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^{13}C NMR SPECTRA OF BIOLOGICALLY ACTIVE COMPOUNDS

IX. * DIASTEREOMERS OF (±)-16-ARYLOXY-11-DEOXYPROSTAGLANDINS OF THE E_1 AND F_1 SERIES

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The diastereomeric effects on the ^{13}C NMR chemical shifts of thirteen epimeric pairs of 16-aryloxy-11-deoxyprostaglandins of the E_1 and F_1 series caused by the change in the configuration of the 15-hydroxy group, which are differential parameters for assigning epimers to the 15α- and 15β-stereochemical series, have been determined.

We have previously published details of the ^{13}C NMR spectroscopy of α-homo and ω-aryloxy analogs of the 11-deoxyprostaglandins E_1 [2, 3]. As differential parameters for determining the epimeric prostaglandins (PGs) and other compounds having two and more chiral centers, we have proposed the diastereomeric effects on the ^{13}C NMR chemical shifts (CSs) determined by the difference in the screening of the characteristic carbon atoms:

$$\Delta_{diasCi} = \delta_{CiA} - \delta_{CiB}.$$

In the present paper we consider the ^{13}C NMR spectra of ten new 16-aryloxy-11-deoxy-PGE_1's (I-X) and three pairs of 16-aryloxy-11-deoxy-PGF_1's (XI-XIII) epimeric at the C-15 hydroxy group and the observed values of the diastereomeric effects in the chemical series discussed (see scheme on following page).

The racemic compounds (I-XIII) each have three chiral centers (at C-8, C-12, and C-15), which makes the existence of four diastereomers probable. Thanks to the fact that in the course of chemical synthesis [4] the precursors of the prostanoids had the correct stereochemistry at C-8 and C-12 and only the oxo function at C-15 was subjected to transformation, only pairs of epimers at the C-15 alcohol groups were obtained, each of which was isolated in the individual form with the aid of column chromatography on silica gel and was characterized spectrally (Table 1). In the spectra of the individual compounds, all the characteristic signals corresponding to the prostanoid structure were detected. In the weakest field there were the signals of the 9-keto and the carboxy groups. The carbon atoms of the double bond and of the aromatic ring resonated in the 114-158 ppm region. In contrast to the values given in]5], we found that for compound (I) the doublet signal at 70.7 ppm corresponded to C-15, and the triplet signal at 71.8 ppm to C-16. Two doublets at 54.5 and 45.6 ppm characterized the C-8 and C-12 atoms. The other triplet signals in the strong-field region related to the methylene groups of the α-chain and of the cyclopentane ring.

The differences in the spectra of the two stereoisomers were very slight and exceeded the error of the measurements (±0.03 ppm) only for a few of the carbon atoms — C-3–C-6, C-8, and C-12–C-15. These diastereomeric effects were not connected with the change in

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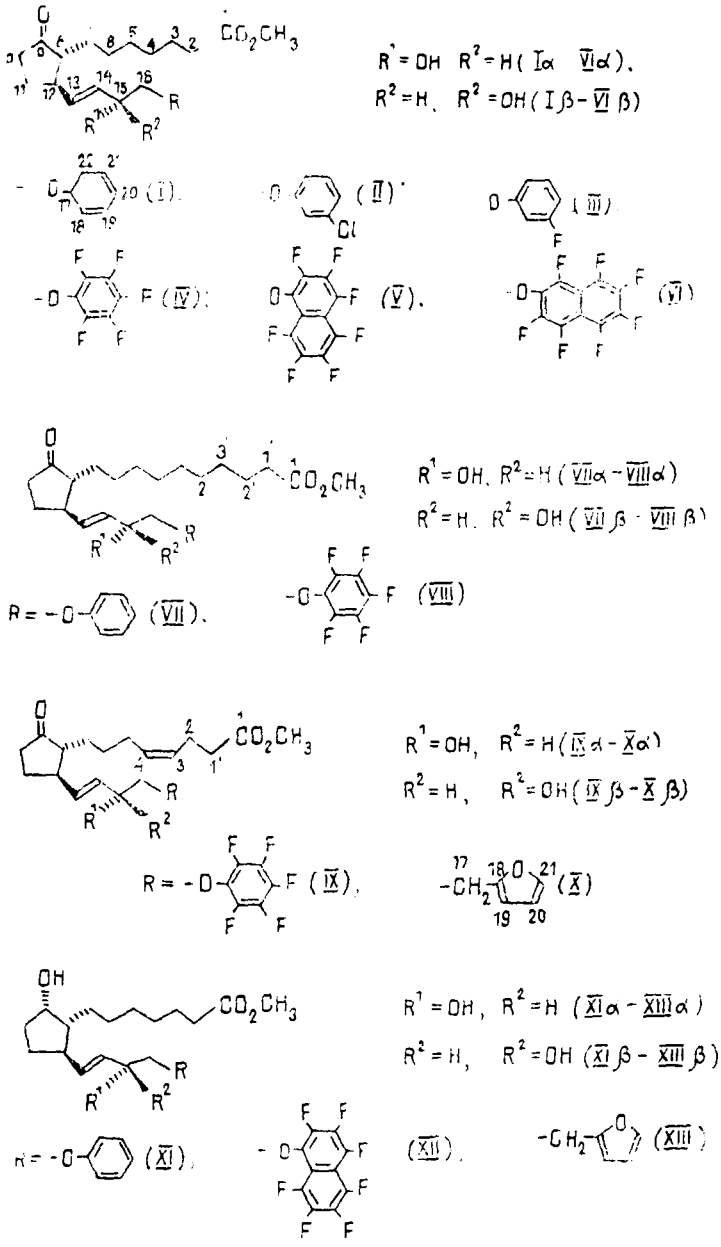

in the relative configurations of the chiral centers at C-8 and C-12, since their maximum value was less than 0.3 ppm. It has been shown previously [3] that such effects amount to several ppm. A comparison with these facts showed that in our case the α- and ω-chains had the trans-orientation relative to one another.

The observed values of the diastereomeric effects were due to the difference in the stereochemical orientation of the C-15 hydroxy group relative to the C-12 chiral center. The maximum positive effect (0.29 ppm) was detected for the C-13 atom of the double bond. Also positive were the effects for the C-12 and C-15 chiral centers. The signs and magnitudes of these effects were due to the presence of erythro-steric interactions in the 15β-epimer (the RS and SR enantiomeric pair) caused by the screening of the signal, in contrast to the 15α-epimer (RR and SS enantiomeric pair). An exception was the C-14 signal, which apparently does not participate in the interaction.

Interesting is the existence of positive effects for the methylene groups of the α-chain. A consideration of molecular models, and also the results of X-ray structural analysis show that the α- and ω-chains in the prostaglandins are spatially close, a consequence of which is the different screening of the methylene groups of the α-chain and, in particular, of the C-5 atom, which is located opposite the C-15 hydroxy group.

TABLE 1. ^{13}C NMR Chemical Shifts of Prostaglandins (I-XIII) [δ, ppm, ($J_{^{13}C,^{19}F}$, Hz) $CDCl_3$, 25°C]

Number of the carbon atom	Prostaglandin Iα	Iβ	$\Delta\delta_{\alpha-\beta}$	Prostaglandin IIα	IIβ	$\Delta\delta_{\alpha-\beta}$	Prostaglandin IIIα	IIIβ	$\Delta\delta_{\alpha-\beta}$
1	174,25	174,29	−0,04	174,28	174,35	−0,07	174 28	174,35	−0,07
2	34,01	33,98	0,03	33,98	34,08	−0,03	34,01	33,94	0,07
3	24,81	24,74	0,07	24,81	24,74	0,07	24,81	24,74	0,07
4	28,89	28,82	0,07	28,85	28,78	0,07	28.92	28,79	0 13
5	29,41	29,31	0,10	29,37	29,31	0,06	29,37	29,24	0,13
6	26,57	26,50	0,07	26,57	26,47	0,10	26,63	26,44	0,19
7	27,68	27,64	0,04	27,71	27,68	0,03	27,74	27,68	0,06
8	54,57	54,51	0,06	54,44	54,51	−0,07	54,51	54,44	0,07
9	219,46	219,46	0,00	219,46	219,43	0,03	219,46	219,39	0,07
10	37,66	37,66	0,00	37,63	37,66	−0 03	37,67	37,60	0,07
11	27,78	27,81	- 0,03	27,78	27,84	−0 06	27,74	27,81	−0,07
12	45,63	45,56	0,07	45,63	45,63	0,00	45,70	45 56	0,14
13	135,84	135,55	0,29	135,94	135,81	0,13	135,97	135 78	0,19
14	128,66	128,79	−0,13	128,60	128,66	−0,06	128.66	128 66	0,00
15	70,70	70,60	0,10	70,53	70,53	0,00	70,57	70,43	0,14
16	71,77	71,77	0,00	72,07	72,07	0,00	72,13	72,07	0,06
17	158,36	158,39	−0,03	159,18	159.18	0,00	159,83 (10,3)	159,76 (10,3)	0,07
18	114,59	114,59	0,00	115,05	115,08	−0,03	102,45 (25,0)	102 38 (25,0)	0,07
19	129,51	129,51	0,00	134,93	134,93	0,00	163,61 (245,6)	163,55 (245,6)	0,06
20	121,29	121,25	0,04	121,42	121,45	−0,03	108,10 (20,6)	108,04 (20,6)	0,06
21	129,51	129,51	0,00	130,29	130,29	0,00	130,32 (10,3)	130,26 (10,3)	0 06
22	114,59	114,59	0,00	113,09	113,12	−0,03	110.38 (3,0)	110,32 (2 9)	0,06
CO_2-CH_3	51,47	51,44	0,03	51,47	51,50	−0,03	51,50	51,44	0,06

Number of the carbon atom	Prostaglandin IVα	IVβ	$\Delta\delta_{\alpha-\beta}$	Prostaglandin Vα	Vβ	$\Delta\delta_{\alpha-\beta}$	VIα	Prostaglandin VIβ	$\Delta\delta_{\alpha-\beta}$
1	174,42	174,42	0.00	174,29	174,37	−0,08	174,29	174,35	−0,06
2	34,01	33,94	0,07	33,98	33,98	0,00	34,01	33,93	0,08
3	24,81	24,67	0,14	24,80	24,74	0,06	24,81	24,74	0,07
4	28 85	28,72	0.13	28,80	28,67	0,13	28,85	28,79	0,06
5	29,31	29,24	0,07	29,37	29 31	0,06	29,37	29,24	0,13
6	26,50	26.37	0 13	26,54	26,46	0,08	26,57	26,44	0,13
7	27,68	27 61	0 07	27,80	27,84	−0,06	27,81	27,68	0,13
8	54,44	54,44	0,00	54,43	54,48	−0,05	54,44	54,44	0,00
9	219,52	219,52	0,00	219,39	219 39	0,00	219,33	219,33	0,00
10	37,66	37,66	0,00	37,67	37,67	0,00	37,66	37,66	0,00
11	27,81	27,81	0.00	27,67	27,67	0,00	27,81	27,81	0,00
12	45,63	45 56	0,07	45,61	45,61	0,00	45,69	45,63	0,06
13	136,36	136,23	0,13	136,29	136 16	0,13	136.49	136,36	0,13
14	127,75	128,01	−0.21	127,91	128,08	−0,17	127,75	128,98	−0,23
15	70,89	70,89	0,00	71,01	71,0.	0,00	71,09	71,02	0,07
CO_2CH_3	51,50	51,50	0.00	51,45	51,47	0,02	51,44	51,44	0,00

Number of the carbon atom	Prostaglandin VIIα	VIIβ	$\Delta\delta_{\alpha-\beta}$	Prostaglandin VIIIα	VIIIβ	$\Delta\delta_{\alpha-\beta}$
1	174,29	174,34	−0,06	174.35	174,35	0,00
2	29,21	29,18	0,03	29,24	29,24	0,00
3	29,41	29,44	−0,03	29,24	29,24	0,00
4	29,41	29,44	−0,03	29,44	29,44	0,00
5	29,83	29,83	0,00	29,70	29,70	0,00
6	26.83	26,83	0,00	26,83	26,83	0,00
7	27,81	27,81	0,00	27,81	27.81	0,00
8	54,51	54,51	0,00	54,51	54,51	0,00
9	219,52	219.72	−0.20	219,33	219,40	−0,07
10	37,66	37,66	0,00	37,66	37,66	0,00
11	27,81	27,81	0,00	27,81	27,81	0,00
12	45,63	45,50	0,13	45,56	45,50	0 06
13	135,97	135,39	0,58	136,62	136,36	0.26
14	128,60	128,66	−0,06	127,61	127,61	0,00
15	70,76	70,43	0,33	71,02	70,89	0,13
16	71,81	71,81	0,00	78,59	78,46	0,13
17	158.36	158,36	0,00			

TABLE 1. (continued)

Number of the carbon atom	Prostaglandin VIIα	VIIβ	$\Delta\delta_{\alpha-\beta}$	Prostaglandin VIIIα	VIIIβ	$\Delta\delta_{\alpha-\beta}$
18	114,59	114,56	0,03			
19	129,51	129,51	0,00			
20	121,25	121,22	0,03			
21	129,51	129,51	0,00			
22	114,59	114,56	0,03			
1′	34,07	34,07	0,00	34,14	34,14	0,00
2′	24,94	24,94	0,00	24,94	24,94	0,00
3′	29,11	29,18	−0,07	29,24	29,24	0,00
CO_2CH_3	51,40	51,44	−0,04	51,44	51,44	0,00

Number of the carbon aton	Prostaglandin IXα	IXβ	$\Delta\delta_{\alpha-\beta}$	Prostaglandin Xα	Xβ	$\Delta\delta_{\alpha-\beta}$	Prostaglandin XIα	XIβ	$\Delta\delta_{\alpha-\beta}$
1	174,36	174,76	0,40	173,70	173,71	−0,01	174,38	174,35	0,02
2	22,78	22,85	−0,07	22,84	22,78	0,06	34,05	34,03	0,03
3	127,81	127,81	0,00	130,95	130,88	0,07	24,84	24,76	0,08
4	130,88	130,88	0,00	133,69	133,62	0,07	29,07	28,99	0,08
5	26,76	26,76	0,00	26,83	26,76	0,07	29,61	29,47	0,15
6	27,29	27,48	−0,19	27,48	27,35	0,13	27,06	26,98	0,08
7	27,29	27,35	−0,07	27,28	27,35	−0,07	28,09	28,01	0,08
8	54,31	54,38	−0,07	54,51	54,51	0,00	51,55	51,47	0,08
9	219,20	219,20	0,00	219,52	219,46	0,06	73,98	73,90	0,08
10	37,66	37,60	0,06	37,66	37,66	0,00	33,84	33,75	0,09
11	27,68	27,81	−0,13	27,87	28,00	−0,13	29,91	29,91	0,00
12	45,63	45,69	−0,06	45,50	45,56	−0,06	45,92	45,78	0,14
13	136,36	136,23	0,13	133,36	133,49	−0,13	138,10	137,73	0,37
14	127,81	127,94	−0,13	127,75	127,75	0,00	127,59	127,65	−0,06
15	70,95	70,89	0,06	71,61	71,69	−0,08	71,09	70,92	0,17
16				35,51	35,51	0,00	72,03	72,00	0,03
17				24,02	24,09	−0,07	158,53	158,48	0,05
18				155,55	155,55	0,00	114,70	114,65	0,05
19				104,97	104,97	0,00	129,55	129,49	0,06
20				110,12	110,12	0,00	121,20	121,15	0,05
21				140,87	140,93	0,06	129,55	129,49	0,06
22							114,70	114,65	0,05
1′	34,07	34,07	0,00	34,07	34,14	−0,07			
CO_2CH_3	51,57	51,57	0,00	51,57	51,57	0,00	51,55	51,47	0,08

Number of the carbon atom	Prostaglandin XIIα	XIIβ	$\Delta\delta_{\alpha-\beta}$	Prostaglandin XIIIα	XIIIβ	$\Delta\delta_{\alpha-\beta}$
1	174,34	174,35	−0,01	174,35	174,38	−0,03
2	34,08	33,81	0,27	33,98	33,98	0,00
3	24,87	24,76	0,11	24,81	24,71	0,10
4	29,04	28,93	0,11	28,98	28,92	0,06
5	29,79	29,75	0,04	29,54	29,44	0,10
6	27,03	26,98	0,05	26,99	26,96	0,03
7	28,06	28,01	0,05	28,07	27,97	0,10
8	51,58	51,53	0,05	51,56	51,57	−0,01
9	74,01	73,96	0,05	73,73	73,83	−0,10
10	34,08	34,03	0,05	35,51	35,48	0,03
11	29,90	29,91	−0,01	29,96	30,02	−0,06
12	45,94	45,89	0,05	45,76	45,63	0,13
13	138,54	138,38	0,16	136,07	135,71	0,36
14	126,78	126,84	−0,06	128,27	128,27	0,00
15	71,41	71,35	0,06	72,07	71,87	0,20
16				33,78	33,75	0,03
17				24,12	24,05	−0,07
18				155,72	155,75	−0,03
19				104,80	104,80	0,00
20				110,06	110,06	0,00
21				140,77	140,77	0,00
CO_2CH_3	51,58	51,53	0,05	51,44	51,47	−0,03

*No signals of C-16 and of the aryloxy substituents were observed because of splitting on the ^{19}F nuclei.

The introduction of a chlorine atom into the meta position of the aryloxy fragment [compound (II)] led to an increase in the number of signals of the aromatic ring in the spectrum because of the loss of a local axis of symmetry. The values of the diastereomeric effects for the transition from the (IIα) to the (IIβ) epimer were somewhat smaller than in the preceding case, but the main features were retained. In the epimeric pair (IIIα) and (IIIβ), the fluorine atom located in the meta position led to the splitting of the signals of the aromatic ring. The maximum value of the $^{13}C,^{19}F$ spin-spin coupling constant of 245.6 Hz was observed for the carbon atom linked directly to the fluorine atom and decreased with an increase in the number of separating bonds [6].

The introduction into the prostaglandin molecule of a perfluoroaromatic ring [compound (VI)] led to the practical disappearance of the signals of the C-16–C-22 atoms through splitting on the ^{19}F nuclei. For the same reason, the signals of the carbon atoms of perfluorinated naphthyloxy substituents in compounds (V) and (VI) disappeared.

In order to exclude concentration and temperature influences, the spectrum of the epimeric pair (V) was obtained in a 1:2 mixture of compounds (Vα) and (Vβ) on an instrument with a working frequency of 75.47 MHz. In this case, the error of the measurements was 0.01 ppm, while the value of the diastereomeric effects for the majority of the carbon atoms amounted to ±0.06-0.013 ppm. The greatest values of the effects were observed for the carbon atoms of the double bond. The signals of the carbon atoms of the cyclopropane fragment were less sensitive to isomerism of position 15. The retention in this case of the general laws of diastereomeric effects characteristic of the whole series of compound presented leads us to state on a sure foundation that the difference in the chemical shifts in the spectra of the α and β epimers is due to differences in the orientations of the C-15 hydroxy groups.

The presence of three additional groups in the α-chain of the prostaglandins (VII) and (VIII) leads to an increase in the number of signals and to the coincidence of some of them in the strong-field region. The diastereomeric effects for C-13 and C-15 were more pronounced than in the preceding cases, and practically no interaction of the α- and ω-chains was observed.

In compounds (IX) and (X), the double bond in the α-chain had the cis configuration, as was readily determined in the upfield shifts of the signals of the C-2 and C-5 atoms in comparison with the compounds considered above. The presence of a double bond in the α-chain led to negative values of the diastereomeric effects for the ω-chain, apparently because of a change in its conformation.

In the PGF_1 series (XI-XIII) there is an additional chiral center at C-9, which leads to a doubling of the number of possible stereoisomers. The selected strategy of synthesis [4] made it possible to obtain only the two desired diastereomers, which were isolated in the individual form by column chromatography. On the basis of the diagnostic C-13 and C-15 signals it was shown that the isomers obtained consisted of epimers differing by the configuration of the C-15 hydroxy group. To establish the configuration of the C-9 hydroxyl we used model compounds with the 9α and 9β configurations of the OH group [5]. The position of the C-9 signal in the strong-field region through cis-interaction with the α-chain (74 ppm) unambiguously indicated the 9α configuration of the hydroxy group. The observed values of the diastereomeric effects for the C-12–C-15 atoms practically coincided with those for the 9-keto analogs.

EXPERIMENTAL

^{13}C NMR spectra were recorded on a JEOL FX90Q spectrometer (22.5 MHz) with broad-band and incomplete suppression of coupling with protons. The solvent was $CDCl_3$, and the resolution of the ADC was 0.75 Hz. The spectrum of compound (V) was taken on a Bruker AM-300 spectrometer (75.47 Mz). The synthesis of the compounds has been described in [4].

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SYNTHESIS OF DODEC-5E-EN-1-OL — THE PHEROMONE OF TRICIMBA CINCTA — AND TETRADEC-5E-1-YL ACETATE — AN IMITATOR OF THE PHEROMONE OF RHYNCHOPACHA SP.

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On the basis of a modified Knoevenagel reaction starting from octanol and decanal, the stereodirected synthesis has been effected of dodec-5E-en-ol (the pheromone of the grass fly Tricimba cincta — and tetradec-5E-en-yl acetate) an imitator of the pheromone of the moth Rhynchopacha sp.

The attractant activity of dodec-5E-en-1-ol (I) for females of the grass fly Tricimba cincta (Diptera, Chloropidae) and of tetradec-5-en-1-yl acetate (II) for males of the moth Rhynchopacha sp. (Lepidoptera, Gelechiidae) has been established. The synthesis of these compounds based on the formation of an E-double bond on the opening of the cyclopropane rings in the corresponding alkyl cyclopropyl carbinols has been described [1].

Continuing investigations of the synthesis of alk-E-enols and their acetates on the basis of a modified Knevenagel reaction [2, 3], we propose a new approach to the synthesis of the attractants (I) and (II) (see scheme on following page).

The condensation of octanal (III) and decanal (IV) with malonic acid in boiling p-xylene in the presence of catalytic amounts of piperidine yielded dec-3-enoic (V) and dodec-3-enoic (VI) acids with yields of 68 and 70%, respectively. These acids were converted by the action of lithium tetrahydroaluminate in absolute ether into dec-3-en-1-ol (VII) and dodec-3-en-1-ol (VIII) with yields of 65 and 60%, respectively. The bromination of the latter with PBr_3 in ether in the presence of traces of pyridine gave 1-bromodec-3E-ene (IX) and 1-bromododec-3E-ene (X) with yields of 67 and 60%, respectively. The condensation of the bromides (IX) and (X) with malonic ester in n-butanol in the presence of sodium butanolate, as described in [4], led, after alkaline hydrolysis, to a mixture of dec-3E-enylmalonic acid (XI) and its monobutyl ester (XII) or a mixture of dodec-3E-en-1-ylmalonic acid (XIII) and its monobutyl ester (XIV).

Subsequent thermal decarboxylation in the presence of Ionol gave the corresponding mixtures of dodec-5E-enoic acid (XVI) and its n-butyl ester (XVI) and tetradec-5E-enoic acid (XVII) and its n-butyl ester (XVIII). The yield of the acid (XV) was 47.6%, calculated on the bromide (IX) and that of its n-butyl ester (XVI) 12.8%; the yield of the acid (XVII) calculated on the bromide (X) was 40.6%, and that of its ester 14.7%. Reduction of the mixtures (XV and XVI) and (XVII and XVIII) of the alk-E-enoic acids and their butyl esters with lithium tetrahydroaluminate gave dodec-5E-en-1-ol (I) and tetradec-5E-en-1-ol (XIX) with yields of 72 and 76.6%, respectively. Acetylation of the alcohol (XIX) gave the attractant (II) with a yield of 77.2%.

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