SYNTHESIS OF PYRYLIUM AND PYRIDINE DERIVATIVES OF BENZOFURAN

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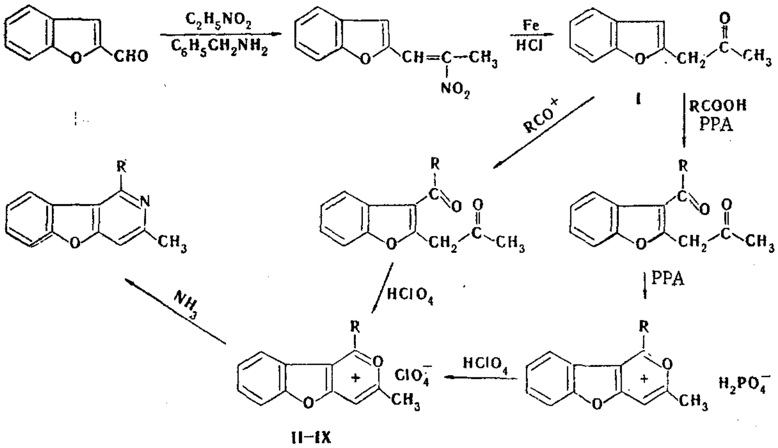
Acylation of benzo[b]-2-furyl acetone was used to synthesize 2,9-disubstituted benzofuro[3,2-c]pyrylium perchlorates, which were converted in high yields to the corresponding benzofuro[3,2-c]pyridines. The molecular diagram of the pyrylium cation is examined. The IR, UV, and NMR spectra of the synthesized compounds are discussed.

Previously one of us and co-workers developed a general method for the attachment of pyrylium and pyridine rings to compounds of the furan [1], thiophene [2], and indole [1, 3] series by catalytic acylation of the corresponding heteryl acetones with acid anhydrides in the presence of perchloric acid. In the present paper, we report the results of an investigation of the application of this method for the preparation of pyrylium and pyridine derivatives of benzofuran. We studied the acylation of benzo[b]-2-furyl acetone, which was obtained by reduction [4] of the product of alkaline condensation of 2-formylbenzofuran [5] with nitroethane via the following scheme:



II R=CH_3; III R=C_2H_5; IV R=C_3H_7; V R=C_6H_5; VI R=$CH_2C_6H_5$; VII R=p-$CH_3OC_6H_4$; VIII R=3,4-$(CH_3O)_2C_6H_3$; IX R=$CH{=}CHC_6H_5$.

It was shown that 2,9-dialkyl-substituted benzofuro[3,2-c]pyrylium salts (II-IV) are formed in good yields (Table 1) in the acylation of I with aliphatic acid anhydrides (acetic, propionic, and butyric).

The acylation of I with aromatic and aliphatic-aromatic acids in the presence of polyphosphoric acid (PPA) proceeds under mild conditions, and the 2-aryl- and 2-aralkyl-9-methylbenzofuro[3,2-c]pyrylium orthophosphates formed in the reaction are readily converted to crystalline perchlorates upon the addition of 70% perchloric acid (Table 1).

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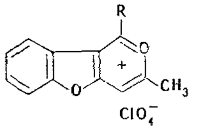
TABLE 1



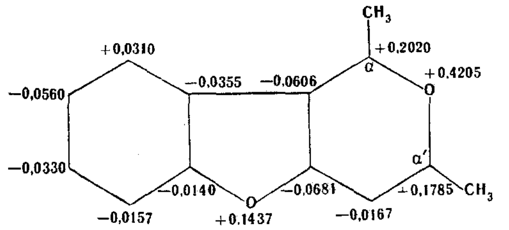
Compound	R	mp, °C	Empirical formula	Found, % C	Found, % H	Found, % Cl	Calc., % C	Calc., % H	Calc., % Cl	IR spectrum, ν, cm^{-1}	UV spectrum λ_{max}, nm	UV spectrum lg ε	Yield, %
II	CH_3	161	$C_{13}H_{11}ClO_6$	52,6	3,8	11,7	52,3	3,7	11,9	1652, 1600, 1582, 1534, 1454, 1083	255 266 320	4,25 4,23 3,69	66,4
III	C_2H_5	151	$C_{14}H_{13}ClO_6$	53,5	4,4	10,8	53,8	4,2	11,4	1650, 1602, 1580, 1530, 1470, 1094	254 265 313	4,25 4,22 3,65	75,2
IV	C_3H_7	143	$C_{15}H_{15}ClO_6$	55,0	4,7	11,3	55,1	4,6	10,9	1652, 1622, 1584, 1540, 1460, 1096	255 266 315	4,00 3,93 3,65	65,3
V	C_6H_5	199	$C_{18}H_{13}ClO_6$	59,6	3,8	10,0	59,9	3,6	9,9	1625, 1600, 1555, 1518, 1440, 1093	253 284 370	3,48 4,00 3,69	73,7
VI	$CH_2—C_6H_5$	178	$C_{19}H_{15}ClO_6$	60,6	4,2	9,6	60,9	4,0	9,5	1644, 1620, 1574, 1530, 1090			69,6
VII	*p*-$CH_3O—C_6H_4$	221	$C_{19}H_{15}ClO_7$	58,4	3,8	9,1	58,0	4,0	9,0	1640, 1607, 1560, 1530, 1500, 1450, 1090	250 295 395	4,18 4,23 3,63	49,0
VIII	$3,4(CH_3O)_2C_6H_3$	271	$C_{20}H_{17}ClO_8$	57,2	4,0	8,4	57,1	4,0	8,4	1630, 1620, 1560, 1504, 1090	250 267 310 425	3,63 3,66 3,47 3,60	44,0
IX	$CH{=}CH—C_6H_5$	232	$C_{20}H_{15}ClO_6$	62,3	4,0	9,1	62,1	3,9	9,2	1640, 1620, 1660, 1520, 1455, 1095	255 308 420	4,14 4,23 4,45	37,0

TABLE 2. Chemical Shifts of the Protons of the Pyrylium Salts

Compound	CH_3, δ, ppm	α-Substituent				Aromatic protons, δ, ppm	Concn., %
		R	δ, ppm	Signal character	J, Hz		
II	3,15	CH_3	3,51	Singlet	—	7,81, 7,91, 8,00, 8,17, 8,20	10
III	3,20	$\overset{1}{C}H_2—\overset{2}{C}H_3$	3,86 1,88	1 quartet 2 triplet	7,2	7,36, 7,57, 7,58, 7,64, 7,76	10
IV	3,12	$\overset{1}{C}H_2—\overset{2}{C}H_2—\overset{3}{C}H_3$	3,74 2,07 1,33	1 triplet 2 sextet 3 triplet	7,2	7,88, 7,93, 8,13, 8,28, 8,38	10
V	2,65	C_6H_5	—	—	—	7,41, 7,50, 7,59, 7,67	7
VI	2,60	$C_6H_5CH{=}CH$	—	—	—	6,93, 7,26, 7,75, 7,98	10
VII	2,60	$3,4\text{-}(CH_3O)C_6H_3$	3,61	Singlet (6H)	—	7,05, 7,28, 7,38, 7,61	10

The structure of the compounds was confirmed by IR and NMR spectroscopy. The IR spectra of the pyrylium salts contain absorption bands at 1650 and 1530 cm^{-1}, which correspond to the symmetrical and asymmetrical stretching vibrations of the heteroring. The characteristic bands of the benzofuran ring [6, 7] appear at 1600-1622, 1270-1280, and 1084-1110 cm^{-1}. The absorption band of the ClO_4^- anion is found at 1083-1095 cm^{-1}.

The signals of the α'-CH_3 group (3H), the chemical shift of the protons of which depends on the character of the substituent in the α position of the pyrylium ring, are observed in the NMR spectra of the salts: in the case of alkyl substituents (CH_3, C_2H_5, and C_3H_7), this group resonates at δ 3.15-3.22 ppm; when the alkyl substituents are replaced by aryl and aralkyl substituents, the signal of these protons is shifted to stronger field (2.60-2.65 ppm). This fact is explained by shielding of the CH_3 group by the π electrons of the benzene ring of the substituent in the 2 position. Two singlets of the protons of α- and α'-methyl groups at, respectively, δ 3.15 and 3.51 ppm are observed in the spectrum of 2,9-dimethylbenzofuro[3,2-c]py-



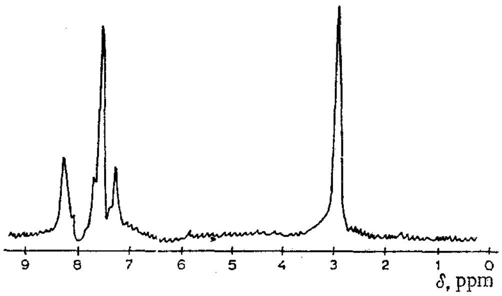


Fig. 1

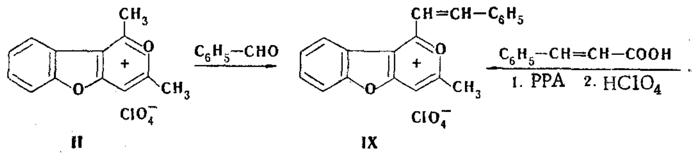
Fig. 2

Fig. 1. Molecular diagram of the benzofuropyrylium cation.

Fig. 2. NMR spectrum of 2-styryl-9-methylbenzofuro[3,2-c]pyrylium perchlorate (in trifluoroacetic acid).

rylium perchlorate. This sort of shift in the position of the signals of the methyl groups to weak field is due to the overall effect of their deshielding by the heteroatom of the pyrylium ring and the π electrons of the benzofuran system. Data on the chemical shifts and spin-spin coupling constants of the pyrylium salts are presented in Table 2.

According to the results of quantum-mechanical calculations† of the pyrylium cation (by the Pariser–Parr–Pople method [8]), the maximum positive-charge densities are observed on the 2 and 9 (α and α') carbon atoms, and the negative charge is concentrated on the 8 carbon atom (Fig. 1). Since the positive-charge density is a maximum on the 2 carbon atom, attack by nucleophilic reagents should occur primarily at this position. We have shown that a salt with a styryl substituent in the 2 position is formed in the condensation of 2,9-dimethylbenzofuro[3,2-c]pyrylium perchlorate with benzaldehyde in glacial acetic acid (IX):



The assumption of the possibility of the formation of a mixture of two products or of a condensation product containing two styryl substituents was rejected. We isolated precisely IX; this was proved by identifying it with the compound obtained by acylation of I with cinnamic acid in the presence of PPA. Only a single signal of the protons of the α'-methyl group is observed in the NMR spectrum of IX at δ 3.15 ppm. Hence one can conclude that the condensation occurred entirely at the α-methyl group (Fig. 2).

Strong absorption bands at 253, 256, and 310 nm are observed in the UV spectra of salts II-IV. The system of energy levels calculated by the Pariser–Parr–Pople method with allowance for the configuration interaction of 20 singly excited orbitals for II correlates quite well with the spectra of the pyrylium salts and makes it possible to assign the long-wave absorption band to a $\pi \rightarrow \pi^*$ transition; the large extinction value (Table 1) also indicates this type of transition.

The 2,9-disubstituted benzofuro[3,2-c]pyrylium salts readily exchange an oxygen atom of the pyrylium ring for a nitrogen atom. 2,9-Disubstituted benzofuro[3,2-c]pyridines (Table 3) are isolated in high yields when ammonia is passed through alcohol suspensions of the salts.

The structure of the pyridines was confirmed by the IR and NMR spectra. A single signal of the protons of the α'-CH_3 group is observed in the NMR spectra of the pyridines. The signals of the protons of the alkyl substituents in the α position of the pyridine ring lie at 2.61-2.70 ppm, compared with 2.56 ppm in the case of aryl substituents. This shift is explained by the same reason as in the case of the pyrylium salts, but the effect of deshielding from the nitrogen atom of the pyridine ring and the aromatic substituent in the α position is less than from the oxygen atom (Table 4).

Data on the UV spectra of the pyridine bases are presented in Table 3. The same reasoning that was used for the corresponding pyrylium salts remains valid for them.

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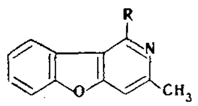
† We thank V. I. Minkin and co-workers for the calculations.

TABLE 3

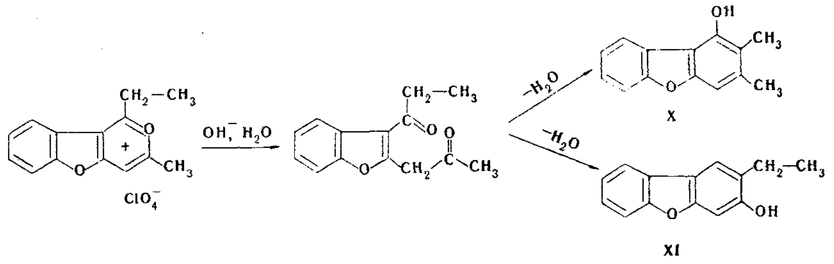


Compound	R	mp, °C	Empirical formula	Found, %			Calc., %			IR spectrum, ν, cm^{-1}	UV spectrum		Yield, %
				C	H	N	C	H	N		λ_{max}, nm	lg ε	
XIII	CH_3	64	$C_{13}H_{11}NO$	79,1	5,4	7,2	79,2	5,6	7,1	1635, 1600, 1443, 1328, 1233, 1188, 1070, 736	255 282 289 300	4,17 4,14 4,04 4,08	90,9
XIV	C_2H_5	42	$C_{14}H_{13}NO$	79,8	6,2	6,8	79,6	6,2	6,6	1630, 1600, 1580, 1450, 1190, 1220, 1110, 855, 754	255 280 289 302	4,60 4,44 4,38 4,43	93,4
XV	C_3H_7	55	$C_{15}H_{15}NO$	79,8	6,4	5,8	80,0	6,7	6,2	1630, 1600, 1575, 1456, 1190, 1110, 830, 751	254 280 289 299	4,17 4,00 3,96 3,94	96,6
XVI	p-CH_3O—C_6H_4	137	$C_{19}H_{15}NO_2$	78,5	5,2	—	78,9	5,2	—	1600, 1520, 1250, 1100, 840, 750	260 304	4,17 4,04	93,3
XVII	CH=CH—C_6H_5	101	$C_{20}H_{15}NO$	83,8	5,4	—	84,2	5,3	—	1600, 1460, 1380, 1200, 1100, 750	257 300 333	4,33 4,07 4,00	96,3

TABLE 4. Chemical Shifts of the Protons of Benzofuro[3,2-c]pyridines

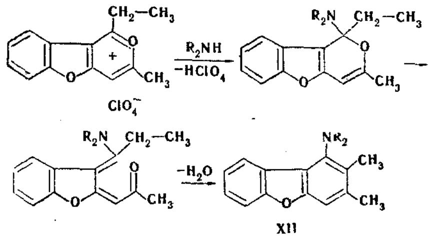
Compound	CH_3, δ, ppm	α Substituent				Aromatic protons, δ, ppm	Concn., %
		R	δ, м. д.	Signal character	J, Hz		
XIII	2,68	CH_3	2,55	Singlet	—	7,00, 7,23, 7,36, 7,69	10
XIV	2,62	$\overset{1}{CH_2}$—$\overset{2}{CH_3}$	3,23 1,40	1 quartet 2 triplet	7,0	7,03, 7,30, 7,46, 7,84	10
XV	2,61	$\overset{1}{CH_2}$—$\overset{2}{CH_2}$—$\overset{3}{CH_3}$	3,18 1,74 0,78	1 triplet 2 sextet 3 triplet	7,2	7,40, 7,50, 7,65, 7,78	9
XVI	2,58	p-$C_6H_4OCH_3$	3,77 (OCH_3)	Singlet	—	6,80, 6,95, 7,06, 7,31 7,61, 7,76	10

The ability of pyrylium salts to readily undergo conversion to aromatic systems [9] is extremely unusual. We have studied the conversion of the benzofuro[3,2-c]pyrylium salts in alkaline media. Chromatographically pure 1-hydroxy-2,3-dimethyldibenzofuran (X) is obtained when 2-ethyl-9-methylbenzofuro[3,2-c]pyrylium perchlorate is heated in aqueous alcoholic sodium hydroxide solution:



It is seen from the scheme presented above that there is a possibility for the formation of two isomeric products. In this connection, it was necessary to prove that X rather than XI or a mixture of X and XI is formed. The NMR spectrum of the phenolic product contains singlets of the protons of the methyl groups in the 2 and 3 positions at δ 1.88 and 2.31 ppm, respectively. The spectrum does not contain the triplet–quartet that is characteristic for the ethyl group; a diffuse signal of the lone proton of a hydroxyl group is observed at 4.85 ppm (Fig. 3). The IR spectrum also confirms the presence of a phenolic hydroxyl group (3653 cm^{-1}).

The ability of pyrylium salts to undergo conversion to dialkylanilines on reaction with secondary amines is well known [10, 11]. 1-Dimethylamino-2,3-dimethyldibenzofuran (XII) is formed via the following scheme in the reaction of 2-ethyl-9-methylbenzofuro[3,2-c]pyrylium perchlorate with aqueous alcoholic dimethylamine:



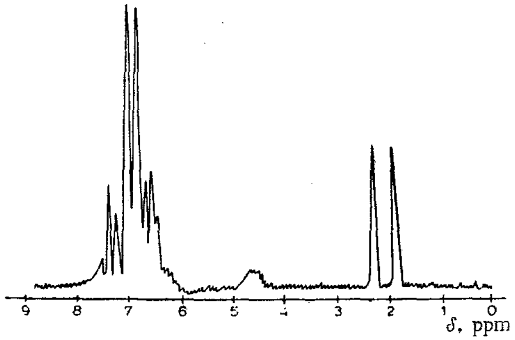


Fig. 3. NMR spectrum of 1-hydroxy-2,3-dimethyldibenzofuran (in benzene).

EXPERIMENTAL

The IR spectra of mineral-oil pastes of the compounds were recorded with a UR-20 spectrometer. The NMR spectra of 10% solutions of the compounds were recorded with an RYa-2305 spectrometer with an operating frequency of 60 MHz at room temperature with tetramethylsilane as the standard. Trifluoroacetic acid was used as the solvent for the pyrylium salts, while carbon tetrachloride was used for the pyridine compounds. The UV spectra were recorded with a Specord UV Vis spectrometer.

1-(2-Benzofuryl)-2-nitropropene. A mixture of 30.6 g (0.21 mole) of 2-formylbenzofuran, 22.26 g (0.21 mole) of benzylamine, and 50-70 ml of benzene was refluxed for 30 min on a boiling-water bath, after which the benzene was removed by distillation on a boiling-water bath under vacuum (water aspirator). The mixture was then cooled, 15.7 ml (0.21 mole) of nitroethane and 50 ml of glacial acetic acid were added, and the mixture was heated on a boiling-water bath for 20-30 min. It was then cooled, and the precipitate was removed by filtration and washed successively with glacial acetic acid, alcohol, and ether to give 27 g of product. Water was added to the filtrate to precipitate another 13 g of product to give a total of 40 g (92.8%) of bright-yellow crystals with mp 85° (from alcohol). Found: C 65.1; H 4.5; N 6.8%. $C_{11}H_9NO_3$. Calculated: C 65.3; H 4.4; N 6.9%.

2-Benzofuryl Acetone (I). Toluene (40 ml), 100 ml of water, 40.3 g of iron powder or filings, and 0.8 g of anhydrous ferric chloride were added to 40 g of 2-nitro-3-(2-benzofuryl)propene, and the mixture was stirred and heated at 75° for 1.5 h, after which 72 ml of concentrated hydrochloric acid was added. After all of the acid had been added, the mixture was heated for 30 min and steam-distilled until 2.5 liter of distillate had been collected. The toluene layer was separated, and the aqueous layer was extracted with ether. The ether extract was combined with the toluene layer and dried over calcium chloride. The solvent was removed by distillation, and the residue was vacuum-distilled to give 9.1 g (24.6%) of a colorless liquid with bp 153° (11 mm). Found: C 70.4; H 5.5%. $C_{11}H_{10}O_2$. Calculated: C 70.7; H 5.7%. The semicarbazone was obtained as needles with mp 138° (from alcohol). Found: C 62.6; H 6.0%. $C_{12}H_{13}N_3O_2$. Calculated: C 62.3; H 5.6%.

2,9-Dimethylbenzofuro[3,2-c]pyrylium Perchlorate (II). An acylating mixture obtained from 5 ml of acetic anhydride and 1 ml (0.01 mole) of 70% perchloric acid was added to 1.74 g (0.01 mole) of I, during which the mixture warmed up and turned reddish-brown. After 10 min, a copious precipitate began to form; this was filtered off immediately to give 1.98 g (66.4%) of a colorless crystalline product with mp 161° (from glacial acetic acid).

Perchlorates III and IV were similarly obtained (Table 1).

2-Phenyl-9-methylbenzofuro[3,2-c]pyrylium Perchlorate (V). A mixture of 0.37 g (2 mmole) of I, 0.25 g (2 mmole) of benzoic acid, and 5 g of polyphosphoric acid was heated with vigorous stirring on a boiling-water bath for 30 min. It was then poured over ice and triturated to give a dark-green orthophosphate, which was converted to the perchlorate by the addition of 0.3 ml of 70% perchloric acid to an aqueous suspension of the salt. The precipitate was removed by filtration and washed with ether to give 0.56 g (73.7%) of dark-green crystals with mp 199° (from glacial acetic acid).

Perchlorates VI-VIII were similarly obtained (Table 1).

2-Styryl-9-methylbenzofuro[3,2-c]pyrylium Perchlorate (IX). A mixture of 0.3 g (1 mmole) of II, 0.16 g (1.5 mmole) of benzaldehyde, 2 ml of glacial acetic acid, and 1 drop of 70% perchloric acid was heated for 1.5 h, after which it was cooled, and 0.25 g (66%) of orange crystals with mp 230° (from glacial acetic acid) was removed by filtration. The product did not depress the melting point of a sample obtained by acylation of I with cinnamic acid.

1-Hydroxy-2,3-dimethyldibenzofuran (X). A solution of 1.6 g of sodium hydroxide in 3 ml of water was added to 2 g (6.4 mmole) of perchlorate III in 10 ml of alcohol, and the mixture was refluxed for 6 h. It was then cooled, diluted with 60 ml of water, and extracted with ether. The aqueous layer was acidified with hydrochloric acid to give 0.6 g (44.25%) of yellow crystals with mp 146° (from alcohol). Found: C 78.9; H 5.2%. $C_{14}H_{12}O_2$. Calculated: C 79.2; H 5.6%.

1-Dimethylamino-2,3-dimethyldibenzofuran (XII). A mixture of 0.4 g (1.2 mmole) of perchlorate III, 0.1 ml of 33% aqueous dimethylamine solution, and 3 ml of alcohol was heated on a boiling-water bath, after which the solvent was removed by distillation and sodium hydroxide solution was added until the mixture was alkaline. It was then extracted with ether. The ether extract was washed with water and dried with calcium chloride. The ether was evaporated to give XI. Purification by chromatography with a column filled with aluminum oxide (with chloroform as the solvent) gave 0.2 g of light-gray crystals (65.5%) with mp 171°. Found: C 80.8; H 6.7; N 5.6%. $C_{16}H_{17}NO$. Calculated: C 80.5; H 7.0; N 5.8%.

2,9-Dimethylbenzofuro[3,2-c]pyridine (XIII). Gaseous ammonia was passed through a suspension of 1 g (3 mmole) of 2,9-dimethylbenzofuro[3,2-c]pyrylium perchlorate in ethanol for 10 min, after which the mixture was poured into ice water. The aqueous mixture was extracted with ether, and the extract was dried with calcium chloride. The alcohol was evaporated to give a yellow oily product. Purification by chromatography with a column filled with aluminum oxide (with chloroform as the solvent) gave 0.6 g (90.9%) of yellow crystals with mp 64°. The picrate had mp 254° (from alcohol).

Compounds XIV-XVII were obtained via a similar method (Table 3).

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