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Note

Gas chromatography of 3,7,11-trimethyl-11-hydroxy- (or -methoxy-) -2,4-dodecadienoic acids and related compounds as their methyl or trimethylsilyl esters

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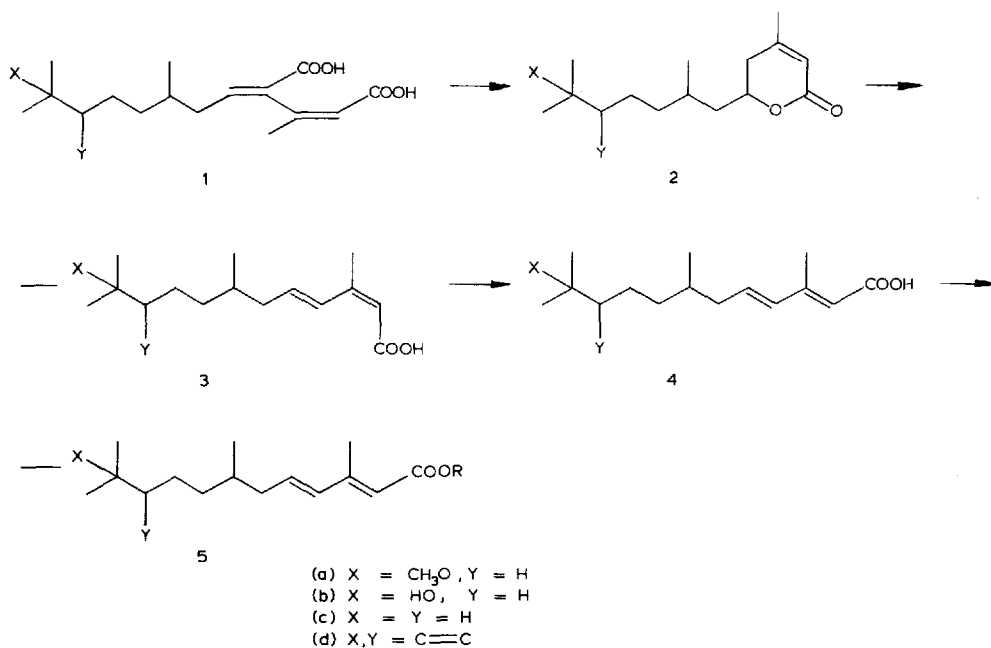
and

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The 3,7,11-trimethyl-2,4-dodecadienoic acids (4a, 4c) are valuable intermediates in the syntheses of methoprene (5a, R = iso-C₃H₇) and hydroprene (5c, R = C₂H₅) (Zoecon Corp.). Henrick *et al.*¹ obtained these compounds as follows:



Compounds 1a, 3a, 4a and 1c, 3c, 4c were separated by gas-liquid chromatography (GLC) on OV-101 or DPEAS stationary phases, after esterification of these acids with diazomethane. However, as no details of the procedure were published,

we have studied the use of GLC for the monitoring of each step of these syntheses and for the determination of the purity of the products. We have also tried to replace the diazomethane method of derivatization by alternative procedures.

EXPERIMENTAL

Materials

The compounds investigated were obtained as described by Henrick *et al.*¹. Their identities and purities were determined by high-performance liquid chromatography (HPLC) together with IR and NMR spectroscopy; purities were generally >95%.

To prepare diazomethane in ether solution, N-nitroso-N-methylurea was treated with 40% aqueous potassium hydroxide and the product was immediately dissolved in diethyl ether and dried over potassium hydroxide pellets before use. Dimethylformamide dimethyl acetal, trimethylchlorosilane, N,O-bis(trimethylsilyl)acetamide and hexamethyldisilazane were Fluka reagent grade products.

Instruments and columns

GLC was performed using Chrom 4, Chrom 5 (Laboratorni Přistroje, Prague) and Pye Unicam 104 Model gas chromatographs with nitrogen and argon as carrier gas and flame ionization detectors. The stationary phases used were dimethyl polysiloxanes and polyethylene glycol. The column characteristics and test conditions are summarized in Table I.

TABLE I

CHARACTERISTICS OF THE GLC COLUMNS USED AND SEPARATION CONDITIONS

Stationary phase	Support	Column		Column temperature (°C)	Pressure drop or flow-rate
		Length (m)	I.D. (mm)		
3% OV-101	Gas-Chrom Q	2.5	3	210	200 kPa N ₂
5% SE-30	Gas-Chrom Q	2.5	3	210	200 kPa N ₂
10% Carbowax 20M	Chromosorb W	3	2.6	200	200 kPa N ₂
3% SE-30	Diatomite Q	1.5	4	200	40 ml/min Ar

Sample preparation

Esterification with diazomethane. A solution of diazomethane in diethyl ether was added to solid samples dissolved in diethyl ether or to neat liquids to give a persistent yellow colour. To achieve complete esterification, it is advisable to let the solvent evaporate and treat the residue once again with excess of diazomethane.

Esterification with dimethylformamide dimethyl acetal. Equal volumes (0.2 µl) of a 1–5% solution of the sample in methanol and of dimethylformamide dimethyl acetal were taken up into a syringe, and the resulting mixture was directly injected on the GLC column. This method proved to be useful in the case of monocarboxylic acids 3 and 4. With compounds 1 and 2, 1 µl of dimethylformamide dimethyl acetal

was added to 1 μ l of test sample and the mixture was allowed to stand for 30 min before injection (0.2 μ l).

Silylation. The silylation was performed in the usual way² using dry pyridine (Py) as solvent and the reagents trimethylchlorosilane (TMCS), hexamethyldisilazane (HMDS) and N,O-bis(trimethylsilyl)acetamide (BSA).

RESULTS

The by-products formed during the preparation of methoprene (5a, R = iso-C₃H₇) have structures in which X = OH and Y = H, or in which X,Y = a double bond. Using dimethyl polysiloxanes as stationary phase, no separation could be obtained between the hydroxylated and methoxylated derivatives. The more polar polyethylene glycol gives, however, an excellent separation.

The impurities formed in the preparation of hydroprene (5c, R = C₂H₅) are derivatives in which X,Y = a double bond, and whose separation involved no difficulties.

Although the *Z-E* isomers 3a-d and 4a-d could be separated on both types of stationary phases, the best results were obtained on dimethyl polysiloxanes.

The esterification procedure with diazomethane described in the Experimental gave unambiguous results. On the other hand, dicarboxylic acids 1 gave lactones 2 and methyl esters of the monocarboxylic acids 3, when coinjected with dimethylformamide dimethyl acetal. Similar chromatograms were obtained with pure lactones 2. This phenomenon may be explained by rapid lactonization and decarboxylation of dicarboxylic acids 1 followed by thermal lactone ring opening and subsequent esterification.

This difficulty could be overcome by allowing the reaction mixture to stand for 30 min at room temperature prior to injection onto the column². In this way, no decomposition of the formed methyl esters occurred. However, under all conditions investigated, the 11-hydroxy compounds 1b, 2b, 3b and 4b eliminated water in the presence of dimethylformamide dimethyl acetal and were eluted as the corresponding 10-unsaturated derivatives 1d, 2d, 3d and 4d. As demonstrated by HPLC, this reaction takes place quantitatively either during the sample preparation or at the evaporation step.

TABLE II

RETENTION TIMES (min) OF METHYL CARBOXYLATES 1-4 ON POLYETHYLENE GLYCOL OR DIMETHYL POLYSILOXANES AS STATIONARY PHASE

Compound	t_R	Compound	t_R	Compound	t_R	Compound	t_R	Chromatographic conditions
1a	10	2a	21	3a	4	4a	4.5	Carbowax 20M, 200°C, 200 kPa N ₂
1b	18	2b	40	3b	8	4b	9	
1c	4	2c	8	3c	1.5	4c	1.7	
1d	5	2d	10	3d	2	4d	2.2	
		2a	10.2	3a	6.4	4a	7.4	OV-101, 215°C, 180 kPa N ₂
		2b	9.3	3b	5.8	4b	6.7	
		2c	5.5	3c	3.4	4c	4.0	
		2d	6.2	3d	3.8	4d	4.4	

The retention times of lactones 2a-d and of the methyl esters of diacids 1a-d and monoacids 3a-d and 4a-d are shown in Table II.

The various silylating agents (TMCS-Py, HMDS-Py, BSA-Py) were used only in the analysis of monocarboxylic acids 3c and 4c because the TMS esters derived from dicarboxylic acids 1a were eluted as 1d as a consequence of methanol elimination at the sample chamber temperature of 250°C required for effective evaporation. On the other hand, the acids 3b and 4b gave three different products depending on the silylation conditions used:

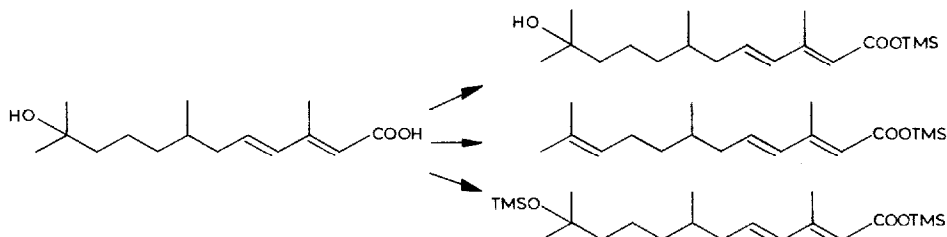


Fig. 1 shows a chromatogram of a mixture of the 11-methoxydodecadienoic acid (4a) with 15% of the corresponding 11-hydroxy compound (4b) (as determined by HPLC), after silylation of *N,O*-bis(trimethylsilyl)acetamide in pyridine. The trimethylsilyl ester of the 2*Z*-isomer (3a) ("impurity") is well separated, but the tri-

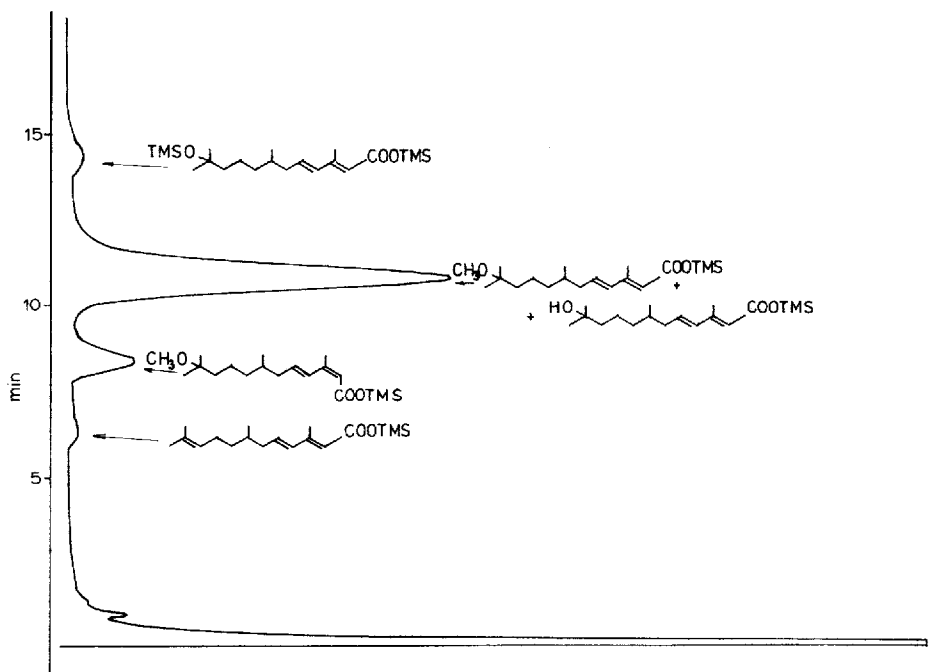


Fig. 1. Chromatogram of (2*E*,4*E*)-11-methoxy-3,7,11-trimethyl-2,4-dodecadienoic acid (4a) containing 11% of the (2*Z*,4*E*) isomer 3a after silylation with BSA. Chromatograph: Pye Unicam 104. Stationary phase: 3% SE-30 on Diatomite Q in a glass-bis (1.5 m × 4 mm I.D.). Column temperature: 200°C. Flow-rate of argon carrier gas: 40 ml/min. The sample was silylated in pyridine solution with BSA at room temperature for 0.5 h.

methylsilyl esters of 4d and of 11-trimethylsilyloxy-3,7,11-trimethyl-2,4-dodecadienoic acid were also formed during the silylation reaction. The trimethylsilyl ester of the acid 4b having a free HO-C(11) group was eluted together with the TMS ester of 4a on dimethyl polysiloxanes.

In the analysis of the acid 3d obtained during the hydroprene preparation, the silylation proceeded without difficulty. Fig. 2 shows the separation of the TMS esters of the mixture, corresponding to the acids 3c, 3d, 4c and 4d.

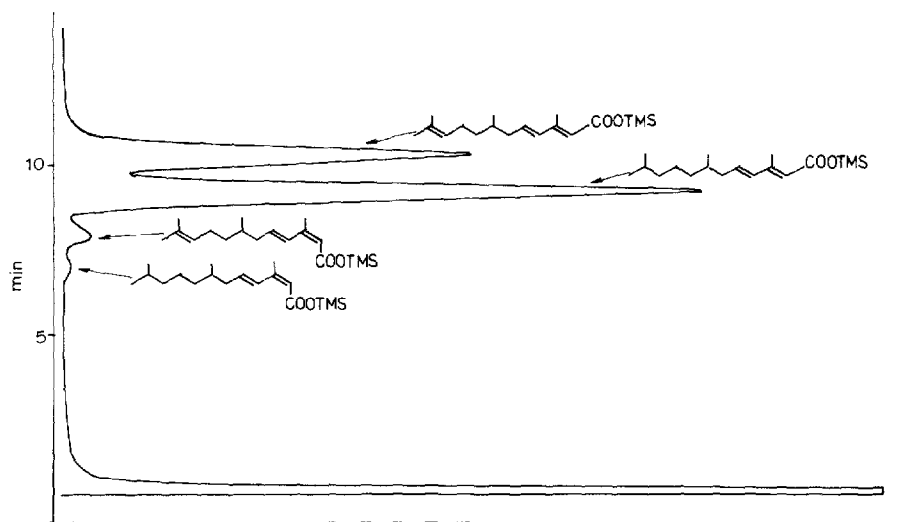


Fig. 2. Separation of (2Z,4E)-3c and (2E,4E)-3,7,11-trimethyl-2,4-dodecadienoic acid (4c) and the corresponding 2,4,10-dodecatrienoic acids (3d and 4d) as their trimethylsilyl esters. Instruments, sample preparation and GLC conditions as in Fig. 1, except column temperature (180°C).

CONCLUSION

GLC on dimethyl polysiloxanes or polyethylene glycol proved to be suitable for the analysis of the methyl esters of 3,7,11-trimethyl-11-hydroxy (or -methoxy)-2,4-dodecadienoic acids (3a, b and 4a, b) and of 3,7,11-trimethyl-2,4,10-dodecatrienoic acids (3d, 4d).

REFERENCES

- 1 C. A. Henrick, W. E. Willy, J. W. Baum, T. A. Baer, B. A. Garcia, T. A. Mastre and S. M. Chang, *J. Org. Chem.*, 40 (1975) 1.
- 2 *Handbook and General Catalog 1979-80*, Pierce Eurochemie B.V., Rotterdam, p. 196.