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Chemical Conversion of Kobusine: Cleavage of the Bridged C-C Bond by a Novel Fragmentation Reaction

Kobusine was converted into the secondary amine (**9**). The bridged C_{14}-C_{20} bond was cleaved by treating the chloramine (**10**) obtained from the amine with sodium methoxide in methanol.

An aconite alkaloid, kobusine[1] (**1**) has the most rigid carbon-nitrogen skeleton among diterpene alkaloids. Several aconite alkaloids including ignavine[2] and some spiraea alkaloids as spiradine A[3] have also the same framework. In the structure of kobusine, ring fusions forming bonds between N and C_6 and between C_{14} and C_{20} are characteristic comparing with other diterpene alkaloids such as atisine (**2**). We have been interested in cleaving C_{14}–C_{20} bond with respect to the reactivity, because this bond is involved in a bicyclo[3,2,1]octane system and this cleavage is thought to be one of the key steps in a series of the conversion reactions of kobusine into atisine or other diterpenoids. In this communication, we wish to report the successful conversion of kobusine into the secondary amine (**9**) and the cleavage of C_{14}–C_{20} bond by a novel fragmentation reaction *via* the chloramine (**10**).

Reduction of **1** with sodium in *n*-propanol, followed by acetylation with acetic anhydride and pyridine gave **3**, $C_{22}H_{29}O_2N$, mp 119—120°,[4] in 80% yield. Of various reagents such as cyanogen bromide, ethyl chloroformate, and carbobenzoxy chloride used to open C_6–N bond, phenyl chloroformate[5] proved to be the most satisfactory. The acetate (**3**) was treated with excess phenyl chloroformate in refluxing *o*-dichlorobenzene to afford the carbamate (**4**) in 90% yield, mp 149—150°. *Anal.* Calcd. for $C_{29}H_{33}O_4N$: C, 75.79; H, 7.24; N, 3.05. Found: C, 75.72; H, 7.31; N, 3.30. IR ν_{max}^{KBr} cm^{-1}: 1720 (C=O), 1600, 1595. NMR ($CDCl_3$) δ: 1.01 (3H, s, 18-CH_3), 1.82 (3H, d, $J=2$ Hz, 17-CH_3), 2.00 (3H, s, -$OCOCH_3$), 5.12 (1H, broad s, -CH-OAc), 5.57 (1H, q, $J=2$ Hz, 15-CH), 5.72, 6.07 (each 1H, ABX, $J_{AB}=10$ Hz, -CH=CH-), 6.96—7.40 (5H, m, Ar). When **4** was hydrogenated over Pd–C in methanol, $\Delta^{15(16)}$-double bond was saturated stereoselectively and the sole product (**5**) was obtained in 94% yield, $C_{29}H_{35}O_4N$, mp 133°. NMR ($CDCl_3$) δ: 0.91 (3H, d, $J=7$ Hz, 17-CH_3), 0.98 (3H, s, 18-CH_3), 2.05 (3H, s, -$OCOCH_3$), 5.09 (1H, d, $J=2$ Hz, -CH-OAc), .556 (2H, s, -CH=CH-), 6.96—7.40 (5H, m, Ar). Further reduction was carried out by platinum catalyst in acetic acid to afford **6** in 75% yield, $C_{29}H_{37}O_4N$, mp 139—140°. Then, acetyl group of **6** was removed by hydrolysis with hydrochloric acid in methanol to give **7** in 92% yield, $C_{27}H_{35}O_3N$, mp 176—177°. Under various hydrolytic conditions, the secondary amine (**9**) could not be obtained in appreciable yield. Even under a rigorous condition such as refluxing **7** with potassium hydroxide in diethylene glycol and water (3: 2) for 200 hours, **9** was obtained in only 30% yield. So, the carbamate (**7**) was converted into the benzyl derivative (**8**) by treating with benzylalcohol and sodium hydride in dimethoxyethane in 90% yield, which gave **9** smoothly on hydrogenoly-

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4) Satisfactory spectral data (infrared (IR), nuclear magnetic resonance (NMR), and Mass) were obtained for all compounds. All crystalline compounds gave correct analytical results. Only some spectral data of special significance are reported.

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sis over Pd–C in methanol containing few drops of hydrochloric acid in 95% yield, mp 190°.[6] *Anal.* Calcd. for $C_{20}H_{31}ON$: C, 79.68; H, 10.37; N, 4.64. Found: C, 79.93; H, 10.47; N, 4.72. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 3340 (NH), 3200. NMR ($CDCl_3$) δ: 0.88 (3H, s, 18-CH_3), 0.89 (3H, d, J=7 Hz, 17-CH_3), 2.60 (1H, s, –NHC$\underline{H}$–), 2.63, 2.81 (each 1H, ABq, J=12 Hz, –NHC$\underline{H}_2$–), 3.94 (1H, broad s, –C$\underline{H}$–OH).

Chlorination of **9** with N-chlorosuccinimide in dichloromethane furnished the chloramine (**10**) in 85% yield. The chloramine (**10**) was refluxed with sodium methoxide in methanol

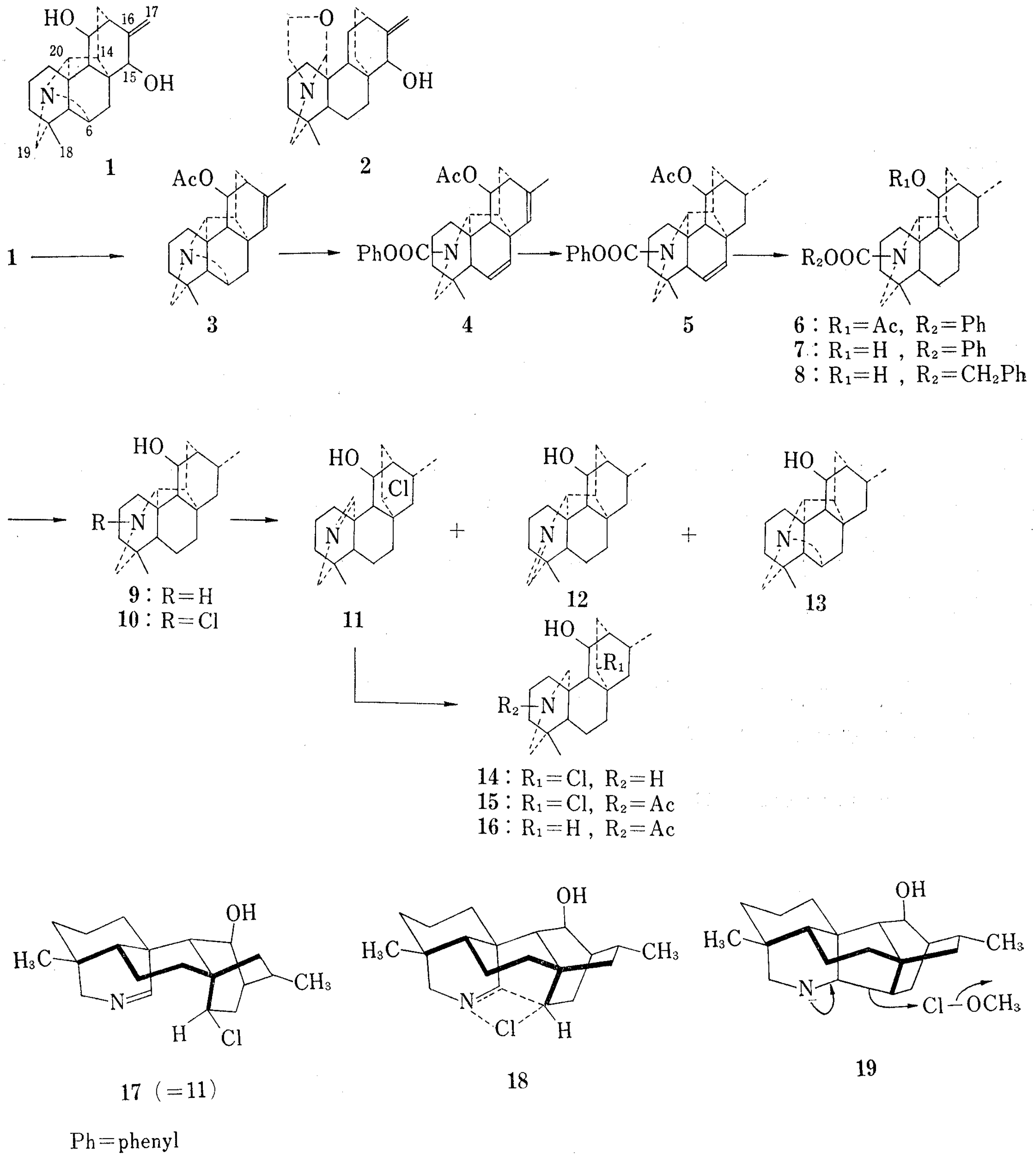

Fig. 1

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[6] E.H. Flynn, H.W. Murphy, and R.E. McMahon, *J. Am. Chem. Soc.*, 77, 3104 (1955); W.H. Hartung and R. Simonoff, "Organic Reactions," Vol. VII, John Wiley and Sons, Inc., New York, 1953, pp. 263—326.

for 24 hours to give the cleaved product (**11**) in 38% yield, mp 243.5—244° (decomp.), *Anal.* Calcd. for $C_{20}H_{30}ONCl$: C, 71.51; H, 9.00; N, 4.17; Cl, 10.56, Found: C, 71.37; H, 9.16; N, 4.51; Cl, 10.22, IR $\nu_{\max}^{\mathrm{KBr}}$ cm^{-1}: 3200 (OH), 1645 (C=N), NMR ($CDCl_3$) δ: 0.84 (3H, s, 18-CH_3), 1.08 (3H, d, J=7 Hz, 17-CH_3), 3.44 (2H, d, J=2 Hz, =N-CH_2-), 4.08—4.32 (2H, m, >$C\underline{H}$-OH and >CH-Cl), 7.60 (1H, s, -CH=N), accompanied by the imine (**12**), $C_{20}H_{29}ON$, mp 211—212°, and the compound (**13**), $C_{20}H_{29}ON$, mp 214—217°, in 28% and 13% yield respectively. The presence of imino group in **11** was demonstrated as follows. Reduction of **11** with sodiumborohydride in methanol gave the amine (**14**) quantitatively, $C_{20}H_{32}ONCl$, mp 169—171°, which, after acetylation with acetic anhydride and pyridine, was hydrolyzed with hydrochloric acid in methanol to afford the N-acetate (**15**) in 60% yield, $C_{22}H_{34}O_2NCl$, mp 211—212°. Dechlorination was effected by Raney nickel hydrogenolysis of **15** in ethanol at 85° under 70 kg/cm^2 of hydrogen to give **16** in 50% yield, $C_{22}H_{35}O_2N$, mp 179°.

The structure and stereochemistry of **11** was finally determined by X-ray analysis of **11**⁷⁾ and was established as **17**. The chlorine atom was introduced from the rear side of the bond cleaved and the configuration of 17-methyl group was α. To the best of our knowledge there is no example of this type of reaction *via* chloramine.⁸⁾ We can provide no definitive explanation of the formation of **11** on the basis of presently available data. But, nitrenium ion intermediate⁹⁾ would not be involved, since both thermal and silver ion ($AgBF_4$) catalyzed methanolysis of **10** offered **12** and **13**, but **11** was not detected. At least the concerted mechanism as illustrated in **18** could be eliminated, because in this mechanism the chlorine atom must be introduced from the same side of the cleaved bond. A Hofmann-Löffler-Freytag type radical condition (H_2SO_4-AcOH, $h\nu$) gave a complex mixture in which **11** was not involved. Considering the fact that the reaction proceeded in methanol with basic condition and methoxide was not introduced in **11**, the nitrogen anion intermediate as shown in **19** might be concerned in the reaction. Formation of **12** and **13**¹⁰⁾ is well rationalized by nitrenium ion intermediate.

We are continuing our studies on the mechanism of this reaction and application to other systems.

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