# The Total Synthesis of Dihydrocostunolide

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A seven-step synthesis of the sesquiterpene dihydrocostunolide (1) from santonin (5) is described. The key elements of this approach, the first to yield a synthetic sesquiterpene in the cyclodecadiene series, are the photolytic cleavage of the hexahydronaphthalene derivative 10 to form a cyclodecatriene (13) and the subsequent selective hydrogenation to a cyclodeca-1,5-diene (1).

Dihydrocostunolide (1) and costunolide (2) are members of a group of sesquiterpenes possessing a ten-membered carbocyclic unit. They are of particular interest because of this structural feature and also as possible biogenetic links between farnesol and certain polycarbocyclic sesquiterpenes, especially the guaianolide and eudesmolide (santonin) types.[1,2] The carbon skeleton of the known sesquiterpenes having a ten-

1   2
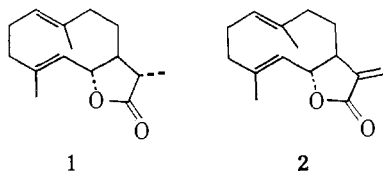
membered ring can be derived formally from farnesol (3) by cation–olefin cyclization and this formulation of the biogenesis is an attractive possibility. However, the laboratory synthesis of these sesquiterpenes by

3   4
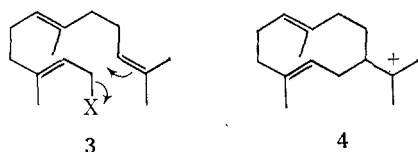
such a cyclization has not yet been realized, despite its apparent simplicity and, moreover, the application of the well-known classical synthetic operations for ring formation offers little promise. As a consequence, these novel structures present an intriguing synthetic problem and are of special interest to the chemists who seek to extend synthetic methodology. We describe here a short synthesis of dihydrocostunolide (1) by a new approach which also would seem to be applicable to other sesquiterpenoid structures. Dihydrocostunolide was first obtained by catalytic hydrogenation of the related natural product costunolide (2).[3] However, more recent studies indicate that dihydrocostunolide is also a naturally occurring substance.[4,5]

The point of origin for this synthesis (see Chart I) was the known keto lactone 8 which was prepared from santonin[6] (5) by a three-step sequence involving first the previously described hydrogenation of santonin[7] which gives the saturated, *trans*-fused tetrahydro ketone 6

Chart I

5   6   4-epi 6

9   8   7

11   10   13   1

14   12   16
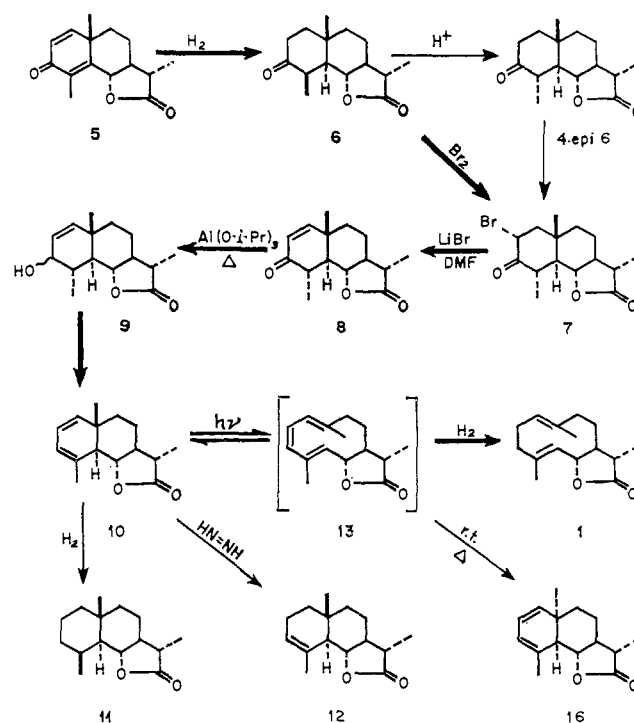
in *ca.* 35% yield. The 4-epimer of 6 can be obtained from the residual product of the hydrogenation by treatment with hydrochloric acid–ethanol and in this way an additional 14% of saturated ketone is recovered. Bromination of 6 or the 4-epimer affords 2α-bromo-3-oxo-5αH, 4,6,11βH-eudesman-6,13-olide (7) (60% yield) in a process involving equilibration at C-4 as well as halogenation at C-2.[8,9] Treatment of 7 with collidine was previously reported to give 4,5-dihydrosantonin 8 in <18%[9] and in 45%[7] yields; in our hands the yield of 8 was only 30% and therefore a better method was sought for the preparation of this intermediate. The lithium halide–dimethylformamide dehydrohalogenation method, first reported by Holysz[10] and later em-

(1) For recent reviews of medium-ring containing sesquiterpenes see F. Sorm, *Fortschr. Chem. org. Naturstoffe*, 19, 1 (1961); T. G. Halsall and D. W. Theobald, *Quart. Rev.* (London), 16, 1 (1962).

(2) A discussion of biogenetic relationships can be found in (a) L. Ruzicka, *Experientia*, 9, 357 (1953); *Proc. Chem. Soc.*, 341 (1959); (b) J. B. Hendrickson, *Tetrahedron*, 7, 82 (1959); (c) J. H. Richards and J. B. Hendrickson, "The Biosynthesis of Steroids, Terpenes, and Acetogenins," W. A. Benjamin, Inc., New York, N. Y., 1964, Chapter 8.

(3) A. S. Rao, G. R. Kelkar, and S. C. Bhattacharyya, *Tetrahedron*, 9, 275 (1960), and earlier papers.

(4) A. S. Rao, A. Paul, D. Sadgopal, and S. C. Bhattacharyya, *ibid.*, 13, 319 (1961).

(5) For a preliminary announcement of this work see E. J. Corey and A. G. Hortmann, *J. Am. Chem. Soc.*, 85, 4033 (1963).

(6) Previously made by total synthesis by Y. Abe, T. Harukawa, H. Ishikawa, T. Miki, N. Sumi, and T. Toga, *Proc. Japan Acad.*, 28, 425 (1952); 29, 113 (1953); 30, 116, 119 (1954).

(7) J. B. Hendrickson and T. L. Bogard, *J. Chem. Soc.*, 1678 (1962).

(8) W. Cocker and T. B. H. McMurry, *ibid.*, 4549 (1956). The nomenclature used is that of Cocker and McMurry with provision for the recently revised configuration of santonin at C-11: see (a) J. D. M. Asher and G. A. Sim, *Proc. Chem. Soc.*, 111 (1962); (b) J. W. Huffman, *J. Org. Chem.*, 28, 601 (1963); (c) M. Nakazaki and H. Arakawa, *Proc. Chem. Soc.*, 151 (1962); (d) D. H. R. Barton, T. Miki, J. T. Pinhey, and R. J. Wells, *ibid.*, 112 (1962).

(9) M. Yanagita and A. Tahara, *J. Org. Chem.*, 20, 959 (1955).

(10) R. P. Holysz, *J. Am. Chem. Soc.*, 75, 4432 (1953).

ployed in the preparation of steroidal Δ^1-3-ketones,[11,12] gave excellent results. Thus, treatment of **7** with lithium bromide–lithium carbonate in dimethylformamide at 120° produced the pure dihydrosantonin **8** consistently in 80–90% yield.

The enone lactone **8** was next converted to the diene lactone **10**, a key intermediate in the synthesis, by way of the hydroxy lactone **9**. However, some initial difficulties were experienced in the reduction of **8** to the allylic alcohol and these deserve mention. On attempted reduction with sodium borohydride, a mixture of saturated and allylic alcohols was obtained, which, on oxidation with manganese dioxide produced a ca. 1:3 mixture of **8** and an unchanged alcohol exhibiting no resonance peaks due to vinyl protons in the n.m.r. Treatment of **8** with lithium aluminum tri-*t*-butoxyhydride in tetrahydrofuran at 0° for 4 hr. gave a 50% yield of the 4-epimer of **6** and only minor amounts of the desired product. It appears that the initial reduction of **8** with hydride occurs at the carbon–carbon double bond. Some similar examples have been cited in connection with the chemistry of cedrelone.[13] Nonetheless, it was possible to obtain the allylic alcohol **9** in 90% yield (as a mixture of 3-epimers) by reduction of the enone **8** with aluminum isopropoxide–isopropyl alcohol, and in consonance with structure **9** this product could be oxidized to **8** by treatment with manganese dioxide in essentially quantitative yield. The key intermediate, diene **10** was obtained from the alcohol **9** (44% yield) by heating with pyridine-treated alumina[14,15] at 220–230°. In agreement with structure **10** the product exhibited a peak in the ultraviolet (CH_3OH) at 262 mμ (ϵ 4900) and infrared absorption (CCl_4) at 1785 (s), 1640 (w), and 1585 (w) cm.$^{-1}$. The integrated n.m.r. spectrum in deuteriochloroform showed peaks at 0.93 (3 H, singlet; C-14 methyl), 1.21 (3 H, doublet, $J = 7$ c.p.s.; C-12 methyl), 1.98 (3 H, singlet; C-15 methyl), 4.08 (1 H, multiplet; 6β-H), and 5.68 (3 H, multiplet, complex; 1-, 2-, and 3-H) p.p.m. downfield from tetramethylsilane as an internal standard. The multiplet at 4.08 p.p.m. appeared to be an ABC quartet exhibiting $J_{AC} \approx 9$ c.p.s. and $J_{BC} \approx 11.5$ c.p.s. in agreement with a dihedral angle of approximately 180° between the 6β-H and the vicinal α-oriented hydrogens at C-5 and C-7.

Further evidence for structure **10** was provided by hydrogenation of the diene with platinum in acetic acid–methanol to yield a compound identical in its melting point and infrared spectrum (Nujol) with santanolide "c" (**11**).[3] Partial reduction of the diene **10** with diimide gave the known 3-santenolide (**12**).[8,16]

The transformation of the diene **10** to a ten-membered carbocycle was accomplished photochemically using the now well-known photofission of 1,3-cyclohexadiene systems.[17,18] The irradiation of **10** was carried out in

methanol solution at $-18°$ under an argon atmosphere using a low-pressure mercury discharge tube (Hanovia Type SC-2537, 96.5% of total ultraviolet (ca. 10-w.) emitted at 2537 Å.) and a filter of chlorine gas at 1 atm. All but 25 cm.^{2} of the surface area of the light source was masked and the source, filter, and quartz jacket were surrounded by the externally cooled solution of diene **10**. Spectroscopic analysis of the cold solution at several-minute intervals during irradiation indicated the gradual appearance of a strong absorption peak at 211 mμ and the diminution of the original diene band at ca. 265 mμ. After about 1 hr. a photostationary state was reached in which the ratio of the optical density at 211 mμ to that at 265 mμ was 3.4 (initial value, 0.1); ca. 50–55% of diene **10** remained in the steady-state mixture which resulted under the conditions of the experiment.

The other component of the mixture is considered to be triene **13** both on the basis of existing analogy and because of the subsequent conversion to dihydrocostunolide. Inspection of models indicates that the geometry of triene **13** is not such as to allow extensive π-conjugation and so the occurrence of the main absorption maximum at 211 mμ rather than at longer wave length is not regarded as inconsistent with this structure.

Essentially the same results were obtained when the irradiation of the diene **10** was performed using *n*-pentane as solvent at $-70°$. It was found that the product of irradiation underwent a thermal transformation which could be followed by measuring changes in the ultraviolet absorption spectrum; the absorption at 218 mμ decreased and that at ca. 265 mμ increased. In methanol as solvent the half-life for this reaction was ca. 2 hr. at $+5°$ whereas in pentane the half-life was ca. 1 hr. It thus appeared that the triene **13** was thermally unstable and as a consequence all operations involving this intermediate were conducted at temperatures below $-15°$ using methanol as solvent.

Assuming the formation of the triene lactone **13** in the irradiation of the diene **10**, the synthesis of dihydrocostunolide then becomes a matter of selective reduction of the disubstituted double bond of **13**. As expected from the generally greater rate of catalytic hydrogenation of dialkylated double bonds as compared with trialkylated olefins and also from the fact that the trisubstituted double bonds of constunolide (**2**) are relatively inert to hydrogenation at room temperature,[8] it was possible to obtain dihydrocostunolide from the photolysis mixture by catalytic hydrogenation. Selective reduction was accomplished simply by bubbling hydrogen through a cold ($-18°$), methanolic solution of the photolysis products after addition of Raney nickel. The hydrogenation product obtained was a mixture consisting mainly of santanolide "c" (**11**), 3-santenolide (**12**), and dihydrocostunolide. The presence of dihydrocostunolide (**1**) could be demonstrated by the appearance of two characteristic peaks in the n.m.r. spectrum (CCl_4) at 1.67 and 1.41 p.p.m. due to the methyl hydrogens in the CH=CMe groupings in **1**. The upfield peak (1.41 p.p.m.) is due to the methyl

(11) R. Joly, J. Warnant, G. Nominé, and D. Bertin, *Bull. soc. chim. France*, 366 (1958).

(12) R. Joly and J. Warnant, *ibid.*, 367 (1958).

(13) R. Hodges, S. G. McGeachin, and R. A. Raphael, *J. Chem. Soc.*, 2515 (1963).

(14) E. von Rudolff, *Can. J. Chem.*, **39**, 1860 (1961).

(15) L. Beránek, M. Kraus, K. Kochloefl, and V. Bažant, *Collection Czech. Chem. Commun.*, **25**, 2513 (1960).

(16) The diene **10** has also been prepared from **8** by Professor G. Büchi and Dr. D. W. Hutchinson using different procedures for reduction and elimination: personal communication from Dr. Büchi.

(17) The classical case of such a reaction is the formation of precalciferol from ergosterol in the light-promoted synthesis of vitamin D: see (a) E. Havinga, R. J. deKock, and M. P. Rappoldt, *Tetrahedron*, **11**,

276 (1960), and previous papers; (b) L. Velluz, B. Goffinet, and G. Amiard, *ibid.*, **4**, 241 (1958); (c) H. H. Inhoffen, *Fortschr. Chem. org. Naturstoffe*, **17**, 70 (1959).
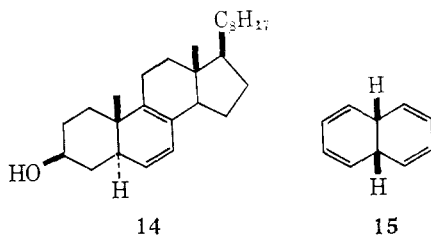
(18) D. H. R. Barton, *Helv. Chim. Acta*, **42**, 2604 (1959); D. H. R. Barton and G. Quinkert, *J. Chem. Soc.*, 1 (1960).

protons in one such grouping which are shielded by the transannular π-electrons of the other $-CH=Me-$ grouping. This effect, which has previously been observed for costunolide,[19] was found in the present work to extend to dihydrocostunolide (1), an authentic sample of which was prepared from natural costunolide (2)[20] as previously described.[3] The vinyl hydrogens of dihydrocostunolide are also shifted upfield in a characteristic manner and appear in the crude hydrogenation products as a multiplet with major peaks at 4.58 and 4.47 p.p.m. Thin layer chromatography on silica gel G–25% silver nitrate[21,22] showed spots having the same R_f values as 11, 12, and 1 after development with iodine vapor.

When the crude hydrogenation product was chromatographed on silicic acid at room temperature, monitoring the collected fractions by n.m.r. analysis, very little dihydrocostunolide (1) was found to survive. However, chromatography of the hydrogenation product on silicic acid, programming the temperature from -23 to $+5°$, led to considerable reduction of rearrangements and afforded pure synthetic dihydrocostunolide (1), identical in its melting point, rotation, and infrared, ultraviolet, and n.m.r. spectra with an authentic specimen. The yield of 1 was 10% based on the amount of diene actually photolyzed in the irradiation step.

The synthesis of dihydrocostunolide demonstrates the feasibility of producing by synthesis sesquiterpenes of this type. It is clear from the above discussion that the experimental complications are not trivial and that great care must be exercised especially in the diene photolysis, triene hydrogenation, and in the isolation of the relatively unstable 1,5-cyclodecadiene system.

To our knowledge the transformation of the diene 10 to the cyclodecatriene derivative 13 is the first example of the successful utilization of the photofission of 1,3-cyclohexadienes to the synthesis of a medium ring system. However, it has been considered that the product from the irradiation[23] of isodehydrocholesterol (14) is the 5-epimer formed *via* an intermediate cyclodecatriene.[24] Of some relevance is the report that attempts to synthesize cyclodecapentaene by photolysis of the *cis*-fused dihydronaphthalene 15 were not successful.[25]

14   15

The thermal decomposition of the triene 13 was also investigated. A solution of the diene 10 was irradiated at $-18°$ until the absorption of the photolysis solution at λ_{max}^{MeOH} 262–265 mμ had been reduced to one-half its

original intensity. After the resulting solution had been kept at 25° for 6 hr., the final absorption intensity at 265 mμ was found to have reverted to a value almost identical with that of the solution of 10 before irradiation. The solution obtained in this way was evaporated to dryness and the residue was subjected to spectroscopic analysis. The n.m.r. spectrum was found to exhibit two sharp peaks of identical height (≈ 1.5 H each) at 0.89 and 0.96 p.p.m. corresponding, respectively, to the protons on the C-14 methyl group of the starting diene 10 and a newly formed product. The mixture, in amounts up to 0.5 mg., could be cleanly separated into its components by vapor phase chromatography (v.p.c.) using a 4-ft. column of cyanosilicon rubber (5%) on Diatoport S. However, a very practical separation which yielded the new diene in pure form was achieved by chromatography on silica gel–10% silver nitrate. The new diene, isomeric with 10, had m.p. 69.5–70.5°, ultraviolet maximum 265 mμ (ϵ 4800, methanol), n.m.r. peaks at 0.98 (3 H, singlet), 1.15 (3 H, doublet, $J = 7$ c.p.s.), 1.95 (3 H, singlet), 3.79 p.p.m. (1 H, ABC triplet), and a series due to three olefinic protons at 5.2 to 6.0 p.p.m. This diene is regarded tentatively as the *cis*-fused $\Delta^{1,3}$-diene 16 on the basis of the n.m.r. data and the findings of Vogel and Marvell[26] and co-workers that *trans, cis, trans*-1,6-dimethyl-1,3,5-triene, an analog of 13, affords by thermal cyclization *cis*-1,2-dimethylcyclohexa-3,5-diene stereospecifically. The ABC triplet in the n.m.r. spectrum of the diene can be assigned to the 6β-proton being split by neighboring hydrogens at C-5 and C-7 with J_{AC} and $J_{BC} \approx 10$ c.p.s. Of the two possible *cis* dienes only isomer 16 can account for the observed magnitude of these coupling constants.

It is noteworthy that the irradiation of the diene 16 did not lead to the development of triene absorption at 211 mμ.

Experimental Section[27]

3-Oxo-4,5αH,6,11βH-eudesman-6,13-olide (6). By Hydrogenation of Santonin over 2% Palladium on Strontium Carbonate. The method of Hendrickson and Bogard[7] was followed. Santonin (5, 7.7 g., 0.03 mole), ethyl acetate (250 ml.), and a previously reduced suspension of 2% palladium on strontium carbonate (3.35 g.) were stirred in an atmosphere of hydrogen at room temperature and pressure for 15 min. The hydrogen uptake ceased at 0.066 mole. The catalyst was removed, and the solvent was evaporated. Fractional crystallization of the product from aqueous acetone, followed by recrystallization from aqueous ethanol, gave a total yield of 2.65 g. (34%) of 3-oxo-4,5αH, 6,11βH-eudesman-6,13-olide (6) as plates, m.p. 145.5–147° (lit.[7,8] m.p. 146°, 143°).

2α-Bromo-3-oxo-5αH,4,6,11βH-eudesman-6,13-olide (7). A solution of 3-oxo-4,5αH,6,11βH-eudesman-6,13-olide (6, 2.0 g., 0.008 mole), m.p. 145.5–147°, in chloroform (70 ml.) at 0° was treated with 0.93

(19) R. B. Bates and D. M. Gale, *J. Am. Chem. Soc.*, 82, 5749 (1960).
(20) The authors wish to express their appreciation for samples of authentic costunolide received from Dr. V. Herout (Prague, Czechoslovakia) and Dr. S. C. Bhattacharyya (Poona, India).
(21) C. B. Barrett, M. S. J. Dallas, and F. B. Padley, *Chem. Ind.* (London), 1050 (1962).
(22) B. deVries, *ibid.*, 1049 (1962).
(23) A. Windaus and G. Zühlsdorff, *Ann. Chem.*, 536, 204 (1938).
(24) P. de Mayo and S. T. Reid, *Quart. Rev.* (London), 15, 393 (1961).
(25) E. E. van Tamelen and B. Pappas, *J. Am. Chem. Soc.*, 85, 3296, (1963).

(26) (a) E. Vogel, W. Grimme, and E. Dinne, *Tetrahedron Letters*, No. 7, 391 (1965); (b) E. N. Marvell, G. Caple, and B. Schatz, *ibid.*, No. 7, 385 (1965).
(27) All melting points are corrected. Rotations were measured in chloroform. The infrared spectra were recorded on a Perkin-Elmer Infracord and the ultraviolet spectra were measured on a Cary 11 M recording spectrophotometer. The n.m.r. spectra were taken in carbon tetrachloride on a Varian A-60 spectrometer and reported in units of p.p.m. downfield from tetramethylsilane as an internal standard.

M bromine–carbon tetrachloride solution (9.1 ml., 0.00846 mole) all at once. Stirring was continued at 0° for 45 min. after disappearance of the bromine color. Water was added and the chloroform layer was washed successively with saturated sodium bicarbonate and saturated sodium chloride solutions, dried over anhydrous sodium sulfate, and reduced to dryness *in vacuo* at room temperature. Recrystallization (twice) from ethanol–water gave 1.67 g. (63%) of 2α-bromo-3-oxo-5αH,4,6,11βH-eudesman-6,13-olide (7) as prisms, m.p. 148° dec. (lit.[8,9] m.p. 145–147°, 147–148°).

When treated similarly, the 4βH-isomer of the saturated ketone 6 gave the same product and yield.

 3-Oxo-5αH,4,6,11βH-eudesm-1-en-6,13-olide (8). *A. By Collidine Dehydrobromination of 7.* A solution of 2α-bromo-3-oxo-5αH,4,6,11βH-eudesman-6,13-olide (7, 1.67 g., 0.005 mole) in 20 ml. of γ-collidine was heated at reflux temperature for 3.5 hr. under nitrogen. The product was isolated as described,[7] twice sublimed *in vacuo*, and finally recrystallized from benzene–hexane to give 0.43 g. (30%) of 3-oxo-5αH,4,6,11βH-eudesm-1-en-6,13-olide (8) as needles, m.p. 140–142° (lit.[7] m.p. 138–140°).

 B. By Lithium Bromide–Lithium Carbonate–Dimethylformamide Dehydrobromination[10–12] *of 7.* To a stirred suspension of dry lithium bromide (3.0 g.) and lithium carbonate (4.0 g.) in dry dimethylformamide (50 ml.) at 120° under nitrogen was added 7.26 g. (0.022 mole) of 2α-bromo-3-oxo-5αH,4,6,11βH-eudesman-6,13-olide (7). Stirring was continued for 75 min. at 120–125°. The reaction mixture was cooled, poured into dilute acetic acid, and extracted with methylene chloride. The extracts were washed with water (the washings were back extracted) and saturated sodium chloride solution and dried over anhydrous sodium sulfate. Crystallization from benzene–hexane gave 3-oxo-5αH,4,6,11βH-eudesm-1-en-6,13-olide (8) as needles, m.p. 141.5–142.5° (lit.[7] m.p. 138–140°), yield 4.62 g. (85%). Mixture melting point with an authentic sample of 8 prepared by method A was 140–141.5°.

Compound 8 showed $\nu_{max}^{CHCl_3}$ 1780 and 1680 cm.$^{-1}$; the n.m.r. spectrum (CDCl$_3$) exhibited the previously reported AB pattern ($J = 9.5$ c.p.s.) centered at 5.92 and 6.80 p.p.m. due to the H-1–H-2 interactions.

 3-Hydroxy-5αH,4,6,11βH-eudesm-1-en-6,13-olide (9). A solution of 3-oxo-5αH,4,6,11βH-eudesm-1-en-6,13-olide (8, 18.7 g., 0.075 mole) and aluminum isopropoxide (26 g., Eastman, practical grade) in dry 2-propanol (150 ml.) was allowed to boil gently in a 250-ml. flask fitted with a 20-cm. Vigreux column. The acetone vapor formed was allowed to escape from the reaction mixture. After 6 hr. the 2-propanol was distilled and the reaction mixture was reduced to *ca.* a 50-ml. volume. Cold 1 *N* hydrochloric acid was added, and the resulting acidic solution was extracted with methylene chloride. The extracts were washed with saturated sodium bicarbonate and saturated sodium chloride solutions and dried over sodium sulfate. Crystallization from acetone–hexane gave 3-hydroxy-5αH,4,6,11βH-eudesm-1-en-6,13-olide (9) as a mixture of needles and plates: m.p. 156–172°; yield 16.9 g. (90%); $\nu_{max}^{CHCl_3}$ 3700 (m), 3580 (m), 1770 (s), and 698 (w) cm.$^{-1}$.

Repeated recrystallization produced very little change

in the melting point, indicating a probable mixture of 3-isomers.

A solution of the alcohol mixture 9 (0.045 g.) in 5 ml. of chloroform was stirred at room temperature for 18 hr. with 0.5 g. of freshly prepared manganese dioxide.[28] The oxidant was removed by gravity filtration, and the filtrate was evaporated to dryness. Crystallization of the residue from hexane gave 0.038 g. (85%) of 3-oxo-5αH,4,6,11βH-eudesm-1-en-6,13-olide (8), m.p. 141–143.5° (lit.[7] m.p. 138–140°), identical in the infrared spectrum with an authentic sample of 8 prepared as described above.

 Unsuccessful Attempts at the Preparation of 3-Hydroxy-5αH,4,6,11βH-eudesm-1-en-6,13-olide (9). *A. Reduction of 3-Oxo-5αH,4,6,11βH-eudesm-1-en-6,13-olide* (8) *by Lithium Aluminum Tri-t-butoxyhydride.* A solution of the unsaturated ketone 8 (0.240 g., 0.00097 mole) in tetrahydrofuran (5 ml.) at 0° was treated with lithium aluminum tri-*t*-butyoxyhydride (1.0 g., 0.0039 mole) in tetrahydrofuran (5 ml.). Stirring was continued for 4 hr. at 0°. The excess reducing agent was decomposed by careful addition of dilute acetic acid. The product was extracted into methylene chloride; crystallization from aqueous ethanol gave 0.120 g. of 4-epi 6 (50%) as plates, m.p. 137.5–145°. One recrystallization raised the melting point to 146–151°.

The product exhibited $\nu_{max}^{CHCl_3}$ 1780 (vs) and 1712 (s) cm.$^{-1}$; the melting point was undepressed when the product was admixed with an authentic sample (m.p. 151.5–154°) of 3-oxo-5αH,4,6,11βH-eudesman-6,13-olide.

The mother liquors contained additional saturated ketone and a small amount of hydroxylic material which was not further investigated.

 B. Reduction of 3-Oxo-5αH,4,6,11βH-eudesm-1-en-6,13-olide (8) *with Sodium Borohydride.* Attempts to reduce the unsaturated ketone with sodium borohydride in ethanol–water at 0–10° gave a *ca.* 1:3 ratio of a 3-hydroxyeudesm-1-en-olide and a 3-hydroxyeudesmanolide, respectively, by n.m.r. analysis and manganese dioxide oxidation product analysis (infrared, ultraviolet, and n.m.r.).

 5αH,6,11β-Eudesm-1,3-dien-6,13-olide (10). A finely ground mixture of 3.00 g. (0.012 mole) of 3-hydroxy-5αH,4,6,11βH-eudesm-1-en-6,13-olide (9) and 8.4 g. of alumina (Woelm, grade I, neutral) which had been previously treated with 2% (v./w.) of pyridine[14,15] was evenly distributed on a glass "boat" consisting of a 20-cm. length of Pyrex tubing (25 mm. o.d.) which had split in half lengthwise. The boat was inserted into the heated section (30 cm.) of a 120-cm. length of Pyrex tubing (30 mm. o.d.) under an atmosphere of preheated nitrogen (flow rate *ca.* 350 ml./min. at STP). (The tube was heated by means of an electric furnace (Hevi Duty Elec. Co., Milwaukee, Wis.) and was allowed to attain equilibrium temperature of 230° before insertion of the loaded boat.) After a few minutes the product began to distil out of the heated portion of the tube and to condense as a partially crystalline solid at a cooler portion. After 1.75 hr. the tube was cooled, the boat was removed, and the condensed product was collected (yield 1.93 g.). The combined product (7.65 g.) obtained from four runs

(28) J. Attenburrow, *et al.*, *J. Chem. Soc.*, 1094 (1952).

was dissolved in methylene chloride and adsorbed on a column of Florisil (200 g., 100–200 mesh, packed in n-pentane–benzene (1:1)). Elution with n-pentane–benzene (1:1, 3 1.) gave 5.04 g. of crystalline solid which was dissolved in hot n-heptane (50 ml.) and clarified by filtration through Supercel. Crystallization afforded 4.44 g. (40%) of 5αH,6,11βH-eudesm-1,3-dien-6,13-olide (10) as heavy plates, m.p. 96.5–98.5°. The mother liquor gave an additional 0.17 g., m.p. 93.5–96.5°.

An analytical sample of 10 exhibited m.p. 95–97°; $[\alpha]^{29}D$ +70.5° (c, 0.6); λ_{max}^{MeOH} 262 mμ (ε 4900); ν_{max}^{CCl4} 1785 (s), 1640 (w), 1585 (w), 1455 (m), 1445 (m, shoulder), 1230 (ms), 1190 (ms), 1155 (ms), 1120 (ms), 1020 (s), 1000 (s), 985 (m, shoulder), 865 (m), and 726 (s) cm.$^{-1}$; the n.m.r. spectrum (in CDCl₃) exhibited resonance peaks at 0.93 (3 H, singlet), 1.21 (3 H, doublet, J = 7 c.p.s.), 1.98 (3 H, singlet), 4.08 (1 H, multiplet), and 5.68 (3 H, multiplet) p.p.m.

Anal. Calcd. for $C_{15}H_{20}O_2$: C, 77.55; H, 8.68. Found: C, 77.71; H, 8.80.

Further elution of the column with chloroform (1.1 1.) gave 2.26 g. of yellow gum which crystallized from n-heptane–acetone to yield 1.27 g. as plates, m.p. 132–140°. The infrared spectrum exhibited bands at 1780 (s) and 1710 (s) cm.$^{-1}$ and was essentially identical with that of 3-oxo-5αH,4,6,11βH-eudesman-6,13-olide.

The residual alumina from the above four runs was combined and washed with methylene chloride containing 10% methanol. The filtered washings were evaporated to dryness to yield 1.95 g. of a yellow oil which appeared to be mainly a mixture of keto–lactones (infrared) and was not further investigated.

Hydrogenation of 5αH,6,11βH-Eudesm-1,3-dien-6,13-olide (10). *A. Partial Reduction with Hydrazine–Hydrogen Peroxide (Diimide).* The diene 10 (223 mg., 0.96 mmole) was dissolved in 100 ml. of methanol containing 0.3 ml. of cupric acetate solution (10^{-3} M) and cooled to −12°. To the solution was added, in ten equal portions at 8-min. intervals, a total of 60 ml. (144 mmoles) of 30% aqueous hydrogen peroxide (15 ml.) in methanol (45 ml.). Each addition was followed immediately by addition of 0.2 ml. (6 mmoles) of 95% hydrazine. Temperature was maintained at −5 to −10° during the addition and for 30 min. afterwards. Water (20 ml.) was added and the methanol was removed at room temperature *in vacuo*. The concentrated solution was extracted with chloroform and worked up as usual to yield 220 mg. of crystalline material, $\lambda\lambda_{max}^{MeOH}$ 203 mμ (ε 4000) and 262 mμ (ε 770). The product was chromatographed on 22 g. of silica gel–10% silver nitrate (Fischer silica gel, 28–200 mesh; slurried with an equivalent amount of 10% silver nitrate solution, and taken to dryness at room temperature *in vacuo*).[21,22] Elution with benzene–ligroin (1:1) gave 162 mg. (72%) of 5αH,6,11βH-eudesm-3-en-6,13-olide (12) as feathery needles, m.p. 129–133°. Six recrystallizations from a variety of solvent combinations gave 65 mg. of 12; m.p. 134.0–137.3°; $[\alpha]^{29}D$ +83.2° (c 0.8) (lit.[8] m.p. 136–137°, $[\alpha]^{29}D$ +90.6° (c 0.13, CHCl₃)); the n.m.r. showed peaks at 0.92 (3 H, singlet), 1.16 (3 H, doublet, J = 7 c.p.s.), 1.80 (3 H, broad singlet), 3.79 (1 H, multiplet), and 5.32 (1 H, multiplet) p.p.m.

Further elution of the column with increasing pro-

portions of benzene gave 28 mg. (12.5%) of the starting diene 10.

B. Catalytic Hydrogenation over Platinum. To a suspension of prereduced platinum oxide (12.5 mg.) in acetic acid–methanol (1.5 ml., 2:1) was added 116 mg. (0.5 mmole) of the diene 10 in 2.5 ml. of methanol. After 1 hr. of stirring at 33° the uptake of hydrogen had ceased at 25.0 ml. (theor., 25.1 ml.). The suspension was filtered and the filtrate was diluted with water to yield 106 mg. (90%) of 4:5αH,6,11βH-eudesman-6,13-olide (11) (santanolide "c") as plates, m.p. 149–154°. Two recrystallizations from n-hexane gave m.p. 154–155°, $[\alpha]^{29}D$ +63.6° (c 0.5) (lit.[3] m.p. 154–155°, $[\alpha]D$ +55.1° (c 3.5, CHCl₃)). The infrared spectrum (Nujol) was identical with that reported[3] for santanolide "c." The integrated n.m.r. spectrum of 16 exhibited sharp peaks at 0.95 (1.5 H), 1.03 (3 H), 1.08 (3 H), and 1.20 (1.5 H) p.p.m., and characteristic multiplets at 2.21 and 3.80 p.p.m. for the 6β and 11β hydrogens, respectively.

Photolysis of 5αH,6,11βH-Eudesm-1,3-diene-6,13-olide (10). *A. Preliminary Experiments.* The photolysis apparatus consisted of a Pyrex jacket (i.d. 54 mm.) with side arm and fitted with a gas inlet tube at the bottom. Into this vessel was inserted a quartz Hanovia immersion well (o.d. 50.5 mm.), the coolant chamber of which was filled with chlorine gas at 1 atm. Irradiation was effected with a custom-built, quartz, low-pressure mercury discharge tube (Hanovia Type SC-2537 (U-shaped); total length 70 cm., i.d. 8 mm.; 96.5% of total ultraviolet emitted at 2537 Å.) powered by a Jefferson outdoor-type transformer[29] (Catalog No. 721-561, 120 ma.).

In a typical experiment the apparatus containing a solution of the diene 10 (5.8 mg.) in methanol (100 ml.) was degassed by passing argon through the solution for *ca.* 30 min. For this experiment the entire mercury discharge tube was masked except for a 1-cm.^{2} "window." During irradiation agitation was achieved by continuous bubbling of argon gas through the solution. The temperature was maintained at −15 to −18° (ice-salt bath). Samples (3.2 ml.) were withdrawn at time intervals with a cooled hypodermic syringe and transferred to a precooled cell; their ultraviolet absorption spectra were measured immediately at λ_{max} 265 mμ, and at a newly formed band at λ_{max} 211 mμ (see Table I; redetermination of the optical density (o.d.) values after *ca.* 1 min. showed <3% change). After 12–13 min. at ambient temperature the o.d. of absorption at λ_{max} 211 mμ was found to have decreased by *ca.* 40%. This decrease was accompanied by a simultaneous increase in the o.d. at 265 mμ due to thermal isomerization of the photoproduct 13 (λ_{max} 211 mμ) to a new diene 16 (see part B) exhibiting ultraviolet absorption similar to that of the starting *trans*-fused diene 10. A value of −3.5 was obtained for the average ratio Δo.d.$_{211\ m\mu}/\Delta$o.d.$_{265\ m\mu}$ due to thermal isomerization of 13 to 16 in samples withdrawn at irradiation times of 12, 18, 24, and 48 min. An average value of −3.4 for this ratio was obtained from the data corresponding to irradiation of 10 to 13 from t = 12 to t = 48 min. (see Table I). These values correspond to a value of λ_{max}^{MeOH} 211 mμ (ε 16,800) for the new photoproduct 13. The values of the ratio o.d.$_{211\ m\mu}/$o.d.$_{265\ m\mu}$ were also determined and found to be a useful measure of the extent

(29) Jefferson Electric Co., Bellwood, Ill.

of reaction in the preparative scale experiments described below. After $t = 60$ min. the value of this ratio was found to remain relatively constant, possibly due to photoequilibrium.

Table I. Results of Irradiation of
5αH,6,11βH-Eudesm-1,3-dien-6,13-olide (10)

Irradiation time (t), min.	O.d. at 211 mμ	O.d. at 265 mμ	O.d. at 211 mμ/ o.d. at 265 mμ	Thermal isomerization,[a] Δo.d. at 211 mμ/ Δo.d. at 265 mμ
0	0.13	1.15	...	...
6	0.52	1.02	0.51	...
12	0.81	0.93	0.87	3.72
18	1.02	0.85	1.20	3.42
24	1.22	0.79	1.54	3.46
36	1.55	0.69	2.25	3.44
48	1.83	0.63	2.90	...
60	1.92	0.57	3.37	...
80	1.91	0.51	3.74	...
220	1.69	0.47	3.60	...

[a] Absolute value, measured after samples withdrawn at time t had been allowed to stand at ambient temperature for 10–13 min., corresponding to a decrease of ca. 40% in o.d.$_{211\ m\mu}$ and a simultaneous increase in o.d.$_{265\ m\mu}$.

Solutions of the irradiated diene 10 in methanol for 1 hr. showed the new photoproduct 13 to be isomerized to the cis-fused diene 16 to the extent of ca. 25% at 5°; ca. 3% at −15°, and 0% at −70°. Irradiation of the diene 10 in n-pentane at −70° gave rise to absorption at λ_{max} 218 mμ. The photoproduct 13 in n-pentane was similarly isomerized to 16 to the extent of 45% in 45 min. at 5°. Photolysis of the cis-fused diene 16 under the same conditions as described above gave rise only to high end absorption and was >5 times slower in initial rate when compared to that of the trans-fused diene 10.

B. Formation of 10-Epi-5αH,6,11β H-eudesm-1,3-dien-6,13-olide (16) by Thermal Isomerization of the Photolysis Product 13. A solution of the diene 10 (405 mg., 1.74 mmoles) in methanol (135 ml.) was photolyzed at −18° exactly as described below (see part C). After 40 min. the lamp was shut off and the cooling bath was removed. The reaction mixture was allowed to remain at room temperature for 6 hr., evaporated to dryness in vacuo, and chromatographed on silica gel–10% AgNO₃[21,22] (30 g., 28–200 mesh) packed in benzene–ligroin (35:65). Elution with benzene–ligroin (60:40) gave 202 mg. of crude crystalline material which was dissimilar from the starting diene 10 in its infrared spectrum. Crystallization from n-hexane afforded 108 mg. (27%) of 10-epi-5αH,6,11βH-eudesm-1,3-dien-6,13-olide (16) as plates, m.p. 67–69.5°; two recrystallizations yielded an analytical sample of 16: m.p. 69.5–70.5°; $[\alpha]^{29}D$ +375°, λ_{max}^{MeOH} 265 mμ (ε 4800), $\nu_{max}^{CCl_4}$ 1780 (vs), 1450 (ms), 1185 (ms), 1120 (ms), 1050 (ms), 985 (m), and 728 (s) cm.⁻¹; the n.m.r. spectrum of 16 showed peaks at 0.98 (3 H, singlet), 1.15 (3 H, doublet, $J = 7$ c.p.s.), 1.95 (3 H, singlet), 3.79 (1 H, ABC triplet, $J_{AC} \approx 10$ c.p.s., $J_{BC} \approx 10$ c.p.s.), and a series of vinyl H peaks (3 H) occurring between 5.2 and 6.0 p.p.m.

Anal. Calcd. for $C_{15}H_{20}O_2$: C, 77.55; H, 8.68. Found: C, 77.65; H, 8.71.

Further elution of the column with benzene gave 61 mg. of starting diene 10. The remaining material appeared to have decomposed on the column during the long contact time necessary for clean separation.

The crude product (before chromatography) showed two sharp n.m.r. peaks of identical height (≈ 1.5 H each) at 0.89 and 0.96 p.p.m. corresponding, respectively, to the C-14 protons of the trans-fused diene 10 and the cis-fused diene 16. The mixture (maximum 0.5 mg.) of 10 and 16 could be separated into its components by v.p.c. using a 4-ft. column of cyanosilicon rubber (5%) on Diatoport S. Retention times of 14.25 and 9.4 min. were observed for 10 and 16, respectively, using a column temperature of 175° and a helium flow rate of 60 ml./min.

C. Synthesis of Dihydrocostunolide (1). A solution of the diene 10 (400 mg., 1.72 mmoles) in 135 ml. of methanol was photolyzed at −18° as in part A. The jacket used had an i.d. of 59 mm. and the mercury discharge tube described was partially masked, leaving 25 cm.² of surface area exposed for the passage of radiated light. After 38 min. irradiation time an aliquot (0.05 ml.) of the photolysis solution was withdrawn by means of a precooled syringe and added to 3.2 ml. of methanol at 0°. The ultraviolet absorption ratio (o.d.$_{211\ m\mu}$/o.d.$_{265\ m\mu}$) was 2.96 corresponding to 45–50% photochemical conversion (use Table I) of the diene 10 to the new photoproduct 13 absorbing at λ_{max}^{MeOH} 211 mμ. The photolysis solution was immediately hydrogenated at −15 to −18° by addition of 1.3 g. of moist Raney nickel[30] (ca. 50% suspension; washed with methanol before addition) followed by passage of hydrogen through the resulting suspension. After 30 min. an additional 1.3 g. Raney nickel was added. After a total of 75 min.,[31] the hydrogen gas was replaced by nitrogen, the immersion well was removed, and the reduced photolysis solution was filtered by gravity. The filtrate was evaporated to dryness at room temperature in vacuo and the oily residue was dissolved in ether. The ethereal solution was washed with 5% sodium bicarbonate and saturated sodium chloride solutions, dried over anhydrous sodium sulfate, and evaporated to dryness to yield 362 mg. of semicrystalline solid.

The crude product was chromatographed at −23° on 10 g. of silicic acid (Mallinckrodt, 100 mesh) packed in benzene–methylene chloride (1:1). The column was eluted with the same mixture (150 ml.) followed by methylene chloride–benzene–chloroform (1:1:1, 85 ml., then 1:1:2, 140 ml.) until only traces of crystalline material showing n.m.r. peaks for C-14 methyl groups were eluted. Combination of the eluted material gave 216 mg. of crystalline solid consisting mainly of the 3-ene 12, a small amount of santanolide "c" (11), and some unidentified minor products (n.m.r. analysis). The column was warmed to +5°. Elution was continued with methylene chloride–benzene–chloroform (1:1:2, 300 ml.) yielding 142 mg. of pale yellow oil which exhibited n.m.r. peaks indicating the presence

(30) Obtained from W. R. Grace and Co., Davison Chemical Division, Cincinnati, Ohio.

(31) Previous experiments using slightly smaller amounts of catalyst had demonstrated that after 1 hr. of hydrogenation time the value of the ultraviolet absorption at 265 mμ of reduced solutions which had been allowed to isomerize thermally at room temperature for 30 min. was <5% that of the starting diene solution.

of a variety of vinyl methyl groups. Treatment of the oil with *n*-hexane–ether and storage at −23° for 2 days gave 27 mg. of crude crystalline material which, after recrystallization from *n*-hexane–ether, gave 13.5 mg. of dihydrocostunolide (1), m.p. 76.0–78.0°. Chromatography (−23°) of the mother liquors on 2.3 g. of silicic acid gave an additional 6 mg. of 1, m.p. 74.5–78°; total yield, 19.5 mg. (10%) based on amount of diene 10 actually transformed on photolysis.

Recrystallization afforded pure synthetic dihydrocostunolide (1), m.p. 76.5–78.0°, $[\alpha]^{26}$D +110.8° (*c* 0.8) (lit.[3] m.p. 77–78°, $[\alpha]$D +113.6° (*c* 3.0, CHCl₃)); the n.m.r. spectrum of 1 exhibited peaks at 1.19 (3 H, doublet, $J = 6.5$ c.p.s.), 1.40 (3 H, doublet, $J \approx$ 1.5 c.p.s.), 1.67 (3 H, doublet, $J \approx 1.0$ c.p.s.), 4.39 and 4.52 (2 H, multiplet), and 4.75 (1 H, multiplet) p.p.m. The synthetic material showed no depression in its melting point when admixed with an authentic specimen prepared from costunolide (2)[3]; it was identical in all respects with this specimen in its infrared and ultraviolet (ϵ 10,300 at 207 mμ) spectra.

In another experiment 56 mg. of dihydrocostunolide (1), m.p. 74.5–76.0°, was obtained in the same manner as described above from the photolysis of 1.20 g. of diene 10.

Studies in Mass Spectroscopy. III.[1]
Mass Spectra of β-Keto Esters

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Contribution from the University Chemical Laboratory, Cambridge, England, and the Department of Organic Chemistry, Aarhus University, Aarhus C, Denmark. Received August 9, 1965

The spectra of 16 β-keto esters are reported and discussed. Ethyl acetoacetate and its derivatives, in which one of the active methylene hydrogens has been replaced by a substituent, break down in a well-defined manner upon electron impact. The spectra of some substituted ethyl benzoylacetates are noteworthy for the probable occurrence of an intramolecular acylation of the aromatic ring which takes place in an acylium ion fragment.

In view of the importance of β-keto esters and their derivatives as synthetic intermediates, it was thought desirable that the mass spectra of representative members of this class should be determined and interpreted. Prior to the present study, the only mass spectrum of a member of this series which has been discussed appears to be that of methyl 3-oxooctadecanoate.[2]

The mass spectra of ethyl acetoacetate (I) and seven derivatives (II–VIII) are recorded in Table I and Figures 1 and 2. The parent compound I and all the derivatives II–VI break down to a large extent by the general sequence which is outlined in Scheme I. The formation of enolic fragment ions (see M − 42), from processes involving hydrogen rearrangement in the mass spectrometer, has previously been demonstrated.[3a] Moreover, the elimination of ethylene from the M − 42 ion closely parallels the loss of an olefin from vinyl ethers[3a] and acetals.[3b]

(1) Part II: R. Grigg, M. V. Sargent, J. Knight, and D. H. Williams, *Tetrahedron*, in press.
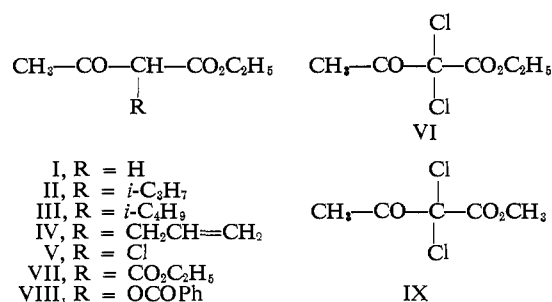(2) R. Ryhage and E. Stenhagen, *Arkiv Kemi*, 15, 545 (1960).
(3) (a) S. Meyerson and J. D. McCollum, *Advan. Anal. Chem. Instr.*, 2, 179 (1963); (b) R. A. Friedel and A. G. Sharkey, *Anal. Chem.*, 28, 940 (1956).

Scheme I[a]
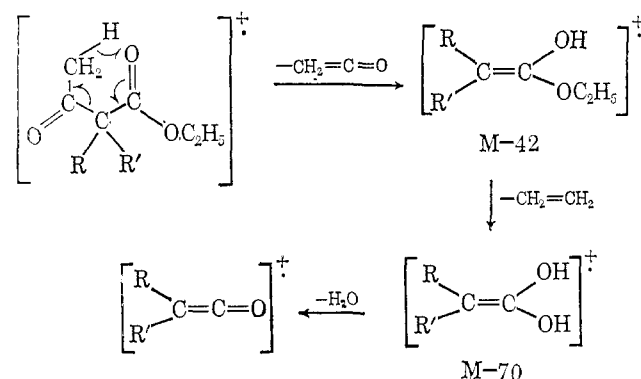
[a] Throughout this paper, specific structures have been drawn for fragment ions primarily to give a self-consistent rationale for the interpretation of the spectra. Although exact mass measurements confirm the composition of the fragment ions in many instances, some structures are nominal only.

The sequence indicated in Scheme I is supported by a number of appropriate metastable peaks in many of the

$$CH_3\!-\!CO\!-\!CH\!-\!CO_2C_2H_5 \qquad CH_3\!-\!CO\!-\!\underset{\underset{Cl}{|}}{\overset{\overset{Cl}{|}}{C}}\!-\!CO_2C_2H_5$$
$$\overset{|}{R} \qquad\qquad\qquad\qquad VI$$

I, R = H	
II, R = *i*-C₃H₇	
III, R = *i*-C₄H₉	$CH_3\!-\!CO\!-\!\underset{\underset{Cl}{|}}{\overset{\overset{Cl}{|}}{C}}\!-\!CO_2CH_3$
IV, R = CH₂CH=CH₂	
V, R = Cl	
VII, R = CO₂C₂H₅	
VIII, R = OCOPh	IX

spectra. It is noteworthy that the M − 42, M − 70, and M − 88 ions are all odd electron fragments and therefore, depending on the nature of R and R', a