Tetrahedron, 1966, Vol. 22, pp. 259 to 264. Pergamon Press Ltd. Printed in Northern Ireland

VITAMIN A ANALOGUES—I

SYNTHESIS OF 4-THIA-IONONE

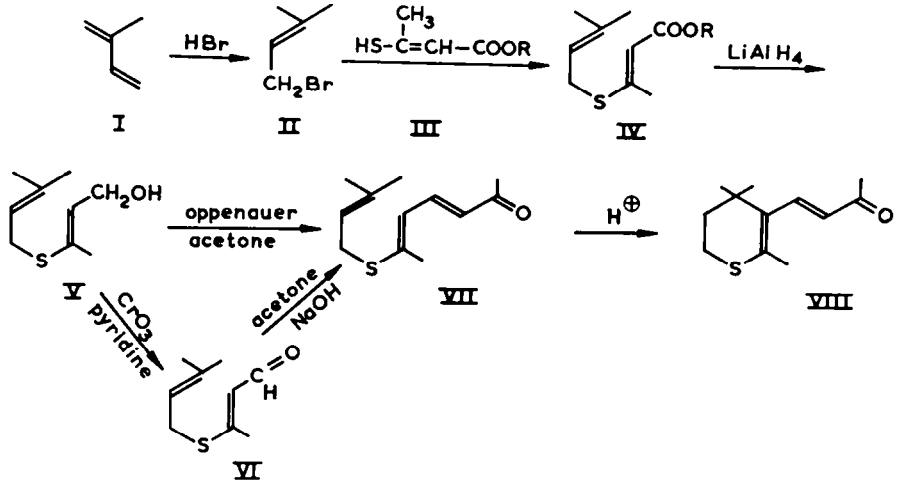
J. L. BAAS*, A. DAVIES-FIDDER and H. O. HUISMAN†
Laboratory for Organic Chemistry, University of Amsterdam,
Nieuwe Achtergracht 129, Amsterdam, The Netherlands

(*Received* 23 *April* 1965)

Abstract—In connection with investigations‡ on the relationship between chemical structure and biological activity of vitamin A, the synthesis of the 4-thia-ionone, a suitable intermediate for the synthesis of 4-thia-vitamin A, is described.

THE synthetic route leading to 4-thia-ionone (VIII) is based upon the acid catalysed cyclization of 1,5-dienes, in a manner analogous to the conversion of pseudo-ionone into a mixture of the α- and β-ionones.[1] It may be anticipated that by cyclization of thia-pseudo-ionone the β-isomer (VIII) will be the main product.

The synthesis of 4-thia-ionone is carried out as follows:



Compound II could be easily obtained in a yield of 60% by addition of HBr to isoprene.[2] Compound III was prepared in 76% yield according to a method described

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

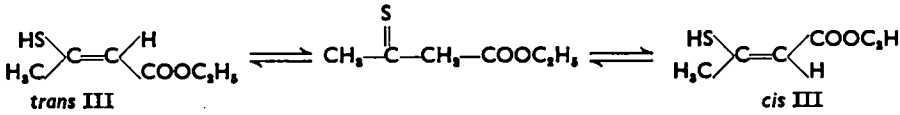
† Part of the lecture presented at the *IUPAC International Symposium on the Chemistry of Natural Products*. Kyoto, Japan, 12–18th April (1964).

‡ These investigations have been carried out in collaboration with the Laboratories of N. V. Philips-Duphar, Weesp, The Netherlands.

[1] V. A. Smit, A. V. Semenovskii, V. M. Medvedera and V. F. Kucherov, *Dokl. Akad. Nauk. SSSR.* **124**, 1080 (1959).

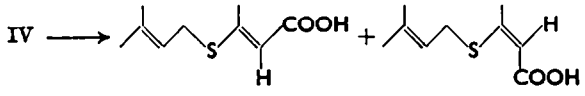
[2] L. F. Fieser, *J. Amer. Chem. Soc.* **49**, 857 (1927); E. H. Farmer and F. C. B. Marshall, *J. Chem. Soc.* **129**, (1931).

by Mitra[3] and Mayer.[4] It consists of a mixture of the following isomers:



trans III *cis* III

Condensation of the compounds II and III may be expected to yield a mixture of the *trans*- and *cis*- isomers of the corresponding reaction product IV. That this indeed is the case, was shown by hydrolysis of the isomeric esters (IV) to the corresponding acids which were separated by fractional crystallization.



trans *cis*

The structure of the two geometric isomers was confirmed by the NMR spectra of the corresponding methyl esters. (Figs. 1 and 2).

Reduction of the *trans*- and *cis*-esters IV with LAH furnished a mixture of geometric isomers of the corresponding alcohols (V). These alcohols proved to be unstable substances which underwent a very rapid acid catalysed rearrangement. A similar rearrangement, as evidenced by IR spectra, also occured when the alcohols were allowed to stand at room temperature for some time.*

The *cis*- and *trans*- alcohols (V) could be obtained in high yields by extracting the hydrolysed reaction mixture at −30°. Due to their instability the alcohols were not purified but used directly in the next reaction step.

The mixture of alcohols was converted into the corresponding isomeric thia-pseudo-ionones by two different ways: a. via the aldehyde VI, followed by acetone condensation, b. by an Oppenauer oxidation in acetone.

a. Upon oxidation of the *cis*- and *trans*- alcohols (V) into the corresponding aldehydes by means of MnO_2, a partial rearrangement of the alcohols took place before oxidation of the latter could occur.

A better method proved to be oxidation by means of CrO_3 in pyridine at low temperature.[5] The stability of the aldehydes seemed to be greater than that of the corresponding alcohols. The aldehydes were characterized as their crystalline N,N-dimethylglycine hydrazones, prepared as described by Viscontini.[6]

Condensation of the aldehydes with acetone converted then into a mixture of geometric isomers of thia-pseudo-ionones. This mixture was purified via the corresponding crystalline N,N-dimethylglycine hydrazones. However it proved to be impossible to isolate the four possible isomeric hydrazones in their pure form by fractional crystallization of the mixture. Only *one* isomer, in all probability the *all-trans* isomer, was obtained in relatively pure form after several fractional crystallizations.

* The product of this transformation and the rearrangement reaction itself are currently under investigation.

[3] S. K. Mitra, *J. Indian Chem. Soc.* **10**, 71 (1933).
[4] R. Mayer, I. Morgenstern and J. Fabian, *Angew. Chem.* **76**, 157 (1964).
[5] J. R. Holum, *J. Org. Chem.* **26**, 2814 (1961).
[6] M. Viscontini and J. Meier, *Helv. Chim. Acta* **33**, 1773 (1950).

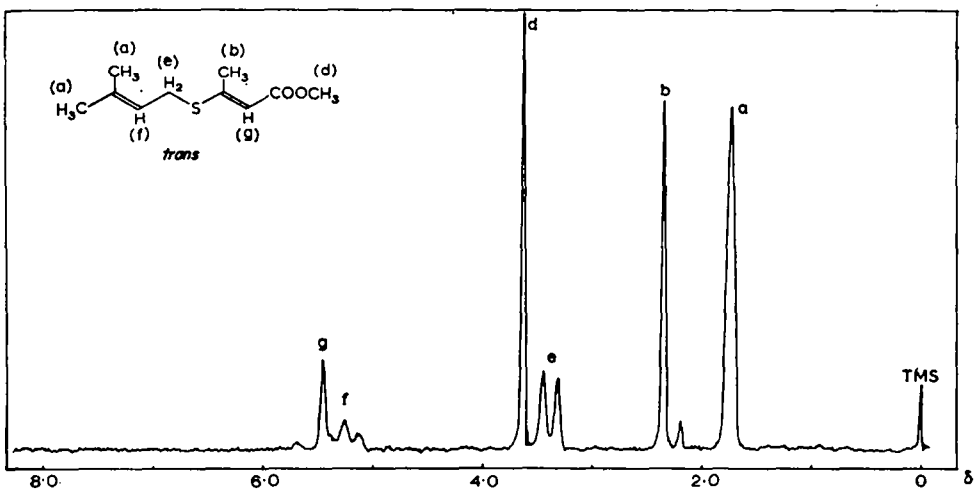


FIG. 1

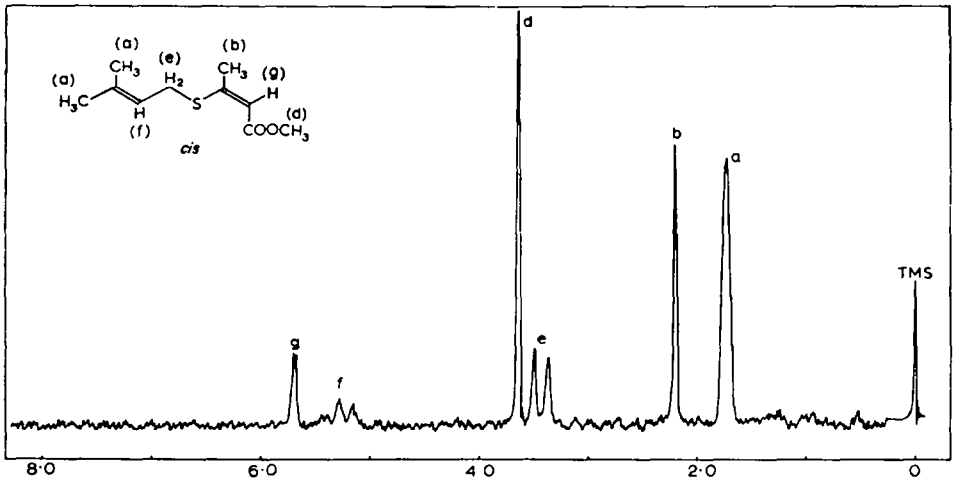


FIG. 2

b. Upon Oppenauer oxidation of the alcohols (V) the crude thia-pseudo-ionones were isolated in high yield. Purification was carried out as described under (a).

We have studied the cyclization of thia-pseudo-ionone under reaction conditions comparable with those in which optimal yields of β-ionone have been reportedly obtained from pseudo-ionone.[1]

In our experiments the best results were obtained by carrying out the cyclization of thia-pseudo-ionone with concentrated sulphuric acid in nitromethane at $-15°$. Optimum time for the reaction was about 30 minutes. The crude 4-thia-ionone was purified via the crystalline N,N-dimethylglycine hydrazone followed by regeneration from the latter. The yield of the pure product was 70–80%.

The structure was proved by NMR spectrometry. It could also be proved by

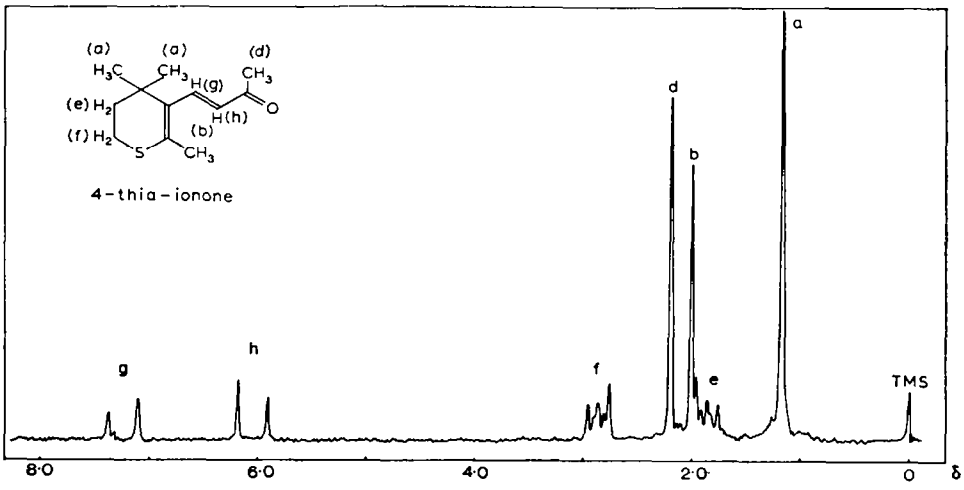


FIG. 3

NMR spectrometry that the 4-thia-ionone obtained has the *trans* configuration as could be expected from Pauling's rule[7] (Fig. 3).

The UV-spectrum of 4-thia-ionone shows two maxima ($\lambda = 333$ nm, $\varepsilon = 12{,}800$; $\lambda = 233$ nm, $\varepsilon = 9{,}000$). The absorption of the main band is shifted by about 40 nm to higher wavelength in comparison with that of β-ionone.

EXPERIMENTAL

IR spectra were taken with a Unicam SP 200 Spectrophotometer and the UV spectra with a Zeiss RPQ 20C Spectrophotometer.

NMR spectra were obtained with a Varian A 60 Analytical Spectrometer. The compounds were measured as 10% solutions in CCl_4. Chemical shifts δ are given from tetramethylsilane as an internal reference. The spectrometer calibration was checked by the procedure given by Jungnickel.[8]

M.ps—determined with a Kofler m.p. microscope—and b.ps are uncorrected.

2-methyl-4-bromobutene-2 (II)

Dry HBr (110 g; 1·4 mole) was passed into cooled (−15°) isoprene, stabilized by 0·06% t-butyl catechin. The reaction mixture was directly distilled *in vacuo*. The first fraction consisted of unchanged isoprene and the second of compound II; b.p. (30 mm) ≈ 40–43°; yield 89 g = ca. 60%.

Ethyl thio-acetoacetate (III)

This compound was prepared as described by Mitra;[8] b.p. (0·1 mm) = 34–41°, yield 76%.

2,6-dimethyl-1-carbethoxy-3-thia-hepta-1,5-diene (IV)

To a solution of 0·5 mole EtONa in 500 ml EtOH 63 g (0·5 mole) III was added at room temp. After stirring for ½ hr the EtOH was evaporated and 500 ml benzene was added to the residue. While stirring 75 g (0·5 mole) of II was added and after 1 hr the reaction mixture was poured into cold water and extracted with benzene. The extract was washed with water, dil. HCl, $NaHCO_3$aq and water. After drying over $MgSO_4$ the solvent was evaporated and the residue distilled *in vacuo*; b.p. (0·5 mm) = 75–123°; yield 82 g = 76%.

The mixture of esters (5 g) were saponified with 5 g KOH in 70 ml MeOH by refluxing for 17 hr.

[7] L. Pauling and L. Zechmeister, *Fortschr. der Chemie Org. Naturstoffe* **3**, 203 (1939); L. Pauling, *Helv. Chim. Acta* **32**, 2241 (1949); L. Zechmeister, *Chem. Rev.* **34**, 267 (1944).

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

After cooling the mixture was diluted with water and the non-acidic impurities were extracted with ether. The water layer was acidified with cold dil. HCl and the acids extracted with ether. After drying the solvent was removed *in vacuo*. The crude acids (3·64 g = 80%) were dissolved in boiling pet. ether (40–60°) and allowed to cool very slowly. The crystals were filtered off and recrystallized from ether. This substance had a m.p. of 97·5–99° (*trans*-isomer).

The pet. ether mother liquor was concentrated and a second quantity of crystals obtained. After recrystallization from ether the m.p. was 151–153° (*cis*-isomer). (Found for the *trans*-isomer: C, 58·1; H, 7·6; O, 16·7; S, 16·8. Found for the *cis*-isomer: C, 57·8; H, 7·6; O, 17·2; S, 17·0. Calc. for $C_9H_{14}O_2S$ (186·26): C, 58·02; H, 7·59; O, 17·12; S, 17·21%.)

The structure of the *trans*- and *cis*-isomers was proved by NMR spectra. The acids were converted into their corresponding methyl esters by diazomethane (Figs 1 and 2):

$$\begin{array}{l} -S-\underset{\displaystyle CH_3}{\underset{|}{C}}=CH-COOCH_3 \quad -CH_3\text{: } \textit{trans}\text{-}\delta = 2{\cdot}34 \text{ (singlet)}, \textit{cis}\text{-}\delta = 2{\cdot}20 \text{ (singlet)}, \\ \qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad -H\text{: } \textit{trans}\text{-}\delta = 5{\cdot}44 \text{ (singlet)}, \textit{cis}\text{-}\delta = 5{\cdot}68 \text{ (singlet)}. \end{array}$$

UV spectra (cyclohexane): *trans*-acid: $\lambda = 216$ nm; $\varepsilon = 4{,}600$; $\lambda = 278$ nm; $\varepsilon = 16{,}300$; *cis*-acid: $\lambda = 221$ nm; $\varepsilon = 1{,}900$; $\lambda = 289$ nm; $\varepsilon = 8{,}600$; *trans*-methylester: $\lambda = 211$ nm; $\varepsilon = 4{,}500$; $\lambda = 274$ nm; $\varepsilon = 16{,}500$; *cis*-methylester: $\lambda = 284$ nm; $\varepsilon = 12{,}400$. IR spectra (cap): C=O (COOMe): 1700 cm^{-1}; C=C (conjugated): 1585 cm^{-1}.

3,7-*dimethyl*-4-*thia*-*octa*-2,6-*diene*-1-*ol* (V)

The mixture of the *trans*- and *cis*-esters (IV; 30 g; 0·14 mole) was reduced with 6 g LAH in 300 ml ether at 0°. After 1 hr stirring the reaction mixture was cooled to −30°, and cooled dil. HCl was added till the mixture was neutralized. After extraction with ether at a low temp and drying over $MgSO_4$ at −30° the solvent was evaporated; the residue obtained was a mixture of the *trans*- and *cis*-alcohols (V), yield 23·5 g = 97%.

The conversion of the esters into the alcohols was shown by their IR spectra (cap): OH: 3390 cm^{-1}; C=C (conjugated): 1625 cm^{-1}; C=C (isolated): 1660 cm^{-1}.

Attempts to make crystalline derivatives of the alcohols failed owing to their instability.

3,7-*dimethyl*-4-*thia*-*octa*-2,6-*diene*-1-*al* (VI)

The crude alcohols (V; 21 g; 0·12 mole) were added to a cooled (0°) solution of 40 g of CrO_3 in 600 ml dry pyridine. After stirring for 2 hr and keeping the mixture for 14 hr at 0°, 300 ml ether was added and the organic layer isolated by filtering. This layer was treated with dil. HCl, $NaHCO_3$aq and water respectively. After drying over $MgSO_4$ and removing the solvent *in vacuo*, a mixture of 14·3 g (70%) of the corresponding aldehydes was isolated. UV spectrum (EtOH): $\lambda_{max} = 299$ nm; $\varepsilon = 13{,}200$; IR spectrum (cap): C=O (—CHO): 1665 cm^{-1} C=C (conjugated): 1585 cm^{-1}.

The aldehydes were characterized as their corresponding N,N-dimethylglycine hydrazones as described earlier.[8,9]

Separation of the *trans*- and *cis*-isomers by fractional crystallization was unsuccessful. The N,N-dimethylglycine hydrazones of the *trans*- and *cis*- aldehyde mixture had a melting range of 110–116°. (Found: C, 57·8; H, 8·5; N, 15·6; S, 11·8. Calc. for $C_{13}H_{23}N_3OS$ (269·40): C, 57·95; H, 8·61; N, 15·60; S, 11·90%.)

UV spectrum (cyclohexane): $\lambda_{max} = 308$ nm; $\varepsilon = 27{,}000$.

6,10-*dimethyl*-7-*thia*-*undeca*-3,5,9-*triene*-2-*one* (VII)

(a) *From the aldehydes* VI. A mixture of the geometric isomers of VI (10·6 g; 0·06 mole) were dissolved in 440 ml acetone and added to 160 ml 1N NaOH. The mixture was then shaken during 16 hr and extracted with ether. The organic layer was dried over $MgSO_4$, the solvent evaporated and the crude thia-pseudo-ionones isolated.

The thia-pseudo-ionones were converted into their crystalline N,N-dimethylglycine hydrazones and regenerated from the latter with HCl in EtOH solution, yield 50%.

[9] H. O. Huisman, A. Smit, P. H. van Leeuwen and J. H. van Rij, *Rec. Trav. Chim.* **75**, 977 (1956).

A sample of the hydrazones had, after several recrystallizations a m.p. of 100·5–104·5°. (Found; C, 62·1; H, 8·8; O, 5·4; N, 13·6; S, 10·3; Calc. for $C_{16}H_{27}N_3OS$ (309·47): C, 62·09; H, 8·79: O, 5·17; N, 13·66; S, 10·35%.)

UV spectrum (cyclohexane): $\lambda_{max} = 328$ nm; $\varepsilon = 28{,}600$.

After regeneration of the above hydrazone with HCl in EtOH the thia-pseudo-ionone—in all probability the *all-trans*-isomer—showed the following UV absorption spectrum (cyclohexane): $\lambda_{max} = 329$ nm, $\varepsilon = 18{,}500$.

IR spectrum (cap): C=O: 1660 cm^{-1}, C=C (conjugated): 1585–1605 cm^{-1}.

(b) *From the alcohol* V. The alcohols V (21·8, 0·12 mole) and 31 g aluminium isopropylate were dissolved in a mixture of 700 ml acetone and 1700 ml benzene. After boiling for 30 hr the mixture was cooled, washed with water till it was neutralized and dried over $MgSO_4$; then the organic solvents were evaporated. The thia-pseudo-ionone was purified as described under (a), yield 55%.

1-(2′,4′,4′-*Trimethyl*-1′-*thia-cyclohex*-2′-*ene*-3′-*yl*)-*but*-1-*ene*-3-*one* (VIII) (*4-thia-ionone*)

A mixture of the geometric isomers of VII (21 g; 0·1 mole) was dissolved in 60 ml nitromethane. While stirring the solution was added to a cooled (−15°) mixture of 50 ml of 100% H_2SO_4 and 70 ml nitromethane. After ½ hr the mixture was poured into ice and extracted with pet. ether (40–60°). After drying over $MgSO_4$ the solvent was evaporated. The residue consisted of 17 g (80%) crude 4-thia-ionone.

Purification was carried out via the N,N-dimethylglycine hydrazone; m.p. 96·5–98°. (Found: C, 62·3; H, 8·8; N, 13·7; S, 10·1; Calc. for $C_{16}H_{27}N_3OS$ (309·51): C, 62·09; H, 8·79; N, 13·66; S, 10·35%.) UV spectrum (cyclohexane): $\lambda_{max} = 322$ nm; $\varepsilon = 17{,}000$; λ_{max} 257 nm; $\varepsilon = 14{,}200$.

After regeneration with HCl in an EtOH solution the pure 4-thia-ionone was isolated. UV absorption spectrum (cyclohexane): λ_{max} 333 nm; $\varepsilon = 12{,}800$; λ_{max} 223 nm; $\varepsilon = 9{,}000$; IR spectrum (cap): C=O: 1660 cm^{-1}, C=C (conjugated): 1570–1600 cm^{-1}.

The structure of the 4-thia-ionone was proved by NMR spectrometry (Fig. 3):

gem-dimethyl	$\delta = 1{\cdot}17$ (singlet),
mono-methyl (to the ring)	$\delta = 2{\cdot}00$ (singlet),
mono-methyl (side-chain)	$\delta = 2{\cdot}19$ (singlet),
side-chain protons	$\delta = 6{\cdot}05, 7{\cdot}24$, (doublets).

Couplings constant of the side-chain vinyl protons: J = 16 c/s indicating a *trans*- double bond.

Acknowledgements—Thanks are due to Drs. P. J. van der Haak, Drs. P. K. Korver, Mr. C. Kruk, and Mr. M. P. F. van Noort of our Spectrometry Department for valuable assistance with the NMR, IR and UV spectra and to Mr. H. Pieters, Mr. W. J. Buis and Mr. J. F. van Duyl of our Micro-analytical Department for carrying out the elementary analyses.