SYNTHESIS OF FUNCTIONALIZED PYRIMIDO[1,2-a]-BENZIMIDAZOLES FROM (BENZIMIDAZOL-2-YL)CYANAMIDE AND β-DICARBONYL COMPOUNDS USING NICKEL COMPLEXES OR SALTS

V. A. Dorokhov, M. F. Gordeev,
Z. K. Dem'yanets, M. N. Bochkareva,
and V. S. Bogdanov

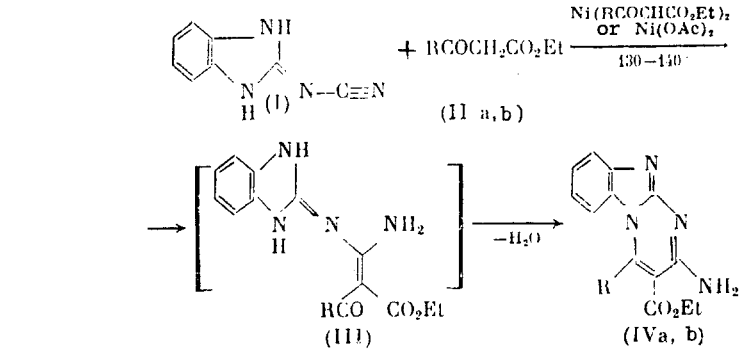
UDC 542.97:542.953:547.785.5:547.442.3

It was found that cyclocondensation of (benzimidazol-2-yl)cyanamide with β-diketones and β-ketoesters proceeds in the presence of β-ketoenolates or nickel(2+) acetate with the formation of 2-aminopyrimido[1,2-a]benzimidazole derivatives. Protonation (deuteration) and methylation of substituted 2-aminopyrimido[1,2-a]benzimidazoles takes place at the N^{10} atom, while acylation by carboxylic acid anhydrides gives the 2-acylamino derivatives exclusively.

We have recently shown that Ni(2+) β-ketoenolates catalyze the addition of β-diketones and β-ketoesters to the C≡N group of cyanamide or monosubstituted cyanamides [1, 2]. This path of formation of the C–C bond can be used for constructing heterocyclic systems. We have previously developed a convenient one-stage method of synthesis of functionalized pyrimidines from active-methylene groups containing β-dicarbonyl compounds (DCC) and N-cyanoamidines [3].

In the present work, we studied the cyclocondensation of (benzimidazol-2-yl)cyanamide (I) containing a cyanoguanidine fragment with β-ketoesters and β-diketones (see also the preliminary publications [4, 5]). In the presence of the corresponding Ni(2+) β-ketoenolates this process proceeds with the formation 2-aminopyrimido[1,2-a]benzimidazole (APB) derivatives (see schemes 1, 2 and Tables 1, 2). The optimal yields of APB are attained on carrying out

Scheme 1



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

the reaction in a DCC medium using the equimolar amounts of (I) and Ni(2+) complexes. Instead of the later, $Ni(OAc)_2$ can also be used; in such a case, although the APB are obtained in lower yields, the necessity of the preparation of Ni β-ketoenolates from the corresponding DCC is avoided.

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. 2600-2608, November, 1990. Original article submitted December 28, 1989.

 0568-5230/90/3911-2354$12.50

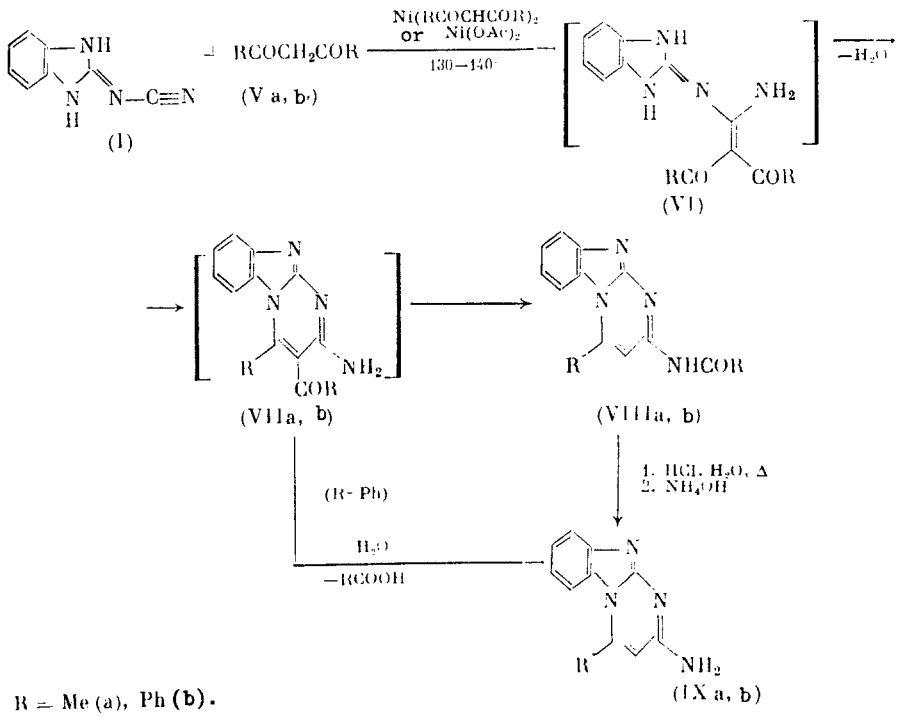
TABLE 1. Derivatives of 2-Aminopyrimido[1,2-a]benzimidazole (APB)

APB	Yield, %	Mp, °C	Found/Calculated, %			Empirical formula	Mass spectrum, m/z	IR spectrum (KBr, ν, cm^{-1})
			C	H	N			
(IVa)	63 (49)[a]	245–246 (EtOH)	64,95 / 62,21	5,45 / 5,22	20,53 / 20,73	$C_{14}H_{14}N_4O_2$	270 $[M]^{+\cdot}$	3400 (NH), 3300–2800 (NH, CH), 1690 (CO), 1645, 1612, 1585, 1509
(IVb)	62 (48)[a]	304–305 (EtOH)	68,40 / 68,66	4,32 / 4,85	16,63 / 16,86	$C_{19}H_{16}N_4O_2$	332 $[M]^{+\cdot}$	3445, 3295 (NH), 3250–2800 (NH, CH), 1700 (CO), 1645, 1580, 1547, 1521
(VIIa)	7	243–247 (dec., MeCN)	64,52 / 64,98	5,18 / 5,03	23,10 / 23,32	$C_{13}H_{12}N_4O$	240 $[M]^{+\cdot}$	3600–2800 (NH, CH), 3160 (NH), 1684 (CO), 1660, 1647, 1592
(VIIIa)	81 (95)[b]	324–325 (dec., DMF)	65,19 / 64,98	5,30 / 5,03	23,02 / 23,32	$C_{13}H_{12}N_4O$	240 $[M]^{+\cdot}$	3293, 3250 (NH), 3200–2800 (NH, CH), 1740 (CO), 1635, 1610, 1570, 1540
(VIIIb)	54 (9)[b]	301–303 (dec., DMF)	75,98 / 75,81	4,69 / 4,43	15,31 / 15,38	$C_{23}H_{16}N_4O$	364 $[M]^{+\cdot}$	3420 (NH), 3200–2870 (NH, CH), 1695 (CO), 1630, 1596, 1564, 1540[c]
(VIIIc)	80[b]	259–260 (dec., toluene)	71,03 / 71,51	4,80 / 4,67	18,25 / 18,53	$C_{18}H_{14}N_4O$	302 $[M]^{+\cdot}$	3410 (NH), 3200–2800 (NH, CH), 1695 (CO), 1630, 1607, 1570, 1543[c]
(IXa)	80 (33)[a]	319–320 (dec., MeCN)	66,56 / 66,65	5,20 / 5,09	28,20 / 28,27	$C_{11}H_{10}N_4$	198 $[M]^{+\cdot}$	3430, 3300 (NH), 3240–2700 (NH, CH), 1665, 1640, 1610, 1585, 1547
(IXb)	65 (31)[a]	364–366 (dec., DMF)	73,69 / 73,83	4,62 / 4,65	21,22 / 21,53	$C_{16}H_{12}N_4$	260 $[M]^{+\cdot}$	3445, 3310 (NH), 3250–2700 (NH, CH), 1655, 1615, 1600, 1583, 1540
(XII)	98 (95)[d]	331–333 (dec., reprecipitated by Et_2O from MeOH)	56,08 / 56,29	5,03 / 4,72	24,17 / 23,88	$C_{11}H_{10}N_4 \cdot HCl$[e]	198 $[M-HCl]^{+\cdot}$	3500–2400 (NH, CH), 1668, 1600, 1525, 1510
(XIIIa)	94	278–280 (dec., reprecipitated by Et_2O from MeOH)	42,16 / 42,37	4,19 / 3,85	16,50 / 16,47	$C_{12}H_{12}N_4 \cdot HI$[f]	212 $[M-HI]^{+\cdot}$	3600–2800 (NH, CH), 1660, 1610, 1587, 1520
(XIIIb)	94	298–300 (dec., reprecipitated by Et_2O from MeOH)	44,03 / 43,99	4,01 / 3,96	14,60 / 14,66	$C_{14}H_{14}N_3O \cdot HI$[g]	254 $[M-HI]^{+\cdot}$	3260–2600 (NH, CH), 1727 (CO), 1652, 1610, 1581, 1511

[a]The yield on using $Ni(OAc)_2$ in the reaction is given in brackets.
[b]The yield of the acylation reaction of (IX) is given in brackets.
[c]In CH_2Cl_2.
[d]The yield in the reaction of (IXa) with aqueous HCl is given in brackets.
[e]Found: Cl 15.38%. Calculated: Cl 15.11%.
[f]Found: I 37.06%. Calculated: I 37.31%.
[g]Found: I 32.70%. Calculated: I 33.20%.

The corresponding 2-amino-3-ethoxycarbonylpyrimido[1,2-a]benzimidazoles (IVa, b) were obtained by the reaction of (I) with β-ketoesters (IIa, b).

Scheme 2



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

The reaction of (I) with β-diketones (Va, b) gives instead of the expected 2-amino-3-acylpyrimido[1,2-a]benzimidazoles (VIIa, b), their isomeric 2-acylaminopyrimido[1,2-a]-benzimidazoles (VIIIa, b) as the main products in yields of 81 and 54%, respectively. Only in the reaction of (I) with (Va), compound (VIIa), together with (VIIIa), was isolated by column chromatography in a yield of 7%. In the case of the reaction of (I) with (Vb) together with (VIIIb), 2-amino-4-phenylpyrimido[1,2-a]benzimidazole (IXb) was also formed, and isolated by preparative TLC in a yield of 12%. The reaction of (I) with (Va, b) in the presence of Ni(2+) salts or complexes can be used as a convenient method for the preparation of APB (IXa, b), if after the removal of excess DCC, the reaction mixture is treated at the boiling point with aqueous HCl with boiling, and then neutralized with NH_4OH. The yield of (IXa, b) thereby reaches 80 and 65%, respectively.

It should be noted that in the absence of Ni(2+) complexes or of $Ni(OAc)_2$, APB cannot be synthesized from (I) and DCC, even on using acidic (TsOH) or alkaline (EtONa) catalysts (compound (I), is thus recovered from the reaction mixtures). On the contrary, $Ni(acac)_2$ reacts in the absence of free DCC, with (I) with DMF at 130-140°C (the course of the process was monitored by IR spectroscopy from the disappearance of the absorption band $\nu_{C\equiv N} \sim 2180$ cm^{-1}). In this case, on boiling the reaction mixture with aqueous HCl and subsequent treatment with NH_4OH, a mixture of compounds (VIIa) and (IXa) was obtained in a molar ratio of ~1:2 (overall yield ~30%). It is possible that, as in the case of the reaction of DCC with cyanamides, previously studied by us in [1, 2], the nucleophilic attack of the CH group of Ni(2+) β-ketoenolate at the C≡N bond of (I) and the formation of intermediates (III) or (VI), which further cyclize with splitting of H_2O into (IV) or (VII), play the key role in processes (1) and (2). The possibility of the electrophilic activation of the C≡N group by coordination of (I) with a Ni(2+) salt or complex also must be taken into account (the ability of compounds of the 2-aminobenzimidazole series to form complexes with transition metals is well known [6]).

The structure of APB (IVa, b), (VIIa), (VIIIa, b) and (IXa, b) was confirmed by spectral methods (IR, ^1H and ^{13}C NMR spectroscopy, and mass spectrometry). The mass spectra of these compounds show intense peaks of molecular ions. The IR spectra of compounds (IVa, b), (VIIa) and (VIIIa, b) include absorption bands of the CO groups in the 1710-1680 cm^{-1} region.

TABLE 2. PMR Spectra of 2-Aminopyrimido[1,2-a]benzimidazole (APB) Derivatives

APB	Solvent	PMR spectrum, δ, ppm
(IVa)	DMSO-d_6	7,95 d (H^9), 7,55 d (H^6), 7,35 t (H^7), 7,34 br.s (NH_2), 7,14 t (H^8), 4,38 q (OCH_2), 3,00 s (Me), 1,33 t ($CH_2\underline{Me}$)
(IVb)	DMSO-d_6	7,75–7,53 m (Ph and NH_2), 7,50 d (H^9), 7,20 d (H^6), 6,71 t (H^7), 5,59 t (H^8), 3,90 q (OCH_2), 0,70 t (Me)
(VIIa)	DMSO-d_6	7,93 d (H^9), 7,55 d (H^6), 7,33 t (H^7), 7,25 br.s (NH_2), 7,13 t (H^8), 2,85 s (Me), 2,57 s (MeCO)
(VIIIa)	DMSO-d_6	11,15 s (NH), 8,13 d (H^9), 7,75 d (H^6), 7,73 s (H^3), 7,48 t (H^7), 7,30 t (H^8), 3,02 s (Me), 2,13 s (MeCO)
(VIIIa)	CD_3COOH	8,25 s (H^3), 8,23 s (H^9), 7,87 d (H^6), 7,71 t (H^7), 7,57 t (H^8), 3,17 s (Me), 2,34 s (MeCO)
(VIIIb)	$CDCl_3$	9,04 s (NH), 8,09 s (H^3), 8,00 d (2 *o*-H(Ph)), 7,89 d (H^9), 7,78–7,50 m (8H phenyl), 7,43 t (H^8), 7,00 t (H^7), 6,65 d (H^6)
(VIIIc)	DMSO-d_6	11,46 s (NH), 8,14 d (H^9), 8,08 d (2 *o*-H(Ph)), 7,87 s (H^3), 7,78 d (H^6), 7,63 t (*p*-H(Ph)), 7,53 t (2 *m*-H(Ph)), 7,48 t (H^7), 7,30 t (H^8), 3,06 s (Me)
(IXa)	DMSO-d_6	7,86 d (H^9), 7,51 d (H^6), 7,27 d (H^7), 7,20 br.s (NH_2), 7,09 t (H^8), 6,13 s (H^3), 2,82 s (Me)
(IXa)	CD_3COOD	8,02 d (H^9), 7,68 d (H^6), 7,56 t (H^7), 7,45 t (H^8), 6,70 s (H^3), 2,95 s (Me)
(IXb)	DMSO-d_6	7,75–7,56 m (Ph), 7,50 d (H^9), 7,43 br.s (NH_2), 7,17 t (H^8), 6,75 t (H^7), 6,17 s (H^3), 6,12 d (H^6)
(XII)	DMSO-d_6	8,67 br.s (NH), 8,44 br.s (NH), 8,07 d (H^9), 7,62 d (H^6), 7,54 t (H^7), 7,39 t (H^8), 6,57 s (H^3), 2,89 s (Me)
(XIIIa)	DMSO-d_6	8,65 br.s (NH), 8,62 br.s (NH), 8,09 d (H^9), 7,81 d (H^6), 7,57 t (H^7), 7,42 t (H^8), 3,77 s (10-Me), 2,91 s (4-Me)
(XIIIb)	DMSO-d_6	11,90 s (NH), 8,43 d (H^9), 8,20 s (H^3), 8,10 d (H^6), 7,85 t (H^7), 7,76 t (H^8), 4,00 s (10-Me), 3,20 s (4-Me), 2,26 s (MeCO)

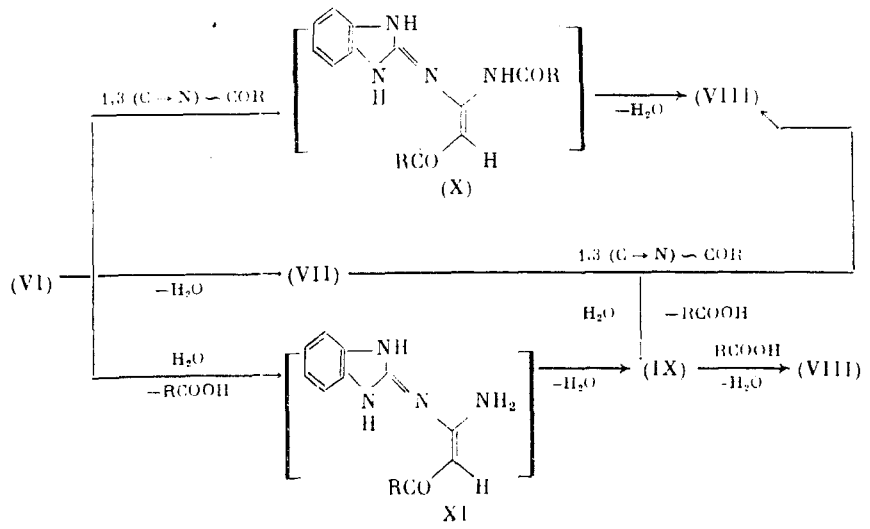
The assignment of signals in high resolution ^{13}C NMR spectra of compounds (IVa), (VIIa), (VIIIa, b) and (IXa, b) was carried out taking into account the SSCC, the multiplicity of the signals and on the basis of the spectra of the model compound – 2-amino-1-methylbenzimidazole (when necessary the method of the $^{13}C-\{^1H\}$ double resonance was used). The ^{13}C NMR spectra of (VIIIa, b) contain doublets of the C^3 atom. Thus, in the spectrum of (VIIIa), the signal of this atom is observed at δ 99.03 ppm ($^1J_{C^3,H}$ = 175.0 Hz), and in APB (IXa) at δ 98.06 ppm ($^1J_{C^3,H}$ = 170.0 Hz), while in compound (VIIa), isomeric with (VIIIa), this signal appears in the form of a broadened singlet at δ 111.93 ppm.

The formation of compounds (VIII) from β-diketones (Va, b) and (I) can be represented as a result of the 1,3- (C → N) acyl migration in the molecule of ketene amimal (VI) or in the product of its intramolecular condensation (VII). However, the transformation of (VIIa) into (VIIIa) could not be obtained on boiling this compound for 12 h in xylene or for 2 h in (Va) in the presence of $Ni(acac)_2$ or its absence [(VIIa) practically does not change under these conditions]. Another probable path includes the protolytic C-deacylation of intermediates (VI) or (VII) with the formation of (IX) and carboxylic acid acylating (IX) under the reaction conditions at the NH_2 group (see Scheme 3 on following page).

The following arguments can be presented in favor of this scheme. Firstly, it is known that salts and complexes of transition metals are capable of catalyzing the protolytic C-deacylation of DCC [7] and diacylketene aminals [8]. Secondly, we found that the reaction of (IXa) with AcOH at 130-140°C proceeds readily with the formation of (VIIIa). Thirdly, compound (IXb) was isolated from the products of the reaction of (I) with (Vb). It must be admitted however, that the above considerations do not permit an unequivocal solution to the problem of the formation mechanism of compounds (VIII).

Compounds of the 2-aminopyrimido[1,2-a]benzimidazole series have not yet been reported. The synthesis of 2-amino-3-ethoxycarbonylpyrimido[1,2-a]benzimidazole from 2-aminobenzimidazole and ethoxymethylenecyanoacetic ester was reported in [9], but it was later proved that

Scheme 3

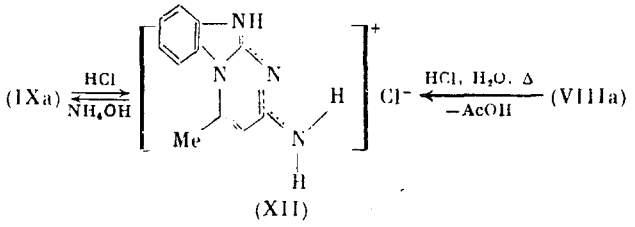


this reaction gives a mixture of 4-amino-3-ethoxycarbonylpyrimido[1,2-a]benzimidazole and 3-cyano-1H-pyrimido[1,2-a]benzimidazol-4-one [10].

We studied certain transformations of APB: protonation (deuteration), methylation and acylation.

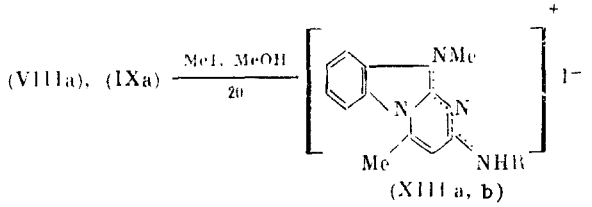
On treating APB (IXa) with aqueous HCl, the hydrochloride (XII) was obtained, which by the action of NH_4OH again gives the initial base (IXa). Salt (XII) was also isolated on boiling the N-acetyl derivative of APB (VIIIa) with aqueous HCl

Scheme 4



Methylation of APB (VIIIa) and (IXa) by the action of MeI in MeOH proceeds at 20°C at the N atom of the benzimidazole fragment and gives the corresponding salts (XIIIa, b) in high yields.

Scheme 5



R = H (a), Ac (b).

Compounds (XII), (XIIIa, b) are stable crystalline substances (for example, (XIIIa) does not change after 2 h at 100°C in a DMSO-d_6 solution).

The mass spectra of salts (XIIIa, b) contain intense peaks of $[M-HI]^+$ and $[M-HI-Me]^+$ ions, while the spectrum of hydrochloride (XII) contains the peak of the $[M-HCl]^+$ ion.

The regiospecificity of the protonation (deuteration) and methylation reactions of APB was confirmed by the spectral data (^1H, ^{13}C and ^{15}N NMR spectroscopy). In the ^{13}C spectra of (VIIIa) and (IXa) in CD_3COOD a strong-field shift of the C^{9a} atom is observed, compared with its signal in the spectra of these APB in DMSO-d_6, by not less than 13.49 and 9.28 ppm,

TABLE 3. ^{13}C NMR Spectra of 2-Aminopyrimido[1,2-a]benzimidazole (APB) Derivatives

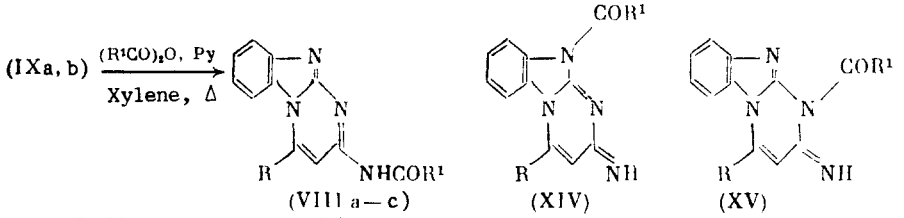
APB	Solvent	^{13}C NMR spectrum, δ, ppm (J, Hz)*
(IVa)	DMSO-d_6	165,42 (CO), 157,19 (C^{10a}), 151,32 (C^2), 151,22 q (C^4, $^2J_{C^4, Me} = 7,6$), 145,22 d.d. (C^{9a}), 128,88d.d. (C^{5a}), 124,64 d, 119,37 d (C^7 and C^8), 117,37d (C^9), 114,82 d (C^6), 102,13 m (C^3), 61,67 t (CH_2, $^1J_{C, H} = 151,0$), 18,54 q (Me, $^1J_{C, H} = 132,0$), 13,72 q (MeCH$_2$, $^1J_{C, H} = 127,0$)
(VIIa)	DMSO-d_6	201,51 (CO), 156,61 s (C^{10a}), 151,69 s (C^2), 147,00 q (C^4, $^2J_{C^4, Me} = 6,0$), 145,09 d.d (C^{9a}), 128,94 d.d (C^{5a}), 124,49 d.d ($^1J_{C, H} = 161,0$, $^2J_{C, H} = 8,0$), 119,36 d.d ($^1J_{C, H} = 161,0$, $^2J_{C, H} = 7,0$) (C^7 and C^8), 117,46 d.d (C^9, $^1J_{C, H} = 162,0$, $^2J_{C, H} = 8,0$), 114,66 d.d (C^6, $^1J_{C, H} = 164,0$, $^2J_{C, H} = 8,0$), 111,93 br.s (C^3), 32,29 q MeCO, $^1J_{C, H} = 128,0$), 18,13 q (Me, $^1J_{C, H} = 132,0$)
(VIIIa)	DMSO-d_6	170,16 (CO), 154,97 s (C^{10a}), 150,75s (C^2), 150,36 (C^4), 144,46 d.d (C^{9a}), 127,98 d.d (C^{5a}), 124,90 d, 120,16 d (C^7 and C^8), 118,12 d (C^9), 114,90 d (C^6), 99,03 d (C^3, $^1J_{C^3, H}$, 175,0), 24,10 q (MeCO), 20,45q (Me)
(VIIIa)	CD_3COOD	174,22 (CO), 160,26 (C^{10a}), 155,77 (C^2), 149,72 (C^4), 135,18, 128,62 (C^{9a} and C^{5a}), 130,41, 126,22 (C^7 and C^8), 118,08, 116,66 (C^6 and C^9), 105,68 (C^3), 25,89 (MeCO), 22,50 (Me)
(VIIIb)	DMSO-d_6	166,60 (CO), 155,29 (C^{10a}), 150,63 (C^2), 149,87 (C^4), 144,49, (C^{9a}), 133,11, 132,20, 132,05, 130,68, 128,97, 128,08, 128,01 (12 C, 2Ph), 127,25 (C^{5d}), 124,93, 119,91 (C^7 and C^8), 118,56 (C^9), 113,47 (C^6), 100,99 (C^3, $^1J_{C^3, H} = 176,0$)
(IXa)	DMSO-d_6	160,62 s (C^{10a}), 153,32 br.s (C^2), 147,20 m (C^4, $^2J_{C^4, H^3} = 3,3$), 144,05 m (C^{9a}), 128,56 m (C^{5a}), 123,72 d.d ($^1J_{C, H} = 161,0$, $^2J_{C, H} = 7,0$), 118,96 d.d ($^1J_{C, H} = 160,0$, $^2J_{C, H} = 8,0$), (C^7 and C^8), 116,94 d.d (C^9, $^1J_{C, H} = 162,0$, $^2J_{C, H} = 8,0$), 113,54 d.d (C^6, $^1J_{C, H} = 164,0$, $^2J_{C, H} = 8,0$), 98,06 d.q.t (C^3, $^1J_{C^3, H} = 170,0$, $^3J_{C^3, Me} = 4,9$, $^3J_{C^3, NH_2} = 5,5$), 19,80 q.d (Me, $^1J_{C, H} = 129,0$, $^3J_{C, H} = 5,0$)
(IXa)	CD_3COOD	163,24 s (C^{10a}), 149,85 br.d (C^4, $^2J_{C^4, H} = 6$), 149,01 s (C^2), 130,56 d.d, 126,63 d.d (C^{9a} and C^{5a}), 127,37 d.d ($^1J_{C, H} = 164,0$), 124,06 d.d ($^1J_{C, H} = 165,0$), 115,21 d.d ($^1J_{C, H} = 172,0$), 113,30 d.d ($^1J_{C, H} = 169,0$) (C^6, C^7, C^8 and C^9), 102,50 d (C^3, $^1J_{C^3, H} = 174,0$), 19,91 q (Me, $^1J_{C, H} = 131,0$)
(IXb)	DMSO-d_6	160,30 s (C^{10a}), 153,31 br.s (C^2), 147,67 m (C^4), 144,50 d.d (C^{9a}), 132,34 m (C^1—Ph), 130,43 d (*p*-CPh, $^1J_{C, H} = 165,0$), 129,00 d ($^1J_{C, H} = 162,0$), 128,23 d $^1J_{C, H} = 161,0$, 2*o*-C and 2*m*-CPh), 123,56 d.d ($^1J_{C, H} = 158,0$), 118,37 d d ($^1J_{C, H} = 159,0$) (C^7 and C^8), 117,32 d.d (C^9, $^1J_{C, H} = 159,0$), 112,22 d.d (C^6, $^1J_{C, H} = 164,0$), 127,87 (C^{5a}), 99,36 d.d (C^3, $^1J_{C^3} = 171,0$, $^3J_{C, NH_2} = 5,7$)
(XIIIa)	DMSO-d_6	162,06 (C^{10a}), 149,12 (C^4), 147,85 (C^2), 131,31, 125,16 (C^{9a} and C^{5a}), 126,39, 123,51 (C^7 and C^8), 115,14, 111,14 (C^6 and C^9), 101,19 (C^3), 28,96 (MeN), 20,03 (Me)
2-Amino-1-methylbenzimidazole	DMSO-d_6	155,37 q ($^3J_{C^2, Me^{3,0}}$, C^2), 142,66 d.d ($^2J_{C^{3a}, H} = 8,5$, $^3J_{C^{3a}, H} = 5,5$, C^{3a}), 134,88 m ($^2J_{C^{7a}, H} = 8,5$, $^3J_{C^{7a}, H} = 7,0$, C^{7a}), 120,26 d.d ($^1J_{C, H} = 158,7$, $^2J_{C, H} = 7,3$), 118,00 d.d ($^1J_{C, H} = 159,9$, $^2J_{C, H} = 7,9$) (C^5 and C^6), 114,64 d.d (C^4, $^1J_{C^{4a}, H} = 159,3$, $^2J_{C^4, H} = 7,3$), 107,29 d.d (C^7, $^1J_{C^7, H} = 160,5$, $^2J_{C^7, H} = 7,9$), 28,35 q (Me, $^1J_{C, H} = 139,2$)

*The SSCC and the multiplicity of the signals are shown in cases where they were necessary for making assignments.

respectively (cf. [11]: the protonation of 1-methylbenzimidazole at N^3 leads to a 10.13 ppm shift of the signal of the C^{3a} atom to a strong field). The PMR spectra of APB (VIIIa), (IXa) in CD_3COOD and of the corresponding salts (XII), (XIIIa, b) in DMSO-d_6, and also the ^{13}C NMR spectra of (IXa) in CD_3COOD and (XIIIa) in DMSO-d_6 are similar to one another, which indicates a structural similarity of the protonated (deuterated) forms of these compounds and the products of their methylation (XIII). In the ^{15}N spectra of salts (XII) and (XIIIa) in DMSO-d_6 (35°C) triplets are observed of the NH_2 group (δ = −278.35 ppm, ^1J = 90.0 Hz and δ = −274.71 ppm, ^1J 90.0 Hz, respectively), which excludes protonation or alkylation at the amino group. The PMR spectra of (XII) and (XIIIa) in DMSO-d_6 reveal the nonequivalency of the NH_2 group protons, indicating the presence of a rotation barrier around the C^2—NH_2 bond as a result of delocalization of the multiple bonds (compare: the spectra of APB (VIIa) and (IXa, b) in DMSO-d_6 contain only one signal of the NH_2 group).

The reaction of APB (IXa, b) with carboxylic acid anhydrides in boiling xylene proceeds regiospecifically and leads to compounds with an exocyclic acylamino group (VIIIa, b) identical to products isolated in the reaction of β-diketones (Va, b) with (I) (see Schemes 2 and 6). In a similar way, compound (VIIIc) was synthesized from (IXa) and Bz_2O

Scheme 6



R = R^1=Me (a), R = R^1=Ph (b), R = Me, R^1 = Ph (c).

On the basis of the spectral data, structures (XIV) and (XV), alternative to (VIII), can be excluded. In fact, in the spectra of (VIIIa, b) there are signals of the C^{9a} atoms with chemical shifts (CS) of 144.46 and 144.49 ppm, respectively, Table 3), which are very close in their values to the CS of C^{9a} in compounds (IVa), (VIIa), (IXa, b) (144.09-145.22 ppm). The IR spectra of (VIIIb, c) in CH_2Cl_2 show NH absorption bands in the region of 3410-3420 cm^{-1} (as known the NH signals of the imino group of the amidine system are usually observed at 3310-3330 cm^{-1} [12]).

The PMR spectrum of (VIIIa) reveals a deutero exchange in the 4-Me group, proceeding slowly in the solution of this compound in CD_3COOD at ∿20°C.

The method of constructing the pyrimido[1,2-a]benzimidazole system from DCC and (benzimidazol-2-yl)cyanamide in the presence of Ni(2+) salts of complexes, discussed in the present work, is a novel example of the use of the strategy of chelate organic synthesis for the preparation of heterocyclic comopunds (see also [3, 13-15]).

EXPERIMENTAL

The PMR spectra were recorded on a "Bruker WM-250" spectrometer, while the ^{13}C NMR spectra of compounds (IVa), (VIIa), (VIIIa, b), (IXa, b), (XIIIa) and the ^{15}N NMR spectra of salts (XII), (XIIIa) were taken on a "Bruker AM-300" spectrometer (the CS in the ^{15}N NMR spectra were measured relative to $MeNO_2$ as external standard). The IR spectra were recorded on a UR-20 spectrophotometer. The mass spectra were obtained on a "Varian MAT CH-6" mass spectrometer.

Cyanamide (I) was synthesized according to [16], and the Ni(2+) complexes of the β-ketoesters according to [17].

2-Amino-4-methyl(phenyl)-3-ethoxycarbonylpyrimido[1,2-a]benzimidazoles (Va, b) and 2-Amino-4-methyl(phenyl)pyrimido[1,2-a]benzimidazoles (XIa, b). A mixture of 6 mmoles of (I), 6 mmoles of Ni(2+) β-ketoenolate or acetate and 24 mmoles of DCC (IIa, b), (Va, b) was stirred for 40 min in a dry Ar atmosphere at 130-140°C. In experiments with (IIa, b), (Va), the excess DCC was removed in vacuo, and in the reaction with (Vb) by washing the reaction mixture with a hexane—Et_2O (1:1) mixture. In the synthesis of (IVa, b), the residue remaining after removal of excess DCC was dissolved in 1.5 N HCl in EtOH at 30-40°C, the solvent

was distilled off, and the residue was washed with a pentane–Et_2O (1:1) mixture, a 25% NH_4OH solution, and (IVa, b) was obtained. In the synthesis of (IXa, b), the residue was boiled with 30 ml of aqueous concentrated HCl for 2.5 h (in the case of (Va)) or for 5 h (in the case of (Vb)). In the reaction with (Va), 25% NH_4OH was added to the mixture (to pH ∿8), the precipitate was filtered off, washed with a 25% NH_4OH solution (to decoloration of the filtrate) and MeCN, and (IXa) was obtained (in the reaction using $Ni(OAc)_2$, the crude product was crystallized from MeCN). In the synthesis of (IXb), the precipitate that separated out from the acid solution on cooling was filtered off, washed with Et_2O and a 25% NH_4OH solution, crystallized from DMF, and compound (IXb) was obtained. The crude products were dried in vacuo over P_2O_5. The analytical preparations were obtained by crystallization from a suitable solvent (Table 1).

The yields, physicochemical properties and elemental analysis data of compounds (IVa, b) and (IXa, b) are given in Table 1.

2-Amino-3-acetyl-4-methylpyrimido[1,2-a]benzimidazole (VIIa) and 2-Acetylamino-4-methylpyrimido[1,2-a]benzimidazole (VIIIa). As in the synthesis of (IXa), the reaction mixture obtained from (I), (Va), and $Ni(acac)_2$, after the removal of excess (Va) was heated with 5 ml of AcOH for 30-40 min at 60-70°C (according to the data of control experiments, APB (VIIa), (VIIIa) do not change under these conditions). After cooling, a 25% solution of NH_4OH was added in small portions (to pH 8), the precipitate that separated out was filtered off, washed with a 25% NH_4OH solution, and then with 5 × 7 ml of MeCN, dried in vacuo over P_2O_5, and (VIIIa) was obtained. The MeCN solvent was distilled off from the filtrate, and the residue was chromatographed on a column with SiO_2 40/100 μm (eluent $CHCl_3$–EtOH, 10:1), and compound (VIIa) was obtained (R_f 0.2) (Table 1).

2-Benzoylamino-4-phenylpyrimido[1,2-a]benzimidazole (VIIIb) and (IXb). As in the synthesis of (IXb) (see above), the reaction mixture obtained from (I), (Vb) and $Ni(dbm)_2$ was partitioned on plates with SiO_2 Silpearl UV-254 (eluent $CHCl_3$–MeOH, 20:1) and compounds (IXb) (R_f 0.2) and (VIIIb) (R_f 0.5) were obtained, yield 12 and 54%, respectively (Table 1).

Synthesis of (VIIa) and (IXa) from $Ni(acac)_2$ and (I). A mixture of 0.158 g (1 mmole) (I) and 0.257 g (1 mmole) of $Ni(acac)_2$ in 2 ml of absolute DMF was heated under Ar for 45 min at 130-140°C. The solvent was distilled off under vacuum (1 torr), the residue was boiled for 2 h with 5 ml of concentrated HCl. The solvent was distilled off, the residue was stirred for 2 h with 10 ml of a 25% NH_4OH solution. The precipitate was filtered off, washed with water, and dried in vacuo over P_2O_5 to give 0.070 g of a mixture of (VIIa) and (IXa). According to the PMR spectral data in DMSO-d_6, the yields were 11 and 22%, respectively.

2-Amino-4-methylpyrimido[1,2-a]benzimidazole Hydrochloride (XII). a) Synthesis of (IXa). A 1 ml portion of concentrated aqueous HCl was added to a suspension of 0.232 g of (IXa) in 10 ml of MeOH, and stirring was continued for 1 h at 20°C. The solvent was distilled off, and the residue was dried in vacuo over P_2O_5. Compound (XII) was obtained (Table 1).

b) Synthesis of (VIIIa). A solution of 0.600 g of (VIIIa) in 7 ml of concentrated aqueous HCl was boiled for 2 h. The solvent was distilled off, and the residue was dried in vacuo over P_2O_5. Compound (XII) was obtained (Table 1).

Synthesis of (IXa) from (XII). A suspension of 0.469 g of (XII) in 5 ml of a 25% solution of NH_4OH was stirred for 30 min, then filtered and washed with H_2O. After drying in vacuo over P_2O_5, 0.341 g (86%) of (IXa) was obtained.

2-Amino-4,10-dimethylpyrimido[1,2-a]benzimidazolium Iodide (XIIIa) and 2-Acetylamino-4-, 10-dimethylpyrimido[1,2-a]benzimidazolium Iodide (XIIIb). A suspension of 2 mmoles of (VIIIa) or (IXa) in 20 ml of MeOH was stirred with 1 ml of MeI for 24 h at 20°C. A 40 ml portion of Et_2O was added, the precipitate of the salt was filtered off, and compounds (XIIIa) or (XIIIb) were obtained.

Synthesis of (VIIIa) from (IXa). a) A mixture of 0.198 g (1 mmole) of (IXa), 0.153 g (1.5 mmoles) of Ac_2O and 0.095 g (1.2 mmoles) of Py in 25 ml of xylene was boiled for 6 h. The solvent was distilled off, the residue was washed with Et_2O, and compound (VIIIa) was obtained (Table 1).

b) A solution of 0.050 g of (IXa) in 0.6 ml of AcOH was heated for 30 min in a sealed ampul at 130-140°C, AcOH was then distilled off in vacuo (1 torr). Compound (VIIIa) was obtained in 83% yield.

Synthesis of (VIIIb) from (IXb). In a similar way as in the synthesis of (VIIIa), compound (VIIIb) was obtained from (IXb) and Bz_2O (Table 1).

2-Benzoylamino-4-methylpyrimido[1,2-a]benzimidazole (VIIIc). In a similar way as in the synthesis of (VIIIa, b), compound (VIIIc) was obtained from (IXa) and Bz_2O (Table 1).

LITERATURE CITED

1. V. A. Dorokhov, M. F. Gordeev, and V. S. Bogdanov, et al., Izv. Akad. Nauk SSSR, Ser. Khim., No. 6, 1431 (1988).
2. V. A. Dorokhov, M. F. Gordeev, Z. K. Dem'yanets, et al., Izv. Akad. Nauk SSSR, Ser. Khim., No. 8, 1806 (1989).
3. V. A. Dorokhov, M. F. Gordeev, A. V. Komkov, and V. S. Bogdanov, Izv. Akad. Nauk SSSR, Ser. Khim., No. 1, 145 (1990).
4. V. A. Dorokhov and M. F. Gordeev, Izv. Akad. Nauk SSSR, Ser. Khim., No. 2, 458 (1987). Khim., No. 2, 458 (1987).
5. V. A. Dorokhov, M. F. Gordeev, and Z. K. Dem'yanets, Khim. Geterotsikl. Soedin., No. 10, 1424 (1987).
6. A. D. Garnovskii, O. A. Osipov, and V. N. Sheinker, Koordinats. Khim., 6, No. 1, 3 (1980).
7. K. Uehara, F. Kitumara, and M. Tanaka, Bull. Chem. Soc. Jpn., 49, 493 (1976).
8. V. A. Dorokhov, M. F. Gordeev, A. V. Komkov, and V. S. Bogdanov, Izv. Akad. Nauk SSSR, Ser. Khim., No. 2, 401 (1990).
9. A. De Cat and A. Van Dormel, Bull. Soc. Chim. Belg., 60, No. 1-2, 69 (1951).
10. A. W. Chow, D. R. Jakas, B. P. Trotter, et al., J. Heterocycl. Chem., 10, No. 1, 71 (1973).
11. R. Benassi, R. Grandi, M. Ugo, et al., Magn. Reson. Chem., 24, No. 5, 415 (1984).
12. D. S. Prevorsek, J. Phys. Chem., 66, No. 5, 769 (1962).
13. M. F. Gordeev and V. A. Dorokhov, Izv. Akad. Nauk SSSR, Ser. Khim., No. 7, 1690 (1988).
14. V. A. Dorokhov and M. F. Gordeev, Izv. Akad. Nauk SSSR, Ser. Khim., No. 12, 2874 (1989).
15. V. A. Dorokhov and S. V. Baranin, Izv. Akad. Nauk SSSR, Ser. Khim., No. 4, 954 (1987).
16. B. Serafin, Z. Konopsky, and L. Stolarczyk, Roczn. Chem., 51, No. 12, 2355 (1977).
17. R. W. Hay and G. E. R. Hook, Aust. J. Chem., 5, 601 (1984).