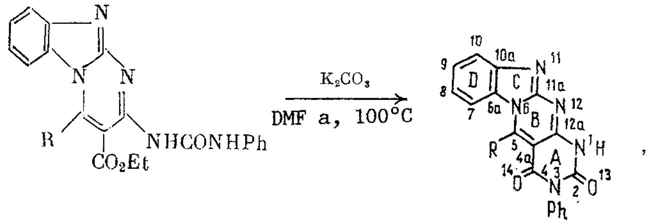
SYNTHESIS OF DERIVATIVES OF THE NEW HETEROCYCLIC SYSTEM PYRIMIDO[4′,5′:4,5]PYRIMIDO[1,2-a]BENZIMIDAZOLE

V. A. Dorokhov, M. F. Gordeev, Z. K. Dem'yanets,
L. G. Vorontsova, M. G. Kurella, V. I. Andrianov,
and O. A. Rekhlova

UDC 542.953:547.781:547.442.3

3-Phenyl-5-methyl(phenyl)-1H,3H-pyrimido[4′,5′:4,5]pyrimido[1,2-a]benzimidazole-2,4-diones were obtained by the cyclization of N-phenyl-N′-[3-ethoxycarbonyl-4-methyl(phenyl)pyrimido[1,2-a]benzimidazol-2-yl]ureas by the action of potassium carbonate. 2-Methyl-5-phenyl-1H-pyrimido[4′,5′:4,5]pyrimido[1,2-a]benzimidazol-4-one was obtained by the reaction of N′-3-ethoxycarbonyl-4-phenylpyrimido[1,2-a]benzimidazol-2-yl]-N,N-dimethylacetamidine with ammonium acetate in ethanol. The synthesized compounds are members of a new heterocyclic system. The molecular and crystal structure of the solvate of 3-phenyl-5-methyl-1H,3H-pyrimido[4′,5′:4,5]pyrimido[1,2-a]benzimidazole-2,4-dione with two molecules of DMF was studied by x-ray crystallographic analysis.

Earlier we synthesized new functionally 2-substituted derivatives of pyrimido[1,2-a]benzimidazole (amines, ureas, amidines, and guanidines) [1-3]. In the present work by means of the ureas and amidines of this series we obtained derivatives of a new heterocyclic system – pyrimido[4′,5′:4,5]pyrimido[1,2-a]benzimidazole. Thus, the intramolecular cyclization of the ureas (Ia, b), containing vicinal carbamide and ethoxycarbonyl groups in the pyrimidine ring, takes place under the influence of potassium carbonate and leads to the formation of 1H,3H-pyrimido[4′,5′:4,5]pyrimido[1,2-a]benzimidazole-2,4-diones (IIa, b) with yields of 61 and 56% respectively.

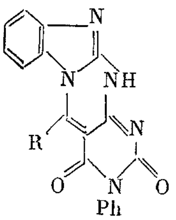


(1)

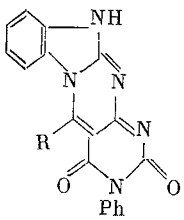
(IIa,b)

(Ia, b)
R = Me (a), Ph (b).

The tetracyclic compounds (IIa, b) are yellow crystalline substances poorly soluble in most organic solvents but moderately soluble in DMSO and DMF. Their mass spectra contain strong peaks for the molecular ions [M]$^{+\cdot}$ The IR spectra of (IIa, b) contain absorption bands for C=O at 1745-1730 and 1695-1685 cm^{-1}. The PMR spectra do not contain signals for the EtO group. However, the spectral data do not make it possible to eliminate fully the tautomeric structures A or B for the obtained heterocycles.



A



B

N. D. Zelinskii Institute of Organic Chemistry, Academy of Sciences of the USSR, Moscow. Translated from Izvestiya Akademii Nauk SSSR, Seriya Khimicheskaya, No. 11, pp. 2587-2592, November, 1991. Original article submitted December 4, 1990.

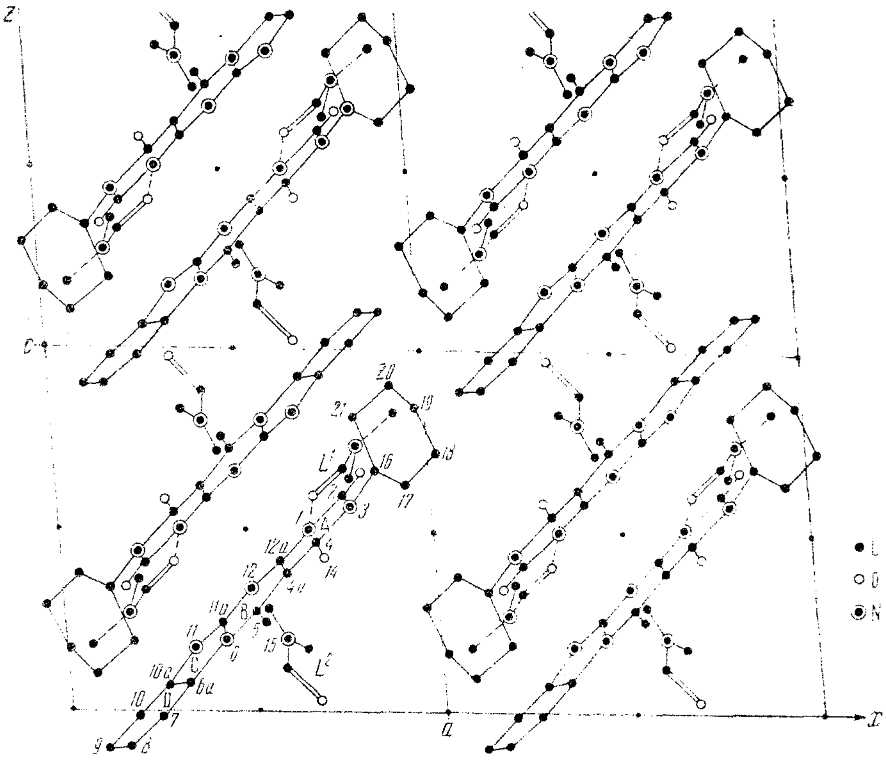


Fig. 1. Molecular and crystal structure of (IIa)·DMF in a projection onto the xz plane of the crystals.

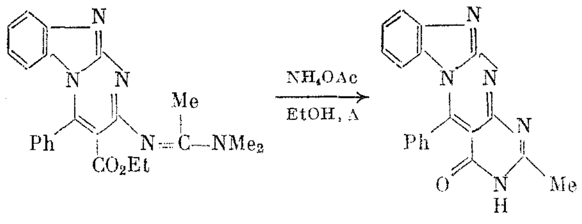
We investigated the molecular and crystal structure of the product from the cyclization of compound (Ia) in the form of a solvate with two molecules of DMF by x-ray crystallography and confirmed that its structure corresponded to the formula (II).

The tetracyclic skeleton of the molecule of (IIa)·2DMF is practically planar. (The numbering of the atoms is given in Fig. 1 and in scheme 1.) The dihedral angles between the planes of the component rings A, B, C, and D are as follows: A/B 1.33; B/C 1.0; C/D 1.40; A/D 2.76°. The deflections of the nonhydrogen atoms from the mean-square planes of A, B, C, D do not exceed 0.01 Å. In rings A, B, C, and D almost all the bond angles deviate from 120° and mainly vary between 114.3 and 126°. In ring C the exocyclic bond angles at the N^6 (132.8) and C^{6a} (133.0°) atoms are increased significantly in comparison with the endocyclic angles at the N^{11} (103.4°), N^6 (105.8°), C^{6a} (102.7°) and C^{11a} (113.60°) atoms. The sum of the bond angles at all the tertiary nitrogen atoms N^1, N^3, and N^6 amounts to 360° (the H atom at N^1 was localized by x-ray diffraction), i.e., the planar trigonal conformation of the N bonds is preserved. In the imidazole ring (C) the double bond is localized between the N^{11} and C^{11a} atoms (1.313 Å), the N^{11}–C^{10a} (1.378) and C^{10a}–C^{6a} (1.381 Å) bonds have an order of 1.5, and the C^{6a}–N^6 (1.427) and N^6–C^{11a} (1.400 Å) bonds are close to single N_{sp^2}–C_{st^2} (1.44 A) [4]. This shows that the unshared electron pair (UEP) of the N^6 atom interacts with the C^5–C^{4a} double bond (1.381 Å) of ring B, although as a rule the UEP of the pyrrole nitrogen atom in benzimidazole derivatives participates in the general delocalization of the π electrons of the bicyclic system (e.g. see [5-7]). In the pyrimidone imine fragment (ring B and the N^{11} atom) the lengths of the C^{11a}–N^{12} (1.345) and N^{12}–C^{12a} (1.315 Å) bonds appreciably exceed the standard length of the $N_{sp^2} = C_{sp^2}$ (1.279 Å), double bond, while the N^6–C^{11a} (1.400 Å) and (C^{4a}–C^{12a} (1.409 Å) bonds are close to single. In ring A, which can be compared with the pyrimidine ring of uracil, the N^3–C^4 (1.386), C^4–C^{4a} (1.471) and C^{4a}–C^{12a} (1.409 Å) bonds are longer than the corresponding bonds in uracil and its derivatives [8,9]. The C^2–O^{13} and C^4–O^{14} distances practically coincide with the lengths of the C=O bonds in tetrasubstituted ureas (e.g., see [10]). Thus, in the molecule of (IIa) it is possible to distinguish a planar zigzag chain $C^{10a} \cdots N^{11} \cdots C^{11a} \cdots N^{12} \cdots C^{12a} \cdots N^1 \cdots C^2 \cdots O^{13}$ with clearly defined delocalization of the electron density. We note that the N^3 atom does not participate in p–π conjugation with the phenyl group, since the plane of the latter forms an angle of 84.1° with ring A. The N^3–C(Ph) (1.466 Å) bond corresponds to a single C_{sp^2}–N_{sp^2} bond.

The included DMF molecules are planar (except for the H atoms). One molecule of DMF (L^1) is practically coplanar with the skeleton of (IIa) (the dihedral angle between the planes is 8.4°) and forms a strong intermolecular hydrogen bond N^1–H...O=C(L^1) with parameters N^1...O (2.78), (N^1)H...O (1.70 Å) and $\angle N^1$–H...O 158(4)°. The other molecule of DMF (L^2) does not participate in the formation of hydrogen bonds and is perpendicular to L^1, and the L^1/L^2 angle is 94.7°. The packing of the molecules in the crystal is of the layer type (Fig. 1). The molecules of (IIa) and L^1, related by a center of symmetry (0,0,0 and ½,½,½), form infinite "double" layers in stacks along the b axis. The layers are parallel to the $(\bar{1}01)$ plane. In each layer the long axis of the (IIa) molecule is extended along the (101) direction, and the molecules are packed in the "head-to-tail" fashion. In the "double" layer the van der Waals contacts between the planar fragments of the (IIa) molecules are shortened to 3.35 Å. In the stacks the "double" layers are separated by columns of L^2 molecules, which as it were support the planar fragments of the molecule (IIa) and thereby create a rigid architecture in the crystal.

It should be noted that compounds (IIa, b), which contain a fragment similar in structure to uracil, will probably be of interest as potential biologically active compounds (e.g., cf. the familiar antiallergens of the pyrimido[4,5-d]pyrimidine series [11]).

(Pyrimido[1,2-a]benzimidazol-2-yl)amidines, containing suitable functional groups at position 3 of the pyrimidine ring, can also be used to construct the pyrimido[4′,5′:4,5]-pyrimido[1,2-a]benzimidazole system. Thus, 1H-pyrimido[4′,5′:4,5]pyrimido[1,2-a]benzimidazol-4-one (IV) was obtained in the form of a yellow crystalline substance moderately soluble in DMSO and DMF by boiling the amidine (III) [3] in ethanol with ammonium acetate. Its mass spectrum contained a strong molecular ion peak, while its IR spectrum contained a band for the carbonyl group at 1700 cm^{-1}. The data from the PMR spectrum of this compound correspond to structure (IV).



(III) (IV)

(2)

EXPERIMENTAL

The PMR spectra were recorded on a Bruker WM-250 instrument (δ, ppm). The IR spectra were obtained on a UR-20 instrument (ν, cm^{-1}). The mass spectra were obtained on a Varian MAT CH-6 mass spectrometer (m/z).

Compounds (Ia, b), (III) were obtained by the method in [3].

3-Phenyl-5-methyl-1H,3H-pyrimido[4′,5′:4,5]pyrimido[1,2-a]benzimidazole-2,4-dione (IIa). A mixture of 1 mmole of (Ia) and 1 mmole of potassium carbonate was heated in 15 ml of DMF on a water bath at 100°C for 4 h. The solvent was distilled, the residue was washed with water, and the product was recrystallized from DMF and kept under vacuum (1 mm Hg) at 140°C. We obtained 0.208 g (61%) of (IIa); mp ~360°C (decomp.). Found %: C 66.30; H 3.80; N 20.52. $C_{19}H_{13}N_5O_2$. Calculated %: C 66.46; H 3.82; N 20.40. Mass spectrum: 343 $[M]^{+\cdot}$. IR spectrum in potassium bromide: 3500-2630 (NH, CH), 1730, 1685, 1650, 1605 (C=O, C=N). PMR spectrum in DMSO-d_6: 12.26 br.s (NH) 8.26 d (H^{10}), 7.82 d (H^7), 7.60-7.30 m ($7H_{arom}$), 3.60 s (Me).

3,5-Diphenyl-1H,3H-pyrimido[4′,5′:4,5]pyrimido[1,2-a]benzimidazole-2,4-dione (IIb). The compound was obtained similarly to (IIa) with a yield of 56%; mp ~360°C (decomp.). Found %: C 70.82; H 3.87; N 17.02. $C_{24}H_{15}N_5O_2$ Calculated: C 71.10; H 3.73; N 17.28. Mass spectrum: 405 $[M]^{+\cdot}$ IR spectrum in potassium bromide: 3500-2720 (NH, CH), 1735, 1695, 1630, 1605 (C=O, C=N). PMR spectrum in DMSO-d_6: 7.76-7.20 m ($12H_{arom}$), 6.92 t (H^8), 5.66 d (H^7).

2-Methyl-5-phenyl-1H-pyrimido[4′,5′:4,5]pyrimido[1,2-a]benzimidazol-4-one (IV). A solution of 0.110 g (0.27 mmole) of (III) and 0.5 g of ammonium acetate in 10 ml of ethanol was boiled for 1 h. The solvent was distilled, and the residue was recrystallized from DMF.

TABLE 1. Atomic Coordinates of Compound (IIa)·2DMF (Nonhydrogen atoms $\times 10^4$, Hydrogen atoms $\times 10^3$)

Atom	*X*	*Y*	*Z*
N^1	6964(4)	5591(4)	4777(6)
C^2	7813(5)	4681(5)	5583(8)
N^3	7731(4)	3631(4)	5360(6)
C^4	6863(5)	3214(5)	4404(8)
C^{4a}	5598(5)	4018(5)	3538(7)
C^5	5105(5)	3761(5)	2505(8)
N^6	4349(4)	4597(4)	1793(6)
C^{6a}	3340(5)	4645(5)	0700(8)
C^7	2773(5)	3877(6)	−0050(8)
C^8	1762(6)	4252(7)	−1052(9)
C^9	1362(6)	5301(8)	−1223(10)
C^{10}	1941(6)	6053(6)	−0478(9)
C^{10a}	2978(5)	5709(5)	0516(8)
N^{11}	3669(4)	6328(4)	1379(6)
C^{11a}	4478(5)	5642(5)	2125(8)
N^{12}	5349(4)	5899(4)	3126(6)
C^{12a}	6075(5)	5102(5)	3772(7)
O^{13}	8586(3)	4787(3)	6447(5)
O^{14}	6888(4)	2254(4)	4301(5)
C^{15}	4898(5)	2678(6)	2083(9)
C^{16} *	8583(5)	2850(5)	6306(8)
C^{17}	9683(6)	2887(6)	5787(9)
C^{18}	10498(6)	2181(7)	6725(11)
C^{19}	10194(6)	1417(6)	8094(10)
C^{20}	9079(6)	1405(6)	8525(9)
C^{21}	8240(5)	2112(6)	7637(9)
O^{22} (L^1)	7165(4)	7433(4)	5510(6)
N^{28} (L^1)	8470(5)	8452(5)	6749(7)
C^{24}	8043(6)	7516(6)	6413(9)
C^{25}	7947(10)	9501(8)	6054(14)
C^{26}	9466(9)	8438(9)	7856(13)
O^{27} (L^2)	6976(6)	−1091(5)	0178(9)
N^{28} (L^2)	6035(5)	−0573(6)	1822(9)
C^{29}	6663(9)	0548(8)	1503(16)
C^{30}	5129(7)	−0865(10)	2873(13)
C^{31}	6243(6)	−1285(8)	1116(14)
HC^7	319(5)	310(5)	−068(7)
HC^8	140(5)	370(5)	−174(7)
HC^9	052(7)	543(7)	−168(10)
HC^{10}	145(6)	677(6)	−048(8)
H^1C^{15}	417(7)	236(6)	224(9)
H^2C^{15}	563(9)	232(9)	215(13)
H^3C^{15}	484(7)	281(7)	097(9)
HN^1	685(5)	614(5)	518(7)

---

*The $C^{16}...C^{21}$ atoms belong to the benzene ring (D), $O^{22}...C^{26}$ to the DMF (L^1) molecule, and $O^{27}...C^{31}$ to the DMF (L^2) molecule.

We obtained 0.040 g (45%) of (IV); mp ~340°C (decomp.). Found %: C 69.84; H 4.24; N 22.12. $C_{19}H_{13}N_5O$. Calculated %: C 69.71; H 4.00; N 21.39. Mass spectrum: 327 $[M]^{+\cdot}$. IR spectrum in potassium bromide: 3300-2500 (NH, CH), 1700, 1610 (C=O, C=N). PMR spectrum in DMSO-d_6: 12.40-11.85 br.s (NH), 8.02-7.30 m ($7H_{arom}$), 6.95 t (H^8), 5.77 d (H^7), 2.39 s (Me).

X-Ray Crystallographic Analysis of (IIa)·2DMF. Single crystals of (IIa)·2DMF in the form of yellow extended four-phase prisms, grown from DMF, were unstable in air. The sample taken for analysis was therefore packed in paraffin. The crystals are triclinic: a = 11.33(1), b = 12.334(2), c = 9.332(2) Å, α = 72.42(1), β = 97.35(1), γ = 97.45(1)°, V = 1227.97 Å^3, space group $P\bar{1}$, Z = 2.

The unit cell parameters and a full set of intensities with $I \geq 2\sigma$ were obtained on an RED-4 four-circle autodiffractometer (CuK_α) with a graphite monochromator, $\omega = \theta/2\theta$ scan, $\theta \leq 60°$, and 2493 reflections. The preliminary treatment for the experiment was conducted by means of the DEM IOKh program on the ES-1022 computer.

A model of the structure was obtained by a combination of the direct method with the automatic method of successive approximations [12].

Initially the direct method did not give results in the $P\bar{1}$ space group. However, after changing to the P1 space group it was possible to reveal all 72 nonhydrogen atoms of the structure after 10 iterations. Analysis of the results showed that the molecules in the unit cell are related by a center of symmetry, and subsequent refinement of the structure was made in the P$\bar{1}$ space group. It is noteworthy that the search for the model in the P$\bar{1}$ space group also revealed the correct initial fragment of the structure. As found, however, it was displaced by 1.2 Å in relation to the true center of symmetry.

The structure was refined by least-squares treatment in isotropic-anisotropic full-matrix approximation. A large part of the hydrogen atoms (20) were localized from difference syntheses, and seven hydrogen atoms were introduced by geometry. The absorption of the crystal was taken into account by means of the DIFABS program. The final R value was 0.079. All the calculations on the interpretation of the structure were conducted on an ES-1045 computer with the AREN software [13]. The atomic coordinates are given in Table 1. The accuracy of the determination of the bond lengths for the nonhydrogen atoms was 0.007-0.009 Å, and the accuracy of the bond angles was 0.6-0.8°.

LITERATURE CITED

1. V. A. Dorokhov and M. F. Gordeev, Izv. Akad. Nauk SSSR, Ser. Khim., No. 2, 458 (1987).
2. V. A. Dorokhov, M. F. Gordeev, Z. K. Dem'yanets, et al., Izv. Akad. Nauk SSSR, Ser. Khim., No. 12, 2600 (1990).
3. M. F. Gordeev, Z. K. Dem'yanets, M. N. Bochkareva, and V. A. Dorokhov, Izv. Akad. Nauk SSSR, Ser. Khim., No. 12 (1991).
4. F. H. Allen, O. Kennard, D. G. Watson, et al., J. Chem. Soc. Perkin Trans. II, 51 (1987).
5. H. P. Weber and F. Trokler, Helv. Chim. Acta, 57, No. 8, 23 (1974).
6. S. Sprang and M. Sundaralingam, Acta Crystallogr., 29, No. 10, 1910 (1973).
7. D. Kohne, K. Praetcke, T. Derz, et al., Angew. Chem., 98, No. 17, 627 (1986).
8. G. N. Reeke and R. E. Marsh, Acta Crystallogr., 20, No. 6, 703 (1966).
9. R. F. Steward and L. H. Jensen, Acta Crystallogr., 23, 1102 (1967).
10. A. I. Kitaigorodskii, P. M. Zorkii, and V. K. Bel'skii, Structure of Organic Material [in Russian], Nauka, Moscow (1988), p. 441.
11. Eur. Pat. Appl., 163.599; Chem. Abs., 104, 1864394 (1986).
12. V. I. Andrianov, T. A. Shibanova, and V. I. Simonov, Kristallografiya, 32, No. 1, 41 (1987).
13. V. I. Andrianov, Kristallografiya, 32, No. 1, 228 (1987).