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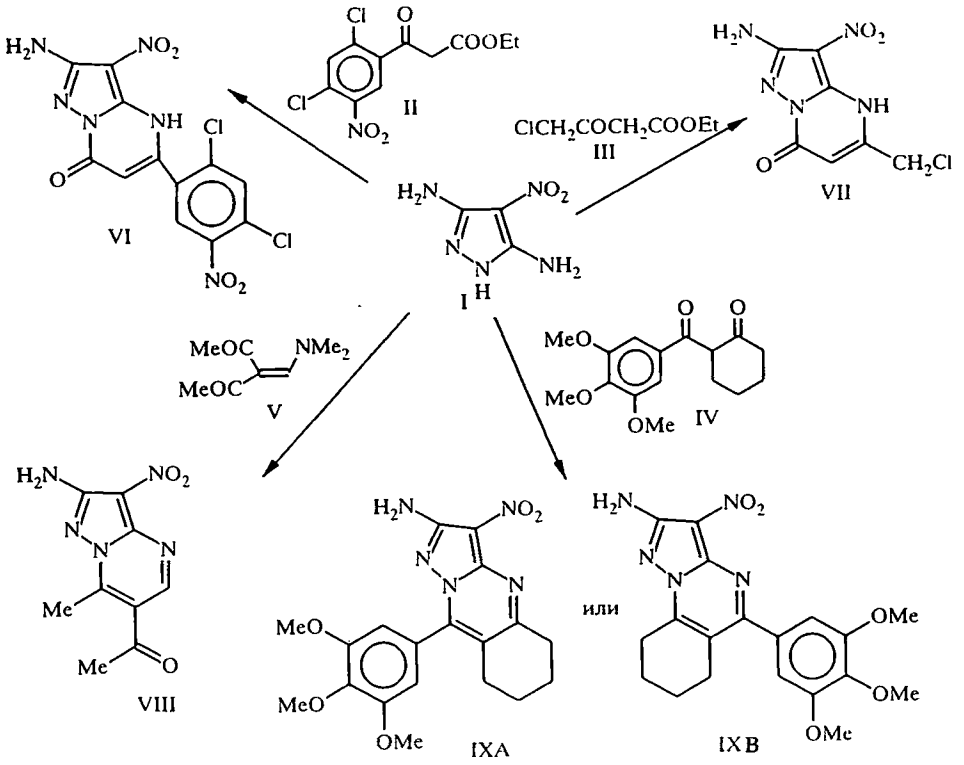
SYNTHESIS OF PYRAZOLO[1,5-*a*]PYRIMIDINES BY THE REACTION OF β-DICARBONYL COMPOUNDS WITH 3,5-DIAMINO-4-NITROPYRAZOLE

V. A. Makarov, V. A. Tafeenko, and V. G. Granik

The reaction of 3,5-diamino-4-nitropyrazole with asymmetrical β-dicarbonyl compounds gave polysubstituted pyrazolo[1,5-*a*]pyrimidines, which are used in reactions with both nucleophilic and electrophilic reagents. The structure of the compounds obtained was demonstrated by x-ray diffraction structural analysis.

The reaction of 3,5-diamino-4-nitropyrazole (I) obtained in our previous work [1] with β-dicarbonyl compounds with additional functional substituents was studied in the framework of an investigation of the synthesis of pyrazolo[1,5-*a*]pyrimidines. Such β-dicarbonyl compounds permit us to study some chemical transformations of this compound class and develop an approach to the synthesis of substituted pyrazolopyrimidines, which may hold interest for biological research.



Center for Pharmacological Chemistry, All-Russian Pharmaceutical Chemistry Institute, 119815 Moscow and M. V. Lomonosov Moscow State University, 119899 Moscow, Russia. E-mail: makar-cl@ropnet.ru. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 12, pp. 1676-1681, December, 1998. Original article submitted November 29, 1997.

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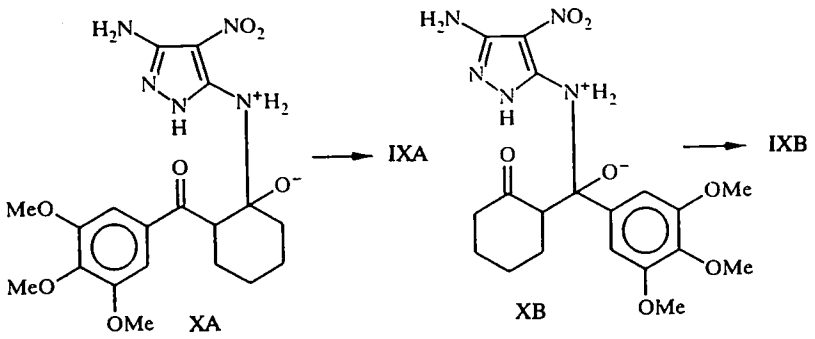
Ethyl 2,4-dichloro-5-nitrobenzoylacetate (II), ethyl β-chloroacetoacetate (III), 2-(3,4,5-trimethoxybenzoyl)cyclohexanone (IV), and an enaminodiketone, namely, 2-diaminomethylenacetylacetone (V) were taken as the starting λ-dicarbonyl compounds [2]. The reaction was carried out under conditions described in our previous work [3] in the presence of methanolic hydrogen chloride. The pyrazolopyrimidine products (VI-X) were obtained in good yield. The first step in the case of β-diketones is condensation of a keto group at the primary amino group in I with subsequent cyclization of the ethoxycarbonyl group at the cyclic NH group. In previous work [4], we showed that the first step in the reaction of aminopyrazole I with enaminocarbonyl compounds is transamination. Hence, the identification of VI and VII as 5-substituted oxo derivatives and of VIII as the 6-acetyl-7-methyl derivative is certain. The reaction with IX is more complicated since starting diketone V may react with diaminonitropyrazole through two pathways to give tricyclic products IXA or IXB.

The PMR spectra (see Experimental section) do not provide sufficient information for reliable resolution of the question of the product structure. However, these spectra suggest that the reaction of I and V gives not a mixture of IXA and IXB, but rather only one of these products. From general concepts, the path yielding IXA appears favored since examination of the structures of the corresponding intermediates XA and XB shows that conjugation of the carbonyl group with the aryl moiety is retained in XA, while conjugation energy is lost in the case of XB. Hence, we conclude that intermediate XA has lower energy and this reaction pathway is more likely.



Unequivocal proof for the structure of this product as IXA was obtained by x-ray diffraction analysis (see Fig. 1).

The experimental bond lengths and angles are given in Tables 1 and 2. Atoms $C_{(14)}$ and $C_{(15)}$ in the six-membered unsaturated ring are twisted relative to the corresponding atoms of the other configuration $C_{(141)}$ and $C_{(151)}$. Refinement of the multiplicity of these atoms showed that the two configurations are equally probable. The coordinates of all the hydrogen atoms at $C_{(13)}$-$C_{(16)}$ were calculated and taken into account in determining the structural

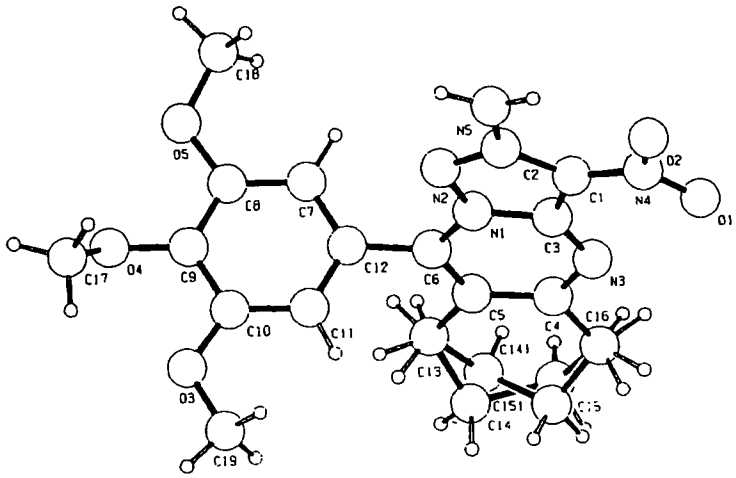


Fig. 1. General view of a molecule of IXA.

TABLE 1. Bond Lengths in the Structure of IXA

Bond	Length, Å	Bond	Length, Å
$O_{(1)}$—$N_{(4)}$	1,241(4)	$C_{(4)}$—$C_{(5)}$	1,411(5)
$O_{(2)}$—$N_{(4)}$	1,249(4)	$C_{(4)}$—$C_{(16)}$	1,506(5)
$O_{(3)}$—$C_{(10)}$	1,354(5)	$C_{(5)}$—$C_{(6)}$	1,389(5)
$O_{(3)}$—$C_{(19)}$	1,401(5)	$C_{(5)}$—$C_{(13)}$	1,496(5)
$O_{(4)}$—$C_{(9)}$	1,375(4)	$C_{(6)}$—$C_{(12)}$	1,486(5)
$O_{(4)}$—$C_{(17)}$	1,440(5)	$C_{(7)}$—$C_{(8)}$	1,386(5)
$O_{(5)}$—$C_{(8)}$	1,380(4)	$C_{(7)}$—$C_{(12)}$	1,393(5)
$O_{(5)}$—$C_{(18)}$	1,411(5)	$C_{(8)}$—$C_{(9)}$	1,383(5)
$N_{(1)}$—$C_{(6)}$	1,352(5)	$C_{(9)}$—$C_{(10)}$	1,393(5)
$N_{(1)}$—$C_{(3)}$	1,380(4)	$C_{(10)}$—$C_{(11)}$	1,390(5)
$N_{(1)}$—$N_{(2)}$	1,388(4)	$C_{(11)}$—$C_{(12)}$	1,372(6)
$N_{(2)}$—$C_{(2)}$	1,336(5)	$C_{(13)}$—$C_{(14)}$	1,49(3)
$N_{(3)}$—$C_{(4)}$	1,325(5)	$C_{(13)}$—$C_{(141)}$	1,53(2)
$N_{(3)}$—$C_{(3)}$	1,336(5)	$C_{(14)}$—$C_{(15)}$	1,58(4)
$N_{(4)}$—$C_{(1)}$	1,376(5)	$C_{(15)}$—$C_{(16)}$	1,57(3)
$N_{(5)}$—$C_{(2)}$	1,342(5)	$C_{(141)}$—$C_{(151)}$	1,49(3)
$C_{(1)}$—$C_{(3)}$	1,403(5)	$C_{(151)}$—$C_{(161)}$	1,46(2)
$C_{(1)}$—$C_{(2)}$	1,416(5)		

factors. The most reliable values for the $C_{(14)}$-$C_{(15)}$ and, thus, $C_{(141)}$-$C_{(151)}$ bond lengths were obtained using this method. The four hydrogen atoms bound respectively to $C_{(13)}$ and $C_{(16)}$ depicted in the Fig. 1 reflect only the position of the hydrogen atoms of the different configurations of the six-membered ring. The nitro and amino groups are coplanar to the five-membered ring. The values of the shortened $C_{(2)}$-$N_{(5)}$ (1.342(5) Å) and $C_{(1)}$-$N_{(4)}$ bond lengths (1.376(5) Å) suggest that these groups are strongly conjugated to each other. The phenyl ring is twisted relative to the conjugated bicyclic system by 75°. The $O_{(5)}$-$C_{(18)}$ and $O_{(3)}$-$C_{(10)}$ (meta) methoxy groups only slightly extrude from the phenyl ring plane, while the $O_{(4)}$-$C_{(17)}$ (para) methoxy group is twisted at an angle of 61°. Intramolecular hydrogen bonding exists between a nitro group oxygen atom and amino group hydrogen atom, $O_{(2)}$-$H_{(51)}$, 2.16 Å.

Several reactions of VII and VIII indicate the broad scope for using these compounds in the synthesis of pyrazolo[1,5-*a*]pyrimidines using the reaction of 3,5-diamino-4-nitropyrazole with β-dicarbonyl compounds studied in our previous work.

Thus, pyrazolopyrimidine VII readily reacts with nucleophilic reagents to give the corresponding derivatives, XIa, XIb, XIc, and XId. Product VIII has an active methyl group, as demonstrated by the reaction of this compound with dimethylformamide acetal to give XIII. In this case, we simultaneously observe the reaction of the acetal with the free amino group to give the corresponding amidine.

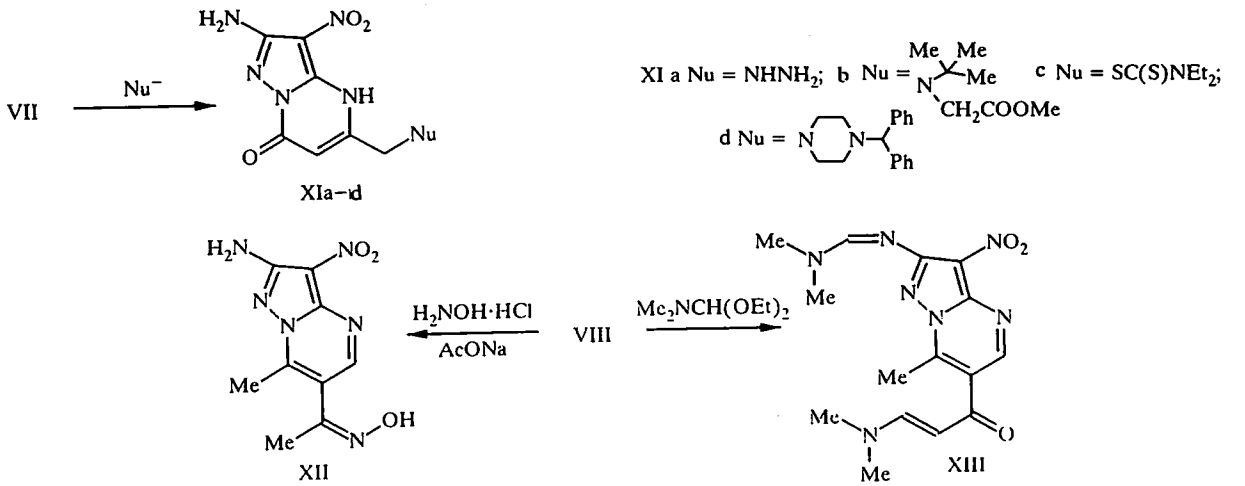


TABLE 2. Valence Angles in the Structure of IXA

Bond angle	ω, deg	Bond angle	ω, deg
C(10)—O(3)—C(19)	118,4(3)	N(1)—C(6)—C(5)	117,6(4)
C(9)—O(4)—C(17)	117,2(3)	N(1)—C(6)—C(12)	118,4(4)
C(8)—O(5)—C(18)	116,8(4)	C(5)—C(6)—C(12)	123,9(4)
C(6)—N(1)—C(3)	122,0(4)	C(8)—C(7)—C(12)	117,9(4)
C(6)—N(1)—N(2)	124,2(3)	O(5)—C(8)—C(9)	115,5(4)
C(3)—N(1)—N(2)	113,6(3)	O(5)—C(8)—C(7)	122,7(4)
C(2)—N(2)—N(1)	103,5(3)	C(9)—C(8)—C(7)	121,7(4)
C(4)—N(3)—C(3)	116,8(4)	O(4)—C(9)—C(8)	118,5(4)
O(1)—N(4)—O(2)	122,4(4)	O(4)—C(9)—C(10)	121,8(4)
O(1)—N(4)—C(1)	119,4(4)	C(8)—C(9)—C(10)	119,6(4)
O(2)—N(4)—C(1)	118,2(4)	O(3)—C(10)—C(11)	125,2(4)
N(4)—C(1)—C(3)	126,8(4)	O(3)—C(10)—C(9)	115,8(4)
N(4)—C(1)—C(2)	126,7(4)	C(11)—C(10)—C(9)	119,0(4)
C(3)—C(1)—C(2)	106,1(4)	C(12)—C(11)—C(10)	120,8(4)
N(2)—C(2)—N(5)	120,2(4)	C(11)—C(12)—C(7)	121,0(4)
N(2)—C(2)—C(1)	112,3(4)	C(11)—C(12)—C(6)	117,9(4)
N(5)—C(2)—C(1)	127,5(5)	C(7)—C(12)—C(6)	121,1(4)
N(3)—C(3)—N(1)	121,9(4)	C(14)—C(13)—C(5)	115,4(13)
N(3)—C(3)—C(1)	133,6(4)	C(5)—C(13)—C(141)	111,9(8)
N(1)—C(3)—C(1)	104,4(4)	C(13)—C(14)—C(15)	110(3)
N(3)—C(4)—C(5)	124,5(4)	C(16)—C(15)—C(14)	112(2)
N(3)—C(4)—C(16)	115,1(4)	C(151)—C(141)—C(13)	109(2)
C(5)—C(4)—C(16)	120,4(5)	C(16)—C(151)—C(141)	112(2)
C(6)—C(5)—C(4)	117,3(4)	C(151)—C(16)—C(4)	109,5(9)
C(6)—C(5)—C(13)	120,0(4)	C(4)—C(16)—C(15)	115,5(10)
C(4)—C(5)—C(13)	122,7(4)		

EXPERIMENTAL

The IR spectra were taken on a Perkin—Elmer spectrophotometer for Vaseline mulls. The NMR spectra were taken on an Oxford Unity 400 spectrometer with TMS as the internal standard. The mass spectra were taken on a Varian SSQ-700 spectrometer with direct sample inlet to the ion source. The purity of the products and course of the reactions were monitored by thin-layer chromatography on Silufol UV-254 plates. The physicochemical indices of the products are given in Table 3.

X-ray Diffraction Structural Study. Crystals of IXA were studied on a CAD4 four-circle diffractometer using MoKα radiation, graphite monochromator, and ω-scanning. The unit cell parameters were determined using 25 reflections in the region θ 7-10° by self-induction and refined using 24 reflections in the region θ 12-15°; a = 9.522(2), b = 15.457(4), c = 13.458(4) Å, β = 106.54(2), V = 1904.8(9) Å^3, space group $P2_1/C$, Z = 4. A total of 2997 nonzero reflections were determined in the range θ 2-24°. A correction for absorption was not introduced.

The structural pattern was determined by the MULTAN direct method in the SDP program package. Refinement of the positional and temperature parameters of the nonhydrogen atoms was carried out anisotropically using the full-matrix approximation and the SHELX93 program package. The coordinates of the hydrogen atoms were determined using both the Fourier map and calculation, R_{factor} = 0.059 for 1358 reflections with intensity $I > 2\sigma(I)$. The designations of the atoms are given in Fig. 1.

3-Amino-4-nitropyrazolo[1,5-*a*]pyrimidines (VI, VII, VIII, and IXA). A sample of 9 mmoles of the corresponding dicarbonyl compound was added to a suspension of 1.0 g (7 mmoles) 3,5-diamino-4-nitropyrazole in 30 ml methanol and heated to reflux. A sample of 2 ml 9% (0.2 mmole) HCl/MeOH was added to the reaction mixture at reflux with vigorous stirring. The reaction mixture was maintained at reflux until a yellow precipitate formed and the starting pyrazole disappeared as indicated by thin-layer chromatography and cooled to room temperature. The precipitate of the pyrazolopyrimidine product was filtered off and washed with water, cold methanol, and ether. The product was crystallized from the corresponding solvent (Table 3). Light yellow monocrystals of pyrazolopyrimid-

TABLE 3. Physicochemical Indices of Products

Compound	Chemical formula	Found, % / Calculated, %			Mp, °C	Solvent*	M^+	Yield, %
		C	H	N				
VI	$C_{12}H_6Cl_2N_6O_5$	37,2 37,4	1,4 1,6	22,1 21,8	> 270 (dec)	DMF./H_2O	385	72
VII	$C_7H_6ClN_5O_3$	34,0 34,5	2,4 2,5	28,8 28,8	> 270 (dec)	DMF	242	87
VIII	$C_9H_9N_5O_3$	45,9 46,0	4,0 3,9	30,0 29,8	272...274	DMF	235	85
IXA	$C_{19}H_{21}N_5O_5$	57,3 57,1	5,4 5,3	17,6 17,5	> 270	DMF	399	67
XIa	$C_7H_9N_7O_3$	35,2 35,2	3,8 3,8	41,2 41,0	> 270 (dec)	DMF	239	78
XIb	$C_{14}H_{20}N_6O_5$	47,6 47,7	5,6 5,7	23,7 23,8	> 270	IPA	352	58
XIc	$C_{12}H_{16}N_6O_3S_2$	40,5 40,4	4,5 4,5	23,4 23,6	> 290	IPA	356	83
XId	$C_{24}H_{25}N_7O_3$	49,4 49,6	4,8 4,9	28,9 29,0	207...209	IPA	290	71
XII	$C_9H_{10}N_6O_3$	43,3 43,2	4,2 4,0	34,0 33,6	> 290	DMF./H_2O	250	93
XIII	$C_{17}H_{22}N_6O_3$	59,3 59,6	6,7 6,5	24,6 24,5	257...259	IPA	342	68

*For crystallization.

ine IXA were obtained by the evaporation from solution in 2-propanol. PMR spectra for IXA in DMSO-d_6: 1.70 and 1.84 (4H, m, β-CH_2 and β^1-CH_2), 2.49 (2H, t, α-CH_2), 2.88 (2H, t, α^1-CH_2), 3.73 (3H, s, *p*-OCH_3), 3.76 (6H, s, 2 *m*-OCH_3) and 6.83 (2H, s, 2 *o*-H_{arom}).

3-Amino-4-nitro-6-R-methylpyrazolo[1,5-*a*]pyrimidines (XIa, XIb, XIc, XId). A sample of 4.5 mmoles of corresponding nucleophilic reagent was added to a suspension of 1 g (4.11 mmole) pyrazolopyrimidine VII in 40 ml methanol. The reaction mixture was heated until starting pyrazolopyrimidine VII disappeared as indicated by thin-layer chromatography and cooled (in the case of XIc, the mixture was diluted with cold water). The precipitate of pyrazolopyrimidine XI was filtered off and crystallized from a suitable solvent (Table 3).

3-Amino-4-nitro-7-(1-oximinoethyl-1)-8-methylpyrazolo[1,5-*a*]pyrimidine (XII). A sample of 0.2 g (2.89 mmoles) dry hydroxylamine hydrochloride and 0.24 g (2.89 mmoles) sodium acetate were added to a hot solution of 0.5 g (2.12 mmoles) VIII in 5 ml DMF. The reaction mixture was heated for 1 h on a water bath at 90°C. The inorganic salts were filtered off the hot solution. The mother liquor was cooled and filtered to give 0.49 g light yellow fine-crystalline XI.

3-Dimethylaminomethylene-4-nitro-7-(1-oxo-3-dimethylamino-2-propen-1-yl)-8-methylpyrazolo[1,5-*a*]pyrimidine (XIII). A sample of 2 ml (16.00 mmoles) dimethylformamide dimethylacetal was added to 1 g (4.25 mmoles) dry pyrazolopyrimidine VIII. The reaction mixture was heated for 7-10 min until the precipitate completely dissolved, maintained for 10 min at 100-110°C, and cooled in a refrigerator for 12 h. Filtration gave 0.89 g large yellow crystals of XIII.

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