Chemistry of Heterocyclic Compounds, Vol. 32, No. 4, 1996

CONDENSED PYRIDINE BASES. ELECTROPHILIC SUBSTITUTION IN 1,7-DIMETHYL-3(2H)-BENZO[*b*]FURO[2,3-*c*]PYRIDONE

S. V. Tolkunov, M. N. Kal'nitskii, S. N. Lyashchuk,
S. Yu. Suikov, M. Yu. Zubritskii, and V. I. Dulenko

Nitration, bromination, thiocyanation, and acylation of 1,7-dimethyl-3(2H)-benzo[b]furo[2,3-c]pyridone were investigated. It was shown that either the 4-nitro- or the 4,6-dinitro derivative is formed as a function of the nitration conditions. Bromination with bromine and thiocyanation with dithiocyanogen yields a bromo derivative at position 4. The product of substitution at the $C_{(6)}$ *atom is obtained in acylation with acetyl chloride, and the product of substitution at atoms* $C_{(4)}$ *and* $C_{(6)}$ *is obtained with benzoyl chloride. The results of the calculations were generalized in the MNDO approximation.*

In continuing our study of β-carboline isosteres [1-3], we investigated the characteristics of electrophilic substitution in 1,7-dimethyl-3(2H)-benzo[*b*]furo[2,3-*c*]pyridone (I). Compound I is interesting because electrophilic substitution in it can be directed both to the condensed benzene ring and to position 4 of the pyridine ring [4, 5]. Actually, calculations of the electronic structure of 1-methyl-3(2H)-benzo[*b*]furo[2,3-*c*]pyridone and its protonated form in the MNDO approximation [6] show that the highest negative charge is concentrated on the $C_{(4)}$ atom of the pyridine ring (Fig. 1), and in going from the unprotonated to the protonated form, both an absolute and a relative increase in the negative charge on the indicated atom is observed:

$$Q(C_{(4)}) : Q(C_{(6)}) : Q(C_{(8)}) \text{ (neutr.)} = 1 : 0{,}93 : 0{,}77\ ;$$
$$Q(C_{(4)}) : Q(C_{(6)}) : Q(C_{(8)}) \text{ (cation)} = 1 : 0{,}51 : 0{,}46$$

The opposite situation is observed for the HOMO AO coefficients

$$\psi^2(C_{(4)}) : \psi^2(C_{(6)}) : \psi^2(C_{(8)}) \text{ (neutr.)} = 1 : 0{,}29 : 0{,}13;$$
$$\psi^2(C_{(4)}) : \psi^2(C_{(6)}) : \psi^2(C_{(8)}) \text{ (cation)} = 1 : 16{,}7 : 18{,}4.$$

Since electrophilic substitution reactions are conducted in media with high acidity, the direction of this process should be predicted with the electronic characteristics of the cation. Based on the results of the calculations and previous studies [1-3], we can hypothesize that "hard" electrophiles (NO_2^+, for example) will primarily attack the $C_{(4)}$ atom of the pyridinium ring of the cation, since Coulomb interactions in the reactions of such electrophiles are dominant. Position 6 is much less subject to electrophilic attack by a "hard" electrophile, although it is not excluded in principle and can take place in harsher reaction conditions. A different situation is observed in the reaction of pyridone with "soft" electrophiles (CH_3CO^+, for example), which basically takes place at atoms with maximum HOMO AO coefficients. Coulomb interactions in this case have a much smaller effect on the orientation and can only appear when the AO coefficients of the different atoms are close. Since $\psi^2C_{(8)} \sim \psi^2C_{(6)}$, but $[Q(C_{(8)})] < [(C_{(6)})]$, the $C_{(6)}$ atom is the predicted direction of attack of the acylium cation. When a "moderately hard" electrophile ($PhCO^+$) is used, its equally probably reaction with the cation at positions 4 and 6 should be predicted.

L. M. Litvinenko Institute of Physical Organic Chemistry and Carbon Chemistry, National Academy of Sciences of Ukraine, Donetsk 340114. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 4, pp. 534-541, April, 1996. Original article submitted June 28, 1995; revision submitted February 9, 1996.

TABLE 1. Characteristics of Compounds II-XI

Compound	Empirical formula	Found, %				Calculated, %				Mp, °C	R_f	System for TLC	Yield, % (method)
		C	H	N	Br (S)	C	H	N	Br (S)				
II	$C_{13}H_{10}N_2O_4$	60,5	3,9	10,8	–	60,5	3,9	10,9	–	>350	0,62	Benzene-ethanol, 6 : 1	68
III	$C_{13}H_{19}N_3O_6$	49,9	6,1	13,4	–	49,8	6,1	13,4	–	>350	0,21	Benzene-ethanol, 20 : 1	65
IV	$C_{13}H_{10}NO_2Br$	53,4	3,5	4,7	27,3	53,5	3,5	4,8	27,4	276...279 (decomp.)	0,42	Benzene-ethanol, 10 : 1	51 (A), 57 (B)
V	$C_{13}H_{13}NO_3$	70,5	5,2	5,5	–	70,6	5,1	5,5	–	117,5...119	0,81	Benzene-ethyl acetate, 1 : 1	90
VI	$C_{13}H_{12}NO_3Br$	54,0	3,6	4,2	24,0	53,9	3,6	4,2	23,9	126,5...128	0,74	Benzene-ethyl acetate, 1 : 1	79
VII	$C_{14}H_{10}N_2O_2S$	62,2	3,8	10,3	(11,9)	62,2	3,7	10,4	(11,9)	>350	0,42	Methanol	26
VIII	$C_{15}H_{13}NO_3$	70,6	5,1	5,5	–	70,6	5,1	5,5	–	291...294	0,27	Benzene-ethanol, 10 : 1	84 (A), 64 (B)
IX	$C_{27}H_{19}NO_4$	76,9	4,6	3,3	–	77,0	4,5	3,3	–	286...289	0,91	Benzene-ethanol, 20 : 1	29 (A), 48 (B)
X	$C_{20}H_{15}NO_3$	75,7	4,7	4,4	–	75,7	4,8	4,4	–	134...136	0,79	Benzene-ethanol, 6 : 1	82
XI	$C_{20}H_{15}NO_3$	75,7	4,8	4,5	–	75,7	4,8	4,4	–	320 (decomp.)	0,67	Benzene-ethanol, 6 : 1	85

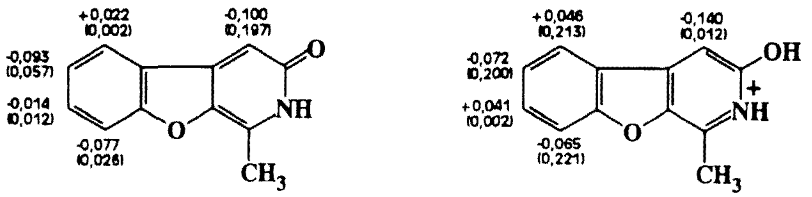
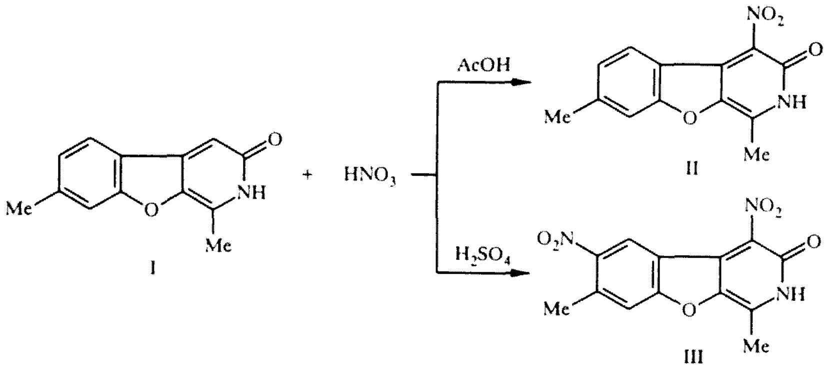
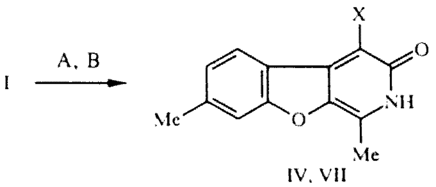


Fig. 1. Effective charges on the atoms of 1-methyl-3(2H)-benzo[*b*]furo[2,3-*c*]pyridone and its protonated form (the squares of the HOMO AO coefficients are indicated in parentheses).

Our results are in good agreement with the arguments reported above. Nitration of benzofuropyridone I with 99% nitric acid in acetic acid medium yields 4-nitro derivative (II) with a good yield (see Table 1). In harsher conditions — in nitration with a mixture of concentrated sulfuric and 99% nitric acids — 4,6-dinitro derivative (III) is formed.



Bromination of compound I with one equivalent of bromine in acetic acid in the presence of sodium acetate (A) results its 4-bromo-substituted derivative (IV). It was predicted that when two equivalents of bromine are used, the reaction will also take place at the 1-CH_3 group, since we previously showed that in these conditions, 1-methyl-substituted benzo[*b*]furo[2,3-*c*]pyridines are easily brominated with formation of a mixture of monobromomethyl and dibromomethyl derivatives [7]. However, in the case of benzo[*b*]furo[2,3-*c*]pyridone I, use of an excess of bromine did not yield products of bromination at the methyl group and only bromide IV was obtained. It is perhaps formed first and subsequently removed from the reaction sphere due to poor solubility.



A Br_2, AcOH, AcONa; B KSCN, Br_2, AcOH, IV X = Br, VII X = SCN

It should be noted that in the case of 1,7-dimethyl-3-acetoxybenzo[*b*]furo[2,3-*c*]pyridine (V), a "fixed" enol form of compound I, bromination with N-bromosuccinimide selectively takes place at the 1-methyl group and the corresponding 1-bromomethylpyridine (VI) is obtained with a 79% yield.

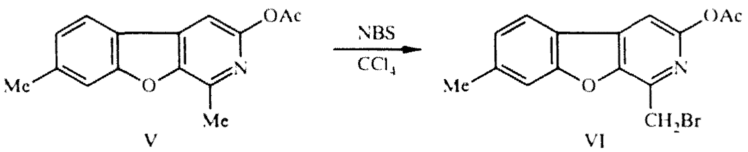


TABLE 2. Spectral Characteristics of Compounds II-XI

Compound	IR spectrum, cm^{-1}	PMR spectrum, ppm, SSCC (*J*), Hz						
		1-CH_3 c	7-CH_3 c	4-H c	5-H	6-H	8-H c	Other protons
II	1340, 1510 (NO_2), 1640 (C=O)	2,39	2,63	–	8,32 d, *J* = 10,0	7,18 d, *J* = 10,0	7,42	–
III	1340, 1510 (NO_2), 1640 (C=O)	2,63	2,79	–	9,07 s	–	7,75	–
IV	1640 (C=O), 520 (C–Br)	2,39	2,58	–	8,51 d, *J* = 8,4	7,20 d, *J* = 8,4	7,42	–
V	1690 (O–C=O)	2,63	2,59	7,45	7,90 d, *J* = 10,0	7,42 d, *J* = 10	7,65	2,70 s (CH_3CO)
VI	1670, 1690 (O–C=O), 570 (C–Br)	–	2,58	7,43	7,91 d, *J* = 10,0	7,41 d, *J* = 10,0	7,65	2,77 s (CH_3CO), 4,63 s (1-CH_2Br)
VII	1640 (C=O), 1410 (C=S)	2,41	2,61	–	8,40 d, *J* = 8,0	7,19 d, *J* = 8,0	7,40	–
VIII	1640, 1690 (C=O)	2,69	2,67	7,37	8,63 s	–	7,46	2,76 s (CH_3CO)
IX	1640, 1670 (C=O)	2,49	2,76	–	8,23 s	–	*	7,30...7,60 m (4 *m*-HP_h; 2-*p*-HP_h, 8-H), 7,89 d, *J* = 8,6 (2 *o*-HP_h); 8,19 d, *J* = 8,8 (2 *o*-HP_h)
X	1680 (O–C=O)	2,40	2,73	7,49	7,93 d, *J* = 8,0	7,19 d, *J* = 8,0	7,74	7,47 t (1-*p*-HP_h); 7,58 t (2 *m*-HP_h); 8,39 d, *J* = 7,1 (2 *o*-HP_h)
XI	1640, 1670 (C=O)	2,40	2,73	7,33	8,17 s	–	7,56	7,49 t (2 *m*-HP_h), 7,58 t (1 *p*-HP_h), 7,99 d, *J* = 7,1 (2 *o*-HP_h)

---

*Signal is overlapped by the HP_h multiplet.

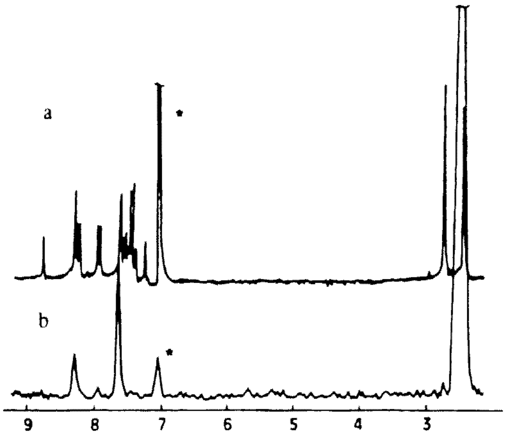
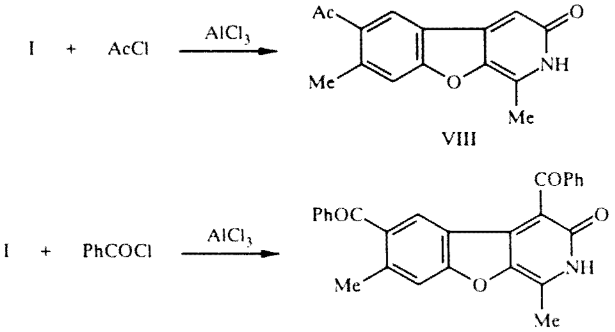


Fig. 2. PMR spectrum of compound IX: a) 1M spectrum; b) 2M spectrum (section over the frequency of the methyl group at 2.76 ppm, an artifact — a "turned" TMS signal — is indicated by the asterisk).

Thiocyanation of pyridone I (B) takes place similar to bromination and 4-thiocyanogen derivative (VII) is formed with a low yield. Acylation of pyridone I with acetyl chloride in the presence of $AlCl_3$ at 130-135°C results in a single product — 6-acetyl derivative (VIII). In benzoylation of compound I, we only separated product (IX) containing two benzoyl groups in positions 4 and 6. This dibenzoyl derivative is formed both with an equimolar ratio of the reagents and when a three-fold excess of the acylating agent is used.

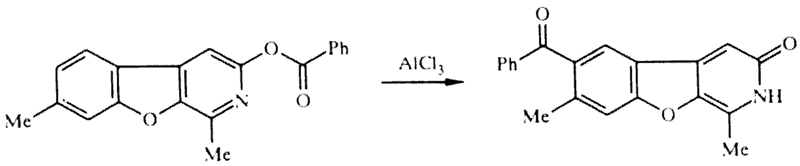


VIII

IX

An attempt was made to conduct Fries rearrangement with 3-acetoxypyridine V to obtain 4-acetyl-3-hydroxypyridine. However, instead of the expected product, compounds VIII with a yield of 64% and pyridone I were obtained. In the case of 3-benzoylhydroxypyridine (X), the yield of 6-benzoyl derivative (XI) was 85%, and pyridone I was not separated.

$$V \xrightarrow{AlCl_3} VIII + I$$



X

XI

We used the PMR data and IR spectra to demonstrate the structure of the synthesized compounds (Table 2). In the case of product IX, due to overlapping of the signals of the *m*- and *p*-protons of the two PhCO substituents and the signals of the aromatic protons of benzofuropyridone, it was difficult to draw any conclusion concerning the site of addition of these benzoyl groups. To solve this problem, we used the 2M COSY method. There are two cross peaks with signals of aromatic protons in the 2M spectrum (Fig. 2) at only one of the methyl groups (2.76 ppm) which we assigned to 7-CH_3, and the cross-peak intensities differ by more than two times. It was thus possible to identify the signals of the two protons of the condensed benzene ring and to show that their positions are not the same with respect to the methyl group. This is only possible for the skeleton of the molecule when the benzoyl group is in position 6. The lack of a cross peak at the 1-CH_3 group indicates that the second benzoyl group is in position 4 of the condensed pyridine ring.

The examples examined and the results obtained previously [2, 3] thus indicate that use of the effective charges and squares of the HOMO AO coefficients as statistical reactivity indexes for estimations of the most probable directions of electrophilic substitution in β-carboline isosteres is totally justified.

EXPERIMENTAL

The PMR spectra were recorded on a GEMINI-200 (200 MHz) in pyridine-D_5 (TMS internal standard) in the case of compounds II-IV, VII-XI, or chloroform-D (HMDS internal standard) for compounds V, VI. The IR spectra were recorded on a Specord M-80 in KBr pellets. The characteristics of the synthesized compounds are reported in Table 1, and the PMR data and IR spectra are given in Table 2. The purity and concentration of isomers was monitored with TLC on Alufol (VII) and Silufol UV-254 plates (remaining compounds).

The data from elemental analysis of compounds II-XI for C, H, Br, N, and S correspond to the calculations (see Table 1).

The starting benzofuropyridone I was synthesized by the method in [8].

1,7-Dimethyl-4-nitro-3(2H)-benzo[*b*]furo[2,3-*c*]pyridone (II). Here 1.25 ml of nitric acid (*d* 1.520) was added by drops to a suspension of 4.7 mmole of compound I in 7 ml of glacial acetic acid, maintaining the temperature at 13-15°C. The reaction mixture was subsequently held at 25-30°C for 20 min, the sediment was dissolved, and then a yellow sediment of product II precipitated almost immediately, was filtered off, washed on the filter with a small amount of cold ether, and dried in air.

1,7-Dimethyl-4,6-dinitro-3(2H)-benzo[*b*]furo[2,3-*c*]pyridone (III). At −5 to 0°C while stirring, 5 ml of nitric acid (*d* 1.520) was added by drops to a solution of 4.7 mmole of compound I in 10 ml of sulfuric acid (*d* 1.832). The reaction mixture was held at the indicated temperature for 1 h, and was then poured on ice with ammonia. The sediment of product III was filtered off, washed with water, dried in air, and recrystallized from benzene—ethanol mixture.

4-Bromo-1,7-dimethyl-3(2H)-benzo[*b*]furo[2,3-*c*]pyridone (IV). Method A. Here 2.5 mmole of bromine was added by drops to a suspension of 2.34 mmole of compound I in 5.5 ml of glacial acetic acid containing 0.3 g of sodium acetate. Pyridone I was dissolved simultaneously, and sediment of bromide IV formed. The reaction mixture was held for 1 h at 18-20°C. Product IV was filtered off, washed on the filter successively with water (four times), acetone, and ether, dried in air and recrystallized from DMF.

Method B. Product IV identical to the sample synthesized by Method A (R_f, mp) was also obtained from pyridone I with the method described above, but using 5 mmole of bromine.

3-Acetyoxy-1,7-dimethylbenzo[*b*]furo[2,3-*c*]pyridine (V). A mixture of 1.41 mmole of compound I and 30 ml of acetic anhydride was boiled for 20 min, the excess acetic anhydride was distilled off, ether was added to the residue, the sediment of product V was filtered off, washed with ether, dried in air, and recrystallized from benzene—hexane mixture.

3-Acetoxy-1,7-bromomethyl-7-methylbenzo[*b*]furo[2,3-*c*]pyridine (VI). Here 1.45 mmole of N-bromosuccinimide was added to a solution of 1.45 mmole of compound I in 15 ml of carbon tetrachloride. The mixture was boiled until the sediment disappeared (16 h). The succinimide was filtered off and washed with carbon tetrachloride. The filtrate was evaporated, and the residue — product VI — was recrystallized from benzene—hexane mixture.

1,7-Dimethyl-4-thiocyanogen-3(2H)-benzo[*b*]furo[2,3-*c*]pyridone (VII). Here 3.50 mmole of bromine was added to a solution of 4.22 mmole of KSCN in 5 ml of glacial acetic acid cooled to 15°C and the mixture obtained was added to a suspension of 1.41 mmole of compound I in 5 ml of glacial acetic acid. The reaction mass was held at 15°C for 6 h; it was poured in water, the precipitated sediment was filtered off, washed on the filter with water, dried in air, and chromatographed in a column with aluminum oxide (methanol eluent), collecting the fraction with R_f 0.42. The eluent was evaporated, and the residue — product VII — was recrystallized from benzene—methanol mixture.

6-Acetyl-1,7-dimethyl-3(2H)-benzo[*b*]furo[2,3-*c*]pyridone (VIII). Method A. A mixture of 2.6 mmole of compound I, 7.8 mmole of aluminum chloride, and 7.8 mmole of acetyl chloride was held at 130-135°C for 3 h. The cooled reaction mass was transferred to acidified ice water, and the sediment of product VIII was filtered off, washed on the filter with water, dried in air, and recrystallized from chloroform—ethanol mixture.

Method B. A mixture of 0.56 g (2.19 mmole) of compound V and 1.47 g (11 mmole) of aluminum chloride was held at 140-145°C for 3 h (conditions of Fries rearrangement). The reaction mass was then cooled, transferred to water, and the sediment was filtered off, washed on the filter with water, dried in air, and chromatographed in a column with silica gel. Then 0.36 g of compound VIII was eluted with benzene—ethanol mixture, 10:1, and 0.14 g of pyridone I was then eluted with ethanol. The mixed sample of substance VIII obtained with the different methods (A, B) did not exhibit any depression of the melting point.

4,6-Dibenzoyl-1,7-dimethyl-3(2H)-benzo[*b*]furo[2,3-*c*]pyridone (IX). Method A. A mixture of 2.6 mmole of compound I, 7.8 mmole of aluminum chloride, and 3.0 mmole of benzoyl chloride was held at 130-135°C for 3 h, cooled, transferred to strongly basic ice water, and the sediment of product IX was filtered off, washed on the filter with water, dried in air, and recrystallized from benzene—chloroform mixture.

Method B. Product IX was obtained with the method described above, but using 7.8 mmole of benzoyl chloride and 7.8 mmole of aluminum chloride. The mixed sample of compound IX prepared with Methods A and B did not exhibit any depression of the melting point.

3-Benzoyloxy-1,7-dimethyl-3(2H)-benzo[*b*]furo[2,3-*c*]pyridine (X). While stirring, 3.51 mmole of benzoyl chloride was added to a suspension of 2.34 mmole of compound I in 20 ml of chloroform containing triethylamine. The mixture was boiled in a water bath for 15 min, cooled, poured in water, the organic layer was separated, then washed with an aqueous solution of sodium bicarbonate and water, and dried over magnesium sulfate. The solvent was eliminated, and the residue of product X was recrystallized from ethyl acetate.

6-Benzoyl-1,7-dimethyl-(2H)-benzo[*b*]furo[2,3-*c*]pyridone (XI). A mixture of 1.48 mmole of compound X and 7.41 mmole of aluminum chloride was held at 140-145°C for 3 h. The cooled reaction mass was transferred to strongly basic water, the sediment of product XI was filtered off, washed on the filter with water, dried in air, and recrystallized from chloroform—ethanol mixture.

REFERENCES

1. S. V. Tolkunov, M. N. Kal'nitskii, and V. I. Dulenko, Khim. Geterotsikl. Soedin., No. 5, 706 (1993).
2. S. V. Tolkunov, M. N. Kal'nitskii, S. N. Lyashchuk, and V. I. Dulenko, Khim. Geterotsikl. Soedin., No. 5, 701 (1994).
3. S. V. Tolkunov, M. N. Kal'nitskii, V. I. Dulenko, and S. N. Lyashchuk, Khim. Geterotsikl. Soedin., No. 5, 694 (1995).
4. R. M. Kanojia, J. B. Press, O. W. Lever, L. Williams, J. J. McNally, A. J. Tobia, R. Falotico, and J. Moor Jr., J. Med. Chem., **31**, 1363 (1988).
5. J. B. Press and J. J. McNally, J. Heterocycl. Chem., **25**, 1571 (1988).
6. M. T. S. Dewar and W. Thiel, J. Am. Chem. Soc., **99**, 4899 (1977).
7. S. V. Tolkunov, M. N. Kal'nitskii, A. I. Khizhan, S. Yu. Suikov, M. Yu. Zubritskii, and V. I. Dulenko, Khim. Geterotsikl. Soedin., No. 8, 1124 (1995).
8. S. V. Tolkunov, M. N. Kal'nitskii, and E. A. Zemskaya, Khim. Geterotsikl. Soedin., No. 11, 1552 (1991).