Ultrasound in Lipid Chemistry, Cyclopropanation of Unsaturated Fatty Esters and Triglycerides

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Concomitant ultrasonic irradiation during the Simmons-Smith reaction facilitated the cyclopropanation of ethylenic fatty esters and triglycerides. Methyl ricinoleate furnished predominantly the corresponding hydroxy cyclopropanoid ester when the reaction was carried out at 85–95 C under ultrasound in the presence of zinc, while a C_{18} furanoid fatty ester gave a novel tricyclo derivative (methyl 9,12-epoxy-9,10;11,12-dimethanooctadecanoate).

This work is a continuation of studies (1) on fatty acids. The use of ultrasound to accelerate chemical reactions in nonaqueous media has become more widespread, as research workers can readily find this source of energy for their experiments through the use of a laboratory ultrasonic cleaner (2). Repic et al. recently have shown that concomitant ultrasonic irradiation during the Simmons-Smith reaction permits cyclopropanation of olefins to proceed smoothly, reproducibly and in high yield (3). Extension of their method to a large scale cyclopropanation reaction involving methyl oleate confirmed their claim (4). Prior to the use of ultrasonic irradiation, the zinc used in such reactions was modified (usually to the zinc-copper couple) or the reaction was catalyzed in order to achieve ready cyclopropanation across the olefin bonds (5,6). Activation of a zinc-copper couple with ultrasonic irradiation permitted even the less reactive dibromomethane to be used in the Simmons-Smith reaction instead of the usual diiodomethane (7). The mechanism underlying the Simmons-Smith cyclopropanation reaction is understood to involve a carbenoid (organozinc complex) and not a free carbene species, which allows the delivery of methylene stereospecifically to an olefinic bond. However, such reactions are not restrictive to olefinic systems, but are also found to transform hydroxy groups to the methoxy derivatives, as reported by Osman et al. (8,9) in the cyclopropanation of methyl ricinoleate.

The occurrence of cyclopropane fatty acids in bacterial lipids (10) and in certain seed oils (11) prompted this investigation. Attempts were directed to the cyclopropanation of unsaturated triglycerides and to extend this technique to furanoid fatty esters by making use of the effects of ultrasound in the Simmons-Smith reaction.

RESULTS AND DISCUSSION

We confirm the high yield (over 90%) in the cyclopropanation of methyl oleate under ultrasonic irradiation using zinc alone and diiodomethane. A time study of the cyclopropanation of methyl linoleate suggests a stepwise transformation of this diunsaturated fatty ester, first to the monounsaturated cyclopropanoid intermediate during the first half of the reaction period, then reaching to about 80% yield of the dicyclopropanoid derivative at the end of six hr of reaction as shown by gas chromatographic analysis (Fig. 1). Extension of this ultrasonic assisted cyclopropanation reaction to triglycerides was performed smoothly, and complete cyclopropanation across the olefinic bonds was achieved as indicated by the absence of ethylenic proton signals in the ^{1}H-NMR spectrum of the products and by the appearance of signals corresponding to the cyclopropane protons at 0.6 and -0.3δ. Our experience has shown that such reaction results could not be achieved in the absence of ultrasonic irradiation, not even when the zinc was activated by copper.

In considering the effects of ultrasound on the cyclopropanation reaction, the success of the transfer of a methylene group across an olefinic bond could be attributed to the acoustic cavitation of the solvent. Under ultrasonic irradiation the solvent (1,2-dimethoxyethane) allowed the rapid formation, growth and implosive collapse of unstable microbubbles, generating short-lived but extremely high pressure and high temperature "hot spots" within the system (12), which accelerated the slow carbenoid production from zinc. Secondly, the rapid movement of the solvent caused by variation of sonic pressure allowed the zinc metal surface to be activated, thus promoting carbenoid complex formation during the ultrasonic assisted reaction.

When methyl ricinoleate was treated under similar ultrasonic assisted Simmons-Smith reaction conditions, it became readily apparent that the products and yields depended substantially on the operating temperature of the heating bath in which these reactions were carried out. Thus, at a bath temperature between 120–130 C, methyl ricinoleate gave low yields of methyl methoxy and/or hydroxycyclopropanoid C_{18} esters, but high amounts of polymerized products. Efforts were therefore directed to the prevention of excessive polymerization. It was consequently realized that by maintaining a bath temperature of 85–95 C, methyl ricinoleate furnished about 75% of methyl 12-hydroxy-9,10-methyleneoctadecanoate. Only small amounts (ca. 5%) of the corresponding methoxy cyclopropanoid ester were detected in addition to some polymerized material. The methyl 12-hydroxy-9,10-methyleneoctadecanoate was converted to the methyl 12-oxo-9,10-methyleneoctadecanoate by the Brown's two-phase oxidation procedure (13).

Dauben and Berezin noted the accelerating and stereo-directing effects of a hydroxy function in cyclic allylic alcohols during the classical Simmons-Smith

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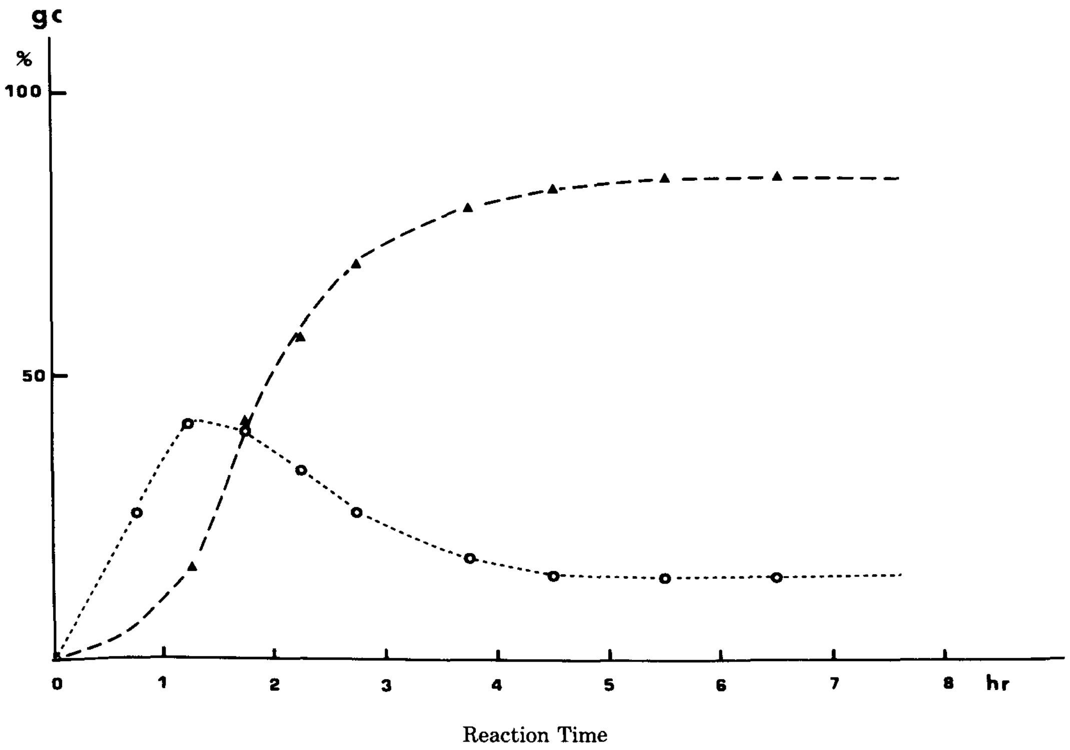
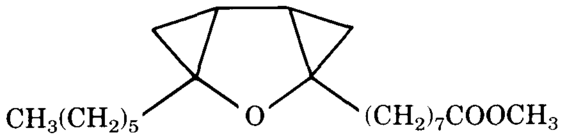


FIG. 1. Cyclopropanation of methyl linoleate with zinc and diiodomethane with concomitant ultrasonic irradiation. ○ - - - - - ○, yield of monocyclopropanated intermediate (C18:1, △). ▲ - - - - - ▲, yield of dicyclopropanated product (methyl 9,10;12,13-dimethyleneoctadecanoate.

reactions involving such substrates, but reported no etherification of the hydroxy function (14). However, Osman et al. attributed the etherification of methyl ricinoleate to a similar concept as suggested by Dauben and Berezin that the zinc of the carbenoid reagent could further complex with the lone pair electrons of the oxygen of the hydroxy group permitting the transformation of the latter to a methoxy group. In Osman's cyclopropanation reaction of methyl ricinoleate, the zinc-copper couple produced at the onset of the reaction all the required carbenoid species for cyclopropanation (if not in excess, due to deliberate increase in molar proportions of reagent versus substrate). As a result, the high initial concentration of carbenoid species in the reaction mixture caused etherification in addition to cyclopropanation across the olefinic bonds. In our ultrasonic assisted cyclopropanation reactions, the slow reacting zinc produced carbenoid species at a steady rate but not in excess quantities, allowing the transfer of methylene to occur preferentially across the double bonds. When these more reactive olefinic systems had been cyclopropanated, excess carbenoid species would direct the reaction toward the hydroxy function, causing etherification to take place. This concept concurred with the results when the reaction periods were extended, resulting in the production of large amounts of methoxy cyclopropanoid ester.

Our described reaction conditions further suggested that the optimum reaction temperature of 85–95 C provided control over the generation of carbenoid species for the purpose of adequate cyclopropanation of the olefinic bonds. But when the reaction temperature was raised to 120–130 the reactivity of the zinc under ultrasonic irradiation enhanced the production of carbenoid species at such a rate to influence the side reaction leading to etherification of the hydroxy function and apparently causing undesired polymerization reactions to take place simultaneously. It could be concluded that ultrasonic assisted Simmons-Smith reactions involving zinc, diiodomethane in 1,2-dimethoxyethane provide a unique method for the cyclopropanation of olefinic bonds in substrates which also contain hydroxy groups.

A novel tricyclo derivative (I) was obtained when a C_{18} furanoid ester (methyl 9,12-epoxy-9,11-octadecadienoate) was treated similarly.



(I)

Methyl 9,12-epoxy-9,10;11,12-dimethanooctadecanoate

METHODS

Methyl oleate and linoleate were obtained from the Department of Chemistry, University of St. Andrews, Scotland. Methyl ricinoleate was isolated from castor oil. Triolein was obtained from Sigma Chemical Co., St. Louis, Missouri. Groundnut oil was purchased locally and contained a total of about 80% oleic and linoleic acids. Methyl 9,12-epoxy-9,11-octadecadienoate was synthesized as described earlier (15). A laboratory ultrasonic cleaner (Bransonic, model 321, 150W, 55 KHz, bath temperature maintainable at 65 C) manufactured by Branson Co., Shelton, Connecticut was used. Analytical (AR) grade solvents were used and, where required, solvents were dried and distilled before use. Flash column chromatography was carried out as described by Still et al. (16). Gas chromatography-mass spectrometric analyses were conducted on a Hewlett Packard HP5970B gas chromatograph fitted with a mass sensitivity detector and mounted with an OV-101 capillary column. High resolution mass spectral analysis was conducted on a VG 7070F mass spectrometer. ^1H and ^{13}C nuclear magnetic resonance spectra were obtained on a JEOL FX90 (90 MHz) instrument.

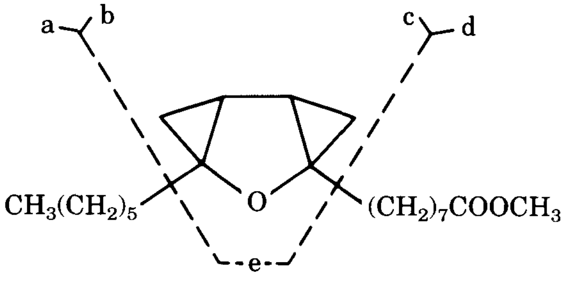
General procedure for ultrasonic assisted cyclopropanation reactions. A mixture of zinc filing (1.1 g, Merck #3764) and 1,2-dimethoxyethane (5 ml) was placed in a quickfit test tube fitted with a water-cooled condenser and dipped to a depth of 10 cm into a 400-ml beaker containing water and a 0.5-cm layer of paraffin oil and carrying a variac controlled submersible heating rod. The beaker carrying the reaction set up was then partially submersed into the ultrasonic cleaner filled with water, which was maintained at 65 C. The level of the paraffin oil inside the beaker was levelled with that of the water inside the ultrasonic bath. The reaction mixture was sonicated for 1 1/2 hr. The substrate (example: methyl ricinoleate, 0.77 g) was added to the reaction mixture followed by careful addition of diiodomethane (1.4 g) through the condenser. The entire reaction mixture was sonicated for 1 hr at 65 C. Thereafter the temperature inside the beaker was raised and maintained at 85–95 C and the system sonicated for a further 3 hr. The reaction mixture was cooled and treated with saturated aqueous ammonium chloride (5 ml) and the product extracted with petroleum ether or diethyl ether, depending on the polar nature of the substrate. The organic extract was washed with saturated aqueous sodium chloride, dried over anhydrous sodium sulfate and the solvent removed under reduced pressure. The residual oil was purified by flash column chromatography using a 2.5-cm i.d. glass column and about 15 cm of silica (Merck, art. 9385, 0.04–0.063 mm, 230-400 ASTM mesh). The eluent in the case of methyl 12-hydroxy-9,10-methyleneoctadecanoate was a mixture of petroleum ether:diethyl ether, 7:3, v/v. For non-hydroxylated substrates a mixture of petroleum ether:diethyl ether, 85:15, v/v, was used. Fractions of 20 ml each were taken and the purity of the eluted products checked by thin layer chromatography before pooling the fractions for further analysis.

Preparation of methyl 12-hydroxy-9,10-methyleneoctadecanoate. A mixture of zinc (1.1 g), 1,2-dimethoxyethane (5 ml), diiodomethane (1.4 g), methyl ricinoleate (0.77 g) was allowed to react as described above. Flash column chromatographic separation furnished methyl 12-hydroxy-9,10-methyleneoctadecanoate (0.61 g, 75%). GC analyses: ECL = 20.6 (OV-101), 25.3 (SP2300); ir (cm^{-1}):3460(s), 1745(s); ^1H-NMR (δ):-0.23(2H), 0.69(2H), 0.93(3H), 1.3–1.6(20H), 1.6–1.8(4H), 3.38(1H), 3.66(3H).

Preparation of methyl 12-oxo-9,10-methyleneoctadecanoate. Methyl 12-hydroxy-9,10-methyleneoctadecanoate (0.6 g) was dissolved in diethyl ether (40 ml) and chromic acid (10 ml, prepared from 20 g $Na_2Cr_2O_7$, 28 g H_2SO_4 and 65 ml water) was added over a period of 15 min at room temperature; the mixture was stirred for a further 15 min. The ethereal solution was successively washed with water (20 ml) and sodium bicarbonate (10%, 20 ml) and dried over sodium sulfate. Flash column chromatographic separation yielded methyl 12-oxo-9,10-methyleneoctadecanoate (0.44 g, 72%). GC analysis: ECL = 20.4 (OV-101), 26.3 (SP2300); ir (cm^{-1}):3060 (w), 1740(s), 1720(s). ^1H-NMR (δ):-0.22(2H), 0.68(2H), 0.88(3H), 1.2–1.5(20H), 2.2–2.5(6H), 3.66(3H).

Reaction of methyl 9,12-epoxy-9,11-octadecadienoate with zinc and diiodomethane. Methyl 9,12-epoxy-9,11-octadecadienoate (0.2 g) was reacted with zinc (0.5 g), diiodomethane (0.7 g) and 1,2-dimethoxyethane (5 ml) under ultrasonic irradiation. Purification of the product gave methyl 9,12-epoxy-9,10;11,12-dimethanoctadecanoate (I, 0.125 g, 57%). GC analysis: ECL = 19.6 (OV-101), 22.5 (SP2300); ir (cm^{-1}):3040(w), 1745(s), 1100(m); ^1H-NMR (δ):0.38–0.78(6H), 0.93(3H), 1.2–1.8(22H), 2.3(2H), 3.66(3H); ^{13}C-NMR (ppm) (see Scheme 1).

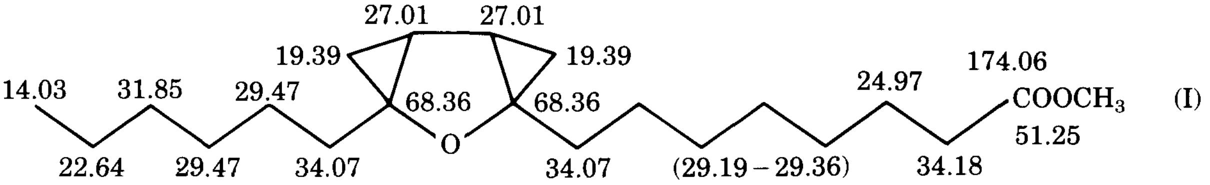
Mass spectrometric analysis: m/z (fragment, relative intensity) 43(CH_3CO^+,100), 55($C_4H_7^+$,46), 85(a,22.4), 94(e,3.6) 95(e+1,12.6), 97(f-16,19.6), 113(f,47.1), 125(d-32,20.9), 126(d-31,2.3), 157(d,0.8) 179(c,5.9), 185(g,19.7), 251(b,3.7), 305(M-31,2.7), 336(M^+,1.9).



$f = CH_3(CH_2)_5C{\equiv}O^+$

$g = {}^+O{\equiv}C(CH_2)_7COOCH_3$

High resolution mass spectral analysis gave: m/z = 335.9786 (M^+,calc. $C_{21}H_{36}O_3$ = 336.2664); microanal-



SCHEME 1.

ysis: obs. 75.24% C, 10.65% H, 14.11% O, calc. 75% C, 10.71% H, 14.29% O.

Time study of cyclopropanation of methyl linoleate under ultrasonic condition in the preparation of methyl 9,10;12,13-dimethyleneoctadecanoate. Methyl linoleate (0.1 g) was reacted with zinc (0.4 g), diiodomethane (1.7 g) and 1,2-dimethoxyethane (5 ml) under ultrasonic irradiation. Samples of the reaction mixture were drawn at timed intervals. The products were isolated and analyzed by gas liquid chromatography on an OV-101 column. The ECL values of the components were: methyl linoleate (17.60), methyl 9,10/12,13-methyleneoctadecenoate (18.50) and methyl 9,10;12,13-dimethylenoctadecanoate (19.60). The conversion of methyl linoleate to the mono and dimethylene derivatives is given in Figure 1.

Cyclopropanation involving groundnut oil and triolein. Groundnut oil or triolein (0.2 g), zinc (0.9 g), diiodomethane (3.7 g) and 1,2-dimethoxyethane (5 ml) were reacted under ultrasonic irradiation for 6 hr. The products were isolated, and the ^{1}H-NMR analysis of each product indicated the absence of ethylenic proton signals and the appearance of signals at -0.3 and 0.6 δ indicative of the protons attached to the cyclopropane system.

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