

Stereoselectivity of the Base-Induced Conversion of Epoxides into Allylic Alcohols

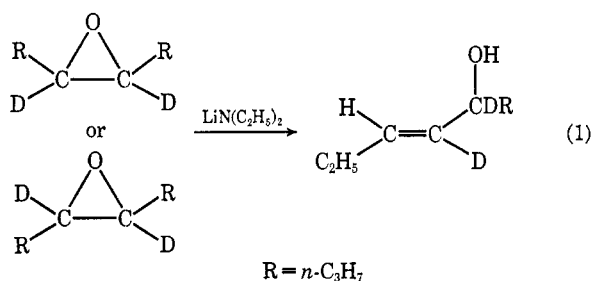
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Very high selectivity is observed in the reaction of unsymmetrical epoxides with lithium diethylamide, leading to allylic alcohols. The proton abstraction occurs most readily from the least substituted carbon in open-chain systems, with large factors separating primary from secondary from tertiary proton abstraction. Thus 2-pentene oxide yields 1-penten-3-ol as the exclusive allylic alcohol product, and 2-methyl-3-heptene oxide gives only 2-methyl-4-hepten-3-ol. Nearly statistical product distribution is observed from 2-methyl-2-butene oxide, which gives 2-methyl-3-buten-2-ol (41%) and 3-methyl-3-buten-2-ol (59%). High selectivity is also observed in the reaction of mixed *cis*- and *trans*-3-methylcyclohexene oxide, where at most a few per cent of the trisubstituted olefin product is formed. Conformational effects also play an important role in determining the selectivity of this reaction, as shown by the conversion of *trans*-4-*t*-butylcyclohexene oxide into *trans*-5-*t*-butyl-2-cyclohexenol (97%), accompanied by only 3% *trans*-4-*t*-butyl-2-cyclohexenol. Similar results are obtained with *trans*-2-octalin oxide. The exclusive formation of contrathermodynamic, least-substituted olefin from the open-chain epoxides is unique among elimination reactions.

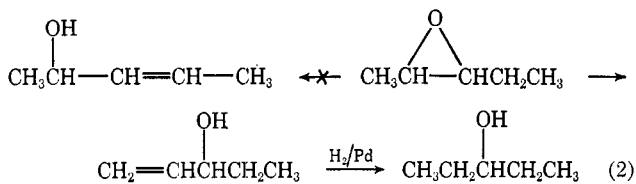
The reaction of an epoxide with a strong base such as lithium diethylamide may take a number of courses depending on the structure of the oxirane.^{2,3} The dominant pathway with most simple alkyl-substituted epoxides is rearrangement into an allylic alcohol. Cope and Heeren⁴ have shown that, with both *cis*- and *trans*-4-octene oxide, the elimination occurs *via* abstraction of a proton from a carbon adjacent to the epoxide ring. Interestingly, both epoxides give a single allylic alcohol (*trans* olefin), to the exclusion of the *cis* isomer (eq 1).⁴



This high selectivity is certainly unusual for base induced elimination reactions, and suggested that the reaction might have other features of specificity. The present study was undertaken to determine the selectivity of proton abstraction from unsymmetrically substituted epoxides.

Results

Different mixtures of *cis*- and *trans*-2-pentene oxide treated with lithium diethylamide in ether gave, after hydrolysis, neutral product in good yield. Of the two possible positional isomer allylic alcohols, only that formed by abstraction of a proton from the primary carbon is obtained, as shown in eq 2.

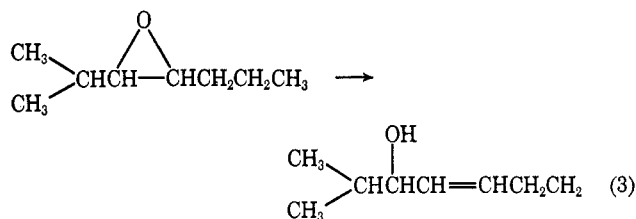


(1) Alfred P. Sloan Fellow, 1967-1969.

(2) A. C. Cope, M. M. Martin, and M. A. McKervey, *Quart. Rev. (London)*, **20**, 119 (1966).

A small amount of pentanone is also formed if the reaction mixture is allowed to stand for extended periods; this material proved to be 3-pentanone. Isomeric 2-pentanone was excluded by direct vpc analysis of the allylic alcohol crude product, and by the absence of 2-pentanol after reduction.

Competition between secondary and tertiary proton abstraction was examined by using 2-methyl-3-heptene oxide. Again a single allylic alcohol was obtained, presumably the *trans*⁴ (ir 970 cm⁻¹) isomer of 2-methyl-4-hepten-3-ol (eq 3). The position of the hydroxyl



group was established by catalytic reduction and vpc comparison with the two possible saturated alcohols, and by nmr analysis of the unsaturated material. Less than 1% of the alternate isomer was formed in this reaction.

Similar treatment of a mixture of *cis*- and *trans*-3-methylcyclohexene oxide (*cis* \approx *trans*) gave a mixture (two essentially equal area peaks by vpc) of allylic alcohols. Analysis was accomplished by catalytic reduction to a mixture of methylcyclohexanols and ketone,⁵ which in turn was oxidized by chromic acid (eq 4).

The problem of analysis of the four isomeric 2- and 3-methylcyclohexanols has been discussed previously.⁷ The saturated ketone product obtained from this sequence (eq 4) is mainly 2-methylcyclohexanone, although a product (3.5%) with the same retention

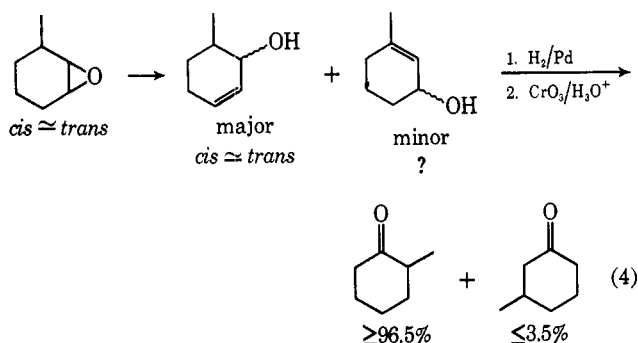
(3) (a) J. K. Crandall, *J. Org. Chem.*, **29**, 2830 (1964). (b) J. K. Crandall and L. Chang, *ibid.*, **32**, 435, 532 (1967). (c) J. K. Crandall and L. C. Lin, *J. Amer. Chem. Soc.*, **89**, 4526, 4527 (1967).

(4) A. C. Cope and J. K. Heeren, *ibid.*, **87**, 3125 (1965).

(5) Several catalysts were used for the reduction of the allylic alcohols; all caused small amounts of rearrangement to the corresponding ketone (up to 10%). In the open-chain systems, analysis was facilitated by further catalytic reduction of the ketone. Hydrogenation catalysts have been used previously to effect the conversion of allylic alcohols into carbonyl compounds.⁶

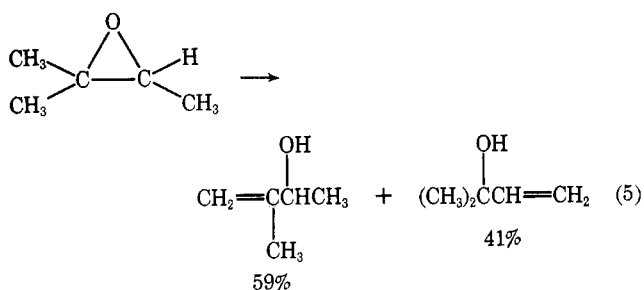
(6) M. B. Green and W. J. Hickinbottom, *J. Chem. Soc.*, 3262 (1957).

(7) B. Rickborn and W. E. Lamke, *J. Org. Chem.*, **32**, 537 (1967).

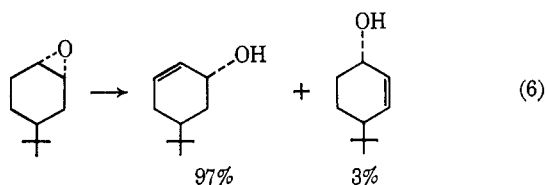


time (two columns) as 3-methylcyclohexanone was also observed. Again very high selectivity is noted for the elimination reaction, with secondary proton greater than tertiary proton abstraction.

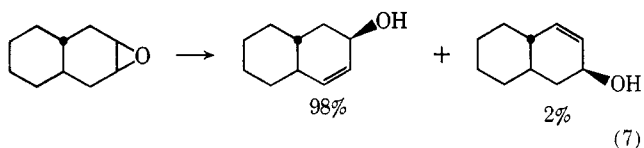
When only one type of hydrogen (primary) is available for reaction, the elimination occurs in an essentially statistically predicted manner as shown by the reaction of 2-methyl-2-butene oxide (eq 5).



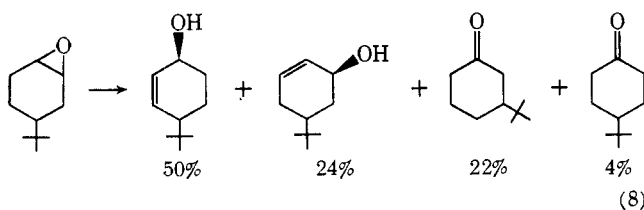
A very different result is observed, however, with cyclic olefin epoxides where strong conformational preference exists. Thus *trans*-4-*t*-butylcyclohexene oxide⁸ reacts readily with lithium diethylamide in refluxing ether to give nearly pure *trans*-5-*t*-butyl-2-cyclohexenol (eq 6) high yield.



Analogous behavior is observed with *trans*-2-octalin oxide (eq 7).



In contrast, *cis*-4-*t*-butylcyclohexene oxide shows very little selectivity in its reaction with lithium diethylamide (eq 8).



Discussion

Crandall and his coworkers⁹ have reported that 1-methylcycloalkene oxides in general react with lithium diethylamide to form 2-methylenecycloalkanols, accompanied by varying amounts of isomeric materials presumed to be formed by subsequent rearrangement. The preference for primary proton abstraction in these systems has thus been demonstrated and attributed to a combination of steric effects and preferred geometry.⁹ The subsequent rearrangement makes it difficult with the 1-methylcycloalkene oxides to establish limits on the selectivity of the elimination reaction.

The present work demonstrates that a very high degree of selectivity exists for acyclic systems; since *ca.* 1% alternate isomers could have been detected (eq 2 and 3), lower limits for the relative rates of proton abstraction are established as primary ≥ 100 secondary ≥ 100 tertiary. The magnitude of selectivity exceeds that of the Hofmann elimination, where typically the rate of primary proton abstraction ≥ 20–40 that of secondary proton abstraction.¹⁰

The bulk of the relatively large lithium diethylamide undoubtedly plays a major role in determining the course of the reaction with an epoxide. Crandall and Chang^{3b} have shown that reaction of cyclopentene oxide with this reagent yields mostly the nucleophilic opening product (amino alcohol), while the even larger lithium diisopropylamide gives more allylic alcohol. Electronic effects, *i.e.*, the enhanced "acidity" of primary hydrogen, may also be important, but no straightforward method of distinguishing these two features is evident. The observed direction of elimination, assuming substantial bulk requirements for the attacking base, is in keeping with the steric model for E2 reactions proposed by Brown.¹¹

The formation of 3-pentanone in the reaction of 2-pentene oxide was shown to be time dependent, increasing on continued reflux after the epoxide was consumed. In a separate experiment, a sample of 1-penten-3-ol was treated with lithium diethylamide in refluxing ether, and slow conversion into 3-pentanone was observed. Although a number of mechanisms for direct formation of ketone from epoxide are conceivable and have been discussed by other authors, subsequent rearrangement of the allylic alcohol appears to be a general reaction,⁹ and may be the only viable route to carbonyl compounds from simple aliphatic epoxides. No 2-pentanone was observed at any stage in the reaction of 2-pentene oxide, strengthening the proposal that no ketone is formed directly from epoxide in this instance.

Both of the β-unsymmetrical open-chain epoxides lead exclusively to the least-substituted, contrathermodynamic olefinic product. This feature, along with the very high selectivity observed with the cyclic olefin epoxides, greatly enhances the synthetic utility of this reaction. For instance, the allylic alcohols may be

(8) B. Rickborn and J. Quartucci, *J. Org. Chem.*, **29**, 2476 (1964).

(9) J. K. Crandall and L. C. Lin, *ibid.*, **33**, 2375 (1968).

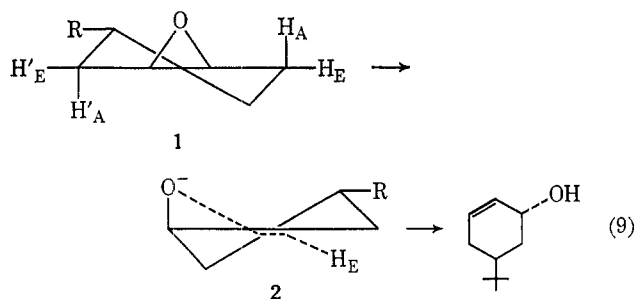
(10) A. C. Cope, N. A. LeBel, H. Lee, and W. R. Moore, *J. Amer. Chem. Soc.*, **79**, 4720 (1957). The Hofmann elimination is of course usually carried out at much higher temperatures than used here, and hence no absolute comparison is possible. Very little *cis-trans* selectivity is observed in the Hofmann elimination.

(11) (a) H. C. Brown and R. L. Klimisch, *ibid.*, **88**, 1425 (1966). (b) H. C. Brown, I. Moritani, and Y. Okamoto, *ibid.*, **78**, 2193 (1956).

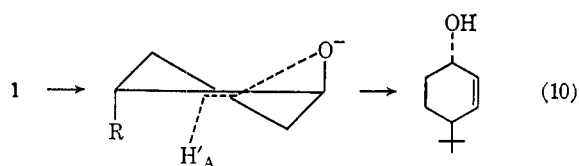
oxidized to specific enones, which are widely used synthetic intermediates. The overall sequence of epoxidation, treatment with base, and reduction can be used for the specific hydration of any properly substituted olefin; thus a 2-alkene can be selectively converted into the corresponding 3-alkanol.

It should be noted that for both eq 2 and 3, both possible allylic alcohol products are secondary alcohols. Arguments regarding thermodynamic stability thus rest on the degree of substitution of the olefinic center. As Young and Franklin¹² have pointed out, the enhanced stability of a more highly substituted alcohol can override the effects of alkyl substitution on the double bond. In the reaction of 2-methyl-2-butene oxide (eq 5) the tertiary alcohol product may be the more stable of the two allylic products formed. The observed product distribution from this epoxide, which has only primary protons available for elimination, suggests that product stability and secondary steric effects play at most a very minor role. The distribution closely approximates that predicted on a purely statistical basis (67% secondary, 33% tertiary alcohol), showing that the lithium diethylamide does not significantly differentiate between the two kinds of primary protons in this acyclic system. This result may be contrasted with that of Price and Carmelite,¹³ who found the same epoxide on treatment with *t*-butoxide in DMSO to give 80% tertiary, 15% secondary alcohol.

Marked conformational effects are apparent in the reactions of *trans*-4-*t*-butylcyclohexene oxide and *trans*-2-octalin oxide (eq 6 and 7). The stereochemistry of this elimination reaction (*i.e.*, whether *cis* or *trans*) is unknown at present, and consequently it is not clear whether H_A or H_E is abstracted in this process (eq 9).¹⁴



If *trans* elimination is assumed, it follows that abstraction of quasiequatorial H_E will form the major product from this system. A transition state (2) involving partial bonding between the centers of the cleaved C-O bond, and transoid geometry, fixes the retained C-O bond in the quasi-axial position. Similar requirements for a possible transition state involving abstraction H_A' places the group R in the unfavorable axial position (eq 10). Although this pathway may account

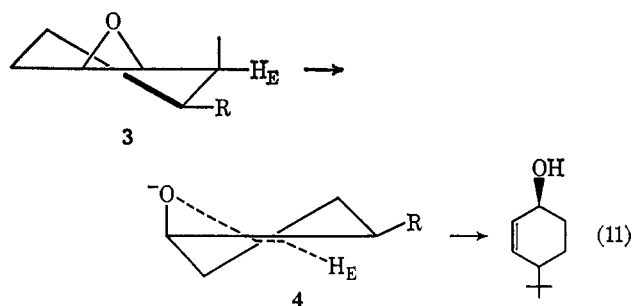


(12) W. G. Young and J. S. Franklin, *J. Amer. Chem. Soc.*, **88**, 785 (1966).

(13) C. C. Price and D. D. Carmelite, *ibid.*, **88**, 4039 (1966).

for the minor product as shown in eq 10, an alternate mechanism, perhaps involving a twist transition state, is needed to account for the minor product from *trans*-2-octalin oxide. The latter system does demonstrate, in its direct analogy with *trans*-4-*t*-butylcyclohexene oxide, that the observed selectivity is not associated with any steric effect of the bulky alkyl group.

Such an effect apparently is operative, however, in the reaction of *cis*-4-*t*-butylcyclohexene oxide (eq 8). Abstraction of H_E from the favored conformation 3



through transition state 4 would lead to the major observed allylic alcohol; steric interaction of the attacking base and the *t*-butyl group is evident. Steric inhibition of this otherwise favorable process implies that 3 should react more slowly than 1, and this is in fact observed. The *trans* epoxide is totally consumed after 7 hr, while 10% of *cis* epoxide is unreacted after 45 hr under otherwise identical conditions. This rate difference was used to prepare nearly pure *cis* epoxide from the 60% *cis*-40% *trans* mixture obtained by peracid treatment of the olefin.¹⁵

The substantial amounts of ketone formed in the reaction of the *cis* epoxide may be associated with the longer time required for this elimination (eq 8). Assuming this to be the case, the essentially complete lack of selectivity in this reaction is shown by the ratio of total 3-*t*-butyl to 4-*t*-butyl derivatives. The relative amounts of ketone formed suggest that the *cis*-5-*t*-butyl-2-cyclohexenol is more readily rearranged than the 4-*t*-butyl isomer. This could be associated with quasi-axial preferred geometry for allylic proton abstraction, a point which is being explored further.

Experimental Section

Epoxides.—In general the epoxides were prepared by treating the corresponding olefin with peracetic acid following the procedure of Korach and coworkers.¹⁶ The yields were moderate to high. The 2-pentene oxide used in this work was a spinning-band distillation fraction, bp 83.2–84.8°, which consisted of 56% *trans* and 44% *cis* material. The 2-methyl-3-heptene, bp 109–112°, was prepared in 50% yield by the method of Schlosser and Christmann¹⁷ from isobutyraldehyde and *n*-butyltriphenylphosphonium bromide. Epoxidation gave material (72%), bp 52–53° (14 mm), which was 88% *cis*, 12% *trans* epoxide. The 3-methylcyclohexene oxide⁷ and *trans*-4-*t*-butylcyclohexene oxide⁸ have

(14) Work is currently underway to determine the stereochemistry of this reaction. Results with deuterium-labeled cyclohexene oxides indicate that reaction occurs by a *syn*-elimination mechanism.

(15) B. Rickborn and S. Lwo, *J. Org. Chem.*, **30**, 2212 (1965).

(16) M. Korach, D. R. Nielsen, and W. H. Rideout, *J. Amer. Chem. Soc.*, **82**, 4328 (1960).

(17) M. Schlosser and K. F. Christmann, *Angew. Chem.*, **76**, 683 (1964).

been described previously. The 2-methyl-2-butene oxide was prepared from commercial olefin and distilled, bp 73°. *cis*-4-*t*-Butylcyclohexene oxide was prepared by refluxing 200 g of mixed epoxide¹⁶ (1.30 mol) with 2.1 mol of lithium diethylamide in ether for 19 hr. The ether solution was washed with water, dilute acid, and base, dried, and evaporated and the residue was distilled to give 32 g of unreacted epoxide, bp 72–75° (5 mm). Analysis was accomplished by LiAlH₄ reduction of a small sample followed by conversion into the acetates as described previously.¹⁵ This material (94% *cis*) was used directly in further reactions with lithium diethylamide, with product analysis corrected for the small amount of *trans* epoxide present.

Following the procedure of Johnson and coworkers,¹⁸ a mixture of *trans*- (70%) and *cis*- Δ^2 -octalin (30%), 69.5 g, was prepared. Very careful distillation through a Teflon spinning-band column gave 20 g of pure *trans* olefin, bp 116–117° (100 mm); the olefins are separable and were analyzed on a Carbowax 4M vpc column at 195°. As expected, the *trans* compound has the shorter retention time. This product was converted to the epoxide in 28% yield, bp 99° (12 mm).¹⁸

Lithium Diethylamide Promoted Rearrangements of Epoxides.—The general procedure of Crandall and Chang^{2b} was followed; a 2.5 molar ratio of lithium diethylamide (generated from commercial butyllithium in hexane) to epoxide was used in refluxing ether solvent. Progress of the reaction was checked by withdrawing samples, quenching with a small volume of water, and analysis by vpc. Reaction times were varied to ensure total consumption of the epoxide. On completion, the ether solutions were washed with a small volume of dilute hydrochloric acid (salted for lower molecular weight products). This treatment does not cause any rearrangement of the allylic alcohols, but serves to remove any amino-alcohol side product.³ Yields of neutral material from small scale runs (0.01 mol) ranged from about 60 to 90%, as determined by vpc analysis.

A larger scale reaction of 2-pentene oxide (12.0 g) gave 8.2 g (68%) of pure distilled 1-penten-3-ol, bp 114–115°. Similarly, 3-methylcyclohexene oxide (6.25 g) gave 4.23 g (68%) of distilled allylic alcohol.

Product Identification.—The neutral products from 2-pentene oxide and 2-methyl-2-butene oxide were reduced catalytically (10% Pd-C, 1 atm) to give known products. Using a TCEOP vpc column at 75°, it was shown that as little as 1% 2-pentanol could have been detected in the product from 2-pentene oxide.

A sample of 2-methyl-3-heptene oxide was reduced by LiAlH₄ to give a mixture of 2-methyl-3- and 2-methyl-4-heptanol. The

latter was excluded (<1%) as a product from the catalytically reduced allylic alcohol from this epoxide.

A previously described procedure, involving catalytic reduction followed by chromic acid oxidation, was used to analyze the products from 3-methylcyclohexene oxide. Using the TCEOP column, a peak (3.5%) with retention time corresponding to 3-methylcyclohexanone was observed; the remainder was unequivocally shown to be 2-methylcyclohexanone by comparison with an authentic sample.

The products from both *trans*- and *cis*-4-*t*-butylcyclohexene oxide were identified by catalytic reduction and conversion of the resulting saturated alcohols into the acetate derivative. Analysis was accomplished as described previously.¹⁵ Additional evidence bearing on the allylic alcohols was obtained by comparison with the LiAlH₄ reduction products of 5-*t*-butyl-2-cyclohexenone.²⁰ The major (94%, *cis*) and minor (6%, *trans*) alcohols were formed in an essentially identical ratio with that reported previously by Goering and Blanchard²² for the reduction of 5-methyl-2-cyclohexenone.

The products from *trans*-2-octalin oxide were also identified by catalytic reduction. Comparison samples were obtained by LiAlH₄ reduction of the epoxide (90% axial, 10% equatorial alcohol) and of *trans*-2-decalone, which gave about 90% equatorial, 10% axial alcohol.

Samples of all the major product allylic alcohols were collected, either by distillation or preparative vpc, and gave the anticipated ir and integrated nmr spectra.

Registry No.—2-Pentene oxide (*cis*), 3203-99-4; 2-pentene oxide (*trans*), 3203-98-3; 2-methyl-3-heptene (*cis*), 20488-34-0; 2-methyl-3-heptene (*trans*), 692-96-6; 2-methyl-3,4-epoxyheptan (*cis*), 21438-79-9; 2-methyl-3,4-epoxyheptane (*trans*), 21438-80-2; 2-methyl-2-butene oxide, 5076-19-7; *trans*- Δ^2 -octalin, 2001-50-5; *trans*-2,3-epoxyoctalin, 21438-82-4.

Acknowledgments.—The authors wish to thank the National Science Foundation (9383) for financial support and Mr. Sam Tokuyama for preparing some of the epoxides used in this work.

(20) This sample was prepared by the method of Garbisch²¹ from 3-*t*-butylcyclohexanone, followed by careful fractional distillation. This compound is in fact more easily accessible from 4-*t*-butylcyclohexene oxide via the reaction with lithium diethylamide described here.

(21) E. W. Garbisch, Jr., *J. Org. Chem.*, **30**, 2109 (1965).

(22) H. L. Goering and J. P. Blanchard, *J. Amer. Chem. Soc.*, **76**, 5405 (1954).

(18) W. S. Johnson, V. J. Bauer, J. L. Margrave, M. A. Frisch, L. H. Dreger, and W. N. Hubbard, *J. Amer. Chem. Soc.*, **83**, 606 (1961).

(19) H. Hunsdiecker, *Chem. Ber.*, **80**, 137 (1947).