Reduction of 14a with Lithium Aluminum Hydride. Compound **14a** (0.020 g) on treatment with lithium aluminum hydride (0.025 g) in THF (3 mL) under reflux for 4 h gave cycloheptenol (0.012 g), found to be identical with an authentic sample.

Oxidation of Limonene (15). **15** (0.525 g, 3.8 mmol) on oxidation under conditions described earlier gave after chromatography the enone **16** (0.130 g, 23%) as an oil: IR ($CHCl_3$) 1670, 1615 cm^{-1}; NMR ($CDCl_3$) δ 1.02 (s, 3 H), 1.55 (s, 3 H), 2.0 (s, 3 H), 2.3–2.9 (m, 4 H), 5.65 (m, 1 H); MS, m/e 150 (M^+).

Oxidation of Fluorene (17). **17** (0.347 g, 2.1 mmol) under the same conditions of oxidation and after the usual workup yielded unreacted starting material (0.030 g) and fluorenone (**18**; 0.342 g, 99.5%) as a yellow solid (mp 80–81 °C), found to be identical with an authentic sample.

Oxidation of Diphenylmethane (19). **19** (0.332 g, 2.1 mmol) under the same conditions yielded after flash chromatography unreacted starting material (0.076 g) and benzophenone (0.211 g, 76%; mp 49–50 °C), found to be identical with an authentic sample.

Oxidation of Tetralin (21). Tetralin (**21**; 0.311 g, 2.35 mmol) under similar conditions of oxidation afforded unreacted starting material (0.010 g) and α-tetralone (**22**; 0.26 g, 78%), found to be identical with an authentic sample.

Registry No. **1**, 604-35-3; **2**, 809-51-8; **3**, 1755-01-7; **4**, 5530-96-1; **5**, 150-84-5; **6**, 60857-06-9; **7**, 771-98-2; **8**, 4556-09-6; **9**, 80-56-8; **10**, 80-57-9; **11**, 13466-78-9; **12**, 81800-50-2; **12a**, 107493-44-7; **13**, 628-92-2; **14**, 1121-66-0; **14a**, 110314-39-1; **15**, 138-86-3; **16**, 491-09-8; **17**, 86-73-7; **18**, 486-25-9; **19**, 101-81-5; **20**, 119-61-9; **21**, 119-64-2; **22**, 529-34-0; *tert*-butyl hydroperoxide, 75-91-2; pyridinium dichromate, 20039-37-6; 3-cycloheptenol, 4096-38-2.

The Case of the Troubling Doubling. Isoatisine and 19-Epiisoatisine from the Chinese Herb Guan-Bai-Fu (*Aconitum koreanum*)

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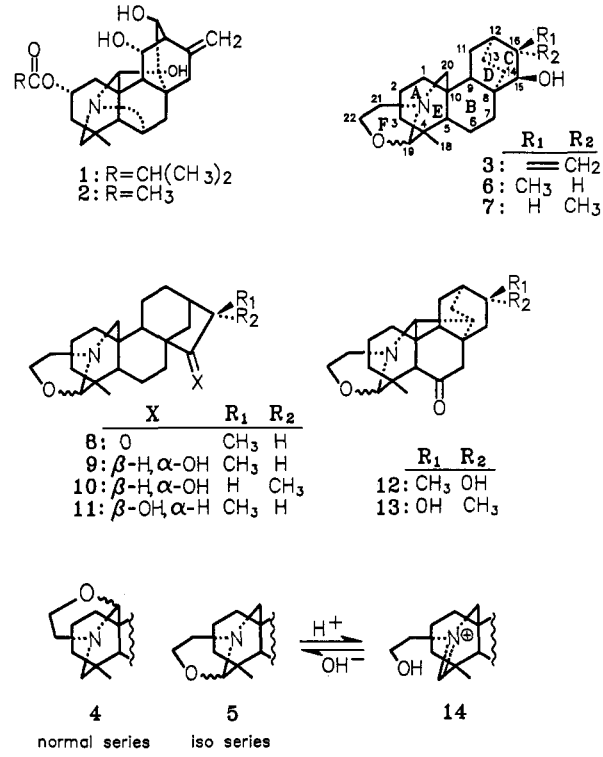
Received April 16, 1987

The Chinese herbal drug guan-bai-fu [*Aconitum koreanum* (Levl.) Raipacs] has recently been shown to contain two new hetisine-type alkaloids, guan-fu base Z (**1**)[1] and guan-fu base Y (**2**).[2] Gradient elution (cyclohexane–ethyl acetate–diethylamine) silica gel chromatography of the chloroform extracts of the strongly basified (pH 11) 1% HCl solution of the original ethanol extracts of the drug gave a TLC-homogeneous, crystalline substance (mp 143–144 °C from methanol) that appears to be a mixture of the known alkaloid isoatisine (**3**) (mp 148–152 °C)[3] and a small amount of its elusive 19-epimer.

The identification of the major component as isoatisine rests primarily on comparison (Table I) of its ^{13}C NMR with literature[4] values and is supported by its mass spectrum, which displays the expected molecular ion at m/e 343 and a base peak at m/e 342 arising from the typical[5] M – H fragmentation of 2-*H*-1,3-diheterocycles,

Chart I

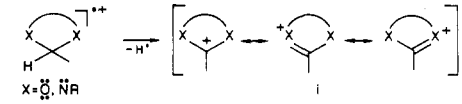


in this case the oxazolidine F ring. Furthermore, the ^1H NMR spectrum (Table I) is very similar to that in the literature,[6] taking into account the differences expected for a 60 vs. a 300 MHz instrument. In particular the characteristic unequal doubling of the C-18 methyl signal at δ 0.93 and 1.07 is observed.

This doubling is found in many C-20 diterpenoid alkaloids containing an oxazolidine F ring and was originally ascribed to conformational isomerism involving the piperidine E ring.[6] An alternative explanation[7] involving the presence of C-20 epimers in the normal series (**4**) (atisine and veatchine) was confirmed by the doubling of certain peaks in the ^{13}C NMR spectra of these alkaloids[4] and the demonstration by X-ray diffraction that crystalline veatchine exists as a disordered 60:40 mixture of C-20 epimers.[8] However, neither ^{13}C NMR[4] nor X-ray diffraction studies[9] revealed the presence of the analogous C-19 epimers in the iso series (**5**) (isoatisine and garryine) so that the origin of the C-18 methyl doubling in the ^1H NMR was once again attributed to conformational isomerism, but this time of the oxazolidine F ring.[9] This latest rationale is debatable since the much smaller conformational energy barriers expected for five- compared to six-membered saturated heterocyclic molecules[10] (0.3 vs. 6

(1) Reinecke, M. G.; Watson, W. H.; Chen, D. C.; Yan, W. M. *Heterocycles* **1986**, *24*, 49.
(2) Reinecke, M. G.; Minter, D. E.; Chen, D. C.; Yan, W. M. *Tetrahedron* **1986**, *42*, 6621.
(3) Edwards, O. E.; Singh, T. *Can. J. Chem.* **1954**, *32*, 465.
(4) Mody, N. V.; Pelletier, S. W. *Tetrahedron* **1978**, *34*, 2421.

(5) Although little work has been published on the mass spectra of oxazolidines, closely related systems such as 1,3-dioxolans, 1,3-dioxanes, and hexahydropyrimidines all show M – 1 base peaks as expected for the resonance-stabilized ion (i). Porter, Q. N. *Mass Spectrometry of Heterocyclic Compounds*, 2nd ed.; John Wiley and Sons: New York, 1985; p 313, 328, 734.



(6) Pelletier, S. W.; Oeltmann, T. N. *Tetrahedron* **1968**, *24*, 2019.
(7) Pradhan, S. K.; Girijavallabhan, V. M. *J. Chem. Soc. D* **1970**, 644. Pradhan, S. K. *Tetrahedron Lett.* **1978**, 263.
(8) DeCamp, W. H.; Pelletier, S. W. *Science (Washington, D.C.)* **1977**, *198*, 726.
(9) Pelletier, S. W.; DeCamp, W. H.; Mody, N. V. *J. Am. Chem. Soc.* **1978**, *100*, 7976.

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Table I. Spectral Data for Isoatisine (3)

	^{13}C NMR			^{1}H NMR	
		this work[a]			
carbon[b]	lit.[b]	**3A** (major)	**3B** (minor)[c]	lit.[d]	this work[a]
				17-CH_2	
16	156.2	156.5	156.6		
17	109.6	109.8	109.7	5.05 t	5.02 s (1)
19	98.4	98.5	96.3		5.08 s (1)
15	76.8	76.9	76.8	18-CH_3	
22	58.6	58.7	64.6	0.91 s (0.4)	0.93 s (0.6)
21	54.9	54.9	52.2	1.06 s (2.6)	1.07 s (2.4)
20	49.8	49.8	51.4	19-CH	
5	48.6	48.6	50.9	3.95 s	3.96 s (0.84)
1	40.6	40.6	40.9		3.78 s (0.16)
3	40.0	40.0	34.5	20-CH_2	
9	39.6	39.7	39.0	2.78 bs	2.79 dd (2)
4	38.1	38.1	38.5		
8	37.5	37.48	37.51	mass spectrum[e]	
12	36.4	36.4	36.3	343 (26)	
10	35.9	35.9	35.2	342 (100)	
7	31.9	31.9	32.0	91 (16)	
11	28.1	28.2	28.5	86 (17)	
13	27.6	27.6	27.2	85 (10)	
14	26.4	26.4	26.3	79 (13)	
18	24.3	24.3	24.2	72 (11)	
2	22.1	22.1	22.2	56 (14)	
6	19.2	19.2	17.4	55 (12)	

[a] In $CDCl_3$ with TMS reference on a Varian XL300 instrument operating at 75.429 (^{13}C) and 299.944 MHz (^{1}H). [b] Reference 3. [c] Assignments based on comparison to **3A** peaks with respect to proximity, relative intensity, and, in the few instances where overlap and base-line noise do not interfere, off-resonance decoupling. The region 34–40 ppm is somewhat tentative. [d] Reference 6. [e] Taken at 70 eV on a Finnegan 1020 OWA instrument; all ions above m/e 45 with relative intensity greater than 10 are reported.

kcal/mol) should not permit the observation of doubled C-18 methyl signals in the ^{1}H NMR spectrum at room temperature.[4,7,11,12] Furthermore, several compounds (**6–11**) closely related to isoatisine and garryine do exist as C-19 epimers according to the doubling of several signals in their ^{13}C NMR spectra.[13]

A close inspection of the ^{13}C NMR spectrum of our sample of isoatisine (**3**) (Table I) also reveals doubling of all signals at 15–30% of their intensity due to minor alkaloid **3B**. Particularly noteworthy is the carbinolamine ether carbon resonance at 96.3 ppm, which establishes the presence of an oxazolidine ring and hence predicts that the mass spectrum of the minor alkaloid also will display a base peak at M – H[5] with an intensity of 15–30% that of the isoatisine (**3**) base peak at m/e 342. Since no such peak is observed (Table I), the base peaks of the minor alkaloid and isoatisine must coincide, i.e., the compounds are isomeric.

The possibility that **3B** is residual atisine[14] or any other normal series (**4**) diterpenoid alkaloid can be specifically excluded since the carbinolamine ether carbon resonance (96.3) is well outside the expected range (92.7–94.8 ppm).[4,13] On the other hand, comparison of the ^{13}C parameters of the major (**3A**) and minor (**3B**) components of our sample of isoatisine reveals that the largest differences occur at just those atoms (3, 5, 6, 19, 20, 21, 22) whose environment would be expected to change most drastically upon epimerization at C-19. The same is true for several other iso series (**5**) diterpenoid alkaloids (**6–11**) that exist as C-19 epimeric mixtures.[13] Furthermore, the chemical shifts of all of the above carbon atoms as well as the absolute magnitude of their epimeric shifts ($|\delta_{\text{epimer A}} - \delta_{\text{epimer B}}|$) are very similar for **3** and **6–11**,[15] thereby strongly supporting the hypothesis that **3A** and **3B** are also C-19 epimers. Confirmatory evidence is provided by the ^{1}H NMR spectrum of **3** (Table I), which in addition to the two 18-methyl resonances mentioned earlier, shows two distinct singlets of unequal area at 3.96 (0.84 H) and 3.78 (0.16 H) ppm assignable to the 19-H of **3A** and **3B**, respectively, and which give the best measure of the epimeric composition of **3**. Similar pairs of proton resonances arising from mixtures of epimers at the 19-position are observed at 4.25 and 3.68 ppm in the alkaloids spirasine V (**12**) and VI (**13**),[17] where the anisotropy of the 6-keto group apparently leads to a larger difference in chemical shift.[18]

The failure to observe 19-epiisoatisine in the X-ray studies[9] is not surprising since several of the spirasine alkaloids exist as 1:1 mixtures of 19-epimers in solution but only as the 19*S* epimer in the crystal.[17,19] With simpler oxazolidine derivatives the epimer that crystallizes from solution may even be the thermodynamically less stable

(10) Riddell, F. G. *The Conformational Analysis of Heterocyclic Compounds*; Academic Press: New York, 1980; pp 60, 84–87, and references cited therein.

(11) Pelletier, S. W.; Mody, N. V. *J. Am. Chem. Soc.* **1977**, *99*, 284. Pelletier, S. W.; Mody, N. V. *Tetrahedron Lett.* **1977**, 1477.

(12) Cited[9] in support of this oxazolidine hypothesis is the observation that the ^{1}H NMR of α-oxoisoatisine (**5**, C-21 carbonyl) shows a sharp singlet for the C-18 methyl group. This statement may be in error since the paper[6] that is indicated as containing this spectrum contains only that of α-oxoatisine (**4**, C-21 carbonyl), which shows a single C-18 methyl signal in spite of the fact that atisine exists as C-20 epimers. This latter point indicates that the NMR of the α-oxo derivative is not likely to provide information regarding the origin of the doubling of the C-18 methyl signals in the atisine and isoatisine series.

(13) Pelletier, S. W.; Mody, N. V.; Desai, H. K.; Finer-Moore, J.; Nowacki, J.; Joshi, B. S. *J. Org. Chem.* **1983**, *48*, 1787.

(14) Atisine readily isomerizes to isoatisine in the presence of base or by refluxing in hydroxylic solvents such as methanol.[13] Isoatisine could therefore be an artifact of the isolation procedure.

(15) Only the absolute value of $\Delta\delta$ is considered since the direction of steric compression shifts in the ^{13}C NMR is a function of the relative geometry of the interacting groups,[16] a factor that might be affected by changes in the C/D rings as in **3** vs. **9–11**. Such effects have been observed in several normal series (**4**) alkaloids.[4,13]

(16) Wehrli, F. W.; Wirthlin, T. *Interpretation of Carbon-13 NMR Spectra*; Heyden and Son: London, 1976; pp 27–29.

(17) Sun, F.; Liang, X.; Yu, D.; Xu, C.; Clardy, J. *Tetrahedron Lett.* **1986**, *27*, 275.

(18) Jackman, L. M. *Applications of NMR Spectroscopy in Organic Chemistry*; Pergamon Press: New York, 1959; p 122.

(19) Sun, F.; Liang, X.; Yu, D. *Heterocycles* **1987**, *26*, 19.

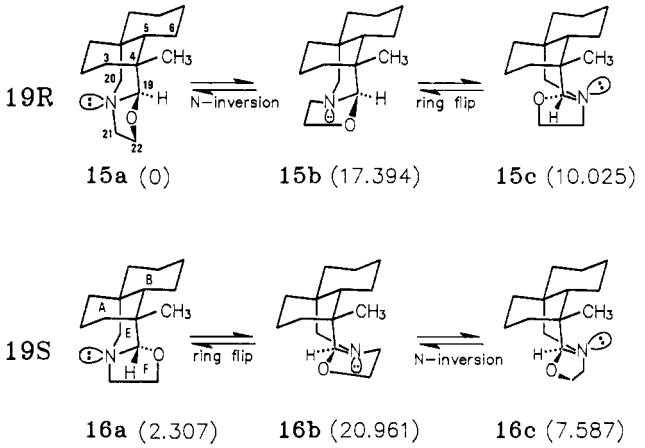
Table II. Steric Relationships[a] in C-19 Epimers of Isoatisine

path	effect	relationship in 19*R* (15a)	relationship in 19*S* (16a)
O, C-19, C-4, C-5	γ	anti	gauche
O, C-19, C-4, C-3	γ	gauche	anti
O, C-19, N, C-20	γ	anti	gauche
C-22, C-21, N, C-20	γ	anti	gauche
O, C-19, C-4, C-5, C-6	δ	extended	syn, axial

[a] Nomenclature of ref 28.

one.[20] The absence of doubling in previous ^{13}C NMR spectra of isoatisine[4] may be due to the lower resolution and sensitivity with a 15- vs. a 75-MHz instrument. Alternatively, extensive recrystallization from solvents that do not permit epimerization at C-19[21] might remove the small amount of **3B** originally present from basification of the isoatisinium salt **14**. Exactly this process has been observed upon recrystallization of a C-20 epimeric mixture of homoveatchine acetates.[13] An insufficient amount of our isoatisine sample was available to permit such extensive recrystallization, which may account for its slightly lower melting point as well as the doubled ^{13}C signals.

Although the question of which 19-epimer of isoatisine is the most stable would seem to have been answered by X-ray analysis[9] in favor of the 19*S* isomer **15a**, as noted



above such a conclusion might be unwarranted in solution.[17,19,20] Molecular mechanics calculations[22] for the A/B/E/F ring system and the 18-methyl group of both possible C-19 epimers of isoatisine (**3**) give the relative energies shown (in kJ/mol) and indicate that E-chair conformations **15a** for the 19*R* and **16a** for the 19*S* epimers are by wide margins the lowest energy. A smaller difference in energy is calculated between the two epimers with the 19*R* isomer (**15a**) favored by only 2.3 kJ/mol over the 19*S* (**16a**). Since these correspond to trans and cis E/F ring-fusions, respectively, this relative stability is consistent with those found by experiment and calculation for other 6/5 fused ring systems such as hydrindane,[24] indolizidine,[25] and hexahydro-3*H*-oxazolo[3,4-*a*]pyridine.[26] On the other hand it is inconsistent with the suggestion that the structure of isoatisine (**3**) in the crystal (19*S*)[9] is also the more stable epimer in solution. While this discrepancy might signal the intervention of crystal packing effects, it also could reflect the accuracy limits of the molecular mechanics calculation in a heteroatom system[27] especially when the C and D rings, structural variations of which sometimes alter the chemistry of the oxazolidine ring of the C-20 diterpenoid alkaloids,[13] have been omitted from the calculations.

This ambiguity was resolved by relating the ^{13}C chemical shifts of **3A** and **3B** to stereochemical differences between the two most stable conformations **15a** and **16a**. As can be seen from Table II, the one δ- and four γ-effects change in a way that permits the prediction of relative chemical shifts in the two epimers. Since the *shielding* γ-effects are greater in the gauche than in the anti conformation,[28] the 19*S* epimer should have the higher field resonance at C-5, C-20, and C-22 and the lower field one at C-3. Similarly the *deshielding* δ-effect will be greatest in the synaxial conformation, thereby predicting that the 19*S* epimer will have the lower field C-6 resonance. All five of these predictions are borne out only if the 19*S* epimer is the major one in solution as well as in the crystal.[9]

In conclusion, it may be noted that the **3A**:**3B** ratio of 84:16 is very close to the 8:2 ratio reported[13] for the garryine derivatives **9**–**11**, which suggests that their major epimers might also have the 19*S* configuration. In view of the present results with isoatisine (**3**), it is probably worth reinvestigating the ^{13}C NMR spectra of other "nonepimeric" iso series (**5**) alkaloids such as garryine[4,13] to determine if small amounts of their 19-epimers are in fact produced if extensive recrystallization after regeneration from the iminium salts (**14** → **5**) is avoided.

Acknowledgment. This research was supported by the TCU Research Fund and the Tarrant County Charitable Foundation Trust. The Varian XL-300 NMR was purchased with a generous gift from Dr. Malcolm K. Brachman. Translations of the Chinese articles and of correspondence between our laboratories was kindly provided by Mr. Chen-yi Qian. The hospitality of the Department of Chemistry of the University of British Columbia and especially Professor James P. Kutney during the preparation of this manuscript is gratefully acknowledged.

(20) Agami, C.; Rizk, T. *Tetrahedron* **1985**, *41*, 537.
(21) While some 2-aryloxazolidines epimerize at the carbinolamine ether carbon even in nonpolar solvents,[20] there is disagreement on whether atisine-type alkaloids do[7] or do not.[4,8,11] Our sample of isoatisine was recrystallized from methanol, a solvent that probably[13] permits such epimerization.
(22) MM2 program of N. L. Allinger[23] available from Quantum Chemistry Exchange Program of Indiana University, Bloomington, IN 47401.
(23) Allinger, N. L. *J. Am. Chem. Soc.* **1977**, *99*, 8127.
(24) Burkert, U.; Allinger, N. L. *Molecular Mechanics*, ACS. Monograph 177; American Chemical Society: Washington, DC, 1982; p 109, 177 and references cited therein.
(25) Reference 24, p 232 and references cited therein.
(26) Takeuchi, Y.; Chivers, P. J.; Crabb, T. A. *J. Chem. Soc., Perkin Trans. 2* **1975**, 51 and references cited therein.
(27) The standard deviation between experimental and calculated heats of formation is greater for heteroatom-containing molecules than hydrocarbons (ref 24, pp 180–183), although for the system most closely related to **3**, indolizidine,[25] the experimental and calculated differences in the cis and trans conformation differ by only 0.92 kJ/mol.
(28) Reference 16, pp 37–40.

Practical Large-Scale Oxidation of 1,4-Hydroquinones to 1,4-Benzoquinones Using Hydrogen Peroxide/Catalytic Diphenyl Diselenide

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Received April 24, 1987

In connection with a synthesis project, we required an inexpensive source of a large quantity (>1 kg) of 2-meth-

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0022-3263/87/1952-5053$01.50/0