REDUCTION OF ETHYL 2-ALKYL- AND 2,3-DIALKYL-2-CYCLOPROPENE-1-CARBOXYLATES AND THE CORRESPONDING CYCLOPROPENOLS WITH LITHIUM ALUMINUM HYDRIDE

I. N. Domnin, K. Dumon,
M. Vincens, and M. Vidal

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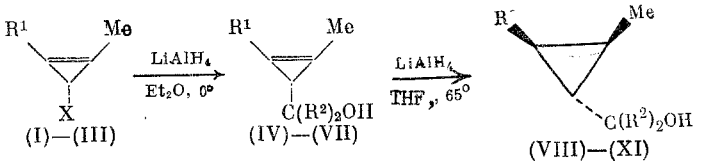
Compounds of the cyclopropene series are good models for the study of stereoselectivity in addition reactions. We have studied the reduction reactions of esters and alcohols of the cyclopropene series containing various substituents at the double bond in order to investigate the stereospecificity and regioselectivity of the process



(I)—(III) (IV)—(VII) (VIII)—(XI)

X = CO_2Et, R^1 = Et (I); X = CO_2Et, R^1 = *i*-Pr (II); X = CO_2Et, R^1 = *t*-Bu (III); R^1 = Et, R^2 = H (IV), (VIII); R^1 = *i*-Pr, R^2 = H (V), (IX); R^1 = *t*-Bu, R^2 = H (VI), (X); R^1 = *t*-Bu, R^2 = Me (VII), (XI).

Earlier it was shown that if phenyl substituents are present at the cyclopropene double bond the simultaneous reduction of the ethoxycarbonyl group and the double bond is observed even at low temperatures [1]. On the other hand, in the case of ethyl 2,3-dibutyl-2-cyclopropene-1-carboxylate reduction can occur either with retention of the cyclopropene double bond or with the formation of the corresponding cyclopropane ring [2, 3], depending on the reaction temperature, and in the latter case the alkyl groups are in the trans position with respect to the alcohol group. Somewhat more recently for the case of ethyl monoalkylcyclopropenecarboxylates it was shown that reduction with lithium aluminum hydride is regiospecific and stereospecific; initial attack by the hydride ion at the double bond always corresponds to the formation of the most stabilized carbanion [4].

In the case of the esters (I-III) reduction in an ether solution of lithium aluminum hydride at 0 to −10°C leads exclusively to the corresponding primary alcohols of the cyclopropene series (IV-VI); if the reaction is realized in THF at 65°C, the formation of the cyclopropanols (VIII-X) is observed. In the IR spectra of compounds (IV-VII) there is a characteristic absorption band for the disubstituted cyclopropene double bond in the region of 1860-1870 cm^{-1} [5]. In the PMR spectra the chemical shifts of the CH_3 group (δ 2.03 ppm) and the proton in the cyclopropene ring (δ 1.45 ppm) are also characteristic [4].

The stereochemical configuration of the cyclopropanols (VIII-XI) was established by high-resolution PMR spectroscopy at 250 MHz. The spin–spin coupling constant $^3J_{H^1H^3} \sim 5$ Hz indicates the trans position for the H^1 and H^2 protons and also the H^1 and H^3 protons. Our results confirm that the reduction is stereospecific; in all cases both alkyl and hydroxymethyl groups are in the trans position in relation to each other.

Initial attack by the hydride ion can occur either at the C^2 atom or at the C^3 atom of the three-membered ring. In order to obtain data on the regioselectivity of this reaction we realized the reduction by two methods.

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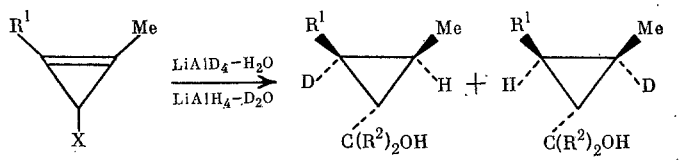
TABLE 1. Data on the Regioselectivity in the Reduction of 2,3-Dialkyl-Substituted Cyclopropenes

Initial compound	Ratio of isomers A:B, %	
	$LiAlD_4/H_2O$	$LiAlH_4/D_2O$
(I)	63 : 37	35 : 65
(II)	75 : 25	23 : 77
(III)	73 : 27	–
(VI)	–	26 : 74
(VII)	95 : 5	5 : 95



(I)-(III), (VI), (VII) A B

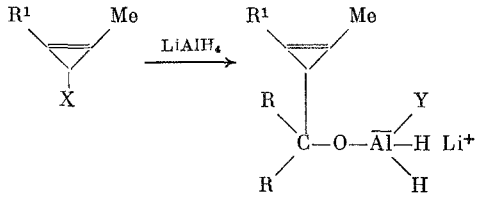
In each case the reaction leads to two isomeric cyclopropanols A and B, in which the position of the deuterium was determined by means of the high-resolution PMR spectra (250 MHz). Investigation of the spectra in the region of 0.1-0.9 ppm, where the signals for the protons of the cyclopropane ring H^1, H^2, and H^3 lie, makes it possible to determine the percentage content of the H and D atoms at the C^2 and C^3 atoms in relation to the signal for the H^1 proton. Here it was shown by special tests that the signals of the H^1 proton can actually be selected as standard, since H^1—D exchange hardly takes place at all under the conditions of reduction and subsequent hydrolysis. The same results were obtained during determination of the ratio of the areas of the CH_3 groups at the C^3 atoms in isomers A and B. With suppression of spin—spin coupling with the D atom the signal for the CH_3 group in the A isomer is observed in the form of a doublet, while in the B isomer it takes the form of a singlet. The experimental results on the regioselectivity of reduction are given in Table 1.

As seen from these data, irrespective of the type of reagent employed ($LiAlH_4$ or $LiAlD_4$) the regioselectivity of initial nucleophilic attack hardly changes at all; thus, the isotope effect can be considered negligibly small. It can also be seen that the reduction of the cyclopropene double bond is regioselective; attack by the hydride ion takes place preferentially at the most substituted C^2 atom and corresponds to the formation of the most stable carbanion. Particularly high regioselectivity is observed during the reduction of the tertiary alcohol (VII).

Since the rate of reduction of the ethoxycarbonyl group in the ethyl esters (I-III) greatly exceeds the rate of reduction of the cyclopropene double bond, the aluminum alcoholate is formed at the initial stage of the reaction. On the other hand, the observed stereospecificity in the reduction process indicates that initial attack at the C^2 and C^3 atom takes place in the cis position in relation to the ethoxycarbonyl group. This fact is sometimes unexpected, since nucleophilic attack by the hydride ion usually takes place from the side of the three-membered ring with the largest steric hindrances. However, this effect finds an explanation if it is assumed that the initial attack takes place by an intramolecular mechanism and the reducing agent is the alcoholate group. This hypothesis is consistent with published data [6, 7, 8]; in particular, it has been shown that the reduction of 7-hydroxybicyclo[2.2.1]heptadiene with lithium aluminum hydride takes place by an intramolecular mechanism [9].

In order to confirm this hypothesis we compared the reduction rates of the primary (VI) and tertiary (VII) cyclopropenols. Since the formation of the aluminum alcoholate precedes reduction of the double bond to an equal degree for both alcohols, the alcoholate of the tertiary alcohol, possessing higher nucleophilicity than the alcoholate of the primary alcohol, must lead the reduction at a higher rate. In fact, under identical conditions the reduction of the tertiary alcohol (VII) is approximately ten times faster than the reduction of the initial alcohol (VI).

It is known that the carbanions formed from compounds of the cyclopropane series without electron withdrawing substituents retain their configuration fully or partially. Protonation, halogenation, and carbonization of organometallic cyclopropanes take place with retention of the configuration of the C atom in the ring [10, 11]. The same relationship can be adopted for the hydrolysis of the organometallic complex during reduction with lithium aluminum hydride. The following general mechanism can be proposed for the reduction reaction; the formation of the aluminum alcoholate occurs at the first stage:



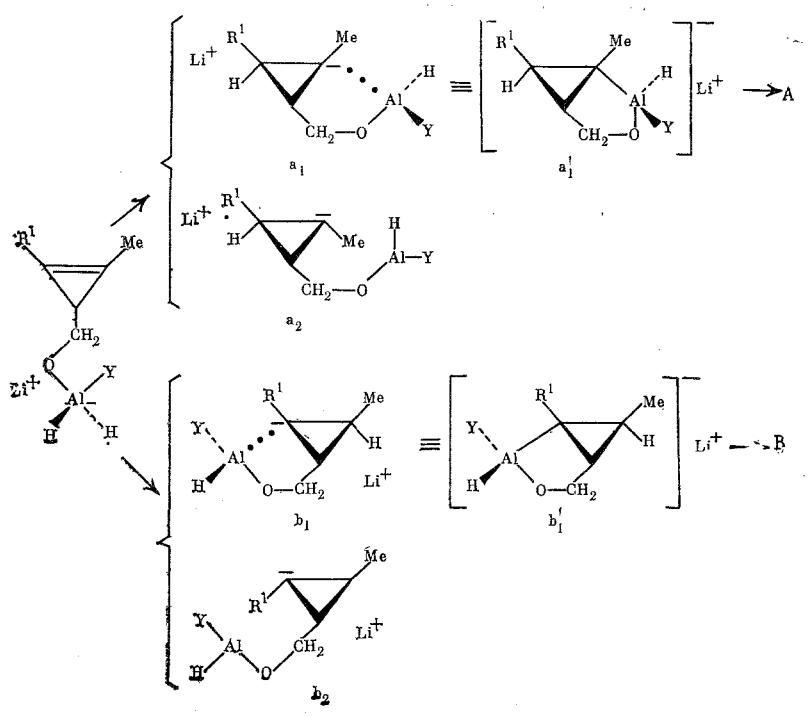
X = CO_2Et, CH_2OH, $C(Me)_2OH$; R^2 = H, Me; Y = OEt, H.

Subsequent nucleophilic attack by the $OAlH_2Y^-$ group on the C^2 and C^3 atoms of the cyclopropene double bond can lead to the formation of two pairs of diastereoisomeric carbanions ($a_1 - a_2$) and ($b_1 - b_2$).

In view of the capacity of such carbanions to retain their geometric configuration, it is natural to suppose that they will not undergo epimerization during reduction. During kinetically controlled formation of the carbanions the $OAlH_2Y^-$ group is in an approximately bisecting conformation in relation to the ring, and this makes formation of structures a_2 and b_2 unfavorable for steric reasons.

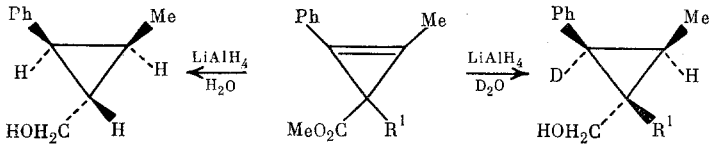
It should be noted that in organometallic compounds of types a_1 and b_1 there is strong interaction between the negative charge and the aluminum atom, since in none of the investigated cases did we observe opening of the three-membered ring [11] or addition of the carbanion at the cyclopropene double bond [5]. Clearly, intramolecular C^- ... Al coordination is in fact observed in these organometallic compounds.

The regioselectivity of the initial attack is evidently determined by the relative stability of the carbanions a_1 and b_1; here the carbanion with the charge at the less substi-



Y = OEt, H

tuted atom is more stable. This hypothesis was confirmed during investigation of the reduction of methyl 2-methyl-3-phenyl-2-cyclopropene-1-carboxylate (XII) and its analog deuterated at the C^1 atom (XV)



(XIII) (XII), (XV) (XIV), (XVI)

R^1 = H (XII), (XIV); D (XV), (XVI).

In this case the reaction is stereospecific; initial attack by the hydride ion takes place exclusively at the C^3 atom, as a result of which a carbanion stabilized by conjugation with the benzene ring is formed. The configurations of the cyclopropanols (XIII, XIV, XVI) were proved by high-resolution PMR spectroscopy.

Finally, it is necessary to mention the increase in the regioselectivity of reduction in the transition from the primary alcohol (VI) to the tertiary alcohol (VII), which is also consistent with the proposed mechanism of reduction. The large steric hindrances in (VII) prevent initial attack at the C^3 atom.

EXPERIMENTAL

The IR spectra were obtained on Perkin-Elmer 521 and UR-20 instruments. The PMR spectra were recorded in tablets and in carbon tetrachloride on Perkin-Elmer R10 (60 MHz) and Cameca (250 MHz) instruments with TMS as internal standard.

The ethyl esters (I-III) were obtained by the method in [12], the carbinols (IV-VI) by the method in [3], and (VII) by the method in [13]. The methyl ester (XII) was synthesized by the method in [14], and its deutero analog (XV) [14] by the reaction of methyl D-diazoacetate [15] with 1-phenylpropyne.

General Method for Reduction of the Cyclopropene Esters (I-III) to the Corresponding Cyclopropenols (IV-VI)

To a solution of 0.1 mole of the cyclopropene ester in 250 ml of absolute ether we added dropwise a suspension of 0.2 mole of lithium aluminum hydride in 250 ml of absolute ether. The mixture was stirred at 0°C for 1 h, poured into water and ice, and extracted with ether. The extracts were dried with magnesium sulfate, and after removal of the solvent the residue was distilled under vacuum. The yields of the cyclopropenols (IV-VI) were 80-90%.

2-Ethyl-3-methyl-1-hydroxymethylcyclopropene (IV), bp 40°C (2 mm Hg), n_D^{20} 1.4560. IR spectrum (ν, cm^{-1}): 1870 (C=C), 3390 (OH). PMR spectrum (δ, ppm): 1.12 t (3H, $CH_2\underline{CH_3}$), 2.40 q (2H, $\underline{CH_2}CH_3$), 2.03 s (3H, CH_3), 1.44 s (%H, H), 3.30 m (2H, $\underline{CH_2}OH$). Found %: C 75.23; H 10.45. $C_7H_{12}O$. Calculated %: C 74.95; H 10.78.

2-Isopropyl-3-methyl-1-hydroxymethylcyclopropene (V). The compound was purified by preparative GLC on a 3 m × 10 mm column with 20% Carbowax 20M on Chromosorb WAW 60/80 (nitrogen, column temperature 130°C). IR spectrum (ν, cm^{-1}): 1870 (C=C), 3400 (OH). PMR spectrum (δ, ppm): 1.16 d (6H, $(\underline{CH_3})_2CH$), 2.33 hept [1H, $(CH_3)_2\underline{CH}$], 2.04 s (3H, CH_3), 1.45 s (1H, H of ring), 3.35 m (2H, $\underline{CH_2}OH$). Found %: C 76.73; H 11.27. $C_8H_{14}O$. Calculated %: C 74.95; H 10.78.

2-tert-Butyl-3-methyl-1-hydroxymethylcyclopropene (VI). bp 63°C (3.5 mm Hg), n_D^{20} 1.4475. IR spectrum (ν, cm^{-1}): 1850 (C=C), 3400 (OH). PMR spectrum (δ, ppm): 1.12 s [9H, $(CH_3)_3C$], 2.02 s (3H, CH_3), 1.50 s (1H, H of ring), 3.37 m (2H, $\underline{CH_2}OH$). Found %: C 77.81; H 11.17. $C_9H_{16}O$. Calculated %: C 77.08; H 11.50.

General Method for Reduction of the Esters (I-III) and Cyclopropenols (IV) and (VII) to the Corresponding Cyclopropanols (VIII-XI)

To a solution of 15 mmole of the cyclopropene compound in 40 ml of absolute THF we added dropwise a suspension of 31 mmole of lithium aluminum hydride in 100 ml of absolute THF. The mixture was boiled and stirred for 4 h. It was then poured into water and ice and extracted with ether. The extract was dried with magnesium sulfate, and after removal of the solvent the alcohols (VIII-XI) were purified by preparative GLC on a 4 m × 10 mm column with SE-30 on Chromosorb WAW 60/80 (nitrogen, column temperature 150°C). The yields were 40-60%.

2-Ethyl-3-methyl-1-hydroxymethylcyclopropane (VIII). IR spectrum (ν, cm^{-1}): 1015, 1090 (cyclopropane ring), 3440, (OH). PMR spectrum (δ, ppm): 0.99 t (3H, CH_3CH_2), 1.34 m (2H, CH_3CH_2), 1.05 d (3H, CH_3), 0.64 m (1H, H^3), 0.49 m (1H, H^2), 0.40 m (1H, H^1), $J_{H^2H^1}$ = 5.0 Hz, 3.4 m (2H, CH_2OH). Found %: C 73.75; H 12.07. $C_7H_{14}O$. Calculated %: C 73.67; H 12.36.

2-Isopropyl-3-methyl-1-hydroxymethylcyclopropane (IX). IR spectrum (ν, cm^{-1}): 1030, 1100 (cyclopropane ring), 3445 (OH). PMR spectrum (δ, ppm): 0.96 d [6H, $(CH_3)_2CH$], 1.00 m [1H, $(CH_3)_2CH$], 1.08 d (3H, CH_3), $^3J_{CH-H^2}$ = 10.00 Hz, 0.66 m (1H, H^3), 0.30 m (1H, H^2), 0.44 m (1H, H^1), 3.34 m (2H, CH_2OH), $^3J_{H^1H^2}$ = 5.0 Hz. Found %: C 75.32; H 12.91. $C_8H_{16}O$. Calculated %: C 74.94; H 12.58.

2-tert-Butyl-3-methyl-1-hydroxymethylcyclopropane (X). IR spectrum (ν, cm^{-1}): 1015, 1090 (cyclopropane ring), 3440 (OH). PMR spectrum (δ, ppm): 0.98 s [9H, $C(CH_3)_3$], 1.22 d (3H, CH_3), 0.64 m (1H, H^3), 0.41 m (1H, H^2), 0.75 m (1H, H^1), 3.33 m (2H, CH_2OH), $J_{H^1H^2}$ = 5.0. Found %: C 76.42; H 12.54. $C_9H_{16}O$. Calculated %: C 75.97; H 12.75.

2-tert-Butyl-3-methyl-1-hydroxyisopropylcyclopropane (XI). IR spectrum (ν, cm^{-1}): 1020, 1100 (cyclopropane ring), 3440 (OH). PMR spectrum (δ, ppm): 0.94 s [9H, $(CH_3)C$], 1.11 d (3H, CH_3), 1.19 s [6H, $(CH_3)_2OH$], 0.79 m (1H, H^3), 0.56 m (2H, H^2 and H^1). Found %: C 77.85; H 12.67. $C_{11}H_{22}O$. Calculated %: C 77.58; H 13.02.

2-Phenyl-3-methyl-1-hydroxymethylcyclopropane (XIII). To a suspension of 0.2 g (5.2 mmole) of lithium aluminum hydride in 10 ml of absolute ether at 0°C while stirring we added 0.5 g (2.5 mmole) of the ester (XII) [13] in 10 ml of absolute ether. The reaction mixture was stirred at 0°C for 2 h, poured into water and ice, and extracted with ether. The extracts were dried with magnesium sulfate. After removal of the solvent the residue was distilled under vacuum; bp 92.5°C (0.3 mm Hg), n_D^{20} 1.5420. The yield was 60%. IR spectrum (ν, cm^{-1}): 3375 (OH). PMR spectrum (δ, ppm): 0.79 d (3H, CH_3), 0.94 m (1H, H^3), 1.88 m (1H, H^2), 1.23 m (1H, H^1), 7.1 m (5H, C_6H_5), 3.49 m (2H, CH_2OH), $^3J_{H^1H^3}$ = $^3J_{H^1H^2}$ = 5 Hz, $^3J_{H^2H^3}$ = 9, $^3J_{H^3-CH_3}$ = 6, $^3J_{H^1-CH_2OH}$ = 6, $^3J_{CH_2OH}$ = 12 H.

The cyclopropanols (XIV) and (XVI) were obtained by a similar method.

2-Phenyl-2-deutero-3-methyl-1-hydroxymethylcyclopropane (XIV). bp 93°C (0.3 mm Hg), n_D^{20} 1.5440. The yield was 48%. IR spectrum (ν, cm^{-1}): 3370 (OH). PMR spectrum (δ, ppm): 0.79 d (3H, CH_3), 0.94 m (1H, H^3), 1.23 m (1H, H^1), 3.49 m (2H, CH_2OH), 7.1 m (5H, C_6H_5), $^3J_{H^1H^3}$ = 5 Hz.

1,3-Dideutero-2-phenyl-3-methyl-1-hydroxymethylcyclopropane (XVI). bp 92.5°C (0.3 mm Hg), n_D^{20} 1.5445. The yield was 60%. IR spectrum (ν, cm^{-1}): 3360 (OH). PMR spectrum (δ, ppm): 0.79 d (3H, CH_3), 0.94 m (1H, H^3), 3.47 m (2H, CH_2OH), 7.1 m (5H, C_6H_5).

CONCLUSIONS

1. The reduction of ethyl 2,3-dialkylcyclopropane-1-carboxylates either take place with retention of the double bond in the ring or leads to the corresponding alcohols of the cyclopropane series, depending on the reaction conditions.

2. Complete reduction takes place stereospecifically; in the products the hydroxymethyl group is in the trans position in relation to the alkyl substituents.

3. The regioselectivity of the reduction process (the direction of initial attack by the hydride ion) is determined by the possibility of the formation of the most stable carbanion.

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REDUCTION OF THE CONJUGATED CYCLOPROPENE BOND AND DOUBLE BOND OF SUBSTITUTED METHYLENECYCLOPROPANE WITH LITHIUM ALUMINUM HYDRIDE

I. N. Domnin, K. Dumon,
M. Vincens, and M. Vidal

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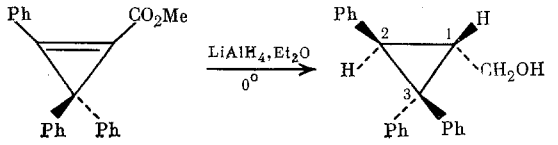
The present communication is a continuation of investigations into the reduction of the exo- and endo-double bonds of the three-membered carbon ring with lithium aluminum hydride. In the literature there is fairly comprehensive information describing the stereochemistry of the reduction of the triple bond in α,β-acetylenic esters, ketones, and aldehydes [1-6]. It was shown that for these compounds in the absence of Lewis acids the initial attack by the hydride ion is regioselective and takes place exclusively at the carbon atom at the α position to the carbonyl group. The reaction also takes place with a high degree of stereoselectivity; the double bond in the reduction product has the preferred E configuration. In view of the certain similarity in the characteristics of the triple bond and the cyclopropene double bond [7, 8], it seemed to us of interest to compare the reduction of compounds containing bonds of this type with lithium aluminum hydride.

In contrast to the ethyl 2,3-dialkyl-2-cyclopropene-1-carboxylates, the reduction of methyl 2,3,3-triphenyl-2-cyclopropene-1-carboxylate (I) with an excess of lithium aluminum hydride at 0°C takes place with the reduction of the cyclopropene double bond and leads exclusively to the cyclopropanol (II).



(I) (II)

The reaction is stereospecific; the hydroxymethyl group is at the trans position in relation to the phenyl group at the C^2 atom. Stereochemical investigation of the structure of the cyclopropane alcohol (II) was undertaken by PMR spectroscopy.

The spin–spin coupling constant $^3J_{H^1H^2}$ = 5 Hz indicates the trans configuration for these protons. In the literature $^3J_{H^1H^2}$ = 10 Hz was given for the cis isomer of this compound and 6 Hz for the trans isomer [9, 10]. Such an assignment of the configuration can also be confirmed by determination of the spin–spin coupling constants and chemical shifts of the diastereotopic protons of the CH_2OH group. The signal of each of these protons represents the AB component of an ABX system, consisting of eight resonance lines.

The three possible rotamers of (II) (A, B, and C), differing in the mutual arrangement of the A and B protons of the CH_2OH group in relation to the other substituents at positions 2 and 3, are given below.

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