tion of the redistribution of the nucloephilic centers in the benzene ring. However, it must be observed that the changes in the charges on the atoms of the aromatic nucleus are fairly considerable and involve a migration of reaction centers. Consequently, on passing to excited S_1 and T_1 states the reaction properties of the phenolate anion will be different from those in the ground state – the positions of the nucleophilic centers in the benzene change, which leads to a change of the direction of attack of electrophilic reagents.

SUMMARY

The passage of ionized lignin chromophores (phenolate anions) into electronically excited state is accompanied by the transfer of negative charge between the individual functional groups and by a redistribution of the electron density in the aromatic ring, which leads to a change in the donor-acceptor properties of the excited phenolate anions of compounds modeling the structural unit of lignin and, consequently, to a change on their reactivity in electrophilic and nucleophilic reactions as compared with their ground thermodynamic state.

LITERATURE CITED

1. N. N. Shorygina, V. M. Reznikov, and V. V. Elkin, The Reactivity of Lignin [in Russian], Moscow (1976), p. 368.
2. V. M. Burlakov, D. D. Chuvashev, and G. V. Ratovskii, Theoretical Problems of New Methods of Delignifying Wood [in Russian], Bratsk, 1985, p. 23.
3. V. M. Burlakov, É. I. Chupka, D. D. Chuvashev, and G. V. Ratovskii, Cellulose Chem. Technol., No. 6, 651 (1986).
4. V. M. Burlakov, É. I. Chupka, D. D. Chuvashev, G. V. Ratovskii, and L. B. Maksimova, Khim. Prir. Soedin., 265 (1988) [in this issue].
5. M. J. S. Dewar, J. Am. Chem. Soc., 99, No. 15, 4899 (1977).
6. L. V. Vilkov, V. S. Mastryukov, and N. I. Sadova, Determination of the Electronic Structures of Free Molecules [in Russian], Leningrad (1978), p. 224.
7. V. V. Ershov, G. A. Nikiforov, and A. A. Volod'kin, Sterically Hindered Phenols [in Russian], Moscow (1972), p. 352.

^1H and ^{13}C NMR SPECTRA OF BIOLOGICALLY ACTIVE COMPOUNDS. III. DIASTEREOMERS OF (±)-7-THIA- AND 13-THIA-16-ARYLOXY ANALOGS OF 11-DEOXYPROSTAGLANDINS OF THE E_1 SERIES

L. M. Khalluov, A. A. Panasenko
E. V. Vasil'eva, N. A. Danilova,
Ya. L. Vel'der, and G. A. Tolstikov

UDC 543.422.25+547.915

The structure has been established and stereochemical assignments have been made of two complete sets of diastereomers of the 7-thia and 13-thia analogs of 11-deoxyprostaglandins of the E_1 series by the ^{13}C NMR method. It is proposed to determine the diastereomeric effects of the ^{13}C NMR chemical shifts, which are differential parameters bearing information on the stereochemistry of the molecules. Diagnostic diastereomeric effects have been found for assigning stereoisomers with respect to the C-15-hydroxy group and also with respect to the C-8 and C-12 chiral centers of the cyclopentane ring.

The introduction of a sulfur atom into the α- or ω-chain of a prostaglandin molecule may lead to considerable changes in its biological activity [2]. It is also known that the properties of prostaglandins depend substantially on the mutual configurations of the chiral centers [3].

Institute of Chemistry of the Bashkir Branch of the USSR Academy of Sciences, Ufa.

Translated from Khimiya Prirodnykh Soedinenii, No. 2, pp. 282-287, March-April, 1988. Original article submitted June 3, 1987; revision submitted September 29, 1987.

0009-3130/88/2402-0241$12.50

TABLE 1. Chemical Shifts and Multiplicities of the ^{13}C NMR Signals of Stereoisomers of 11-Deoxy-13,14-didehydro-13-thia-16-aryloxy-17,18,19,20-tetranorprostaglandins E_1 (I-VIII) (δ, ppm, $J_{^{13}C-^{19}F}$, Hz, $CDCl_3$)

C atom	I	II	III	IV
C-1	173,86 s	173,83 s	173,90 s	173,90 s
C-2	34,22 t	34,24 t	34,31 t	34,30 t
C-3	24,79 t	24,79 t	24,81 t	24,81 t
C-4	28,79 t	28,78 t	28,82 t	28,81 t
C-5	29,17 t	29,24 t	29,08 t	29,09 t
C-6	29,21 t	29,08 t	27,30 t	27,07 t
C-7	26,46 t	26,46 t	25,14 t	25,11 t
C-8	54,90 d	54,80 d	54,22 d	54,20 d
C-9	217,80 s	217,69 s	216,98 s	216,94 s
C-10	37,06 t	37,04 t	34,55 t	34,47 t
C-11	28,04 t	28,07 t	27,37 t	27,37 t
C-12	46,08 d	45,88 d	46,99 d	46,50 d
C-13				
C-14	34,22 t	34,18 t	34,31 t	34,47 t
C-15	69,59 d	69,24 d	69,67 d	68,87 d
C-16	70,24 t	70,24 t	70,28 t	70,33 t
C-17	158,30 s	158,30 s	158,33 s	158,36 s
C-18	114,46 d	114,46 d	114,53 d	114,53 d
C-19	129,51 d	129,51 d	129,57 d	129,54 d
C-20	121,22 d	121,22 d	121,32 d	121,32 d
C-21	60,21 t	60,18 t	60,23 t	60,22 t
C-22	14,22 q	14,22 q	14,26 q	14,26 q

C atom	V	VI	VII	VIII
C-1	173,86 s	173,80 s	173,90 s	173,88 s
C-2	34,27 t	34,24 t	34,27 t	34,26 t
C-3	24,81 t	24,77 t	24,81 t	24,80 t
C-4	28,82 t	28,82 t	28,82 t	28,81 t
C-5	29,24 t	29,21 t	29,24 t	29,25 t
C-6	29,24 t	29,11 t	29,24 t	29,12 t
C-7	26,47 t	26,47 t	26,50 t	26,51 t
C-8	54,93 d	54,80 d	54,96 d	54,83 d
C-9	217,57 s	217,60 s	217,77 s	217,73 s
C-10	37,11 t	37,08 t	37,18 t	37,08 t
C-11	28,10 t	28,10 t	28,13 t	28,11 t
C-12	46,22 d	45,89 d	46,18 d	45,97 d
C-13				
C-14	34,27 t	34,24 t	34,27 t	34,26 t
C-15	69,45 d	69,03 d	69,59 d	69,21 d
C-16	70,76 t	70,76 t	71,18 t	71,13 t
C-17	156,93 s	156,96 s	154,54 d(2)	154,56 d (2)
C-18	115,83 d	115,83 d	115,59 d (8)	115,57 d (8)
C-19	129,41 d	129,41 d	115,52 d(22)	115,90 d (23)
C-20	126,10 s	126,15 s	157,43 d(239)	157,45 d(239)
C-21	60,25 t	60,25 t	60,28 t	60,25 t
C-22	14,26 q	14,26 q	14,26 q	14,25 q

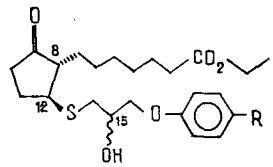
In the present paper we consider the influence of stereochemistry of the molecules of thia analogs of prostaglandins on the ^{13}C NMR spectral parameters. We have defined the difference in the chemical shifts (CSs) of monotypical carbon atoms in diastereomeric pairs A and B as the ^{13}C NMR diastereomeric effect:

$$\Delta_{\text{dias C-i}} = \delta_{\text{C-}i\text{ A}} - \delta_{\text{C-}i\text{ B}}.$$

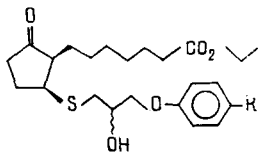
The presence of three chiral centers, C-8, C-12, and C-15 in 11-deoxy-13,14-didehydro-13-thia-16-aryloxy-17,18,19,20-tetranorprostaglandins E_1 should lead to the formation of eight enantiomers or four stereoisomers. In actual fact, a detailed analysis of the final product of synthesis by high-performance liquid chromatography (HPLC) showed the presence of four stereoisomers which were then isolated in the individual form, and the ^{13}C spectra of each of them were obtained. The CSs and multiplicities for all the signals for all the diastereomers (I-IV) are given in Table 1.

TABLE 2. Diastereomeric Effects of the ^{13}C NMR Chemical Shifts in a Series of Stereoisomers of 11-Deoxy-13,14-didehydro-13-thia-16-aryloxy-17,18,19,20-tetranorprostaglandins E_1 (I-VIII) $\Delta_{i\ dias}^{AB} = (\delta_{C\text{-}iA} - \delta_{C\text{-}iB})$ ppm

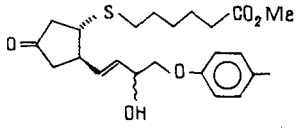
C atom	I–II	III–IV	I–III	II–IV	V–VI	VII–VIII
C-1	+0,03	0,00	−0,04	−0,07	+0,06	+0,02
C-2	−0,02	+0,01	−0,09	−0,06	+0,03	+0,01
C-3	0,00	0,0	−0,02	−0,02	+0,04	+0,01
C-4	+0,01	+0,01	−0,03	−0,03	0,00	+0,01
C-5	−0,07	−0,01	+0,09	+0,13	+0,03	−0,01
C-6	+0,13	+0,23	+1,91	+2,01	+0,13	+0,12
C-7	0,00	+0,02	+1,32	+1,36	0,00	−0,01
C-8	+0,10	+0,02	+0,68	+0,60	+0,13	+0,13
C-9	+0,11	+0,04	+0,82	+0,55	−0,03	+0,04
C-10	+0,02	+0,08	+2,51	+2,54	+0,03	+0,10
C-11	−0,03	0,00	+0,67	+0,70	0,00	+0,02
C-12	+0,20	+0,49	−0,91	−0,62	+0,33	+0,21
C-13						
C-14	+0,04	−0,16	−0,09	−0,29	+0,03	+0,01
C-15	+0,35	+0,80	−0,08	+0,37	+0,42	+0,38
C-16	0,00	−0,05	−0,04	−0,09	0,00	+0,05
C-17	0,00	−0,03	−0,03	−0,06	−0,03	−0,02
C-18	0,00	0,00	−0,07	−0,07	0,00	+0,02
C-19	0,00	+0,03	−0,06	−0,03	0,00	+0,02
C-20	0,00	0,00	−0,10	−0,10	−0,05	−0,02
C-21	0,03	+0,01	−0,02	−0,04	0,00	−0,03
C-22	0,00	0,00	−0,04	−0,04	0,00	+0,01



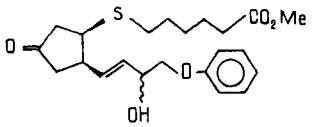
I, II, V–VIII



III, IV



IX, X



XI, XII

R=H (8R*, 15S*) (I), R=H (8R*, 15R*) (II),
R=H (8S*, 15S*) (III), R=H (8S*, 15R*) (IV),
R=Cl (8R*, 15S*) (V), R=Cl (8R*, 15R*) (VI),
R=F (8R*, 15S*) (VII), R=F (8R*, 15R*) (VIII).
(8S*, 15S*) (IX), (8R*, 15S*) (XI),
(8S*, 15R*) (X), (8R*, 15R*) (XII).

The signals of the carbons of the ketone carbonyl of the cyclopentanone fragment (216-217 ppm) and of the carboxy group (173 ppm) are observed in the weakest field. The aromatic carbon atoms resonate in the form of four signals in the 121-158 ppm region. Two doublet signals at 45-54 ppm characterize the methine carbon atoms C-8 and C-12 of the cyclopentanone ring. A triplet at 70 ppm and a doublet at 68-69 ppm characterize methylene and methine carbon atoms linked to oxygen atoms. Signals at 60 and 14 ppm relate to the ethoxy group. The other signals of methylene groups are located in the 24-37 ppm region.

The difference in the CSs of corresponding carbon atoms of the diastereomeric pairs (I), (II); (III), (IV); (I), (III); and (II), (IV), characterizing the diastereomeric effects are given in Table 2. The considerable positive value of the diastereomeric effects Δ_{dias} for C-6–C-11 in the isomeric pairs (I), (III), and (II), (IV) is caused by the existence of 1,2-cis interactions of the α and ω-chains of the cyclopentanone ring. The maximum value of Δ_{dias} amounts to 2.54 ppm for C-10. The negative value of Δ_{dias} for C-12 on passing from the 8,12-trans

TABLE 3. ^1H Chemical Shifts (δ, ppm) and Spin-Spin Coupling Constants $J_{H\text{-}A-H\text{-}B}$ (Hz) for Protons at C-14 and the ABX System of the Stereoisomers (I-IV)

Compound	$\delta_{H\text{-}A}$	$\delta_{H\text{-}B}$	$^2J_{H\text{-}A-{}'H\text{-}B}$	$^3J_{H\text{-}A-{}'H\text{-}15}$	$^3J_{H\text{-}B-{}'H\text{-}15}$
I	2 87	2,87	0	5,6	5,6
II	2,80	2,96	13,0	6,0	5,0
III	2,85	2,85	0	5,6	5,6
IV	2,80	2,92	13,0	6,0	4,5

TABLE 4. Chemical Shifts and Multiplicities of the ^{13}C NMR Signals of the Stereoisomers of 11-Deoxy-10-keto-16-phenoxy-7-thia-17,18,19,20-tetranorprostaglandin E_1 (IX-XII) (δ, ppm, $CDCl_3$)

C atom	IX	X	XI	XII
C-1	173,96 s	173,96 s	174,02 s	174,02 s
C-2	33,78 t	33,78 t	33,85 t	33,85 t
C-3	24,38 t	24,38 t	24,45 t	
C-4	29,28 t	29,24 t	29,15 t	29,11 t
C-5	28,23 t	28,23 t	28,36 t	28,33 t
C-6	31,37 t	31,33 t	31,50 t	31,46 t
C-7				
C-8	45,89 d	45,89 d	45,89 d	45,86 d
C-9	46,09 t	45,96 t	45,56 t	45,59 t
C-10	214,53 s	214,59 s	215,22 s	215,19 s
C-11	44,22 t	44,13 s	42,59 t	42,36 t
C-12	45,89 d	45,79 d	43,37 d	43,25 d
C-13	132,71 d	132,61 d	130,26 d	130,13 d
C-14	130,13 d	130,13 d	131,60 d	131,69 d
C-15	70,37 d	70,30 d	70,60 d	70,66 d
C-16	71,74 t	71,71 t	71,74 t	71,71 t
C-17	158,36 s	158,39 s	158,39 s	158,43 s
C-18	114,59 d	114,59 d	114,60 d	114,66 d
C-19	129,47 d	129,47 d	129,51 d	129,51 d
C-20	121,19 d	121,15 d	121,29 d	121,25 d
C-21	51,50 q	51,47 q	51,54 q	51,54 q
C-22				

to 8,12-cis stereochemical series apparently caused by the paramagnetic influence of the sulfur atom in the cis isomers proved to be unexpected. The diastereomeric effects in the stereoisomeric pairs (I), (II) and (III), (IV) due to stereochemical differences in the lateral ω-chain proved to be finer. As was to be expected, the most informative proved to be the positive magnitude Δ_{dias} = +(0.20-0.80) ppm for the C-12 and C-15 chiral centers, considerably exceeding the experimental error (0.03 ppm). The diastereomeric effect $\Delta_{dias\ C\text{-}6}$ = +(0.13-0.23 ppm) shows the steric interaction of the α and ω side chains, which depends on the orientation of the 15-hydroxy group.

A clear confirmation of the stereochemical assignments made was given by the characteristics of the ^1H NMR spectra, fragments of the AB part (C-14) of the ABX system of which are described in Table 3. For the 15α epimers ((I) and (III), threo isomers) the methylene protons at C-14 are observed in the form of a doublet due to interaction with the H-15 proton. In the case of the 15β epimers ((II) and (IV), erythro isomers), there is a loss of magnetic equivalence of the diastereotopic protons. In the ^1H NMR spectrum, both geminal and vicinal spin-spin coupling constants are observed.

The laws of the changes of the ^{13}C NMR chemical shifts as functions of the configuration of the 15-hydroxy group that have been found are also valid for the stereoisomeric pairs with para-Cl (V and VI) and para-F (VII and VIII) substitution of the phenoxy group.

The next objects selected for the investigation of spectrochemical correlations consisted of the quartet of stereoisomers of the 10-keto-16-phenoxy-7-thia analog of PGE_1. Elimination of the keto group in the C-10 position from the upper side chain creates certain difficulties in the assignment of the signals of the C-8, -9, -11, and -12 atoms, which are present in an extremely narrow CS interval (42-46 ppm) (Table 4). In spite of this, a knowledge of the

TABLE 5. Diastereomeric Effects of the ^{13}C Chemical Shifts in the Series of Stereoisomers of 11-Deoxy-10-keto-6-phenoxy-7-thia-17,18,19,20-tetranorprostaglandin E_1 (IX-XII) $\Delta_{i\ dias\ AB} = (\delta_{C\text{-}i\ A} - \delta_{C\text{-}i\ B})$ (ppm)

C atom	IX–X	XI–XII	IX–XI	X–XII
C-1	0,00	0,00	−0,06	−0,06
C-2	0,00	0,00	−0,07	−0,07
C-3	0,00	0,00	−0,07	−0,07
C-4	+0,04	+0,04	+0,09	+0,13
C-5	0,00	+0,03	−0,13	−0,10
C-6	+0,04	+0,04	−0,17	−0,13
C-7	—	—	—	—
C-8	0,00	+0,03	0,00	+0,03
C-9	+0,13	−0,03	+0,53	+0,37
C-10	−0,06	+0,03	−0,69	−0,60
C-11	+0,09	+0,23	+1,63	+1,77
C-12	+0,10	+0,12	+2,52	+2,54
C-13	+0,10	+0,13	+2,45	+2,48
C-14	0,00	−0,09	−1,47	−1,56
C-15	+0,07	−0,06	−1,23	−0,36
C-16	+0,03	+0,03	0,00	0,00
C-17	−0,03	−0,04	−0,03	−0,04
C-18	0,00	−0,06	−0,01	−0,07
C-19	0,00	0,00	−0,04	−0,04
C-20	+0,04	+0,04	−0,10	−0,10
C-21	+0,03	0,00	−0,04	−0,07

general laws and the availability of the spectra of all four individual stereoisomers, separated by the HPLC method, permitted a clear identification of the stereochemistries of the α and ω-chains and also of the orientation of the 15-OH group.

The C-11, C-12, and C-13 signals, the strong-field values of which indicate that compounds (XI) and (XII) are 8,12-cis isomers, were used as diagnostic characteristics for assignment to the cis or the trans stereochemical series in relation to C-8 and C-12.

The values of the diastereomeric effects on passing from the trans to the cis stereochemical series was a maximum for C-12. The practical absence of effects for the methine atom, C-8 linked to the sulfur atom (compare $\Delta_{dias\ C\text{-}12}$) in (IX-XII) proved to be unexpected, and so did the negative value of the effect (−0.60 ppm) for the C-10 carbonyl atom.

The differences in the diastereomeric pairs (IX), (X), and (XI), (XII), with unlike orientations of the hydroxy group, proved to be finer. It must be mentioned that the signal of the C-15 chiral center differed on passing from one stereoisomer to the other by not more than 0.07 ppm, which is within the limits of the errors of measurement. The C-13 signals [4] and also the positive values of the C-11 and C-12 diastereomeric effects on passing from the 15α epimers (IX, XI) to the 15β epimers are more informative.

EXPERIMENTAL

The ^{13}C NMR spectra were taken on a JEOL FX-90-Q (22.5 MHz) spectrometer with broad-band and off-resonance decoupling from protons. ^1H NMR spectra were recorded on a Tesla BS 567 (100 MHz) spectrometer with stabilization of the field on the deuterium of the solvent. The solvent used was $CDCl_3$, and the internal standard TMS.

The synthesis of the (±)-7-thia- and 13-thia-16-aryloxy analogs of the 11-deoxyprostaglandins of the E_1 series have been described elsewhere.

SUMMARY

1. The structures have been established and stereochemical assignments have been made of two complete sets of diastereomers of 7-thia and 13-thia analogs of 11-deoxyprostaglandins of the E_1 series by the ^{13}C NMR method.

2. A definition of the diastereomeric effects of ^{13}C NMR chemical shifts, which are differential parameters bearing stereochemical information on the molecule, has been proposed.

3. Diagnostic diastereomeric effects have been found for the assignment of stereoisomers at the C-15 hydroxy group, and also at the C-8 and C-15 chiral centers of the cyclopentane ring.

LITERATURE CITED

1. G. A. Tolstikov, L. M. Khalilov, A. A. Panasenko, N. A. Danikova, and M. S. Miftakhov, Khim. Prir. Soedin., 610 (1985).
2. L. Novak, P. Kolonits, and C. S. Czantay, Tetrahedron, 38, 153 (1982).
3. T. Pekhk, T. Vilimyaé, and N. Samel', Izv. Akad. Nauk ESSR, Khimiya, 31, 85 (1982).
4. G. A. Tolstikov, L. M. Khalilov, A. A. Panasenko, F. A. Valeev, and M. S. Miftakhov, Khim. Prir. Soedin., 315 (1985).
5. G. A. Tolstikov, M. S. Miftakhov, N. A. Danilova, and O. V. Shitikova, Zh. Org. Khim., 72, Vol, 6, 1204 (1986).

^1H AND ^{13}C NMR SPECTRA OF BIOLOGICALLY ACTIVE COMPOUNDS.

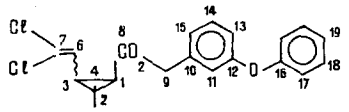
IV. DIASTEREOMERS OF PYRETHROIDS AND THEIR INSECTICIDAL ACTIVITY

G. A. Tolstikov, L. M. Khalilov,
F. Z. Galin, E. V. Vasil'eva,
D. B. Amirkhanov, M. G. Migranov,
and A. A. Panasenko

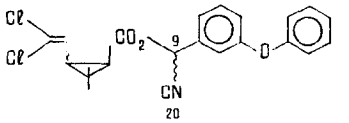
UDC 543.422.25+632.951.2

The stereochemistry of the diastereomers of permethrin has been confirmed by ^{13}C NMR spectroscopy and the stereochemistry of the 9-CN derivative (cypermethrin) has been established. Diagnostic values of the diastereomeric effects have been determined for identifying diastereomers with respect to the cyclopropane ring and to the gem-dimethyl groups. It has been shown that the insecticidal activity of pyrethroids depends both on the stereochemistry of the cyclopropane fragment and on the orientation of a CN substituent in the side chain.

Synthetic pyrethroids are a new class of highly effective insecticides, with a low toxicity for warm-blooded animals, that do not pollute the environment [2]. For the majority of pyrethroids, the cyclopropane ring is the main fragment of the acid component the stereochemistry of which determines insecticidal activity [3]. In addition, the presence of chiral centers in the alcoholic component increases the number of possible stereoisomers.



Ia (1R*, 3S*)
Ib (1R*, 3R*)



IIa (1R*, 3S*, 9S*)
IIb (1R*, 3R*, 9S*)
IIc (1R*, 3S*, 9R*)
IId (1R*, 3R*, 9R*)

The ^{13}C NMR spectra of some synthetic pyrethroids and, in particular, permethrin, have been described previously [4]. In order to study the dependence of the insecticidal activity on the stereochemistry of the pyrethroids, we have obtained the ^{13}C and ^1H NMR spectra of m-phenoxybenzyl 3-(7,7-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylate (permethrin, (Ia, b) and α-cyano-m-phenoxybenzyl 3-(β,β-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylate (cypermethrin IIa, b, c, d).

Permethrin (Ia, b) consists of a mixture of two enantiomeric pairs, 1R,3S and 1S,3R (1R*, 3S*) (Ia) and 1R,3R and 1S,3S (1R*,3R*) (Ib), and cypermethrin of a mixture of four entiomeric pairs:

1R, 3S, 9S and 1S, 3R, 9R (1R*, 3S*, 9S*) (IIa),
1R, 3R, 9S and 1S, 3S, 9R (1R*, 3R*, 9S*) (IIb),
1R, 3S, 9R and 1S, 3R, 9S (1R*, 3S*, 9R*) (IIc),
1R, 3R, 9R and 1S, 3S, 9S (1R*, 3R*, 9R*) (IId)

Institute of Chemistry and Division of Biochemistry and Phytochemistry, Bashkir Branch, USSR Academy of Sciences, Ufa. Translated from Khimiya Prirodnykh Soedinenii, No. 2, pp. 287-292, March-April, 1988. Original article submitted July 16, 1987; revision submitted September 29, 1987.

 0009-3130/88/2402-0246$12.50