Mechanism of Dehydroacetoxylation of Methyl 3-Acetoxy-3-aryl-2-halogenopropanoates

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The rate of sodium methoxide-induced dehydroacetoxylation of the diesters *p*-$RC_6H_4CH(OAc)CXHCO_2Me$ (X = Br or Cl) has been studied as a function of the *para*-substituent. The results correspond to the *para*-substituent effects expected for proton abstraction from C-2, as estimated from the diastereoisomerisation of model compounds [*p*-$RC_6H_4CH(OMe)CXHCO_2Me$] under similar conditions. This suggests that the elimination occurs *via* a carbanion mechanism, with C(2)–H bond-breaking rate-determining. The apparent insensitivity of the kinetic behaviour to configuration differences, together with the response of the reactions to the effect of the 3-substituent, is interpreted in terms of inductive stabilisation by the 2-halogen atom, which tends to localise the incipient negative charge at C-2, inhibiting distortion of its tetrahedral geometry.

An attempt to obtain information about the influence of configurational differences on the alkene-producing dehydroacetoxylation of methyl 3-acetoxy-2-bromo-3-phenylpropanoate (**1**; X = Br, R = H) showed that the methoxide-promoted elimination rate coefficients were completely independent of the diastereoisomeric character of the substrate. A similar kinetic

$$p\text{-}RC_6H_4CH(OAc)CXHCO_2Me \qquad (1)$$

insensitivity was observed with the 2-chloro-derivative (**1**; X = Cl, R = H) under the same conditions.

Kinetic evidence has been presented indicating that in 1,2-eliminations involving hydrogen made acidic by an acetyl (or a benzoyl) group,[1,2] the acetate leaving group is expelled by an *E*1cB process, with carbon–hydrogen bond-breaking rate-determining. It was therefore thought that elimination reactions in systems of type (**1**) would merit further examination, since they would allow some stereochemical features to be studied and provide an opportunity of testing and extending the applicability of the $(E1cB)_I$ mechanism. We describe here results of a kinetic study of the methanolic methoxide-induced elimination of acetic acid from (**1**; X = Br or Cl, R = OMe, Me, H, Cl, or NO_2) together with some aspects of the stereochemical course of the reaction.

Results and Discussion

The elimination products were isolated from the reaction mixtures; ^1H n.m.r. and u.v. spectra showed that they were the only products formed. All compounds (pure diastereoisomers or diastereoisomeric mixtures) gave exclusively the most stable olefin, (*Z*)-*p*-$RC_6H_4CH{=}CXCO_2Me$.[3] Blank experiments showed that the products did not isomerise under the reaction conditions. Further, the ^1H n.m.r. spectra of samples from interrupted-reaction mixtures showed the absence of isomerisation of the starting material.

The rates of reactions with the acetoxy halides were followed by monitoring the appearance of the corresponding olefin, by u.v. spectroscopy. A full spectrum of the elimination product after fifteen half-lives was superimposable on a spectrum of the appropriate olefin at the same concentration. Good first-order kinetics in both substrate and base were obtained up to at least 85% reaction. Results are summarised in Table 1.

The substrates were diastereoisomerically pure by ^1H n.m.r. analysis except for two chloro-derivatives (**1**; X = Cl, R = Me or Cl) which were obtained as mixtures containing various proportions of the diastereoisomers. For each of the latter compounds, reactions with different initial isomeric compositions led to the same rate of appearance of the product, indicating that the isomer rate coefficients were identical within the limits of the estimated experimental error. This was further verified by evaluating relative rate constants ($k_{R,R}/k_{R,S}$) by ^1H n.m.r. The n.m.r. method involved determination of the ratio of unchanged starting isomers during the course of the reaction. The values of $k_{R,R}/k_{R,S}$ so obtained were close to unity.

Table 1. Kinetic data for dehydroacetoxylation of *p*-$RC_6H_4CH(OAc)CXHCO_2Me$ with MeO in MeOH at 30 °C

X	R	Isomer	$10^{-1}\ k$ [a]
Br[b]	MeO	*R,R*	0.412
	Me	*R,R*	0.510
	H	*R,R*	0.832
		R,S	0.842
	Cl	*R,R*	1.833
	NO_2	*R,R*	7.750
Cl[c]	MeO	*R,R*	0.698
	Me	*R,R*/*R,S*	0.965[d]
	H	*R,R*	1.575
		R,R/*R,S*	1.551[d]
	Cl	*R,R*/*R,S*	3.475[d]
	NO_2	*R,R*	16.616[e]

[a] ln $dm^3\ mol^{-1}\ s^{-1}$. [b] [substrate] 0.001 mol dm^{-3}, [base] 0.002 mol dm^{-3}. [c] [substrate] 0.000 85 mol dm^{-3}, [base] 0.0015 mol dm^{-3}. [d] Average of values obtained with isomeric mixtures of different composition. [e] Based on the relative values of $k_{p\text{-}NO_2}$ and $k_{p\text{-}H}$ for elimination with triethylamine in methanol.

The observed kinetics are compatible with the *E*2, the pre-equilibrium, or the irreversible *E*1cB mechanism.[4] However, the lack of hydrogen–deuterium exchange at position 2, of the diastereoisomerisation of the substrate, precludes the second possibility.

The rate coefficients were correlated with the 'normal' Hammett σ constants; the plot exhibited satisfactory linearity with ρ = 1.24 (correlation coefficient 0.9987) and ρ = 1.31 (correlation coefficient 0.9994) for the 2-bromo- and 2-chloro-derivatives, respectively. These values argue for development of negative charge in the transition state,[5] and this is consistent either with the $(E1cB)_I$ process, or with a mechanism of the *E*2 type wherein the transition state has appreciable carbanion character. According to the variable transition-state theory of the *E*2 reaction offered by Bunnett (*E*1-like–*E*1cB-like

Table 2. Kinetic data for equilibration of (*R,R*)-*p*-$RC_6H_4CH(OMe)CXHCO_2Me$[a] with MeO^-[b] in MeOH at 30 °C

X	R	k[c]
	MeO	0.370
	Me	0.474
Br	H	0.682
	Cl	1.510
	NO_2	8.750
	MeO	0.438
	Me	0.585
Cl	H	0.964
	Cl	2.300
	NO_2	9.362

[a] [substrate] 0.0366 mol dm^{-3}. [b] [base] 0.0024 mol dm^{-3}. [c] ln dm^3 mol^{-1} s^{-1}.

spectrum),[6] a concerted transition state of the present reactions would be one in which considerable proton removal accompanies little breaking of the C–OAc bond and partial π-bond formation. It seems reasonable to assume that this developing double bond would be susceptible to through-conjugation with $-M$ substituents in the *para*-position of the aromatic ring. However, the rate-enhancing effect observed for the nitro group is lower than would be expected from any of the σ^- constants used in reactions in which direct conjugation between the substituent and the reaction centre occurs. Thus, the fact that a better correlation is achieved with the ordinary σ_{NO_2} value (0.78) argues against the concerted pathway and seems to favour a two-step process with only proton removal rate-determining. Further, if the concerted process near the *E*1cB end of the *E*2 spectrum is operative, it is rather difficult to see why an electron-releasing substituent such as MeO should not facilitate the concerted reaction through a favourable influence on the removal of the leaving group, shifting the transition state character to the paenecarbonium side and showing a curved Hammett plot.[7]

In order to obtain further information about the nature of the rate-controlling step of these eliminations, we have evaluated the influence of the *p*-phenyl substituents on the rate of proton transfer of suitable model compounds. The methanolic methoxide-catalysed hydrogen–deuterium exchange reaction at the carbon atom adjacent to the methoxycarbonyl group in the *R,R*-methoxy ester (**2**; R = H, X = Br or Cl) was found to occur

$$p\text{-}RC_6H_4CH(OMe)CXHCO_2Me \qquad (2)$$

with equilibration to mixtures of the *R,R*- and *R,S*-isomers. The two processes were shown to proceed at identical rates. It may be concluded that equilibration and hydrogen exchange are both controlled by the same pathway, *viz.* heterolysis of the C(2)–H bond followed by protonation (deuteronation) of the intermediate carbanion, which would partition between *R,R*- and *R,S*-forms as determined by the relative stability of the isomers [reaction (i)].

$$(R,R)\text{-}(2;\ R = H) + MeO^- \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} PhCH(OMe)\bar{C}XCO_2Me + MeOH \underset{k_2}{\overset{k_{-2}}{\rightleftharpoons}} (R,S)\text{-}(2;\ R = H) + MeO^- \qquad (i)$$

Since these 2-halogeno esters may reasonably be regarded as very weak acids in the present base–solvent systems, their ionisation rates must be much lower than the rates of reprotonation, $k_1 \gg (k_{-1} + k_{-1})$ [MeOH]. Thus, the rate of equilibration of the *R,R*-isomer may be taken as a measure of its rate of ionisation. The equilibration reactions of the methoxy halides; (**2**; X = Br or Cl, R = MeO, Me, H, Cl, or NO_2) were started with the pure *R,R*-isomers and followed by integration of the methoxycarbonyl proton signals in the n.m.r. spectra. Good pseudo-first-order coefficients (k_1) were obtained. Second-order rate constants were calculated by dividing k_1 by the base concentration (Table 2). The Hammett ρ values for these reactions were determined from the slopes of the logarithms of relative reactivity of the substituted and the unsubstituted compounds ($k_{p\text{-R}}/k_{p\text{-H}}$) against σ values. For (**2**; X = Br), ρ = 1.32 (r = 0.9979); for (**2**; X = Cl), ρ = 1.26 (r = 0.9974).

Table 3. Relative rates for the elimination reactions of methyl 2-halogeno-3-acetoxy- and 2,3-dihalogeno-3-phenylpropanoates[a] with MeO^-[b] in MeOH at 30 °C

x/*y*	k_x/k_y
(*R,R*)-2-Chloro-3-acetoxy-/(*R,S*)-2,3-Dichloro-	1.78
(*R,R*)-2-Bromo-3-acetoxy-/(*R,S*)-2,3-dibromo-	3.14
(*R,S*)-2-Chloro-3-bromo-/(*R,S*)-2,3-dichloro-	0.82
(*R,S*)-2,3-Dibromo-/(*R,S*)-2-bromo-3-chloro-	0.76

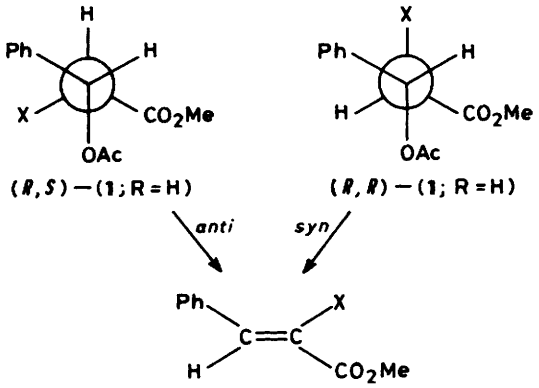
[a] [substrates] 0.04 mol dm^{-3}. [b] [base] 0.04 mol dm^{-3}.

The observation that the response of reactivity of the model compounds to substituent effects closely parallels that of the eliminations may be regarded as indication that transition states of similar character are involved in the two cases. Again, this observation reinforces the idea that rate-limiting carbanion formation is involved.

The observed k^{OAc}/k^{OMe} values (12.3 for the bromo- and 16.2 for the chloro-unsubstituted substrates) appear larger than would be expected on the basis of a Taft correlation for C-2 carbanion-forming reactions in carbonyl compounds.[2] However, Stirling's measurements have shown that the sensitivity of these processes to substitution adjacent to the reaction centre varies with the carbanion-stabilising group and depends on the degree of delocalisation of the charge. Although ρ* values for ionisation of the present 2-halogeno esters are not available, it is possible that whereas a relatively small ρ* value for esters of the type ZCH_2CO_2Me[8] would be expected, partly because much of the charge is distributed onto the methoxycarbonyl group, the inductive influence exerted by a 2-halogen atom might result in electrostatic inhibition of delocalisation of the charge over the carbonyl group and an increased sensitivity of ionisation to polar effects. Accordingly, the aforementioned difference in rates may reasonably be attributed to a response of the kinetic acidity of the C-2 hydrogen atom to the influence of the 2-substituent. An alternative explanation is that the role of the acetoxy group also includes some degree of intramolecular interaction between the carbonyl oxygen atom and the C-2 hydrogen atom in the transition state leading to the carbanionic intermediate. An enhanced effect might be expected for a deprotonation stage in which this neighbouring group participation facilitates proton abstraction by the base. Consistent with this hypothesis seems to be the effect of changing the leaving group from acetoxy to halogen. The similarity in rates for the eliminations with the acetoxyhalogeno- and the dihalogeno-compounds (Table 3) suggests that these reactions are all occurring by the same mechanism. Furthermore, the smallness and direction of the dependence of reactivity on the leaving group (3-acetoxy > 3-chloro > 3-bromo) argues against a concerted elimination. In the case of the dihalogeno-compounds, the very slight difference in rates suggests that, if anything, the sensitivity of the reaction to the leaving group is that expected of the inductive ability of the latter to stabilise the incipient carbanion. However, the

response of the rate to the influence of the 3-acetoxy group, as compared with that of the corresponding 3-halogeno-compounds (3-acetoxy > 3-chloro and 3-acetoxy > 3-bromo), shows a reversal of the normal electronic effect of the 3-substituent. It is thus tempting to ascribe the reactivity of the acetoxy compounds to some direct assistance exerted by the acetoxy group which increases the lability of the C-2 hydrogen atom.

A notable feature of these eliminations is that the same isomeric olefin is obtained irrespective of the configuration of the starting material. It is possible to justify these observations on the basis of a mechanism in which the intermediate has a long enough life to lose its original diastereoisomeric identity before expulsion of the leaving group to lead to the more stable olefin. However, the stereochemical requirement that hydrogen and the leaving group be *anti* in concerted 1,2-eliminations is less strict for the paenecarbanion region of the variable transition-state theory, and *syn*-eliminations are sometimes also observed in *E*1cB-like reactions.[9] Thus, the stereoconvergent course of the present eliminations could be consistent with *anti* and *syn* *E*1cB-like transition states from the *R,S*- and *R,R*-isomers, respectively [reaction (ii)]. If this were the case, then a



(ii)

qualitative evaluation of the non-bonded repulsions would suggest that the appropriate conformation for the elimination from the *R,R*-isomer should be more stable than that for the *R,S*-isomer. On the other hand it seems not unreasonable to expect that, owing to the favourable orbital overlap accompanying *anti*-eliminations, the transition state arising from the *R,S*-isomer would be energetically favoured with respect to the transition state arising from the *R,R*-isomer. Thus some degree of coincidence would be required of these two pathways in order to be consistent with the apparent equivalence in activation parameters that may be inferred from the kinetic identity observed within the limits of experimental uncertainty. Although the evidence against the latter possibility does not seem conclusive, it appears more likely that the elimination proceeds by a mechanism with carbanion formation rate-determining where the transition state undergoes no conformational change with respect to the initial state, so that the kinetic behaviour of the isomers is not affected by differential steric factors. This could be compatible with the fact that since the adjacent halogen is also available to stabilise the transition state leading to the carbanionic system, the extent of delocalisation of the incipient charge into the carbonyl group may be significantly reduced and this will result in little deviation from the tetrahedral geometry about the carbanionic carbon atom. This interpretation is in line with the apparent enhanced carbanion character of the transition state of these reactions already suggested to account for the sensitivity of the substrates to the influence of the 3-substituent.

Although the foregoing results do not rigorously discount the operation of the concerted mechanism, we feel that the balance of the evidence tends to favour irreversible carbanionic elimination.

Experimental

Materials.—Sodium methoxide solutions were prepared by reaction of clean pieces of sodium with methanol under nitrogen. Concentrations were determined by titration against standard acid. Solutions containing the required concentrations of reagents were prepared immediately before use by suitable dilution of stock solutions.

The (*R,R*)-acetoxy bromides (**1**; X = Br, R = MeO, Me, H, or Cl)[10] were prepared by reactions of the corresponding (*E*)-methyl cinnamate (0.2M) and *N*-bromosuccinimide (0.22M) in acetic acid containing a small proportion of mercury(II) acetate (0.04M) in order to prevent formation of dibromides. After the appropriate reaction period at 60 °C, the cooled mixture was poured into water and extracted with chloroform. Removal of the solvent left a residue which ^{1}H n.m.r. spectroscopy showed to contain the corresponding (*R,R*)-acetoxy bromide contaminated with minor amounts of the *R,S*-isomer. The crude products were purified as follows. The *p*-methyl- and *p*-chloro-compound (**1**; X = Br, R = Me or Cl) were recrystallised from ethanol at −10 °C. The unsubstituted acetoxy bromide (**1**; X = Br, R = H) was purified by chromatography on a silica gel column with benzene–carbon tetrachloride (1:2) as eluant. The *p*-methoxy compound (**1**; X = Br, R = MeO) was chromatographed on silica gel using carbon tetrachloride–chloroform (1:1) as eluant. The *p*-nitro-compound (**1**; X = Br, R = NO_2) was similarly prepared except that the reaction temperature was 30 °C and mercury(II) acetate was omitted. The crude product obtained after the usual work-up was recrystallised from ethanol at −10 °C yielding pure (R,R)-*methyl 3-acetoxy-2-bromo-3-(p-nitrophenyl)propanoate*, m.p. 94.5—96.0 °C (Found: C, 41.4; H, 3.6; N, 4.0. $C_{12}H_{12}BrNO_6$ requires C, 41.6; H, 3.5; N, 4.05%). The configurational assignment was based on ^{1}H n.m.r. comparison with the known (*R,R*)- and (*R,S*)-(**1**; X = Br or Cl);[10] δ(CCl_4) 8.35 (2 H, d, aromatic), 7.70 (2 H, d, aromatic), 6.15 (1 H, d, *J* 8 Hz, H-3), 4.46 (1 H, d, *J* 8 Hz, H-2), 3.90 (3 H, s, CO_2CH_3), and 2.05 (3 H, s, $OCOCH_3$). (*R,S*)-Methyl 3-acetoxy-2-bromo-3-phenylpropanoate was prepared from methyl (*R,S*)-2-bromo-3-hydroxy-3-phenylpropanoate according to the method reported by Wilson.[10]

The (*R,R*)- and (*R,S*)-acetoxy chlorides (**1**; X = Cl; R = H) were also prepared by acetylation of the corresponding chlorohydrins as described by de la Mare.[11] The *p*-methyl- and *p*-chloro-acetoxy chlorides (**1**; X = Cl, R = Me or Cl) were obtained as mixtures of the *R,R*- and *R,S*-isomers in the ratio *ca.* 7:3 by reaction of the appropriate (*E*)-methyl cinnamate (0.2M) with t-butyl hypochlorite (0.26M) and mercury(II) acetate (0.06M) in acetic acid at 30 °C. Chromatography on a column of silica gel eluted with carbon tetrachloride–chloroform (1:1) gave pure mixtures containing different amounts of the two isomers. The (*R,R*)-*p*-nitro- and *p*-methoxy-acetoxy chlorides (**1**; X = Cl, R = NO_2 or OMe)[12] were prepared in the same manner as the *p*-methyl and *p*-chloro analogues. For the *p*-methoxy-acetoxy chloride the crude product consisted of the *R,R*-compound contaminated with 7% of the *R,S*-isomer. Chromatography on silica gel eluted with carbon tetrachloride–chloroform (1:1) afforded pure (*R,R*)-(**1**; X = Cl, R = OMe). In the case of the *p*-nitro-acetoxy chloride the residue containing *R,R*- and *R,S*-isomers in the ratio 81:19 was recrystallised from methanol–light petroleum (b.p. 30—60 °C) (9:1), yielding pure (*R,R*)-(**1**; X = Cl, R = NO_2).

Methyl (*R,R*)-2-bromo-3-methoxy-3-phenylpropanoate[3] was obtained diastereoisomerically pure by bromination of (*E*)-

Table 4. ^{1}H N.m.r. spectra of p-$RC_6H_4CH(OCH_3)CBrHCO_2CH_3$

R	Isomer	Chemical shifts (δ)[a] 3-H	2-H	$COCH_3$	CO_2CH_3	$J_{2,3}$/Hz
OCH_3	*R,R*	4.29	3.93	3.08	3.71	10.0
	R,S	4.28	4.06	3.13	3.41	9.0
CH_3	*R,R*	4.28	3.95	3.10	3.71	10.0
	R,S	4.26	4.08	3.15	3.41	9.0
Cl	*R,R*	4.28	3.92	3.13	3.72	10.0
	R,S	4.33	4.06	3.21	3.45	9.0
NO_2[b]	*R,R*	4.58	4.10	3.20	3.78	10.0
	R,S	4.63	4.25	3.29	3.58	8.0

[a] In CCl_4 unless otherwise stated. [b] In $CDCl_3$.

Table 5. ^{1}H N.m.r. spectra of p-$RC_6H_4CH(OCH_3)CClHCO_2CH_3$

R	Isomer	Chemical shifts (δ)[a] 3-H	2-H	$COCH_3$	CO_2CH_3	$J_{2,3}$/Hz
OCH_3	*R,R*	4.22	3.94	3.09	3.72	9.5
	R,S	4.28	4.08	3.15	3.43	8.0
CH_3	*R,R*	4.26	3.97	3.09	3.71	9.5
	R,S	4.32	4.11	3.16	3.42	8.0
Cl	*R,R*	4.31	3.96	3.13	3.72	9.5
	R,S	4.37	4.10	3.20	3.48	8.0
NO_2	*R,R*	4.56	4.17	3.18	3.78	9.5
	R,S	4.75	4.34	3.24	3.62	6.5

[a] In CCl_4.

methyl cinnamate (0.2M) with *N*-bromosuccinimide (0.24M) in methanol in the dark at 30 °C. Work-up as in the procedures already described gave material which was recrystallised from ethanol at −10 °C. Similarly prepared were the methyl (*R,R*)-*p*-methoxy, *p*-methyl, and *p*-chloro analogues. The crude products were purified by recrystallisation from ethanol at −10 °C, except for the *p*-methoxy compound which was chromatographed on silica gel with 1:1 carbon tetrachloride–chloroform as eluant. (R,R)-*Methyl 2-bromo-3-methoxy-3-(p-methoxyphenyl)propanoate* had m.p. 43.0—45.0 °C (Found: C, 47.3; H, 4.8. $C_{12}H_{15}BrO_4$ requires C, 47.5; H, 5.0%); (R,R)-*methyl 2-bromo-3-methoxy-3-(p-methylphenyl)propanoate* had m.p. 70.0—71.0 °C (Found: C, 49.8; H, 5.2. $C_{12}H_{15}BrO_3$ requires C, 50.2; H, 5.3%); (R,R)-*methyl 2-bromo-3-methoxy-3-(p-chlorophenyl)propanoate* had m.p. 71.5—72.5 °C (Found: C, 42.6; H, 3.95. $C_{11}H_{12}BrClO_3$ requires C, 42.9; H, 3.9%). The *p*-nitro compound was prepared by esterification of the corresponding acid obtained *via* methoxymercuriation of (*E*)-*p*-nitrocinnamic acid. Mercury(II) acetate (0.026 mol) and (*E*)-*p*-nitrocinnamic acid (0.025 mol) in methanol (125 ml) were heated under reflux for 12 days. The mixture was concentrated to one-half of its original volume and the resulting precipitate was filtered off and dissolved in aqueous potassium bromide. The liquid was refiltered to remove some dark-brown solid and a solution of bromine (0.025 mol) in water (50 ml) containing potassium bromide was added dropwise under illumination from a 70 W Hanau mercury lamp. After addition was complete the mixture was acidifed with hydrobromic acid and extracted with ether, and the solvent was removed. The ^{1}H n.m.r. spectrum of the resulting white solid was consistent with the presence of a 1:1 mixture of (*R,R*)- and (*R,S*)-2-bromo-3-methoxy-3-(*p*-nitrophenyl)propionic acid. The mixture was partially dissolved in aqueous sodium carbonate (10%; 30 ml). Treatment of the remaining solid with 2.5M-hydrochloric acid afforded the *R,R*-acid contaminated with 3% (^{1}H n.m.r.) of the *R,S*-isomer. Crystallisation from chloroform–hexane (3:1) gave the pure *R,R*-acid, m.p. 178 °C. The acid was converted into the ester by refluxing with methanol in the presence of sulphuric acid. (R,R)-*Methyl 2-bromo-3-methoxy-3-(p-nitrophenyl)propanoate* had m.p. 75.0—76.0 °C (Found: C, 41.1; H, 3.75; N, 4.3. $C_{11}H_{12}BrNO_5$ requires C, 41.5; H, 3.8; N, 4.4%).

The ^{1}H n.m.r. data of the new (*R,R*)-methoxy bromides are summarised in Table 4 together with those of the *R,S*-isomers obtained from the equilibration reactions. The configurational assignment followed from stability considerations and comparison of their ^{1}H n.m.r. spectra with those of the (*R,R*)- and (*R,S*)-methoxy bromides as described previously.[3]

Methyl (*R,R*)-2-chloro-3-methoxy-3-phenylpropanoate and its *p*-methoxy, *p*-methyl, *p*-chloro, and *p*-nitro analogues were prepared by reactions of the appropriate (*E*)-methyl cinnamates with t-butyl hypochlorite.[3] The usual work-up afforded the desired compound contaminated with small proportions of the corresponding *R,S*-isomer (*ca.* 9%). Recrystallisation from ethanol at −10 °C gave a pure sample of the *R,R*-isomer except with the *p*-methoxy compound, for which attempted purification by direct crystallisation or chromatography failed. Finally, this compound was freed of the *R,S*-isomer by dry trituration of the oily solid mixture over a porous plate followed by recrystallisation from methanol. (R,R)-*Methyl 2-chloro-3-methoxy-3-(p-methoxyphenyl)propanoate* had m.p. 37.0—39.0 °C (Found: C, 55.2; H, 5.7. $C_{12}H_{15}ClO_4$ requires C, 55.7; H, 5.8%); (R,R)-*methyl 2-chloro-3-methoxy-3-(p-methylphenyl)propanoate* had m.p. 45.0—47.0 °C (Found: 59.5; H, 6.15. $C_{12}H_{15}ClO_3$ requires C, 59.4; H, 6.2%); (R,R)-*methyl 2-chloro-3-methoxy-3-(p-chlorophenyl)propanoate* had m.p. 71.0—71.5 °C (Found: C, 49.8; H, 4.5. $C_{11}H_{12}Cl_2O_3$ requires C, 50.2; H, 4.6); (R,R)-*methyl 2-chloro-3-methoxy-3-(p-nitrophenyl)propanoate* had m.p. 80.0—80.5 °C (Found: C, 47.8; H, 4.4. $C_{11}H_{12}ClNO_5$ requires C, 48.3; H, 4.4%). The ^{1}H n.m.r. data of the new (*R,R*)-methoxy chlorides and their *R,S*-isomers are shown in Table 5. As before, the assignment of configurations was based on stability grounds.

(*R,S*)-Methyl 2,3-dibromo-[3] and (*R,S*)-methyl 2,3-dichloro-3-phenylpropanoate[13] were obtained, contaminated with the corresponding *R,R*-isomers, according to the reported procedures. Crystallisation of the mixtures from ethanol at −10 °C gave the pure *R,S*-compounds. (*R,S*)-Methyl 3-bromo-2-chloro-3-phenylpropanoate was prepared by esterification of the acid;[14] m.p. 104.5—105.0 °C (MeOH–H_2O, 9:1), δ(CCl_4) 7.23 (5 H, s, aromatic), 5.05 (1 H, d, *J* 11.5 Hz, H-3), 4.56 (1 H, d, *J* 11.5 Hz, H-2), and 3.80 (3 H, s, CO_2CH_3). (*R,S*)-Methyl 2-bromo-3-chloro-3-phenylpropanoate was similarly prepared from the corresponding acid;[14] m.p. 110.5—112.0 °C (EtOH), δ(CCl_4) 7.20 (5 H, s, aromatic), 5.06 (1 H, d, *J* 11.0 Hz, H-3), 4.40 (1 H, s, *J* 11.0 Hz, H-2), and 3.77 (3 H, s, CO_2CH_3).

Kinetic Procedure.—Rates were measured at 30 ± 0.05 °C. Elimination reactions were initiated by adding methanolic sodium methoxide (10 ml; 0.14 mmol) to a solution of the appropriate substrate in methanol (60 ml; 0.07 mmol) with maximum precautions to exclude atmospheric carbon dioxide. For the more rapid reactions addition was carried out quickly from a calibrated syringe while the solution was being stirred. Samples (5 ml) were withdrawn by calibrated automatic pipette at various times and mixed with nineteen volumes of aqueous 0.1M-hydrochloric acid (except for the reaction with the *p*-nitro compounds for which the quenching was carried out with aqueous acetic acid in order to prevent hydrogen chloride addition to the resulting olefin), and their absorption was recorded at the appropriate absorption maximum. The wavelengths used with 312 (*p*-OMe), 296 (*p*-Me), 286 (*p*-H), 294 (*p*-Cl), and 310 nm (*p*-NO_2). Rate coefficients were calculated by

standard methods for second-order reactions from the data obtained by measuring the optical densities. Transparency of the starting materials at the wavelengths mentioned was demonstrated in all cases except with the *p*-nitro substrate. For this compound the fraction of elimination product (x) was calculated from the equation $x = (O.D._t - O.D._0)/(O.D._\infty - O.D._0)$ where $O.D._0$, $O.D._t$, and $O.D._\infty$ are the optical densities obtained from samples drawn initially, after time t, and after 15 half-lives, respectively. In the other cases x was calculated directly from $O.D._t/O.D._\infty$. All runs were conducted at least in triplicate; the average rate coefficients agreed within ±2% or less, except that with the *p*-nitro-acetoxy chloride (**1**; X = Cl, R = NO_2) for which the accuracy was no better than ±8%. In this case a more accurate result was obtained by using the fact that comparison of the lower rates of triethylamine-induced dehydroacetoxylation of the remaining *para*-substituted derivatives with that of the parent compound leads to $k_{p\text{-R}}/k_{p\text{-H}}$ values almost identical with those corresponding to the reaction with sodium methoxide. The desired rate coefficient was thus calculated by multiplying $k_{p\text{-NO}_2}/k_{p\text{-H}}$ for the former reaction by the $k_{p\text{-H}}$ for the elimination with sodium methoxide.

For the ^{1}H n.m.r. measurements the reactions with mixtures of *R,R*- and *R,S*-isomers were carried out similarly except that larger volumes of solutions were used in order to obtain convenient amounts of residue. The samples were prepared by quenching the reaction with water containing a slight excess of hydrochloric acid. The products were removed by extraction with dichloromethane. After drying, the solvent was removed by careful evaporation and a solution (10%) was made with carbon tetrachloride for ^{1}H n.m.r. analysis. The relative rates were measured using the intensity of the methoxy carbonyl resonances of the starting material relative to the methoxy carbonyl signals of the product.

For the competition reactions with the acetoxy-halogeno and the dihalogeno substrates a methanolic solution (10 ml) containing the particular pair of compounds such that the initial concentration of each reactant was 0.08M, was treated with methanolic sodium methoxide (0.08M; 10 ml). The reaction mixture was worked up as before and the amounts of unchanged starting materials were determined by relative integration of the 2-proton peak areas and the area corresponding to the total methoxy-proton resonances. The rate ratios were calculated from the equation (iii), which is independent of time.

$$k_x/k_y = \log(\text{fraction of unchanged } x)/\log(\text{fraction of unchanged } y) \quad \text{(iii)}$$

The values were estimated to have an experimental error of ±2.5% after triplicate experiments and multiple integrations.

The equilibration reactions were started by transferring 5 ml of methanolic sodium methoxide into a flask containing the solution of the corresponding methoxy-halogeno compound in methanol (10 ml) such that the initial concentrations were 0.05M (substrate) and 0.001M (base). Samples (3 ml) were periodically withdrawn with an automatic pipette and quenched by shaking with a mixture of 0.5 ml of $CDCl_3$ and 7.5 ml of 0.1M-hydrochloric acid in a centrifuge tube. The mixture was centrifuged and the chloroform layer transferred to a n.m.r. tube by hypodermic syringe. The proportions of the equilibrated material were estimated by integration of the areas under the methoxy carbonyl signals. Equilibration rate coefficients were calculated from the pseudo-first-order equation (iv), where

$$\ln\{[R,R]/([R,R] - x) = kt \quad \text{(iv)}$$

$[R,R]$ is the initial concentration of the *R,R*-isomer and x the fraction of $[R,R]$ converted into equilibrium mixture at time t. Since for the equilibration $[R,R] = [R,S]/K_{eq}$, x is given by the expression $x = [R,S] + [R,S]/K_{eq}$, where $[R,S]$ is the amount of *R,S*-isomer at time t. Triplicate runs gave a reproducibility of ±2%.

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