Chem. Pharm. Bull. 26(10)3199—3207(1978)

UDC 547.944.7.04 : 581.192

Chemical Conversion of Kobusine. Cleavage and Regeneration of the Bridged C_{14}–C_{20} Bond[1)]

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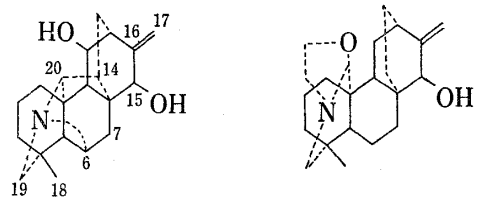
(Received June 27, 1978)

An aconite alkaloid, kobusine (**1**) was converted to a C_{14}–C_{20} bond cleaved derivative (**12**) by a novel fragmentation reaction *via* a chloramine (**11**). Possible mechanisms were discussed in which participation of anionic nitrogen was proposed. The C_{14}–C_{20} bond regeneration in compound (**12**) was also accomplished by an intramolecular Grignard type reaction.

Keywords——aconitum; diterpene alkaloid; kobusine; fragmentation reaction; chloramine; intramolecular Grignard reaction

An aconite alkaloid kobusine (**1**)[3)] is the one having the most rigid and complex carbon-nitrogen skeleton among diterpene alkaloids. Strained bonds between N and C_6, and between C_{14} and C_{20} are characteristic of the kobusine structure to be compared with other C_{20}-type diterpene alkaloids such as atisine (**2**). Ever after isolation and structural determination of kobusine, the cleavage of the C_{14}–C_{20} bond has been posing a continuing challenge to our laboratory for the following reasons. (1) The cleavage of the bond is necessary in order to convert kobusine to other diterpenes such as atisine, (−)-kaurene, and gibberellines. (2) The cleavage of the bond is chemically interesting by itself with respect to the reactivity of the bond since the bond constitutes a bicyclo[3.2.1]octane system and cannot be converted to a double bond (Bredt's rule).[4)] Consequently, there is no simple conventional way to cleave the bond.



1 **2**

Chart 1

Here we have succeeded in converting kobusine to a bond-cleaved compound (**12**) by a novel reaction *via* a chloramine derivative (**11**). In addition we have also succeeded in regenerating the C_{14}–C_{20} bond in **12** using an intramolecular Grignard-type reaction. This bond formation method may provide a useful tool in planning a total synthesis of kobusine since one of the difficulties for the synthesis is presumed to be the formation of this strained bond.

Because of the expected sensitivity of the allylic alcohol group, kobusine (**1**) was transformed to the compound (**3**) by reduction with sodium in *n*-propanol in 90% yield. The

1) Preliminary communication: T. Yatsunami, T. Isono, I. Hayakawa, and T. Okamoto, *Chem. Pharm. Bull.* (Tokyo), **23**, 3030 (1975).
2) Location: *Hongo, Bunkyo-ku, Tokyo.*
3) T. Okamoto, M. Natsume, H. Zenda, and S. Kamata, *Chem. Pharm. Bull.* (Tokyo), **10**, 883 (1962); T. Okamoto, M. Natsume, H. Zenda, S. Kamata, and A. Yoshino, Abstracts of Papers, I.U.P.A.C. 3rd Symposium on Natural Products, Kyoto, 1964, p. 115; S.W. Pelletier, L.H. Wright, M.G. Newton, and H. Wright, *Chem. Commun.*, **1970**, 98.
4) G. Koebrich, *Angew. Chem. internat. Ed.*, **12**, 464 (1973).
5) S. Sakai, A. Kubo, K. Katano, and K. Sasago, *Yakugaku Zasshi*, **93**, 1165 (1973); J.D. Hobson and J.G. McClusky, *J. Chem. Soc.* (*C*), **1967**, 2015.

next step toward our goal involves cleavage of the N–C_6 bond. A number of attempts including von Braun reaction, Cope reaction, or Hofmann reaction were proved unsuccessful because of easy regeneration of the bond. After acetylation of **3** with acetic anhydride in pyridine, the acetate (**4**) was treated with a large excess of phenyl chloroformate[5] in boiling *o*-dichlorobenzene to give a carbamate (**5**) in 90% yield. This compound was very stable and the structure was supported by nuclear magnetic resonance (NMR) spectrum. Other chloroformates such as ethyl chloroformate and carbobenzoxy chloride[6] failed to give the expected carbamates in several selected conditions. The saturation of the double bonds in

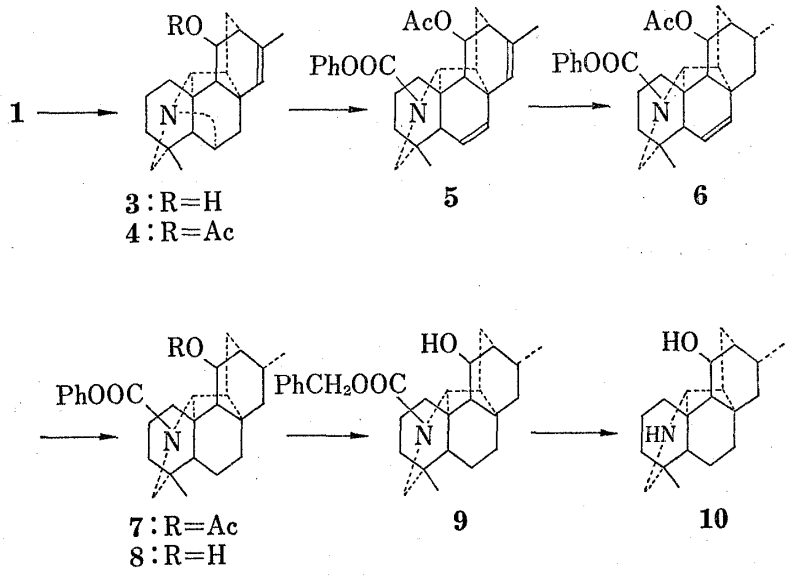


Chart 2

5 was required since the presence of the double bond at C_6–C_7 caused the reformation of C_6–N bond when subjected to hydrolysis of the carbamoyl group. When **5** was hydrogenated using palladium-carbon in methanol, the sole product (**6**) was obtained in 94% yield. Further reduction was carried out by platinum black in acetic acid to give **7** in 75% yield. The configuration of the 17-methyl group was unknown at this stage, but determined later to be alpha by X-ray analysis. Though the hydrogenation of both of the double bonds in **5** by platinum black in acetic acid proceeded, the product was a mixture of two configurational isomers regarding the 17-methyl group. The acetyl group of **7** was easily removed by hydrochloric acid to give **8**. In the next step we met a big difficulty to remove the phenoxy carbonyl group. Conventional reaction conditions such as potassium hydroxide in ethanol, hydrochloric acid in methanol, or hydrobromic acid in acetic acid resulted in the complete recovery of the starting compound (**8**). Under a very vigorous condition such as refluxing **8** with potassium hydroxide in diethylene glycol–water (2: 3) for 300 hr, a partial hydrolysis proceeded and the secondary amine (**10**) was obtained in 32% yield. Attempts using *n*-butyl lithium or methyl lithium[7] were also discouraging with the yield of **10** only about 20%. Expecting a reductive cleavage of the carbobenzoxyamine (**9**)[6b,8] the compound (**8**) was treated with benzyl alcohol and sodium hydride in dimethoxyethane. The ester exchange reaction proceeded satisfactorily and **9** was obtained in 90% yield. Hydrogenolysis of **9** over palladium-carbon in methanol containing hydrochloric acid gave the secondary amine (**10**) in 95% yield. Without hydrochloric acid, the yield of **10** dropped to 44—55%. Various attempts

6) *a*) W. Bright and H. Brabander, *J. Org. Chem.*, **26**, 4057 (1961); *b*) E. Flynn, H. Murphy, and R. MacMahon, *J. Am. Chem. Soc.*, **77**, 3104 (1955).
7) A.G. Anastassiou and R. Elliot, *Chem. Commun.*, **1973**, 601.
8) W.H. Hartung and R. Simonoff, "Organic Reactions," Vol. 7, ed. by R. Adams, John Wiley and Sons, Inc., New York, 1953, pp. 263—326.

on **10** to cleave the C_{14}–C_{20} bond or to functionalyze C_{20} position were unsuccessful. To test the reactivity of chloramine was a choice for the present purpose. Chlorination of the amine (**10**) with N-chlorosuccinimide in methylene chloride at room temperature furnished the chloramine (**11**) in 85% yield. When the chloramine (**11**) was refluxed with sodium methoxide in methanol, a chlorine containing compound (**12**) was obtained in 38% yield, along with an imine (**13**) and a compound (**14**) having C_6–N bond in 28 and 13% yields respectively. The structure of **12** was determined chemically and by X-ray crystallographic analysis as the

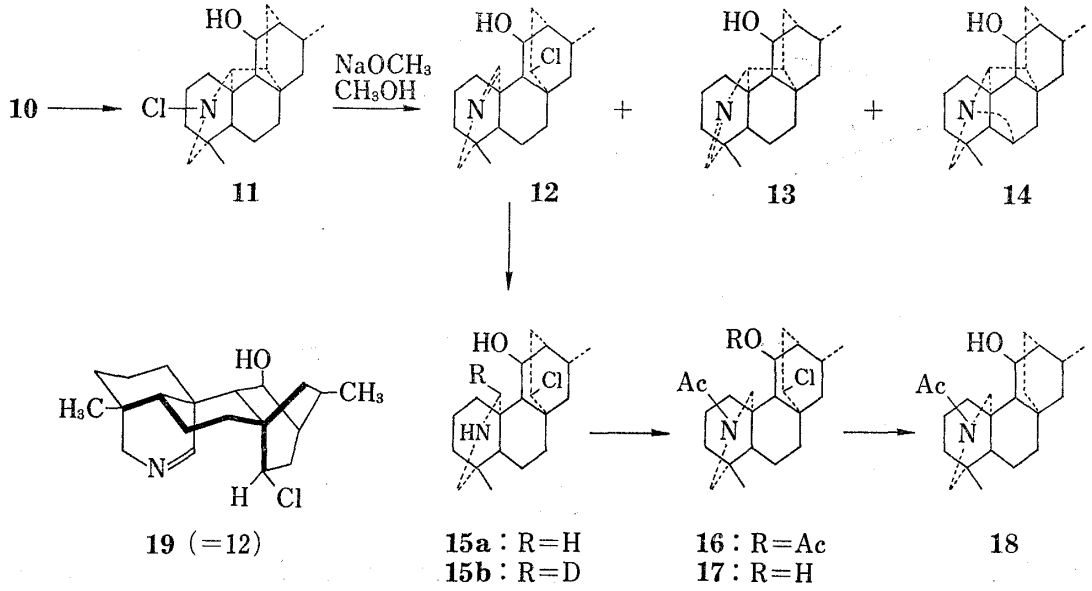


Chart 3

expected compound. The elemental analysis and mass spectral (MS) data suggested the molecular formula $C_{20}H_{30}ClNO$. The infrared (IR) spectrum showed the presence of an imino bond at 1645 cm^{-1}. The NMR spectrum suggested the presence of CH–Cl group and a partial structure C–CH_2–N=CH–C, which were indicated by the absorption of one proton at δ 4.20 (m), two protons at 3.44 (d, J=2 Hz), and one proton at 7.60 (s). The above partial structure was further confirmed by reduction of **12** using sodium borohydride and sodium borodeuteride which gave secondary amines (**15a**) and (**15b**), respectively. The NMR spectrum of **15a** showed two sets of AB quartet signals centered at 2.65 and 2.96 which could be assigned to the two methylene groups adjacent to the nitrogen atom. On the other hand, in the spectrum of the deuterated compound (**15b**) one proton signal at 3.02 as a singlet due to C_{20}-hydrogen was observed in place of the AB quartet signals at 2.96 of the spectrum of **15a**. The position of the chlorine atom could not be determined but supposed to be at C_{14}. The amine (**15a**) was further converted to a dechlorinated compound (**18**) by sequential steps of diacetylation, partial hydrolysis, and hydrogenolysis by Raney nickel catalyst. The X-ray crystallographic analysis of **12** determined the structure and stereochemistry unequivocally.[9] The result proved the anticipated structure as shown in **19**. It was firmly established that the C_{14}–C_{20} bond was cleaved since the distance between the carbon atoms C_{14} and C_{20} was 3.15 Å. The chlorine atom was introduced from the rear side of the C_{14}–C_{20} bond. The configuration of the 17-methyl group was proved to be alpha.

Since there was no example of such a fragmentation reaction *via* a chloramine, we were interested in a mechanism of the reaction. The following facts led us to a tentative conclusion that the mechanism involves anionic nitrogen intermediate. (i) When the chloramine

9) X-ray analysis was carried out by Drs. A. Itai and Y. Iitaka, and the result will be published in *Acta Cryst.*, in preparation.

(**11**) was refluxed in the presence of silver tetrafluoroborate in methanol, a reaction condition to form a nitrenium ion (N^+) as established by Gassman,[10] products were **13**, **14**, and **20** in yields of 33, 4, and 40%, respectively, but **12** was not detected. Methanolysis of **11** in the absence of silver ion also provided only **13** and **14**. These results eliminated the participation of a nitrenium ion as shown in **21**. The configuration of the chlorine atom in **12** also

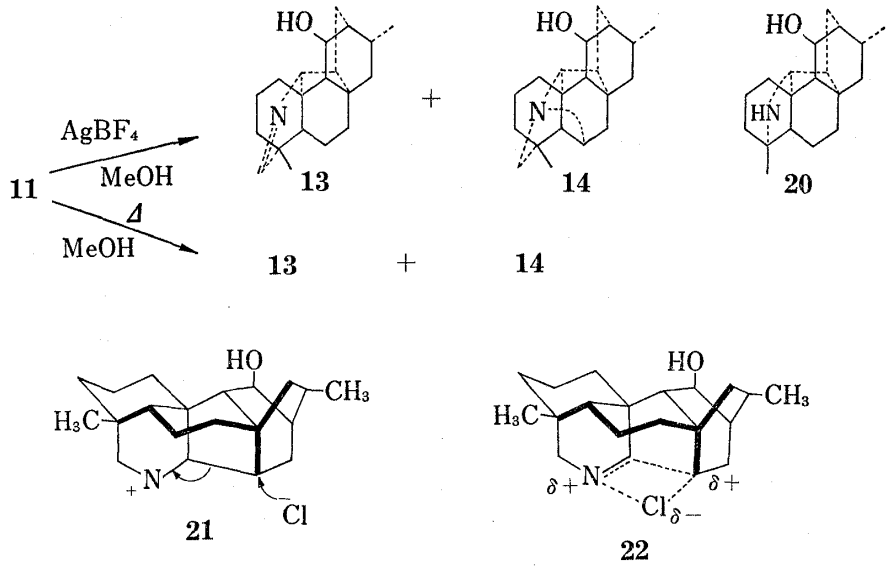


Chart 4

disproved a possible intramolecular concerted rearrangement of the chlorine atom *via* a nitrenium ion as illustrated in **22** since the chlorine atom should be introduced from the same side as the cleaved bond by this mechanism (the same is true in other concerted intramolecular mechanisms). (ii) The chloramine was refluxed in the presence of a radical initiater, azobisisobutyronitrile. However, the major product was **13**, but **12** was not detected. A Hofmann–Loeffler type condition (H_2SO_4, AcOH, ***hν***) either did not give **12** but afforded a complex mixture. Consequently, a homolytic mechanism appears to be unlikely. (iii) The anionic mechanism illustrated in **24** is another possibility. This may be partially supported by the fact that treatment of the chloramine with sodium methoxide in the presence of N-bromoacetamide as a possible positive bromine source[11] gave a mixture of **12** and **23**. This novel fragmentation reaction may reflect the strained nature of the bond, and we are studying the generality of the reaction and the mechanism.

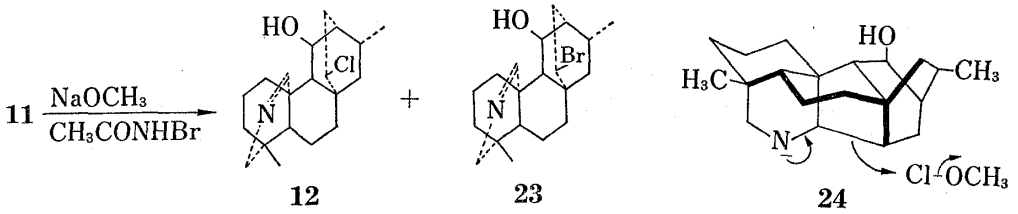


Chart 5

The by-product imine (**13**) was structure-determined by spectral data and was converted to a deaminated derivative (**26**). Treatment of **13** with sodium nitrite and acetic acid gave the hemiacetal (**25**) which, without isolation, was subjected to Wolff–Kishner reduction afford-

10) P.G. Gassman, *Accounts Chem. Res.*, 3, 26 (1970).
11) H. Rapoport, C.H. Lovell, H.R. Reist, and M.E. Warren, Jr., *J. Am. Chem. Soc.*, **89**, 1942 (1967).

ing **26**.[12] The configuration of C_{20}-hydroxy group was deduced to be alpha based on the NMR coupling constant of C_{20}–H and C_{14}–H. The structure of **14** was determined by spectral data and identified with an authentic sample prepared from **6** by reaction with potassium hydroxide in ethylene glycol. The structure of **20** was suggested by molecular formula and NMR spectrum which showed the presence of only one hydrogen at 2.89 assignable to a hydrogen on the carbon adjacent to the nitrogen atom and the 18-methyl signal occurring at lower field than usual. Formation of **13**, **14**, and **20** may be interpreted by a common ionic mechanism as shown in Chart 6. Dehydrochlorination gave the imine (**13**) (route a). Hydride shift to nitrogen, followed by C_6–N bond regeneration[13] afforded **14** (route b). The C_4–C_{19} bond migration to nitrogen and subsequent hydrolysis gave **20** (route c). These three processes *via* nitrenium ion are well documented.[10,14]

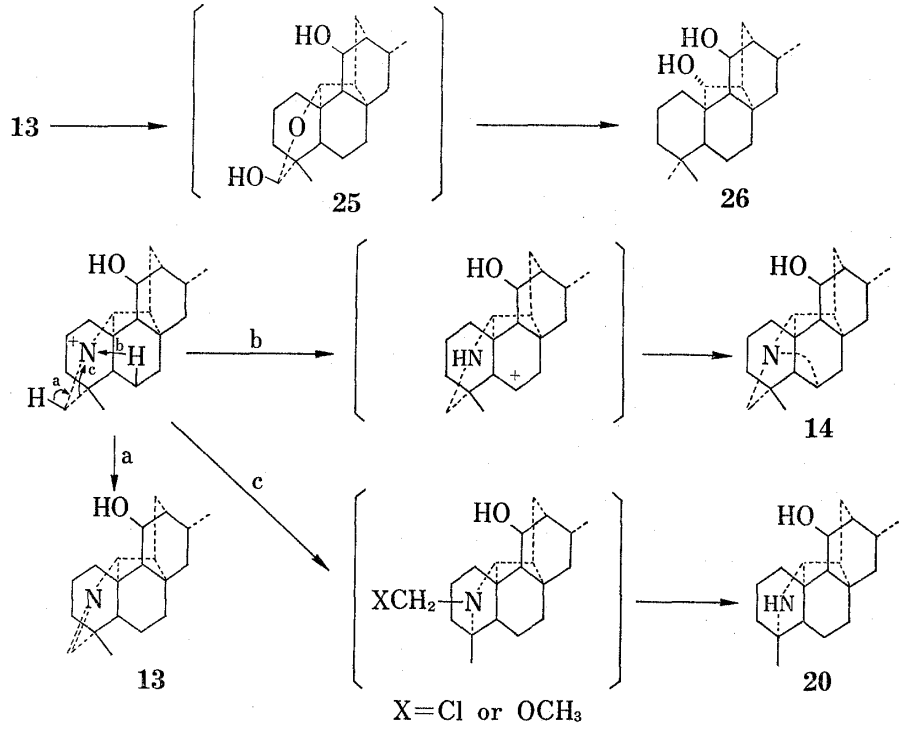


Chart 6

Thus our initial objective was completed. Our next effort was directed to regenerating the C_{14}–C_{20} bond since **12** is well functionalyzed and the distance between the two atoms is close enough for the bond formation. Grignard type reactions were attempted. Refluxing a solution of **12** with ordinary magnesium in tetrahydrofuran resulted in the complete recovery of the starting compound. Activated magnesium[15] proved to be some success, though the yield of **10** was only 12%. The use of lithium in tetrahydrofuran brought a more satisfactory yield of 43%. This C_{14}–C_{20} bond formation, together with C_6–N bond formation described above (*i.e.* **11**→**14**),

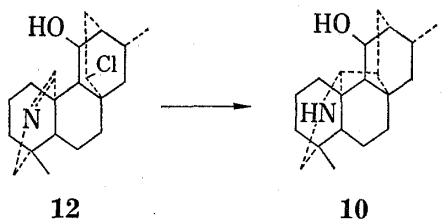


Chart 7

12) J.W. ApSimon, O.E. Edwards, and R. Howe, *Can. J. Chem.*, **40**, 630 (1962); W. Nagata, T. Wakabayashi, M. Narisada, Y. Hayase, and S. Kamata, *J. Am. Chem. Soc.*, **93**, 5740 (1971).
13) O.E. Edwards, D. Vocell, J.W. ApSimon, and F. Haque, *J. Am. Chem. Soc.*, **87**, 678 (1965); G. Adams and K. Schreider, *Angew. Chem.*, **76**, 752 (1964).
14) P.G. Gassman and R.L. Cryberg, *J. Am. Chem. Soc.*, **91**, 2047 (1969).
15) R.D. Rieke and S.E. Bales, *J. Am. Chem. Soc.*, **96**, 1775 (1974).

may be very useful from the standpoint of a total synthesis of kobusine since these two bond formations are the most important key steps in constructing the kobusine skeleton from atisine type structure.

Experimental

Melting points were determined with Yanagimoto micro melting point apparatus and uncorrected. IR spectra were recorded on a JASCO DS-402G. NMR spectra were recorded using a JNM-PS-100 (100 MHz) spectrometer with tetramethylsilane as an internal standard. Mass spectra were recorded on a JEOL JMS-01SG-2 spectrometer.

Reduction of Kobusine (1) with Sodium in *n*-Propanol——To a solution of **1** (10.1 g) in dry *n*-PrOH (800 ml) was added Na (55 g) in portions over a period of 3 hr with vigorous stirring under gentle reflux. After refluxing for an additional 1 hr, the mixture was cooled and the excess Na was decomposed by the cautious addition of CH_3OH, diluted with water and extracted with $CHCl_3$. The extract was washed with water, dried over Na_2SO_4, and evaporated *in vacuo* to give an oily residue, which was subjected to a short column chromatography over alumina and recrystallized from acetone to give **3** (8.45 g, 90%) as plates, mp 199°. *Anal.* Calcd. for $C_{20}H_{27}NO$: C, 80.76; H, 9.15; N, 4.71. Found: C, 80.83; H, 9.32; N, 4.82. IR ν_{max}^{KBr} cm^{-1}: 3120, 1660 (C=C). NMR ($CDCl_3$) δ: 0.96 (3H, s, 18-CH_3), 1.82 (3H, d, $J=1$, 17-CH_3), 2.34, 2.48 (each 1H, AB quartet, $J=12$, NCH_2), 2.48 (1H, s, N-C_{20}H), 3.19 (1H, br. s, N-C_6H), 3.98 (1H, q, $J=8$ and 4, CHOH), 5.60 (1H, d, $J=1$, C=CH).

Acetylation of 3——A solution of **3** (29.7 g) in pyridine (950 ml) and acetic anhydride (450 ml) was left to stand overnight at room temperature. The solvent was evaporated *in vacuo* and the residue was dissolved in $CHCl_3$, washed with aq. $NaHCO_3$ and water, dried over Na_2SO_4, and evaporated. The resulting crude acetate was passed through a short column over alumina and recrystallized from acetone to give **4** (30.3 g, 90%) as plates, mp 119—120°. *Anal.* Calcd. for $C_{22}H_{29}NO_2$: C, 77.84; H, 8.61; N, 4.13. Found: C, 77.90; H, 8.71; N, 4.41. IR ν_{max}^{KBr} cm^{-1}: 1725 (Ac). NMR ($CDCl_3$) δ: 1.97 (3H, s, $COCH_3$).

Reaction of 4 with Phenyl Chloroformate——To a solution of the acetate **4** (208 mg) in dry *o*-dichlorobenzene (20 ml) was added phenyl chloroformate (520 mg, 5.4 equiv.) and the mixture was refluxed for 37 hr. The solvent was evaporated *in vacuo*, and the residue was dissolved in $CHCl_3$, washed successively with 2 N NaOH, 2 N HCl and water. The $CHCl_3$ layer was dried over Na_2SO_4 and evaporated to give an oily residue which was purified by a column of neutral alumina (*n*-hexane–$CHCl_3$) and recrystallized from *n*-hexane–acetone to give **5** (254 mg, 90%) as leaflets, mp 149—150°. *Anal.* Calcd. for $C_{29}H_{33}NO_4$: 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 (CO), 1595. NMR ($CDCl_3$) δ: 1.00 (3H, s, 18-CH_3), 1.80 (3H, s, 17-CH_3), 2.00 (3H, s, $COCH_3$), 5.57 (1H, s, C=CH), 5.72, 6.07 (each 1H, AB quartet-like, $J=10$, HC_6=C_7H), 6.96—7.40 (5H, m, aromatic protons).

Hydrogenation of 5 over Pd-C——A stirred solution of the carbamate **5** (38.2 g) was hydrogenated over 5% Pd-C (14 g) at room temperature under atmospheric pressure. After the uptake of hydrogen ceased, the catalyst was filtered off and the filtrate was evaporated *in vacuo*. The residue was recrystallized from *n*-hexane–acetone to give **6** (36 g, 94%) as white powder, mp 133°. *Anal.* Calcd. for $C_{29}H_{35}NO_4$: C, 75.46; H, 7.64; N, 3.05. Found: C, 75.19; H, 7.65; N, 3.02. IR ν_{max}^{KBr} cm^{-1}: 1710, 1725. NMR ($CDCl_3$) δ: 0.91 (3H, d, $J=7$, 17-CH_3), 0.98 (3H, s, 18-CH_3), 5.56 (2H, s, HC_6=C_7H), 6.96—7.40 (5H, aromatic protons).

Hydrogenation of 6 over Pt-black——To a solution of **6** (36.5 g) in acetic acid (600 ml) was added PtO_2 (3 g) and the mixture was stirred in hydrogen gas. The catalyst was removed by filtration and the solvent was evaporated *in vacuo* to give an oily residue, which was dissolved in $CHCl_3$, washed with aq. $NaHCO_3$ and water, dried over Na_2SO_4 and evaporated. Purification by column chromatography over neutral alumina ($CHCl_3$) followed by recrystallization from *n*-hexane–acetone afforded **7** (27.3 g, 75%) as prisms, mp 139—140°. *Anal.* Calcd. for $C_{29}H_{37}NO_4$: C, 75.13; H, 8.05; N, 3.02. Found: C, 75.08; H, 8.13; N, 3.21. IR ν_{max}^{KBr} cm^{-1}: 1705, 1730. NMR ($CDCl_3$) δ: 0.83 (3H, d, $J=7$, 17-CH_3), 0.94 (3H, s, 18-CH_3), 2.05 (3H, s, $COCH_3$), 3.20—3.41 (3H, m, $CHNCH_2$), 5.13 (1H, s, CHOAc), 7.05—7.41 (5H, aromatic protons).

Hydrolysis of 7 with HCl——A solution of **7** (27 g) in methanol (500 ml) and conc. HCl (100 ml) was refluxed for 3 hr. The solvent was removed *in vacuo* and the residue was dissolved in CH_2Cl_2, washed with 5% Na_2CO_3 and water, dried over Na_2SO_4 and evaporated to dryness. Recrystallization from *n*-hexane–CH_2Cl_2 gave **8** (22.6 g, 92%) as needles, mp 176—177°. *Anal.* Calcd. for $C_{27}H_{35}NO_3$: C, 76.92; H, 8.37; N, 3.32. Found: C, 76.84; H, 8.54; N, 3.45. IR ν_{max}^{KBr} cm^{-1}: 3500 (OH). NMR ($CDCl_3$) δ: 0.87 (3H, d, $J=7$, 17-CH_3), 0.95 (3H, s, 18-CH_3), 3.08—3.55 (3H, m, CH_2NCH), 3.99 (1H, s, CHOH), 7.04—7.46 (5H, aromatic protons).

Conversion of 8 to 9——To a suspension of NaH (1.34 g of 50% dispersions, 27.8 mmol, washed twice with dry *n*-hexane) in dry dimethoxyethane (300 ml) was added benzyl alcohol (10 ml), and the mixture was stirred overnight at room temperature. To the resulting solution of sodium salt of benzyl alcohol, was added compound **8** (3.9 g, 9.26 mmol) and refluxed for 7 hr under nitrogen. The mixture was evaporated *in vacuo* and the residue was dissolved in $CHCl_3$, washed with successively with water, 5% HCl, 5% $NaHCO_3$ and water, dried over Na_2SO_4 and evaporated. Purification by chromatography over alumina using benzene

as eluent gave **9** (3.64 g, 90%) as an amorphous solid whose crystallization was unsuccessful. The amorphous solid was analyzed. *Anal.* Calcd. for $C_{28}H_{37}NO_3$: C, 77.21; H, 8.56; N, 3.21. Found: C, 77.46; H, 8.70; N, 3.25. IR ν_{max}^{KBr} cm^{-1}: 1680. NMR ($CDCl_3$) δ: 0.81 (3H, d, J=7, 17-CH_3), 0.91 (3H, s, 18-CH_3), 5.12, 5.20 (each 1H, AB quartet, J=12.5, CH_2Ph), 7.36 (5H, br. s, aromatic protons). MS *m/e*: 435 (M^+).

Hydrogenation of 9——A solution of **9** (3.55 g) in methanol (70 ml) and conc. HCl (2 ml) was hydrogenated over 10% Pd-C (0.7 g). Removal of the catalyst and evaporation of the solvent gave the hydrochloride of **10** which was basified by 5% Na_2CO_3 and taken up in CH_2Cl_2. The methylene chloride layer was washed with water, dried over Na_2SO_4 and evaporated *in vacuo* to give free amine **10**. Recrystallization from CH_2Cl_2–ether afforded 2.36 g (95%) of pure **10** as plates, mp 190°. *Anal.* Calcd. for $C_{20}H_{31}NO$: C, 79.67; H, 10.37; N, 4.65. Found: C, 79.41; H, 10.32; N, 4.64. IR ν_{max}^{KBr} cm^{-1}: 3340, 3200. NMR ($CDCl_3$) δ: 0.88 (3H, s, 18-CH_3), 0.89 (3H, d, J=7, 17-CH_3), 2.60 (1H, s, NCH), 2.63, 2.81 (each 1H, AB quartet, J=12, NCH_2), 3.94 (1H, br.s, CHOH). MS *m/e*: 301 (M^+).

Hydrolysis of 8 with KOH in Diethyleneglycol-Water——A mixture of **8** (406 mg), KOH (1.0 g), diethyleneglycol (64 ml) and water (96 ml) was refluxed with vigorous stirring under nitrogen for 300 hr. The reaction mixture was diluted with CH_2Cl_2 and extracted with dil. HCl. The HCl layer was basified with Na_2CO_3 and extracted with CH_2Cl_2. The extract was washed with water, dried over Na_2SO_4 and evaporated to give basic residue. Recrystallization from CH_2Cl_2–*n*-hexane afforded **10** (93 mg, 32%). Comparison of the melting points and IR spectra proved the identity with the sample obtained from **9**.

Reaction of 8 with *n*-Butyl Lithium——To an ice-cooled solution of **8** (250 mg) in dry ether (50 ml) was added 5 ml (19 mmol) of *n*-butyl lithium *n*-hexane solution under argon. After stirring for 6 hr, the mixture was diluted with water and CH_2Cl_2 and extracted with dil. HCl. The HCl layer was basified with K_2CO_3 and extracted with $CHCl_3$. The extract was washed with water, dried over Na_2SO_4 and evaporated to give almost pure **10** (46 mg, 26%). Comparison of the IR spectra proved the identity with the sample prepared from **9**.

Reaction of 8 with Methyl Lithium——To an ice-cooled solution of **8** (133 mg) in dry dimethoxyethane (20 ml) was added 3 ml (2.5 mmol) of methyl lithium etherial solution over a period of 3.5 hr under argon. The mixture was worked up as described above to give almost pure **10** (19 mg, 20%). Comparison of the IR spectra proved the identity with the sample prepared from **9**.

Chlorination of 10——To an ice-cooled solution of **10** (1.0 g) in CH_2Cl_2 (150 ml) was added dropwise N-chlorosuccinimide (486 mg, 1.1 equiv.) in CH_2Cl_2 (50 ml) over a period of 2 hr. After stirring for 1 hr at room temperature, the mixture was made basic with 5% Na_2CO_3 and the CH_2Cl_2 layer was washed with water, dried over Na_2SO_4 and evaporated. Purification by chromatography over alumina with CH_2Cl_2–*n*-hexane gave **11** (943 mg, 85%) as an oil. IR ν_{max}^{KBr} cm^{-1}: 3340. NMR ($CDCl_3$) δ: 0.89 (3H, d, J=7, 17-CH_3), 0.97 (3H, s, 18-CH_3), 2.56 (1H, s, NCH), 2.96, 3.08 (each 1H, AB quartet, J=11, NCH_2). MS *m/e*: 337 (M^++2), 335 (M^+).

Reaction of the Chloramine (11) with Sodium Methoxide——To a solution of sodium methoxide (prepared from 1.2 g of sodium) in anhydrous methanol (40 ml) was added the chloramine **11** (856 mg) in anhydrous methanol (10 ml) and the mixture was refluxed for 24 hr under nitrogen. The solvent was removed and the residue was dissolved in CH_2Cl_2, washed with water, dried over Na_2SO_4 and evaporated to afford a crystalline residue. Recrystallization from methanol gave 214 mg of **12**. The mother liquor was subjected to column chromatography over alumina using $CHCl_3$–*n*-hexane as eluent to afford an additional **12** (109 mg), imine (**13**) (216 mg, 28%), and **14** (100 mg, 13%). **12**: a total yield was 323 mg (38%) needles from methanol, mp 243.5—244° (dec.). *Anal.* Calcd. for $C_{20}H_{30}ClNO$: C, 71.37; H, 9.16; Cl, 10.56; N, 4.51. Found: C, 71.51; H, 9.00; Cl, 10.22; N, 4.17. IR ν_{max}^{KBr} cm^{-1}: 3200, 1645 (C=N). NMR ($CDCl_3$) δ: 0.84 (3H, s, 18-CH_3), 1.08 (3H, d, J=7, 17-CH_3), 3.44 (2H, d, J=2, NCH_2), 4.08—4.32 (2H, m, CHOH and CHCl), 7.60 (1H, br. s, CH=N). MS *m/e*: 337 (M^++2), 335 (M^+). **13**: needles from acetone, mp 221.5—222°. *Anal.* Calcd. for $C_{20}H_{29}NO$: C, 80.22; H, 9.76; N, 4.68. Found: C, 80.29; H, 9.95; N, 4.67. IR ν_{max}^{KBr} cm^{-1}: 3280, 1638 (C=N). NMR ($CDCl_3$) δ: 0.92 (3H, d, J=7, 17-CH_3), 1.02 (3H, s, 18-CH_3), 3.01 (1H, br.s, C=N–CH), 4.06 (1H, s, CHOH), 7.28 (1H, br.s, CH=N). MS *m/e*: 299 (M^+). **14**: plates from CH_2Cl_2–*n*-hexane, mp 214—217°. *Anal.* Calcd. for $C_{20}H_{29}NO$: C, 80.22; H, 9.76; N, 4.68. Found: C, 79.80; H, 9.55; N, 4.67. IR ν_{max}^{KBr} cm^{-1} 3110. NMR ($CDCl_3$) δ: 0.92 (3H, d, J=7, 17-CH_3), 0.97 (3H, s, 18-CH_3), 2.33 and 2.49 (each 1H, AB quartet, J=12, N–CH_2), 2.39 (1H, s, N–$C_{20}H$), 3.18 (1H, br.s, N–C_6H), 4.08 (1H, d, J=5, CHOH). MS *m/e*: 299 (M^+). Comparison of melting points and IR spectra proved the identity with the sample obtained from **6**.

Conversion of 6 to 14——A mixture of **6** (150 mg), KOH (800 mg), and ethylene glycol (16 ml) was refluxed for 6 hr. The mixture was diluted with CH_2Cl_2, washed with water, dried over Na_2SO_4 and evaporated. Recrystallization from CH_2Cl_2–*n*-hexane afforded 51 mg of **14**, mp 213—217°.

Reduction of 12 with Sodium Borohydride——To a solution of **12** (35 mg) in methanol (15 ml) was added $NaBH_4$ (100 mg) in small portions over 5 hr with stirring at room temperature. The solvent was evaporated and the residue was dissolved in CH_2Cl_2, washed with water, dried over Na_2SO_4, and evaporated. Recrystallization from CH_2Cl_2 afforded **15a** (8 mg) as prisms, mp 169—171°. *Anal.* Calcd. for $C_{20}H_{32}ClNO$: C, 71.08; H, 9.55; N, 4.14. Found: C, 70.61; H, 9.54; N, 3.98. IR ν_{max}^{KBr} cm^{-1}: 3350, 3215. NMR ($CDCl_3$) δ: 0.72 (3H, s, 18-CH_3), 1.06 (3H, d, J=7, 17-CH_3), 2.57, 2.73 (each 1H, AB quartet, J=12, N–$C_{19}H_2$), 2.87, 3.03 (each 1H, AB quartet, J=12, N–$C_{20}H_2$). MS *m/e*: 339 (M^++2), 337 (M^+).

Reduction of 12 with $NaBD_4$——A solution of **12** (16 mg) in methanol (10 ml) was treated with $NaBD_4$ (30 mg) and worked up in a similar manner described above. Purification by chromatography over Al_2O_3 and recrystallization from CH_2Cl_2 gave 5 mg of **15b**. NMR ($CDCl_3$) δ: 0.72 (3H, s, 18-CH_3), 1.06 (3H, d, J=7, 17-CH_3), 2.57 and 2.73 (each 1H, AB quartet, J=12, NC_{19}–H_2), 3.02 (1H, s, NC_{20}–H).

O,N-Diacetylation of 15a——A mixture of **15a** (25 mg), Ac_2O (2 ml) and pyridine (7 ml) was allowed to stand overnight at room temperature. The solvent was removed *in vacuo* and the residue was dissolved in CH_2Cl_2, washed successively with dil. HCl, dil. Na_2CO_3 and water, dried over Na_2SO and evaporated. Chromatography over Al_2O_3 afforded 25 mg of the O,N-diacetate (**16**) as an amorphous solid. IR ν_{max}^{KBr} cm^{-1}: 1740 (OAc), 1645 (NAc). NMR ($CDCl_3$) δ: 2.05, 2.07 (each 3H, s, NAc and OAc). MS *m/e*: 423 (M^++2), 421 (M^+), 385 (M^+—HCl).

Hydrolysis of 16——A solution of the above O,N-diacetate (**16**) (15 mg) in a mixture of conc. HCl (0.7 ml) and CH_3OH (4 ml) was refluxed for 5 hr. The reaction mixture was diluted with CH_2Cl_2, washed with aq. $NaHCO_3$ and water, dried over Na_2SO_4 and evaporated to dryness. Recrystallization from acetone gave **17** (8 mg) as needles, mp 211—212°. *Anal.* Calcd. for $C_{22}H_{34}ClNO_2$: C, 69.54; H, 9.02; N, 3.68. Found: C, 69.72; H, 9.23; N, 3.94. IR ν_{max}^{KBr} cm^{-1}: 3340, 1610 (NAc). NMR ($CDCl_3$) δ: 0.85 (3H, s, 18-CH_3), 1.05 (3H, d, J=7, 17-CH_3), 2.05 (3H, s, NAc). MS *m/e*: 381 (M^++2), 379 (M^+), 343 (M^+—HCl).

Dechlorination of 17——A mixture of **17** (135 mg), Raney-nickel catalyst (W-7) prepared from 1.5 g of Ni–Al alloy, and absolute EtOH (30 ml) was shaken in an autoclave under 70 kg/cm^2 of hydrogen pressure at 85° for 7 hr. After cooling, the catalyst was removed and the solvent was evaporated. The residue was subjected to chromatography over Al_2O_3 and recrystallized from acetone–*n*-hexane to give **18** (60 mg, 49%) as plates, mp 179°. *Anal.* Calcd. for $C_{22}H_{35}NO_2$: C, 76.47; H, 10.21; N, 4.05. Found: C, 76.16; H, 10.33; N, 4.23. IR ν_{max}^{KBr} cm^{-1}: 3340, 1615 (NAc). NMR ($CDCl_3$) δ: 0.84 (3H, s, 18-CH_3), 0.98 (3H, d. of slight splitting, J=7, 17-CH_3), 2.07 (3H, s. of slight splitting, NAc), A complex signal pattern due to five protons was observed over the range 2.5 to 4.5 ppm, which may reflect the equilibrium of N-containing ring conformation. MS *m/e*: 345 (M^+), 327 (M^+—H_2O), 302 (M^+—Ac).

Methanolysis of 11 in the Presence of $AgBF_4$——A solution of **11** (377 mg) and $AgBF_4$ (439 mg, 2 equiv.) in absolute CH_3OH (30 ml) was refluxed for 5 hr. The reaction mixture was diluted with ether and basified with aq. Na_2CO_3. The ether layer was separated and washed with water, dried over Na_2SO_4 and evaporated to give 392 mg of residue. The residue showed four spots on TLC (Al_2O_3, $CHCl_3$–CH_3OH), but, the spot due to **12** could not be detected. Three main products were purified by repeated chromatography over Al_2O_3 and **20** (130 mg, 40%), **13** (111 mg, 33%) and **14** (12 mg, 4%) were obtained. Compounds **13** and **14** were identified with corresponding samples obtained from the reaction of **11** with $NaOCH_3$ described above by TLC, melting points, and IR spectra after recrystallization. Compound (**20**) was recrystallized from CH_2Cl_2–*n*-hexane to give powder, mp 157—159°. *Anal.* Calcd. for $C_{19}H_{29}NO$: C, 79.39; H, 10.17; N, 4.87. Found: C, 79.03; H, 10.25; N, 4.75. IR ν_{max}^{KBr} cm^{-1}: 3260. NMR ($CDCl_3$) δ: 0.93 (3H, d, J=7, 17-CH_3), 1.09 (3H, s, 18-CH_3), 2.89 (1H, s, N-C_{20}H), 3.80 (1H, br.s, CHOH).

Methanolysis of 11 in the Absence of Silver Ion——A solution of **11** (55 mg) in absolute CH_3OH (8 ml) was refluxed for 24 hr. The reaction mixture was basified with aq. Na_2CO_3 and extracted with CH_2Cl_2, washed with water, dried over Na_2SO_4 and evaporated to give 43 mg of residue. The residue was subjected to chromatography over Al_2O_3 to give **13** (20 mg, 40%) and **14** (10 mg, 21%).

Methanolysis of 11 in the Presence of AIBN——A solution of **11** (30 mg) and AIBN (12 mg) in absolute MeOH (10 ml) was refluxed under argon for 10 hr. The solvent was removed *in vacuo* and the residue was dissolved in CH_2Cl_2, washed with aq.Na_2CO_3 and water, dried over Na_2SO_4 and evaporated. Chromatography over Al_2O_3 ($CHCl_3$) gave 21 mg of **13** and trace of **14**. The spot due to compound (**12**) could not be detected on TLC (Al_2O_3, $CHCl_3$–CH_3OH).

Reaction of 11 with $NaOCH_3$ in the Presence of N-Bromoacetamide——To a solution of $NaOCH_3$ (prepared from 200 mg of Na) in CH_3OH (50 ml) was added **11** (50 mg) and N-bromoacetamide (206 mg, 10 equiv.), and the mixture was refluxed for 15 hr. The solvent was removed *in vacuo* and the residue was dissolved in CH_2Cl_2, washed with water, dried over Na_2SO_4 and evaporated to dryness. The pattern of spots on TLC (Al_2O_3, $CHCl_3$–CH_3OH) was very similar to the case of reaction in the absence of N-bromoacetamide. Chromatographic separation over Al_2O_3 afforded 15 mg of crystalline substance having the same *Rf* value as **12**, which was recrystallized from MeOH to give 8 mg of needles, mp 210—214°. The result of GLC analysis showed that the crystals consisted of two components in nearly equal amounts. The fragmentation pattern of mass spectrum suggested that these components were **12** and **23**. NMR spectrum of the crystals was superimposable on that of **12** except a slight splitting of signals assignable to 17-methyl group and broadning of multiplet signals around at 4.20. GLC: 1.5% OV 101 on Shimalite W (80 cm), carrier gas: N_2 (1 kg/cm^2), column temp. 195°, retention time: 8 and 10.5 min. MS *m/e*: 381, 379 (M^++2, 59% and M^+, 62% of **23**), 366, 364 (M^++2—Me, 34 and M^+—Me, 34 of **23**), 337, 335 (M^++2, 30 and M^+, 67 of **12**), 322, 320 (M^++2—Me, 18 and M^+—Me, 49 of **12**), 300 (M^+—HBr of **23** and M^+—HCl of **12**, 100). Fragmentation pattern below 300 was superimposable upon that of **12**. NMR ($CDCl_3$) δ: 0.84 (6H, s, 18-CH_3 of **12** and **23**), 1.06 (3H, d, J=7, 17-CH_3 of **23**), 1.08 (3H, d, J=7, 17-CH_3 of **12**), 3.44 (4H, d, J=2, NCH_2 of **12** and **23**), 4.04—4.48 (4H, m, CHOH of **12** and **23**, CHCl, CHBr), 7.60 (2H, s, CH=N of **12** and **23**).

Diol (26)——To an ice-cooled solution of **13** (100 mg), NaOAc (250 mg) and $NaNO_2$ (250 mg) in a mixture of dioxane (10 ml) and water (7 ml) was added dropwise a solution of AcOH (0.5 ml) in dioxane (4 ml) over 2 hr under argon with stirring. After standing at 4° for 20 hr, the reaction mixture was diluted with CH_2Cl_2, washed with aq. $NaHCO_3$ and water, dried over Na_2SO_4 and evaporated to give 123 mg of residue containing the hemiacetal (**25**). A mixture of the above residue (89 mg), anhydrous hydrazine (4 ml, bp 112—113.5°), hydrazine dihydrochloride (500 mg) and diethylene glycol (9.5 ml) was heated at 160° (bath temp.) for 22 hr. After addition of KOH (2.0 g), the temperature was slowly raised to 220° by distilling the low boiling material out and the mixture was heated at this temperature for 3 hr. The reaction mixture was diluted with CH_2Cl_2, washed with water, dried over Na_2SO_4 and evaporated *in vacuo* to give 82 mg of residue. Chromatography over silica gel (CH_2Cl_2) afforded 13 mg of **26**, mp 200—203° (recrystallized from CH_2Cl_2–*n*-hexane). *Anal.* Calcd. for $C_{20}H_{32}O_2$: C, 78.89; H, 10.60; N, 0.00. Found: C, 78.77; H, 10.69; N, 0.00. IR ν_{max}^{KBr} cm^{-1}: 3300. NMR ($CDCl_3$) δ: 0.89 (3H, d, $J=7$, 17-CH_3), 0.92 (6H, s, 18-CH_3 and 19-CH_3), 3.45 (1H, s, C_{20}–H), 3.91 (1H, br.s, C_{11}–H). MS *m/e*: 304 (M^+), 286 (M^+-H_2O).

Conversion of 12 to 10 with Lithium——To a suspension of Li cut to small pieces (450 mg) in dry THF (30 ml) was added **12** (65 mg), and the mixture was refluxed for 40 hr under argon. After filtration of the resulting precipitate and unreacted Li, the filtrate was evaporated *in vacuo* below 40°. The residue was dissolved in CH_2Cl_2 and extracted with dil. HCl. The HCl layer was basified with aq. NaOH and extracted with CH_2Cl_2. The extract was then washed with water, dried over Na_2SO_4 and evaporated *in vacuo* to give 39 mg of oily residue which was subjected to chromatography over Al_2O_3 giving crystalline **10** (23 mg, 43%). Comparison of the IR and NMR spectra proved the identity with the authentic sample.

Conversion of 12 to 10 with activated Magnesium——To a suspension of activated Mg prepared from K (450 mg), $MgCl_2$ (1.0 g) and a small amount of I_2 according to the procedure by Rieke[15] in dry THF (50ml), was added **12** (45 mg) and the mixture was refluxed for 3.5 hr under nitrogen. The reaction mixture was worked up in a similar manner described above to give 55 mg of an oily residue. Purification by chromatography over Al_2O_3 afforded 5 mg (12%) of **10** which was identified by comparison of IR spectra with the authentic sample.