Chemistry of Heterocyclic Compounds, Vol. 34, No. 10, 1998

SYNTHESIS OF 2-AMINO-4,5,7-TRIARYLIMIDAZO[1,5-*b*]PYRIDAZINES

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The reaction of 4-aryl-1,2-diaminoimidazoles with 1-aryl-2,3-dibromo-3-(4-nitrophenyl)propanones, 2-bromo-1-phenyl-3-(4-chlorophenyl)propenone, and 1,3-diarylpropynones yields 2-amino-4,5,7-triarylimidazo[1,5-b]-pyridazines. The structure of one of these products was determined by x-ray diffraction analysis.

Diaminoimidazoles hold interest in light of their dual reactivity. Both imidazotriazepins [1, 2] and imidazopyrimidines [3] are formed in their reactions with carbonyl compounds. In the present work, we studied the cyclocondensation of 4-aryl-1,2-diaminoimidazoles (I and II) with chalcone dibromides (IVa-IVh). This reaction was carried out upon heating diamines I and II with ketones IVa-IVh in methanol at reflux for 6-8 h using N-methylmorpholine as the catalyst.

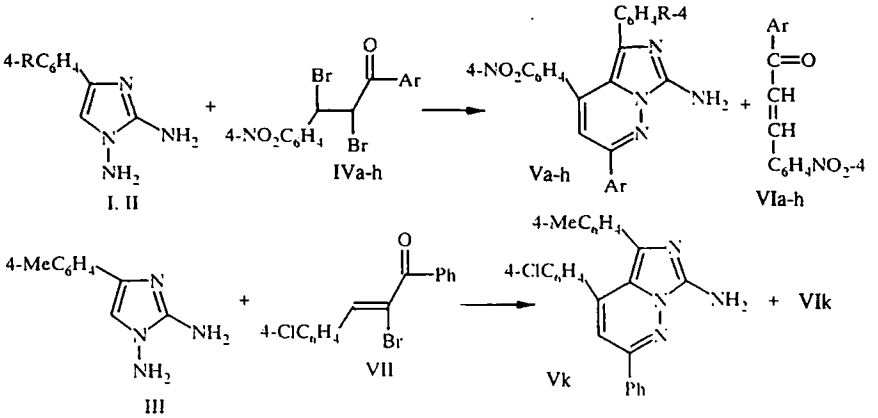
The reaction of aromatic o-diamines with α,β-dibromochalcones proceeds through a series of steps involving formation of an α-bromochalcone as the result of the elimination of HBr, addition of the diamine at the C=C bond to give a β-adduct, and separation of a β-enaminochalcone or the product of its cyclization, namely, 1,5-diazepin, from the reaction mixture [4, 5].

Products Va-Vh and chalcones VIa-VIh were isolated from the reaction mixture under the conditions described, indicating participation of tertiary amines in the reduction of the resultant α-bromochalcones [6]. This behavior may account for the low yields of Va-Vh. Indirect evidence for initial dehydrobromination of ketones IVa-IVh is found in the formation of Vk in the reaction of diamine III with α-bromochalcone VII. Products Vi and Vj were isolated in satisfactory yield in the reaction of diamines I and II with acetylenic ketones VIII and IX. The IR spectra of these products show bands at 3280 and 3452 cm^{-1} assigned to primary amino group stretching vibrations and bands at 1637-1652 cm^{-1} (superposition of stretching bands $\nu_{C=N}$ and $\nu_{C=C}$). The electronic absorption spectra of imidazopyridazines Va-Vk show a strong band in the vicinity of 290 nm and long-wavelength band at 490-500 nm.

The PMR spectra of Va, Ve, and Vi (see Experimental section) show aromatic proton signals at 6.9-8.2 ppm and a broad singlet at 6.5 ppm assigned to NH_2 group protons, which disappears upon the addition of methanol. The signal for the pyridazine ring proton is sometimes overlapped by the aromatic proton multiplet but is readily determined by analyzing the integral signals.

The mass spectrum of Ve shows quasimolecular ions $[M + H]^+$ with m/z 518.9, 520.9, and 522.9, which corresponds to the isotopic composition of the molecule assuming the presence of one bromine atom and one chlorine atom. The mass spectrum also shows fragmentation ions with m/z 504 $[M-O]^+$ and m/z 474 $[M-NO]^+$.

The stoichiometry of this reaction indicates the loss of two molecules of HBr and one molecule of water in the synthesis of Va-Vk.



Kharkov State University, 310077 Kharkov, Ukraine. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 10, pp. 1397-1403, October, 1998. Original article submitted November 21, 1997.

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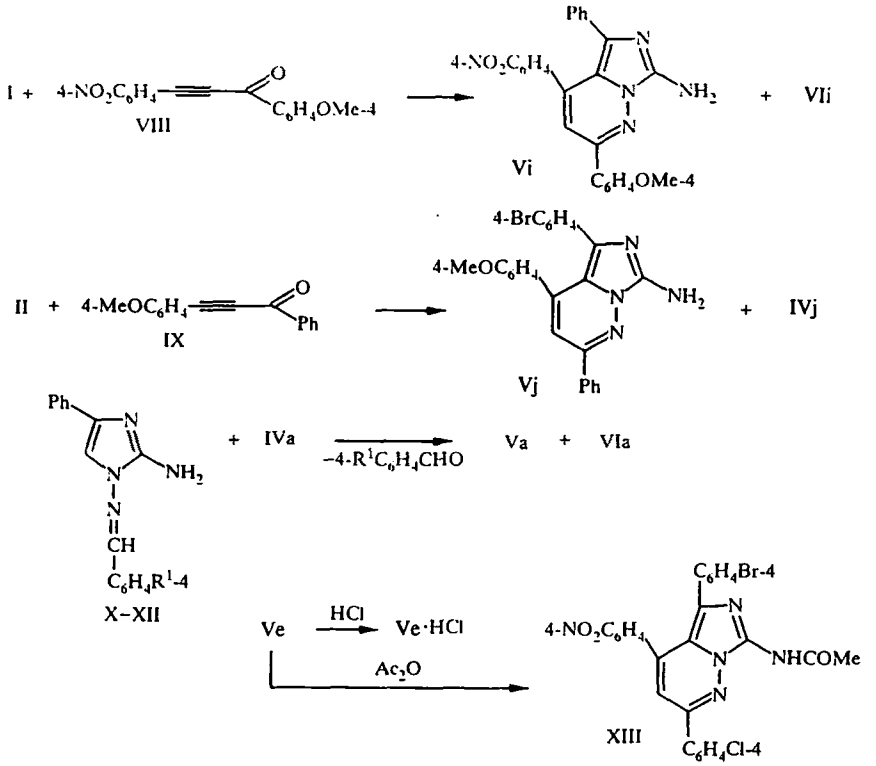

I, Va-c, i R = H; II, Vd-h R = Br; IVa,d, VIa,d Ar = Ph; IVb,g, Vb,g, VIb,g Ar = 4-$NO_2C_6H_4$; IVe, Ve, VIe Ar = 4-ClC_6H_4; IVf, Vf, VIf Ar = 4-BrC_6H_4; VIi Ar = 4-$MeOC_6H_4$; IVc, Vc, VIc Ar = 2-thienyl; IVh, Vh, VIh Ar = 5-Br-2-thienyl; X R^1 = H; XI R^1 = NMe_2; XII R^1 = NO_2

Thus, these results indicate cyclocondensation involving only one amino group.

The structures of Va-Vk were determined by x-ray diffraction analysis for the case of Vk, which, according to the data obtained, is 2-amino-7-(p-bromophenyl)-4-(p-methylphenyl)-5-phenylimidazo[1,5-b]pyridazine. The bicyclic imidazopyridazine system in Vk is planar. The amino group nitrogen atom has planar trigonal configuration. The phenyl substituent at $C_{(2)}$ (Fig. 1) is somewhat twisted relative to the plane of the bicyclic system (the $N_{(2)}$—$C_{(2)}$—$C_{(19)}$—$C_{(20)}$ torsion angle is 16.9°), which is likely a consequence of the short intramolecular contacts $H_{(20)}\cdots N_{(2)}$ 2.48 Å (the sum of the van der Waals radii is 2.66 Å [7]) and $H_{(24)}\cdots H_{(3)}$ 2.18 Å (2.32 Å). The conjugation between the π-electron systems of the arene substituents and imidazopyridazine fragment is significantly violated due to twisting of the aromatic rings about C—C bonds (torsion angles $C_{(3)}$—$C_{(4)}$—$C_{(13)}$—$C_{(18)}$ 59.0° and $C_{(5)}$—$C_{(6)}$—$C_{(7)}$—$C_{(12)}$ 46.9°). This twisting is probably a result of the repulsion between these substituents (short intramolecular contacts $C_{(7)}\cdots C_{(14)}$ 3.30 Å (3.42 Å) and $C_{(13)}\cdots C_{(12)}$ 3.28 Å).

The molecules of Vk in the crystal form centrosymmetric dimers due to intermolecular hydrogen bonds $H_{(4a)}\cdots N_{(3')}$ (1 − x, −y, 1 − z) (H···N 2.20 Å, N—H···N 156°). Since the features of Vk are in accord with the data obtained for the other compounds of this series, Va-Vi are also substituted imidazo[1,5-b]pyridazines.

Products V could not be obtained in the reactions of diamines I-III with chalcone dibromides lacking a nitro group in the benzylidene fragment. This failure may be attributed both to the higher rate of HBr elimination in dibromides IVa-IVh and the greater electrophilicity of the β-position of the α-bromo-β-nitrophenylchalone intermediates.

Thus, diamines I-III in their reactions with ketones IVa-IVh and VII-IX behave as typical 1,3-dinucleophiles. $C_{(5)}$ in the imidazole ring proves most susceptible to electrophilic attack in I-III. Alkylation by the unsaturated ketones occurs specifically at this atom followed by heterocyclization.

This sequence of steps is in good accord with the formation of imidazopyridazine Va in the reactions of hydrazones X-XII with chalcone dibromide IVa in the presence of N-methylmorpholine. The tendency of hydrazones to undergo hydrolysis decreases with increasing electron-withdrawing properties of the aromatic ring in the carbonyl component. Thus, the total rate of the cyclocondensation involving hydrazones X-XII is expected to drop in the series: XI (R^1 = NMe_2) > X (R^1 = H) > XII (R^1 = NO_2). For example, trace amounts of product Va are detected chromatographically in the case of hydrazone XII only after 14 h heating at reflux in 1:1 DMF−MeOH.

TABLE 1. Physical Indices for Va-Vk

Compound	Chemical formula	Found, % / Calculated, %	mp, °C	IR spectrum, cm^{-1}		UV spectrum, λ_{max}, nm ($\varepsilon \cdot 10^{-3}$)	Yield, %
				$\nu_{C=C}$, $\nu_{C=N}$	ν_{NH_2}		
Va	$C_{24}H_{17}N_5O_2$	17,3 / 17,2	317...318	1640	3447 3292	286(29,1) 492(2,7)	52
Vb	$C_{24}H_{16}N_6O_4$	18,6 / 18,5	281...282	1640	3400 3278	280(26,7) 498(2,9)	35
Vc	$C_{22}H_{17}N_5O_2S$	16,8 / 16,9	309...310	1640	3430 3290	282(27,2) 483(2,8)	30
Vd	$C_{24}H_{16}BrN_5O_2$	14,4 / 14,4	296...297	1642	3453 3296	271(25,0) 491(2,3)	43
Ve	$C_{24}H_{15}BrClN_5O_2$	13,3 / 13,4	289...290	1645	3423 3282	278(30,0) 495(2,6)	57
Vf	$C_{24}H_{15}Br_2N_5O_2$	12,4 / 12,4	291...292	1642	3420 3284	286(34,7) 495(2,4)	47
Vg	$C_{24}H_{15}BrN_6O_4$	15,8 / 15,8	273...274	1652	3392 3272	281(31,5) 492(2,6)	32
Vh	$C_{22}H_{13}Br_2N_5O_2S$	12,1 / 12,3	281...282	1637	3428 3286	274(32,8) 496(2,2)	35
Vi	$C_{25}H_{19}N_5O_3$	15,9 / 16,0	303...304	1642	3444 3289	292(25,2) 494(2,6)	61
Vj	$C_{25}H_{19}BrN_4O$	14,2 / 14,2	248...249	1640	3435 3292	270(18,8) 495(2,3)	38
Vk	$C_{25}H_{19}ClN_4$	14,2 / 14,1	257...258	1645	3433 3293	273(23,9) 491(2,1)	52

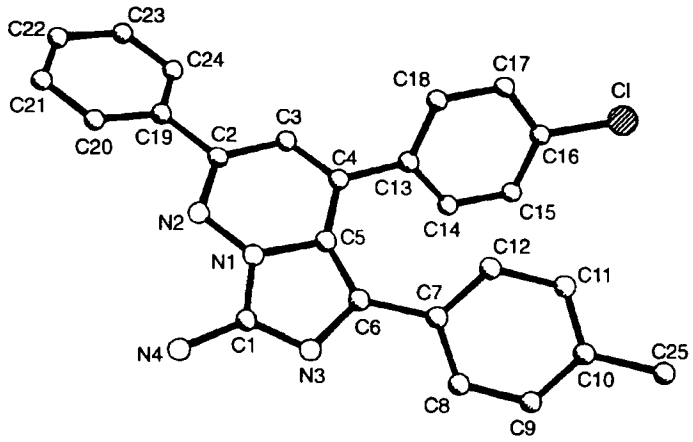

Fig. 1. Molecular structure of Vk.

Products Va-Vk are colored compounds. The long-wavelength UV band disappears after acylation achieved by heating in acetic anhydride at reflux or salt formation with HCl. The color is restored after decomposition of its salt by the action of ethanolic alkali. These reactions proceed with the participation of the amino group in the meso position of the imidazole ring. Thus, it acts as an efficient auxochrome in Va-Vk facilitating charge transfer from the imidazole ring to the pyridazine ring.

EXPERIMENTAL

The IR spectra of Va-Vk were taken for KBr pellets on a Specord IR-75 spectrometer and the electronic absorption spectra were taken on a Specord M-40 spectrometer in acetonitrile. The PMR spectra were taken on a Gemini-200 spectrometer using TMS as the standard for solutions in DMSO-d_6. The mass spectrum of Ve was taken using plasma desorption spectroscopy by Cf^{252} division fragments. The purity of the samples of Va-Vk were monitored by thin-layer chromatography on Silufol UV-254 plates with ethyl acetate as the eluent.

TABLE 2. Bond Lengths and Angles in the Structure of Vk

Bond	d, Å	Bond angle	ω, deg	Bond angle	ω, deg
Cl—C(16)	1,751(5)	C(1)—N(1)—N(2)	123,9(4)	C(10)—C(9)—C(8)	122,0(5)
N(1)—C(1)	1,372(5)	C(1)—N(1)—C(5)	108,3(4)	C(11)—C(10)—C(9)	117,6(5)
N(1)—N(2)	1,389(5)	N(2)—N(1)—C(5)	127,8(4)	C(11)—C(10)—C(25)	121,2(6)
N(1)—C(5)	1,434(5)	C(2)—N(2)—N(1)	114,7(4)	C(9)—C(10)—C(25)	121,2(6)
N(2)—C(2)	1,315(6)	C(1)—N(3)—C(6)	107,2(4)	C(10)—C(11)—C(12)	121,0(5)
N(3)—C(1)	1,345(5)	N(3)—C(1)—N(4)	127,6(5)	C(7)—C(12)—C(11)	121,2(5)
N(3)—C(6)	1,384(5)	N(3)—C(1)—N(1)	110,4(4)	C(14)—C(13)—C(18)	118,1(4)
N(4)—C(1)	1,369(5)	N(4)—C(1)—N(1)	121,9(4)	C(14)—C(13)—C(4)	122,1(4)
C(2)—C(3)	1,452(6)	N(2)—C(2)—C(3)	122,7(4)	C(18)—C(13)—C(4)	119,7(4)
C(2)—C(19)	1,500(6)	N(2)—C(2)—C(19)	115,5(4)	C(15)—C(14)—C(13)	122,0(5)
C(3)—C(4)	1,371(6)	C(3)—C(2)—C(19)	121,8(5)	C(16)—C(15)—C(14)	118,4(5)
C(4)—C(5)	1,441(6)	C(4)—C(3)—C(2)	122,4(5)	C(17)—C(16)—C(15)	121,7(4)
C(4)—C(13)	1,505(6)	C(3)—C(4)—C(5)	117,6(4)	C(17)—C(16)—Cl	119,3(4)
C(5)—C(6)	1,407(6)	C(3)—C(4)—C(13)	122,2(4)	C(15)—C(16)—Cl	119,0(4)
C(6)—C(7)	1,490(6)	C(5)—C(4)—C(13)	120,1(4)	C(16)—C(17)—C(18)	118,7(5)
C(7)—C(8)	1,399(6)	C(6)—C(5)—N(1)	103,6(4)	C(13)—C(18)—C(17)	121,0(4)
C(7)—C(12)	1,402(6)	C(6)—C(5)—C(4)	141,6(4)	C(20)—C(19)—C(24)	118,0(5)
C(8)—C(9)	1,395(6)	N(1)—C(5)—C(4)	114,8(4)	C(20)—C(19)—C(2)	120,1(5)
C(9)—C(10)	1,392(7)	N(3)—C(6)—C(5)	110,5(4)	C(24)—C(19)—C(2)	121,9(5)
C(10)—C(11)	1,388(7)	N(3)—C(6)—C(7)	119,7(4)	C(19)—C(20)—C(21)	120,4(6)
C(10)—C(25)	1,537(7)	C(5)—C(6)—C(7)	129,8(4)	C(22)—C(21)—C(20)	121,4(6)
C(11)—C(12)	1,407(6)	C(8)—C(7)—C(12)	117,4(4)	C(23)—C(22)—C(21)	118,2(6)
C(13)—C(14)	1,394(6)	C(8)—C(7)—C(6)	119,4(5)	C(22)—C(23)—C(24)	121,0(6)
C(13)—C(18)	1,400(6)	C(12)—C(7)—C(6)	123,2(5)	C(19)—C(24)—C(23)	121,0(6)
C(14)—C(15)	1,390(6)	C(9)—C(8)—C(7)	120,7(5)		
C(15)—C(16)	1,390(6)				
C(16)—C(17)	1,386(6)				
C(17)—C(18)	1,402(6)				
C(19)—C(20)	1,381(6)				
C(19)—C(24)	1,385(7)				
C(20)—C(21)	1,398(7)				
C(21)—C(22)	1,380(8)				
C(22)—C(23)	1,364(8)				
C(23)—C(24)	1,398(7)				

X-ray Diffraction Study. The unit cell parameters of triclinic crystals of Vk at 20°C are: a = 9.091(2), b = 10.112(3), c = 13.678(3) Å, a = 103.57(2)°, β = 99.97(2)°, γ = 112.42(2)°, V = 1080.6(5) Å^3, d_{calc} = 1.263 g/cm^3, space group P1, Z = 2. The unit cell parameters and intensities of 1260 independent reflections (R_{int} = 0.030) were measured on a Siemens p3/PC diffractometer (using λMoKα radiation, graphite monochromator, $\theta/2\theta$ scanning, $2\theta_{max}$ = 45°). Absorption was taken into account by direct integration over the crystal (T_{min} = 0.9713, T_{max} = 0.9810).

The structure was solved by the direct method using the SHELXTL PLUS program package [8]. The positions of the hydrogen atoms were calculated geometrically and refined using the "horseman" model with fixed $U_{iso} = nU_{eq}$ of the nonhydrogen atom attached to give the hydrogen atom (n = 1.5 for methyl groups and 1.2 for the other hydrogen atoms). Anisotropic refinement relative to F^2 by the full-matrix method of least squares for the nonhydrogen atoms using 1204 reflections was carried out to wR^2 = 0.091 (R^1 = 0.039 for 1132 reflections with $F > 4\sigma(F)$, S = 1.07). The coordinates of the nonhydrogen atoms are given in Table 3.

2-Amino-4,7-diphenyl-5-(4-nitrophenyl)imidazo[1,5-b]pyridazine (Va). A. A solution of 0.4 g (2.2 moles) diamine I and 0.95 g (2.2 moles) ketone IVa was heated in 30 ml methanol with 0.3 ml N-methylmorpholine at reflux for 6 h. The precipitate of Va was washed with hot chloroform and then crystallized from 4:1 MeCN–DMF to give 0.47 g (52%) Va, mp 317-318°C. IR spectrum: 1640 (C=C, C=N), 3447, 3292 cm^{-1} (NH_2). Found: N, 17.3%. Calculated for $C_{24}H_{17}N_5O_2$: N, 17.2%. PMR spectrum in DMSO-d_6: [8.28-8.31 (2H, d), 8.13-8.09 (2H, d), 7.80-7.60 (6H, m), 7.21-7.18 (2H, d), 6.90-6.86 (2H, d) arom.], 7.04 (1H, s, CH), 6.51 ppm (2H, br.s, NH_2).

TABLE 3. Coordinates ($E\times10^4$) and Equivalent Isotropic Temperature Parameters ($E^2\times10^3$) of Nonhydrogen Atoms in the Structure of Vk

Atom	x	y	z	U(eq)
Cl	10398(2)	11349(2)	7344(1)	93(1)
N(1)	6107(4)	2446(4)	3605(3)	55(1)
N(2)	5697(5)	2130(4)	2522(3)	61(1)
N(3)	6286(5)	2003(4)	5133(3)	57(1)
N(4)	5031(5)	-157(4)	3514(3)	74(1)
C(1)	5781(6)	1357(5)	4081(4)	54(1)
C(2)	6100(6)	3332(6)	2220(4)	59(2)
C(3)	6932(6)	4868(5)	2959(4)	58(1)
C(4)	7334(6)	5174(5)	4026(4)	50(1)
C(5)	6872(5)	3904(5)	4408(3)	48(1)
C(6)	6932(5)	3555(5)	5347(4)	51(1)
C(7)	7604(6)	4584(5)	6459(4)	52(1)
C(8)	8625(7)	4318(6)	7202(4)	75(2)
C(9)	9312(7)	5287(7)	8242(4)	95(2)
C(10)	9018(8)	6547(7)	8587(4)	84(2)
C(11)	7961(7)	6789(6)	7863(4)	72(2)
C(12)	7253(6)	5818(5)	6813(4)	61(2)
C(13)	8207(6)	6768(5)	4790(3)	47(1)
C(14)	9691(6)	7279(5)	5574(4)	58(1)
C(15)	10408(6)	8698(5)	6343(4)	62(2)
C(16)	9604(7)	9622(5)	6322(4)	57(1)
C(17)	8170(7)	9192(5)	5530(4)	62(1)
C(18)	7474(6)	7756(5)	4762(3)	53(1)
C(19)	5645(6)	3014(6)	1054(4)	60(2)
C(20)	4499(8)	1588(7)	383(4)	107(2)
C(21)	4074(10)	1284(8)	-705(5)	122(3)
C(22)	4795(10)	2383(9)	-1139(5)	104(2)
C(23)	5917(8)	3794(8)	-477(5)	106(2)
C(24)	6352(8)	4115(7)	613(4)	96(2)
C(25)	9814(8)	7618(7)	9731(4)	136(3)

B. The reaction of 0.52 g (2.2 moles) phenylhydrazone X and 0.95 g (2.2 mmoles) ketone IVa under identical conditions (6 h) gave 0.33 g (38%) Va, while hydrazone XI after 6 h reaction gave 0.26 g (30%) Va. In the case of hydrazone XII, product Va was detected chromatographically after 14 h (R_f 0.65, ethyl acetate as the eluent).

Products Vb-Vh were obtained according to method A. PMR spectra in DMSO-d_6: Ve: [8.34-8.31 (2H, d), 8.11-8.07 (2H, d), 7.83-7.67 (4H, m), 7.20-7.16 (2H, d), 6.88-6.84 (2H, d) arom], 7.08 (1H, CH), 6.53 ppm (2H, br.s, NH_2). Compound Vi: [8.21-8.16 (2H, d), 8.05-8.01 (2H, d), 7.54-7.58 (2H, d), 6.94-7.01 (8H, m) arom.], 6.36 (2H, br.s, NH_2), 3.00-3.01 ppm (3H, s, OMe).

2-Amino-4-(4-bromophenyl)-7-(4-chlorophenyl)-5-(4-nitrophenyl)imidazo[1,5-b]pyridazine (Vi). A solution of 0.4 g (1.8 mmole) diamine II and 0.64 g (1.8 mmole) ketone VIII was heated at reflux in 20 ml methanol for 2 h. The precipitate of imidazopyridazine Vi was washed with hot chloroform and crystallized from 4:1 MeCN–DMF to give 0.4 g (61%) Vi, mp 303-304°C.

Product Vj was obtained analogously.

2-Amino-4-(p-tolyl)-7-phenyl-5-(4-chlorophenyl)imidazo[1,5-b]pyridazine (Vk). A mixture of 0.4 g (2.2 mmoles) diamine III and 0.78 g (2.2 mmoles) ketone VII was heated in 30 ml methanol with 0.3 ml N-methylmorpholine at reflux for 4 h. The precipitate of imidazopyridazine Vk was washed with hot chloroform and crystallized from 4:1 MeCN–DMF to give 0.52 g (52%) Vk, mp 257-258°C.

2-Acetylamino-4-(4-bromophenyl)-5-(4-nitrophenyl)-7-(4-chlorophenyl)imidazo[1,5-b]pyridazine (XIII). A solution of 0.2 g (1 mmole) Ve in 5 ml acetic anhydride was heated at reflux for 2 h. Cooling led to the precipitation of 0.23 g (94%) acetylamine XIII, mp 254°C. IR spectrum: 1725 (C=O), 3075 cm^{-1} (NH). Found: N, 13.1%. Calculated for $C_{25}H_{17}N_5O_2\cdot BrCl$: N, 13.0%.

Hydrochloride Salt of 2-Amino-4-(4-bromophenyl)-5-(4-nitrophenyl)-7-(4-chlorophenyl)imidazo[1,5-b]pyridazine. A sample of 0.2 g (1 mmole) Ve was dissolved in 15 ml acetonitrile and 0.5 ml 30% hydrochloric acid was added.

Cooling led to the precipitation of 0.2 g (80%) orange crystals of the hydrochloride salt, which decompose at 150°C. The hydrochloride is converted by the action of ethanolic alkali into the starting imidazopyridazine Ve.

This work was carried out with the financial support of the State Basic Research Fund of Ukraine (Project 3.4/56).

REFERENCES

1. M. V. Povstyanoi, N. A. Klyuev, E. Kh. Dank, V. A. Idzikovskii, and V. P. Kruglenko, Zh. Org. Khim., **19**, No. 2, 433 (1983).
2. A. Bernadini, P. Viallefont, and R. Zniber, J. Heterocycl. Chem., **15**, No. 6, 937 (1978).
3. V. D. Orlov, S. M. Desenko, V. P. Kruglenko, V. P. Gnidets, N. A. Klyuev, and M. V. Povstyanoi, Khim. Geterotsikl. Soedin., No. 8, 1136 (1986).
4. N. H. Cromwell, R. D. Badson, and C. E. Harris, J. Am. Chem. Soc., **65**, 312 (1943).
5. N. N. Kolos, V. D. Orlov, and E. Yu. Yur'eva, Khim. Geterotsikl. Soedin., No. 7, 947 (1992).
6. T. S. Kaitmazova, N. P. Gambaryan, and E. M. Rokhlin, Usp. Khim., **58**, 2011 (1989).
7. Yu. V. Zefirov and P. M. Zorkii, Usp. Khim., **58**, 713 (1989).
8. G. M. Sheldrick, SHELXTL PLUS. PC Version. A System of Computer Programs for the Determination of Crystal Structure from X-Ray Diffraction Data. Rev. 5.02.1994.