: C 47.52; H 6.93; N 13.86.

The checking of the purity of the starting materials and the analysis of the product of the alkylation of cyanoacetic ester with 1,2-dibromoethane were carried out by GLC in a Varian Aerograph-2800 chromatograph with a flame-ionization detector. A metal column (0.3 × 150 cm) filled with 5% of SE-30 on Chromaton N-Super (0.125-0.160 mm) was used. The carrier gas was helium. IR spectra were recorded on a UR-20 instrument. The PMR spectrum was taken on a Jeol C-60 HL (60 MHz) spectrometer. The values of the molecular ions were found on a MKh-1310 instrument.

REFERENCES

1. L. E. Burroughs, Nature (London), **179**, No. 4555, 360 (1957).
2. D. O. Adams and S. F. Yang, Proc. Natl. Acad. Sci. USA, **76**, No. 1, 170 (1979).
3. O. I. Romanovskaya, N. V. Kurushina, M. I. Shtil'man, and M. Ya. Kornakov, Izv. Latv. Akad. Nauk, No. 4, 36 (1986).

4. Jpn. Pat. Appl. 61-204121 (1986).
5. G. Robin, Plant Physiol., **77**, No. 4, 922 (1985).
6. M. Ya. Kornakov, A. M. Tsatsakis, Yu. A. Davidovich, and M. I. Shtilman, Izv. Vuzov. Khim. Khim. Tekhnol., **36**, No. 1, 13 (1993).
7. H. W. Liu, R. Auchus, and C. T. Walsh, J. Am. Chem. Soc., **106**, No. 18, 5335 (1984).
8. Handbook of Chemistry [in Russian], Leningrad (1964), p. 572.
9. N. S. Zefirov, T. S. Kuznetsova, S. I. Kozhushkov, L. S. Surmina, and S. A. Rashchupkina, Zh. Org. Khim., **19**, No. 3, 541 (1983).