

Reactions of Fused Carbonyl-containing Spirodihydrofurans with Hydrogen Sulfide and Acids

O.V. Fedotova, M.I. Skuratova, M.A. Panov, and S.P. Mushtakova

Chernyshevskii Saratov State University, Saratov, 410012 Russia
e-mail: fedotova@chem.sgu.ru

Received August 18, 2004

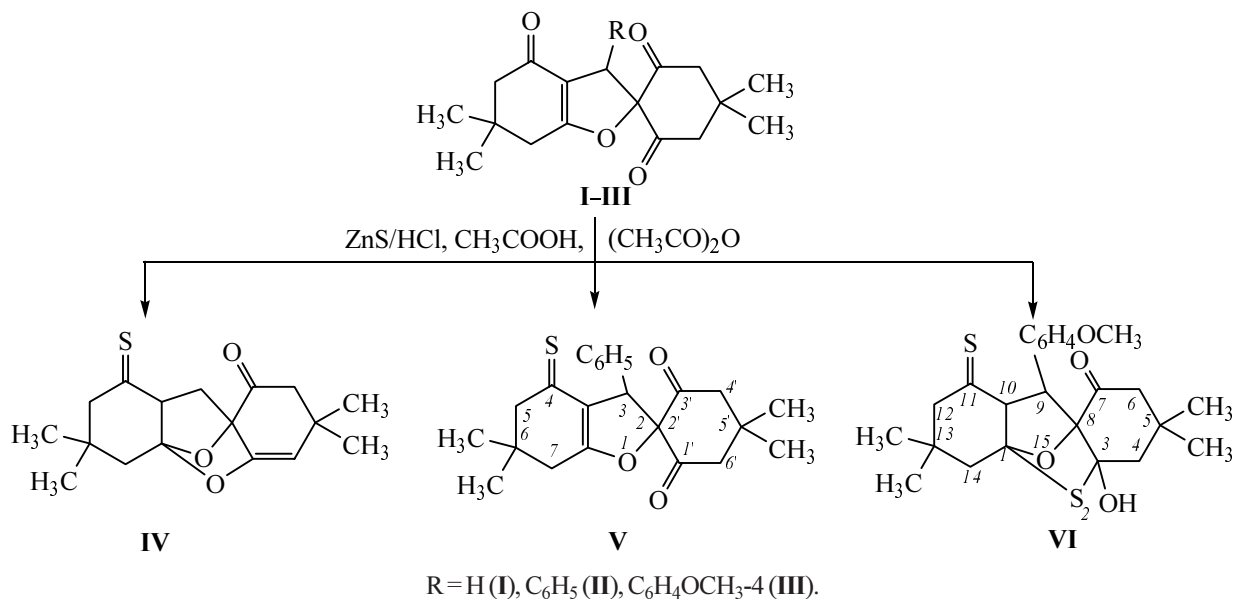
Abstract— Reactions were studied of fused spirodihydrofurans originating from 1,3-cyclohexanedione with hydrogen sulfide arising *in situ*. Depending on a substituent at the atom C³ of the heterocycle the reaction ended by thionation of the conjugated carbonyl group followed by heterocyclization involving the spirodimedonyl fragment. A quantum-chemical forecasting of the protonation stages of substrates and their thionated analogs was performed applying the semiempirical PM3 procedure. A probable mechanism of investigated transformations of the spirodihydrofurans was suggested.

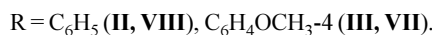
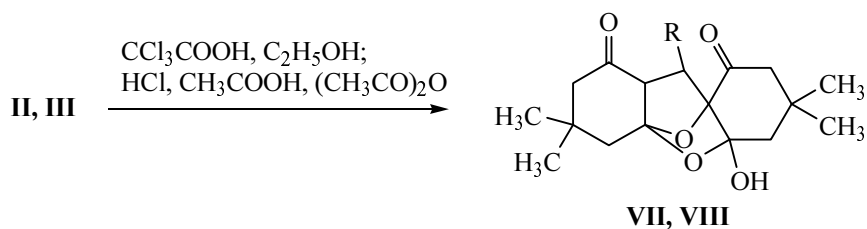
Research in the field of carbonyl-containing fused spirodihydro(pyrans)chromans is among the promising and rapidly developing domains of chemistry related to the natural heterocyclic compounds, biologically active substances [1], unique thermo- and photochromes [2].

Although the fused spirodihydrofurans originating from the 1,3-cyclohexanedione (dimedone) [3] contain several reactive sites (conjugated and nonconjugated carbonyl groups, dihydrofuran ring, spiroheterocycle, and spiroalkyl ring) and thus are valuable substrates for the synthesis of complex cyclic systems, the compounds are virtually unexplored. The only known facts concern the possibility of δ -ketoacids formation under alkaline hydrolysis by the

opening of the spirodimedonyl fragment [4], and the formation involving the latter of 3,4-dihydropyridin-2-ones at treating with ammonium acetate in the acetic acid [5].

In extension of systematic research on nucleophilic reactions involving spirodihydrofurans we studied reactions of 3-R-6,6-dimethyl-4-oxo-2,3,4,5,6,7-hexahydrobenzofuran-2-spiro-2'-(5',5'-dimethylcyclohexane-1',3'-diones) **I–III** with hydrogen sulfide formed *in situ* (from ZnS/HCl in a mixture of acetic acid and acetic anhydride, 2:1), and the dependence of the path taken by the reaction was revealed on the character of the carbonyl function, on the substituent at the C³ atom of the hetero fragment, and on the reagents ratio. We found a tendency





common for spirans **I–III** to a conversion of the conjugated carbonyl of the fused ring into a thiocarbonyl group.

Therewith whereas 5,5,13,13-tetramethyl-7-oxo-11-thioxo-2,15-dioxatetracyclo[7.6.1.0.^{1,10}0^{3,8}]pentadec-3-ene (**IV**) formed at equimolar reagents amounts (60°C, 40 h), the preparation of 5,5,13,13-tetramethyl-9-(4-methoxyphenyl)-7-oxo-11-thioxo-15-oxa-2-thiatetracyclo[7.6.1.0.^{1,10}0^{3,8}]pentadecan-3-ol (**VI**) required a significant excess of zinc sulfide (1:12, 60 h) favoring thiahemiketalization of substrate **III**. At the insufficient amount of the hydrogen sulfide (1:1) the reaction afforded the oxygen-containing analog of compound **VI**, 5,5,13,13-tetramethyl-9-(4-methoxyphenyl)-7,11-dioxo-2,15-dioxatetracyclo[7.6.1.0.^{1,10}0^{3,8}]pentadecan-3-ol (**VII**).

Unlike oily compounds **IV** and **VI** that were crystallized in 2-propanol, 6,6-dimethyl-4-thioxo-3-phenyl-2,3,4,5,6,7-hexahydrobenzofuran-2-spiro-2'-(5',5'-dimethylcyclohexane-1',3'-dione) (**V**) was isolated in a crystalline form in 20 h at the use of a double excess of ZnS, all the other conditions being the same. Therefore it presumably is the cause why no (thia)hemiketalization was observed in this case that was characteristic of compounds **I** and **III**. The product of hemiketalization **VIII** was successfully obtained from spirane **II** by boiling in the presence of ethanol in the trichloroacetic acid diluted with acetic acid

The composition and structure of compounds obtained are confirmed by the data of elemental analysis, IR and ¹H NMR spectra. The ¹H NMR spectra of (thia)hemiketals **VI–VIII** are similar in the main pattern. The proton signals of the hydroxy groups disappear at exchange with deuterium oxide. The IR spectra of compounds **VI–VIII** in contrast to those of the initial spirodihydrofurans **II** and **III** contain absorption bands of hydroxy groups in the region 3400–3100 cm⁻¹, of carbonyl at 1720 (**VI**), 1722 (**VII**), 1714 (**VIII**) cm⁻¹, and of the C–O–C group from the tetrahydrofuran moiety at 1168–1038 cm⁻¹. The presence of the double bonds C=C in the alicyclic and dihydrofuran structures in compounds **IV** and **V** is in-

dicated by the absorption bands at 1662 and 1650 cm⁻¹ respectively.

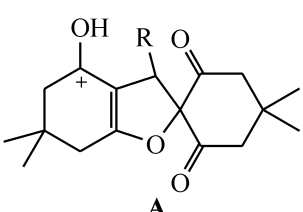
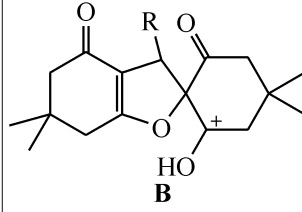
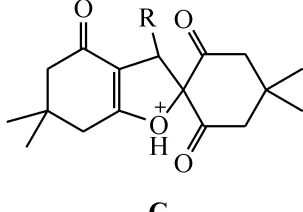
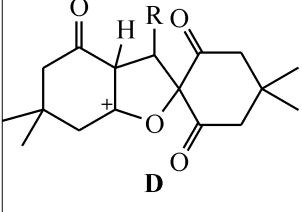
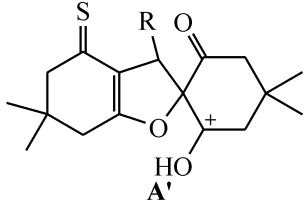
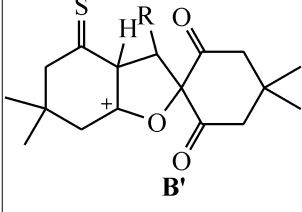
Inasmuch as the molecules of spirodihydrofurans **I–III** possess several reactive sites and the first stage of the reaction with the hydrogen sulfide formed *in situ* should be the protonation of one of the carbonyl groups or the multiple bond of the heterocycle we have carried out a quantum-chemical calculation by the semiempirical PM3 method of the most probable place of the proton addition to the substrate and of the spatial and electronic structure of the arising carbocation.

The largest partial negative charges are located on the oxygen atoms of various carbonyl groups (conjugated, nonconjugated), and also on the carbon atom of the endocyclic double bond of the dihydrofuran ring. The charges on the carbonyl groups have a minor difference. This fact suggests the lack of a charge control of the protonation. In keeping with the electronic characteristics of the initial molecular systems **I–III** we revealed four types of possible cations **A–D**. For each type and also for the transition states we calculated the standard heats of formation. The thermodynamically most feasible proved to be the proton addition to the oxygen of the conjugated carbonyl group (cation **A**). The energy barrier of the reaction for cations **B–D** is considerably higher, but the protonation of the double bond in the spirodihydrofuran **I** cannot be ruled out (cation **D**). In the substituted compounds **II** and **III** the double bond is sterically shielded by aromatic substituents.

Further transformations of the thioxospirans involve the protonation of the multiple bond in the heterocycle or the carbonyl group of the alicycle. The calculation results for the standard heats of formation of the transition states (cations **A'**, **B'**) permitted the choice of the most favorable structure of carbocation **A'** which further takes part in the heterocyclization affording products of addition of hydrogen sulfide or water.

Thus the data of the quantum-chemical calculations suggest the most probable mechanism of the reaction

Standard heats of formation of the intermediate cations^a

Cation	R	ΔH_f , kJ/mol	$\Delta\Delta E$, kJ/mol	Cation	R	ΔH_f , kJ/mol	$\Delta\Delta E$, kJ/mol
 A	H	-5.82	669	 B	H	95.0	770
	C ₆ H ₅	143	662		C ₆ H ₅	234	753
	C ₆ H ₄ OCH ₃	-18.2	660		C ₆ H ₄ OCH ₃	68.7	747
 C	H	143	818	 D	H	44.5	719
	C ₆ H ₅	272	791		C ₆ H ₅	179	698
	C ₆ H ₄ OCH ₃	107	785		C ₆ H ₄ OCH ₃	23.5	702
 A'	H	388	772	 B'	H	346	733
	C ₆ H ₅	519	771		C ₆ H ₅	463	715
	C ₆ H ₄ OCH ₃	356	767		C ₆ H ₄ OCH ₃	301	712

$$^a \Delta\Delta E = \Delta H_{f\text{cation}} - \Delta H_{f\text{initial}}$$

between spirodihydrofurans and hydrogen sulfide in acid medium supporting the experimental data obtained.

EXPERIMENTAL

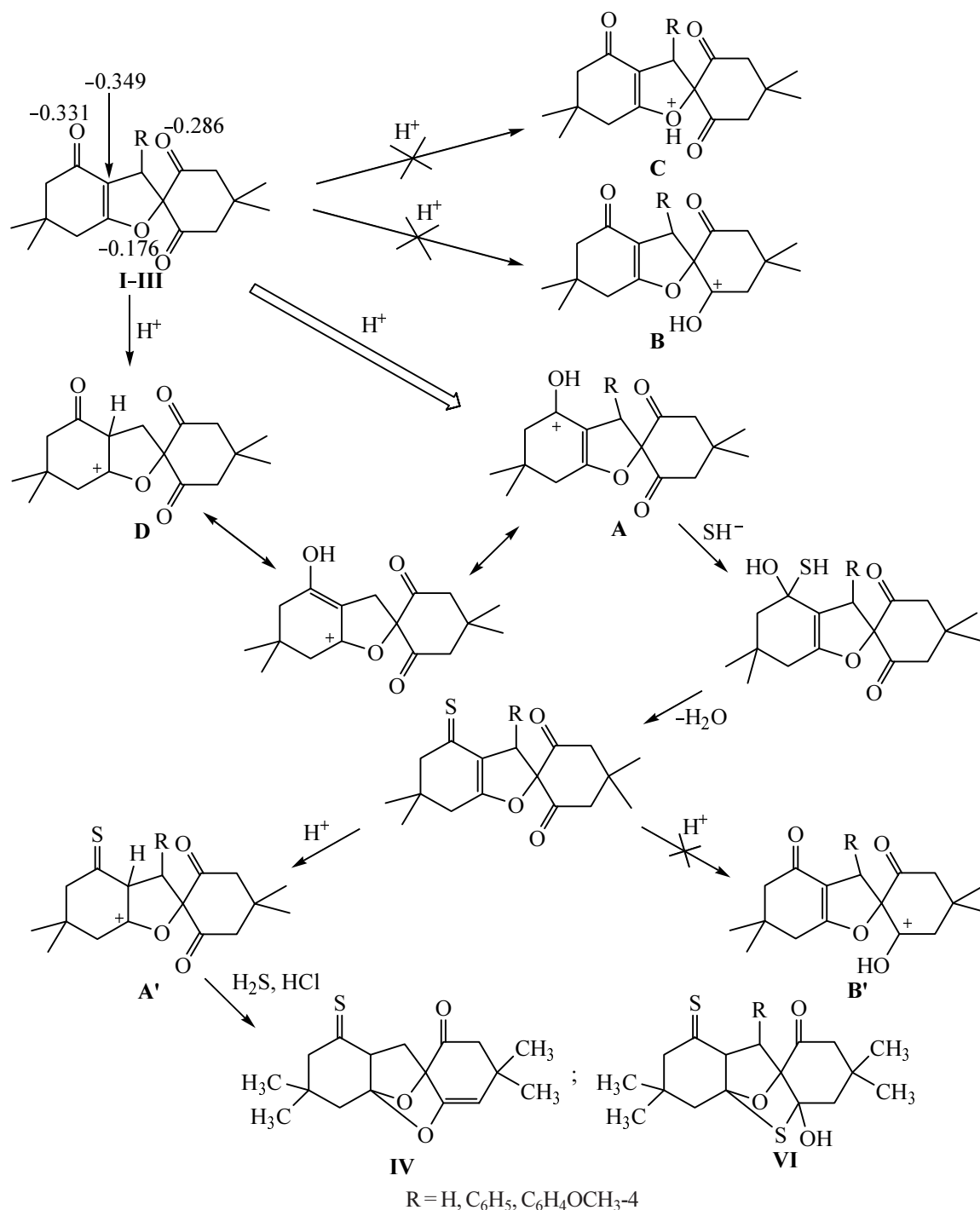
IR spectra were recorded on a spectrophotometer Specord M-80. ¹H NMR spectra were registered on a spectrometer Varian FT-80A from solutions in CDCl₃, internal reference TMS. The monitoring of the reactions progress and checking the homogeneity of the compounds obtained was performed by TLC on Silufol UV-254 plates (eluent hexane–ether–chloroform, 3:2:2).

5,5,13,13-Tetramethyl-7-oxo-11-thioxo-2,15-dioxatetracyclo[7.6.1.0^{1,10}.0^{3,8}]pentadec-3-ene (IV). Into a flat-bottom flask of 100 ml capacity was charged 1 g (3.4 mmol) of spirodihydrofuran **I**, and 0.4 g (4.1 mmol) of zinc sulfide, 10 ml of acetic anhydride and 20 ml of glacial acetic acid was added thereto, and the reaction mixture was stirred till all the reagents dissolved completely. Then 6 ml of concn. HCl was added dropwise at 20–25°C. The stirring of the content of the tightly stoppered flask was continued for 40 h with intermittent heating to 60–70°C. The precipitate (inorganic salts) was filtered off, the filtrate was diluted with water, and the reaction products were extracted into chloroform (3×

20 ml), the combined extracts were dried with anhydrous magnesium sulfate, and evaporated. The oily residue was treated in succession with hexane and diisopropyl ether. Yield of compound **IV** 0.4 g (38%), lilac crystals, mp 149–151°C (2-propanol). ¹H NMR spectrum, δ , ppm: 1.00 m (12H, CH₃), 2.27–2.46 m (6H, H⁶, H¹², H¹⁴), 4.44 s (1H, H⁴), 2.84–2.95 d (2H, H⁹), 3.24 t (1H, H¹⁰). Found, %: C 66.60; H 7.28; S 10.00. C₁₇H₂₂O₃S. Calculated, %: C 66.63; H 7.24; S 10.46.

6,6-Dimethyl-4-thioxo-3-phenyl-2,3,4,5,6,7-hexahydrobenzofuran-2-spiro-2'-(5',5'-dimethylcyclohexane-1',3'-dione) (V) was obtained in the same way as compound **IV** from 1.5 g (4.1 mmol) of substrate **II** and 0.8 g (8.2 mmol) of zinc sulfide in 10 ml of acetic anhydride and 10 ml of glacial acetic acid in the presence of 2 ml of concn. HCl within 20 h. Yield 0.7 g (45%), pink crystals, mp 229–230°C (2-propanol). ¹H NMR spectrum, δ , ppm: 0.77–1.06 m (12H, CH₃), 2.05 s (2H, H⁵), 2.93–3.12 d (2H, H⁷), 2.60 m (4H, H^{4,6}), 4.54 t (1H, H⁹), 7.24 m (5H, Ar). Found, %: C 72.55; H 6.76; S 7.96. C₂₃H₂₆O₃S. Calculated, %: C 72.25; H 6.85; S 8.38.

5,5,13,13-Tetramethyl-9-(4-methoxyphenyl)-7-oxo-11-thioxo-15-oxa-2-thiatetracyclo-



[7.6.1.0^{1,10}.0^{3,8}]pentadecan-3-ol (VI) was obtained in the same way as compound **IV** from 1 g (2.7 mmol) of spirocompound **II** and 2.98 g (30 mmol) of zinc sulfide in 10 ml of acetic anhydride and 20 ml of glacial acetic acid in the presence of 6 ml of concn. HCl within 60 h. Yield 0.6 g (50%), light-yellow crystals, mp 181–182°C (2-propanol). ¹H NMR spectrum, δ, ppm: 1.08 m (12H, CH₃), 2.16 s (6H, H⁶, H¹², H¹⁴), 2.40 s (1H, H⁴), 5.08–

5.24 d (1H, H⁹), 4.36–4.52 d (1H, H¹⁰), 6.56–6.96 m (4H, Ar), 1.52 s (1H, OH). Found, %: C 64.32; H 6.12; S 14.53. C₂₄H₃₀O₄S₂. Calculated, %: C 64.54; H 6.73; S 14.36.

5,5,13,13-Tetramethyl-9-(4-methoxyphenyl)-7,11-dioxo-2,15-dioxatetracyclo[7.6.1.0^{1,10}.0^{3,8}]pentadecan-3-ol (VII) was obtained in the same way as compound **IV** from 1 g (2.5 mmol) of spirocompound

III and 0.98 g (10 mmol) of zinc sulfide in 20 ml of glacial acetic acid and 4 ml of concn. HCl. In 8 days was isolated an oily substance that was treated with hexane and diisopropyl ether. Yield 0.4 g (39%), light-rosy crystals, mp 178–180°C (2-propanol). ¹H NMR spectrum, δ , ppm: 0.75–1.19 m (12H, CH₃), 2.46 s (6H, H⁶, H¹², H¹⁴), 2.18 s (1H, H⁴), 4.60 d (1H, H⁹), 5.32 d (1H, H¹⁰), 6.68–7.00 m (4H, Ar), 4.63 C (1H, OH). Found, %: C 69.52; H 7.15. C₂₄H₃₀O₆. Calculated, %: C 69.54; H 7.30.

5,5,13,13-Tetramethyl-7,11-dioxo-9-phenyl-2,15-dioxatetracyclo[7.6.1.0^{1,10}.0^{3,8}]pentadecan-3-ol (VIII). A mixture of 1.5 g (4.1 mmol) of spirocompound **II**, 20 ml of acetic acid, 10 ml of anhydrous ethanol, and 1 g (6.1 mmol) of trichloroacetic acid was boiled for 59 h, and evaporated. The oily residue was subjected to column chromatography on Al₂O₃ (*l* 100 mm, *d* 20 mm, eluent hexane–diisopropyl ether, 3:2). Fraction of *R_f* 0.71 was collected and evaporated. The residue was treated with hexane. Yield 0.9 g (39%), light-orange crystals, mp 135–136°C (2-propanol). ¹H NMR spec-

trum, δ , ppm: 1.05 m (12H, CH₃), 2.52–2.68 s (6H, H⁶, H¹², H¹⁴), 2.16 s (1H, H⁴), 2.84–2.95 d (1H, H⁹), 4.80–4.92 d (1H, H¹⁰), 7.28 m (5H, Ar), 6.41 s (1H, OH). Found, %: C 71.56; H 7.94. C₂₃H₂₈O₅. Calculated, %: C 71.85; H 7.34.

The study was carried out under financial support of the Russian Foundation for Basic Research (grant no. 03-03-33026a).

REFERENCES

1. Evstigneeva, R.P., Volkov, N.M., and Chudinov, V.V., *Aiol. Membrany*, 1998, vol. 15, no. 12, p. 119.
2. Shapiro, A.A., Lobkovskaya, R.M., Malkin, Ya.N., and Shibaeva, R.P., *Dokl. Akad. Nauk SSSR*, 1982, vol. 264, no. 3, p. 619.
3. Lielbriedis, I.S. and Gudrinietse, E. Yu., *Izv. Akad. Nauk Latv. SSR*, 1968, p. 192.
4. Grenberg, F.N., *J. Org. Chem.*, 1965, vol. 30, p. 1251.
5. Skuratova, M.I., Tedotova, O.V., and Reshetov, P.V., *Khim. Geterotsykl. Soedin.*, 2002, p. 710.