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SYNTHESIS OF CONJUGATED SYSTEMS BASED ON 3-(5-METHYLFUR-2-YL)-2-(3-OXOBUTYL)BENZOFURANS

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Methods were developed for the synthesis of 3-butyl-2-(3-oxobutenyl)benzofurans and 3-(3-furylbenzofuran-2-yl)acrylic acids on the basis of 3-furyl-2-(3-oxobutyl)benzofurans.

Keywords: 3-furyl-2-(3-oxobutyl)benzofurans, 3-furyl-2-(3-oxobutenyl)benzofurans, 3-(3-furylbenzofuran-2-yl)acrylic acids, bromination, dehydrobromination.

Derivatives of benzofuran possess a wide range of biological activity. In the series of 2-alkyl-3-arylbenzofurans compounds exhibiting antiarrhythmic [1], local anesthetic [2], antiallergic [3], antimicrobial [4], and other pharmacological activities have been discovered. The 3-hetaryl derivatives have been studied much less, and in this connection the 3-(5-methylfur-2-yl)-2-(3-oxobutyl)benzofurans **1**, produced easily by the condensation of salicylaldehyde derivatives with sylvane [5], are of interest.

In the present work we describe the synthesis, from compounds **1**, of the unsaturated ketones **2** and the 2-benzofuranylacrylic acid derivatives **3**, study of the biological activity of which is extremely promising since elongation of the conjugation chain and the introduction of the propenone fragment may create additional centers of complementarity with the biosubstrate [6] and lead to new biologically active substances. In addition, compounds **2**, like the hetero analogs of the chalcones, may prove to be useful intermediates for the synthesis of pharmacologically active substances. For example, the construction of nitrogen-containing heterocycles by the condensation of chalcones or their benzofuran analogs with various binucleophiles has been described many times [7-9].

The classical sequence of bromination and dehydrobromination was used to convert ketones **1** into the unsaturated compounds **2**. Here the choice of reagents was made in such a way that the two reactions were conducted as a one-pot synthesis. As mild brominating agent we chose pyridinium bromide-perbromide [10]. We used sodium hydroxide, ammonia, pyridine, and piperidine for dehydrobromination, but triethylamine proved most suitable. In other cases resinification occurred, and this became stronger with increase in the basicity of the reagent. The best solvents for the reaction were dry ether, tetrahydrofuran, and dioxane.

Attempts to isolate the intermediate bromination products in the individual state by column chromatography were unsuccessful because these substances were quickly transformed into the corresponding unsaturated ketones as a result of the elimination of HBr under the influence of the adsorbent (silica gel or aluminum oxide). Only bromide **4b**, containing a nitro group at position 5 of the benzofuran ring and purified by recrystallization from hexane, was sufficiently stable for undertaking a set of analyses. The IR spectrum of compound **4b** contains a band for the stretching vibrations of the carbonyl group at 1710 cm^{-1} (Table 1), as also in the spectra of the initial ketones **1** [5].

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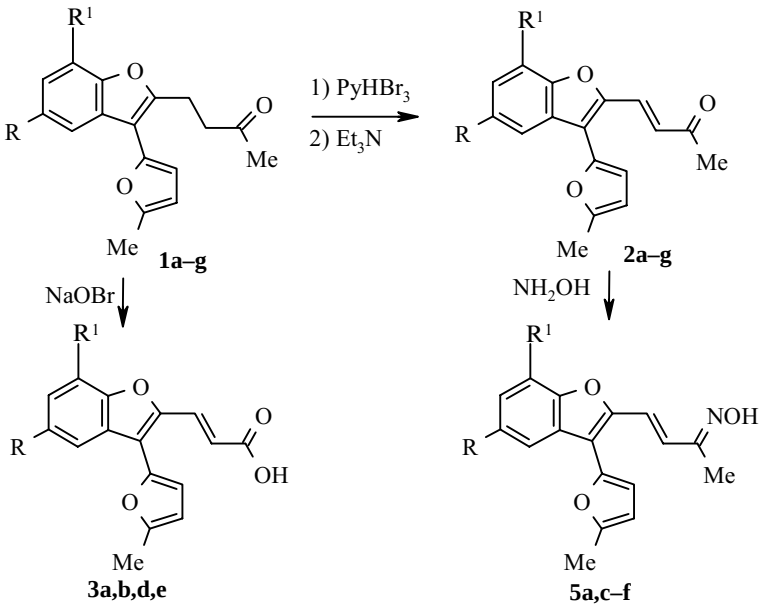
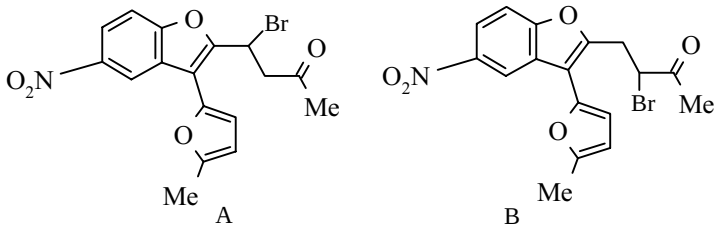


1-5a-e R^1 = H; **a** R = H; **b** R = NO_2; **c** R = Cl; **d** R = Br; **e** R = Me; **f** R = R^1= I; **g** R = R^1= Br

The ^{1}H NMR spectra of the synthesized compounds contain signals for the protons of the benzofuran and furan fragments (Table 2), which do not require special discussion. A distinguishing feature of the ^{1}H NMR spectrum of bromide **4b** is the presence of two multiplets for the methylene and methine protons in the region of 3.72-3.85 and 4.79-4.86 ppm respectively (see the experimental section). We note that the signals of both the α and the β protons are shifted downfield compared with the signals of the analogous protons in the initial ketone **1b** [5] as a result of the descreening effect of the bromine. The data from the ^{1}H NMR spectrum only make it possible to consider with certainty that the methyl group is not brominated (its three-proton signal at 2.44 ppm is present in the spectrum of compound **4b**), but it does not make it possible to reach an unambiguous conclusion about the direction of bromination, i.e., at the β-methylene unit (structure A) or at the α-methylene unit in relation to the carbonyl group (structure B) of compound **1b** during the formation of the bromine derivative **4b**.



In the IR spectra of the unsaturated benzofuran ketones there is a typical shift of the absorption band of the carbonyl group, which is in conjugation, into the region of 1655-1665 cm^{-1} (Table 1). In the ^{1}H NMR spectra of these compounds there are signals for the protons of the vinylene fragment with a constant of 15.8 Hz, indicating that it has the *trans* configuration (Table 2). Here the signals of the α protons resonate in the region of 6.90-6.95 ppm, while the signals of the β protons resonate in the upfield region at 7.80-8.00 ppm owing to the effect of conjugation with the carbonyl group.

As a result of the haloform oxidation of compounds **1** we isolated not 3-(5-methylfur-2-yl)-2-benzofuranylpropionic acid, as expected, but the corresponding unsaturated acid. Bromination clearly took place simultaneously at the methyl group and at one of the methylene groups, but the basic medium promoted dehydrobromination with the formation of an exocyclic double bond. The nature of the substituent in the benzofuran ring has a significant effect on the course of the reaction. Thus, in the case of the nitro derivative **3b** the reaction was complete after an hour, whereas the other derivatives required a significant increase in the reaction time and also an increase in the concentration of the hypobromite.

TABLE 1. The Physicochemical Characteristics of the Synthesized Compounds

Compound	Empirical formula	Found, % / Calculated, %		mp, °C*	IR spectrum, ν, cm^{-1}	Yield, %
		C	H			
2a	$C_{17}H_{14}O_3$	76.59 / 76.67	5.21 / 5.30	115-116	1650 (C=O)	54
2b	$C_{17}H_{13}NO_5$	65.71 / 65.59	4.09 / 4.21	189-190	1670 (C=O)	85
2c	$C_{17}H_{13}ClO_3$	68.01 / 67.89	4.45 / 4.36	127-129	1660 (C=O)	42
2d	$C_{17}H_{13}BrO_3$	59.02 / 59.15	3.85 / 3.80	114-115	1660 (C=O)	29
2e	$C_{18}H_{16}O_3$	77.23 / 77.12	5.82 / 5.75	154-156	1670 (C=O)	17
2f	$C_{17}H_{12}I_2O_3$	39.35 / 39.41	2.30 / 2.34	154-155	1665 (C=O)	44
2g	$C_{17}H_{12}Br_2O_3$	48.07 / 48.14	2.71 / 2.85	142-144	1670 (C=O)	11
3a	$C_{16}H_{12}O_4$	71.49 / 71.63	4.53 / 4.51	>200 (decomp.)	1675 (C=O)	76
3b	$C_{16}H_{11}NO_6$	61.29 / 61.34	3.42 / 3.54	>220 (decomp.)	1670 (C=O)	30
3d	$C_{16}H_{11}BrO_4$	55.49 / 55.35	3.26 / 3.19	>220 (decomp.)	1665 (C=O)	71
3e	$C_{17}H_{14}O_4$	72.24 / 72.33	5.11 / 5.00	218-220	1680 (C=O)	82
4b	$C_{17}H_{14}BrNO_5$	62.13 / 62.21	4.42 / 4.30	105-106	1710 (C=O)	41
5a	$C_{17}H_{15}NO_3$	72.47 / 72.58	5.29 / 5.38	207-208	1605 (C=N)	98
5c	$C_{17}H_{14}ClNO_3$	64.73 / 64.67	4.40 / 4.47	234-235	1605 (C=N)	98
5d	$C_{17}H_{14}BrNO_3$	56.81 / 56.69	4.01 / 3.92	248-249	1605 (C=N)	96
5e	$C_{18}H_{17}NO_3$	73.17 / 73.20	5.72 / 5.80	229-230	1605 (C=N)	98
5f	$C_{17}H_{13}I_2NO_3$	38.37 / 38.30	2.53 / 2.46	213-214	1605 (C=N)	97

* Compounds **2** were crystallized from a mixture of benzene and hexane, compounds **3** from ethanol, compound **4b** from hexane, and compounds **5** from benzene.

The IR spectra of acids **3** contain absorption for $\nu_{C=O}$, represented by a strong band in the region of 1665-1680 cm^{-1} (Table 1), which is typical of aromatic α,β-unsaturated acids in the dimeric state. In addition, the IR spectra of acids are characterized by the absorption of the hydroxyl groups with low intensity in the region of 2500-2800 cm^{-1}. Acids **3**, like ketones **2**, have the *trans* configuration for the olefinic fragment, as indicated by the spin–spin coupling constant (15.6 Hz) for the protons of the vinylene fragment in the ^1H NMR spectra of these compounds (Table 2). Here the signals of the α-protons are shifted by an average of 0.4 ppm upfield, compared with the signals of the corresponding protons in ketones **2**, as a result of the smaller direct negative inductive effect of the carboxyl group, whereas the signals of the β-protons remain in practically the same region.

Oximes **5** were obtained with quantitative yields by the condensation of compounds **2** with hydroxylamine. The IR spectra of compounds **5** are characterized by the absence of the absorption of the carbonyl group and the presence of a $\nu_{C=N}$ band at 1605 cm^{-1} (Table 1), also shifted toward the shortwave region on account of conjugation. In the ^1H NMR spectra of these compounds the signals of the β-protons are shifted upfield by 0.6 ppm compared with the analogous signals in the spectra of ketones **2** as a result of the smaller descreening effect of the oxime group. The chemical shifts of the α protons here remain unchanged.

TABLE 2. The ^{1}H NMR Spectra of Compounds **2**, **3**, **5**

Compound	Chemical shifts, δ, ppm									
	Benzofuryl			Furyl*			CH_3, s	α-CH, d*[2]	β-CH, d	Other signals and SSCC, *J*, Hz
	4-H	6-H	7-H	3-H, d	4-H, d	CH_3, s				
2a	7.78 m	7.22-7.44 m*[3]		6.71	6.20	2.41	2.46	6.91	7.97	
2b	8.76 d	8.32 dd	7.56 d	6.81	6.24	2.43	2.49	6.95	7.93	$J_{4,6}$ = 2.6; $J_{6,7}$ = 9.0
2c	7.80 s	7.36 s		6.69	6.20	2.41	2.48	6.92	7.93	
2d	7.96 d	7.49 dd	7.34 d	6.70	6.20	2.41	2.48	6.91	7.92	$J_{4,6}$ = 1.9; $J_{6,7}$ = 8.7
2e	7.63 br. s	7.13-7.46 m		6.73	6.20	2.41	2.48	6.89	7.99	2.43 (3H, s, CH_3)
2f	8.09 d	8.03 d		6.68	6.20	2.43	2.46	6.98	7.88	$J_{4,6}$ = 1.6
2g	7.84 d	7.61 d		6.64	6.18	2.43	2.46	6.94	7.81	$J_{4,6}$ = 1,8
3a		7.30-8.07 m*[4]		7.05	6.37	2.40		6.49	7.99	12.50 (1H, br. s, COOH)
3b	8.60 d	8.29 dd	7.80 d	7.02	6.36	2.41		6.49	7.83	12.65 (1H, br. s, COOH); $J_{4,6}$ = 2,2; $J_{6,7}$ = 9.2
3d	8.12 s	7.63 s		7.09	6.37	2.41		6.51	7.95	12.56 (1H, br. s, COOH)
3e	7.78 s	7.32 d	7.52 d	7.04	6.37	2.41		6.46	7.99	2.45 (3H, s, CH_3); 12.48 (1H, br. s, COOH); $J_{6,7}$ = 8.5
5a	7.92 m	7.28-7.62 m*[3]		6.91	6.32	2.41	2.05	7.00	7.31	11.35 (1H, br. s, NOH)
5c	7.88 d	7.40 dd	7.59 d	6.93	6.31	2.41	2.05	6.99	7.26	11.45 (1H, br. s, NOH); $J_{4,6}$ = 1.9; $J_{6,7}$ = 8.7
5d	8.00 s	7.54 s		6.92	6.31	2.42	2.06	6.99	7.25	11.44 (1H, br. s, NOH)
5e	7.70 s	7.22 d	7.47 d	6.92	6.32	2.42	2.05	6.96	7.31	2.44 (3H, s, CH_3); 11.43 (1H, br. s, NOH); $J_{6,7}$ = 8.3
5f	8.09 s	8.00 s		6.91	6.30	2.42	2.05	6.98	7.22	11.51 (1H, br. s, NOH)

* J_{34} = 3.2 Hz.

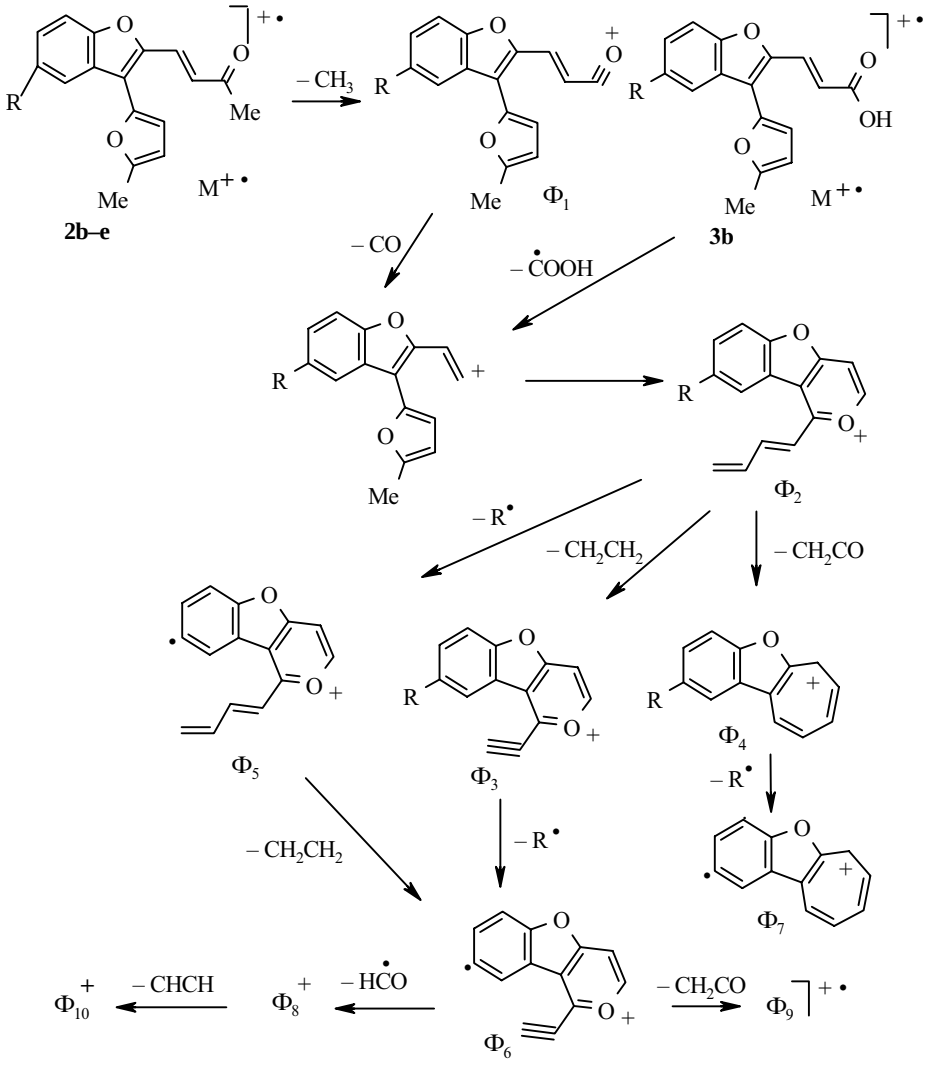
*[2] $J_{\alpha\beta}$ = 15.8 Hz for compounds **2**; 15.6 for **3**; 16.2 for **5**.

*[3] Multiplet of three protons, including 5-H.

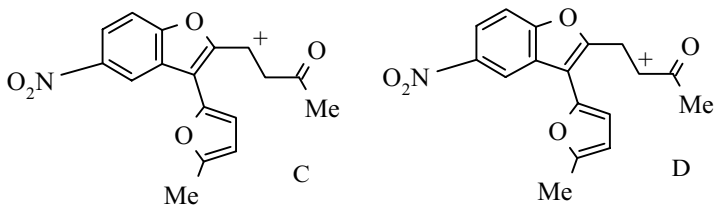
*[4] Multiplet of four protons, including 5-H.

Analysis of the mass spectra of ketones **2b-e** (Table 3) showed a general type of fragmentation (Table 4). Compounds **2b-e** are resistant to electron impact, and their molecular ions have maximum intensity in the spectra. (The main fragmentation paths are indicated in Scheme 1.) In all cases the dissociation of $M^{+\cdot}$ begins with two-stage elimination of the CH_3CO radical (m = 43). The question of where the fragment with a mass of 43 comes from – from the ketone chain or from the methylfuryl substituent – was resolved in favor of the first direction on the basis of the mass spectrum of acid **3b**. Fragmentation of the molecular ion of this compound begins with extrusion of the HCOO radical (m = 45) with the formation of the Φ_2 cation, the further dissociation of which coincides fully with the dissociation of the same cation formed from the molecular ion of ketone **2b**.

Scheme 1

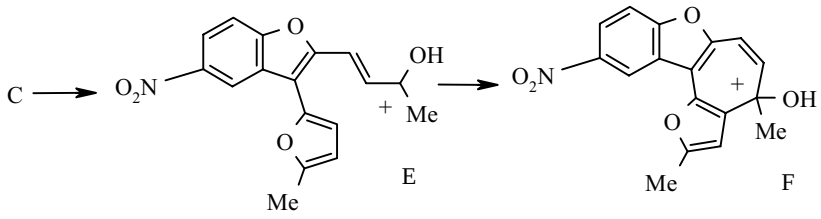


The fragmentation of the molecular ion of compound **4b** differs greatly in nature from the fragmentation of the unsaturated ketones **2** (Table 3). It begins with ejection of the halogen with the formation of the [M-Br] cation, which has high intensity (98.96%). Of the two possible cations the C stabilized by conjugation with the benzofuran ring is undoubtedly more stable.



The second fragmentation step is the ejection of a hydrogen atom with the formation of a radical-cation (*m/z* 311), the structure of which may correspond to the radical-ion of the unsaturated ketone **2b**. In fact, the mass spectrum of compound **4b** contains fragments characteristic of the dissociation of ketone **2b** (Table 4). At the same time the mass spectrum of ketone **4b** contains a peak of maximum intensity with *m*/*z* 256, which is absent in the spectrum of compound **2b**, indicating a different fragmentation path. It was therefore suggested that in the dissociation of the [M-Br] cation intramolecular cyclization occurs at the β position of the furan ring, similar to that which we described earlier [11].

Of the two possible cations with mass [M-Br] only the cation C is capable of isomerizing to the ion E, which in turn can attack the β position of the furan ring with the ejection of a hydrogen atom and the formation of the radical-cation F (*m*/*z* 311), the further fragmentation of which is shown in Scheme 2.



The high stability of the cation with *m*/*z* 256 may be due to resonance and to the capacity for prototropic tautomerism. Its further fragmentation supports to some extent the proposed structure F.

TABLE 3. The Mass Spectra of Compounds **2b-e**, **3b**, **4b**

Com-pound	*m/z* (I_{rel}, %)*
2b	312 (18.17), 311 (100.00), 296 (13.01), 269 (10.78), 268 (17.23), 250 (10.03), 240 (18.55), 222 (19.83), 221 (10.75), 194 (18.73), 165 (19.44), 139 (11.55), 63 (10.49), 53 (11.83)
2c	302 (34.55), 301 (20.31), 300 (100.00), 285 (33.47), 259 (14.32), 258 (22.69), 257 (44.28), 231 (11.84), 230 (11.06), 229 (33.08), 222 (28.00), 215 (24.60), 194 (13.83), 179 (10.85), 165 (17.03), 151 (10.47), 150 (11.14), 75 (12.01), 53 (20.17)
2d	347 (17.10), 346 (93.58), 345 (30.62), 344 (100.00), 331 (17.37), 329 (14.06), 304 (20.60), 303 (33.35), 302 (23,98), 301 (31,76), 299 (10,41), 275 (15.11), 273 (22.79), 261 (16.65), 259 (15.98), 223 (23.58), 222 (56.05), 194 (40.70), 165 (30.41), 151 (15.81), 150 (15.47), 139 (10.26), 75 (10.83), 53 (15.23)
2e	282 (10.21), 281 (17.66), 280 (100.00), 265 (19.04), 238 (27.20), 237 (40.63), 225 (12.12), 222 (10.11), 209 (42.62), 195 (32.79), 193 (10.69), 165 (17.73)
3b	314 (14.04), 313 (100.00), 268 (38.26), 267 (21.56), 253 (11.59), 240 (15.37), 223 (12.88), 222 (33.27), 221 (20.23), 194 (30.11), 193 (15.36), 165 (16.24), 152 (12.95), 139 (17.53), 57 (11.51)
4b	393 (17.82), 391 (22.97), 313 (48.33), 312 (98.86), 311 (43.71), 296 (20.41), 270 (47.98), 269 (17.21), 268 (20.51), 257 (16.01), 256 (100.00), 253 (12.35), 240 (11.72), 234 (24.86), 224 (20.34), 223 (17,40), 222 (20.34), 210 (43.78), 208 (18.85), 194 (10.67), 181 (14.95), 180 (12.75), 179 (15.91), 178 (36.25), 177 (10.81), 165 (16.83), 151 (26.83), 150 (16.49), 149 (24.97), 126 (10.28), 119 (20.55), 81 (15.17), 80 (22.54), 79 (21.43), 77 (22.89), 63 (23.58), 59 (20.31), 53 (16.08), 51 (39.23)

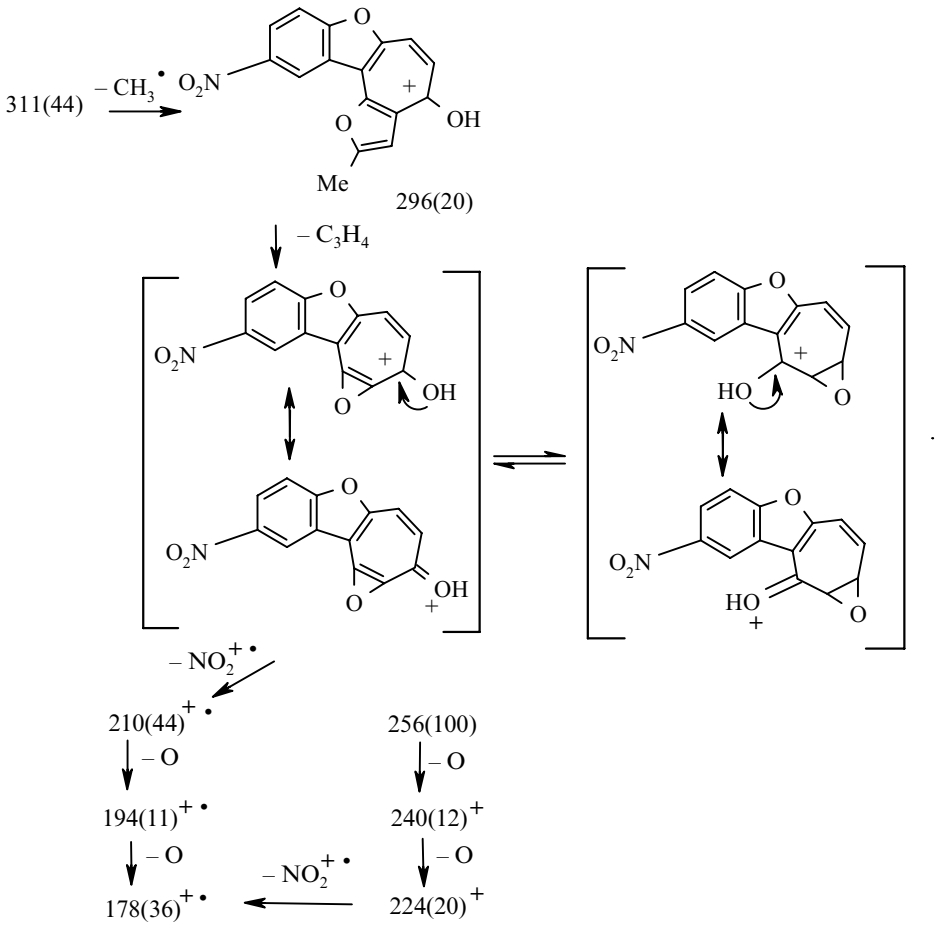
* The peaks with $I \geq 10.00$ are given.

TABLE 4. The Characteristic Peaks in the Spectra of Compounds **2b-e**, **3b**, **4b**

Compound	*m/z* (I_{rel}, %)										
	M^+	Φ_1	Φ_2	Φ_3	Φ_4	Φ_5	Φ_6	Φ_7	Φ_8	Φ_9	Φ_{10}
2b	311 (100)*	296 (13.01)	268 (17.23)	240 (18.55)	226 (6.42)	222 (19.83)	194 (18.73)	180 (4.73)	165 (19.44)	152 (6.60)	139 (11.55)
2c	302 (34.55) 300 (100)	287 (5.83) 285 (33.47)	259 (14.32) 257 (44.28)	231 (11.84) 229 (33.08)	217 (9.47) 215 (24.60)	222 (28.00)	194 (13.83)	180 (>4)	165 (17.03)	152 (4.11)	139 (6.46)
2d	346 (93.58) 344 (100)	331 (17.37) 329 (14.06)	303 (33.35) 301 (31.76)	275 (15.11) 273 (22.79)	261 (16.65) 259 (15.98)	222 (56.05)	194 (40.70)	180 (7.16)	165 (30.41)	152 (3.67)	139 (10.26)
2e	280 (110)	265 (19.04)	237 (40.63)	209 (42.62)	195 (32.79)						
3b	313 (100)		268 (38.26)	240 (15.37)	226 (7.56)	222 (33.27)	194 (30.11)	180 (7.25)	165 (16.24)	152 (12.95)	139 (17.53)
4b	311 (43.71)*	296 (20.41)	268 (20.51)	240 (11.72)	226 (6.12)	222 (24.09)	194 (10.67)	180 (12.75)	165 (16.83)	152 (7.38)	

* Fragment of molecular dissociation.

Scheme 2



Thus, on the basis of the mass-spectrometric data structure A would be assigned to the bromine derivative **4b**. An X-ray crystallographic analysis of a single crystal was undertaken in order to establish the structure of compound **4b** conclusively (Fig. 1, Tables 5-7). We were unable to grow a single crystal of good quality, and the experiment gave high *R* values. We are not therefore discussing the geometric parameters of this molecule, but it was established at a qualitative level that the compound had structure B. The formation of the cation C under electron impact probably takes place through the bromonium state.

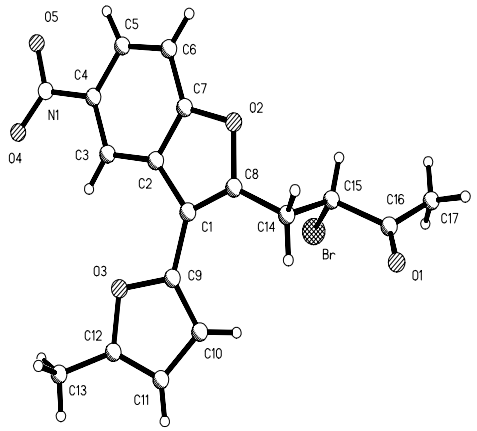


Fig. 1. Projection of the three-dimensional model of the molecule of 2-(2-bromo-3-oxobutyl)-3-(5-methylfur-2-yl)-5-nitrobenzofuran **4b**.

TABLE 5. The Coordinates of the Non-hydrogen atoms (Å × 10^4) and the Temperature Factors (Å^2 × 10^3) in the Molecule of Compound **4b**

Atom	*x*	*y*	*z*	*U(eq)*
Br	5335(2)	1645(1)	1825(1)	72(1)
O(1)	4005(10)	2806(8)	3447(3)	60(2)
O(2)	3172(7)	4772(6)	1183(3)	42(2)
O(3)	-618(7)	1639(6)	530(3)	38(1)
O(4)	248(9)	3620(8)	-1639(3)	64(2)
O(5)	1906(10)	5174(9)	-1888(4)	81(3)
N(1)	1271(11)	4430(9)	-482(4)	49(2)
C(1)	1523(11)	3045(8)	963(4)	32(2)
C(2)	1755(11)	3765(8)	344(4)	33(2)
C(3)	1235(11)	3637(9)	-330(4)	38(2)
C(4)	1783(11)	4562(9)	-769(4)	39(2)
C(5)	2786(12)	5608(10)	-579(5)	44(3)
C(6)	3284(11)	5767(9)	70(5)	39(2)
C(7)	2751(11)	4819(9)	510(4)	38(2)
C(8)	2390(11)	3672(8)	1438(4)	35(2)
C(9)	527(11)	1838(9)	1028(4)	34(2)
C(10)	490(13)	857(10)	1481(5)	50(3)
C(11)	-770(14)	-26(10)	1250(5)	51(3)
C(12)	-1389(12)	455(9)	668(5)	44(3)
C(13)	-2705(14)	51(11)	201(6)	64(3)
C(14)	2724(11)	3441(9)	2166(4)	42(2)
C(15)	4556(11)	3188(9)	2313(4)	41(2)
C(16)	4955(14)	2977(10)	3083(7)	59(3)
C(17)	6753(16)	3008(12)	3246(6)	81(4)

Methods for the synthesis of unsaturated carbonyl compounds – benzofuran derivatives – were developed in order to investigate the pharmacological activity of the obtained substances. The series of compounds **1** and **2** exhibited antihypoxia [12] and antiarrhythmic, antianginal, and hypotensive activity [13]. Increased activity was observed in the derivatives of 3-furyl-2-(3-oxobutenyl)benzofuran **2**, in contrast to the unconjugated analogs **1**.

TABLE 6. The Bond Lengths (*l*) in the Molecule of Compound **4b**

Bond	*l*, Å	Bond	*l*, Å
Br–C(15)	1.955(9)	C(2)–C(3)	1.402(12)
O(1)–C(16)	1.081(12)	C(3)–C(4)	1.363(12)
O(2)–C(7)	1.376(11)	C(4)–C(5)	1.385(13)
O(2)–C(8)	1.385(10)	C(5)–C(6)	1.352(13)
O(3)–C(9)	1.358(10)	C(6)–C(7)	1.376(12)
O(3)–C(12)	1.385(10)	C(8)–C(14)	1.486(13)
O(4)–N(1)	1.205(10)	C(9)–C(10)	1.344(12)
O(5)–N(1)	1.226(10)	C(10)–C(11)	1.428(14)
N(1)–C(4)	1.475(12)	C(11)–C(12)	1.342(13)
C(1)–C(8)	1.328(12)	C(12)–C(13)	1.459(14)
C(1)–C(2)	1.448(11)	C(14)–C(15)	1.529(14)
C(1)–C(9)	1.475(12)	C(15)–C(16)	1.572(15)
C(2)–C(7)	1.376(12)	C(16)–C(17)	1.486(17)

TABLE 7. The Bond Angles (ω) in the Molecule of Compound **4b**

Angle	ω, deg.	Angle	ω, deg.
C(7)–O(2)–C(8)	106.1(7)	C(2)–C(7)–O(2)	109.8(8)
C(9)–O(3)–C(12)	106.8(7)	C(1)–C(8)–O(2)	111.5(7)
O(4)–N(1)–O(5)	123.1(8)	C(1)–C(8)–C(14)	134.4(8)
O(4)–N(1)–C(4)	119.3(8)	O(2)–C(8)–C(14)	114.1(8)
O(5)–N(1)–C(4)	117.5(9)	C(10)–C(9)–O(3)	110.7(8)
C(8)–C(1)–C(2)	106.6(8)	C(10)–C(9)–C(1)	134.0(9)
C(8)–C(1)–C(9)	128.3(8)	O(3)–C(9)–C(1)	115.3(7)
C(2)–C(1)–C(9)	125.1(8)	C(9)–C(10)–C(11)	106.0(8)
C(7)–C(2)–C(3)	117.7(8)	C(12)–C(11)–C(10)	107.5(8)
C(7)–C(2)–C(1)	105.9(8)	C(11)–C(12)–O(3)	109.0(8)
C(3)–C(2)–C(1)	136.3(8)	C(11)–C(12)–C(13)	134.5(9)
C(4)–C(3)–C(2)	116.9(8)	O(3)–C(12)–C(13)	116.4(9)
C(3)–C(4)–C(5)	123.4(9)	C(8)–C(14)–C(15)	111.7(7)
C(3)–C(4)–N(1)	117.6(9)	C(14)–C(15)–C(16)	112.8(8)
C(5)–C(4)–N(1)	118.9(8)	C(14)–C(15)–Br	111.2(6)
C(6)–C(5)–C(4)	120.9(8)	C(16)–C(15)–Br	108.2(6)
C(5)–C(6)–C(7)	115.5(8)	O(1)–C(16)–C(17)	124.5(12)
C(6)–C(7)–C(2)	125.5(9)	O(1)–C(16)–C(15)	122.6(10)
C(6)–C(7)–O(2)	124.6(9)	C(17)–C(16)–C(15)	112.9(11)

EXPERIMENTAL

The IR spectra of compounds **2**-**4** were recorded in Vaseline oil on a Specord 75-IR spectrometer, and those of compounds **5** were recorded in tablets with potassium bromide on a Specord M-80 spectrometer. The ^{1}H NMR spectra were recorded on a Bruker AC-200P instrument (200 MHz, internal standard TMS) in deuterochloroform (**2**, **4**) and DMSO-d_6 (**3**, **5**).

X-ray Crystallographic Analysis of Compound 4b. The monoclinic crystals of compound (**4b**) with the composition $C_{17}H_{14}NBrO_5$ were grown from a mixture of hexane and toluene. Unit cell parameters: a = 8.101(2), b = 10.159(2), c = 19.879(4) Å; β = 91.18(3)°; V = 1635.7(6) Å^3. Space group $P2(1)/c$, Z = 4. The unit cell parameters and the intensities of 792 unique reflections with $I > 2\sigma(I)$ were obtained on an automatic diffractometer Enraf-Nonius CAD4 without a monochromator (MoKα radiation, θ/2θ scan to 2θ = 45°). The structure was interpreted by the direct method by means of the SHELXTL Plus software (PC version) and refined in anisotropic approximation (isotropic for the hydrogen atoms) to divergence factors R = 0.0480 and R_w = 0.1299.

3-(5-Methylfur-2-yl)-2-(3-oxobutenyl)benzofurans (2). (General Procedure). Pyridinium bromide-perbromide (3.84 g, 0.012 mol) was added in portions with stirring to a solution of compound **1** (0.01 mol) in absolute tetrahydrofuran (15 ml). After 0.5 h the precipitated pyridinium bromide was filtered off, anhydrous triethylamine (5 ml, 0.05 mol) was added to the mother solution, and the mixture was stirred for a further 20 min. Triethylamine hydrobromide was then filtered off, the solvent was distilled off, and the residue (an oil) was dissolved by heating in a 1:4 benzene–hexane mixture (30 ml). The hot solution was passed through a layer of silica gel and left to crystallize. The reaction was monitored by TLC on Silufol UV-254 plates in the 1:1 benzene–hexane system with development in iodine vapor.

The product **2g** was purified from the initial ketone **1g** by column chromatography on silica gel L5/40 (30 × 2 cm). Compound **1g** was eluted with carbon tetrachloride and compound **2g** with diethyl ether.

3-[3-(5-Methylfur-2-yl)benzofuran-2-yl)acrylic Acids (3a,d,e). Bromine (2 ml, 0.039 mol) was added dropwise with stirring and cooling to a solution of sodium hydroxide (6.6 g, 0.165 mol) in water (15 ml). A solution of compound **1** (0.005 mol) in dioxane (7 ml) was added to the obtained solution of NaOBr with stirring at room temperature. The reaction mixture was stirred for 5 h, and water (100 ml) was then added. The water-insoluble impurities were extracted with diethyl ether (6 × 20 ml). To the aqueous layer acetic acid (10 ml) was

added carefully, and the mixture was stirred for 16 h. The crystalline product was filtered off, dried, washed with benzene, and recrystallized from aqueous ethanol. The reaction was monitored by TLC on Silufol UV-254 plates in the 2:1 benzene–diethyl ether system.

3-[3-(5-Methylfur-2-yl)-5-nitrobenzofuran-2-yl]acrylic Acid (3b). Bromine (0.8 ml, 0.015 mol) was added dropwise with stirring and cooling to a solution of sodium hydroxide (2 g, 0.05 mol) in water (20 ml). A solution of compound **1b** (1.57 g, 0.005 mol) in dioxane (10 ml) was gradually added with stirring to the obtained solution of NaOBr at room temperature. The mixture was stirred for 1 h, water (40 ml) was added, and the organic layer was separated. The water-insoluble impurities were extracted with diethyl ether (10 × 25 ml), and the aqueous layer was cautiously acidified with acetic acid (3-5 ml) and kept for 16 h. The crystalline product was filtered off and recrystallized from aqueous ethanol.

2-(2-Bromo-3-oxobutyl)-3-(5-methylfur-2-yl)-5-nitrobenzofuran (4b). Pyridinium bromide-perbromide (3.2 g, 0.01 mol) was added in several portions with stirring to a solution of compound **1b** (3.13 g, 0.01 mol) in absolute tetrahydrofuran (20 ml) at room temperature. When all the brominating agent had been used up (after about 2 h), the mixture was filtered from the obtained pyridinium bromide, and the solvent was distilled off under vacuum. The obtained oil was dissolved in boiling hexane (30 ml), and the hot solution was passed through a layer of adsorbent (silica gel or aluminum oxide). The crystals that separated from the mother solution were filtered off, and 1.6 g of the bromide **4b** was obtained. Yield 41%.

^{1}H NMR spectrum, ppm: 2.44 (3H, s, CH_3); 2.46 (3H, s, CH_3); 3.72-3.85 (2H, m, β-CH_2); 4.79-4.86 (1H, m, α-CH); 6.19 (1H, d, J = 3.2 Hz, 4-H_{Fur}); 6.66 (1H, d, J = 3.2 Hz, 3-H_{Fur}); 7.53 (1H, J = 9.0 Hz, 7-H); 8.25 (1H, dd, J = 2.4, 9.0 Hz, 6-H); 8.73 (1H, d, J = 2.4 Hz, 4-H).

Oximes of Ketones 2 (5). A solution of compound **2** (0.01 mol) and hydroxylamine (4.2 g, 0.06 mol) hydrochloride in dry pyridine (20 ml) was boiled with a reflux condenser for 20 min. The mixture was then poured into cold water (200 ml). The precipitated oxime was filtered off, dried, and dissolved in boiling benzene. The hot solution was passed through a layer of silica gel, and the purified oxime crystallized from the mother solution.

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