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Nitrative and Brominative Cleavage of Cyclotriveratrylene[1]

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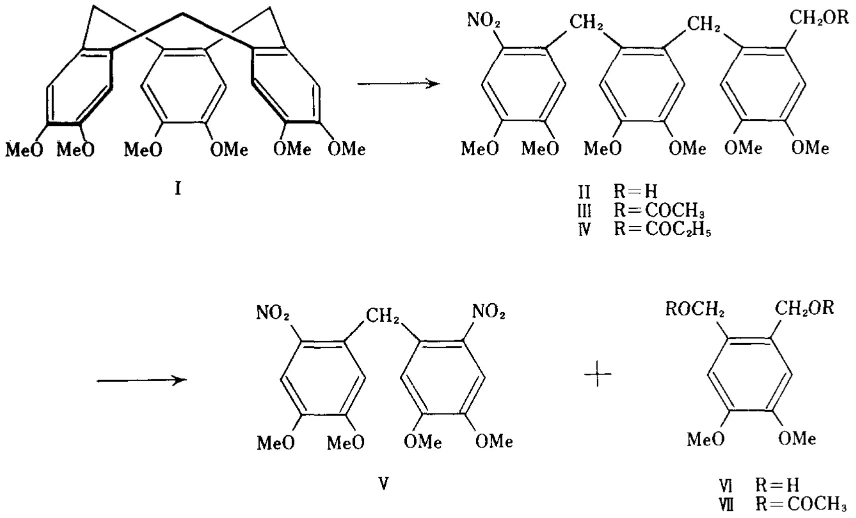
The condensation reaction of veratryl alcohol, or veratrole with formaldehyde in the presence of acid produced a cyclic product, for which dimeric[2] and hexameric structures[3] have been proposed. Later, Lindsey[4] and Erdtman[5] have revised the structure as trimeric based on the molecular weight determination. The compound I, named cyclotriveratrylene,[4] has a pyramidal structure incorporating a nine-membered ring in a crown conformation as shown in the figure. Isolation and conformational study of a cyclic tetramer have also been described.[5,6]

In this paper, we wish to describe the attempted nitration and bromination reactions of the compound I aiming at the preparation of the nuclear substituted derivatives for optical resolution.[7] We also hope to clarify a rather conflicting observation by Robinson,[2] who obtained 6,6'-dinitro-3,3',4,4'-tetramethoxydiphenylmethane (V) by the treatment with nitric acid of the compound which she considered to be dimeric but now believed to be trimeric compound I.

The nitration reaction of I, examined by using varying amounts of cupric nitrate trihydrate in acetic anhydride, afforded no compounds preserving the cyclotriveratrylene structure but induced extensive cleavage reactions. The treatment with the excess reagent (1.5 molar equivalents or more) at 40-50° for 30 min produced 82% yield of V, mp 181-183°.[2] The rest of the molecule was isolated from the last portions of chromatography as 4,5-dimethoxy-o-xylene-α,α'-diol (VI), mp 107-110.5°,[8] which was considered to be formed initially as the diacetate VII but was hydrolyzed during chromatography (see below). The formation of V was also observed by the nitration with nitric acid-acetic

Scheme 1



anhydride (79% yield) or with mixed acid.

When I was treated with one-half molar equivalent of cupric nitrate, two new compounds were isolated. The major product, which was obtained as pale yellow solid, mp 119-121°, was deduced to be nitro acetate from the IR spectrum. Another product having a nitro alcohol structure was isolated by chromatography as pale yellow powder, mp 124-124.5°. Hydrolysis of the nitro acetate furnished the nitro alcohol. Based on analytical data and molecular weight determinations, the formulas for the nitro alcohol and acetate were established as $C_{27}H_{31}O_9N$ and $C_{29}H_{33}O_{10}N$ respectively. The NMR spectra data supported structure II for the nitro alcohol and structure III for its acetate. An optimum yield of III reached 76.5%, whereas that of II was dependent on the work-up procedure and varied from experiment to experiment.

The NMR spectrum of II determined in $CDCl_3$-C_6D_6 showed aryl proton absorption as six singlets of equal intensity between δ 6.34-7.49, indicating that the substitution pattern of each of the benzene rings is 1,2,4,5-tetrasubstituted type and six positions available for substitution in I are still left unoccupied.

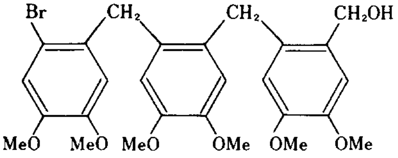
Benzyl methylene signals appeared as three two-proton singlets at δ 3.84, 4.26, and 4.40. A singlet at δ 1.24 due to a hydroxy proton disappeared on dilution with D_2O. The NMR spectrum of nitro acetate III was much like that of II with the exception of a new sharp singlet due to an acetoxyl methyl signal at δ 1.80 and loss of the signal for the hydroxyl proton. Both of these cleavage products were also obtainable by the reaction with nitric acid-acetic anhydride. The reaction with benzoyl nitrate in chloroform also produced II.

It is interesting to know whether this nitrative cleavage reaction is inherent to a rigid, overcrowded cyclotriveratrylene ring system, or ascribable to a substituted polymethoxydiphenylmethane structure. Also interesting is the mode of formation of the double cleavage products, which may be formed either by simultaneous attack of the nitrating reagent on I or by a stepwise reaction through intermediacy of II or III. To make choice between these possibilities, nitro acetate III was further treated with cupric nitrate-acetic anhydride. The reaction produced V in 65.7% yield together with VI thus favoring the stepwise reaction (scheme 1).

The substitution or addition reaction of cupric nitrate or nitric acid in acetic anhydride is regarded to involve acetyl nitrate and dinitrogen pentoxide as the reactive species.[9] The nitrative cleavage reaction is facilitated by the following two reasons, i) high electron density at the para position of a methoxy group for electrophilic attack, and ii) stabilization of veratryl cation as a good leaving group. The formation of alcohols II and VI may be due to hydrolysis of acetates or nitrates. Partial or complete hydrolysis of acetates occurred during chromatography (Woelm neutral alumina or Florisil).

Predominant formation of III suggests the involvment of acetyl nitrate as the major reactive species. Relevant to this the reaction of I with cupric nitrate-propionyl anhydride produced nitro propionate IV as pale yellow solid (crude), from which II was obtained on hydrolysis. The NMR spectrum of IV determined in $CDCl_3$-C_6D_6 was essentially similar to that of acetate III except that a singlet due to a methyl signal at δ 1.80 was replaced by ethyl absorption which appeared as a three-proton triplet at δ 1.00 and a two-proton quartet at δ 2.12.

Bromination of I, under various conditions, afforded bromo alcohol VIII, mp 145-146°. The structure was confirmed by elemental analysis, molecular weight dtermination, and spectra data. The NMR spectrum showed six one-proton singlets for aryl protons between δ 6.37-6.96 and three two-proton singlets for methylene groupings at δ 3.84, 3.91, and 4.44 together with methoxy signals.



VIII

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