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OXIRANYL β-AMINOVINYL KETONES.
7*. SYNTHESIS OF 5-HYDROXY-3-(1-OXO-2,3-EPOXYALKYL)BENZOFURANS

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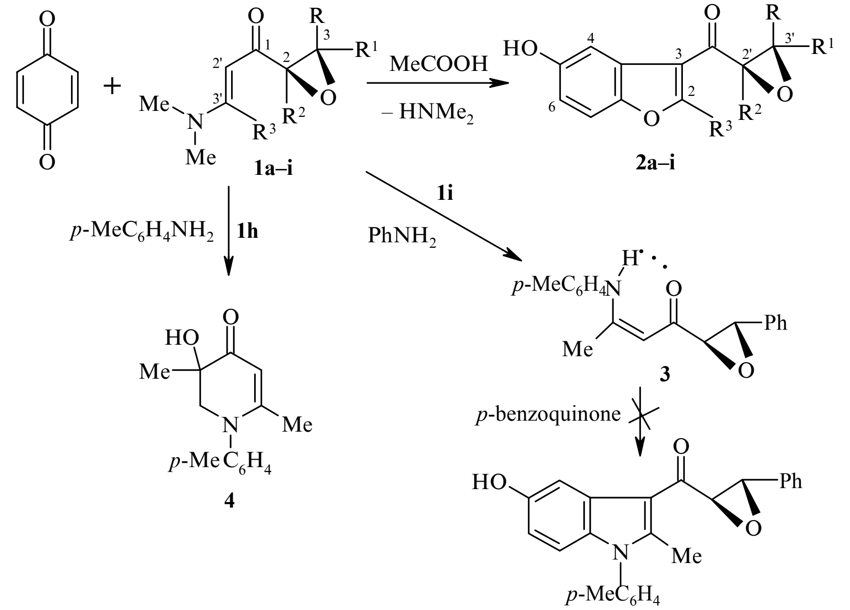
5-Hydroxy-3-(1-oxo-2,3-epoxyalkyl)benzofurans were obtained with yields of up to 81% by the reaction of p-benzoquinone with oxiranyl β-dimethylaminovinyl ketones in acetic acid.

Keywords: acetyloxirane, *p*-benzoquinone, 5-hydroxy-3-(1-oxo-2,3-epoxyalkyl)benzofuran, oxiranyl β-aminovinyl ketone, Nenitzescu reaction, spectral characteristics.

Various derivatives of 5-hydroxyindoles and 5-hydroxybenzofurans, obtained by the Nenitzescu reaction [2, 3] by the condensation of *p*-benzoquinones with enaminocarbonyl compounds, are of interest as anticonvulsive, antihypertensive, antidepressant, and other physiologically active substances [4, 5].



1, **2** **a** $R = R^1 = R^2 = R^3 = H$; **b** $R = R^1 = R^3 = H$, $R^2 = Me$; **c** $R = R^2 = R^3 = H$, $R^1 = Me$;
d $R = R^1 = Me$, $R^2 = R^3 = H$; **e** $R^1 = R^2 = Me$, $R = R^3 = H$; **f** $R = R^3 = H$, $R^1 + R^2 = (CH_2)_4$;
g $R = R^2 = R^3 = H$, $R^1 = Ph$; **h** $R = R^1 = H$, $R^2 = R^3 = Me$; **i** $R = R^2 = H$, $R^3 = Me$, $R^1 = Ph$

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* For Communication 6, see [1].

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In order to obtain 5-hydroxybenzofuran structures containing the highly reactive 1-oxo-2,3-epoxyalkyl fragment at position 3, in the present work we studied the reaction of 2-(3-dimethylaminoacryloyl)oxiranes **1a**-**g** and 2-(3-dimethylamino-3-methylacryloyl)oxiranes **1h**,**i** variously substituted in the oxirane ring with *p*-benzoquinone. As a result we obtained the corresponding 5-hydroxy-3-[1-oxo-2,3-epoxy(cyclohexyl)-alkyl]benzofurans **2a**-**i**.

The reaction of the epoxyaminovinyl ketones **1a**-**i** with benzoquinone was conducted at room temperature in glacial acetic acid.

For the ketones **1a**-**e**,**g** without the β substituent at the double bond the yield of the benzofurans **2a**-**e**,**g** amounted to 68-81%. In the case of the ketone **1e**, containing the epoxycyclohexane fragment, and the ketones **1h**,**i**, having a methyl group at the double bond at the β-position to the carbonyl group, the yield of the respective products **2** was substantially lower, due probably to the fairly rigorous steric control of the formation of the benzofuran system.

It is known [6] that the N-aryleneamines of acetylacetone, containing electron-donating substituents in the benzene ring, in reaction with *p*-benzoquinone form 5-hydroxy-2-methylindole exclusively. In order to obtain an epoxyaminovinyl ketone capable of condensation with *p*-benzoquinone to form the corresponding 5-hydroxyindole we brought the ketone **1i** into transamination with *p*-toluidine. The obtained ketone **3** was then condensed with *p*-benzoquinone.

TABLE 1. The Characteristics of Compounds **1h**-**i**, **2a**-**i**, **3**, **4**

Compound	Empirical formula	Found, % / Calculated, % C	H	N	mp, °C*	Yield, %
1h	$C_9H_{15}NO_2$	63.67 63.88	8.77 8.93	8.43 8.28	56-58	36
1i	$C_{14}H_{17}NO_2$	72.86 72.70	7.52 7.41	6.29 6.06	89-90	57
2a	$C_{11}H_8O_4$	64.55 64.71	4.04 3.95	—	175-176 (dec.)	76
2b	$C_{12}H_{10}O_4$	66.26 66.05	4.65 4.62	—	169-170	68
2c	$C_{12}H_{10}O_4$	66.21 66.05	4.43 4.62	—	206-208	71
2d	$C_{13}H_{12}O_4$	67.11 67.23	5.23 5.21	—	214-215	78
2e	$C_{13}H_{12}O_4$	67.32 67.23	5.44 5.21	—	156-157	81
2f	$C_{15}H_{14}O_4$	69.58 69.76	5.59 5.46	—	174-176	32
2g	$C_{17}H_{12}O_4$	73.04 72.85	4.27 4.32	—	201-202	77
2h	$C_{13}H_{12}O_4$	67.36 67.23	5.49 5.21	—	155-156	21
2i	$C_{18}H_{14}O_4$	73.22 73.46	4.96 4.79	—	233-234 (dec.)	43
3	$C_{19}H_{19}NO_2$	77.63 77.79	6.38 6.53	5.02 4.77	121-122	88
4	$C_{14}H_{17}NO_2$	72.46 72.70	7.22 7.41	6.27 6.06	144-145	66

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* Solvents: ether–hexane, 1:1 (compounds **1h**,**i**), 2-propanol (compounds **2a**,**c**), methanol (compounds **2b**,**d**, **3**, **4**).

TABLE 2. The Spectral Data of the Obtained Compounds

Compound	IR spectrum, ν, cm^{-1}*	^{1}H NMR spectrum, δ, ppm. (SSCC, J, Hz)
1h	1607, 1553, 1413, 1385, 1200, 1107, 1027, 938, 880, 847	1.51 (3H, s, 2-CH$_3$); 2,57 (3H, s, 3'-CH$_3$); 2.73 (2H, s, 3,3'-H$_2$); 3.12 (6H, s, 3'-N(CH$_3$)$_2$); 5.25 (1H, s, 2'-H)
1i	3020, 1600, 1533, 1414, 1387, 1027, 867, 720, 694	2.58 (3H, s, 3'-CH$_3$); 3.10 (6H, s, 3'-N(CH$_3$)$_2$); 3.25 (1H, d, J_{32} = 2.1, 3-H); 3.83 (1H, d, J_{23} = 2.1, 2-H); 5.23 (1H, s, 2'-H); 7.39 (5H, s, C$_6$H$_5$)
2a	3587, 3327, 1653, 1534, 1467, 1201, 1174, 1147, 907, 867	2.85-3.20 (2H, 3',3'-H$_2$); 3.96 (1H, m, 2'-H); 6.95 (1H, dd, J_{64} = 2.8, J_{67} = 8.8, 6-H); 7.46 (1H, d, J_{76} = 8.8, 7-H); 7.68 (1H, d, J_{46} = 2.8, 4-H); 8.41 (1H, s, 2-H); 8.87 (1H, s, 5-OH)
2b	3587, 3363, 1640, 1606, 1533, 1200, 1147, 900, 840, 721	1.61 (3H, s, 2'-CH$_3$); 2.95, 3.14 (2H, AB, J_{AB} = 5.4, 3',3'-H$_2$); 6.93 (1H, dd, J_{67} = 8.8, J_{64} = 2.8, 6-H); 7.63 (1H, d, J_{76} = 8.8, 7-H); 7.73 (1H, d, J_{46} = 2.8, 4-H); 8.38 (1H, s, 2-H); 8.77 (1H, s, 5-OH)
2c	3267, 3047, 1647, 1597, 1525, 1240, 1207, 1133, 913, 860, 787, 707	1.43 (3H, d, J = 5.4, 3'-CH$_3$); 3.35 (1H, d. q, J = 5.4, J = 1.6, 3'-H); 3.75 (1H, d, J = 1.6, 2'-H); 6.97 (1H, dd, J_{67} = 8.8, J_{64} = 2.5, 6-H); 7.45 (1H, d, J_{76} = 8.8, 7-H); 7.68 (1H, d, J_{46} = 2.5, 4-H); 8.41 (1H, s, 2-H); 8.83 (1H, s, 5-OH)
2d	3586, 3340, 1640, 1602, 1545, 1465, 1406, 1245, 1200, 1180, 1150, 1115, 970, 923, 875, 834, 795, 766	1.27 (3H, s, 3'-CH$_3$); 1.50 (3H, s, 3'-CH$_3$); 4.00 (1H, s, 2'-H); 6.94 (1H, dd, J_{67} = 9.1, J_{64} = 2.9, 6-H); 7.48 (1H, d, J_{76}= 9.1, 7-H); 7.66 (1H, d, J_{46}= 2.9, 4-H); 8.40 (1H, s, 2-H); 8.80 (1H, s, 5-OH)
2e	3587, 3347, 1640, 1613, 1533, 1467, 1200, 1147, 927, 873, 720, 730	1.45 (3H, d, J = 5.5, 3'-CH$_3$); 1.59 (3H, s, 2'-CH$_3$); 3.32 (1H, q, J = 5.5, 3'-H); 6.93 (1H, dd, J_{67} = 8.6, J_{64} = 2.8, 6-H); 7.72 (1H, d, J_{46} = 2.8, 4-H); 7.77 (1H, d, J_{76} = 8.6, 7-H); 8.35 (1H, s, 2-H); 8.79 (1H, s, 5-OH)
2f	3580, 3340, 1633, 1600, 1533, 1460, 1205, 1150, 907, 847, 720	1.00-2.83 (8H, m, 2',3'-(CH$_2$)$_4$); 3.39 (1H, br. s, 3'-H); 6.92 (1H, dd, J_{64} = 2.2, J_{67} = 9.8, 6-H); 7.43 (1H, d, J_{76} = 9.8, 7-H); 7.75 (1H, d, J_{46} = 2.2, 4-H); 8.35 (1H, s, 2-H); 8.83 (1H, s, 5-OH)
2g	3400, 3295, 1655, 1600, 1544, 1465, 1418, 1250, 1217, 1175, 1155, 1123, 978, 870, 817, 794, 718, 700 (KBr)	4.19 (1H, d, J_{32} = 1.7, 3'-H); 4.29 (1H, d, J_{23} = 1.7, 2'-H); 6.94 (1H, dd, J_{64} = 2.5, J_{67} = 9.2, 6-H); 7.41 (5H, br. s, 3'-C$_6$H$_5$); 7.46 (1H, d, J_{76} = 9.2, 7-H); 7.69 (1H, d, J_{46} = 2.5, 4-H); 8.45 (1H, s, 2-H); 8.86 (1H, s, 5-OH)
2h	3587, 3330, 1654, 1634, 1594, 1560, 1468, 1201, 1181, 961, 934, 867, 721	1.65 (3H, s, 2'-CH$_3$); 2.77 (3H, s, 2-CH$_3$); 2.98 (2H, s, 3',3'-H); 6.83 (1H, dd, J_{67} = 8.4, J_{64} = 2.8, 6-H); 7.33 (1H, d, J_{76} = 8.4, 7-H); 7.43 (1H, d, J_{46} = 2.8, 4-H); 8.31 (1H, s, 5-OH)
2i	3453, 1665, 1625, 1598, 1464, 1422, 1210, 1180, 1058, 984, 904, 870, 860, 765, 705 (KBr)	2.59 (3H, s, 2-CH$_3$); 4.43 (1H, d, $J_{3'2'}$ = 1.9, 3'-H); 4.58 (1H, d, $J_{2'3'}$ = 1.9, 2'-H); 7.20-7.64 (7H, m, 3'-C$_6$H$_5$, 6-, 7-H); 7.98 (1H, d, J_{46} = 2.1, 4-H); 8.46 (1H, s, 5-OH)
3	3147, 1613, 1560, 1514, 1414, 1334, 1281, 1154, 1027, 812	2.10 (3H, s, p-$\underline{CH_3}$C$_6$H$_4$); 2.43 (3H, s, 3'-CH$_3$); 3.32 (1H, d, J = 1.6, 3-H); 3.92 (1H, d, J = 1.6, 2-H); 5.40 (1H, s, 2'-H); 7,17 (4H, AABB, J_{AB} = 8.6, NC$_6$H$_4$); 7.40 (5H, s, C$_6$H$_5$); 12.73 (1H, br. s, NH)
4	3410, 1628, 1550, 1508, 1473, 1423, 1273, 1207, 1158, 979, 943, 837, 760	1.29 (3H, s, 3-CH$_3$); 1.83 (3H, s, 6-CH$_3$); 2.38 (3H, s, p-$\underline{CH_3}$C$_6$H$_4$); 2.89 (1H, s, 3-OH); 3.49, 3.82 (2H, AB, J_{AB} = 12.5, 2,2-H$_2$); 4.95 (1H, s, 5-H); 7.24, 7.30 (4H, AABB, J_{AB} = 8.6, p-C$_6$H$_4$)

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* The IR spectra of compounds **1h**,**i**, **2a-c**,**e**,**f**,**h**, **3** were recorded in CCl$_4$, and those of **2d**,**g**,**i**, **4** in potassium bromide.

The reaction was carried out at various temperatures in acetone, dioxane, methanol, and acetic acid. In all cases, however, resinification of the reaction mixture was observed. It was only possible to identify the initial ketone **3** and quinhydrone.

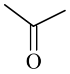
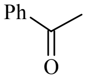
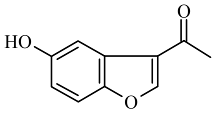
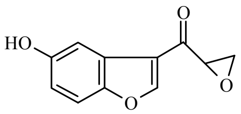
In the reaction of compound **1h** with *p*-toluidine 3-hydroxy-3,6-dimethyl-1-(*p*-tolyl)-1,2,3,4-tetrahydropyridin-4-one (**4**) was obtained with a yield of 65% instead of the expected transamination product.

The structure of the synthesized compounds **1h**-**j**, **2a**-**i**, **3**, **4** was fully confirmed by elemental analysis (Table 1) and spectral characteristics (Table 2).

In the IR spectra of the benzofurans **2a**-**i** the band of the carbonyl absorption lies in the region of 1670-1640 cm^{-1}, which is appreciably lower than the frequency of a carbonyl conjugated with an aromatic system.

The force constant and the frequency of the stretching vibrations of the double bond are directly related to its π order. Delocalization of the π electrons during conjugation reduces this order and, consequently, the frequency of the bond [7]. The frequencies of the carbonyl stretching vibrations of acetone, acetophenone, 3-acetyl-5-hydroxybenzofuran, and benzofuran **2a** calculated by the semiempirical PM3 method [8] for the geometry optimized by the INDO method [9] using the HyperChem 5.1 software are close to the experimental values of the frequencies of the carbonyl vibrations for the indicated compounds (Table 3), confirming the direct relation between the frequency of the carbonyl vibration and its π order. The lower value of the latter for the carbonyl group in the benzofuran **2a** compared with those for 3-acetyl-5-hydroxybenzofuran makes it possible to suppose that there is definite conjugation between the carbonyl in the benzofurans **2a**-**i** and the epoxide ring.

TABLE 3. The Charges, Bond Orders, Force Constants, and Frequencies of the Carbonyl Stretching Vibrations in Some Carbonyl Compounds and Benzofuran **2a**

Formula	Charges at C and O of C=O bond (INDO)	Order of C=O π bond (INDO)	Force constant, mdyn/Å	Obtained frequency of C=O bond, cm^{-1} (INDO, PM3)	Experimental frequency, cm^{-1}*
	0.308 -0.332	0.81486	11.84	1713	1719 [12]
	0.295 -0.331	0.79318	11.52	1698	1693 [12]
	0.295 -0.345	0.78655	11.37	1677	1667
	0.292 -0.345	0.78175	11.06	1654	1653

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* Solvent, CCl_4.

EXPERIMENTAL

The IR spectra of 0.15 M solutions of compounds **1h-i**, **2a-c**,**e**,**f**,**h** and **3** (in CCl_4) were obtained on a Specord IR-75 spectrophotometer, and those of compounds **2d**,**g**,**i** and **4** were obtained on a UR-20 spectrophotometer (in tablets with potassium bromide). The ^{1}H NMR spectra were recorded on a Tesla BS-467 spectrometer (60 MHz) in deuteroacetone (**2a-f**), deuterochloroform (**1h**), carbon tetrachloride (**1i** and **3**), and deuteropyridine (**2i**) with HMDS as standard. The ^{1}H NMR spectra of compounds **2g**,**h** and **4** were obtained in deuteroacetone on a Bruker AC-300 spectrometer (200 MHz) with TMS as standard.

The reactions and the purity of the synthesized compounds were monitored on Silufol plates. The eluent was a 1:1 to 1:3 mixture of acetone and hexane, and the developer was iodine vapor or 4% potassium permanganate solution.

The characteristics of the compounds **1h-i** and **3**, **2a-i** and **4** are presented in Tables 1 and 2.

The epoxyaminovinyl ketones **1a-g** were obtained as described earlier [1, 10].

3-Acetyl-5-hydroxybenzofuran. The carbonyl absorption is given in Table 3. The compound was synthesized according to the method in [11]. The force constants f given in Table 3 were determined in the two-atom approximation using the formula $f = 4\pi^2 v^2 C^2 M$, where v is the calculated frequency (cm^{-1}), C is the velocity of light, and M is the reduced mass of the atoms in the carbonyl group.

2-(3-Dimethylamino-3-methylacryloyl)-2-methyloxirane (1h). The methanol was distilled from a solution of 2-acetyl-2-methyloxirane (10.1 g, 0.1 mol) and N,N-dimethylacetamide dimethyl acetal (17.3 g, 0.13 mol) in toluene (50 ml), while ensuring that the boiling point did not exceed 75°C. The end of the reaction was determined from the amount of methanol distilled. The toluene was then removed on a rotary evaporator. The residue was cooled. The crystals of the product **1h** that separated were filtered off, washed with dry ether, and crystallized from a 1:1 mixture of ether and hexane.

***trans*-2-(3-Dimethylamino-3-methylacryloyl)-3-phenyloxirane (1i)**. The compound was obtained similarly to compound **1h** from *trans*-2-acetyl-3-phenyloxirane and dimethylacetamide dimethyl acetal.

***trans*-3-Phenyl-2-(3-*p*-toluidino-3-methylacryloyl)oxirane (3) and 3-Hydroxy-3,6-dimethyl-1-(*p*-tolyl)-1,2,3,4-tetrahydropyridin-4-one (4)**. A solution of *p*-toluidine (0.01 mol) and the respective ketone **1i** or **1h** (0.008 mol) in 80% acetic acid (15 ml) was kept at room temperature for 24 h and was then diluted with water (40 ml). The crystals of the product were filtered off and crystallized from methanol.

5-Hydroxy-3-(1-oxo-2,3-epoxyalkyl)benzofurans (2a-i). To a solution of the ketone **1a-i** (0.1 mol) in acetic acid (50 ml) at room temperature we added with stirring *p*-benzoquinone (0.1 mol). When the quinone had dissolved the reaction mixture was kept at room temperature for 4 h. The crystals of the product **1a-i** that separated were filtered off, washed with 50% acetic acid and with water, and dried in a Fischer drying pistol.

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