Registry No.—$ArCONMe_2$ (Ar = 4-ClC_6H_4), 14062-80-7; $ArCONMe_2$ (Ar = 3-ClC_6H_4), 24167-52-0; $ArCONMe_2$ (Ar = 4-$O_2NC_6H_4$), 7291-01-2; $ArCONMe_2$ (Ar = 3-$O_2NC_6H_4$), 7291-02-3; $ArCONMe_2$ (Ar = 3,5-di$O_2NC_6H_3$), 2782-45-8; $ArCONMe_2$ (Ar = 2-pyrrolyl), 7126-47-8; $ArCONMe_2$ (Ar = 2-furyl), 13156-75-7; $ArCONMe_2$ (Ar = 2-thienyl), 30717-57-8; *N*-(4-methoxybenzoyl)morpholine, 7504-58-7; *N*-(4-methylbenzoyl)morpholine, 63833-44-3; *N*-(4-chlorobenzoyl)morpholine, 19202-04-1; ethyl 2,4-dimethylpyrrole-3-carboxylate, 2199-51-1; phosphoryl chloride, 10025-87-3; 2-benzoylpyrrole, 7697-46-3; *N*-benzoylmorpholine, 1468-28-6; *N,N*-diethyl-3-pyridinecarboxamide, 59-26-7; pyrrole, 109-97-7; 4-nitro-*N,N*-dimethylbenzamide, 7291-01-2.

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N-Nitroaziridines: Synthesis, Thermal Stability, and Solvolytic Reactivity

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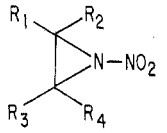
The syntheses of 3β-acetoxy-5β,6β-*N*-nitroaziridinylcholestane (**5**) and 10-methyl-1,9-(*N*-nitroaziridino)decalin (**6**), the first known *N*-nitroaziridines, are described. Their thermal rearrangements and their reactivity in the presence of protic solvents are also examined.

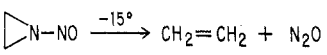
Synthetic and naturally occurring aziridines and nitro-substituted heterocycles are rich sources of important pharmaceuticals, veterinary medicines, and agrichemicals.[1] *N*-Nitroaziridines (**1**) are representative of both classes, but until



1

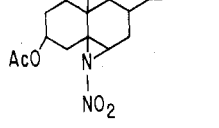
R_1, R_2, R_3, R_4 = H or ALKYL

now were unknown. Research in this area may have been inhibited by the impression that these aziridines would be too unstable to isolate, since *N*-nitrosoaziridines are known to decompose spontaneously at −15 °C, giving nitrous oxide and olefin.[2]

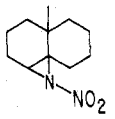


2 **3** **4**

We now wish to report the synthesis of two stable *N*-nitroaziridines (**5** and **6**) by a novel route. Both compounds are



5



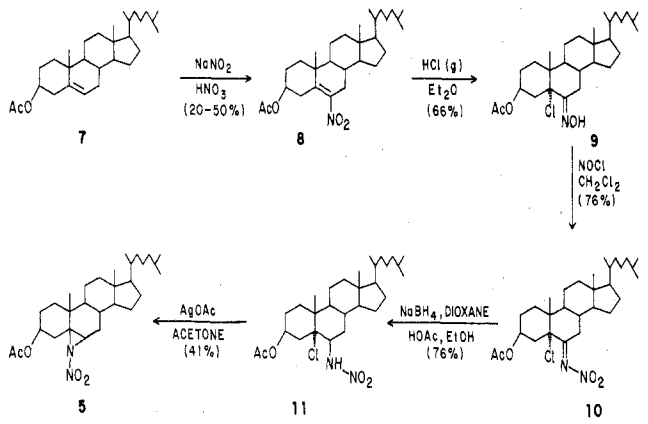
6

stable at room temperature, but undergo unique thermal rearrangements at elevated temperatures.

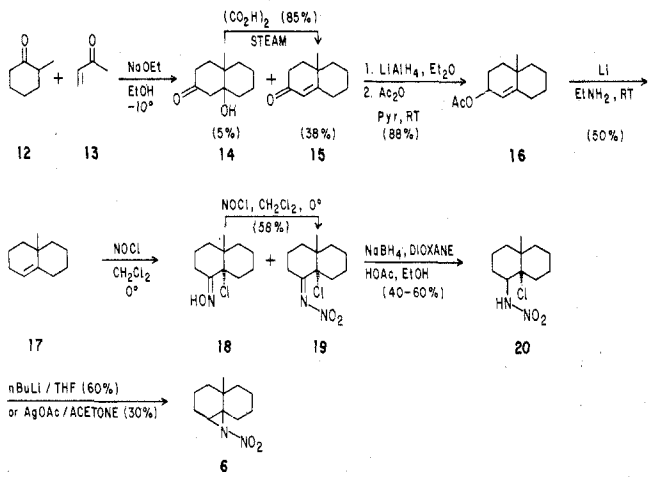
Synthesis

The synthesis of *N*-nitroaziridine **5** began with nitration of cholesteryl acetate (**7**) to give 6-nitrocholesteryl acetate (**8**) (Scheme I). This reaction proved quite capricious with yields from 20 to 50% even under identical conditions, probably because of variations in quality of the sodium nitrite and nitric acid. Conversion to the chlorooxime **9** was effected with dry hydrogen chloride in ether.[3] Direct addition of nitrosyl chloride to cholesteryl acetate, followed by acidic isomerization to chlorooxime **9**, was an unacceptable alternative because steroidal olefins give chloronitro derivatives rather than the

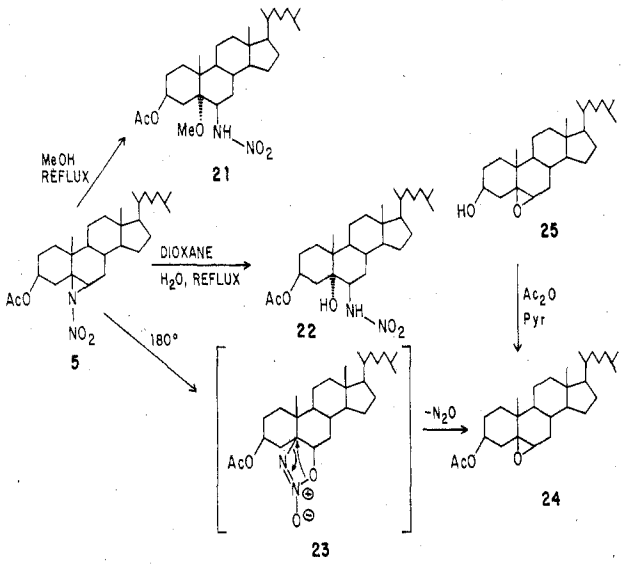
Scheme I



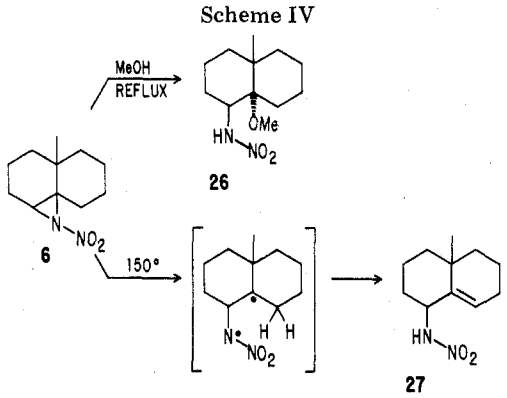
Scheme II



Scheme III



Scheme IV



desired chloronitroso compounds upon addition of nitrosyl chloride.[4-6]

Nitrosyl chloride was used[3,7] to convert 3β-acetoxy-5α-chloro-6-oximinocholestane (**9**) to 3β-acetoxy-5α-chloro-6-nitriminocholestane (**10**). The nitrimino moiety in **10** was reduced to the nitramine **11** in 15% yield with sodium borohydride in dioxane and ethanol. However, yields of 76% could be obtained by adding glacial acetic acid to the reaction mixture.[8]

Ring closure to the *N*-nitroaziridine **5** was obtained by the novel reaction of the chloronitramine **11** with silver acetate in acetone. Although silver acetate appears insoluble in acetone, there is sufficient solubility to allow the reaction to proceed. Silver chloride is precipitated as a purple solid. Periodic filtering and addition of fresh silver acetate[9] are required for acceptable yields. *n*-Butyllithium treatment of **11** afforded only trace amounts of *N*-nitroaziridine. By comparison, treatment of 5α-fluoro-6β-nitraminocholestan-3β-ol acetate with base gave no *N*-nitroaziridine.[10] 3β-Acetoxy-5β,6β-*N*-nitroaziridinylcholestane (**5**) was a stable, crystalline solid melting at 134–135 °C.

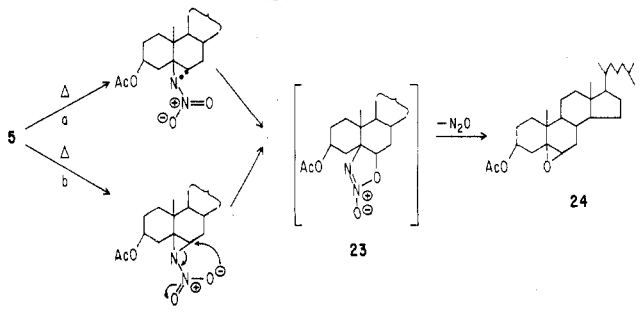
10-Methyl-1,9-(*N*-nitroaziridino)decalin (**6**) was prepared in more direct fashion from the known[11,12] 10-methyl-$\Delta^{1,9}$-octalin (**17**) (Scheme II). Nitrosyl chloride addition to **17** gave a 50:50 mixture of 1-oximino-9-chloro-10-methyldecalin (**18**) and 1-nitrimino-9-chloro-10-methyldecalin (**19**). The oxime **18** could be isolated and treated again with nitrosyl chloride to give the nitramine **19** in 58% yield. Reduction of **19** with sodium borohydride afforded 1-nitramino-9-chloro-10-methyldecalin (**20**); again glacial acetic acid was added to facilitate reduction of the C=N bond. Ring closure to the *N*-nitroaziridine **6** was accomplished with either silver acetate in acetone or *n*-butyllithium in tetrahydrofuran. In contrast to the steroidal system, the best results were obtained with *n*-butyllithium rather than silver acetate because traces of silver acetate remain in solution during filtration of the reaction mixture. This impurity proved difficult to remove from this *N*-nitroaziridine because it is an oil. Distillation afforded pure *N*-nitroaziridine, but decomposition during distillation considerably lowered the yield. The *n*-butyllithium route, on the other hand, afforded pure *N*-nitroaziridine without further purification. 10-Methyl-1,9-(*N*-nitroaziridino)decalin (**6**) is a clear oil boiling at 63–75 °C (0–1 mm).

Discussion

The syntheses of 3β-acetoxy-5β,6β-*N*-nitroaziridinylcholestane (**5**) and 10-methyl-1,9-(*N*-nitroaziridino)decalin (**6**) have shown *N*-nitroaziridines to be stable, isolable compounds. They undergo characteristic solvolytic opening of the aziridine ring in the presence of protic solvents (Schemes III and IV). When either **5** or **6** is heated to reflux in methanol, the corresponding methoxynitramines **21** and **26**, respectively, are obtained; and, when **5** is heated in a dioxane/water mixture, the alcoholic nitramine **22** is produced. However, this reactivity does not extend to all protic solvents, since the steroidal *N*-nitroaziridine **5** can be recrystallized without change from isopropyl alcohol.

Thermal transformations of *N*-nitroaziridines appear unique to each system. When *N*-nitroaziridine **6** is heated to 150 °C under vacuum, the allylic nitramine **27** is produced. Presumably the mechanism involves thermal homolytic

Scheme V

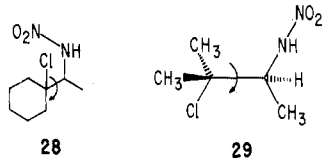


opening of the aziridine ring followed by hydrogen transfer to give an allylic nitramine. In contrast, when the steroidal N-nitroaziridine **5** is heated in neat solution to 180 °C, only traces of olefinic material are seen. The primary product isolated is the β-epoxide **24** (Scheme V), whose structure was established by independent synthesis from the known 5β,6β-oxocholesterol.[10,13] This is supported by mass spectrometric analysis of **5**, which shows no molecular ion, but instead exhibits a strong peak at *m/e* 444 corresponding to loss of $\cdot N_2O$ to give the epoxide **23**. The formation of the epoxide can best be attributed to intramolecular opening of the aziridine ring to give a nonisolable intermediate **23**, which promptly loses N_2O.

The intermediate **23** can be thought to arise from a vinylcyclopropane–cyclopentene type rearrangement of the N-nitroaziridine. Alternatively, attack on the aziridinyl carbon by the negatively polarized oxygen would also lead to **23**. Although **6** is also capable of undergoing such a rearrangement, formation of the allylic nitramine (**27**) appears more facile. No epoxide was isolated from the thermolysis of **6** or seen in the crude thermolysis mixture. Since both epoxide formation routes appear available equally to **5** and **6**, the fact that **6** does not form an epoxide thermally does not eliminate either route from consideration. Reasons for the diverse thermolysis pathways of **5** and **6** remain unclear, particularly in view of their structural similarities.

Although **6** displays notable thermal and solvolytic activity, it is remarkably unreactive under various conditions. When treated in ether solution with either dry hydrogen chloride, acetic anhydride, methyl iodide, or sodium borohydride, the N-nitroaziridine was recovered unchanged. Treatment with lithium aluminum hydride gave unidentified complex reaction products.

There are distinct structural limitations to ring closure of chloronitramine precursors. Ring closure of 1-chloro-1-(α-nitraminoethyl)cyclohexane (**28**) to its corresponding N-



nitroaziridine could not be forced using either base or Ag^+ under a variety of conditions: silver acetate/acetone; silver tetrafluoroborate/ether; silver tetrafluoroborate/ether, triethylamine; silver hexafluorophosphate/acetone; triethylamine/ether; silver oxide/acetone; sodium hydride/ether; potassium *tert*-butoxide/dimethyl sulfoxide; and *n*-butyllithium/tetrahydrofuran. To determine if aziridine formation was inhibited by strain introduced by the incipient spiro system, ring closure of 3-chloro-3-methyl-2-nitraminobutane (**29**) was attempted. Again, the N-nitroaziridine did not form with either Ag^+ or base (NaH or *n*-BuLi). The optimal configuration for aziridine formation is a trans-diaxial alignment of the chloro and nitramino groups. Both **11** and **20** are held rigidly in this configuration and the aziridine forms readily. Although chloronitramines **27** and **28** can achieve a trans-diaxial configuration, relatively free rotation about the central C–C bond does not make this preferred, and there is less chance of ring closure.

N-Nitroaziridines are relatively stable compounds which are easily synthesized provided certain structural limitations are considered. They possess unique thermal properties that make them interesting compounds for future study.

Experimental Section

6-Nitrocholesteryl Acetate (8). To a vigorously stirred suspension of 100 g (0.23 mol) of cholesteryl acetate in 1700 mL of concentrated nitric acid with a water bath for cooling was added 100 g of sodium nitrite in small portions over 30 min. The pink solution turned yellow and brown fumes evolved. After stirring overnight at room temperature, the mixture was filtered and the precipitate washed well with water to give a yellow solid, which was recrystallized from methanol/ether to give 52.49 g (0.11 mol, 47%) of 6-nitrocholesteryl acetate, mp 102–104 °C.

The spectral data were: IR ($CHCl_3$) 3.38 (s), 3.48, 5.80 (s), 6.59 (s), 6.82, 6.96, 7.30, 7.99, 9.62 μm; NMR ($CDCl_3$) τ 5.37 (m, 1 H –COOCH<), 7.70–9.25 (m, 28 H, aliphatic), 7.98 (s, 3 H, CH_3CO–), 8.87 (s, 3 H, C-19 methyl), 9.10 (br s, 6 H, C-26 and C-27 methyls), 9.19 (br s, 3 H, C-21 methyl), 9.31 (s, 3 H, C-18 methyl).

Anal. Calcd for $C_{29}H_{47}NO_4$: C, 73.53; H, 10.00; N, 2.96. Found: C, 73.81; H, 9.74; N, 2.65.

3β-Acetoxy-5α-chloro-6-oximinocholestane (9). The procedure of Komeichi et al. was used.[3] A stream of anhydrous hydrogen chloride was bubbled into a stirred solution of 6-nitrocholesteryl acetate (47.74 g, 0.101 mol) in 1300 mL of ether for 3 h at 0 °C. The reaction mixture was allowed to stand at 0 °C for 2 days, followed by 2 days at room temperature. The ether and hydrogen chloride were then removed in vacuo, and the residue was taken up in ether, washed with water, dried, filtered, and concentrated in vacuo to give a red oil, which was taken up in 50 mL of ether and 100 mL of acetone. The ether was boiled off and crystallization occurred on cooling to room temperature. Recrystallization from acetone gave 33.11 g (0.0672 mol, 66%) of 3β-acetoxy-5α-chloro-6-oximinocholestane, mp 153.5–155 °C dec.

The spectral data were: IR ($CHCl_3$) 2.92, 3.36, 5.76 (s), 5.82 (s), 6.80, 6.92, 7.32, 8.02, 8.57, 8.70, 9.58, 9.76, 10.22, 10.47, 10.82, 10.92, 11.12, 12.12 μm; NMR ($CDCl_3$) τ 1.0–2.0 (br s, 1 H, NOH), 4.40–5.00 (m, 1 H, COOCH<), 7.98 (s, 3 H, CH_3CO–), 8.00–9.25 (m, 28 H, aliphatic), 9.03 (s, 3 H, C-19 methyl), 9.07 (br s, 6 H, C-26 and C-27 methyls), 9.18 (br s, 3 H, C-21 methyl), 9.33 (s, 3 H, C-18 methyl).

3β-Acetoxy-5α-chloro-6-nitriminocholestane (10). The procedure of Komeichi et al. was used.[3] A solution of 3.5 g (7.1 mmol) of 3β-acetoxy-5α-chloro-6-oximinocholestane in 300 mL of methylene chloride was stirred at 0 °C, while nitrosyl chloride was slowly bubbled into the solution for ca. 10 min until a deep brownish red color appeared. The stoppered flask was allowed to stand at 10 °C overnight, and then the contents was poured into water. The organic layer was washed with water and brine, dried, filtered, and concentrated in vacuo to give a clear oil which crystallized upon addition of ether/methanol. Recrystallization from ether/methanol yielded 2.8 g (5.4 mmol, 76%) of 3β-acetoxy-5α-chloro-6-nitriminocholestane, mp 121–123 °C.

The spectral data were: IR ($CHCl_3$) 3.38, 3.48, 5.82 (s), 6.15, 6.36, 6.80, 6.92, 7.22, 7.30, 7.55, 8.02, 8.60, 9.57, 9.80, 10.20, 10.80, 11.40 μm; NMR ($CDCl_3$) τ 4.50–5.00 (m, 1 H, –COOCH<), 7.80–9.25 (m, 28 H, aliphatic), 7.98 (s, 3 H, CH_3CO–), 8.95 (s, 3 H, C-19 methyl), 9.10 (br s, 6 H, C-26 and C-27 methyls), 9.18 (br s, 3 H, C-21 methyl), 9.35 (s, 3 H, C-18 methyl).

3β-Acetoxy-5α-chloro-6β-nitraminocholestane (11). The acidification technique of Meyers and Nabeya[8] was modified for this imine reduction. To a stirred solution of 1.00 g (1.91 mmol) of 3β-acetoxy-5α-chloro-6-nitriminocholestane in 25 mL of dioxane, 25 mL of absolute ethanol, and 5 drops of glacial acetic acid with an ice/acetone bath for cooling was added 1.22 g (32.2 mmol) of sodium borohydride in small portions to control frothing. The mixture was allowed to stir for 30 min at reduced temperature, 15 drops of glacial acetic acid were added, and stirring was continued for 60 min at reduced temperature, followed by 30 min at room temperature. The reaction was then carefully diluted with 100 mL of 3% aqueous acetic acid and extracted thoroughly with methylene chloride. The combined organic extracts were dried, filtered, and concentrated in vacuo to give a white solid, which was recrystallized from acetone to give 760 mg (1.45 mmol, 76%) of 3β-acetoxy-5α-chloro-6β-nitraminocholestane,

mp 206–206.5 °C dec.

The spectral data were: IR (Nujol) 2.90, 3.00, 3.30, 5.85 (s), 6.20 (s), 6.88, 7.10, 7.40, 7.60, 7.71, 7.95, 8.12, 8.19, 8.33, 8.70, 9.30, 9.41, 9.60, 9.81, 10.08, 10.40, 10.55, 10.77, 10.88, 11.09, 11.39, 11.80, 12.15, 12.94, 13.19 μm; NMR [$(CD_3)_2SO$] τ 4.50–5.10 (m, 1 H, –COOCH<), 7.72–9.28 (m, 30 H, aliphatic), 8.01 (s, 3 H, CH_3CO–), 8.81 (s, 3 H, C-19 methyl), 9.10 (br s, 6 H, C-26 and C-27 methyls), 9.20 (br s, 3 H, C-21 methyl), 9.31 (s, 3 H, C-18 methyl).

Anal. Calcd for $C_{29}H_{49}N_2O_4Cl$: C, 66.32; H, 9.50; N, 5.33; Cl, 6.75. Found: C, 66.40; H, 9.29; N, 5.16; Cl, 6.83.

3β-Acetoxy-5β,6β-*N*-Nitroaziridinylcholestane (5). A suspension of 2.61 g (4.98 mmol) of 3β-acetoxy-5α-chloro-6β-nitraminocholestane and 5.00 g of silver acetate in 150 mL of acetone was stirred under nitrogen for 1 day and 5.22 g of silver acetate was added. After stirring for another day, the mixture was filtered and the precipitate washed with acetone. The acetone was removed in vacuo, the solid residue was taken up in 150 mL of acetone, and 6.95 g of fresh silver acetate was added. The suspension was stirred for 1 day and 6.46 g of silver acetate was added. After stirring for an additional day (4 days total), the mixture was filtered and the filtrate concentrated in vacuo to give a white solid. Recrystallization from isopropyl alcohol gave 1.00 g (2.05 mmol, 41%) of 3β-acetoxy-5β,6β-*N*-nitroaziridinylcholestane, mp 134.5–135 °C.

The spectral data were: IR ($CHCl_3$) 3.35, 5.84 (s), 6.45 (s), 6.81, 6.93, 7.34, 7.74, 7.79, 7.99, 8.51, 9.63, 10.19, 11.14 μm; NMR ($CDCl_3$) τ 4.86–5.44 (m, 1 H, COOCH<), 6.72 (m, 1 H, >CHN), 7.55–9.25 (m, 28 H, aliphatic), 7.99 (s, 3 H, CH_3CO–), 8.83 (s, 3 H, C-19 methyl), 9.09 (br s, 6 H, C-26 and C-27 methyls), 9.18 (br s, 3 H, C-21 methyl), 9.35 (s, 3 H, C-18 methyl).

Anal. Calcd for $C_{29}H_{48}N_2O_4$: C, 71.27; H, 9.90; N, 5.73. Found: C, 71.32; H, 9.54; N, 5.40. MS shows no molecular ion; only a large M – 44 peak. Calcd for $C_{29}H_{48}O_3$: 444.3601. Found 444.3601.

3β-Acetoxy-5β,6β-oxocholestane (24) from Thermolysis of 3β-Acetoxy-5β,6β-*N*-nitroaziridinylcholestane (5). A sample of 3β-acetoxy-5β,6β-*N*-nitroaziridinylcholestane (590 mg) was heated under vacuum to 190–193 °C for 30 min until bubbling ceased. After cooling to room temperature, the darkened product was chromatographed on two 20 cm × 20 cm × 2 mm plates of silica gel (E. Merck, according to Stahl). After one development with chloroform, the plate was divided into three bands. The second band from the top contained 70 mg of 3β-acetoxy-5β,6β-oxocholestane, whose NMR and IR were identical with authentic material obtained in the following experiment.

The spectral data were: IR ($CHCl_3$) 3.40, 5.71, 5.96, 6.81, 7.31, 8.12, 8.90, 9.00, 9.81 μm; NMR ($CDCl_3$) τ 4.25–4.80 (m, 1 H, COOCH<), 7.70–9.20 (m, 29 H, aliphatic), 7.82–7.95 (m, 3 H, CH_3CO–), 8.78 (br s, 3 H, C-19 methyl), 9.08 (br s, 6 H, C-26 and C-27 methyls), 9.18 (s, 3 H, C-21 methyl), 9.28 (s, 3 H, C-18 methyl).

Anal. MS Calcd for $C_{29}H_{48}O_3$: 444.3601. Found: 444.3588.

3β-Acetoxy-5β,6β-oxocholestane (24). A mixture of 20 mg of 5β,6β-oxocholesterol,[12] 0.1 mL of pyridine, and 5 mL of acetic anhydride was heated to gentle reflux for 1 h under nitrogen followed by stirring overnight at room temperature. The mixture was concentrated in vacuo to give 20 mg of 3β-acetoxy-5β,6β-oxocholestane, whose spectral data were identical with those of the thermolysis product of 3β-acetoxy-5β,6β-*N*-nitroaziridinylcholestane.

Methanolysis of 3β-Acetoxy-5β,6β-*N*-nitroaziridinylcholestane (5). A solution of 500 mg (1.02 mmol) of 3β-acetoxy-5β,6β-*N*-nitroaziridinylcholestane in 40 mL of methanol was refluxed for 4 h, and the methanol was removed under a stream of nitrogen, giving a white solid. The solid was recrystallized from methanol, giving 340 mg (0.65 mmol, 64%) of 3β-acetoxy-5α-methoxy-6β-nitraminocholestane, mp 209–210 °C.

The spectral data were: IR ($CHCl_3$) 2.90, 3.39, 3.48, 5.77 (s), 6.30 (s), 6.80, 7.31, 7.51, 7.97, 8.55, 9.29, 9.69, 10.36 μm; NMR ($CDCl_3$) τ 4.24–4.76 (m, 1 H, –COOCH<), 6.67 (s, 3 H, CH_3O–), 7.70–9.25 (m, 30 H, aliphatic), 7.98 (s, 3 H, CH_3CO–), 8.88 (s, 3 H, C-19 methyl), 9.08 (br s, 6 H, C-26 and C-27 methyls), 9.17 (br s, 3 H, C-21 methyl), 9.30 (s, 3 H, C-18 methyl).

Anal. Calcd for $C_{30}H_{52}N_2O_5$: C, 69.19; H, 10.06; N, 5.38. Found: C, 69.08; H, 10.13; N, 5.35.

3β-Acetoxy-5α-hydroxy-6β-nitraminocholestane (22). A 1.00-g (2.04 mmol) sample of 3β-acetoxy-5β,6β-*N*-nitroaziridinylcholestane in 25 mL of dioxane and 10 mL of water was refluxed for 1 h, diluted with methylene chloride and water, extracted with methylene chloride (3×), dried, filtered, and concentrated in vacuo to give 1.16 g of white solid. The solid was recrystallized from acetone, giving 460 mg (0.908 mmol, 44%) of 3β-acetoxy-5α-hydroxy-6β-nitraminocholestane, mp 241–242 °C.

The spectral data were: NMR (Me_2SO-d_6) τ 7.70–9.70 (m); IR (Nujol) 2.84, 3.10, 3.20, 3.40 (s), 5.84 (s), 6.30, 6.84, 7.05, 7.26, 7.37, 7.50, 7.66, 7.90, 8.05, 8.25, 8.58, 8.90, 9.23, 9.71, 10.39, 10.88, 11.49 μm.

Anal. Calcd for $C_{29}H_{50}N_2O_5$: C, 68.74; H, 9.95; N, 5.53. Found: C, 69.02; H, 9.59; N, 5.65.

10β-Methyl-$\Delta^{1,9}$-octal-2-one (15). The procedure of Marshall and Fanta was followed.[11] A mixture of 28.17 g (0.154 mol) of *cis*-10-methyl-2-decalon-9-ol and 300 mL of 10% aqueous oxalic acid was steam-distilled. The distillate was saturated with sodium chloride and ether-extracted. The combined ether extracts were dried, filtered, and concentrated in vacuo to give 19.03 g (0.116 mol, 75%) of 10β-methyl-$\Delta^{1,9}$-octal-2-one.

***cis*-10-Methyl-2-decalon-9-ol (14) and 10β-Methyl-$\Delta^{1,9}$-octal-2-one (15)** The procedure of Marshall and Fanta[11] was followed. To a stirred mixture of 4.90 g (72 mmol) of sodium ethoxide in 25 mL of absolute ethanol and 400 g (3.57 mol) of 2-methylcyclohexanone at −10 to 0 °C was added dropwise 250 g (3.57 mol) of methyl vinyl ketone over 1.5 h under nitrogen. The thick mixture was stirred for 5 h at −10 to 0 °C, diluted with ether and brine, and extracted with ether. The combined ether extracts were washed with brine, dried, filtered, and concentrated in vacuo to ca. 900 mL. The ether was boiled off while volume was maintained with hexane. Cooling to room temperature overnight gave 32.08 g (0.176 mol, 5%) of *cis*-10-methyl-2-decalon-9-ol, mp 120–121 °C (lit.[11] mp 120–121 °C). Hexane was removed from the mother liquors in vacuo, and the residue was distilled giving: fraction 1, 75 °C (30 mm), 144.52 g of 2-methylcyclohexanone; and fraction 2, 135 °C (0.1 mm), 171.55 g of 10β-methyl-$\Delta^{1,9}$-octal-2-one. Steam distillation of the pot residue with 300 mL of 10% aqueous oxalic acid followed by ether extraction, drying, and concentration in vacuo gave an additional 49.21 g of enone. The total yield of 10β-methyl-$\Delta^{1,9}$-octal-2-one was 220.76 g (1.34 mol, 38%).

10-Methyl-$\Delta^{1,9}$-octal-2-ol Acetate (16). The procedure of Marshall and Hochstetler was followed.[12] To a stirred solution of 50.00 g of lithium aluminum hydride in 2 L of ether was added 204.0 g (1.24 mol) of 10β-methyl-$\Delta^{1,9}$-octal-2-one in 200 mL of ether over 45 min. A ice bath was used for cooling during the addition and then removed. After stirring for 3 h at room temperature, the mixture was cautiously treated with a mixture of 100 mL of water and 80 mL of 10% aqueous sodium hydroxide. An ice bath was used for cooling during the addition and then removed. After stirring for an additonal 2 h, the mixture was filtered and concentrated in vacuo to give a yellow liquid (204.5 g) whose NMR and IR were consistent with an allylic alcohol.

The crude alcohol was dissolved in 1300 mL of pyridine and 355 mL of acetic anhydride was added. The clear solution was stirred under nitrogen at room temperature for 23 h, 5 L of brine was added, and the mixture was extracted with ether. The combined ether extracts were washed with water, 2% aqueous sulfuric acid, and brine. The ether layer was then dried, filtered, and concentrated in vacuo to give a light yellow liquid which was distilled, giving 228.58 g (1.10 mol, 88%) of 10-methyl-$\Delta^{1,9}$-octal-2-ol acetate, bp 117 °C (2.5 mm) [lit.[12] bp 62–63 °C (0.08 mm)].

10-Methyl-$\Delta^{1,9}$-octalin (17) and 2-Hydroxy-10-methyldecalin. The procedure of Marshall and Hochstetler was followed.[12] To a stirred solution of 60.0 g (0.288 mol) of 10-methyl-$\Delta^{1,9}$-octal-3-ol acetate in 75 mL of ethylamine was added 20.0 g (225 cm, 2.88 mol) of lithium cut in small pieces. After ca. 15 min, a deep blue color appeared and the mixture was stirred at room temperature for 40 min more. Solid ammonium chloride was added carefully to neutralize the lithium salts and destroy any excess lithium metal. Ether was added to maintain volume and an ice bath was used to control the reaction. When most of the lithium had been destroyed, a small amount of water was added to speed the hydrolysis. When all the lithium had been destroyed, the mixture was diluted with 2 L of brine and extracted with ether. The combined ether extracts were washed with water, 2% aqueous sulfuric acid, and brine, and then dried, filtered, and concentrated in vacuo to give a yellow liquid which was vacuum distilled to give 21.25 g (0.141 mol, 49%) of 10-methyl-$\Delta^{1,9}$-octalin, bp 70 °C (0.7 mm) [lit.[12] bp 86–88 °C (26 mm)], and 16.13 g (0.096 mol, 29%) of 2-hydroxy-10-methyldecalin, bp 90–95 °C (0.8 mm).

The spectral data for 10-methyl-$\Delta^{1,9}$-octalin were identical with those reported in the literature.[12] The spectral data for 2-hydroxy-10-methyldecalin were: NMR ($CDCl_3$) τ 6.1–6.7 (br m, 1 H, –OH), 7.9–9.0 (br m, 16 H, aliphatic), 9.15 (s, 3 H, methyl); IR ($CHCl_3$) 2.74, 2.91, 3.42, 3.50, 6.88, 7.26, 7.34, 8.06, 8.53, 9.19, 9.49, 9.74, 9.16, 10.56 μm.

Anal. Calcd for $C_{11}H_{18}$: C, 87.93; H, 12.07. Found: C, 87.90; H, 12.08. MS calcd for $C_{11}H_{18}$: 150.1408. Found: 150.1407. Anal. Calcd for $C_{11}H_{20}O$: C, 78.51; H, 11.98. Found: C, 78.44; H, 11.84. MS calcd for $C_{11}H_{20}O$: 168.1514. Found: 168.1526.

1-Oximino-9-chloro-10-methyldecalin (18) and 1-Nitri-

mino-9-chloro-10-methyldecalin (19). A solution of 58.0 g of 10-methyl-$\Delta^{1,9}$-octalin in 1 L of methylene chloride at 0 °C was stirred while nitrosyl chloride was slowly bubbled in for 20 min. The reddish brown solution was stirred at 0 °C for 3 h and concentrated in vacuo to give a light green solid which was washed with cold hexane and filtered, giving 22.72 g (0.105 mol, 27%) of 1-oximino-9-chloro-10-methyldecalin, mp 128–132 °C dec. The filtrate was concentrated in vacuo to give a dark oil, which was chromatographed on a 6.5 cm × 34.5 cm column of silicic acid (Mallinckrodt, Silic AR, CC-7) slurry packed in 10% chloroform in hexane. Elution in 500-mL fractions gave: fraction 1, 1.38 g of unidentified oil; fractions 2–4, 25.05 g (0.102 mol, 26%) of 1-nitrimino-9-chloro-10-methyldecalin; and fraction 5, 2.13 g.

The spectral data for 1-oximino-9-chloro-10-methyldecalin were: NMR (CCl_3) τ 1.30 (s, 1 H, =NOH), 6.50–8.90 (m, 14 H, aliphatic), 9.00 (s, 3 H, methyl); IR ($CHCl_3$) 2.68, 3.01, 3.36, 6.86, 6.99, 7.26, 7.36, 7.61, 8.33, 8.70, 9.86, 10.26, 10.58, 11.30, 11.37, 11.65, 12.15, 12.32 μm.

The spectral data for 1-nitrimino-9-chloro-10-methyldecalin were: NMR ($CDCl_3$) τ 6.70–9.00 (m, 14 H, aliphatic), 8.89 (s, 3 H, methyl); IR ($CHCl_3$) 3.45, 3.52, 6.19, 6.38, 6.90, 6.96, 7.30, 7.65, 7.76, 7.90, 8.10, 8.70, 9.05, 9.50, 9.62, 9.96, 10.24, 10.33, 11.04, 11.21, 11.80, 12.20 μm.

Anal. Calcd for $C_{11}H_{18}NOCl$: C, 61.25; H, 8.41; N, 6.49; Cl, 16.43. Found: C, 61.41; H, 8.30; N, 6.35; Cl, 16.12. MS Calcd for $C_{11}H_{18}NOCl$: 215.1077. Found: 215.1075. Anal. Calcd for $C_{11}H_{17}N_2O_2Cl$: C, 53.99; H, 7.00; N, 11.45. Found: C, 54.22; H, 7.16; N, 11.11.

1-Nitrimino-9-chloro-10-methyldecalin (19). A solution of 22.73 g (0.105 mol) of 1-oximino-9-chloro-10-methyldecalin in 1.5 L of methylene chloride at 0 °C was stirred while nitrosyl chloride was slowly bubbled in for 30 min. The reddish brown solution was stirred at 0 °C for 5.5 h, poured into water, washed with water and brine, dried, filtered, and concentrated in vacuo to give a yellow oil which was chromatographed on a 3.5 cm × 39.5 cm column of silicic acid (Mallinckrodt, Silic-AR, CC-7) slurry packed in 10% chloroform in hexane. Elution in 200 mL fractions gave: fraction 1, nil; fractions 2–5, 14.49 g (0.059 mol, 56%) of 1-nitrimino-9-chloro-10-methyldecalin; and fraction 6, 160 mg.

A small sample of 1-nitrimino-9-chloro-10-methyldecalin was recrystallized from ethanol, yielding white crystals which melted at 61–62 °C.

1-Nitramino-9-chloro-10-methyldecalin (20). The acidification technique of Meyers and Nabeya[8] was modified for the imine reduction. To a stirred solution of 14.49 g (59.2 mmol) of 1-nitrimino-9-chloro-10-methyldecalin in 420 mL of dioxane, 420 mL of absolute ethanol, and 107 drops of glacial acetic acid at 0 °C was added 22.00 g (0.579 mol) of sodium borohydride as fast as possible while still controlling frothing. The mixture was stirred at 0 °C for 30 min, and 3.8 mL (306 drops) of glacial acetic acid was added. Stirring was continued for 1 h at 0 °C followed by 1 h at room temperature. The mixture was then diluted with 1700 mL of 3% aqueous acetic acid and extracted with methylene chloride. The organic extracts were washed with water, dried, filtered, and concentrated in vacuo to give a white solid which was washed with hexane, filtered, and vacuum dried to give 10.24 g (41.5 mmol, 70%) of 1-nitramino-9-chloro-10-methyldecalin, mp 136 °C dec.

The spectral data were: NMR ($CDCl_3$) τ 0.90–1.50 (br m, 1 H, >NH), 5.28–5.51 (br m, 1 H, $-CHNHNO_2$), 7.32–9.16 (m, 14 H, aliphatic), 8.80 (s, 3 H, methyl); IR ($CHCl_3$) 2.96, 3.09, 3.42, 3.49, 6.24, 6.38, 6.74, 6.84, 7.09, 7.29, 7.44, 7.53, 7.75, 7.88, 8.14, 8.44, 8.58, 8.85, 9.16, 9.31, 9.84, 10.99, 11.20, 11.43, 11.79 μm.

Anal. Calcd for $C_{11}H_{19}N_2O_2Cl$: C, 53.55; H, 7.76; N, 11.35; Cl, 12.97. Found: C, 53.52; H, 7.62; N, 11.30; Cl, 12.99.

10-Methyl-1,9-(*N*-nitroaziridino)decalin (6) by the Silver Acetate Route. A mixture of 1.03 g (4.17 mmol) of 1-nitramino-9-chloro-10-methyldecalin and 2.13 g of silver acetate in 200 mL of acetone was stirred at room temperature under nitrogen for 8 h and 2.18 g of fresh silver acetate was added. Stirring was continued for 89 h more. The mixture was filtered and the filtrate was concentrated in vacuo to give a dark oil which was taken up in methylene chloride, washed with water, dried, filtered, and concentrated in vacuo to give a dark oil, which was vacuum distilled on a Kugelrohr distillation apparatus at 73–75 °C (0.1 mm), giving 260 mg (1.24 mmol, 30%) of 10-methyl-1,9-(*N*-nitroaziridino)decalin.

The spectral data were: NMR ($CDCl_3$) τ 6.89 (br d, 1 H, J = 5.6 Hz, >CHN<), 7.50–9.50 (m, 14 H, aliphatic), 8.78 (s, 3 H, methyl); IR ($CHCl_3$) 3.39, 3.47, 6.43, 6.83, 6.93, 7.27, 7.78, 7.96, 8.19, 8.71, 8.88, 9.23, 9.51, 10.07, 10.18, 10.45, 11.23, 11.92, 12.03, 12.38, 12.59 μm.

Anal. Calcd for $C_{11}H_{18}N_2O_2$: C, 62.83; H, 8.63; N, 13.32. Found: C, 63.39; H, 8.84; N, 13.17. No molecular ion was found in MS; however, a strong peak from the loss of $\cdot NO_2$ was found. Calcd for $C_{11}H_{18}N$: 164.1438. Found: 164.1433.

10-Methyl-1,9-(*N*-nitroaziridino)decalin (6) by the *n*-Butyllithium Route. To a solution of 4.76 g (19.3 mmol) of 1-nitramino-9-chloro-10-methyldecalin in 475 mL of dry tetrahydrofuran at room temperature under nitrogen was added 23.2 mmol of *n*-butyllithium. The solution was stirred and refluxed for 1 h and then stirred at room temperature for 24 h. The mixture was diluted with 1.5 L of methylene chloride, washed with water, dried, filtered, and concentrated in vacuo to give 2.42 g (11.5 mmol, 60%) of 10-methyl-1,9-(*N*-nitroaziridino)decalin.

Thermolysis of 10-Methyl-1,9-(*N*-nitroaziridino)decalin (6). A neat sample of 10-methyl-1,9-(*N*-nitroaziridino)decalin (500 mg, 2.38 mmol) was heated to 149 °C under nitrogen for 5 min. After sitting at room temperature for several days, the oil crystallized and was chromatographed on a 20 cm × 20 cm × 2 mm plate of silica gel (E. Merck, according to Stahl). After one development with chloroform, the plate was divided into four bands: the second band from the bottom contained 170 mg (0.81 mmol, 34%) of 1-nitramino-10-methyl-Δ^8-decalin, which was recrystallized from hexane to give white crystals, mp 97.5–98.5 °C; the third band contained 5 mg of starting *N*-nitroaziridine; and the first and fourth bands contained a total of 10 mg of unidentified material.

The spectral data were: NMR ($CDCl_3$) τ 1.28–1.68 (br m, 1 H, >NH), 4.18 (t, 1 H, J = 3.5 Hz, vinyl), 5.35–5.64 (br m, 1 H, $>CHNHNO_2$), 7.65–8.80 (m, 12 H, aliphatic), 8.87 (s, 3 H, methyl); IR ($CHCl_3$) 2.90, 3.03, 3.38, 6.35, 6.86, 6.93, 7.23, 7.38, 7.47, 7.65, 7.77, 8.53, 9.27, 9.51, 9.88, 11.02 μm.

Anal. Calcd for $C_{11}H_{18}N_2O_2$: C, 62.83; H, 8.63; N, 13.32. Found: C, 62.75; H, 8.88; N, 13.52.

Methanol Solvolysis of 10-Methyl-1,9-(*N*-nitroaziridino)-decalin (6). A solution of 500 mg (2.38 mmol) of 10-methyl-1,9-(*N*-nitroaziridino)decalin in 100 mL of methanol was stirred and refluxed under nitrogen for 16 h. The methanol was removed in vacuo to give an oil which crystallized. The solid was washed with hexane, filtered, and vacuum dried to give 160 mg (0.66 mmol, 28%) of 1-nitramino-9-methoxy-10-methyldecalin as a cream-colored solid, mp 120–125 °C.

NMR analysis of the crude reaction mixture showed it to also contain trace amounts of 1-nitramino-10-methyl-Δ^8-decalin.

The spectral data were: NMR ($CDCl_3$) τ 1.16–1.70 (br m, 1 H, >NH), 5.40–5.75 (br m, 1 H, $>CHNHNO_2$), 6.80 (s, 3 H, OCH_3), 7.75–9.35 (m, 14 H, aliphatic), 8.87 (s, 3 H, aliphatic methyl); IR ($CHCl_3$) 2.92, 3.40, 6.32, 6.68, 6.93, 7.14, 7.34, 7.49, 8.55, 9.24, 10.46, 11.44, 11.79, 14.34 μm.

Anal. Calcd for $C_{12}H_{22}N_2O_3$: C, 59.48; H, 9.15. Found: C, 59.84; H, 9.25. No molecular ion was found in MS; however, a strong peak due to loss of $\cdot NO_2$ was found. Calcd for $C_{12}H_{22}NO$: 196.1700. Found: 196.1695.

1-Chloro-1α-nitrosoethylcyclohexane.[14] A solution of 50.0 g (0.454 mol) of ethylidenecyclohexane in 250 mL of ether at −78 °C was stirred while nitrosyl chloride was bubbled in for ca. 20 min. The solution rapidly turned dark brown, and a precipitate began to form after ca. 10 min. The mixture was stirred for 1 h, and the precipitate was filtered, washed with ice-cold ether, and vacuum dried to give 52.98 g (0.302 mol, 66%) of 1-chloro-1α-nitrosoethylcyclohexane, mp 130–131.5 °C (lit.[14] mp 134–135 °C). Both NMR and IR were in agreement with the reported spectra.[14]

Methyl 1-Chlorocyclohexylketoxime.[14] A suspension of 20.00 g (113.9 mmol) of 1-chloro-1α-nitrosoethylcyclohexane was stirred in 600 mL of ether at room temperature, while anhydrous hydrogen chloride was bubbled in for 45 min. The suspension was allowed to stir overnight at room temperature, was filtered, and the ether and hydrogen chloride were removed in vacuo. The resultant white solid was recrystallized from hexane to give 13.71 g (78.0 mmol, 68%) of methyl 1-chlorocyclohexylketoxime, mp 80.0–80.5 °C (lit.[14] mp 70–71 °C). Both NMR and IR were in agreement with the reported spectra.[14]

Methyl 1-Chlorocyclohexylnitroketimine.[14] A solution of 11.02 g (62.7 mmol) of methyl 1-chlorocyclohexylketoxime in 800 mL of chloroform at 0 °C was stirred while nitrosyl chloride was slowly bubbled in for ca. 15 min until the solution became reddish brown. The mixture was allowed to return to room temperature while stirring for 1 h. Solid sodium carbonate (15.0 g) was added and stirring was continued for 2.5 h. The mixture was filtered and concentrated in vacuo to give a blue liquid which was taken up in methylene chloride, washed with water and brine, dried, filtered, and concentrated in vacuo to give a blue liquid which was distilled, giving 4.83 g (23.6 mmol, 38%) of methyl 1-chlorocyclohexylnitroketimine, bp 52 °C (0.2 mm). Both NMR and IR were in agreement with the reported spec-

tra.[14]

1-Chloro-1-(α-nitraminoethyl)cyclohexane (28). The acidification technique of Meyers and Nabeya[8] was modified for this imine reduction. To a stirred solution of 4.00 g (19.5 mmol) of methyl 1-chlorocyclohexylnitroketimine in 100 mL of dioxane, 100 mL of absolute ethanol, and 24 drops of glacial acetic acid with an ice/acetone bath for cooling was added 12.8 g of sodium borohydride in small portions to control frothing. The mixture was allowed to stir for 30 min at reduced temperature, 60 drops of glacial acetic acid was added, and stirring was continued for 60 min at reduced temperature, followed by 30 min at room temperature. The mixture was carefully diluted with 400 mL of ca. 3% aqueous acetic acid and extracted with methylene chloride. The organic extracts were dried, filtered, and concentrated in vacuo to give a yellow oil which crystallized from hexane. Recrystallization from hexane yielded 1.66 g (8.03 mmol, 41%) of 1-chloro-1-(α-nitraminoethyl)cyclohexane, mp 84–85 °C (lit.[14] mp 91–92.5 °C). Both NMR and IR were in agreement with the reported spectra.[14]

3-Chloro-3-methyl-2-nitroiminobutane. A solution of 200 g (2.85 mol) of 2-methyl-2-butene in 1200 mL of methylene chloride was stirred at 0 °C while nitrosyl chloride was slowly bubbled into the solution for 1.3 h. The resultant blue solution was stirred for 1.5 h at 0 °C and concentrated in vacuo without heating to give ca. 200 g of 3-chloro-3-methyl-2-butanone oxime as an oily blue-green solid. Further purification was not attempted.

The 200 g of 3-chloro-3-methyl-2-butanone oxime in 1600 mL of methylene chloride was stirred at 0 °C while nitrosyl fluoride was slowly bubbled into the solution for 1.25 h. The green solution was stirred at 0 °C for 3.5 h, followed by 1.5 h at room temperature. The mixture was slowly poured into saturated aqueous sodium carbonate and washed with saturated aqueous sodium carbonate, water, and brine. The organic layer was dried, filtered, and concentrated in vacuo to give a blue oil which was distilled giving 21.00 g (0.128 mol, 4% overall) of 3-chloro-3-methyl-2-nitroiminobutane, bp 48–50 °C (0.5 mm).

The spectral data for the oxime were: IR ($CHCl_3$) 3.01, 3.32, 3.81 (br), 6.36, 6.96, 7.24, 7.32, 7.76, 8.13, 8.71, 9.01, 9.86, 10.06, 10.56, 11.11 μm; NMR ($CDCl_3$) τ 0.56 (s, 1 H, C=NOH), 7.95 (s, 3 H, CH_3C=NOH), 8.23 (s, 6 H, $(CH_3)_2CCl$).

The spectral data for the nitrimine were: IR (neat) 3.40, 3.47, 6.17, 6.36 (s), 6.92, 7.34, 7.65, 7.85, 8.12, 8.72, 9.01, 9.82, 10.12, 10.52, 10.94, 11.52, 11.87, 13.32 μm; NMR ($CDCl_3$) τ 7.76 (s, 3 H, $-C(CH_3)$=N–), 8.17 (s, 6 H, $(CH_3)_2CCl$).

Anal. Calcd for $C_5H_9N_2O_2Cl$: C, 36.49; H, 5.51; N, 17.02; Cl, 21.54. Found: C, 36.30; H, 5.59; N, 17.27; Cl, 21.51.

3-Chloro-3-methyl-2-nitraminobutane (29). The acidification technique of Meyers and Nabeya[8] was modified for this imine reduction. To a stirred solution of 4.04 g (24.6 mmol) of 3-chloro-3-methyl-2-nitroiminobutane in 100 mL of dioxane, 100 mL of absolute ethanol, and 24 drops of acetic acid at 0 °C was added 5.18 g (136 mmol) of sodium borohydride as fast as possible while still controlling frothing. The mixture was allowed to stir for 20 min at 0 °C, 60 drops of glacial acetic acid were added, and stirring was continued for 1 h at 0 °C, followed by 15 min at room temperature. The mixture was carefully diluted with 400 mL of ca. 3% aqueous acetic acid and extracted with methylene chloride. The combined organic extracts were dried, filtered, and concentrated in vacuo to give a light yellow liquid which was taken up in ether, washed with water (to remove dioxane), dried, filtered, and concentrated in vacuo to give a light yellow liquid which was distilled, giving 1.73 g (10.4 mmol, 42%) of 3-chloro-3-methyl-2-nitraminobutane as a clear liquid, bp 60 °C (0.1 mm).

The spectral data were: IR ($CHCl_3$) 2.90, 3.30, 6.35, 6.88, 7.25, 7.45, 7.74, 8.23, 8.75, 8.85, 9.17, 9.68, 11.00, 12.15 μm; NMR ($CDCl_3$) τ 1.45 (br m, 1 H, >NH), 5.56 (br q, 1 H, J = 6.5 Hz, $>CHNHNO_2$), 8.33 (s, 3 H, $CH_3C(Cl)<$), 8.36 (s, 3 H, $CH_3C(Cl)<$), 8.61 (d, 3 H, J = 6.5 Hz, $>C(CH_3)NH–$).

Anal. Calcd for $C_5H_{11}N_2O_2Cl$: C, 36.05; H, 6.66; N, 16.81; Cl, 21.28. Found: C, 36.09; H, 6.52; N, 16.28; Cl, 21.49.

Registry No.—**5,** 63866-33-1; **6,** 63866-34-2; **7,** 604-35-3; **8,** 1912-54-5; **9,** 31239-32-4; **10,** 31239-36-8; **11,** 63215-89-4; **17,** 13943-77-6; **18,** 63866-35-3; **19,** 63866-36-4; **20,** 63866-37-5; **21,** 63866-38-6; **22,** 63866-39-7; **24,** 1256-31-1; **25,** 4025-59-6; **26,** 63866-40-0; **27,** 63866-41-1; **29,** 63215-91-8; nitric acid, 7697-37-2; 2-hydroxy-10-methyldecalin, 2547-28-6; 2-methyl-2-butene, 513-35-9; 3-chloro-3-methyl-2-nitriminobutane, 63215-90-7; 3-chloro-3-methyl-2-butanone oxime, 3238-16-2.

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Chirality of Nucleophilic Reactions of Axial Aldehydes and Methyl Ketones in the Diterpene Series

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The conformation of the 4β aldehyde and methyl ketone groups in the podocarpane series has been reinvestigated. Felkin's hypothesis on the geometry of the most favored transition state for a nucleophilic reaction on these aldehydes and ketones combined with a calculation of the energy profile for the rotation around the C_α—C=O bond gives explanations for both chemical results and NMR data.

I. Introduction

The determination of the most stable conformation of the axial aldehyde group (4β) in the podocarpane **1** or ursane **2** series relies upon the following arguments.[1] (a) In the ^1H NMR spectra the signal associated with the aldehyde proton in a compound such as **3a** appears as a doublet (J = 1.6 Hz)[2] which has been shown to be due to long-range ^4J coupling with the 3α proton. The conformation of 3β-hydroxyaldehyde **4a**