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Synthesis and Luminescence-Spectral Properties of Benzoheterocyclic β-Diketones and Their Complexes with Europium

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Abstract—In order to solve some environmental and biomedical problems, we synthesized fluorinated heterocyclic β-diketones and estimated the luminescence-spectral properties of these compounds complexes with the ions of rare-earth elements as the possible reagents for immunofluorescence analysis.

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The development of advanced diagnostic technologies for environmental and biomedical analysis of low molecular weight compounds, proteins, and nucleic acids is based on the implementation of new long-living luminescent markers for biomolecules. In many analytical applications of immunofluorescence analysis lanthanide β-diketonate complexes are used, most commonly the complexes of Eu^{3+} ions [1,2]. Besides unique luminescent and spectral characteristics (large, >200 nm, Stokes shift; long, up to 800 μs lifetime of excited state; narrow, ~14 nm, band of the luminescence emission in the region 613–616 nm), the β-diketonate complexes containing aromatic rings have high quantum efficiency (εφ), and the peak position of their luminescence excitation lies at ≥ 340 nm, which allows elimination of the natural luminescence of the sample, the substrate, and interfering impurities. These properties are essential at the instrumental implementation of biospecific methods of analysis. However, for developing the multianalytical biochips based on the nanotechnology approaches, it is necessary to use the lanthanide complexes of different types, that makes expedient the synthesis and study of new heterocyclic chelates using a number of β-diketones.

The preparation of new fluorinated β-diketones in this work was carried out by the examples of condensed benzoheterocyclic fragments that include nitrogen, oxygen, or sulfur atoms, to provide a variation in the sensitizing effect by changing the conjugation in these systems. These heteroatoms of different polarizability contain unshared *n*-electrons and contribute to the complexation with rare earth elements through *n–d* and *n–f* interactions [3]. The β-diketones of benzofuran, benzothiophene, and indole series containing a trifluoromethyl group have been first obtained in [4–6] as the precursors of drugs, their luminescence properties have been first disclosed in a patent of the Russian Federation [7].

We continue the study of the methods of the synthesis of fluorinated benzoheterocyclic β-diketones and of their spectral properties and the properties of their complexes with Eu^{3+}. In particular, we studied the use of different basic reagents in the Claisen condensation: sodium methoxide, sodium and lithium hydrides. To prepare the benzofuran-containing β-diketone **I** in the reaction of 2-acetylbenzofuran with methyl trifluoroacetate the use of sodium methoxide is the most effective. The yield of β-diketone **I** in this case is 48% or higher, while at the application of metal hydrides it does not exceed 30%.

The synthesis of β-diketone **II** containing benzothiophene fragment proceeds in the presence of sodium methoxide less efficiently. Therefore the β-

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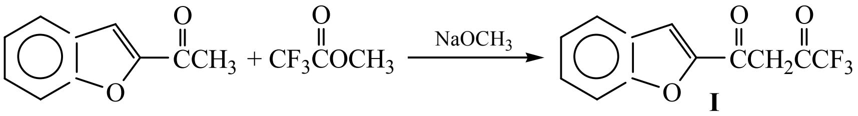
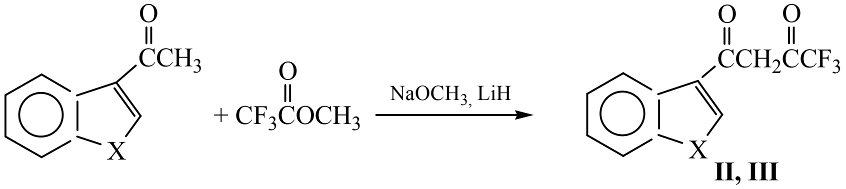
[†] Deceased.



I

diketone **II** was prepared from 3-acetylbenzothiophene in the presence of lithium hydride (use of lithium hydride for the synthesis of fluorinated β-diketones has been described in [8]). The formation of β-diketone **III** with indolyl fragment proceeded satisfactorily only when sodium methoxide was taken in double excess and the reaction conditions were more hard.

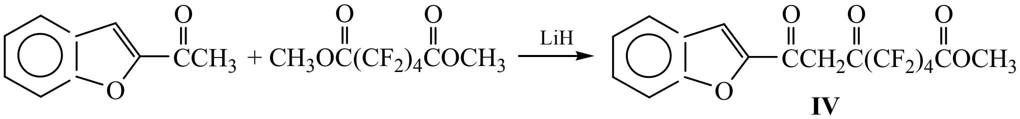


II, III

X = S (**II**), NH (**III**).

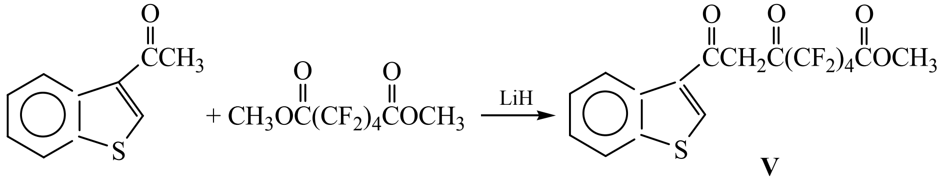
It seemed interesting to study the condensation of acetylbenzoheterocyclic compounds with the perfluorodicarboxylic acids diesters. It is known that the reactions of 2-acetylnaphthalene with perfluorodicarboxylic acids diesters results in the formation of the compounds of tetraketone and diketoester series, which are valuable due to the possibility of obtaining synthetic nano- and microparticles owing to the presence of the reactive group, and as labels in the immuno assay [9].

The reaction of 2-acetylbenzofuran with an excess of dimethyl perfluoroadipate to form diketoester **IV** was carried out in the presence of lithium hydride in boiling ether.

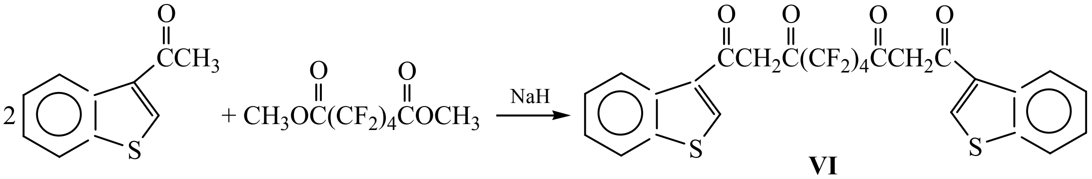


IV

3-Acetylbenzothiophene reacts with excess dimethyl perfluoroadipate under similar conditions in the presence of lithium hydride forming diketoester **V**, which was isolated in 14% yield. The formation of tetraketone **VI** in this case was registered in the reaction mixture only by NMR spectroscopy. In contrast, carrying out the condensation in the presence of sodium hydride allows effective isolation of tetraketone **VI** in 16% yield.



V

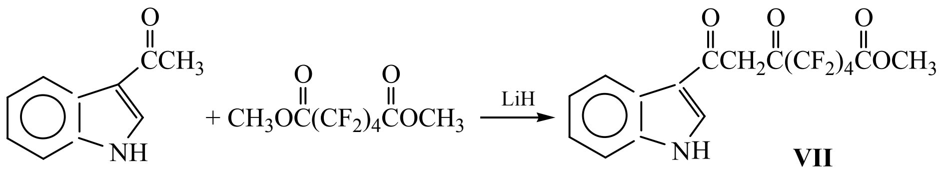


VI

Table 1. Luminescence-spectral characteristics of Eu^{3+} complexes of the synthesized compounds

Comp. no.	pH	λ_{abs}, nm	$\varepsilon \times 10^{-4}$, $mol^{-1}\,l\,cm^{-1}$	λ_{exc}, nm	I_{max}, rel. units	τ, μs
I	3.2	355	1.18	357	226	656±2.8
	7.2	358	4.61	355	366	625.1±21.0
II	3.2	340	1.13	348	286	812±4.0
	7.2	340	3.13	350	239	801.7±14.7
III	3.2	350	0.27	350	8	718±10.3
	7.2	360	1.31	358	39	695.9±22.4
IV	3.2	355	0.92	358	189	632.5±10.2
	7.2	355	2.02	355	380	606.1±4.9
V	3.2	345	1.17	348	236	802.0±8.7
	7.2	340	1.24	350	485	807.6±4.0
VI	3.2	345	2.24	345	202	743.6±23.3
	7.2	350	2.54	350	282	645.6±15.3
VII	3.2	363	0.68	360	6	710.0±17.0
	7.2	340	1.08	355	1	526.8±76.9
2-Naphthoyltrifluoroacetone	3.2	340	1.13	342	275	754.9±8.6
	7.2	340	1.54	340	375	745.3±16.9

The acylation of 3-acetylindole with dimethyl perfluoroadipate in the presence of sodium hydride failed even at prolonged heating under severe conditions. This reaction was possible only at prolonged heating in the presence of lithium hydride in tetrahydrofuran medium, the diketoester **VII** was isolated in a low yield of ~7%.



VII

Summing up briefly the study of the Claisen reaction with acetylbenzoheterocyclic compounds, it should be noted that the condensation reaction with acetylindole requires more rigid conditions than with acetylbenzofuran and acetylbenzothiophene. In general, methyl trifluoroacetate reacts faster than dimethyl perfluoroadipate. In some cases the compounds are formed in a low yield (less than 10%). We could not identify the patterns of the influence of the basic reagents on the condensation process.

Table 1 lists the luminescence-spectral properties of complex compounds of the diketones with Eu^{3+}.

All the luminescence characteristics were obtained in aqueous solutions containing 5×10^{-5} M trioctylphosphine oxide and 0.1% of Triton X-100. For neutral (0.05 M of the Tris-buffer, pH 7.2) and acidic (the “enhancement solution” medium, pH 3.2) media the results are shown obtained for the ligand–Eu^{3+} complexes of stoichiometric composition 3:1 (concentration ratio ligand:ion = 10^{-5}:3.3×10^{-6} M).

The data listed in Table 1 indicate that the compounds obtained form with Eu^{3+} the complexes that luminesce with long afterglow in neutral and acidic media, the luminescence lifetime is 500 to 800 μs, which is sufficient to implement most of the analytical techniques of immunofluorescence assay with time resolution. Complex compounds of the indole series **III** and **VII** have low luminescence level, which is unexpected and difficult to explain. In acidic medium, good luminescent characteristics showed the complexes of compounds **I, II**, and **VI:** the intensity of the luminescence signal was comparable with that of the complex of reference β-diketone 2-naphthoyltrifluoroacetone used in the analysis along the “DELFIA” method [10]. The compounds **IV** and **V** containing the reactive methoxycarbonyl group can be used to produce nano- and micro-particles with covalently bonded ligands.

EXPERIMENTAL

Spectra of solutions of compounds in DMSO-d_6 were recorded on a Bruker AC-300 spectrometer with

Table 2. Physicochemical characteristics, yields, data of elemental analysis, ^{1}H and ^{19}F NMR and IR spectra of compounds **I–VII**

Comp. no.	Yield, %	bp, °C (Topp)	mp, °C	Found, %			Formula (*M*)	Calculated, %			δ_H [δ_F], ppm (*J*, Hz)	ν, cm^{-1}
				C	H	N		C	H	N		
I	48	91 (2)	74	56.68	2.50	–	$C_{12}H_7F_3O_3$ (256.18)	56.26	2.75	–	6.75 s (1H, =CH), 7.35 t (1H, H_{arom}, *J* 6), 7.6 t (1H, H_{arom}, *J* 6), 7.75 d (1H, H_{arom}, *J* 6.5), 7.8 d (1H, H_{arom}, *J* 6.5), 7.95 s (1H, H_{fur}) [–74.1 (3F, CF_3)]	1640 w, 1720 s, 2950 w, 3200 s
II	62	–	57	52.76	2.75	–	$C_{12}H_7F_3O_2S$ (272.24)	52.94	2.57	–	7.0 s (1H, =CH), 7.5 m (2H, 2H_{arom}), 7.95 d (1H, H_{arom}, *J* 7), 8.65 d (1H, H_{arom}, *J* 7), 9.2 s (1H, H_{thioph}), [–76.1 (3F, CF_3)]	1655 m, 1720 s, 3000 w, 3250 s
III	25	–	199	56.85	3.24	5.21	$C_{12}H_8F_3O_2N$ (255.19)	56.48	3.16	5.49	6.65 s (1H, =CH), 7.2 m (2H, 2H_{arom}), 7.5 m (1H, H_{arom}), 8.2 m (1H, H_{arom}), 8.52 s (1H, H_{ind}), 12.35 br.s (1H, NH), [–73.3 (3F, CF_3)]	1640 m, 1700 s, 2980 w, 3150 v.s
IV	62	180 (2)	56	46.11	2.40	–	$C_{17}H_{10}F_8O_5$ (446.27)	45.74	2.24	–	6.77 s (1H, =CH), 7.37 t (1H, H_{arom}, *J* 7), 7.57 t (1H, H_{arom}, *J* 7), 7.73 d (1H, H_{arom}, *J* 7.5), 7.83 d (1H, H_{arom}, *J* 7,5), 8.15 s (1H, H_{fur}), 3.98 s (3H, Me), [–118.5 m (4F, CF_2), –122.2 m (4F, 2 CF_2)]	1640 m, 1720 s, 1760 s, 2980 w, 3250 s
V	14	200 (2)	186	45.01	2.40	–	$C_{17}H_{10}F_8O_4S$ (462.33)	44.16	2.16	–	7.07 s (1H, =CH), 7.5 m (2H, 2H_{arom}), 8.1 d (1H, H_{arom}, *J* 7), 8.57 d (1H, H_{arom}, *J* 7), 9.35 br.s (1H, H_{thioph}), 3.85 s (3H, Me) [–120.5 m (4F, CF_2), –124.1 m (4F, 2CF_2)]	1610 w, 1720 s, 1750 s, 2980 w, 3300 v.s
VI	16	–	221	51.54	2.46	–	$C_{26}H_{14}F_8O_4S_2$ (606.17)	51.49	2.31	–	7.1 br.s (2H, =CH), 7.55 m (4H, 2H_{arom}, *J* 7.5), 8.17 d (2H, H_{arom}, *J* 7.5), 8.62 d (2H, H_{arom}, *J* 7.5), 9.41 s (2H, H_{thioph}) [–118.2 m (4F, CF_2), –123.1 m (4F, 2CF_2)]	1620 w, 1730 m, 2950 w, 3250 s
VII	7	–	>300	45.29	3.12	3.40	$C_{17}H_{11}F_8O_4N$ (445.29)	45.84	2.47	3.15	6.65 s (1H, =CH), 7.2 m (2H, 2H_{arom}), 7.5 m (1H, H_{arom}), 8.2 m (1H, H_{arom}), 8.52 s (1H, H_{ind}), 12.35 br.s (1H, NH) [–116.3 m (4F, CF_2), –121.8 m (4F, 2 CF_2)]	1640 m, 1720 s, 1780 s, 2980 w, 3250 v.s

the operating frequency 300.13 MHz (^{1}H NMR). ^{19}F NMR spectra were recorded on a Bruker WP-200 SY spectrometer at operating frequency 188.31 MHz. Chemical shifts (δ) are given in ppm with respect to external references: TMS (^{1}H) and $CFCl_3$ (^{19}F). The IR spectra (ν, cm^{-1}) of substances in mineral oil were obtained on a FSM 1201 spectromerter. The ^{1}H, ^{19}F NMR and IR spectra, physicochemical characteristics, the data of elemental analysis, and the yields of substances are listed in Table 2.

Luminescence properties of the obtained complex compounds with Eu^{3+} were studied in the wavelength range 300–650 nm on a luminescence spectrometer Perkin Elmer LS5B with time-resolved luminescence.

We used commercial reagents and solvents prepared in accordance with known recommendations [11].

2-(4,4,4-Trifluoro-1,3-dioxobutyl)benzofuran (I). 0.58 g of sodium metal was dissolved in dry methanol (7 ml), the reaction mixture was evaporated to dryness, anhydrous diethyl ether (20 ml) was added, and to the suspended reaction mixture was added within 15 min 3.2 g of methyl trifluoroacetate and then a solution of 1.33 g of 2-acetylbenzofuran in diethyl ether (10 ml). The reaction mixture was refluxed for 7 h while stirring, then cooled to room temperature, and treated with 20% solution of sulfuric acid with ice. The organic layer was separated, washed with distilled water (3× 25 ml), evaporated in a vacuum, and the residue was fractionated in a vacuum. 1.0 g of β-diketone **I** was isolated as a crystalline substance.

3-(4,4,4-Trifluoro-1,3-dioxobutyl)benzothiophene (II). To a suspension of 0.2 g of lithium hydride in anhydrous diethyl ether (40 ml) was added within 15 min 3.2 g of methyl trifluoroacetate and then a solution of 1.7 g of 2-acetylbenzothiophene in diethyl ether (10 ml). The reaction mixture was refluxed for 7 h with stirring, then cooled to room temperature and treated with 20% solution of sulfuric acid with ice. The organic layer was separated and washed with distilled water (5×25 ml), evaporated in a vacuum, and fractionated to give the β-diketone **II,** 1.4 g, as a crystalline substance.

3-(4,4,4-Trifluoro-1,3-dioxobutyl)indole (III). 0.28 g of sodium metal was dissolved in anhydrous methanol (5 ml), then the reaction mixture was concentrated to dryness, anhydrous diethyl ether (50 ml) was added to it and then were added in succession 1.5 g of methyl trifluoroacetate and 0.8 g of 3-acetylindol. The resulting suspension was refluxed while stirring for 15 h, then cooled to room temperature and treated with 20% solution of sulfuric acid with ice. The organic layer was separated, washed with distilled water (3×10 ml), and evaporated in a vacuum. The dry residue was recrystallized from chloroform (65 ml) and washed with chloroform (3× 5 ml) to yield 0.32 g of crystalline β-diketone **III**.

2-(7-Methoxycarbonyl-1,3-dioxo-2,2-dihydroperfluoroheptyl)benzofuran (IV). To a suspension of 0.05 g of lithium hydride in anhydrous ether (40 ml) was added dropwise in the cold 1.8 g of dimethyl perfluoroadipate over 30 min, then 0.3 g of 2-acetylbenzofuran. The resulting suspension was heated while stirring under reflux for 8 h, then cooled to room temperature and treated with 20% solution of sulfuric acid with ice. The organic layer was separated and washed with distilled water (3×10 ml), evaporated in a vacuum of 20 Torr, and fractionated to yield 0.51 g of β-diketone **IV** as a viscous substance, solidifying at room temperature.

2-(7-Methoxycarbonyl-1,3-dioxo-2,2-dihydroperfluoroheptyl)benzothiophene (V). To a suspension of 0.05 g of lithium hydride in anhydrous diethyl ether (40 ml) was added dropwise in the cold over 30 min 1.65 g of dimethyl perfluoroadipate, followed by a solution of 0.3 g of 3-acetylbenzothiophene. The reaction mixture was refluxed for 6.5 h with stirring, cooled to room temperature, and treated with 20% solution of sulfuric acid with ice. The organic layer was separated and washed with distilled water (5× 25 ml), evaporated in vacuo, yielding 0.12 g of crystalline β-diketone **V**.

1,10-Di(benzothiophen-3-yl)-1,3,8,10-tetrahydroxy-2,2,9,9-tetrahydroperfluorodecane (VI). Sodium hydride, 0.13 g, was suspended in anhydrous diethyl ether (40 ml) and over 30 min to it was added dropwise in the cold 1.65 g of dimethyl perfluoroadipate, and then a solution of 0.3 g of 3-acetylbenzothiophene. The reaction mixture was refluxed for 7 h with stirring, then cooled to room temperature, and treated with 20% solution of sulfuric acid with ice. The organic layer was separated and washed with distilled water (5× 25 ml), the tetraketone **VI** precipitate, 0.16 g, was filtered off and dried in a vacuum.

2-(7-Methoxycarbonyl-1,3-dioxo-2,2-dihydroperfluoroheptyl)indole (VII). To a suspension of 0.06 g of lithium hydride in anhydrous THF (40 ml) was added dropwise over 30 min in the cold 2.26 g of dimethyl perfluoroadipate, then 0.38 g of 3-acetylindole. The resulting suspension was heated at reflux with stirring for 72 h, cooled to room temperature, treated with 20% solution of sulfuric acid with ice. The organic layer was separated, washed with distilled water (3×10 ml), and evaporated in a vacuum to give 0.07 g of β-diketone **VII** as a resinous substance.

REFERENCES

1. Osin, N.S. and Pomelova, V.G., *Frontiers in Research, Humana Press*, 2008, vol. 1 (24), p. 233.
2. Chudinov, A.V., Savitskii, A.P., and Zlobin, V.N., *Vestnik Ross. Akad. Med. Nauk*, 1999, no. 8, p. 15.
3. Yatsimirskii, K.B., Kostomina, N.A., Sheka, Z.A., Davidenko, N.K., Kriss, E.E., and Ermolenko, V.I., *Khimiya kompleksnykh soedinenii redkozemel'nykh elementov* (The Chemistry of Complex Compounds of Rare Earth Elements), Kiev: Naukova Dumka, 1966.
4. Barkley, L.B. and Levine, R., *J. Am. Chem. Soc*., 1951, vol. 73, no. 10, p. 4625.
5. Penning, T.D., Talley, J.J., Bertenshaw, S.R., Carter, J.S., Collins, P.W., Docter, S., Graneto, M.J., Lee, L.F., Malecha, J.W., Miyashiro, J.M., Rogers, R.S., Rogier, D.J., Yu, S.S., Anderson, G.D., Burton, E.G., Cogburn, J.N., Gregory, S.A., Koboldt, C.M., Perkins, W.E., Seibert, K., Veenhuizen, A.W., Zhang, Y.Y., and Isakson, P.C., *J. Med. Chem*., 1997, vol. 40, p. 1347.
6. Singh, S.K., Saibaba, V., Raoa, K.S., Reddya, P.G., Dagaa, P.R., Rajjaka, S.A., Misrab, P., and Raoa, Y.K., *Eur. J. of Med. Chem*., 2005, vol. 40, p. 977
7. RF Patent no. 2373200, *Byul. Izobret.*, 2009, no. 32.
8. Slepukhin, P.A., Boltacheva, N.S., Filyakova, V.I., Charushin, V.N., *Izv. Akad. Nauk, Ser. Khim*., 2007, no. 6, p. 1195.
9. Romanov, D.V., Vasil'ev, N.V., Lyamin, A.I., Ivanovskaya, N.P., and Osin, N.S., *Russ. Chem. Bull*., 2006, vol. 55, no. 2, pp. 1–5.
10. Hemmila, I., *Anal. Biochem*., 1984, vol. 137, p. 335.
11. Gordon, A.J. and Ford, R.A., *The Chemist's Companion. A Handbook of Practical Data, Techniques and References*, New York: Wiley, 1972.