ACETALS OF LACTAM AND AMIDE ACIDS.

59.* SYNTHESIS OF DERIVATIVES OF BIS(BENZOFURYL-3)KETONES

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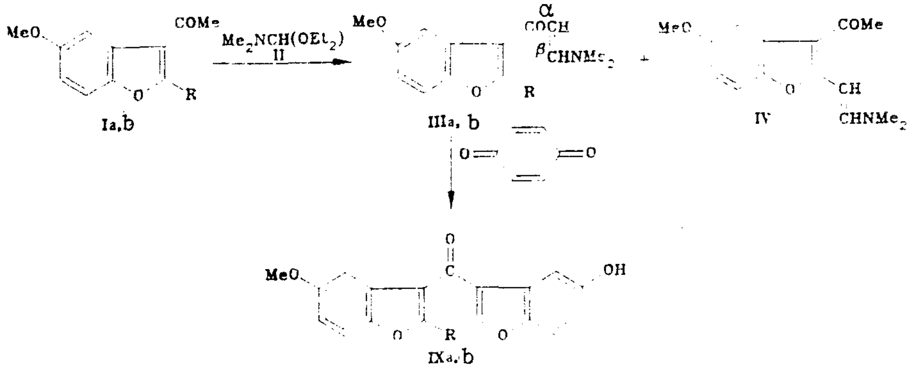
The reaction of substituted 3-acetylbenzofurans with dimethylformamide diethylacetal gave the corresponding enaminoketones, which reacted with p-benzoquinone to give bis(benzofuryl-3)ketone derivatives.

In recent years, some derivatives of bis(benzofuryl-2)ketones have been found to exhibit a wide spectrum of biological activity [2-4]. For this reason we have sought to develop a method of obtaining some previously unreported structural analogs of bis(benzofuryl-3)ketones.

These compounds were synthesized starting from the available 3-acetyl- and 2-methyl-3-acetyl-5-methoxybenzofurans (Ia, b) [5, 6]. The condensation of benzofuran Ia with dimethylformamide diethylacetal (II) took place smoothly, and gave (β-dimethylamino)vinyl(5-methoxybenzofuryl-3)ketone (IIIa) in reasonably good yield. On the other hand, the reaction of benzofuran Ib with excess acetal II was more complicated and the reaction mixture was shown by TLC to contain two reaction products; these were isolated by column chromatography and shown by elemental analysis and mass spectral data (M^+ 259) to be isomers.



I, III, IX a R=H, b R=Me

The enaminoketone IIIa and 2-(β-dimethylaminovinyl)-3-benzoyl-5-methoxybenzofuran (V) [5] were used as model compounds for the assignment of the ^{1}H and ^{13}C NMR signals in compounds IIIb and IV; compound V was obtained from 2-methyl-3-benzoyl-5-hydroxybenzofuran (VI) [5] via the intermediate compound VIII. The benzofuran VI was obtained from (β-dimethylamino-β-methyl)vinylphenylketone (VII) [7] in higher yields than those reported in the literature [8].

A comparison of the ^{1}H NMR spectra of the enaminoketones IIIa, b (Table 1) shows that the chemical shifts corresponding to the vinyl protons are approximately the same in both compounds, indicating that they are very similar, i.e., both contain a dimethylaminovinylketone fragment at position 3 of the benzofuran ring. Comparison of the spectra of the enamines IV and V does not give such clear confirmation of the structure of compound IV, since there is a difference of 0.46 ppm in chemical shifts associated with the vinyl protons in compounds IV and IIIb (see Table 1).

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*See [1] for Communication 58.

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TABLE 1. ^{1}H NMR Spectra of Synthesized Compounds

Compound	Chemical shifts, (DMSO), δ, PPM (coupling constant, Hz)*						
	2-H (IIIa), 2-CH_3 (IIIb)	3-COCH=CHN$(CH_3)_2$ (IIIa, IIIb), 2-CH=CHN$(CH_3)_2$ (IV, V)	3-$COCH_3$ (IV), 3-COC_6H_5 (V)	4-H	6-H	7-H	5-OCH_3
IIIa	8,10 s	5,50 d (J=12); 7,77 d (J=12); 2,98**	—	7,78 d (J=3)	6,92 q.d (J_1=9, J_2=3)	7,37d (J=9)	3,88 s
IIIb	2,69 s	5,52 d (J=12); 7,79 d (J=12); 3,0**	—	7,37 d	6,83 q.d	7,30 d	3,86 s
IV	—	6,04 d (J=13); 7,55 d (J=13); 3,0 br.s	2,58 s	7,26d	6,71 q.d	7,18 d	3,86s
V	—	5,58 d (J=13); 7,50 d (J=13); 2,9 br.s	7,50...7,74 m	—	6,70 m	7,17 d	3,66 s

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*The coupling constant for the aromatic protons of compounds IIIb, IV, and V are similar to those for compound IIIa.

**Very broad signal.

TABLE 2. ^{13}H NMR Spectra of Compounds IIIb and IV

Compound	Chemical shifts, δ, ppm (coupling constant, Hz)												
	$C_{(2)}$	$C_{(3)}$	$C_{(3a)}$	$C_{(4)}$	$C_{(5)}$	$C_{(6)}$	$C_{(7)}$	$C_{(7a)}$	CO	—CH=	=CH	OCH_3	CH_3	N$(CH_3)_2$
IIIb	158,7 q (J=7,5)	118,7 m	127,6 d (J=5,8)	104,7q.d (J_1=161; J_2=4,5)	155,9 m	111,6 q. d (J_1=162; J_2=5,0)	110,7d (J=164)	148,3 m	181,7 t (J_1=J_2=4,5)	96,0 d (J=156)	152,9 d. m (J=168)	55,7s	14,5q	—*
IV	165,4t (J_1=J_2=5,3)	109,2 m	128,4 d (J=5,5)	105,7 q.d (J_1=161; J_2=5,0)	156,4 m	109,2q. d (J_1=162; J_2=5,0)	109,3d (J=164)	147,1 m	192,4 q (J=6,0)	85,5 d (J=162)	147,6d (J=166)	55,7s	30,5 q	40,0 br.q

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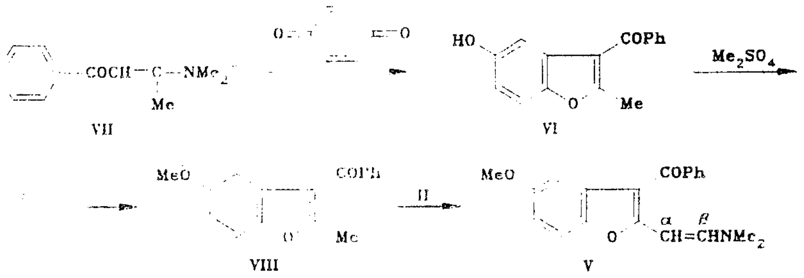
*Very broad signal.



Similar information on the structure of compounds IIIb and IV was obtained from ^{13}C NMR spectra (Table 2). Interaction with protons of the methyl and dimethylaminovinyl substituents causes splitting of the signals from both the benzofuran ring $C_{(2)}$ atom and the carbonyl carbon atom. Thus, in the spectrum of compound IIIb, the splitting of the signal from the $C_{(2)}$ atom to give a quartet at 158.7 ppm (J = 7.5 Hz) and the carbonyl carbon atom to give a triplet at 184.7 ppm ($J_1 = J_2 = 4.5$ Hz) is in complete agreement with the enaminoketone structure. In the spectrum of the enamine IV, a different signal splitting is seen because of the change in structure: The signal from the $C_{(2)}$ (165.4 ppm) is now a triplet ($J_1 = J_2 = 5.3$ Hz), and the signal from the carbon atom of the CO group (192.4 ppm) becomes a quartet (J = 6.0 Hz).

The condensation of the acetal II proceeds not only at the acetyl CH_3 groups, but also at the methyl group at position 2 of the benzofuran ring. It should be noted that the condensation at both positions did not take place at the same time; this can be seen from the mass spectra of the unpurified compounds. This suggests that introduction of an enamino group at either of these positions decreases the electron-attracting ability of the carbonyl group and thereby deactivates the methyl group. A steric effect due to increasing the size of the neighboring group when a methyl or acetyl group substituent is replaced by a β-dimethylaminovinyl group also cannot be excluded.

We have used the enaminoketones IIIa, b as starting compounds in a new synthesis of bis(benzofuryl-3)ketones. The condensation of these compounds with p-benzoquinone proceeded smoothly to give the desired (5-methoxy-5'-hydroxy)bis-(benzofuryl-3)ketones (IXa, b) in satisfactory yield.

EXPERIMENTAL

UV spectra were taken on a Perkin–Elmer 275 using ethanol as solvent. NMR spectra were recorded on a Varian XL-200, internal standard TMS. Mass spectra were obtained on a Varian MAT-112 mass spectrometer (70 eV) with direct introduction of the sample into the ion source. The purity of the compounds was confirmed by TLC on Silufol UV-254 plates using a 9:1 benzene–acetone mixture as solvent; spots were visualized in UV light.

Elemental analysis data agreed with calculated values.

2-Acetyl- and 2-methyl-3-acetyl-5-methoxybenzofurans (Ia, b) were obtained by the method described earlier [5, 6], (β-dimethylamino-β-methyl)vinylphenylketone by the method given in [7].

3-(β-Dimethylaminovinyl)(5-methoxybenzofuryl-3)ketone (IIIa, $C_{14}H_{15}NO_3$). A solution of benzofuran Ia (19 g, 100 mmoles) in acetal II (25 ml) was stirred for 5 h at 110°C with simultaneous evaporation of alcohol. Excess acetal II was removed under vacuum. The residue was triturated with ether (150 ml), then filtered and dried to give 17.6 g (72%). mp 82-83°C (from hexane). UV spectra, λ_{max} (log ε): 210 (4.46), 260 (4.54), 340 nm (4.43).

3-(β-Dimethylaminovinyl)(2-methyl-5-methoxybenzofuryl-3)ketone (IIIb, $C_{15}H_{17}NO_3$) and 2-(β-Dimethylaminovinyl)-3-acetyl-5-methoxybenzofuran (IV, $C_{15}H_{17}NO_3$). To a solution of benzofuran Ib (5 g, 24.5 mmoles) in toluene (40 ml) was added the acetal II (6 ml), and the mixture refluxed for 7 h. A further 2 ml of the acetal was then added and refluxing continued for another 7 h. The solvents and excess acetal II were evaporated, the residue triturated with ether (60 ml), and compound IIIb filtered off to give 2.4 g (38%), mp 95°C (from heptane). UV spectrum, λ_{max} (log ε): 208 (4.52), 243 (4.50), 337 nm (4.44). Found: M^+ 259. Calculated: M 259.

The ethereal mother liquors were chromatographed on a silica gel column (30 × 1.5 cm) and eluted with ether. The starting benzofuran Ib was the first to be isolated, yield 0.8 g (13%); the melting point was in agreement with the literature value [6]. The enamine IV was obtained next in 13% yield (0.8 g), mp 96-97°C (from heptane). UV spectrum, λ_{max} (log ε): 217 (4.35), 269 (4.50), 309 (4.55), 401 nm (4.54). Found: M^+ 259. Calculated: M 259.

The melting point of a sample of mixed enamines IIIb and IV was depressed.

5-(Hydroxybenzofuryl-3)(5-methoxybenzofuryl-3)ketone (IXa, $C_{18}H_{12}O_5$). To technical grade enamine IIIa (6.4 g, 26 mmoles) in glacial acetic acid (10 ml) at about 20°C with mixing was added p-benzoquinone (2.3 g, 21 mmoles) in glacial acetic acid (10 ml). The reaction mixture was left overnight, the crystalline material which separated was filtered off, washed on the filter with 50% acetic acid, and dried to give 4.1 g (63%) of IXa with mp 197-198°C (from acetic acid). IR spectrum: 1635 (C=O), 3550 cm^{-1} (OH).

2-Methyl-3-benzoyl-5-hydroxybenzofuran (VI) was obtained in the same way as IXa, from technical grade (β-dimethylamino-β-methyl)vinylphenylketone (19 g, 100 mmoles) and p-benzoquinone (10 g, 93 mmoles) in glacial acetic acid (90 ml); 8.1 g (35%) was obtained. The melting point was in agreement with the literature value [5].

The **ketone IXb ($C_{19}H_{14}O_5$)** was obtained in the same way as compound IXa in 59% yield, mp 185-187°C (from acetic acid).

2-Methyl-3-benzoyl-5-methoxybenzofuran (VIII, $C_{17}H_{14}O_3$). To a suspension of the benzofuran VI (5 g, 20 mmoles) in dioxane (25 ml) was added 10% potassium hydroxide (14 ml, 24 mmoles). As the phenolate formed, dimethyl sulfate (2.7 g, 21 mmoles) was gradually added and the mixture was stirred and heated on a boiling water bath for 10 h. The reaction mixture was diluted with 5 volumes of water and cooled with ice. The crystalline material which separated was filtered off, washed on the filter with water, and dried to give 4.2 g (79%), mp 65°C (from hexane). IR spectrum: 1660 cm^{-1} (C=O).

2-(β-Dimethylaminovinyl)-3-benzoyl-5-methoxybenzofuran (V, $C_{20}H_{19}NO_3$). A mixture of the benzofuran VIII (2.2 g, 8.3 mmoles), acetal II (2.5 ml), and DMF (5 ml) was refluxed for 30 min. The solvent and excess acetal were evaporated, and ether (5 ml) was added to the residue. The precipitated material was filtered off and dried to give 2.2 g (83%), mp 109-110°C (from heptane). Found: M^+ 321. Calculated: M 321.

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