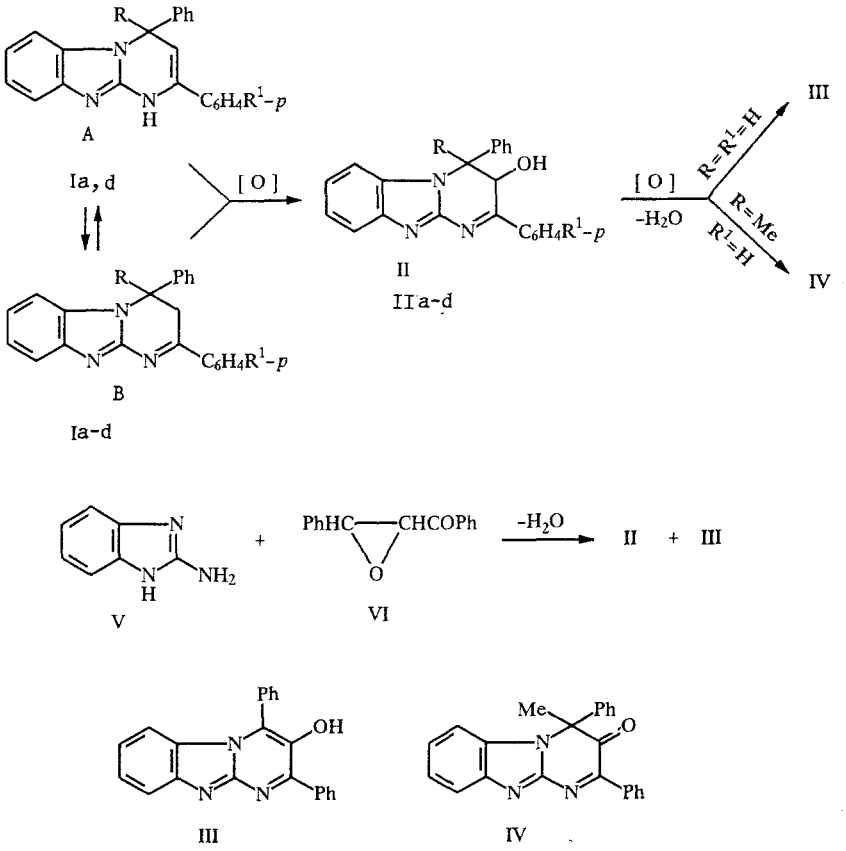
3-HYDROXYPYRIMIDO[1,2-*a*]BENZIMIDAZOLES

**S. M. Desenko, V. D. Orlov, V. V. Lipson,
O. V. Shishkin, S. V. Lindeman,
and Yu. T. Struchkov**

The oxidation of aromatic derivatives of 1,4- and 3,4-dihydropyrimido[1,2-a]benzimidazoles gave the corresponding 3-hydroxy-3,4-dihydro derivatives and the dehydrogenation of these compounds was carried out. An x-ray diffraction structural analysis was carried out on 2-(4-dimethylaminophenyl)-3-hydroxy-4-phenyl-3,4-dihydropyrimido[1,2-a]benzimidazole.

In previous work [1, 2], we reported that dihydro derivatives of pyrazolo- and triazolo[1,5-*a*]pyrimidines may undergo oxidation by atmospheric oxygen to give the corresponding 6-hydroxy derivatives. In the present work, we studied the oxidation of aromatic derivatives of dihydropyrimido[1,2-*a*]benzimidazole Ia-Id, leading to 3-hydroxy-3,4-dihydropyrimido[1,2-*a*]benzimidazoles IIa-IId. The rate of the oxidation reaction increases with increasing electron donor capacity of substituent R^1.



I, IIa – c R = H, d R = Me; a, d R^1 = H, b R^1 = MeO, c R^1 = Me_2N

Kharkov State University, Kharkov, Ukraine 310077. A. N. Nesmeyanov Institute of Organometallic Compounds, Russian Academy of Sciences, Moscow 117813. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 5, pp. 688-693, May, 1993. Original article submitted June 15, 1992.

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TABLE 1. Indices of II-IV

Compound	Chemical formula	mp, °C	IR spectrum, cm^{-1}		λ_{max}, ($\varepsilon \cdot 10^{-3}$)	Chemical shift (ppm) of protons* (DMSO-d_6)				Reaction time, h	Yield, %
			$\nu_{C=N}$ (KBr)	ν_{OH} (CCl_4)		3-H, d**	4-H, S	OH, d**	CH_3, S		
IIa	$C_{22}H_{17}N_3O$	202...205	1612	3566	355 (13,5)	5,15	6,02	6,83	—	1,5	91
IIb	$C_{23}H_{19}N_3O_2$	182...184	1605	3568	366 (15,8)	5,10	5,96	6,81	3,82	1,5	85
IIc	$C_{24}H_{22}N_4O$	246...247	1604	3564	297 (6,3); 420 (35,9)	5,10	5,89	6,62	3,33	1,0	90
IId	$C_{23}H_{19}N_3O$	165...167	1615	3560	357 (16,6)	5,23	—	6,64	2,38	0,5	88
III	$C_{22}H_{15}N_3O$	275...278 (dec.)	1601	3569	350 (16,5) 440 (3,6)	—	—	8,17 s	—	1,0	70
IV	$C_{23}H_{17}N_3O$	138...140 (dec.)	1620, 1681***	—	400 (3,9)	—	—	—	2,38	1,0	95

*The aromatic protons in II-IV are at 6.5-8.2 ppm.

**The coupling constants range from 5.8-7.2 Hz.

***$\nu_{C=O}$.

The structures of IIa-IIc would appear to facilitate ready dehydration. However, as in the case of analogous hydroxy derivatives of dihydropyrazolo[1,2-*a*]pyrimidine [1], IIa remains unchanged upon heating in solution in DMF or ethanol with HCl, KOH, $ZnCl_2$, or *p*-toluenesulfonic acid at reflux in an inert atmosphere. Heating of the same solutions with access to air led to the formation of 3-hydroxy-2,4-diphenylpyrimido[1,2-*a*]benzimidazole III. This reaction is especially facile in ethanolic KOH. This facility may be related to the partial ionization of IIa under these conditions. Benzimidazole IId, whose heteroaromatization is hindered by having two substituents at $C_{(4)}$, was oxidized to 3-oxo derivative IV under these conditions in ethanolic KOH.

The convergent synthesis of IIa and III was carried out by the condensation of 2-aminobenzimidazole (V) with epoxyketone VI. The reaction conditions featuring heating in DMF at reflux, which are more vigorous than in the case of the oxidation of Ia, led to significant imposition of a second dehydrogenation process of IIa to give heteroaromatic analog III as the major product of this cyclocondensation.

The IR spectra of II-IV in KBr pellets show C=N stretching bands at 1604-1615 cm^{-1} and a C=O stretching band for IV at 1681 cm^{-1}. The spectra of IIa-IId and III in CCl_4 also show a ν_{OH} band at 3560-3569 cm^{-1} (Table 1). In previous work [3], we found that dihydropyrimido[1,2-*a*]benzimidazoles Ia, Ib, and Id crystallize exclusively in the enamine dihydro form A, while dimethylamino derivative Ic crystallizes in imine tautomer form B. In particular, this is evident in the IR spectra of Ia, Ib, and Id (in KBr pellets) by the strong C=C stretching band at 1660-1690 cm^{-1}, which is absent in the spectrum of Ic [3]. The absence of this band in the spectra of hydroxy derivatives IIa-IId indicates the imine tautomer structure of all these compounds in the solid phase.

The electronic absorption spectra of hydroxy derivatives IIa-IId are similar on the whole and feature a long-wavelength band at 355-420 nm (Table 1), whose position is virtually the same as for the band of tautomer B of Ia-Id [3].

PMR spectroscopy indicates 3,4-dihydro structure for IIa-IId in solution in DMSO-d_6 (Table 1). These spectra show signals for aromatic protons, the CR−CHOH fragment, and R^1. The lack of signals for NH protons in the PMR spectra of these compounds eliminates the possibility that these compounds exist as their 1,4- or 4,9-dihydro forms within the limits of the sensitivity of PMR spectroscopy. Comparison of this result with the data of our previous work [3], showing that the concentration of tautomer A in solutions of Ia-Id in DMSO-d_6 ranges from 40-100%, indicates relative stabilization of the imine tautomer form of dihydropyrimido[1,2-*a*]benzimidazoles in going from I to 3-hydroxy forms II. The observed effect should be attributed to a decrease in the CH-acidity of IIa-IId due to the electron donor effect of the hydroxy group introduced.

The two chiral sites in IIa-IId permit the existence of different spatial isomers or their mixtures. The PMR spectra of these compounds are characteristic for pure compounds. The spectra of IIa-IIc (R = H) do not show spin−spin coupling of

TABLE 2. Some Bond (ω) and Torsion Angles (τ) in IIc

Angle	ω, deg	Angle	τ, deg
$C_{(7)}N_{(1)}C_{(1)}$	106,3(2)	$N_{(1)}C_{(1)}C_{(6)}N_{(2)}$	1,2(2)
$N_{(1)}C_{(1)}C_{(6)}$	105,0(2)	$C_{(1)}C_{(6)}N_{(2)}C_{(7)}$	0,0(2)
$C_{(1)}C_{(6)}N_{(2)}$	110,5(2)	$C_{(6)}N_{(2)}C_{(7)}N_{(1)}$	-1,2(2)
$C_{(6)}N_{(2)}C_{(7)}$	104,4(2)	$N_{(2)}C_{(7)}N_{(1)}C_{(1)}$	1,9(2)
$N_{(2)}C_{(7)}N_{(1)}$	113,7(2)	$C_{(7)}N_{(1)}C_{(1)}C_{(6)}$	-1,8(2)
$N_{(1)}C_{(7)}N_{(3)}$	122,5(2)	$C_{(8)}N_{(3)}C_{(7)}N_{(1)}$	-7,8(3)
$C_{(7)}N_{(3)}C_{(8)}$	118,5(2)	$C_{(7)}N_{(3)}C_{(8)}C_{(9)}$	-5,3(3)
$N_{(3)}C_{(8)}C_{(9)}$	121,9(2)	$N_{(3)}C_{(8)}C_{(9)}C_{(10)}$	31,7(2)
$C_{(8)}C_{(9)}C_{(10)}$	112,6(2)	$C_{(8)}C_{(9)}C_{(10)}N_{(1)}$	-41,9(2)
$N_{(1)}C_{(10)}C_{(9)}$	107,3(2)	$N_{(3)}C_{(7)}N_{(1)}C_{(10)}$	-8,8(3)
$C_{(7)}N_{(1)}C_{(10)}$	122,8(2)	$C_{(8)}C_{(9)}C_{(10)}C_{(11)}$	82,7(2)
$N_{(1)}C_{(10)}C_{(11)}$	112,7(2)	$N_{(3)}C_{(8)}C_{(9)}O$	-91,3(2)
$C_{(8)}C_{(9)}O$	106,9(2)	$N_{(3)}C_{(8)}C_{(17)}C_{(18)}$	-22,7(2)

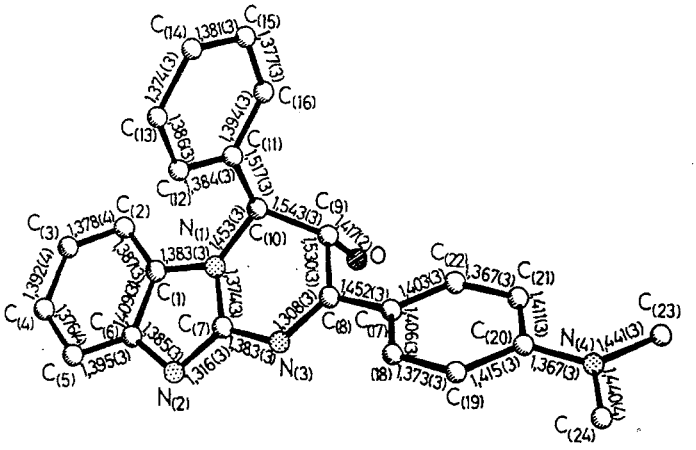

Fig. 1. Molecular structure of IV (without hydrogen atoms) with bond lengths (Å).

3-H and 4-H (Table 1). This finding is related to the corresponding H–C–C–H torsion angle in the predominant conformation of IIa-IIc, which is close to 90°. The structural data of analogous molecular systems [1] indicate that such an arrangement of 3-H and 4-H is possible only in *trans* isomers with diaxial orientation of the substituents at $C_{(3)}$ and $C_{(4)}$. This finding, however, does not unequivocally indicate steric selectivity in formation of IIa-IIc in light of the possibility of *cis–trans* isomerization through a prior tautomeric conversion to the 1,4-dihydro form.

The PMR spectrum of III has signals for protons of the aromatic and hydroxy groups, while the spectrum of IV has signals only for aromatic protons (Table 1).

The preference for the formation of IIa-IIc in comparison with the dehydrogenation reaction, which is usual for dihydroheteroaromatic systems, as well as the unexpected stability of these compounds relative to dehydrating reagents are nontrivial findings. The spectral evidence for the structure of IIa-IId was thus not considered sufficient and we undertook an x-ray diffraction structural analysis of IIc, which unequivocally proved its structure (Fig. 1, Tables 2 and 3).

The benzimidazole system in IIc is planar. The extrusion of the atoms of this system from the mean square plane does not exceed 3s. The dihydropyrimidine ring has a somewhat distorted sofa conformation and $N_{(3)}$, $C_{(7)}$, $N_{(1)}$, and $C_{(10)}$ lie in a single plane to within $\pm 3\sigma$. The extrusions of $C_{(8)}$ and $C_{(9)}$ from this plane are 0.29(1) and 0.67(1) Å, respectively. The conformational parameters of this ring in accord with Zefirov et al. [4] are S = 0.54, $\Theta = 46.8°$, and $\varphi = 26.8°$.

The *trans*-arranged substituents at $C_{(9)}$ and $C_{(10)}$ occupy quasiaxial positions, which confirms the proposed three-dimensional structure for IIc based on analysis of its PMR spectroscopy. The lack of pronounced coupling of $H_{(9)}$ and $H_{(10)}$ is in good accord with the $H_{(9)}C_{(9)}C_{(10)}H_{(10)}$ torsion angle equal to 84(2)°. This indicates a similar three-dimensional structure for IIc in solution and in the solid phase.

TABLE 3. Coordinates of Non-Hydrogen ($\times 10^4$) and Hydrogen Atoms ($\times 10^3$) in IIc

Atom	x	y	z	Atom	x	y	z
O	2358(1)	-415(2)	1924(1)	$C_{(22)}$	758(2)	356(2)	3434(1)
$N_{(1)}$	4672(1)	283(2)	2467(1)	$C_{(23)}$	-2196(2)	1275(3)	4556(2)
$N_{(2)}$	5113(1)	2487(2)	2573(1)	$C_{(24)}$	-1266(3)	3048(3)	5409(2)
$N_{(3)}$	3424(1)	1809(2)	3127(1)	$H_{(O)}$	203(2)	-137(2)	182(1)
$N_{(4)}$	-1213(2)	1995(2)	4787(1)	$H_{(2)}$	621(2)	-149(2)	182(1)
$C_{(1)}$	5691(2)	405(2)	2136(1)	$H_{(3)}$	788(2)	-68(2)	132(1)
$C_{(2)}$	6393(2)	-540(3)	1807(2)	$H_{(4)}$	835(2)	160(2)	138(1)
$C_{(3)}$	7373(2)	-58(3)	1538(2)	$H_{(5)}$	710(2)	319(2)	192(1)
$C_{(4)}$	7634(2)	1308(3)	1584(2)	$H_{(9)}$	251(2)	-122(2)	306(1)
$C_{(5)}$	6935(2)	2247(3)	1905(2)	$H_{(10)}$	412(2)	-155(2)	222(1)
$C_{(6)}$	5944(2)	1790(2)	2199(1)	$H_{(12)}$	556(2)	-9(2)	390(1)
$C_{(7)}$	4385(2)	1553(2)	2729(1)	$H_{(13)}$	608(2)	-111(2)	516(1)
$C_{(8)}$	2709(2)	837(2)	3172(1)	$H_{(14)}$	539(2)	-318(2)	553(1)
$C_{(9)}$	2864(2)	-522(2)	2734(1)	$H_{(15)}$	414(2)	-433(2)	462(1)
$C_{(10)}$	4072(2)	-924(2)	2686(1)	$H_{(16)}$	364(2)	-329(2)	333(1)
$C_{(11)}$	4508(2)	-1579(2)	3490(1)	$H_{(18)}$	234(2)	262(2)	440(1)
$C_{(12)}$	5254(2)	-955(2)	4032(1)	$H_{(19)}$	74(2)	310(2)	507(1)
$C_{(13)}$	5580(2)	-1569(2)	4782(1)	$H_{(21)}$	-82(2)	13(2)	365(1)
$C_{(14)}$	5168(2)	-2806(3)	5001(2)	$H_{(22)}$	76(2)	-31(2)	300(1)
$C_{(15)}$	4443(2)	-3451(2)	4455(2)	$H_{(23A)}$	217(2)	25(2)	461(1)
$C_{(16)}$	4120(2)	-2851(2)	3707(1)	$H_{(23B)}$	244(2)	137(2)	398(2)
$C_{(17)}$	1716(2)	1081(2)	3615(1)	$H_{(23C)}$	276(2)	152(2)	487(1)
$C_{(18)}$	1662(2)	2099(2)	4229(1)	$H_{(24A)}$	-82(2)	287(2)	590(2)
$C_{(19)}$	718(2)	2378(3)	4630(1)	$H_{(24B)}$	200(2)	320(2)	561(1)
$C_{(20)}$	-257(2)	1681(2)	4419(1)	$H_{(24C)}$	102(2)	390(2)	522(1)
$C_{(21)}$	-195(2)	651(2)	3810(2)				

The mutual orientation of the hydroxy group and $H_{(10)}$ is cisoid (the $H_{(10)}C_{(10)}C_{(9)}O$ torsion angle is $-37(1)°$) and is unfavorable for the dehydration reaction [5]. This finding accounts for the relative stability of hydroxy derivatives II.

The torsion angles of the benzalaminobenzimidazole fragment do not exceed 23° (Table 2), which indicates retention of conjugation of the π-electron systems of the $C_{(17)}\cdots C_{(22)}$ phenyl substituent, azomethine group, and benzimidazole system. This conjugation is also evident in some contraction of the $C_{(8)}-C_{(17)}$ bond (1.452 (3) Å) in comparison with the standard value (1.467 Å [6]). However, the twist of the $C_{(17)}\cdots C_{(22)}$ phenyl ring relative to the plane of the azomethine bond ($-22.7(3)°$) is much greater than in analogous dihydro derivatives of pyrazolo (8.9(9)° [1]) and 1,2,4-triazolo[1,5*a*]pyrimidines (18.2(9)° [7]).

In the crystal, molecules of IIc form chains due to $OH\cdots N_{(3)'}$ hydrogen bonds (the $H\cdots N_{(3)'}$ bond length is 1.88(1) Å and the $OH\cdots N_{(3)'}$ angle is 166.8(8)°).

EXPERIMENTAL

X-Ray Diffraction Structural Analysis. Crystals of 2-(4-Dimethylaminophenyl)-3-hydroxy-4-phenyl-3,4-dihydropyrimido[1,2-*a*]benzimidazole (IIc, $C_{24}H_{22}N_4O$). The unit cell parameters of the monoclinic crystals of IIc at 20°C are as follows: a = 12.310(2), b = 9.897(1), c = 15.913(2)°, β = 91.88(2)°, Z = 4, d_{calc} = 1.311 g/cm^3, F(000) = 808, space group $P2_1/n$. The unit cell parameters and intensities of 2229 independent reflections with $F > 4\sigma(F)$ were taken on a Siemens P3/PC automatic four-circle diffractometer using λMoK_α radiation, graphite monochromator, and $\theta/2\theta$ scanning; $2\theta_{max} = 50°$.

The structure was solved by the direct method using the SHELTX PLUS programs. All the hydrogen atoms were revealed in the difference map. Anisotropic refinement for the non-hydrogen atoms and isotropic refinement for the hydrogen atoms gave R = 0.042 [R_w = 0.047, $w^{-1} = \sigma^2(F) + 0.003(F^2)$]. The atomic coordinates are given in Table 3.

The IR spectra of II-IV were taken in KBr pellets and CCl_4 solution ($c = 10^{-4}$-10^{-3} mole/liter) on a Specord IR-75 spectrometer. The UV spectra were taken on a Specord M-40 spectrometer in ethanol [$c = (2\text{-}4)\cdot 10^{-5}$ mole/liter]. The PMR spectra were taken for solutions in DMSO-d_6 on a Gemini-200 spectrometer using HMDS as the internal standard. The reaction

course and purity of the products were monitored using thin-layer chromatography on Silufol UV-254 plates with 10:1 benzene–methanol as the eluent.

The nitrogen contents found were in accord with the calculated values.

3-Hydroxy-2,4-diphenyl-3,4-dihydropyrimido[1,2-*a*]benzimidazole (IIa). Air was passed through a solution of 0.20 g (0.62 mmole) 2,4-diphenyl-3,4-dihydropyrimido[1,2-*a*]benzimidazole (Ia [3]) in 100 ml chloroform at 50-55°C for 1.5 h. The solution was evaporated to 20 ml and, after cooling, was filtered to give 0.19 g (91%) IIa with mp 202-205°C (from chloroform).

Products IIb-IId were obtained analogously.

2,4-Diphenyl-3-hydroxypyrimido[1,2-*a*]benzimidazole (III). A. A sample of 0.20 g (0.59 mmole) IIa was dissolved in 10 ml 2% methanolic KOH, heated at reflux for 1 h with free access to air, mixed with 50 ml water, neutralized by adding a solution obtained by adding one part concentrated hydrochloric acid and one part water, and filtered to give 0.14 g (70%) III with mp 275-278°C (from 2-propanol).

Product IV was obtained analogously.

B. A solution of 0.27 g (2 mmoles) 2-aminobenzimidazole (V) and 0.45 g (2 mmoles) epoxyketone VIc in 1 ml DMF was heated at reflux for 10 min, cooled, mixed with 20 ml benzene, washed with water, and dried over anhydrous Na_2SO_4. The solvent was distilled off. The residue was dissolved in 10 ml 2-propanol. The solution was cooled and filtered to give 0.20 g (26%) III. Products IIa (R_f 0.25) and III (R_f 0.30) were identified in the filtrate by thin-layer chromatography.

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