USE OF DOUBLE PROTON RESONANCE TO ESTABLISH THE STRUCTURE OF LIGNANS OF THE ARYLNAPHTHALENE SERIES. THE STRUCTURE OF DAURINOL

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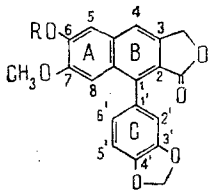
UDC 547.99

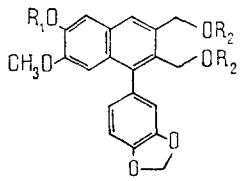
On the basis of the results of a study of PMR spectra with the use of double proton resonance, the promising nature of this method for determining the structures of lignans of the arylnaphthalene series has been shown and the structure of a new lignan, daurinol, isolated from *Haplophyllum dauricum* has been established as the lactone of 6-hydroxy-3-hydroxymethyl-7-methoxy-1-(3',4'-methylenedioxyphenyl)-2-naphthoic acid.

In determining the structures of lignans of the arylnaphthalene series on the basis of an analysis of only the chemical shifts of the Ar—H, Ar—CH_2—O— and —OCH_3 protons in the PMR spectrum, indications have been observed from which it is possible to distinguish the position of the lactone ring and of the methoxy groups in such compounds [1-3]. In determining the structure of a new arylnaphthalene lignan, daurinol, from *Haplophyllum dauricum* (L) G. Don, we used double-resonance methods — collapse and NOE — for the first time [4]. However, the mutual positions of the —OH and —OCH_3 groups were not determined unambiguously. In the present paper we give the results of an unambiguous determination of the structures of lignans of the arylnaphthalene series with the aid of double proton resonance (collapse and NOE). Here, substantial assistance is provided by the study of the spectra at various temperatures both of the initial lignans and of their reduction products. The details of the PMR spectra are given in Table 1 and in Fig. 1.

As has been shown previously [4], in the PMR spectrum of daurinol acetate (Ia), an unambiguous assignment of the signals of the aromatic protons H_5 and H_8 in ring A with the aid of double resonance is made difficult by virtue of the fact that the Ar—$\underline{CH_2}$—O protons exhibit long-range spin—spin coupling with both H_5 and H_8. A similar pattern is observed in the case of justicidin B (Ib). Without a strict assignment of the H_5 and H_8 signals it is impossible to determine the mutual positions of the OH and OCH_3 groups in ring A. To resolve this question we performed the opening of the lactone rings of daurinol and of justicidin B by reduction with lithium tetrahydroaluminate, with the formation of compounds (IIa) and (IIb), respectively. Acetylation of the latter led to the triacetate (IIIa) from daurinol and the diacetate (IIIb) from justicidin B.



I. R = H
Ia R = $COCH_3$
Ib R = CH_3



IIa $R_1 = R_2 = H$
IIb $R_1 = CH_3$, $R_2 = H$
IIIa $R_1 = R_2 = COCH_3$
IIIb $R_1 = CH_3$, $R_2 = COCH_3$

Institute of the Chemistry of Plant Substances, Academy of Sciences of the Uzbek SSR, Tashkent. Translated from Khimiya Prirodnykh Soedinenii, No. 1, pp. 19-23, January-February 1983. Original article submitted February 2, 1982.

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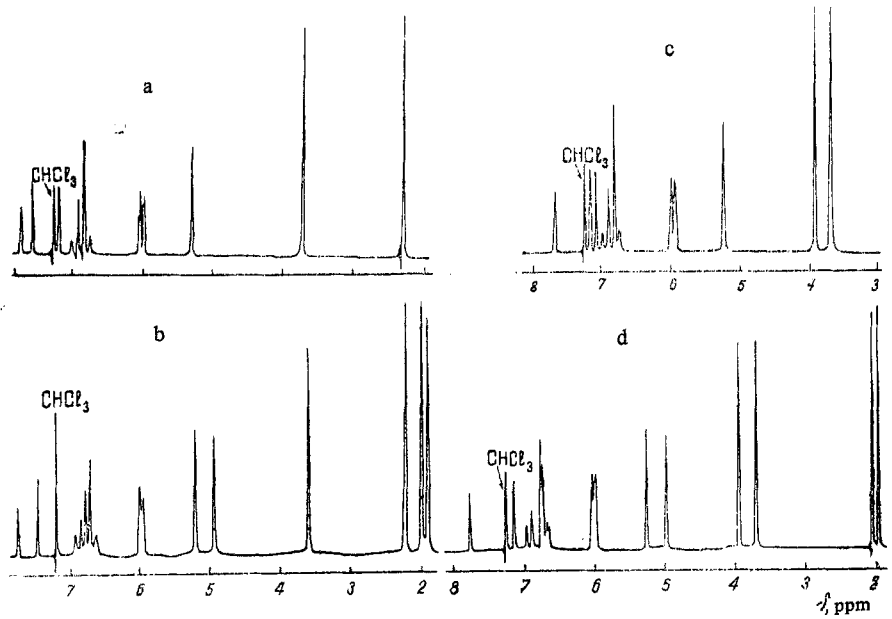

Fig. 1. PMR spectra of daurinol acetate (a), of the acetate of the reduction product of daurinol (b), of justicidin B (c), and of the products of the reduction of justicidin B (d) in $CDCl_3$.

In the PMR spectra of (IIIa) and (IIIb) at room temperature the signal of one of the aromatic protons of ring A is appreciably shifted upfield (see Table 1 and Fig. 1) as compared with the others. It is quite obvious that the reduction of the lactone C=O has a greater effect on the change (increase) of the electron density of the C_8 carbon atom than of the C_5 atom, as a result of which the H_8 signal must correspondingly undergo an upfield shift considerably greater than that of the H_5 signal. The signals of H_8 aromatic protons in compounds (Ia), (Ib), (IIIa), and (IIIb) are located in a relatively strong field as compared with the H_5 signal, and from this, therefore, flows the unambiguous assignment of the H_8 and H_5 signals shown in Table 1. As another confirmation of this we can give the fact that in a comparison of the chemical shifts the signals of the protons taken at room temperature and with heating to + 60° (see Table 1), the signals of all the protons shift upfield with the exception of one strong-field signal of the aromatic proton which undergoes a slight paramagnetic shift. This is apparently due to the different influences of the diamagnetic anisotropy of the benzene ring C with a change in the temperature on the H_8 proton of ring A, since a similar influence of ring C on H_5 is probably excluded. When the OCH_3 protons (δ 3.60 ppm) were irradiated with an additional field, H_2, the intensity of the signal of the aromatic H_8 proton (δ 6.68 ppm) increased by approximately 30%, i.e., an appreciable NOE was observed between H_8 and Ar—OCH_3 in (III) which indicates the location of the —OCH_3 group at C_7 in ring A in daurinol. This, in its turn, permits an unambiguous selection of the C_6 position for the OH group of daurinol and the establishment of its structure in the form of (I).

The results of a NOE measurement in justicidin B and its derivative (IIIb) between the protons of the Ar—OCH_3 group and H_5 and H_8 shows that the signal of the —OCH_3 protons at C_6 appears in a weaker field (δ 3.96-3.89) than the signal of the —OCH_3 group at C_7 (δ 3.73-3.58 ppm). In addition to this, as a characteristic indication of the position of the methylenedioxy group in ring C at C_3'-C_4' in lignans of the arylnaphthalene series it is possible to take the nonequivalence of the CH_2 protons of this group, which, in the PMR spectra of such lignans, give two doublets at 5.90 and 5.97 ppm with $J \approx 1.2$ Hz [2, 5]. It is obvious that the nonequivalence of these protons is due to the noncoplanar position of ring C with respect to the remainder of the molecule. In the spectra of (Ia) and (Ib) taken at + 60°C, these protons become almost equivalent and give a two-proton singlet at 5.89-5.90 ppm (see Table 1 and Fig. 1). It is known that in the case where the —OCH_2O-group is present in ring A, the CH_2 protons are, as a rule, equivalent and give a signal in the form of a two-proton singlet [5-7]. As already mentioned, in order to decide on the position of the lactone carbonyl at C_2 or C_3 in the lignans under consideration one starts from the different chemical shifts of the Ar—$\underline{CH_2}$—O—C=O and H_4 protons [1-3, 8].

TABLE 1. Details of the PMR Spectra of Lignans of the Arylnaphthalene Series ($CDCl_3$)

Compound	Chemical shifts (ppm; O – HMDS) and SSCCs (J, Hz)											
	Temperature deg C	H_4	H_5	H_8	$H_{2'}$, $H_{5'}$, $H_{6'}$	7-OMe	6-OMe	3-CH_2O–	2-CH_2O–	–OCH_2 O–	Ar–$OCOCH_3$	Ar–CH_2–O–C(=O)–CH_3
Justicidin B (Ib)	22	7,58	7,06	6,98	6,74	3,73	3,96	5,24 br.s	—	5,90 d	—	—
	60	7,52	7,05	7,03	6,71	3,69	3,91	5,19 s	—	5,97 d J=1,2 5,89 s	—	—
Daurinol acetate (Ia)	22	7,62	7,45	7,07	6,72	3,67	—	5,25	—	5,89 d	2,30	—
										5,97 d J=1,2		
	60	7,58	7,44	7,11	6,72	3,65	—	5,22	—	5,90 br.s	2,26	
Acetate of the product of the reduction of justicidin B (IIIb)	22	7,65	7,02	6,62–6,65	6,65	3,64	3,92	5,22	4,93	5,93 dd J=1,2	—	2,04; 1,92
	60	7,61	7,00	6,64		3,63	3,89	5,24	4,95	5,90 br.s	—	2,00; 1,92
Acetate of the product of the reduction of daurinol (IIIa)	22	7,65	7,37	6,68	6,57	3,60	—	5,20	4,92	5,92 dd J=1,2	2,25	2,02; 1,93
	60	7,63	7,35	6,73		3,58	—	5,22	4,97	5,89	2,24	2,01; 1,93

We consider that by the method of double proton resonance it is also possible reliably to select one of the alternative positions of the Ar—CH_2—O group in the aromatic ring, at C_2 or C_3, from the presence or absence of spin–spin coupling between the Ar—CH_2—O protons (δ 5.30-4.90 ppm) and H_4. Thus, for all the compounds studied — (Ia), (Ib), (IIIa), and (IIIb) — a long-range interaction was found between the Ar—CH_2—O and H_4 protons by the double-resonance method, since on irradiation of the Ar—$\underline{CH_2}$ protons with a H_2 field the half-width of the H_4 signal decreased and its intensity increased. By the same method we have established that in compounds (IIIa) and (IIIb) the signals in the weak field at 5.22 and 5.24 ppm, respectively, relate to the protons of CH_2—OAc groups attached to the C_3 atoms, since the CH_2 protons interact with H_4. Consequently, the signal in the stronger field relates to CH_2—OAc at C_2, and the relative diamagnetic shift of the CH_2—O—Ac protons of at C_2 as compared with those at C_3 can be explained by the screening of the former by the benzene ring at C in (IIIa) and (IIIb).

Thus, the double-resonance method is an extremely effective and promising one in the establishment of the structures of lignans of the arylnaphthalene series.

EXPERIMENTAL

The PMR spectra were obtained on a JNM-4H-100/100 MHz instrument in $CDCl_3$, 0 — HMDS, and the mass spectrum on a MKh-1310 instrument. The homogeneity of the substances was checked by the TLC method on Silufol UV-254 in the chloroform—ethyl acetate (1 : 1) system.

Reduction of Daurinol with $LiAlH_4$. With constant stirring, 300 mg of lithium tetrahydroaluminate was added in portions to a solution of 0.2 g of daurinol in 25 ml of absolute tetrahydrofuran. The mixture was stirred at room temperature for 4 h and was then boiled on the water bath under reflux for 30 min. After this, 25 ml of ethyl acetate was added to it and the excess of the reagent was decomposed with dilute hydrochloric acid. The layer of organic solvent was separated off, washed with distilled water, and dried with anhydrous sodium sulfate, filtered, and evaporated. The residue was twice recrystallized from ethanol, giving 158 mg of (IIa) with mp 209-211°C, R_f 0.24.

Mass spectrum of (IIa): M^+ 354 (100), 338 (22), 337 (15), 336 (68), 308 (13), 307 (29), 306 (6), 305 (9), 291 (6), 278 (7), 277 (9), 275 (7), 263 (9), 249 (6), 235 (8), 234 (5), 205 (6), 199 (7, 5), 176 (5), 165 (5), 153 (8), 139 (7), 88 (6), 73 (7).

Acetylation of (IIa). A solution of 25 mg of (II) in 0.5 ml of pyridine was treated with 1 ml of acetic anhydride and the mixture was left at room temperature. After 24 h, the acetyl derivative was isolated in the usual way.

Preparation of (IIa) and (IIIb). The reduction of 120 mg of justicidin B with 160 mg of lithium tetrahydroaluminate by the method described above gave 96 mg of (IIb) in the form of a colorless oily substance with R_f 0.31. Acetylation of the product obtained with acetic anhydride in the presence of pyridine led to (IIIb).

SUMMARY

On the basis of the results of a study of PMR spectra using double proton resonance the promising nature of this method in the determination of the structures of lignans of the arylnaphthalene series has been demonstrated and the structure of the new lignan daurinol has been established unambiguously as the lactone of 6-hydroxy-3-hydroxymethyl-7-methoxy-1-(3', 4'-methylenedioxyphenyl)-2-naphthoic acid.

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