

CYCLIZATION OF POLYENES XX¹

BROMO ETHERIFICATION OF UNSATURATED ALCOHOLS AND KETONES

Tadahiro KATO^{*}, Isao ICHINOSE, Takeo HOSOGAI^{**}

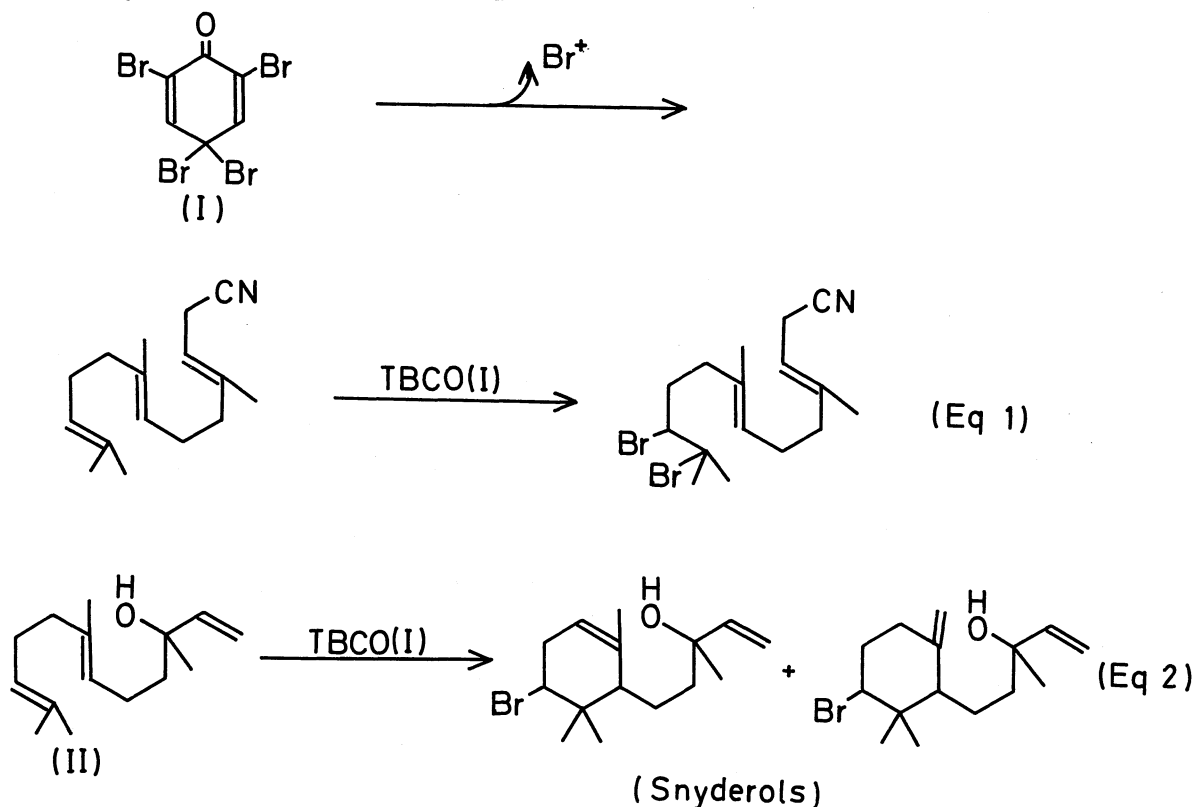
and (the late) Yoshio KITAHARA

Department of Chemistry, Faculty of Science,

Tohoku University, Sendai 980

By the reaction of 2,4,4,6-tetrabromocyclohexadienone (I, TBCO) with unsaturated alcohols (III and VI) and ketones (IX), it was found that the corresponding bromo ethers (IV and VIII) and (X) were obtainable in moderate yields.

In conjunction with our interest in developing efficient bromination reagent of polyenes for projected synthesis of brominated terpenoids², we have investigated the chemistry of 2,4,4,6-tetrabromocyclohexa-2,5-dienone (I, abbreviated as TBCO)³



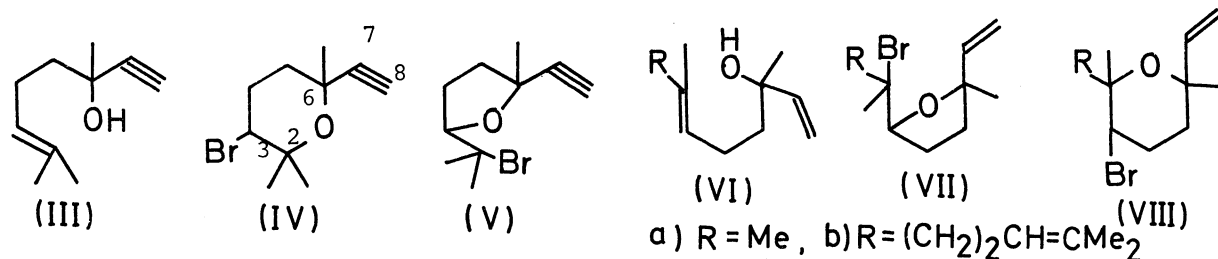
and have found that TBCO reacts with polyenes in two different fashions⁴. One is the selective bromination of terminal double bond of polyenes as exemplified in eq 1⁵. The other is the brominative cyclization as typified by eq 2⁶, in which the objectives, dl-synderols, were obtained although in low yields. In this reaction, however, formation of bromo ethers was observed as a major reaction product. Further studies on the reactivity of TBCO revealed that I was an efficient reagent for bromo etherification of unsaturated alcohols and ketones. The results are described in this paper.

I. Reaction of δ,ϵ -Unsaturated Alcohols.

A mixture of dl-dehydrolinalool (III, 1.52 g), TBCO (4.11 g) and anhydrous CH_2Cl_2 (50 ml) was kept at room temperature for 8 hrs under N_2 atmosphere and the resulting mixture was shaken with aq NaOH to remove the resultant tribromophenol (3.06 g). The neutral portion was passed through a short SiO_2 column to obtain a mixture of bromo ethers (1.90 g, 82%). The crude product was suggested to be a 4 : 1 mixture of IV and V by NMR and TLC, the latter showing two closely located spots. By repeated SiO_2 column chromatographies, IV was isolated in 50% yield (1.16 g) accompanying the decomposition of the other isomer (V). PMR (IV), 1.27 and 1.39 ($\text{C}_2\text{-Me}_2$), 1.61 ($\text{C}_6\text{-Me}$), 2.29 ($\text{C}_8\text{-H}$), and 3.77 ($\text{C}_3\text{-H}$, dd, 4 and 12 Hz) ppm; CMR 20.9, 30.7, and 32.1 ($\text{Me} \times 3$), 29.3 and 41.2 (C_5 and C_4), 57.4 (C_3), 67.2 and 77.1 (C_6 and C_2), 72.6 and 87.1 (C_7 and C_8) ppm. Catalytic reduction of IV (Pd/C in EtOH) afforded the corresponding tetrahydro derivative. PMR, 1.27 and 1.33 ($\text{C}_2\text{-Me}_2$), 3.97 ($\text{C}_3\text{-H}$, t, 7 Hz), 1.07 ($\text{C}_6\text{-Me}$), and 0.87 ($-\text{CH}_2\text{Me}$, t, 7 Hz) ppm⁷.

The acetylenic bond of IV is inert toward the excess of TBCO, suggesting that TBCO might be a useful bromination reagent based on eq 1 for double bond of polyenes containing triple bond. It is of interest to compare the reactivity of TBCO with that of NBS. Demole and Enggist have reported that tetrahydrofuran derivatives (VIIa, b) are the major products when NBS in CCl_4 was employed to the δ,ϵ -unsaturated alcohols (VIa, b)^{8,9}. Treatment of III with NBS in CCl_4 resulted in the formation of a mixture of IV (minor) and V (major). PMR (V), 1.49 ($-\text{OCMe}$), 1.71 and 1.73 ($-\text{CBrMe}_2$), and 4.01 (OCH- , m) ppm. On the other hand, the isomer (VIIIa)¹⁰ was suggested by NMR for the main product obtained by the reaction of VIa with TBCO. PMR (VIIIa), 1.10, 1.27 and 1.33 ($\text{OCMe} \times 3$), and 3.83 ($-\text{CHBr}$, dd, 5 and 12 Hz) ppm. From these findings it could be concluded that δ,ϵ -unsaturated alcohol was mainly converted to the six membered bromo ether by TBCO (in CH_2Cl_2) while NBS (in CCl_4) afforded the

isomeric five membered derivative¹¹.



II. Reaction of γ,δ -Unsaturated Ketones.

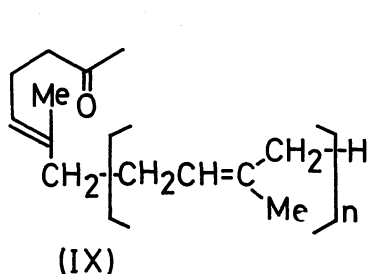
When 2.2 mol equivalents of TBCO were reacted with polyene ketones (IXa, b, c), the corresponding dibromo ethers (Xa, b, c) were obtained in almost quantitative yield. Structure of the product was confirmed by the following evidence. (Xb), PMR, 1.30, 1.63, 1.69, and 1.90 (Me x 4), 2.87 (C₄-protons, br.d, 8 Hz), 4.14 (C₅-H, t, 8 Hz), and 5.10 (C=CH, br.t, 6 Hz) ppm. Mass 354, 352, and 350 (M⁺). (Xc), PMR, 1.30, 1.70, 1.90 (Me x 3), 1.60 (Me x 2), 2.88 (C₄-protons, br.d, 8 Hz), 4.15 (C₅-H, t, 8 Hz) and 5.10 (C=CH x 2) ppm. Mass 422, 420 and 418 (M⁺). As expected, dibromo ether (Xa) was converted to methoxy ether (XI)¹² in 39% yield when treated with HCl in MeOH at room temperature. (XI), mp 52-57°, PMR, 1.30, 1.38, 1.52, and 3.30 (Me x 4), 2.44 (C₄-H, dt, 8 and 3 Hz), 2.90 (C₄-H, ddd, each 8 Hz), 3.83 (CHBr, dd, 8 and 3 Hz), and 3.90 (CHBr, dd, 8 and 3 Hz) ppm. Hydration of enol ether grouping of Xa with aq HCl followed by treatment with 2N-NaOH afforded the methyl ketone (XII)¹³. IR (neat), 1715 cm⁻¹, PMR 1.35 (Me x 2), 2.23 (COMe), 4.04 (1H, t, 8 Hz), and 4.18 (1H, t, 8 Hz) ppm.

When equimolar amount of TBCO was employed, ca 50% of the starting polyene was converted to dibromo ether (X), indicating that C₃ position of enol ether (H instead of Br in X) is more reactive than the terminal double bond of IX. It has been thus found that TBCO is an efficient reagent for bromo etherification of polyene alcohol and ketone^{14,15}.

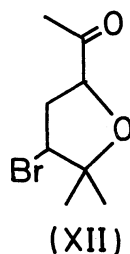
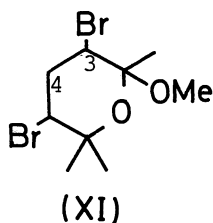
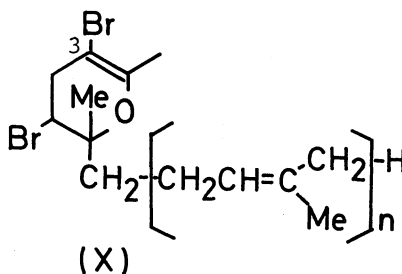
References

- * To whom correspondence should be addressed.
- ** Research fellow from Central Research Laboratories, Kuraray Co. Ltd., Kurashiki.
- 1. Part XIX of this series, T. Kato, I. Ichinose, and Y. Kitahara, Chem. Commun., 518 (1976).
- 2. For a leading reference, J. F. Siuda and J. F. DeBernardis, Lloydia, 36, No. 2 107 (1973).
- 3. T. Kato, I. Ichinose, S. Kumazawa, and Y. Kitahara, Bioorg. Chem., 4, 188 (1975).

4. Reactivity of TBCO depends on not only the functional group present in a molecule but also the solvent employed.
5. Y. Kitahara, T. Kato, and I. Ichinose, Chem. Lett., 283 (1976).
6. see ref 1.
7. Relative stereochemistry of bromine atom with respect to C₆-substituents of IV remains unsolved.
8. E. Demole and P. Enggist, Helv. Chim. Acta, 54, 465 (1971).
9. E. Demole, P. Enggist, and C. Borer, *ibid.*, 54, 1945 (1971).
10. As E. Demole and P. Enggist have observed, VII and VIII were fairly unstable, VII decomposed during SiO₂ chromatography.
11. Although formation of stereoisomers could not be ruled out, one isomer was predominantly formed in the cases of IV, V, VII and VIII.
12. Only one stereoisomer was isolated from several stereoisomeric mixture by SiO₂ column chromatography. Methoxy group of XI was presumably trans equatorial with respect to two equatorial bromine atoms since difference of chemical shift of two gem-methyls was quite small.
13. Only one stereoisomer was isolated from the reaction mixture.
14. An example of application of TBCO for the synthesis of natural product is described in the following paper.
15. All the compounds described herein have satisfactory analytical and/or mass spectral data.



a) $n=0$, b) $n=1$, c) $n=2$



(Received September 7, 1976)