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REVISION OF THE STEREOCHEMISTRY OF KOUMIDINE

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Key Word Index—*Gelsemium sempervirens*; Loganiaceae; stereochemistry revision; sarpagine-type alkaloid; koumidine.

Abstract—In the course of assigning the ^{1}H and ^{13}C NMR spectra of the alkaloid koumidine it was found necessary to revise the stereochemistry of C-18 from the *E* to the *Z* configuration.

INTRODUCTION

In previous investigations on natively growing *Gelsemium* plants, i.e. *G. sempervirens* and *G. rankinii* (Loganiaceae), we have reported the isolation of several oxindole alkaloids [1–4] and cytotoxic pregnane derivatives [5]. In this short report, we wish to revise the stereochemistry of the side chain of koumidine (**1**), a sarpagine-type alkaloid isolated from *G. sempervirens*.

RESULTS AND DISCUSSION

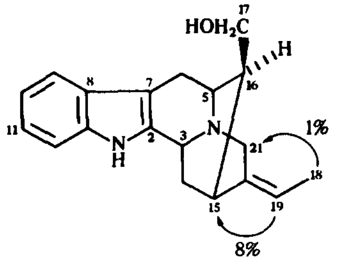
Koumidine (**2**) was first obtained from the entire plant of Chinese *Gelsemium* (*G. elegans*) [6] and shown to be a C-16 (*S*) isomer of normacusine B.

The compound **1** was obtained from *G. sempervirens* and its acetate revealed identical mp, MS, $[\alpha]_D$ and ^{1}H NMR spectra with those of published koumidine (**2**) and its acetate, except that high resolution NMR spectroscopy has permitted unambiguous assignment of the ^{1}H NMR spectrum using homonuclear COSY techniques. Recent reports on the chemical shifts of H-6, H-5, and H-16 indicate that significant differences exist between the C-16 isomers of sarpagine type alkaloids [7, 8]. From these data the C-16 stereochemistry of koumidine and normacusine B could be confirmed.

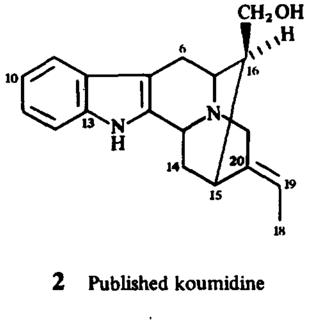
The ^{13}C NMR spectral assignments of compound **1** in DMSO-d_6 or pyridine-d_5, which have not been discussed previously, were established unambiguously through CSCM 1D experiments [9] for the protonated carbons, and SINEPT experiments [10] for the quaternary carbons. Comparison of the ^{13}C NMR spectral data of koumidine with those reported for normacusine B *O*-acetate (16*R*) [11] showed nearly identical aliphatic regions for koumidine and gardnerine, except for the resonances of C-15 and C-21, while normacusine B *O*-acetate was closer to that of 16-epigardnerine. The significantly different chemical shifts observed for gardnerine and its 16-epimer at C-6 (−4.5 ppm), C-14 (−6.5), C-17 (−4.2), C-19 (−3.1), C-20 (+2.9) were also noted for isolated koumidine and normacusine B *O*-acetate. In this way the C-16 stereochemistry of koumidine was further confirmed.

It has long been believed that the ethylidene side chain of naturally occurring monoterpenoid indole alkaloids generally possesses the *E* configuration, i.e. C-18 is oriented *cis* to C-15 [12]. Gardneramine, found in several *Gardneria* spp. of Loganiaceae, whose structure was elucidated by X-ray analysis, was determined to be the first natural indole alkaloid with a rigorously established *Z* configuration for the 19,20-double bond [13]. Subsequently, indole alkaloids possessing this rare *Z*-configuration, i.e. 16-*epi*-*Z*-isositsirikine, have been found in other plants of the Apocynaceae [14]. It was also noted that several sarpagine type indole alkaloids, e.g. gardnerine, coexisted in the same *Gardneria* spp. revealing the normal *E* geometry side chain as deduced through NOE experiments [15].

The presence in koumidine of an 8% NOE between H-19 and H-15, and a 1% NOE between H-18 and H-21, respectively, together with the different ^{13}C NMR chemi-



1 Revised koumidine



2 Published koumidine

cal shifts of C-15 and C-21 from those of gardnerine, which are diagnostic for the configuration of the side chain double bond between C-19 and C-20 [13], indicated that the configuration of C-18 in koumidine should be revised to be *trans* to C-15 (*Z* configuration) instead of the *E* configuration of normal sarpagine-type alkaloids. Koumidine therefore has the structure 1.

EXPERIMENTAL

For general details on methods, see refs [1–5]. Plant material was collected in the spring of 1983 from Texas, U.S.A. by Dr W. Morden. Specimens are deposited in the S. M. Tracy Herbarium, Texas A & M University, College Station, Texas, and the Field Museum of Natural History, Chicago, Illinois.

Isolation and purification of koumidine. The isolation of the crude alkaloid mixture was carried out as previously described [1–4]. The total alkaloid extract was subjected to Si gel CC eluting with mixtures of petrol, EtOAc and MeOH of increasing polarity. From the petrol–EtOAc–MeOH 8:5:0.1 eluent, which was further purified by prep. TLC (petrol–C_6H_6–EtOAc–Et_2NH 25:10:10:4) on precoated Si gel plates, koumidine was isolated at R_f 0.14 as white needles (0.0005 % of the dry stem, 0.001 % of leaf, and 0.0012 % of root) exhibiting mp 201–203 °C (acetone); $[\alpha]_D$ $-11°$ (MeOH 0.07 *c*,); UV λ_{max}^{MeOH} nm 230 (log ε 4.56), 282 (3.90), and 292 (3.82); IR ν_{max}^{KBr} cm^{-1} 3218, 1709, 1620, 1590, 1560, 1450, and 1030; ^1H NMR (360 MHz, DMSO-d_6) δ, 10.79 (1H, *s*, D_2O exchangeable, NH), 7.34 (1H, *dd*, J = 1.4, 7.0 Hz, H-9), 7.26 (1H, *dd*, J = 1.4, 7.0 Hz, H-12), 7.00 (1H, *ddd*, J = 1.4, 7.0, 7.0 Hz, H-11), 6.92 (1H, *ddd*, J = 1.4, 7.0, 7.0 Hz, H-10), 5.23 (1H, *q*, J = 6.7 Hz, H-19), 3.98 (1H, *dd*, J = 3.6, 9.3 Hz, H-3), 3.30–3.60 (2H, masked by H_2O in DMSO, H-21), 3.42 (1H, *m*, J = 5.3 Hz, H-5), 3.27 (1H, *dd*, J = 6.4, 10.4 Hz, H-17), 2.92 (1H, *dd*, J = 5.6, 15.7 Hz, H-17), 2.84 (1H, *d*, J = 15.7 Hz, H-6β), 2.69 (1H, dd, J = 5.6, 15.7 Hz, H-6α), 2.35 (1H, *m*, H-15), 2.04 (1H, *m*, H-16), 1.72 (2H, *m*, H-14), and 1.54 (3H, *d*, J = 6.7 Hz, H-18); ^1H NMR (360 MHz, pyridine-d_5) δ, 11.93 (1H, *s*, D_2O exchangeable, NH), 7.73 (1H, *d*, J = 7.4 Hz, H-9), 7.60 (1H, *d*, J = 7.4 Hz, H-12), 7.30 (1H, *ddd*, J = 0.9, 7.4, 7.4 Hz, H-11), 7.25 (1H, *ddd*, J = 0.9, 7.4, 7.4 Hz, H-10), 5.33 (1H, *q*, J = 6.8 Hz, H-19), 4.31 (1H, *dd*, J = 2.8, 11.3 Hz, H-3), 4.03 (1H, *dd*, J = 6.9, 10.4 Hz, H-17), 3.87 (1H, *d*, J = 17.7 Hz, H-21α), 3.75 (1H, *d*, J = 5.7 Hz, H-5), 3.72 (1H, *m*, H-17), 3.66 (1H, *d*, J = 17.9 Hz, H-21β), 3.37 (1H, *d*, J = 15.5 Hz, H-6β), 3.24 (1H, *dd*, J = 5.8, 15.5 Hz, H-6α), 2.77 (1H, *d*, J = 2.5 Hz, H-15), 2.64 (1H, *m*, H-16), 2.10 (1H, *dt*, J = 3.0, 12.2 Hz, H-14β), 1.87 (1H, *dd*, J = 11.3, 12.2 Hz, H-14α), and 1.54 (3H, *d*, J = 6.8 Hz, H-18); ^{13}C NMR (90.8 MHz, DMSO-d_6) δ, 143.36 (C-20), 138.54 (C-2), 136-14 (C-13), 126.25 (C-8), 120.57 (C-11), 118.52 (C-10), 117.88 (C-9), 112.75 (C-19), 111.25 (C-12), 104.77 (C-7), 59.27 (C-17), 53.81 (C-21), 52.25 (C-5), 49.24 (C-3), 42.88 (C-16), 33.79 (C-15), 28.68 (C-14), 22.58 (C-6), and 12.60 (C-18); ^{13}C NMR (90.8 MHz, pyridine-d_5) δ, 144.19 (C-20), 139.82 (C-2), 137.46 (C-13), 127.46 (C-8), 121.04 (C-11), 119.12 (C-10), 118.44 (C-9), 112.99 (C-19), 111.72 (C-12), 105.96 (C-7), 60.80 (C-17), 54.60 (C-21), 53.39 (C-5), 50.41 (C-3), 44.23 (C-16), 35.08 (C-15), 29.45 (C-14), 23.41 (C-6), and 12.55 (C-18); EIMS 70 eV, *m/z* (rel. int.): 294 $[M]^+$ (77), 277 (10), 249 (9), 222 (2), 182 (11), 169 (100), and 168 (67).

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