Tetrahedron, 1966, Vol. 22, pp. 277 to 284. Pergamon Press Ltd. Printed in Northern Ireland

VITAMIN A ANALOGUES—III*

DETERMINATION OF THE STEREOCHEMICAL CONFIGURATION OF SOME POLYENES OF THE 4-THIA-VITAMIN A SERIES BY NMR SPECTROMETRY

P. K. KORVER, C. KRUK, P. J. VAN DER HAAK, J. L. BAAS† and H. O. HUISMAN‡
Laboratory for Organic Chemistry, University of Amsterdam
Nieuwe Achtergracht 129, Amsterdam, The Netherlands

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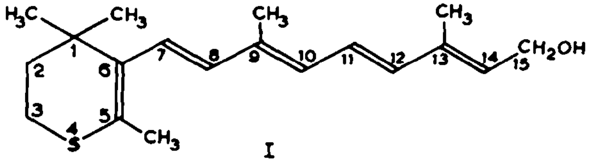
Abstract—The determination of the stereochemical configuration of several intermediates obtained in the synthesis of 4-thia-vitamin A is described by comparing the NMR spectra of these compounds with those of the carbocyclic analogues of known structure.

IN CONNECTION with the synthesis of 4-thia-vitamin A (I)[1] (Fig. 1) the stereochemical configuration of the intermediates was determined by comparing the NMR spectra of these compounds with those of the carbocyclic analogues of known structure.[2]

Since in all cases only one of the possible stereoisomeric thia-compounds was isolated (the *all-trans* isomer), a direct comparison of the spectra of the *cis*- and the *trans*-compounds was not possible. The use of NMR spectrometry takes advantage of the fact that the hetero-atom exerts very little influence on the absorption patterns of protons attached to the side chain, thus making the comparison with the spectra of the carbocyclic compounds, a straightforward procedure. This method is superior to that of UV spectrometry, since the introduction of the hetero-atom produces marked changes in the UV spectrum.[1]

The NMR spectra of several polyenes of the vitamin A series have been reported by von Planta *et al.*[3] These authors, however, limit their discussion to the absorptions of the methyl groups.



I

FIG. 1 All-*trans*-thia-vitamin A.

During the course of the synthesis it was essential to ascertain the correct stereochemical configuration of the intermediates obtained.

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* Part II: J. L. Baas, Mrs. A. Davies-Fidder, F. R. Visser and H. O. Huisman, *Tetrahedron* **22**, 265 (1966).

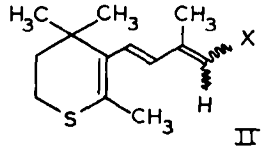
† Part of the Thesis of J. L. Baas, University of Amsterdam (1964).

‡ Part of the lecture presented at the *IUPAC International Symposium on the Chemistry of Natural Products.* Kyoto, Japan 12–18 April (1964).

[1] Part II of this series. *Tetrahedron* **22**, 265 (1966).

[2] Thanks are due to Dr. P. H. van Leeuwen *et al.* of the Laboratories of N. V. Philips-Duphar, Weesp, The Netherlands for supplying the samples.

[3] C. von Planta, U. Schwieter, L. Chopard-dit-Jean, R. Rüegg, M. Kofler and O. Isler, *Helv. Chim. Acta* **45**, 548 (1962).

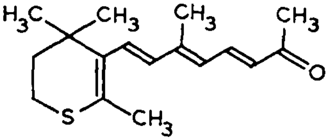


II

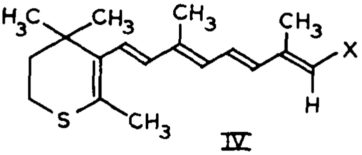
IIa X = CN

b X = $COOCH_3$

c X = CHO



III

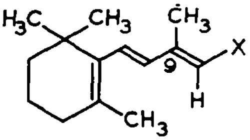


IV

IVa X = $COOCH_3$

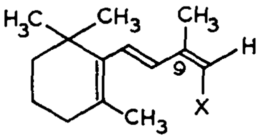
b X = CH_2OAc

FIG. 2



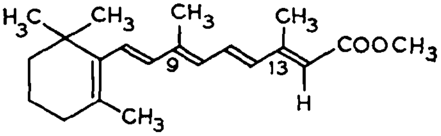
V 9-*trans* Va X = CN'

b X = $COOCH_3$

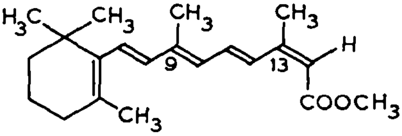


VI 9-*cis* VIa X = CN

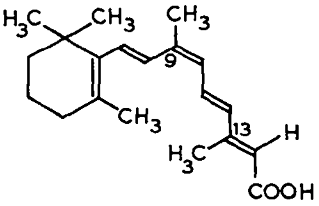
b X = $COOCH_3$



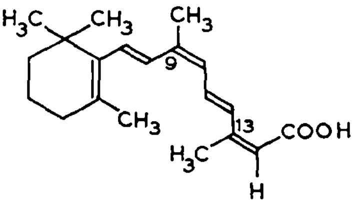
VII 9-*trans*-13-*trans*



VIII 9-*trans*-13-*cis*



IX 9-*cis*-13-*trans*



X 9-*cis*-13-*cis*

FIG. 3

The following 4-thia-vitamin A intermediates (II-IV) were studied (Fig. 2).

The carbocyclic reference compounds which were used to obtain the necessary NMR spectral correlations are listed in Fig. 3.

DISCUSSION

For the present purpose two regions of the spectra are important:

1. the CH_3 absorptions between $\delta = 1{\cdot}5$ and $\delta = 2{\cdot}5$
2. the absorptions between $\delta = 5{\cdot}5$ and $\delta = 8{\cdot}0$ due to the olefinic protons.

If the substituent at the terminal double bond is in a *trans*-position, it will cause a downfield shift[4] of the absorption of the methyl group attached to this double bond ($C_{(9)}$—CH_3 in V; $C_{(13)}$—CH_3 in VII and IX). The influence of the substituent on the absorption of the olefinic proton $C_{(8)}$—H (in V) or $C_{(12)}$—H (in VII and IX) will be relatively small. Similarly, *cis*-substitution of the terminal double bond will result in a downfield shift of the olefinic proton.

The chemical shifts of these methyl- and vinyl-protons are given in Table 1.

TABLE 1

Compound	Chemical shifts*			
	CH_3		$C{=}C\diagdown H$	
Va		2·20	6·17	
VIa	2·04			6·64
Vb		2·32	6·11	
VIb	2·02			7·72
VII		2·36	6·30	
VIII	2·08			7·85
IX		2·36		
X	2·09			

* Cf. Experimental part.

From the data of Table 1 (compounds V to X incl.) it is clear that although the magnitude of the shift is dependent upon the nature of the substituent, the differences between the *cis* and *trans* structures are very pronounced.

It is possible to use the aforementioned resonance peaks for a quantitative determination of the composition of mixtures of *cis* and *trans* isomers. The accuracy of this determination is sufficient for the purposes outlined above. An example is given in Table 2.

TABLE 2

%-age *trans*	
prepared by weighing	found
21	24
87	89

Determination of the composition of mixtures of *cis*- and *trans*-isomers (Vb) and (VIb).

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[4] L. M. Jackman, *Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry*, 7.3. Pergamon Press, London (1959).

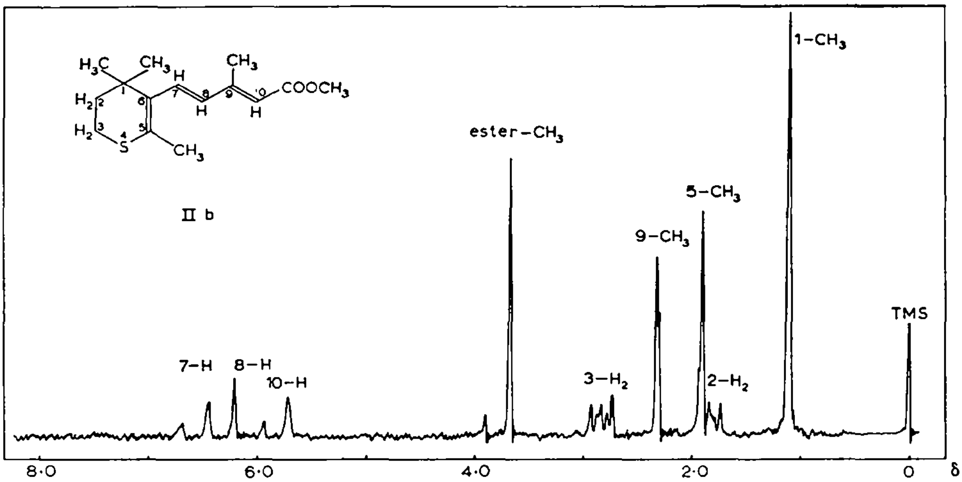

FIG. 4

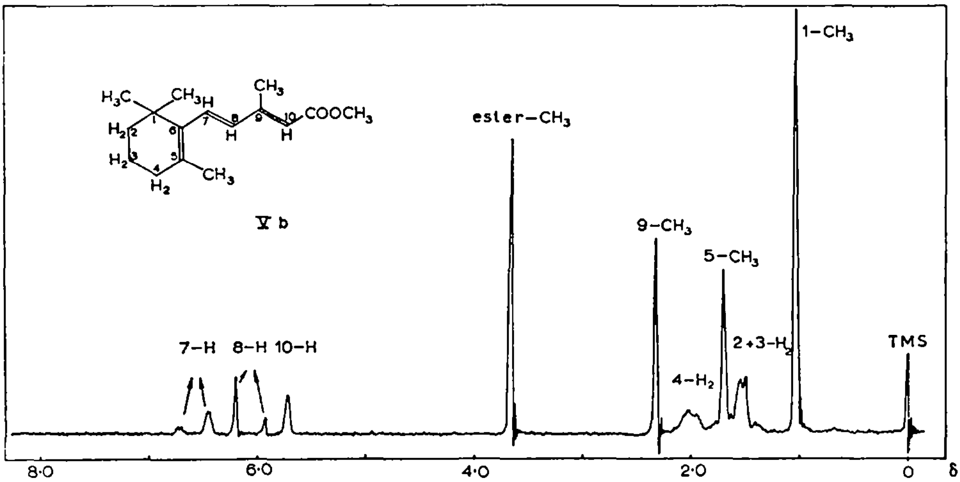

FIG. 5

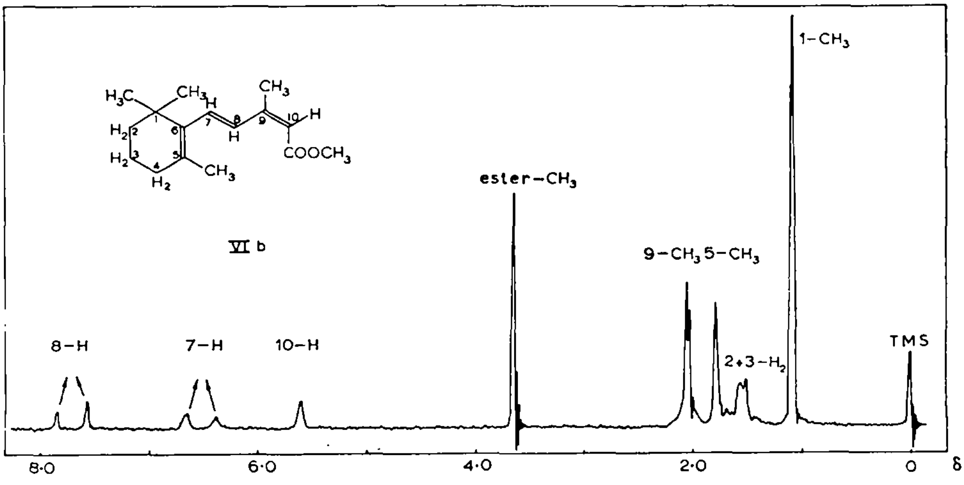

FIG. 6

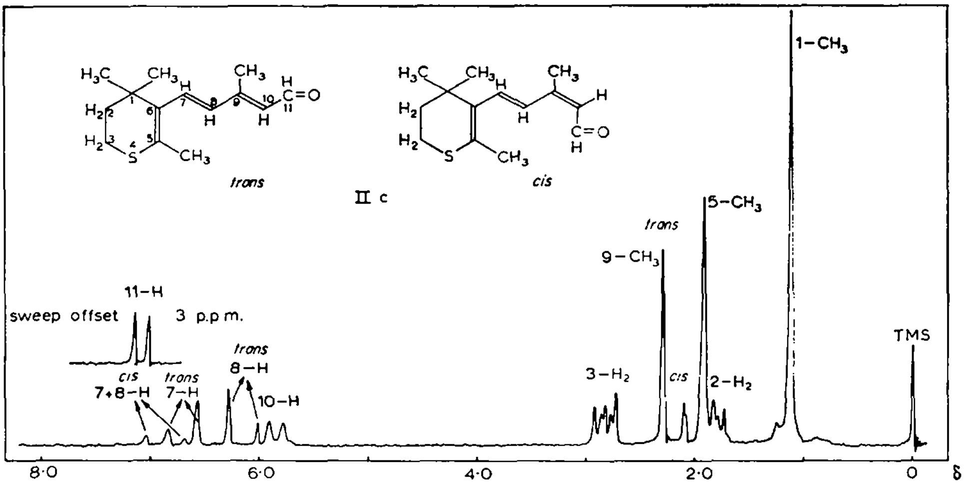

FIG. 7

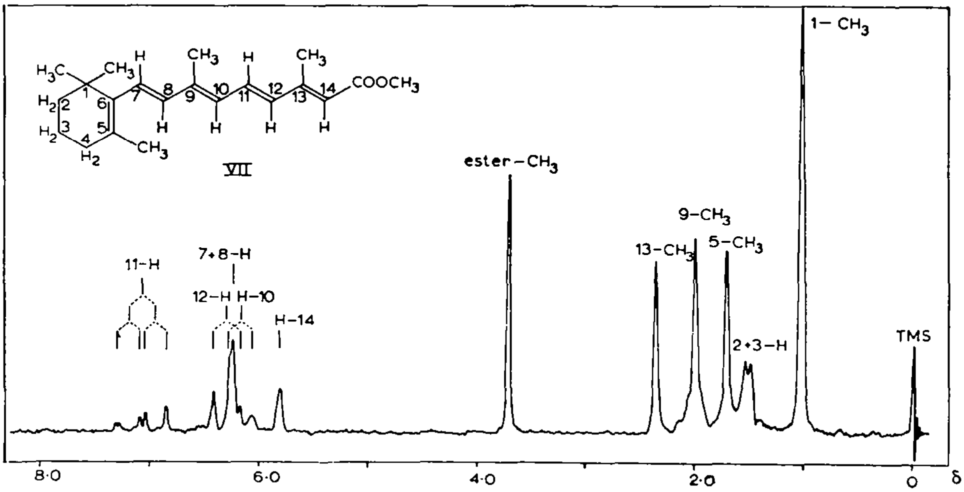

FIG. 8

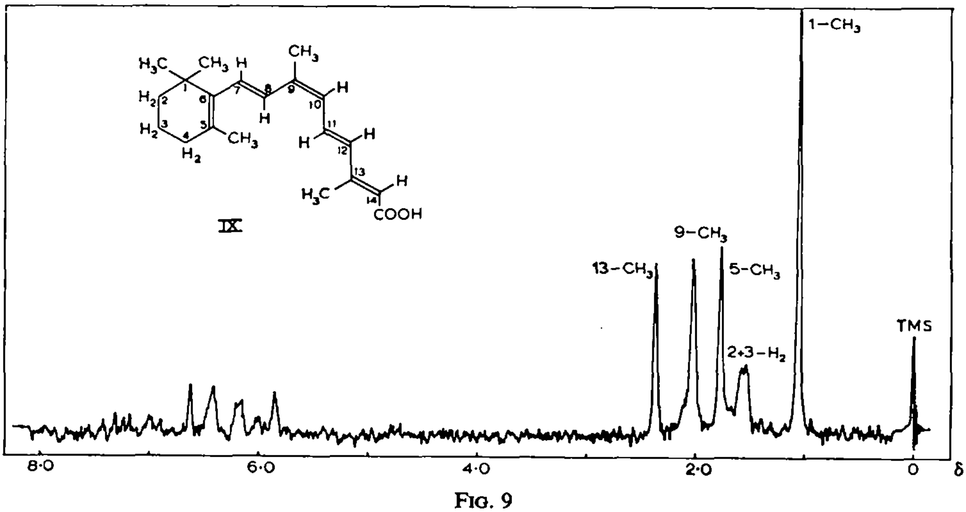

FIG. 9

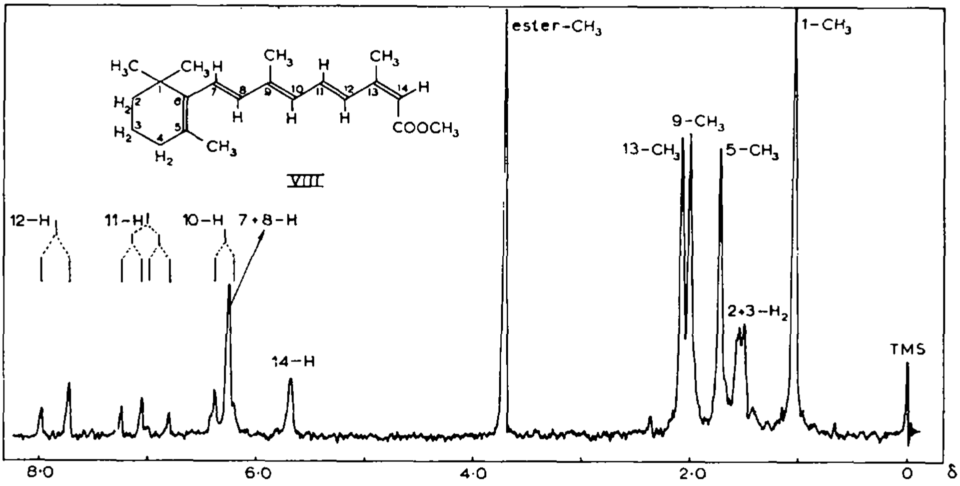

FIG. 10

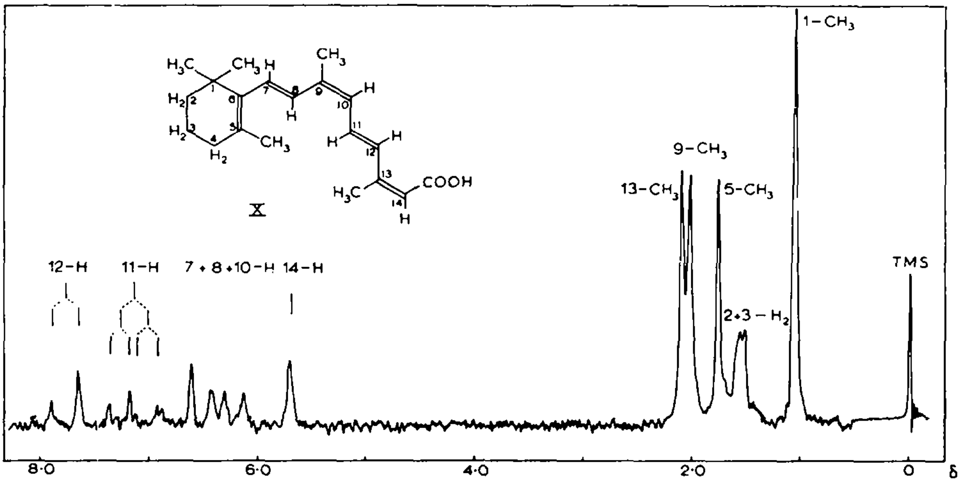

FIG. 11

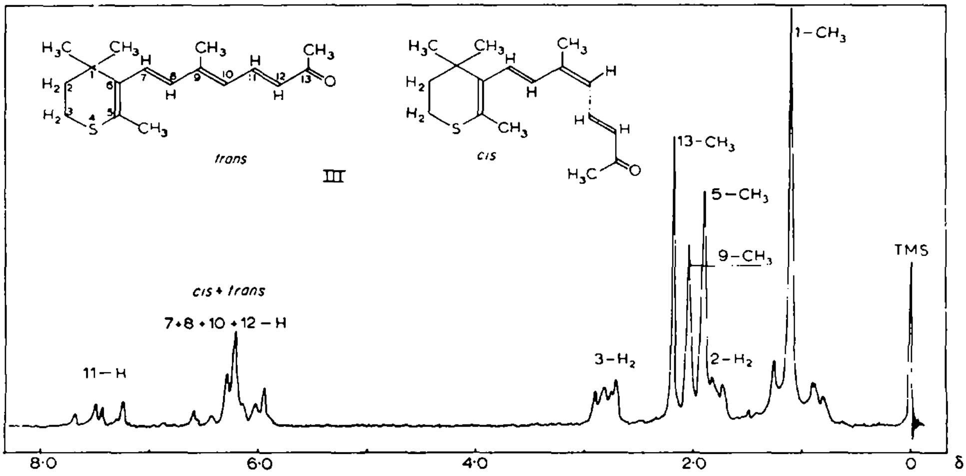

FIG. 12

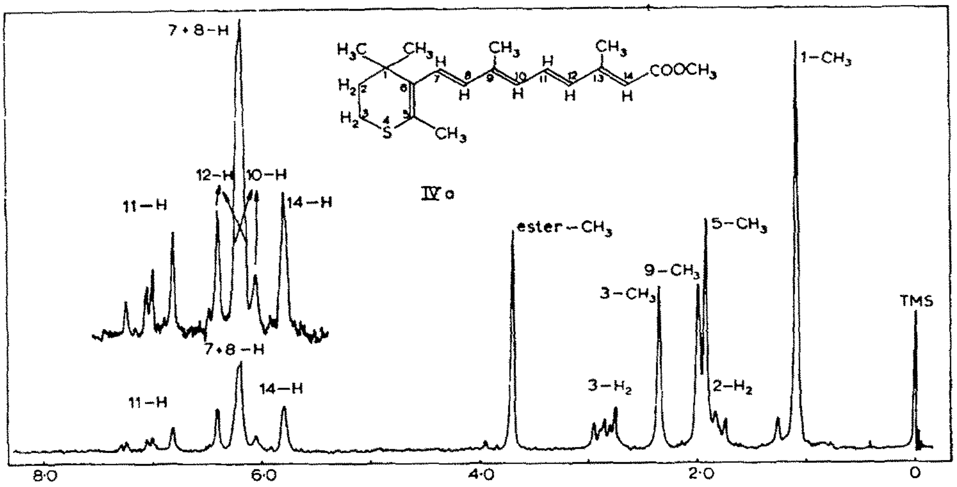

FIG. 13

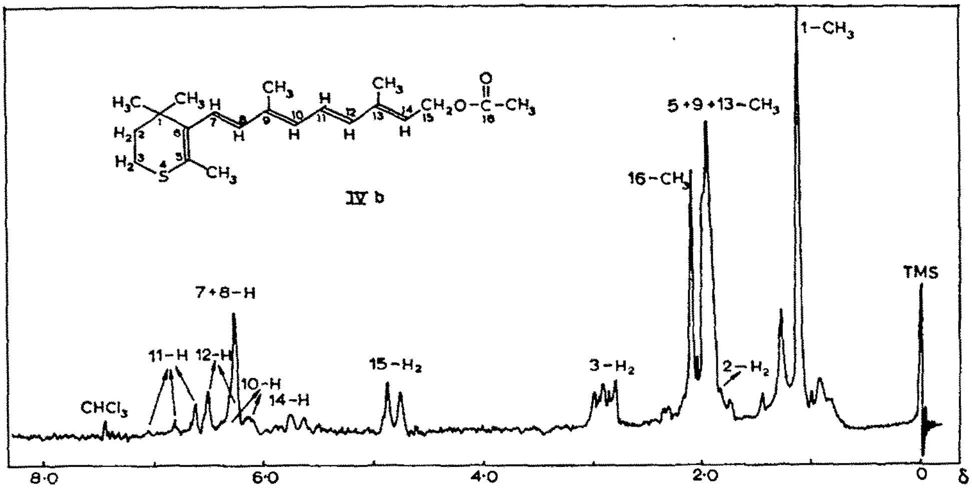

FIG. 14

APPLICATIONS

1. *Compound* IIa. The NMR spectrum is a superposition of the spectra of Va and VIa with the exception of the absorptions due to protons in the immediate vicinity of the hetero-atom, namely $C_{(5)}$—CH_3 and $C_{(3)}$—H_2. Therefore, the sample must be a mixture of *cis*- and *trans*-IIa. Quantitative evaluation of the spectrum showed the sample to contain 65% *trans*-IIa.

2. By comparison with the spectra of the relevant carbocyclic analogues IIb was shown to consist of the pure *trans* isomer. This is illustrated by the NMR spectra described in Figs. 4, 5 and 6.

3. In some cases the data so far obtained, permit the determination of the stereochemical configuration of a 4-thia-polyene system even when no carbocyclic analogue is available. This is demonstrated for compound IIc. The NMR spectrum (Fig. 7)

shows two absorptions due to methyl groups attached to the terminal double bond: a strong one at $\delta = 2{\cdot}29$ and a weaker one at $\delta = 2{\cdot}09$. The interpretation of the absorption pattern of the olefinic protons is shown. By comparison with the data given in Table 2 one can deduce that the sample contains predominantly *trans*-IIc. The *cis*-isomer content is approximately 16%.

4. Compounds VII and IX (Fig. 3) have a different configuration at the 9,10 double bond only. The same is true for VIII and X. From their spectra (Figs. 8, 9, 10 and 11) one can see that when the 9,10 double bond is *trans* substituted, protons $C_{(7)}$—H and $C_{(8)}$—H have the same chemical shift and therefore give rise to one sharp band. In the case of a 9,10 *cis*-double bond however, these protons give a broad, complicated absorption pattern. This empirical correlation was applied to the 4-thia compounds III and IV.

The sample of III (spectrum Fig. 12) is a mixture of 9,10-*cis*- III and 9,10-*trans*-III (approximately 70% *trans*).

Both IVa and IVb (spectra Figs. 13 and 14) have a 9,10-trans-double bond.

It should be remarked that in IVb the influence of the acetate group on the absorption of the $C_{(13)}$—CH_3 is very small. Consequently, in this case it is not possible to determine the stereochemical configuration of the terminal double bond by this method.

EXPERIMENTAL

For details of the syntheses see part II[1] of this series and Refs quoted therein.

NMR spectra were obtained with a Varian A-60 Analytical Spectrometer. The compounds were measured as 10% solutions in CCl_4 or $CDCl_3$. Chemical shifts δ are given from tetramethylsilane which was employed as an internal reference. The spectrometer calibration was checked by the procedure given by Jungnickel.[5]

[5] J. L. Jungnickel, *Analyt. Chem.* 35, 1985 (1963).