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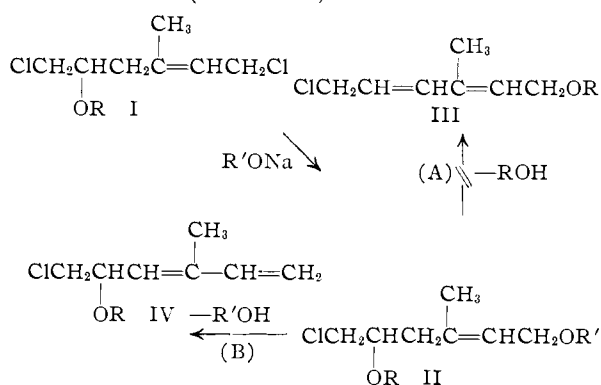
The Dealcoholation of a Series of Unsaturated Diethers

BY JAMES N. COKER, AUGUST S. BJORNSON, THOMAS E. LONDERGAN, TED F. MARTENS AND JOHN R. JOHNSON

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The dealcoholation of a series of 1,5-dialkoxy-2-hexenes has been investigated in an effort to prepare a 1-alkoxy-2,4-hexadiene. Though the dealcoholation reaction could be accomplished in several ways, a 2,4-hexadiene structure was not obtained. Instead, the corresponding 5-alkoxy-1,3-hexadienes resulted in good yield. The infrared absorption characteristics of these compounds are described.

Various 3-methyl-6-chloro-2-hexenes (II), containing an alkoxy group in the 5-position and an alkoxy or acetoxy group in the 1-position, have been described in an earlier publication.¹ These compounds have been examined as possible precursors of the vitamin A side chain. With this objective in mind, the 1,5-dialkoxy compounds have been subjected to a dealcoholation in the presence of *p*-toluenesulfonic acid. The product desired from this dealcoholation was the corresponding 1-alkoxy-2,4-hexadiene (III), formed by an elimination of the internal alkoxy group (reaction A), but this product was not obtained. Instead the terminal alkoxy group was eliminated and 5-alkoxy-1,3-hexadiene (IV) was isolated as the principal product of the reaction (reaction B).



I (a) R = C₂H₅; (b) *i*-C₃H₇; (c) C₆H₅CH₂
 II (a) R = C₂H₅; R' = CH₃; (b) R = C₂H₅, R' = *n*-C₄H₉; (c) R = *i*-C₃H₇, R' = CH₃; (d) R = *i*-C₃H₇; R' = *n*-C₄H₉; (e) R = *i*-C₃H₇, R' = C₆H₅CH₂; (f) R = *i*-C₃H₇, R' = C₆H₅; (g) R = C₆H₅CH₂, R' = CH₃; (h) R = C₂H₅, R' = COCH₃; (i) R = *i*-C₃H₇, R' = COCH₃; (j) R = COCH₃, R' = CH₃
 IV (a) R = C₂H₅; (b) R = *i*-C₃H₇; (c) R = C₆H₅CH₂

The dealcoholation reaction was carried out initially with 1-methoxy-3-methyl-5-ethoxy-6-chloro-2-hexene (IIa). This compound could be dealcoholated in several ways. The most effective method employed a catalytic amount of anhydrous *p*-toluenesulfonic acid in boiling toluene. The main product formed under these conditions was 3-methyl-5-ethoxy-6-chloro-1,3-hexadiene (IVa). It was observed that the rate of dealcoholation of the 1-methoxy-5-ethoxy compound (IIa) was not affected markedly by varying the amount of the toluene in the reaction mixture. However, cyclohexane proved to be quite inferior to toluene as a reaction solvent. When the reaction was catalyzed with

oxalic acid instead of *p*-toluenesulfonic acid, the same 1,3-diene (IVa) was formed, but the reaction proceeded very slowly. No appreciable reaction was observed when sodium bisulfate was used as the dealcoholation catalyst. Dealcoholation was also accomplished by pyrolysis over alumina at a temperature of 150–200°. The same 5-ethoxy-1,3-hexadiene (IVa) was isolated as the predominant product of this pyrolysis.

In order to determine the effect of various alkoxy groups upon the course of the dealcoholation reaction, other 3-methyl-6-chloro-2-hexene derivatives (IIb-g) have been studied. The basis for this investigation has been the assumption that the formation of the desired 2,4-hexadiene (III) could be accomplished if appropriate dissimilar alkoxy residues were present in the parent 2-hexene system (II). Presumably, the presence of either a relatively stable group in the 1-position or a relatively labile group in the 5-position of the compound would favor the selective elimination of the group in the 5-position. The latter approach has been favored mainly because the presence of a stable ether group in the 1-position might be expected to lower the biological activity of any vitamin A structure obtained from the compound.²

The dealcoholation of 2-hexenes containing three other pairs of alkoxy groups in the 1- and 5-positions (IIb-d) has been observed to proceed in the same manner as the reaction observed with the 1-methoxy-5-ethoxy adduct (IIa). The failure of these compounds to yield the desired 2,4-hexadiene structure (III) has prompted an investigation of several compounds (IIe-g) containing either benzyloxy or phenoxy groups.

Benzyl ethers in general readily undergo cleavage in the presence of acidic reagents.³ The dealcoholation of a 2-hexene containing a 5-benzyloxy group might be expected therefore to yield a 2,4-hexadiene derivative. The dealcoholation of such a compound, 1-methoxy-3-methyl-5-benzyloxy-6-chloro-2-hexene (IIg), did not bear out this contention, however. In fact, the product of the reaction, 3-methyl-5-benzyloxy-6-chloro-1,3-hexadiene (IVc) was shown on the basis of spectroscopic data to be more stable to the conditions of the dealcoholation than had been observed previously for 3-methyl-5-ethoxy-6-chloro-1,3-hexadiene (IVa).

The unexpected stability of 3-methyl-5-benzyloxy-6-chloro-1,3-hexadiene (IVc) to the conditions of the dealcoholation reaction has suggested that a

(1) J. N. Coker, A. S. Bjornson, T. E. Londergan and J. R. Johnson, THIS JOURNAL, **77**, 5542 (1955).

(2) O. Isler, Section 10, paper 98, XIIth International Congress of Pure and Applied Chemistry, New York City, September, 1951.

(3) B. W. Tronow and L. W. Ladigina, *Ber.*, **62**, 2844 (1929).

Discussion of Infrared Absorption Data⁷

The complex nature of both the products of the dealcoholation reaction (IV) and the 2-hexene precursors (I and II) has made the use of infrared absorption spectra invaluable in the assignment of structures to these compounds. With regard to the parent 1,5-dichloro-2-hexenes (I), a consideration of individual absorption spectra clearly brings out characteristics relating all of these materials. The absorption spectrum of 1,6-dichloro-5-ethoxy-2-hexene (Ia without the 3-methyl group) contains the 10.36 μ band associated with a *trans*-RCH=CHR structure as well as a broad ether absorption at 9.1 μ . The absorption at 13.4 μ is in the proper region for a C-Cl group while absorptions at 8.0 and 14.7 μ are characteristic of the allyl chloride structure, $-\text{C}(\text{R})=\text{CH}-\text{CH}_2\text{Cl}$. The presence of a methyl group in the 3-position, or an isopropoxy instead of an ethoxy group in the 5-position, introduces only the expected changes in the general absorption pattern. The observed similarities establish, therefore, that all of the prepared isoprene- α -chloroether adducts had the same basic structure.

Methoxylation and acetoxylation of the 1,6-dichloro-2-hexene compounds resulted in the removal of the bands at 8.0 and 14.7 μ which are attributed to C-Cl. The acetoxy group in compound IIh is readily distinguished by absorption maxima at 5.8 and 8.0 μ . All of the alkoxyated and acetoxyated adducts (IIa-i) which have been prepared have been found to have infrared absorption spectra similar to that observed for compound IIa. Inasmuch as the structure of the latter was established by ozonolysis, all of these materials are indicated to be 3-methyl-6-chloro-2-hexenes (IIa-j), having oxygen-containing groups in the 1- and 5-positions.

The infrared spectra of the dienes (IVa-c) prepared by the dealcoholation of the 2-hexenes (II) just described are characterized by an absorption doublet at 10.1 and 11.1 μ . This doublet is ascribed to terminal unsaturation of the type RCH=CH₂. Moreover, the resulting conjugated system of double bonds is established by the presence of an absorption band at 6.2 μ and by characteristic ultraviolet absorption maxima. The strong absorption at 7.3 μ is attributed largely to the presence of a 3-methyl side chain rather than to one or more methyl groups present in the 5-alkoxy group. It should be noted that the intensity of this absorption band remains relatively undiminished in 3-methyl-5-benzyloxy-6-chloro-1,3-hexadiene (IVc) where there can be no contribution from the 5-alkoxy group. The presence of an internal double bond corresponding to RCH=CHR was not noted in any of the diene spectra examined. This type of double bond would have been formed if the ether group in the 5-position had been eliminated to produce the desired 2,4-hexadiene (III).

The use of infrared absorption spectra also has

(7) Because of space limitations, the infrared absorption spectra discussed are not included. These scans have been deposited as Document number 4602 with the ADI Auxiliary Publications Project, Photoduplication Service, Library of Congress, Washington 25, D. C. A copy may be secured by citing the Document number and by remitting \$3.75 for photoprints, or \$2.00 for 35 mm. microfilm in advance by check or money order payable to: Chief, Photoduplication Service, Library of Congress.

afforded a means of studying critically the sulfonic acid-catalyzed dealcoholation reaction. Relative changes in the intensity of characteristic absorption maxima have been used to determine the progress of this reaction. As an illustration, three such maxima were used to follow the dealcoholation of the 1-methoxy-5-ethoxy adduct (IIa). Changes in the intensity of these absorptions are plotted in Graph I. The absorption at 11.1 μ is attributed to the 1,3-diene formed in the reaction; this absorption reached a maximum in one and one-half hours at the boiling point of toluene and then decreased rapidly as heating was continued. The diminishing maximum at 3.6 μ , on the other hand, is indicative of the methoxyl group initially present in the 1-methoxy-5-ethoxy adduct (IIa) and is useful for determining the relative concentration of starting material at various stages of the reaction. The appearance of an uncharacterized compound, apparently formed at the expense of the 1,3-diene and represented by the absorption at 5.9 μ , also has been noted in the graph.

Infrared absorption spectra has facilitated the study of the dealcoholation of three other 1,5-dialkoxy-2-hexenes. The 1-methoxy-5-benzyloxy adduct (IIg) was observed to undergo reaction more slowly than the 1-methoxy-5-ethoxy adduct (IIa); the 11.1 μ absorption reached a maximum intensity only after three to four hours had elapsed. Moreover, the 5-benzyloxy-1,3-hexadiene (IVc), once formed, appeared to be more stable to the conditions of the dealcoholation than the corresponding 5-ethoxy analog (IVa). Even after prolonged heating of this diene with a catalytic amount of *p*-toluenesulfonic acid in boiling toluene, the presence of the degradation product represented by an absorption maximum at 5.9 μ was not noted. The dealcoholation of the 1-benzyloxy-5-isopropoxy compound (IIe), on the other hand, proceeded rapidly, and the lability of the resulting 5-isopropoxy-1,3-hexadiene (IVb) was comparable to that observed for the 5-ethoxy analog (IVa). While the complexity of the infrared scans obtained during the dealcoholation of the 1-phenoxy-5-isopropoxy adduct (IIf) did not permit an entirely adequate analysis of this reaction, these scans did establish that a 2,4-diene structure (III) was not formed.

Experimental

3-Methyl-5-ethoxy-6-chloro-1,3-hexadiene (IVa).—To 100 ml. of dry toluene was added 0.95 g. (0.05 mole) of *p*-toluenesulfonic acid monohydrate and the mixture refluxed vigorously for 15 minutes under a condenser equipped with a water trap. An anhydrous solution of the reagent resulted. After 20.6 g. (0.1 mole) of 1-methoxy-3-methyl-5-ethoxy-6-chloro-2-hexene had been introduced in a single portion, the solution was refluxed 1.5 hours. After three water washings to remove the *p*-toluenesulfonic acid, the solution was dried over sodium sulfate. The toluene was removed under reduced pressure and a vacuum flash distillation was used to separate the other distillable components. Finally, a fractionation of the products through a 20" \times 1/4" rotating platinum-band still yielded 11.4 g. (0.065 mole) (65%) of 3-methyl-5-ethoxy-6-chloro-1,3-hexadiene, b.p. 35–37° (1.0 mm.), n_D^{20} 1.4752. This product was characterized by its infrared absorption spectrum and by elemental analysis.

Anal. Calcd. for C₉H₁₅OCl: C, 61.89; H, 8.59; Cl, 20.34. Found: C, 61.78, 62.10; H, 8.59, 8.59; Cl, 20.35.

3-Methyl-5-benzyloxy-6-chloro-1,3-hexadiene (IVc).—Ten grams (0.37 mole) of 1-methoxy-3-methyl-5-benzyloxy-6-chloro-2-hexene was dissolved in 50 ml. of dry toluene,

containing 0.32 g. (0.002 mole) of anhydrous *p*-toluenesulfonic acid, and the solution was refluxed gently for four hours. Three water washings removed the *p*-toluenesulfonic acid. The solution was dried over sodium sulfate and the toluene separated under reduced pressure. A flash distillation in a high vacuum removed the distillable components and these materials were fractionated through a 20" X 1/4" rotating platinum-band column. Three and eight-tenths grams (0.016 mole) (45%) of 3-methyl-5-benzyloxy-6-chloro-1,3-hexadiene, b.p. 86–89° (0.2 mm.), n_D^{20} 1.5301, was isolated. This product was characterized by its infrared absorption spectrum and by elemental analysis.

Anal. Calcd. for $C_{14}H_{17}OCl$: C, 71.04; H, 7.19; Cl, 13.60. Found: C, 71.00, 70.96; H, 7.07, 7.20; Cl, 13.85, 13.60.

Use of Infrared Absorption Spectra to Follow the Dealcoholation Reaction.—The required amount of *p*-toluenesulfonic acid monohydrate was dissolved in toluene. The solution was dehydrated by vigorous refluxing for 15 minutes under a condenser equipped with a water trap. The anhydrous solution was cooled to 40–50°, and the compound to be dealcoholated was added in a single portion. The first 1.0-ml. aliquot was removed immediately. The reac-

tion mixture was brought to reflux temperature, and 1-ml. aliquots were then removed at regular intervals. The infrared absorption scans were obtained for each aliquot immediately after removal from the reaction mixture. Graphs showing changes in intensity of various characteristic absorptions were then prepared.

In Fig. 1, the dealcoholation of 1-methoxy-3-methyl-5-ethoxy-6-chloro-2-hexene is described. In this run, a 20:1 molar ratio of adduct to *p*-toluenesulfonic acid was used; the concentration of adduct in the toluene was 17% by weight. In the plotting of the absorption data obtained, the variance in reactant concentration and cell thickness was corrected to a concentration of 20 g. adduct/100 ml. of toluene with an absorption path of 1 mm. In the graph, curve A is a plot of infrared absorptions at 3.6 μ and represents a decrease in concentration of the starting material. Curve B is a plot of infrared absorptions at 11.1 μ and shows changes in concentration of the 1,3-diene formed in the reaction. Changes in intensity of infrared absorptions at 5.9 μ are described by plot C; this plot represents the appearance of an uncharacterized product, presumed to be formed largely at the expense of the 1,3-diene.

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Synthesis of a Series of Substituted Phenylpropionic Acids

By MELVIN S. NEWMAN AND STEWART H. MERRILL¹

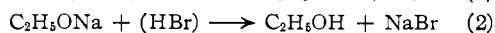
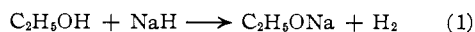
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The synthesis of phenylpropionic and of *o*-, *m*- and *p*-chloro-, methoxy- and nitrophenylpropionic acids is described. A new procedure for alkaline dehydrohalogenation is illustrated in several of the syntheses.

The reasons for the synthesis of a series of *ortho*-, *meta*- and *para*-substituted phenylpropionic acids are given in the accompanying paper.² In this paper are described the synthesis of phenylpropionic acid and the *o*-, *m*- and *p*-chloro, nitro and methoxy analogs.

In the synthetic work prime attention was paid to purity of product so that the yields reported do not reflect efforts to reach a maximum. All of the acids were prepared by dehydrobromination of the corresponding dibromocinnamic acid or ester. In each case by-products were obtained which rendered the isolation of pure propionic-type acid difficult. Since each case was different no attempt at generalization concerning conditions for reaction or purification will be made. Rather each experimental procedure will be described.

A new procedure was used for some of the alkaline dehydrobrominations. This procedure involves addition of a small excess of sodium hydride to a benzene solution of the dibromocinnamate followed by small additions of absolute alcohol. The alcohol reacts with sodium hydride to form sodium ethoxide and hydrogen (equation 1). The sodium ethoxide then removes hydrogen bromide from the dibromoester thereby regenerating alcohol (equation 2).



The fact that sodium ethoxide is the real dehydrobrominating agent is shown by the failure of the

(1) Holder of a National Science Foundation Fellowship, 1952–1953.

(2) M. S. Newman and S. H. Merrill, *THIS JOURNAL*, **77**, 5552 (1955).

benzene solution of dibromoester to react with sodium hydride, even at reflux. Indeed it is important that the benzene–dibromide solution be inert to sodium hydride else a violent reaction might occur on adding the relatively large amount of sodium hydride needed.

In principle a small amount of alcohol could suffice to complete a large scale reaction. In practice occasional small additions of alcohol are needed. In any event this method drastically reduces the amount of alcohol present and, in certain cases at least, markedly improves the yield. For example, with sodium ethoxide in ethanol ethyl dibromocinnamate was converted mainly into ethyl β -ethoxycinnamate³ whereas by our procedure a good yield of pure phenylpropionic was obtained. However, our procedure could not be used for any of the nitrocinnamic ester dibromides.

The sodium hydride procedure could be generalized by using alcohols other than ethyl or any compound which will react with sodium hydride to form a conjugate base capable of effecting dehydrohalogenation. Since the solvent is mainly benzene the tendency for solvolytic side reactions with certain types of halogen compounds should be minimized.

Experimental⁴

Phenylpropionic Acid.—A solution of 115 g. (0.65 mole) of ethyl cinnamate in 250 ml. of methylene chloride was

(3) V. L. Leighton, *Am. Chem. J.*, **20**, 136 (1898). The procedure in "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., p. 515, uses potassium hydroxide in 95% alcohol and is preferable to that of Leighton.

(4) All melting points are corrected and were determined with calibrated Anschütz total immersion thermometers.