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On the Structure of Thromboxane A_2

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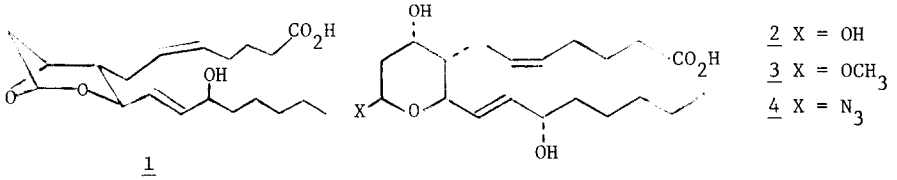
Abstract. The reactions of the 2-alkoxyoxetane 5 with sodium azide and methanol yield the α-azidoether 7 and the dimethyl acetal 8, respectively, paralleling reactions reported for TXA_2. The hydrolysis of 5 reported by Bruice to involve general acid catalysis proceeds at a rate similar to that reported for TXA_2. All these cleavage reactions are most likely to proceed by the same mechanism. These findings support structure 1 for TXA_2.

Thromboxane A_2, an important vasoactive metabolite of arachidonic acid has been assigned structure 1 by Hamberg et al.[1] This structure rests largely on the conversions of 1 to TXB_2, 2, ($t_{1/2}$ at pH 7.4 = 32 sec), to the methyl acetal 3 upon addition of methanol and to the azide 4 upon addition of 5 M sodium azide. Both 2 and 3 have been synthesized by unambiguous routes[2] and their structures are firmly established.



1

2 X = OH
3 X = OCH_3
4 X = N_3

TXA_2 has not been prepared by total synthesis nor has the enzymatic route yielded sufficient material for spectroscopic examination. In the absence of direct spectroscopic evidence, structure 1 has been considered with some skepticism particularly because of the proposal[1] that "the acetal carbon binding two oxygens in the very strained bicyclic structure should be susceptible to attack by nucleophiles". Although there is no question as to the correctness of structures 2 and 3, such a mechanism for their formation is implausible. 2-Alkoxyoxetanes, simpler versions of structure 1, had been prepared and their chemistry studied prior to the discovery of TXA_2, but no comparison was made between their known chemistry and that of TXA_2.

It is the purpose of this paper to show that the chemical properties of 2-alkoxyoxetanes reported in the literature and new findings presented here are fully consonant with structure 1 for TXA_2. Two routes are available for the synthesis of 2-alkoxyoxetanes, the Paterno-Büchi photocycloaddition of ketones and vinyl ethers,[3] or the base catalyzed cyclization of β-sulfonyloxy hemiacetals.[4] Refluxing 2-alkoxyoxetanes with primary, secondary or tertiary alcohols furnished acetals of the parent β-hydroxyaldehydes.[5] Insight into the unusual sol-

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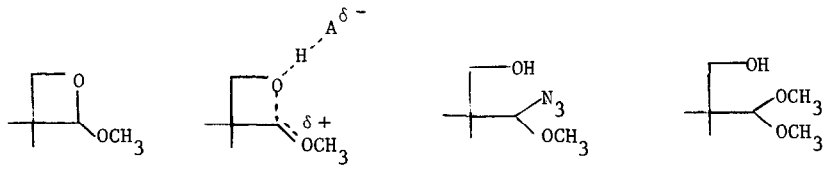
volytic behavior of 2-alkoxyoxetanes was afforded by the work of Atkinson and Bruice[6] who showed that the first step in the hydrolysis of 5 occurred with general acid catalysis, rather than by an A-1 process characteristic of the hydrolysis of simple acetals. The parallelism in the hydrolytic behavior of this model and that of TXA_2 became readily apparent when the bimolecular rate constant of hydrolysis for 5, $k_1 = 2.24 \times 10^5$, was used to calculate the half life at pH = 7.4, $t_{1/2}$ = 69 sec, which turned out to be twice that reported for TXA_2.[1] Bruice and Atkinson ascribed this tremendous rate enhancement to relief of strain in the transition state for ring opening, which involves proton donation concerted with bond breaking as shown in structure 6.[6] One may conclude from the similarity in the rate constants for hydrolysis that ring opening in TXA_2 proceeds by the mechanism established for oxetane 5 by Bruice rather than by nucleophilic attack at the acetalic carbon. It is furthermore likely that the reaction of TXA_2 with 5 M sodium azide leading to the azido ether 4 should pass through a similar transition state. Moreover, 5 should yield the open azido ether 7 at a comparable rate. Indeed, the reaction of 5 (300 µl) with THF/5 M sodium azide 1:5 (18 ml, pH = 9.35) for 16 hours at 25° produced as the sole product the azido ether 7, 185 mg after flash chromatography. ^{1}H NMR (500 MHz): δ 4.34 (s 1H, CHN_3OCH_3) 3.55 (s 3H, OCH_3) 3.49 (dd J = 6, 11 Hz, 1H) and 3.42 (dd J = 5.5, 11 Hz, 1H, CH_2OH) 1.97 (t 1H, OH) 0.97 (s 3H, CH_3). IR: 2,100 cm^{-1} (N_3), Anal. C, 46.01; H, 8.31; N, 24.59.



5 6 7 8

The reaction of 5 with methanol/0.05 M pH 7 phosphate buffer 25:1 at 25° for 30 min was performed simulating the conditions used by Hamberg et al., with TXA_2.[1] The dimethyl acetal 8 was formed in addition to a small amount of hydroxy aldehyde. The acetal was identical with an authentic sample obtained by refluxing 5 with methanol.[5] ^{1}H NMR: δ 4.00 (s 1H, $CH(OCH_3)_2$) 3.52 (s 6H, OCH_3) 3.43 (d J = 5.8 Hz, 2H, CH_2OH) 2.60 (t J = 5.8 Hz, 1H, OH) 0.92 (s 6H, CH_3).

It is concluded that the reactions reported for TXA_2 by Hamberg et al., are in full accord with those of simple 2-alkoxyoxetanes. The presence of an additional ring in TXA_2 contributes little to the reactivity of the system.

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