DERIVATIVES OF IMIDAZO[4,5-e]-2,1-BENZISOXAZOLE AND SYNTHESIS OF SUBSTITUTED BENZIMIDAZOLES FROM THEM

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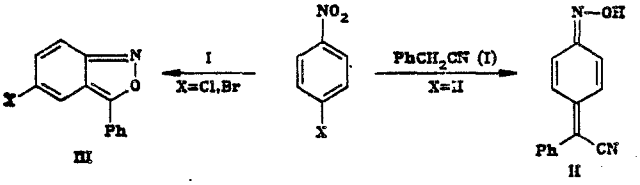
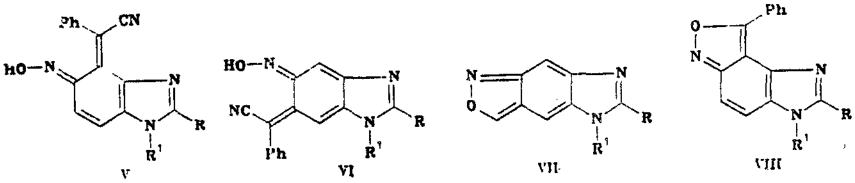
A series of imidazo[4,5-e]-2,1-benzisoxazole derivatives was synthesized by reacting benzyl cyanide with 1,2-disubstituted 5-nitrobenzimidazoles; their reduction gave 1,2-disubstituted 4-benzoyl-5-aminobenzimidazoles. Acylation, oximation, and diazotization reactions with subsequent replacement of the diazo group by iodine were investigated. In the reaction with DMFA diethyl acetal, amidines were obtained, whose cyclization by the action of ammonia leads to imidazo[4,5-f]quinazoline derivatives.

The reaction of nitrobenzene with benzyl cyanide (I) leads to a compound with a quinoid structure II [1], at the same time, in the reaction of p-halonitrobenzenes with compound I, substituted anthranils III are obtained [2, 3].



A similar reaction with the participation of nitro derivatives of heteroaromatic compounds has not yet been described in the literature, and the aim of the present work was to study this reaction on the example of 1,2-disubstituted 5-nitrobenzimidazoles IVa-d. In analogy with the nitrobenzene derivatives, the reaction of compounds IVa-d could lead to o-cyanomethylenequinone oximes of types V, VI or anthranils of types VII, VIII.



In the reaction of nitrobenzimidazoles IV with compound I in methanol in the presence of an excess of sodium hydroxide, compounds were obtained in good yields, which according to the elemental analysis data correspond to structures VII and VIII. In their IR spectra, absorption bands of the cyano and hydroxy groups were absent, which also excluded the structures of oximes V, VI. The choice between structures VII and VIII could easily be made from the PMR spectra: The doublet signals in the 7-8 ppm region with SSCC 9-10 Hz, corresponding to the aromatic protons in the 7- and 8-positions, unequivocally indicated structure VIII.

Thus, as the result of reaction of substituted nitrobenzimidazoles IVa-d with nitrile I, derivatives of a new heterocyclic system — imidazo[4,5-e]-2,1-benzisoxazoles (VIIIa-d) — are formed. They may serve as suitable starting compounds for the synthesis of new benzimidazole derivatives, and also of condensed systems, containing a benzimidazole fragment.

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TABLE 1. Characteristics of Synthesized Compounds

Compound	T_{mp}, °C*	Found, %			Empirical formula	Calc., %			Yield, %
		C	H	N (Hal)		C	H	N (Hal)	
VIIIa	182—184	77,6	4,7	12,9	$C_{21}H_{15}N_3O$	77,5	4,6	12,9	78
VIIIb	186,5—187	77,4	4,3	13,6	$C_{20}H_{13}N_3O$	77,2	4,2	13,5	70
VIIIc	168—169	68,7	4,8	15,3	$C_{16}H_{13}N_3O_2$	68,8	4,7	15,0	84
VIIId	189—190	69,7	5,3	14,6	$C_{17}H_{15}N_3O_2$	69,6	5,1	14,3	80
IXa	175—177	77,5	5,3	13,1	$C_{21}H_{17}N_3O$	77,0	5,2	12,8	89
IXb	161—162	78,9	4,9	13,4	$C_{20}H_{15}N_3O$	78,7	4,8	13,4	89
IXc	166—168	68,6	5,6	15,2	$C_{16}H_{15}N_3O$	68,3	5,4	14,9	78
IXd	212—213	69,5	6,1	14,4	$C_{17}H_{17}N_3O_2$	69,1	5,8	14,2	70
Xa	210—212	71,6	5,4	8.0	$C_{31}H_{27}N_3O_5$	71,4	5,2	8,0	83
Xb	201—203	78,6	4,8	10,0	$C_{28}H_{21}N_3O_2$	77,9	4,9	9,8	75
Xc	146—148	75,6	5,2	9,3	$C_{29}H_{23}N_3O_3$	75,5	5,0	9,1	58
Xd	196—198	68,7	4,4	10,4 (8,6)	$C_{23}H_{18}ClN_3O_2$	68,4	4,5	10,4 (8,8)	62
Xe	220—222	74.6	5,2	11,2	$C_{23}H_{19}N_3O_2$	74,8	5,2	11,4	78
XIa	270—271,5	73,7	5,3	16,4	$C_{21}H_{18}N_4O$	73,7	5,4	16,3	88
XIb	255—256	73,3	4,8	17,2	$C_{20}H_{16}N_4O$	73,2	4,9	17,1	85
XIIa	232,5—234	57,8	3,6	16,2 (29,2)	$C_{21}H_{15}IN_2O$	57,5	3,4	16,4 (29,0)	50
XIVa	238—240	75,2	6,1	14,8	$C_{24}H_{22}N_4O$	75,4	5,8	14,6	74
XIVb	158—160	74,9	5,6	15.0	$C_{23}H_{20}N_4O$	75,0	5,5	15.2	62
XIVc	197—199	68,2	6.2	16,7	$C_{19}H_{20}N_4O_2$	67,8	6,0	16,6	83
XIVd	202—203	68.2	6.3	16,2	$C_{20}H_{22}N_4O_2$	68,6	6,3	16,0	85
XVa	193—195	78.6	5,0	16,8	$C_{22}H_{16}N_4$ †	78,6	4,8	16,6	50
XVb	228—230	77,6	4.6	17,4	$C_{21}H_{16}N_4$	77,8	5,0	17,3	43
XVc	178—179	70,3	5,0	19,4	$C_{17}H_{16}N_4O$	69,8	5,5	19,2	45

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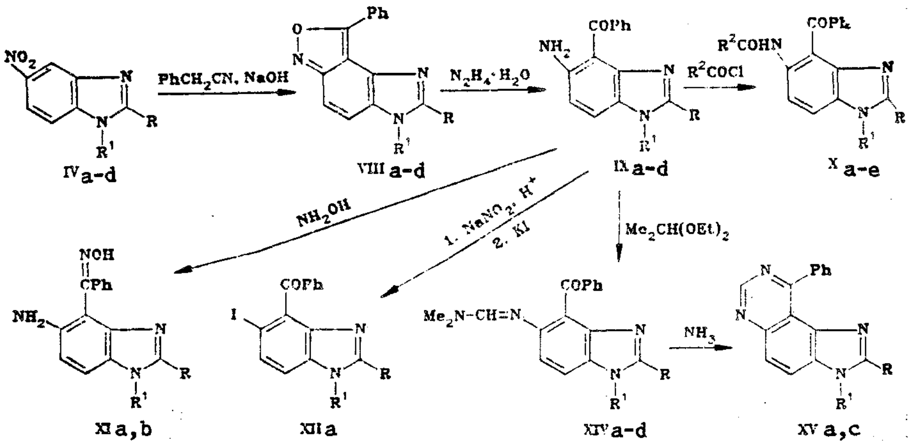
*Compound VIIIa was crystallized from a mixture of benzene and ethanol; VIIIb-d, IXa-d, Xa-e – from ethanol, XIa, XIIa from DMFA; Xib – from a mixture of DMFA and water; XIVa, b XVa-c – from absolute ethanol, XIVc, d – from a mixture of absolute alcohol and toluene.

†Found: M^+ 336. Calculated: M 336.

Thus, by the reduction of the tricyclic compounds VIIIa-d by hydrazine hydrate in the presence of Raney nickel, o-amino-ketones IXa-d were synthesized in high yields. Reduction of compounds VIII and IX can be also effected by means of iron in acetic acid, but this method is less convenient, and amino ketones are formed in lower yields. Various benzimidazole derivatives were synthesized from amino-ketones IXa-d; their acylation gave a series of 5-acyl-amino derivative Xa-d, oximation of ketones IXa led to the corresponding oximes XIa, b, and by diazolization of compound IXa, followed by treatment with potassium iodide, 4-benzoyl-5-iodobenzimidazole (XIIa) was synthesized.



IV, VIII, IX a R=Me, R^1=Ph; b R=H, R^1=Ph; X R=Me, R^1=Ph; a R^2=3,4,5-(MeO)$_3$C$_6$H$_2$, b R^2=Ph: c R^2=PhOCH$_2$, d R^2=CH$_2$Cl, e R^2=Me; XI, XII, XIV, XV c R=H, R^1=CH$_2$CH$_2$OH; d R=CH$_3$, R^1=CH$_2$CH$_2$OH

The presence of keto and amino groups at the ortho-positions of compounds IXa-d ensures the possibility of the preparation from them of condensed tricyclic systems. As an example, a reaction of amino-ketones IXa-d with DMFA diethyl acetal (XIII) was carried out, as the result of which formamidines XIVa-d were obtained. Imidazo[4,5-f]quinazolines (XVa-c) were synthesized by heating amidines XIVa-c with an alcoholic solution of ammonia in a bomb.

In the IR spectra of quinazolines XV, the absorption bands of an aromatic keto group characteristic for the initial formamidines XIVa-c are absent, and in the PMR spectra, the signals of N,N-dimethyl groups are absent. At the same time, in the PMR spectra of compounds XV in DMFA-D$_7$, besides the signals of aromatic protons of the condensed benzene ring, phenyl and benzoyl substituents in the 1- and 4-positions (in the 7.5-8.5 ppm region) and signals of the CH_3 group (2.19 ppm for compound XVa) and the CH_2CH_2OH group (3.86 t CH_2; 4.49, t, OCH_2; 4.80, OH, for XVc), signals are observed of 6-H protons at the 2-position of the pyrimidine ring at 9.24 (XVa), 9.30 (XVb) and 9.25 ppm (XVc), which corresponds to the data in [4] for the quinazoline ring protons. In the mass spectrum of the tricyclic compound XVa, the peak of the molecular ion M^+ 336 is the most intense.

Thus, with the method that we developed an approach can be made to the synthesis of previously unobtainable benzimidazole derivatives, which may serve, in particular, as starting compounds in the preparation of new condensed heterocycles.

EXPERIMENTAL

The IR spectra were run on an UR-20 spectrophotometer in KBr tablets, and the PMR spectra on a Tesla BS-497 spectrometer (100 MHz), using HMDS as internal standard. The mass spectrum was measured on a Varian MAT-112 spectrometer. The melting points were determined on a Boetius apparatus. The individual state of the compounds obtained was verified by chromatography in a thin layer (Silufol UV-254).

The characteristics of synthesized compounds are given in Table 1.

3,6-Diphenyl-5-methylimidazo[4,5-e]-2,1-benzisoxazole (VIIIa). A 15.44 g (60 mmoles) portion of compound IVa and 21.08 (180 moles) of nitrile I are added at 60°C to a solution of 96.0 g (2400 mmoles) of sodium hydroxide in 500 ml of methanol. The solution is brought to boiling, held for 5 h, and cooled to 20°C. After 500 ml of water have been added, the precipitate is filtered, washed with water to pH 7, and then with alcohol. Yield 15.21 g. Compounds VIIIb-d are obtained in a similar way.

1-Phenyl-2-methyl-4-benzoyl-5-aminobenzimidazole (IXa). A 10% Raney nickel catalyst is added to a suspension of 12.5 g (38.5 mmoles) of compound VIIIa in 140 ml of ethanol. The mixute is heated to boiling, and 35 ml of hydrazine hydrate are added dropwise in the course of 1 h. The mixture is boiled for 4 h, activated charcoal is added, boiling is continued for 10 min, and the carbon is removed by filtration. When cool the precipitate is filtered, washed with cold ethanol, and dried. Yield, 11.16 g. Compounds IXb-d are obtained in a similar way.

1-Phenyl-2-methyl-4-benzoyl-5-trimethoxybenzamidobenzimidazole (Xa). A 4.24 g portion (40 mmoles) of finely ground sodium carbonate is added to a suspension of 6.54 g (20 mmoles) of ketone IXa in 50 ml of methanol acetate. Then, 6 g (26 mmoles) of trimethoxybenzoyl chloride in 30 ml of benzene are added dropwise at 20°C in the course of 30 min, and the mixture is left to stand for 8 h. The precipitate is filtered, washed with water, and dried. Yield, 8.65 g. Compounds Xb-e are obtained in a similar way.

1-Phenyl-2-methyl-4-benzoyl-5-aminobenzimidazole oxime (XIa). A 3.15 g portion (45 mmoles) of hydroxylamine hydrochloride is added to a solution of 4.08 g (15 mmoles) of ketone IXa in 30 ml of pyridine, the mixture is brought to boiling and held for 3 h. It is then cooled to 20°C, 100 ml of water are added, and the precipitate is filtered, washed with water, acidified with HCl, and dried. Yield, 3.52 g. Compound XIb is obtained in a similar way.

1-Phenyl-2-methyl-4-benzoyl-5-iodobenzimidazole (XIIa). A 5.2 ml portion of concentrated HCl is added to a solution of 6.54 g (20 mmoles) of compound IXa in 50 ml of acetic acid. The mixture is cooled to 6°C, and a solution of 1.38 g (20 mmoles) sodium nitrite in 10 ml of water is added dropwide very slowly (in the course of 1 h to 1 h 30 min). The mixture is left to stand for 1 h and then the diazonium salt is added to a solution of 3.32 g (20 mmoles) of potassium iodide in 10 ml of water, cooled to 5°C. The evolution of nitrogen is complete after 3 h, and towards the end of the holding time, the mixture is heated to 30-35°C. The precipitate is filtered and washed with ethanol. Yield, 4.38 g.

1-Phenyl-2-methyl-4-benzoyl-5-dimethylaminomethyleneaminobenzimidazole (XIVa). A 6 ml portion (40 mmoles) of a 70% DMFA diethyl acetal is added in the course of 4 h, at the boiling point, to a suspension of 6.54 g (20 mmoles) of ketone IXa in 20 ml of toluene. The reaction mixture is cooled, filtered (in the case of compound XIVb, evaporated), and the product is washed with a small amount of absolute ethanol. Yield, 5.67 g. Compounds XIVb-d are obtained in a similar way.

4,7-Diphenyl-6-methylimidazo[4-5-f]quinazoline (XVa). A mixture of 4 g (11 mmoles) of compound XIVa and 30 ml of a 10% alcoholic solution of ammonia is heated for 12-15 h in a bomb at 140-145°C and at a pressure of 13-15 atm. The reaction mixture is cooled and evaporated. The residue is treated with 10 ml of absolute ethanol and filtered. Yield, 1.42 g (40%). Compounds XVb,c are obtained in a similar way.

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