Necic Acid Synthons. Part 4.[1] Regioselectivity in the Reactions of Chloro and Iodo Derivatives of Selected 3-Hydroxy-2-methylenealkanoate Esters with Ethyl 2-Methyl-3-oxobutanoate

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Iodination of 3-hydroxy-2-methylenealkanoate esters with HI–H_3PO_4 proceeds with exclusive rearrangement, whereas in some cases, chlorination with hexachloroacetone–triphenylphosphine affords both *normal* and *rearranged* products. Substituent and solvent effects on the regioselectivity of nucleophilic displacement in these halogeno derivatives are discussed.

The potential of 2-bromomethylalk-2-enoate esters as versatile synthons in a 'general' necic acid synthesis,[2] and the use of ethyl (*Z*)-2-bromomethylbut-2-enoate in a specific synthesis of integerrinecic acid[3] have been reported previously. We now describe the preparation and use of selected chloro and iodo analogues as alternative necic acid synthons.

Halogenation Studies.—Questions of regioselectivity in the halogenation of allylic alcohols have been reviewed elsewhere.[4] In the alcohols discussed here, however, perturbation of the allylic system by the ethoxycarbonyl group may be expected to enhance the electrophilicity of the vinylic carbon, C-3′ [Figure (a)], and thus influence the *regioselectivity* of halogenation.

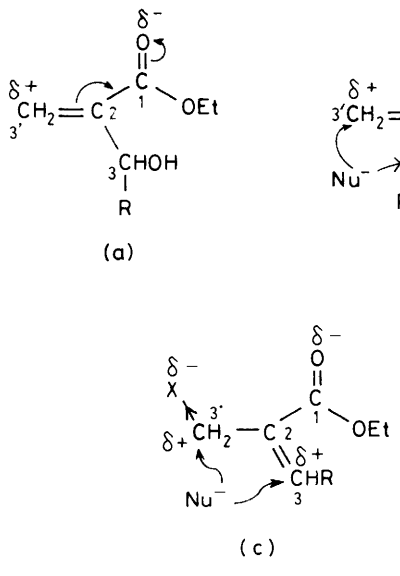
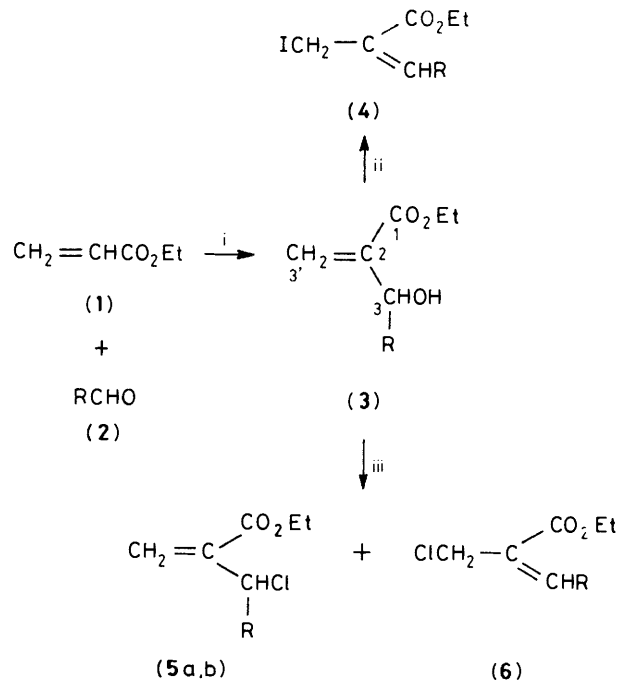


Figure.

The ready oxidation of HI by H_2SO_4 precludes the use of conc. HI–conc. H_2SO_4 as an iodinating mixture analogous to the conc. HBr–conc. H_2SO_4 brominating mixture used previously.[2] A combination of conc. HI and conc. H_3PO_4, however, effectively iodinates the hydroxy esters (**3**) as indicated in the Scheme. The *regioselectivity* of the iodination (involving exclusive substitution at the electrophilic vinylic carbon, C-3′) follows the trend observed in the bromination study.[2] The hydroxy esters (**3**) were also treated with hexachloroacetone–triphenylphosphine (HCA–Ph_3P),[5] at *ca.* 0 °C, to give the chloro derivatives indicated in the Scheme. Since secondary allylic alcohols typically react with HCA–Ph_3P to give mixtures



Relative product distribution [(**5**):(**6**)] *

	R	(5)	(6)
a;	Me	1	1
b;	Pr	1	1
c;	Ph	0	1

* As determined from ^1H n.m.r. spectra of reaction mixtures after work-up.

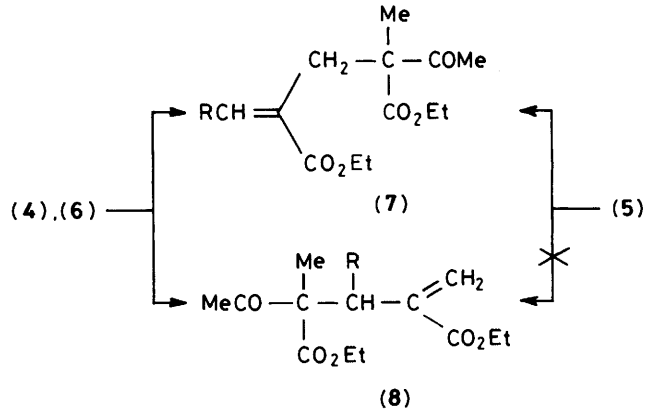
Scheme. *Reagents:* i, DABCO; ii, conc. HI–conc. H_3PO_4; iii, HCA–Ph_3P

of S_N (*normal*) and $S_{N'}$ (*rearranged*) products, in which the former predominates,[5] it may be argued that the *ca.* 1:1 isomer distributions obtained in the reactions of the secondary allylic alcohols (**3a**) and (**3b**) reflect the enhanced electrophilicity of the vinylic carbon, C-3′. Exclusive formation of the *rearranged* phenyl system (**6c**) may be attributed to conjugative effects.

Regioselectivity Studies.—The product distributions observed in the reactions of the halogeno esters (**4**)—(**6**) with ethyl 2-methyl-3-oxobutanoate enolate (Table 1) reveal the effect of changing (i) the position of the double bond, and (ii) the halogen leaving group (X).

In the chloro compounds having a terminal double bond

Table 1. Percentage relative distribution between products (7) and (8) in the reactions of halogeno esters (4)—(6) with ethyl 2-methyl-3-oxobutanoate enolate



Substrate	Base–solvent system	Relative product distribution (%)[a] (7) (*E*)	(7) (*Z*)	(8)
(5a)	NaH–THF[b]	83	17	0
	NaOEt–EtOH	75	25	0
(5b)	NaH–THF	85	15	0
	NaOEt–EtOH	67	33	0
(4a)	NaH–THF	64	0	36[e]
	NaOEt–EtOH	100	0	0[c]
(4b)	NaH–THF	100	0	0
	NaOEt–EtOH	100	0	0
(4c)	NaH–THF	100	0	0
	NaOEt–EtOH	100	0	0
(6a)	NaH–THF	44	0	56[e]
	NaOEt–EtOH	100	0	0[c]
(6b)	NaH–THF	68	0	32[e]
	NaOEt–EtOH	100[d]	0	0
(6c)	NaH–THF	20	0	80[e]
	NaOEt–EtOH	100	0	0

[a] Determined by ^{1}H n.m.r. spectroscopy of reaction mixture after work-up. [b] THF = tetrahydrofuran. [c] In some cases a small quantity (10—20%) of this regioisomer is formed. [d] Reaction mixture, after work-up, comprised compound (8) and an ethoxy derivative (35%). [e] Mixture of diastereoisomers.

[(5a) and (5b)] substitution occurs exclusively at the electrophilic vinylic centre, C-3′ [Figure, (b)] with consequent rearrangement of the allylic system. Similar *regioselectivity* is observed in both solvent systems (THF and EtOH). However, these reactions are not *diastereoselective* since ^{1}H and ^{13}C n.m.r. spectrometry clearly indicate the formation of both (*E*)- and (*Z*)-products. The reactions of the chloro compounds having a non-terminal double bond [(6a) and (6b)] and their iodo analogues [(4a) and (4b)] follow the general trends observed for the bromo esters,[2] substitution occurring at both vinylic (C-3) and allylic (C-3′) centres [Figure, (c)]. Substitution at the allylic carbon, C-3′, is *diastereospecific* (the alkene configuration being retained) and is enhanced by changing: (i) the alkyl substituent (R) from methyl to propyl; (ii) the leaving group (X) from Cl to I; and (iii) the base-solvent system from NaH–THF to NaOEt–EtOH. For the 2-halogenomethyl-3-phenylpropenoate systems in THF the degree of nucleophilic substitution at the allylic carbon, C-3′, decreases in the order I[(4c), 100%] > Br(88%)[2] > Cl[(6c), 20%]. In fact, the chloro compound (6c) reacts very slowly (the reaction being incomplete after several days) giving a mixture of three products, *viz.*, the *rearranged* diastereoisomers, (8c) and (8c′) (as indicated by the doubling of certain ^{1}H and ^{13}C n.m.r. signals), and the *normal* substitution product (7c). Compound (7c) and one of the diastereoisomers, (8c), were isolated by column chromatography. The other *rearranged* products [(8a) and (8b), obtained from the corresponding chloro or iodo compounds] were also shown by ^{13}C and/or ^{1}H n.m.r. spectroscopy to comprise mixtures of the corresponding diastereoisomers.

Stereochemical Aspects.—^{13}C N.m.r. studies of isomeric necic acids[6] and of the bromo analogues[1] of compounds (4) and (6) have illustrated the sensitivity of the ^{13}C chemical shift of the allylic carbon [*e.g.* C-3′, Figure, (c)] to a change in double-bond geometry. The configurational assignments for the *normal* substitution products [(7), Table 1] are based on a comparison of their C-3′ signals [(*E*)-isomers, δ 29.7 ± 0.3 p.p.m.; (*Z*)-isomers, δ 37.9 ± 0.1 p.p.m.] with the corresponding signals for retronecic acid [(*E*)-isomer, δ 28.4] and isatinecic acid [(*Z*)-isomer, δ 37.3]. The chloro and iodo esters [(4) and (6) respectively] are assumed to belong to the (*Z*)-series since they react *diastereospecifically* to give the same [*i.e.* (*E*)] substitution products (7) as those obtained from the corresponding (*Z*)-bromo esters. Not surprisingly, variation of the halogen (X) affects the C-3′ chemical shifts markedly, but within each halogeno series the observed shifts are comparable [(*Z*)-bromo (25.1 ± 1.5 p.p.m.); chloro (37.7 ± 1.2 p.p.m.); and iodo (1.9 ± 1.7 p.p.m.)].

Experimental

N.m.r. spectra (^{1}H and ^{13}C) were obtained from $CDCl_3$ solutions on Varian T60 or FT80A n.m.r. spectrometers. Analytical data for the new compounds are given in Table 2. H.p.l.c. separations were effected on a Waters preparative LC/System 500A chromatograph.

Halogenation.—Iodination and chlorination of the 3-hydroxy-2-methylenealkanoate esters (3a—c)[2] are illustrated by the following examples.

Ethyl (Z)-2-*iodomethylbut*-2-*enoate* (4a). Conc. HI (51%, 53 ml) and then conc. H_3PO_4 (46 ml) was added dropwise with stirring to ethyl 3-hydroxy-2-methylenebutanoate (3a) (20 g, 0.138 mol). After stirring at room temp. for 4 days, a slurry of sodium metabisulphite in H_2O was added and the resulting mixture was stirred vigorously for 0.5 h before being extracted with Et_2O. The solvent was evaporated under reduced pressure from the dried extract and the residual oil was distilled to give *ethyl* (Z)-2-*iodomethylbut*-2-*enoate* (4a) (22.6 g, 64%).

Ethyl 3-*chloro*-2-*methylenebutanoate* (5a) *and ethyl* (Z)-2-*chloromethylbut*-2-*enoate* (6a). Ph_3P (13.5 g, 0.051 mol) was added in small portions to a stirred solution of ethyl 3-hydroxy-2-methylenebutanoate (3a) (7.2 g, 0.05 mol) in HCA (98%, 30.6 g) maintained at *ca.* 0 °C.* When the addition was complete the mixture was allowed to warm to room temperature and filtered, and the solid residue washed with light petroleum (30—40 °C). The combined filtrate and washings were stirred vigorously with 1M-Na_2CO_3 (25 ml) for 1.5 h and the resulting mixture was then extracted with Et_2O. Evaporation of the solvent under

* Increasing the temperature for the reaction of the hydroxy ester (3a) did not appear to influence the product distribution significantly, although less charring was observed at lower temperatures.

Table 2. Characterisation of new compounds

Compound	M.p. (°C) or B.p. (°C/mmHg)	Found (%)		Molecular formula	Required %	
		C	H		C	H
(4a)	96/2	*m/z*	253.9807	$C_7H_{11}IO_2$[a]	M^+, *m/z*	253.9763
(4b)	102—104/6	*m/z*	282.0114	$C_9H_{15}IO_2$[a]	M^+, *m/z*	282.0076
(4c)	47—48	45.4	4.25	$C_{12}H_{13}IO_2$	45.5	4.1
(5a)	40—42/3.5	52.0	6.8	$C_7H_{11}ClO_2$	51.7	6.8
(5b)	75—76/4.5	57.1	8.0	$C_9H_{15}ClO_2$	56.7	7.9
(6b)	80/4.5	56.5	7.8	$C_9H_{15}ClO_2$	56.7	7.9
(6c)	125/2	64.3	6.0	$C_{12}H_{13}ClO_2$	64.1	5.8
(7b)	140—145/4	64.3	9.1	$C_{16}H_{26}O_5$	64.4	8.8
(8b)	140—145/4	64.3	9.0	$C_{16}H_{26}O_5$	64.4	8.8
(8c)	160—170/4	68.6	7.3	$C_{19}H_{24}O_5$	68.7	7.3

[a] Material too labile to purify for microanalysis.

reduced pressure from the dried extract gave a residual oil (5.9 g) comprising a 1:1 mixture of the chloro derivatives (**5a**) and (**6a**). Chromatography [h.p.l.c.; elution with light petroleum (40—60 °C)–EtOAc (19:1)] of the distilled mixture afforded *ethyl 3-chloro-2-methylenebutanoate* (**5a**) and ethyl (*Z*)-2-chloromethylbut-2-enoate (**6a**).

Regioselectivity Studies.—The results of the regioselectivity studies [involving the reaction of the halogeno compounds (**4**)—(**6**) with ethyl 2-methyl-3-oxobutanoate] are summarised in Table 1. The general procedures used in these studies have been described previously.[2] The reaction of ethyl 2-chloromethyl-3-phenylbut-2-enoate (**6a**) with ethyl 2-methyl-3-oxobutanoate enolate in THF during 3 days afforded, after work-up, a mixture shown by ^1H and ^{13}C n.m.r. spectroscopy to contain starting material, the (*E*)-regiosomer (**7c**), and the diastereoisomers (**8c**) and (**8c'**). Fractional distillation afforded the starting material (**6c**) and a mixture which was then chromatographed [elution with light petroleum (40—60 °C)–EtOAc (19:1) on silica gel] to give diethyl (*E*)-4-methyl-5-oxo-1-phenylhex-1-ene-2,4-dicarboxylate (**7c**) and *diethyl 4-methyl-5-oxo-3-phenylhex-1-ene-2,4-dicarboxylate* (**8c**); the diastereoisomeric compound (**8c'**), which was not isolated, was identified (by ^1H and ^{13}C n.m.r. spectroscopy) in mixtures with (**7c**) and with (**8c**).

Acknowledgements

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