Esters of α-Arylalkanoic Acids from 'Masked' α-Halogenoalkyl Aryl Ketones and Silver Salts: Synthetic, Kinetic, and Mechanistic Aspects

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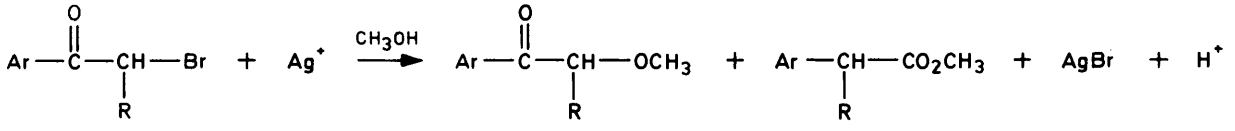
A method for the synthesis of alkyl esters of α-arylalkanoic acids is given, based on silver-ion-assisted ($AgBF_4$, $AgOSO_2CF_3$, $AgSbF_6$, $AgNO_3$) solvolysis of alkyl acetals of primary and secondary α-halogenoalkyl aryl ketones (Hal = I, Br, Cl) in an alcoholic medium (methanol, ethanol). The reaction is quite selective and alkyl esters are the only reaction products; ethers, which are possible substitution products, are not found. The importance of masking the carbonyl as the acetal is emphasised. The reaction is found to be first-order in $AgBF_4$ and in the primary α-halogeno acetal. A three-point Hammett correlation ($\rho = -3.29$) between σ^+ and the rate constants suggests a large cationic contribution as well as strong aryl participation in the transition state.

The role played by the oxygen of the acetal group in the specificity of the reaction is discussed in comparison with the reactivity of analogous compounds with saturated skeletons and of α-halogenoalkyl aryl ketones.

THE use of masking reagents [1] that alter the normal reactivity of a functional group is a convenient artifice for performing synthetic operations to reverse the reactivity pattern of the substrate. Thus, the reactivity of such reagents is becoming an essential part of synthetic strategies.

In this paper we report the synthesis of esters of α-arylalkanoic acids from α-halogenoalkyl aryl ketones, the success of which depends on masking the carbonyl group present in the starting ketones. Esters, so obtained, are converted by hydrolysis into the corresponding α-arylalkanoic acids; the importance of this class of compounds is well known.[2,3]

Synthesis of esters of α-arylalkanoic acids from masked alkyl aryl ketones have been reported previously; thus, the intermediate formation of masked carbonyls as the hemiacetals has been postulated in the oxidative rearrangement of alkyl aryl ketones with thallium(III) [4] and lead(IV) [5] salts to esters of α-arylalkanoic acids. Moreover, masked carbonyls (as acetals) have been invoked to explain the formation of methyl esters of α-arylalkanoic acids in the reaction of α-bromoalkyl aryl ketones with silver salts in methanol [6] (Scheme 1).



SCHEME 1

This method suffers from limitations which are related to the presence of the carbonyl group in equilibrium with the acetal: the presence of the carbonyl favours substitution (α-methoxyalkyl aryl ketones are the main reaction by-products,[6] Scheme 1) and elimination reactions (formation of α,β-unsaturated ketones [6]). We thought that these disadvantages might be overcome by converting the carbonyl group of the starting α-halogenoalkyl aryl ketones into an acetal group. The acetal group changes the stereoelectronic properties of the carbonyl group by inhibiting substitution reactions, thus favouring the migration of the aryl group.

This last consideration is substantiated by the reaction between chalcones and thallium(III) salts,[7] where it is underlined by the more facile aryl migration in aryl acetals with respect to aryl ketones. Some data concerning the silver hexafluoroantimonate-assisted rearrangement of *tertiary and benzylic secondary* α-bromoalkyl aryl acetals have been reported in connection with work related mainly to the substitution or elimination of bromine in α-bromoalkyl aryl ketones by nucleophiles.[8,9] However, this work does not give an idea of the general synthetic potential of this kind of rearrangement.

As a matter of fact, to the best of our knowledge, the rearrangement of *primary and non-benzylic secondary* α-halogenoalkyl aryl acetals (which are the most important from a practical point of view; [2,3] see Table, entries n, o, q, and t) has never been reported.

RESULTS AND DISCUSSION

Our method consists of the addition at 40 °C of a silver salt (silver tetrafluoroborate, hexafluoroantimonate, trifluoromethanesulphonate, or nitrate), to an alcoholic solution of a primary or secondary α-halogenoalkyl aryl acetal. Generally, the acetal is generated *in situ* from the corresponding α-halogenoalkyl aryl ketone, a trialkyl orthoformate (trimethyl orthoformate or triethyl orthoformate) and an alcohol (methanol or ethanol) in the presence of a catalytic amount of acid (Scheme 2, Table).

Yields of esters, based on the converted α-halogeno-acetals, are almost quantitative; the unchanged α-halogeno-acetals can be recovered as such or as free α-halogeno-ketones. The converted silver can be recovered, at the end of the reaction, as a silver halide

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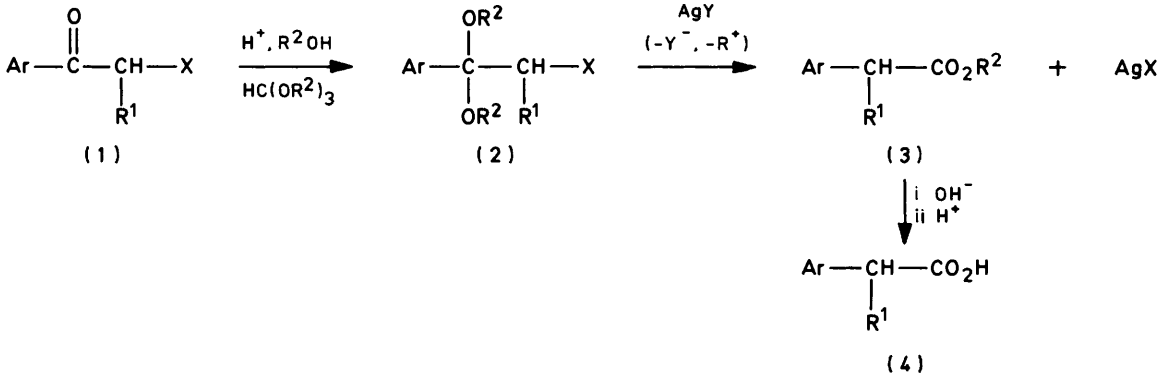
(AgX) by simple filtration; the unchanged silver can be precipitated with gaseous hydrogen chloride and recovered as above.

The amount of ester is related stoicheiometrically to the converted silver salt, determined as the silver halide (AgX). The method has been applied successfully to the preparation of methyl and ethyl esters of 2-(6-methoxy-2-naphthyl)propionic acid (Table, entries n, q, and t) and the methyl ester of 2-(4-isobutylphenyl)propionic acid (Table, entry o); after hydrolysis these esters give rise to the formation of the free acids which are well known as anti-inflammatory drugs under the commercial names of Naproxen and Ibuprofen, respectively.

stituents (although this was calculated on a limited number of substituents) and the corresponing rate constants has been found: $\rho = -3.29$ ($r^2 = 0.994$).

Thus, the rearrangement rate is strongly influenced by the polar character of the substituents; electron-releasing groups increase and electron-withdrawing groups decrease the reaction rate. This has synthetic implications, as shown by the results in the Table. For example, 95% of the methyl acetal of 2-bromo-4'-methoxyacetophenone (entry a) is converted in 2 h, whereas only 17% of the methyl acetal of 2-bromo-3'-chloroacetophenone (entry j) is converted in 48 h.

The strong polar effect of aryl substituents indicates a



SCHEME 2

Silver tetrafluoroborate, hexafluoroantimonate, and trifluoromethanesulphonate are preferred to silver nitrate because they, unlike the last-named salt, are very soluble in the alcoholic medium and a high concentration can be used.

It is worth noting that no formation of substitution products has been observed with silver nitrate, which is known to give α-keto-nitrates [10] with α-halogeno-ketones. Moreover, substitution products are not formed with α-iodo-acetals.

The specificity and the consequent considerable synthetic interest of the rearrangement prompted us to investigate the kinetics of the reaction in order to acquire a deeper understanding of its mechanism. The kinetic study was carried out for the reaction between the methyl acetals of primary α-bromoalkyl aryl ketones and silver tetrafluoroborate in methanol at 25 °C (see Experimental section). Second-order kinetics were observed for at least two half-lives. The reaction was first-order in $AgBF_4$ and in the α-bromo-acetal, clearly indicating that the rate-determining step occurs in the interaction between the α-bromo-acetal and the silver ion. The following rate constants were calculated: 6.24×10^{-4} l mol^{-1} s^{-1} ($r^2 = 0.994$), 1.23×10^{-5} l mol^{-1} s^{-1} ($r^2 = 0.995$), and 1.80×10^{-6} l mol^{-1} s^{-1} ($r^2 = 0.996$) for 2-bromo-1,1-dimethoxy-1-(4'-methoxyphenyl)-ethane, 2-bromo-1,1-dimethoxy-1-(4'-methylphenyl)-ethane and 2-bromo-1,1-dimethoxy-1-phenylethane, respectively.

A good Hammett correlation between σ^+ of the sub-

large cationic contribution or a strong aryl-participation in the transition state (Scheme 3). Moreover, the order of reactivity of the α-halogeno-acetals (I > Br > Cl) is that expected on the basis of the C–X bond energy,[11] taking into account the fact that the C–X bond is broken in the rate-determining step. Thus, 87% of the methyl acetal of 2-iodo-4'-methoxyacetophenone is converted in 15 min at 15 °C, 47% of the methyl acetal of 2-bromo-4'-methoxyacetophenone is converted in 1 h at 25 °C, and less than 1% of the methyl acetal of 2-chloro-4'-methoxyacetophenone is converted in 1 h at 25 °C.*

Comparison of the rates of the silver-ion-assisted methanolyses of 2-aryl-1-bromoalkanes with those of the structurally related 1-aryl-2-bromo-1,1-dimethoxy-alkanes (which differ only from the former in the presence of 1-methoxy-groups) should give information on the effect of the presence of methoxy-groups on the solvolysis. Such a comparison was possible because the silver-ion-assisted ($AgBF_4$) methanolysis of primary bromo-alkanes provides 1-methoxyalkanes,† under our standard solvolysis conditions, in high yields.

The results of the competitive solvolysis (see Experi-

* The different reaction conditions are required because of the observed low stability of the α-iodoketone and of the α-iodoacetal.

† A convenient procedure to convert 1-bromoalkanes into 1-methoxyalkanes was developed during our investigations. According to this new procedure, the 1-bromoalkane was dissolved into a solution of silver ions in $BF_3 \cdot 2CH_3OH$ (See Experimental section) and allowed to react at 25 °C for a few hours.

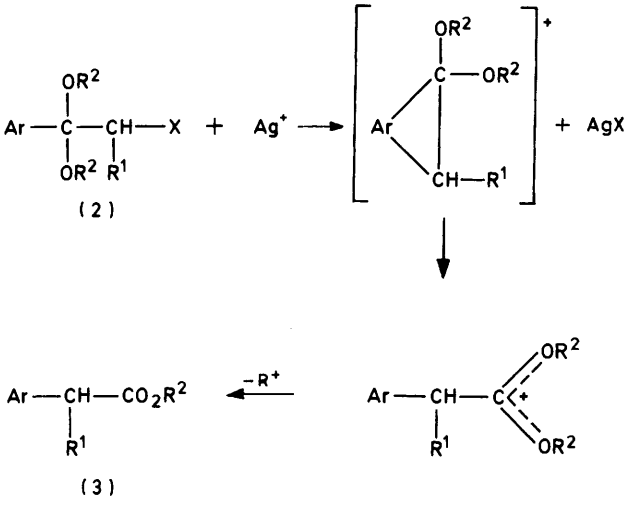
TABLE [a]

Conversion of alkyl acetals of α-halogenoalkyl aryl ketones (2) into α-arylalkanoic acids (4) (Scheme 2)

Entry	Aryl group	R^1	R^2	X	AgY	Reaction time (h)	Conversion [b] (%)	Ester (3) yield (%) [c]	Acid (4) [c] m.p. (°C) (solvent)	Lit. m.p. (°C)
a	4-Methoxyphenyl	H	Me	Br	$AgBF_4$	2	95	98	86—88 (water)	83—84 [23]
b	2-Methoxyphenyl	H	Me	Br	$AgBF_4$	3	94	98	123 (water)	124 [h]
c	3-Methoxyphenyl	H	Me	Br	$AgBF_4$	22	55	98	68—70 (water)	68—69 [23]
d	4-Methylphenyl	H	Me	Br	$AgBF_4$	6	85	98	94 (benzene)	91 [i]
e	Biphenyl-4-yl	H	Me	Br	$AgBF_4$	15	78	98	160 (water)	161—162 [j]
f	2-Naphthyl	H	Me	Br	$AgBF_4$	14	72	98	141—143 (water)	141—142 [k]
g	1-Naphthyl	H	Me	Br	$AgBF_4$	16	80	98	133 (water)	132.5 [l]
h	Phenyl	H	Me	Br	$AgBF_4$	20	67	98	77 (hexane)	77 [m]
i	4-Chlorophenyl	H	Me	Br	$AgBF_4$	38	55	98	105—106 (water)	105 [22]
j	3-Chlorophenyl	H	Me	Br	$AgBF_4$	48	17	98	77—78 (hexane)	77 [n]
k	4-Methoxyphenyl	H	Me	I	$AgBF_4$	0.25		87 [d,e]	86—88 (water)	83—84 [23]
l	4-Methoxyphenyl	H	Me	Cl	$AgBF_4$	2	44	98	86—88 (water)	83—84 [23]
m	4-Methoxyphenyl	H	Et	Br	$AgBF_4$	3	95	98	86—88 (water)	83—84 [23]
n	6-Methoxy-2-naphthyl	Me	Me	Br	$AgBF_4$	1	98 [f]	98	154—155 (acetone–hexane)	150—151 [24]
o	4-Isobutylphenyl	Me	Me	Cl	$AgBF_4$	16	*g*	82 [e]	76 (hexane)	75—77 [o]
p	4-Methoxyphenyl	Me	Me	Br	$AgBF_4$	1.5	96	98	57 (hexane)	56—57 [p]
q	6-Methoxy-2-naphthyl	Me	Et	Br	$AgBF_4$	2	95 [f]	98	154—155 (acetone–hexane)	150—151 [24]
r	4-Methoxyphenyl	H	Me	Br	$AgNO_3$	4	90	98	86—88 (water)	83—84 [23]
s	4-Methoxyphenyl	H	Me	Br	$AgNO_3$	24	65	98	94 (benzene)	91 [i]
t	6-Methoxy-2-naphthyl	Me	Me	Br	$AgNO_3$	3	96 [f]	98	154—155 (acetone–hexane)	150—151 [24]

[a] Unless otherwise noted, the reaction conditions for the rearrangements are as given in the Experimental section. [b] Unless stated otherwise, conversions are referred to the starting α-halogeno-acetals and are calculated on the basis of n.m.r. analysis carried out on the crude reaction products. [c] Yields of alkylesters, based on the converted α-halogeno-acetals, are referred to the α-arylalkanoic acids obtained by hydrolysis of the crude reaction products. The free acids (4) are identified by comparison with authentic samples. [d] The reaction conditions differ slightly from the others; acetalization: methanol (20 ml), trimethyl orthoformate (2.12 g, 2 ml, 20 mmol), toluene-*p*-sulphonic acid (0.6 mmol) and 2-iodo-4′-methoxyacetophenone (10 mmol). Reaction temperature: 25 °C; reaction time: 3 h. The reaction solution was cooled to 15 °C and silver tetrafluoroborate added (15 mmol). Reaction temperature: 15 °C. The different reaction conditions are required because of the observed low stability of the α-iodo-ketone and of the α-iodo-acetal. [e] Yield calculated on the introduced α-halogeno-alkyl aryl ketone. [f] The (+)-enantiomer (Naproxen) is well known as a commercial anti-inflammatory drug. [g] The acid (Ibuprofen) is on the market as an anti-inflammatory drug. [h] S. Sugasawa and H. Shigehara, *Chem. Ber.*, 1941, **74**, 459. [i] K. Kindler, W. Metzendorf, and Dschi-yin-kwok, *Chem. Ber.*, 1943, **76**, 308. [j] K. Kindler, *Chem. Ber.*, 1941, **74**, 314. [k] J. D. Fulton and R. Robinson, *J. Chem. Soc.*, 1939, 200. [l] P. D. Barlett and E. N. Trachtenberg, *J. Am. Chem. Soc.*, 1958, **80**, 5808. [m] L. Kofler and A. Kofler, 'Termo-Mickro Methoden,' Weinheim, 1954. [n] N. Campbell and J. E. McKail, *J. Chem. Soc.*, 1948, 1251. [o] 'The Merck Index,' 9th edn., Merk and Co., Rahway, New York, 1976, p. 649. [p] W. M. Lauer and L. Hansen, *J. Chem. Soc.*, 1939, **61**, 3039.

mental section) between 2-bromo-1,1-dimethoxy-1-phenylethane and the structurally related compound 1-bromo-2-phenylethane indicate that the presence of the acetal-oxygens strongly depresses the solvolysis rate: thus, under conditions where 1-bromo-2-phenylethane was almost completely converted into 1-methoxy-2-phenylethane, 2-bromo-1,1-dimethoxy-1-phenylethane was almost unchanged.



SCHEME 3

Similar behaviour was shown by other primary bromoalkanes, such as 1-bromo-3-phenylpropane and 1-bromooctane (see Experimental section). This implies that acetal-oxygens, because of their inductive, electron-withdrawing effect, reduce the extent of the interaction between the bromine atom and the silver ion, thus making the solvolysis reaction difficult. A similar interpretation has been used to explain the decreased rate observed in the solvolysis of 1-halogeno-2-methoxyalkanes with respect to 1-halogenoalkanes.[12]

From the above considerations and from the available data[13a] on the silver-ion-assisted alcoholysis of α-halogenoalkyl aryl ketones it is seen that the solvolysis rate for Ar = phenyl increases in the order: α-halogenoalkanes ≃ α-halogeno-ketones ≫ α-halogeno-acetals.[13b] The difference in behaviour between α-halogeno-ketones and α-halogeno-acetals is mainly due to the polarizability of the carbonyl group, which makes the formation of substitution products [14] easier.

The difference in reactivity between α-halogeno-acetals and α-halogeno-ketones towards substitution is thus well established. To explain correctly the difference in behaviour between α-halogeno-acetals and α-halogeno-ketones towards rearrangement, the following has to be kept in mind: it is likely that, in the silver-ion-assisted methanolysis of α-bromoalkyl aryl ketones,[6] which provides esters and ethers (Scheme 1), the small amount of acetals and hemiacetals present in equilibrium with the ketones strongly contributes to ester formation; this means that aryl migration is not favoured for primary and secondary α-bromoalkyl aryl ketones. This was expected on the basis of the available data on the silver-ion-ethanolysis [13a] in which only ethers are formed; the reaction is quite insensitive to the substituents on the phenyl ring ($\rho = 0$) and therefore is not assisted by the aromatic ring.[13b]

The difference in migratory aptitude of the aryl group observed in α-halogenoalkyl aryl acetals with respect to α-halogenoalkyl aryl ketones is, in our opinion, related to their different setereoelectronic characteristics. The sp^3 hybridization of the carbon which is bonded to the aromatic ring in the acetal structures should favour aryl migration with respect to the sp^2 hydridization of the same carbon in the ketones.

The two oxygens of the acetal group should destabilize the positive charge present in the transition state less than the carbonyl group, thus favouring the formation of the cationic (Scheme 3) precursor of the alkyl ester of α-arylalkanoic acids.

The present procedure constitutes the method of choice for the conversion of α-halogenoalkyl aryl ketones into α-arylalkanoic acids. Moreover, this method, based on the masking of a functional group, provides an additional and significant example of the importance of changing the normal nature of a functional group in planning a synthetic strategy.

EXPERIMENTAL

Unless stated otherwise, ^{1}H n.m.r. spectra were taken at 60 MHz for solutions in deuteriochloroform, relative to internal tetramethylsilane. The chemical shifts are expressed in δ(p.p.m.).

In general, spectra were recorded for convenience on a 2 Hz/mm scale; for this reason the shifts given are not more accurate than ±0.03 p.p.m., and the coupling constants are not more accurate than 1.8 Hz; however, these are sufficiently precise for our work. I.r. spectra were taken for Nujol mulls; positions of interesting absorption are quoted to ±5 cm^{-1}. Vapour-phase chromatography analysis was performed on a Hewlett-Packard 7620 A instrument using a Glass column (2 m × 2 mm), containing UCCW 9821 10% on Chromosorb W AW-DMCS, 80—100 mesh. Analytical t.l.c. was performed on precoated silica-gel with a fluorescent indicator supplied by Merck. Visualization was accomplished under u.v. light. The removal of the solvent under reduced pressure refers to the evaporation of the solvent at aspirator pressure on a Büchi rotary evaporator. M.p.s, measured on a Köfler apparatus, are not corrected. Elemental analyses were carried out on a Hewlett-Packard instrument (C ±0.2; H ±0.2%).

Anhydrous silver tetrafluoroborate was purchased from Fluka, as were 1-bromo-3-phenylpropane and 1-bromooctane. 1-Bromo-2-phenylethane was prepared according to a known procedure.[15]

The crude α-arylalkanoic acids obtained by hydrolysis of the reaction mixture were isolated pure and identified by comparison with authentic samples. The α-bromoalkyl aryl ketones and 2-iodo-4′-methoxyacetophenone are known and were prepared according to previously reported procedures.[16-19]

Preparation of 2-Chloro-4′-methoxyacetophenone.—Chloro-

acetyl chloride (11.3 g, 8 ml, 0.1 mol) was added dropwise during 30 min with stirring at −10 °C to a mixture of aluminium chloride (14.6 g, 0.11 mol) in methylene dichloride (100 ml). The reaction mixture was stirred at −10 °C for an additional 30 min. Anisole (10.8 g, 10.9 ml, 0.1 mol) was added during 1 h with stirring at −10 °C and the reaction mixture was allowed to warm to room temperature and then stirred for 2 h. It was then poured into a mixture of concentrated hydrochloric acid and crushed ice and extracted with methylene dichloride (2 × 200 ml). The combined organic extracts were washed with 2% aqueous sodium hydrogen carbonate and water and dried (Na_2SO_4). Evaporation of the solvent under reduced pressure gave 2-chloro-4'-methoxyacetophenone (14.5 g, 0.0785 mol, 78.5%). An analytically pure product was obtained by crystallization from methanol, m.p. 97—98 °C (lit.,[20] m.p. 96—99 °C), δ 3.83 (s, 3 H), 4.63 (s, 2 H), and 6.8—8.1 (AA'BB', 4 H); $\nu_{max.}$ 1 685 cm^{-1} (CO).

Preparation of 2-Chloro-4'-isobutylpropiophenone.—A mixture of anhydrous copper(II) chloride (13.5 g, 0.1 mol), lithium chloride (3.2 g, 0.076 mol), 4'-isobutylpropiophenone (9.33 g, 0.049 mol), and dimethylformamide (40 ml) was stirred at 80 °C for 3 h. The solution was poured into 2% hydrochloric acid and extracted with diethyl ether (3 × 50 ml). The combined organic extracts were washed with water and dried (Na_2SO_4). Evaporation of the solvent under reduced pressure gave a residue which, after crystallization from methanol, gave 2-chloro-4'-isobutylpropiophenone (6.36 g, 0.028 mol, 58%) as an analytically pure product, m.p. 53.5—54.5 °C; δ(CCl_4) 0.89 (d, 6 H, *J* 7 Hz), 1.75 (d, 3 H, *J* 7 Hz), 1.80 (m, 1 H), 2.53 (d, 2 H, *J* 7 Hz), 5.20 (q, 1 H, *J* 7 Hz), and 7.1—8.1 (AA'BB', 4 H); $\nu_{max.}$ 1 680 cm^{-1} (CO).

Preparation of Alkyl Acetals of Primary α-Halogenoalkyl Aryl Ketones and their Reaction with Silver Salts.—General procedure. A mixture of the α-halogenoalkyl aryl ketone (10 mmol), trialkyl orthoformate (20 mmol), alcohol (10 ml), and anhydrous toluene-*p*-sulphonic acid (0.6 mmol) was stirred at 40 °C until the α-halogeno-ketone had been completely converted into the α-halogeno-acetal (the reaction time is reported below for each compound). The reaction was monitored by ^1H n.m.r. of the reaction solution and significant changes in the resonances of the aromatic protons were observed.

In parallel experiments, the reaction solution was poured, with vigorous stirring, into saturated aqueous sodium carbonate and extracted with diethyl ether (3 × 50 ml). The combined organic extracts were washed with 2% aqueous sodium hydrogen carbonate and dried (Na_2CO_3). Evaporation of the solvent under reduced pressure gave the α-halogenoalkyl aryl acetal as the crude product.

Reaction time and physical data for the α-halogeno-acetals. 2-Bromo-1,1-dimethoxy-1-(4-methoxyphenyl)-ethane (2a), 1 h, m.p. 56—58 °C (methanol); δ 3.20 (s, 6 H), 3.60 (s, 2 H), 3.79 (s, 3 H), and 6.7—7.5 (AA'BB', 4 H); 2-bromo-1,1-dimethoxy-1-(2-methoxyphenyl)ethane (2b), 3 h; 2-bromo-1,1-dimethoxy-1-(3-methoxyphenyl)ethane (2c), 4 h; 2-bromo-1,1-dimethoxy-1-(*p*-tolyl)ethane (2d), 1 h; 1-biphenyl-4-yl-2-bromo-1,1-dimethoxyethane (2e), 3 h, m.p. 86—88 °C (methanol), δ 3.22 (s, 6 H), 3.63 (s, 2 H), and 7.0—7.8 (m, 9 H); 2-bromo-1,1-dimethoxy-1-(2-naphthyl)ethane (2f), 3 h; 2-bromo-1,1-dimethoxy-1-(1-naphthyl)ethane (2g), 7 h; 2-bromo-1,1-dimethoxy-1-phenylethane (2h), 2 h, m.p. 46—47 °C (sublimed at 0.25 mmHg) [lit.,[21] m.p. 46—46.9 °C]; δ 3.18 (s, 6 H), 3.58 (s, 2 H), and 7.3 (m, 5 H); 2-bromo-1-(4-chlorophenyl)-1,1-dimethoxyethane (2i), 3 h; 2-bromo-1-(3-chlorophenyl)-1,1-dimethoxyethane (2j), 16 h; 2-iodo-1,1-dimethoxy-1-(4-methoxyphenyl)ethane (2k), 3 h; 2-chloro-1,1-dimethoxy-1-(4-methoxyphenyl)ethane (2l), 1 h; and 2-bromo-1,1-diethoxy-1-(4-methoxyphenyl)ethane (2m), 3 h, m.p. 55—56 °C (methanol); δ 1.23 (t, 6 H, *J* 7 Hz), 3.47 (q, 4 H, *J* 7 Hz), 3.57 (s, 2 H), 3.80 (s, 3 H), and 6.7—7.5 (AA'BB', 4 H).

Rearrangement procedure. The general procedure for rearrangement is given for the preparation of the methyl ester of 4-methoxyphenylacetic acid (entry a, Table): anhydrous silver tetrafluoroborate (2.92 g, 15 mmol) was added, with stirring and under nitrogen, at 40 °C to the previously prepared solution of 2-bromo-1,1-dimethoxy-1-(4-methoxyphenyl)ethane (10 mmol) and the mixture stirred at 40 °C for 2 h in a dark-glass reactor. The insoluble material was filtered off, washed with methanol and diethyl ether, and dried *in vacuo* in the dark to give silver bromide (1.78 g, 9.5 mmol, 95% based on the starting acetal). The organic layer of the mother liquor was poured into distilled water (100 ml) and extracted with diethyl ether (3 × 80 ml). The combined organic extracts were washed with water and dried (Na_2SO_4). Evaporation of the solvent under reduced pressure gave the methyl ester of 4-methoxyphenylacetic acid (1.71 g, 9.5 mmol, 95%) as an oil. An analytically pure sample was obtained by distillation, b.p. 142—143 °C at 16 mmHg [lit.,[22] b.p. 141—142° at 16 mmHg]; δ 3.48 (s, 2 H), 3.59 (s, 3 H), 3.67 (s, 3 H), and 6.6—7.2 (AA'BB', 4 H); $\nu_{max.}$ 1 740 cm^{-1} (CO).

In a parallel experiment, the crude reaction mixture was dissolved in a solution of 30% aqueous sodium hydroxide (15 ml) in methanol (50 ml) and stirred at room temperature for 4 h. It was then poured in water, extracted with diethyl ether (2 × 50 ml) and the aqueous phase acidified with concentrated hydrochloric acid and extracted with diethyl ether (3 × 80 ml). The organic extract was washed with water and dried (Na_2SO_4). Evaporation of the solvent under reduced pressure gave 4-methoxyphenylacetic acid (1.53 g, 9.2 mmol, 92%), m.p. 86—88 °C (lit.,[23] m.p. 83—84 °C); δ 3.59 (s, 2 H), 3.80 (s, 3 H), 6.8—7.3 (AA'BB', 4 H), and 11.40 (s, 1 H); $\nu_{max.}$ 1 710 (CO) and 3 120 cm^{-1} (OH).

Preparation of Alkyl Acetals of Secondary α-Halogenoalkyl Aryl Ketones and their Reaction with Silver Salts.—Preparation of 2-bromo-1,1-dimethoxy-1-(6-methoxy-2-naphthyl)-propane. A mixture of 2-bromo-1-(6-methoxy-2-naphthyl)propan-1-one (25.7 g, 0.088 mol), trimethyl orthoformate (27.2 g, 27.7 ml, 0.26 mol), methanesulphonic acid (0.17 g, 0.0017 mol), and methanol (70 ml) was stirred at 45 °C for 24 h. The reaction mixture then was poured, with vigorous stirring, into saturated aqueous sodium carbonate and extracted with diethyl ether (2 × 200 ml). The combined organic extracts were washed with 2% aqueous sodium hydrogen carbonate and dried (Na_2CO_3). Evaporation of the solvent under reduced pressure gave 2-bromo-1,1-dimethoxy-1-(6-methoxy-2-naphthyl)propane (29 g, 0.086 mol, 98%) as the crude product. Crystallization from methanol gave the bromo-acetal (23 g, 0.068 mol, 80%) as the analytically pure product, m.p. 87—89 °C; δ 1.53 (d, 3 H, *J* 7 Hz), 3.26 (s, 3 H), 3.43 (s, 3 H), 3.90 (s, 3 H), 4.50 (q, 1 H, *J* 7 Hz), and 7.0—8.0 (m, 6 H).

Preparation of 2-chloro-1,1-dimethoxy-1-(4-isobutylphenyl)-propane. A mixture of 2-chloro-4'-isobutylpropiophenone (11.2 g, 0.05 mol), trimethyl orthoformate (21.2 g, 20 ml,

0.2 mol), methanesulphonic acid (0.8 g, 0.008 mol), and methanol (50 ml) was stirred and heated under reflux, for 24 h. The reaction solution was poured, with vigorous stirring, into saturated aqueous sodium carbonate and extracted with diethyl ether (2 × 50 ml). The combined organic extracts were washed with 2% aqueous sodium hydrogen carbonate and dried (Na_2CO_3). Evaporation of the solvent under reduced pressure gave 2-chloro-1,1-dimethoxy-1-(4-isobutylphenyl)propane (13 g, 0.0485 mol, 97%) as an oil; δ 0.90 (d, 6 H, *J* 7 Hz), 1.28 (d, 3 H, *J* 7 Hz), 1.80 (m, 1 H), 2.46 (d, 2 H, *J* 7 Hz), 3.16 (s, 3 H), 3.33 (s, 3 H), 4.33 (q, 1 H, *J* 7 Hz), and 6.7—7.6 (AA'BB', 4 H).

Preparation of 2-bromo-1,1-diethoxy-1-(6-methoxy-2'-naphthyl)propane. A solution containing 2-bromo-1,1-dimethoxy-1-(6-methoxy-2-naphthyl)propane (33.9 g, 0.1 mol), triethyl orthoformate (13.4 g, 0.09 mol), and methanesulphonic acid (1 g, 0.01 mol) in ethanol (300 ml) was kept at 45 °C for 2 h. It was then poured, with vigorous stirring, into saturated aqueous sodium carbonate and extracted with diethyl ether (2 × 150 ml). The combined organic extracts were washed with 2% aqueous sodium hydrogen carbonate and dried (Na_2CO_3). Evaporation of the solvent under reduced pressure gave 2-bromo-1,1-diethoxy-1-(6-methoxy-2-naphthyl)propane (36.7 g, 0.1 mol, 100%) as an oil; δ(CCl_4) 1.23 (t, 6 H, *J* 7 Hz), 1.53 (d, 3 H, *J* 7 Hz), 3.43 (q, 4 H, *J* 7 Hz), 3.90 (s, 3 H), 4.50 (q, 1 H, *J* 7 Hz), and 7.0—8.0 (m, 6 H).

Rearrangement procedure. The general procedure of rearrangement is given for the preparation of the methyl ester of 2-(6-methoxy-2-naphthyl)propionic acid (entry n, Table): anhydrous silver tetrafluoroborate (2.92 g, 15 mmol) was added, with stirring and under nitrogen, at 40 °C, to a solution of 2-bromo-1,1-dimethoxy-1-(6-methoxy-2-naphthyl)propane (3.39 g, 10 mmol) and trimethyl orthoformate (2.12 g, 2.16 ml, 20 mmol) in methanol (10 ml). The reaction mixture was stirred at 40 °C for 1 h in in a dark-glass reactor. The insoluble material was filtered off, washed with methanol and diethyl ether, and dried in the dark to give silver bromide (1.88 g, 10 mmol, 100% based on the starting acetal). The remaining solution was poured into distilled water (100 ml) and extracted with diethyl ether (3 × 80 ml). The combined organic extracts were washed with water and dried (Na_2SO_4). Evaporation of the solvent under reduced pressure gave the methyl ester of 2-(6-methoxy-2-naphthyl)propionic acid (2.42 g, 9.9 mmol, 99%) as a solid residue. An analytically pure product was obtained by crystallization from methanol, m.p. 87—88 °C (lit.,[24] m.p. 88 °C); δ 1.64 (d, 3 H, *J* 7 Hz), 3.72 (s, 3 H), 3.94 (q, 1 H, *J* 7 Hz), 3.98 (s, 3 H), and 7.0—7.8 (m, 6 H); $\nu_{max.}$ 1 740 cm^{-1} (CO).

In a parallel experiment the crude reaction mixture was dissolved in a solution of 30% aqueous sodium hydroxide (15 ml) in methanol (50 ml) and stirred at room temperature for 4 h. It was then poured into water, extracted with diethyl ether (2 × 50 ml) and acidified with concentrated hydrochloric acid. The precipitate was filtered off, washed with water and dried at 80 °C *in vacuo*. 2-(6-Methoxy-2-naphthyl)propionic acid (2.26 g, 9.8 mmol, 98%) was obtained, m.p. 153—154 °C (lit.,[24] m.p. 150—152 °C); δ 1.55 (d, 3 H, *J* 7 Hz), 3.85 (q, 1 H, *J* 7 Hz), 3.88 (s, 3 H), 7.0—7.8 (m, 6 H), and 10.80 (br, 1 H); $\nu_{max.}$ 1 710 (CO) and 3 080 cm^{-1} (OH).

Kinetic Data.—Determination of the reaction order and rate constants for the reaction between the methyl acetal of some primary α-halogenoalkyl aryl ketones and silver tetrafluoroborate. A mixture of the 2-bromoalkyl aryl ketone (10 mmol), trimethyl orthoformate (20 mmol), anhydrous toluene-*p*-sulphonic acid (0.6 mmol) and methanol (20 ml) was kept, with stirring and under nitrogen, at 25 °C (±0.1 °C) for 12 h. Silver tetrafluoroborate (1.95 g, 10 mmol) was added to the reaction solution and it was kept at 25 °C (±0.1 °C). Aliquots (2 ml) were removed at suitable intervals, filtered and diluted with water; benzyl acetate or methylbenzoate was added (as internal standard) and the mixture extracted with diethyl ether (3 × 20 ml). The combined extracts were washed with water, dried (Na_2SO_4), and analyzed by g.l.c. in order to determine the amount of methyl ester of the arylacetic acid present.

A plot of the reciprocal of $a - x$ (a = molar initial concentration of methyl acetal; x = molar concentration of the methyl ester of the arylacetic acid) *versus* time was found to be linear for at least two half-lives; the slope gave the k value for the following compounds. 2-Bromo-1,1-dimethoxy-1-(4-methoxyphenyl)ethane: k 6.24×10^{-4} l mol^{-1} s^{-1} ($r^2 = 0.994$); 2-bromo-1,1-dimethoxy-1-(4-methylphenylethane: k 1.27×10^{-5} l mol^{-1} s^{-1} ($r^2 = 0.995$); 2-bromo-1,1-dimethoxy-1-phenylethane: k 1.80×10^{-6} l mol^{-1} s^{-1} ($r^2 = 0.966$).

Competitive silver-assisted methanolysis between 1-bromoalkanes and 2-bromo-1,1-dimethoxy-1-phenylethane. A mixture of 2-bromoacetophenone (0.995 g, 5 mmol), trimethyl orthoformate (1 ml, 10 mmol), methanol (9 ml), and anhydrous toluene-*p*-sulphonic acid (0.05 g, 0.3 mmol) was kept at 25 °C, with stirring and under nitrogen, for 3 h. 1-Bromo-2-phenylethane (0.925 g, 0.68 ml, 5 mmol) and then anhydrous silver tetrafluoroborate (1.95 g, 10 mmol) were added to this solution. The reaction mixture was kept at 25 °C with stirring and in the dark, for 4 h and 2-methoxynaphthalene (0.50 g, 3 mmol) was then added as internal standard. A sample was taken, filtered, poured into 2% aqueous sodium hydrogen carbonate, extracted with diethyl ether and analyzed by g.l.c. It was found to contain 1-methoxy-2-phenylethane (0.56 g, 4.5 mmol, 90%); the methyl ester of phenylacetic acid (less than 2%).

Following to the above procedure, a competitive reaction between 1-bromo-3-phenylpropane and 2-bromo-1,1-dimethoxy-1-phenylethane (reaction time 4 h) gave the following results: 1-methoxy-3-phenylpropane (0.74 g, 4.91 mmol, 98%); the methyl ester of phenylacetic acid (less than 2%).

Similarly a competitive reaction between 1-bromo-octane and 2-bromo-1,1-dimethoxy-1-phenyl-1-ethane (reaction time 4 h) gave the following result: 1-methoxyoctane (0.54 g, 3.75 mmol, 75%); the methyl ester of phenylacetic acid (less than 2%).

Preparation of 1-methoxyalkanes. 1-Methoxyalkanes, used as reference products, were prepared according to the following, new procedure: silver carbonate (8.27 g, 30 mmol) was added, at 25 °C, in portions to a stirred mixture of $BF_3 \cdot 2CH_3OH$ (15 g, 113 mmol), trimethyl orthoformate (3.92 g, 4 ml, 40 mmol) and methanol (20 ml). After evolution of carbon dioxide had ceased, 1-bromo-2-phenylethane (7.4 g, 5.44 ml, 40 mmol) was added dropwise during 5 min to the above solution. The reaction mixture was stirred at 25 °C for 2 h in the dark. The insoluble material was filtered off, washed with diethyl ether, and dried in the dark to give the silver bromide (6.74 g, 36 mmol, 90% based on the starting bromoalkane). The remaining solution was poured into water (150 ml) and extracted with diethyl ether (3 × 80 ml). The combined organic extracts

were washed with water and dried (Na_2SO_4). Evaporation of the solvent under reduced pressure left 1-methoxy-2-phenylethane as the crude product. An analytically pure sample was obtained by distillation, b.p. 82—83 °C at 18 mmHg (lit.,[25] 192—193 °C at 766 mmHg).

Following the above procedure 1-methoxy-3-phenylpropane, b.p. 142—144 °C at 68 mmHg (lit.,[25] 213 °C at 766 mmHg) and 1-methoxyoctane, b.p. 130—132 °C at 760 mmHg, were obtained as analytically pure products.

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REFERENCES

[1] D. Seebach, *Angew. Chem.*, 1979, **91**, 259; *Angew. Chem., Int. Ed. Engl.*, 1979, **18**, 239.
[2] D. Lednicer and L. A. Mitscher, ' The Organic Chemistry of Drugs Synthesis,' John Wiley & Sons, New York, 1977, ch. 6; T. Y. Shen, *Angew. Chem.*, 1972, **84**, 512; *Angew. Chem., Int. Ed. Engl.*, 1972, **6**, 460; S. H. Ferreira and J. R. Vane, *Anti-inflammatory Drugs*, Springer–Verlag, Berlin–Heidelberg, New York, 1979, p. 321.
[3] *Scrip World Pharmaceutical News*, ed. J. P. B. Publ. Limited, United Kingdom, 1980, **497**, 10.
[4] A. McKillop and E. C. Taylor, *Endeavour*, 1978, **35**, 88.
[5] B. Myrboh, H. Ila, and H. Junjiappa, *Synthesis*, 1981, 126.
[6] C. Giordano, G. Castaldi, F. Casagrande, and L. Abis, *Tetrahedron Lett.*, 1982, 1385 and references cited therein; G. Castaldi, Ph.D. Thesis, University of Milan, 1980.
[7] E. C. Taylor, R. A. Conley, D. K. Johnson, and A. McKillop, *J. Org. Chem.*, 1977, **42**, 4167.
[8] J. P. Bègué and D. Bonnet, *Tetrahedron*, 1974, **30**, 141.
[9] D. Baudry and M. Charpentier-Morize, *Tetrahedron Lett.*, 1973, 3013.
[10] D. N. Kevill and N. H. Cromwell, *J. Org. Chem.*, 1964, **29**, 499.
[11] T. L. Coltrell, ' The Strengths of Chemical Bonds,' 2nd edn., Academic Press Inc., New York, 1958.
[12] B. Capon and S. P. McManus, ' Neighboring Group Participation,' Plenum Press, New York, 1976, vol. 1.
[13] (*a*) D. J. Pasto and K. Garves, 1967, **32**, 778; (*b*) It is worth noting that the reactivity of α-halogeno-acetals depends on the nature of the substituent on the aryl group, while that of α-halogeno-ketones is not affected by the polarity of substituents. As a matter of fact, in principle, α-halogeno-acetals having electron-donating groups on the aromatic ring could become more reactive than the corresponding α-halogeno-ketones.
[14] F. G. Bordwell and W. T. Branner, *J. Am. Chem. Soc.*, 1964, **86**, 4645.
[15] A. I. Vogel, ' Practical Organic Chemistry,' Longmans–Green and Co., New York, 1954.
[16] M. I. Cheuchuck and A. V. Dombrowski, *Zh. Obshch. Khim.*, 1963, **33**, 1135.
[17] C. B. Radcliffe, I. R. Sherwood, and W. F. Short, *J. Chem. Soc.*, 1931, 2293.
[18] J. W. Baker, *J. Chem. Soc.*, 1932, 1148.
[19] A. Marquet and J. Jaques, *Bull. Soc. Chim. Fr.*, 1962, 90.
[20] A. L. Wilds and T. L. Johnson, *J. Am. Chem. Soc.*, 1945, **67**, 286.
[21] R. Tanaka, M. Rodgers, R. Simonaitis, and S. I. Miller, *Tetrahedron*, 1971, **27**, 2651.
[22] J. F. J. Dippy and F. R. Williams, *J. Chem. Soc.*, 1934, 161.
[23] J. A. King and F. H. McMillan, *J. Am. Chem. Soc.*, 1946, **68**, 2335.
[24] I. T. Harrison, B. Lewis, P. Nelson, W. Rooks, R. Ruzkowki, A. Tomolonis, and J. H. Fried, *J. Med. Chem.*, 1970, **13**, 203.
[25] J. R. Knowles and R. O. C. Norman, *J. Chem. Soc.*, 1961, 3888.