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1,2,3,4-TETRAHYDROPYRIMIDO-[1,2-*a*]BENZIMIDAZOL-2- AND -4-ONES

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We have studied the reaction of 2-aminobenzimidazole with esters of substituted cinnamic acids and arylidene derivatives of Meldrum's acid, and have established the direction of formation of the tetrahydrooxopyrimidine ring. We have conducted an x-ray diffraction study of 2-phenyl-1,2,3,4-tetrahydropyrimido[1,2-a]benzimidazol-4-one.

Keywords: 2-aminobenzimidazole, arylidene derivatives of Meldrum's acid, partially hydrogenated pyrimido[1,2-*a*]benzimidazoles, esters of substituted cinnamic acids, X-ray diffraction study, ring condensation.

Among partially hydrogenated azolopyrimidines with a node nitrogen atom, the corresponding pyrimido[1,2-*a*]benzimidazoles have been the least studied. At the same time, these are original systems for pharmacological studies [1,2] and convenient models for analysis of stability and conformational features of annelated dihydro- and tetrahydroheteroaromatic systems [3,4].

By condensation of 2-aminobenzimidazole (**1**) with α,β-unsaturated ketones and hydrochlorides of Mannich bases, we have obtained various aryl-substituted 1,4(3,4)-dihydropyrimido[1,2-*a*]benzimidazoles [2,3]. In trying to expand the range of reagents that can be used in synthesis of partially hydrogenated azolopyrimidines, we have studied the condensation of esters of substituted cinnamic acids **2a-g** and arylidene derivatives of Meldrum's acid **3a,b** with amine **1** under various conditions.

We found that when equimolar amounts of amine **1** are boiled with both esters **2a-f** and arylidene derivatives of Meldrum's acid **3a,b** in nitrobenzene, the compounds 1,2,3,4-tetrahydropyrimido[1,2-*a*]-benzimidazol-2-ones (**4a-f**) are formed. The same products **4a-f** are obtained when the condensation between amine **1** and esters **2a-f** is carried out in DMF. In the case of the ester of α-chlorocinnamic acid **2g**, additional cleavage of HCl and formation of compound **5** occur.

In the IR spectra of compounds **4a-f** and **5** (Table 1), there are bands typical of the amide moiety ν_{N-H} (3250-3050 cm^{-1}) and $\nu_{C=O}$ (1700-1684 cm^{-1}). In the ^1H NMR spectra of compounds **4a,d**, we identify signals from the aryl protons, the NH group, and the ABX system of protons of the moiety –CH–CH_2– of the pyrimidine ring (Table 2). The ^1H NMR spectrum of compound **5** contains a broad singlet from the NH group, a multiplet from the aryl protons, and a singlet from the proton found in the 3 position of the pyrimidine ring. The downfield (11.5-12.7 ppm) position of the signal from the NH group in the spectra of compounds **4,5** is typical for azolopyrimidones containing an NH–C=O moiety [6], and indicates that the direction of formation of the pyrimidine ring corresponds to acylation with participation of the amino group, rather than an endocyclic reaction center.

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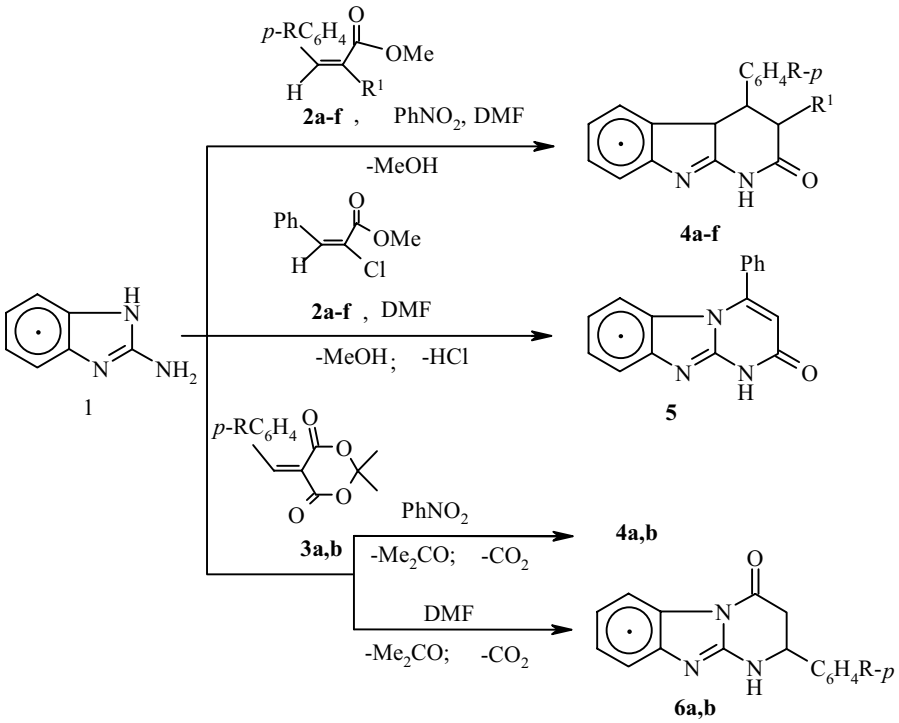

When arylidene-substituted Meldrum's acid **3a,b** is reacted with amine **1** in DMF, we obtain the products **6a,b** which have the same nitrogen content and molecular weight as the 2-oxo derivatives **4a,b** (see Table 1) but have different melting points and spectral characteristics. In the IR spectra of compounds **6a,b**, the $\nu_{C=O}$ band is shifted to 1732 cm^{-1}. In the ^1H NMR spectra, the signal from the NH group is shifted upfield by 3 ppm compared

TABLE 1. Characteristics of Synthesized Compounds

Compound	Empirical formula	Found, % / Calculated, % — N	mp, °C*	IR spectrum (KBr), ν, cm^{-1}	[M+H] / [M-H]	Yield, %
4a	$C_{16}H_{13}N_3O$	16.02 / 15.97	289-291*[2]	3056-2650, 1684, 1636, 1588	264 / 262	61 (48)*[3]
4b	$C_{16}H_{12}N_4O_3$	18.03 / 18.18	260-261	3250-2700, 1684, 1584, 1352		57 (54)*[3]
4c	$C_{17}H_{15}N_3O_2$	14.20 / 14.33	243-245	3048-2650, 1696, 1632, 1580		56
4d	$C_{16}H_{12}FN_3O$	14.90 / 14.95	242-244	3100-2600, 1700, 1636, 1588		67
4e	$C_{17}H_{15}N_3O$	14.95 / 15.16	255 (dec.)	3060-2736, 1688, 1640, 1588		50
4f	$C_{22}H_{17}N_3O$	12.40 / 12.39	250-251	3056-2650, 1692, 1636, 1588		52
5	$C_{16}H_{11}N_3O$	16.12 / 16.09	278-279	3080, 2900-2500, 1684, 1656, 1580		58
6a	$C_{16}H_{13}N_3O$	16.03 / 15.97	297-299	3100-2900, 1732, 1648, 1592	264 / 262	63
6b	$C_{16}H_{12}N_4O_3$	18.10 / 18.18	>300	3100-3916, 1732, 1648, 1524	309 / 307	60

* Compounds **4a-f, 6a,b** were recrystallized from a DMF–2-propanol mixture; compound **5** was recrystallized from 2-propanol.

*[2] 289-290°C [5].

*[3] According to procedure B.

TABLE 2. ^{1}H NMR Spectra for Synthesized Compounds in DMSO-d_6 (δ, ppm; Spin–spin Coupling Constants (*J*), Hz)

Com-pound	NH (1H, br. s)	H_{arom}, m	$CH(H_X)$	CH_2 (H_A, H_B)
4a	11.7	7.0-7.3 (9H)	5.95 (1H, dd, J_{AX} = 7.1, J_{BX} = 3.5)	3.50 (1H, dd) 2.90 (1H, dd, J_{AB} = -16.0)
4b	11.8	7.1-8.2 (8H)	6.16 (1H, dd, J_{AX} = 7.3, J_{BX} = 3.0)	3.62 (1H, dd) 3.04 (1H, J_{AB} = -16.4)
4c*	11.7	6.9-7.4 (8H)	5.84 (1H, dd, J_{AX} = 7.0, J_{BX} = 3.6)	3.43 (1H, dd) 2.88 (1H, J_{AB} = -16.5)
4d	11.5	7.0-7.5 (8H)	5.91 (1H, dd, J_{AX} = 7.1, J_{BX} = 3.4)	3.47 (1H, dd) 2.91 (1H, J_{AB} = -16.5)
4e*[2]	11.7	6.6-7.5 (9H)	5.54 (1H, d, J_{AB} = 5.0)	3.12 (1H, m)
4f	12.0	6.9-7.5 (14H)	6.09 (1H, d, J_{AB} = 4.0)	4.41 (1H, d)
5	12.7	6.9-7.7 (9H)	5.92 (1H, s)	—
6a	8.6	7.0-7.9 (9H)	5.02 (1H, t *J* = 7.4)	3.12 (2H, d)
6b	8.8	6.95-8.35 (8H)	5.20 (1H, t, *J* = 6.6)	3.17 (2H, d)

* Signal from protons of the OCH_3 group: 3.69 ppm (3H, s).
*[2] Signal from protons of the CH_3 group: 1.23 ppm (3H, d, *J* = 7.5 Hz).

with those signals for compounds **4g,d**, which suggests a change in the relative position of the NH and C=O groups. The nature of the splitting of the signals for protons of the CH–CH_2 moiety also changes: it corresponds to an A_2X system rather than an ABX system (Table 2). Based on the data presented, we assign the structure of 1,2,3,4-tetrahydropyrimido[1,2-*a*]benzimidazol-4-ones to compounds **6a,b**, which is confirmed by the results of an X-ray diffraction study for compound **6a**.

According to X-ray diffraction data (Fig. 1, Table 3), the tetrahydropyrimidine ring in compound **6a** is found in the chair conformation. The deviation of the $C_{(7)}$ atom from the mean-square plane of the rest of the ring atoms is 0.57 Å.

The phenyl substituent has an equatorial orientation (torsional angle $C_{(11)}$–$C_{(7)}$–$C_{(8)}$–$C_{(9)}$ 168.0(4)°). The $C_{(7)}$–$C_{(11)}$ bond (1.553(6) Å) is lengthened slightly compared with the mean value of 1.513 Å [7].

In the crystal of molecule **6a**, centrosymmetric dimers are formed because of the very weak intermolecular hydrogen bond $N_{(2)}$–$H_{(2N)}$···$N_{(1)}$ (-*x*, -*y*, -*z*); H···N 2.37 Å, N–H···N 132°.

Thus reaction of 2-aminobenzimidazole with arylidene derivatives of Meldrum's acid **6a,d** in nitrobenzene and DMF occurs in different directions, and leads to 2- or 4-oxo derivatives of tetrahydropyrimido[1,2-*a*]-benzimidazole. A similar dependence of the direction of condensation on reaction conditions was observed in the reaction of compound **3a** with 3-amino-1,2,4-triazole [8].

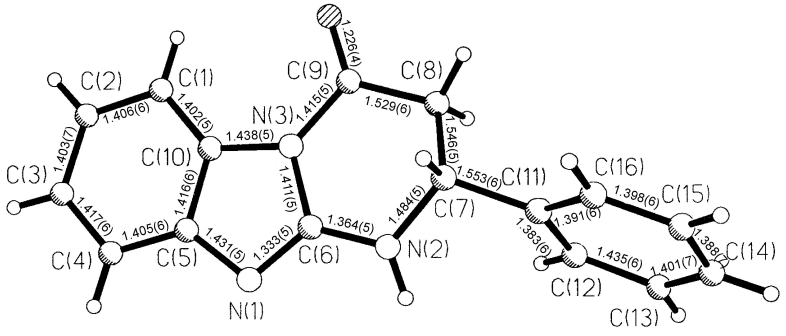

Fig. 1. Structure of molecule **7a** (without hydrogen atoms) with bond lengths (Å).

TABLE 3. Coordinates ($\times 10^4$) and Equivalent Isotropic Temperature Factors ($Å^2 \times 10^3$) of Non-hydrogen Atoms in Molecule **7a**

Atom	*x*	*y*	*z*	U_{eq}
$O_{(1)}$	3026(2)	5523(6)	2148(2)	67(1)
$N_{(1)}$	1438(2)	-324(6)	491(2)	51(1)
$N_{(2)}$	270(2)	2228(6)	856(2)	51(1)
$N_{(3)}$	2168(2)	2766(6)	1268(2)	47(1)
$C_{(1)}$	4132(3)	2029(10)	1386(3)	64(1)
$C_{(2)}$	4751(3)	466(10)	1136(2)	73(2)
$C_{(3)}$	4302(3)	-1431(10)	662(2)	70(2)
$C_{(4)}$	3196(3)	-1859(9)	419(2)	64(1)
$C_{(5)}$	2563(3)	-318(8)	664(2)	47(1)
$C_{(6)}$	1242(3)	1530(8)	854(2)	42(1)
$C_{(7)}$	149(3)	4650(8)	1116(2)	55(1)
$C_{(8)}$	1103(3)	5223(8)	1817(2)	53(1)
$C_{(9)}$	2187(3)	4611(7)	1770(2)	49(1)
$C_{(10)}$	3038(3)	1589(8)	1139(2)	47(1)
$C_{(11)}$	-920(3)	4818(8)	1259(2)	47(1)
$C_{(12)}$	-1231(4)	3108(10)	1656(3)	70(2)
$C_{(13)}$	-2230(4)	3259(10)	1770(3)	72(2)
$C_{(14)}$	-2882(4)	5208(11)	1471(3)	76(2)
$C_{(15)}$	-2577(4)	6939(10)	1074(3)	78(2)
$C_{(16)}$	-1597(4)	6718(9)	975(3)	64(1)

EXPERIMENTAL

X-ray Diffraction Study. Crystals of 1,2,3,4-tetrahydro-2-phenylpyrimido[1,2-*a*]benzimidazol-4-one monoclinic, $C_{16}H_{13}N_3O$: a = 13.427(4), b = 5.641(2), c = 19.295(6) Å; β = 110.01°; V = 1373.2(8) $Å^3$; M_r = 263.29, Z = 4, space group $P2_1/n$, d_{calc} = 1.274 g/cm^3, μ = 0.083 mm^{-1}, $F(000)$ = 552, the unit cell parameters and intensities of 2319 reflections (2223 independent, R_{int} = 0.05) were measured on a Siemens P3/PC automatic four-circle diffractometer (MoKα, graphite monochromator, $2\theta/2\theta$ scanning, $2\theta_{max}$ = 50°).

The structure was deciphered by the direct method using the SHELXTL PLUS software package [9]. The positions of the hydrogen atoms were calculated geometrically and refined by the "horse and rider" model with fixed $U_{iso} = 1.2U_{eq}$ for the nonhydrogen atom bonded to a given hydrogen. Full-matrix least-squares refinement with respect to F^2 in the anisotropic approximation for the non-hydrogen atoms using 2535 reflections resulted in wR_2 = 0.178 from 2223 reflections (R_1 = 0.071 from 1061 reflections with $F > 4\sigma(F)$, S = 0.942). The coordinates of the atoms are presented in Table 3.

The IR spectra were recorded on a Specord M-82 spectrometer for KBr pellets; the ^{1}H NMR spectra were recorded on Bruker AM-300 and Bruker AM-100 spectrometers for solutions in DMSO-d_6, internal standard TMS. The mass spectra were obtained on an MSBC SELMI spectrometer (10 μC ^{252}Cf source) for positive and negative ions with accelerating voltage ±20 kV. The purity of the compounds obtained was monitored by TLC on Silufol UV-254 plates; eluent 2:2:1 ethyl acetate–benzene–methanol.

4-Phenyl-1,2,3,4-tetrahydropyrimido[1,2-*a*]benzimidazol-2-one (4a). A. A solution of cinnamic acid methyl ester **2a** (0.32 g, 2 mmol) and 2-aminobenzimidazole **1** (0.36 g, 2 mmol) in DMF (1 ml) was boiled for 5 min until a crystalline precipitate formed. This was cooled and then mixed with 2-propanol and then 0.32 g compound **4a** was filtered off (from a DMF–2-propanol mixture).

Compounds **4b-f** were obtained similarly from amine **1** and esters.

B. A mixture of 5-benzylidene-2,2-dimethyl-1,3-dioxane-4,6-dione **3a** (2.32 g, 0.01 mol) and amine **1** (1.33 g, 0.01 mol) in nitrobenzene (2 ml) was boiled for 1 h. This was cooled, methanol (5 ml) was added, and the precipitate of product was separated by filtration. Obtained 1.26 g of compound **4a**.

Compound **4b** was obtained similarly from amine **1** and dione **2b**.

4-Phenyl-1,2-dihydropyrimido[1,2-*a*]benzimidazol-2-one (5). A solution of α-chlorocinnamic acid methyl ester **2g** (0.39 g, 2 mmol) and amine **1** (0.36 g, 2 mmol) in DMF (1 ml) was boiled for 15 min, cooled, and then mixed with 2-propanol (5 ml). Compound **5** (0.3 g) was filtered off.

2-Phenyl-1,2,3,4-tetrahydropyrimido[1,2-*a*]benzimidazol-4-one (6a). A mixture of dione **3a** (2.32 g, 0.01 mol) and amine **1** (1.33 g, 0.01 mol) in DMF (2 ml) was boiled for 10 min. This was cooled and of 2-propanol (10 ml) was added. The precipitate was separated by filtration. Obtained 1.66 g of product **6a**.

Compound **6b** was obtained similarly from amine **1** and dione **3b**.

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