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REACTIONS OF NITROPHENYLPYRIMIDINES WITH BENZYL CYANIDE. SYNTHESIS OF PYRIMIDINYL-2H-INDAZOLES BY THE REDUCTIVE CYCLIZATION OF SUBSTITUTED DIBENZOYLAZOXYBENZENES

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The reaction of 2- and 5-(p-nitrophenyl)pyrimidines with benzyl cyanide in a strongly alkaline medium at 65°C gives pyrimidinyl derivatives of dibenzolyazoxybenzene. The conversion of these reagents is low at lower temperatures and a complex product mixture is obtained. The reduction of the azoxybenzene derivatives obtained leads to substituted 2H-indazoles.

In a continuation of a study of the effect of the pyrimidinyl substituent on the properties of aromatic nitro derivatives [1], we investigated the reaction of *p*-nitrophenylpyrimidines with benzyl cyanide in a strongly alkaline medium [2, 3]. The reaction of aromatic nitro compounds with substituted benzyl cyanides is used in the synthesis of 2,1-benzisoxazoles [3, 4] and of their reduction products, namely, *o*-aminobenzophenones, which are starting reagents for the preparation of various polymers [8]. Among the heterocyclic compounds used in this reaction, we employed 1-substituted 5-nitrobenzimidazoles, which led to the corresponding imidazobenzisoxazoles. These products were then reduced to N-substituted 5-amino-6-benzoylbenzimidazoles [9].

There have been reports of the complex course of this reaction depending on the medium, concentration of the starting reagents, nature of the substituent in the aromatic ring containing the nitro group, and other factors [10-12] and the possibility of obtaining various products due to complex oxidation–reduction reactions has been indicated [13].

The starting reagents were 2- and 5-(*p*-nitrophenyl)pyrimidines (Ia-c). The reaction of benzyl cyanide with Ib in methanol in the presence of KOH at 0-5°C, i.e., under the conditions of the reaction of benzyl cyanide with 4-nitrodiphenyl, 4′-chloro-4-nitrodiphenyl, and 4′-bromo-4-nitrodiphenyl [14], does not take place (Table 1, procedure A) and hardly proceeds with Ia and Ib up to 45°C. These results indicate reduced reactivity of the nitroaromatic substrate upon the replacement of the aryl substituent by an electron-withdrawing pyrimidinyl substituent [15].

Up to 80% of Ia and Ib were converted in this temperature range using DMSO as the solvent (procedure C) or a mixture of methanol and N-methylpyrrolidone and increasing the amount of base (procedure D). The products of these reactions were complex mixtures. In the case of 5-(*p*-nitrophenyl)pyrimidine (Ia), the high-resolution mass spectral data of the chromatographically-separated individual components of this mixture indicate the presence of 5-(5-pyr-imidinyl)-3-phenyl-2,1-benzisoxazole (IIa), 2-amino-5-(5-pyrimidinyl)benzophenone (IIIa), and 4,4′-di(5-pyrimidinyl)-azobenzene (IVa). Analogously, in the case of 5-(*p*-nitrophenyl)-2-phenylpyrimidine (Ib), benzisoxazole (IIb) and aminobenzophenone (IIIb) were detected.

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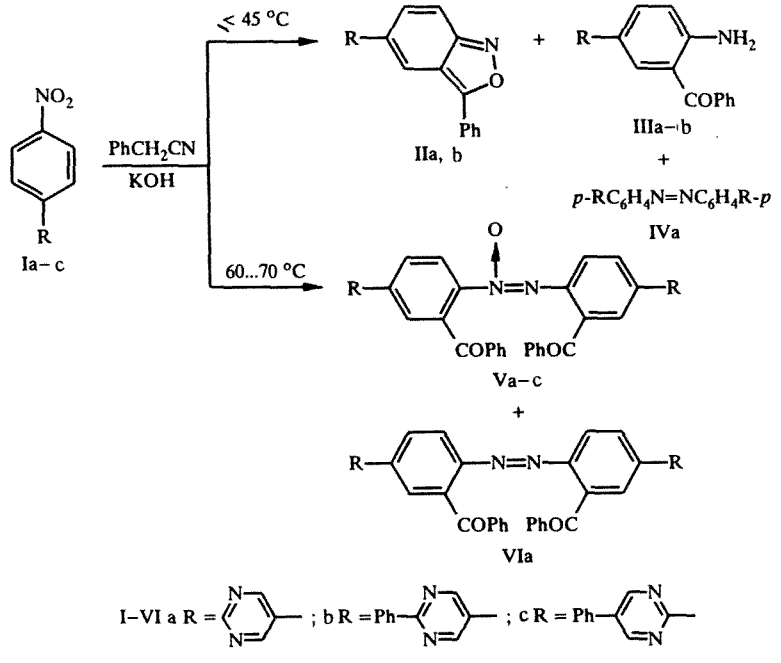
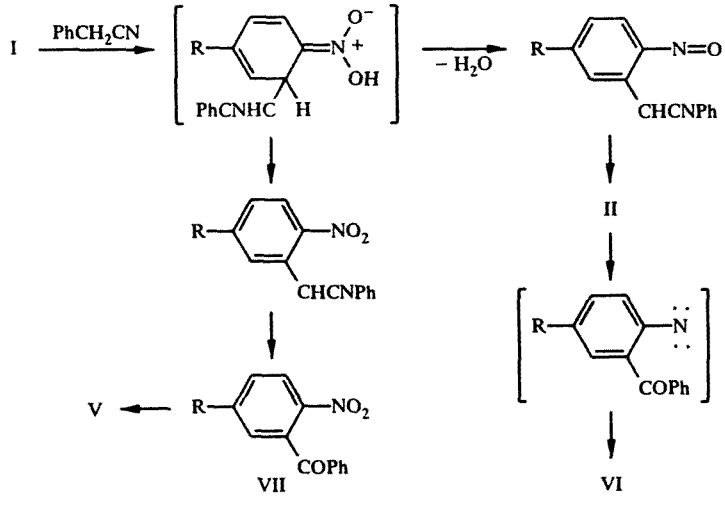


When the reaction temperature is brought to 65°C (procedure E), benzyl cyanide and nitro derivative Ia give predominantly a single product. Mass spectral analysis indicated that this product was not the expected benzisoxazole (IIa), but rather 2,2′-dibenzoyl-4,4′-di(5-pyrimidinyl)azoxybenzene (Va) with a trace of azobenzene (VIa). Under the same conditions, the reaction of benzyl cyanide with Ib and Ic led to the corresponding colored azoxy compounds Vb and Vc. The IR spectra of products Va-Vc (Table 2) show aromatic ketone C=O stretching bands at 1665-1675 cm^{-1} and lack N–H stretching bands at 3100-3500 cm^{-1}. The PMR spectrum of Va taken in $CDCl_3$ (Table 3) shows two downfield separate signals for the pyrimidine 2-H protons with 1:1 integral intensity ratio, indicating lack of equivalence of the two pyrimidinyl substituents. The signals for 4-H and 6-H of the pyrimidinyl groups in the spectrum of Vb appear as two singlets with 2:2 intensity ratio, while they appear as one four-proton singlet in the spectrum of Va in $CDCl_3$. Makosza et al. [12, 13] have noted the formation of azoxy derivatives both with and without an *o*-benzoyl group in the aromatic ring. An increase in the reaction temperature was found to lead to an increase in the yield of the azoxy derivative with disappearance of the substituted 2,1-benzisoxazole in the reaction mixture [12].



The formation of various products in the reaction of benzyl cyanide with aromatic nitro compounds usually is attributed to a series of parallel transformations, which may lead to azobenzophenones (VI) or azoxybenzophenones (V). Thus, in accord

TABLE 1. Conditions and Results of the Reaction of Nitrophenylpyrimidines Ia-Ic with Benzyl Cyanide

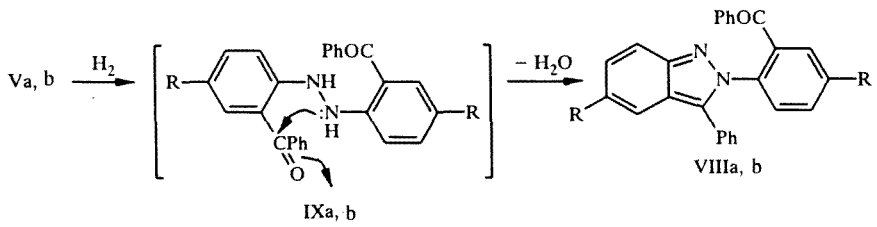
Procedure	Starting compound	Reaction conditions					Reaction results	
		I:benzyl cyanide: base mole ratio	solvent	amount of solvent, ml/mmole I	T,°C	reaction time, h	recovery of I, %	reaction products*2
A	Ib	1 : 1,6 : 32	MeOH	7	0...20...60	7	97	—
B	Ia	1 : 1,2 : 18	MeOH-MAP 3 : 1	8	45	42	95	—
C	Ia	1 : 1,2 : 18	DMSO	11	25	24	80	—
D	Ia	1 : 1,2 : 32	MeOH-MAP 3 : 1	8	45	33	80	IIa, IIIa, IVa
	Ib	1 : 1,2 : 32	MeOH-MAP 3 : 1	8	45	38	92	IIb, IIIb
E	Ia	1 : 1,2 : 32	MeOH-MAP 3 : 2	6	65	7	—	Va, VIa (traces)
	Ib	1 : 1,2 : 32	MeOH-MAP, 3 : 2	6	65	1,5	—	Vb
	Ic	1 : 1,2 : 32	MeOH-MAP 3 : 2	6	65	1,5	—	Vc

*KOH was used in procedures A, B, D, and E, while NaOH was used in procedure C; MAP) N-methyl-α-pyrrolidone. The reaction was carried out at 0°C for 4 h, at 20°C for 1 h, and at 60°C for 2 h in procedure A [14].

*2The yields are given in Table 2. The separation and identification of products other than those indicated in Table 1 were not carried out in the experiments using procedures C and E.

with the results of Davis and Pizzini [16], one pathway involves formation of benzisoxazoles II, which may give intermediate nitrenes [3] and then azo compounds VI. Oxidation–reduction processes are proposed for the other pathway, proceeding in a system containing a carbanion and nitro compound, where azoxy derivatives become the major reaction products [13]. These transformations predominate at higher temperatures and may lead to the formation of III, IV, V, and VII in the reaction studied.

The hydrogenation of isolated epoxy derivatives Va and Vb gave compounds lacking NH and NH_2 groups as indicated by spectral data and failure of the qualitative reaction with *p*-dimethylaminobenzaldehyde. The three-dimensional structure of one of these compounds was established by x-ray diffraction structural analysis [17] as 2-[2-benzoyl-4-(5-pyrimidinyl)phenyl]-5-(5-pyrimidinyl)-3-phenyl-2H-indazole (VIIIa). Correspondingly, VIIIb is a close analog with a phenyl group in the pyrimidinyl ring. The mass spectra of 2H-indazoles VIIIa and VIIIb show characteristic lines for M^+, $(M-29)^+$, $(M-COPh)^+$, $PhCO^+$, and Ph^+, while their IR spectra show C=O stretching bands at 1670 cm^{-1} characteristic for benzophenones. The PMR spectra of VIII and VIIIb show two downfield pyrimidine proton signals indicating lack of equivalence of the two pyrimidine rings in these compounds (Table 4). Intermediates IXa and IXb formed upon hydrogenation are readily cyclized to the corresponding indazole derivatives due to the proximity of the NH and C=O groups.



The tendency of azo-, azoxy-, and hydrazobenzenes to form indazoles when carbonyl groups are present in the *ortho* position is well known [18-20]. Thus, a substituted indazole was obtained in the reduction of 2,2'-dibenzoylazobenzene [18].

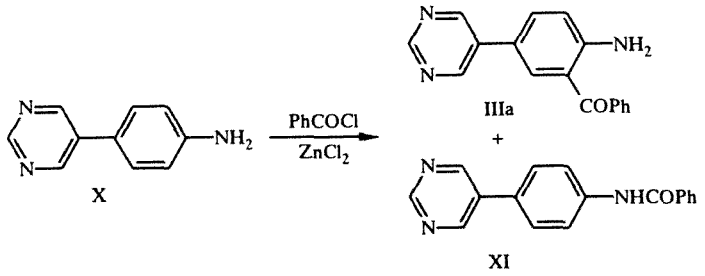
Azoxybenzenes Va-Vc have a strong UV band at 360-370 nm. This band disappears upon going to the hydrogenation products, namely, indazoles VIII, which absorb at 310-312 nm.

TABLE 2. Characteristics of Synthesized Compounds

Compound	Chemical formula	mp, °C	IR spectrum, cm^{-1}		UV spectrum		Yield, %
			C=O	NH	solvent	λ_{max}, nm (lg ε)	
IIIa*	$C_{17}H_{13}N_3O$	147...149	1615	3325, 3430	Ethanol	252 (4,32), 308 (4,23), 395 (3,70)	10
Va	$C_{34}H_{22}N_6O_3$	254...257	1675	—	DMF	360 (4,35)	53
Vb	$C_{46}H_{30}N_6O_3$	309...312	1675	—	DMF	285 (4,69), 368 (4,57)	65
Vc	$C_{46}H_{30}N_6O_3$	297...300	1665	—	DMF	312 (4,71), 365 (4,49)	40
VIIIa	$C_{34}H_{22}N_6O$	238...242	1670	—	Ethanol	263(4,75), 312 sh (4,37)	80
VIIIb	$C_{46}H_{30}N_6O$	244...247	1670	—	DMF	300 (4,82)	83
XI	$C_{17}H_{13}N_3O$	212...213	1670	3300	Ethanol	220 sh (4,25), 295 (4,43)	17

*The characteristics of the sample synthesized from X are given.

Having observed the presence of aminobenzophenone IIIa in the product mixture from the reaction of Ia with benzyl cyanide and expecting the formation of the same compound in the reduction of azoxy derivative Va, we carried out the convergent synthesis of aminobenzophenone IIIa by the benzoylation of 5-(*p*-nitrophenyl)pyrimidine (X) with benzoyl chloride in the presence of $ZnCl_2$.



This gave low yields of IIIa and 4-(5-pyrimidinyl)benzanilide (XI), whose structure was indicated by spectral data (Tables 2 and 3). The UV spectrum of C-benzoylation product IIIa, in contrast to the spectrum of benzanilide XI, shows a bathochromic shift of the long-wavelength absorption band. Benzoylation of X in the presence of $AlCl_3$ led only to benzanilide XI.

EXPERIMENTAL

The PMR spectra of the compounds synthesized were taken on a Bruker WP-200SY spectrometer with TMS or DMSO (2.50 ppm) as the standard. The IR spectra were taken on a Specord M-80 spectrometer for KBr pellets or chloroform solutions. The UV spectra were taken on a Specord UV-VIS spectrophotometer. The mass spectra were taken on a Finnigan MAT-8200 spectrometer. The physicochemical and spectra data are given in Tables 2 and 3.

The elemental analysis data for C, H, and N corresponded to the calculated values.

Starting (*p*-nitrophenyl)pyrimidines Ia-Ic were synthesized by the reaction of the corresponding trimethinium salts with amidines in the presence of base according to our improved procedure [21]. The indicated reagents were used in mole ratios 1.0:1.5:1.5 (CH_3ONa as the base) or 1.0:1.5:1.0 (NaOH as the base). This permitted us to obtain Ia in 46% yield, Ib in 97% yield, and Ic in 81% yield as lightly colored products suitable for use without further purification.

TABLE 3. Mass Spectral and PMR Data for the Synthesized Compounds

Compound	Mass spectrum, *m/z*	PMR spectrum, δ, ppm, coupling constant (H), Hz*			
		solvent	H_{Het}		H_{Ar}
			2-H (1H, c)	4-H, 6-H (c)	
IIIa*[2]	275 (M^+), 198 ($M-C_6H_5$), 170 ($M-C_6H_5CO$), 143, 116, 105 (C_6H_5CO), 89, 77 (C_6H_5)	$CDCl_3$	9,06	8,76 (2H)	8,07...8,58 (4H, m), 7,58...7,38 (3H, m), 6,86 (1H, d, *J* = 8,5)
V a	562 (M^+), 546, 502 (M-60), 457 ($M-C_6H_5CO$), 105 (C_6H_5CO), 77 (C_6H_5)	$CDCl_3$	9,24, 9,21	8,93 (4H)	7,85...7,30 (16H, m),
		DMSO-d_6	9,24, 9,20	9,24 (2H), 9,20 (2H)	8,09...7,97 (4H, m), 7,66...7,61 (6H, m), 7,60...7,45 (6H, m)
V b	714 (M^+), 698, 654 (M-60), 609 ($M-C_6H_5CO$), 505, 105 (C_6H_5CO), 77 (C_6H_5)	DMSO-d_6	—	9,35 (2H), 9,31 (2H)	8,49...8,42 (4H, m), 8,19...8,06 (5H, m), 7,79...7,64 (6H, m), 7,61...7,51 (11H, m)
V c	714 (M^+, *I*≤2%), 609 ($M-C_6H_5CO$), 466, 450, 105 (C_6H_5CO), 77 (C_6H_5)	DMSO-d_6	—	9,31 (4H)	8,89...8,11 (7H, m), 8,11...7,73 (9H, m), 7,73...7,43 (10H, m)
VIIIa	530 (M^+), 501 (M-29), 453 ($M-C_6H_5$), 425 ($M-C_6H_5CO$), 149, 105 (C_6H_5CO), 77 (C_6H_5)	$CDCl_3$	9,20, 9,11	8,98 (2H), 8,9	7,83...7,19 (11H, m), 7,33 (5H, s)
VIIIb	682 (M^+), 653 (M-29), 605 ($M-C_6H_5$), 577 ($M-C_6H_5CO$), 447, 105 (C_6H_5CO), 77 (C_6H_5)	DMSO-d_6	—	9,36 (2H), 9,29 (2H)	8,45 (4H, m), 8,23...8,07 (3H, m), 7,78...7,64 (5H, m), 7,55 (8H, m)
XI	275 (M^+), 105 (C_6H_5CO), 77 (C_6H_5)	$CDCl_3$	9,17	8,93 (2H)	7,91...7,84 (2H, d.d, *J* = 8,5 and 1,8), 7,81 (2H, d, *J* = 8,5), 7,58 (2H, d, *J* = 8,5), 7,54...7,43 (3H, m)

*The signals for the protons of the NH_2 (IIIa) and NH groups (XI) appear as broad singlets at 6.29 and 8.02 ppm, respectively.

*[2]The characteristics of the sample obtained by the benzoylation of X are given.

Reaction of Benzyl Cyanide with Ia and Ib (procedures A-D). A suspension of benzyl cyanide and Ia or Ib in the solvent was added to a solution of KOH in methanol (or NaOH in DMSO in procedure C). The reaction mixture was stirred for several hours at 0-45°C (Table 1) and then water was added, followed by 10% hydrochloric acid to bring the solution to pH 5-6. The precipitate formed containing largely starting I was filtered off and washed with methanol or ethyl acetate. The filtrate (method D) was extracted with ether. The extract was dried over $MgSO_4$, combined with the methanol or ethyl acetate sample used to wash the precipitate, and evaporated. The residue was subjected to chromatography on a silica gel column using 1:1 petroleum ether–ether, ether, 1:3 ether–ethyl acetate, and ethanol consecutively as the eluents. The individually collected fractions were evaporated and analyzed using mass spectroscopy. In the case of starting Ia, the following compounds were identified in the corresponding fractions: Ia, 5-(5-pyrimidinyl)-2,1-benzisoxazole (IIa, M^+ found: 273.0915, calculated for $C_{17}H_{11}N_3O$: 273.0902), 2-amino-5-(5-pyrimidinyl)benzophenone (M^+ found: 275.1046, calculated for $C_{17}H_{13}N_3O$: 275.1058), and 4,4′-di(5-pyrimidinyl)benzophenone (IIIa, M^+ found: 338.1251, calculated for $C_{20}H_{14}N_6$: 338.1279). Product IIIa was found identical to a sample obtained by benzoylation of Xa using mass spectroscopy and thin-layer chromatography (R_f value and qualitative reaction for an amino group with dimethylaminobenzaldehyde).

In the case of starting Ib (procedure D), the following compounds were identified in the fractions: Ib, 5-(2-phenyl-5-pyrimidinyl)-2,1-benzisoxazole (IIb, M^+ found: 349.1238, calculated for $C_{23}H_{15}N_3O$: 349.1215) and 2-amino-5-(2-phenyl-5-pyrimidinyl)benzophenone (IIIb, M^+ found: 351.1343, calculated for $C_{23}H_{17}N_3O$: 351.1371).

2,2′-Dibenzoyl-4,4′-di(5-pyrimidyl)azoxybenzene (Va) (procedure E). A hot solution of 2.8 g (0.014 g mole) Ia and 2.0 g (0.017 mole) benzyl cyanide in a mixture of 40 ml methanol and 50 ml N-methylpyrrolidone was added to a solution of 25.2 g (0.45 mole) KOH in 70 ml methanol. The reaction mixture was stirred at 60-70°C for 7 h and cooled to room tem-

perature. A sample of 150 ml water was added, followed by 10% hydrochloric acid to bring the solution to pH 5-6. The precipitate formed was filtered off, washed with methanol and water, heated at reflux with 50 ml methanol or ethyl acetate, again filtered off, and crystallized twice from DMF to give 2.1 g product. Mass spectral analysis indicated that this product consisted of Va (M^+ found: 562.1782, calculated for $C_{34}H_{22}N_6O_3$: 562.1752) with a trace of VIa (M^+ found: 546.1823, calculated for $C_{34}H_{22}N_6O_2$: 546.1803). An analytical sample of azoxybenzene Va was obtained by further purification of this product. The latter was placed on a silica gel column, washed consecutively with ether, ethyl acetate, and methanol, eluted with hot DMF, precipitated from the cooled solution in DMF by adding water, and recrystallized from DMF.

Analogously, azoxy derivatives Vb and Vc were obtained from Ib and Ic, respectively.

2-[2-Benzoyl-4-(5-pyrimidinyl)phenyl]-5-(5-pyrimidinyl)-3-phenyl]-2H-indazole (VIIIa). A sample of 0.5 g (0.1 mmole) Va was hydrogenated in a mixture of 25 ml ethanol and 25 ml acetic acid with hydrogen at atmospheric pressure in the presence of 0.05 g Pd/C (4%) until no further hydrogen was absorbed. The catalyst was filtered off and the filtrate was evaporated. The residue was treated with a solution of $NaHCO_3$ and extracted with chloroform. The extract was evaporated and the residue was crystallized from ethanol to give 0.33 g VIIIa.

Analogously, indazole VIIIb was obtained from azoxy derivative Vb.

2-Amino-5-(5-pyrimidinyl)benzophenone (IIIa) and 4-(5-Pyrimidinyl)benzanilide (XI). A sample of 1.9 g (0.011 mole) Xa was added in portions over 30 min to a mixture of 3.4 g (0.024 mole) benzoyl chloride and 2.3 g (0.017 mole) anhydrous $ZnCl_2$ heated to 140°C. The mass obtained was maintained for 1 h at 200°C and cooled to 100°C. Then, 7 ml 60% acetic acid was added dropwise over 45 min, followed by 11 ml concentrated hydrochloric acid. The mixture was heated at reflux for 5 h and left overnight. The reaction mixture was poured into 100 ml ice and extracted with methylene chloride. The extract was washed with 50 ml 3 N hydrochloric acid and three 50-ml portions of 5 N NaOH and dried over $MgSO_4$. The solvent was evaporated. The residue was triturated with 50 ml benzene. Filtration gave 0.5 g XI, mp 212-213°C (from ethanol). The mother liquor was passed through a layer of silica gel and evaporated to give 0.3 g IIIa, mp 147-149°C (from petroleum ether).

Under the same conditions but in the presence of $AlCl_3$ (instead of $ZnCl_2$), XI was obtained in 21% yield, mp 208-210°C.

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