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STEREOCHEMICAL STRUCTURES OF PYRETHROSIN, CYCLOPYRETHROSIN ACETATE AND ISOCYCLOPYRETHROSIN ACETATE

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Absolute stereoformulas Ia and IIa have been proposed for pyrethrosin and its acid cyclization product cyclopyrethrosin acetate, respectively, by Barton et al.(1). The NMR spectrum of cyclopyrethrosin acetate*, m.p. 175°, which was prepared from pyrethrosin in our laboratory according to their method, however, revealed it to be a (1:1) mixture** of two components bearing a close resemblance. Therefore, the substances were subjected to a reinvestigation.

Repeated crystallizations or silica gel adsorption chromatography of cyclopyrethrosin acetates+ (II) hardly affected the ratio of the components. However, the dihydro-derivatives (III) obtained by hydrogenation of II over palladised charcoal or nickel boride catalyst(2), gave a (1:2) mixture, m.p. 183-185°, after seven times recrystallization, and a (2:1) mixture, m.p. 166-168°, from the mother liquor of the first recrystallization++. Treatment of a (2:3) mixture of the diacetates (III) with aqueous sodium hydrogen carbonate gave a (3:5) mixture of monoacetates (IV), m.p. 205-206°, which was then

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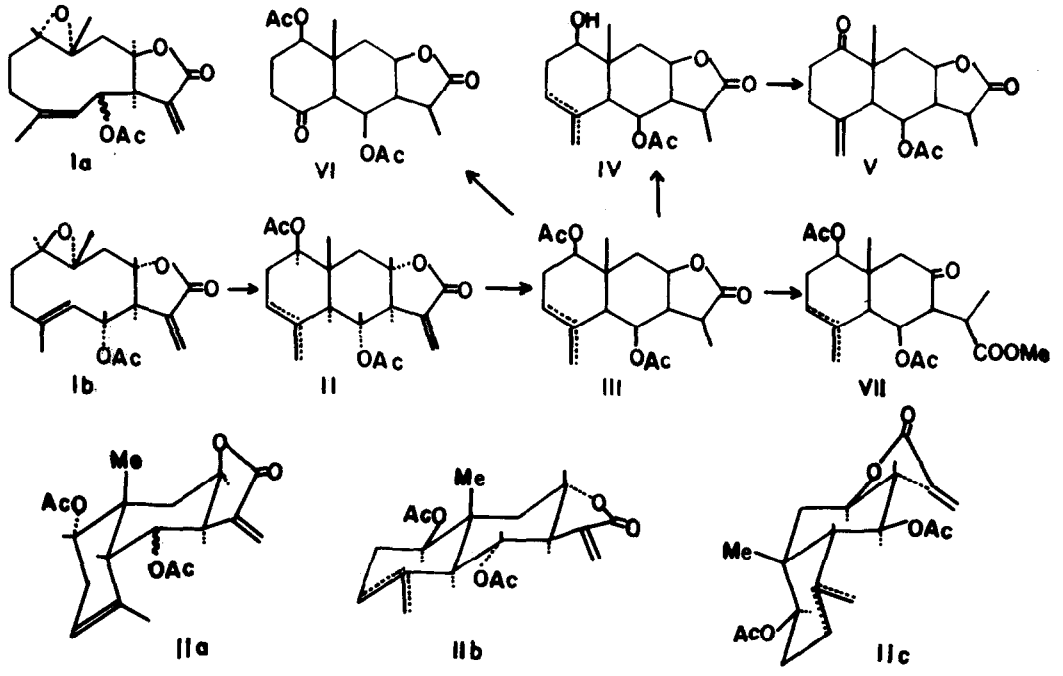
* The identity of our sample of cyclopyrethrosin acetate was confirmed by m.p. and IR spectra with the authentic specimen kindly sent us from Prof. Barton whom we acknowledge.

** The ratio of the components was determined by the intensity ratio of the NMR signals due to angular methyl groups. The NMR spectra were measured on JNM-4H-100 spectrometer(100 Mc) in $CDCl_3$ solution with TMS serving as internal reference. The chemical shift is expressed in δ(p.p.m.) and the coupling constant(J) in c.p.s.

\+ The suffix "s" denotes a mixture.

++ A comparison of the NMR spectra of cyclopyrethrosin acetates and their dihydro-derivatives indicated that the hydrogenation of the former to the latter compounds had probably occurred in a stereospecific manner.



oxidized with chromic acid. The product was isolated and filtered through acid-treated alumina in benzene-hexane(7:3) to afford a keto-acetate, m.p. 168-168.5°, which was clearly a single compound on the basis of its NMR spectrum. In the spectrum, a pair of one-proton singlets which is assigned to the exomethylene protons unconjugated with the γ-lactone was clearly observed at δ5.08 and 4.65. This suggests that the compound is an isomer which should be designated as isoketoacetate(V) containing $\Delta^{4(15)}$, instead of Δ^{3} in the cyclopyrethrosin acetate series which was described by Barton et al. Further, the lowest one-proton triplet(J=10) at δ5.37 which is assigned to a proton(H-6) attached to carbon carrying the acetoxyl group shows that H-6 is an axial proton coupled with two axial protons. A one-proton sextet (J=4, 11.5 and 11.5) at δ4.03 which is due to a proton(H-8) on carbon bearing the lactone ether oxygen indicated that H-8 is an axial proton flanked by two axial and one equatorial protons. Thus four hydrogens, H-5, H-6, H-7 and H-8, in V were all demonstrated to be in trans diaxial relationship with each other.

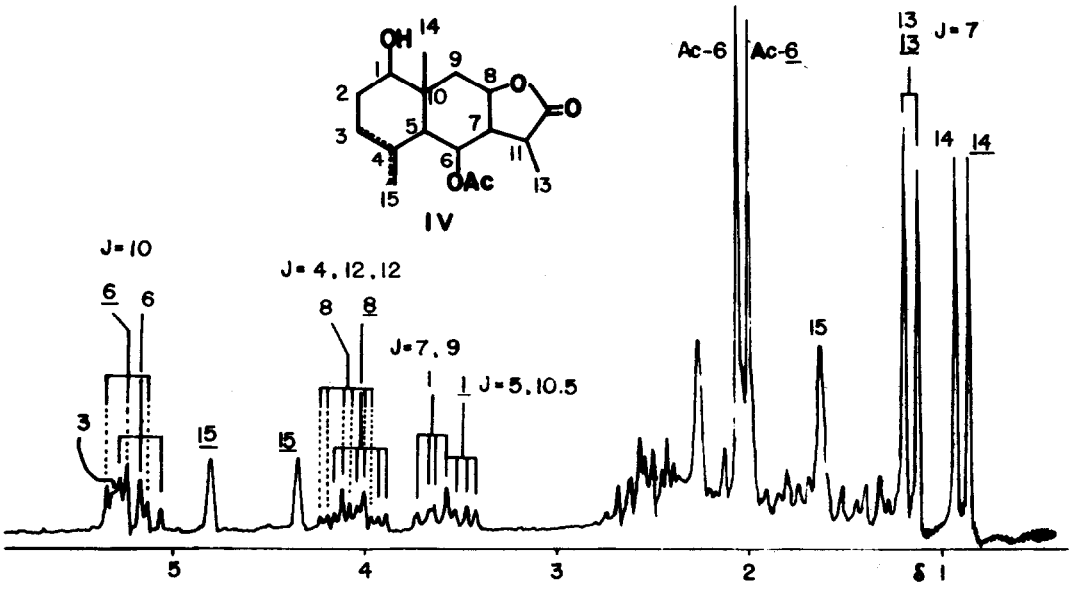


FIG. 1

100 Mc NMR Spectrum of a (1:1) Mixture of Monoacetate(Δ^3) and Isomonoacetate($\Delta^{4(15)}$)(IV)*.

When the dihydro-compounds(III), the NMR spectrum of which indicated the absence of the exomethylene conjugated with the γ-lactone, was ozonised in ethanol-free chloroform and steam distilled, formaldehyde was obtained as the dimedone-derivative in 18% yield, while Barton et al. have described that the dihydro-compound did not give a significant amount of formaldehyde. The neutral part of the residue after steam distillation was chromatographed on alumina to afford the norketone(VI), m.p. 213-214.5°, derived from the dihydro-iso-compound. The NMR spectrum of VI not only supported the above evidence obtained from the spectrum of V, but also revealed that the one-

* Figures not underlined belong to Δ^3-isomer and those underlined belong to $\Delta^{4(15)}$-isomer. In a (3:5) mixture the signals of the underlined figures become stronger. The superimposed signals of H-8 and H-8 are observed in an intensity ratio of (1:1:1:3:2:2:3:1:1:1) which is in complete agreement with the expected value.

proton quartet(J=5.5 and 11.5) at δ5.10 should be assigned to H-1 which is an axial proton adjacent to methylene protons(one axial and one equatorial).

A comparison of the NMR spectrum of a (1:1) mixture of IV with that of its (3:5) mixture permitted the assignment illustrated in FIG. 1 which clearly showed that the above results obtained from the NMR spectra of the iso-series are also applicable to the cyclopyrethrosin acetate series except for double bond position. Thus cyclopyrethrosin acetates are concluded to be a (1:1) mixture of cyclopyrethrosin acetate containing Δ^3 and $\Delta^{4(15)}$-isomer designated as isocyclopyrethrosin acetate. This conclusion is reasonable in view of the cyclization mechanism of pyrethrosin suggested by the previous authors and is also well supported by a close and comparative examination of the 100 and 60 Mc NMR spectra of cyclopyrethrosin acetates(II) and dihydrocyclopyrethrosin acetates(III). As the solubility of the $\Delta^{4(15)}$-isomer is smaller in the case of III, the mixture rich in $\Delta^{4(15)}$-isomer has been obtained after recrystallization.

Absolute β-orientation of the angular methyl in II has been established by Barton et al. through the correlation of II with ψ-santonin. This fact together with the evidences cited above leaves only two possible stereoformulas IIb(trans form) and IIc(nonsteroid-like cis form) for cyclopyrethrosin acetates, excluding the possibility of IIa(steroid-like cis form) presented earlier by them.

Norketone(VI) and 8-keto-esters(VII), m.p. 113-116.5°, which was prepared according to the method of the above authors both exhibited a strong negative Cotton effect(molecular amplitude: a= -51 and -37, respectively). This indicates that the structure of cyclopyrethrosin acetates is IIb rather than IIc, because the octant rule(3) predicts that VI and VII derived from IIb will show a strong negative Cotton effect while the ketones from IIc would exhibit a positive Cotton effect*.

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* As the norketone derived from IIa is predicted to show a positive Cotton effect, the structure IIa is again denied. The possibility that a cis norketone from IIa may have been isomerized to the stable trans form is easily excluded by the NMR spectra.

Further an angular proton(H-5) of VI which is observed at δ2.66 as a doublet(J=10) in $CDCl_3$ is shifted to higher field by 0.67 ppm in benzene. This observation showing that H-5 is an axial proton adjacent to a ketone in the cyclohexanone ring of VI(4) is compatible with the above conclusion based on ORD data. Thus IIb is the most favourable structure for cyclopyrethrosin acetates.

β-Configuration of the acetoxyl group at C-1 in IIb is in disagreement with the proposal of the previous authors in which α-orientation has been presented on the basis of the molecular-rotation difference method(5). Since the NMR and ORD data usually present more direct and reliable evidence than the molecular-rotation method, we consider that the configuratio of the asymmetric centers of cyclopyrethrosin acetates should be represented by IIb and accordingly, that of pyrethrosin by Ib* in taking account of the mechanism of the cyclization reaction.

Geometry of the endocyclic double bond in pyrethrosin is not determined in our experiment.

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* It is noted that our structure(Ib) for pyrethrosin contains a trans epoxy contrary to a cis epoxy in the previous structure(Ia). Incidentally, the presence of a trans epoxy was recently established by X-ray analysis(6) in heliangine, a ten-membered sesquiterpene lactone similar to pyrethrosin.

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