Beckmann Rearrangements in Bicyclo[2.2.1]heptan-2-one Oximes

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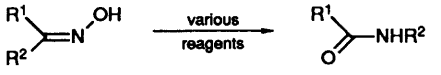
Although Beckmann rearrangement of norcamphor oxime **1** was unsatisfactory, proceeding in poor yield to give a mixture of lactam products, rearrangement of the *E*/*Z* oxime **9**, or the pure *E*-isomer **10**, upon treatment with methanesulfonyl chloride and triethylamine, gave the lactam **12** in good yield.

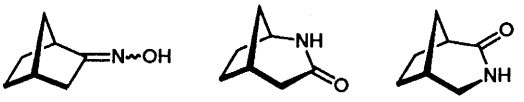
Since its discovery over 100 years ago,[1] the Beckmann rearrangement has been used widely in organic chemistry.[2] The treatment of oximes with a variety of reagents provides a simple way of inserting a nitrogen atom into a carbon framework (Scheme 1). The scope of the reaction is broad and it is usually



Scheme 1

stereospecific with the migrating group being *anti* to the oxime hydroxy. In cases where the *syn* group appears to migrate it is often a result of oxime isomerisation *before* the rearrangement occurs.

Stimulated by our interest in the mechanistic aspects of the Beckmann rearrangement,[3] we were intrigued by the conflicting accounts, summarised in a comprehensive review on nitrogen insertion reactions of bridged bicyclic ketones,[4] of the rearrangement of the oxime **1** derived from bicyclo[2.2.1]heptan-2-one (norcamphor). This is reported to give the two possible lactam products **2** and **3** in varying ratios, with fragmentation products being formed in some cases, and hence the situation is far from straightforward. The early claims in the patent literature, that under acidic conditions the rearrangement gives exclusively the 2-aza product **2**, have not been substantiated,[5] other workers obtaining mixtures of products under a variety of conditions.[6] However, one of the subsequent studies did report conditions (boron trifluoride–diethyl ether in tetrachloroethane), without experimental detail, under which the lactam **2** was obtained as the sole product in 91% yield.[7]



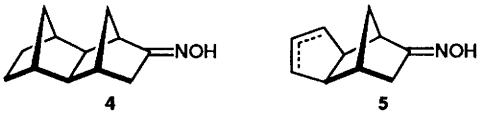
1 **2** **3**

In view of the uncertainty associated with the above results, we decided to reinvestigate the Beckmann rearrangement of oximes derived from bicyclo[2.2.1]heptanones, and we now report our results in full. During the course of our investigation and before the publication of our preliminary communication,[8] Pappalardo and co-workers reported some complementary results.[9]

Results and Discussion

Norcamphor oxime **1** was prepared in 97% yield by a standard method and subjected to the acidic conditions (85% sulfuric acid) described in the literature.[5] The product obtained in 44% yield was a clear oil, the spectroscopic properties of which indicated that it was a mixture of the lactams **2** and **3**. Likewise, when the oxime **1** was treated with tosyl chloride and sodium hydroxide[6a] a mixture (21%) of lactams was obtained, thereby confirming the doubts[6] associated with the original patent report.[5] We were unable to effect the Beckmann rearrangement of oxime **1** using boron trifluoride–diethyl ether in 1,1,2,2-tetrachloroethane.

Since conformational and torsional effects are thought to be important in nitrogen insertion reactions of bridged bicyclic ketones,[4] we considered the possibility that the problems with norcamphor oxime **1** compared with, say, the high-yielding regiospecific Beckmann rearrangement of the oxime derived from bicyclo[2.2.2]octan-2-one,[10] might be conformation related. A further indication of these effects comes from the fact that bicyclo[2.2.1]heptanone oximes such as **4** and **5**, which contain an additional ring bridging the 5- and 6-positions, which undoubtedly alters the conformation of the bicyclic system, are reported to undergo regioselective Beckmann rearrangement to give the corresponding 2-aza lactams.[6a,11]



4 **5**

Therefore, we decided to investigate the Beckmann rearrangement of the oxime **9** in which the additional dioxolane ring possibly alters the conformation of the bicyclo[2.2.1]heptane system. The reason that Pappalardo and his co-workers also chose to investigate this system was because they wished to retain a 'masked alkene' at the 5- and 6-positions, the Beckmann rearrangement of the oxime of the bicyclic alkene ketone itself (dehydronorcamphor) being unsuccessful due to competing fragmentation reactions.[9]

The required ketone **8** was prepared from commercially available norborn-5-en-2-ol (Scheme 2) following a literature procedure.[12] Thus, *cis*-hydroxylation using catalytic osmium tetroxide and trimethylamine *N*-oxide gave the triol **6**, which although it was isolated as a crystalline solid on one occasion, was normally converted directly into the acetonide **7**. Oxidation with pyridinium dichromate (PDC) gave the ketone **8**, which was converted into the oxime **9** by reaction with hydroxylamine. The oxime **9** was initially obtained as a mixture of *E*- and *Z*-isomers, a colourless oil which slowly solidified after a prolonged period under high vacuum. In an effort to distinguish the two isomers, the oxime *O*-methyl ether was prepared, but it did not facilitate the separation. Eventually it was found that recrystallisation from boiling cyclohexane gave the pure *E*-

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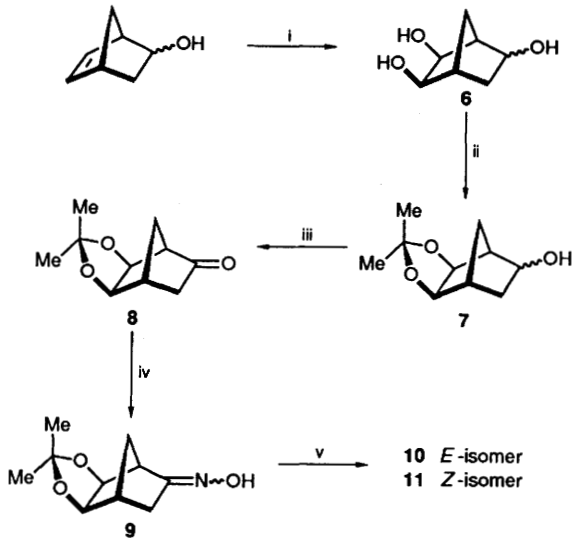


Scheme 2 *Reagents:* i, cat. OsO_4, Me_3NO, Bu^{t}OH, py, H_2O; ii, $MeC(OMe)_2Me$, acetone, Dowex resin; iii, PDC, py TFA, CH_2Cl_2; iv, NH_2OH·HCl, NaOAc, MeOH, H_2O; v, recrystallise from cyclohexane

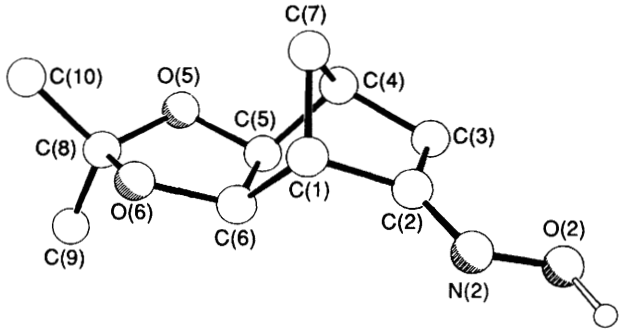


Fig. 1 X-Ray crystal structure of (*E*)-5-*exo*,6-*exo*-(isopropylidenedioxy)bicyclo[2.2.1]heptan-2-one oxime **10** showing crystallographic numbering

oxime **10**, m.p. 143–144 °C. Concentration of the mother liquors gave an oily residue which slowly solidified to the *Z*-oxime **11**, m.p. 113–114 °C. The *Z*-oxime was readily converted into the *E*-isomer by heating it above its melting point. The structure of the *E*-isomer **10** was confirmed by X-ray crystallography (Fig. 1).

Our first attempts to effect the Beckmann rearrangement were carried out on the isomeric mixture of oximes **9**. Initial experiments using acidic conditions (85% sulfuric acid), tosyl chloride or triphenylphosphine and chlorine[13] were unsuccessful. However, treatment of the oximes **9** with methanesulfonyl chloride and triethylamine in ether gave the 2-aza lactam **12** in 25% yield. Changing to the more polar solvent acetonitrile increased the yield to 63%. When the pure *E*-oxime **10** was subjected to the same conditions, the lactam **12** was isolated in 73% yield. Treatment of the *Z*-oxime **11** also gave the same lactam product, albeit in lower yield (44%), perhaps indicating that the oximes pre-equilibrate. In all cases, there was no evidence for the formation of the isomeric lactam, the 3-azabicyclo[3.2.1]octanone system.

The exclusive formation of the lactam **12** was expected on the basis of the preferred migration of the bridgehead atom, and in the case of the pure *E*-oxime **10**, the preferred *anti*-migration in the Beckmann rearrangement. The structure was confirmed by 2-D ^{1}H NMR studies, and by X-ray crystallography (Fig. 2).

We conclude that the Beckmann rearrangement of oximes derived from bicyclo[2.2.1]heptan-2-ones are indeed complicated, and that differences in conformation brought about by

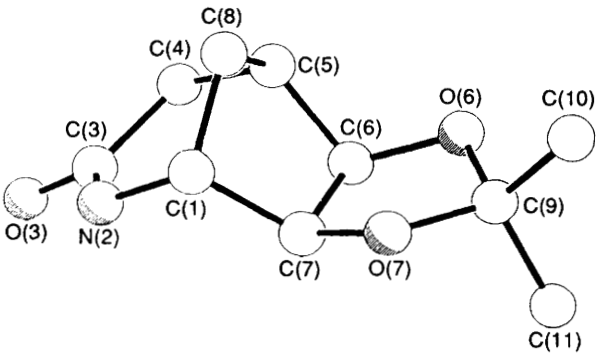
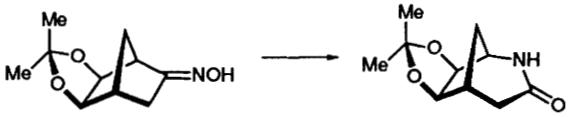


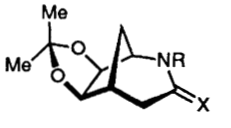
Fig. 2 X-Ray crystal structure of 6-*exo*,7-*exo*-(isopropylidenedioxy)-2-azabicyclo[3.2.1]heptan-3-one **12** showing crystallographic numbering



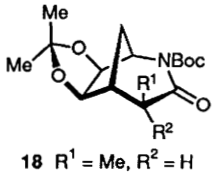
9 *E/Z*-mixture
10 *E*-isomer
11 *Z*-isomer
12

the fusion of an additional ring, as well as the presence of the 5,6-double bond which is responsible for the alternative fragmentation pathway,[9] may play an important role.

Finally, with the development of a synthetic route to the 2-azabicyclo[3.2.1]octan-2-one **12**, we briefly investigated the chemistry of this ring system. Thus, treatment with sodium hydride in dimethylformamide followed by iodomethane, allyl bromide, or di-*tert*-butyl oxydiformate (BOC anhydride) gave the corresponding *N*-methyl **13**, *N*-allyl **14** and *N*-*tert*-butoxycarbonyl **15** derivatives in 55, 71 and 75% yield respectively. Conversion of **12** and **14** into the corresponding thiones **16** and **17** by reaction with Lawesson's reagent in refluxing toluene also proceeded in a perfectly standard manner. However, attempted functionalisation of the 4-position by deprotonation and quenching with electrophiles, proved surprisingly difficult. Using lithium diisopropylamide (LDA) as base, the enolate of *N*-allyl lactam **14** was apparently formed as evidenced by the deuterium incorporation on addition of D_2O, although addition of more 'useful' electrophiles, to either this enolate, or the one derived from **15**, proved unsuccessful. However, on changing the base to potassium hexamethyldisilazide, a good yield of methylated products was obtained on quenching with iodomethane. Both mono- **18** and di-methyl **19** derivatives were formed in 21 and 34% yield respectively, and although the reaction apparently showed good *exo*-selectivity in terms of the mono-substitution product **18**, the disubstitution could not be suppressed.



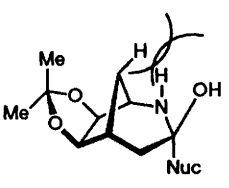
12 R = H, X = O
13 R = Me, X = O
14 R = $CH_2CH{=}CH_2$, X = O
15 R = Boc, X = O
16 R = H, X = S
17 R = $CH_2CH{=}CH_2$, X = S



18 R^1 = Me, R^2 = H
19 R^1 = R^2 = Me

Finally, it should be noted that the amide bond in the lactams **14** and **15** is extremely resistant to cleavage by hydrolytic methods. A variety of acidic and basic conditions were used all without success; the products observed resulted from removal of

the *N*-substituent or opening of the acetonide ring. The reasons for this are unclear; it seems unlikely that the approach of a nucleophile to the lactam carbonyl is completely hindered, *viz.* the successful conversion into thiolactams. One possibility is steric compression in the tetrahedral intermediates **20** or **21** formed by either *exo* or *endo* attack on the carbonyl. Similar reasons are presumably responsible for the stability of the lactone **22** towards nucleophiles such as ammonia.[14]



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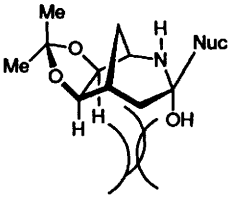

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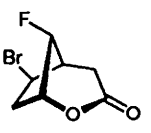

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Experimental

Tetrahydrofuran was distilled from potassium benzophenone ketyl and stored under nitrogen or used immediately. Dichloromethane which was to be used as a reaction solvent was distilled from phosphorus pentoxide and used under nitrogen. Triethylamine, pyridine and diisopropylamine were distilled and stored over potassium hydroxide. Norborn-5-en-2-ol was purchased from Aldrich Chemical Company and was purified before use by dry flash filtration column chromatography (eluent light petroleum to diethyl ether to ethyl acetate). Light petroleum, which refers to the fraction with b.p. 40–60 °C, and pentane were distilled after purchase and then stored normally. All remaining reagents and chromatography solvents were used, as purchased, without further purification.

Analytical TLC was carried out using Merck 0.2 mm silica gel 60 GF_{254} aluminium-backed plates, which were visualised using UV light (254 and 360 nm), iodine vapour, and/or molybdenum dip. The molybdenum dip was prepared in the following manner. Ammonium molybdate (5 g) was dissolved in a solution of concentrated sulfuric acid (10 g) in water (75 cm^3). This solution was allowed to stand overnight or until the dissolution process was complete. Wet flash and dry flash column chromatography[15] was carried out on Merck silica gel 60 H with hand bellows providing a low pressure force for the wet flash technique and a water aspirator providing the suction needed for the dry flash technique.

IR spectra were recorded on a Perkin-Elmer model 1710 IR Fourier transform spectrometer and samples were analysed as thin films, Nujol mulls, or in solution as indicated. Proton Fourier transform NMR spectra were recorded on either a Bruker WM 250 (250 MHz), or a JEOL GSX 270 (270 MHz) spectrometer). Chemical shifts are reported in ppm downfield of tetramethylsilane by referencing to tetramethylsilane itself or the residual proton resonances of the solvents as the appropriate internal standard. Coupling constants (J) in Hz are included where possible. Carbon-13 Fourier transform NMR spectra were recorded on either a Bruker WM 250 (62.9 MHz), or a JEOL GSX 270 (67.9 MHz) spectrometer and were referenced to the solvent. Electron ionisation mass spectra were performed on either A.E.I. MS 12 or VG Micromass 7070 B instruments and run at either 14 or 70 eV source potentials. All accurate mass determinations were performed by the SERC mass spectrometry service centre at the chemistry department University of Swansea.

Norcamphor Oxime **1**.—Norcamphor (5.5 g, 0.05 mmol) was dissolved in methanol (20 cm^3) and aqueous solutions (20 cm^3 each) of sodium acetate (6.55 g, 0.08 mol) and hydroxylamine hydrochloride (6.6 g, 0.1 mol) were also prepared. The three solutions were mixed together and the resultant solution was stirred overnight. The mixture was diluted with water, extracted with ether (3 × 45 cm^3) and the combined ether layers were washed with a saturated aqueous sodium carbonate (20 cm^3). The ether layer was dried ($MgSO_4$) and evaporated to give the title compound **1** (6.06 g, 97%) as a colourless solid, m.p. 50–51 °C (lit.,[6a] m.p. 50–51.5 °C) (Found: M^+, 125.0841. Calc. For $C_7H_{11}NO$: M, 125.0841); ν_{max}(Nujol)/cm^{-1} 3128 (OH), 1690 (C=N), 1466 and 955; δ_H(270 MHz; $CDCl_3$), 1.2–1.5 (4 H, m), 1.55–1.8 (2 H, m), 2.1 (1 H, dd, J 17.1 and 3.4), 2.3 (1 H, J 17.6, 3.9 and 2.0), 2.5 (1 H, br s), 2.85 (1 H, br s) and 9.2 (1 H, br s, OH); m/z 125 (M^+, 90%), 108 (40), 96 (35), 93 (22), 80 (35), 67 (100) and 59 (73).

Beckmann Rearrangement of Norcamphor Oxime.—(A) *Sulfuric acid route*. Norcamphor oxime **1** (1 g, 8 mmol) was placed in a round-bottomed flask and 85% concentrated sulfuric acid (10 cm^3) was poured directly, slowly, onto it. After a short induction period of *ca.* 10 s, vigorous effervescence was observed and the colourless, solid, starting material was rapidly turned into a black viscous oil. This oil was diluted with water (10 ml) and neutralised with a 24% aqueous potassium hydroxide. The precipitate was filtered off, washed with chloroform (2 × 25 cm^3) and combined with the chloroform extracts (5 × 30 cm^3) of the aqueous phase. These extracts were washed once with water (30 cm^3), dried (Na_2SO_4), and the solvent removed under reduced pressure. The oily residue was distilled to give a mixture of the lactams **2** and **3** (0.449 g, 45%) as a pale oil, b.p. 150 °C at 20 mmHg (Found: M^+, 125.0841. Calc. for $C_7H_{11}NO$: M, 125.0841); ν_{max}(neat)/cm^{-1} 3226 (NH, 1667 (CO), 1496, 1346, 1294 and 1135; δ_H(250 MHz; $CDCl_3$) 1.5–2.1 (6 H, m), 2.15–2.7 (3 H, m), 3.8 (1 H, br d, J 4.4) and 7.0 (1 H, br s, NH); m/z 125 (M^+, 50%), 96 (100, M^+ − HCO), 82 (10), 67 (29), 54 (12) and 41 (20).

(*B*) *Sodium hydroxide/tosyl chloride route*. Norcamphor oxime **1** (1 g, 8 mmol) was taken up into aqueous sodium hydroxide (5 mol dm^{-3}; 11 cm^3) and, with stirring, tosyl chloride (1.66 g, 8.7 mmol) was added to it. This slow addition took 20 min and a further 1 h was allowed for the reaction. After this time the solution was extracted with chloroform (5 × 35 cm^3), dried (Na_2SO_4) and the solvent removed under reduced pressure. The oily residue was distilled and gave a mixture of lactams **2** and **3** as a pale oil (0.213 g, 21%, b.p. 150 °C at 20 mmHg).

5-exo,6-exo-*Isopropylidenedioxybicyclo*[2.2.1]*heptan*-2-*ol* **7**.—To norborn-5-en-2-ol (24 g, 0.218 mol) and trimethylamine *N*-oxide (33 g, 0.297 mol) in freshly distilled *tert*-butyl alcohol (440 cm^3), water (132 cm^3) and pyridine (17.4 cm^3) was added a freshly prepared solution of osmium tetroxide in *tert*-butyl alcohol (0.5% w/v; 17.4 cm^3, 87 mg). The solution was refluxed for 3 h and then cooled and aqueous sodium metabisulfite (20%; 174 cm^3) was added dropwise quickly, followed by HCl (2 mol dm^{-3}; 250 cm^3); the *tert*-butyl alcohol was then removed under reduced pressure. Acetone (200 cm^3) was then added and the mixture stirred for 1 h after which the acetone was removed. Ethyl acetate (100 cm^3) was added and both layers were filtered through Celite. The aqueous layer was continuously extracted for 3 days before the combined ethyl acetate layers were dried $MgSO_4$) and the solvent removed to give a brown viscous oil. (On one occasion a colourless solid was isolated which was the pure triol **6**, data given below, although on most occasions an oily product, a mixture of protected and unprotected alcohols, was obtained). This oil was taken up in a mixture of acetone (400 cm^3) and 2,2-dimethoxypropane (75 cm^3) with freshly activated Dowex 50-X200 cation exchange resin (5 g) and stirred at room temperature for 4 h. The solution was filtered, concentrated, and taken up in ether (350 cm^3) and washed

successively with water (50 cm^3), and saturated aqueous sodium hydrogen carbonate (50 cm^3). The ether layer was dried ($MgSO_4$) and the solvent removed to give the title compound **7** as a pale brown viscous oil (31.9 g, 80%) comprised of the two alcohol isomers. The spectroscopic data for this mixture was consistent with a combination of the literature data[12] for the individual isomers, b.p. 107 °C at 0.3 mmHg (Found: C, 65.2; H, 8.9. Calc. for $C_{10}H_{16}O_3$: C, 65.2; H, 8.7%); ν_{max}(neat)/cm^{-1} 3425 (OH), 1384 and 1375 [$C(Me)_2CH$ def.], 1270, 1207, 1163, 1049, 886 and 852; δ_H[250 MHz; $(CD_3)_2CO$] 0.7 (1 H, dt, 3-H, J_{3ab} 13.1, 3.7), 1.1–1.6 (3 H, m), 1.2 (3 H, s, Me-acetonide), 1.35 (3 H, s, Me-acetonide), 1.9 (1 H, ddd, 3-H, *J* 5.6, 10.3, J_{3ab} 13.1), 2.2 (1 H, m), 2.9 (2 H, br d), 4.05 and 4.6 (2 H, br d, 5-H and 6-H, $J_{5,6}$ 5.6); *m/z* 184 (M^+, 0.1%), 169 (100, M^+ − Me), 109 (56), 82 (41), 81 (45) and 59 (42).

5-exo,6-exo-*Bicyclo*[2.2.1]*heptane*-2,5,6-*triol* **6**.—The *title compound* was isolated, as an intermediate from the above reaction, m.p. 120 °C (decomp.) (Found: C, 58.1; H, 8.3. $C_7H_{12}O_3$ requires C, 58.3; H, 8.4%); ν_{max}(Nujol)/cm^{-1} 3355 (OH); δ_H[270 MHz; $(CD_3)_2CO$] 0.7 (1 H, dt, 3-H, J_{3ab} 13.1, 3.4), 1.1 (1 H, dt, *J* 10.3, 1.5), 1.7 (1 H, dt, *J* 10.5, 1.4), 1.85 (1 H, ddd, *J* 12.9, 10.3, 5.4), 1.97 (1 H, br d, *J* 4.6), 2.1 (1 H, m), 2.9 (1 H, br s, OH), 3.65 (1 H, br s), 3.8 (1 H, br s), 4.1 (2 H, br d) and 4.3 (1 H, br s); *m/z* 126 ($M^+ - H_2O$, 1%), 108 [3, $M^+ - 2(H_2O)$], 100 [3, (126) − C_2H_2], 97 (2), 95 (2), 82 [19, (126) − MeCHO], 41 (24), 39 (42), 31 (46), 29 (69) and 27 (100).

5-exo,6-exo-*Isopropylidenedioxybicyclo*[2.2.1]*heptan*-2-*one* **8**.—To a slurry of pyridinium dichromate (PDC) (63.7 g, 0.172 mol), silica gel (Kieselgel 60, 70–230 mesh, 127.3 g) and pyridinium trifluoroacetate (2.787 g, 14 mmol) in dichloromethane (275 cm^3) was added a solution of the two alcohol isomers **7** (12.56 g, 0.068 mol) in dichloromethane (104 ml). This mixture was stirred, under nitrogen, for 88 h at room temperature before being diluted with ether (325 cm^3) and filtered through Celite. The solid was washed with ether (325 cm^3) and the combined ether solvent was removed under reduced pressure to give an off-white solid. This crude product was recrystallised from boiling pentane to give an initial crop of the title compound **8** (9.6 g, 77%) as colourless crystals. The mother liquor was concentrated and after another recrystallisation gave a second crop of the title compound (1.43 g, 12%) (total yield 11.03 g, 89%). The spectroscopic data obtained for this solid matched well that recorded within the literature,[12] m.p. 80 °C, (lit.,[12] 74–75 °C); ν_{max}($CHCl_3$)/cm^{-1} 1758 (CO), 1458, 1410, 1383 and 1375 [$C(Me)_2$, CH def.], 1270, 1208, 1163, 1133, 1096, 1056, 1007, 959 and 866; δ_H(270 MHz; $CDCl_3$), 1.29 (3 H, s, Me-acetonide), 1.45 (3 H, s, Me-acetonide), 1.6–1.7 (2 H, m), 2.0–2.15 (2 H, m), 2.6–2.8 (2 H, m), 4.25 (1 H, d, 5-H or 6-H, $J_{5,6}$ 4.9), and 4.30 (1 H, d, 5-H or 6-H, $J_{5,6}$ 4.9); *m/z* 182 (M^+, 1%), 167 (100, M^+ − Me), 125 (47), 107 (41), 95 (39), 82 (38), 79 (63), 59 (53) and 43 (98).

5-exo,6-exo-*Isopropylidenedioxybicyclo*[2.2.1]*heptan*-2-*one Oxime* **9**, **10**, **11**.—The bicyclic ketone **8** (0.1414 g, 0.777 mmol) was dissolved in methanol (0.2 cm^3) and aqueous solutions (0.2 cm^3 each) of sodium acetate (0.1019 g, 1.24 mmol) and hydroxylamine hydrochloride (0.1019 g, 1.47 mmol) were also prepared. The three solutions were mixed together and the resultant solution was stirred overnight. The mixture was then diluted with water, extracted with ether (3 × 15 cm^3) and the combined ether layers were washed with a saturated aqueous sodium carbonate (20 cm^3). The ether layer was dried ($MgSO_4$) and evaporated to give the *title compound* (0.1246 g, 98%) as a clear colourless oil which became solid after an extended period under high vacuum, m.p. 118–120 °C. The isomeric mixture of oximes produced by this method were separated by recrystallisation of the solid mixture, from cyclohexane, which gave the pure *E*-isomer **10** in the first crop. Repeated recrystallisations managed to extract all of the *trans* form and enable the *Z*-form **11** to crystallise out, m.p. (*E*) 148 °C, (*Z*) 111–113 °C (starts to sublime). Data for *E*-isomer (Found: C, 61.2; H, 7.7; N, 7.1. $C_{10}H_{15}NO_3$ requires C, 60.9; H, 7.7; N, 7.1%); ν_{max}($CHCl_3$)/cm^{-1} 3600, 3294 (OH), 1383 and 1374 [$C(Me)_2$, CH def.], 1 270, 1209 and 1058; δ_H(270 MHz; $CDCl_3$) 1.3 (3 H, s, Me-acetonide), 1.4 (1 H, dt, 7b-H, J_{7ab} 10.3, 1.2), 1.47 (3 H, s, Me-acetonide), 1.95 (1 H, m, 7a-H, J_{7ab} 10.3), 2.0 (1 H, d, 3_{exo}-H, J_{3ba} 18.3), 2.3 (1 H, dd, 3_{endo}-H, J_{3ab} 18.3, $J_{3endo,4}$ 4.9), 2.5 (1 H, d, 4-H, $J_{4,3endo}$ 4.9), 2.92 (1 H, s, 1-H), and 4.2 (2 H, dd, 5-H and 6-H, $J_{5,6}$ 5.4); *m/z* 197 (M^+, 1%), 182 (46, M^+ − Me), 166 (80), 152, (34), 106 (59), 94 (54), 79 (65) and 59 (100); the NMR spectrum for the *Z*-isomer was identical with that for the *E*-isomer.

5-exo,6-exo-*Isopropylidenedioxybicyclo*[2.2.1]*heptan*-2-*one O*-*Methyloxime*.—A solution of the oxime **9** (393 mg, 2 mmol) in dimethylformamide (5 cm^3) was added to sodium hydride (50% dispersion; 210 mg, 2.2 mmol) under nitrogen. This mixture was stirred for 25 min before methyl iodide (0.14 cm^3, 2.2 mmol) was added *via* a syringe. Stirring was continued for a further 35 min before the reaction mixture was poured onto ice (15 g) and extracted with ether (3 × 30 cm^3). These extracts were dried ($MgSO_4$), and evaporated to give the *title compound* as an oil (211 mg, 50%), b.p. 85 °C at 20 mmHg (Found: M^+, 211.1208. $C_{11}H_{17}NO_3$ requires M, 211.1208); ν_{max}(neat)/cm^{-1} 2988 and 2939 (CH def.), 1462, 1385 and 1374 [$C(Me)_2CH$ def.], 1271, 1208, 1163, 1047, 886 and 849; δ_H(270 MHz; $CDCl_3$) 1.2 (3 H, s, Me-acetonide), 1.3 (1 H, dt, 7a-H, J_{7ab} 10, 1.7), 1.4 (3 H, s, Me-acetonide), 1.75–1.85 (1 H, dd, 3_{exo}-H, J_{3ba} 18.3, 4), 1.85–1.92 (1 H, m, 7b-H, J_{7ab} 10, 1.7), 2.15 (1 H, dd, 3_{endo}-H, J_{3ab} 18.3, $J_{3endo,4}$ 5.0), 2.4 (1 H, d, 4-H, $J_{4,3endo}$ 5.0), 2.8 (1 H, br s, 1-H), 3.75 (3 H, s, C=N–O–Me) and 4.2 (2 H, dd, 5-H and 6-H, $J_{5,6}$ 5.4); *m/z* 211 (M^+, 8%), 196 (78, M^+ − Me), 167 (23), 153 (19), 124 (100), 92 (68), 81 (73) and 66 (69).

6-exo,7-exo-*Isopropylidenedioxy*-2-*azabicyclo*[3.2.1]*octan*-3-*one* **12**.—The *E*-oxime **10** (307 mg, 1.56 mmol) was dissolved in acetonitrile (25 cm^3). Triethylamine (242 mm^3, 1.74 mmol) was added to this solution, followed by methanesulfonyl chloride (129 mm^3, 1.66 mmol). This mixture was heated and stirred at 78 °C for 21 h after which it was allowed to cool and the solvent removed under reduced pressure. The yellow/brown residue was pre-adsorbed onto silica gel and columned directly using the dry flash technique (eluent light petroleum to diethyl ether to ethyl acetate) to give the *title compound* **12** (221 mg, 73%) as a colourless solid, m.p. 164–166 °C (from diethyl ether–ethyl acetate) (Found: C, 60.8; H, 7.7; N, 6.9. $C_{10}H_{15}NO_3$ requires C, 60.9; H, 7.7; N, 7.1%); ν_{max}(CCl_4)/cm^{-1} 3201 (NH), 1669 (CO), 1383 and 1374 [$C(Me)_2CH$ def.], and 1209; δ_H(250 MHz; $CDCl_3$) 1.28 (3 H, s, Me-acetonide), 1.42 (3 H, s, Me-acetonide), 1.65 (1 H, d, 8b-H, J_{8ab} 12.5), 2.13 (1 H, m, 8a-H, J_{8ab} 12.5, 1.5), 2.25 (1 H, d, 4_{endo}-H, J_{4ab} 17.5), 2.41 (1 H, t, 5-H, $J_{5,4exo}$ 5), 2.57 (1 H, dd, 4_{exo}-H, J_{4ab} 17.5, $J_{5,4exo}$ 6), 3.56 (1 H, t, 1-H, *J* 5), 4.50 [2 H, ddd, 6-H and 7-H, $J_{8b,(6\text{ or }7)}$ 1.5, $J_{6,7}$ 6] and 6.42 (1 H, br s, NH); δ_C(62.9 MHz; $CDCl_3$) 23.77 (Me-acetonide), 25.63 (Me-acetonide), 29.21 (8-C), 36.22 (4-C), 37.54 (5-C), 55.09 (1-C), 83.99 (6-C or 7-C), 84.88 (6-C or 7-C), 110.22 (9-C) and 170.91 (3-C); *m/z* 197 (M^+, 19%), 182 (100, M^+ − Me), 138 [58, $(182)^+$ − MeCHO], 122 [29, $(182)^+ - CH_3CO_2H$], 101 (87), 96 (59) and 43 [54, $(MeCO)^+$].

6-exo,7-exo-*Isopropylidenedioxy*-2-*methyl*-2-*azabicyclo*-[3.2.1]*octan*-3-*one* **13**.—A solution of the lactam **12** (52.6 mg,

0.27 mmol) in dimethylformamide (5 cm^3) was added to sodium hydride (50% dispersion; 14 mg, 0.29 mmol) under nitrogen. This mixture was stirred for 1 h before methyl iodide (18 mm^3, 0.29 mmol) was added *via* a syringe. Stirring was continued for a further 30 min before the reaction mixture was poured onto ice (*ca.* 3 g) and extracted with ether (3 × 15 cm^3). These extracts were dried ($MgSO_4$), and evaporated to give the *title compound* **13** (31 mg, 55%) as an oil, which could not be obtained in analytical purity, b.p. 110 °C at 20 mmHg; $\nu_{max}(CCl_4)/cm^{-1}$ 1661 (CO), 1397, 1383 and 1374 [$C(Me)_2CH$ def.], 1267, 1209, 1075, 1047, 894 and 861; δ_H(250 MHz; $CDCl_3$) 1.26 (3 H, s, Me-acetonide), 1.40 (3 H, s, Me-acetonide), 1.68 (1 H, d, 8a-H, J_{8ab} 12.5), 2.10 (1 H, m, 8b-H, J_{8ab} 12.5), 2.21 (1 H, d, 4_{endo}-H, J_{4ab} 18), 2.40 (1 H, t, 5-H, $J_{5,4exo}$ 5), 2.55 (1 H, dd, 4_{exo}-H, J_{4ab} 18, $J_{4exo,5}$ 6), 2.92 (3 H, s, NMe), 3.44 (1 H, m, 1-H) and 4.44 (2 H, m, 6-H and 7-H); *m/z* 211 (M^+, 41%), 196 (28, M^+ − Me), 152 (74), 111 (100), 110 (76), 101 (46), 97 (41) and 57 (52).

2-*Allyl*-6-exo,7-exo-*isopropylidenedioxy*-2-*azabicyclo*[3.2.1]-*octan*-3-*one* **14**.—A solution of the lactam **12** (374 mg, 1.9 mmol) in dimethylformamide (20 cm^3) was added to sodium hydride (50% dispersion; 100 mg, 1.1 mmol) under nitrogen. This mixture was stirred for 50 min before allyl bromide (0.18 cm^3, 1.1 mmol) was added *via* a syringe. Stirring was continued for a further 100 min before the reaction mixture was poured onto ice (15 g) and extracted with ethyl acetate (3 × 25 cm^3). These extracts were dried ($MgSO_4$), and evaporated to give the crude product as an oil which was purified by flash column chromatography (eluent light petroleum to diethyl ether to ethyl acetate) to give the *title compound* **14** (317 mg, 71%) as a solid, m.p. 54–55 °C (Found: C, 65.6; H, 8.2; N, 5.9. $C_{13}H_{19}NO_3$ requires C, 65.8; H, 8.1; N, 5.9%); $\nu_{max}(CCl_4)/cm^{-1}$ 1662 (CO); δ_H(250 MHz; $CDCl_3$) 1.28 (3 H, s, Me-acetonide), 1.42 (3 H, s, Me-acetonide), 1.64 (1 H, d, 8b-H, J_{8ab} 12.5), 2.14 (1 H, m, 8a-H, J_{ab} 12.5), 2.25 (1 H, d, 4_{endo}-H, J_{4ab} 18.7), 2.41 (1 H, t, 5-H, $J_{4a,5}$ 5), 2.6 (1 H, dd, 4_{exo}-H, $J_{4a,5}$ 5, J_{4ab} 18.7), 3.5–3.62 (2 H, dd and br s, 1-H and 12a-H, *J* 6.3, 15), 4.3–4.5 (3 H, dd and br s, 12b-H, 6-H and 7-H, J_{67} 5), 5.1–5.2 (2 H, m, 14-H) and 5.73 (1 H, m, 13-H); *m/z* 237 (M^+, 73%), 222 (23%, M^+ − Me), 178 (41, [222] − MeCHO), 137 (75, [178] − allyl), 136 (55, [178] − CH_2CCH_2 + H), 101 (44), 68 (26) and 41 (100, $[allyl]^+$).

2-tert-*Butoxycarbonyl*-6-exo,7-exo-*isopropylidenedioxy*-2-*azabicyclo*[3.2.1]*octan*-3-*one* **15**.—A solution of the lactam **12** (277 mg, 1.41 mmol) in dimethylformamide (30 cm^3) was added to sodium hydride (50% dispersion; 93 mg, 1.1 equiv.). This mixture was stirred at room temperature for 35 min before a solution of di-*tert*-butyl oxydiformate (BOC anhydride) (1.5343 g, 5 equiv.) in dimethylformamide (5 cm^3) was added. The reaction was allowed to proceed for a further 35 min and then the mixture was poured onto ice (15 g). The resulting aqueous solution was extracted with ethyl acetate (5 × 40 ml) and the extracts were dried ($MgSO_4$), and the solvent was removed under reduced pressure. The residue was purified using dry flash column chromatography (eluent light petroleum to diethyl ether) to give the *title compound* **15** (323 mg, 75%) as a colourless solid, m.p. 118 °C (decomp.) (Found: C, 60.3; H, 7.8; N, 4.7. $C_{15}H_{23}NO_5$ requires C, 60.6; H, 7.8; N, 4.7%); $\nu_{max}(CHCl_3)/cm^{-1}$ 1769 and 1719 (CO), 1151, 1385 and 1372 [$C(Me)_2CH$ def.]; δ_H(250 MHz; $CDCl_3$) 1.30 (3 H, s, Me-acetonide), 1.45 (3 H, s, Me-acetonide), 1.55 (9 H, s, BOC), 1.68 (1 H, d, 8b-H, J_{8ab} 12.5), 2.2 (1 H, m, 8a-H, J_{8ab} 12.5), 2.4 (2 H, m, 5-H and 4_{endo}-H), 2.7 (1 H, dd, 4_{exo}-H, $J_{4a,5}$ 6, J_{4ab} 18.5) and 4.5 (3 H, dd, 1-H, 6-H and 7-H, $J_{6,7}$ 4.7, $J_{8b,6}$ 1.5); *m/z* 282 (M^+ − Me, 24%), 241 (23), 182 [63, (282) − BOC], 138 [35, (182) − CH_2CO], 122 [19, (182) − CH_3CO_2H], 101 (48), 96 (34) and 57 (100, $[Bu^t]^+$).

6-exo,7-exo-*Isopropylidenedioxy*-2-*azabicyclo*[3.2.1]*octane*-3-*thione* **16**.—The lactam **12** (173 mg, 0.878 mmol) was dissolved in dry toluene (10 cm^3) under nitrogen. To this was added Lawesson's reagent (213 mg, 0.527 mmol) and the mixture was heated to reflux. After being heated under reflux for 1.5 h the solution was allowed to cool and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography (eluent light petroleum to diethyl ether) to give the *title compound* **16** (125 mg, 67%) as a colourless solid, m.p. 174 °C (decomp.) (Found: C, 56.0; H, 7.1; N, 6.5. $C_{10}H_{15}NO_2S$ requires C, 56.3; H, 7.1; N, 6.6%); $\nu_{max}(CHCl_3)/cm^{-1}$ 3171 (NH), 1551, 1515, 1385 and 1377 [$C(Me)_2CH$ def.], 1266, 1209, 1122, 1082, 1049 and 974; δ_H(270 MHz; $CDCl_3$) 1.29 (3 H, s, Me-acetonide), 1.43 (3 H, s, Me-acetonide), 1.73 (1 H, d, 8b-H, J_{8ab} 12.2), 2.17 (1 H, m, 8a-H, J_{8ab} 12.2), 2.4 (1 H, t, 5-H, *J* 5.1), 2.85 (1 H, dt, 4_{endo}-H, J_{4ab} 20.0, *J* 1.7), 3.2 (1 H, dd, 4_{exo}-H, J_{4ab} 20.0, $J_{4,5}$ 5.6), 3.7 (1 H, t, 1-H, *J* 4.6), 4.5–4.6 (2 H, dd, 6-H and 7-H, $J_{6,7}$ 5.4, $J_{8b,6}$ 1.6) and 9.6 (1 H, br s, NH); *m/z* 213 (M^+, 72%), 198 (16, M^+ − Me), 154 [46, (198) − CH_3CHO or CS], 138 [33, (198) − CH_3CO_2H], 126 (154) − CO], 112 [84, (154) − CH_2CO], 81 (67) and 43 [100, $(CH_3CO)^+$].

2-*Allyl*-6-exo,7-exo-*isopropylidenedioxy*-2-*azabicyclo*[3.2.1]-*octane*-3-*thione* **17**.—The allyl lactam **14** (276 mg, 1.16 mmol) was dissolved in dry toluene (10 cm^3) under nitrogen. To this was added Lawesson's reagent (283 mg, 0.699 mmol) and the mixture was heated to reflux. After being heated under reflux for 0.5 h the solution was allowed to cool and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography (eluent light petroleum to diethyl ether) to give the *title compound* **17** (211 mg, 72%) as a colourless solid, m.p. 121–123 °C (needles form from 118 °C onwards) (Found: C, 61.5; H, 7.7; N, 5.4. $C_{13}H_{19}NO_2S$ requires C, 61.6; H, 7.6; N, 5.5%); $\nu_{max}(CHCl_3)/cm^{-1}$ 1495 (C=S coupling bands with C–N vib.), 1385 and 1377 [$C(Me)_2CH$ def.], 1191, 1077 and 1046 (C=S str.); δ_H(270 MHz; $CHCl_3$) 1.3 (3 H, s, Me-acetonide), 1.44 (3 H, s, Me-acetonide), 1.71 (1 H, d, 8b-H, J_{8ab} 12.5), 2.2 (1 H, m, 8a-H, J_{8ab} 12.5), 2.38 (1 H, t, 5-H, *J* 5.2), 2.9 (1 H, d, 4_{endo}-H, J_{4ab} 19.5), 3.2 (1 H, dd, 4_{exo}-H, J_{4ab} 19.5, $J_{4,5}$ 5.8), 3.8 (1 H, d, 1-H, *J* 3.9), 4.11 (1 H, dd, 12a-H, J_{12ab} 6.3, $J_{12a,3}$ 14.7), 4.45 (2 H, dd, 6-H and 7-H, $J_{6,7}$ 5.6, $J_{8b,6}$ 1.7), 5.18 (1 H, dd, 12b-H, $J_{12a,13}$ 6.3, J_{12ab} 14.7), 5.27 [1 H, dd, (*trans*)14a-H, $J_{14a,13}$ 5.1, J_{14ab} 1.2], 5.33 [1 H, dd, (*cis*)14b-H, $J_{14b,13}$ 2.7, J_{14ab} 1.2] and 5.85 (1 H, m, 13-H); *m/z* 253 (M^+, 25%), 238 (100, M^+ − Me), 196 [2, (238) − CH_2CO], 178 [5, (238) − CH_3CO_2H], 152 [5, (196) − CS], 112 [6, (152) − CH_2CCH_2], 81 (16) and 41 [21, $(CH{=}CHCH_2)^+$].

Methylation of the BOC Protected Lactam **15**.—The BOC protected lactam **15** (97.4 mg, 0.317 mmol) was dissolved in freshly distilled THF (10 cm^3) and this solution was cooled to −78 °C. A solution of KHMDS (0.5 mol dm^{-3} solution in toluene; 0.7 cm^3, 1.1 equiv.) was added, and the mixture was stirred for 30 min. Methyl iodide (59.3 mm^3, 3 equiv.) was added and the solution was allowed to reach room temperature. The solution was diluted with water (10 cm^3) and extracted with ethyl acetate (5 × 20 cm^3); these organic layers were combined, dried ($MgSO_4$), filtered, and the solvent was removed under reduced pressure. The yellow oily residue was purified by dry flash column chromatography (eluent light petroleum to diethyl ether) and to give (i) a small amount of starting material **15** (7.3 mg, 9% recovery), (ii) 2-tert-*butoxycarbonyl*-4-exo-*methyl*-6-exo,7-exo-*isopropylidenedioxy*-2-*azabicyclo*[3.2.1]*octan*-3-*one* **18** (20.9 mg, 21%), m.p. 114–115 °C (decomp.) (Found: M^+ − CH_3, 296.1498, $C_{15}H_{22}NO_5$ requires $M - CH_3$ 296.1498); $\nu_{max}(CCl_4)/cm^{-1}$ 1776 (BOC C=O), 1723 (lactam CO), 1383 and 1371 [$C(Me)_2CH$ def.], 1289, 1268, 1241, 1214, 1158, 1122, 1075,

Table 1 Atom coordinates ($\times 10^4$) with esds in parentheses for compound **10**

Atom	*x*	*y*	*z*
C(1)	3 837(1)	3 031(2)	7 468(1)
C(2)	3 171(1)	3 607(2)	6 983(1)
N(2)	2 869(1)	3 076(2)	6 088(1)
O(2)	2 257(1)	3 852(2)	5 830(1)
C(3)	2 971(1)	4 903(2)	7 733(1)
C(4)	3 549(1)	4 915(2)	8 649(1)
C(5)	3 479(1)	3 537(2)	9 402(1)
O(5)	3 988(1)	3 519(1)	10 311(1)
C(6)	3 677(1)	2 234(2)	8 599(1)
O(6)	4 278(1)	1 629(1)	9 130(1)
C(7)	4 151(1)	4 493(2)	7 924(1)
C(8)	4 307(1)	2 095(2)	10 314(1)
C(9)	3 930(1)	1 012(3)	11 061(2)
C(10)	5 035(1)	2 280(3)	10 684(2)

Table 2 Atom coordinates ($\times 10^4$) with esds in parentheses for compound **12**

Atom	*x*	*y*	*z*
C(1)	116(8)	504(6)	3646(3)
N(2)	1895(6)	1123(4)	4148(3)
C(3)	3800(8)	812(5)	4079(3)
O(3)	5324(6)	1390(3)	4465(2)
C(4)	4169(9)	−357(5)	3492(4)
C(5)	2263(9)	−860(5)	2950(3)
C(6)	1446(8)	131(6)	2242(3)
O(6)	149(7)	−498(5)	1537(2)
C(7)	−77(0)	997(5)	2687(3)
O(7)	−2017(6)	735(4)	2227(2)
C(8)	533(9)	−950(5)	3532(3)
C(9)	−1696(10)	163(6)	1378(3)
C(10)	−3419(13)	−774(10)	1090(4)
C(11)	−1487(12)	1295(8)	710(4)

1049, 1008, 945, 893 and 859; δ_H(270 MHz; $CDCl_3$) 1.28 (3 H, s, Me-acetonide), 1.32 (3 H, d, 4_{exo}-Me, J_{4ab} 7.6), 1.45 (3 H, s, Me-acetonide), 1.5 (9 H, s, BOC), 1.7 (1 H, d, 8b-H, J_{8ab} 12.9), 2.05 (1 H, dtd, 8a-H, J_{8ab} 12.9, *J* 4.6, 1.7), 2.15 (1 H, br, d, 5-H, *J* 4.6), 2.4 (1 H, q, 4_{endo}-H, J_{4ab} 7.6) and 4.4–4.5 (3 H, m, 1-H and 6-H and 6-H and 7-H); *m/z* 311 (M^+, 0.2%), 296 (14, M^+ − Me), 255 (18), 196 [39, (296) − BOC], 153 (19), 110 (23), 101 (41) and 57 (100, $[Bu^t]^+$), and (iii) 2-tert-*butoxycarbonyl*-4,4-*dimethyl*-6-exo,7-exo-*isopropylidenedioxy*-2-*azabicyclo*[3.2.1]*octan*-3-*one* **19** (35.1 mg, 34%), m.p. 134 °C (decomp. starts at 120 °C) (Found: $M^+ - CH_2$, 311.1687. $C_{16}H_{25}NO_5$ requires 311.1691); $\nu_{max}(CHCl_3)/cm^{-1}$ 1766 (BOC C=O), 1718 (lactam CO), 1386 and 1372 [$C(Me)_2CH$ def.], 1293, 1269, 1150, 1048 and 1022; δ_H(270 MHz; $CDCl_3$) 1.25 (3 H, s, 4_{endo}-Me), 1.27 (3 H, s, 4_{exo}-Me), 1.30 (3 H, s, Me-acetonide), 1.42 (3 H, s, Me-acetonide), 1.49 (9 H, s, BOC), 1.85 (1 H, d, 8b-H, J_{8ab} 12.7), 2.0–2.13 (2 H, m, 8a-H and 5-H), 4.3 (1 H, br t, 1-H, *J ca.* 2) and 4.4 and 4.7 (2 H, dd, 6-H and 7-H, $J_{6,7}$ 5.4, 1.7); *m/z* 325 (M^+, 0.2%), 310 (13, M^+ − Me), 269 [14, (310) − (2 × Me)], 210 [42, (310) − BOC], 167 (17), 101 (33), 81 (26) and 57 (100, Bu^{t+}).

Crystal Data.—(E)-5-exo,6-exo-*Isopropylidenedioxybicyclo*-[2.2.1]*heptan*-2-*one Oxime* **10**.—Crystal data $C_{10}H_{15}NO_3$, *M* = 197.2, monoclinic, *a* = 19.762(4), *b* = 8.936(2), *c* = 11.542(2) Å, β = 91.88(2)°, *U* = 2037 Å^3, space group *C*2/*c*, *Z* = 8, D_c = 1.29 g cm^{-3}, Cu radiation, λ = 1.541 78 Å μ(Cu-Kα) − 7 cm^{-1}, *F*(000) = 848. Data were measured on a Nicolet R3m diffractometer with Cu-Kα radiation (graphite monochromator) using ω-scans. 1374 Independent reflections were measured ($2\theta \leqslant 116°$), of which 1255 had $|F_o| > 3\sigma(|F_o|)$ and were considered to be observed. The data were corrected for Lorentz and polarisation factors; no absorption correction was applied. The structure was solved by direct methods. The non-hydrogen atoms were refined anisotropically. The hydroxy proton on O(2) and the protons on C(1) and C(4) were located from a Δ*F* map and refined isotropically. The positions of the remaining hydrogen atoms were idealised, C–H = 0.96 Å, assigned isotropic thermal parameters, $U(H) = 1.2\ U_{eq}(C)$, and allowed to ride on their parent carbon atoms. The methyl groups were refined as rigid bodies. Refinement was by block-cascade, full-matrix least-squares to $R = 0.039$, $R_w = 0.045$ [$w^{-1} = \sigma^2(F) + 0.000\,71F^2$]. The maximum and minimum residual electron densities in the final Δ*F* map were 0.18 and −0.12 eÅ^{-3} respectively. The mean and maximum shift/error in the final refinement were 0.008 and 0.097 respectively. Computations were carried out on an Eclipse S140 computer using the SHELXTL program system.[16,*]

6-exo,7,exo-*Isopropylidenedioxy*-2-*azabicyclo*[2.3.1]*heptan*-3-*one* **12**. Crystal data: $C_{10}H_{15}NO_3$, *M* = 197.2, monoclinic, *a* = 6.554(3), *b* = 10.247(5), *c* = 15.141(7) Å, β = 96.78(4)°, *U* = 1010 Å^3, space group $P2_1/a$, *Z* = 4, D_c = 1.30 g cm^{-3}, Cu radiation, λ = 1.541 78 Å, μ(Cu-Kα) = 8 cm^{-1}, *F*(000) = 424. Data were measured on a Nicolet R3m diffractometer with Cu-Kα radiation (graphite monochromator) using ω-scans. 853 Independent reflections were measured ($2\theta \leqslant 100°$), of which 815 had $|F_o| > 3\sigma(|F_o|)$ and were considered to be observed. The data were corrected for Lorentz and polarisation factors; no absorption correction was applied. The structure was solved by direct methods. The non-hydrogen atoms were refined anisotropically. The amide proton was located from a Δ*F* map and refined isotropically. The positions of the remaining hydrogen atoms were idealised, C–H = 0.96 Å, assigned isotropic thermal parameters, $U(H) = 1.2\ U_{eq}(C)$, and allowed to ride on their parent carbon atoms. The methyl groups were refined as rigid bodies. Refinement was by block-cascade, full-matrix least-squares to $R = 0.084$, $R_w = 0.105$ [$w^{-1} = \sigma^2(F) + 0.00209F^2$]. The maximum and minimum residual electron densities in the final Δ*F* map were 0.26 and −0.22 e Å^{-3} respectively. The mean and maximum shift/error in the final refinement were 0.025 and 0.127 respectively. Computations were carried out on an Eclipse S140 computer using the SHELXTL program system.[16,*]

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* Bond lengths, bond angles, thermal parameters and hydrogen atom coordinates for this work are available on request from the Director of the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW. Any request should be accompanied by the full literature citation for this paper.

References

1 E. Beckmann, *Chem. Ber.*, 1886, **19**, 988.
2 R. E. Gawley, *Org. React.*, 1988, **35**, 1.
3 P. A. Hunt and H. S. Rzepa, *J. Chem. Soc., Chem. Commun.*, 1989, 623.
4 G. R. Krow, *Tetrahedron*, 1981, **37**, 1283.
5 Swiss Patent, 270546 (1951) (*Chem. Abstr.*, 1952, **46**, 780); Swiss Patent, 287863 (1953) (*Chem. Abstr.*, 1955, **49**, 2490).
6 (*a*) H. K. Hall, *J. Am. Chem. Soc.*, 1960, **82**, 1209; (*b*) R. C. Elderfield and E. T. Losin, *J. Org. Chem.*, 1961, **26**, 1703; (*c*) B. L. Fox and J. E. Reboulet, *J. Org. Chem.*, 1968, **33**, 3639; (*d*) B. L. Fox and H. M. Rosenberg, *J. Chem. Soc., Chem. Commun.*, 1969, 1115; (*e*) G. H. Schmid and P. H. Fitzgerald, *Can. J. Chem.*, 1968, **46**, 3758.

7 R. T. Conley and S. Ghosh, in *Mechanisms of Molecular Migrations*, ed. B. S. Thyaguragan, Wiley, New York, 1971, vol. 4, pp. 230–233.
8 Preliminary communication, P. A. Hunt and C. J. Moody, *Tetrahedron Lett.*, 1989, **30**, 7233.
9 D. G. VerHaeghe, G. S. Weber and P. A. Pappalardo, *Tetrahedron Lett.*, 1989, **30**, 4041.
10 K. I. Morita and Z. Suzuki, *J. Org. Chem.*, 1966, **31**, 233; G. Reinisch, H. Bara and H. Klare, *Chem. Ber.*, 1966, **99**, 856.
11 M. Gates and S. P. Malchick, *J. Am. Chem. Soc.*, 1957, **79**, 5546.
12 R. C. Cookson, P. J. Dudfield and D. I. C. Scopes, *J. Chem. Soc., Perkin Trans. 1*, 1986, 393.
13 I. Sakai, N. Kawabe and M. Ohno, *Bull. Chem. Soc. Jpn.*, 1979, **52**, 3381.
14 C. A. Fletcher, H. Hilpert, P. L. Myers, S. M. Roberts and R. Storer, *J. Chem. Soc., Chem. Commun.*, 1989, 1707.
15 L. M. Harwood and C. J. Moody, *Experimental Organic Chemistry: Principles and Practice*, Blackwells Scientific Publications, Oxford, 1989.
16 G. M. Sheldrick, SHELXTL, An Integrated System for Solving, Refining and Displaying Crystal Structures from Diffraction Data, University of Gottingen, Germany, Revision 4.1, 1983.

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