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INTRAMOLECULAR CYCLOADDITIONS OF NITRONES JOINED BY AMIDES TO OLEFINS

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Abstract—Six nitrones joined by amides to olefins were prepared *in situ* from the related ketones **1–3** with N-methyl- and benzylhydroxylamines. The nitrones added intramolecularly to the olefins, and the cycloadditions gave the 6-lactams **4–9** stereoselectively and regiospecifically. Chemical correlations, CMR spectroscopy and two X-ray crystallographic analyses established that the relative stereochemistries of the six cycloadducts **4–9** were identical.

INTRODUCTION

Discovered by Cope and LeBel,[1-2] intramolecular cycloadditions of nitrones to olefins were developed by the latter and others from a puzzle[2] to a powerful synthetic method.[3-6] C-alkenylnitrones cyclize to carbocycles fused to isoxazolidines,[7-12] and two of these were used to synthesize the α-bisabolols.[13] N-alkenylnitrones ultimately give azacycles like cocaine[14-15] and luciduline.[16-17] When a heteroatomic chain links the cycloaddenda, they give isoxazolidines fused to heterocyclic ethers,[18-19] an amine,[20] a Schiff's base[21] and a thioether from which biotin was synthesized.[22-23]

Were a heteroatomic chain comprising amides of β,γ-unsaturated carboxylic acids and α-aminoketones to link the olefin to the nitrone carbon, cycloadditions should yield isoxazolidines fused to 6-membered lactams. We sought some of these 6-lactams as intermediates.

From ketones **1–3** we prepared six nitrones with N-methyl- and benzylhydroxylamines. We report that these nitrones cyclized *in situ*, giving the 6-lactams **4–9** stereoselectively and regiospecifically (Table 1). The relative stereochemistries of the six cycloadducts were identical. The cycloadditions induced asymmetry at four of the chiral centers of adducts **6–7**, because of prochirality at C_1 of ketone **2**.

Sequential N-demethylation, hydrolysis and hydrogenolysis beginning with **4** yielded the triply functionalized perhydroquinolizine **18**. Hydrogenolyses of **5** and **7** also gave **18**. These changes completed an asymmetric synthesis founded on closure of the C_4–C_5 bonds of 6-lactams by intramolecular cyloadditions of nitrones joined by amides to olefins.

[a]Dedicated to the memory of Robert Burns Woodward, this paper will be included in the Book version of the special Woodward Memorial Supplement.

STARTING MATERIALS

We assembled the starting materials for these cyloadditions from the aminoketal **10** and unsaturated carboxylic acids. To obviate self-condenstation we protected the latent ketone of **10** as the dimethyl ketal, and to provide a variety of amides we chose readily available acids. Ketalization of 2-acetylpyridine with trimethylorthoformate and catalytic reduction of the product gave **10**. It was amidated, and the resulting amideketals were hydrolyzed by dilute aqueous acid to the ketones **1–3** and **11**.

As expected, ketone **1** was a mixture of diastereomers; its CMR spectrum showed 17

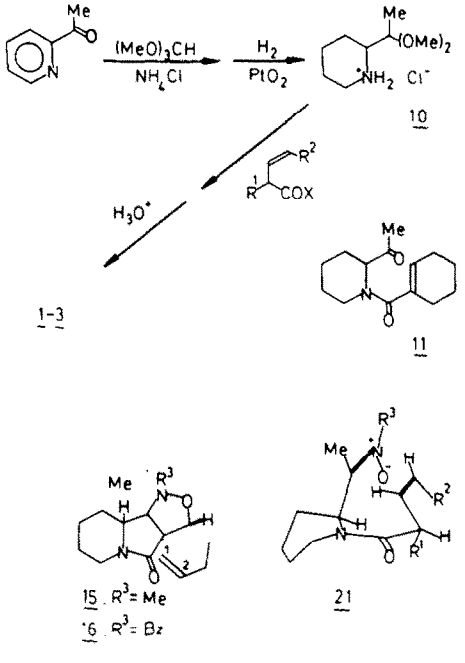
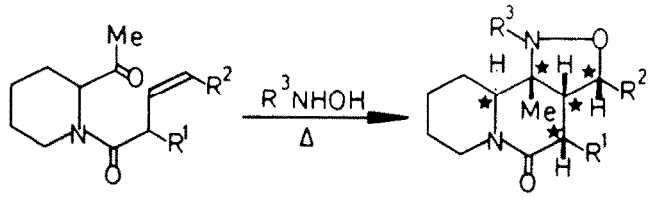
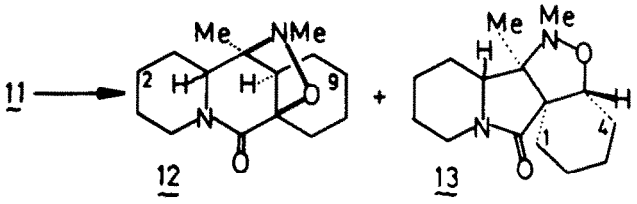


Table 1. Intramolecular cycloadditions of nitrones joined by amides to olefins



KETONE	R^1 R^2	ADDUCT	R^3	YIELD (%)
1	$-(CH_2)_3-$	4	Me	51
	$-(CH_2)_3-$	5	Bz	60[a]
2	$-(CH)_2CH_2-$	6	Me	3
	$-(CH)_2CH_2-$	7	Bz	32[a]
3	H H	8	Me	45
	H H	9	Bz	21

[a]Estimated; see Experimental.



resonances. Important, this observation implied we were not predetermining the stereochemistry of **4** and **5** by using only one diastereomer of ketone **1**.

Intramolecular cycloadditions

Excess N-methylhydroxylamine in hot ethanol consumed both diastereomers of ketone **1**, but formed cycloadduct **4** exclusively (tlc). Crystallization routinely isolated pure **4** in a yield of 51%. Although the crude product was sometimes chromatographed lest regio- or stereoisomers be overlooked, none were found.

Gratifying no less because it was foreseen,[4,6] the absence of regioisomers was a premiss of our plan. That of stereoisomers at once emphasized the exquisite discrimination of intramolecular cycloadditions[4,6] and defined the usefulness of these. The structures, acceptable relative stereochemistry, and chemistry of cycloadducts **4** and **8** later proved them to be intermediates we sought. Cycloadduct **8** was prepared like **4**.

We hoped to press other intermediates into service and to exact another diastereoselective response to nitrones larger and smaller than those employed before. We treated N-benzylhydroxylamine[24] with ketones **1** and **3**, and ketone **2** with both N-methyl- and benzylhydroxylamines. Cycloadduct **5** resulted and served as desired. Like the others obtained (**6–7, 9**), however, it bore the same relative stereochemistry as **4** and **8**.

We made cycloadduct **7** to functionalize its double bond subsequently. At first we obtained only 3% of this substance, a middling yield neither beneath notice nor above contempt. Changing the solvent of cycloaddition from ethanol to benzene increased the yield tenfold, but evidently optimized it. Despite prolonged treatment (119 hr) of **2** with N-benzylhydroxylamine in benzene at 50°, no reaction occurred (tlc). Briefer treatment (23 hr) of **2** with this reagent in boiling toluene gave not **7** but a complex mixture instead (tlc). Indeed, each of the foregoing six reactions was complicated by the formation of impurities.

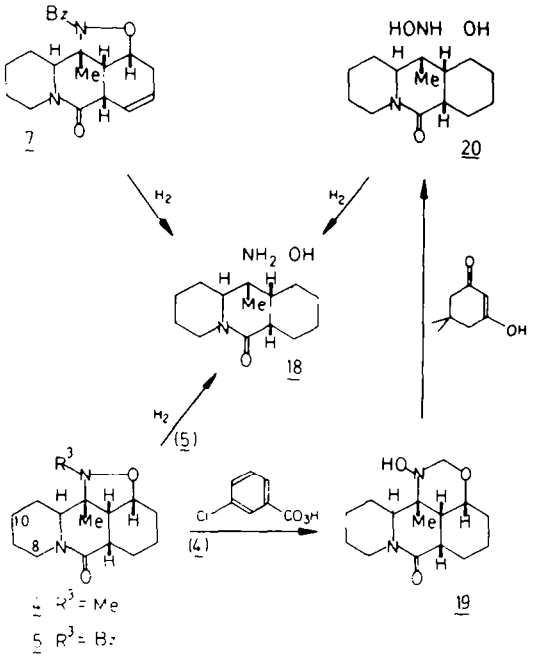
Chromatography isolated four of these impurities: N-benzyl-C-phenylnitrone,[25–26] and cycloadducts **14–16**. This nitrone contaminated adducts **5**, **7** and **9** (PMR). Although we prepared N-benzylhydroxylamine from this nitrone,[24] it did not contaminate the samples of the hydroxylamine used to make cycloadducts **5**, **7** and **9** (tlc, PMR, mp). We speculate that self-condensation of the hydroxylamine formed the nitrone during the cycloadditions.†

Evidently N-methylhydroxylamine also underwent self condensation. The structure of **14**,‡ formed by **2** and this reagent, was formally that of an adduct of N-methylnitrone and **6**.

Cycloadducts **15** and **16** contaminated compounds **6** and **7**. The structures of **15** and **16** implied that one double bond of ketone **2** or of its

†Dehydration of the N-alkylhydroxylamine to the corresponding imine, followed by addition of the hydroxylamine to the imine and elimination of ammonia, would account for the formation of the nitrone.

‡The regioisomeric structure of **14** followed from the frequency (ν 1640, 6-lactam) of its carbonyl absorption and from the three vicinal couplings (9.5, 9.0 and 5.0 Hz) of H_{7a} in it. In the regioisomer of **14**, these couplings would have numbered two. In **14** and **4**, the signals of H_{6a} and H_{2a} were broad 1-proton multiplets at δ4.2–3.9 ppm respectively. These facts allowed us to assign the signals of H_{6a} and H_{7a} in **14**. Its spectrum showed only two signals in this region.



nitrones suffered conjugation to the amide carbonyl. This raises the question of whether we would have detected cycloadducts **12** and **13** in crude **4**.

Had **1** or its N-methylnitrones been isomerized *in situ* to ketone **11** or to its N-methylnitrone, adducts **12** and **13** would have contaminated **4**. They did not, as direct comparison of **12** and **13** to crude **4** showed. We concluded that little isomerization, if any, occurred.

We prepared **12** and **13** from **11** and isolated them by chromatography in a yield of 70% and a ratio of 1:13, respectively. They were distinguishable from **4**, **12** by tlc and **13** by IR. IR spectroscopy not only distinguished **13** from **4** but from **12** as well.

Differentiation of 5- and 6-lactams

In general, IR and CMR spectroscopy distinguished the isomeric 5- and 6-membered lactams (**13**, **15-16** and **12**, **6–7**, respectively). The carbonyls of the former absorbed at higher frequencies and resonated at lower fields than those of the latter. In particular, the signals of the other oxygenated carbons of **12** and of **13** were a singlet (C_{6a}) and a doublet (C_{4a}), respectively. These distinctions were independent of the relative stereochemistries of the cycloadducts.

Assume the illustrated assignment of partial relative stereochemistry to **15** and **16**. Then support for the distinction between them and **6–7** lies in the differential chemical shift ($\nabla\delta$ $[H_2-H_1]$ = 0.8 ppm) of the olefinic protons of **15** and **16**. In stereomodels of the spirocycloadducts **15** and **16**, the planes of the amides and olefins were nearly perpendicular. Consequently anisotropic shielding of H_1 by the carbonyls of **15–16** accounts for the differential chemical shift. Adducts **6–7**, however, should show no such anisotropy. In them, the differential chemical shift of H_4 from H_5 was naught.

The distinction between **15** and **6** was consistent with the differential chemical shift ($\nabla\delta$ = 9 ppm) of the olefinic carbon resonances of **15**. We were unable to assign the olefinic carbon resonances of **15** uniquely, but steric compression of its C_1-carbon by its *cis*, vicinal C_{6a}-methyl group would explain the observed $\nabla\delta$-value. In **6** no effect was observed ($\nabla\delta$ $[C_4-C_5]$ = 1 ppm), and none expected.

Assignments of relative stereochemistry

We assigned the illustrated partial relative stereochemistries to compounds **12–13** and **15–16** for two reasons. Nitrone-olefin cycloadditions are *cis*-stereospecific[28] and other structures manifesting this specificity would be improbably strained. In them the reciprocal fusions of the 5-membered rings and the bridging of the lactam of **12** by its epoxyimino group would be *trans*.

Although we were unable to determine the stereochemistry of spirocycloadducts **15** and **16** at C_{6b}, their comparable CMR chemical shifts were identical. This showed they had the same relative stereochemistry.

So, too, did all six cycloadducts **4–9** have the same relative stereochemistry. Single-crystal X-ray analyses of cycloadduct **4** and of perhydroquinolizinone **17** not only established their complete structures but also demonstrated the identical natures of their common relative stereochemistries. Reduction of **8** with zinc was the source of **17**.

CMR spectroscopy established that the relative stereochemistries of the common chiral centers of **6** and **8** were identical to those of **7** and **9**, respectively. The relevant chemical shifts (Table 2) were within 1 ppm of one another.

We converted cycloadducts **5** and **7** to the same perhydrobenzoquinolizidine **18**, showing the identity of their relative stereochemistries. Oxidative N-demethylation of **4** to **19**,[14-15,27] hydrolysis of **19** to **20**,[27] and hydrogenolysis of **20** also gave **18**. These changes related **5** and **7** to **4**, and they completed elucidation of the relative stereochemistries of **4–9**. From the structural relations of products **4–9**, we inferred that the cycloadditions were indifferent to the nitrones they consumed.

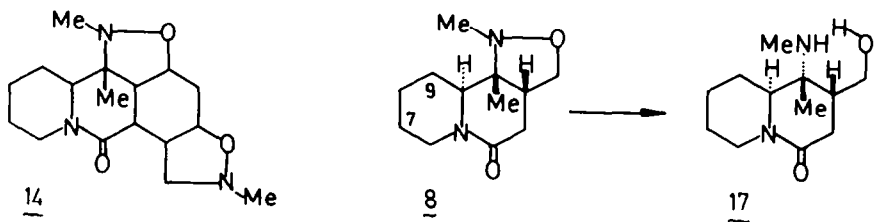


Table 2. ^{13}CMR chemical shifts (δ($CDCl_3$), ppm)[a]

No./C	2a	11c	5a	6	8	9	10	11	11a	11b	Me	3
6	73.7	40.3[b]	48.8	170.8	39.6[b]	22.7[c]	23.8[c]	26.2	58.4	70.0	16.9	20.5
7	73.9	40.2[b]	48.1	169.4	39.3[b]	22.6[c]	23.8[c]	26.2	58.3	70.0	16.5	20.5
	3	3a	4	5	7	8	9	10	10a	10b	Me	
8	71.0	44.8[b]	31.3	168.5	42.4[b]	23.1[c]	24.0[c]	26.7	60.7	66.0	16.5	
9	71.0	45.8[b]	31.8	168.6	42.4[b]	23.1[c]	24.0[c]	26.6	60.6	66.3	17.0	

[a]Assignments were aided by off-resonance spectra. [b,c]Interchangeable.

DISCUSSION

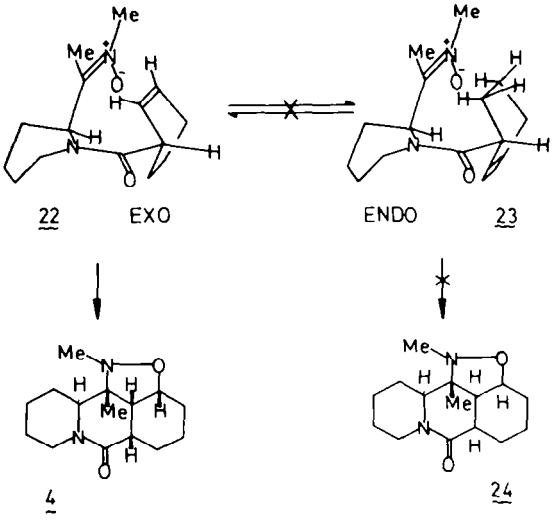
Omnivorous, the cycloadditions yielding **4**–**9** had identical diastereoselectivities. These were independent of the sizes of the N-substituents of the nitrones, of the presence or absence of a cyclohexene and of its size. They implied a common nitrone conformer cyclizing, we presume,† under kinetic control.[29]

We adduce **21** as the nitrone conformer common to the cycloadditions yielding **4**–**9**. Our inspection of stereomodels suggested that its transition to cycloadducts was least hindered in each series. In stereomodels its variable substituents were remote from the intramolecular site of cycloaddition.

Both diastereomers of **1** were consumed but yielded only half the theoretical amount of cycloadduct **4**. Therefore neither the diastereomers of ketone **1** nor those of its N-methylnitrones were interconverted.

If both diastereomeric nitrones of **1** formed, relatively slow cycloaddition of one would explain the absence of any diastereomeric adduct. Inspection of stereomodels suggested that the cycloadditions of the diastereomeric nitrone conformers **22** and **23** were the least hindered of the respective series. Leading to a sterically disfavored *endo* transition state,[30] **23** may consequently cyclize more slowly than **22**. A less crowded *exo* transition state corresponds to **22**. Uncyclized to the *trans*-fused **24**, unepimerized and unisolated, **23** may have been destroyed rapidly by another (unknown) reaction.

We defer to another report an account of how the structures and stereochemistry of these cycloadducts served. Save for an exposition of the crystallographic findings, we conclude divulging that the diastereoselectivity of these cycloadditions frustrated our greatest hope. *Woodward's Epigram* describes this plight: "...bad planning on Nature's part."‡



X-*ray crystallography*

The crystal structures of cycloadduct **4** and of perhydroquinolizinone **17** were solved by direct methods by use of MULTAN 76.[31] Atomic positional and thermal parameters (anisotropic C, N, O; isotropic H) were refined by full-matrix least-squares calculations to R ($=\Sigma||F_o|-|F_c||/\Sigma|F_o|$) values of 0.050 for **4** over 1185 reflections and 0.049 for **17** over 1189 reflections. Final atomic positional and thermal parameters are in Tables 3 and 4. Figures 1 and 2 provide views of the solid-state conformations as well as the atom numbering scheme; bond lengths and angles are reported in Figs. 3 and 4.

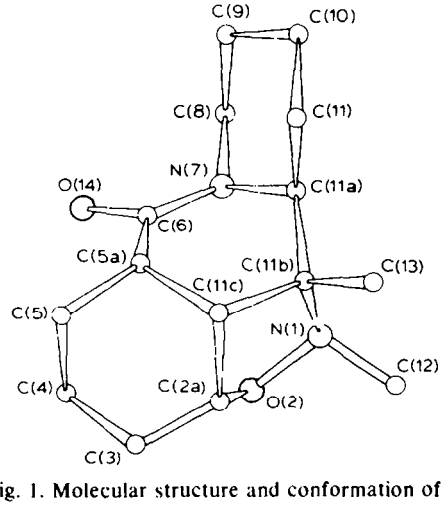


Fig. 1. Molecular structure and conformation of **4**.

†For example, cycloadduct **4** could be distilled under atmospheric pressure at 220° (temp. of Kofler block).

‡R. B. Woodward (6.XII.1971, Basel, Switzerland) firmly postponing—not abandoning—a scheme to synthesize $PGF_{2\alpha}$ (*cf* I. Ernest, *Angew. Chem.* Int. Ed. **15**, 207 (1976)).

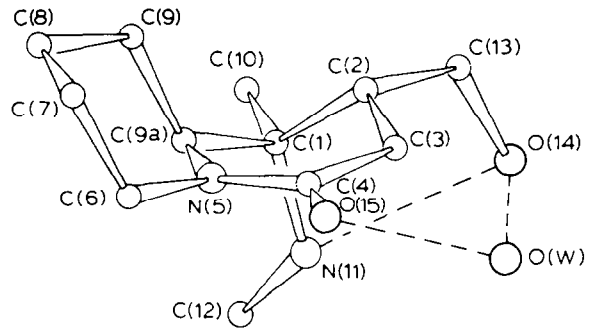


Fig. 2. Molecular structure and conformation of **17**: broken lines denote hydrogen bonds.

Crystals of **4** contain discrete molecules separated by normal van der Waals distances. Molecules of **17**, however, in addition to having an intramolecular N–H...O ($N_{11}...O_{14}$ 2.98 Å) H-bond, are associated further in the solid state through H-bonds involving the water molecule [$O_{14}...O_W$ 2.77 Å; $O_{15}...O_W$ (at $x, y, 1+z$) 2.71 Å; $O_{14}...O_W$ (at $(1/2)-x, 1-y, (1/2)+z$) 2.62 Å].

Endocyclic torsion angles characterizing the ring conformations in **4** and **17** are in Table 5. The piperidine rings in both compounds adopt slightly distorted chair conformations in which the means

Table 3. Fractional atomic co-ordinates (x10^4; x10^3 for hydrogen atoms) and thermal parameters (x10^3) for **4**, with estimated standard deviations in parentheses. Hydrogen atoms bear the same labels as the atoms to which they are bonded. Anisotropic thermal parameters are in the form: $\exp[-2\pi^2(U_{11}h^2a^{*2}+U_{22}k^2b^{*2}+U_{33}l^2c^{*2}+2U_{12}hka^*b^*+2U_{13}hla^*c^*+2U_{23}klb^*c^*]$

Atom	*x*	*y*	*z*	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
N(1)	7545(3)	5910(2)	3054(2)	55(2)	37(1)	36(1)	-10(1)	1(1)	-1(1)
O(2)	8469(2)	5053(2)	2970(2)	56(1)	45(1)	55(1)	-6(1)	7(1)	4(1)
C(2a)	8636(4)	4681(3)	4219(3)	52(2)	49(2)	57(2)	-5(2)	-22(2)	01(2)
C(3)	9361(4)	3654(3)	4191(5)	38(2)	65(2)	106(3)	2(2)	-14(2)	11(2)
C(4)	8518(4)	2778(3)	3716(3)	49(2)	42(2)	59(2)	8(2)	2(2)	9(2)
C(5)	7257(4)	2708(3)	4454(4)	66(2)	37(2)	72(2)	8(2)	10(2)	18(2)
C(5a)	6433(3)	3707(2)	4350(3)	53(2)	34(1)	45(2)	1(1)	17(2)	11(1)
C(6)	5703(3)	3768(2)	3126(3)	42(2)	28(1)	54(2)	-5(1)	6(2)	-8(1)
N(7)	5184(3)	4696(2)	2814(2)	46(1)	30(1)	33(1)	-3(1)	1(1)	-5(1)
C(8)	4031(4)	4724(3)	1998(3)	52(2)	48(2)	44(2)	-6(2)	-3(2)	-3(2)
C(9)	2777(4)	4734(3)	2784(4)	49(2)	64(2)	60(2)	-5(2)	4(2)	6(2)
C(10)	2817(4)	5614(3)	3738(4)	56(2)	62(2)	59(2)	13(2)	17(2)	3(2)
C(11)	4073(4)	5609(3)	4503(3)	72(2)	42(2)	47(2)	7(2)	18(2)	-5(1)
C(11a)	5277(4)	5611(2)	3631(3)	60(2)	25(1)	29(1)	1(1)	5(1)	-2(1)
C(11b)	6681(3)	5702(2)	4170(3)	64(2)	27(1)	26(1)	-6(1)	1(2)	-3(1)
C(11c)	7233(4)	4680(3)	4724(3)	59(2)	43(2)	21(1)	2(2)	-4(1)	-1(1)
C(12)	8335(5)	6866(3)	3099(4)	105(3)	42(2)	75(2)	-31(2)	12(3)	6(2)
C(13)	6702(4)	6571(3)	5144(3)	90(3)	48(2)	42(2)	-7(2)	-1(2)	-20(1)
O(14)	5504(3)	2986(2)	2487(3)	68(2)	38(1)	111(2)	-3(1)	-18(2)	-33(1)

Atom	*x*	*y*	*z*	*U*	*Atom*	*x*	*y*	*z*	*U*
H(2a)	912(4)	521(3)	475(4)	74(12)	H(10α)	268(4)	629(3)	329(4)	73(12)
H(3α)	1025(3)	370(3)	386(3)	59(10)	H(10β)	205(3)	561(3)	426(3)	56(10)
H(3β)	958(4)	352(4)	520(4)	87(14)	H(11α)	409(4)	622(3)	503(4)	75(12)
H(4α)	830(3)	285(3)	285(3)	48(9)	H(11β)	416(4)	499(3)	505(4)	71(12)
H(4β)	899(3)	209(2)	380(3)	35(8)	H(11a)	513(2)	626(2)	310(2)	18(6)
H(5α)	673(3)	218(3)	424(3)	45(9)	H(11c)	716(4)	476(3)	556(4)	71(12)
H(5β)	757(4)	270(3)	539(4)	79(13)	H(12A)	884(4)	688(4)	236(4)	77(14)
H(5a)	565(3)	360(2)	493(3)	31(7)	H(12B)	769(4)	746(3)	305(4)	76(11)
H(8α)	409(4)	535(3)	153(3)	63(11)	H(12C)	897(5)	689(4)	387(4)	104(12)
H(8β)	411(4)	414(3)	145(4)	69(12)	H(13A)	762(3)	666(3)	544(3)	54(10)
H(9α)	193(3)	484(3)	225(3)	59(11)	H(13B)	618(4)	639(3)	579(3)	58(10)
H(9β)	264(4)	401(4)	312(4)	93(14)	H(13C)	629(4)	729(3)	477(4)	76(13)

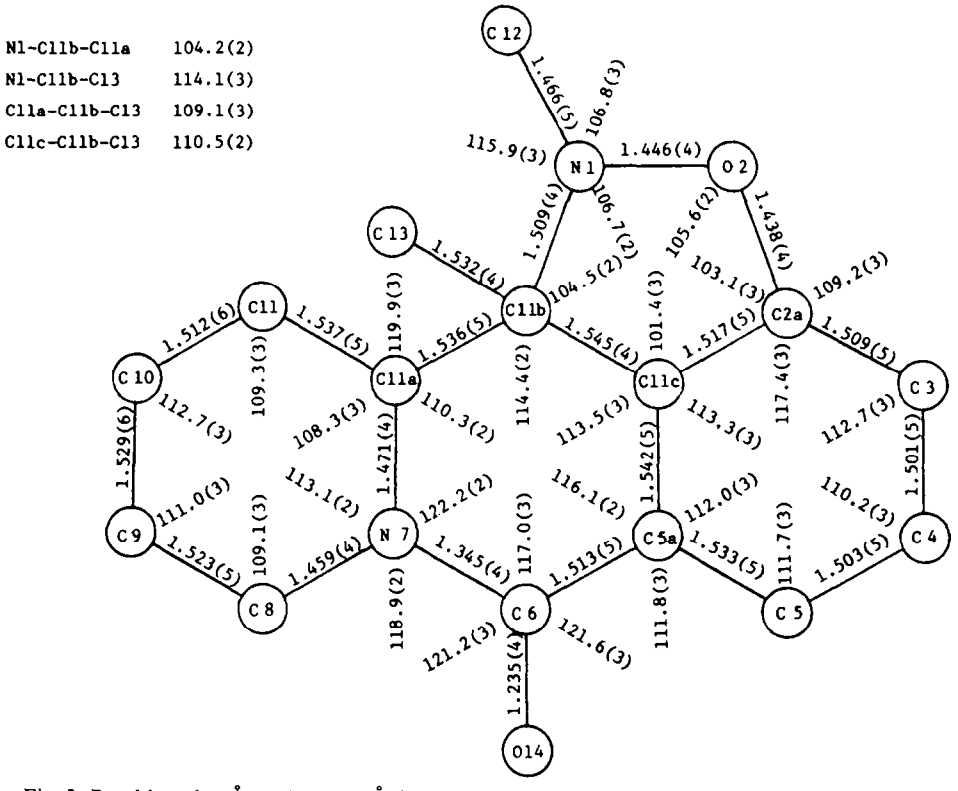


Fig. 3. Bond lengths (Å) and angles (°) in **4**, with estimated standard deviations in parentheses.

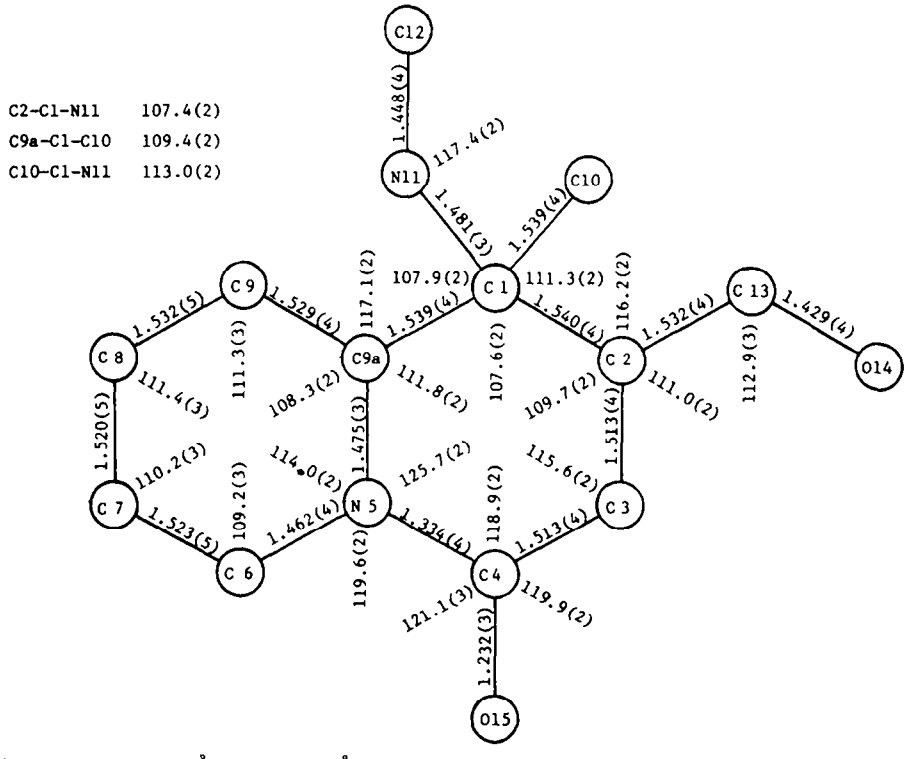


Fig. 4. Bond lengths (Å) and angles (°) in **17**, with estimated standard deviations in parentheses.

Table 4. Fractional atomic co-ordinates ($\times 10^4$; $\times 10^3$ for hydrogen atoms) are thermal parameters ($\times 10^3$) for **17**, with estimated standard deviations in parentheses. Hydrogen atoms bear the same labels as the atoms to which they are bonded. Anisotropic thermal parameters are in the same form as those reported in Table 3

Atom	*x*	*y*	*z*	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
C(1)	1531(2)	2346(2)	3203(3)	36(1)	44(1)	30(1)	-2(1)	-3(1)	-1(1)
C(2)	887(3)	3130(2)	4045(4)	37(1)	42(1)	40(1)	0(1)	0(1)	4(1)
C(3)	1605(3)	3376(2)	5576(3)	42(1)	38(1)	36(1)	0(1)	5(1)	-2(1)
C(4)	2032(2)	2617(2)	6630(3)	39(1)	44(1)	33(1)	-6(1)	4(1)	-2(1)
N(5)	1948(2)	1806(1)	6034(3)	43(1)	39(1)	33(1)	-5(1)	-7(1)	1(1)
C(6)	2134(3)	1058(2)	7125(4)	53(2)	41(1)	43(1)	-1(1)	-12(2)	7(1)
C(7)	880(4)	602(2)	7404(4)	74(2)	46(1)	52(2)	-5(2)	7(2)	9(2)
C(8)	308(3)	331(2)	5776(5)	67(2)	48(1)	59(2)	-17(1)	0(2)	4(2)
C(9)	210(3)	1109(2)	4599(4)	50(1)	49(1)	46(2)	-14(1)	-3(1)	-2(1)
C(9a)	1478(3)	1567(2)	4395(3)	40(1)	37(1)	32(1)	0(1)	-1(1)	-5(1)
C(10)	860(3)	2100(2)	1598(4)	53(2)	63(2)	35(1)	-7(1)	-9(1)	-1(1)
N(11)	2868(2)	2581(2)	2958(3)	38(1)	47(1)	36(1)	-3(1)	3(1)	-1(1)
C(12)	3617(3)	2006(2)	2943(4)	45(1)	68(2)	48(2)	5(1)	8(1)	-6(2)
C(13)	649(3)	3936(2)	2969(5)	60(2)	48(1)	59(2)	5(1)	-9(2)	7(2)
O(14)	1782(2)	4359(1)	2464(3)	75(1)	46(1)	45(1)	-4(1)	10(1)	5(1)
O(15)	2447(2)	2755(2)	8015(3)	89(2)	55(1)	31(1)	-16(1)	-11(1)	-5(1)
O(W)	2988(3)	4305(1)	-542(3)	103(2)	44(1)	63(1)	-9(1)	13(2)	-6(1)

Atom	*x*	*y*	*z*	*U*	*Atom*	*x*	*y*	*z*	*U*
H(2)	0(3)	295(2)	446(4)	40(8)	H(10A)	-8(3)	212(2)	177(5)	56(8)
H(3α)	233(2)	366(2)	525(3)	32(7)	H(10B)	120(3)	154(2)	118(4)	51(8)
H(3β)	105(2)	376(2)	619(3)	33(6)	H(10C)	110(3)	254(2)	71(4)	49(12)
H(6α)	275(3)	62(2)	660(4)	52(8)	H(11)	291(3)	324(2)	267(4)	45(10)
H(6β)	251(3)	129(2)	806(4)	49(8)	H(12A)	442(3)	227(2)	187(5)	62(10)
H(7α)	90(3)	10(2)	823(4)	65(10)	H(12B)	329(3)	190(2)	105(4)	60(9)
H(7β)	31(3)	109(2)	790(4)	51(9)	H(12C)	366(3)	141(2)	248(4)	58(9)
H(8α)	93(3)	-16(2)	522(4)	55(9)	H(13A)	11(3)	438(2)	364(5)	64(10)
H(8β)	-56(4)	10(3)	587(6)	104(15)	H(13B)	15(3)	378(2)	191(4)	61(10)
H(9α)	-10(2)	86(2)	354(4)	37(7)	H(14)	222(-)	434(-)	138(-)	55(8)
H(9β)	-32(2)	155(2)	488(5)	64(10)	H(OWA)	279(-)	373(-)	-108(-)	70(12)
H(9a)	212(3)	113(2)	389(4)	42(7)	H(OWB)	308(-)	482(-)	-130(-)	70(12)

of the moduli of the endocyclic torsion angles are 57.0 and 56.7°, respectively. Fusion of the cyclohexane ring to the isoxazolidine and 2-piperidone rings in **4** results in a significantly flattened chair form wherein the torsion angles range from 38.1 to 61.1° with a mean value of 49.3°. The isoxazolidine ring in **4** has an envelope conformation with C_{2a} as the out-of-plane atom. Non-bonded interactions between the nearly eclipsed N_1-and C_{11b}-methyl substituents associated with this particular envelope conformation are accomodated by a combination of bond lengthening (N_1–C_{11b} at 1.509 Å is significantly longer than the mean of 1.465 Å for the other three non-lactam C–N single bonds in **4** and **17**) and bond angle deformations [C_{11b}–N_1–C_{12} (115.9°) is much larger than C_{12}–N_1–O_2 (106.8°), and N_1–C_{11b}–C_{13} (114.1°) is greater than tetrahedral]. Although the C–C–N–C lactam moieties are nearly planar in both compounds, the conformations adopted by the 2-piperidone rings are distinctly different. In **17**, where the ring conformation in the solid state is undoubtedly influenced to some extent by hydrogen bonding, a form approximating to a half-chair with a C_2 axis bisecting the C_4–C_5 and C_1–C_2 bonds is found. Constraints imposed by the multiple ring fusions in **4** force the 2-piperidone ring to adopt a distorted boat form.

EXPERIMENTAL

Uncorrected m.ps were determined on a Kofler block (Thomas Model 40), IR spectra (CH_2Cl_2) on a Perkin-Elmer 727B spectrophotometer, PMR and CMR (TMS in $CDCl_3$) on Varian CFT-20 or XL-100 instruments, and medium-resolution mass spectra on a Varian CH5 spectrometer. For tlc, commercial silica gel (F-254, E. Merck) and alumina (GF, Analtech) plates were used; developed plates were visualized in I_2 vapor. For column chromatography, silica gel (0.063–0.200 mm, E. Merck) and basic alumina (Woelm; deactivated with H_2O to grade IV) were purchased. Although all chiral compounds prepared were racemic, only one enantiomer is depicted.

2 - (1, 1 - *Dimethoxyethyl*) - *pyridine*. 2 - Acetylpyridine (180g), trimethylorthoformate (246ml), NH_4Cl (24g) and MeOH (1.8 l) were boiled 60 hrs under reflux, cooled, mixed with Na_2CO_3 (47g) and evaporated. The residue was extracted from H_2O with CH_2Cl_2, dried ($MgSO_4$) and distilled giving the ketal (92.9g, 37%), b.p. 44–53°/0.1 mm after redistillation. PMR: 8.74–8.55 (m, 1H), 7.79–7.52 (m,

Table 5. Endocyclic torsion angles (°) in **4** and **17**, with estimated standard deviations in parentheses

(a) Compound 4

Cyclohexane ring		Piperidine ring	
C(11c)-C(2a)-C(3)-C(4)	44.4(3)	C(11a)-N(7)-C(8)-C(9)	-61.5(3)
C(3)-C(2a)-C(11c)-C(5a)	-38.1(3)	C(8)-N(7)-C(11a)-C(11)	63.8(3)
C(2a)-C(3)-C(4)-C(5)	-54.6(4)	N(7)-C(8)-C(9)-C(10)	53.4(3)
C(3)-C(4)-C(5)-C(5a)	61.1(3)	C(8)-C(9)-C(10)-C(11)	-51.9(3)
C(4)-C(5)-C(5a)-C(11c)	-55.1(3)	C(9)-C(10)-C(11)-C(11a)	53.6(3)
C(5)-C(5a)-C(11c)-C(2a)	42.4(3)	C(10)-C(11)-C(11a)-N(7)	-57.6(3)
2-Piperidone ring		**Isoxazolidine ring**	
C(11c)-C(5a)-C(6)-N(7)	-35.8(3)	C(11b)-N(1)-O(2)-C(2a)	-27.9(3)
C(6)-C(5a)-C(11c)-C(11b)	27.2(3)	O(2)-N(1)-C(11b)-C(11c)	1.9(2)
C(5a)-C(6)-N(7)-C(11a)	-1.8(3)	N(1)-O(2)-C(2a)-C(11c)	43.0(3)
C(6)-N(7)-C(11a)-C(11b)	44.0(3)	O(2)-C(2a)-C(11c)-C(11b)	-40.1(3)
N(7)-C(11a)-C(11b)-C(11c)	-48.4(3)	N(1)-C(11b)-C(11c)-C(2a)	22.9(3)
C(11a)-C(11b)-C(11c)-C(5a)	14.3(3)		

(b) Compound 17

2-Piperidone ring		Piperidine ring	
C(9a)-C(1)-C(2)-C(3)	62.5(2)	C(9a)-N(5)-C(6)-C(7)	-61.7(3)
C(2)-C(1)-C(9a)-N(5)	-50.9(2)	C(6)-N(5)-C(9a)-C(9)	60.2(2)
C(1)-C(2)-C(3)-C(4)	-43.1(2)	N(5)-C(6)-C(7)-C(8)	56.6(3)
C(2)-C(3)-C(4)-N(5)	11.2(3)	C(6)-C(7)-C(8)-C(9)	-53.9(3)
C(3)-C(4)-N(5)-C(9a)	0.6(3)	C(7)-C(8)-C(9)-C(9a)	53.6(3)
C(4)-N(5)-C(9a)-C(1)	20.6(2)	C(8)-C(9)-C(9a)-N(5)	-54.4(3)

2H), 7.34–7.07 (m, 1H), 3.23 (s, OMe, 6H), 1.65 (s, Me, 3H); MS: 136 (M–OMe, 36), 122 (22), 104 (100).

2-(1,1-*Dimethoxyethyl*)-*piperidine hydrochloride* (**10**). The filtrate from hydrogenation (20.5 hr, 25°, 60 psi of H_2, Paar shaker) of the foregoing ketal (32.0 g) with PtO_2 (6.2 g) in MeOH (600 ml) and trimethylorthoformate (21 ml) containing NH_4Cl (10.3 g) was concentrated to 100 ml and colorless **10** (36.7 g, 92%), m.p. 140.0–142.0°, pptd. with Et_2O. (Found: N.E. 207; Calc. ($C_9H_{20}ClNO_2$): 210.) Crystallization did not change the m.p. but acceptable microanalytical data could not be obtained. IR (KBr): 2720; PMR (DMSO-d_6): 9.9–7.7 (br, 2H), 3.6–2.6 (br), 3.18 (s, OMe) and 3.14 (s, OMe), 1.70 (br, 6H), 1.36 (s, CMe); MS: 173 (M, free base), 84.

2-*Cyclohexenyl*-1-*carbonyl chloride*. This was prepared according to Pearlman[32] from fresh oxalyl chloride and 2-cyclohexenyl-1-carboxylic acid[33] in benzene (25°) and was used without purification.

Vinylacetic anhydride. After being stirred overnight at 25°, the mixture from vinylacetic acid (28.4 g containing 10 mole % crotonic acid (PMR)), dicyclohexylcarbodiimide (34.1 g) and CH_2Cl_2 (125 ml) was filtered and concentrated; the product, b.p. 105–110°/35 mm (lit.[34] b.p. 98–100°/17 mm) was usually used without purification.

1,4-*Dihydrobenzoic anhydride*. Like vinylacetic anhydride, this was prepared from the corresponding acid[33] and dicyclohexylcarbodimide in CH_2Cl_2, and was used without purification.

Preparation of the amideketals. Equivalent amounts of **10**, $(i\text{-}Pr)_2NEt$ and the corresponding acid chlorides or anhydrides in CH_2Cl_2 (0–5° for 1–2 hr, then 25° overnight) gave these compounds. Lest *both* ketal *and* amide be hydrolyzed, the aqueous work-up was kept basic. When purification was deemed necessary, the crude products were chromatographed on silica gel and eluted with 1–5% MeOH in $CHCl_3$; otherwise the crude products were used directly.

2 - (1,1 - *Dimethoxyethyl*) - *piperidine* 2 - *cyclohexenyl* - 1 - *carboxamide*. A sample of this was distilled, b.p. 120–122°/0.05 mm; PMR: 5.99–5.41 (br m, 2H), 4.98–4.75 (m, 1H), 3.75–3.09 (en), 3.27 (s) and 3.26 (s) (2 OMe) (8H), 2.52–1.00 (en) and 1.31 (s, CMe) (16H); MS: 281, 90.

2 - (1,1 - *Dimethoxyethyl*) - *piperidine* 1,4 - *dihydrobenzamide*. This was prepared from the corresponding anhydride and was used directly.

2 - (1,1 - *Dimethoxyethyl*) - *piperidine* 1 - *cyclohexenyl* - 1 - *carboxamide*. This was prepared from commercial 1 - cyclohexenyl - 1 - carbonyl chloride. IR: 1610, 1430.

2 - (1,1 - *Dimethoxyethyl*) - *piperidine vinylacetamide*. A sample was distilled, b.p. 91–97°/0.05 mm. IR: 1620, 1430; PMR: 6.3–5.7 (m), 5.25–4.95 (m), 4.0–2.9 (br), 3.25 (s, OMe), 2.1–1.1 (en), 1.33 (s, CMe). Samples of this compound were contaminated by small amounts of the corresponding crotonamide which was inseparable by chromatography or distillation.

Preparation of the Amideketones (**1–3** and **11**). Compounds **1** and **2** were best prepared from the corresponding ketals by careful hydrolysis (dil aq HCl, 0–5°, 30–60 min, Et_2O; then aq $NaHCO_3$ workup). Some samples of the ketals contained an unidentified basic impurity, and acidification (to pH 2 with a minimum of conc HClaq) was necessary lest the ketals be recovered. Exposure to HClaq was minimized *lest the amide bonds be hydrolyzed*; Et_2O served this purpose better than THF. When purification was deemed necessary, the crude products were chromatographed on silica gel and eluted with 0.5–2% MeOH in $CHCl_3$; otherwise the crude products were used directly.

2 - *Acetylpiperidine* 2 - *cyclohexenyl* - 1 - *carboxamide* (**1**). The crude ketal (from 0.283 mole of the acid) in cold Et_2O (180 ml) was filtered, the unidentified ppt. discarded, the filtrate mixed with cold 0.1N HCl (300 ml), acidified (pH 2, conc HCl) and stirred 1 hr at 0–5°. Extraction (Et_2O), washing (1N $NaHCO_3$, H_2O, brine), drying (Na_2SO_4) and evaporating gave **1** (45.7 g,

61%). A chromatographed, distilled sample, b.p. 120–125°/0.05 mm was a yellow liquid. IR: 1710, 1630, 1420; PMR: 5.89 (br d, 1H) and 5.60 (br d, 1H) (2H), 5.24 (s, $W_{h/2}$ = 9, COCH), 3.87 (br d, 1H, NCH), 3.57–2.89 (en, 2H), 2.51–1.13 (en) and 2.12 (s, COMe) (15H); CMR: 207.2 (COMe), 171.4 (CON), 129.7, 125.1 and 124.6 (olefin C, unequal intensities), 59.0 (NCH), 44.1 (NCH_2), 38.9 and 38.6 (equal intensity, COCH), 26.9, 25.8, 25.5, 24.9, 24.7, 21.1, 21.0, 20.7 (CH_2 and COMe); MS: 235 (M), 192, 84 (100).

2 - *Acetylpiperidine* 1,4 - *dihydrobenzamide* (**2**). This compound was prepared from 1,4-dihydrobenzoic anhydride similarly to **3**; a sample of the crude product (31.1 g, 27% from 0.491 mole of the acid) crystallized, m.p. 83.0–85.5° (Et_2O), after chromatography on silica gel. (Found: C, 72.07; H, 8.07; N, 6.07. Calc. ($C_{14}H_{19}NO_2$): C, 72.07; H, 8.21; N, 6.00%). IR: 1720, 1640, 1420; PMR: 6.20–5.53 (m, 4H, vinyl), 5.26 (br, s, 1H, CHCON), 4.27–3.87 (br m, 2H, CH_2N), 3.17 (br t, 12, 1H, CHCOMe), 2.72 (br d, 9, 1H, CH_2 (vinyl)$_2$), 2.14 (s, 3H, COMe), 1.67–1.12 (en, 6H, $(CH_2)_3$); MS: 190 ($M-C_2H_3O$, 75), 84 (100).

2 - *Acetylpiperidine* 1 - *cyclohexenyl* - 1 - *carboxamide* (**11**). The crude ketal (9.27 g) in THF (27 ml) and 1N HCl (54 ml) was acidified (pH 2, conc HCl) and stirred 2 hrs at 0–5°; extraction (Et_2O), washing (H_2O, 1N Na_2CO_3, brine) and evaporating gave crude, oily **11** (5.80 g, 74%). IR: 1720, 1620, 1420; PMR: 5.79 (br m, 1H), 4.25–3.67 (br, 1H), 3.17–2.72 (br, 1H), 2.67–1.89 (br) and 2.16 (s) (9H), 1.90–1.11 (br m, 9H); MS: 235, 192, 109 (100).

2 - *Acetylpiperidine vinylacetamide* (**3**). The crude ketal (32.4 g) in THF (100 ml) and 0.1N HCl (200 ml) was stirred 2.5 hrs at 33°; basic aq work-up similar to that for **1** gave **3** (16.8 g, 68%). Chromatographed **3** was distilled, b.p. 100–110°/0.05 mm. IR: 1720, 1640, 1430; PMR: 6.2–5.7 (m, 1H), 5.3–5.0 (m, 2H) (vinyl), 3.74 (br d, 13, $1H_2$), 3.20 (d of t, 6.0, 1.2, $COCH_2$) and 3.3–2.9 (br, overlapping, CH_2N) (4H), 2.13 (s, 3H, COMe), 1.95–1.10 (en, 6H); MS: 152 (M-43), 83 (100).

1,11β - *Dimethyl* - 2aβ,3,4,5,5aβ,8,9,10,11aα, 11*b*, 11cβ - *dodecahydro* - 2H - *isoxazolo* [5,4,3-kl] *benzo* [b] *quinolizin* - 6 - *one* (**4**). Crude **1** (24.3 g), MeNHOH HCl (17.2 g), (i-Pr)$_2$NEt (36.0 ml) and EtOH (115 ml) were boiled 34 hr under reflux, evaporated, diluted with H_2O (450 ml) and extracted ($CHCl_3$). Chromatography of the extract (Al_2O_3, elution with Et_2O, or silica gel and elution with 1% MeOH–$CHCl_3$) followed by crystallization (Et_2O) gave **4** (13.94 g, 51%), m.p. 111–114°; alternatively, washing the extract with 1N HCl, basifying (pH 11, 50% aqNaOH), extracting ($CHCl_3$) and crystallizing (Et_2O) gave **4**, m.p. 108–110°, without chromatography. Recrystallization gave colorless prisms, m.p. 109.5–111.5° (Et_2O–hexanes). (Found: C, 68.10; H, 9.43; N, 10.62. Calc. ($C_{15}H_{24}N_2O_2$): C, 68.15; H, 9.15; N, 10.60%). IR: 1640, 1460, 1440; PMR: 4.54 (br d, 13, H_{8eq}) and 4.28 (br, H_{2a}) (2H), 3.32 (br dd, 10 and 2, H_{11a}), 2.84–2.25 (en) and 2.64 (s, NMe) (7H), 2.08–1.06 (en) and 1.24 (s, CME) (14H); H_{8eq} suffered the greatest deshielding in the presence of Eu(fod)$_3$; CMR: 171.7 (s, C_6), 74.9 (d, C_{2a}), 65.6 (s, C_{11b}), 61.9 (d, C_{11a}), 48.4 (d, C_{11c}), 44.2 (t, C_8), 38.4 (q, NMe), 35.0 (d, C_{5a}), 27.5 (t, C_{11}), 25.5, 24.5, 24.0, 23.0, 18.6 (q, CMe), 16.2 (t); MS: 264 (25), 152 (100).

Reaction of **1** *and* BzNHOH. Ketone **1** (2.86 g), BzNHOH[24] (3.00 g, freshly crystallized) and C_6H_6 (25 ml) were boiled 71 hr under reflux, concentrated and chromatographed on silica gel. Elution with 0.5% MeOH–$CHCl_3$ gave an oily mixture (3.26 g) of **5** (PMR) and N-benzyl-α-phenylnitrone, inseparable by crystallization or by rechromatography on silica gel or Al_2O_3 with many eluants; the mixture was hydrogenolyzed to **16**. Calculating the square root of the overall yield of **16** from **1** gave an estimate of the yield of **5**.

Reaction of **2** *and* MeNHOH. Ketone **2** (10.0 g), MeNHOH HCl (7.17 g), (*i*-Pr)$_2$NEt (15.0 ml) in EtOH (50 ml) were boiled 21 hr under reflux in N_2, and worked-up (neutral conditions) as described for **4**; chromatography (Al_2O_3, elution with Et_2O) gave a yellow oil (1.65 g, two components (tlc)) which was reserved for rechromatography.

4b, 5, 9 - *Trimethyl* - 1, 2, 3, 4, 4a, 4b, 4c, 6a, 7, 7a, 9, 10, 10a, 10b - 11H - *tetradecahydrodiisoxazolo* [5, 4, 3-k, 1:4, 5-h] benzo [b] quinolizin - 11 - *one* (**14**). Continued elution (Et_2O) gave a yellow oil crystallizing to pure **14** (0.413 g, 3%), m.p. 93–94° (Et_2O). (Found: C, 63.18; H, 8.48; N, 13.20; Calc. ($C_{17}H_{27}N_3O_3$): C, 63.52; H, 8.47; N, 13.07%). IR: 1640, 1440; PMR: 4.25 (br sextet, 9.5, 9.0, 5.0, H_{7a}), 4.2–3.9 (en, $1H_{6a}$), 3.76–2.26 (en), 2.75 (s, NMe) and 2.56 (s, NMe) (12H), 2.26–1.02 (en) and 1.18 (s, CMe) (13H); MS: 321 (9), 56 (100).

1, 11β - *Dimethyl* - 2aβ, 3, 5aβ, 8, 9, 10, 11, 11aα, 11b, 11cβ - *decahydro* - 2H - *isoxazolo* [5, 4, 3-k,1] *benzo* [b] *quinolizin* - 6 - *one* (**6**). Rechromatography on silica gel of the reserved 1.65-g sample and elution with 2.5% MeOH–$CHCl_3$ gave the less polar isomer **6** (0.387 g, 3%) crystallizing from Et_2O, m.p. 88.0–89.0°. (Found: C, 68.95; H, 8.76; N, 11.09; Calc. ($C_{15}H_{22}N_2O_2$): C, 68.67; H, 8.45; N, 10.68%.) IR; 1640, 1440; PMR: 5.89 (complex m, H_4 and H_5), 4.65 (d of t, J_{2a-11c} = 8, $J_{2a-3\alpha}$ = $J_{2a-3\beta}$ = 5, H_{2a}), 3.74–2.87 (en, H_{11a}) (4H), 2.74 (dd, 8 and 10, H_{11c}) and 2.64 (s, NMe) (4H), 2.28 (m, 2H), 2.09–1.06 (en, $2H_9$, $2H_{10}$ and $2H_{11}$) and 1.18 (s, Me) (9H); CMR: 127.1 (d, C_4 or C_5), 126.1 (d, C_5 or C_4), 39.3 (NMe); MS: 262 (7), 56 (100).

6, 6a - *Dimethyl* - 3, 4, 6, 6a, 6b, 7, 8, 9 - *octahydro* - 10H, 12H - *indolizino* [3,2-c] *indoxazin* - 12 - *one* (**15**). Continued elution of the foregoing column with Et_2O gave the more polar isomer **15** (0.715 g, 6%) crystallizing from Et_2O, m.p. 131.5–133.0°. (Found: C, 68.45; H, 8.51; N, 10.62%; Calc. ($C_{15}H_{22}N_2O_2$).) IR: 1680, 1440; PMR: 6.21 (d of t, $J_{2-3\alpha}$ = $J_{2-3\beta}$ = 4.5, J_{2-1} = 9, H_2), 5.38 (br d, 9, H_1), 4.35–4.02 (overlapping m of H_{10eq}) and 4.26 (t, 4, H_{4a}), 3.16 (dd, 12, 3, H_{6b}), 2.78 (br d, 12.5, H_{10ax}), 2.59 (s, NMe), 2.34–0.83 (en) and 0.97 (s, CMe) (13H); CMR: 173.3 (C_{12}), 133.2 (C_2 or C_1), 124.6 (C_1 or C_2), 78.3 (C_{4a}), 71.7 (C_{6a}), 63.6 (C_{6b}), 61.0 (C_{12a}), 40.8 (C_{10}), 36.2 (NMe), 29.4 (C_7), 25.6, 24.8, 24.4, 20.0, 11.0; MS: 262 (6), 56 (100).

Reaction of **2** *and* BzNHOH. Ketone **2** (11.8 g, *ca* 80% purity), BzNHOH[24] (9.97 g) in C_6H_6 (75 ml) were boiled under reflux, evaporated and chromatographed on silica gel.

N - *Benzyl* - C - *phenylnitrone*. Elution with 0.75% MeOH–$CHCl_3$ gave an oil (10.6 g) crystallizing from Et_2O to give the nitrone (2.03 g, 24%), m.p. 82.0–82.5° (lit.[25-26] m.p. 81.5–83.5°, 82–83°). (Found: C, H, and N within 0.2%; Calc. ($C_{14}H_{13}NO$).)

1 - *Benzyl* - 11bβ-*methyl* - 2aβ, 3, 5aβ, 8, 9, 10, 11, 11aα, 11b, 11cβ - *decahydro* - 2H - *isoxazolo* [5, 4, 3-k, 1] *benzo* [b] *quinolizin* - 6 - *one* (**7**). Continued elution, rechromatography on silica gel of selected pooled fractions and elution with 1%MeOH–$CHCl_3$ gave a small oily sample of the less polar isomer **7** (containing 10 wt% of the nitrone (PMR)). IR: 1640, 1430; PMR: 7.5–7.2 (m, C_6H_5), 5.90 (m, vinyl), 4.68 (d of t, J_{2a-11c} = 8.5, $J_{2a-3\alpha}$ = $J_{2a-3\beta}$ = 5, H_{2a}), 3.95 (s, CH_2Ph), 3.78–3.20 (en) and 3.29 (br d, 10 and 2, H_{11a}) (4H), 2.84 (dd, 8.5 and 8.5, H_{11c}), 2.28 (m, 2H), 2.15–1.20 (en) and 1.24 (s, CMe) (9H); CMR: 128.6, 128.3, 127.0, 126.8, 126.3, 55.0 (CH_2Ph); MS: 338 (4), 91 (100). Four crystallizations ((Et_2O, EtOAc–hexanes) gave a nitrone-free (tlc, PMR) sample, m.p. 108–122°. (Found: c, 74.56; H, 8.03; N, 8.02; Calc. ($C_{21}H_{26}N_2O_2$): C, 74.52; H, 7.74; N, 8.28%.) More **7** (pure by tlc or PMR) was gleaned by repeated rechromatography and recrystallization; the estimated yield of **7** was 32%.

6 - *Benzyl* - 6a - *methyl* - 3, 4, 4a, 6a, 6b, 7, 8, 9, 10, 11a - *decahydro* - 10H, 12H - *indolizino* [3, 2-c] *indoxazin* - 12 - *one* (**16**). Rechromatography on Al_2O_3 of selected pooled fractions and elution with 75% Et_2O–hexanes gave the more polar isomer **16**, m.p. 162.5–163.5° (Et_2O). (Found: C, 74.46; H, 7.83; N, 8.24%; Calc. ($C_{21}H_{26}N_2O_2$).)

IR: 1680, 1450; PMR: 7.5–7.1 (m, C_6H_5), 6.20 (d of t, $J_{2-3\alpha} = J_{2-3\beta} = 4.5$, $J_{2-1} = 10$, H_2), 5.40 (br d, 10, H_1), 4.38–3.99 (overlapping m of H_{10eq}) and 4.25 (t, 4, H_{4a}) (2H), 3.85 (s, CH_2–Ph), 3.24 (dd, 13, 2, H_{6b}), 2.69 (br t, 12, H_{10ax}), 2.25–0.81 (en) and 1.04 (s, CMe); CMR: 173.4 (C_{12}), 138.2, 133.3 (C_2 or C_1), 128.3, 128.0, 127.1, 124.6 (C_1 or C_2), 78.4 (C_{4a}), 71.7 (C_{6a}), 63.7 (C_{6b}), 60.9 (C_{12a}), 53.5 (CH_2–Ph), 40.8 (C_{10}), 29.2 (C_7), 23.5, 24.7, 24.4, 20.3, 12.2; MS: 338 (4), 91 (100).

11, N - *Dimethyl* - 6a, 11-*epoxyimino* - 1, 3, 4, 6, 6a, 7, 8, 9, 10, 10a, 11, 11a - *dodecahydro* - 2H - *benzo* [b] quinolizin - 6 - one (**12**). Ketone **11** (5.80 g), MeNHOH HCl (8.10 g), (i-Pr)$_2$NEt (17.2 ml) and EtOH (25 ml) were boiled 19 hrs under reflux, evaporated, worked-up (neutral conditions) as described for **4**, and chromatographed on silica gel. Elution with 2% MeOH–$CHCl_3$ and crystallization gave the less polar isomer **12** (0.346 g, 5.3%), m.p. 168.5–170.5° (Et_2O). (Found: C, 68.28; H, 9.32; N, 10.62%; Calc. ($C_{15}H_{24}N_2O_2$).) IR: 1640, 1440; PMR: 4.63 (br q, 12, 2.5, H_{4eq}), 3.09–2.89 (overlapping m) and 2.83 (s, NMe) (4H), 2.57–0.75 (en) and 1.22 (s, CMe) (19H); CMR: 169.4 (s, C_6), 77.9 (s, C_{6a}), 67.9 (d, C_{11a}), 65.8 (s, C_{11}), 48.9 (d, C_{10a}), 42.7 (t or q, C_4 or NMe), 41.7 (q or t, NMe or C_4), 26.1, 25.5, 24.8, 24.3, 24.1, 24.0, 21.1 (t), 13.6 (q, CMe); MS: 264 (16), 56 (100).

6, 6a - *Dimethyl* - 1, 2, 3, 4, 4a, 6a, 6b, 7, 8, 9, 10, 11a - *dodecahydro* - 10H, 12H - *indolizino* [3, 2-c] *indoxazin* - 12 - *one* (**13**). Continued elution of the foregoing column gave the more polar isomer **13** (4.22 g, 64.7%) as a yellow oil crystallizing from hexanes, m.p. 78.0–79.5°. (Found: C, 68.21; H, 9.27; N, 10.79%; Calc. ($C_{15}H_{24}N_2O_2$).) IR: 1670, 1450; PMR: 4.30–3.95 (overlapping m, H_{10eq} and H_{4a}), 3.23 (dd, 11, 3, H_{10ax}), 2.86–2.48 (overlapping m, H_{6b}) and 2.63 (s, NMe) (4H), 2.70–2.14 (en) and 1.10 (s, CMe) (17H); CMR: 174.2 (s, C_{12}) 78.5 (d, C_{4a}), 71.0 (s, C_{6a}), 60.4 (s, C_{12a}), 59.8 (d, C_{6b}), 40.5 (t, C_{10}), 36.5 (q, NMe), 28.9 (t, C_7), 25.7, 24.8, 24.7, 24.4, 18.5, 17.7, 11.6 (q, CMe); MS: 264 (36), 56 (100).

1, 10bβ-*Dimethyl* - 3, 3aβ, 4, 5, 7, 8, 9, 10, 10aα, 10b - *decahydro* - 1H - *isoxazolo* [5, 4-a] *quinolizin* - 5 - *one* (**8**). Chromatographed **3** (17.0 g), MeNHOH HCl (21.8 g) (i-Pr)$_2$NEt (45.6 ml) and EtOH (129 ml) were boiled under reflux in N_2 for 25 hr and evaporated; the residue in H_2O (300 ml) was extracted ($CHCl_3$), and the extract chromatographed on silica gel. 5% MeOH–$CHCl_3$ eluted oily **8** (7.80 g, 40%); rechromatography of a forerun gave another 0.93 g (5%) of **8** IR: 1630, 1440; PMR: 4.47–4.00 (overlapping m, H_{8eq}) and 4.26 (t, 8, $H_{3\alpha}$ or $H_{3\beta}$), 3.56 (t, 8, $H_{2\beta}$ or $H_{3\alpha}$) and 3.35 (br dd, 10, 2, H_{10a}) (3H), 3.05–2.40 (overlapping m, H_{3a} (irradiation at 2.8 affected $H_{3\alpha}$ and $H_{3\beta}$), J_{7ax}, $2H_4$) and 2.61 (s, NMe) (7H), 2.10–1.30 (en, 6H), 1.19 (s, CMe); CMR: 39.0 (NMe); MS: 224 (15), 84 (100).

1 - *Benzyl* - 10bβ - *methyl* - 3, 3aβ, 4, 5, 7, 8, 9, 10, 10aα, 10b - *decahydro* - 1H - *isoxazolo* [5, 4-a] *quinolizin* - 5 - *one* (**9**). Crude **3** (3.00 g), BzNHOH[24] (3.79 g) and EtOH (23 ml) were boiled 4 days under reflux, concentrated, and chromatographed on silica gel. Elution with 2% MeOH–$CHCl_3$, rechromatography on silica gel and elution with 1% MeOH–$CHCl_3$ gave pure (tlc), oily **9** (0.968 g, 21%). IR: 1640, 1440; PMR: 7.31 (br s, C_6H_5), 4.64–4.21 (overlapping m, H_{7eq}) and 4.16 (t, 8, $H_{3\alpha}$ or $H_{3\beta}$) (2H), 3.50 (t, 8, $H_{3\beta}$ or $H_{3\alpha}$) and 3.34 (br, overlapping dd, 10, 2, H_{10a}) (2H), 3.00–2.38 (en, H_{3a}, $2H_4$, H_{7ax}) (4H), 2.10–1.02 (en, $-(CH_2)_3-$) and 1.26 (s, CMe) (9H); CMR: 138.2, 128.5, 128.4, 127.2, 55.4 (CH_2Ph); MS: 300 (3), 91 (100).

1 - *Hydroxy* - 12bβ - *methyl* - 1, 2, 3aβ, 4, 5, 6, 6aβ, 9, 10, 11, 12, 12aα, 12b, 12cβ - *tetradecahydrooxazino* [6, 5, 4-k, 1] benzo [b] - *quinolizin* - 2 - *one* (**19**). After 1 hr at 0–5°, a soln of mCPBA (1.64 g, 80–90%), **4** (2.14 g) and CH_2Cl_2 (75 ml) was chromatographed on silica gel. $CHCl_3$–MeOH-conc. aq. NH_3 (97.5–2.25–0.25) eluted **19** (1.30 g, 57%), m.p. 226.5–228.0° (MeOH). (Found: C, 64.39; H, 8.83; N, 9.96; Calc. ($C_{15}H_{24}N_2O_3$): C, 64.26; H, 8.63; N, 9.99%). IR (Nujol): 3225, 1620; PMR: 7.88 (s, ex, OH), 4.42 (br d, 12, H_{9eq}), 4.21 (d, 9.5) and 4.18 (d, 9.5) ($2H_2$), 3.93 (br q, H_{3a}), 3.48 (br d, 11, H_{12a}), 2.3–1.1 (en), 1.20 (s, CMe); MS: 280 (13), 84 (100).

10α - *Hydroxy* - 11α - *hydroxylamino* - 11β - *methyl* - 1, 3, 4, 6, 6aβ, 7, 8, 9, 10, 10aβ, 11, 11aα - *dodecahydro* - 2H - *benzo* [*b*] *quinolizin* - 6 - *one* (**20**). After 18.5 hr at 25°, the mixture from **19** (0.800 g), dimedone (0.841 g) and 50% aq EtOH (16 ml) was filtered, the ppt crystallized giving dimedone-formaldehyde (0.77 g, 92%), m.p. 188.0–191.0° (MeOH) (lit.[35] 191–191.5°), and the filtrate chromatographed on silica gel. $CHCl_3$–MeOH-conc aq NH_3 (95–4.5–0.5) eluted **20** (0.487 g, 64%), m.p. 208–212° (EtOAc–MeOH). (Found: C, 62.86; H, 9.17; N, 10.28; Calc. ($C_{14}H_{24}N_2O_3$): C, 62.66; H, 9.01; N, 10.44%.) IR (KBr): 3420, 3250, 1610; PMR (DMSO-d_6): 4.48 (br d, 13, H_{4eq}), 4.12 (br s, H_{10}), 3.20–1.00 (en), 1.18 (s, CMe); MS: 268 (8), 84 (100).

11α - *Amino* - 10α - *hydroxy* - 11β - *methyl* - 1, 3, 4, 6, 6aβ, 7, 8, 9, 10aβ, 11, 11aα - *dodecahydro* - 2H - *benzo* [b] *quinolizin* - 6 - *one* (**18**)

A. From **5**. The mixture from hydrogenolysis (2 days, 25°, 60 psi of H_2, Paar shaker) of crude **5** (3.20 g) with 20% $Pd(OH)_2$ on C (2.6 g) in EtOH (50 ml) was filtered and the concentrated filtrate crystallized giving **18** (1.11 g, 36% (2 steps)), m.p. 196.0–198.0° (EtOAc). (Found: C, 67.03; H, 9.91; N, 11.24. Calc. ($C_{14}H_{24}N_2O_2$): C, 66.63; H, 9.59; N, 11.10%.) IR: 3600, 3400, 1630, 1440; PMR: 4.64 (br d, 12, H_{4eq}), 4.36 (br s, $W_{h/2} = 6$, H_{10a}), 3.34 (br d, 11,2, H_{11a}), 2.74–0.78 (en), 1.45 (s, ex, NH_2) and 1.24 (s, CMe) (21H); CMR: 172.5 (s, C_6), 67.2 (d, C_{10}), 65.3 (d, C_{11a}), 51.7 (s, C_{11}), 50.6 (d, C_{6a}), 43.2 (dd, C_4), 35.2 (d, C_{10a}), 34.1 (t, C_1), 26.7, 26.2, 25.9, 25.2, 24.8, 16.3 (t); MS: 252 (4), 84 (100).

B. From **7**. The filtered, concentrated product from hydrogenolysis (2 days, 25°, 60 psi of H_2, Paar shaker) of **7** (1.21 g) with 20% $Pd(OH)_2$ on C (1.2 g) in EtOH (100 ml) was chromatographed on silica gel. $CHCl_3$–MeOH-conc aq NH_3 (90-9-1) eluted **18** (0.169 g, 23%), identified by tlc, IR and PMR.

C. From **20**. The filtered, concentrated product from hydrogenolysis (69 hr, 25°, 60 psi of H_2, Paar shaker) of **20** (0.40 g) with 20% $Pd(OH)_2$ on C (0.40 g) in EtOH (25 ml) was crystallized (EtOAc) giving **18** (0.181 g, 48%), m.p. 193–196.5°, identified by tlc, IR, PMR, and m.m.p. (191.5–193.5°).

2α - *Hydroxymethyl* - 1β - *methyl* - 1α - *methylamino* - 1, 2, 3, 4, 6, 7, 8, 9aα - *octahydro* - 9H - *quinolizin* - 4 - *one* (**17**). Reduction of **8** (0.612 g) with excess Zn in HOAc-H_2O at 75°, basifying (pH 11, 50% aq NaOH), and extracting ($CHCl_3$) gave oily **17** (0.521 g, 84%) crystallizing from Et_2O–CH_2Cl_2, m.p. 106–109°. (Found: C, 63.90; H, 9.96; N, 12.51. Calc. ($C_{12}H_{22}N_2O_2$): C, 63.88; H, 9.80; N, 12.38%.) IR ($CHCl_3$): 3300 (intramolecularly H-bonded (dilution experiments)), 1620; PMR: 4.78 (br d, $J_{6eq-6ax} = 13.5$, H_{6eq}), 4.09 (dd, $J_{gem} = 11.5$, $J_{2ax-CH(H)OH} = 3$, $CH(H)OH$), 3.70 (dd, $J_{gem} = 11.5$, $J_{2ax-CH(H)OH} = 3$, $CH(H)OH$), 3.88 (dd, $J_{9a-9ax} = 10.5$, $J_{9a-9eq} = 3$, H_{9a}), 2.88 (dd, $J_{gem} = 18.6$, $J_{3ax-2ax} = 12.6$, H_{3ax}), 2.65–2.20 (en, H_{3eq}, H_{6a} and OH) and 2.34 (s, NMe) (6H), 2.00 (complex m, H_2), 1.85–1.20 (en) and 1.25 (s, CMe) (9H) (the assignments of H_{6eq}, CH_2OH, H_{9a}, H_{3ax} and H_2 were made or confirmed by reciprocal double resonance experiments); CMR: 168.7 (s, C_4), 62.9 (t, CH_2OH), 62.3 (d, C_{9a}), 56.0 (s, C_1), 45.0 (dd, C_6), 37.9 (d, C_2), 30.8 (t, C_3), 29.2 (t, C_9), 27.6 (q, NMe), 25.4 (C_7 or C_8), 25.5 (C_8 or C_7), 20.1 (q, CMe); MS: 226 (1), 84 (100).

Crystal data.–$C_{15}H_{24}N_2O_2$ (**4**), $M = 264.4$, Orthorhombic, $a = 10.094(5)$, $b = 12.845(6)$, $c = 10.776(5)$ Å, $U = 1397$ Å^3, $Z = 4$, $D_c = 1.257$ g cm^{-3}, $F(000) = 576$. Cu-K_α radiation, $\lambda = 1.5418$ Å; μ(Cu-K_α) = 6.7 cm^{-1}. Space group $P2_12_12_1$(D_2^4) uniquely from systematic absences: $h00$ when $h \neq 2n$, $0k0$ when $k \neq 2n$, $00l$ when $l \neq 2n$.

$C_{12}H_{22}N_2O_2 \cdot H_2O$ (**17**), $M = 244.3$, Orthorhombic, $a = 10.645(5)$, $b = 15.266(7)$, $c = 8.166(4)$ Å, $U = 1327$ Å^3, $Z =$

4, $D_c = 1.223\ g\ cm^{-3}$, $F(000) = 536$. $\mu(Cu\text{-}K_\alpha) = 7.2\ cm^{-1}$. Space group $P2_12_12_1(D_2^4)$ uniquely as for (4).

Crystallographic measurements. Preliminary unit-cell parameters and space group information were obtained from oscillation and Weissenberg photographs (Cu-K_α radiation) and from precession photographs (Mo-K_α radiation, $\lambda = 0.7101$ Å). Crystals of dimensions *ca* $0.28 \times 0.30 \times 0.54$ mm (4) and $0.20 \times 0.40 \times 0.50$ mm (17) were then oriented in turn on an Enraf-Nonius CAD-3 automated diffractometer (Ni-filtered Cu-K_α radiation) for intensity measurements, and one octant to $\theta = 67°$ was surveyed by means of the θ-2θ scanning technique as described previously.[36] From totals of 1448 (4) and 1378 (17) independent intensity measurements, only those 1185 and 1189, respectively, with $I > 2.0\sigma(I)$ [$\sigma^2(I)$ = scan count + total background count] were used in the structure analysis after the usual Lorentz and polarization corrections had been applied. Refined unit-cell parameters were derived by least-squares treatment of the diffractometer setting angles for 40 reflections widely separated in reciprocal space.

Structure analysis. Initial structure models for both compounds were obtained by use of the MULTAN76 series of programs.[31] Refinement of non-hydrogen atom positional and thermal parameters by full-matrix least-squares calculations proceeded smoothly to R values of 0.125 (4) and 0.119 (17). Hydrogen atom positional and isotropic thermal parameters, save those on the hydroxy group and water molecule in crystals of 17, were included as variables in the subsequent least-squares iteration which converged to $R = 0.050$ for 4 and 0.049 for 17. Final atomic positional and thermal parameters are in Tables 3 and 4.

Atomic scattering factors used in all structure-factor calculations were those for C, N, and O from Ref. 37 and for H from Ref 38. In the least-squares calculations, $\Sigma w\Delta^2$ ($\Delta = ||F_o| - F_c||$) was minimized; the weighting scheme used, $\sqrt{w} = 1$ when $|F_o| < K$ and $\sqrt{w} = K/|F_o|$ when $|F_o| > K$ ($K = 10.0$ for 4, and $K = 7.0$ for 17), showed only random variations of $\langle w\Delta^2 \rangle$ when analyzed in ranges of $|F_o|$ and $\sin\theta$.

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