Tetrahedron Letters Vol. 21, pp 777 - 780
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0040-4039/80/0222-0777$02.00/0

THE REACTION OF EREMANTHIN AND ISOEREMANTHIN WITH BROMINE. UNPRECEDENTED SIMULTANEOUS ADDITION OF Br_2 TO TWO ISOLATED BUT TOPOGRAPHICALLY RELATED DOUBLE BONDS.

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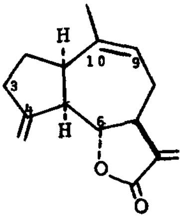
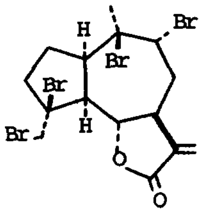
Summary: The reaction of 1 with Br_2 in $CHCl_3$ proceeds with the simultaneous and stereospecific incorporation of two moles of Br_2 to give 2 thus providing strong experimental evidence for the existence of Br_3^-.

As part of a program of chemical modifications of eremanthin (1)[1] we needed a selective protection for the 9,10-double bond. Electrophilic addition of Br_2 seemed an appropriate choice[2] and the reaction was investigated.

To our surprise, when 1 was allowed to react with one mole of Br_2 in $CHCl_3$ at -70° C an equimolar mixture of 1 and the relatively unstable tetrabromide 2[3] could be detected by ^1H NMR spectroscopy. Addition of a second mole of Br_2 led exclusively to 2.

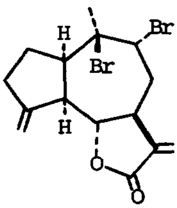


1



2

Trans addition to the 9,10-double bond was indicated by observing the quantitative formation of 1 upon reaction of 2 with Zn in methanol. The stereochemistry at this site as indicated was suggested by comparison of the ^1H NMR properties of 2 with those of the dibromides 3 and 4[4].



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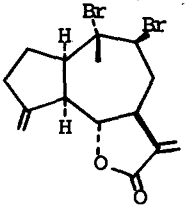

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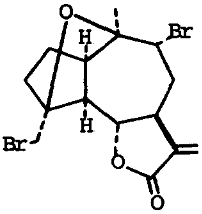

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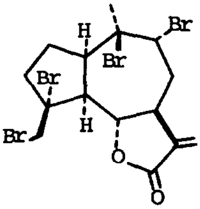
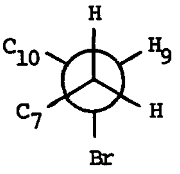
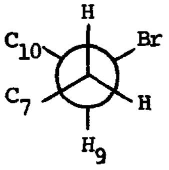


6

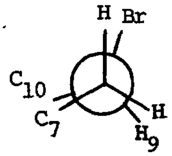
While 2 and 3 showed H-9 as a collapsed doublet of doublets ($J_{8,9} \simeq 3.5$ Hz) centered at 4.81 and 4.78 δ respectively, compound 4 had the corresponding signal as doublet of doublets (J = 6 and 10 Hz) centered at 4.67 δ. On the other hand, the signal corresponding to the C_{10}-CH_3 appeared at 1.99 δ in 2, 1.95 δ in 3 and 1.85 δ in 4. Further, it is relevant to note that the signals (multipicity) corresponding to H-9 in 2 and 3 are superimposable with that of H-9 in the conformationally rigid dibromoether 5. This finding strongly indicates that 2 and 3 exist mainly in a chair conformation as implicit in A. The latter explains nicely the relatively low chemical shift of H-6 in 2 (5.14 δ) and 3 (4.73 δ) as compared with 4 (4.10 δ)[5]. It is important to note that while the chair conformation as implicit in A is the only conformation which explains the NMR properties of 2, the spectral properties of compound 4 may be explained by the same chair conformation as expressed in A' (bromines trans-diequatorial), or, in the alternative chair conformation B in which the bromines are trans-diaxial.



A



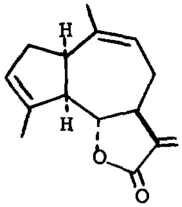
A'



B

A solution of 2 in $CHCl_3$ left at room temperature for 10 days gave the tetrabromide 6 as shown by its ^1H NMR spectrum. The signals corresponding to H-9 and the C_{10}-CH_3 were superimposable with those of 2 but H-6 appeared at 5.07 δ and C_{14}-H_2 appeared as two doublets (J = 10.5 Hz) centered at 4.09 and 4.53 δ. (4.13 and 4.46 δ in 2). We believe that the proposed inversion of configuration at C-4 is triggered by stereoelectronic repulsion between the β-oriented bromine atoms at C-4 and C-10.

On the other hand, reaction of isoeremanthin (7) with one mole of Br_2 in $CHCl_3$ or ether at -70°C led to a more complex mixture of products as shown below (isolated yields are given):



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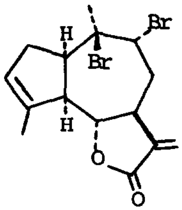

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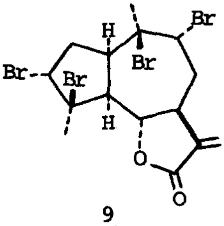
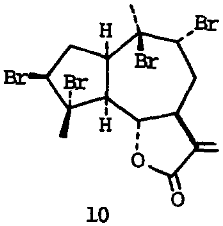


9



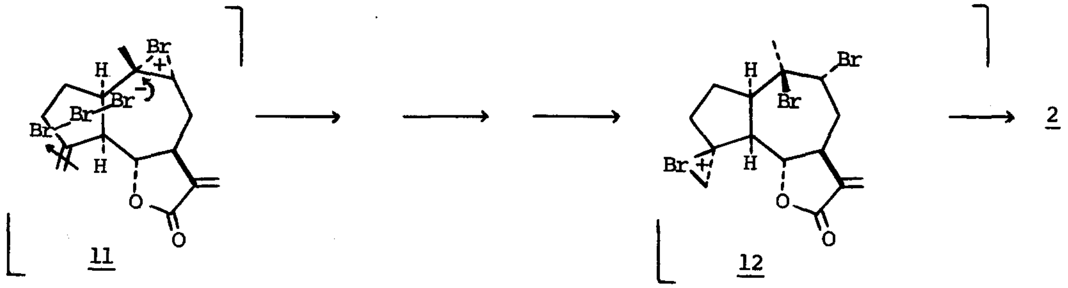
10

$CHCl_3$	26	18	15	3	(%)
ETHER	16	53	traces	3	(%)

As already indicated for 2 and 3 the 7-membered ring of the bromides 8, 9 and 10 also seem to adopt the chair conformation as implicit in A. Thus, the signal corresponding to C_{10}-CH_3 appear at 2.00, 1.95 and 1.96 δ respectively and the H-9 signal is a collapsed doublet of doublets ($J \simeq 3.5$ Hz) centered at 4.79 δ. Further, the ^{1}H NMR spectra of 9 and 10 are almost identical in other regions of the spectrum too: H-6 appears at 5.19 δ (4.87 δ in 8) and the signal corresponding to H-3 is a doublet ($J \simeq 3.5$ Hz) centered at 4.88 δ. This spectral identity suggests that if 9 and 10 have the same conformation at the 7-membered ring, they must differ in the puckering of the 5-membered ring. While 9 is suggested to have C-4 above the plane of the cyclopentane ring, 10 would have C-3 above the said plane thus avoiding the eclipsing between the bromine at C-3 and the methyl at C-4[6].

On the other hand, reaction of 8 with Br_2 in ether or chloroform leads to 10 exclusively thus demonstrating that 8 is not an intermediate in the formation of 9.

Kinetic studies of bromine addition to olefins in nonpolar solvents show a second order dependence on bromine suggesting the presence of the linear and electrophilic tribromide ion as the acting nucleophile[7]. On the other hand electrophilic addition reactions to 1 have always yielded 9,10-disubstitued derivatives resulting by approach of the reagent from the less hindered α face[2]. It is reasonable therefore to assume that reaction of 1 with Br_2 leads initially to the bromonium ion intermediate 11. Reaction of this latter ion with Br_3^- would result in the simultaneous and efficient interaction at C_{10} (electrophilic site) and the π system at the 4,14-double bond (nucleophilic site) leading to a charge transference complex which collapses into the β-oriented bromonium ion intermediate 12. The sequence is completed by nucleophilic attack at the softer[8] and less hindered C_{14} to yield 2.



An identical argument readily explains the formation of 9 from 7. In this latter case however, the π system at the 5-membered ring is not parallel to the path of the incoming Br_3^- thus diminishing the efficiency in the formation of a β-oriented 3,4-bromonium ion intermediate Part of the nascent bromine leaves therefore the surface of 8 which in a consecutive reaction leads, thru an α-oriented 3,4-bromonium ion, to 10. In ether where the acting nucleophile is more likely to be Br^- [9] the main observed product is the dibromide 8.

To our knowledge the work described above represents the first direct experimental evidence in favor of the tribromide ion as the acting nucleophile in bromination reactions in nonpolar solvents[10].

REFERENCES AND NOTES

1 . Part 8 in the series "Chemical Transformations of Abundant Natural Products". Part 7 is the preceding paper. Financial support for this and the previous papers was provided by the Ministry of Planning (FINEP), the National Research Council of Brazil (CNPq), and the Research Council of the University (CEPG).

2 . The most nucleophilic olefin in 1 is the 9,10-double bond. For example, reaction of 1 with equimolar amount of peracids leads almost exclusively to the 9,10-α-epoxide. W. Vichnewski and B. Gilbert, Phytochem. 11, 2563 (1972).

3 . All new compounds reported gave analytical and spectral data in complete agreement with the structures as proposed.

4 . Dibromides 3 and 4 were obtained as minor products in the reaction of 1 with Br_2 in dioxane-water and ether respectively.

5 . See preceding paper and references therein.

6 . While 9 and 10 can hardly be differentiated from their spectral properties, they may be easily distinguished by thin layer chromatography using plates coated with silica gel and eluting with a mixture of hexane/ ethyl acetate (7/3; v/v). Compound 9 has a Rf = 0,79 and gives a pink spot when sprayed with a solution of ceric sulphate and heated at 100^{o}. In contrast, 10 has a Rf ~ 0.75 and gives a green spot when similarly treated.

In addition compound 9 is relatively unstable compared to 10. Thus when in solution or in the solid state it undergoes decomposition to a complex mixture of unidentified substances. As with 2 we attribute this relative instability to the interaction between the β-oriented bromine atoms at C_4 and C-10.

7 . R.C. Fahey, "Topics in Stereochemistry", vol. 3, E.L. Eliel, N.L. Allinger, Eds., Interscience (J.W.), New York (1969) , p. 237. A more recent reference on the subject is A. Modro, G.H. Schmid and K. Yates, J. Org. Chem., 42, 3673 (1977).

8 . J.E. Dubois, M.H. Durand, G. Mouvier and J. Chretien, Tetrahedron Lett., 2993 (1975).

9 . The reaction of dioxane with Br_2 yields dioxane dibromide, a useful brominating reagent. L.F. Fieser and M. Fieser, "Reagents for Organic Synthesis", J. Wiley and Sons Inc., New York (1967), p. 333, and references therein.

10. Attack of 11 by Br_2 also explains satisfactorily the formation of 2. However , considering the equilibrium: $Br_2 + Br^- \rightleftharpoons Br_3^-$, two lines of reasoning may be developed to rule out this possibility. Firstly, if the equilibrium favored the formation of Br_3^- (an almost certain fact in a nonpolar solvent), one would be led to accept that Br_2 is a better nucleophile than Br_3^- . Secondly, if the equilibrium were displaced to the left, and knowing that no dibromides are formed in the reaction of 1 with Br_2 in $CHCl_3$, one would be forced to accept the even less likely conclusion that Br_2 is a stronger nucleophile than Br^-.

(Received in USA 26 November 1979)