SYNTHESIS OF 3-AMINO DERIVATIVES OF BENZO[b]FURO[2,3-c]PYRIDINES

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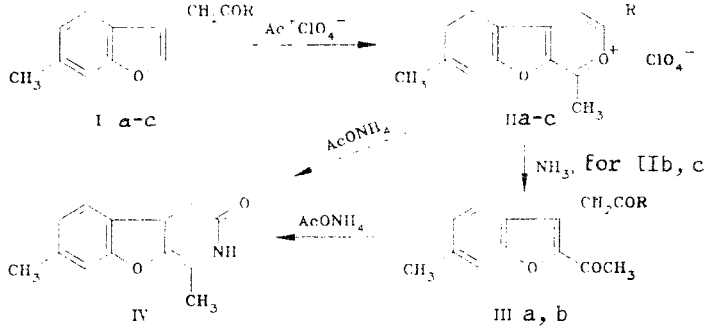
The reaction of 1,7-dimethyl-3(2H)-benzo[b]furo[2,3-c]pyridone with phosphoric acid amides gave 1,7-dimethyl-3-dimethylamino(morpholino)benzo[b]furo[2,3-c]pyridines. A method for the synthesis of 3-amino derivatives of 4-nitrobenzo[b]furo[2,3-c]pyridines, which consists in heating 1,7-dimethyl-4-nitro-3(2H)-benzo[b]furo[2,3-c]pyridone with hexamethyldisilazane and secondary or primary amines in pyridine, was developed.

It is known that α-amino derivatives of condensed pyridine bases have a broad spectrum of biological activity. Thus derivatives of 3-aminoisoquinolines are neuroleptics and antihypertonic agents [1, 2], while 3-amino-β-carbolines are selective antagonists of the sedative action of diazepam [3].

The aim of the present research was to obtain 3-amino-substituted benzo[b]furo[2,3-c]pyridines. According to our data [4, 5], benzo[b]furo[2,3-c]pyrylium salts are convenient intermediates in the synthesis of benzo[b]furo[2,3-c]pyridines. In developing this method we synthesized 1,7-dimethyl-3-dimethylamino(morpholino)-benzo[b]furo[2,3-c]pyrylium perchlorates IIb, c by acylation of the corresponding amides Ib, c in acetic anhydride in the presence of perchloric acid (see Table 1).

When we treated salts IIb, c with an alcohol solution of ammonia, we isolated 2-acetyl-6-methylbenzo[b]furan-3-ylacetic acid amides IIIa, b instead of the expected 3-dialkylaminobenzo[b]furo[2,3-c]pyridines, while 1,7-dimethyl-3(2H)-benzo[b]furo[2,3-c]pyridone (IV) was isolated in the case of refluxing with ammonium acetate in acetic acid. Compound IV was also obtained by heating acetamides IIIa, b with ammonium acetate in acetic acid and from perchlorate IIa under the same conditions.



The direct replacement of the 3-oxo group in pyridone IV may be another method for the synthesis of 3-amino derivatives of benzo[b]furo[2,3-c]pyridines. As has been previously demonstrated, hexamethylphosphoric triamide has been successfully used as a donor of an $N(CH_3)_2$ group in reactions involving the nucleophilic substitution of an activated OH group in aromatic systems [6], as well as for the dimethylamination of compounds containing a —CONH— grouping [7, 8]. In fact, the corresponding 1,7-dimethyl-3-dimethylamino(morpholino)-benzo[b]furo[2,3-c]pyridines Va, b are formed when IV is heated with hexamethylphosphoric triamide or trimorpholino phosphate.

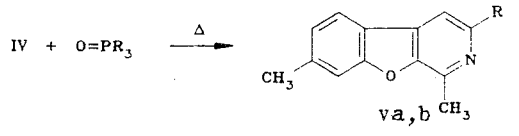


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TABLE 1. Characteristics of I-IV

Compound	Empirical formula	R*	T_{mp} °C**	R_f***	Yield, %
Ib	$C_{13}H_{15}NO_2$	$N(CH_3)_2$	100...101	—	80
Ic	$C_{15}H_{17}NO_3$	$N(CH_2)_4O$	81	—	75
IIa	$C_{13}H_{11}ClNO_7$	OH	(205)	—	65
IIb	$C_{15}H_{16}ClNO_6$	$N(CH_3)_2$	269...270	—	60
IIc	$C_{15}H_{18}ClNO_7$	$N(CH_2)_4O$	269...270	—	62
IIIa	$C_{15}H_{17}NO_3$	$N(CH_3)_2$	86...87	—	74
IIIb	$C_{17}H_{18}NO_4$	$N(CH_2)_4O$	124...125	—	71
IV	$C_{13}H_{11}NO_2$		336...337	0,45	80
Va	$C_{15}H_{16}N_2O$	$N(CH_3)_2$	114...115	0,36	70
Vb	$C_{17}H_{18}N_2O_2$	$N(CH_2)_4O$	154...155	0,40	53
VI	$C_{13}H_{10}N_2O_4$		(250)	0,62	68
VIIa	$C_{21}H_{20}N_6O_3$		(205)	0,72	94
VIIb	$C_{23}H_{24}N_6O_3$		(262)	0,76	84
VIIc	$C_{23}H_{22}N_3O_5$		(207)	0,74	91
VIId	$C_{20}H_{17}N_3O_3$		(270)	0,86	75

*Ia R = OH; for VIIa-d the designation of R is given under the scheme.
**The compounds were crystallized: Ia, b from hexane, IIa-c from acetic anhydride, IIIa, b from aqueous alcohol, IV from acetic acid, and Va, b from ether.
***Elution with the following solvent systems: benzene—ethanol (6:1) for IV, VI, and VIIc, d, ethyl acetate—benzene (6:1) for Va, ethyl acetate—benzene (1:6) for Vb, and benzene—ethanol (18:1) for VIIa, b.

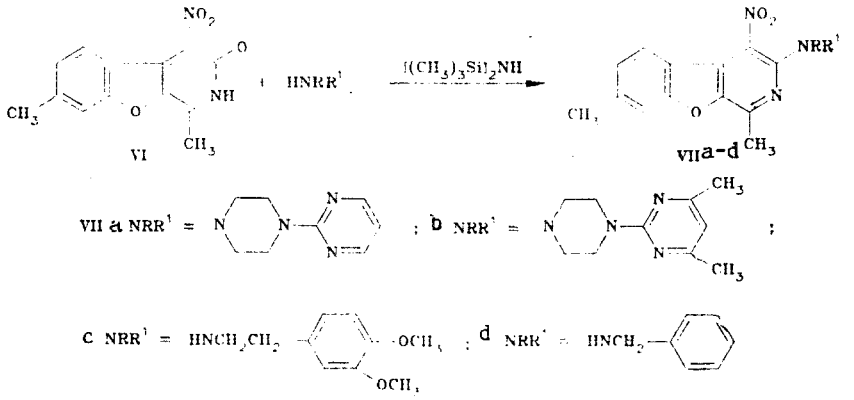
TABLE 2. Spectral Characteristics of IV-VII

Compound	IR spectrum ν, cm^{-1}*	Solvent for PMR	PMR spectrum, δ, ppm (J, Hz)
IV	1650 (—NHCO), 1645, 1610, 1560	C_5D_5N	2,41 (3H, s 7-CH_3); 2,77 (3H, s 1-CH_3); 7,15 (1H, d J=10, 6-H); 7,20 (1H, s 4-H); 7,46 (1H, s 8-H); 7,97 (1H, d J=12, 5-H)
Va		C_5D_5N	2,41 (3H, s 7-CH_3); 2,77 (3H, s 1-CH_3); 2,90 (6H, s $N(CH_3)_2$); 7,15 (1H, d J=10, 6-H); 7,20 (1H, s 4-H); 7,46 (1H, s 8-H); 7,97 (1H, d J=12, 5-H)
Vb	1640, 1600	C_5D_5N	2,41 (3H, s 7-CH_3); 2,77 (3H, s 1-CH_3); 2,59 (2H, q CH_2); 3,88 (2H, q CH_2); 7,15 (1H, d J=10, 6-H); 7,20 (1H, s 4-H); 7,46 (1H, s 8-H); 7,97 (1H, d J=12, 5-H)
VI	1645, 1605, 1545, 1510	CF_3COOH	2,68 (3H, s 7-CH_3); 3,12 (3H, s 1-CH_3); 7,60 (1H, d J=3,3, 6-H); 7,73 (1H, s 8-H); 8,90 (1H, d J=3,0, 5-H)
VIIa	1610, 1580, 1550, 1510	CF_3COOH	2,68 (3H, s 7-CH_3); 3,12 (3H, s 1-CH_3); 3,77 (4H, q $(CH_2)_2$); 4,47 (4H, q $(CH_2)_2$); 7,23 (1H, t, H**); 7,60 (1H, d J=3,3, 6-H); 7,73 (1H, s 8-H); 8,78 (2H, d J=8,3, H**); 8,90 (1H, d J=3,0, 5-H)
VIIb	1610, 1580, 1550, 1510	CF_3COOH	2,59 (6H, s $(CH_3)_2$**); 2,68 (3H, s 7-CH_3); 3,12 (3H, s 1-CH_3); 3,77 (4H, q $(CH_2)_2$); 4,47 (4H, $(CH_2)_2$); 6,97 (1H, s, H**); 7,60 (1H, d J=3,3, 6-H); 7,73 (1H, s 8-H); 8,90 (1H, d J=3,0, 5-H)
VIIc	1610, 1580, 1550, 1510	C_5D_5N	2,38 (3H, s 7-CH_3); 2,60 (3H, s 1-CH_3); 3,05 (2H, s CH_2); 3,35 (2H, s, CH_2); 3,70 (6H, s $(OCH_3)_2$); 6,80...8,00 (6H, m Harom); 8,60 (1H, t NH)
VIId	1615, 1580, 1550, 1510	C_5D_5N	2,38 (3H, s 7-CH_3); 2,60 (3H, s 1-CH_3); 3,50 (2H, s CH_2); 6,8...8,0 (8H, t Harom); 8,65 (1H, t NH)

*In mineral oil.
**Pyrimidine.

Compounds Va, b were obtained in good yields; however, the method is limited by the availability of the corresponding phosphoric acid amides. It is known that trimethylsilylation can activate groupings such as amide and lactam groupings, which makes it possible to carry out substitution reactions [9]. Subjecting pyridone IV to the silylation—amination reaction was unsuccessful — the starting IV was isolated. However, 1,7-dimethyl-4-nitro-

3(2H)benzo[b]furo[2,3-c]pyridone (VI) is readily aminated under these conditions to give 3-amino derivatives — 4-nitrobenzo[b]furo[2,3-c]pyridines VIIa-d. The method consists in heating VI with a twofold amount of the corresponding primary or secondary amine and hexamethyldisilazane in pyridine.



The structures of VIIa-d are confirmed by the IR and PMR spectral data (Table 2). A characteristic of VIIa-d is the fact that hydrolysis of the dialkyl(alkyl)amino group and the formation of VI occur when they are heated in solvents containing water; this was confirmed by TLC and the IR spectral data.

EXPERIMENTAL

The IR spectra of suspensions of the compounds in mineral oil were recorded with a UR-20 spectrometer. The PMR spectra were obtained with a Gemini-200 spectrometer (200 MHz) with tetramethylsilane (TMS) as the internal standard. The purity of the products obtained was monitored by TLC on Silufol UV-254 plates.

The results of elementary analysis of I-VII for C, H, Cl, and N were in agreement with the calculated values.

6-Methylbenzo[b]furan-3-ylacetic acid (Ia) was obtained by the method in [10]. Compound Ib was synthesized by a known method [11], while Ic was obtained by the method in [12].

Perchlorates IIa-c. A 2-ml sample of 70% $HClO_4$ was added to a solution of 0.01 mole of Ia-c in 10 ml of acetic anhydride, and the mixture was maintained at room temperature for 24 h. The precipitated crystals were removed by filtration, washed successively with acetic anhydride—ether (1:1) and ether, and dried in vacuo.

2-Acetyl-6-methylbenzo[b]furan-3-ylacetic Acid Amides. A 20-ml sample of an alcohol solution of ammonia was added to 0.01 mole of IIb, c, and the mixture was refluxed for 1 h. It was then cooled and poured into 100 ml of water, and the precipitated crystals were removed by filtration.

1,7-Dimethyl-3(2H)-benzo[b]furo[2,3-c]pyridone (IV). A mixture of 0.01 mole of IIa-c or IIIa, b, 10 g of ammonium acetate, and 60 ml of glacial acetic acid was refluxed for 3 h, after which it was cooled and poured into 50 ml of water, and the precipitated crystals were removed by filtration.

1,7-Dimethyl-3-dimethylamino(morpholino)benzo[b]furo[2,3-c]pyridines Va, b. A mixture of 0.01 mole of pyridone IV and 25 g of the corresponding triamido phosphate was heated for 12 h at 200-220°C, after which it was cooled and treated with 100 ml of 5% NaOH. The mixture was then extracted with chloroform, and the extract was dried over Na_2SO_4. The solvent was removed, and the residue was purified by column chromatography on silica gel by elution with benzene—ethyl acetate (6:1).

1,7-Dimethyl-4-nitro-3(2H)-benzo[b]furo[2,3-c]pyridone (VI). A 30-mmole sample of 97% HNO_3 was added with stirring at 13-15°C to a suspension of 4.7 mmole of IV in 7 ml of glacial acetic acid, after which the mixture was maintained for 20 min at 30°C and then poured over ice. The resulting precipitate was removed by filtration and washed with a small amount of cold ether.

1,7-Dimethyl-3-R,R^1-amino-4-nitrobenzo[b]furo[2,3-c]pyridines VIIa-d. A mixture of 0.01 mole of VI, 0.02 mole of the corresponding amine, and 0.01 mole of hexamethyldisilazane in 40 ml of dry pyridine was refluxed for 16 h, after which the pyridine was removed in vacuo. The residue crystallized on cooling. The mixture was filtered, and the crystals were washed with methylene chloride.

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CONDENSATION OF 6-METHYL-3-AZAPYRYLIUM SALTS TO PYRIDO[1,2-C]PYRIMIDINIUM DERIVATIVES

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Under the influence of DMF/Ac_2O 2,4-diphenyl-6-methyl-3-azapyrylium perchlorates undergo condensation to give pyrido[1,2-c]pyrimidinium perchlorates. The structure of one of the perchlorates was proved by x-ray diffraction analysis.

Little study has been devoted to the properties of 3-azapyrylium salts. We have recently observed [1] that the acid-catalyzed acylation of 4-methyl-substituted 3-azapyrylium salts at the methyl group is accompanied by a previously unknown recyclization to give difficult-to-obtain 4-acylaminopyrylium salts. This opens up prospects for the profound modification of 3-azapyrylium salts by the action of not only nucleophilic reagents but also electrophilic reagents.

Our recently developed [2] method for obtaining 6-alkyl-3-azapyrylium salts has made it possible to begin a systematic study of the reactivities of the alkyl groups of this class of heterocyclic cations, viz., pathways of functionalization and subsequent transformations of the products formed.

We found that pyrido[1,2-c]pyrimidinium salts IIIa, b are formed when 3-azapyrylium perchlorates Ia, b are refluxed in DMF/Ac_2O, which is normally used to obtain N,N-dimethylaminovinyl-substituted pyrylium salts [3]. Carrying out this reaction at 20°C probably gives N-benzoylaminovinyl derivatives B of pyridine, which are converted to pyridines IVa, b by the action of aqueous alkali, whereas they are converted to salts IIIa, b by heating in acetic anhydride.

The formation of perchlorates IIa, b can be explained by a scheme that provides for deprotonation of 3-azapyrylium salts Ia, b to anhydro bases IIa, b. The latter are capable of reacting with electrophilic reagents, which in this case are starting salts Ia, b. Reactions of this sort in series of other heterocyclic systems have been previously described [4-6]. The subsequent recyclization of adducts A leads to perchlorates B, which undergo cyclization to salts IIIa, b on heating (see Table 1).

The scheme presented below is confirmed by the fact that the same products IIIa, b and IVa, b were synthesized in the reactions of salts Ia, b with anhydro bases IIa, b. The latter were obtained by deprotonation of the starting perchlorates Ia, b with triethylamine.

The structure of product IIIb was proved unequivocally by an x-ray study of its perchlorate (see Fig. 1 and Tables 2 and 3), which was also of independent structural-chemical interest, since, according to the Cambridge structural data base [7], the structure of pyrido[1,2-c]pyrimidinium derivatives has not been previously studied.

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