to warm to ambient temperature and stirred for an additional 1 h. The precipitated salts were removed by filtration and washed with 300 mL of hot toluene and then 300 mL of hot CH_2Cl_2. The organic phase of the filtrate was separated, dried with $MgSO_4$, and concentrated in vacuo to yield 11.58 g (theoretical, 10.72 g) of clear oil, which was 77% pure by GLC (SE-30). This was used without further purification.

3,4,5,10,11,11a-Hexahydro-1,5-methano-10,10-dimethyl-1*H*-pyrido[1,2-*a*][1,3]diazocin-6(2*H*)-one (2a). To a refluxing solution of THF (185 mL) containing 4.5 g (35 mmol) of nipecotamide (**6**), 3.0 mL (39 mmol) of trifluoroacetic acid, and 9.0 g (75 mmol) of anhydrous $MgSO_4$ under nitrogen was added 4.5 g (35 mmol) of 3,3-dimethylglutaraldehyde[8] in 75 mL of THF over a period of 20 min. After 3 h, the reaction mixture was cooled, filtered, and concentrated to 11.24 g of brown oil. This material was dissolved in CH_2Cl_2, washed with 15% NaOH and then brine, dried with $MgSO_4$, and concentrated to yield 6.10 g (79%) of brown oil, which was 96% pure product by gas chromatographic analysis (SE-30). As indicated in Table I, the ratio of isomers was 83:17. The diastereomers were separated, and the product was further purified by column chromatography on silica gel with an elution system of 5:1 methyl ethyl ketone/$CHCl_3$. A sample of the major isomer was recrystallized from acetonitrile to obtain a crystal appropriate for X-ray analysis. The free base was converted to the 2-naphthalenesulfonate with 1 equiv of the acid in a mixture of ether and ethanol to give analytically pure product in 48% yield, mp 223-225 °C. Major isomer, cis: free base ^1H NMR ($CDCl_3$, TMS) δ 1.1 (s, 6 H, 2 CH_3), 1.4 (br d, 1 H), 1.5-1.7 (m, 1 H), 1.7-1.9 (m, 3 H), 2.1 (br d, 1 H), 2.5 (br s, 1 H), 2.9 (dt, 1 H), 3.2 (d, 1 H), 3.3 (br d, 2 H), 4.6 (dd, 1 H, NCHN), 4.9 (d, 1 H, NC*H*=CH), 7.1 (d, 1 H, NCH=C*H*); IR 1637 (C=O) cm^{-1}. Minor isomer, trans: free base ^1H NMR ($CDCl_3$, TMS) δ 1.0 (s, 3 H, CH_3), 1.1 (s, 3 H, CH_3), 1.4 (br d, 1 H), 1.5-1.9 (m, 4 H), 2.1 (br d, 1 H), 2.4 (br s, 1 H), 2.9-3.1 (m, 3 H), 3.15 (br d, 1 H), 4.2 (dd, 1 H, NCHN), 4.9 (dd, 1 H, NCH=C*H*), 7.05 (d, 1 H, NC*H*=CH); IR 1638 (C=O) cm^{-1}. Anal. Calcd for $C_{13}H_{20}N_2O/C_{10}H_8O_3S$: C, 64.46; H, 6.59; N, 6.54. Found: C, 64.52; H, 6.67; N, 6.51.

3,4,5,10,11,11a-Hexahydro-1,5-methano-10,10-diphenyl-1*H*-pyrido[1,2-*a*][1,3]diazocin-6(2*H*)-one (2b). This material was synthesized from 3,3-dimethylglutaraldehyde and **6** by the procedure given for **2a**. Reflux time was 4 h. The crude product was converted directly into a 2-naphthalenesulfonic acid salt for analysis. Anal. Calcd for $C_{23}H_{24}N_2O/C_{10}H_8O_3S$: C, 71.72; H, 5.84; N, 5.07. Found: C, 71.82; H, 6.09; N, 4.97.

3,4,5,10,11,11a-Hexahydro-1,5-methano-1*H*-pyrido[1,2-*a*][1,3]diazocin-6(2*H*)-one (2c). This material was synthesized from anhydrous glutaraldehyde and **6** by the procedure described for **2a**. Reflux time was 1 h. The crude oil obtained after workup was flash chromatographed on silica gel with 10% acetone/CH_2Cl_2 as the elutant to yield a crystalline isomer mixture (see Table I). Trituration three times with cyclohexane gave pure cis isomer. Anal. Calcd for $C_{11}H_{16}N_2O$: C, 68.72; H, 8.39; N, 14.57. Found: C, 68.74; H, 8.43; N, 14.53.

2,3,4,5a,6,7-Hexahydro-7,7-dimethyl-1*H*-dipyrido[1,2-*a*:1′,2′-*c*]imidazol-11-one (1a). This material was obtained from 3,3-dimethylglutaraldehyde and **5** by the same procedure described for **2a**. Reflux time was 22 h. The crude product was a brown solid, which was recrystallized twice from hexane with decolorizing charcoal to yield white needles for analysis. Anal. Calcd for $C_{13}H_{20}N_2O$: C, 70.87; H, 9.15; N, 12.72. Found: C, 70.91; H, 9.23; N, 12.71.

2,3,4,5a,6,7-Hexahydro-7,7-diphenyl-1*H*-dipyrido[1,2-*a*:1′,2′-*c*]imidazol-11-one (1b). This material was obtained from 3,3-diphenylglutaraldehyde and **5** by the same procedure described for **2a**. Reflux time was 48 h. The crude product was flash chromatographed on silica gel with 20% ethyl acetate/hexane as the elutant. The crystals obtained were washed with ethanol and ether prior to analysis. Major isomer, cis: ^1H NMR ($CDCl_3$ TMS) 1.15-1.35 (1 H, m), 1.35-1.7 (3 H, m), 1.9 (1 H, d), 2.05 (1 H, d), 2.15 (1 H, t), 2.25 (1 H, t), 2.6 (1 H, d), 2.75 (1 H, dt), 3.0 (1 H, br d), 3.75 (1 H, d, NCHN), 5.4 (1 H, dd, NC*H*=CH), 6.95 (1 H, d, NCH=C*H*), 7.1-7.4 (10 H, m, aromatics). Anal. Calcd for $C_{23}H_{24}N_{20}$: C, 80.20; H, 7.02; N, 8.13. Found: C, 80.21; H, 7.09; N, 8.13. A small sample was dissolved in ethanol/ethyl acetate, and crystals were allowed to slowly separate for X-ray analysis (see Figure 1). IR spectra of the two isomers were examined for the prescence of Bohlman bands. Indeed, the major isomer had the characteristic series of peaks indicative of a cis relationship of the bridgehead protons. These were absent in the minor isomer. Major isomer: IR 3010, 2948, 2860, 2799, 2708 (CH), 1714 (C=O) cm^{-1}. Minor isomer: IR 3012, 2946, 2864 (CH), 1706 (C=O) cm^{-1}.

2,3,10,10a-Tetrahydro-9,9-dimethyl-1*H*,9*H*-1,4-ethanopyrido[1,2-*a*]diazapin-5(4*H*)-one (3a). This material was synthesized from 3,3-dimethylglutaraldehyde and **7** by the same procedure described for **2a** except that dimethylformamide was used for the reaction solvent in order to dissolve starting material **7**. The reaction mixture was heated at 90 °C for 5.5 h. The crude product was converted to the 2-naphthalenesulfonic acid salt, which was recrystallized from ethanol to yield white needles for analysis: mp 231-233 °C; free base ^1H NMR ($CDCl_3$ TMS) 1.1 (6 H, s, 2 CH_3), 1.5-2.5 (6 H, m), 2.6-3.4 (5 H, m), 4.35 (1 H, dd, NCHN), 4.8 (1 H, br d, NC*H*=CH), 6.9 (1 H, d, NCH=C*H*). Anal. Calcd for $C_{13}H_{20}N_{20}/C_{10}H_8O_3S$: C, 64.46; H, 6.59; N, 6.54. Found: C, 64.35; H, 6.64; N, 6.60.

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Registry No. *cis*-**1a**, 110392-30-8; *trans*-**1a**, 110454-62-1; *cis*-**1b**, 110392-31-9; *trans*-**1b**, 110454-63-2; *cis*-**2a**, 110392-27-3; *trans*-**2a**, 110454-61-0; *cis*-**2b**, 110392-28-4; *cis*-**2b** (2-naphthalenesulfonic acid salt), 110454-66-5; *trans*-**2b**, 110454-64-3; *trans*-**2b** (2-naphthalenesulfinc acid salt), 110507-65-8; *cis*-**2c**, 110392-29-5; *trans*-**2c**, 110454-65-4; **3a**, 110392-32-0; **3a** (2-naphthalenesulfonic acid salt), 110392-33-1; **5**, 19889-77-1; **6**, 4138-26-5; **7**, 39546-32-2; glutaraldehyde, 111-30-8; 3,3-diphenylglutaraldehyde, 64516-58-1; diethyl 3,3-diphenylglutarate, 3531-26-8; 3,3-dimethylglutaraldehyde, 67402-86-2.

Supplementary Material Available: Details of the X-ray analysis of **1b** are included (3 pages). Ordering information is given on any current masthead page.

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tert-Butyl Hydroperoxide–Pyridinium Dichromate: A Convenient Reagent System for Allylic and Benzylic Oxidations

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A number of methods are currently available for allylic and benzylic oxidations using chromium(VI) complexes.[1] Some of these traditional methods of oxidation suffer from drawbacks such as the use of a very large excess of reagent, large volumes of solvent, and long reaction times. There is a continual search for milder, inexpensive, and more convenient methods for effecting these transformations. More recently, the use of *tert*-butyl hydroperoxide–chro-

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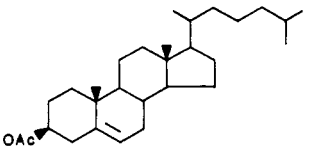
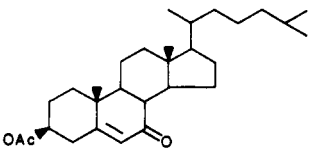
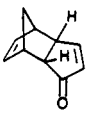
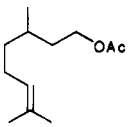
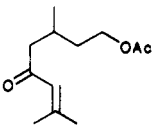
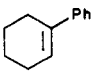
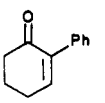
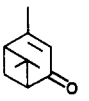
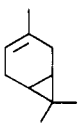
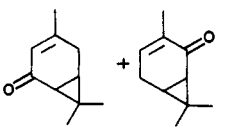
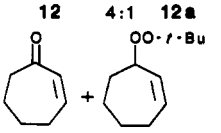
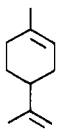
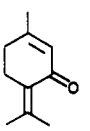
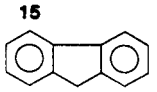
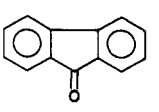
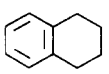
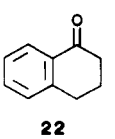
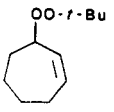
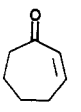
Table I. Oxidations with *tert*-Butyl Hydroperoxide and Pyridinium Dichromate at 25 °C

entry	substrate	substrate: t-BuOH:PDC	reactn time, h	product	conversion, %	yield, %
1	 **1**	1:4:4	4	 **2**	84	81
2	 **3**	1:2:2	7	 **4**	74	44
3	 **5**	1:2:2	11	 **6**	69	40
4	 **7**	1:2:2	9	 **8**	60	30
5	 **9**	1:2:2	9	 **10**	64	37
6	 **11**	1:2:2	9	 **12** 4:1 **12a**	55	29
7	 **13**	1:3:3	9	 **14** 2.5:1 **14a**	57	58
8	 **15**	1:2:2	9	 **16**	48	23
9	 **17**	1:4:4	14	 **18**	90	99.5
10	$PhCH_2Ph$ **19**	1:4:4	14	 **20**	77	76
11	 **21**	1:2.5:2.5	6.5	 **22**	82	78
12	 **14a**	1:2:2	2	 **14**	100	90

mium hexacarbonyl catalyst,[2] *tert*-butyl hydroperoxide–2,4-dimethylpentane-2,4-diol cyclic chromate catalyst,[3] and PCC/Celite in benzene under reflux[4] has been reported to give good yields in benzylic oxidations. These results prompt us to report our findings in this area of benzylic oxidations using readily available *tert*-butyl hydroperoxide and pyridinium dichromate.[5]

Although *tert*-butyl hydroperoxide and pyridinium dichromate do not effect allylic and benzylic oxidations independently, a combination of these two in a 1:1 molar ratio turns out to be a very good reagent system for carrying out these transformations under very mild conditions. A number of examples of successful oxidations are presented in Table I. The experiments were generally carried out at 25 °C in dry benzene containing 2 equiv of *tert*-butyl hydroperoxide and 2 equiv of pyridinium dichromate for 4–14 h. In order to put the present results in the right perspective, they have to be compared with some of the other methods for effecting the same transformations. For example, **2** was obtained from cholesteryl acetate with Collins' reagent (yield 74%)[6] or by heating with *tert*-butyl hydroperoxide and highly toxic $Cr(CO)_6$ catalyst (yield 80%),[2] whereas the present method affords **2** in 81% yield in a very short time.

In a typical example of benzylic oxidation, tetralone (**22**), was obtained from tetralin (**21**) with 5 equiv of chromium trioxide in acetic acid/acetone (yield 55%),[7] 15 equiv of bipyridinium chlorochromate (yield 63%),[8] or 7 equiv of *tert*-butyl hydroperoxide and a catalytic amount of chromium(VI) complex (yield 65%),[3] whereas the present method (yield 78%) is far superior.[9] An interesting feature in the allylic oxidation using the present methodology is exemplified in the oxidation of limonene (**15**) and 1-phenylcyclohexene (**7**), where high regioselectivity is observed. Many of the existing methods of allylic oxidation of limonene give a mixture of carvone and isopiperitenone as major products of the reaction, whereas with present methodology piperitenone (**16**, 23%) was the only product formed. 1-Phenylcyclohexene (**7**) gave exclusively 2-phenyl-2-cyclohexenone (**8**).

In the case of allylic oxidation of cycloheptene (**13**), apart from the enone **14** (41%) the *tert*-butyl peroxy compound **14a** (17%) was also isolated. The peroxy derivative was not formed if pyridinium dichromate was not used in the reaction. Similar observations on the formation of peroxy compounds in benzylic oxidations have been reported by Muzart recently.[3] The peroxy compound **14a** on treatment with *tert*-butyl hydroperoxide/PDC gave rise to the enone **14**, indicating that compounds of this type are potential intermediates in the pathway leading to the ketones. Compound **14a** on reduction with lithium aluminum hydride yielded cycloheptenol.

At the present time the mechanism of this oxidation remains unclear. It is likely that chromium peroxo species formed in situ are responsible for this oxidation process. Recently, Firouzabadi[18] reported the use of chromium peroxo complexes in the oxidation of alcohols to carbonyl compounds.

In summary, the present method of allylic and benzylic oxidations using *tert*-butyl hydroperoxide–pyridinium dichromate is extremely useful in terms of both yield and operational simplicity. We believe that it will find wide application in organic synthesis.

Experimental Section

Infrared spectra were determined on a Perkin-Elmer 1320 spectrometer and NMR spectra on Varian EM-390 and Bruker WP-80 spectrometers. Melting points are uncorrected.

General Procedure for Allylic and Benzylic Oxidations: Oxidation of Cholesteryl Acetate. To a stirred solution of cholesteryl acetate (1; 0.430 g, 1 mmol) in benzene (12 mL) and Celite (1.2 g) was added pyridinium dichromate (1.5 g, 4 mmol) followed by the addition of 70% *tert*-butyl hydroperoxide (0.360 g, 4 mmol) at 10 °C. After 15 min at 10 °C, the reaction mixture was stirred for 4 h at 25 °C. Ether (30 mL) was added, and the reaction mixture was filtered through a pad of Celite and washed twice with 20-mL portions of ether. Combined filtrate was evaporated, and the residue was purified by flash chromatography (10% ethyl acetate in petroleum ether 40–60 °C) to afford unreacted starting material (0.069 g, 16%) and the enone **2** (0.279 g, 81%) as a white solid: mp 152–153 °C (lit.[2,10] mp 155–156 °C); IR (KBr) 1730, 1670 cm^{-1}.

Oxidation of Dicyclopentadiene (3). Compound **3** (0.413 g, 3.1 mmol) in benzene (12 mL) and Celite (2.5 g), pyridinium dichromate (2.35 g, 6.2 mmol), and *tert*-butyl hydroperoxide (0.563 g, 6.2 mmol) were treated as above (7 h). Flash chromatography afforded unreacted starting material (0.110 g) and the enone **4** (0.146 g 44% based on starting material consumed) as a colorless solid, mp 75–77 °C (lit.[11,12] mp 77–79 °C).

Oxidation of Citronellol Acetate (5). Compound **5** (0.401 g, 2 mmol) under similar conditions yielded the enone **6** (0.172 g, 40%) as an oil: IR (thin film) 1730, 1680 cm^{-1}; NMR (CCl_4) δ 0.9 (d, 3 H), 1.95 (s, 3 H), 4.0 (t, 2 H), 5.95 (m, 1 H); MS, *m/e* 212 (M^+).

Oxidation of 1-Phenylcyclohexene (7). Compound **7** (0.625 g, 3.95 mmol) in benzene (25 mL) and Celite (2.97 g), PDC (2.97 g, 7.9 mmol), and *tert*-butyl hydroperoxide (0.71 g, 7.9 mmol) under similar reaction conditions gave after chromatography unreacted starting material (0.26 g) and enone **8**: 0.120 g, 30%; mp 94–95 °C (lit.[13] mp 95–96 °C); IR (KBr) 1660, 1600 cm^{-1}; NMR (CCl_4) δ 2.1–2.45 (m, 4 H), 2.75 (t, 2 H), 6.3 (m, 1 H), 7.45 (m, 5 H).

Oxidation of α-Pinene (9). Compound **9** (0.270 g, 1.98 mmol) under similar reaction conditions afforded after chromatography verbenone (**10**; 0.109 g, 37%). The IR and NMR data of the product were identical with that in the literature.[14,15]

Oxidation of Δ^3-Carene (11). Compound **11** (0.527 g, 3.87 mmol) under similar reaction conditions afforded after chromatography car-3-en-2-one (**12a**; 0.036 g, 6.2%) and car-3-en-5-one (**12**; 0.130 g, 22.4%). The IR and NMR data of the products were identical with those of the literature reports.[16,17]

Oxidation of Cycloheptene (13). Cycloheptene (**13**; 0.288 g, 3 mmol) under the same conditions of oxidation gave the enone **14** (0.151 g, 46%; identical with an authentic sample) and the peroxy compound **14a** (0.063 g, 12%) as an oil. **14a**: IR (thin film) 1198, 788, 760 cm^{-1}; NMR ($CDCl_3$) δ 1.2 (s, 9 H), 5.7 (s, 1 H); MS, *m/e* 95 ($C_7H_{11}^+$), 73 ($C_4H_9O^+$), 57 ($C_4H_9^+$).

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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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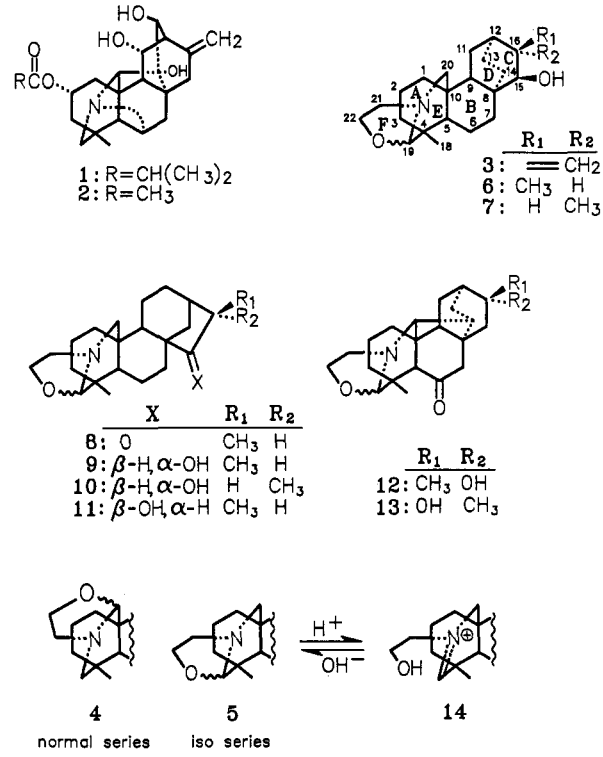
The Chinese herbal drug guan-bai-fu [*Aconitum koreanum* (Levl.) Raipacs] has recently been shown to contain two new hetisine-type alkaloids, guan-fu base Z (**1**)[1] and guan-fu base Y (**2**).[2] Gradient elution (cyclohexane–ethyl acetate–diethylamine) silica gel chromatography of the chloroform 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

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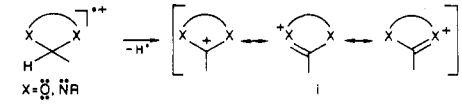

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