Copper Chromite-catalyzed Conversion of Some Glycols to Dioxenes

R. K. SUMMERBELL, DONALD M. JERINA,[1] AND ROBERT J. GRULA

Chemical Laboratory of Northwestern University, Evanston, Illinois

Received July 23, 1962

Dioxenes are prepared from several dialkylene glycols by copper chromite-catalyzed dehydrogenation–dehydrations. Contrary to a previous report, no dioxanone is produced from 4-oxaheptane-2,6-diol, and the unsaturated compound from 3-oxahexane-1,5-diol is 2-methyl-*p*-dioxene rather than 5-methyl-*p*-dioxene. With these amended observations, a simple sequence of expected reactions correlates the observed phenomena. Several related diols have been studied.

The study and use of dioxenes has been limited by a dearth of synthetic methods for their preparation in quantity or with a variety of substituents. Bell[2] recently made the important discovery that dioxenes were produced along with the previously observed dioxanones[3] when dialkylene glycols were treated with copper chromite in the liquid phase. We have found the Bell reaction to be a useful synthetic tool, but our experimental results have differed from his in several details. In this paper, these differences and several extensions and variations of the reaction are reported.

In Chart I, we present our concept of the sequence of reactions. The diol *A* is dehydrogenated to a hydroxy aldehyde or hydroxy ketone *B*, which may form a hemiacetal *C* that in turn should readily dehydrate to the dioxene *D*. Alternatively, *B* may be dehydrogenated to the dicarbonyl compound *E*, which may undergo a Cannizarro-like reaction to F, *if at least one of the carbonyl groups* of E is an aldehyde. In other words, to prepare a lactone, one of the alcohol groups in *A* must be primary.

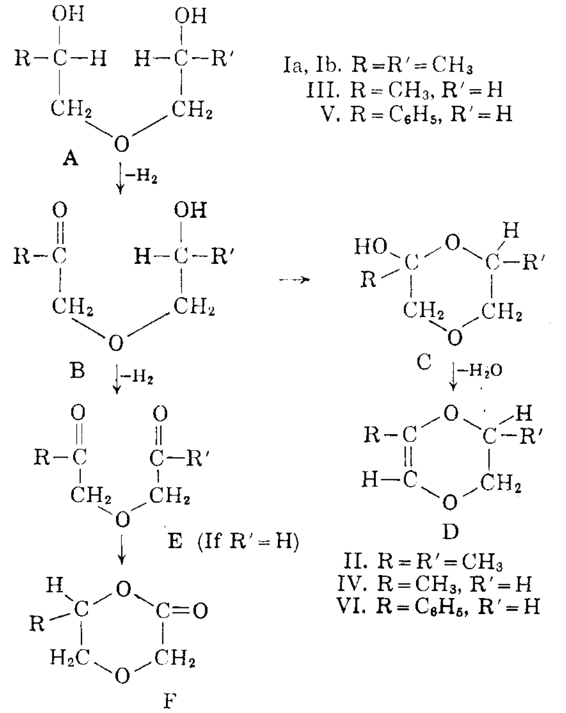

Chart I

On the basis of this simple mechanism, one would predict that 4-oxaheptane-2,6-diol (I)[4] should give 2,6-dimethyldioxene, but no dioxanone, because in this case, both carbonyls of *E* are ketones. Bell[2] reports a yield of 23% of the dioxene as predicted, but also, contrary to prediction, a 50% yield of 3,5-dimethyl-2-*p*-dioxanone. Likewise, according to our theory, the secondary alcohol of 3-oxahexane-1,5-diol (III) should dehydrogenate more readily than the primary, so the predicted predominant product *D* should be 2-methyl-*p*-dioxene (IV); the reported product[2] is 5-methyl-*p*-dioxene. We have repeated both of these syntheses and found the products predicted by our simple theory rather than those previously reported.

We took particular pains as to the authenticity of our starting material, 4-oxaheptane-2,6-diol (I) which was prepared by the method of Sexton and Britton,[5] employing the alkoxide catalyzed condensation of propylene oxide and propylene glycol. The "dipropylene glycol" was fractionated from starting material and higher condensation products by distillation and was further purified by crystallization from ether at Dry Ice temperatures to give a white solid of appropriate melting point, infrared spectrum, and derivatives. This previously known form of I will be called Ia. When this pure sample of Ia was heated with copper chromite at a temperature permitting slow distillation of products, an 83% yield of 2,6-dimethyl-*p*-dioxene (II) was obtained. When a more rapid distillation was conducted, some unchanged Ia was identified in the distillate along with a lesser yield of II. No dimethyldioxanone was found when Ia was the starting material.

II was identified by hydrogenation over palladium–charcoal catalyst to a mixture of 2,6-dimethyl-*p*-dioxanes in which the *cis* isomer predominated.[6] In another run, not carried to com-

---

[1] National Science Foundation Undergraduate Summer Research Participant, 1960–1961.

[2] John Barr Bell, U. S. Patent 2,807,629, September 24, 1957.

[3] R. W. McNamee and C. M. Blair, U. S. Patent 2,142,033, December 27, 1938.

[4] Wherever practical, we have named the dialkene glycols in such a way as to emphasize the two alcohol groups and their distance apart, matters of major importance in the reaction being studied. Bell[2] calls this compound dipropylene glycol but gives the structural formula of this specific isomer. Sexton and Britton call it 1,1-oxydi-2-propanol.

[5] A. R. Sexton and E. C. Britton, *J. Am. Chem. Soc.*, **75**, 4357 (1953).

[6] R. K. Summerbell, Anna Burlingame, David R. Dalton, and Cecile Kaplan Dalton, *J. Org. Chem.*, **27**, 4365 (1962).

pletion, unchanged Ia was found in the pot, but no other isomeric variety of dipropylene glycol could be found there. This evidence, coupled with the absence of 2,5-dimethyldioxanes in the product obtained by hydrogenating II, indicates that our dehydrogenation catalyst was not also an ether rearrangement catalyst under our experimental conditions. Glycols obtained by rearranging I could give dioxanones.

In previous work,[2] the finding of product dioxanones may have been due to the use of commercial "dipropylene glycol" which is usually represented by supply houses as primarily 3-oxaheptane-2,6-diol. Parallel experiments using such a commercial starting material did yield lactone and 2,5-dimethyl-*p*-dioxene along with II.

While preparing Ia, we encountered evidence of a hitherto unreported form of I. Since I possesses two equivalent asymmetric centers, it should exist in *meso* and in *racemic* modifications. While the alkaline-catalyzed condensation of propylene oxide with propylene glycol would be expected to yield predominantly forms of I rather than the other "dipropylene glycols,"[7] there is no compelling reason to expect *meso* or *racemic* to predominate. The mother liquors from which our starting sample of the previously known form of I, Ia, were crystallized yielded a *p*-nitrobenzoate derivative differing in melting point from any reported for the three known dipropylene glycols. In solution this derivative was almost identical with the derivative of Ia in infrared spectra, but the melting point of a mixture of the derivatives was depressed markedly. These phenomena are explained by assuming that the higher melting, less soluble form of I, Ia, crystallized, leaving the more soluble form of I, Ib, in the mother liquor. Attempts to isolate the new isomer in a state pure enough to solidify were not successful.

This second form, Ib, is probably the chief diglycol component in the mother liquor, since the crude dipropylene glycol obtained therefrom gave primarily 2,6-dimethyl-*p*-dioxene on treatment with copper chromite. The other dipropylene glycols would have given also dioxanones and 2,5-dimethyl-*p*-dioxenes. Since the "dipropylene glycol" from the alkaline condensation of propylene oxide and glycol is thus predominantly a mixture of the *meso* and *racemic* forms of I and since both forms of I dehydrogenate–dehydrate to 2,6-dimethyl-*p*-dioxene with a minimum of side reactions, this particular dioxene now becomes readily available.

The synthesis of 3-oxahexane-1,5-diol (III) was accomplished by the alkaline condensation of propylene oxide with a large excess of ethylene glycol. On treatment with copper chromite, the only dioxene isolated was 2-methyl-*p*-dioxene (IV), as proved by the hydrolysis products from the halogen addition compound, methylglyoxal and ethylene glycol. The 5-methyl-*p*-dioxene would have given glyoxal and propylene glycol.

The preparation of 2-phenyl-*p*-dioxene (VI) by the reaction of phenyllithium with 2,3-dichloro-*p*-dioxane has been reported.[8] Prepared by this method, VI was difficult to purify and to preserve so that an alternative method of preparation seemed desirable. Alkaline condensation of styrene oxide with ethylene glycol yielded an impure sample of the 1-phenyl-3-oxapentane-1,5-diol (V), the structure of which was proved by acidic–azeotropic dehydration to the known phenyl-*p*-dioxane.[9]

Treatment of the diol (V) with copper chromite catalyst yielded dioxene VI, but in no better yield and in an even less stable condition than the previous method. The present catalytic method could possibly be improved by using a less acidic form of the catalyst; however, some acidity may be necessary in the dehydration step.

The reaction may be used to prepare a bicyclic dioxene. Propylene glycol by alkaline condensation with cyclohexene oxide formed 1-(2-hydroxycyclohexyl)-1,2-propanediol. After treatment with copper chromite, the distillate consists of two fractions; in the higher boiling one, carbonyl bands were pronounced, while the other absorbed at 5.87 μ consistent with a highly substituted dioxene structure.[10] The dioxene was not obtained in pure form, but its presence in major quantity was indicated by derivatives.

All of the preparations so far involved a glycol that could give a six-membered ring. To find out whether a seven-membered ring could be made, we synthesized 4-oxaheptane-1,6-diol. On treatment with the catalyst, two major products were obtained, acetol and propanal, but the spectrum of the propanal indicated an unsaturated impurity, possibly acrolein. The mechanism is not obvious. Perhaps the aldehyde–ketone analogous to *E* formed by dehydrogenation breaks into acrolein and acetol, and the propanal is produced by the almost, but not quite, complete hydrogenation of the double bond of the acrolein. A related glycol, 1,6-hexanediol, reacted in a rather complex manner, forming a black sponge rubber-like material as the main product, together with minor quantities of organic liquid, one component of which was 2-methylcyclopentanone.

Our attempt to make a five-membered unsaturated ether, dihydrofuran, as the analogue of a dioxene, was unsuccessful. When 1,4-butenediol was subjected to our catalyst and experimental

---

[7] H. C. Chitwood and B. T. Freure, *J. Am. Chem. Soc.*, **68**, 680 1946).

[8] R. K. Summerbell, M. Smedley, D. M. Jerina, and D. R. Berger, *J. Org. Chem.*, **27**, 4078 (1962).

[9] R. K. Summerbell and L. N. Bauer, *J. Am. Chem. Soc.*, **57**, 2364 (1935). See also M. J. Astle and B. E. Jacobson, *J. Org. Chem.*, **24**, 1767 (1959), who reported the preparation of phenyldioxane by acid-catalyzed condensation of styrene oxide with ethylene glycol but characterized their liquid product only by boiling point.

[10] J. B. Miller, *ibid.*, **25**, 1279 (1960).

conditions, the yield of butyrolactone was almost quantitative. We could detect no dihydrofuran.

Some of the differences between our results and those of Bell could be due to a difference in catalyst. A catalyst sufficiently acidic to cause an ether rearrangement of the diglycols or a combination of catalyst and conditions that would promote rehydration of the dioxenes to other diglycols could lead to some of the products that Bell observed, but that we did not.

Experimental

Copper Chromite Catalyst. The catalyst was prepared by the method of Lazier and Arnold,[11] using the Mozingo[12] modification in the decomposition step. Samples of catalyst prepared on different occasions by different persons independently did not differ perceptibly in activity.

4-Oxaheptane-2,6-diol (I). The method is essentially that of Sexton and Britton.[5] A blanket of nitrogen was laid over 760 g. (10 moles) of freshly distilled propylene glycol in a 3-l. flask. Sodium metal (8 g.) was dissolved by warming, and the propylene oxide, 580 g. (10 moles) was added under the surface, with vigorous stirring, at a reaction temperature *ca.* 105–120°. Time, 4.5 hr. A Dry Ice–acetone cold finger seldom collected any liquid during the addition. Distillation at atmospheric pressure through a 4-plate Vigreux column yielded 648 g. (48%) of I, b.p. 217–224°. When the distillate was dissolved in ether and cooled over night at Dry Ice temperatures, the solid which separated (Ia) amounted to about half of the total I. On recrystallization from ether, it melted at 46–48°, boiled at 220–222° (754 mm.), gave a *bis-p-nitrobenzoate*, m.p. 146–148°[5] in 97% yield, and a bis-trityl ether, m.p. 143–144°[5]. The mother liquor, on evaporation of solvent gave a liquid, Ib. The bis-*p*-nitrobenzoate prepared from Ib in 84% yield melted after several recrystallizations at 125.5–126°.

Anal. Calcd. for $C_{20}H_{20}N_9$: C, 55.5; H, 4.66; N, 6.48. Found: C, 55.64; H, 4.54; N, 6.66.

A melting point of the two bis-*p*-nitrobenzoates mixed in a 1:1 ratio was depressed to 118°. No trityl ether was obtained from Ib. The infrared spectra of the two bis-*p*-nitrobenzoates taken in chloroform solution were duplicates; those taken in potassium bromide pellets showed minor differences. The infrared spectra of Ia and Ib are almost identical, the latter having all of the lines of Ia, with a few minor additions. The boiling point of redistilled Ib was 226.5–228° (755 mm.).

Preparation of 2,6-dimethyl-*p*-dioxene (II).—A 1-l. flask was fitted with a Vigreux column of four plates, on the top of which was placed a Claissen head with a thermometer and a water-jacketed condenser, which in turn was attached to a receiving flask equipped with a hose for venting hydrogen out of the window. The diglycol Ia (268 g., 2 moles) was mixed with 10 g. of copper chromite and heated at such a rate that slow distillation occurred. Hydrogen evolution started at 35°. Of the two layers of products formed, the lighter layer was dried with sodium hydroxide, then distilled to yield 187.5 g. (82.5%) of 2,6-dimethyl-*p*-dioxene. In other parallel experiments, the rate of distillation was increased, resulting in a lowered yield of dioxene and the recovery of Ia, identified as the bis-*p*-nitrobenzoate, from the distillate. Fractions of distillate with intermediate boiling points on redistillation were resolved into II, water, and Ia. No lactone was found. A sample of II distilled twice from sodium had b.p. 126–126.5 (749 mm.) and n^{20}D 1.4320. Reduction of II with hydrogen (5% palladium on charcoal, microhydrogenation apparatus) produced predominantly *cis*-2,6-dimethyl-*p*-dioxane with a small admixture of *trans*-2,6-dimethyl-*p*-dioxane, as judged by an infrared spectra, but no 2,5-dimethyl-*p*-dioxanes could be detected.

In a similar experiment, Ib was substituted for Ia with parallel results, except that the dimethyldioxane reduction product contained traces of *cis*- and *trans*-2,5-dimethyl-*p*-dioxanes. The yield of crude dimethyldioxenes was 67% on a small run with high mechanical losses. When commercial dipropylene glycol was the starting material, more 2,5-dimethyldioxanes were produced on reduction of the dimethyl-*p*-dioxene fraction. Infrared spectra of the higher boiling fractions (204–210°) of the original dehydrogenation product indicate the presence of carbonyl.

3-Oxahexane-1,5-diol (III).—Ethylene glycol was substituted for propylene glycol in the above preparation of I. A refractionated sample boiled at 234–235° (751 mm.), n^{23}D 1.4437. A bis-p-nitrobenzoate was prepared in 72% yield, m.p. 108–109°.

Anal. Calcd.: C, 54.54; H, 4.34. Found: C, 54.29; H, 4.11.

2-Methyl-*p*-dioxene (IV). A 60-g. sample (0.5 mole) of III was mixed with 5 g. of catalyst and heated slowly for 2.5 hr. The methyldioxene fraction was separated from water, dried over potassium hydroxide, and doubly distilled from sodium to obtain 9 g. of pure methyl-*p*-dioxene, b.p. 115.5–116° and n^{23}D 1.4393. Three milliliters of the methyldioxene was dissolved in pentane, cooled to ice temperatures, and titrated with a pentane solution of bromine until the bromine color persisted. Solvent evaporation resulted in an oil which solidified. Water (30 ml.) was added and the solution heated on the steam bath for 10 min. To half the solution was added phenylhydrazine and acetic acid and after work-up, the osazone melted at 143–145°. The other half of the hydrolysate was used to prepare the dibenzoate of ethylene glycol, m.p. 67–68°, by usual methods. The infrared spectra of the 2-methyl-*p*-dioxene and of the derivatives were identical with those of an authentic specimen previously described.[13]

2-Phenyl-*p*-dioxene (VI).—The requisite glycol, 1-phenyl-3-oxapentane-1,5-diol (V), was prepared from ethylene glycol (6 moles) and styrene oxide (3 moles) by the usual alkaline procedure. The pot temperature during styrene oxide addition was *ca.* 110° and total reaction time 3 hr. The product, a light yellow liquid, b.p. 184–187° (13 mm.), weighed 256 g. (1.4 moles, 47%). Because the analysis was too low in carbon to be satisfactory, a portion was dehydrated by azeotroping with benzene, using *p*-toluenesulfonic acid as a catalyst to the known phenyl-*p*-dioxane, m.p. 46°,[14] in 73% yield. It was identified by comparison with an authentic sample as to infrared spectra, melting point and mixed melting point. The dehydrogenation was carried out in the usual fashion with 91 g. (0.5 mole) of the glycol V at such a temperature that the distillate mixture boiled below 175°. Yield, 50 g. On redistillation under vacuum, this was reduced to 17 g. (21%). White crystals, m.p. 43° from ligroin, were identified as 2-phenyl-*p*-dioxene by comparison with a sample of that compound prepared by the action of phenyllithium with 2,3-dichloro-*p*-dioxane.[8] By the next morning, even the best crystalline samples of VI had become a viscous liquid.

1-(2-Hydroxycyclohexyl)-1,2-propanediol (VII).—Condensation of 98 g. (1 mole) of cyclohexene oxide with a large excess (8 moles) of propylene glycol in which 6 g. (0.25 mole) of sodium had been dissolved was carried out at 170° in 3.5 hr. The cooled reaction mixture was neutralized with phosphoric acid, the excess glycol distilled, and the

---

[11] W. A. Lazier and H. R. Arnold, "Organic Synthesis," Coll. Vol. II, 1943, p. 142.

[12] R. Mozingo, *J. Am. Chem. Soc.*, **71**, 3528 (1949). (See footnote 2 of this reference.)

[13] R. K. Summerbell, G. H. Kalb, E. S. Graham, and L. Allred, *J. Org. Chem.*, **27**, 4461 (1962).

[14] R. K. Summerbell and L. N. Bauer, *J. Am. Chem. Soc.*, **57**, 2364 (1935).

remainder fractionated under vacuum to produce 110 g. (90% yield) of a white viscous liquid, b.p. 132–134° (4.5 mm.). The liquid, when dissolved in the minimum amount of dry ether and cooled to Dry Ice temperatures, deposited as a solid which melted over a wide range up to room temperature.

Anal. Calcd. for $C_9H_{18}O_3$: C, 62.04; H, 10.41. Found: C, 61.94; H, 10.60.

Catalytic Treatment of VII.—On heating 87 g. (0.5 mole) of the diol VII with 2.6 g. (3%) of the catalyst, hydrogen was rapidly evolved and a two-phase material distilled. When hydrogen no longer evolved, the remainder in the pot was distilled at vacuum. Refractionation at 0.5 mm. gave 20 g., b.p. 42–44°, and 40 g., b.p. 68–105°. Infrared spectrum indicated that the lower boiling fraction had a double bond contaminated with some carbonyl, and that the higher boiling fraction was a carbonyl compound. A satisfactory analytical sample of the olefin was not obtained.

Anal. Calcd. for $C_9H_{14}O_2$: C, 70.09; H, 9.15. Found: C, 69.03; H, 9.16.

However, addition of chlorine followed by hydrolysis and treatment with *p*-nitrophenylhydrazine gave an osazone, m.p. 235–237°. The known *p*-nitrophenylosazone of 1,2-cyclohexanedione is 236–237°.[15] This derivative indicates the presence of a major quantity of 2-methyl-5,6,7,8-tetrahydro-1,4-benzodioxane in the olefin fraction. A similar series of experiments on the condensation products of cyclohexene oxide with ethylene glycol produced only an impure sample of what was believed to be a lactone. No product corresponding to a dioxene was found.

Abnormal Dehydrogenation of 4-Oxaheptane-1,6-diol.—The diol was prepared in 36% yield by alkaline condensation of propylene oxide with an excess of 1,3-propanediol. When a slurry of 67 g. (0.5 mole) of the crude diol with 4 g. (6%) of the catalyst was heated, hydrogen was evolved. The liquid distillation products on refractionation gave 14 g., b.p. 50–54°, and 10.5 g., b.p. 146–150°. The lower boiling fraction was identified as propanal by the formation of the *p*-nitrophenylhydrazone, m.p. 123–124° (lit. m.p. 125°), and of the 2,4-dinitrophenylhydrazone, m.p. 153° (lit. m.p. 154°).[16] The higher boiling fraction was identified as acetol by the formation of the phenylosazone, m.p. 149–150° (lit.,[17] 150°). Spectra of both samples were consistent with these assignments, with the qualification that the propanal contained an unsaturated impurity.

Preparation of Butyrolactone.—A slurry of 90 g. (1 mole) of 1,4-butanediol and 4.5 g. (5%) of catalyst was heated to evolution of hydrogen and distillation of product, *ca.* 200°. On redistillation, 79 g. of butyrolactone, b.p. 204–205°, resulted for a yield of 92%.

Polymer from 1,6-Hexanediol.—The catalyst, 3.5 g., was suspended in 118 g. (1 mole) of melted 1,6-hexanediol and the mixture heated gradually. Hydrogen was evolved and liquid products distilled normally at about 130°. After about 50 ml. of liquid had been collected, the reaction became exothermic, the rate of gas evolution increased markedly and a black, spongy material, not unlike foam rubber, filled the flask, distilling column, and condensers. The liquid contained several components, one of which was identified as 2-methylcyclopentanone by the formation of a semicarbazone, m.p. 181°, after sublimation (lit.,[18] m.p. 182°).

Acknowledgment.—We wish to thank Dr. James G. Traynham for discussions and the loan of facilities during the preparation of this manuscript.

---

[15] G. Moeyes and N. Schoorl, *Pharm. Weekblad*, **71**, 1026–1029 (1935).

[16] N. D. Cheronis and J. B. Entrikin, "Semimicro Qualitative Organic Analysis," 2nd ed., Interscience Publishers, Inc., New York, N. Y., 1957, p. 582.

[17] J. U. Nef, *Ann.*, **335**, 255 (1904).

[18] C. D. Hodgman, "Tables for Identification of Organic Compounds," Chemical Rubber Publishing Co., 2310 Superior Ave., Cleveland 14, Ohio, 1960, p. 84.

Decarboxylation and Deuterium Exchange in Some Azabicyclic Ketone Systems[1]

HERBERT O. HOUSE AND HANSPETER C. MÜLLER

Department of Chemistry, Massachusetts Institute of Technology, Cambridge 39, Mass.

Received July 12, 1962

Studies of the decarboxylation of the keto acid **2** (to form **1b**) and of deuterium exchange with the bicyclic amino ketones **1** (to form **3**) indicate that both of these reactions proceed *via* monocyclic intermediates.

Studies of the synthesis of the azabicyclic ketones **1**[2,3] had shown that boiling 20% hydrochloric acid would effect the hydrolysis and decarboxylation of the ester, **2**, to produce **1b** in 60–70% yield. We have found that this same reaction, utilizing 20% deuterium chloride in deuterium oxide, forms the dideuterio ketone, **3b**. However, application of the same reaction conditions to the keto acid, **4**, previously reported[4] to be thermally stable, resulted in no reaction and application of this decarboxylation precedure to the diester, **5**, resulted in the formation of the diacid, **6a**, characterized as its ester, **6b**. It is also pertinent to note that compounds **7**[5] and **8**[6] have been found stable to thermal decarboxylation, whereas compounds containing the systems **9**[7,8] and **10**[9,10] have been decarboxylated successfully at temperatures above

---

[1] This research has been supported by grants from the National Institutes of Health (RG-8761) and the McNeil Laboratories, Inc.

[2] W. Schneider and H. Götz, *Naturwiss.*, **47**, 397 (1960); *Arch. Pharm.*, **294**, 506 (1961).

[3] H. O. House, P. P. Wickman, and H. C. Müller, *J. Am. Chem. Soc.*, **84**, 3139 (1962).

[4] A. C. Cope and M. E. Synerholm, *ibid.*, **72**, 5228 (1950).

[5] C. Mannich and W. Brose, *Ber.*, **56B**, 833 (1923).

[6] V. Prelog, P. Barman, and M. Zimmermann, *Helv. Chim. Acta*, **32**, 1284 (1949).

[7] H. Meerwein, F. Kiel, G. Klosgen, and E. Schoch, *J. prakt. Chem.*, [2] **104**, 161 (1922).

[8] V. Prelog and R. Seiwerth, *Ber.*, **74**, 1644 (1941).

[9] O. E. Edwards, L. Marion, and D. K. R. Stewart, *Can. J. Chem.*, **34**, 1315 (1956).