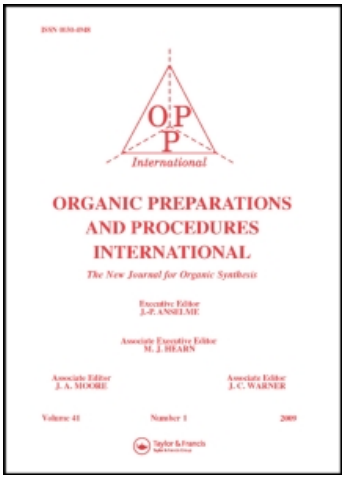

Organic Preparations and Procedures International
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

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To cite this Article Atchley, Ralph W. and Tolbert, Bert M.(1971) 'SYNTHESIS OF 5,6-0-ALKYLIDENE DERIVATIVES OF L-ASCORBIC ACID BY THE ORTHOFORMATE METHOD', Organic Preparations and Procedures International, 3: 6, 299 — 302
To link to this Article: DOI: 10.1080/00304947109356079
URL: http://dx.doi.org/10.1080/00304947109356079

ORGANIC PREPARATIONS AND PROCEDURES, INT. 3(6), 299-302 (1971)

SYNTHESIS OF 5,6-O-ALKYLIDENE DERIVATIVES OF L-ASCORBIC ACID BY THE ORTHOFORMATE METHOD

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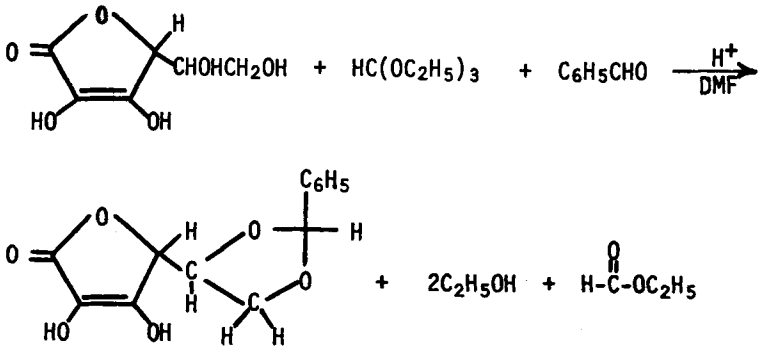

The 5,6-O-alkylidene derivatives of ascorbic acid are important intermediates in the synthesis of the 2- and 3-sulfate and phosphate esters of this compound. Recent work in this laboratory and a report by Mead and Finamore[2] indicate that a sulfate ester of ascorbic acid is present in biological systems. In developing a synthesis of these compounds, we found that existing procedures for the preparation of 5,6-O-alkylidene derivatives were in various ways unsatisfactory for our purposes. For example, the only available preparation for the benzylidene derivative gave a 12% yield.[3] The procedures for the only known remaining isopropylidene and cyclohexylidene derivatives appeared too inconvenient or too frequently gave lower yields than reported, in our hands.[4,5] This prompted our search for a more suitable method.

We now report the synthesis of the 5,6-O-benzylidene, cyclopentylidene and isopropylidene derivatives of L-ascorbic acid by application of the orthoformate method so successfully used by Chladek and Smrt in their preparation of the cyclohexylidene, isopropylidene, cyclopentylidene and p-anisylidene derivatives of ribonucleosides.[6] The method consists of dissolving the ascorbic acid in dry dimethylformamide (DMF), adding a stoichiometric amount or up to a double molar amount of the aldehyde or ketone, followed by a two to four fold excess of ethyl orthoformate and a catalytic amount of trifluoracetic acid. The reaction is run at room temperature. Yields appeared high, 80% or above, as judged visually from TLC analysis. The course and extent of the reaction was followed by this means in order to determine the best point to begin work-up. For example, a TLC analysis of the benzylidene after one hour reaction time indicated about a 90% conversion. After stripping off the volatile components under good vacuum (150 microns or better) at no higher than 40°, a TLC analysis of the syrupy residue showed the complete disappearance of the ascorbic acid indicating a quantitative conversion. The light colored unpurified product was used directly in the next reaction. Proof of the benzylidene derivative was obtained by the melting point of recrystallized material from benzene and TLC agreement with that in the only existing literature report.[3] It needs to be mentioned that the benzylidene group is very sensitive to removal by hydrolysis in the presence of an acid such as benzoic acid which can be an impurity from oxidation of benzaldehyde. For this reason and from a practical standpoint, recrystallization for this compound is not recommended in serial synthesis work. If recrystallized pure material is absolutely necessary, then one must use completely dry benzene and work in a dry box. Even so, recrystallization is slow and difficult.

SYNTHESIS OF 5,6-O-ALKYLIDENE DERIVATIVES OF L-ASCORBIC ACID

The isopropylidene derivative prepared by the orthoformate method was identified by a TLC comparison with a sample prepared by the Salomon method.[4] The preparation of the new cyclopentylidene derivative was indicated by its position on the chromatogram relative to the other derivatives. The compound remains to be isolated, purified and further characterized.

The TLC analysis used the solvent system chloroform, methanol and water (65:25:4). Brinkman precoated Silica Gel F_{254} plates, both 10 and 20 cm lengths, were employed. Detection was with iodine vapor and uv. R_f values were 0.38, 0.40, 0.30 respectively for cyclopentylidene, benzylidene and isopropylidene derivatives and 0.10 for L-ascorbic acid.

EXPERIMENTAL

5,6-O-Benzylidene-L-Ascorbic Acid.[7] A solution of 0.880 g (5 mM) of L-ascorbic acid in 5 ml of DMF (distilled, dried over P_2O_5 and redistilled) was treated with 0.65 ml (5 mM) of dried, redistilled benzaldehyde, 3 ml (20 mM) of ethyl orthoformate and about 5 drops of trifluoracetic acid. The reaction mixture was allowed to stand at room temperature with occasional shaking and sampled periodically for TLC analysis. After 1 hour when the reaction was nearly complete, the mixture was transferred to a Roto-Vac and the volatile components were removed under 150 micron or better vacuum at about 40°. The resulting syrup has been used directly in sulfation procedures. For identification, the 5,6-O-benzylidene ascorbic acid was recrystallized from very dry benzene. The recrystallization proceeded slowly over a period of at least a week with only a very small amount of product obtained. The melting point after one such recrystallization was the same as the literature reported value, 167-168° C.

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1. (a) Author to whom inquires should be addressed.

   (b) Acknowledgment is made of a grant from the NSF Summer Research Participation Fund for College Teachers which enabled R. Atchley to perform the experimental work.

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7. The structure of this compound is given as the first product on the title page of this paper.

(Received August 17, 1971; in revised form November 9, 1971)