CHEMICAL MODIFICATION OF ANTITUMOR ALKALOID CAMPTOTHECIN.[1] ACID-CATALYZED CONVERSION OF 7-HYDROXYMETHYLCAMPTOTHECIN INTO THE ALDEHYDE AND ITS ACETALS

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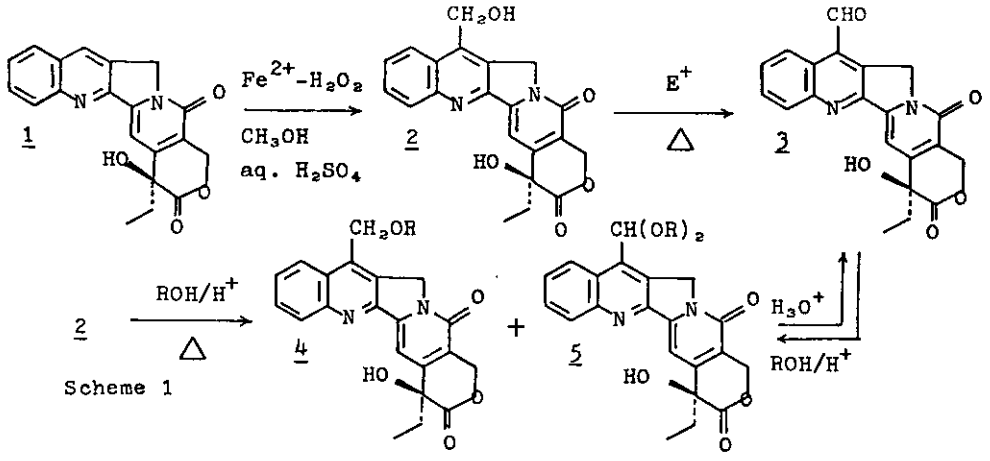
Abstract —— Camptothecin-7-carbaldehyde (3) was prepared from 7-hydroxymethylcamptothecin (2) by treatment with such cationoid agent as sulfuric acid, acetic acid, p-toluenesulfonyl chloride, phosphoryl chloride, thionyl chloride, or triphenylphosphine-carbon tetrachloride. On heating with sulfuric acid in an alcoholic solution, 2 afforded 7-alkoxymethylcamptothecin (4) and 7-dialkoxymethylcamptothecin (5), the product-ratio depending upon the acid-concentration.

(+)-Camptothecin (1), isolated first from Camptotheca acuminata (NYSSACEAE) by Wall and co-workers in 1966,[2] has attracted much attention because of its significant inhibitory activity toward L1210 in mice and Walker 256 tumor in rats.[3] This alkaloid is not clinically utilized at present, except in China, because of its high toxicity;[4] however, it is still one of the most potent substances having antitumor activity. Many attempts to obtain lower toxicity derivatives with activity as high as 1 have appeared in literatires.[5] We have been conducting a study of the chemical modification of 1 using naturally occurring 20(S)-camptothecin as a starting material.[1] This article describes novel processes to convert 7-hydroxymethylcamptothecin (2) into the aldehyde (3) and its acetals (5) by treatment with various cationoid agents (E^+) without any conventional oxidizing agent.

The hydroxymethyl compound 2 was obtained in satisfactory yield by the reaction of 1 with hydrogen peroxide-ferrous sulfate in a mixture of aqueous sulfuric acid-methanol.[6] Acylation of 2 gave 7-acyloxymethylcamptothecin in good yield by

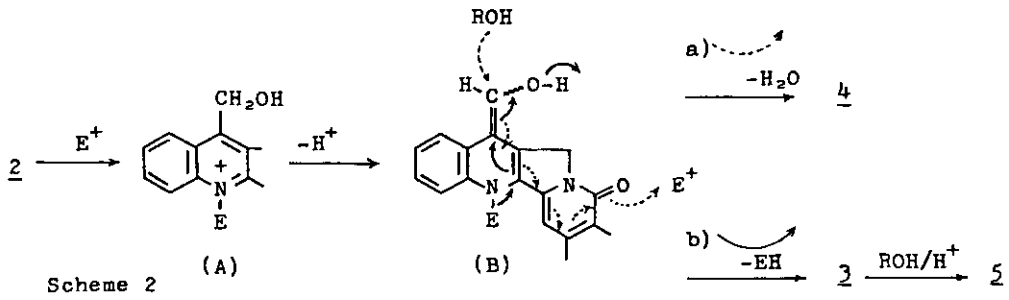
the treatment with such acid anhydrides as acetic, propionic, and butyric anhydrides, whereas acylation with acid chloride such as benzoyl or phenylacetyl chloride afforded considerable amounts of the aldehyde 3[7] in addition to the corresponding acyloxymethyl compound. p-Toluenesulfonyl chloride in hot pyridine also effected the conversion of 2 into 3 in 68% yield, under which condition 7-acyloxymethyl compounds were recovered unchanged. Attempted chlorination of 2 with such chlorinating agents as phosphoryl chloride, thionyl chloride, and triphenylphosphine-carbon tetrachloride resulted in the formation of the aldehyde 3 in moderate yields, no chloromethyl compound being formed in a detectable amount. Conversion of 2 to 3 was more conveniently conducted by heating in aqueous sulfuric acid or in acetic acid.

Heating of the alcoholic solution of 2 in the presence of catalytic amount of sulfuric acid or boron trifluoride etherate furnished the corresponding 7-dialkoxymethylcamptothecins (5, R=C_2H_5, n-C_4H_9) in good yield, which were easily hydrolyzed into 3 with aqueous mineral acids. However in an alcoholic solution of high acid concentration(e.g. 5 ml conc. H_2SO_4 in 20 ml of n-butanol), 7-alkoxymethylcamptothecin (4, R=n-C_4H_9) was obtained as major product with a trace amount of the acetal (5, R=n-C_4H_9).



Scheme 1

A possible mechanism for the formation of the aldehyde 3 from 2 is depicted in Scheme 2. The intermediate anhydrobase (B) is readily formed via deprotonation from the cationoid adduct (A). Rearomatization of the B-ring with loss of a hydride in terms of EH furnishes 3. Another protonation of (B) with the participation of heteroannular conjugation with the carbonyl in the D-ring could accelerate the formation of the ether 4 and the acetal 5 in highly acidic medium.



Scheme 2

References and Notes

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6) Cf. W. Buratti, P. G. Gardini, F. Minisci, F. Bertini, R. Galli, and M. Perchinunno, Tetrahedron, 27, 3655 (1971).

7) Yellow prisms, m.p. 256-260° (dec.), IR(KBr): 1750(lactone), 1690(CHO), 1655(pyridone). NMR(in $CDCl_3$): 11.20(CHO). MS: m/e 376.1077 $[M^+]$ for $C_{21}H_{16}N_2O_5$ = 376.1059.

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