Synthesis and Resolution of 2-Hydroxyundec-10-enoic Acid

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The synthesis of 2-hydroxyundec-10-enoic acid from undec-10-enoic acid is described. The optically pure enantiomers of the former acid have been obtained through fractional crystallization of the salts of optically active α-phenethylamine. The course of resolution is conveniently followed by thin-layer chromatography. The methyl esters of the optically pure enantiomers of 2-hydroxyundec-10-enoic acid, as well as the methyl esters of the corresponding 2-methoxy-derivatives, have been prepared. The mass spectra of methyl 2L-hydroxy-undec-10-enoate and methyl 2L-methoxyundec-10-enoate are discussed.
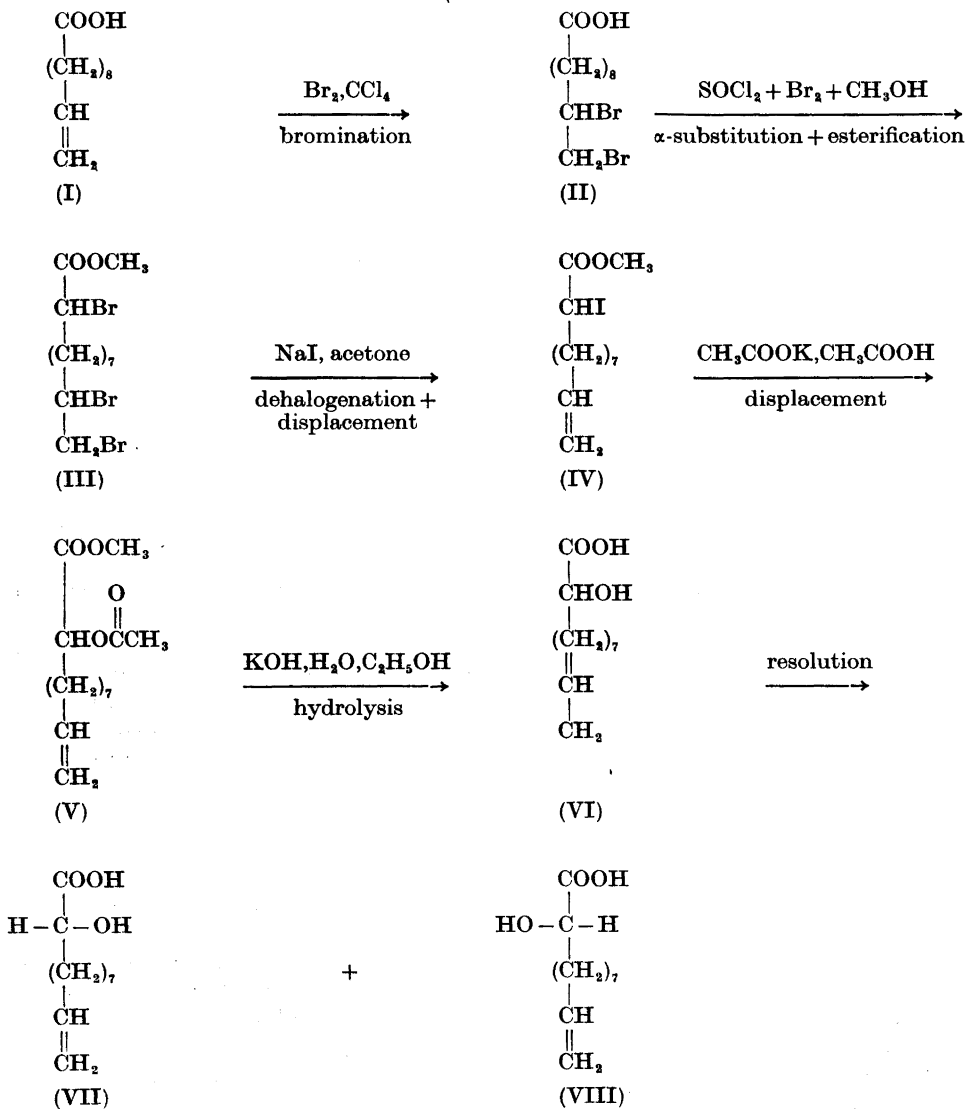
ω-Unsaturated methyl branched optically active units of moderate size have recently proved suitable intermediates in the synthesis of very long chain polymethyl-substituted natural fatty acids.[1] Methyl esters of this type can be oxidatively cleaved to yield the corresponding optically active half-ester, which may subsequently be chain-lengthened to a desired molecular size with mixed anodic coupling (Kolbe electrosynthesis). Starting with 2D-methyloct-7-en-1-ol, it was possible to synthesize 2D,4D,6D,8D-tetramethyl-octacosanoic acid *via* a step-wise build-up with diethyl methylmalonate, and successive resolution of diastereoisomers by preparative gas chromatography. The synthesis afforded conclusive proof that this structure is identical with the so-called C_{32}-mycocerosic acid, isolated from tubercle bacilli.[2]

The work has now been extended to a study of possible synthetic sequences, leading to optically active structures with substituents consisting of hydroxyl and methoxyl groups. The readily available ω-unsaturated undec-10-enoic acid was considered a suitable starting material. Its conversion to the corresponding 2-hydroxy derivative does not appear to have been described in the literature. The preparation of 2-bromoundec-10-enoic acid is described by Hunsdiecker in a German patent.[3] The synthesis involves debromination of 2,10,11-tribromoundecanoic acid with zinc dust in ethanol. This experiment was repeated, following the directions given, but we were unable to obtain the desired ω-unsaturated bromo acid.

SYNTHESIS

The required acid can, however, be obtained as outlined in Chart 1. Addition of bromine to undec-10-enoic acid (I), dissolved in a small amount of carbon tetrachloride, afforded 10,11-dibromoundecanoic acid (II). This was refluxed in an excess of thionyl chloride, to give the corresponding acid chloride. Repeated addition of bromine to the acid chloride in thionyl chloride yielded

Chart 1.

COOH
|
$(CH_2)_8$
|
CH
‖
CH_2
(I)

$\xrightarrow[\text{bromination}]{Br_2, CCl_4}$

COOH
|
$(CH_2)_8$
|
CHBr
|
CH_2Br
(II)

$\xrightarrow[\text{$\alpha$-substitution + esterification}]{SOCl_2 + Br_2 + CH_3OH}$

COOCH$_3$
|
CHBr
|
$(CH_2)_7$
|
CHBr
|
CH_2Br
(III)

$\xrightarrow[\substack{\text{dehalogenation +}\\\text{displacement}}]{\text{NaI, acetone}}$

COOCH$_3$
|
CHI
|
$(CH_2)_7$
|
CH
‖
CH_2
(IV)

$\xrightarrow[\text{displacement}]{CH_3COOK, CH_3COOH}$

COOCH$_3$
|
$\quad$ O
$\quad$ ‖
CHOCCH$_3$
|
$(CH_2)_7$
|
CH
‖
CH_2
(V)

$\xrightarrow[\text{hydrolysis}]{KOH, H_2O, C_2H_5OH}$

COOH
|
CHOH
|
$(CH_2)_7$
‖
CH
|
CH_2
(VI)

$\xrightarrow{\text{resolution}}$

COOH
|
H−C−OH
|
$(CH_2)_7$
|
CH
‖
CH_2
(VII)

+

COOH
|
HO−C−H
|
$(CH_2)_7$
|
CH
‖
CH_2
(VIII)

2,10,11-tribromoundecanoyl chloride, from which the solvents were subsequently removed. Addition of the tribromo-substituted acid chloride to a large excess of methanol afforded methyl 2,10,11-tribromoundecanoate (III).

Debromination of a *vic*-dibromide grouping is usually performed with zinc dust in boiling ethanol (*cf.* Hunsdiecker [3]), with zinc dust in acetic acid, or with zinc dust in an ether solution, containing a little acetic acid. In this case, none of the methods gave the desired ω-double bond as indicated by the absence of the characteristic band at 910 cm^{-1} in the infrared spectrum.[4] However, a smooth debromination was obtained by the less frequently used alternative method, involving refluxing the *vic*-dibromide in acetone with sodium iodide. It may be assumed that the α-bromine atom is displaced by iodine in this reaction.

Conventional displacement of the α-halogen atom by acetate was subsequently brought about with potassium acetate in hot acetic acid, yielding methyl 2-acetoxyundec-10-enoate (V). After hydrolysis, crude 2-hydroxyundec-10-enoic acid was obtained. It should be pointed out that the route of synthesis so far described involves no step of purification, the end product consequently being rather heterogeneous. However, filtration through silicic acid, followed by two crystallizations from light petroleum, gave pure (VI) in the form of colourless lustrous plates of m.p. 60.4 − 60.9° (corrected).

As already mentioned, the preparation of optically active methoxy-substituted fatty acids was also considered of interest. It has been shown previously that optically active methyl 3-hydroxynonanoate can conveniently be transformed into the corresponding 3-methoxy derivative without racemization,[5] utilizing the method of Müller *et al.*[6] Here, diazomethane in ether, in the presence of boron trifluoride etherate, is used as methylating agent. It was found that also optically active methyl 2D-methoxyundec-10-enoate can be synthesized by this method (62 %) from optically active methyl 2D-hydroxyundec-10-enoate.

RESOLUTION

It was found that the two enantiomers (VII and VIII) of 2-hydroxyundec-10-enoic acid could be conveniently obtained in optically pure form *via* fractional crystallization of the salts of optically active α-phenethylamine. The specific rotations of the two enantiomers thus obtained were numerically equal, $[\alpha]_D \pm 4.1°$ in chloroform.

The subject of optically active, natural and synthetic 2-hydroxy acids has been reviewed several times, the most recent papers being those of Horn and Pretorius (1954),[7] Mislow and Bleicher (1954),[8] Downing (1961),[9] Radin 1965),[10] and Brettle and Latham (1968).[11] The direct correlation between the sign of optical rotation and steric configuration is complicated by the fact that the sign and absolute value of the specific rotation is highly solvent dependent. For example, 2-hydroxyhexanoic acid, prepared by Horn and Pretorius by anodic coupling with the monoethyl ester of L-acetoxymalic acid, shows the following specific rotations: $[\alpha]_D - 1.6°$ (H_2O: *c*, 4.40), $[\alpha]_D - 1.5°$ (C_2H_5OH: *c*, 6.76), and $[\alpha]_D + 5.6°$ ($CHCl_3$: *c*, 6.84).[5] However, Horn and Pretorius analogously prepared a series of optically active 2-hydroxy acids of different chain lengths, including 2-hydroxybutanoic, 2-hydroxyoctanoic,

2-hydroxydecanoic, and 2-hydroxyhexadecanoic acid. These were all dextro-rotatory in chloroform.[7] The finding suggests that the dextrorotatory (in chloroform) acid now described possesses L-configuration. Additional support for the conclusion is based on the following consideration. It is known that 2-hydroxy-acids of L-configuration show a shift in the rotation towards the left, in passing from the free acids to the salts.[12] The enantiomer of $[\alpha]_D + 4.1°$ in chloroform is levorotatory in pyridine ($[\alpha]_D - 6.3°$). This fact may be attributed to an increase in degree of ionisation, in going from chloroform to pyridine. We conclude therefore that there is justification for assigning L-configuration to the enantiomer which is dextrorotatory in chloroform (VIII, Chart 1). The corresponding rotations in the R,S-system are 2S-hydroxyundec-10-enoic acid (VIII) and 2R-hydroxyundec-10-enoic acid (VII).

It is known that amine salts of carboxylic acids, at elevated temperatures eliminate water and rearrange to the corresponding carboxylic acid amide. Pascher [13] has recently demonstrated that the diastereoisomeric α-phenethyl-amides of 2-hydroxy-substituted fatty acids separate excellently by thin layer chromatography in certain solvents. This finding represents a very convenient way of following the degree of resolution on a milligram scale.

In Fig. 1, a thin layer chromatogram of amides (designated a – c), derived from three representative salts in the course of resolution, has been reproduced. (a) represents the mother liquor salt obtained in the second crystallization.
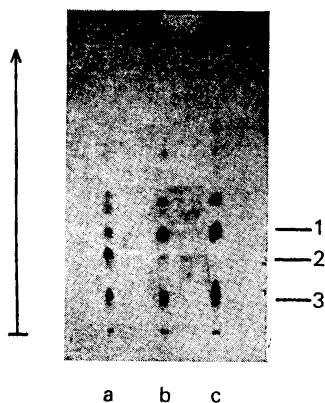

Fig. 1. Thin-layer chromatogram of (+)-α-phenethylamides of 2-hydroxyundec-10-enoic acid. 1) amide of 2D-hydroxyundec-10-enoic acid; 2) amide of 2L-hydroxy-undec-10-enoic acid; 3) 2-hydroxyundec-10-enoic acid. a) mother liquor from second crystallization; b) crystals from second crystallization; c) crystals from final crystallization. Adsorbent: Silica Gel G, Fluka. Solvent: light petroleum (b.p. 60 – 80°):ethyl acetate:acetic acid (70:30:2 v/v/v).

Clearly the spot corresponding to the (+)-α-phenethylamide of 2L-hydroxy-undec-10-enoic acid (VIII) dominates in preference to that of 2D-hydroxy-undec-10-enoic acid (VII). The opposite is true for the crystals of the same crystallization (b). The (+)-α-phenethylamide of optically pure (VII) (after five crystallizations) is seen in (c).

MASS SPECTROMETRIC INVESTIGATIONS

The mass spectrum of methyl 2L-hydroxyundec-10-enoate, identical with that of the antipode, is reproduced in Fig. 2. The mass spectrum shows a molecular ion peak at m/e 214, expected for a mono-unsaturated hydroxy-substituted C_{11} methyl ester.
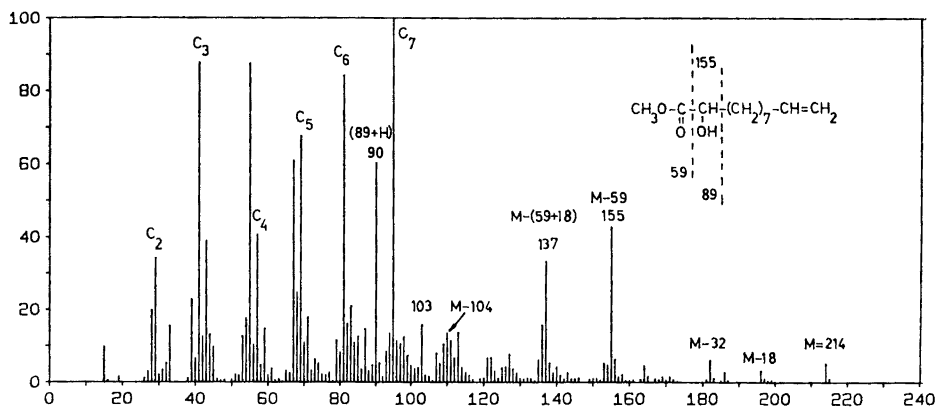
Fig. 2. Mass spectrum of methyl 2L-hydroxyundec-10-enoate.

The prominent peak at m/e 155 ($= M - 59$) is very likely formed through 1,2-cleavage with loss of the methoxycarbonyl group. The ion may, however, also be due to elimination of the three carbon fragment $-\overset{2}{H}\overset{}{C}-\overset{3}{C}H_2-\overset{4}{C}H_2-$
                                                                 $|$
                                                                OH

plus one hydrogen atom, followed by recombination analogous to the formation of ions of m/e M − 43 in the spectra of normal chain esters.[14,15] High resolution work on this compound revealed that the former mode of fragmentation accounts for about 98 % of the ions, whereas the latter only for 2 %. Additional loss of a molecule of water gives rise to very abundant fragments at m/e 137 [$= M - (59 + 18)$].

A prominent rearranged ion due to 2,3-cleavage is observed at m/e 90. It corresponds to the radical ion of m/e 74 also observed in spectra of normal chain methyl esters.[14-16] 4,5-Cleavage with charge retention on the oxygen containing fragment gives rise to the peak at m/e 103.
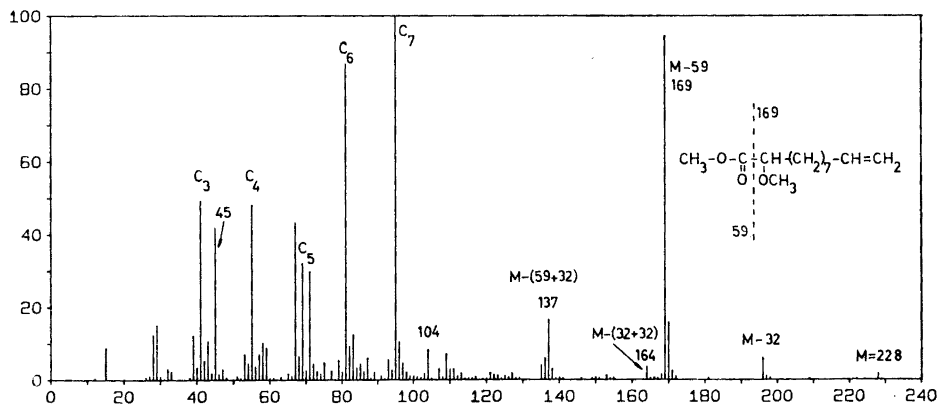

Fig. 3. Mass spectrum of methyl 2L-methoxyundec-10-enoate.

Other abundant fragments in the high mass range, corresponding to loss of a molecule of water or methanol are observed at m/e 196 and m/e 182, respectively. On the whole, the characteristic fragmentations resemble those of methyl 2DL-hydroxyoctadecanoate.[15]

Fig. 3 shows the mass spectrum of methyl 2L-methoxyundec-10-enoate. A small peak at m/e 228 indicates the expected molecular weight of the compound. The molecule readily looses fragments of 32 a.m.u., as shown by abundant ions at m/e 196 (loss of one methoxyl group plus a hydrogen atom) and at m/e 164 (loss of both methoxyl groups plus two hydrogen atoms). 1,2-Cleavage with charge retention on the larger part of the molecule results in a very prominent peak at m/e 169 ($= M - 59$). Additional loss of the methoxyl group and a hydrogen atom gives rise to fragments of m/e 137.

The previously mentioned 2,3-cleavage, involving McLafferty rearrangement, here leads to an ion of m/e 104. Such ions are observed in the spectrum.

EXPERIMENTAL

10,11-Dibromoundecanoic acid (II). 368 g (2.0 mol) of undec-10-enoic acid (Fluka, *purum* quality) was dissolved in 100 ml of carbon tetrachloride, and the mixture was cooled ($+4°$). To the stirred solution was drop-wise added 330 g (2.06 mol) of bromine during 1 h. The stirring was allowed to continue for half an hour. The crude (II) thus obtained was not isolated.

Methyl 2,10,11-tribromoundecanoate (III). To the above solution was added 500 ml of thionyl chloride, and the mixture was refluxed for 3 h. To the still refluxing mixture was then drop-wise added 330 g (2.1 mol) of bromine during 1 h, and the reaction was completed by refluxing for a further period of 3 h. The excess of thionyl chloride and solvent were distilled off at reduced pressure, and the residue was drop-wise added to 500 ml of methanol during 1 h. The reaction mixture was left overnight at room temperature. The excess of methanol was removed at reduced pressure on the water bath. 865 g (theoretically 874 g) of crude (III) was obtained as a brownish viscous liquid.

Methyl 2-iodoundec-10-enoate (IV). 865 g of (III) was dissolved in 2 l of acetone, and the solution was heated to reflux temperature. 900 g of sodium iodide was added in portions, and the slurry refluxed with stirring overnight. The still hot reaction mixture was filtered with suction, cooled, refiltered, and then distributed between water and methylene chloride. The organic layer was washed successively with water, sodium hydrogen sulphite and water, dried with magnesium sulphate, and evaporated to dryness. A residue of 511 g (theoretically 642 g) of crude (IV) was obtained. An infrared spectrum of the product showed strong absorption at 910 cm^{-1}, characteristic for the $=CH_2$ group.

Methyl 2-acetoxyundec-10-enoate (V). 600 g of potassium acetate was dissolved in 750 ml of glacial acetic acid, and the solution was heated to almost boiling. The iodo-ester (IV) (511 g) was then drop-wise added to the stirred, still hot solution. After heating overnight and subsequent cooling, the reaction mixture was distributed between ether and water, and the organic phase was washed several times with water, dried (MgSO$_4$), and evaporated to dryness. Yield, 330 g of dark brown crude (V).

2-Hydroxyundec-10-enoic acid (VI). The crude (V) (330 g) was carefully added to a solution of 455 g potassium hydroxide in 500 ml of distilled water and 200 ml of methanol. After the initial evolution of heat had ceased, the mixture was refluxed for 3 h and then shaken with water and ether. The organic layer contained practically no organic material. The aqueous layer was acidified with hydrochloric acid in water (1:1 v/v) to pH 2, and extracted twice with ether. The combined organic phases were washed three times with water, dried (MgSO$_4$), and evaporated to dryness. 185 g of an almost black residue of crystalline appearance was obtained.

This was dissolved in 350 ml of hot light petroleum (b.p. $60-85°$) and allowed to crystallize at $+4°$ overnight. The dark brown, rather smeary mass of crystals (145 g) was dissolved in 400 ml of an ether:light petroleum mixture (1:10 v/v), and filtered through

200 g of silicic acid in the same solvent. 71 g of yellowish (VI) was eluted. A forerun, consisting of non-crystallizable material (12 g), was discarded, and so was the strongly adsorbed black tarry material on the column. (VI) was recrystallized twice from 200 ml of light petroleum (b.p. 60 − 85°). Yield, 50.0 g of (VI), in the form of colourless lustrous plates of m.p. 60.4 − 60.9°.

2L-Hydroxyundec-10-enoic acid (VIII). 32.5 g (0.16 mol) of (VI) was dissolved in 150 ml of dry ether and 19.7 g (0.16 mol) (−)-α-phenethylamine dissolved in 450 ml of light petroleum (b.p. 60 − 85°). The solutions were mixed and set for crystallization at + 4° overnight. 21.6 g of salt crystals was obtained in the form of large colourless plates. A second crop of crystals (16.7 g) was obtained, when the mother liquor dissolved in 200 ml of an ether:light petroleum (7.5:92.5 v/v) mixture was allowed to crystallize at + 4°. The course of resolution was followed by TLC of the corresponding amides after each crystallization, as previously described. The combined crops of crystals (38.3 g) were then recrystallized successively from 400 ml of ether:light petroleum (1:10 v/v), 560 ml of ether:light petroleum (1:1 v/v), 1000 ml of ether:light petroleum (3:1 v/v), 1000 ml of ether, 1100 ml of ether, and finally from 1400 ml of ether. After seven crystallizations, 7.9 g of salt (mother liquor 1.8 g) was obtained. The corresponding amides appeared optically pure when tested, using the TLC technique.

Decomposition of the salt with hydrochloric acid in water (1:3 v/v) followed by extraction with ether afforded 4.9 g of 2L-hydroxyundec-10-enoic acid. The acid isolated from the mother liquor (0.7 g) of m.p. 64.9 − 65.5° showed the same optical rotation. α_D^{25} − 0.051° (pyridine, l 0.2, c 4.00); $[\alpha]_D^{25}$ − 6.3 ± 0.3°; $[M]_D^{25}$ − 12.5 ± 0.5. α_D^{25} + 0.033° (chloroform, l 0.2, c 4.00); $[\alpha]_D^{25}$ + 4.1 ± 0.2°; $[M]_D^{25}$ + 8.2 ± 0.4.

2D-Hydroxyundec-10-enoic acid (VII). The partially resolved, slightly dextrorotatory hydroxy acid (25.4 g) (0.13 mol), obtained from the decomposed mother liquors of the four first crystallizations, was dissolved in 205 ml of an ether:light petroleum (b.p. 60 − 85°) mixture, and added 15.5 g (0.13 mol) of (+)-α-phenethylamine. After standing overnight at + 4°, 22.3 g of colourless crystals were isolated. These were successively recrystallized from 300 ml ether:light petroleum (1:10 v/v), 450 ml of ether:light petroleum (1:1 v/v), 1200 ml of ether:light petroleum (3:1 v/v), and twice from 1500 ml of ether. 8.4 g of optically pure salt was obtained as indicated by TLC. Decomposition of the salt yielded 5.1 g of (VII), m.p. 65.0 − 65.5°. α_D^{25} + 0.051° (pyridine, l 0.2, c 4.00); $[\alpha]_D^{25}$ + 6.3 ± 0.3°; $[M]_D^{25}$ + 12.5 ± 0.5. α_D^{25} − 0.033° (chloroform, l 0.2, c 4.00); $[\alpha]_D^{25}$ − 4.1 ± 0.2°; $[M]_D^{25}$ − 8.2 ± 0.4.

TLC check on the course of resolution. Samples (a few mg) of salt and mother liquor crystals were heated at 140° for 4 h, during which time the α-phenethylamine salt partly changed into the corresponding α-phenethylamide. A 3 % solution of the reaction product in chloroform was subsequently analyzed on a thin layer plate (Silica Gel G, Fluka) with light petroleum (b.p. 60 − 80°):ethyl acetate:acetic acid (70:30:2 v/v/v). Iodine vapours served as developer of the spots (Fig. 1).

(+)-Methyl 2D-methoxyundec-10-enoate. 3.0 g of (VII) was dissolved in 50 ml of dry ether, and added to a solution of diazomethane in ether (conventionally prepared from *N*-nitrosomethylurea) until the yellow colour persisted. The solvent and excess of reagent were distilled off, and the residual crude hydroxy ester dissolved in 125 ml of dry ether, containing 1 % by weight of boron trifluoride etherate.[5] 180 ml of the above diazomethane solution was then added drop-wise with continuous stirring at + 4°. After an additional stirring for 15 min, the reaction mixture was analyzed by gas chromatography (at 160° on HI-EFF-4B as stationary phase). It contained in addition to the desired methoxy derivative about 40 % of unreacted hydroxy ester. Another 100 ml of the diazomethane solution was therefore run in. GLC now indicated a satisfactory yield of methoxy ester. The reaction mixture was evaporated to dryness, dissolved in about 50 ml of light petroleum (b.p. 40 − 60°), filtered, and then re-evaporated. The residue was finally chromatographed on 50 g of silicic acid (100 − 200 mesh) with ether:light petroleum (b.p. 40 − 60°) (1:10 v/v). 2.1 g (61.5 %) of gas chromatographically pure methyl 2D-methoxyundec-10-enoate was obtained. α_D^{23} + 0.282° (chloroform, l 0.2, c 4.00); $[\alpha]_D^{23}$ + 35.3 ± 0.3°; $[M]_D^{23}$ + 80.5 ± 0.5.

(−)-Methyl 2L-methoxyundec-10-enoate. From 6.6 g of (VIII) was analogously obtained 4.4 g of chromatographically pure methyl 2L-methoxyundec-10-enoate. α_D^{23} − 0.280° (chloroform, l 0.2, c 4.00); $[\alpha]_D^{23}$ − 35.0 ± 0.3°; $[M]_D^{23}$ − 80.0 ± 0.5.

Optical rotations were measured with a Bendix-Ericsson type 143 photoelectric polarimeter at the sodium D-lines.

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