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REACTION OF AMIDINES OF ALIPHATIC CARBOXYLIC ACIDS WITH DIMETHYL ACETYLENEDICARBOXYLATE

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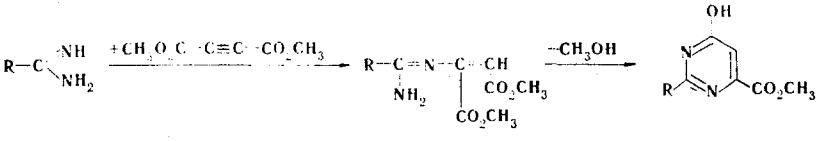
It was established that dimethyl acetylenedicarboxylate reacts with acetamidine to give methyl 4-hydroxy-2-methylpyrimidine-6-carboxylate, with formamide to give a linear addition product, and with trichloroacetamide to give cyclic and linear reaction products. The structures of the products were proved by alternative synthesis and the IR and mass spectra.

The literature does not contain data on the addition of carboxylic acid amidines to dimethyl acetylenedicarboxylate (DMAD).

In the present research we studied the addition of acetamidine, trichloroacetamidine, and formamidine to DMAD. One might have expected that esters (II) of 2-substituted 4-hydroxypyrimidine-6-carboxylic acids would be obtained via this reaction as a result of cyclization of the linear addition products (I).

Only a cyclization product — methyl 4-hydroxy-2-methylpyrimidine-6-carboxylate (IIa) — was isolated in the reaction of acetamidine with DMAD in methanol in the presence of sodium methoxide.



I-II a R = CH_3; b R = CCl_3; c R = H

Ia-c

IIa-c

The structure of IIa was confirmed by elementary analysis and identification with a sample of the ester obtained from 4-hydroxy-2-methylpyrimidine-6-carboxylic acid [1]. The reaction of acetamidine with DMAD at various temperatures (—15, 0, 20, and 65°C) was always accompanied by a great deal of resinification, and IIa was obtained in up to 15% yield. This is probably explained by the low stability of the acetamidine base and its Ia derivative.

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Depending on the temperature at which the reaction is carried out, trichloroacetamidine reacts with DMAD to give primarily Ib or IIb. Addition product Ib was obtained in up to 35% yields at −8°. Pyrimidinecarboxylic acid ester IIb was obtained in refluxing benzene solution due to cyclization of Ib. Both products were isolated at 20°. We were probably able to isolate Ib because the presence of an electronegative group makes it more stable than Ia, just as trichloroacetamidine is considerably more stable than acetamidine (pK_a 6.6 and 12.4).

The structure of Ib was confirmed by its mass spectrum. A triplet of molecular ion peaks at 302-306,* the ratio of the intensities of which indicates the presence of three chlorine atoms in the investigated compound, is observed in the mass spectrum, and the molecular weight corresponds to the elementary composition of Ib; this confirms the presence of two ester groupings. The principal pathway of fragmentation of the molecular ion is successive elimination of an OCH_3 radical and a CO molecule to give ion peaks at 271-275 and 243-247. These processes are confirmed by the corresponding metastable transitions. In addition, a number of peaks of ions with 185-189 and 157-161, which are formed by successive splitting out of CO_2CH_2 and CO particles by the molecular ion, are observed in the mass spectrum.†

The structure of IIb was confirmed by comparison of the IR spectra of IIa and IIb. The spectra of these compounds are identical, except that a band of a C-Cl group (700-800 cm^{-1}) is also observed in the case of IIb.

Formamidine hydrochloride reacts vigorously with DMAD in methanol containing one equivalent of sodium methoxide to give Ic. Pronounced resinification occurs at 20°, and Ic is obtained in 34% yield when the mixture is cooled (at −10° for 1 h). The results of elementary analysis give the empirical formula $C_7H_{10}N_2O_4$, in conformity with Ic, which has two ester groups.

A molecular ion peak at 186 is observed in the mass spectrum of Ic. The fragmentation of the molecular ion involves elimination of an OCH_3 radical and a CH_3OH molecule to give intense ion peaks at 155 and 123. This indicates the presence of two ester groups in the molecule. Both successive transitions are confirmed by the presence of peaks of metastable ions in the mass spectrum.

EXPERIMENTAL

The IR spectra of KBr pellets of the compounds were recorded with a UR-20 spectrometer. The mass spectra were obtained with an LKV-900 mass spectrometer at an ionizing-electron energy of 70 eV and 100° (the temperature of the system for introduction of the samples into the ion source). The individuality of the synthesized compounds was monitored by thin-layer chromatography (TLC) on activity II aluminum oxide in a benzene–methanol system (10:1); the chromatograms were developed in UV light.

Reaction of Acetamidine with Dimethyl Acetylenedicarboxylate. Methyl 4-Hydroxy-2-methylpyrimidine-6-carboxylate (IIa). A solution of 3.74 g (0.04 mole) of acetamidine hydrochloride in 15 ml of absolute methanol was added slowly with cooling (ice water) to a solution of 0.04 mole of sodium methoxide (from 0.92 g of sodium) in 20 ml of absolute methanol, after which the mixture was filtered to remove the NaCl, and the filtrate was added with vigorous stirring in the course of 5-7 min to a solution of 5.68 g (0.04 mole) of dimethyl acetylenedicarboxylate in 10 ml of absolute methanol, and the mixture was refluxed for 1 h. Ether was then added, and the resulting precipitate was dissolved in 10 ml of water. The solution was neutralized with 2 N HCl, and the precipitate was removed by filtration to give 0.95 g (14%) of a product with mp 224-226° (from ethanol). Found: C 49.9; H 4.9; N 16.5%. $C_7H_8N_2O_3$. Calculated: C 49.9; H 4.9; H 16.6%. No melting-point depression was observed for a mixture of this product with a sample obtained by esterification of the acid. Their IR spectra were also identical: 1560, 1620, 1690, 1750, 2930, and 3030 cm^{-1}.

Methyl 4-Hydroxy-2-methylpyrimidine-6-carboxylate (IIa). A 1.5-g (6 mmole) sample of silver oxide and 1 g (7.3 mmole) of methyl iodide were added to a solution of 1 g (6 mmole) of 2-methyl-4-hydroxypyrimidine-6-carboxylic acid [1] in 35 ml of absolute methanol, and the

*Here and subsequently, the numbers characterizing the ions are the mass-to-charge ratios (m/e).

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suspension was shaken for 30 min, after which it was refluxed for 2 h, cooled, and filtered to remove the silver iodide (1.6 g). The filtrate was evaporated to give 0.6 g (60%) of IIa with mp 226-228°. Found: C 49.8; H 4.8; N 16.6%. $C_7H_8O_3N_2$. Calculated: C 50.0; H 4.8; N 16.7%.

Methyl 4-Hydroxy-2-trichloromethylpyrimidine-6-carboxylate (IIb). A solution of 1.6 g (0.01 mole) of trichloroacetamidine in 15 ml of absolute benzene was added with stirring to a solution of 1.42 g (0.01 mole) of dimethyl acetylenedicarboxylate in 7 ml of absolute benzene, and the mixture was refluxed for 1 h. It was then cooled, and the precipitate was removed by filtration to give 0.4 g (14%) of a product with mp 165-167° (from benzene). Found: C 31.2; H 2.1; Cl 39.5%. $C_7H_5Cl_3N_2O_3$. Calculated: C 31.0; H 1.9; Cl 39.3%. IR spectrum: 1570, 1600, 1690, and 1760 cm^{-1}.

N-(1,2,-Dimethoxycarbonylvinyl)trichloroacetamidine (Ib). A solution of 1.9 g (0.012 mole) of trichloroacetamidine in 30 ml of absolute methanol was added with vigorous stirring and cooling (−10°) to a solution of 1.7 g (0.012 mole) of dimethyl acetylenedicarboxylate in 15 ml of absolute methanol, after which the mixture was allowed to stand at −8° for 24 h. It was then vacuum evaporated, and 40 ml of absolute benzene was added to the residue. The resulting precipitate was removed by filtration to give 1.1 g (35%) of a product with mp 98-100°. Found: C 31.9; H 2.9; Cl 35.2; N 9.5%. $C_8H_9Cl_3N_2O_4$. Calculated: C 31.7; H 3.0; Cl 35.0; N 9.2%. IR spectrum: 1715, 1740, 3355, and 3460 cm^{-} . Mass spectrum, m/e values (relative intensities of the ion peaks in percent relative to the maximum peak): 15 (36), 18 (4), 27 (5), 28 (18), 29 (8), 30 (4), 31 (7), 36 (14), 38 (6), 39 (6), 40 (9), 41 (7), 42 (6), 43 (8), 44 (9), 45 (3), 47 (4), 52 (3), 53 (12), 55 (4), 66 (3), 67 (13), 68 (71), 69 (11), 70 (11), 75 (13), 77 (6), 82 (13), 83 (7), 84 (5), 85 (5), 91 (4), 98 (3), 99 (4), 100 (100), 101 (6), 109 (8), 110 (26), 111 (4), 112 (15), 114 (5), 117 (6), 118 (4), 119 (6), 125 (4), 126 (4), 145 (6), 157 (2), 159 (1), 161 (1), 176 (4), 177 (4), 178 (3), 185 (7), 186 (6), 187 (2), 189 (1), 215 (6), 243 (2), 245 (2), 247 (2), 271 (4), 273 (13), 275 (1), 302 (10), 304 (10), 306 (3).

N-(1,2-Dimethoxycarbonylvinyl)formamidine (Ic). A solution of 1.97 g (0.024 mole) of formamidine hydrochloride in 30 ml of absolute methanol was added slowly at −10° to a solution of 0.024 mole of sodium methoxide (from 0.56 g of sodium) in 10 ml of absolute methanol, after which the mixture was filtered to remove the NaCl. The filtrate was added with stirring to a solution of 3.5 g (0.022 mole) of dimethyl acetylenedicarboxylate in 10 ml of absolute methanol at −15°, and the mixture was stirred for 1 h. The precipitate was removed by filtration and washed with absolute methanol to give 1.52 g (34%) of a product with mp 110° (dec., from benzene). Found: C 45.2; H 5.5; N 15.2%. $C_7H_{10}N_2O_4$. Calculated: C 42.2; H 5.4; N 15.0%. IR spectrum: 1680, 1730, and 3350 cm^{-1}. Mass spectrum: 32 (7), 96 (3), 99 (7), 122 (4), 123 (12), 124 (6), 139 (12), 154 (100), 155 (83), 156 (86), 157 (10), 186 (74).

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