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CHEMISTRY OF HETEROANALOGUES OF ISOFLAVONES. 15*. SYNTHESIS AND STUDY OF THE REACTION OF LANTHANIDE

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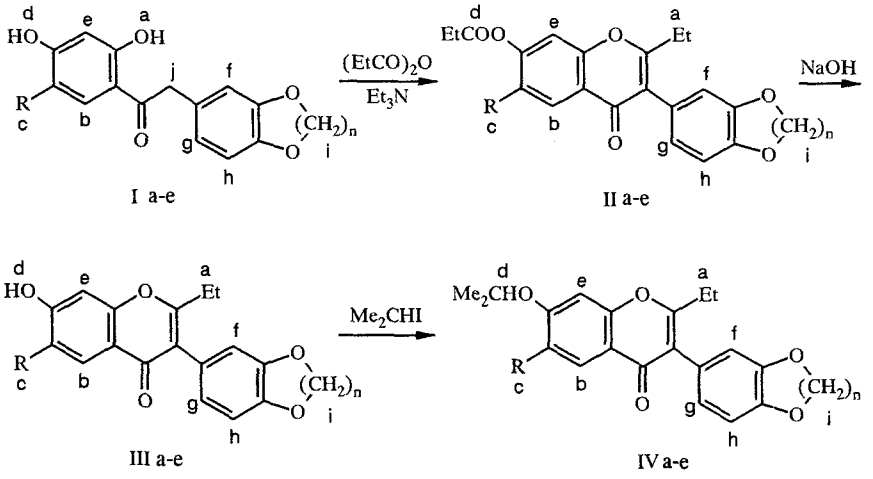
2-Ethyl substituted isoflavones have been synthesized. 7-Isopropyloxyisoflavones carrying 1,3-benzodioxole and 1,4-benzodioxan nuclei have been obtained from them. The spectral characteristics of the compounds obtained are discussed. The reaction of several of the products with various lanthanide shift reagents (LSR) has been studied. The preferred conformation of compounds in solution has been determined. It was shown that optically active LSR must not be used for obtaining quantitative data on the molecular conformation of a substrate due to the lack of effective axial symmetry in the adduct.

It is known from the literature that 7-isopropyloxy-isoflavones and their derivatives possess anabolic activity and are used for the treatment of ischemia [2]. Preparations have been found among the 7-isopropyloxy-chromones which possess antiallergic action and are used for the treatment of bronchial asthma and dermatitis [3]. Based on this information we have attempted to synthesize the corresponding 7-isopropyloxy derivatives in the isoflavone series modified by 1,3-dioxole and 1,4-dioxan nuclei. The initial ketones (Ia, b, e) were synthesized under the conditions described by us previously [4].

The ketones (Ia-e) were heated in a mixture of propionic anhydride and triethylamine in order to synthesize the 2-ethyl-7-propionyloxyisoflavones (IIa-e). The 2-ethyl-7-propionyloxyisoflavones (IIa-e) were converted by boiling for a short time with 5% alkali solution into the 2-ethyl-7-hydroxyisoflavones (IIIa-e). The compounds (IVa-e) were formed by alkylating the 2-ethyl-7-hydroxyisoflavones (IIIa-e) with isopropyl iodide in acetone in the presence of potassium carbonate.



I a-e II a-e

III a-e IV a-e

I-IV a R = Et, n = 1; b R = Pr, n = 1; c R = H, n = 2; d R = Et, n = 2; e R = Pr, n = 2

Biological screening of the new isoflavones enabled compounds possessing significant hypolipidemic, hypoglycemic, and anabolic activities to be revealed. Biological testing of the promising compounds is being continued.

Physical constants, spectral data, and yields of the starting materials and of the new compounds are given in Table 1. There are signals for all the proton-containing groups in the PMR spectra of the products studied. The absorption regions and

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TABLE 1. Physicochemical Constants and PMR Spectral Data for the Compounds Synthesized

Compound	Empirical formula	Mp, °C	PMR* Spectra, δ, ppm									Yield, %
			a•2	b	c•2	d•2	e	f	g	h	i	
Ia	$C_{17}H_{16}O_5$	122...123	12,40	7,72	2,52; 1,13	10,63	7,72	6,87	6,71	6,89	5,98	58
Ib	$C_{18}H_{18}O_5$	127...128	12,39	7,73	2,45; 1,52; 0,87	10,81	7,73	6,87	6,72	6,89	5,96	72
Ie	$C_{19}H_{20}O_5$	126...127	12,41	7,76	2,50; 1,57; 0,90	10,61	7,70	6.2-7	6.2-7	6.2-7	4,23	63
IIa	$C_{23}H_{22}O_6$	103...105	2,58; 1,19	7,94	2,58; 1,19	2,67; 1,19	7,51	6,83	6,71	6,98	6,08	61
IIb	$C_{24}H_{24}O_6$	81...82	2,62; 1,18	7,93	2,62; 1,56; 0,88	2,62; 1,18	7,50	6,82	6,71	6,98	6,07	58
IIc	$C_{22}H_{20}O_6$	159...160	2,62; 1,20	8,22	7,11	2,62; 1,29	7,27	6,77	6,72	6,91	4,28	79
IId	$C_{24}H_{24}O_6$	155...156	2,62; 1,16	7,94	2,62; 1,16	2,62; 1,16	7,50	6,77	6,70	6,92	4,29	72
IIe	$C_{25}H_{26}O_6$	130...131	2,63; 1,23	8,07	2,63; 1,64; 0,95	2,63; 1,33	7,22	6,76	6,70	6,94	4,29	76
IIIa	$C_{20}H_{18}O_5$	230...231	2,58; 1,16	7,72	2,58; 1,16	10,74	6,86	6,79	6,67	6,95	6,06	96
IIIb	$C_{21}H_{20}O_5$	235...236	2,55; 1,16	7,70	2,55; 1,59; 0,90	10,68	6,87	6,80	6,67	6,96	6,07	99
IIIc	$C_{19}H_{19}O_5$	239...240	2,49; 1,15	7,80	6,89	10,69	6,84	6,72	6,67	6,74	4,26	96
IIId	$C_{21}H_{20}O_5$	258...259	2,53; 1,16	7,71	2,53; 1,16	10,72	6,87	6,71	6,66	6,89	4,28	97
IIIe	$C_{22}H_{22}O_5$	210...211	2,50; 1,13	7,67	2,50; 1,55; 0,87	10,64	6,83	6,69	6,62	6,85	4,25	75
IVa	$C_{23}H_{24}O_5$	135...136	2,54; 1,17	7,75	2,54; 1,17	4,83; 1,35	7,14	6,81	6,69	6,97	6,07	97
IVb	$C_{24}H_{26}O_5$	108...109	2,60; 1,19	7,72	2,60; 1,58; 0,88	4,84; 1,32	7,14	6,79	6,69	6,96	6,07	52
IVc	$C_{22}H_{22}O_5$	95,5...96	2,53; 1,18	7,89	7,00	4,83; 1,31	7,11	6,73	6,68	6,90	4,28	80
IVd	$C_{24}H_{26}O_5$	118...120	2,54; 1,16	7,75	2,54; 1,16	4,84; 1,34	7,12	6,72	6,67	6,89	4,28	100
IVe	$C_{25}H_{28}O_5$	111...112	2,55; 1,18	7,71	2,55; 1,57; 0,87	4,83; 1,32	7,12	6,72	6,66	6,88	4,28	89

*The PMR spectra of compounds (IIc, e) were measured in deuterochloroform and the remainder in DMSO-d_6. Coupling constants ^3J for aliphatic protons were close to 7 Hz, ^3J for aromatic protons of the chromone nucleus were 8.5 Hz, ^4J was 2.5 Hz. In the benzodioxan and benzodioxole nuclei ^3J = 8.0 Hz, ^4J = 2.0 Hz. The singlet for proton j in compound (I) had δ 4.19 ppm.

†The chemical shifts of protons in substituents are numbered in order of their distance from the heterocyclic nucleus.

the coupling constants were within the usual limits for such values. The skeletal structure of the products synthesized follows from the PMR spectra. However it was not possible to draw any conclusions from these spectra on the mutual orientation of the heterocyclic fragments, although a solution to this problem is of interest since cases of atropisomerism were detected and studied previously for similar chromones [5]. We attempted to clarify this problem with lanthanide shift reagents (LSR).

Successful application of LSR is possible when the molecule studied contains a functional group capable of interacting with the LSR and forms secondary complexes (adducts) existing in a state of rapid exchange with the uncoordinated LSR molecules. In this case lanthanide induced shifts (LIS) are observed in the PMR spectra, the values of which grow on increasing the relative content of LSR. The PMR spectra in the presence of LSR proved to be structurally informative since the LIS for protons usually have a pseudocontact nature and comply with the McConnell–Robertson relationship, which has the following form for axially symmetrical adducts.

$$\Delta H_i = K \frac{(3\cos^2\Theta_i - 1)}{r_i^3} ,$$

where θ and r_i are the polar coordinates of the protons of the substrate molecule relative to the lanthanide ion located at the origin of coordinates. The axial symmetry of adducts is provided by the rapid exchange between coordinated and uncoordinated substrate molecules and by the presence of a definite acceptable range of angles between the principal magnetic axis of the LSR and the direction of the coordination of the substrate molecule [6].

An increase in the steric interference near the coordination center leads to a reduction in the size of the LIS. In addition a bulky LSR molecule may exert an influence on the conformation of substituents located near the coordination center. Consequently a study of sterically hindered molecules, which the compounds synthesized are, by the LSR method will give rise to some scepticism. the study of such substances requires a special approach. First of all it is necessary to be convinced of the possibility of using formula (1) for quantitative calculations. We studied one of the products (IVc) in more detail for this purpose.

Values are given in Table 2 for the chemical shifts and specific LIS (shifts at a molar ratio of LSR:substrate = 1:1) of PMR signals of the isopropyloxychromone (IVc) found on coordinating it with $Eu(FOD)_3$, $Yb(FOD)_3$, and $Eu(HFBC)_3$. FOD and HFBC are residues of the β-diketones 1,1,1,2,2,3,3-heptafluoro-7,7-dimethyl-4,6-octanedione and 3-(2,2,3,3,4,4,4,-heptafluoro-1-hydroxyethylidenebutyl)-D-camphor respectively. Values of the relaxation time T_1 in the presence of the relaxant $Gd(FOD)_3$ are also given. As is seen from Table 2 the greatest LIS is observed when using the ytterbium reagent but the broadening of the peaks by this also proved to be significant. The europium reagents did not cause strong broadening of the signals at room temperature. However broadening of individual signals for the adduct of (IVc) with $Eu(FOD)_3$ also took place on reducing the temperature. The LIS values found using $Eu(FOD)_3$ and $Yb(FOD)_3$ varied in parallel from proton to proton. This is characteristic of adducts in which significant contact LIS are absent. At the same time the use of the LSR with the other β-diketonate ligand leads to a significant change in the LIS values for individual protons. This is particularly marked for the protons of the benzodioxan fragment of the molecule. In the adduct with $Eu(FOD)_3$ the signal of proton g is shifted more significantly than the others, while in the adduct with $Eu(HFBC)_3$ the greatest LIS was noted for the signal of proton f. There may be several reasons for the observed differences of LIS. Firstly the adducts of the (IVc) molecule with the various LSR may have different structures. Secondly, the different LSR may exert different effects on the conformation of the benzodioxan substituent. Finally, it is possible that there is a significant nonaxial contribution to the LIS. A reliable explanation of the reasons for the anomalies is important in order to determine whether the LIS can be used for structural conclusions in this series of compounds, since if the LSR exerts an influence on the conformation of the molecule, it is impossible to use it to establish the conformation of the benzodioxan fragment.

We have made a calculation of the disposition of the lanthanide ion in the adducts of (IVc) with the europium LSR by the method of [7]. Since the orientation of the benzodioxan fragment of the molecule was previously unknown, the only data used for the calculations were those on the LIS of protons of the chromone nucleus and of the substituents in it remote from the coordination center. It turned out that the adducts with both $Eu(FOD)_3$ and $Eu(HFBC)_3$ have structures close to one another. The europium ion is located 2.8-3.0 Å from the carbonyl oxygen atom near the axis of its unshared electron pair towards the side of the benzodioxan substituent. From the calculated geometry of the adduct it is possible to calculate the size of the LIS for the protons of the benzodioxan substituent, the orientation of which was previously unknown. The appropriate data are given in Fig. 1a, b in the form of graphs of the relationship of the size of the LIS and the torsion angle between the heterocyclic fragments of the (IVc) molecule. The points on the curves correspond to the experimental LIS at room temperature. As follows from Fig. 1 negative values of LIS are observed for proton h within a certain range of angles of φ which indicates that this

TABLE 2. Values of the Chemical Shifts and LIS Found for Adducts of LSR and the Isopropoxychromones (IVa-e)

Compound	LSR*	PMR Spectra, δ, ppm								
		a†2	b	c†2	d†2	e	f	g	h	i
IV a	1	1,9; 1,5	5,7	0,3; -0,3	0,7; 0,3	1,4	3,7	7,0	0,3	-0,7
IVb	1	2,9; 2,1	6,6	-0,4; -0,5; -0,5	0,7; 0,3	1,5	4,1	7,5	0,3	-0,7
IV c	1	2,3; 1,3	5,5	0,1	0,4; 0,1	1,3	3,4	5,0	-0,3	-0,4
	2	6,5; 4,1	19,4	0,3	1,0; 0,4	4,1	10	14	0,6	-0,8
	3	1,7; 1,0	3,2	-0,6	0,1; -0,1	0,9	3,2	2,3	-1,1	-0,1
	4	1,2; 1,0	5,4	1,3	1,6; 1,2	1,3	5,0	6,1	2,5	1,1
IVd	1	2,3; 1,5	6,6	-0,2; 0,3	0,3; 0,6	2,1	4,3	8,2	0,2	-0,3
IV e	1	2,9; 2,0	6,1	0,2; 0,4; -0,3	0,7; 0,3	1,4	4,9	8,5	0,8	-0,3

*Lanthanide shift reagents: 1) $Eu(FOD)_3$; 2) $Yb(FOD)_3$; 3) $Eu(HFBC)_3$; 4) $Gd(FOD)_3$. For the last reagent the factor for the reduction of relaxation time T_1 on adding a small quantity of relaxant to the solution in deuterochloroform is given.
†Numbered in order of distance of protons in substitutents from the heterocyclic nucleus.

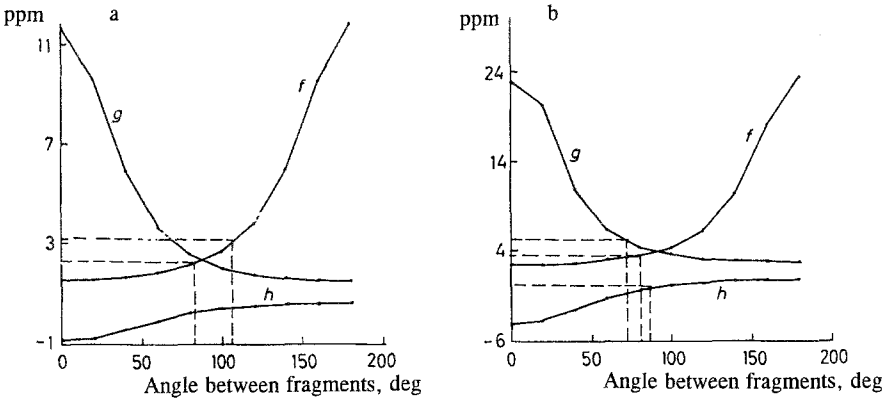

Fig. 1. Calculated values of the LIS for the protons of the benzodioxan fragment in adducts with LSR: a) adduct with $Eu(HFBC)_3$; b) adduct with $Eu(FOD)_3$. Values are given in the figures for the calculated angles between the chromone and benzodioxan fragments estimated using the LIS of the various protons of the benzodioxan nucleus [protons are designated as in formula (IV)].

proton may be in an area of diamagnetic shielding by the europium atom [angle θ in equation (1) > 54°]. In principle it is possible to find the conformation of the benzodioxan fragment of the molecule from the size of the LIS of each of the protons of this substituent. For this it is sufficient to find the angle corresponding to the experimental LIS (from Table 2) on the appropriate curves of Fig. 1. It is evident that a good agreement is observed for the results obtained from the LIS of various protons for the adduct of $Eu(FOD)_3$ with compound (IVc). The angles φ are in the range 75-85° which indicates a good compliance of the LIS with formula (1) and correspondingly the effective axial symmetry of the adduct. The agreement is significantly worse for the adduct with $Eu(HFBC)_3$. Thus the angle φ corresponding to the LIS of proton f of the benzodioxan fragment is 112°. If the LIS of proton g is used then the angle φ proves to be equal to 93°. The experimental LIS of proton h generally does not lie in the rnage of LIS values of this proton calculated for various angles φ. The reason for the divergence from the calculations is evidently the significant contribution of a nonaxial term of equation (1) to the LIS for the adduct with $Eu(HFBC)_3$. As was shown previously this contribution increases on increasing the angle between the main magnetic axis of the complex and the vector linking a given proton with the lanthanide ion in the adduct [8]. This angle is largest for proton h consequently the greatest anomaly is observed for it.

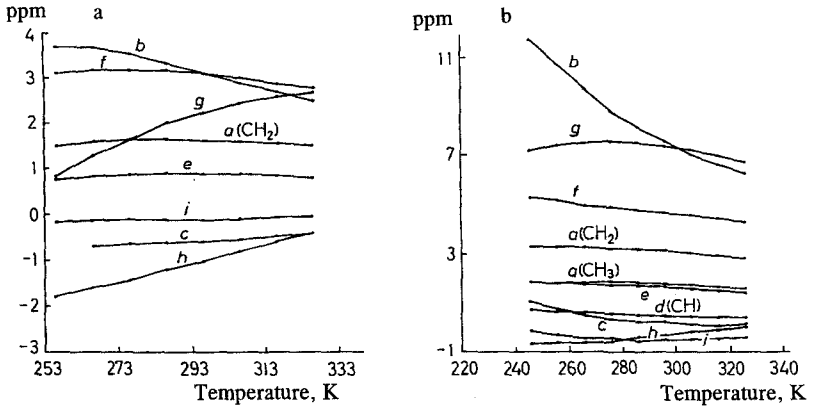

Fig. 2. Temperature dependencies of the LIS for the adducts of (IVc) with LSR: a) adduct with $Eu(HFBC)_3$; b) adduct with $Eu(FOD)_3$ [protons are designated as in formula (IV)].

We also studied the dependence of the experimental LIS on temperature in the range 246-326 K. The temperature dependencies found are given in Fig. 2. It is evident from Fig. 2 that an increase in the LIS occurs on reducing the temperature for the majority of the protons of compound (IVc), as follows from the theory of pseudocontact shifts. On the other hand the LIS for proton g of the benzodioxan fragment is reduced on reducing the temperature, particularly for the adduct of (IVc) with $Eu(HFBC)_3$. This indicates a change in the mean orientation of the benzodioxan fragment. On increasing the temperature of the adduct of (IVc) with $Eu(HFBC)_3$ to 333 K the sizes of the LIS for protons f and g practically coincide. As is evident from Fig. 1, this is possible at a mutually perpendicular orientation of the heterocyclic fragments in the (IVc) molecule. An increase in temperature therefore leads to a growth in the noncoplanarity of the benzodioxan and chromone fragments of the (IVc) molecule. This is exactly the situation when the LSR exerts a steric effect on the conformation of the substrate molecule.

The ratio of the LIS for protons f and g in the adduct of (IVc) with $Eu(FOD)_3$ on varying the temperature in the range 333-273 K proved to be practically unchanged, i.e. growth in the kinetic energy of the fragments in this adduct on increasing the temperature does not lead to a change in the mean conformation of the benzodioxan fragment of the molecule. Thus $Eu(FOD)_3$ proves to be a more successful reagent than $Eu(HFBC)_3$ for studying the conformation of these molecules. Use of the latter reagent for quantitative calculations is probably inexpedient.

We also attempted to determine the conformation of the (IVc) molecule using the LIS data of all the protons in it. However it turned out that for any angle between the heterocyclic fragments it was possible to find a point at which a good agreement of calculated and experimental LIS was observed. As the angle φ increases the calculated position of the lanthanide in the adduct is further displaced from the plane of localization of the chromone fragment. The size of this displacement at $\varphi = 90°$ may reach 2 Å. Since the geometry of the adduct found in this way does not agree with the usual stereochemistry of complex formation, we assume that this result is linked with the extreme nature of the solution of a system of equations (1) made up for the considered protons of the substrate molecule. The solution which was found previously, using the LIS of the protons of the chromone fragment only, proved not to be the best from a mathematical point of view. The large values of the LIS for the protons of the benzodioxan fragment compared to the protons of the chromone nucleus contribute to this.

The use of data on the influence of $Gd(FOD)_3$ on the relaxation time of individual signals, as it turned out, did not assist in the localization of the lanthanide in the adduct with (IVc). In calculations using the dependence of relaxation time on the $Gd-H_i$ vector length ($1/r^6$) no regions were found with a satisfactory correlation of calculated and experimental relaxation times.

The investigations carried out therefore show that $Eu(FOD)_3$ is the best reagent for establishing the structure of 3-heterylchromones. This LSR induces high LIS values, it proves to have less effect on the conformation of the substrate molecule being studied, and the adducts with it possess effective axial symmetry, which makes the calculations more correct.

We also studied the reaction of $Eu(FOD)_3$ with the chromones (IVa), (IVb), (IVd), and (IVe) (see Table 1). The LIS observed proved to be close to the values found for product (IVc). The introduction of alkyl substituents at position 6 of the chromone nucleus reduces the LIS somewhat, however an increase in the volume of such a substituent does not affect the induced shifts significantly. If the data for molecules having various heterocyclic residues in position 3 of the chromone nucleus are compared, other conditions being equal, the LIS differ little. This indicates identical structures for the adducts of these

chromones with the LSR and the closely similar conformations of the substituents. These conclusions were confirmed by calculating the structures of the adducts of (IVa-e) with $Eu(FOD)_3$.

EXPERIMENTAL

The PMR spectra were measured on a Bruker WP 100-SY spectrometer with an operating frequency of 100 MHz. The sizes of chemical shifts are given relative to TMS (internal standard). Commercial samples of LSR were used without further purification. The temperature measurements were made on a standard B-VT-1000 spectrometer adapter. The precision of establishing the temperature was ± 1 K. The relaxation times of magnetic nuclei were determined using the Carr–Purcell–Maybaum–Hill impulse sequence.

The purity of the compounds obtained and the course of reactions were checked by TLC on Silufol UV-254 plates. A mixture of benzene and ethanol (9:1) was used as eluent.

The elemental analysis data of new compounds corresponded with calculated values.

2-Ethyl-3-heteryl-7-propionyloxychromones (IIa-e). A mixture of the appropriate ketone (Ia-e) (20 mmole), propionic anhydride (12.9 ml: 100 mmole), and triethylamine (11.2 ml: 80 mmole) was heated for 7-8 h at 120-130°C. The reaction mixture was then poured into cold water (250 ml) containing hydrochloric acid (1 ml). The precipitated solid was filtered off and recrystallized from ethyl acetate.

2-Ethyl-3-heteryl-7-hydroxychromones (IIIa-e). A 5% solution of sodium hydroxide (24 ml: 30 mmole) was added to a hot solution of the appropriate 2-ethyl-7-propionyloxy-isoflavone (IIa-e) in ethanol (150 ml) and the mixture boiled for 10 min. The mixture was neutralized with dilute hydrochloric acid to pH 7. The precipitated solid was filtered off. Compounds (IIIa, b, d) were crystallized from isopropanol and compounds (IIIc, e) from aqueous ethanol.

2-Ethyl-3-heteryl-7-isopropyloxychromones (IVa-e). Isopropyl iodide (1 ml: 10 mmole) and freshly calcined potassium carbonate (4.14 g: 30 mmole) were added to a hot solution of the appropriate 2-ethyl-3-heteryl-7-hydroxy-chromone (IIIa-e) (10 mmole) in dry acetone (200 ml) and the mixture boiled for 29-34.5 h. The inorganic solid was filtered off and washed several times on the filter with hot acetone. The acetone was distilled off in vacuum with a water-jet pump and the residue crystallized from ethanol.

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