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

IV. DIASTEREOMERS OF PYRETHROIDS AND THEIR INSECTICIDAL ACTIVITY

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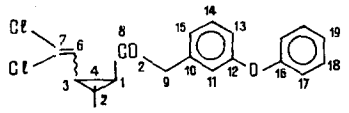
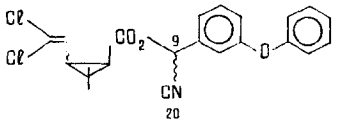
The stereochemistry of the diastereomers of permethrin has been confirmed by ^{13}C NMR spectroscopy and the stereochemistry of the 9-CN derivative (cypermethrin) has been established. Diagnostic values of the diastereomeric effects have been determined for identifying diastereomers with respect to the 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)

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TABLE 1. Parameters of the ^{13}C NMR Spectra of the Stereo-Isomers of Permethrin (Ia, b) and Cypermethrin (IIa-d) (δ, ppm, $CDCl_3$, 25°C)

C	Ia	Ib	IIa	IIb	IIc	IId
C-1	31,78d	32,93d	30,93d	33,75d	30,96d	33,81d
C-2	27,66s	29,02s	28,69s	30,15s	28,82s	30,26s
C-3	32,70d	34,56d	33,37d	33,83d	33,20d	33,89d
C-4	14,95q	20,01q	14,78q	19,94q	14,71q	19,99q
C-5	28,34q	22,49q	28,01q	22,32q	28,01q	22,35q
C-6	124,80d	126,83d	124,02d	126,03d	123,97d	126,08d
C-7	120,77s	122,00s	121,96s	122,99s	121,69s	123,18s
C-8	170,21s	170,70s	168,40s	169,12s	168,42s	169,15s
C-9	65,75t	65,90t	62,23d	62,47d	62,28d	62,63d
C-10	137,95s	137,90s	133,64s	133,64s	133,42s	133,69s
C-11	118,25d	118,15d	117,49d	117,46d	117,62d	117,71d
C-12	157,52s	157,45s	158,10s	158,12s	158,04s	158,23s
C-13	118,41d	118,35d	120,01d	120,04d	119,98d	120,12d
C-14	129,90d	129,80d	130,58d	130,58d	130,55d	130,58d
C-15	123,45d	123,41d	123,72d	124,04d	123,86d	124,04d
C-16	156,90s	156,80s	156,15s	156,17s	156,15s	156,34s
C-17	119,03d	118,97d	119,31d	119,33d	119,25d	119,33d
C-18	129,79d	129,70d	129,93d	129,95d	129,90d	129,95d
C-19	122,67d	122,59d	121,96d	121,93d	122,02d	122,07d
C-20			115,84s	115,81s	115,95s	115,95s

TABLE 2. Diastereomeric Effects in the ^{13}C NMR Spectra of Permethrin (Ia, b) and Cypermethrin (IIa-d), $\Delta_{dias\ a,b} = \delta_{cia} - \delta_{Cib}$ (ppm)

Ci	Δ_{dias} Ib,a	Δ_{dias} IIb,a	Δ_{days} IId,b	Δ_{dias} IIc,a	Δ_{dias} IId,b
C-1	1,15	2,82	2,85	0,03	0,06
C-2	1,36	1,46	1,44	0,13	0,11
C-3	1,86	0,46	0,60	—0,08	0,03
C-4	5,06	5,16	5,28	—0,07	0,05
C-5	—5,85	—5,69	—5,66	0,00	—0,03
C-6	2,03	2,01	2,11	—0,05	0,05
C-7	1,23	1,03	1,49	—0,27	—0,19
C-8	0,49	0,72	0,73	0,02	0,03
C-9	0,15	0,24	0,35	0,05	0,16
C-10	—0,05	0,00	0,27	—0,22	0,05

The enantiomeric pairs or diastereomers (Ia, b) and (IIa, b, c, d) were isolated by high-performance liquid chromatography in the individual form, and the ^{13}C NMR spectra (Table 1) and ^{1}H NMR spectra (Table 2) of each of them were obtained.

The ^{13}C spectra of the stereoisomers (Ia) and (Ib) contained all the characteristic signals corresponding to a carboxy group (170.21, 170.70 ppm) and two aromatic and olefinic carbons (118-157 ppm), two doublet (31-34 ppm) and a singlet (27-29 ppm) signals for a penta-substituted (sic) cyclopropane ring, and quartet signals of methyl groups in the strongest fields (14-28 ppm). The most informative for the stereochemical difference were the signals of the gem-dimethyl groups. The existence of two cis-interactions in isomer (Ia) for one of the methyl groups (C-4) led to a substantial diamagnetic shift of the signal in the spectrum relative to the signal of the other methyl group (δ C-5 = 28.34 ppm) [4].

In the case of isomer (Ib), for each methyl group there was one cis-interaction, thanks to which the values of the chemical shifts (CSs) differed by less than 3 ppm [5]. The greatest stereochemical difference were observed for the signals of the carboxy groups (0.5 ppm) and the α-C atom of the dichlorovinyl (2.0 ppm). The signals of the carbon atoms of the cyclopropane ring also underwent diamagnetic shifts of from 1 to 2 ppm in the sterically more stressed structure (Ia) with the cis-configuration of the substituents.

For compound (II), the presence of the nitrile group at the benzyl α-carbon atom led to the appearance of an additional, third, chiral center and to an increase in the number of stereoisomers to four (a-d).

TABLE 3. Parameters of the ^1H NMR Spectra of the Diastereomers (Ia, b) and (IIa-d) (δ, ppm; $^3J_{^1H-^1H}$, Hz, $CDCl_3$, 25°C)

H*l*	Ia	Ib	IIa	IIb	IIc	IId
HC-1	1,87, d, 8,0	1,64, d, 5,0	1,89, d, 9,0	1,67, d, 5,2	1,88, d, 8,4	1,65, d, 5,6
HC-3	2,04, t, 8,0	2,24, d, 9,0, d, 5,0	2,15, t, 9,0	2,31, d, 8,0, d, 5,2	2,12, t, 8.4	2,27, d, 8,0, d, 5,6
HC-6	6,25, d, 8,0	5,60, d, 9,0	6,18, d, 9,0	5,61, d, 8.0	6,17, d, 8,4	5,59, d, 8,0
HC-9	5,06, s	5,09, s	6,36, s	6,38, s	6,31, s	6,37, s
PhOPh	6,97—7,45, m	6,98—7,48, m	6,97—7,45, m	6,98—7,50, m	6,97—7,46, m	6,97—7,52, m
Me-4	1,23, s	1.26 s	1,23, s	1.23, s	1,23 s	1,32, s
Me-5	1,23, s	1,17, s	1,18, s	1,16, s	1,27, s	1,22, s

TABLE 4. Biological Activity of Permethrin (Ia, b), and of Cypermethrin (IIa-d) in Relation to Colorado Beetle Imagoes

Compound	LD_{50}, μg/g	Confidence interval (P = 0.05)	Relative toxicity, %
Mixture of the isomers (Ia):(Ib) = 1:1	0,244	0,194—0,308	100
Ia	0,044	0,0338—0,0572	554
Ib	0,498	0,376—0,660	49
Mixture of the isomers (IIa)-(IId).	0,0457	0,0364—0,0574	100
IIa	0,0129	0,0104—0,0160	354
IIb	0,0378	0,0307—0,0465	121
IIc	0,0641	0,0402—0,1020	71
IId	0,281	0,187—0,424	16

The stereochemical difference in the isomeric pairs (IIa), (IIb), and (IIc), (IId), are due to the cis- and trans-orientations of the substituents at C-1 and C-3 and are easily determined from the diagnostic signals of the gem-dimethyl groups in the same way as for stereoisomers (Ia) and (Ib) (Table 1). The changes in the spectra characterizing the orientation of the nitrile group relative to the C-1 chiral center are finer. On comparing the spectra of the stereoisomeric pairs (IIa), (IIc), and (IIb), (IId) it can be observed that the small diamagnetic shifts of the C-2 signal (from 0.11 to 0.13 ppm) are stable and determine the stereochemistry of the nitrile group. Thus, in the case of isomers (IIa) and (IIb) we are dealing with a RS and a SR enantiomeric pair in which the erythro-interaction of the nitrile group with the most substituted, C-2, atom of the cyclopropane ring causes diamagnetic shifts of this signal in comparison with RR and SS enantiomeric pairs in the threo isomers (IIc) and (IId).

The values of the direct carbon-proton spin-spin coupling constants (SSCCs) depend weakly on the stereochemistry of the molecule. Thus, for example, for C-9 $^1J_{^{13}C-^1H}$ (147.8 ± 0.5) Hz (Ia, Ib); (154.4-155.0) Hz (IIa-IId). Table 2 gives the values of the diastereomeric effects of the ^{13}C chemical shifts due to the differences of the screening of the corresponding carbon atoms in the diastereomeric pairs. An analysis of this table permits an evaluation of the degree to which each signal is diagnostic for stereochemical assignments. Such parameters in the identification of the 1,3-diastereomers are the positive value of the diastereomeric effects for C-1—C-4 and the negative value for C-5 on passing from the 1,3-trans- to the 1,3-cis-isomeric pairs (C-4 and C-5 being the carbon atoms of the two 2-methyl groups). As already mentioned, a diagnostic parameter for identifying the stereochemistry of the nitrile group is the maximum positive value of the diastereomeric effect at C-2 on passing from the 9S-CN threo epimers to the 9R-CN erythro epimers.

The results obtained by the ^{13}C NMR method agree completely with those of ^1H NMR (Table 3). In this case the more suitable for diagnosis are not the CSs of the gem-dimethyl groups but the values of the vicinal SSCCs $^3J_{^1H-^1H}$ of the cyclopropane protons at C-1 and C-3. Thus, for the 1,3-cis isomers the value of this constant amounts to from 8.0 to 9.0 Hz, while in the 1,3-trans isomers it is 5.0-5.6 Hz [6].

The signals of the protons of the gem-dimethyl groups, unlike those from the carbon atoms, are close to one another in the 1,3-cis isomers (from 0.1 to 0.05 ppm) and in the 1,3 trans-isomers (from 0.7 to 0.10 ppm).

Apparently, in proton spectroscopy the steric effects may be masked by the effects of the anisotropy of the bonds, etc., and therefore they cannot be used to the same extent as ^{13}C NMR in making stereochemical assignments.

Informative parameters for stereochemical control are the diamagnetic shifts of the signals of the protons of the gem-dimethyl groups on passing from the erythro isomers (IIa and b) to the threo isomers (IIc and d). The individual stereoisomers of permethrin (Ia, Ib) and of cypermethrin (IIa-d) and mixtures of them in various ratios were subjected to toxicological evaluation for insecticidal activity on Colorado beetle imagoes (Table 4).

The trials showed that the greatest insecticidal activity of the individual permethrin compounds (Ia, b) was possessed by cis-permethrin (Ia), which was 11.3 times more active than trans-permethrin (Ib) and 5.5 times more active than a mixture of (Ia) + (Ib) in a ratio of 1:1.

The insecticidal evaluation of the individual cypermethrin compounds (IIa-d) showed that the greatest activity was possessed by compounds (IIa) and (IIb). Thus, for example, compound (IIa) was 5 times more effective than compound (IIc), and compound (IIb) was 7.5 times more effective than compound (IId). Consequently the insecticidal efficacy of cypermethrins is determined primarily by the presence of compounds (IIa) and (IIb), but (IIa) is three times more active than (IIb). It is interesting to note the higher biological activity of compound (IIa) than of compound (Ia).

EXPERIMENTAL

^{13}C NMR spectra were recorded on a JEOL FX 90 Q (22.5 MHz) spectrometer with broad-band off-resonance suppression in relation to proteins and in the "monoresonance" regime. The solvent used was $CDCl_3$, and the standard was TMS. The field scan was 5000 Hz, and the resolution of the ADC was 0.6 Hz.

^{1}H HMR spectra were recorded on a Tesla BS 567 (100.0 MHz) spectrometer in the pulsed regime with Fourier transformation. The solvent was $CDCl_3$ and the standard TMS. The resolution of the ADC was 0.3 Hz.

The compounds were synthesized as described in [7].

The insecticidal activities of permethrin and cypermethrin and their stereoisomers were evaluated on imagoes of the Colorado beetle Leptinotarsa decemlinenta Say taken from a natural population. The mean weight of the beetles was 151.5 mg. The beetles were treated by the topical method [8] with ethanolic solutions of the insecticides in a dose of 1 μl per individual. Each compound was tested in six concentrations with a dilution factor of 2. The cutting-off concentrations for each compound were selected on the basis of preliminary experiments. Beetles treated with ethanol in the same dose were used as controls. The deaths of the pests were counted 72 h after treatment. The insecticidal activities of the compounds were evaluated from the LD_{50} (mean lethal dose) index: the dose of insecticide causing on a single application the deaths of 50% of individuals of a group of homogeneous organisms. The LD_{50} values were calculated by the Miller-Tainter method of probit analysis [9].

SUMMARY

1. The stereochemistry of the diastereomers of m-phenoxybenzyl 3-(β,β-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylate (permethrin, Ia, b) has been studied by ^{13}C NMR spectroscopy, and the stereochemistry of the diastereomers of the derivative with a CN group in the α-benzyl position (IIa-d) has been established.

2. The diagnostic values of the diastereomeric effects ($\Delta_{dias}\ C_2$) for identifying stereoisomers with respect to the cyclopropane ring of the side chain of pyrethroids in the ^{13}C NMR spectra and of the diamagnetic chemical shifts of the protons of the gem-dimethyl group in the erythro isomers have been determined.

3. It has been shown that insecticidal activity in pyrethroids depends both on the stereochemistry of the cyclopropane fragment of the molecule (the acid component) and on the orientation of a CN-substituent in the side chain (alcoholic component).

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