METHODS OF DRUG SYNTHESIS AND PRODUCTION TECHNOLOGY

ACETALS OF ACID LACTAMS AND AMIDES. 76.[1] A NEW APPROACH TO THE SYNTHESIS OF BENZOFURO[3,2-c]PYRIDINE DERIVATIVES

T. I. Mukhanova,[2] L. M. Alekseeva,[2] E. F. Kuleshova,[2] and V. G. Granik[2]

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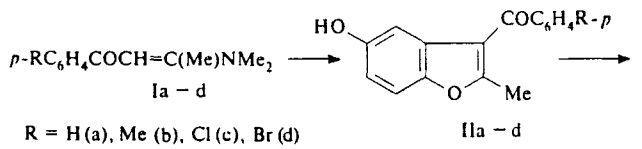
Among the derivatives of benzofuro[3,2-c]pyridine, the hydroxoanalogs of γ-carbolines, a number of compounds were reported to possess analgetic, psychotropic, and other types of biologial activity [2 – 4]. The purpose of this work was to develop a new scheme for the preparative synthesis of derivatives of this system and obtain key compounds that can be used for the creation of new biologically active substances (a preliminary communication about the new approach was published in [5]).

Earlier [5, 6] we have established that tertiary enaminoketones, β-dimethylamino-β-methylacrylophenones (Ia, b), readily enter into the Nenitzescu reaction with para-benzoquinone to form 2-methyl-3-benzoyl-5-hydroxybenzofurans (IIa, b) [5, 6]. The subsequent O-methylation of the latter compounds proceeds smoothly at room temperature under the conditions of interphase catalysis. The corresponding 5-methoxy derivatives (IIIa, b) can be obtained with a quantitative yield [5]. Under similar conditions, we synthesized benzofurans (IIc, d and IIIc, d) proceeding from enamines Ic and Id.

Protons of the 2-methyl group of IIIa – d are sufficiently mobile and, on heating with dimethylformamide diethylacetal, these compounds are converted with a high yield into enamines IVa – d. Because the presence of an electron-donor enamine group in the position 2 of these compounds decreases the reaction ability of acyl carbonyls, we may expect that the formation of oximes upon the treatment of IV with hydroxylamine is hardly probable. It is also known that interaction of 3-formyl-5-nitro-2-(β-dimethylaminovinyl)indole with hydroxylamine leads to the formation of 2-cyanomethyl-3-formyl-5-nitroindole, while the aldehyde group remains intact [7]. On this basis, it was anticipated that the interaction of benzofurans IVa – d with hydroxylamine would initially lead to a transamination with the formation of N-hydroxyenamines. On boiling in dimethylformamide, the latter were expected to exhibit a Beckmann rearrangement of the second kind with the formation of the corresponding nitriles (Va – d) [7, 8]. However, the reactions proceeded by different pathways. The IR spectra of the products did not contain the absorption bands in the region of 1600 – 2500 cm^{-1} characteristic of the carbonyl and cyano groups. The mass spectra of these compounds exhibited, besides the peaks of molecular ions, the intense peaks of $[M–O]^+$ and $[M–OH]^+$ ions. There are also intense peaks due to the $[M–H]^+$ ions. A proton donor for the formation of these peaks is apparently an aryl substituent in the α-position with respect to nitrogen atom of the pyridine ring. Note that the loss of oxygen is caused not only by fragmentation of the molecular ion but by thermodestruction of molecules in the ion source of the mass spectrometer as well. The spectra exhibit a change in the course of measurements and the $[M–O]^+$ peak becomes dominating.

A combination of these data allowed us to conclude that the interaction of compounds IVa – d with hydroxylamine leads to the formation of N-oxides of benzofuro[3,2-c]pyridines (VIa – d). The ^1H NMR spectra agreed with the proposed structures of compounds VI (see the experimental part below).



[1] For communication No. 75 see [1].

[2] Center for Drug Chemistry, All-Russia Research Institute of Pharmaceutical Chemistry, Moscow, Russia.

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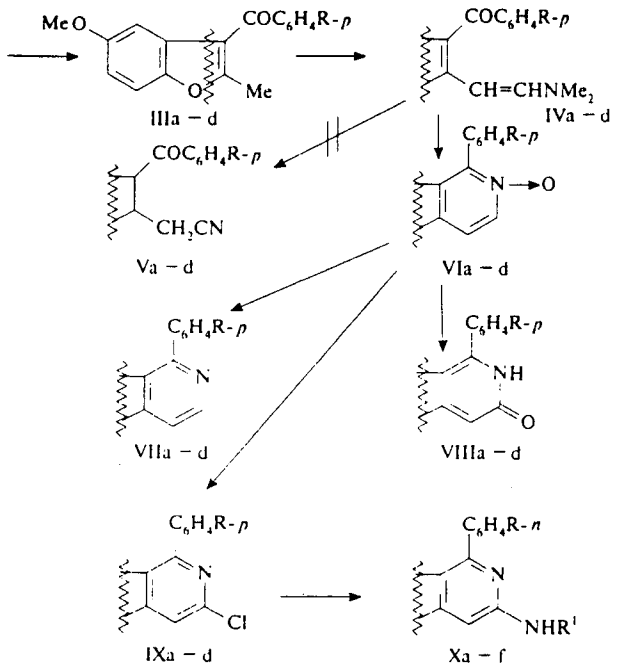
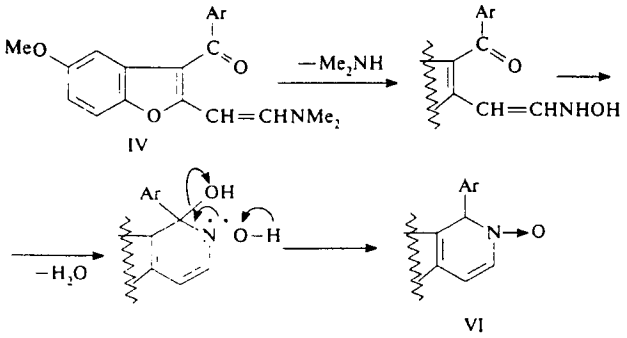


Xa: R = H, R^1 = $(CH_2)_2OH$;
b: R = H, R^1 = CH_2Ph;
c: R = H, R^1 = $N(CH_2CH_2)_2O$;
d: R = Me, R^1 = CH_2Ph;
e: R = Br, R^1 = CH_2Ph;
f: R = Cl, R^1 = $(CH_2)_2OH$.

We believe that the formation of N-oxides VIa – d is based on the initial transamination of IV with detachment of dimethylamine, with the subsequent attack of the NH group of the hydroxylamine fragment at the carbonyl carbon and by closure of the pyridine ring. This is followed by dehydration of the intermediate product:



An additional evidence for the N-oxide nature of the synthesized compounds was provided by the reduction of VIa – d by zinc in acetic acid with the formation of 1-phenyl-8-methoxybenzofuro[3,2-c]pyridines (VIIa – d). The structure of these products was confirmed by data of mass spectrometry and ^1H NMR spectroscopy.

On boiling compounds VIa – d in acetic anhydride medium, the N-oxides transform into tricyclic 2-pyridones (VIIIa – d). The latter appear in a mixture with their acetoxy derivatives ($\nu_{CO\text{-ether}}$, 1765 cm^{-1}; $\nu_{CO\text{-amide}}$, 1665 cm^{-1}).[3] The unseparated mixtures are hydrolyzed by heating in alcohol solutions of hydrochloric acid to obtain compounds VIIIa – d. The mass spectra of these, in contrast to isomeric N-oxides, contain no peaks due to $[M–O]^+$ and $[M–OH]^+$ ions, but exhibit the characteristic peaks of $[M–CONH]^+$ ions.

Another characteristic reaction of N-oxides is the transformation into chlorine derivatives under the action of phosphorus oxychloride [10]. Using this reaction, we synthesized a series of 2-chlorine derivatives (IXa – d) by boiling N-oxides VIa – d with $POCl_3$. The presence of chlorine atom in position 2 of the pyridine ring gives us possibility to perform various reactions with nucleophilic reagents. In this work, we used boiling of compounds IXa – d with excess of various amines to synthesize 2-amino derivatives (Xa – f).

Some characteristics of the newly synthesized compounds are listed in Tables 1 and 2.

EXPERIMENTAL CHEMICAL PART

The IR absorption spectra were measured on a Perkin-Elmer Model 457 spctrophotometer (USA) using samples prepared as nujol nulls. The mass spectra were obtained using a Varian MAT-112 (70 eV) spectrometer with direct injection of samples into the ion source. The ^1H NMR spectra were recorded on a Varian XL-200 spectrometer (USA) using DMSO-d_6 as the solvent and 1HTMS as the internal standard for the chemical shift determination. The course of reactions was monitored by thin-layer chromatography (TLC) on Silufol UV-254 plates in the system benzene – CH_3OH, 9 : 1 (except syntheses of compounds IXa – d). The results of elemental analyses coincided with the analytically calculated values. Enamines Ia – d were obtained according to [11]. 2-Methyl-3-benzoyl-5-hydroxybenzofurans IIa – d were obtained as described in [5].

2-Methyl-3-benzoyl-5-methoxybenzofurans (IIIa – d). To 0.01 mole of IIa – d is added 0.03 mole dimethylsulfate, 0.015 mole NaOH, 0.001 mole triethylbenzylammonium chloride (TEBAC), 50 ml CH_2Cl_2, and 50 ml water, and the mixture is stirred for 2 – 3 h at room temperature. The course of the reaction is monitored by TLC. Upon completion, the organic layer is separated and the water layer is additionally extracted with CH_2Cl_2. The solvent is distilled off. To the residue is added 150 ml of water and the precipitate is filtered, washed on the filter with water, and dried. Benzofurans IIIa – d are used in the subsequent reactions without additional purification.

2-(β-Aminovinyl)-3-aroyl-5-methoxybenzofurans (IVa – d). A mixture of 0.01 mole of a benzofurans IIIa – d, 5 ml dimethylformamide diethylacetal, and 5 ml DMFA is boiled for 4 – 5 h and monitored by TLC. Upon completion of the reaction, the solvent and excess acetal are distilled off.

[3] The formation of 2-acetoxypyridine by interaction of pyridine N-oxide with acetic anhydride was considered in [9].

The residue is mixed with a minimum amount of *iso*-PrOH, filtered, and dried.

N-Oxides of 1-aryl-8-methoxybenzofuro[3,2-c]pyridines (VIa – d). A mixture of 0.01 mole of compound IVa – d, 0.01 mole of hydroxylamine chlorohydrate, and 5 ml DMFA is boiled for 1 h and cooled to 0 – 5°C. The precipitate of VIa – d is filtered, washed on the filter with water, and dried. An additional amount of crystals is precipitated from the mother liquor by diluting with water, filtered, and dried. The ^{1}H NMR spectrum of VIa, δ, ppm: 3.57 (s, 3H, OMe), 6.31 (d, J 2.7 Hz, 1H, 9-CH), 7.18 (q, J^1 9.1 Hz, J^2 2.7 Hz, 1H, 7-CH), 7.71 (d, J 9.1 Hz, 1H, 6-CH), 7.66 (s, 5H, Ph), 7.85 (d, J 7.2 Hz, 1H, 4-CH), 8.46 (d, J 7.2 Hz, 1H, 3-CH).

TABLE 1. Characteristics of Synthesized Compounds

Compound	M.p., °C	Yield, %	Empirical formula
Ib*	101 – 103	76	$C_{13}H_{17}NO$
Ic	110 – 111	86	$C_{12}H_{14}ClNO$
Id	118 – 120	72	$C_{12}H_{14}BrNO$
IIb	174 – 176	36	$C_{17}H_{14}O_3$
IIc	179 – 180	38	$C_{16}H_{11}ClO_3$
IId	187 – 188	39	$C_{16}H_{11}BrO_3$
IIIb	71 – 72	quant.	$C_{18}H_{16}O_3$
IIIc	128 – 130	quant.	$C_{17}H_{13}ClO_3$
IIId	105 – 106	quant.	$C_{17}H_{13}BrO_3$
IVb	126 – 128	91	$C_{21}H_{21}NO_3$
IVc	110 – 111	93	$C_{20}H_{18}ClNO_3$
IVd	112 – 114	92	$C_{20}H_{18}BrNO_3$
VIa	219 – 222	81	$C_{18}H_{13}NO_3$
VIb	192 – 194	85	$C_{19}H_{15}NO_3$
VIc	232 – 234	83	$C_{18}H_{12}ClNO_3$
VId	238 – 240	87	$C_{18}H_{12}BrNO_3$
VIIa	92 – 93	84	$C_{18}H_{13}NO_2$
VIIb	231 – 233**	78	$C_{18}H_{16}ClNO_3$
VIIc	126 – 128	88	$C_{18}H_{12}ClNO_2$
VIId	117 – 118	95	$C_{18}H_{12}BrNO_2$
VIIIa	245 – 247	67	$C_{18}H_{13}NO_3$
VIIIb	262 – 265	50	$C_{18}H_{15}NO_3$
VIIIc	306 – 308	69	$C_{18}H_{12}ClNO_3$
VIIId	306 – 308	60	$C_{18}H_{12}BrNO_3$
IXa	185 – 187	96	$C_{18}H_{12}ClNO_2$
IXb	167 – 168	75	$C_{19}H_{14}ClNO_2$
IXc	183 – 185	87	$C_{18}H_{11}Cl_2NO_2$
IXd	197 – 199	95	$C_{18}H_{11}ClBrNO_2$
Xa	173 – 175	93	$C_{20}H_{18}N_2O_3$
Xb	137 – 139	50	$C_{25}H_{20}N_2O_2$
Xc	182 – 184	92	$C_{22}H_{20}N_2O_3$
Xd	146 – 147	56	$C_{26}H_{21}N_2O_2$
Xe	142 – 144	85	$C_{25}H_{19}BrN_2O_2$
Xf	202 – 204	80	$C_{20}H_{17}ClN_2O_3$

* For the constants of compound Ia, see [11]; for IIa, IIIa, and IVa, see [5, 6].
** Isolated in the form of hydrochloride. Compounds Ib – d, IIIb – d, IVb – d, VIIb – d, Xb, and Xe were recrystallized from *iso*-PrOH; IIb – d, from AcOH, VIa – d, from benzene; VIIIa – d and IXa – d, from DMFA; Xa, c, d, and f, from a MeOH–DMFA mixture.

1-Aryl-8-methoxybenzofuro[3,2-c]pyridines (VIIa – d). To 0.01 mole of compound VIa – d in 20 ml of glacial acetic acid is added on boiling during 30 min by portions 5 g of fine Zn powder. The boiling is continued for 2 – 3 h and the reaction is monitored by TLC. Then the reaction mixture is cooled, and the inorganic residue filtered. The solvent is distilled off, the residue is mixed with 100 – 150 ml of water, and the pH is adjusted at 7.5 – 8. The target product (VIIa – VIId) is filtered, washed with water, and dried. The ^{1}H NMR spectrum of VIIa, δ, ppm: 3.64 (s, 3H, OMe), 7.10 (d, J 2.6 Hz, 1H, 9-CH), 7.16 (q, J^1 2.6 Hz, J^2 2.6 Hz, 1H, 7-CH), 7.67 (d, J 9 Hz, 1H, 6-CH), 7.59 – 7.85 (m, 5H, Ph), 7.69 (d, J 6.7 Hz, 1H, 4-CH), 8.68 (d, J 6.7 Hz, 1H, 3-CH).

1-Aryl-3-oxo-8-methoxybenzofuro[3,2-c]pyridines (VIIIa – d). A mixture of 0.01 mole of compound VIa – d and 25 ml Ac_2O is boiled for 5 h. The reaction mixture is cooled and poured into 250 ml of water. The precipitate is filtered, washed on the filter with water, and dried. To this mixture of 2-pyridones VIIIa – d and their O-acyl derivatives is added 100 – 150 ml MeOH until complete dissolution of the residue and 10 ml of concentrated HCl, and the solution id boiled for 5 h. The course of the reaction was monitored by TLC. After completion of the reaction, the solvent is distilled off and the residue is mixed with water. The target product (VIIIa – d) is filtered and dried. The ^{1}H NMR spectrum of VIIIa, δ, ppm: 3.61 (s, 3H, OMe), 6.40 (s, 1H, 4-CH), 6.66 (d, J 2.7 Hz, 1H, 9-CH), 6.92 (q, J^1 9 Hz, J^2 2.7 Hz, 1H, 7-CH), 7.44 (d, J 9 Hz, 1H, 6-CH), 7.61 – 7.73 (m, 5H, Ph).

TABLE 2. Electron-Impact Mass Spectra of Compounds VIa – d, VIIa, b, VIIIa, b, and IXa – c

Compound	*m/z* (I_{rel}, %)
VIa	292(35), 291(100) $[M]^+$, 290(95), 275(62), 274(64), 260(22), 259(60), 245(15)
VIb	306(18), 305(98) $[M]^+$, 304(100), 289(26), 288(28), 276(32), 273(46), 77(79)
VIc	326(26) (1Cl)*, 325(64) $[M]^+$ (1Cl), 324(62) (1Cl), 310(48) (1Cl), 309(100) (1Cl), 308(88) (1Cl), 294(22) (1Cl), 292(48)
VId	369(30) (1Br)* $[M]^+$, 368(16) (1Br), 353(100) (1Br), 352(77) (1Br), 337(45) (1Br), 322(17) (1Br), 273(26), 202(67)
VIIa	275(100) $[M]^+$, 274(96), 260(11), 259(33), 245(16), 244(8), 203(12), 131(11)
VIIb	289(83) $[M]^+$, 288(100), 273(32), 260(74), 259(14), 216(10), 203(5), 96(4)
VIIIa	291(100) $[M]^+$, 290(40), 276(3), 275(5), 248(14), 219(6), 191(2), 104(8)
VIIIb	305(100) $[M]^+$, 304(40), 290(4), 289(6), 234(4), 145(7), 118(6), 91(4)
IXa	309(100) $[M]^+$ (1Cl)*, 308(60) (1Cl), 293(10) (1Cl), 280(3) (1Cl)
IXb	323(100) $[M]^+$ (1Cl)*, 322(83) (1Cl), 322(83) (1Cl), 307(19) (1Cl), 293(20) (1Cl), 280(5) (1Cl)
IXc	387(82) [M+] (1Cl, 1Br)*, 386(56) (1Cl, 1Br), 357(15) (1Cl, 1Br), 293(14) (1Cl), 265(13) (1Cl), 230(16), 201(20), 175(8)

* The *m/z* values for chlorine and bromine-containing ions are calculated for ^{35}Cl and ^{79}Br isotopes. Mass numbers are presented for the eight most intense peaks in the spectra.

1-Aryl-3-chloro-8-methoxybenzofuro[3,2-c]pyridines (IXa – d). A mixture of 0.01 mole of compound VIa – d and 15 ml of phosphorus chloroxide is boiled for 7 h. The reaction mixture is cooled, and slowly poured onto 75 – 100 g of ice, and the solution pH is adjusted at 9 – 10. The precipitate of IXa – d is filtered and dried.

1-Aryl-3-alkylamino-8-methoxybenzofuro[3,2-c]pyridines (Xa – f). A mixture of 0.01 mole of compound IXa – d and 25 ml of the corresponding amine is boiled until disappearance of the spot of the initial product on Silufol UV-254 plate eluted in the benzene – acetone (9 : 1) system. Then the excess amine is distilled off, and the residue is mixed with 100 – 150 ml of water. The precipitate of Xa – f is filtered and dried.

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