# Synthesis of Physoperuvine (8-Methyl-8-azabicyclo[3.2.1]octan-1-ol), Norphysoperuvine and Dehydro-derivates

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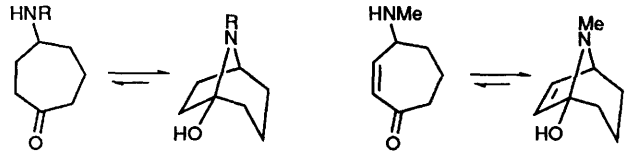
4-Aminocycloheptanones have been synthesised in high yield from cyclohepta-1,3-diene. These compounds exist mainly as the bicyclic tautomers (8-azabicyclo[3.2.1]octan-1-ol derivatives; the title compounds) as shown by $^{13}C$ NMR spectroscopy at low temperatures. 4-Aminocyclohept-2-enones are reactive but show a preference for the monocyclic tautomers; *N*-benzyloxycarbonyl derivatives of the saturated and unsaturated systems are isolated as the monocyclic tautomers.



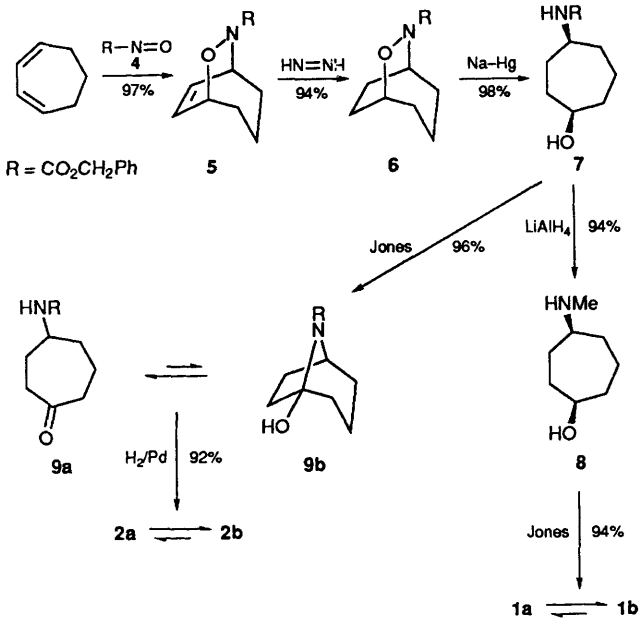
The correct structure for physoperuvine **1** was established only in 1982[1] when it was shown to be 4-(methylamino)cycloheptanone rather than the 3-substituted isomer which had been proposed earlier. The monocyclic amino ketone **1a** was shown to be in equilibrium with the bicyclic tautomer **1b**; the latter predominated and a crystal structure showed that the hydrochloride salt (**1bH**$^+$Cl$^-$) was also exclusively bicyclic.[1b,2] Recently, there has been rapid development of interest in derivatives of the 1-hydroxynortropane skeleton. In particular, the newly-discovered family of hydroxy-derivatives known as the calystegines has attracted attention following their discovery in the root secretions of *Calystegia sepium* and their recognition as growth stimulators for nitrogen-fixing bacteria.[3] Racemic physoperuvine itself has been synthesised earlier using ring enlargement of 4-aminocyclohexanone derivatives with diazomethane to provide 4-substituted cycloheptanones[1a,3a] but overall yields from six-membered ring precursors are low.† We now report a simple route to **1** from cyclohepta-1,3-diene which proceeds cleanly in high overall yield and is also adaptable to the production of the secondary amine norphysoperuvine **2**, *N*-protected derivatives, and to 6,7-dehydro-derivatives such as **3**, although the latter compounds decompose readily.




**1a** R = Me
**2a** R = H
**1b**
**2b**
**3a**
**3b**

Our own earlier syntheses of tropane derivatives from cyclohepta-1,3-diene[5] were based on the cycloaddition of nitroso compounds[6] to derivatise the ring at positions 1 and 4. The work made use of *N*-benzoyl and thence *N*-benzyl derivatives by reduction. However, following conversion of the derivatised seven-membered ring into the tropane skeleton, the *N*-benzyl group was surprisingly difficult to remove, except by hydrogenolysis.[5,7] We turned to the use of the *N*-benzyloxycarbonyl group in the synthesis of *N*-methyl amines in the homotropane series[8] and have modified this approach to produce the family of 1-hydroxytropane derivatives **1**–**3**.

The key intermediate **5** was made in 97% yield from cyclohepta-1,3-diene by addition of the nitroso compound **4** formed *in situ* from benzyl *N*-hydroxycarbamate and tetramethylammonium periodate[5] (Scheme 1). The adduct was reduced with diimide (94%) to **6** followed by reductive cleavage of the NO bond to yield **7** in 98% yield. Reduction with lithium tetrahydroaluminate (94%) followed by Jones oxidation (94%) provided physoperuvine **1** in an overall yield of 79% from cycloheptadiene.

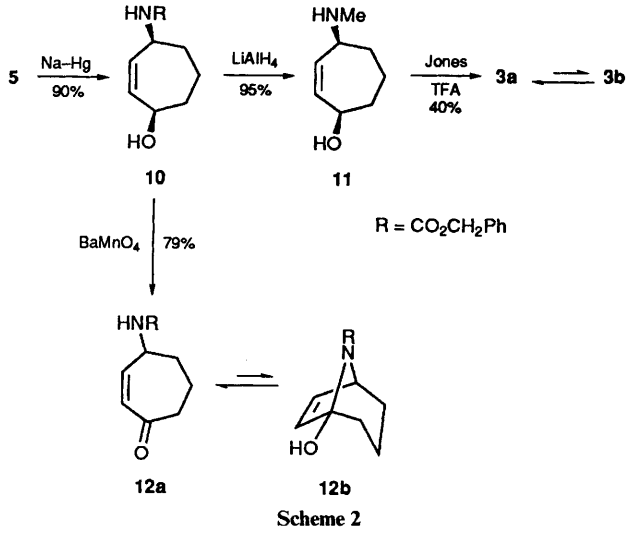



**Scheme 1**

Oxidation of **7** gave the *N*-protected derivative **9** which was easily hydrogenolysed to give norphysoperuvine **2** in a similar overall yield.

We are interested in the effects of incorporation of double bonds into azabicyclic systems with particular emphasis on their ground state properties and on the inversion process at nitrogen.[9,5] We are also investigating the potential influence of bicyclic nitrogen on facial selectivity in attack upon π-bonds in tropane systems (and in lower and higher homologues). The 6,7-double bond in trop-6-enes offers an attractive potential entry to a range of epoxytropanes[10a] (including non-natural analogues of scopine)[10b] and to novel hydroxytropanes.[11] Clearly, the availability of 1-hydroxytrop-6-enes would provide similar opportunities in the 1-hydroxytropane series and an

† Reported yields for the 4-aminocyclohexanone ring enlargements varied from 29% for conversion of 4-(benzylamino)cyclohexanone into *N*-methyl-4-(benzylamino)cycloheptanone (overall yield of physoperuvine from 4-aminocyclohexanol < 10%)[3a] to 71% for the ring enlargement of 4-(methylamino)cyclohexanone[1a] (itself prepared from *p*-methylaminophenol in an overall yield of only 11.4% by catalytic reduction followed by oxidation with chromic acid).[4]




**Scheme 2**

approach to 6,7-dehydrophysoperuvine **3** is summarised in Scheme 2.

Reductive cleavage of compound **5** gave the *cis*-amino alcohol **10** which, after sequential hydride reduction and oxidation, afforded 6,7-dehydrophysoperuvine **3**. Following experiments with a variety of oxidation conditions, direct oxidation of compound **11** was used despite the potential sensitivity of the substrate. Jones oxidation in the presence of trifluoroethanoic acid (to protonate the amino-nitrogen) gave a 40% yield of compound **3** but the product was unstable and difficult to purify. Application of the same conditions to the *N*-benzyl analogue **13** was more successful (85% yield). Direct oxidation of amino alcohol **10** using barium manganate[8] gave the tautomeric mixture **12*** in good yield.

The potential for tautomerism in the case of **1a** ⇌ **1b** was recognised earlier and a tautomer ratio of 1:45 was estimated on the basis of CD measurements.[1b] Similar tautomerism has also been observed more recently in 4-hydroxy- and 4-amino-cyclooctanones and -octenones[12] and in 4-(benzylamino)cycloheptanone (*N*-benzylnorphysoperuvine).[13,]† We have used variable temperature (VT) NMR spectroscopy to study physoperuvine **1** and have also investigated the other amino ketones in the present work. Direct observation of both tautomers of **1** was not possible using NMR at ambient temperature; neither the $^1$H nor the $^{13}$C spectrum was fully analysable, being broad and complex. However, the preference for the bicyclic tautomer **1b** became clear when the $^{13}$C NMR spectrum was measured at lower temperatures. Thus, a characteristic quaternary carbon signal at $\delta$ 88.8 sharpened at 223 K and was assigned to C-1 of **1b**. Additional minor signals confirmed the presence of a small proportion of the monocyclic tautomer but the signal due to the carbonyl carbon was too weak (or broad) to be observed at low temperature and was not resolved at higher temperatures. A ratio for **1a** ⇌ **1b** of approximately 2:98 was estimated from the $^{13}$C NMR spectrum (Table 1), in very good agreement with the earlier estimate.‡ A similar preference was estimated for compound **2** where C-1 of the bicyclic tautomer **2b** appeared at $\delta$ 89.9 at 223 K. Changes in the $^1$H and $^{13}$C NMR spectra of **1** and **2** in [$^2H_8$]toluene above room temperature were consistent with a temperature-dependent equilibrium and the presence of some of the monocyclic tautomer at the higher temperatures. Signal coalescence meant that quantitative estimates could not be obtained for **2** but the observations are in line with measurements in certain homotropan-1-ols in which the proportion of monocycle present at equilibrium increased with increase in temperature.[12] In contrast, the *N*-protected analogue **9** appeared to be completely monocyclic as shown by a carbonyl signal at $\delta$ 213.7 assigned to C-1 of **9a** and by the absence of a signal in the $\delta$ 85–90 region which would have indicated the presence of **9b**. The $^1$H NMR spectrum was consistent with the presence of a single, monocyclic tautomer showing no evidence of the slow N–CO rotation typical of *N*-bridged bicyclic amides and carbamates.[5,8] A similar preference was also seen for the unsaturated *N*-benzyloxycarbonyl derivative **12** where only the monocyclic tautomer **12a** was observed by NMR spectroscopy.

The $^1$H NMR spectra for both compounds **3** and **13** were very similar and showed all of the features associated with the monocyclic tautomers, in particular the low carbonyl stretching

**Table 1** Tautomer ratios for 4-aminocycloheptanone derivatives

| Compound | Ratio monocyclic:bicyclic |
|---|---|
| **1a** ⇌ **1b** | 2:98[a,b] |
| **2a** ⇌ **2b** | *ca.* 0:100[a,c] |
| **3a** ⇌ **3b** | major:minor[d] |
| **9a** ⇌ **9b** | *ca.* 100:0[e] |
| **12a** ⇌ **12b** | *ca.* 100:0[e] |
| **13a** ⇌ **13b** | major:minor[f] |

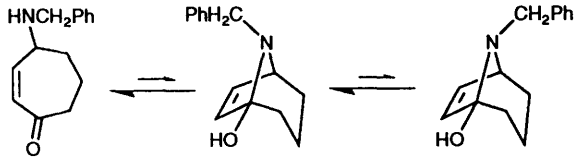
[a] Estimated by $^{13}$C NMR in $CDCl_3$ at 223 K. [b] Compare the value of 1:45 estimated using CD.[1b] [c] Some precipitation from solution occurred at low temperature but only one tautomer was visible and a clear signal at $\delta$ 89.9 (C-1) confirmed that this was the bicyclic form. No minor signals typical of a second tautomer were visible at this temperature but there was evidence for the presence of some of the monocyclic tautomer at higher temperatures (see text). [d] Studied using $^1$H NMR at ambient temperature; the sample contained minor impurities but the essential features of the spectrum were very similar to those observed for the unsaturated analogues **12** and **13**. [e] Measured using $^{13}$C NMR at ambient temperature. The spectrum did not change significantly on addition of acid or base.§ [f] Sharp signals assigned to the monocyclic tautomer were clearly visible at ambient temperature and at 233 K. Additional broad peaks (tentatively associated with the bicyclic tautomer) were observed in the $^{13}$C NMR spectrum at ambient temperature and below, but the picture was complicated, probably by slow inversion at nitrogen in the bicyclic tautomer.

* Attempts to deprotect **12** by hydrolysis were not very successful and losses due to the solubility of the resulting secondary amino alcohol from aqueous solution were considerable.

† The IR spectrum of the *N*-benzyl analogue **1** (R = $CH_2Ph$) showed carbonyl absorption at 1690 cm$^{-1}$ at ambient temperature but the $^1$H and $^{13}$C NMR spectra showed broad signals. At 213 K, the $^{13}$C NMR spectrum showed seven (broadened) signals due to the ring carbons indicating a heavily weighted equilibrium; a signal at $\delta$ 88.9 (assigned to C-1) indicated that the bicyclic tautomer predominated. Similar observations for the *N*-benzyl compound have been reported recently by Boyer *et al.*[3a] who studied the NMR behaviour at higher temperatures but were also unable to resolve the C-1 signal.

‡ The possibility that the minor component might be an invertomer rather than the monocyclic tautomer was considered and rejected on the basis of: (a) the similarity between the behaviour of the *N*-methyl, *N*-benzyl (where carbonyl absorption was observed in the IR spectrum)† and nor-compounds; (b) the close correspondence between the $^{13}$C NMR signals which were resolved for **1a** and those for the heavily monocyclic **9a**; (c) the substantially different coalescence behaviour of C-1 (which involves an unusually large frequency difference between C-1 in the two tautomers) which would not be expected in the case of simple nitrogen inversion.[5]

§ The interconversion of certain analogues in the homotropane series could be influenced by acid and base.[8] However, in the case of **9** and **12**, treatment of solutions in $CDCl_3$ with butyllithium or trifluoroethanoic acid showed no measurable change in the tautomeric preference when monitored by $^1$H and $^{13}$C NMR spectroscopy at room temperature.




**13a** equatorial **13b** axial **13b**



frequency and the substantial chemical shift differences between the two alkene carbons and between the two attached protons, typical of an α,β-unsaturated carbonyl moiety. Double irradiation experiments confirmed the relationship between the protons on C-2, C-3 and C-4 of **13a** and also identified a four-bond coupling through the carbonyl group between 2-H and an α-carbonyl proton on C-7. However, the suggestion that incorporation of a double bond into the bicyclic skeleton to give **13** (and by analogy, **3**) might cause the equilibrium to shift totally to the monocyclic side was surprising in view of work with higher homologues.[12] On closer inspection, additional broad peaks could be discerned in the baseline noise of the $^{13}C$ NMR spectrum of samples of **13** at ambient temperature and new signals appeared as the temperature was lowered to 233 K, including a broad carbonyl carbon signal at $\delta$ 204.8 assigned to the monocycle **13a**. This behaviour suggested the existence of a tautomeric equilibrium and, whilst the low-temperature spectra could not be fully interpreted, strongly supported a qualitative preference for **13a**. The difficulty in interpreting the low-temperature NMR spectra is probably associated with the intrusion of a second temperature-dependent process (nitrogen inversion) which would only be expected for **13b**. Slow inversion at nitrogen has already been shown to cause broadening of the spectra of *N*-benzyl-nortropane and -nortrop-6-ene over a similar temperature range[5] despite the fact that the inversion equilibrium is weighted heavily in favour of the equatorial conformer in each case. Detailed NMR work on **3** could not be performed due to its instability and limited availability but the $^1H$ NMR and IR spectra of **3** and **13** were very similar confirming a similar preference for the monocycle.

Whilst the approach to physoperuvine **2** is convenient and efficient, further work on 6,7-dehydrophysoperuvine **3** itself was considered to be of limited value in view of its instability. Incorporation of substituents at an earlier stage in the synthesis provides a more practical approach to 1-hydroxytropanes bearing functional groups in the two-carbon bridge (at the 6- and 7-positions) and further derivatisation studies are currently under way.[11]

## Experimental

$^1H$ NMR spectra were recorded on Varian EM 390 (90 MHz) or Bruker AM300 (300 MHz) NMR spectrometers. $^{13}C$ NMR spectra were recorded on the Bruker AM 300 spectrometer at 75 MHz. Spectra were measured in $CDCl_3$ with tetramethylsilane (TMS) as internal reference unless indicated otherwise. Signal characteristics are described using standard abbreviations: s (singlet), d (doublet), dd (doublet of doublets), t (triplet), q (quartet), m (multiplet), br (broad); protons identified as NH or OH were shown to be exchangeable with $D_2O$. *J*-Values are given in Hz. In the $^{13}C$ spectra, C, CH, $CH_2$, $CH_3$ are used to indicate quarternary, methine, methylene and methyl carbons respectively, as shown by off-resonance decoupling or DEPT experiments.

IR spectra were recorded on a Perkin-Elmer 298 spectrometer as solutions in $CH_2Cl_2$. Band intensities are described using standard abbreviations: s (strong), m (medium), w (weak), br (broad), v (very).

Mass spectra were measured routinely on VG Micromass 14 or Kratos Concept mass spectrometers using ionisation by electron impact unless stated otherwise; intensities are given as percentages of the base peak. Accurate mass measurements were obtained on the Concept spectrometer or through the SERC service at the University College of Swansea.

Melting point measurements were made using a Kofler hot stage apparatus and are uncorrected.

Combustion analyses were performed by Butterworth Laboratories Ltd., Teddington, Middlesex.

Reactions were performed under dry nitrogen using solvents dried by standard methods. Diethyl ether was dried over sodium wire and distilled from $LiAlH_4$. Dichloromethane and toluene were distilled from calcium hydride. Light petroleum was distilled prior to use. Methanol and ethanol were purified with magnesium and iodine.[14] Tetrahydrofuran was distilled from sodium–benzophenone. All other solvents were dried and purified as described by Perrin and Armarego.[15] Flash chromatography was carried out according to the method of Still *et al.*[16] using Merck Kieselgel 60 (230–400 mesh). Thin-layer chromatography was conducted on standard commercial aluminium sheets pre-coated with a 0.2 mm layer of silica gel (Merck 60–254).

*Benzyl* 8-*Oxa*-9-*azabicyclo*[3.2.2]*non*-6-*ene*-9-*carboxylate* **5**.—This compound was prepared according to the procedure in ref. 5 (compound **3e**) but the yield was further improved (to 97%) following more rigorous purification of the benzyl *N*-hydroxycarbamate prior to use.

*Benzyl* 8-*Oxa*-9-*azabicyclo*[3.2.2]*nonane*-9-*carboxylate* **6**.—To a stirred solution of potassium azodicarboxylate (12.74 g, 65.7 mmol) and compound **5** (3.40 g, 13.12 mmol) in methanol (90 $cm^3$) at 0 °C was added glacial ethanoic acid (7.60 $cm^3$, 139.2 mmol) over 10 min. The mixture was warmed to room temp. and stirred for a further 2 h. The reaction was quenched with water (3 $cm^3$), filtered and the bulk of the solvent distilled under reduced pressure. The residue was partitioned between dichloromethane (70 $cm^3$) and saturated aqueous sodium hydrogen carbonate (20 $cm^3$) and the organic layer washed with further aqueous sodium hydrogen carbonate (10 $cm^3$) and water (20 $cm^3$). The organic layer was separated, dried over anhydrous magnesium sulfate, filtered and then the solvent removed under reduced pressure. The oil was purified by flash column chromatography using 3:7 diethyl ether–light petroleum (b.p. 40–60 °C) to afford the title compound **6** as a colourless oil (3.20 g, 94%); $\delta_H$(300 MHz) 1.59–2.10 (series of m, 10 H), 4.40 (m, 1 H), 4.51 (m, 1 H), 5.19 (s, 2 H) and 7.23–7.38 (m, 5 H); $\delta_C$(75 MHz) (signals shown in italics were broadened due to slow N–CO rotation) 19.2, 21.2, 21.6, *32.3*, 32.7 (5 × $CH_2$) *51.3* (CH), 67.0 ($CH_2$Ph), 76.2 (CH), 127.9 (2 × CH), 128.3 (CH), 136.5 (C) and 154.1 (NC=O); $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 3035w, 2945s, 2875w, 1715s, 1685s, 1495w, 1435br, 1345m, 1325w, 1300m, 1255w, 1210w, 1150w, 1105s, 1085s, 1035w, 1030w, 1000w, 925w and 870w; *m/z* (%) 261 ($M^+$, 5), 218 (5), 217 (28), 149 (7), 132 (4), 126 (6), 92 (21), 91 (100), 81 (4) and 77 (5) (Found: M, 261.136. $C_{15}H_{19}NO_3$ requires *M*, 261.1365).

cis-4-[(*Benzyloxycarbonyl*)*amino*]*cycloheptanol* **7**.—A solution of compound **6** (2.21 g, 8.47 mmol) in dry ethanol (35 $cm^3$) was buffered with sodium phosphate (5.24 g, 36.9 mmol) and stirred for 5 min at 0 °C. Freshly powdered 6% sodium amalgam (33 g) was added and stirring was continued for 1 h. The mixture was then filtered through Celite, and the solvent removed under reduced pressure. The residue solution was partitioned between dichloromethane (30 $cm^3$) and water (20 $cm^3$). The aqueous layer was extracted with further dichloromethane (2 × 25 $cm^3$)

and then the organic layers were combined and dried over anhydrous magnesium sulfate. After filtration the solvent was removed under reduced pressure to afford the title compound **7** as a white solid [2.18 g, 98%, m.p. 70–72 °C after trituration with light petroleum (b.p. 40–60 °C)] which was used without further purification. This compound was prepared earlier by Iida *et al.*[6] in 84% yield (m.p. 72–74 °C) by treatment of *cis*-4-aminocycloheptanol with benzyl chloroformate and base.

cis-4-(*Methylamino*)*cycloheptanol* **8**.—A 100 $cm^3$ flame-dried two-necked flask fitted with a septum cap and reflux condenser was charged with lithium tetrahydroaluminate (220 mg, 5.79 mmol). Dry tetrahydrofuran (5 $cm^3$) was injected into the flask and the system was alternately evacuated and purged with nitrogen gas. The slurry was cooled with stirring to 0 °C and a solution of compound **7** (970 mg, 3.69 mmol) in dry tetrahydrofuran was introduced. The mixture was heated at reflux for 2 h, cooled to 0 °C and then the minimum of water-saturated diethyl ether necessary was added carefully to destroy excess hydride. The suspension was dried with anhydrous sodium sulfate, filtered through Celite and then the inorganic residues were washed with ethyl ethanoate (2 × 7 $cm^3$). The solvent was removed under reduced pressure from the combined organic extracts to give an oil. This was purified by flash chromatography (to remove benzyl alcohol) using 1:4 methanol–dichloromethane saturated with ammonia, to afford the title compound **8** (495 mg, 94%) as a colourless oil which was identical to a sample prepared[7] by hydrogenation of compound **11**. Partition between organic solvents and aqueous solution was avoided since it led to loss of material into the aqueous layer.

4-[(*Benzyloxycarbonyl*)*amino*]*cycloheptanone* **9**.—A solution of compound **7** (1.02 g, 3.88 mmol) in propanone (18 $cm^3$) was titrated at room temperature with a solution of chromic acid prepared from chromium trioxide (12.35 g), concentrated sulfuric acid (11.5 $cm^3$) and water (20 $cm^3$). A persistent orange–brown colour indicated the endpoint. Excess oxidant was destroyed by the dropwise addition of isopropyl alcohol. The solution was filtered and the solvent was removed under reduced pressure. The residual oil was partitioned between water (15 $cm^3$) and dichloromethane (25 $cm^3$). The aqueous layer was extracted with further dichloromethane (2 × 15 $cm^3$), the organic layers combined and then dried over anhydrous magnesium sulfate. Filtration and evaporation of the solvent afforded an oil. Purification by flash column chromatography [4:1 diethyl ether–light petroleum (b.p. 40–60 °C)] gave the title compound **9** (975 mg, 96%) as a waxy solid; $\delta_H$(300 MHz) 1.41 (m, 1 H), 1.60 (m, 2 H), 1.81 (m, 1 H), 2.03 (m, 2 H), 2.46 (m, 4 H), 3.70 (m, 1 H, NCH), 5.06 (s, 2 H), 5.35 (br d, *J* 7.1, NH) and 7.31 (s, 5 H); $\delta_C$(75 MHz) 20.5, 30.4, 36.2, 39.4, 43.4 (5 × $CH_2$), 52.7 (CH), 66.5 ($CH_2$), 128.0 (2 × CH), 128.4 (CH), 136.5 (C), 155.4 (NC=O) and 213.7 (*C*C=O); $\nu_{max}(CH_2Cl_2)$/$cm^{-1}$ 3440m, 3340br, 3030w, 2930m, 2860w, 1705s, 1500s, 1450m, 1405w, 1365w, 1340w, 1310m, 1215s, 1115m, 1065w, 1035w, 1005m, 910w and 875w; *m*/*z* (CI, %) 262 ($MH^+$, 46), 218 (34), 200 (21), 171 (100), 170 (23), 154 (82), 127 (24), 108 (40), 98 (21), 91 (22) and 84 (25) [Found: M, 262.1443. $C_{15}H_{20}NO_3$ requires ($MH^+$) 262.1443].

8-*Methyl* 8-*azabicyclo*[3.2.1]*octan*-1-*ol* (*Physoperuvine*) **1**.—A solution of compound **8** (97 mg, 0.68 mmol) was oxidised using an identical procedure to that described for the preparation of compound **9**. After removal of propanone under vacuum the residual green solution was dissolved in water (6 $cm^3$) and basified to pH 12 using aqueous sodium hydroxide (1 mol $dm^{-3}$). The water was evaporated under reduced pressure and the residue was extracted continuously with chloroform (25 $cm^3$) for 18 h using a Soxhlet apparatus. After removal of the chloroform under vacuum, the title compound **1** was obtained as a white solid (90 mg, 94%), m.p. 73–74 °C after recrystallisation from light petroleum (b.p. 60–80 °C) (lit.,[1a] m.p. 75 °C); $\delta_H$(300 MHz; 298 K) 1.09 (m, 1 H), 1.47 (m, 2 H), 1.68 (m, 2 H), 1.85 (m, 3 H), 2.01 (m, 2 H), 2.36 (s, 3 H), 3.20 (m, 1 H, NCH) and 5.28 (br s, 1 H, exch.); $\delta_C$(75 MHz; 298 K; $CD_2Cl_2$); signals shown in italics were broadened: 18.3, *23.0* and 25.4 (3 × $CH_2$), *29.9* ($CH_3$), *30.3* ($CH_2$), 35.9 ($CH_2$) and 58.8 (CH); the C-1 signal was not visible at this temperature due to coalescence; $\delta_H$(300 MHz; 223 K; $CD_2Cl_2$) 0.86 (br d, $J \approx 12.6$, 1 H), 1.12 (br d, $J \approx 12$, 1 H), 1.37 (br m, 1 H), 1.47–2.03 (series of m, 7 H), 2.25 (s, 3 H), 3.14 (br d, $J \approx 6$, NCH) and 6.65 (br s, 1 H, exch.); $\delta_C$(75 MHz; 223 K; $CD_2Cl_2$) *bicyclic tautomer*: 18.3, 21.1, 25.4 and 27.8 (4 × $CH_2$), 29.2 ($CH_3$), 36.1 ($CH_2$), 58.1 (C-5) and 88.8 (C-1); *monocyclic tautomer*: (low intensity signals; some broadened; not all signals were visible) 19.6, 30.9, 35.2, 39.0 and 63.3. The ratio of major:minor tautomers was estimated to be approximately 98:2 from integration of the $^{13}C$ NMR signals. $\nu_{max}(CH_2Cl_2)$/$cm^{-1}$ 3570w, 3100br, 2940s, 2850m, 2790w, 1695w, 1475m, 1445w, 1325m, 1195m, 1180w, 1145w, 1115m, 1100w, 1040w, 1010m, 975w, 955w, 925w, 910w, 870m and 805w; *m*/*z* (%) 141 ($M^+$, 65), 140 (7), 113 (60), 112 (70), 99 (57), 98 (85), 84 (36), 71 (21) and 70 (100) (Found: M, 141.1153. $C_8H_{15}NO$ requires *M*, 141.1154).

8-*Azabicyclo*[3.2.1]*octan*-1-*ol* (*Norphysoperuvine*) **2**.—A solution of compound **9** (593 mg, 2.27 mmol) in dry ethanol (24 $cm^3$) was hydrogenated at 1 atm in the presence of a catalytic quantity of 5% palladium on charcoal. After 2 h the solution was filtered through Celite, then through a Millipore 0.2 μ Millex-FG disposable filter. The solvent was removed under reduced pressure to give a sample of good purity as shown by $^1H$ NMR (265 mg, 92%). Recrystallisation from toluene–light petroleum (40–60 °C) afforded the title compound **2** (225 mg, 78%) as a pale yellow solid, m.p. 97–101 °C; $\delta_H$(300 MHz; 298 K) 1.41 (m, 1 H), 1.56 (m, 2 H), 1.75 (m, 2 H), 1.97 (m, 5 H), 3.39 (m, 1 H, NCH) and 3.86 (br m, 2 H, exch.); $\delta_C$(75 MHz; 298 K; signals shown in italics were broadened) 19.3, *28.6*, *33.7*, *36.0*, *39.8* (5 × $CH_2$) and 53.8 (CH), the C-1 signal was not resolved at this temperature; $\delta_H$(300 MHz; 223 K) 1.35–1.97 (series of m, 9 H), 2.12 (m, 1 H) and 3.52 (br d, *J* 5.4, 1 H); $\delta_C$(75 MHz; 223 K) 18.7, 26.9, 31.5, 35.0, 38.7 (5 × $CH_2$), 53.3 (CH) and 89.5 (C); $\nu_{max}(CH_2Cl_2)$/$cm^{-1}$ 3660w, 3570w, 3080br, 2930s, 2860m, 1695m, 1590br w, 1445w, 1375w, 1350w, 1325w, 1315w, 1225w, 1185m, 1120m, 1085w, 1025m, 985w, 950w and 880w; *m*/*z* (%) 127 ($M^+$, 81), 99 (80), 98 (76), 85 (30), 84 (67), 82 (7), 71 (16) and 70 (100) (Found: M, 127.0996. $C_7H_{13}NO$ requires *M*, 127.0997).

cis-4-[(*Benzyloxycarbonyl*)*amino*]*cyclohept*-2-*enol* **10**.—A solution of compound **5** (3.12 g, 12.0 mmol) in dry ethanol (75 $cm^3$) was stirred at 0 °C with sodium phosphate (7.70 g, 54.2 mmol) for 5 min. Freshly prepared and powdered 6% sodium amalgam* (44 g) was added to it and stirring was continued at 0 °C for 30 min. The mixture was filtered through Celite and the bulk of the solvent distilled under reduced pressure. The residual solution was partitioned between water (40 $cm^3$) and dichloromethane (70 $cm^3$). The aqueous layer was extracted with further $CH_2Cl_2$ (2 × 40 $cm^3$) and the organic layers combined and dried over anhydrous magnesium sulfate. Filtration and evaporation of the solvent left a solid which was

* A preliminary attempt[5] using sodium amalgam as described above produced only 7% of compound **10**; we now assume that the amalgam used in this case had become deactivated.

recrystallised from ethanol to afford the title compound **10** (2.82 g, 90%) as a white solid, m.p. 143–144 °C (Found: C, 69.1; H, 7.1;, N, 5.3. $C_{15}H_{19}NO_3$ requires: C, 68.94; H, 7.33; N, 5.36%). Spectroscopic properties were identical to those of a sample prepared earlier by a different route and isolated as an oil (compound **4e** in ref. 5 where it was obtained in 95% yield from *cis*-4-aminocyclohept-2-enol by reaction with base followed by benzyl chloroformate).

cis-4-(*Methylamino*)*cyclohept-2-enol* **11**.—This compound[7] was prepared by reduction of compound **10** with lithium tetrahydroaluminate using the method described above for compound **8**. The yield was improved to 95% by working up the reaction mixture using diethyl ether saturated with water to destroy the excess hydride. The ethereal solution was then dried with magnesium sulfate, filtered and evaporated, and then the product was chromatographed using methanol–dichloromethane (1:19) saturated with ammonia. The oily product crystallised on standing. As in the preparation of compound **8**, partition between organic solvents and aqueous solution was avoided since it led to losses.

4-[(*Benzyloxycarbonyl*)*amino*]*cyclohept-2-enone* **12**.—A solution of compound **11** (792 mg, 3.03 mmol) in dichloromethane was stirred at room temperature. Barium manganate (8.50 g, 33.2 mmol) was added to it and stirring was continued for a further 36 h. The slurry was filtered through Celite and the inorganic residues were washed firstly with dichloromethane (2 × 15 $cm^3$) and then with warm ethyl acetate (2 × 15 $cm^3$). The solutions were combined and the solvent was removed under reduced pressure. The residual oil was purified by flash column chromatography [1:1 diethyl ether–light petroleum (40–60 °C)] to afford the title compound **12** as a pale yellow solid (657 mg, 84%), m.p. 56–58 °C [from toluene–light petroleum (40–60 °C)] (Found: C, 69.5; H, 6.5; N, 5.2. $C_{15}H_{17}O_3N$ requires: C, 69.48; H, 6.61; N, 5.40%); $\delta_H$(300 MHz) 1.77 (m, 3 H), 2.11 (m, 1 H), 2.54 (m, 2 H), 4.53 (m, 1 H), 5.08 (s, 2 H, C$H_2$Ph), 5.69 (br d, *J* 8.0, NH), 5.92 (dd, *J* 12.4, 2.2, 1 H), 6.34 (dd, *J* 12.4, 2.9, 1 H) and 7.31 (s, 5 H); $\delta_C$(75 MHz) 18.9, 32.9, 42.9 (3 × $CH_2$), 51.6 (NCH), 66.8 ($CH_2$Ph), 128.0, 128.1, 128.5 (3 × ArCH), 130.9 (=CH), 136.2 (ArC), 146.7 (=CH), 155.6 (C=O) and 202.9 (C=O); $\nu_{max}(CH_2Cl_2)$/$cm^{-1}$ 3440m, 3325br, 3030w, 2960m, 2870w, 1715s, 1665s, 1585w, 1500s, 1450m, 1215s, 1155w, 1125w, 1050w, 1020m, 980w, 900w and 795w; *m*/*z* (%) 259 ($M^+$, 4), 241 (3), 215 (18), 198 (6), 172 (12), 168 (16), 159 (21), 140 (6), 124 (17), 110 (66) and 91 (100).

4-(*Methylamino*)*cyclohept-2-enone* **3a** {⇄8-*Methyl*-8-*azabicyclo*[3.2.1]*oct*-6-*en*-1-*ol* (6,7-*Dehydrophysoperuvine*) **3b**}.—A solution of the amino alcohol **10** (48 mg; 0.34 mmol) in propanone (7 $cm^3$) was acidified with trifluoroethanoic acid (30 $mm^3$, 0.39 mmol) at ambient temperature. The solution was titrated with Jones reagent and stirred for a further 5 min before the addition of excess isopropyl alcohol. The solution was filtered and the solid washed with methanol (2 × 5 $cm^3$). The organic solvent was distilled off under reduced pressure and the residual oil was dissolved in water (5 $cm^3$), and the solution was basified to pH 12 using aqueous sodium hydroxide (2 mol $dm^{-3}$). The solution was extracted with ethyl ethanoate (3 × 7 $cm^3$), the organic layers were combined, dried ($MgSO_4$), filtered, and then the solvent distilled off under reduced pressure to afford the amino ketone **3** as an oil (19 mg; 40%). The compound decomposed during chromatography. Salts of the amine were not easy to handle, for example, the $HBF_4$ salt separated from dry diethyl ether solution as an oil and a pure sample was not obtained. The free amine decomposed over a period of hours. $\delta_H$(300 MHz) 1.75–2.76 (series of m, 6 H), 2.59 (s, 3 H), 3.74 (m, 1 H), 6.01 (dd, *J* 10.2, 0.9, 1 H) and 6.35 (dd, *J* 10.2, 3.2, 1 H); $\nu_{max}(CH_2Cl_2)$/$cm^{-1}$ 3040w, 2920m, 2840w, 2790w, 1665s with shoulders at 1755w and 1700m, 1425w, 1200s, 1180m, 1140m and 905s; *m*/*z* (%) (measured using **3**·HCl) 140 ($MH^+$, 32), 139 ($M^+$, 100), 124 (22), 113 (43), 112 (43), 111 (54), 110 (40), 98 (43), 96 (28), 83 (98), 82 (58), 70 (62), 69 (27), 68 (97), 57 (63) and 55 (91).

The application of other oxidation conditions failed, giving complex product mixtures and/or unchanged starting material. Reagents included barium manganate,[8] pyridinium dichromate, Jones reagent (without TFA) and tetrapropylammonium perruthenate–*N*-methylmorpholine *N*-oxide.[17]

4-(*Benzylamino*)*cyclohept-2-enone* **13a** {⇄8-*Benzyl*-8-*azabicyclo*[3.2.1]*oct*-6-*en*-1-ol **13b**}.—A solution of *cis*-4-(benzylamino)cyclohept-2-enol[5] (84 mg; 0.39 mmol) in propanone (12 $cm^3$) was cooled to 0 °C and acidified with trifluoroethanoic acid (60 $mm^3$; 0.62 mmol). The solution was titrated with Jones reagent until an orange–brown colour persisted and then excess oxidant was destroyed immediately by addition of excess isopropyl alcohol. The solution was filtered through Celite and the remaining solid washed with propanone (3 × 4 $cm^3$). The bulk of the solvent was distilled off under reduced pressure and the resulting green oil was dissolved in water and basified to pH 12 with aqueous sodium hydroxide (2 mol $dm^{-3}$). The solution was extracted with ethyl ethanoate (3 × 10 $cm^3$), the organic layers were combined, washed with brine and then dried ($MgSO_4$). Separation, filtration and distillation of the solvent under reduced pressure afforded the amino ketone **13** as a pale yellow oil (71 mg; 85%) which was approximately 90% pure (NMR integration) but decomposed on standing in solution; $\delta_H$(300 MHz) 1.75 (m, 3 H), 2.11 (m, 1 H), 2.52 (m, 2 H), 3.55 (m, 1 H), 3.84 (ABq, *J* 13.1, 2 H, C$H_2$Ph), 5.97 (ddd, *J* 12.3, 2.3, 1.0, 1 H), 6.56 (ddd, *J* 12.3, 3.7, 1.0, 1 H) and 7.32 (m, 5 H); $\delta_C$(75 MHz) 19.1, 32.2, 42.7 (3 × $CH_2$), 51.5 ($CH_2$Ph), 56.7 (NCH), 127.1, 128.1, 128.5 (3 × ArCH), 130.7 (=CH), 139.5 (ArC) and 149.5 (=CH); the cycloheptenone carbonyl signal was observed only at 233 K ($\delta_C$ 204.8). The $^{13}C$ NMR spectrum at 233 K showed additional signals but the peaks could not be fully assigned; pronounced broadening of the minor signals was probably associated with slow inversion at nitrogen in the bicyclic tautomer. $\nu_{max}(CH_2Cl_2)$/$cm^{-1}$ 3380br w, 3030w, 2940s, 2870m, 1665s with shoulders at 1755w and 1705m, 1610w, 1495w, 1455m, 1395w, 1340w, 1200m, 1140w, 1105w, 1070w, 1030w, 980w and 910s; *m*/*z* (%) (measured using **13**·HCl) 216 ($MH^+$, 14), 215 ($M^+$, 16), 133 (11), 126 (19), 121 (14), 106 (16), 105 (45), 104 (11), 98 (45), 92 (16), 91 (100) and 77 (25) (Found: M, 215.1309. $C_{14}H_{17}NO$ requires *M*, 215.1310).

Attempts to obtain a salt with anhydrous $HBF_4$ in diethyl ether gave only a gum. Passage of anhydrous HCl through a diethyl ether solution of the amino ketone **13** gave a salt which could not be recrystallised but was partially purified by trituration with anhydrous diethyl ether; it was hygroscopic and deteriorated on standing in air.

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