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STERIC INHIBITION OF RESONANCE AND REGIO- AND STEREOSELECTIVITY IN THE RING OPENING OF 1-ARYLSUBSTITUTED EPOXIDES

REACTIONS OF 1-PHENYL-2,2-DIMETHYL-7-OXABICYCLO[4.1.0]HEPTANE UNDER ACIDIC CONDITIONS

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Abstract—The results of the ring opening of 1-phenyl-2,2-dimethyl-7-oxabicyclo[4.1.0]heptane (2) under acidic conditions show a marked diminution in the regioselectivity and in the *cis* stereoselectivity with respect to the corresponding non-methylated epoxide. The percentage composition of the reaction products of epoxide 2 varies significantly with the solvent medium employed. Possible explanations of the observed stereochemical results, particularly with respect to the steric inhibition of resonance of the intermediate carbocation and to the solvent effects, are discussed.

The formation of *cis* adducts that is frequently observed in the ring opening of aryloxiranes in acid media is generally considered to result from the collapse of the ion pair protonated epoxide-anion which probably takes place preferentially via an internal process. The constitution and the stereochemistry of the products are influenced by at least two important factors: (a) the facility with which the benzylic bond can be broken determines the regiospecificity of the attack, and (b) the relative orientation of the anion with respect to the 3-membered ring determines the *cis* stereochemistry of the adduct.[1] Although reaction conditions may alter the amount of *syn* opening,[1,2] the ability of the unsaturated system to delocalize the charge in the carbocation appears to be the dominant factor.[1e,3] In fact the percentage of *syn* opening obtained in the acid hydrolysis of some 1-arylsubstituted epoxycyclohexanes, is directly related to the order of stability of the intermediate benzylic carbocation:[1e,3,4] while, for example, the *p*-methoxy derivative affords almost exclusively the *cis* adduct,[3] the *p*-nitro derivative affords almost exclusively the *trans* product.[1e]

The stabilization of a benzylic carbocation depends on the degree of overlap between the aryl π system and the vacant *p*-orbital on the benzylic C atom.[5,6] According to Hoffmann,[5] the energy of stabilization of a benzylic carbocation, E is a function very close to $E_0 \cos^2 \theta$, where θ is the dihedral angle formed between the overlapping orbitals. Clearly the net stabilization will be at a maximum when the orbitals are parallel ($\theta = 0°$) and will be minimal when the orbitals are perpendicular ($\theta = 90°$).

Examination of molecular models of the two half-chair conformations of 1-phenyl-2,2-dimethyl-7-oxabicyclo[4.1.0]heptane (2) indicates that the two Me groups force the phenyl group to adopt an orientation in which the π-orbitals of the aromatic system are almost perpendicular in the transition state to the developing *p*-orbital on the assumption that the transition state has a geometry not very different from the starting epoxide. On the other hand an NMR study of the parent olefin (1) showed for the phenyl group a nearly perpendicular conformation to the plane of the olefinic system.[7] Therefore the epoxide 2 appeared as a promising substrate for the investigation of the influence of steric effects on the stero- and regioselectivity of epoxide ring opening reactions.

Epoxide 2 was prepared from olefin 1 by epoxidation with peroxybenzoic acid or by treatment with NBA in aqueous dioxane followed by dehydrohalogenation with KOH. From the reaction of 2 with anhydrous HCl in benzene, one obtains a mixture of the three chlorohydrins 3, 4 and 5, which have been separated by TLC on silica gel.

The chlorohydrins 3 and 4 give, on oxidation with Jones reagent, the chloroketone 6; by treatment with alkali, 3 and 5 can be reconverted to the epoxide 1, while 4 is transformed into ketone 7. These reactions define their structure and configuration. The ring opening reaction of 2 with HCl has been carried out in benzene as well as in cyclohexane and $CHCl_3$ and the percentages of the three isomers in the product (Table 1) vary significantly with the nature of the solvent medium employed. The percentage composition of the crude chlorohydrins mixture in each case has been determined by integration of the well separated methyl double singlets in the NMR spectra.

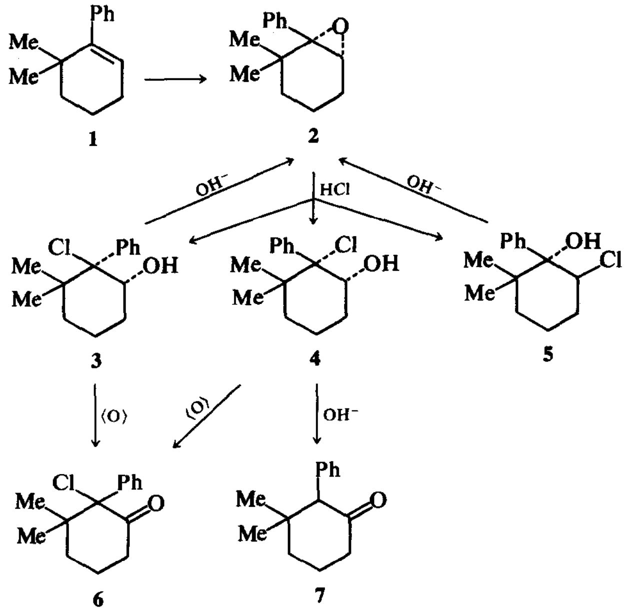
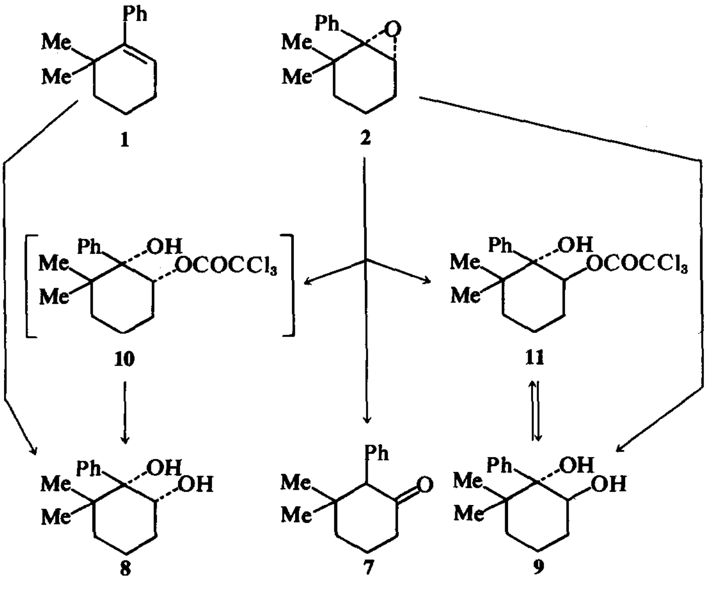


Table 1. Product compositions for the reactions of 2 with HCl

Solvent	%3	%4	%5
Cyclohexane	23	5	72
Benzene	20	25	55
$CHCl_3$	24	44	32

The reactions of **2** with trichloroacetic acid in benzene are much slower than in the case of the unmethylated epoxide (**12**)[1a] and give a mixture of the ketone **7** and of the trichloroacetates **10** and **11**. From the mixture one can isolate the trichloroacetate **11** which on saponification affords **9**. It must be stressed that the isolation of the secondary ester does not imply that all of it is a primary product of the reaction, since it has been shown[1a,b] that the corresponding tertiary esters are rapidly converted into the secondary ones through a particularly facile acyl shift. The diol **9** can also be reconverted to **11** by treatment with trichloroacetyl chloride. The *cis* glycol **8** is obtained by the hydroxylation of **1** with OsO_4, the *trans* diol **9** by treatment of **2** with sulphuric acid in water. Table 2 summarizes the relative percentages of *cis* and

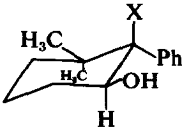


trans diols (**8** and **9**) and ketone **7** obtained in the crude mixture resulting from the alkaline hydrolysis of the reaction product of **2** with trichloroacetic acid in different solvents and from the hydrolysis of **2** in presence of sulphuric acid.

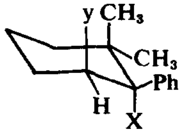
Table 2. Products of trichloroacetolysis and hydrolysis of 2

Solvent	Acid	%7	%8	%9
Cyclohexane	CCl_3COOH	3	2	95
CCl_4	CCl_3COOH	9	3	88
Benzene	CCl_3COOH	16	6	78
$CHCl_3$	CCl_3COOH	18	21	61
CH_2Cl_2	CCl_3COOH	28	35	37
H_2O	H_2SO_4	0·3	0·7	99

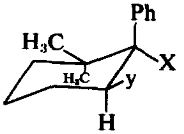
The structures and configurations of all the products mentioned have also been confirmed by NMR spectroscopy and by IR studies in dilute solutions in CCl_4 (Table 3). The NMR and IR data (half-band widths of the methinyl protons β to phenyl group[1b,d,f] and OH stretching frequencies[1f,8]) suggest that the *cis* compounds (**8** and **4**) exist in a conformation (**8a** and **4a**) with the phenyl group equatorial, whereas the half-band width of the methinyl proton resonance[1b,d,f,9] and the IR spectra of the *trans* compounds (**3**, **5**, **9** and **11**) (presence of OH···X hydrogen bonds)[1f,8] are consistent with a twist conformation or a conformation (b) in which the phenyl group occupies an axial position. This is quite reasonable if one considers that, in the *trans* compounds having the phenyl group equatorial (a), the 1,3-diaxial interactions between one of the Me groups and the axial substituent in 2 position with respect to the phenyl group would be very severe.[10,11]



8a: X = OH
4a: X = Cl



9a: X = OH, y = OH
3a: X = Cl, y = OH
5a: X = OH, y = Cl
11a: X = OH, y = $OCOCCl_3$



9b: X = OH, y = OH
3b: X = Cl, y = OH
5b: X = OH, y = Cl
11b: X = OH, y = $OCOCCl_3$

The reactions of the epoxide studied in this work demonstrate a marked diminution in the regioselectivity and in the stereoselectivity with respect to the corresponding parent epoxide **12**. In fact the reaction of **2** with HCl in benzene affords a mixture of products resulting from 45% benzylic attack with only 25% *syn* addition. In contrast, the analogous reaction of epoxide **12** occurs with complete stereo- and regiospecificity with 100% attack at the benzylic C atom to give the *cis* adduct.[12] The only *syn* addition product from epoxide **2** is that which is formed by the attack of the nucleophile at the benzylic carbon.

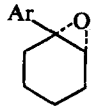
Also in the hydrolysis and trichloroacetolysis of **2** there is a net decrease in the *syn* stereoselectivity. In the reaction with trichloroacetic acid carried out in benzene for **2** there is only 7% retention of configuration, whereas the same reaction of **12** gives 100% retention.[1a] In the hydrolysis of epoxide **12** with aqueous sulphuric acid one obtains 60% of the *cis* product,[4] while with the dimethyl substituted epoxide (**2**) there is a total inversion of configuration. However, in the reactions of **2** carried out in aprotic solvents significant amounts of products arising from a *syn* addition that are particularly sensitive to the solvent effects are still observed.

While there is a little doubt that serious hindrance to conjugation exists in the benzylic carbocation formed from epoxide **2**, the formation of these amounts of *cis* adducts indicate that a limited stabilization of the reaction center can still occur; this may be due to an incomplete orthogonality of the orbitals, or to an inductomeric electron

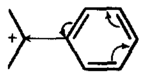
Table 3. NMR and IR data

	NMR (δ, ppm)			IR (cm^{-1})	
Compound	CHX ($W_{1/2}$, Hz)	CH_3		OH Free	OH···X
8	4·47 (16·0)[a]	0·79		3622[e]	3589[d]; 3561[a]
9	3·98 (17·0)[a]	1·12	0·65	3627[e]	3580[a,d]
3	4·55 (16·5)[a]	1·28	0·91	3626[e]	3592[b]
4	4·72 (16·0)[a]	1·03	0·84		3582[b]
5	4·68 (20·5)[b]	1·22	0·61		3574[b]
11	5·23 (12·0)[c]	1·05	0·99	3632[e]	3593[c]

[a]X = OH; [b]X = Cl; [c]X = $OCOCCl_3$; [d]X = Phenyl; [e]Weak band.



12: Ar = C_6H_5
13: Ar = p-$O_2NC_6H_4$

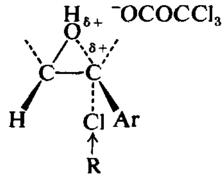


14

release from the phenyl group as shown in **14**. Evidently the diminished stabilization of the benzylic carbocation and the steric hindrance of the two Me groups makes the attack of the nucleophile on the secondary carbon, through a borderline A-2 mechanism, competitive.

The strong solvent effect that is observed in the reactions of epoxide **2** with acids can be explained by a nucleophilic solvation of the intermediate benzylic carbocation which can affect the steric course of the reactions by increasing the contribution of a cationic mechanism.

Since cyclohexane has only weak or no solvating power, the reaction would proceed without any direct or indirect effect attributable to the solvent. In the case of chlorine containing solvents, the polarization of the C—Cl bond would lead to an enhanced solvation of the center of charge in the oxirane ring as shown in **15**, making *cis* attack more competitive. If one compares the results obtained in the chlorinated solvents one can observe (Table 2) that the increase in the amount of *cis* product parallels the order of polarization of the C—Cl bond in the chlorinated solvents, that is CCl_4 $CHCl_3$ CH_2Cl_2. Therefore the amount of *cis* isomer formed in CCl_4, where the polarization of the C—Cl bond is minimal, is less than in CH_2Cl_2 and $CHCl_3$ and it does not differ too much from the value obtained in cyclohexane. Analogously to the chlorinated solvents, benzene can also solvate[13,14] the intermediate carbocation by its π electrons as shown in **16**. An analogous stereochemical result was found by Fahey and McPherson[15] in the reaction of 1,2-dimethylcyclohexene with hydrogen chloride. In fact, they obtained a much higher percentage of *syn* addition in CH_2Cl_2 than in pentane. The authors did not offer, however, any explanation to their results. A substantial agreement is found in the increase of *syn* addition in the case of the reaction of **2** with trichloroacetic acid and in that of epoxide **13**[1e] in the solvent series cyclohexane, CCl_4, benzene, $CHCl_3$, CH_2Cl_2.



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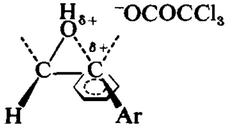

16

The hypothesis of the solvation of the intermediate carbocation by the non protic solvents is confirmed by examining the relative amounts of the ketone **7** formed in the reaction of **2** with trichloroacetic acid. It is possible to observe that the increase of the ketone **7** runs almost parallel to the increase in the percentage of *cis* product. The formation of ketone from epoxides under acidic conditions involves a 1,2-hydride shift through a transition state with a high carbonium ion character.[4,16,17,18] Thus, we can observe the highest percentage of ketone as well as of the *cis* product in that solvent (CH_2Cl_2) where the possibility of the carbocation solvation is greatest. The results we have discussed above show that the steric hindrance of the two Me groups decreases the stability of the carbonium ion, which is however strictly related to the solvent. On the other hand the presence of the two Me groups hinders the attack by an external nucleophile and thus renders the 1,2-shift more efficient thereby producing more ketone than in the case of the same reactions of the non-methylated epoxide **12**.

In the hydrolysis of **2** conducted in aqueous sulphuric acid the water itself can equally solvate the carbocation in a *trans* fashion and contemporarily acts as the nucelophile affording essentially the *trans* adduct **9**.

EXPERIMENTAL

M.ps were determined on a Kofler apparatus and are uncorrected. IR spectra for comparison between compounds were taken on paraffin oil mulls on a Perkin-Elmer Infracord Model 137 and those for the determination of OH stretching bands with a Perkin-Elmer Model 257 double beam grating spectrophotometer in dried (P_2O_5) CCl_4, using the indene band at 3110 cm^{-1} as a calibration standard; a quartz cell of 2 cm optical length was employed, and the concentration of the solns was $5 \cdot 10^{-3}$ M or lower to prevent intramolecular association. NMR spectra were determined an *ca* 10% $CDCl_3$ solns with a JEOL C 60 HL spectrometer using TMS as an internal standard. GLPC were run on a Carlo Erba Fractovap GV apparatus with a flame ionization detector, using a dual column system with glass columns (3 mm × 2 m) packed with 1% neopentyl-glycol succinate on 80–100 mesh silanized Chromosorb W; tems: columns 148°, evaporator 190°, detectors 180°, N_2 flow 45 ml/min. Retention times: **7**, 2 min; **8**, 5 min; **9**, 8 min. The ratio of the three chlorohydrins **3**, **4** and **5** was estimated through the NMR signals of the two Me groups adjacent the phenyl group. Preparative TLC were performed on 2-mm layer silica gel plates (Merk F_{254}) containing a fluorescent indicator; spots were detected under UV light (245 nm). All comparison between compounds were made on the basis of IR and NMR spectra and GLPC. $MgSO_4$ was always used as drying agent. Evaporation were made *in vacuo* (rotating evaporator). Light petroleum refers to the fraction boiling at 30–50°; cyclohexane, CCl_4, $CHCl_3$ and CH_2Cl_2 were refluxed over P_2O_5 and rectified; benzene was washed with concentrated sulphuric acid, refluxed over Na and rectified.

2,2-*Dimethylcyclohexanone*, b.p. 170–172°/760 mm, n_D^{20} 1·4485, was prepared as described before[19] and transformed into 6,6-*dimethyl*-1-*phenylcyclohexene* (**1**), b.p.

86–88°/0·8 mm, n_D^{25} 1·5345 (lit.[20] b.p. 80·5°/0·54 mm, n_D^{20} 1·5324) by the method of Garbisch.[20]

2,2-*Dimethyl*-1-*phenyl*-7-*oxabicyclo*[4.1.0]*heptane* (2)

(a) A soln of 1 (6 g; 32·2 mmole) in 60 ml $CHCl_3$ was treated under stirring with 117 ml of a 0·312 M (35·4 mmole) soln of peroxybenzoic acid,[21] while keeping the temp below 0°. After 70 hr at 5°, the soln was washed with 10% Na_2CO_3 aq, dried and the solvent evaporated under reduced press, to give 5·8 g of a solid residue, which was crystallized from EtOH-water 8/2 (v/v) at −5° to yield 4·6 g of pure 2, m.p. 42–43°, NMR δ 2·97 (m, 1, $W_{1/2}$ 6 Hz, CHO). (Found: C, 83·20; H, 8·84; $C_{14}H_{18}O$ requires: C, 83·12; H, 8·97%).

(b) A soln of 1 (1·0 g, 5·37 mmole) in 70% aqueous dioxane (v/v; 18 ml) was added to a soln of NBA (0·875 g, 6·34 mmole) in 50% aqueous dioxane (v/v; 10 ml), warmed on a steam bath for 4 min, cooled and then treated with a soln of KOH (1·8 g) in water (15 ml). The mixture was warmed on a steam bath for 7 min, diluted with water and extracted with ether. The washed (H_2O) and dried extracts gave, after evaporation, a residue (0·95 g) which was chromatographed through a 1·7 × 30 cm column of neutral Al_2O_3 (act. 2). Elution with light petroleum (90 ml) gave oily products (0·190 mg); further elution with light petroleum (60 ml) and with 9/1 light petroleum-benzene (300 ml) yielded pure 2 (0·480 g).

6,6-*Dimethyl*-1-*phenyl*-r-1-cis-2-*cyclohexanediol* (8)

A soln of 1 (0·200 g, 1·07 mmole) in pyridine (0·4 ml) and anhyd ether was treated with a soln of OsO_4 (0·254 g, 1·0 mmole) in anhyd ether (6 ml) and stored at room temp for 7 days. The ppt was then collected, washed with ether, dissolved in CH_2Cl_2 (20 ml) and treated twice with a soln of NaOH (0·4 g) and mannitol (1·0 g) in water (16 ml). The CH_2Cl_2 soln was then evaporated to yield 8 (0·190 g) which crystallized from light petroleum had m.p. 82–84°. (Found: C, 76·20; H, 8·92; $C_{14}H_{20}O_2$ requires: C, 76·32; H, 9·15%).

Reaction of 2 *with sulphuric acid in water*

A suspension of 2 (0·300 g) in water (27 ml) and 2 N H_2SO_4 aq (3 ml) was stirred at room temp for 4 days and then extracted with ether. Evaporation of the washed (H_2O) and dried extract gave a solid residue (0·305 g) consisting essentially of 9 (Table 2). Crystallization of the residue from light petroleum gave pure 9 (0·210 g), m.p. 85–87°. (Found: C, 76·48; H, 9·12; $C_{14}H_{20}O_2$ requires: C, 76·32; H, 9·15%).

6,6-*Dimethyl*-1-*phenyl*-trans-2-*trichloroacetoxy*-r-1-*cyclohexanol* (11)

(a) A soln of 2 (0·200 g, 0·99 mmole) in benzene (20 ml) was treated with a 1·1 M soln of trichloroacetic acid in benzene (1·1 ml), left at room temp for 40 days, washed with satd $NaHCO_3$ aq, water and evaporated to yield a solid residue (0·315 g) which on crystallization from light petroleum gave 11 (0·180 g), m.p. 96–98·5°, λ_{CO} 5·75 μ. (Found: C, 52·64; H, 5·05; $C_{16}H_{19}O_3Cl_3$ requires: C, 52·53; H, 5·17%).

If the mixture was left only 20 hr at room temp before work-up, mostly unreacted epoxide 2 was recovered.

(b) A mixture of pyridine (0·12 g, 1·5 mmole) and trichloroacetyl chloride (2·7 g, 1·5 mmole) in benzene (3 ml) was added to a soln of 9 (0·22 g, 1·0 mmole) in benzene (3 ml), left at room temp for 12 hr and then refluxed for ½ hr. The mixture was washed with dil HCl, water and evaporated to give 11 (0·35 g).

Reaction of 2 *with trichloroacetic acid in several solvents*

The reactions were carried out in anhyd benzene, cyclohexane, CCl_4, $CHCl_3$, CH_2Cl_2 in the following way: to a soln of 2 (0·100 g, 0·495 mmole) in the solvent was added trichloroacetic acid (0·55 mmole) using a *ca* 1 M soln of the acid in the same solvent. The mixture was allowed to stand 40 days at room temp, washed with satd $NaHCO_3$ aq, water, dried and evaporated to dryness. The crude residue was dissolved in THF (15 ml), treated with 1 M KOH in EtOH (3 ml) and left 5 hr at room temp. Dilution with water, extraction with ether and evaporation of the washed (H_2O) and dried ether layer gave a residue consisting of a mixture of 7, 8 and 9 which was analyzed by GLPC (Table 2).

Reactions of 2 *with* HCl

(a) *In benzene.* Dry gaseous HCl was bubbled through a soln of 2 (0·80 g) in dry benzene (60 ml) to saturation. After 2 hr at room temp the soln was washed with water, satd $NaHCO_3$ aq, water, dried and evaporate to give a residue (0·93 g) consisting of 3, 4 and 5 which was analysed by NMR (Table 1). The crude mixture was subjected to preparative TLC, a 6/4 mixture of light petroleum and ether being used as the eluent. Extraction of the three bands (the faster moving band contains the chlorohydrin 5 and the slowest one contains the chlorohydrin 4) yielded 5 (0·45 g), 3 (0·16 g) and 4 (0·22 g). 5, m.p. 46–47·5° (from light petroleum at −5°). (Found: C, 70·57; H, 8·24; $C_{14}H_{19}OCl$ requires: C, 70·42; H, 8·02%). 3, m.p. 79–80° (from light petroleum at −5°). (Found: C, 70·49; H, 7·80; $C_{14}H_{19}OCl$ requires: C, 70·42; H, 8·02%). 4, m.p. 63–65° (from light petroleum at −5°). (Found: C, 70·20; H, 7·90; $C_{14}H_{19}OCl$ requires: C, 70·42; H, 8·02%).

(b) *In* $CHCl_3$. A soln of 2 (0·10 g) in dry $CHCl_3$ (8 ml) was saturated with dry gaseous HCl, left 2 hr and treated as described in (a). The residue (0·11 g) consisted of a mixture of the chlorohydrins 3, 4 and 5 (NMR) (Table 1).

(c) *In cyclohexane.* Dry gaseous HCl was bubbled to saturation through a soln of 2 (0·10 g) in dry cyclohexane (8 ml) and left 2 hr at room temp. The treatment as described in (a) yielded a residue (0·10 g) consisting of 3, 4 and 5 (NMR) (Table 1).

3,3-*Dimethyl*-2-*chloro*-2-*phenylcyclohexanone* (6)

(a) A soln of 4 (0·100 g, 0·42 mmole) in acetone (10 ml) was treated with Jones reagent[22] (0·150 ml). After 20 min at room temp the mixture was diluted with water and extracted with ether. Evaporation of the washed (H_2O, satd $NaHCO_3$ aq, H_2O) and dried extract gave a solid residue (0·094 g) consisted of 6 which crystallized from MeOH–H_2O at −5°, m.p. 61–62°, λ_{CO} 5·83 μ. (Found: C, 71·02; H, 7·00; $C_{14}H_{17}OCl$ requires: C, 71·02; H, 7·24%).

(b) A soln of 3 (0·015 g, 0·063 mmole) in acetone (5 ml) was treated with Jones reagent[22] (0·02 ml) and left at room temp for 15 min. The treatment as described in (a) gave pure 6 (0·012 g).

When the chlorohydrin 5 was treated as described above it was recovered completely unchanged.

Dehydrohalogenation of 3 *and* 5

(a) A soln of 3 (0·050 g) in 2-propanol (5 ml) was treated with KOH (0·100 g), then refluxed for 25 min, diluted with water and extracted with ether. Evaporation of the washed (H_2O) and dried ether extracts yielded pure 2 (0·042 g).

(b) A soln of 5 (0·025 g) in 2-propanol (5 ml) was treated with KOH (0·100 g) and then refluxed for 25 min. The treatment as described in (a) gave pure **2** (0·010 g).

3,3-*Dimethyl-2-phenylcyclohexanone (7)*

A soln of **4** (0·050 g) in 2-propanol (6 ml) was treated with KOH (0·100 g), then refluxed 25 min, diluted with water and extracted with ether. Evaporation of the washed (H_2O) and dried extracts gave **7** (0·040 g) which crystallized from light petroleum, m.p. 67–68°, λ_{CO} 5·88 μ. (Found: C, 83·27; H, 9·02; $C_{14}H_{18}O$ requires: C, 83·12; H, 8·97%).

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