STUDIES ON ACONITUM SPECIES. XIV.[1] DEOXYGENATION OF PSEUDOKOBUSINE TO KOBUSINE

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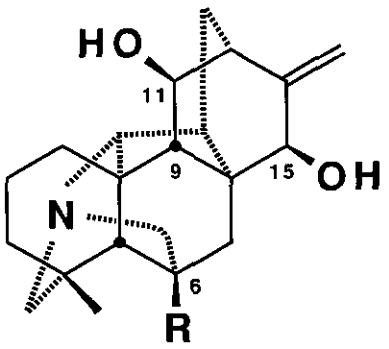
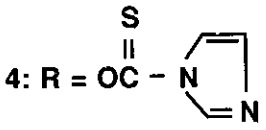
Abstract -- Pseudokobusine (1) was deoxygenated through conversion into the imidazoylthiocarbonyl derivative with N,N'-thiocarbonyldiimidazole and then treated with tri-n-butylstannane. This reaction sequence produced kobusine (2) in a good yield.

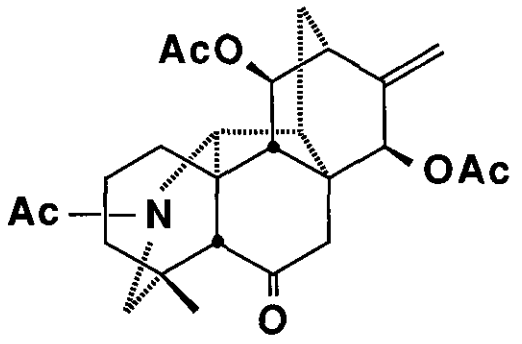
The radical deoxygenations of alcohols have been used to synthesize natural products, e.g. aminoglycosides, carbohydrates,[2] and C_{19}-diterpenoid alkaloids.[3] Meanwhile, the present researchers have reported on the analgesic effect of some C_{20}-diterpenoid derivatives by application of the acetic acid induced writhing method.[4] This deoxygenation was used to produce C_{20}-diterpenoid alkaloids, since C_{20}-diterpenoid derivatives are required to investigate the structure-activity relationship. Firstly, the conversion of pseudokobusine (1) possessing a hydroxy group at C-6 into kobusine (2) was examined. The chemical conversion of a bridgehead hydroxy group at C-6 in C_{20}-diterpenoid alkaloid into H at C-6 was difficult, as acylation of pseudokobusine (1) readily gives rise to N-acyl-N,6-seco-6-dehydro derivative. For example, acetylation of pseudokobusine (1) afforded N,11-O-,15-O-triacetyl-N,6-seco-6-dehydropseudokobusine (3) as its main product.[4] Sakai et al.[5] have reported already on a conversion of pseudokobusine (1) into kobusine (2) which included ring opening, acylation, reduction, ring closing reaction, and hydrolysis. The present report concerns a short-step conversion of pseudokobusine (1) into kobusine (2).

The following preliminary experiments show that the hydroxy group at C-6 in 1 was readily benzoylated. Pseudokobusine (1) has three hydroxy groups, at C-6, C-11, and C-15. Benzoylation (with benzoyl chloride (1.5 eq.) in pyridine, reflux) of



1: R = OH
2: R = H





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pseudokobusine (1) afforded five benzoates: 6-benzoate (21%), 11-benzoate (3%), 15-benzoate (1%), 6,11-dibenzoate (49%), and 6,15-dibenzoate (19%).[6] This result indicates that the increasing order of relative reactivity of the three hydroxy groups on the benzoylation was given as C-15, C-11, and C-6. The β-hydroxy group on C-15 is located in the area of a larger steric hindrance, by reason of the 1,3-diaxial nonbonding interactions between the H on C-9 and the OH group on C-15,[7] and of a neighboring group with exomethylene moiety. Treatment of 1 with N,N'-thiocarbonyldiimidazole in methylene chloride at room temperature gave 6-O-imidazoylthiocarbonylpseudokobusine (4) in 94% yield. This compound was characterized by the presence of thiocarbonyl carbon (180.4 ppm) and three imidazoyl protons (δ 7.07, 7.64, and 8.36) in the ^{13}C- and ^{1}H-nmr spectra. The ^{1}H-nmr spectrum of 4 showed the signal (δ 1.01) of angular methyl at higher field in comparison with that (δ 1.39) of pseudokobusine (1), and the ^{13}C-nmr spectrum of 4 showed a downfield signal (s, 110.7 ppm) compared with that (s, 103.2 ppm) of 1. This suggested that thionosubstituent was attached at the C-6 position. The (thiocarbonyl)imidazolide (4) was treated with tri-n-butyltin hydride in methylene chloride to give kobusine (2) in a high yield (89%). The synthetic compound (2) was identified by comparison of the ^{1}H- and ^{13}C-nmr, ir, and ms spectra, melting points, and tlc behaviors. The conversion process of pseudo-

kobusine (1) into kobusine (2) was thus improved in an overall yield (84%).

EXPERIMENTAL

All melting points are uncorrected. Ir spectra in KBr disks were taken with a JASCO infrared spectrophotometer, model FT/IR-7000. Nmr spectra were measured in a $CDCl_3$ solution with a JEOL GX-270 (270 MHz) spectrometer using TMS as its internal standard. Ms and hrms were measured with a Hitachi M-2000 mass spectrometer.

6-O-Imidazoylthiocarbonylpseudokobusine (4) -- N,N'-Thiocarbonyldiimidazole (30 mg, 0.17 mmol) was added to a solution of pseudokobusine (32 mg, 0.10 mmol) in methylene chloride (5 ml). The mixture was stirred at room temperature for 21 h. After evaporation of the solvent, the residue was purified by silica gel column chromatography (eluent: methanol-$CHCl_3$ = 1:9 v/v) to afford 4 (42 mg, 94%). Amorphous. Hrms (m/z): 439.1956 (M^+, $C_{24}H_{29}N_3O_3S$, calcd 439.1928). Ir (ν, cm^{-1}): 3400, 1700, 1655. Ms (m/z): 439 (M^+), 312 ($M^+-C_4H_3N_2OS$, 100%). ^{1}H-Nmr (δ): 1.01 (3H, s, 18-CH_3), 3.96 (1H, s, C_{15}-H), 4.06 (1H, d, J=4.9 Hz, C_{11}-H), 5.12 and 5.23 (each 1H, s, C=CH_2), 7.07, 7.64, and 8.36 (each 1H, s, imidazoyl-H). ^{13}C-Nmr (ppm): 180.4 (s, C=S), 149.7 (s, C-16), 136.8 (d), 130.7 (d), 117.9 (d), 115.2 (t, C-17), 110.7 (s, C-6), 72.3 (d), 70.2 (d), 67.6 (d), 61.7 (t), 59.8 (d), 53.7 (d), 50.8 (s), 47.4 (s), 41.3 (d), 40.7 (d), 37.2 (s), 35.4 (t), 34.7 (t), 29.6 (q), 29.2 (t), 27.5 (t), 19.4 (t).

Kobusine (2) -- A solution of 4 (10 mg, 0.02 mmol) in methylene chloride (2 ml) was stirred with tri-n-butyltin hydride (0.5 ml, 1.85 mmol) at 50°C for 7 h. The mixture was concentrated to give a residue. Purification by silica gel column chromatography (eluent: methanol-$CHCl_3$ = 1:4, v/v) afforded 2 (6.3 mg, 89%). White plates (acetone-hexane) of mp 257-258°C, mmp 258-260 °C. Hrms (m/z): 313.2029 (M^+, $C_{20}H_{27}NO_2$, calcd 313.2040). Ir (ν, cm^{-1}): 3450, 1660, 890. ^{1}H-Nmr (δ): 0.98 (3H, s, 18-CH_3), 3.89 (1H, s, C_{15}-H), 4.03 (1H, d, J=4.9 Hz, C_{11}-H), 5.08 and 5.19 (each 1H, s, C=CH_2).

REFERENCES

1. Part XIII: K. Wada, H. Bando, and N. Kawahara, Heterocycles, 1990, 31, 1081.
2. W. Hartwig, Tetrahedron, 1983, 39, 2609.
3. P. Kulanthaivel and S. W. Pelletier, Tetrahedron, 1988, 44, 4313.
4. K. Wada, H. Bando, R. Wada, and T. Amiya, Shoyakugaku Zasshi, 1989, 43, 50.
5. S. Sakai, I. Yamamoto, and T. Okamoto, Chem. Pharm. Bull., 1982, 30, 4583.
6. H. Bando, K. Wada, T. Amiya, K. Kobayashi, Y. Fujimoto, and T. Sakurai, Heterocycles, 1987, 26, 2623.
7. S. Sakai, I. Yamamoto, K. Yamaguchi, H. Takayama, M. Ito, and T. Okamoto, Chem. Pharm. Bull., 1982, 30, 4579.

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