24. *A General Stereoselective Synthesis of Olefins.*

By J. W. Cornforth, (Mrs.) R. H. Cornforth, and K. K. Mathew.

The addition of Grignard reagents or lithium alkyls to aliphatic α-chloro-carbonyl compounds is shown to be a stereoselective process. The chlorohydrins produced are converted into olefins by three stereospecific steps, the intermediates being epoxides and iodohydrins. A new procedure for making iodohydrins from epoxides, and a new reagent for reduction of iodohydrins to olefins, are described, as well as a direct but non-stereospecific reduction of epoxides to olefins. The geometry of the two 3-methylpent-2-enes is established by unequivocal synthesis of each isomer.

An olefin is commonly made either from an acetylene by addition of hydrogen or from a more saturated structure by some kind of elimination. By using acetylides most mono-alkylethylenes and 1 : 2-dialkylethylenes can be made, the latter with *cis*- or *trans*-geometry as desired; but unless the chemistry of lithium alkenyls can be developed more widely than at present seems probable, acetylenes show little promise as sources of tri- and tetra-alkylethylenes. On the other hand, ethylenes with any degree of substitution can be made by elimination; but when the groups eliminated are H and X, the hydrogen can often be abstracted from more than one position, so that the product is a mixture of positional and geometrical isomers. When groups X and Y (neither of them hydrogen) are eliminated, the position of the double bond is determined if it is formed in conditions too mild for a prototropic shift; the chemical problem is then to prepare CabX•CcdY, and the stereochemical problem is to obtain this in the desired configuration and to make the elimination stereospecific. Formation of olefins from 1 : 2-dibromides and zinc is one stereospecific (*trans*) elimination, but an olefin is usually the starting point for preparation of the dibromide. In Boord's synthesis[1] a 1 : 2-dibromo-ether reacts with a Grignard reagent to give a substituted 2-bromo-ether from which an olefin is prepared by the action of zinc. This method, which has affinities with the one to be described, is useful for making a carbon chain with a double bond at a particular position, but it is less satisfactory for trisubstituted olefins and neither stage is stereoselective. A related synthesis,[2] the scission by sodium of 2-alkyl-3-chlorotetrahydropyrans, is a useful source of *trans*-4-en-1-ols, but is of limited scope. Wittig and Schöllkopf's admirable method,[3] which has almost every attribute of a truly general synthesis of olefins, suffers from the disadvantage that mixtures of geometrical isomers are formed.

The hydrocarbon squalene, an intermediate in the biosynthesis of cholesterol, has six trisubstituted double bonds of which four can exhibit geometrical isomerism. The problem of synthesising all-*trans*-squalene, and if necessary some of its nine geometrical isomers, impressed on us that no general method existed for obtaining a trisubstituted olefin of predetermined geometry. We were attracted by the possibility of a stereoselective synthesis of a halogenohydrin, followed by stereospecific elimination of the elements of hypohalous acid.

Reaction of α-Chloro-carbonyl Compounds with Organometallic Reagents.—Grignard reagents add normally to the carbonyl group of chloroacetone,[4] though rearrangement may subsequently occur if the reaction mixture is heated.[5] Chloroacetaldehyde likewise can react normally with ethylmagnesium bromide.[6] Our experience confirms that many α-chloro-aldehydes and α-chloro-ketones react smoothly with Grignard reagents to give

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[1] Boord *et al.*, *J. Amer. Chem. Soc.*, 1930, **52**, 651, 3396; 1931, **53**, 1505; 1932, **54**, 751; 1933, **55**, 3293, 4930.

[2] Crombie and Harper, *J.*, 1950, 1707; Crombie, Gold, Harper, and Stokes, *J.*, 1956, 136; cf. Riobé, *Compt. rend.*, 1947, **225**, 334; Brandon, Derfer, and Boord, *J. Amer. Chem. Soc.*, 1950, **72**, 2120.

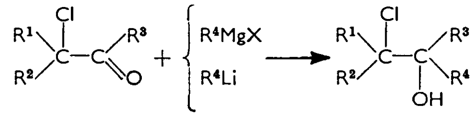
[3] Wittig and Schöllkopf, *Ber.*, 1954, **87**, 1318.

[4] Tiffeneau, *Compt. rend.*, 1902, **134**, 774.

[5] Henry, *ibid.*, 1907, **145**, 24.

[6] Helferich and Speidel, *Ber.*, 1921, **54**, 2636.

chlorohydrins, and we find also that lithium alkyls react in the same sense. The general reaction is:

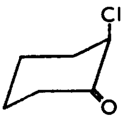


We habitually mix the reagents at —70° and add acetic acid soon afterwards to decompose the complex. This technique, adopted to minimise rearrangement of the complex, is so rapid and convenient that there has been no incentive to compare it with operation at room temperature; with the one (Grignard) reaction where such a comparison was made, the yield at the higher temperature was a little lower. Comparisons of lithium alkyls with Grignard reagents were made more extensively. In general, the Grignard reagent gave the superior yield of chlorohydrin from substances containing the group $^-CO{\cdot}CH_2Cl$, probably because the lithium alkyl induced self-condensation of the ketone. The lithium alkyl had the advantage with more hindered carbonyl compounds; these are less prone to enolisation but are liable to reduction by the Grignard reagent. Comparative yields are assembled in the Table.

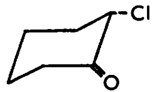
Chloro-carbonyl compound	Yield (%) with		Chloro-carbonyl compound	Yield (%) with	
	Bu^nLi	Bu^nMgBr		Bu^nLi	Bu^nMgBr
$CH_3{\cdot}CH_2{\cdot}CHCl{\cdot}CHO$	65	68	$CH_3{\cdot}CO{\cdot}CHCl{\cdot}CH_3$	79	65
$CH_3{\cdot}CO{\cdot}CH_2Cl$	30 *	67	$(CH_3)_2CCl{\cdot}CHO$	63	25
$CH_3{\cdot}CH_2{\cdot}CO{\cdot}CH_2Cl$	25	75	$(CH_3)_2CCl{\cdot}CO{\cdot}CH_3$	68	10

* Light petroleum, not ether, used as solvent.

The stereochemistry of nucleophilic addition to the carbonyl group of aliphatic α-chloro-carbonyl compounds had never been investigated. We were first attracted to this as a possibly stereoselective process by Corey's statements [7] that 2-chloro*cyclo*hexanone in the liquid state exists entirely in the form (I) with axial chlorine, and that this is in accord with theoretical calculations, the compression of axial substituents in (I) being outweighed by the electrostatic repulsion of C=O and C–Cl dipoles in the " equatorial " conformation (II). Such a repulsion might check free rotation about the C–C bond in aliphatic $^-CO{-}CCl{<}$ and irreversible additions to the C=O group should then be stereoselective. However, it has been shown [8] that the predilection for axial halogen in the related 2-bromo*cyclo*hexanone is not absolute; and work by Bellamy *et al.*[9] with the acyclic α-chloro-carbonyl group (chloroacetone, ω-chloroacetophenone, etc.) indicates that in the liquid state two rotational isomers are present and that in the more stable of these the C=O and C–Cl groups are eclipsed (III).



(I)



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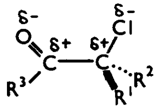

(III)

All these findings were based on measurements of C=O stretching frequencies: when the infrared spectrum of a steroid α-bromo-ketone of known configuration was compared with the spectrum of the parent ketone, the C=O stretching absorption was found at a higher frequency if the C=O and C–Br bonds were approximately in the same plane.[10]

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[7] Corey, *J. Amer. Chem. Soc.*, 1953, **75**, 2301; Corey and Burke, *ibid.*, 1955, **77**, 5418.

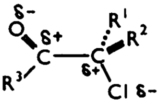
[8] Allinger and Allinger, *Tetrahedron*, 1958, **2**, 64.

[9] Bellamy, Thomas, and Williams, *J.*, 1956, 3704; Bellamy and Williams, *J.*, 1957, 4294.

[10] (*a*) Jones, Ramsay, Herling, and Dobriner, *J. Amer. Chem. Soc.*, 1952, **74**, 2828; (*b*) Jones, *ibid.*, 1953, **75**, 4839; (*c*) Dickson and Page, *J.*, 1955, 447.

The effect was explained as an interaction of dipoles, the polarity of the C–Br bond reducing that of the C=O bond [10a] (Bellamy [11] mistakenly reports the opposite conclusion).

This intramolecular field effect in the eclipsed conformation (III) would thus resist the separation of charge, $\gt C^{\delta+}{=}O^{\delta-}$, on which the electrophilic reactivity of a carbonyl group depends. In the conformation (IV), where the dipoles are antiparallel, the polarisation of the carbonyl group would be easiest; and, if ease of polarisation has a marked effect on the energy required to form the transition state with a nucleophilic agent, the chloro-ketone might react largely in conformation (IV), even though this form made little contribution to the rotational equilibrium in solution. Steric hindrance would operate to favour the attack of the nucleophilic agent on that side of the carbonyl group which is shielded by the smaller of the groups R^1, R^2. The situation is similar to that envisaged in Cram's rule.[12] Thus, when a nucleophilic agent R^4X reacts irreversibly with an α-chloro-ketone (or α-chloro-aldehyde) $R^1R^2ClC\cdot COR^3$, the resulting chlorohydrin would have a preponderance of molecules (V) wherein R^4 is *anti* to the larger (here R^2) of the two groups R^1, R^2 when the chlorine and hydroxyl groups are *anti* to each other.



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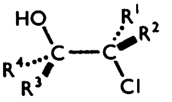

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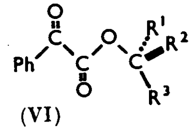
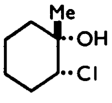


(VI)

It seems possible that Prelog's method [13] for determining the absolute configuration of alcohols may in part owe its success to a similar effect. In considering the steric effects of the groups R^1, R^2, R^3 on the addition of methylmagnesium iodide to the phenylglyoxylate (VI) of an asymmetric alcohol, Prelog assumed that the overwhelming majority of molecules in the ester had the *transoid* conformation (VI). However, the marked exaltation of carbonyl stretching frequencies found in methyl pyruvate [14] suggests that a *transoid* relation of carbonyl groups is not always preferred in α-oxo-esters. On the other hand, the polarisation effects should make the form (VI) the most reactive of all rotational isomers.

Addition of methylmagnesium halide to 2-chloro- and 2-bromo-*cyclo*hexanones has been shown [15,16] to yield predominantly *cis*-halogenohydrins (VII), and reduction of 2-chloro-*cyclo*hexanone by *tert.*-butylmagnesium chloride gives largely *cis*-2-chloro*cyclo*hexanol.[17] Since 2-chloro*cyclo*hexanone normally prefers the conformation with axial chlorine this would be the expected result even if polarisation effects are disregarded, but it is also explained by the arguments developed above which indicate that the conformation with axial chlorine is the more reactive. 2-Methyl*cyclo*hexanone, in contrast, gives a mixture of two isomers by addition of methylmagnesium halide.[18]



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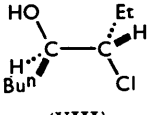

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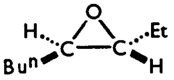

(IX)

To discover whether the addition of organometallic reagents to aliphatic α-chloro-carbonyl compounds was stereoselective in the predicted direction, it was necessary to

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[11] Bellamy, " The Infrared Spectra of Complex Molecules," Methuen, London, 1954, p. 121.

[12] Cram and Elhafez, *J. Amer. Chem. Soc.*, 1952, **74**, 5828.

[13] Prelog, *Helv. Chim. Acta*, 1953, **36**, 308.

[14] Randall, Fowler, Fuson, and Dangl, " Infra-red Determination of Organic Structures," Van Nostrand, New York, 1949.

[15] Tiffeneau and Tchoubar, *Compt. rend.*, 1934, **199**, 360.

[16] Bartlett and Rosenwald, *J. Amer. Chem. Soc.*, 1934, **56**, 1990.

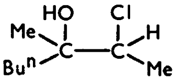
[17] Bartlett, *ibid.*, 1935, **57**, 224.

[18] Chiordoglu, *Bull. Soc. chim. belges*, 1938, **47**, 241.

make by this method a chlorohydrin of ascertainable configuration. A suitable example was 3-chloro-octan-4-ol, which we prepared from 2-chlorobutanol and butylmagnesium bromide or butyl-lithium. The chlorohydrin was converted by aqueous alkali into 3 : 4-epoxyoctane. This type of reaction is well established as a nucleophilic displacement with inversion at the halogen-bearing carbon atom. Thus, if the chlorohydrin had the expected preponderance of the stereoisomeride (VIII), the epoxide would consist mainly of (IX), the product obtainable by (*cis*-)epoxidation of *trans*-oct-3-ene. From 3-octyne, samples of *trans*-oct-3-ene (by reduction with sodium in ammonia [19]) and *cis*-oct-3-ene (by hydrogenation over Lindlar catalyst) were obtained and each was oxidised by monoperphthalic acid. Mixtures of the two epoxides were made and the infrared spectra were compared with that of the epoxide from the chlorohydrin; this epoxide proved to be a mixture containing about 70% of *trans*-epoxide (IX), and the composition was almost the same whether a Grignard reagent or a lithium alkyl had been used to make the chlorohydrin, though the chlorohydrin from the Grignard reaction gave slightly more *trans*-epoxide. Stereoselectivity of this degree * was considered satisfactory in a reaction with an α-chloro-aldehyde. Access to the carbonyl group in an α-chloro-ketone is more restricted: higher selectivity could then be expected and was indeed observed.

Preparation of Olefins from Chlorohydrins.—We abandoned, after several trials, the attempt to eliminate from chlorohydrins the elements of hypochlorous acid. An obvious variant was the conversion of the chlorohydrin *via* the epoxide into a bromohydrin, for bromohydrins have long been known [20] to give olefins on treatment with zinc.† Since formation of the epoxide and of the bromohydrin would each proceed with inversion at one carbon atom, the stereochemistry of the bromohydrin, for the purpose of an elimination, would correspond to that of the chlorohydrin even if the positions of hydroxyl and halogen were partially or wholly interchanged.

Many orienting experiments were made with 2-chloro-3-methylheptan-3-ol (X), prepared from 3-chlorobutan-2-one and butylmagnesium bromide or butyl-lithium. 2 : 3-Epoxy-3-methylheptane (XI) was readily made by stirring the chlorohydrin with aqueous sodium hydroxide. A bromohydrin was prepared by slow addition of hydrobromic acid to a solution of this epoxide in acetone containing lithium bromide and a little Thymol Blue. When the bromohydrin was treated with zinc powder in acetic acid an olefin was obtained, along with a higher-boiling ketonic fraction. The yield of olefin from epoxide was 25%. In a similar experiment using sodium iodide–hydriodic acid instead of lithium bromide–hydrobromic acid the yield was rather better (39%). Reduction of an iodohydrin to an olefin does not seem to have been reported previously.



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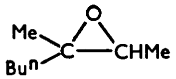

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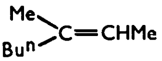

(XII)

When the epoxide (XI) was added to sodium iodide in acetic acid, an iodohydrin was formed rapidly, and subsequent addition of zinc powder gave an olefin, isolated in 56% yield. Two further refinements were then discovered: when the epoxide was added to a

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* The stereochemical purity of our *cis*-oct-3-ene was not proved; if it contained a small proportion of *trans*-oct-3-ene the stereoselectivity in the formation of 3-chloro-octan-4-ol could have been slightly higher than 7 : 3.

† Three apparent exceptions to this rule were reported by Barton, Lewis, and McGhie: [21] it was claimed that 2α- and 2β-bromolanost-8-en-3β-ol and 2α-bromolanostan-3β-ol were reduced to the *alcohols* in 80—85% yields by zinc. When the procedures described for debromination of 2α-bromolanost-8-en-3β-ol and 2β-bromolanost-8-en-3β-ol were repeated in this laboratory, the former was entirely unchanged and the latter gave as principal product lanost-8-en-3-one along with some lanost-8-en-3β-ol, lanost-8-en-3β-yl acetate, and a little lanosta-2 : 8-diene. Dr. McGhie (personal communication) kindly checked our findings and confirmed them; he suggested that the earlier results were obtained with an exceptional batch of zinc.

[19] Henne and Greenlee, *J. Amer. Chem. Soc.*, 1943, **65**, 2020.

[20] Mokiewsky, *J. Russ. Phys.-Chem. Soc.*, 1898, **30**, 900; *Chem. Zentr.*, 1899, I, 591.

cooled stirred mixture of zinc powder, sodium iodide, and acetic acid the olefin was obtained directly in 67% yield (in formic acid, 53%; in propionic acid, 70%). Finally, when the mixture of acetic acid, sodium iodide, and zinc was buffered by sodium acetate a 76% yield of olefin was secured and raised to 82% by working on a larger scale. In this composite process, protonation of the epoxide is presumably followed by nucleophilic addition of iodide ion, and then reduction of the iodohydrin before solvolytic processes can destroy much of it. Iodide ion consumed in the second stage is regenerated in the third, so that a catalytic amount of sodium iodide should, and does, suffice to promote olefin formation; but 3 : 4-epoxyoctane gave a lower yield of oct-3-ene with 0·2 equivalent of sodium iodide than with 2 equivalents.

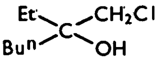
The olefin from reduction of the epoxide (XI) was identified as 3-methylhept-2-ene (XII) by oxidation with the periodate–permanganate reagent,[22] which gave hexan-2-one in good yield. This olefin had not previously been obtained free from positional isomers.[23] The synthesis may be summarised thus:

$$\text{3-Chlorobutan-2-one} \xrightarrow[79\%]{\text{BuLi}} \text{2-Chloro-3-methylheptan-3-ol} \xrightarrow[89\%]{\text{NaOH}}$$

$$\text{2:3-Epoxy-3-methylheptane} \xrightarrow[82\%]{\text{NaI–NaOAc–Zn–AcOH}} \text{3-Methylhept-2-ene,}$$

and the overall yield is 57·5%.

The scope of the synthesis was then explored. To obtain a 1 : 1-disubstituted olefin, 1-chlorobutan-2-one was treated with butylmagnesium bromide to give 3-chloromethylheptan-3-ol (XIII); the epoxide from this was reduced to 2-ethylhex-1-ene (XIV; R = Et). The olefin was identified by periodate–permanganate oxidation to heptan-3-one, and by its infrared spectrum which showed the expected bands at 887, 1647, 1775, and 3090 cm.$^{-1}$. 2-Methylhex-1-ene (XIV; R = Me) was prepared similarly from chloroacetone. 3 : 4-Epoxyoctane gave the 1 : 2-disubstituted ethylene, oct-3-ene. Another trisubstituted ethylene, 2-methylhept-2-ene (XV), was prepared from 2-chloro-2-methylpropanal. Finally the tetrasubstituted 2 : 3-dimethylhept-2-ene (XVI) was made from 3-chloro-3-methylbutan-2-one. Although no search was made for optimum conditions in these syntheses, the yields at all stages were satisfactory (lowest yield 63%). No monosubstituted ethylene (from chloroacetaldehyde) was made; presumably this could be done, but the process would never be so convenient as synthesis *via* an acetylene.



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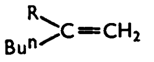

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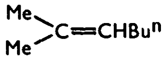

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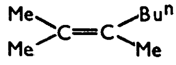

(XVI)

We had hoped that the reduction of iodohydrins to olefins might be a stereoselective *trans*-elimination; but reduction of the epoxide from either *trans*- or *cis*-oct-3-ene gave a mixture containing, as shown by infrared analysis, roughly equal parts of *trans*- and *cis*-olefins. House and Ro[24] recently reported similar results with some 2-bromo-ethers and 2-bromoalkyl acetates. They favoured, after discussion, the explanation that an organozinc compound (XVII) is formed first, and that this equilibrates (XVII $\rightleftharpoons$ XVIII) before (*trans*-)elimination of ZnBr and OR. However, it is hard to see why, if the molecules have no symmetry, forms (XVII) and (XVIII) should be formed in equal amounts; and even harder to devise for the interchange (XVII $\rightleftharpoons$ XVIII) a mechanism not involving separation of the ZnBr group. Once separation has occurred, reattachment of ZnBr to the carbanion is unlikely to be faster than attack by a proton from the medium

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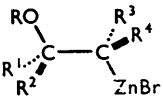
[21] Barton, Lewis, and McGhie, *J.*, 1957, 2907.

[22] Lemieux and Rudloff, *Canad. J. Chem.*, 1955, **33**, 1701.

[23] Church, Whitmore, and McGrew, *J. Amer. Chem. Soc.*, 1934, **56**, 176; cf. Obolentsev and Usof, *J. Gen. Chem. U.S.S.R.*, 1947, **17**, 899.

[24] House and Ro, *J. Amer. Chem. Soc.*, 1958, **80**, 182.

(ethanol or acetic acid). We offer the suggestion that these results and our own are explicable if the first step, as suggested by James, Reed, and Shoppee,[25] is removal of halogen by zinc to give a carbanion. This must be very short-lived to escape reaction with protons from the solvent, and hence elimination of OR may occur before much of the initial energy is dissipated by collisions. The excited state, we suggest, approaches a planar configuration in which the barrier to rotation about the C–C bond offered by the groups R^3, R^4 is lowered and the two states (XIX) and (XX), most favourable for elimination of OR, can equally well be reached. The two geometrical isomers of the olefin, (XXI and XXII), would then be formed in equal amounts.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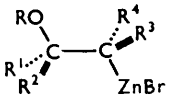
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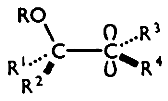
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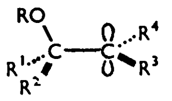
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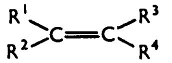

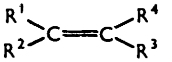
(XXII)

Development of Stereospecific Elimination.—The one-stage reduction of epoxides is a useful method for making olefins when the position of the double bond is important and geometrical isomerism cannot occur or does not matter, but we sought a stereospecific elimination which would preserve the stereoselectivity found in the formation of chlorohydrins. Experiments with oct-3-ene were therefore continued. When the epoxide of *trans*-oct-3-ene was converted into an iodohydrin which was then treated with sodium hydroxide, the recovered epoxide was identical in configuration with the starting material; this proved that addition of hydrogen iodide proceeded, as expected, with inversion, and that elimination was the unselective stage in the formation of olefin.

Various modifications of this stage were then tried: use of smaller amounts of sodium iodide; use of lithium bromide instead of sodium iodide; reduction of the iodohydrin by magnesium, amalgamated aluminium, cadmium, a solution of zinc in mercury, or amalgamated zinc powder. All these procedures gave some oct-3-ene, but this was a 50 : 50 mixture of *cis*- and *trans*-isomers in every experiment except the last-mentioned, which gave a mixture containing 60% of *trans*-oct-3-ene from the *trans*-epoxide. Reduction of the iodohydrin from the *trans*-epoxide by chromous chloride in acetic–hydrochloric acid was more promising, the olefin (47% yield) containing 75—80% of *trans*-oct-3-ene. Finally, when the iodohydrin was reduced by stannous chloride in acetic–hydrochloric acid, a stereospecific elimination was achieved: each olefin, obtained in 70% yield from each epoxide, had an infrared spectrum identical with that of the olefin from which the epoxide was made. The mixture of epoxides obtained from 3-chloro-octan-4-ol, when reduced *via* the iodohydrin by stannous chloride, gave as expected a mixture of oct-3-enes containing about 70% of the *trans*-isomer.

We now required a geometrically isomeric pair of trisubstituted ethylenes. The two 3-methylpent-2-enes prepared by dehydration of 3-methylpentan-3-ol can be separated from each other, and from 2-ethylbut-1-ene, by fractional distillation.[26] We preferred our own method for making the mixture of 3-methylpent-2-enes:

$$\text{3-Chlorobutan-2-one} \xrightarrow[88\%]{\text{EtMgBr}} \text{2-Chloro-3-methylpentan-3-ol} \xrightarrow[88\%]{\text{NaOH}}$$

$$\text{2:3-Epoxy-3-methylpentane} \xrightarrow[76\%]{\text{NaI–NaOAc–Zn–AcOH}} \text{3-Methylpent-2-ene}$$

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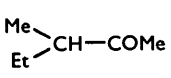
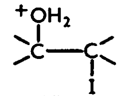
[25] James, Rees, and Shoppee, *J.*, 1955, 1370.

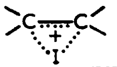
[26] Streiff, Zimmerman, Soule, Butt, Sedlak, Willingham, and Rossini, *J. Res. Nat. Bur. Stand.*, 1948, **41**, 323; Streiff, Soule, Kennedy, James, Sedlak, Willingham, and Rossini, *ibid.*, 1950, **45**, 173.

This product was separated by distillation into the lower-boiling (olefin A) and higher-boiling (olefin B) isomers. These, like the oct-3-enes, were present in about equal amounts. Each was converted into a 2 : 3-epoxy-3-methylpentane (epoxides A and B). It was now possible to assess the stereoselectivity of the reaction between ethylmagnesium bromide and 3-chlorobutan-2-one by infrared analysis of the epoxide obtained from the product. This proved to be a mixture of 80—85% of epoxide B with 15—20% of epoxide A. Further, when 2-chloro-3-methylpentan-3-ol was prepared instead from 2-chloropentan-3-one and methylmagnesium bromide, the epoxide from this chlorohydrin had the infrared spectrum of a mixture of 80—85% of epoxide A and 15—20% of epoxide B.

Epoxides A and B were each converted into iodohydrins; when these were reduced by stannous chloride in acetic–hydrochloric acid, the same mixture of 3-methylpent-2-enes was regrettably produced from both (70% of olefin B + 30% of olefin A). Olefins A and B were each converted into a similar mixture by stannous chloride in acetic–hydrochloric acid. This change did not occur without hydrochloric acid, but treatment of the iodohydrin with stannous chloride in acetic acid gave only a little impure olefin: the main product was 3-methylpentan-2-one (XXIII). Various other modifications were then tried without success. Eventually it was recognised that the reduction of an iodohydrin by stannous chloride–hydrochloric acid was probably a two-step process: the first step would be a concerted elimination of the protonated hydroxyl group (in XXIV) to form a bridged iodonium ion (XXV), from which stannous chloride abstracted iodine in the reducing step. The concerted elimination would certainly require the four centres concerned (O–C–C–I) to be coplanar, with oxygen and iodine *anti* to each other; in the second step the incipient double bond in (XXV) would simply be developed as the iodine atom was withdrawn. The net result is a *trans*-elimination of HOI, as observed in the oct-3-ene series. If this analysis is correct, hydrochloric acid might be supplanted by some reagent which can dehydrate alcohols without isomerising olefins. Phosphoryl chloride in pyridine is such a reagent.

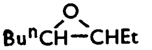

(XXIII)

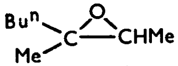

(XXIV)

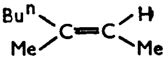

(XXV)

When the iodohydrin from epoxide B was treated with a mixture of phosphoryl chloride and anhydrous stannous chloride in pyridine, olefin B was obtained free from olefin A. Iodohydrin from epoxide A, similarly treated, gave olefin A free from olefin B.

An improvement in the yield of iodohydrin (to 97—100%) was made by treating the epoxide with sodium iodide and sodium acetate in a mixture of acetic and propionic acid at −20°. The reduction was improved in yield and convenience by dissolving stannous chloride in pyridine and adding first the iodohydrin and then a mixture of phosphoryl chloride and pyridine. When 3 : 4-epoxyoctane (XXVI), obtained from the chlorohydrin, was reduced *via* the iodohydrin to oct-3-ene by the new method, the olefin (87% overall yield from epoxide) had the same composition as that obtained by reduction in acetic–hydrochloric acid. Reduction of 2 : 3-epoxy-3-methylheptane (XXVII) by the new method gave a product having an infrared spectrum slightly different from the product of zinc reduction obtained earlier. The new specimen is regarded as being very largely 3-methyl-*trans*-hept-2-ene (XXVIII).

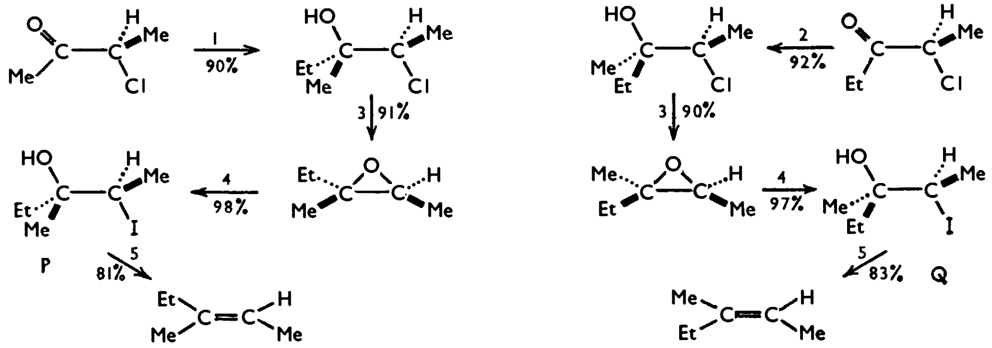

(XXVI)


(XXVII)


(XXVIII)

Reduction of a chlorohydrin (2-chloro-3-methylheptan-3-ol) or a bromohydrin (2-bromo-3-methylpentan-3-ol) by the stannous chloride–phosphoryl chloride–pyridine reagent gave no olefin; nor could phosphoryl chloride be replaced by thionyl chloride, acetyl chloride, or stannic chloride in the reduction of iodohydrins. A by-product of the reduction, especially if the reaction mixture is left for some time, is a small amount of yellow phosphorus; this is easily removed from the product by treatment with water and iodine.

Geometry of the Isomeric 3-Methylpent-2-enes.—The stereoselective synthesis of the 3-methylpent-2-enes proceeds, according to the views developed above, in accordance with the annexed scheme. Here the higher-boiling " olefin B " separated by fractionation of the two hexenes is 3-methyl-*trans*-pent-2-ene and the lower-boiling " olefin A " is 3-methyl-*cis*-pent-2-ene. This assignment would indicate the same stereochemical preference during addition to the carbonyl group of the chloro-ketone as was proved to exist in the synthesis of oct-3-ene. However, in many papers and works of reference, including the recent 3rd Supplement of Beilstein's " Handbuch," it is stated (occasionally with a query) that the lower-boiling isomer is 3-methyl-*trans*-pent-2-ene. The source of this tradition seems to lie in a statement by Goldwasser and Taylor[27] that van Risseghem[28] had assigned the *trans*-configuration to the lower-boiling isomer. No such assignment was, in truth, made in the paper cited; and in a more recent communication[29] van Risseghem seemed to favour the opposite conclusion (although the pictorial formula given for the *trans*-isomer is that of 3-methyl-*cis*-pent-2-ene, and conversely). This opinion was based on debrominations of 2 : 3-dibromo-3-methylpentanes obtained by differing methods; however, it was finally stated that no experimental fact permitted a certain assignment of configuration to either isomeride. We were in need of such an assignment, and therefore set out to prove the configurations by an unequivocal method. Fortunately we had recently made, for a different purpose, 5-hydroxy-3-methyl-*trans*-pent-3-enoic acid (XXIX) and 3-methylpent-3-eno-5-lactone[30] (XXX). These were reduced by lithium aluminium hydride to 3-methyl-*trans*-pent-2-ene-1 : 5-diol (XXXI; X = OH) and 3-methyl-*cis*-pent-2-ene-1 : 5-diol (XXXII; X = OH) respectively; the *cis*-diol was also prepared by reduction of the isomeric lactone (XXXIII). Each diol was converted into the dibromide (XXXI and XXXII; X = Br) by the Rydon method with triphenyl phosphite benzylobromide, and the dibromides were reduced by lithium aluminium hydride in dibutyl ether to the 3-methylpent-2-enes (XXXI and XXXII; X = H).



80–85% of 3-Methyl-*trans*-pent-2-ene, b. p. 70—71°

80—85% of 3-Methyl-*cis*-pent-2-ene, b. p. 68—69°

(Materials P and Q may contain isomers with interchanged positions of OH and I.)
Reagents: 1, EtMgBr. 2, MeMgBr. 3, NaOH. 4, NaI–NaOAc–AcOH–Et·CO_2H. 5, $SnCl_2$–$POCl_3$–C_5H_5N.
Percentages on the arrows are yields.

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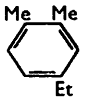
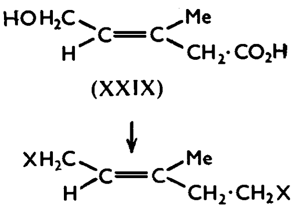
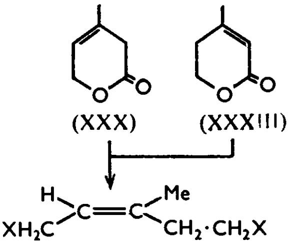
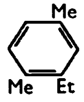
[27] Goldwasser and Taylor, *J. Amer. Chem. Soc.*, 1939, **61**, 1751.
[28] van Risseghem, *Bull. Soc. chim. belges*, 1938, **47**, 47.
[29] *Idem, Bull. Soc. chim. France*, 1952, 177.
[30] Cornforth, Cornforth, Youhotsky, Gore, and Popják, *Biochem. J.*, 1958, **69**, 146.

The methylpentene from the lactone (XXX) had an infrared spectrum almost identical with that of the lower-boiling olefin A; the infrared spectrum of the methylpentene from the hydroxy-acid (XXIX) was almost identical with that of the higher-boiling olefin B.


(XXXIV)

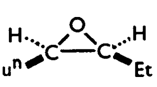

(XXIX) (XXXI)

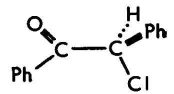

(XXX) (XXXIII) (XXXII)

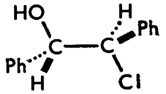

(XXXV)

Harrison and Lythgoe[31] showed that replacement of a primary allylic hydroxyl group by bromine could be effected, without disturbance of the double bond, by triphenyl phosphite benzylobromide; and three reductions of allylic halides by lithium aluminium hydride without isomerisation are also known,[32,33] though an exception with a strongly hindered halide has recently been noted.[34] In any case a quantitative one-step *inversion* of geometrical isomerism in both *cis*- and *trans*-isomers, which would have had to take place here to confuse the two series, has no experimental or theoretical support. It follows that the lower-boiling olefin A is 3-methyl-*cis*-pent-2-ene (XXXII; X = H), and the higher-boiling olefin B is 3-methyl-*trans*-pent-2-ene (XXXI; X = H), in accord with prediction. Van Arkel's rule[35] incidentally leads to the same assignment: 1-ethyl-3 : 4-dimethylbenzene (XXXIV) is less volatile than 2-ethyl-1 : 4-dimethylbenzene[36] (XXXV). The infrared spectra of the two methylpentenes prepared by our method and separated by fractional distillation are in substantially complete agreement with the A.P.I.[37] spectra, provided that the A.P.I. assignments of configuration are reversed.

Reduction of an Aliphatic α-Chloro-ketone by Sodium Borohydride.—Because stereoselective addition to the carbonyl group of an α-chloro-ketone should be possible with other than organometallic reagents, we prepared 3-chloro-octan-4-one by oxidation of the alcohol and reduced it with sodium borohydride in aqueous ethanol. The product was converted by alkali into a 3 : 4-epoxyoctane which proved on infrared analysis to be a mixture of 80—85% of *cis*-epoxide (XXXVI) and 15—20% of *trans*. Reduction by the stereospecific procedure duly gave a mixture of 80—85% of *cis*-oct-3-ene and 15—20% of *trans*-oct-3-ene; the borohydride reduction had therefore been stereoselective in the expected sense.


(XXXVI)


(XXXVII)


(XXXVIII)

Reduction of the chloro-ketone (XXXVII) by lithium aluminium hydride in ether has been stated[38] to give exclusively the *erythro*-chlorohydrin (XXXVIII); but another

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[31] Harrison and Lythgoe, *J.*, 1958, 843.
[32] Hatch and Perry, *J. Amer. Chem. Soc.*, 1949, **71**, 3262.
[33] Trevoy and Brown, *ibid.*, p. 1675.
[34] Corey, Chow, and Scherrer, *ibid.*, 1957, **79**, 5773.
[35] van Arkel, *Rec. Trav. chim.*, 1933, **52**, 1013.
[36] Birch, Dean, Fidler, and Lowry, *J. Amer. Chem. Soc.*, 1949, **71**, 1362.
[37] A.P.I. Research Project 44, " Catalog of Infrared Spectral Data," Nos. 720, 1061.
[38] Lutz, Wayland, and France, *J. Amer. Chem. Soc.*, 1950, **72**, 5511.

paper[39] published about the same time reported equal amounts of the *erythro*- and the *threo*-form. The *threo*-form would be expected to predominate by analogy with the reduction of 3-chloro-octan-4-one. Whether this discrepancy is caused by the presence of aromatic rings or by the use of different reducing agents is uncertain. However, it may be significant that 2-chloro*cyclo*hexanone, which with methylmagnesium bromide[15,16] gives almost entirely the chlorohydrin (VII) and with *tert.*-butylmagnesium chloride is reduced to *cis*-2-chloro*cyclo*hexanol,[17] gives a mixture of *cis*- and *trans*-2-chloro*cyclo*hexanols on reduction by lithium aluminium hydride.[39]

The stereochemistry of addition of some other reagents to α-chloro-ketones is at present being studied.

EXPERIMENTAL

Details of some exploratory experiments mentioned in the general section are not given here, but may be found in the Ph.D. thesis of K. K. M. (University of London, 1958).

General Procedure for Reaction of α-Halogenocarbonyl Compounds with Organometallic Reagents.—A 1·5—2M-ethereal solution of lithium alkyl or the Grignard reagent was prepared under nitrogen, cooled to −70°, and stirred during addition (10 min.) of the α-halogenocarbonyl compound dissolved in a little ether. After 10—15 min. a slight excess of acetic acid in ether was added; the mixture was brought to room temperature and diluted with water. The aqueous layer was extracted once with ether and the combined ethereal solutions were washed with water, aqueous sodium hydrogen carbonate, and water. From the dried ($MgSO_4$) solution the chlorohydrin was isolated by distillation at low pressure. The chlorohydrins were colourless liquids which usually darkened after a time.

3-*Chloro-octan*-4-*ol*.—(*a*) *n*-Butyl-lithium, prepared from lithium (1·8 g.), butyl bromide (17·7 g.), and ether (100 ml.), reacted with 2-chlorobutanal[40] (10 g.) to give 3-*chloro-octan*-4-*ol* (10 g., 64·5%), b. p. 94—96°/20 mm. (Found: C, 58·1; H, 10·3; Cl, 21·5. $C_8H_{17}OCl$ requires C, 58·3; H, 10·4; Cl, 21·5%).

(*b*) *n*-Butylmagnesium bromide, from magnesium (10 g.) and butyl bromide (54·8 g.) in ether (200 ml.), with 2-chlorobutanal (35·5 g.) gave the chlorohydrin (37 g., 67·5%), b. p. 96—99°/25 mm.

2-*Chloro*-3-*methylheptan*-3-*ol*.—(*a*) 3-Chlorobutan-2-one (21·3 g.) with *n*-butyl-lithium (from 3·6 g. of lithium and 34·2 g. of *n*-butyl bromide) gave 2-*chloro*-3-*methylheptan*-3-*ol* (X) (26 g., 79%), b. p. 81—82°/15 mm. (Found: C, 58·5; H, 10·6; Cl, 21·0. $C_8H_{17}OCl$ requires C, 58·3; H, 10·4; Cl, 21·5%).

(*b*) *n*-Butylmagnesium bromide, from magnesium (3·0 g.) and butyl bromide (17·1 g.), with 3-chlorobutan-2-one (10·65 g.) gave the chlorohydrin (10·6 g., 65%), b. p. 81—86°/20 mm., and an appreciable fraction, probably containing 3-chlorobutan-2-ol, b. p. 40—70°/20 mm.

3-*Chloromethylheptan*-3-*ol*.—(*a*) *n*-Butylmagnesium bromide, from magnesium (2·45 g.) and butyl bromide (13·7 g.), with 1-chlorobutan-2-one (8·2 g.) gave 3-*chloromethylheptan*-3-*ol* (XIII) (9·7 g., 75%), b. p. 81—88°/25 mm. Redistilled, it boiled at 85—86°/25 mm. (Found: C, 58·3; H, 10·3; Cl, 21·2. $C_8H_{17}OCl$ requires C, 58·3; H, 10·4; Cl, 21·5%).

(*b*) 1-Chlorobutan-2-one (21·3 g.) reacted with *n*-butyl-lithium to give after three distillations, a product (8 g.; b. p. 84—85°/20 mm.) presumably containing the chlorohydrin but impure (Found: C, 59·8; H, 10·3%).

1-*Chloro*-2-*methylhexan*-2-*ol*.—(*a*) *n*-Butylmagnesium bromide, from magnesium (3·0 g.) and butyl bromide (17·1 g.), with chloroacetone (9·3 g.) gave 1-*chloro*-2-*methylhexan*-2-*ol* (10·0 g., 67%), b. p. 74—78°/20 mm. (Found: C, 55·9; H, 9·9. $C_7H_{15}OCl$ requires C, 55·8; H, 10·0%).

(*b*) The reaction between chloroacetone (7 g.) and *n*-butyl-lithium (from 1·5 g. of lithium and 13·7 g. of butyl bromide) was carried out in light petroleum (b. p. 60—80°) instead of ether. The product (3·5 g.) had b. p. 76—82°/20 mm.

2-*Chloro*-2-*methylheptan*-3-*ol*.—(*a*) *n*-Butyl-lithium (from 1·2 g. of lithium and 12 g. of butyl bromide) with 2-chloro-2-methylpropanal (6·5 g.) gave 2-*chloro*-2-*methylheptan*-2-*ol* (6·3 g., 63%), b. p. 81—86°/20 mm. Redistilled, it had b. p. 82—83°/20 mm. (Found: C, 58·0; H, 10·6; Cl, 21·5. $C_8H_{17}OCl$ requires C, 58·3; H, 10·4; Cl, 21·5%).

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[39] Felkin, *Compt. rend.*, 1950, **231**, 1316.

[40] Stevens, Farkas, and Gillis, *J. Amer. Chem. Soc.*, 1954, **76**, 2696.

(*b*) The chloro-aldehyde (9·5 g.) with *n*-butylmagnesium bromide (from 3·0 g. of magnesium and 17·1 g. of butyl bromide) gave the chlorohydrin (3·6 g., 24%), b. p. 81—85°/20 mm., and a lower fraction (4·0 g.; b. p. 40—70°/20 mm.).

2-*Chloro*-2 : 3-*dimethylheptan*-3-*ol*.—(*a*) *n*-Butyl-lithium (from 1·5 g. of lithium and 13·7 g. of butyl bromide), treated as usual with 3-chloro-3-methylbutan-2-one (10 g.), gave 2-*chloro*-2 : 3-*dimethylheptan*-3-*ol* (10 g., 68%), b. p. 89—94°/25 mm. (91—93°/25 mm. after redistillation) (Found: C, 60·8; H, 11·1. $C_9H_{19}OCl$ requires C, 60·6; H, 10·7%).

(*b*) From the chloro-ketone (8 g.) and *n*-butylmagnesium bromide (from 2·0 g. of magnesium and 11·5 g. of butyl bromide) the major product had b. p. 40—45°/25 mm. and the yield of the chlorohydrin was 8% (1 g.; b. p. 90—98°/25 mm.).

2-*Chloro*-3-*methylpentan*-3-*ol*.—(a) " *Chlorohydrin* α." Methylmagnesium bromide, prepared from magnesium (16·5 g.), methyl bromide (45 ml.), and ether (250 ml.), was treated as usual with 2-chloropentan-3-one (60·25 g.). The product, 2-*chloro*-3-*methylpentan*-3-*ol* α (62·7 g., 92%), was collected at 52—57°/18 mm. (Found: C, 52·5; H, 9·5; Cl, 26·4. $C_6H_{13}OCl$ requires C, 52·7; H, 9·6; Cl, 26·0%).

(b) " *Chlorohydrin* β." Ethylmagnesium bromide, from magnesium (24·3 g.), ethyl bromide (120 g.), and ether (400 ml.), reacted with 3-chlorobutan-2-one (79·9 g.; thrice fractionated to free it from 1-chlorobutan-2-one) to give 2-chloro-3-methylpentan-3-ol (91·8 g., 90%), b. p. 52—56°/16 mm. (Found: C, 52·5; H, 9·6; Cl, 25·9%). Fourneau and Tiffeneau[41] reported b. p. 160—165°.

Preparation of Epoxides.—The chlorohydrin was stirred with a slight excess of N-sodium hydroxide for 1—2 hr. and the product was extracted by ether and distilled.

From 3-chloro-octan-4-ol (7 g.) and N-sodium hydroxide (60 ml.; 1½ hr.) 3 : 4-*epoxyoctane* (4·5 g.) was obtained, having b. p. 47·5—49°/20 mm. (Found: C, 74·9; H, 12·4. $C_8H_{16}O$ requires C, 74·9; H, 12·6%).

2-Chloro-3-methylheptan-3-ol (24·6 g.) and N-sodium hydroxide (190 ml.; 2 hr.) gave 2 : 3-*epoxy*-3-*methylheptane* (17 g.; 88%), b. p. 42—44°/20 mm. (Found: C, 75·1; H, 12·4. $C_8H_{16}O$ requires C, 74·9; H, 12·6%).

1-Chloro-2-ethylhexan-2-ol (7·0 g.) and N-sodium hydroxide (60 ml.; 1½ hr.) gave 1 : 2-*epoxy*-2-*ethylhexane* (1-n-*butyl*-1-*ethyloxiran*) (4·5 g.), b. p. 46°/20 mm., 150°/760 mm. (Found: C, 74·9; H, 12·4. $C_8H_{16}O$ requires C, 74·9; H, 12·6%).

1-Chloro-2-methylhexan-2-ol (7·6 g.) and N-sodium hydroxide (60 ml.; 1 hr.) gave 1 : 2-*epoxy*-2-*methylhexane* (4·0 g.), b. p. 73°/110 mm. (Found: C, 73·2; H, 12·2. $C_7H_{14}O$ requires C, 73·6; H, 12·4%).

2-Chloro-2-methylheptan-3-ol (6·3 g.) and N-sodium hydroxide (50 ml.; 1½ hr.) gave 2 : 3-*epoxy*-2-*methylheptane* (3·9 g.), b. p. 45—46°/25 mm. (Found: C, 74·6; H, 13·1. $C_8H_{16}O$ requires C, 74·9; H, 12·6%).

2-Chloro-2 : 3-dimethylheptan-3-ol (9 g.) and N-sodium hydroxide (70 ml.; 2 hr.) gave 2 : 3-*epoxy*-2 : 3-*dimethylheptane* (5·9 g.), b. p. 57—58°/25 mm. (Found: C, 76·1; H, 12·8. $C_9H_{18}O$ requires C, 76·0; H, 12·8%).

2 : 3-*Epoxy*-3-*methylpentane*.—(a) " *Epoxide* α." 2-Chloro-3-methylpentan-3-ol (" chlorohydrin α; " 62·7 g.) was stirred vigorously with water (25 ml.) whilst 2·5N-sodium hydroxide (225 ml.) was added during ½ hr. After another 1½ hr. 2 : 3-epoxy-3-methylpentane α (41·4 g., 90%) was isolated by extraction with ether and distillation of the dried ($CaCl_2$) extract through a column; it had b. p. 98—103°/748 mm. A redistilled sample had b. p. 100—101° (Found: C, 71·7; H, 12·2. Calc. for $C_6H_{12}O$: C, 72·0; H, 12·1%).

(b) " *Epoxide* β." Prepared as above from " chlorohydrin β " (91·8 g.), 2 : 3-epoxy-3-methylpentane β (61·2 g., 91%) had b. p. 99—101°/750 mm., and 100—101° on redistillation (Found: C, 71·7; H, 12·3%).

cis-3 : 4-*Epoxyoctane*.—To 0·82M-ethereal monoperphthalic acid (75 ml.), *cis*-oct-3-ene (5·6 g.) was added at 5° and the mixture was kept at 0° overnight. Phthalic acid was removed by filtration and extraction with sodium hydroxide, and from the dried ($MgSO_4$) solution cis-3 : 4-*epoxyoctane* (4·0 g.), b. p. 47—49°/20 mm., was recovered (Found: C, 74·7; H, 12·6. $C_8H_{16}O$ requires C, 74·9; H, 12·6%).

trans-3 : 4-*Epoxyoctane*.—From *trans*-oct-3-ene (11·2 g.) and 1·15M-monoperphthalic acid in ether (100 ml.), trans-3 : 4-*epoxyoctane* (9·6 g.), b. p. 47—49°/20 mm., was obtained (Found: C, 74·9; H, 12·5%).

[41] Fourneau and Tiffeneau, *Compt. rend.*, 1907, **145**, 439.

trans-2 : 3-*Epoxy*-3-*methylpentane*.—3-Methyl-*trans*-pent-2-ene (5 g.) with ethereal 0·95M-monoperphthalic acid (80 ml.) gave the epoxide (4·2 g.), b. p. 97—99°. van Risseghem [29] gave b. p. 101·25—101·4° for a product which should be the *trans*-isomer from the method of preparation.

cis-2 : 3-*Epoxy*-3-*methylpentane* (4·35 g.) was prepared similarly from 3-methyl-*cis*-pent-2-ene (5 g.) and had b. p. 98—99° (Found: C, 71·6; H, 12·1. $C_6H_{12}O$ requires C, 72·0; H, 12·1%).

One-stage Preparation of Olefins from Epoxides.—This procedure was designed to permit isolation of the volatile olefins without use of solvents for extraction, and is illustrated by the preparation of 3-methylhept-2-ene. Sodium iodide (21 g.) and sodium acetate (7 g.; anhydrous) were dissolved in acetic acid (42 ml.) and water (3 ml.). To the ice-cooled stirred mixture zinc powder (21 g.) was added, and 2 : 3-epoxy-3-methylheptane (10·5 g.) was added dropwise during 10 min. After ¾—1 hr. the zinc residues were removed and washed with acetic acid. The filtrate after dilution with water was distilled until no more oil came over. The cooled distillate was neutralised by solid potassium hydroxide, and the aqueous layer was removed. The organic layer was dried (KOH) and distilled, to give 3-*methylhept*-2-*ene* (7·53 g., 82%), b. p. 121—123°. Redistilled through a column it had b. p. 121·5°, n_D^{25} 1·4170 (Found: C, 85·2; H, 14·0. C_8H_{16} requires C, 85·6; H, 14·4%). This product is presumably a mixture of about equal parts of *cis*- and *trans*-isomers.

Oxidation of 3-*Methylhept*-2-*ene*.—To the olefin (32 mg.), mixed with water (50 ml.) and potassium carbonate (25 mg.), was added the periodate–permanganate reagent [22] (25 ml.). The mixture was shaken until the oil disappeared (10 min.) and set aside for 18 hr. M-Sodium arsenite (15 ml.) was added and the volatile products were distilled into an ice-cooled receiver. The distillate (20 ml.) was treated with excess of 2 : 4-dinitrophenylhydrazine sulphate; after 1 hr. the solid product was collected (52 mg.; m. p. 98—102°). Recrystallised from dilute ethanol, it had m. p. 104—105° undepressed on admixture with hexan-2-one 2 : 4-dinitrophenylhydrazone, m. p. 106°. In another experiment the distillate was treated with hydroxylamine hydrochloride and titrated potentiometrically to pH 4·1. The acid liberated by oxime formation corresponded to an 84% yield of ketone from the olefin.

2-*Ethylhex*-1-*ene*.—Prepared as above from 1 : 2-epoxy-2-ethylhexane (2·5 g.), 2-ethylhex-1-ene (1·82 g., 80%) had b. p. 117—118° (b. p. 117·5°, n_D^{22} 1·4154, on redistillation) (Found: C, 85·4; H, 14·5. Calc. for C_8H_{16}: C, 85·6; H, 14·4%).

Oxidation of 2-*Ethylhex*-1-*ene*.—The olefin (32 mg.) was oxidised as described for 3-methylhept-2-ene. Formaldehyde was detected in the distillate by chromotropic acid, and was oxidised by treatment with 30% hydrogen peroxide (0·1 ml.) and 0·05N-sodium hydroxide (4 ml.). Back-titration showed consumption of 1·25 ml. of 0·05N-alkali. Excess of 2 : 4-dinitrophenylhydrazine sulphate was added and the solid product (35 mg.) was collected and recrystallised from aqueous ethanol; it had m. p. 78—82° and a mixture with heptan-3-one 2 : 4-dinitrophenylhydrazone (m. p. 79—81°) had m. p. 78—80°.

2-*Methylhex*-1-*ene*.—1 : 2-Epoxy-2-methylhexane (3 g.) was reduced as usual to give 2-methylhex-1-ene (1·8 g.), b. p. 92—93° after redistillation (Found: C, 85·1; H, 14·8. Calc. for C_7H_{14}: C, 85·6; H, 14·4%).

2-*Methylhept*-2-*ene*.—2 : 3-Epoxy-2-methylheptane (1·5 g.) similarly gave 2-methylhept-2-ene (0·9 g.; b. p. 122—125°), b. p. 122—123°, n_D^{22} 1·4172, on redistillation (Found: C, 84·8; H, 14·6. Calc. for C_8H_{16}: C, 85·6; H, 14·4%).

2 : 3-*Dimethylhept*-2-*ene*.—2 : 3-Epoxy-2 : 3-dimethylheptane (2 g.) gave 2 : 3-dimethylhept-2-ene (1·2 g.; b. p. 145—148°), b. p. on redistillation 145—146°, n_D^{24} 1·4300 (Found: C, 85·1; H, 14·7. Calc. for C_9H_{18}: C, 85·6; H, 14·4%). The physical properties agree with those reported by Levina *et al.*[42] but not with those given by Whitmore and Evers.[43] The b. p. observed by the American authors is lower than would be expected from comparison with analogous octenes.

Oct-3-*ene*.—3 : 4-Epoxyoctane (1·5 g.) was reduced in the usual manner, complete reduction at 5° needing about 2 hr. Oct-3-ene (0·9 g.; b. p. 122—124°) when redistilled had b. p. 122°, n_D^{22} 1·4122 (Found: C, 85·4; H, 14·1. Calc. for C_8H_{16}: C, 85·6; H, 14·4%). The infrared spectrum was that of a 1 : 1 mixture of *cis*- and *trans*-oct-3-ene.

3-*Methylpent*-2-*ene* (*Mixture of Geometrical Isomers*).—2 : 3-Epoxy-3-methylpentane (epoxide

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[42] Levina, Fainsilberg, and Itenberg, *Doklady Akad. Nauk S.S.S.R.*, 1950, **75**, 39.

[43] Whitmore and Evers, *J. Amer. Chem. Soc.*, 1933, **55**, 814.

α; 120 g.) was added during ¾ hr. to an ice-cooled, stirred mixture of sodium iodide (130 g.), sodium acetate (30 g.), acetic acid (650 ml.), and zinc powder (200 g.). Stirring was continued for 2 hr. and the mixture was worked up as usual to give 3-methylpent-2-ene (76 g.), b. p. 66—70°. Redistillation followed by fractionation in a Podbielniak still separated it into approximately equal amounts of 3-methyl-*cis*- and -*trans*-pent-2-ene which were used to prepare the epoxides. The infrared spectrum of the total product was that of a 1 : 1 mixture of *cis*- and *trans*-isomers.

Stereospecific Reduction of 3 : 4-*Epoxyoctanes by Stannous Chloride–Hydrochloric Acid.*—*trans*-3 : 4-Epoxyoctane (1·5 g.) was added to a solution of sodium iodide (3 g.) in acetic acid (6 ml.) and water (0·5 ml.) at 5°. After 1 hr. the mixture was poured into water, and the iodohydrin was extracted with ether which was then washed with sodium hydrogen carbonate until neutral (a trace of sodium hydrogen sulphite removed free iodine), then with water, dried ($MgSO_4$), and evaporated at low pressure, leaving the nearly colourless iodohydrin (2·9 g.). This iodohydrin, when shaken with N-sodium hydroxide, reverted to an epoxide (1·15 g.; b. p. 49—50°/20 mm.) having an infrared spectrum identical with that of starting material.

The iodohydrin (from 1·28 g. of epoxide) was added to a solution of stannous chloride dihydrate (5 g.) in acetic acid (20 ml.) and hydrochloric acid (8 ml.; *d* 1·18). After 48 hr. the mixture was diluted with water and distilled. From the distillate the olefin (0·8 g.; b. p. 122—124°) was isolated as usual. The infrared spectrum was identical with that of *trans*-oct-3-ene. *cis*-3 : 4-Epoxyoctane (1·0 g.), similarly treated, gave a product (0·6 g.; b. p. 122—126°) having an infrared spectrum almost identical with that of *cis*-oct-3-ene (small C=O band).

The mixture of 3 : 4-epoxyoctanes from 3-chloro-octan-4-ol was reduced in the same way and gave a product having the infrared spectrum of a 7 : 3 mixture of *trans*- and *cis*-oct-3-ene.

Reduction of 2 : 3-*Epoxy*-3-*methylpentanes by Stannous Chloride–Hydrochloric Acid.*—*trans*-2 : 3-Epoxy-3-methylpentane (1 g.) was added to a solution of sodium iodide (2 g.) in acetic acid (6 ml.). After ½ hr. the mixture was added to stannous chloride dihydrate (6 g.) in hydrochloric acid (5 ml.; *d* 1·18) and acetic acid (25 ml.). The yield of olefin obtained after 24 hr. was 0·5 g. (b. p. 69—74°), and there was a higher-boiling fraction (up to 118°). The infrared spectrum of the olefin was that of a 7 : 3 mixture of 3-methyl-*trans*- and -*cis*-pent-2-ene. Reduction of *cis*-2 : 3-epoxy-3-methylpentane in the same way gave a similar yield of an olefin having the same composition. When the concentration of hydrochloric acid was lowered, less olefin and more higher-boiling ketone were formed. More ketone was also found with higher concentrations of hydrochloric acid. The ketonic material from several reactions was pooled; it boiled at 115—118°, and gave a 2 : 4-dinitrophenylhydrazone, m. p. 70°, and a semicarbazone, m. p. 95—96° (the corresponding figures for 3-methylpentan-2-one are 118°, 71·5°, 95°).

Either 3-methyl-*trans*-pent-2-ene or 3-methyl-*cis*-pent-2-ene was rapidly isomerised by stannous chloride–acetic acid–hydrochloric acid to a mixture (7 : 3-*trans* : *cis*) of both isomers. Stannous chloride in acetic acid alone caused very little change.

Stereospecific Reduction of Iodohydrins from cis- *and* trans-2 : 3-*Epoxy*-3-*methylpentane.*—*trans*-2 : 3-Epoxy-3-methylpentane (0·95 g.) was added to a cooled (—20°) solution of sodium iodide (2·5 g.) and sodium acetate (0·25 g.) in acetic acid (5 ml.) and propionic acid (10 ml.). After ½ hr. the mixture was warmed to room temperature and poured into ether and aqueous sodium hydrogen carbonate. The ether was washed with a little sodium hydrogen sulphite and with water, dried ($MgSO_4$), and evaporated at low pressure. The iodohydrin (1·86 g.) was added to a cooled (0°) solution of anhydrous stannous chloride (4 g.) in pyridine (15 ml.). Phosphoryl chloride (1 ml.) in pyridine (3 ml.) was then added with cooling. The mixture solidified after a few minutes. Next day water was added and the olefin was distilled. The distillate was neutralised (Methyl Orange) with sulphuric acid. The upper layer was then shaken with water and successive small quantities of solid iodine until persistence of colour showed that no phosphorus remained; it was then decolorised by sodium thiosulphate, dried (KOH), and distilled, to give 3-methyl-*trans*-pent-2-ene (0·5 g.), b. p. 70—72°. The infrared spectrum was identical with that of the pure *trans*-isomer separated by fractional distillation. *cis*-2 : 3-Epoxy-3-methylpentane (1·52 g.) was treated similarly, except that sodium iodide in acetic acid was used to prepare the iodohydrin. The product, 3-methyl-*cis*-pent-2-ene (0·66 g.), had b. p. 68—71° and its infrared spectrum was identical with that of the pure *cis*-isomer.

Stereospecific Reduction of Iodohydrin from 3 : 4-*Epoxyoctane.*—3 : 4-Epoxyoctane (1·5 g.; prepared from 3-chloro-octan-4-ol) was converted into the iodohydrin by treatment with sodium iodide in acetic acid at 0°. The iodohydrin (3 g.) was added to an ice-cooled solution of anhydrous stannous chloride (4 g.) in pyridine (18 ml.). Phosphoryl chloride (1·2 ml.) in pyridine (4 ml.) was added slowly. Next day the oct-3-ene (1·15 g., 87%) was isolated as above; it had b. p. 122—124°. The infrared spectrum was identified with that of the product obtained by stannous chloride–hydrochloric acid.

Stereospecific Reduction of the Iodohydrin from 2 : 3-Epoxy-3-methylheptane.—The epoxide (1·5 g.) was added to a solution of sodium iodide (4 g.) and sodium acetate (0·5 g.) in acetic acid (8 ml.) and propionic acid (16 ml.) at −25°. After 3 hr. the mixture was poured into ether and aqueous sodium hydrogen carbonate, and the iodohydrin (2·9 g.) was isolated as usual. This was added to a cooled solution of anhydrous stannous chloride (3·5 g.) in pyridine (12 ml.) and treated with phosphoryl chloride (1·2 ml.) in pyridine (4 ml.) with ice-cooling. After 1 hr. water was added and the olefin, after removal of pyridine and phosphorus as before, was dried (KOH) and distilled (0·81 g.; b. p. 123—125°). Redistilled, the 3-methylhept-2-ene had b. p. 124—124·5°, n_D^{25} 1·4177. The infrared spectrum differed in small details from that of the previous specimen.

Stereospecific Reduction of the Iodohydrin from Epoxides α and β.—2 : 3-Epoxy-3-methylpentane α (22 g.) was added to a mixture of sodium iodide (45 g.), sodium acetate (4 g.), acetic acid (40 ml.), and propionic acid (100 ml.) at −30°. After ½ hr. at −30° to −20° the mixture was allowed to warm to 0° and after another ½ hr. it was poured into a mixture of ether and aqueous sodium hydrogen carbonate. The ether was washed with a little sodium hydrogen sulphite solution and with water, dried ($MgSO_4$), and evaporated at low pressure, leaving nearly colourless iodohydrin (49 g., 97%). An ice-cooled solution of anhydrous stannous chloride (70 g.) in pyridine (250 ml.) was added, then, cautiously during 5 min., phosphoryl chloride (18 ml.) in pyridine (50 ml.). The temperature was kept down by occasional cooling until the mixture solidified (10—15 min.). After 2 hr. water (300 ml.) was added and the mixture was worked up as above to give 3-methylpent-2-ene (15 g., 83% on iodohydrin), b. p. 66—70°. Redistilled through a short column it had b. p. 68—69° and the infrared spectrum was that of a mixture of 80—85% of 3-methyl-*cis*-pent-2-ene and 15—20% of 3-methyl-*trans*-pent-2-ene.

2 : 3-Epoxy-3-methylpentane β (40 g.) was treated similarly, to give 3-methylpent-2-ene (25·6 g.), b. p. 69—71°. On redistillation over sodium the b. p. was 69—70°/750 mm., and the infrared spectrum of the distillate was that of a mixture of 80—85% of 3-methyl-*trans*-pent-2-ene and 15—20% of 3-methyl-*cis*-pent-2-ene. Distillation of the two specimens of hydrocarbon in a Podbielniak still provided pure speciments of the *cis*- and *trans*-olefin and confirmed the proportions deduced from the infrared spectra.

*3-Methyl-*cis*-pent-3-eno-5-lactone and 5-Hydroxy-3-methyl-*trans*-pent-3-enoic Acid.*—The preparation of these substances on a small scale has already been described.[30] Methyl vinyl ketone (43 g.) and methyl bromoacetate (85 g.) were dissolved in dry benzene (212 ml.) and 60 ml. of this solution added to activated zinc wool (45 g.) and mercuric chloride (0·4 g.) in benzene (212 ml.). The mixture was refluxed and stirred (bath 85—90°) until vigorous reaction set in (10 min.), then the remainder of the benzene solution was added at a rate which maintained vigorous refluxing (bath at 85°; 30 min.). The mixture was stirred and refluxed for 1 hr. longer, cooled, decomposed by acetic acid (41 ml.) in water (350 ml.), and worked up in the normal manner to give methyl 3-hydroxy-3-methylpent-4-enoate (47·7 g., 60% on methyl bromoacetate), b. p. 66—68°/13·5 mm. This ester (168·8 g.) was converted in two portions as previously described [30] into methyl 5-bromo-3-methylpent-3-enoate; each batch of crude bromide was shaken for 2½ days in dry acetone (2 l.) with anhydrous potassium acetate (330 g.). After filtration and evaporation the combined products were distilled, to give methyl 3-methylpenta-2 : 4-dienoate (53·9 g.) and methyl 5-acetoxy-3-methylpent-3-enoate (79·9 g.). The acetoxy-ester (75 g.) was dissolved in 0·1N-sodium hydroxide (9 l.); next day the neutralised (Phenol Red) solution was evaporated at low pressure, acidified, and extracted with ether. The product on distillation gave crude 3-methyl-*cis*-pent-3-eno-5-lactone (13·9 g.) and 5-hydroxy-3-methylpent-3-enoic acid (10·4 g.). The lactone was purified by washing it in ether with aqueous sodium hydrogen carbonate and redistilling it (b. p. 112°/14 mm.; 8·0 g.). The *trans*-hydroxy-acid was recrystallised from dry ether at −70° to give 8·75 g. of material having m. p. 48—52°. A further quantity (6·8 g.) of the *trans*-hydroxy-acid was obtained by hydrolysing the residue from distillation, which presumably contained polyester. *Methyl 5-hydroxy-3-methyl-*trans*-pent-3-enoate*, prepared by means of diazomethane, had b. p. 72—73°/0·2 mm. (Found: C, 58·5; H, 8·4. $C_7H_{12}O_3$ requires C, 58·3; H, 8·3%).

3-*Methyl*-cis-*pent*-2-*ene*-1 : 5-*diol*.—Lithium aluminium hydride (2·7 g.) in ether (100 ml.) was stirred overnight and cooled to −15°. 3-Methyl-*cis*-pent-3-eno-5-lactone (8·0 g.) in ether (50 ml.) was added during ½ hr. After a further 2·5 hr. ethyl acetate (10 ml.) in ether (20 ml.) was added, and then saturated aqueous ammonium chloride (20 ml.). The residue after filtration was extracted with hot methanol which was then evaporated, and the residue was extracted with ether. The combined ethereal solutions were distilled, giving 3-*methyl*-cis-*pent*-2-*ene*-1 : 5-*diol* (XXXII; X = OH), b. p. 98°/0·6 mm., n_D^{20} 1·4810 (6·7 g., 80%) (Found: C, 62·2; H, 10·3. $C_6H_{12}O_2$ requires C, 62·1; H, 10·3%). The same diol was obtained by reduction of 3-methyl-*cis*-pent-2-eno-5-lactone.[30] The *di*-p-*nitrobenzoate* crystallised from butan-1-ol in colourless rosettes, m. p. 126—127° (Found: C, 57·6; H, 4·3; N, 6·4. $C_{20}H_{18}O_8N_2$ requires C, 58·0; H, 4·3; N, 6·7%).

3-*Methyl*-trans-*pent*-2-*ene*-1 : 5-*diol*.—Reduction of the *trans*-hydroxy-acid (XXIX) and of its methyl ester by lithium aluminium hydride in ether was incomplete. Methyl 5-hydroxy-3-methyl-*trans*-pent-3-enoate (3·3 g.; recovered from attempted reduction in ether) was added to a mixture of lithium aluminium hydride (3 g.) and tetrahydrofuran (60 ml.) which had previously been stirred under reflux for 1 hr. The complex which first separated dissolved overnight. After decomposition with ethyl acetate (18 ml.) and ammonium chloride solution (17 ml.) the mixture was worked up as with the *cis*-diol to give the trans-*diol* (XXXI; X = OH) (1·9 g.), b. p. 100—102°/0·2 mm. (Found: C, 62·2; H, 10·3%). The *di*-p-*nitrobenzoate* crystallised from butan-1-ol in colourless needles, m. p. 104° (Found: C, 57·6; H, 4·4; N, 7·1%).

1 : 5-*Dibromo*-3-*methyl*-cis-*pent*-2-*ene*.—Triphenyl phosphite benzylobromide was best prepared (cf. Harrison and Lythgoe[31]) by heating together benzyl bromide and triphenyl phosphite (4% excess) under nitrogen with exclusion of moisture for 72 hr. at 130—140°. The glassy product was dissolved in warm tetrahydrofuran and the slurry of hygroscopic crystals obtained on cooling was used for reaction with the alcohols.

3-Methyl-*cis*-pent-2-ene-1 : 5-diol (3·5 g.) in tetrahydrofuran (4 ml.) was added to the benzylobromide (50% excess) in tetrahydrofuran. The mixture became warm and the solid largely dissolved. Next day the solvent was removed at low pressure and the residue extracted five times with light petroleum (b. p. 40—60°), which was then shaken with ice-cold 0·5N-sodium hydroxide (5 × 50 ml.), filtered, dried, and evaporated at low pressure. The residue, after two distillations, gave 1 : 5-*dibromo*-3-*methyl*-cis-*pent*-2-*ene* (XXXII; X = Br) (7·01 g., 97%), b. p. 42—46°/0·005 mm. (Found: C, 29·5; H, 4·2; Br, 66·4. $C_6H_{10}Br_2$ requires C, 29·8; H, 4·1; Br, 66·1%).

1 : 5-*Dibromo*-3-*methyl*-trans-*pent*-2-*ene*.—The *trans*-diol (3·3 g.), treated as above, gave 1 : 5-*dibromo*-3-*methyl*-trans-*pent*-2-*ene* (XXXI; X = Br) (5·9 g.), b. p. 46°/0·005 mm. (Found: C, 29·9; H, 4·2; Br, 66·3%).

3-*Methyl*-cis- *and* -trans-*pent*-2-*ene*.—Two reductions of 1 : 5-dibromo-3-methyl-*cis*-pent-2-ene by lithium aluminium hydride in dibutyl ether at 70° were carried out with very poor results; from the dibromide (11·8 g.) a product (1·0 g.; b. p. 67—69°), smelling strongly of butyraldehyde, was obtained. This was shaken with aqueous semicarbazide acetate, washed with water and aqueous sodium hydrogen carbonate, dried ($CaSO_4$), and distilled, to give 3-methyl-*cis*-pent-2-ene (366 mg.), b. p. 69° (Found: C, 85·4; H, 14·8%).

A somewhat better result was then achieved with the *trans*-dibromide. Lithium aluminium hydride (2·5 g.) in dibutyl ether (80 ml.; freed from peroxide by passage through a column of alumina) was stirred for 4 hr. at 70°. 1 : 5-Dibromo-3-methyl-*trans*-pent-2-ene (5·7 g.) was added during 30 min. and the mixture was stirred at 70° for a further 1 hr., a test then showing little remaining organic halide. The mixture was cooled to −15° and water (12 ml.) was cautiously added. After filtration and washing of the residue with dibutyl ether the ethereal solution was distilled through a column. The distillate, b. p. 140°, was treated as above with semicarbazide and refractionated, to give 3-methyl-*trans*-pent-2-ene (702 mg.); b. p. 70—72° (Found: C, 85·2; H, 14·8%).

We suspect that the low yields in these reductions are due to some fission of dibutyl ether by lithium aluminium hydride, to give lithium butoxide which can react with some of the bromide to give a high-boiling ether and the trace of $C{=}CH_2$ (diene ?) indicated by the infrared spectra of the *cis*-pentene.

3-*Chloro*-*octan*-4-*one*.—3-Chloro-octan-4-ol (5 g.) in benzene (50 ml.), and chromium trioxide (6 g.) in water (15 ml.), were cooled in water and stirred during addition (30 min.) of sulphuric acid (7 ml.; *d* 1·84) in water (7 ml.). After 4½ hr. water was added and the benzene layer was washed with aqueous sodium hydrogen carbonate and with water, dried ($CaCl_2$), and distilled, to give 3-*chloro-octan*-4-*one* (4·1 g.); b. p. 83—85°/16 mm. (no infrared hydroxyl band was found) (Found: C, 58·7; H, 9·1. $C_8H_{15}OCl$ requires C, 59·1; H, 9·2%).

Reduction of 3-*Chloro-octan*-4-*one*.—The chloro-ketone (3·25 g.) in ethanol (20 ml.) was mixed with sodium hydrogen carbonate (2 g.) in water (20 ml.), and sodium borohydride (0·38 g.) in water (10 ml.) was added. After ½ hr. water and dilute sulphuric acid were added, and the product was isolated by extraction with ether and distillation. The 3-*chloro-octan*-4-*ol* (2·95 g.) had b. p. 95—97°/18 mm. and no infrared carbonyl band (Found: C, 58·4; H, 10·5. $C_8H_{17}OCl$ requires C, 58·3; H, 10·4%). The chlorohydrin (2·8 g.) was converted as described earlier into 3 : 4-epoxyoctane (1·7 g.; b. p. 54—55°/25 mm.), which was shown by infrared analysis to be a mixture of 80—85% of *cis*-3 : 4-epoxyoctane and 15—20% of *trans*-3 : 4-epoxyoctane. Reduction by the stereospecific procedure described above gave a mixture of 80—85% of *cis*- and 15—20% of *trans*-oct-3-ene.

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