2-CARBOMETHOXYAMINOBENZIMIDAZOLE IN THE SYNTHESIS OF 2-OXO-1,2,3,4-TETRAHYDROPYRIMIDO-[1,2-a]BENZIMIDAZOLE AND ITS DERIVATIVES

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A one-step method was developed for the preparation of 2-oxo-1,2,3,4-tetrahydropyrimido[1,2-a]benzimidazole and its 3-methyl, 4-methyl, 4,4-dimethyl, and 4-phenyl derivatives by heating 2-carbomethoxyaminobenzimidazole with acrylic, methacrylic, crotonic, and cinnamic acids at 140-200°C. A possible scheme for the formation of the indicated compounds is presented.

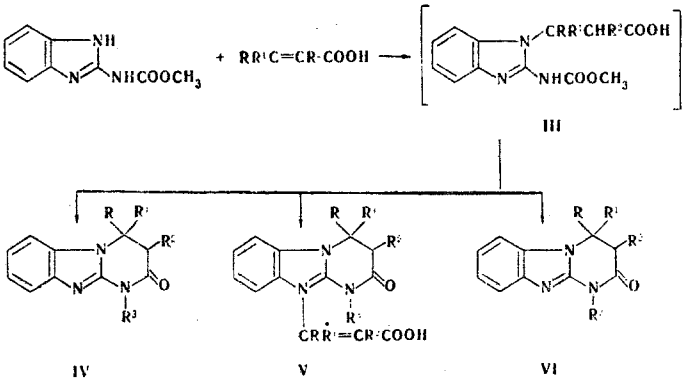
It is known that benzimidazole and its substituted derivatives [1] readily add to acrylonitrile in the presence of triethylbenzylammonium oxide hydrate to give N-β-cyanoethyl derivatives. We have previously [2] shown the possibility of the addition of benzimidazole and its 2-methyl- and phenyl-substituted derivatives to acrylic and methacrylic acids. In this case N-β-carboxyalkyl derivatives of benzimidazole were obtained.

Condensations of 2-carbomethoxyaminobenzimidazole (I) with α,β-unsaturated acids are unknown in the literature. At the same time, the preparation of these compounds is of definite interest, since it is known [3, 4] that amine I itself and 1-butylcarbamoyl-2-carbomethoxyaminobenzimidazole (II, benleit) are broad spectrum fungicides.

With this in mind, we studied the reactions of amine I with acrylic, methacrylic, crotonic, β,β-dimethylacrylic, and cinnamic acids.

We expected that the products of the reaction of amine I with α,β-unsaturated acids would be 1-(β-carboxyalkyl)-2-carbomethoxyaminobenzimidazoles – new analogs of benleit – which could be formed as a result of the addition of amine I to the α,β-unsaturated acid.

However, when we heated amine I with acrylic acid in a ratio of 1 : 2.34 at 140-180°C for 2 h, we obtained a mixture of 2-oxo-1,2,3,4-tetrahydropyrimido[1,2-a]benzimidazole acrylate (V) and 1-(β-carboxypropyl)-2-oxo-1,2,3,4-tetrahydropyrimido[1,2-a]benzimidazole (VI), with predominance of the latter.



III

IV V VI

IV, V $R=R^1=R^2=R^3=H$; VI $R=R^1=R^2=H$, $R^3=-CH_2CH_2COOH$; VII $R=R^1=R^3=H$, $R^2=CH_3$; VIII $R=CH_3$, $R^1=R^2=R^3=H$; IX $R=R^1=CH_3$, $R^2=R^3=H$; X $R=C_6H_5$, $R^1=R^2=R^3=H$

The first step in the reaction is evidently the addition of amine I to acrylic acid to give intermediate 1-(β-carboxypropyl)-2-carbomethoxyaminobenzimidazole (III), which is readily converted to 2-oxo-1,2,3,4-tetrahydropyrimido[1,2-a]benzimidazole (IV) (owing to the formation of a stable six-membered ring).

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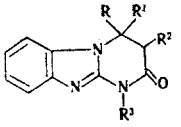
When the reaction of amine I with acrylic acid in a ratio of 1 : 1 is carried out in solvents such as pyridine and dimethylformamide (DMF), only 2-oxo-1,2,3,4-tetrahydropyrimido[1,2-a]benzimidazole (IV) is formed; as seen from the data in Table 1, the yield is higher in the case of DMF than in the case of pyridine.

The structure of IV was proved by its direct preparation from 2-aminobenzimidazole and acrylic acid under the conditions described above and also from the sodium salt of amine I and β-chloropropionic acid in DMF and was confirmed by IR, PMR, and mass spectroscopic data and the results of elementary analysis.

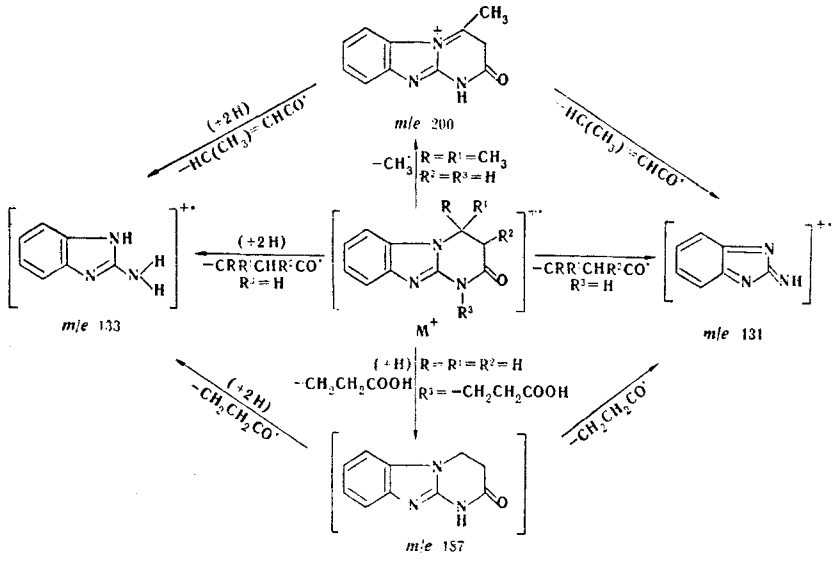
We studied some of the transformations of 2-oxo-1,2,3,4-tetrahydropyrimido[1,2-a]benzimidazole (IV). Brief heating of IV with acrylic acid gave 2-oxo-1,2,3,4-tetrahydropyrimido[1,2-a]benzimidazole acrylate (V), which on more prolonged heating is converted to 1-(β-carboxypropyl)-2-oxo-1,2,3,4-tetrahydropyrimido[1,2-a]-benzimidazole (VI).

Compound VI can be obtained without isolation of acrylate V by heating product IV with excess acrylic acid at 110°C for 2 h. The IR spectrum of IV contains an absorption band of an amide carbonyl group at 1640-1695 (amide I) and 1520, 1580 cm^{-1} (amide II).

The most intense peaks in the mass spectrum of reaction product IV are the ion peaks with m/e 131 and 133, which are formed as a result of elimination of a $-CH_2CH_2CO$ group. The ion peak with m/e 133 is formed by capture of two protons. This fragmentation scheme is characteristic for compounds of the general formula



and the principal pathways of the fragmentation of the molecular ion of these substances are therefore presented below.



M+ 187 R=R¹=R²=R³=H; 201 R=CH₃, R¹=R²=R³=H; 201 R=R¹=R³=H, R²=CH₃; 215 R=R¹=CH₃, R²=R³=H; 263 R=C₆H₅, R¹=R²=R³=H; 259 R=R¹=R²=H, R³=CH₂CH₂COOH

In the PMR spectrum of IV the protons of the aromatic ring appear in the form of a singlet at 7.15 ppm, the triplet at 4.15 ppm corresponds to the protons of the $-CH_2-C=O$ group, and the triplet at 2.9 ppm corresponds to the methylene protons of the $-\overset{|}{N}-CH_2-$ group.

The structure of V was proved by its synthesis from IV and acrylic acid and was confirmed by the mass spectrometric data and the results of elementary analysis. The most intense peak in the mass spectrum of this compound is the ion peak with m/e 133 and the molecular ion peak of acrylic acid with m/e 72.

The structure of VI was proved by its synthesis from 2-oxo-1,2,3,4-tetrahydropyrimido[1,2-a]benzimidazole (IV) and acrylic acid and was confirmed by the PMR and mass spectroscopic data and the results of elementary analysis. In the PMR spectrum of VI the protons of the methylene group attached to the carbonyl

TABLE 1. Characteristics of the Compounds Obtained

Compound	Amount of acid per mole of starting 2-carbomethoxyamino-benzimidazole	Reaction time, h	mp, °C[a]	Found, % C	Found, % H	Found, % N	Empirical formula	Calc., % C	Calc., % H	Calc., % N	Rf (system of solvents	Yield, %
IV[b]	1	6	260—261	63,9	4,9	22,8	$C_{10}H_9N_3O$	64,1	4,8	22,9		44
IV[c]	1	2	" "	63,9	4,9	22,8	" "	64,1	4,8	22,9		18
V	2.34	2	216—217	60,4	4,8	16,0	$C_{13}H_{13}N_3O_3$	60,2	5,0	16,2	—	25
VI	2.34	2	245—246	60,5	4,7	15,8	"	60,2	5,0	16,2	0,2[d]	54
VI	2.34	5	" "	60,5	4,7	15,8	" "	60,2	5,0	16,2	"	79
VII	2	2	260—262	65,3	5,6	20,8	$C_{11}H_{11}N_3O$	65,6	5,5	20,4	0,47[e]	17
VII	1	2	" "	65,3	5,6	20,8	"	65,6	5,5	20,4	"	75
VII	1,17	1.30′	" "	65,3	5,6	20,8	" "	65,6	5,5	20,4	" "	62
VII	1,17	5	" "	65,3	5,6	20,8	" "	65,6	5,5	20,4	" "	82
VIII	1,17	2	256—257	65,8	5,7	20,5	" "	65,6	5,5	20,4	0,5[e]	89
VIII	1,17	2	" "	65,8	5,7	20,5	" "	65,6	5,5	20,4	" "	97
VIII	1	5	" "	65,8	5,7	20,5	" "	65,6	5,5	20,4	" "	75
IX	1,17	2	244—246	66,7	5,7	19,6	$C_{12}H_{13}N_3O$	66,9	6,0	19,5	0,39[f]	33
X	1,17	2	289—290	72,7	4,7	15,5	$C_{16}H_{13}N_3O$	72,9	4,9	15,9	0,34[f]	93

[a]Crystallization solvents: alcohol for IV and VI-X, water for V. [b]The reaction was carried out in DMF at 150-155°C. [c]The reaction was carried out in pyridine at 120-125°C. [d]Methanol–benzene (5 : 0.3). [e]Methanol–benzene (0.5 : 3.1). [f]Methanol–benzene (0.8 : 4).

group (the α-methylene protons) appear in the form of a triplet at 2.61-2.80 ppm, while the protons of the β-methylene group (with respect to the carboxyl group) appear at 2.82-3.11 ppm. In view of their equivalence, the protons of the two endocyclic methylene groups appear in the form of a multiplet at 3.95-4.42 ppm. The aromatic ring protons give a singlet at 7.2 ppm.

The principal peaks in the mass spectrum of this compound (see the scheme above) are the molecular ion peak M^* with m/e 259 and the ion peaks with m/e 72, 131, and 133, the formation of which is confirmed by the presence of the corresponding metastable peaks.

2-Oxo-3-methyl-1,2,3,4-tetrahydropyrimido[1,2-a]benzimidazole (VII) is formed in 82% yield when amine I is heated with methacrylic acid in a ratio of 1 : 1 at 140-180°C. The yield of VII depends on the heating time. Thus VII is obtained in 62% yield when the mixture is heated for 1.5 h, whereas it is obtained in 82% yield when the mixture is heated for 5 h (see Table 1).

When amine I is heated with crotonic, β,β-dimethylacrylic, and cinnamic acids under conditions similar to those for methacrylic acid, 4-methyl-2-oxo- (VIII), 4,4-dimethyl-2-oxo- (IX), and 4-phenyl-2-oxo-1,2,3,4-tetrahydropyrimido[1,2-a]benzimidazole, respectively, are obtained.

It is apparent from the data in Table 1 that the yield of the reaction product in the case of β,β-dimethylacrylic acid is considerably lower than in the case of crotonic and cinnamic acids; this is probably associated with steric hindrance created by two methyl groups attached to the terminal carbon atom.

EXPERIMENTAL

The mass spectra were obtained with an MKh-1303 spectrometer with a system for direct introduction of the samples into the ion source. The ionizing voltage was 3.4 kV, and the temperature was 120-150°C. The PMR spectra of trifluoroacetic acid solutions of the compounds were recorded with a JNM-44-100 spectrometer with tetramethylsilane as the standard (δ scale). The IR spectra of KBr pellets of the compounds were recorded with a UR-10 spectrometer.

2-Oxo-1,2,3,4-tetrahydropyrimido[1,2-a]benzimidazole (IV). A) A mixture of 1.91 g (0.01 mole) of amine I, 0.72 g (0.01 mole) of acrylic acid, and 35 ml of DMF was refluxed for 6 h, after which ether was added, and the mixture was worked up to give 0.84 g (44%) of a product with mp 260-261°C.

B) A mixture of 0.95 g (0.005 mole) of amine I, 0.36 g (0.005 mole) of acrylic acid, and 10 ml of pyridine was refluxed for 2 h. The insoluble material was separated, and the pyridine was removed from the filtrate. The residue was crystallized from alcohol to give 0.17 g (18.2%) of IV with mp 260-261°C.

C) A mixture of 1.33 g (0.01 mole) of 2-aminobenzimidazole, 0.72 g (0.01 mole) of acrylic acid, and 35 ml of DMF was refluxed for 6 h, after which ether was added, and the mixture was worked up to give 0.84 g (44%) of IV with mp 260-261°C.

D) A solution of sodium methoxide was prepared from 0.23 g (0.01 g-atom) of sodium metal and 20 ml of absolute methanol, and 1.91 g (0.01 mole) of amine I and 40 ml of absolute DMF were added to it. A 1.08-g (0.01 mole) sample of β-chloropropionic acid was added to the resulting suspension, and the mixture was stirred at room temperature for 2 h, after which it was heated on a boiling-water bath for 2 h. The insoluble material was separated, and the solvent was removed from the filtrate. The residue was crystallized from alcohol to give 0.1 g (5.8%) of IV with mp 260-261°C.

1-(β-Carboxypropyl)-2-oxo-1,2,3,4-tetrahydropyrimido[1,2-a]benzimidazole (VI). A) A mixture of 1.63 g (0.0085 mole) of amine I and 1.44 g (0.012 mole) of acrylic acid was heated at 140-190°C for 2 h, after which it was cooled, and the precipitated reaction product was crystallized from alcohol to give 1.2 g (54.5%) of VI with mp 245-246°C.

B) A 0.25-g (0.001 mole) sample of acrylate V was heated at 110°C for 2 h, and the mixture was worked up to give 0.25 g (100%) of VI with mp 245-246°C.

2-Oxo-1,2,3,4-tetrahydropyrimidol[1,2-a]benzimidazole Acrylate (V). A) A mixture of 1.63 g (0.0085 mole) of amine I and 1.44 g (0.012 mole) of acrylic acid was heated at 140-190°C for 2 h, after which it was cooled, and the reaction product was crystallized from alcohol to give 1.2 g (54.5%) of VI with mp 245-246°C. The filtrate after separation of the crystals of VI was evaporated to dryness, and the residue was crystallized from water to give 0.56 g (25.4%) of colorless acicular crystals of acrylate V with mp 216-217°C.

B) A 0.18-g (0.001 mole) sample of IV was mixed with 0.72 g (0.01 mole) of acrylic acid, and the mixture was heated to 100°C. It was then allowed to stand at room temperature overnight. The reaction product was converted to a white residue upon treatment with acetone. The residue was then filtered and crystallized from water to give 0.2 g (80%) of acrylate V with mp 216-217°C.

3-Methyl-2-oxo-1,2,3,4-tetrahydropyrimido[1,2-a]benzimidazole (VII). A mixture of 1.63 g (0.0085 mole) of amine I and 0.86 g (0.01 mole) of methacrylic acid was heated at 140-180°C for 2 h. The obtained reaction product was crystallized from alcohol to give 1.3 g (82%) of VII with mp 260-262°C.

4-Methyl-2-oxo-1,2,3,4-tetrahydropyrimido[1,2-a]benzimidazole (VIII). Reaction of 1.63 g (0.0085 mole) of amine I, 0.86 g (0.01 mole) of crotonic acid under the conditions described for VII gave 1.43 g (89.3%) of VIII with mp 256-257°C. IR spectrum: 1690 and 1580 cm^{-1}. Mass spectrum: M* 201, m/e 131, 133.

4,4-Dimethyl-2-oxo-1,2,3,4-tetrahydropyrimido[1,2-a]benzimidazole (IX). A mixture of 1.63 g (0.0085 mole) of amine I and 1.0 g (0.01 mole) of β,β-dimethylacrylic acid was heated at 150-200°C for 2 h, after which the product was extracted with DMF and precipitated by the addition of ether to give 0.6 g (33.3%) of IX with mp 244-246°C. Mass spectrum: M* 215, peaks with m/e 15, 131, 133. PMR spectrum: six-proton singlet at 1.56, CH_2 singlet at 2.9 ppm, and singlet of aromatic protons at 7.35 ppm.

4-Phenyl-2-oxo-1,2,3,4-tetrahydropyrimido[1,2-a]benzimidazole (X). Reaction of 1.63 g (0.0085 mole) of amine I and 1.48 g (0.01 mole) of cinnamic acid under the conditions described for IX gave 1.96 g (93.3%) of X with mp 289-290°C. Mass spectrum: M* 263, peaks with m/e 131 and 133. PMR spectrum: CH_2 protons at 3.1-3.4, methylidyne proton at 5.5-5.8, and aromatic protons at 7.0-7.4 ppm.

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