CONDENSED IMIDAZO-1,2,4-AZINES.

13.* REACTION OF 1,2-DIAMINOBENZIMIDAZOLE WITH 3-BENZOYL-2-PROPANONIC ACIDS

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Refluxing 1,2-diaminobenzimidazole with 3-benzoyl-2-propanonic acids in methanol gives the corresponding salts, viz., 1,2-diaminobenzimidazole 3-benzoyl-2-propanonates, which are converted to 2-benzoylmethyl-1,2,4-triazino[2,3-*a*]-benzimidazol-4H-3-ones upon heating in high-boiling organic solvents.

Continuing our research to ascertain the effect of the structural peculiarities of imidazo[1,2-b]-1,2,4-triazine derivatives on their luminescence [2] and generation [3] characteristics and to synthesize new imidazo-1,2,4-triazines we studied the reaction of 1,2-diaminobenzimidazole (I) with 3-benzoyl-2-propanonic acids IIa-e.

Refluxing equimolar amounts of the starting I and IIa,d in methanol gave salts, viz., 1,2-diaminobenzimidazole 3-benzoyl-2-propanonates IIIa,d, the compositions of which were established on the basis of the results of elementary analysis; the structures were confirmed by IR spectroscopy and mass spectrometry. Absorption bands of stretching vibrations of associated COOH groups ($\nu_{C=O}$ 1695-1715 cm^{-1}, ν_{OH} 2400-3500 cm^{-1}) and NH_2 groups (3285-3400 cm^{-1}), as well as absorption of the carbonyl group of a benzoylmethyl substituent ($\nu_{C=O}$ 1670-1695 cm^{-1}), are observed in the IR spectra of IIIa,d. In addition, the spectra contain absorption bands that are characteristic for a benzimidazole fragment [4].

A molecular ion peak (M^+) corresponding to the product of the chemical reaction of the starting I and IIa is absent in the electron-impact mass spectrum and the chemical-ionization mass spectrum (CI-MS). Ions corresponding to structural fragments of I and IIa (protonated forms in the CI-MS) with m/z 148 and 192, respectively, are observed in both cases. The subsequent independent fragmentation of the indicated pseudomolecular ions of structures I and IIa confirms the formation of salt IIIa. Thus the structural fragment of 1,2-diaminobenzimidazole is characterized by ions with m/z 147 $[C_7H_7N_4]^+$ (A), 132 $[A - NH_2]^+$, 131 $[A - NH_3]^+$, 105 $[(A - NH_2) - HCN]^+$, and 77 $[(A - NH_2) - HCN - N_2]^+$, and the fragment of acid IIa is characterized by ions with m/z: 192 $[C_{10}H_8O_4]^+$ (B), 176 $[B - O]^+$, 175 $[B - OH]^+$, 147 $[B - COOH]^+$, 120 $[CH_3COC_6H_5]^+$, and 105 $[COC_6H_5]^+$. Similar ions with a corresponding shift of +1 amu are observed in the CI-MS, but the intensities of the ions that belong to the fragment of acid IIa are considerably higher.

Taking into account the results of quantum-chemical calculations made by the Pariser–Parr–Pople (PPP) method (Fig. 1), we propose that salt formation proceeds with the participation of the $N_{(3)}$ atom.

Compounds IIIa,d undergo decomposition to the corresponding salts and starting I and IIa,d when they are refluxed in dilute hydrochloric acid or 10% NaOH solution.

It should be noted that IIIa,d behave completely differently when they are heated in anhydrous organic acids. Brief refluxing of salts IIIa,d in glacial acetic acid leads to 2-benzoylmethyl-1,2,4-triazino[2,3-a]benzimidazol-4H-3-ones IVa,d in 80% and 87% yields, respectively. Compounds IVa,d were obtained in considerably lower yields (15% and 17%) when IIIa,d were refluxed for a long time in dimethylformamide (DMF) or hexanol. This fact makes it pos-

*See [1] for communication 12.

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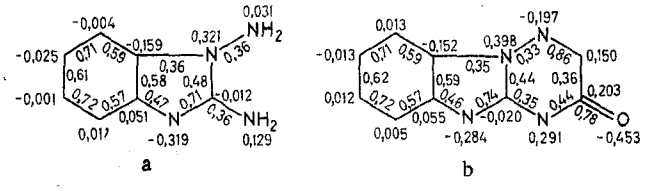
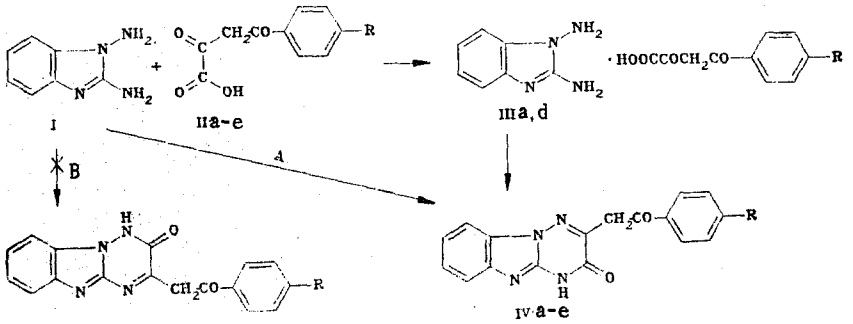


Fig. 1. Molecular diagrams: a) 1,2-diaminobenzimidazole; b) 1,2,4-triazino[2,3-a]benzimidazol-4H-3-one.

sible to conclude that not only the reaction temperature but also the nature of the solvent used affect the conversion of salts IIIa,d to three-ring systems IVa,d. Taking this into account, we studied the reaction of diaminobenzimidazole I with acids IIa-e in various organic solvents (DMF, hexanol, and acetic acid). We found that the corresponding triazinobenzimidazoles IVa-e are formed when starting components I and IIa-e are refluxed in the indicated organic solvents without isolation of intermediates of the III type. The reaction proceeds most successfully with acetic acid as the solvent.

The nonequivalence of the amino groups of starting diamine I predetermines two pathways (A or B) in its reaction with acids IIa-e. Moreover, data from thin-layer chromatography (TLC) and the IR spectra show that one pathway, which leads to the individual desired products, is realized under the experimental conditions.



II—IVa R=H; b R=Cl; c R=Br; d R=CH_3; e R=OCH_3

The choice between the probable pathways of the reaction was made on the basis of the following data. We have shown [5] that the amino group in the 1 position has increased activity as compared with the 2-amino group in 1,2-diaminoimidazoles in the case of condensation with carbonyl reagents. The close structural similarity between 1,2-diaminoimidazole and its benzo analog I makes it possible to expect increased reactivity of the amino group of the hydrazine fragment for the latter. The molecular diagram of I also predicts high nucleophilicity of the NH_2 group in the 1 position. On the basis of these conclusions and taking into account the increased reactivity of the keto group as compared with the carboxy group of α-keto acids [6] and the inertness of the carbonyl group of the benzoylmethyl fragment of 3-benzoyl-2-propanonic acids in reactions with o-diamines [7], pathway A can be considered to be the most preferred pathway.

Finally, the pathway of the reaction of diamine I with acids IIa-e can be established from the unequivocal confirmation of the structures of final products IVa-e.

We have established [8] that substituted imidazo[1,2-b]-1,2,4-triazines have a labile N—N bond of the triazine fragment of the molecule, in connection with which the primary acts in the fragmentation of imidazo-1,2,4-triazines under electron impact are realized with cleavage of the N_1—N_2 and C_5—C_6 bonds of the triazine ring and the elimination of N≡C—R particles in the first step of the fragmentation of the M^+ ion to give charged $[M - NCR]^+$ fragments. Calculation of the electron densities and bond orders for a model of IV (Fig. 1) shows that the presence of a labile N—N bond is also characteristic for them. This is confirmed by data from the mass spectrum of one of the representatives of triazinobenzimidazoles (IVa).

TABLE 1. Characteristics of IVa-e

Compound	mp, °C (from acetic acid)	R_f	IR spectrum, cm^{-1}				Found, %			Empirical formula	Calc., %			Yield, %
			$\nu_{C=O}$ (amide)	$\nu_{C=O}$	ν_{NH}	benzimidazole ring	C	H	N		C	H	N	
IVa	302—303	0,44	1635	1685	3050	1495, 1145, 1000, 860, 760	67,4	4,0	18,2	$C_{17}H_{12}N_4O_2$	67,1	4,0	18,4	69
IVb	299—300	0,50	1640	1690	3070	1495, 1150, 1000, 850, 755	60,2	3,0	16,3	$C_{17}H_{11}ClN_4O_2$	60,3	3,3	16,5	70
IVc	294—295	0,51	1630	1685	3065	1490, 1150, 995, 845, 755	53,5	3,2	14,8	$C_{17}H_{11}BrN_4O_2$	53,5	2,9	14,6	70
IVd	301—302	0,46	1635	1680	3050	1475, 1155, 995, 860, 755	68,0	4,6	17,7	$C_{18}H_{14}N_4O_2$	67,9	4,4	17,6	74
IVe	288—289	0,45	1640	1670	3060	1470, 1175, 995, 860, 775	64,5	4,3	16,8	$C_{18}H_{14}N_4O_3$	64,7	4,2	16,8	60

An M^+ peak with m/z 304 is recorded in the mass spectrum of IVa. The initial acts in the fragmentation of the M^+ ion proceed via two principal pathways: one of them was discussed above and involves the elimination of a neutral $N{\equiv}CCH_2C(O)C_6H_5$ particle and the formation of ion C with m/z 159, and the second pathway involves cleavage of the α bond at the carbonyl group to give a benzoyl ion (m/z 105). Ion C subsequently successively loses C=O (to give an ion with m/z 131) and HCN (to give an ion with m/z 104) particles [9]. Precisely splitting out of a nitrile with the $N{\equiv}CCH_2C(O)C_6H_5$ structure from the M^+ ion (to give ion C) proves the character of the annelation of the imidazole and triazine rings in the IVa molecule in the case of realization of pathway A.

The IR spectral data do not contradict the proposed structure. Thus, in contrast to salts IIIa,d, characteristic absorption bands of carboxy and amino groups are absent in the spectra of three-ring systems IVa-e. In addition, absorption of two carbonyl groups at 1625-1650 and 1670-1695 cm^{-1} and of a cyclic imino group at 3050-3070 cm^{-1} is observed.

EXPERIMENTAL

The IR spectra of KBr pellets of IIIa,d and IVa-e were measured with a UR-20 spectrometer. The electron-impact mass spectrum of triazinobenzimidazole IV was obtained with a Varian MAT-311a spectrometer under standard operating conditions [1]. The CI-MS of IIIa was obtained with a Finnigan-4027 spectrometer under the conditions described in [10]. The purity of the substances obtained was monitored by thin-layer chromatography (TLC) on Silufol UV-254 plates with elution by toluene–isopropyl alcohol (2:1). The chromatograms were developed in UV light.

The properties of the synthesized compounds are presented in Table 1.

1,2-Diaminobenzimidazole 3-Benzoyl-2-propanonate (IIIa). A 0.41-g (2 mmole) sample of acid IIa was added to a solution of 0.3 g (2 mmole) of diamine I in 30 ml of methanol, and the mixture was refluxed for 1 h. It was then cooled, and the resulting white precipitate was removed by filtration, washed with ether, and dried to give 0.53 g (81%) of a product with mp 176-178°C (from methanol). IR spectrum: 3400, 3345, 3295 (NH_2); 3030 (OH); 1695, 1685, 1630 cm^{-1} (C=O). Chemical-ionization mass spectrum (CI-MS), m/z (%): 193 (53) $[B + H]^+$, 177 (12) $[B - O]^+$, 175 (8) $[B - H_2O]^+$, 149 (100), $[A + H]^+$, 147 (17) $[B - COOH]^+$, 134 (41) $[A - NH]^+$, 121 (11) $[CH_3COC_6H_5 + H]^+$, 105 (11) $[C_6H_5CO]^+$, and 77 (14) $[C_6H_5]^+$. Found: C 59.7; H 4.8; N 16.3%. $C_{17}H_{16}N_4O_4$. Calculated: C 60.0; H 4.7; N 16.5%.

Compound IIId. This compound, with mp 171-172°C (from methanol), was similarly obtained in 85% yield. IR spectrum: 3420, 3400, 3330 (NH_2); 3150 (OH); 1715, 1700, 1655 cm^{-1} (C=O). Found: C 60.6; H 5.2; N 16.2%. $C_{18}H_{18}N_4O_4$. Calculated: C 61.0; H 5.1; N 15.8%.

2-Benzoylmethyl-1,2,4-triazino[2,3-*a*]benzimidazol-4H-3-ones IVa-e. A) A solution of 0.45 g (3 mmole) of diamine I and 3 mmole of the corresponding keto acid IIa-e in 20 ml of CH_3COOH was refluxed for 3 h, after which the mixture was cooled, and the resulting white precipitate was removed by filtration, washed with methanol, and dried. Mass spectrum, m/z (%): 43 (99) $[NHCO]^+$, 51 (14), 77 (70), 90 (7), 104 (9), 105 (100), 106 (11), 131 (6), 159 (10), and 304 (13).

B) A solution of 0.34 g (1 mmole) of salt IIIa in 10 ml of acetic acid was refluxed for 2 h, after which it was cooled, and the resulting precipitate was removed by filtration and washed with methanol to give 0.24 g (80%) of IVa.

Triazinobenzimidazole IVd was similarly obtained in 87% yield.

LITERATURE CITED

1. V. P. Kruglenko, N. S. Patalakha, P. B. Kurapov, N. A. Klyuev, V. A. Idzikovskii, I.I. Grandberg, and M. V. Povstyanoi, Khim. Geterotsikl. Soedin., No. 5, 694 (1985).
2. L. V. Chursinova, M. V. Povstyanoi, V. P. Kruglenko, I. I. Grandberg, and P. B. Kurapov, Izv. Timiryazev. Sel'skokhoz. Akad., No. 5, 174 (1982).
3. V. S. Zuev, L. A. Komel'kova, V. P. Kruglenko, O. A. Logunov, M. V. Povstyanoi, A. V. Startsev, Yu. Yu. Stoilov, and A. A. Timoshin, Kvantovaya Elektron., 11, 393 (1984).
4. G. A. Shvekhgeimer and G. A. Mikheichev, Khim. Geterotsikl. Soedin., No. 6, 820 (1974).
5. V. D. Orlov, I. Z. Papiashvili, M. V. Povstyanoi, V. A. Idzikovskii, and O. M. Tsyguleva, Khim. Geterotsikl. Soedin., No. 1, 93 (1983).
6. M. V. Povstyanoi, P. M. Kochergin, E. V. Logachev, E. A. Yakubovskii, V. P. Kruglenko, M. A. Klykov, V. A. Eres'ko, A. V. Shilina, and N. M. Gorban', Summaries of Papers Pre-

sented at the 4th All-Union Conference on the Chemistry of Dicarbonyl Compounds [in Russian], Riga (1976), p. 124.
7. Yu. S. Andreichikov, R. F. Saraeva, and A. L. Fridman, Khim. Geterotsikl. Soedin., No. 2, 259 (1973).
8. M. V. Povstyanoi, V. P. Kruglenko, A. A. Timoshin, N. A. Klyuev, I. I. Grandberg, and Yu. Yu. Stoilov, Izv. Timiryazev. Sel'skokhoz. Akad., No. 5, 155 (1984).
9. V. P. Williams and J. E. Ayling, J. Heterocycl. Chem., 10, 827 (1973).
10. I. Ya. Postovskii, V. A. Zyryanov, V. L. Rusinov, N. A. Klyuev, G. G. Aleksandrov, A. I. Chernyshev, and S. E. Esipov, Khim. Geterotsikl. Soedin., No. 4, 550 (1983).

ANALOGS OF PYRIMIDINE NUCLEOSIDES.

19.* SYNTHESIS, ANTINEOPLASTIC ACTIVITY, AND KINETICS OF THE HYDROLYSIS OF 1-(3-PHTHALIDYL)-5-FLUOROURACILS

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1-(3-Phthalidyl)-5-fluorouracils were synthesized by alkylation of 2,4-bis(trimethylsilyl)-5-fluorouracil with substituted 3-bromophthalides, and the rate constants for hydrolysis at pH 8.0-11.5 were determined. The antineoplastic activity of a number of the compounds was established, and it was assumed that there is a relationship between the biological activity and the rate of hydrolysis.

The extensive use of 1-(2-tetrahydrofuryl)-5-fluorouracil (ftorafur) [2, 3] in the oncological clinics of many countries has promoted an increase in interest in 5-fluorouracil derivatives that can serve as effective transport forms of 5-fluorouracil (5-FU) that release 5-FU under the influence of various enzyme systems. The 5-FU derivatives proposed as transport forms should be sufficiently stable and should not be hydrolyzed in the blood or gastrointestinal tract in the case of oral administration. If this is not the case, they can hardly have substantial advantages over 5-FU and can be replaced by the corresponding medicinal forms of 5-FU.

In this paper we describe the synthesis of 1-(3-phthalidyl)-5-fluorouracils IX-XII. We studied their hydrolytic stabilities and determined their antineoplastic activity in mice with L-1210 lymphatic leukemia and AC-755 adenocarcinoma and their effect on the biosynthesis of DNA in experiments *in vitro* and *in vivo* [4].

We chose the phthalide fragment for introduction into the 5-FU molecule, since it is widely used in the creation of transport forms of antibiotics [5, 6] and is also a structural base and the biosynthetic precursor of microphenolic acid, which is produced by *Penicillium brevicompactum* and has antineoplastic activity [7, 8].

1-(3-Phthalidyl)-5-fluorouracils IX-XII were synthesized by the silyl method.† 3-Bromophthalide (V), 3-bromo-6,7-dimethoxy-phthalide (VI), 3-bromo-4,5,6-trimethoxyphthalide (VII), and 3-bromo-5-hydroxy-4,6-dimethoxyphthalide (VIII) were used as alkylating agents.

Compounds IX-XII are colorless finely crystalline substances that are only very slightly soluble in water and organic solvents. The conditions for the preparation of 1-(3-phthalidyl)-

*See [1] for communication 18.
†After completion of this research, we noted the publication of a paper [9] and a number of patents [10-14] in which the preparation of IX by a two-step synthesis from 3-acyl-5-fluorouracils or by alkylation of 5-fluorouracil with 3-bromophthalide in the presence of alkaline agents was described.

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