SYNTHESIS OF DERIVATIVES OF A NEW HETEROCYCLIC SYSTEM – 1,2,3,4-TETRAHYDROBENZOFURO[3,2-c]PYRIDINE

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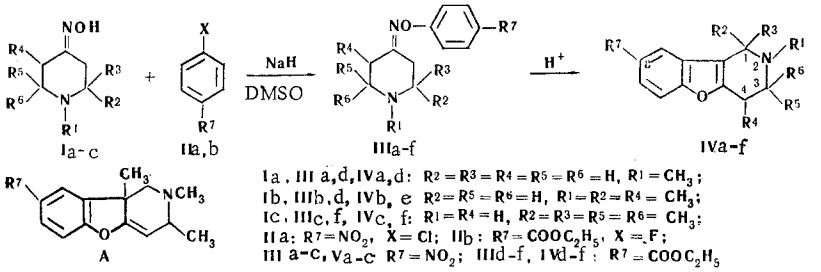
Derivatives (IVa-f) of the heretofore unknown 1,2,3,4-tetrahydrobenzofuro[3,2-c]pyridine heterocyclic system were synthesized by the cyclization of aryl ethers of the oximes of piperidones (IIIa-f) under acid conditions.

Despite the fact that 1,2,3,4-tetrahydro-γ-carboline and its derivatives are widely known and are traditional objects in the search for pharmacologically active substances [1-5], the corresponding oxygen analogs – 1,2,3,4-tetrahydrobenzofuro[3,2-c]pyridines – have not yet been synthesized.

Comparatively recently a new method for the creation of the benzofuran system by the cyclization of aryl ethers of ketoximes was discovered [6-8]. We used this route successfully to obtain the three-ring thiopyrano[4,3-b]benzofuran system [9].

In this paper, we propose the synthesis of 1,2,3,4-tetrahydrobenzofuro[3,2-c]pyridine derivatives (IVa-f):



Ia, IIIa,d, IVa,d: $R^2 = R^3 = R^4 = R^5 = R^6 = H$, $R^1 = CH_3$;
Ib, IIIb,d, IVb, e $R^2 = R^5 = R^6 = H$, $R^1 = R^2 = R^4 = CH_3$;
Ic, IIIc,f, IVc, f: $R^1 = R^4 = H$, $R^2 = R^3 = R^5 = R^6 = CH_3$;
IIa: $R^7 = NO_2$, X = Cl; IIb: $R^7 = COOC_2H_5$, X = F;
IIIa-c, IVa-c $R^7 = NO_2$; IIId-f, IVd-f: $R^7 = COOC_2H_5$

The starting aryl ethers of the oximes (IIIa-f) were obtained in 50-70% yields by the reaction of piperidone oximes (Ia-c) in the sodium salt form in dimethyl sulfoxide (DMSO) with 4-nitrochlorobenzene (IIa) or 4-ethoxycarbonylfluorobenzene (IIb). The IR spectra of III (in the case of IIIa, b) are characterized by a comparatively weak absorption band of a C=N group at 1646-1655 cm^{-1}. There is an absorption maximum at ~306 nm (log ε 4.2) in the UV spectra of III.

Compounds IIIa-IIId were cyclized by refluxing them briefly with a mixture of sulfuric and acetic acids (1:9). The yields of IV range from 10 to 85%.

Absorption at two wavelengths [λ_{max} 248 nm (log ε 4.55) and 286 nm (3.85)] is characteristic for the UV spectra of nitro compounds IVa-c. The IR spectra of IVa, c (in oil) contain a number of bands of high intensity at 1588-1653 cm^{-1} in addition to those typical for aromatic nitro groups at 1526-1530 and 1340-1343 cm^{-1}. The PMR spectrum of IVa (in $CDCl_3$) contained the following signals: 2.5 ppm (3H, singlet, $N-CH_3$), 2.8 ppm [4H, broad symmetric signal of an A_2B_2 system, $C_{(3)}H_2-C_{(4)}H_2$], 3.4 ppm [2H, broad symmetric signal, $C_{(1)}H_2$]. The CH_2-CH_2 signal in the spectrum of a pyridine solution of IVa becomes unsymmetric. If the spectrum of a trifluoroacetic acid solution is recorded, the signals of the protons of the piperi-

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TABLE 1. Ethers of the Oximes (IIIa-f)

Compound	mp, °C	Empirical formula	Found, %				Calc., %				Yield, %
			C	H	N	Cl	C	H	N	Cl	
IIIa	93—94*	$C_{12}H_{15}N_3O_3$	58,1	6,1	16,9		57,8	6,1	16,9		49
IIIa · HCl	171,5—172 (dec.)	$C_{12}H_{15}N_3O_3 \cdot HCl$				12,3				12,4	
IIIb	97—98	$C_{14}H_{19}N_3O_3$	61,4	7,1	15,4		61,5	7,0	15,4		55
IIIb · HCl	196—197 (dec.)	$C_{14}H_{19}N_3O_3 \cdot HCl$				11,3				11,3	
IIIc	78—79*	$C_{15}H_{21}N_3O_3$	61,9	7,3	14,7		61,8	7,3	14,4		70
IIIc · HCl	186—187 (dec.)	$C_{15}H_{21}N_3O_3 \cdot HCl$				10,8				10,8	
IIId	60—61†	$C_{15}H_{20}N_2O_3$	65,0	7,4	10,1		65,2	7,3	10,1		70
IIIe	75—76†	$C_{17}H_{24}N_2O_3$	67,4	7,9	9,5		67,1	7,9	9,2		53
IIIf	56—58‡	$C_{18}H_{26}N_2O_3$	—	—	9,0		—	—	8,8		71

*From heptane.

†From petroleum either.

‡The compound is hygroscopic.

TABLE 2. 1,2,3,4-Tetrahydrobenzofuro[3,2-c]pyridines (IVa-f)

Compound*	mp, °C†	Empirical formula	Found, %				Calc., %				Yield, %
			C	H	N	Cl	C	H	N	Cl	
IVa	145—146	$C_{12}H_{12}N_2O_3$	61,9	5,3	12,0	—	62,0	5,2	12,1	—	78
IVa · HCl	281—282 (dec.)	$C_{12}H_{12}N_2O_3 \cdot HCl$			10,4	13,0			10,4	13,2	
IVb	111—111,5	$C_{14}H_{16}N_2O_3$	64,6	6,4	11,0	—	64,6	6,2	10,8	—	26 ‡
IVc	195—195,5	$C_{15}H_{20}N_2O_3 \cdot HCl$	54,8	6,4	8,5	10,8	54,8	6,4	8,5	10,8	10
IVd	56—57	$C_{15}H_{17}NO_3$	69,4	6,7	5,7	—	69,5	6,6	5,4	—	57
IVe	236—237	$C_{17}H_{21}NO_3 \cdot HCl$	63,0	6,9	4,5	10,8	63,0	6,8	4,3	10,9	71
IVf	>300 (dec.)	$C_{18}H_{23}NO_3 \cdot HCl$	63,6	7,2	4,4	10,5	63,9	7,2	4,1	10,5	85

*In the preparation of IVa, IVd, and IVb,c, the materials were refluxed for 15 min, 10 min, and 5 min, respectively.

†The recrystallization solvents were: absolute alcohol for IVc,f, alcohol for IVa, dilute alcohol for IVb, petroleum ether for IVd, and isopropyl alcohol for IVe.

‡The yield was 43% in the cyclization with BF_3 etherate in acetic acid.

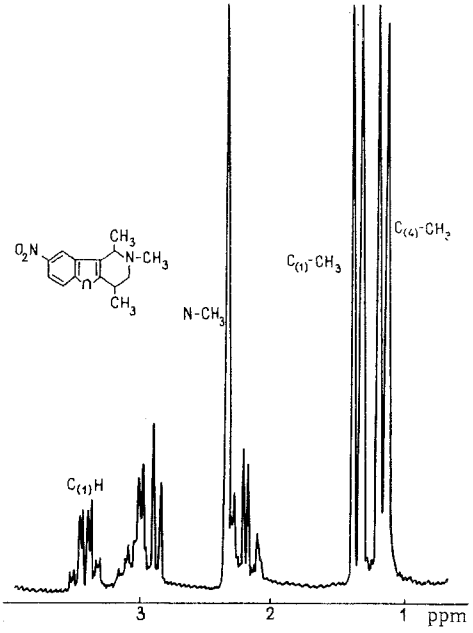

Fig. 1. PMR spectrum (in CCl_4) of 1,2,3,—4-trimethyl-8-nitro-1,2,3,4-tetrahydrobenzofuro[3,2-c]pyridine (IVb).

dine ring and the CH_3 group are shifted to weaker field (N—CH_3 at 2.9 ppm) as a consequence of protonation of the nitrogen atom, and the signals of the protons of this ring assume a complex form (at 3.1-4.8 ppm). Since a structure corresponding not only to formula IVb but also to formula A can be assigned to the product of the cyclization of ether IIIb, the PMR spectrum of this compound was also recorded. The spectral data (Fig. 1) unambiguously confirm structure IVb. Of the characteristic signals of the spectrum, one should note two doublets from $C_{(4)}-CH_3$ and $C_{(1)}-CH_3$ (δ 1.15 and 1.35 ppm), $JC_{(4)}-CH_3$; $C_{(4)}H$ 7 Hz, $JC_{(1)}-CH_3$; $C_{(1)}H$ 6.4 Hz, respectively (the constants were determined at operating frequencies of 100 and 60 MHz), as well as an octet at 3.4 ppm from $C_{(1)}-H$ [$J^1C_{(1)}-H$; $C_{(4)}-CH_3$ 6.4 Hz and $J^2C_{(1)}-H$; $C_{(4)}-H$ 2 Hz].

Thus the direction of cyclization of aryl ethers of the oxime of unsymmetrically constructed piperidone IB differs from the orientation during closing of the indole ring via the Fischer reaction of arylhydrazones of this ketone, for which intramolecular condensation proceeds exclusively with the participation of the α-methylidyne group with the initial formation of idolenines (which spontaneously undergo subsequent rearrangement) [10].

Compound IVd was converted to the corresponding β-dimethylaminoethyl ester (V) by transesterification with β-dimethylaminoethanol.

EXPERIMENTAL

The PMR spectra (in the δ scale) for IVa,b were obtained with an RS-60 spectrometer with an operating frequency of 60 MHz, while the spectrum of IVb was also recorded with a Varian-HA-100 spectrometer with an operating frequency of 100 MHz. The IR spectra were recorded with a UR-10 spectrometer, while the UV spectra were recorded with an SF-4 spectrophotometer.

4-Nitrophenyl Ether of 1-Methyl-4-piperidone Oxime (IIIa). A solution of 8 g (0.062 mole) of 1-methyl-4-piperidone oxime in 45 ml of DMSO was added in 20 min to a suspension of 2 g (0.06 mole) of 75% (with respect to active hydrogen) sodium hydride in 15 ml of DMSO, and the mixture was stirred at 20° for 1 h. A solution of 9.8 g (0.062 mole) of IIa in 20 ml of DMSO was then added, and the reaction mixture was stirred for another hour and poured into water. The resulting precipitate was removed by filtration, washed with water, and dried to give 7.6 g of ether IIIa.

The remaining ethers (IIIb-f) were similarly obtained. The data on IIIa-f are presented in Table 1.

8-Nitro-1,2,3,4-tetrahydrobenzofuro[3,2-c]pyridines (IVa-f). A solution of 0.012 mole of IIIa-f in 30 ml of a mixture of glacial acetic acid and concentrated sulfuric acid (9:1 with respect to volume) was refluxed for 5-15 min, poured into water, and made alkaline. The resulting precipitate was removed by filtration (or extracted with ether in the case of the isolation of the hydrochlorides). The optimum conditions for the preparation of IVe,f are as follows. Compounds IIIe,f were refluxed for 45 min with a 25-30% solution of hydrogen chloride in alcohol, the solvent was evaporated, and the residue was heated with a mixture of glacial acetic and concentrated sulfuric acids, as indicated above.

The physical constants and yields of IVa-f are presented in Table 2.

β-Dimethylaminoethyl 2-Methyl-1,2,3,4-tetrahydrobenzofuro[3,2-c]pyridine-8-carboxylate (V). β-Dimethylaminoethanol (5 ml) and 2-3 mg of sodium were added to 2 g (0.007 mole) of IIId in 20 ml of absolute toluene, and the mixture was refluxed for 1 h with removal of 70% of the toluene by distillation. Another 80 ml of absolute toluene and 4 ml of the amino alcohol were added, and the distillation was repeated. Benzene was added to the residue, the mixture was washed with water, and the benzene was removed by distillation. The residual oil crystallized on standing to give 2.3 g (91%) of amino ester V with mp 83-84° (from heptane). Found: C 67.5; H 7.5; N 9.3%. $C_{17}H_{22}N_2O_3$. Calculated: C 67.5; H 7.3; N 9.3%. The dihydrochloride had mp 285-287° (from alcohol). Found: Cl 18.7; N 7.4%. $C_{17}H_{22}N_2O_3 \cdot 2HCl$. Calculated: Cl 18.9; N 7.5%.

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