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SYNTHESIS OF DERIVATIVES OF SOME CONDENSED SYSTEMS THAT INCLUDE FURAN RINGS AND INVESTIGATION OF THEM BY THE LANTHANIDE-SHIFT-REAGENT METHOD

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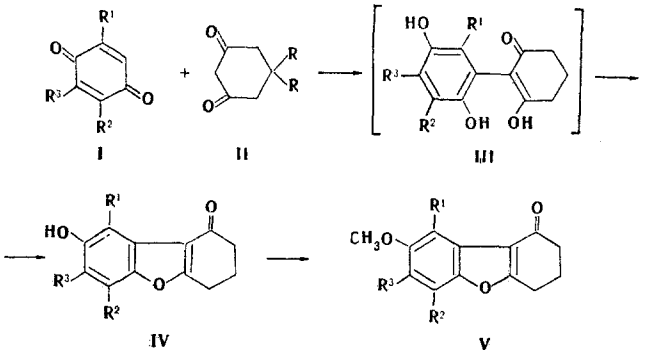
Derivatives of some condensed systems that include furan rings were obtained by condensation of 1,4-benzoquinones with cyclic β-diketones under the conditions of the Michael reaction. The structure of the methoxy derivatives of tetrahydrobenzofuran were established from the PMR spectra with the aid of europium(III) tris(1,1,1,2,2,3,3-heptafluoro-7,7-dimethyl-4,6-octanedionate). The location of the europium ion in the adduct of the lanthanide shift reagent (LSR) with the substrate was determined.

It is known that oxygen-containing heterocycles such as benzo- [1-8] and dibenzofurans [9, 10], as well as benzodifurans [11-14], can be formed in the reaction of p-benzoquinones with β-dicarbonyl compounds or their derivatives. The condensation may take place in the presence of bases (under the conditions of the Michael reaction) and Lewis acids or under the conditions of the Nenitzescu reaction with enamino derivatives of β-dicarbonyl compounds.

We carried out the condensation of alkyl-substituted 1,4-benzoquinones with cyclic β-diketones under the conditions of the Michael reaction and isolated a number of tetrahydrodibenzofuran and benzodifuran derivatives. The structures of the reaction products depend substantially on the structure of the β-diketone used, the ratio of the reacting components, and the conditions under which the condensation is carried out. Thus the reaction of equimolar amounts of quinones I and cyclohexane-1,3-dione (II, R = H) in the presence of piperidine or sodium methoxide leads to 1-oxo-8-hydroxy-1,2,3,4-tetrahydrodibenzofurans IVa-c, which are obtained evidently as a result of intramolecular cyclization of 1,4-addition products III (e.g., see [15]). Compound IVb is formed by refluxing the reaction mixture for



I II III IV V

a $R^1=R^2=R^3=CH_3$, R=H; b $R^1=CH_3$, $R^2=CH(CH_3)_2$, $R^3=H$, R=H;
c $R^1=CH(CH_3)_2$, $R^2=CH_3$, $R^3=H$, R=H

6 h, while isomeric IVc and IVa are obtained by allowing a methanol solution of an equimolar mixture of the reagents to stand at 20°C for a few hours. Methoxy derivatives Va-c, which are readily soluble in chloroform and are therefore more convenient for the measurement of the PMR spectra, were prepared from the corresponding hydroxy compounds IVa-c and dimethyl sulfate. If a methanol solution of dimedone (II, R = CH_3) and thymoquinone (Ib) in a molar

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TABLE 1. Chemical Shifts and Lanthanide Shifts (in parentheses) of Tetrahydrobenzofurans Va-c and Geometrical Parameters of the $Eu(FOD)_3$—Substrate Adducts*

Compound	6-R	7-R	9-R	O—CH_3	4-H	3-H	2-H	r	θ
Va	CH_3 2,38 (1,75)	CH_3 2,31 (1,32)	CH_3 2,81 (9,37)	3,72 (1,08)	3,02 (4,07)	2,20 (3,91)	2,52 (12,88)	2,35	151
Vb	CH_3 1,34 (1,14)	H 6,79 (1,35)	CH_3 2,70 (8,37)	3,90 (0,77)	3,04 (3,46)	2,25 (3,27)	2,63 (11,21)	2,46	155
Vc	CH_3 2,47 (1,47)	H 6,70 (1,77)	CH_3 1,37 (3,85) CH 4,60 (18,66)	3,87 (1,27)	3,02 (3,26)	2,19 (2,23)	2,65 (9,30)	2,80	142

*Symbols: r is the Eu—O distance in angstroms, and θ is the Eu—O—C angle in degrees.

ratio of 2:1 is allowed to stand for 6 days in the presence of sodium methoxide, and the reaction mixture is then treated with hydrochloric acid, benzodifuran VI can be isolated in low yield (up to 5%).

Tetrahydrodibenzofurans Vb and Vc differ with respect to the orientation of the methyl and isopropyl groups in the aromatic ring. To assign the structures of these isomers we recorded their PMR spectra and studied the coupling of Va-c with a lanthanide shift reagent (LSR), viz., europium(III) tris(1,1,1,2,2,3,3-heptafluoro-7,7-dimethyl-4,6-octanedionate) [$Eu(FOD)_3$]. The chemical and lanthanide shifts (LS, ΔH) of the signals of the protons of Va-c are presented in Table 1. Preliminary conclusions regarding the structures of isomers Vb and Vc can be drawn by comparing their PMR spectra with the positions of the proton peaks of Va, the structure of which is determined unambiguously by the starting compounds. Thus, the signal of the 9-CH_3 groups of Va is shifted 0.5 ppm to weak field as compared with the peaks of the other two methyl groups (7- and 6-Me). This can be explained by paramagnetic shielding of the protons of the 9-CH_3 group by the carbonyl group (see [16]). Similar differences in the chemical shifts of the CH_3 and CH groups are observed in the PMR spectra of Vb and Vc. Thus the methyl group bonded to the aromatic ring in Vb and Vc has δ values of 2.70 and 2.47 ppm, respectively, i.e., the CH_3 group in Vb is closer to the carbonyl oxygen atom than in Vc; in addition, the methylidyne proton of the isopropyl group in the Vc molecule experiences paramagnetic shielding: its signal is found at 4.60 ppm (a similar signal appears in the spectrum of Vb at stronger field at 3-3.5 ppm). Thus it is more likely that the methyl group is located in the 9 position in the Vb molecule and in the 6 position in the Vc molecule. We obtained further confirmation of these structural assignments and accomplished an analysis of the origin of the bands in the PMR spectra by the lanthanide-shift-reagent (LSR) method.

All the investigated substances contain two potential coordination centers for the addition of the lanthanide, viz., the oxygen atom of the carbonyl group and the oxygen atom of the methoxy group (virtually no participation of the furan oxygen atom in complexing with LSR has been observed [17]). The small lanthanide shifts (LS) that are observed for the methoxy protons indicate weak coupling of $Eu(FOD)_3$ with the oxygen atoms of these groups, and the most effective coordination center in the Va-c molecules is therefore the oxygen atom of the carbonyl group. This makes it possible to assign the lines of the methylene groups in the spectra: the triplet, for which small LS are observed, corresponds to the 2-CH_2 group. The signals of the protons for which paramagnetic shielding by the carbonyl oxygen atom was noted give the greatest lanthanide shifts, and this confirms our assignment of the Vb and Vc structures (see [16]).

The lengths of the O—Eu bonds in the adducts of Va-c with the LSR found by the method in [18] range from 2.4 to 2.6 Å, and the Eu—O=C valence angles (θ) range from 130 to 150° (Table 1); these values are close to the parameters previously obtained for the adducts of other carbonyl compounds with the LSR [19-21]. The contour maps of the standard deviations (S) of the calculated induced shifts from the experimentally found ΔH values for the adduct of Vb with $Eu(FOD)_3$ are presented in Fig. 1 as an example. The corresponding orthogonal projections of the Dreiding model of the Vb molecule are also shown on the scale of the maps. The crosshatched part of the map corresponds to the minimum of the S values, i.e., the most probable region of location of the lanthanide in the adduct. It is apparent that europium approaches the oxygen atom in the plane of the carbonyl group on the other side relative to the 9-R substituent, which creates steric hindrance to complexing of Vb with the LSR.

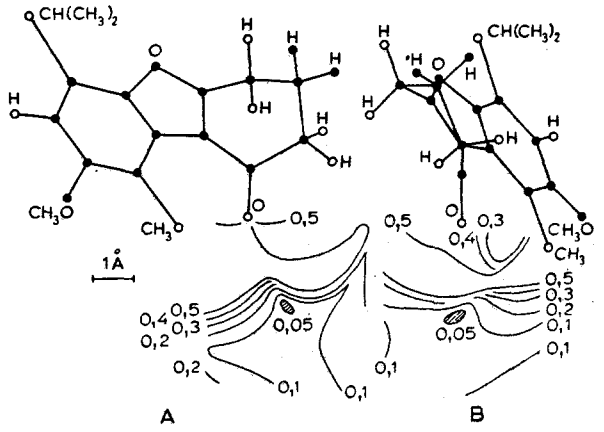
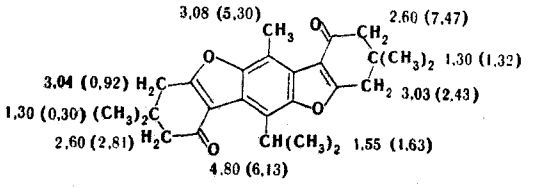


Fig. 1. Contour maps of the standard deviations (S) for the Vb—Eu(FOD)$_3$ adduct and the corresponding projections of the Dreiding model of Vb. The plane of map A passes through the C—CO—C atoms; map B, which is orthogonal to it, passes through the minimum on map A parallel to the C=O bond. The hydrogen atoms used for the calculation are designated by O.

Stuart—Briegleb scale models of the adduct of Vc with the LSR indicate that the isopropyl grouping cannot rotate freely. We found the preferred orientation of this group by the method of contour maps by varying the angle of rotation about the bond between the isopropyl group and the aromatic ring. The conformer in which the methylidyne proton of the isopropyl group and the carbonyl oxygen atom are maximally drawn together gives the best agreement between the calculated lanthanide shifts (LS) and the experimentally observed values.



VI

The molecule of benzodifuran derivative VI can be regarded as a combination of the molecules of tetrahydrodibenzofurans Vb and Vc. Each of the tetrahydrobenzofuran fragments contains a carbonyl group that is capable of coordination with the LSR. The chemical shift and (in parentheses) lanthanide shifts of the proton signals are presented besides the corresponding groups. The lanthanide shift $\Delta H_2-CH_2/\Delta H_4-CH_2$ and $\Delta H_8-CH_2/\Delta H_{10}-CH_2$ ratios for VI are close to the $\Delta H_2-CH_2/\Delta H_4-CH_2$ ratios found for Vb and Vc, respectively. This indicates a similarity in the geometrical structures of the adducts formed due to reaction of the LSR at each of the coordination centers of bifunctional derivative VI and the geometry of the adducts of the corresponding monodentates Vb and Vc. Coordination at each of the carbonyl groups has almost no effect on the chemical shifts of the methylene groups of the other fragment because of their spatial remoteness. The chemical shifts of the analogous groups in each of the fragments virtually coincide, whereas the lanthanide shifts differ appreciably. This is associated with the difference in the ease of coordination of the LSR at each of the carbonyl groups as a consequence of the different sizes of the substituents (methyl and isopropyl) near them, and this leads to different equilibrium constants (K_1 and K_2) for complexing at these groups. The K_1/K_2 ratio is approximately equal to the lanthanide shift $\Delta H_2-CH_2/\Delta H_8-CH_2$ ratio and is $\sim$2.6.

EXPERIMENTAL

The PMR spectra of solutions of the compounds in $CDCl_3$ were measured with a ZKR-60 spectrometer (60 MHz) at 20°C with tetramethylsilane as the internal standard. The IR spectra of KBr pellets were recorded with a UR-20 spectrometer. The contour maps of the standard deviations (S) for the adducts of Va-c with Eu(FOD)$_3$ were obtained by the method in [18]. The coordinates of the hydrogen nuclei in the substrate molecule that are necessary for the calculation of the maps were found from standard Dreiding models of the Va-c molecules constructed in such a way that the distance from the carbonyl oxygen atom to the carbon atom bonded to C_9 was no less than 3.0 Å. The positions of the protons of the CH_3 groups were assigned by the method in [22].

1-Oxo-6,7,9-trimethyl-8-hydroxy-1,2,3,4-tetrahydrodibenzofuran (IVa). A mixture of 7.7 g (0.05 mole) of pseudocumoquinone, 5.60 g (0.05 mole) of cyclohexane-1,3-dione, and 5 ml (0.05 mole) of piperidine in 5 ml of methanol was maintained at 20°C for 7 days, after

which 10 ml of methanol and 10 ml of concentrated HCl were added, and the product that crystallized out was removed by filtration to give 6.37 g (52%) of white needles with mp 211°C (from ethanol). IR spectrum: 3390 (OH) and 1642 cm^{-1} (C=O). Found: C 73.67; H 6.54%. $C_{15}H_{16}O_3$. Calculated: C 73.8; H 6.6%.

1-Oxo-6-isopropyl-8-hydroxy-9-methyl-1,2,3,4-tetrahydrodibenzofuran (IVb). A mixture of 2 g (0.012 mole) of thymoquinone, 1.4 g (0.012 mole) of cyclohexane-1,3-dione, and 1,2 ml (0.012 mole) of piperidine in 2.5 ml of methanol was refluxed for 6 h, after which it was cooled and treated with 4 ml of concentrated HCl, and the product was removed by filtration to give 1.3 g (41%) of a white crystalline powder with mp 206.5°C (from ethanol). IR spectrum: 3275 (OH) and 1655 cm^{-1} (C=O). Found: C 74.3; H 6.9%. $C_{16}H_{18}O_3$. Calculated: C 74.4; H 7.0%.

1-Oxo-9-isopropyl-8-hydroxy-6-methyl-1,2,3,4-tetrahydrodibenzofuran (IVc). A mixture of 2 g (0.012 mole) of thymoquinone, 1.4 g (0.012 mole) of cyclohexane-1,3-dione, and 1.2 ml (0.012 mole) of piperidine in 3 ml of methanol was maintained at 20°C for 26 days, after which the reaction product was removed by filtration to give 0.45 g (11%) of a white powder with mp 258°C (from ethanol). IR spectrum: 3220 (OH) and 1636 cm^{-1}. (C=O). Found: C 74.7; H 6.9%. $C_{16}H_{18}O_3$. Calculated: C 74.4; H 7.0%.

1-Oxo-6,7,9-trimethyl-8-methoxy-1,2,3,4-tetrahydrodibenzofuran (Va). A mixture of 5 g (0.02 mole) of hydroxy derivative IVa, 5 g (0.036 mole) of calcined potassium carbonate, and 5 ml (0.036 mole) of dimethyl sulfate in 20 ml of dry acetone was refluxed for 20 h, after which 50 ml of hot water was added, the mixture was cooled, and the crystalline product was removed by filtration to give 4.98 g (94%) of a white crystalline powder with mp 108°C (from propanol). IR spectrum: 1662 cm^{-1} (C=O). Found: C 74.5; H 7.0%. $C_{16}H_{18}O_3$. Calculated: C 74.4; H 7.0%. Compounds Vb and Vc were similarly obtained.

1-Oxo-6-isopropyl-8-methoxy-9-methyl-1,2,3,4-tetrahydrodibenzofuran (Vb). This compound was obtained in 93% yield. The white crystalline powder had mp 106°C (from ethanol). IR spectrum: 1652 cm^{-1} (C=O). Found: C 75.0; H 7.3%. $C_{17}H_{20}O_3$. Calculated: C 75.0; H 7.4%.

1-Oxo-9-isopropyl-8-methoxy-6-methyl-1,2,3,4-tetrahydrobenzofuran (Vc). This compound was obtained in 85% yield. The white powder had mp 133°C (from ethanol). IR spectrum: 1662 cm^{-1} (C=O). Found: C 75.1; H 7.4%. $C_{17}H_{20}O_3$. Calculated: C 75.0; H 7.4%.

1,7-Dioxo-6-isopropyl-3,3,9,9,12-pentamethyl-1,2,3,4,7,8,9,10-octahydrobenzo[1,2-b:4,5-b']bisbenzofuran (VI). A solution of sodium methoxide, obtained from 0.56 g (0.024 mole) of sodium and 7 ml of anhydrous methanol, was added to 2 g (0.012 mole) of thymoquinone and 3.45 g (0.024 mole) of dimedone, and the mixture was refluxed for 8 h. It was then treated with excess concentrated HCl, and the resinous product was washed thoroughly with water to give 0.27 g (5%) of a white crystalline powder with mp 232°C (from acetone). IR spectrum: 1670 cm^{-1}(C=O). Found: C 76.6; H 7.4%. $C_{26}H_{30}O_4$. Calculated: C 76.8; H 7.4%.

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SYNTHESIS OF 2-CARBETHOXY-3-METHYL-4-HYDROXYBENZOFURAN DERIVATIVES

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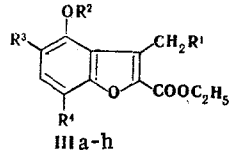
A number of 2-carbethoxy-3-methylbenzofuran derivatives were synthesized. A 5,5-gem-dibromo derivative was obtained in the bromination of 2-carbethoxy-3-methyl-4-oxo-4,5,6,7,tetrahydrobenzofuran. Dehydrobromination of this dibromo derivative gave 2-carbethoxy-3-methyl-4-hydroxy-5-bromobenzofuran. Depending on the structure of the starting compound and the brominating agent, the bromine in the bromination of 2-carbethoxy-3-methyl-4-hydroxy- and 4-acetoxybenzofurans with bromine and N-bromosuccinimide is incorporated either in the methyl group or in 5 and 7 positions of the benzofuran ring. The nitration of 2-carbethoxy-3-methyl-4-hydroxybenzofuran and its bromo derivative leads to 5-nitro- and 5,7-dinitrobenzofuran derivatives. The structures of the synthesized benzofuran derivatives were established by means of the PMR spectra.

In connection with the interest in 4-hydroxybenzofuran derivatives as biologically active compounds [1, 2], we synthesized a number of 2-carbethoxy-3-methyl-4-hydroxybenzofuran derivatives (I).

We used 2-carbethoxy-3-methyl-4-oxo-4,5,6,7-tetrahydrobenzofuran as the starting compound [3]. To convert this compound to the 4-hydroxy derivative by the method that we proposed in [4] we studied the bromination of 2-carbethoxy-3-methyl-4-oxo-4,5,6,7-tetrahydrobenzofuran. However, in this case we were able to obtain only a 5,5-gem-dibromo derivative (II), the dehydrobromination of which leads to 2-carbethoxy-3-methyl-4-hydroxy-5-bromobenzofuran (IIIa). Compound IIIa is also formed in the bromination of 2-carbethoxy-3-methyl-4-hydroxybenzofuran [5] with N-bromosuccinimide (NBS) in the presence of benzoyl peroxide. However, in the case of bromination of 2-carbethoxy-3-methyl-4-acetoxybenzofuran (IIIb) under similar conditions the substituent is not incorporated in the benzene ring but rather in the methyl group in the 3 position to give 2-carbethoxy-3-bromomethyl-4- acetoxybenzofuran (IIIc).

The bromination of I with an equimolar amount of bromine leads to the formation of a mixture of substances, from which we were able to isolate only 2-carbethoxy-3-methyl-4-hydroxy-7-bromobenzofuran (IIId). A 5,7-dibromo derivative (IIIe) is formed in high yield by the action of excess bromine on I.



IIIa-h

IIIa $R^1=R^2=R^4=H$, $R^3=Br$; b $R^1=R^3=R^4=H$, $R^2=COCH_3$; c $R^1=Br$, $R^2=COCH_3$, $R^3=R^4=H$; d $R^1=R^2=R^3=H$, $R^4=Br$; e $R^1=R^2=H$, $R^3=R^4=Br$; f $R^1=R^2=R^4=H$, $R^3=NO_2$; g $R^1=R^2=H$, $R^3=R^4=NO_2$; h $R^1=R^2=H$, $R^3=NO_2$, $R^4=Br$

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