BIOORGANIC CHEMISTRY 4, 188–193 (1975)

Cyclization of Polyenes

XII. Direct Brominative Ring Closure of Polyenes[1]

TADAHIRO KATO, ISAO ICHINOSE, SATORU KUMAZAWA, AND YOSHIO KITAHARA

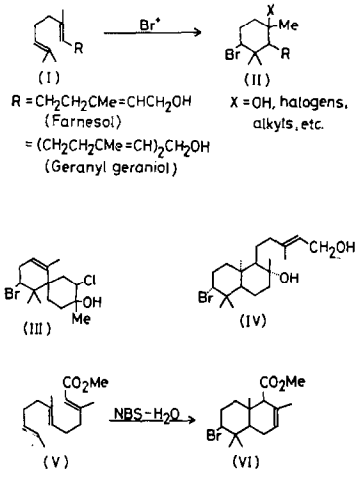
Department of Chemistry, Faculty of Science, Tohoku University, Sendai 980, Japan

Received December 16, 1974

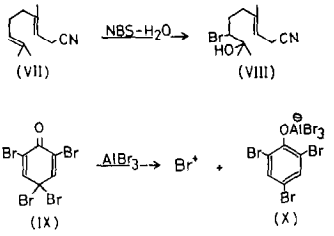
In connection with a program directed toward the biogenetic-type synthesis of bromine-containing terpenoids, we have developed a new reagent system which provides for selective brominative cyclization of polyenes. The mechanism of Br^+-formation in nature is discussed on the basis of the new reagent system.

A few dozen papers have recently been published on the isolation and structural elucidation of naturally occurring halogenated compounds from several sources. In particular, investigations into secondary metabolites of red algae (*2*), sponges (*3*) and sea hares (*4*) have yielded a rich harvest of mono-, sesqui-, and diterpenoids which possess the α,α-dimethylcyclohexyl bromide moiety (**II**). Spirofused sesquiterpenes exemplified by glanduliferol (**III**) (*2d*) and diterpenes typified by aplysin-20 (**IV**) (*4c*) are also good examples for these compounds (*5*).

These terpenoids are of considerable interest from a biogenetic point of view since the partial structure (**II**) is assumed to be derived from the corresponding prenyl compounds (**I**) by the initiation of bromonium ion attack instead of H^+ on the terminal double bond.



[1] See Ref. (*1*) for paper XI in this series.

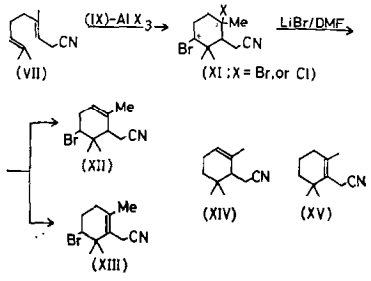


In connection with a program directed toward the biogenetic-type synthesis of bromine-containing terpenoids, we were intrigued to find a system which causes brominative cyclization in such a fashion. Although van Tamelen carried out the direct brominative cyclization of methyl farnesate (**V**) to the bicyclic bromine-containing derivative (**VI**) (*6*) by the use of *N*-bromosuccinimide (NBS) in aqueous organic solvents (*7*), this reagent system was found unsuitable for our purpose. As an example, our preliminary studies revealed that geranyl cyanide (**VII**), a model polyene in our present experiment, was merely converted to the bromohydrin (**VIII**) by treatment with NBS in aqueous acetone without formation of a cyclized product corresponding to **II**. We therefore initiated a search for a new reagent system and found that 2,4,4,6-tetrabromo-2,5-cyclohexadienone (**IX**) (*8*) is effective in the presence of Lewis acid for the execution of the brominative cyclization.

The tetrabromo ketone (**IX**) would be expected to liberate bromonium ion by the action of Lewis acid ($AlBr_3$), which is also involved in the cyclization as an essential catalyst. The resulting tribromophenoxide–$AlBr_3$ complex anion (**X**) might not be so reactive toward the carbonium ion formed initially by Br^+ attack on the terminal double bond, and hence ring formation by participation of the neighboring double bond may not be prevented, resulting in the formation of the brominated cyclization product. As hoped, after $AlBr_3$ in CH_2Cl_2 was dropped into a mixture of equimolar amounts of tetrabromo ketone (**IX**) and geranyl cyanide (**VII**), we easily obtained the cyclized product (**XI**, $X = Br$) in 15% yield by a simple operation. Similarly, treatment of **VII** with $AlCl_3$ under the same conditions afforded a bromo–chloro compound (**XI**, $X = Cl$) in 16% yield. The structure of **XI** was confirmed as follows. The nmr spectrum of **XI** ($X = Br$) shows three sharp signals at 1.08 and 1.32 ppm due to two gem-dimethyls and a tert-methyl geminal to bromine atom at 1.76 ppm in addition to a broad triplet with 8 Hz at 4.00 assigned to a C_4-hydrogen. Upon treatment with LiBr in dimethylformamide at 70°C, **XI** ($X = Br$) was quantitatively dehydrobrominated to give a mixture of olefinic bromides (**XII** and **XIII**) in the ratio of ca. 8:2. The major product (**XII**) of the olefinic bromides exhibited the gem-dimethyl signals at 1.06 and 1.19 and a C_4-hydrogen at 4.13 as a triplet (8 Hz) in the nmr spectrum. The large coupling constant of C_4-hydrogens of both **XI** and **XII**, and the great difference in the chemical shifts between the two gem-dimethyls (1.08 and 1.32) of **XI** as well as the difference of those in **XI** and **XII** (1.32 and 1.19), suggest tentatively that bromine atoms at C_1 and C_4 are axial and equatorial, respectively. Physical data of the bromo–chloro analog (**XI**, $X = Cl$) are quite similar to those of dibromo compound (**XI**, $X = Br$), thus clarifying the assigned structure of the former.

When the mixture of **XII** and **XIII** was submitted to reduction (*9*) with Bu_3SnH, the bromine was removed, resulting in a mixture of **XIV** and **XV** after repeated SiO_2 and

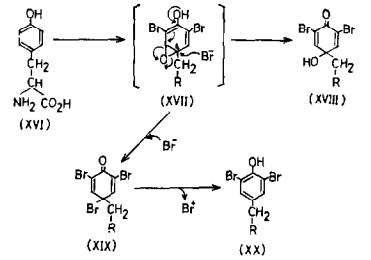
5% $AgNO_3$–SiO_2 column chromatography. The compounds thus derived were identical with authentic samples prepared by the reaction of geranyl cyanide with stannic chloride.



Based on biogenetic considerations, we have thus developed a new method which provides for selective bromination at the terminal double bond of a polyene with concomitant ring closure. We are now attempting to improve the yield as well as apply the method to more complicated polyene systems.

It is of particular interest to speculate on the origin of a bromonium ion in nature. Although adequate amounts of Br^- species may exist in sea water and hence in organisms which produce brominated terpenoids, it is not conceivable that Br^- is oxidized directly to Br^+ in the organism. In contrast, it is reasonably presumed that an organic substance(s) is involved in the oxidation. The following speculation might be acceptable, although lacking in experimental evidence, as a plausible mechanism for the formation of bromonium ion which participates in the biosynthesis of naturally occurring brominated terpenoids.

The 4-hydroxy-2,6-dibromocyclohexadienone derivative (**XVIII**) and its biogenetical equivalent exemplify another type of naturally occurring brominated compound which is widely distributed in nature, especially in coral (*10*), marine sponges (*3a–d*) and also red algae (*11*). It has been suggested (*3d*) that these metabolites are biosynthesized from tyrosine (**XVI**), probably via an arene-oxide (**XVII**). It is speculated that the epoxide ring of **XVII** is converted to a hypothetical tribromo ketone (**XIX**) by an initial attack of Br^-, followed by dehydration as shown in the scheme.



The ketone, structurally similar to our tetrabromide (**IX**), is reasonably assumed to liberate Br^+, which was involved in the brominative cyclization as in the case of our model experiment. The resulting phenol (**XX**) may be oxidized to the original oxide (**XVII**) via phenolic oxidation. Although chemical evidence is lacking for support of the above hypothesis, especially on the formation of **XIX** from **XVII**, it would be of interest to study the chemistry of a compound corresponding to **XIX**.

EXPERIMENTAL

2-Cyanomethyl-1,4-dibromo-1,3,3-trimethylcyclohexane (*XI*). Into a mixture of geranyl cyanide (1.63 g, 10 m*M*), 2,4,4,6-tetrabromo-2,5-cyclohexadienone (4.5 g, 11 m*M*) in anhydrous CH_2Cl_2 (100 ml) was dropped 2.93 g of $AlBr_3$ in 30 ml of CH_2Cl_2 with vigorous stirring under ice-water cooling and nitrogen atmosphere. The reaction mixture was kept for 1 hr under the same conditions and then diluted with excess ether. The organic solution was successively washed with aqueous Na_2CO_3 and then aqueous NaCl solution and dried over $MgSO_4$. Evaporation of the solvent afforded 4.62 g of crude oil, which was passed through a short SiO_2 column with *n*-hexane:AcOEt (19:1) as solvent. The pale yellow oil thus eluted was dissolved in *n*-hexane to obtain 463 mg of crystals of **XI**. The analytical specimen was obtained by recrystallization with *n*-hexane–CH_2Cl_2 (20:1). **XI**, dp 105–111°C. *Anal.*: Calcd for $C_{11}H_{17}NBr_2$: C, 40.89; H, 5.31; N, 4.34; found: C, 41.14; H, 5.32; N, 4.01.

Ir (KBr): 2250 (CN), 1395, 1375 cm^{-1}. Nmr ($CDCl_3$): 1.08, 1.32 and 1.76 (3H each, tert-methyl), 2.59 (dd, 16 and 7 Hz) and 3.05 (dd, 16 and 2 Hz) due to $CNC\underline{H}_2$–, 4.00 (*t*, 8 Hz, C<u>H</u>Br).

4-Bromo-1-chloro-2-cyanomethyl-1,3,3-trimethyl cyclohexane. A mixture of geranyl cyanide (1.63 g, 10 m*M*), tetrabromocyclohexadienone (4.1 g, 10 m*M*) in anhydrous CH_2Cl_2 (130 ml) was cooled with ice water, and a CH_2Cl_2 solution (50 ml) of $AlCl_3$ (1.33 g, 10 m*M*) was dropped into this stirred solution under a nitrogen atmosphere. After continuous stirring for 1 hr, the reaction mixture was diluted with ether and washed with aqueous $NaHCO_3$ and aqueous NaCl solution, and then dried over $MgSO_4$. Evaporation of the solvents gave a crude oil, which was passed through a short SiO_2 column with *n*-hexane–AcOEt (34:1) as solvent. Addition of *n*-hexane to the eluent yielded 407 mg (16%) of 4-bromo-1-chloro-2-cyanomethyl-1,3,3-trimethylcyclohexane: mp 117°C (partly decomposed above 90°C). Nmr ($CDCl_3$): 1.05, 1.31, and 1.56 (3H, each), 3.98 (1H, –C<u>H</u>Br).

Dehydrobromination of XI. A mixture of 2-cyanomethyl-1,4-dibromo-1,3,3-trimethylcyclohexane (**XI**, 149 mg, 0.46 m*M*), $LiBr \cdot H_2O$ (50 mg, 0.48 m*M*) and dimethylformamide (7 ml) was warmed at 75°C for 3 hr with stirring. After being cooled and diluted with ether, the mixture was washed with an aqueous NaCl solution to remove HBr and then dried over $MgSO_4$. Evaporation of the solvents gave a pale yellow oil, which was passed through a short SiO_2 column with *n*-hexane-AcOEt (19:1) as solvent to afford 110 mg of colorless oil (a mixture of **XII** and **XIII**). *Anal.* Calcd for $C_{11}H_{16}NBr$: C, 54.56; H, 6.66; N, 5.78; found: C, 54.07; H, 6.70; N, 5.64. Nmr ($CDCl_3$): 1.06 and 1.19 (3H, each, gem-dimethyls), 1.83 (bs, 3H, olefinic Me), 4.13 (*t*, 8 Hz, C<u>H</u>Br) and 5.43 (*m*, 1H, olefinic H). The integration ratio of peaks at 5.43 vs 4.13 = 0.8, indicating that the isomer (**XIII**) is present in the dehydrobrominated product.

Reduction of olefinic bromides (*XII and XIII*) *with* Bu_3SnH. To a stirred mixture of 150 mg (0.61 m*M*) of olefinic bromides (**XII** and **XIII**), a few milligrams of azobisisobutylnitrile, and 3 ml of anhydrous cyclohexane was dropped 270 mg (0.93 m*M*) of freshly prepared tributyltinhydride under a nitrogen atmosphere, and the mixture was stirred at 60°C for 12 hr under a continuous flow of nitrogen.

Extraction with ether and subsequent evaporation of the solvents afforded an oily substance, which was passed through a short SiO_2 column with *n*-hexane–AcOEt

(24:1) as solvent. The crude eluent was taken up in *n*-hexane–AcOEt (24:1) and chromatographed on 5% $AgNO_3$ column to provide a mixture of cyclohexene derivatives (**XIV** and **XV**, 14 mg). Glc (Golay column, Q-45, Apiezon L) and major peaks in the nmr spectrum of the mixture were identical with material prepared from geranyl cyanide with $SnCl_4$.

Cyclization of geranyl cyanide (VII) with $SnCl_4$. Anhydrous stannic chloride (2.6 g, 10 m*M*) was added to a stirred solution of geranyl cyanide (1.63 g, 10 m*M*) in 30 ml of anhydrous benzene, and the mixture was stirred at room temperature for 12 hr. After being quenched with water, the mixture was extracted with ether. The combined ether solution was successively washed with aqueous $NaHCO_3$ and then NaCl solutions, dried over $MgSO_4$ and evaporated to yield crude cyclized products, which were passed through a short SiO_2 column with *n*-hexane–AcOEt (24:1). The colorless oil (1.31 g) thus isolated is a mixture of **XIV** and **XV** (2:1), as determined by nmr and glc (Golay column, Q-45, Apiezon L).

Reaction of geranyl cyanide (VII) with NBS–aqueous acetone. An acetone (20 ml) solution of geranyl cyanide (**VII**, 1.63 g, 10 m*M*) was saturated with water and cooled in an ice-water bath. NBS, 1.78 g, 10 m*M* was added in several portions to the above solution with stirring and the stirring was continued for 1 hr under the same conditions. After being diluted with ether, the mixture was washed with aqueous $NaHCO_3$ and NaCl solutions, dried over $MgSO_4$ and evaporated to give 2.63 g of colorless bromohydrin (**VIII**). Nmr of VIII: 1.30 and 1.34 (3H, each, gem-dimethyls on carbinol carbon), 1.73 (3H, bs, olefinic Me), 2.52 (1H, OH, disappeared by addition of D_2O), 3.10 (2H, d, 7 Hz, CH_2CN), 3.84 (1H, m, CHBr), and 5.32 (1H, *t*, 7 Hz, olefinic H).

REFERENCES

1. S. KUMAZAWA, Y. NAKANO, T. KATO, AND Y. KITAHARA, *Tetrahedron Lett.*, 1757 (1974).
2. (i) Monoterpenes: (a) N. ICHIKAWA, Y. NAYA, AND S. ENOMOTO, *Chem. Lett.*, 1333 (1974); (ii) sesquiterpenes: (b) J. A. MCMILLAN AND I. C. PAUL, *Tetrahedron Lett.*, 2039 (1974); (c) S. M. WARASZKIEWICZ AND K. L. ERICKSON, *Tetrahedron Lett.*, 2003 (1974); (d) M. SUZUKI, E. KUROSAWA, AND T. IRIE, *Tetrahedron Lett.*, 1807 (1974); (e) A. G. GONZALEZ, J. DARIAS, J. D. MARTIN, AND C. PEREZ, *Tetrahedron Lett.*, 1249 (1974); (f) J. J. SIMS, W. FENICAL, R. M. WING, AND P. RADLICK, *J. Amer. Chem. Soc.*, **95**, 972 (1973); (g) S. S. HALL, D. J. FAULKNER, J. FAYOS, AND J. CLARDY, *J. Amer. Chem. Soc.*, **95**, 7187 (1973); (iii) diterpenes: (h) J. J. SIMS, G. H. Y. LIN, R. M. WING, AND W. FENICAL, *Chem. Commun.*, 470 (1973).
3. (i) 2,6-Dibromocyclohexadienone derivatives: (a) T. HIGA AND P. J. SCHEUER, *J. Amer. Chem. Soc.*, **96**, 2246 (1974); (b) R. J. ANDERSEN AND D. J. FAULKNER, *Tetrahedron Lett.*, 1175 (1973); (c) E. FATTORUSO, L. MINALE, G. SODANO, K. MOODY, AND R. H. THOMSON, *Chem. Commun.*, 752; 751 (1970); (d) G. M. SHARMA AND P. R. BURKHOLDER, *Tetrahedron Lett.*, 4147 (1967); (ii) others: (e) G. E. VAN LEAR, G. O. MORTON, AND W. FULMOR, *Tetrahedron Lett.*, 299 (1973); (f) G. M. SHARMA AND P. R. BURKHOLDER, *Chem. Commun.*, 151 (1971).
4. Terpenes: (a) M. R. WILLCOTT, R. E. DAVIS, D. J. FAULKNER, AND M. O. STALLARD, *Tetrahedron Lett.*, 3967 (1973); (b) D. J. FAULKNER, M. O. STALLARD, J. FAYOS, AND J. CLARDY, *J. Amer. Chem. Soc.*, **95**, 3413 (1973); (c) S. YAMAMURA, AND Y. HIRATA, *Bull. Chem. Soc. Jap.*, **44**, 2560 (1971); others: (d) Y. KATO, P. J. SCHEVER, *J. Amer. Chem. Soc.*, **96**, 2246 (1974).
5. Halogenated compounds from other sources: (a) W. B. J. CRUSE AND M. N. G. JAMES, *Chem. Commun.*, 1278 (1971); (b) J. HARLEY-MASON, A. T. HEWSON, O. KENNARD, AND R. C. PETTERSEN, *Chem. Commun.*, 460 (1972); (c) I. KITAGAWA, T. TANI, K. AKITA, AND I. YOSHIOKA, *Tetrahedron Lett.*, 419 (1972); (d) A. G. GONZALEZ, J. BERMYO, J. L. BRETON, AND J. TRISNA, *Tetrahedron Lett.*,

2017 (1972); (e) T. OSAWA, A. SUZUKI, S. TAMURA, Y. OSHASHI, AND Y. SASADA, *Tetrahedron Lett.*, 5134 (1973).
6. E. E. VAN TAMELEN AND E. J. HESSLER, *Chem. Commun.*, 411 (1966).
7. See also: (a) D. DUFFIN AND J. K. SUTHERLAND, *Chem. Commun.*, 627 (1970); (b) M. A. MCKERVEY AND J. R. WRIGHT, *Chem. Commun.*, 117 (1970); (c) T. C. JAIN, C. M. BANKS, AND J. E. MCCLOSKEY, *Tetrahedron Lett.*, 2387 (1970); (d) K. TAKEDA, I. HORIBE, AND H. MINATO, *Chem. Commun.*, 308 (1971).
8. V. CALO, L. LOPEZ, G. PESCE, AND P. E. TODESCO, *Tetrahedron*, **29**, 1625 (1973); and references therein.
9. G. G. KUIVILA, *Synthesis*, 499 (1970).
10. C. T. MORNER, *Z. Physiol. Chem.*, **88**, 138 (1913).
11. P. J. SCHEUER, "Chemistry of Marine Natural Products," p. 91. Academic Press, New York, 1973.