Tetrahedron. Vol. 27, pp. 2869 to 2875 Pergamon Press 1971. Printed in Great Britain

SYNTHETIC STUDIES IN STEROIDAL SAPOGENINS AND ALKALOIDS—X

SYNTHESES OF TOMATID-5-ENE-3β-OL AND SOLASODINE

S. V. KESSAR, Y. P. GUPTA, M. SINGH and R. K. MAHAJAN

Department of Chemistry, Panjab University, Chandigarh-14, India

(*Received in UK* 30 *December* 1970; *Accepted for publication* 17 *March* 1971)

Abstract—Michael addition of *S* and *R* methyl 5-nitro-2-methylpentonoate to *cis*-5,17(20)pregnadien 3β-ol-20-one affords adducts from which tomatid-5-ene-3β-ol and solasodine are synthesised by a sequence of selective transformations.

SOLANUM alkaloids with spirosolane structure have, of late, acquired considerable commercial importance as a source material for steroidal drugs. These alkaloids, unlike the solanidanes, occur in nature with 25-*S* as well as 25-*R* configuration. In the present work attention was first focussed on the *S*-series since the requisite key intermediates (III and IV) had already been secured in connection with solanidine synthesis.

The first step in the envisaged scheme (Fig 1) required reduction of C-16 CO group in IIIa by a method which left the ester and nitro functions intact. Sodium borohydride reduction seemed promising, but even under mild conditions it led to partial destruction of the nitro group. It seemed that a facile Nef type reaction, probably dependent on proximity of CO and ester functions, was occurring under the reaction conditions. It was, therefore, decided to avoid nitro anion formation by carrying the reduction in acidic medium which, indeed, afforded the desired nitro diol Va in excellent yield. Reduction of the nitro group and subsequent lactam formation (VIIa) proceeded smoothly when this nitro diol was refluxed with zinc and acetic acid. Further reduction of the obtained amide VIIa with LAH yielded the amino alcohol IXa which was converted into its N-chloro derivative. Treatment of this material with sodium methoxide in methanol[1] effected dehydrochlorination which was followed by spontaneous cyclisation. The base XI obtained was identical with natural tomatid-5-ene-3β-ol[2] in all respects. The C-22 isomeric Michael adduct IVa, when carried through the above series of steps, also afforded the same alkaloid in comparable yield. Since both the isomers obtained in Michael addition can be converted into the desired product, the synthesis can be considered stereospecific at each step. Further, this sequence also lends support to the conclusion[3] that adducts III and IV are isomeric only at C-22.

Although IR spectra of intermediate nitro diols (Va and VIa) and hydroxy amides (VIIa and VIIIa) conformed to the assigned structures, some difficulty was experienced

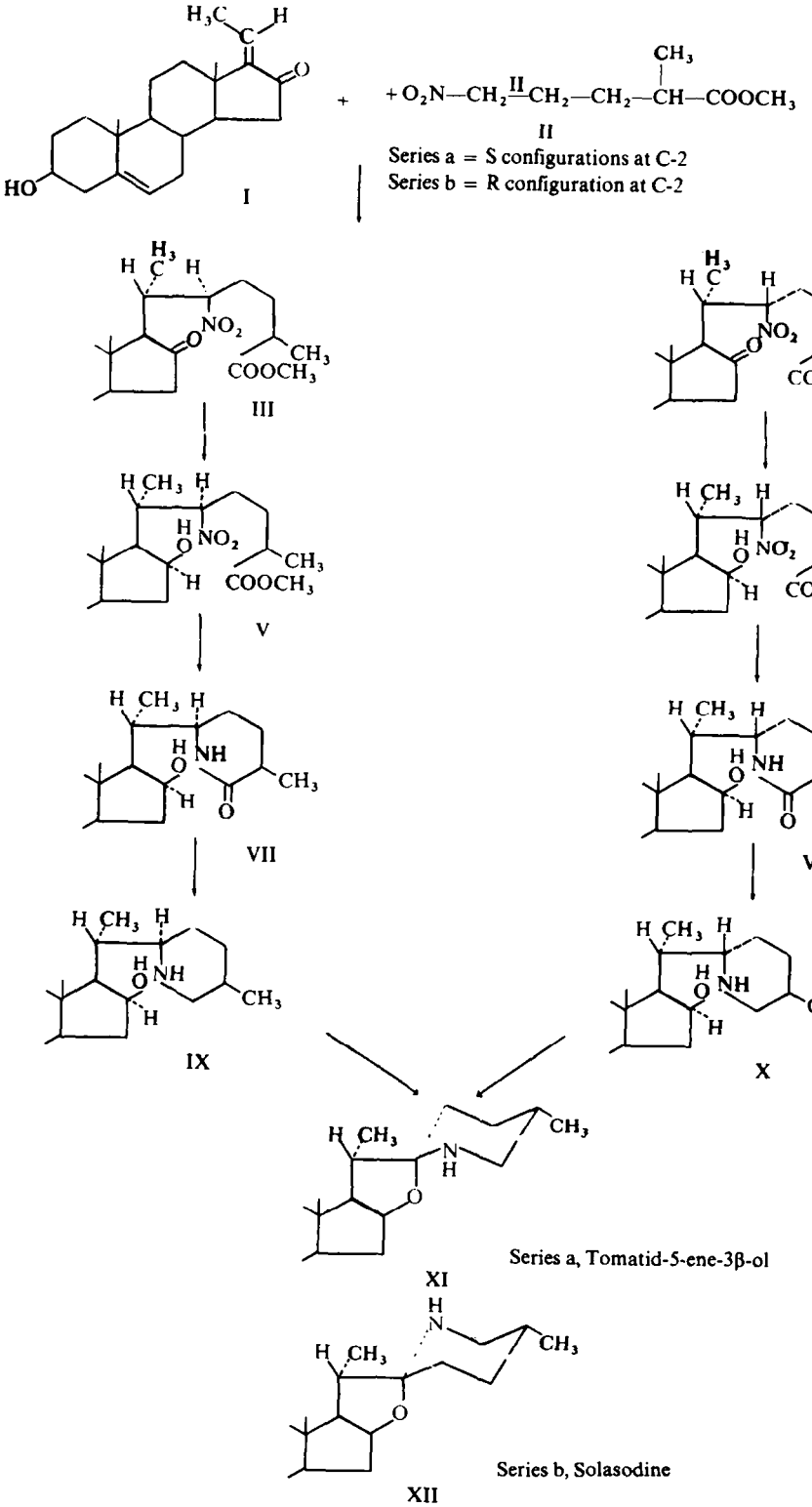
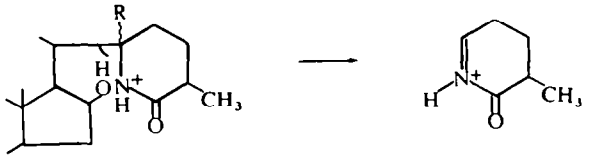

I
II
Series a = S configurations at C-2
Series b = R configuration at C-2
III
IV
V
VI
VII
VIII
IX
X
XI
XII
Series a, Tomatid-5-ene-3β-ol
Series b, Solasodine

FIG 1.

in elemental analysis of these high melting compounds. Additional structural confirmation was, therefore, considered necessary. The mass spectrum of nitro diol Va clearly shows the molecular ion peak at *m/e* 491 (Experimental). The strong peak at *m/e* 473 (M-18) can be attributed to electronic or thermal loss of a water molecule, while the peak at *m/e* 458 [M − (18 + 15)] may be considered to arise from concurrent loss of a Me moiety. Another prominent ion *m/e* 427 [M − (18 + 46)] can be explained on basis of loss of a nitro radical which is a common feature of aliphatic compounds with this function.[4] Elimination of side chain plus 42 mass units (involving C_{15}, C_{16} and C_{17} atoms) along with loss of water is characteristic of many steroidal compounds.[5] Because in V, C-16 bears an additional OH group such fragmentation here should lead to loss of 16 additional mass units, as observed in the prominent peak at *m/e* 213.

In the mass spectrum of amide VIIa and VIIIa molecular ions are observable at *m/e* 429. The fragmentation pattern of the two is very similar to each other as has been observed for other C-22 isomeric pairs of steroidal compounds.[6] In comparison to Va, (M-18) and other ions characteristic of steroid nucleus directed fragmentation are less abundant here. The general pattern resembles that of spirosolane alkaloids[6] in which nitrogen initiated fragmentation is known to predominate. The base peak in spectra of both the amides is observed at *m/e* 112, which can be rationalised on basis of C-20—C-22 bond homolysis as shown.[7] This fragmentation seems to be of excellent diagnostic value for ring F amides.



VIIa; R = ---H
VIIIa; R = –H

m/e 112

FIG 2.

For synthesis of solasodine, methyl-5-nitro-2*R*-methyl pentanoate (IIb) was obtained in 4 steps from partially resolved 2*R*-allyl propionic acid. Its Michael addition to I was carried as in *S*-series. The product obtained was again resolved into IIIb and IVb by thick layer chromatography. Since the separation was very laborious and the asymmetry at C-22 is ultimately eliminated in a subsequent step, the unseparated mixture was carried through the sequence of steps shown in Fig 1 to obtain solasodine identical with a natural sample.[2]

With the above work the primary objective of this project i.e., formal total syntheses of the major structural types in steroidal sapogenins and solanum alkaloids through a common route, was achieved. Elegant syntheses in this area have also been reported by two other groups—sapogenins by Danieli *et al.*[8] and solanum alkaloids by Schreiber *et al.*[9] The present approach is short and stereospecific allowing selective entry into 25-*S* or 25-*R* series. Further, alkaloids and sapogenins with Δ^5 function are accessible directly and easy adaptation to compounds with additional functions in ring F, a variation often encountered in nature, is feasible.[10]

EXPERIMENTAL

Sodium borohydride reduction of 26-*carbomethoxy* (22 R, 25 S) 22-*nitro*-5-*cholesten*-3β-*ol*-16-*one* (IIIa)

(a) A mixture of Michael adduct[3] IIIa (20 mg), EtOH (4 ml) and $NaBH_4$ (40 mg) was refluxed on a water

bath for 3 hr and allowed to stand overnight. It was then decomposed with HCl (10%) and diluted with water. IR spectrum of the obtained solid revealed absence of nitro group.

(b) When the above reaction was carried at 0° for 3 hr and the decomposition effected with AcOH (10%), the solid obtained showed only moderate IR absorption in the nitro region.

(c) A soln of $NaBH_4$ (100 mg) in water (0·6 ml) was gradually added to a soln of IIIa (100 mg) in EtOH (5 ml) during a period of 30 min. The temp of the mixture was kept below 30° by cooling in water and its pH maintained between 3 and 7 by concurrent addition of 3N H_2SO_4. After 15 min at room temp conc H_2SO_4 (5 ml) was added and the mixture diluted with water (40 ml). The solid (90 mg) was filtered off and washed thoroughly with water. Three crystallisations from MeOH gave a white solid, m.p. 131–132°, $(\alpha)_D$ −39°, ν_{max} 1735, 1690, 1530 cm^{-1}; (Mass. 491 (M^+), 473, 458, 442, 441, 427, 425, 355, 271, 213 *m/e*. $C_{28}H_{45}NO_6$ requires mol. wt. 491).

26-Carbomethoxy(22R,25S)*22-nitro-5-cholesten-3,16-diacetate*

The above Va (10 mg) was allowed to stand overnight in Ac_2O (5 drops). On dilution of the mixture with water, a solid was obtained. It was washed with water and crystallised from EtOH yielding a crystalline white solid, m.p. 266–268°, ν_{max} 1720, 1535 cm^{-1}. When acetylation was attempted with pyridine-Ac_2O a mixture of two acetates was obtained. This mixture was identical with that obtained in similar acetylation of 26-carbomethoxy(22*S*,25*S*)22-nitro-5-cholesten-3,16-diol.

Zinc–acetic acid reduction of 26-carbomethoxy(22R,25S)*22-nitro-5-cholesten-3,16-diol* (Va)

Zinc dust (2·5 g) was added, in portions, to a refluxing soln of Va (100 mg) in glacial AcOH (5 ml) during a period of 3 hr. The mixture was further refluxed for 30 min and cooled. The Zn salts formed were removed by filtration and washed with hot glacial AcOH. From the combined filtrate and washings AcOH was distilled off under reduced pressure. The residue was washed with AcOH (10%), water and dried. It was crystallised thrice from acetone to obtain, as a white solid, the hydroxy amide VIIa (45 mg), m.p. 250–253°, $(\alpha)_D$ +79·6°, ν_{max} 1635 cm^{-1}; mass 429 (M^+), 411, 408, 394, 312, 267, 112 *m/e*. $C_{27}H_{43}NO_3$ requires Mol. wt. 429).

Lithium aluminium hydride reduction of (22R,25S)*22,26-imino-26-oxo-5-cholesten-3β-16β-diol* (VIIa)

The above VIIa (35 mg) was refluxed with LAH (100 mg) in dry dioxan (25 ml) on an oil bath (130–140°) for 12 hr. Additional LAH (100 mg) was added and refluxing continued for further 13 hr. The mixture was cooled, decomposed with 2% NaOH aq (0·60 ml) and filtered. The cake was extracted twice with hot THF. From the combined filtrate and extract, the solvent was removed under reduced pressure. The residue was thoroughly triturated with 10% AcOH and filtered. The filtrate on basification with 10% NaOH aq afforded a white solid (24 mg) melting over a range. Comparison by TLC with an authentic sample[11] showed it to be mostly (22*R*,25*S*)-22,26-imino-cholest-5-ene-3β-16β-diol.

Tomatid-5-ene-3β-ol (XI)

A soln of N-chlorosuccinimide (12 mg) in dry CH_2Cl_2 (1 ml) was added, with stirring, to above crude IX (25 mg) in dry CH_2Cl_2 (8 ml) during a period of 30 min while the temp was maintained between −5 and −10°. After additional stirring for 30 min at room temp, the mixture was washed thrice with cold water. The organic layer was dried and the solvent was removed, under reduced pressure at room temp, to obtain the N-chloroderivative of IX as a white solid (15 mg).

The above N-chloro derivative (15 mg) was shaken with NaOMe (prepared from 50 mg Na and 5 ml abs MeOH) for 1 hr at room temp. The resulting soln was diluted with water (50 ml) and the ppt was crystallised from acetone to obtain a white solid XI (12 mg), m.p. 227–229°. It was compared with a sample of natural tomatid-5-ene-3β-ol[2], m.p. 230–232°. The two had superimposable IR spectra, identical R_f values in a number of solvent systems and showed no depression in m.p. on admixture.

26-Carbomethoxy(22S,25S)*22-nitro-5-cholesten-3β,16β-diol* (VIa)

A soln of $NaBH_4$ (200 mg) in water (1 ml) was slowly added to a soln of IVa (200 mg) in EtOH (10 ml) with constant stirring during a period of 90 min. The pH of the mixture was maintained between 3 and 7 by concurrent addition of 3N H_2SO_4 while temp was kept between 10 and 30°. The mixture was worked up as before and the solid obtained was crystallised thrice from MeOH to get a while solid (180 mg), m.p. 126–127°, $(\alpha)_D^{25}$ −30°, ν_{max} 1725, 1530 cm^{-1}. The diacetate was prepared in Ac_2O, as above, m.p. 260–262°, ν_{max} 1715, 1535 cm^{-1}.

(22S,25S)-22,26-*Imino*-26-*oxo*-5-*cholesten*-3β,16β-*diol* (VIIIa)

Zinc dust (3 g) was added gradually to a boiling soln of VIa (120 mg) in glacial AcOH (6 ml) during a period of 3 hr. It was worked up as before to obtain a neutral solid (65 mg). Three crystallisations from MeOH gave white crystalline material, m.p. 262–264°, $(\alpha)_D$ 67·6°, ν_{max} 1635 cm^{-1}; (mass. 429 (M^+), 411, 408, 394, 312, 267, 212, 112 *m/e*. $C_{27}H_{43}NO_3$ requires Mol. wt. 429).

(22S,25S)-22,26-*Imino*-5-*cholesten*-3β,16β-*diol* (Xa)

The above VIIIa (50 mg) was refluxed with LAH (150 mg) in dry dioxan (25 ml) on an oil bath (130–150°) for 12 hr. Additional LAH (100 mg) was added and refluxing continued for further 13 hr. The mixture was then worked up, as before, to obtain a white basic solid (35 mg), melting over a range. Comparison by TLC with an authentic sample[11] showed it to be mostly (22*S*,25*S*)-22,26-imino-5-cholesten-3β,16β-diol.

Tomatid-5-*ene*-3β-*ol* (XI)

The N-chloro derivative (20 mg) was obtained from the above Xa (30 mg) by treatment with N-chlorosuccinimide as described. Its treatment with NaOMe afforded a base (13 mg) which was crystallised from acetone to a white solid XI, m.p. 226–228°. This solid was compared with a sample of natural tomatid-5-ene-3β-ol m.p. 230–232°. The two had superimposable IR spectra, identical R_f values in a number of solvent systems and showed no depression in m.p. on admixture.

2R-*methyl-pent-4-enoic acid*

Partially resolved 2*R*-methyl-pent-4-enoic acid $(\alpha)_D$ −4·6°, was obtained by decomposition of the first two mother liquors in the resolution for 2*S*-methyl-pent-4-enoic acid. This acid (10 g) was reacted with (+)-1-phenylethyl amine (10·4 g) in dry ether (350 ml). The mixture was chilled overnight at −10°. The ppt was collected and decomposed with hydrochloric acid (30%) to afford 2*R*-methyl-pent 4-enoic acid,[12] b.p. 103–104°/20 mm, $(\alpha)_D$ −6·5°.

5-*Bromo*-2R-*methyl-pentanoic acid*

A stream of dry HBr was bubbled through a mixture of the above 2*R*-methyl-pent-4-enoic acid (6·5 g), light petroleum (80–100°, 12 ml), benzoyl peroxide (65 mg) and a drop of water while the temp was maintained at 0°. The supply of gas was discontinued every 15 min and dry air was passed through the mixture for 1 min. The passage of gas was continued for 1 hr beyond saturation of the mixture which was then allowed to stand overnight. The usual work up gave 5-bromo-2*R*-methyl pentanoic acid (9 g) as a pale yellow oil, b.p. 117–120°/3 mm $(\alpha)_D$ −10·2°.

Methyl-5-*bromo*-2R-*methyl pentanoate*

Methylation of the above bromo acid (9 g) with diazomethane gave methyl-5-bromo-2*R*-methyl-pentanoate (8 g), b.p. 78–80°/2 mm, $(\alpha)_D$ −12·6°.

Methyl-5-*iodo*-2R-*methyl pentanoate*

The above bromoester (8 g) was refluxed with NaI (6 g) in dry acetone (100 ml) for 3 hr. The usual work up gave methyl-5-iodo-2*R*-methyl-pentanoate (8 g) as a yellow oil, b.p. 80–82°/1 mm, $(\alpha)_D$ −12·8°.

Methyl-5-*nitro*-2R-*methyl pentanoate* (IIb)

The above iodo ester (7 g) taken in dry ether (25 ml) was added dropwise with stirring to a suspension of $AgNO_2$ (5 g) in dry ether (150 ml) at 0° during a period of 90 min. Light was shut out by wrapping the reaction vessel in black paper. The stirring was continued for 24 hr at 0° and for further 40 hr at room temp. The mixture was then filtered and the cake washed, thoroughly with ether. The solvent was distilled off from the combined ethereal soln. The residue was carefully fractionated to obtain IIb as a pale yellow oil (3 g), b.p. 105–108°/3 mm, $(\alpha)_D$ −13·0° ν_{max} 1725, 1540 cm^{-1}. (Found: N, 7·76 $C_7H_{13}NO_4$ requires: N, 8·0%).

Michael addition of 2R-*methyl*-5-*nitro-pentanoate* (IIb) *to* cis-5,17(20) *pregnadien*-3β-*ol*-16-*one* (I)

A soln of K salt of IIb (from 1·3 g of nitro ester and 130 mg of K-metal) in t-BuOH (4 ml) was added to a soln of *cis*-ketone (1·0 g) in t-BuOH (10 ml). The clear soln was then allowed to stand at room temp. The progress of the reaction was checked after every 48 hr. A small portion of the mixture was withdrawn, made just acidic with dil AcOH, diluted with water and extracted with CH_2Cl_2. The extract was washed with

5% $NaHCO_3$ aq, water, dried and the solvent was evaporated. The residue was tested by TLC to detect any unreacted starting ketone. The addition was complete in 14 days when the whole mixture was made just acidic with 10% AcOH and diluted with water (100 ml). The crude solid was filtered off and crystallised once from MeOH to a white crystalline solid (750 mg), m.p. 140–145°. This solid appeared homogeneous on routine TLC, on silica gel, with a number of solvent systems. However, by eluting (10 cm) 5 times in ether: light petroleum: EtOAc (5:5:2) it was resolved into 2 spots. 120 mg of this material was then separated into two components by preparative TLC.

26-*Carbomethoxy*(22ξ,25R)22-*nitro*-5-*cholesten*-3β-*ol*-16-*one* (IIIb *or* IVb)

From the lower band, R_f 0·52, a white solid (50 mg), m.p. 162–163° (MeOH), ν_{max} 1735, 1535 cm^{-1}, was obtained. (Found: C, 68·45, H, 8·95; $C_{28}H_{43}NO_6$ requires: C, 68·71; H, 8·79%).

26-*Carbomethoxy*(22ξ,25R)22-*nitro*-5-*cholesten*-3β-*ol*-16-*one* (*isomeric at* C-22 *with above*)

From the upper band, R_f 0·58, a white solid (55 mg), m.p. 166–167° (methanol), ν_{max} 1735, 1535 cm^{-1} was obtained. (Found: C, 68·56; H, 8·99. $C_{28}H_{43}NO_6$ requires: C, 68·72; H, 8·79%).

Because the asymmetry at C-22 is ultimately eliminated in one of the subsequent steps for the synthesis of solasodine, subsequent reactions were carried on an unseparated mixture of Michael adducts.

26-*Carbomethoxy*(22ξ,25R)22-*nitro*-5-*cholesten*-3β-16β-*diol* (Vb + VIb)

A soln of $NaBH_4$ (200 mg) in water (1·2 ml) was added dropwise to a soln of unseparated mixture of IIIb and IVb (200 mg) in EtOH (10 ml). The pH of the mixture was maintained between 3 and 7 by concurrent addition of 3N H_2SO_4. The addition was effected during a period of 90 min while the temp was maintained between 10 and 30°. The mixture on work up as in the case of *S*-series gave a white solid (180 mg), m.p. 115–118° (MeOH), ν_{max} 1725, 1535 cm^{-1}.

(22ξ,25R)22,26-*Imino*-26-*oxo*-5-*cholesten*-3β,16β-*diol* (VIIb + VIIIb)

Zinc dust (2·5 g) was added, in portions over a period of 3 hr, to a refluxing soln of above nitro ester (100 mg) mixture in glacial AcOH (5 ml). It was worked up as before and the obtained neutral solid (45 mg) was crystallised from EtOH to give a white solid, m.p. 225–230°, ν_{max} 1630 cm^{-1}.

Lithium aluminium hydride reduction of (22ξ,25R)-22,26-*imino*-26-*oxo*-5-*cholesten*-3β,16β-*diol* (VIIb + VIIIb)

Above hydroxy amide (50 mg) mixture was refluxed with LAH (150 mg) in dry dioxan (25 ml) on an oil bath (130–140°) for 12 hr. Additional LAH (100 mg) was added and refluxing continued for further 13 hr. The mixture was worked up as before when a basic solid (35 mg) was obtained. On TLC in a number of solvent systems it showed only two major spots and its IR spectrum revealed no absorption in the carbonyl region.

Solasodine (XII)

The N-chloro derivative (20 mg) was obtained from the above basic solid (30 mg) by treatment with N-chlorosuccinimide as described earlier. Its treatment with NaOMe (from 60 mg Na and 6 ml MeOH) for 1 hr at room temp afforded a base which was crystallised from EtOH to give a crystalline material (6 mg), m.p. 194–196°. It was compared with a sample of natural solasodine,[2] m.p. 195–197°. The two had superimposable IR spectra, identical R_f values in a number of solvent systems and showed no depression in m.p. on admixture.

REFERENCES

[1] K. Schreiber and G. Adam, *Experientia* **17**, 13 (1961)

[2] We are grateful to Prof. K. Schreiber for natural samples of tomatid-5-ene-3β-ol and solasodine

[3] See the preceding paper

[5] Budzikiewicz, Djerassi and Williams, *Mass Spectrometry of Organic Compounds* p. 512; N. M. M. Nibbering, Th.J. de Boer and H. J. Hofman, *Rec. Trav. Chim.* **84**, 481 (1965)

[5] R. Ryhage and E. Stenhagen, *J. Lipid Res.* **1**, 361 (1960); *Advances in Mass Spectrometry* (Edited by H. J. M. Fitches and R. M. Elliott) Vol. II. Pergamon Press, London (1962)

[6] H. Budzikiewicz, *Tetrahedron* **20**, 2267 (1964)

[7] H. Budzikiewicz, F. Compernolle, K. van cauwenberghe, K. Schulze, H. Wolk and G. Quinkert, *Ibid.* **24**, 6797 (1968)

[8] Y. Mazur, N. Danieli and F. Sondheimer, *J. Am. Chem. Soc.* **82**, 5889 (1960)
[9] K. Schreiber and G. Adam, *Tetrahedron Letters* No 5, **27**,(1960); *Liebigs Ann.* **666**, 155 (1963); *Chem. Abstr.* **59**, 14055 (1963)
[10] S. V. Kessar, A. L. Rampal and Y. P. Gupta, *Tetrahedron* **24**,905 (1968)
[11] K. Schreiber and H. Ronsch, *Ibid.* **21**, 645 (1965)
[12] G. Stallberg, *Acta Chem. Scand.* **11**, 1430 (1957)