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ELECTROPHILIC SUBSTITUTION IN BENZO[b]FURO[2,3-c]PYRIDINES: NITRATION, ACYLATION

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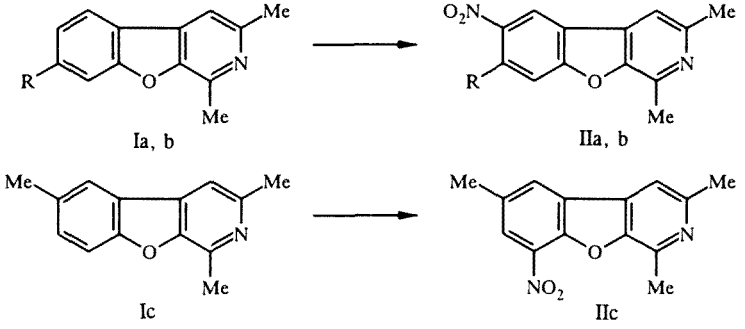
It has been shown that the nitration and acylation of substituted benzo[b]furo[2,3-c]pyridines proceeds exclusively at position 6 of the benzene ring. If position 6 is blocked by a substituent, the product of monosubstitution at the $C_{(8)}$ atom is formed. The molecules that were investigated have been calculated in the MNDO approximation.

The work reported here is a continuation of previous studies of the reactivity of isosteres of β-carbolines, in which we investigated the features of nitration and acylation of benzo[b]thieno[2,3-c]pyridines. It had been shown that, depending on the conditions, either one nitro group is introduced at $C_{(6)}$, or two nitro groups at $C_{(6)}$ and $C_{(8)}$. If position 6 is blocked, a mixture of nitrated products is formed [1]. Acetylation proceeds at position 8, whereas benzoylation leads to a mixture of products from substitution at $C_{(6)}$ and $C_{(8)}$ [2].

In the work reported here, we investigated the nitration and acylation (acetylation, benzoylation) of benzo[b]furo[2,3-c]pyridines [3].

The nitration of the pyridines Ia-c was performed under the same conditions as for the benzo[b]thieno[2,3-c]pyridines reported in [1]. Thus, in the nitration of 1,3-dimethylbenzo[b]furo[2,3-c]pyridine (Ia), we found that only the 6-nitro derivative IIa is formed. An analogous picture was observed for 1,3-7-trimethylbenzo[b]furo[2,3-c]pyridine (Ib). If position 6 is blocked by a methyl group, as in the case of 1,3,6-trimethylbenzo[b]furo[2,3-c]pyridine (Ic), the product of substitution at the $C_{(8)}$ atom (IIc) is formed.



R = H in Ia and IIa; R = Me in IIa and IIb

The acylation of benzo[b]furo[2,3-c]pyridines was performed by heating the corresponding pyridine base or its hydrochloride with a twofold excess of $AlCl_3$ and the acylating agent at 130-135° without solvent (for the benzo[b]thieno[2,3-c]pyridines, the optimal acylation temperature had been found to be 100-110°C). For the furo derivatives, the increase of the reaction temperature from 100° to 130° is necessary in order to obtain acceptable yields of the acyl derivatives; at 100-110°C, the yields are no higher than 30%. We established that both the acetylation and the benzoylation lead to the corresponding 6-derivatives.

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TABLE 1. Characteristics of Compounds II-III

Compound	Empirical formula	Found, % / calculated, %			mp, °C	R_f	Eluent for chromatography	Yield, %
		C	H	N				
IIa	$C_{13}H_{10}N_2O_3$	64,4 / 64,5	4,2 / 4,2	11,7 / 11,6	177...180	0,94	Benzene—chloroform, 2:1*	68
IIb	$C_{14}H_{12}N_2O_3$	65,5 / 65,6	4,7 / 4,7	10,9 / 10,9	169...171	0,46	Benzene—ethyl acetate, 10:1**	71
IIc	$C_{14}H_{12}N_2O_3$	65,5 / 65,6	4,8 / 4,7	10,9 / 10,9	150...153	0,83	Benzene—chloroform, 20:1*	66
IId	$C_{21}H_{17}NO_2$	79,9 / 80,0	5,4 / 5,4	4,4 / 4,4	154...156	0,70	Benzene—ethyl acetate, 1:2**	66
IIe	$C_{19}H_{14}N_2O_3$	71,7 / 71,7	4,4 / 4,4	8,8 / 8,8	282...285	0,92	Benzene—chloroform, 5:1*	86
IIf	$C_{18}H_{11}N_3O_5$	61,8 / 61,9	3,2 / 3,2	12,0 / 12,0	325...327	0,92	Benzene—chloroform, 2:1*	66
IIIa	$C_{15}H_{13}NO_2$	75,4 / 75,3	5,6 / 5,5	5,9 / 5,9	148...150	0,53	Benzene—ethyl acetate, 1:2**	65
IIIb	$C_{21}H_{17}NO_2$	80,0 / 80,0	5,3 / 5,4	4,4 / 4,4	240...242	0,77	Benzene—ethyl acetate, 6:1**	59
IIIe	$C_{21}H_{17}NO_2$	79,9 / 80,0	5,5 / 5,4	4,4 / 4,4	133...134	0,66	Benzene*	59

*Alufol.

**Silufol UV-254.

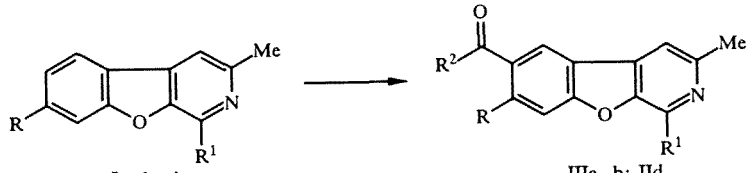
TABLE 2. Spectral Characteristics of Compounds II-V

Compound	PMR spectrum, δ, ppm (and SSCC, J, Hz)
IIa***	2,72 (3H, s, 3-CH_3), 2,79 (3H, s, 1-CH_3), 7,63 (1H, s, 4-H), 7,75 (1H, d, J = 10, 8-H), 8,51 (1H, d, J = 10, 7-H), 9,02 (1H, s, 5-H)
IIb*	2,55 (3H, s, 3-CH_3), 2,64 (3H, s, 1-CH_3), 3,39 (3H, s, 7-CH_3), 7,79 (1H, s, 4-H), 7,81 (1H, s, 8-H), 8,23 (1H, s, 5-H)
IIc***	2,57 (3H, s, 3-CH_3), 2,64 (3H, s, 1-CH_3), 2,79 (3H, s, 3-CH_3), 7,22 (1H, s, 4-H), 7,46 (1H, s, 5-H), 8,74 (1H, s, 7-H)
IId***	1,53 (3H, t, 1β-CH_3), 2,73 (3H, s, 3-CH_3), 2,21 (2H, q, 1α-CH_2), 7,47...7,72 (4H, m, 4-H, 3',4',5'-H_3), 7,79 (1H, d, J = 12,6, 8-H), 8,03 (2H, d, J = 8, 2',6'-H_2), 8,22 (1H, d, J = 12,6, 7-H), 8,65 (1H, s, 5-H)
IIe*	1,49 (3H, t, 1β-CH_3), 3,23 (2H, q, 1α-CH_2), 8,11 (1H, d, J = 10, 8-H), 8,33...8,52 (4H, m, 4-H, 3',4',5'-H_3), 8,58 (1H, d, J = 10, 7-H), 9,12 (2H, d, J = 3,6, 2',6'-H_2), 9,36 (1H, s, 5-H)
IIf***	2,92 (3H, s, 3-CH_3), 7,18 (1H, s, 4-H), J = 7,89 (1H, d, = 10,5, 8-H), 8,51 (2H, d, J = 6,3, 2',6'-H_2), 8,60 (1H, d, J = 10,5, 7-H), 8,71 (2H, d, J = 6,3, 3',5'-H_2), 9,14 (1H, s, 5-H)
IIIa***	2,51 (3H, s, 3-CH_3), 2,54 (3H, s, 1-CH_3), 2,61 (3H, s, 6-Ac), 7,34 (1H, s, 4-H), 7,52 (1H, d, J = 10, 8-H), 8,13 (1H, d, J = 10, 7-H), 8,61 (1H, s, 5-H)
IIIb***	2,42 (3H, s, 3-CH_3), 2,51 (3H, s, 1-CH_3), 2,55 (3H, s, 7-CH_3), 6,86 (1H, s, 4-H), 7,27 (1H, s, 8-H), 7,43 (1H, t, PhCO), 7,49 (2H, d, J = 8, PhCO), 7,62 (1H, t, PhCO), 7,82 (1H, s, 5-H), 7,89 (1H, t, PhCO)
IIIe***	1,55 (3H, t, 1β-CH_3), 2,72 (3H, s, 6-Ac), 3,27 (2H, q, 1α-CH_2), 7,48 (1H, t, 4'-H), 7,60 (2H, t, 3',5'-H_2), 7,78 (1H, d, J = 8, 8-H), 8,37 (1H, d, J = 8, 7-H), 8,42 (2H, d, J = 10, 2',6'-H_2), 8,96 (1H, s, 5-H)
IVe*	1,44 (3H, t, 1β-CH_3), 2,64 (3H, d, 4'-Ac), 2,70 (3H, s, 6'-Ac), 3,18 (2H, q, 1α-CH_2), 7,90 (1H, d, J = 10, 8-H), 8,08 (2H, d, J = 8,6, 2',6'-H_2), 8,25 (1H, d, J = 10, 7-H), 8,31 (2H, d, J = 8,6, 3',5'-H_2), 8,82 (1H, s, 4-H), 8,96 (1H, s, 5-H)
Ve*	1,45 (3H, t, 1β-CH_3), 2,64 (3H, s, 3'-Ac), 2,70 (3H, s, 6-Ac), 3,19 (2H, q, 1α-CH_2), 7,67 (1H, t, 5'-H), 7,90 (1H, d, J = 10, 8-H), 8,03 (1H, d, J = 8, 6'-H), 8,25 (1H, d, J = 10, 7-H), 8,45 (1H, d, J = 8, 4'-H), 8,70 (1H, s, 2'-H), 8,83 (1H, s, 4-H), 8,98 (1H, s, 5-H)

*DMSO-d_6, TMS.

**Chloroform-d, HMDS.

***Pyridine-d_5, TMS.



Ia, b, d — IIIa, b; IId

Ia R = H, R^1 = Me, IbR = R^1 = Me, IdR = Me, R^1 = Et; IIIa R = H, R^1 = R^2 = Me, IIIbR = R^1 = Me, R^2 = Ph; IId R = H, R^1 = Et, R^2 = Ph

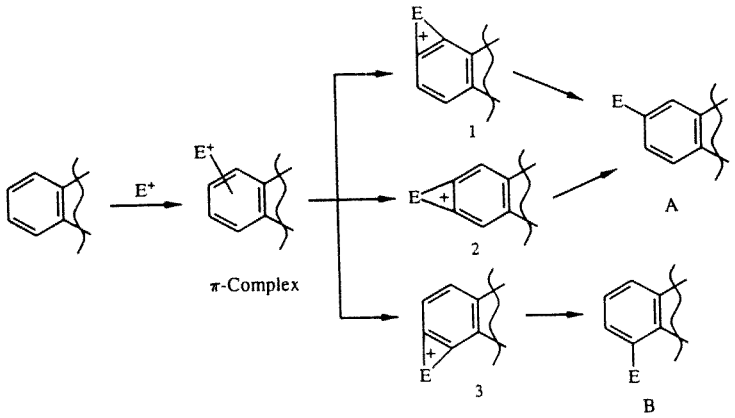
Thus, electrophilic substitution in benzo[b]furo[2,3-c]pyridines is more selective in comparison with electrophilic substitution in benzo[b]thieno[2,3-c]pyridines. In order to elucidate the reason for this difference, we carried out semiempirical quantum-chemical calculations of the benzo[b]furo[2,3-c]pyridines in the MNDO approximation [4] (Table 3). As the initial geometric approximation we used molecular structures obtained by complete optimization of geometry using the method of molecular mechanics (force field MMX [5]).

In comparison with the thio analogs [2], the benzo[b]furo[2,3-c]pyridines have a higher electron density on $C_{(6)}$ and $C_{(8)}$ atoms, as a consequence of a stronger mesomeric influence of the oxygen atom on the benzene fragment of the molecule. However, this difference is not great enough that it can be used as the sole explanation of the observed high positional selectivity of these compounds in electrophilic substitution (see Table 3).

Assuming that three types of σ-complexes are formed in electrophilic substitution, with the participation of the p-AO of the HOMO of the respective atoms $C_{(5-6)}$, $C_{(6-7)}$, and $C_{(7-8)}$, we can estimate the capability of the system for forming these intermediates, assuming that this capability is proportional to the sum of the squares of the AO coefficients of the adjacent atoms.

TABLE 3. Results from Quantum-Chemical Calculations of Benzo[b]furo[2,3-c]pyridines in MNDO Approximation

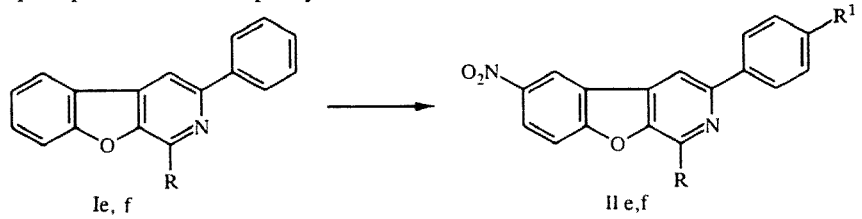
Compound	Effective charges on atoms (au) and squares of LCAO or HOMO coefficients (in parentheses)			
	$C_{(5)}$	$C_{(6)}$	$C_{(7)}$	$C_{(8)}$
Benzo[b]furo[2,3-c]pyridine	0,010 (0,087)	-0,084 (0,143)	-0,026 (0,000)	-0,063 (0,128)
Ia	0,010 (0,068)	-0,084 (0,118)	-0,027 (0,000)	-0,063 (0,106)
6-Methylbenzo[b]furo[2,3-c]-pyridine	0,029 (0,088)	-0,126 (0,162)	-0,010 (0,002)	-0,066 (0,118)
7-Methylbenzo[b]furo[2,3-c]-pyridine	0,006 (0,088)	-0,066 (0,143)	-0,067 (0,000)	-0,047 (0,127)
Cation of benzo[b]furo[2,3-c]-pyridine	0,044 (0,246)	-0,066 (0,193)	0,034 (0,007)	-0,059 (0,251)
Cation of Ia	0,042 (0,234)	-0,066 (0,195)	0,031 (0,005)	-0,060 (0,240)
Cation of 6-methylbenzo[b]furo-[2,3-c]pyridine	0,055 (0,219)	-0,099 (0,247)	0,045 (0,003)	-0,060 (0,162)
Cation of 7-methylbenzo[b]furo-[2,3-c]pyridine	0,043 (0,250)	-0,055 (0,108)	0,005 (0,042)	-0,053 (0,314)



Actually, the ratio $\Sigma(\psi_5^2 + \psi_6^2)/\Sigma(\psi_6^2 + \psi_7^2)/\Sigma(\psi_7^2 + \psi_8^2)$ for the benzo[b]furo[2,3-c]pyridines, 0.230/0.143/0.128, is significantly different from the ratio for benzo[b]thieno[2,3-c]pyridines [2], 0.172/0.104/0.105, indicating that the fraction of substitution in position 6 in the first case should be considerably greater than in the second case. A similar picture is observed for the protonated forms of these compounds: in the first case 0.439/0.200/0.258, and in the second case 0.353/0.157/0.225 [2]. If position 6 is occupied by a substituent, electrophilic substitution should take place in position 8, and this is what is actually observed in experiment.

Thus, information on the HOMOs and AOs obtained by theoretical methods can serve as a convenient means of orientation in predicting a qualitative picture of the direction of preferential positional orientation in processes of electrophilic substitution in isosteres of β-carbolines.

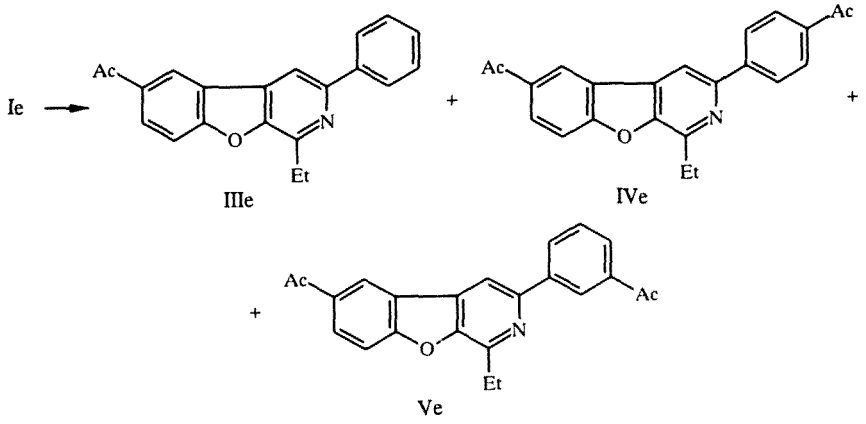
It was of interest to study the features of nitration and acylation in the 1-methyl(ethyl)-3-phenylbenzo[b]furo[2,3-c]pyridines Ie,f, since substitution can proceed both in the annelated benzene ring and in the 3-phenyl substituent. And in fact, when compound Ie is treated with 99% nitric acid at 18-20°C, the 6-nitro derivative IIe is formed, whereas nitration of compound If by a mixture of concentrated sulfuric acid and 99% nitric acid leads to a dinitro derivative, with the second nitro group entering into the para position of the 3-phenyl substituent.



Ie, f IIe,f

Ie R = Et, If R = Me; IIe R = Et, R^1 = H, IIf R = Me, R^1 = NO_2

Acylation of compound Ie by acetyl chloride affords three products of substitution, the main product being the 6-acetyl derivative IIIe. The other two substances are diacetyl derivatives in which one acetyl group is in position 6 of the annelated benzene ring and the second in the para position of the 3-phenyl substituent (IVe) or in the meta position (Ve). We were not able to separate compounds IVe and Ve, since they are very similar in chromatographic mobility (R_f 0-0.18). However, in the PMR spectrum of the mixture (Table 2), we can clearly distinguish signals of protons of the 3-phenyl substituent, which are characteristic for the isomers IVe (two doublets of protons in positions 2′-6′ and 3′-5′) and Ve (singlet 2′-H, two doublets 4′-H and 6′-H and a triplet of the proton in position 5′) (see Table 2).



In the IR spectra of the substitution products from benzo[b]furo[2,3-c]pyridines, we observe absorption bands that are characteristic for the nitro group (1340 and 1510 cm^{-1}) and also bands for acyl groups (1690 cm^{-1} for acetyl, 1670 cm^{-1} for benzoyl).

EXPERIMENTAL

The PMR spectra were taken in a Gemini-200 instrument in DMSO-d_6, chloroform-d, or pyridine-d_5; internal standard TMS or HMDS. The characteristics of compounds II-V and the corresponding PMR spectral data are presented in Tables 1 and 2. The product purity and the contents of isomers were monitored by TLC on Alufol and Silufol UV-254 plates. The isomers were separated by column chromatography on aluminum oxide (neutral) and silica gel (Table 1), with subsequent recrystallization from an appropriate solvent.

Elemental analyses of compounds II-III for C, H, and N matched the calculated values.

Compounds Ia-f were obtained by a procedure given in [3].

General Method for Nitration of Compounds Ia,b,c,e,f. ***A)*** To a solution of 4.7 mmoles of the compound Ia,b,c,e,f in 10 ml of H_2SO_4 (d = 1.832), at −5° to 0°C, 5 ml of nitric acid (d = 1.520) was added dropwise while stirring. The reaction mixture was held at this temperature for 1 h, after which it was poured into water containing ice and ammonia; the resulting precipitate was filtered off, washed with water, and air-dried. ***B)*** A 4.7-mmole quantity of compound Ia,b,c,e,f was added to 4.9 ml of nitric acid (d = 1.520) while cooling the flask with ice water. The reaction mixture was then held at 18-20°C for 1 h, after which it was poured into water containing ice and ammonia, and the precipitate was filtered off, washed with water, and air-dried.

General Method for Acylation of Compounds Ia,b,d,e. A 2.6-mmole quantity of compound Ia,b,d,e was mixed with 5.2 mmoles of aluminum chloride and the appropriate acyl chloride. The mixture was heated at 130-135°C for 3 h. The procedure used in isolating the compound depended on the particular acylating agent used. With acetyl chloride, the reaction mixture was transferred to acidified ice water, and the resulting precipitate was filtered off, washed on the filter with water, and air-dried. With the benzoyl chloride, the reaction mixture was transferred to strongly alkaline ice water, and the precipitate was filtered off, washed on the filter with water, and air-dried.

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