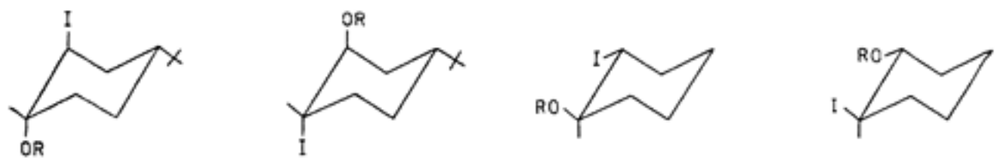
87/ACETOXYIODINATION OF OLEFINS: A NEW METHOD FOR THE PREPARATION OF *trans*-IODOHYDRIN ACETATES (☆)

MICHELANGELO PARRILLI, GASPARE BARONE, MATTEO ADINOLFI and LORENZO MANGONI
Istituto di Chimica organica dell'Università, Napoli.

Summary. — The reaction of 1-methyl-4-*t*-butylcyclohexene and of 1-methylcyclohexene with I_2 and KIO_3 in *Ac*OH has been shown to give mainly the acetoxy-iodides [Ib] and [IIb] and the acetoxy-iodides [IIIb] and [IVb], respectively. Therefore, it may be considered to be a new one-step method for the preparation of *trans*-iodohydrin acetates starting from olefins. Product distribution showed that in the first stage of the reaction the iodonium ions formation is reversible.

Riassunto. — La reazione dell'1-metil-4-*t*-butilcicloesene e dell'1-metilcicloesene con I_2 e KIO_3 in *Ac*OH porta principalmente agli acetossi-ioduri [Ib] e [IIb] ed agli acetossi-ioduri [IIIb] e [IVb] rispettivamente. Essa pertanto costituisce un nuovo metodo per la preparazione diretta degli acetati delle *trans*-iodoidrine a partire dalle olefine. La distribuzione dei prodotti inoltre mostra che nel primo stadio della reazione la formazione degli ioni iodonio è reversibile.

In connection with our research on the reaction of trisubstituted olefins with iodine and silver salts, the iodohydrin acetates [Ib-IVb] were needed (1).



[Ia] R=H
[Ib] R=Ac

[IIa] R=H
[IIb] R=Ac

[IIIa] R=H
[IIIb] R=Ac

[IVa] R=H
[IVb] R=Ac

The way initially chosen in the hope of obtaining both [Ia] and [IIa] from 1-methyl-4-*t*-butylcyclohexene and both [IIIa] and [IVa] from 1-methylcyclohe-

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(☆) This work has been supported by the Naional Research Council (CNR).

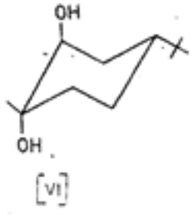
(1) M. Parrilli, M. Adinolfi, V. Dovinola, L. Mangoni, *Gazz. Chim. Ital.*, **104**, 817 (1974).

xene, was the method recently reported by Cornforth and Green (2) (addition of iodine to alkenes in the presence of water and an oxidant).

1-methyl-4-*t*-butylcyclohexene was thus reacted with $I_2/KIO_3/H^+$ in 1:1 water:dioxane. The chromatographic separation of the crude product led to the isolation of a single iodohydrin [Ia] (51%), other products of the reaction being the epoxide [V] (3) (34%) and the *trans*-diol [VI] (3) (8%). As a longer reaction time causes an increase in the yields of [V] and [VI], with concomitant decrease in the yield of [Ia], the epoxide [V] must derive from the slow transformation of [Ia], and the *trans*-diol [VI] originates from the acid-catalyzed *trans*-diaxial opening of [V]. The transformation of [Ia] into the known epoxide [V] and NMR evidence (see the table) firmly establish the structure assigned to the iodohydrin.

The addition of « hypoiodous acid » thus occurs in a completely regiospecific way. Since it may be safely assumed that the intermediate iodonium ions [VII] and [VIII] are produced at about the same rate, owing to the essentially equal ease of attack on both sides of the double bond (4), the regiospecificity observed unequivocally proves that iodonium ion formation is reversible (5).

[V]



[VI]

If this is the case the iodohydrin ratio is governed by the rates of *trans*-diaxial nucleophilic attack on the ions [VII] and [VIII], the mode of attack at the secondary position of [VII] being highly disfavoured, as it leads to anti-Markovnikov addition (6) (see scheme 1). On these grounds, in a less polar hydroxylic solvent, the increased symmetrical bridging (7) of the iodonium ions might have made the attack on the secondary position competitive. The solvent of choice was therefore acetic acid, as it would lead directly to the acetates [Ib] and [IIb]. The use of this solvent, which was further supported by our recent (1) results of the Woodward reactions on 1-methyl-4-*t*-butyl-

(2) G. W. Cornforth, D. T. Green, *J. Chem. Soc.* [*C*], 846 (1970).

(3) P. L. Barili, G. Bellucci, B. Macchia, F. Macchia, G. Parmigiani, *Gazz. Chim. Ital.*, **101**, 300 (1971).

(4) D. J. Pasto, F. M. Klein, *J. Org. Chem.*, **33**, 1468 (1970).

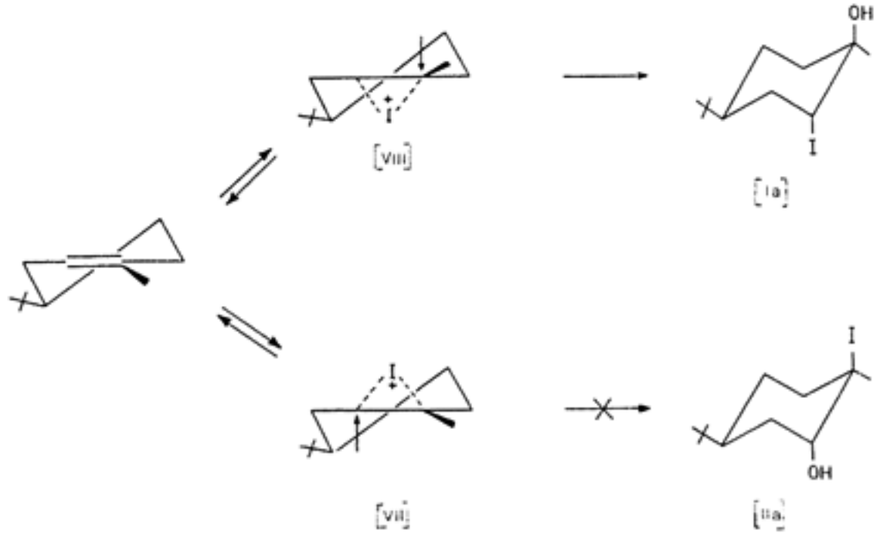
(5) An equilibrium between the two iodonium ions in the Woodward hydroxylation of 1-methyl-4-*t*-butylcyclohexene had been previously suggested by P. L. Barili *et al.* (3): however, see (1).

(6) An analogous interpretation has recently been put forth to explain the regiospecificity in the methoxybromination of the same olefin [D. J. Pasto, J. A. Gontarz, *J. Am. Chem. Soc.*, **93**, 6902 (1971)].

(7) R. E. Buckles, J. M. Bader, R. J. Thurmaier, *J. Org. Chem.*, **27**, 4523 (1962).

cyclohexene, would, in addition, represent a new one-step method for the preparation of *trans*-iodohydrin acetates (8).

SCHEME 1



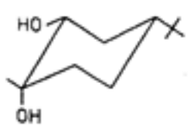
CHEMICAL SHIFTS (δ) IN CCl_4

	CH_3COO—	1-*Me*	2-H
[Ia]	—	1.44	4.43 (dd, $W_{1/2}$ = 4.5 Hz)
[Ib]	1.96	1.64	5.10 (broad s, $W_{1/2}$ = 6 Hz)
[IIa]	—	2.10	4.10 (broad s, $W_{1/2}$ = 6 Hz)
[IIb]	2.00	2.00	5.28 (broad s, $W_{1/2}$ = 5 Hz)
[IIIa]	—	1.33	4.26 (dd, $W_{1/2}$ = 16 Hz)
[IIIb]	1.93	1.58	4.90 (dd, $W_{1/2}$ = 14.5 Hz)
[IVb]	2.02 or 1.97	1.97 or 2.02	5.13 (dd, $W_{1/2}$ = 10.5 Hz)

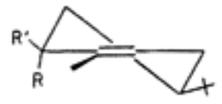
1-methyl-4-*t*-butylcyclohexene was thus reacted at room temperature in acetic acid with iodine (0.5 mole) and potassium iodate (0.25 mole). PLC of the crude product afforded a polar fraction which, through alkaline hydrolysis, gave the *cis*-diol

(8) Disubstituted alkenes have been shown to give *trans*-acetoxy-iodides in high yields with $J_2/KJO_3/AcOH$, [L. Mangoni, M. Adinolfi, G. Barone, M. Parrilli, to be published; *cf.* also L. Mangoni, M. Adinolfi, G. Barone, M. Parrilli, *Tetrahedron Letters*, 4485 (1973)].

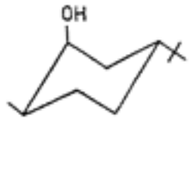
[IX] ([3]) (10%) and three less polar fractions. The first of these fractions was the acetoxy-iodide [Ib] (60%) (NMR: see the table), the second one the allylic acetate [Xb] (5%) (NMR: see Experimental section) and the third one a mixture (16%) of [IIb] and the diequatorial isomer [XI], which we were not able to separate. Besides the signals of [IIb] (see below) the NMR spectrum of this mixture displays signals at δ 4.71 (1H, dd, $W_{1/2}$ = 18.5 Hz) and at δ 1.52 (3H, s), which may be attributed to the CH—I and CH_3—C—O*Ac* protons of [XI]. Integration of the signals due to the CH—I proton of [XI] and CH—O*Ac* proton of [IIb] indicates that the two isomers are in a 1:4 ratio. The obtaining of the alcohols [XII] ([9]) and [XIII] ([9]) by $LiAlH_4$ reduction of the mixture of [IIb] and [XI] confirmed the structure assignment. Thus, even if the reaction in acetic acid actually gives a reasonable yield of the acetoxy-iodide [IIb], our aim of obtaining pure [IIb] was not fulfilled.



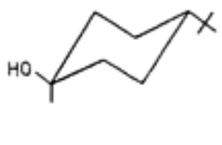
[IX]



[Xa] R=OH , R'=H
[Xb] R=OAc , R'=H
[Xc] R=H , R'=OAc



[XII]



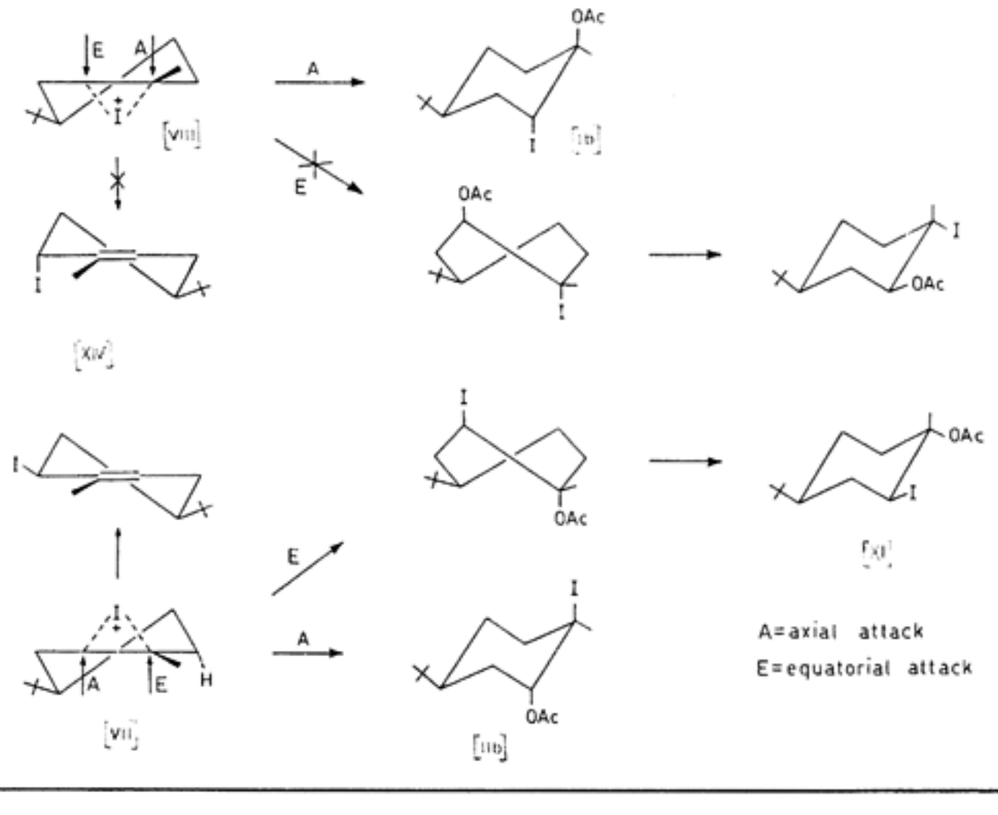
[XIII]

However, the above results deserve some comments, inasmuch as they are of interest to our research on the Woodward reaction of trisubstituted olefins ([1,10]). The iodonium ion [VIII] is opened only *trans*-diaxially, while the diaxial opening of [VII] is not exclusive, a small amount of the acetoxy-iodide [XI] being formed by nucleophilic attack on the more positive tertiary carbon (see scheme 2).

As far as the acetate [Xb] is concerned, the obvious hypothesis that it is formed from [IIb] by elimination can be ruled out by the finding that a sample of [IIb] is unchanged when kept in acetic acid at room temperature even for 48 h. The acetate [Xb] is thus formed from an allylic iodide, this latter having been originated from [VII] and/or [VIII] by loss of a proton ([1]). The fact that only the acetate [Xb] is formed without a trace of its pseudoequatorial epimer [Xc], strongly suggests that it is formed stereospecifically from a single allylic iodide. As in this case retention of configuration by an S_N2' mechanism can quite safely be excluded ([11]), the acetate [Xb] must derive from the allylic iodide [XIV] having the opposite configuration. This implies that of the two iodonium ions only [VII] undergoes (to a small extent) the loss of a proton. This behaviour may be explained

([9]) N. A. LeBel, G. G. Ecke, *J. Org. Chem.*, **30**, 4316 (1965).
([10]) L. Mangoni, V. Dovinola, *Gazz. Chim. Ital.*, **100**, 467 (1970).
([11]) E. S. Gould in « Mechanism and structure in organic chemistry », Holt ed., Reinhart and Wiston, New York, 1959, p. 291.

SCHEME 2



by the lesser tendency of [VII] to undergo the opening of the three-membered ring and/or by the fact that in [VII] the hydrogen atom removed as a proton at C-6 is pseudoaxial and can thus more easily achieve coplanarity with the iodine atom in the transition state for the elimination.

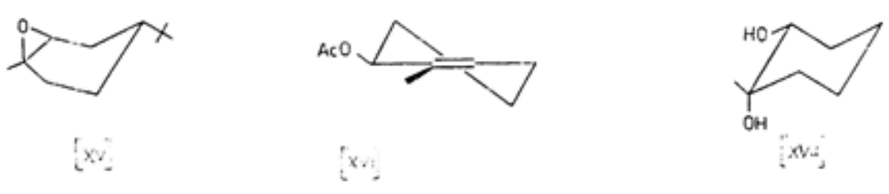
If this is taken into account, the value of the ratio of the products deriving from [VIII], *i.e.* [Ib] and [IX], and those deriving from [VII], *i.e.* [IIb], [XI] and [X], is about 3.3. Thus, in acetic acid the effect of the equilibrium [VII] $\rightleftharpoons$ olefin $\rightleftharpoons$ [VIII] is actually much smaller than in water.

A not very different value was obtained by determination of the products obtained by alkaline hydrolysis of the crude mixture from the reaction with $I_2/KIO_3/AcOH$. These turned out to be the epoxides [V] (58%) and [XV] ([3]) (22%), the *cis*-diol [IX] (11%) and the allylic alcohol [Xa] ([12]) (5%). Since [V] and [IX] must obviously originate from [VIII] and [XV] and [Xa] from [VII], the above ratio is 2.5.

In returning to the preparative aspect of this work, we turned our attention to the reaction of epoxides with NaI/*Ac*OH ([13]), which would allow us to obtain [IIa], starting from [XV]. However, because there is no practical method of ob-

([12]) M. Parrilli, V. Dovinola, L. Mangoni, preceding paper.
([13]) J. W. Cornforth, R. H. Cornforth, K. K. Mathew, *J. Chem. Soc.*, 112 (1959).

taining pure [XV] ([3,9]) a mixture of [V] and [XV], that is easily available from the direct epoxidation of 1-methyl-4-*t*-butylcyclohexene with perbenzoic acid ([9]) was used. The reaction gave 56% of [Ia] and 40% of [IIa] (NMR: see the table), easily isolated by PLC. Acetylation of [Ia] with $Ac_2O/AcOH$ at 60 °C brought out a product identical with [Ib], and acetylation of [IIa] with $Ac_2O/AcOH$ at room temperature easily gave the required acetoxy-iodide [IIb] (NMR: see the table).



[XV] [XVI] [XVII]

In order to obtain [IIIb] and [IVb], the reaction of 1-methylcyclohexene with $I_2/KIO_3/H^+$ in water/dioxane was undertaken. It was found to provide, as its sole product, the iodohydrin [IIIa] (60%) (NMR: see the table) acetylation of which led to the acetoxy-iodide [IIIb] (NMR: see the table). The reaction of 1-methylcyclohexene with $I_2/KIO_3/AcOH$, however, did not turn out to be equally regiospecific. Aside from yielding [IIIb] (66%) and the allylic acetate [XVI] (3%) (NMR: see Experimental section), this reaction in fact gave also the acetoxy-iodide [IVb] (4%) (NMR: see the table), together with a much more polar fraction which gave the *cis*-diol [XVII] ([14]) (2%) after alkaline hydrolysis.

EXPERIMENTAL

1-Methylcyclohexene and 1-methyl-4-*t*-butylcyclohexene were obtained and purified as previously reported ([1]).

M. points were determined on a Kofler apparatus and are uncorrected. IR spectra were made on CCl_4 solutions on a « Perkin-Elmer » model 137E Infracord spectrophotometer. NMR spectra were recorded on a « Perkin-Elmer » model R12A spectrometer on CCl_4 solutions with TMS as an internal standard. Mass spectra were performed on an AEI model 902 spectrometer.

*Reaction of 1-methyl-4-*t*-butylcyclohexene with $I_2/KIO_3/H^+$ in H_2O/dioxane.* — To a suspension of the olefin (500 mg) in H_2O (12.5 ml) and dioxane (12.5 ml) were added 5*N* H_2SO_4 (0.1 ml), I_2 (452 mg) and KIO_3 (191 mg). The mixture was stirred at r.t. for 1 h. Et_2O and solid NaCl were added. The organic layer was washed with sat. $NaHCO_3$, 5*N* $Na_2S_2O_3$, sat. NaCl, dried and evaporated to give an oil (800 mg) which was chromatographed on silica gel (40 g). Elution with 9:1 = n-C_6H_{14}:Et_2O gave [V] (190 mg), oil, NMR spectrum identical with that reported ([3]). Further elution with 7:3 = n-C_6H_{14}:Et_2O gave [Ia] (500 mg) as an oil: ($C_{11}H_{21}OI$, found %: C 44.56; H 7.10; calcd: C 44.60; H 7.14); IR 3 500, 3 350 cm^{-1}; NMR (see the table). Finally [VI] (62 mg), m.p. 117-118 °C [rif. ([3]): m.p. 118.5-119.5 °C], was eluted with Et_2O.

([14]) C. A. Bunton, M. D. Carr, *J. Chem. Soc.*, 710 (1963).

From another experiment on 400 mg of olefin, with 2 h reaction time, [V] (200 mg), [Ia] (166 mg) and [VI] (100 mg) were isolated.

A control experiment showed that in the NMR spectrum of crude reaction product all the peaks due to [V], [Ia] and [VI] are present in the correct ratio. From another experiment, [Ia] was shown to give no epoxide [V] by chromatography on silica gel.

A sample of [Ia] (50 mg) was refluxed in benzene with KOH (0.5 ml of a 10% *MeOH* soln.) for 1 h. Usual work up gave 28 mg of [V].

*Reaction of 1-methyl-4-*t*-butylcyclohexene with I_2/KIO_3/AcOH.* — To a solution of the olefin (500 mg) in glacial *AcOH* (20 ml) were added I_2 (453 mg) and KIO_3 (191 mg). The solution was stirred at room temperature for 3 h. n-C_6H_{14} and sat. NaCl were added. The organic layer was washed with sat. $NaHCO_3$, 5*N* $Na_2S_2O_3$, sat. NaCl, dried and evaporated *in vacuo* at low temperature. The crude product (1.07 g) was chromatographed on silica gel (30 g) to give by elution with 9:1 = n-C_6H_{14}:Et_2O a 850 mg fraction and with Et_2O a 200 mg fraction.

The 200 mg fraction was refluxed in benzene (10 ml) with KOH (2 ml of a 10% *MeOH* soln.) for 2 h. Usual work up gave [IX] (62 mg), m.p. 83-84 °C [rif. ([3]): m.p. 82-84 °C].

The 850 mg fraction by PLC on silica gel (97:3 = n-C_6H_{14}:Et_2O) was separated into three fractions (*A*, *B* and *C*, in order of decreasing polarity).

The fraction *A* (660 mg) was the pure acetoxy-iodide [Ib], oil; IR: 1 740 and 1 240 cm^{-1}; NMR: (see the table); MS: M^+ not detectable, m/e 278 (M^+—*AcOH*), 211 (M^+—I) and 151 (M^+—*AcOH*—I).

The fraction *B* (175 mg) was a mixture of [IIb] and [XI] (see text). Its reduction with $LiAlH_4$ (175 mg) in dry Et_2O (2 h reflux) gave a mixture of [XIII] and [XIV], identified by TLC in comparison with authentic samples ([9]).

The fraction *C* (37 mg) was the pure allylic acetate [Xb], oil; IR: 1 740 and 1 240 cm^{-1}; NMR: δ 1.63 (3H, s, C=C—CH_3), 1.96 (3H, s, CH_3COO—), 5.10 (1H, m, CHO*Ac*) and 5.60 (1H, m, CH=C). [Xb] was identical with an authentic sample obtained by Ac_2O/Py from the known alcohol [Xa] ([12]).

The crude product from an identical experiment was refluxed in benzene (80 ml) with KOH (10 ml of a 10% *MeOH* soln.) for 2 h. Usual work up gave a solid (600 mg) which was chromatographed on silica gel (30 g). Elution with 95:5 = n-C_6H_{14}:Et_2O gave a 2.6:1 mixture (440 mg) of [V] and [XV] [the composition was determined by NMR integration of the signals of the protons at C-2 ([3])]. Elution with 9:1 = n-C_6H_{14}:Et_2O gave [Xa] ([12]) (28 mg). Finally, elution with Et_2O gave [IX] (69 mg).

Reaction of [V] and [XV] with NaI/AcOH. — To a suspension of NaI (1.3 g) and *AcONa* (115 mg) in glacial *AcOH* (1.6 ml) and *AcOEt* (4 ml) at −14 °C was added a mixture of [V] and [XV] (1 g) as obtained by epoxidation of 1-methyl-4-*t*-butylcyclohexene ([9]). The suspension was stirred at −14 °C for 10 min and left in a refrigerator overnight. Ether and sat. NaCl were added. The organic layer was washed with sat. $NaHCO_3$, 5*N* $Na_2S_2O_3$, sat. NaCl, dried and evaporated *in vacuo* at low temperature to give an oil (2 g). By PLC on silica gel (3:1 = n-C_6H_{14}:Et_2O) [IIa] (700 mg), m.p. 44-46 °C (crystallization occurs on long standing in freezer), ($C_{11}H_{21}OI$, found%: C 44.57; H 7.12; calcd: C 44.60; H 7.14). IR 3 450 cm^{-1}, NMR: see the table, and [Ia] (1 g) were isolated.

Acetylation of [Ia]. — [Ia] (1 g) in *AcOH* (4 ml) and Ac_2O (12 ml) was stirred at 60 °C for 15 min. Usual work up followed by chromatography on silica gel (30 g) (9:1 = n-C_6H_{14}:Et_2O), gave unreacted [Ia] (400 mg) and [Ib] (300 mg).

Acetylation of [IIa]. — [IIa] (625 mg) in *Ac*OH (2 ml) and Ac_2O (6 ml) was allowed to stand at room temperature for 24 h. Usual work up afforded [IIb] (500 mg), IR: 1 740 and 1 240 cm^{-1}, NMR: see the table, MS: M^+ not detectable, m/e 211 (M^+—I), 169 (M^+—I—CH_2CO), 151 (M^+—I—*Ac*OH).

[IIb] remained unalterated by *Ac*OH treatment for 48 h at r.t.

A control experiment showed that chromatography of [IIb] on silica gel gives no elimination to [Xb] or to other products.

Reaction of 1-methylcyclohexene with I_2/KIO_3 in H_2O/dioxane. — To a suspension of the olefin (1.35 g) in H_2O (35 ml) and dioxane (35 ml) were added 5*N* H_2SO_4 (0.7 ml), I_2 (1.69 g) and KIO_3 (700 mg). The suspension was stirred at r.t. for 2 h. Work up as above gave [IIIa] (2 g), m.p. 44-45 °C (from *n*-C_6H_{14}) ($C_7H_{13}OI$, found%: C 35.00; H 5.55; calcd: C 35.02; H 5.46); IR: 3 450 and 3 350 cm^{-1}; NMR: see the table.

Acetylation of [IIIa]. — [IIIa] (1.7 g) in *Ac*OH (4 ml) and Ac_2O (12 ml) was allowed to stand at r.t. for 4 days. Usual work up and chromatography on silica gel (40 g) gave [IIIb] (1.4 g), oil; IR: 1 740 and 1 240 cm^{-1}; NMR: see the table; MS: M^+ not detectable, m/e 222 (M^+—*Ac*OH), 155 (M^+—I), 113 (M^+—I—CH_2CO) and 95 (M^+—I—*Ac*OH).

Reaction of 1-methylcyclohexene with I_2/KIO_3/AcOH. — To a solution of the olefin (1.06 g) in glacial *Ac*OH (50 ml) were added I_2 (1.385 g) and KIO_3 (530 mg). The solution was stirred at r.t. for 3 h. Work up was as above. The crude product (2.7 g) was chromatographed on silica gel (80 g) to give by elution with 1:1 = *n*-C_6H_{14}:Et_2O a 2.3 g fraction and with Et_2O a 120 mg fraction.

The latter fraction was refluxed in benzene (5 ml) with KOH (1 ml of a 10% *Me*OH soln.). Usual work up gave [XVII] (27 mg), m.p. 67-68 °C [rif. ([14]): m.p. 67 °C].

The 2.3 g fraction by PLC on silica gel (97:3 = *n*-C_6H_{14}:Et_2O) gave pure [IIIb] (2.07 g), [IVb] (124 mg) and [XVI] (38 mg).

[IVb] was oil; IR: 1 740 and 1 240 cm^{-1}; NMR: see the table; MS: M^+ not detectable, m/e 222 (M^+—*Ac*OH), 155 (M^+—I), 113 (M^+—I—CH_2CO) and 95 (M^+—I—*Ac*OH).

[XVI] was an oil; IR: 1 740 and 1 240 cm^{-1}; NMR: δ 1.52 (3H, s, C=CCH_3), 1.97 (3H, s, CH_3COO—), 5.08 (1H, s, CHO*Ac*) and 5.47 (1H, m, CH=C): it was identical with an authentic sample obtained by acetylation with Ac_2O/Py of the corresponding alcohol ([1]).

A control experiment showed that chromatography of [IVb] on silica gel gives no elimination to [XVI] or to other products.