Tetrahedron Letters, Vol.33, No.2, pp. 277-280, 1992
Printed in Great Britain

0040-4039/92 $3.00 + .00
Pergamon Press plc

MONO-/BICYCLIC TAUTOMERISM IN 4-HYDROXY- AND 4-AMINO-CYCLOOCTANONES AND -OCTENONES

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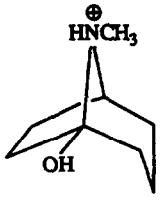
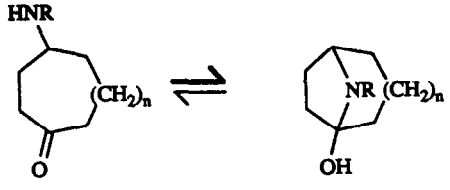
Abstract: 4-Hydroxycyclooctanone and 4-hydroxycyclooct-2-enone are shown to be in equilibrium with their respective bicyclic tautomers; the corresponding 4-aminocyclooctanones and -oct-2-enones have been synthesised and these amino-ketones show similar behaviour. The position of equilibrium varies with substitution (and with temperature in some cases).

The alkaloid physoperuvine has been shown to exist exclusively in the bicyclic amino-alcohol form (1) as the hydrochloride salt but CD and IR data suggest the existence of a tautomeric equilibrium (2) ⇌ (3) for the free base.[1] More recently, investigation of the calystegines has shown that these hydroxylated derivatives of the 1-hydroxy-8-azabicyclo[3.2.1]octane (1-hydroxynortropane) skeleton exist entirely in the bicyclic form.[2] In this paper, we report the observation of tautomeric equilibria in higher homologues of physoperuvine. Mono-/bicyclic ratios are measured by direct NMR methods for 4-aminocyclooctanones (4 ⇌ 5) and also for 4-aminocyclooct-2-enones and the corresponding hydroxy-ketones.



(1)
physoperuvine hydrochloride

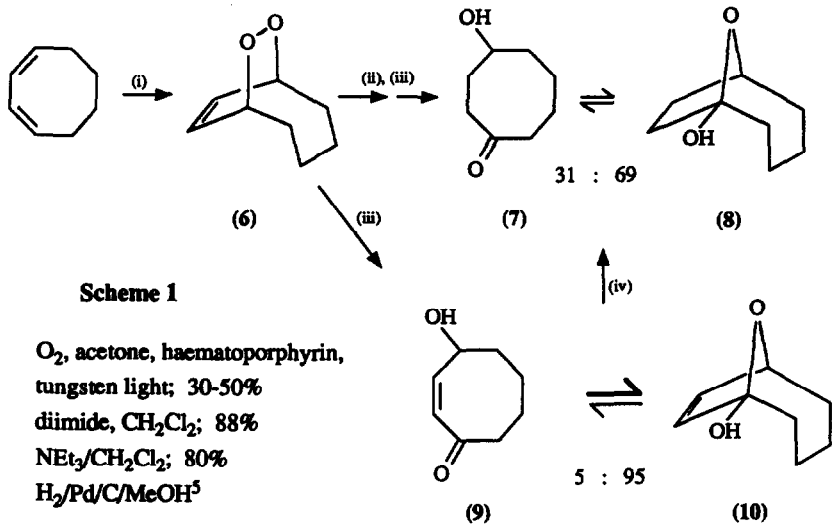


(2) n=1
(4) n=2

(3) n=1
(5) n=2

The synthetic approach to these compounds was based on the addition of singlet oxygen to cycloocta-1,3-diene to yield (6).[3] (Scheme 1)

Reduction of (6) with diimide followed by treatment with triethylamine gave 4-hydroxycyclooctanone, formerly considered to be the monocycle (7),[4] which can be seen by high resolution NMR to be the minor tautomer in equilibrium with 69% of the bicyclic form (8).[9]

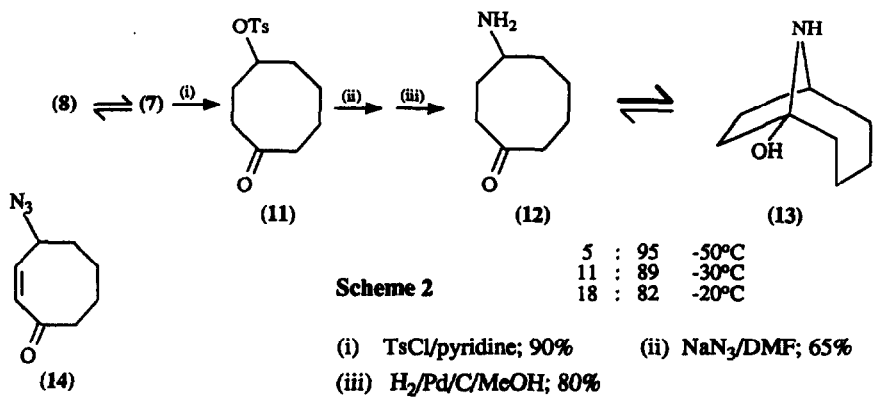


Scheme 1

(i) O_2, acetone, haematoporphyrin, tungsten light; 30-50%
(ii) diimide, CH_2Cl_2; 88%
(iii) NEt_3/CH_2Cl_2; 80%
(iv) $H_2/Pd/C/MeOH$[5]

Treatment of (6) with triethylamine gave the unsaturated analogue (10) which had formerly been thought to be formed irreversibly from (9)[3,4] but which in fact shows signals in the ^{13}C NMR spectrum corresponding to the presence of *ca.* 5% of the monocyclic tautomer (9) at equilibrium.[10] The hydroxy-ketone/hemiacetal equilibrium is finely balanced but the greater preference for the bicyclic (10) on incorporation of the shorter carbon-carbon double bond into the ring system is, perhaps, surprising.

Treatment of (7) ⇌ (8) with tosyl chloride/pyridine led slowly to preferential production of the secondary tosylate (11). Conversion into the azide followed by hydrogenation gave the amino-ketone/amino-alcohol mixture (12) ⇌ (13). Interconversion was relatively slow on the NMR time scale at ambient temperature as shown by broad ^1H and ^{13}C NMR signals but the two tautomers were discernible at lower temperatures as indicated in Scheme 2. The ratio was temperature-dependent as demonstrated by VT NMR and also by VT IR measurements which showed a gradual reduction in the intensity of the carbonyl signal at 1695 cm^{-1} as the temperature of a solution in CH_2Cl_2 was lowered.

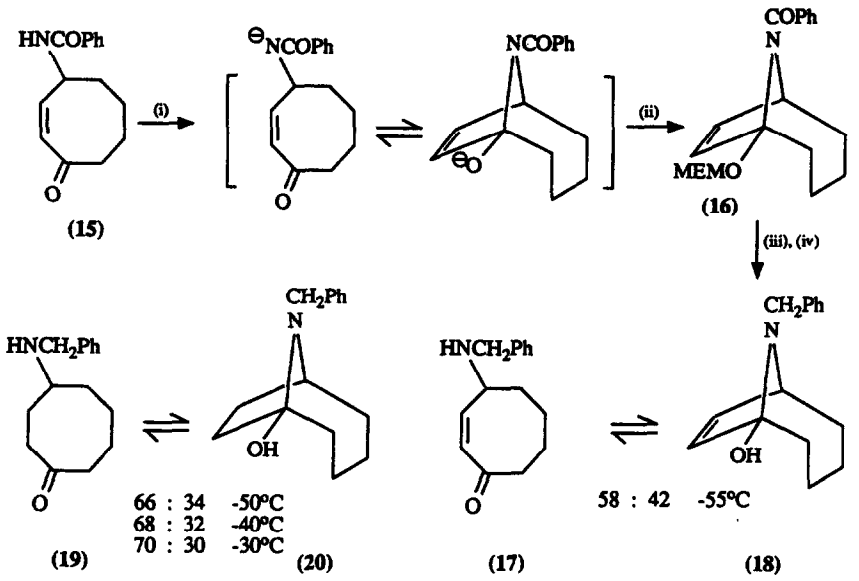


Scheme 2

5 : 95 -50°C
11 : 89 -30°C
18 : 82 -20°C

(i) TsCl/pyridine; 90% (ii) NaN_3/DMF; 65%
(iii) $H_2/Pd/C/MeOH$; 80%

An attempt to follow a similar approach to prepare the unsaturated analogues was thwarted by difficulties with the reduction of the unstable unsaturated azido-ketone (**14**). An alternative approach to the N-benzyl compounds is summarised in Scheme 3.



Scheme 3

(i)	n-BuLi/THF/0°C	(ii)	MEM chloride (65% overall)
(iii)	$LiAlH_4$/THF; 85%	(iv)	TFA/CH_2Cl_2/0°C → RT; 86%

Treatment of the unsaturated amido-ketone (**15**)[6] with base gave the anion(s) which reacted with MEM chloride to yield the protected bicyclic amido-alcohol (**16**). The tautomeric mixture (**17**) ⇌ (**18**)[11] was obtained by reduction of the benzoyl group followed by deprotection with acid.[8] The saturated analogues (**19**) ⇌ (**20**)[12] were obtained in a similar manner starting from the saturated amido-ketone.[7]

The tautomeric equilibrium for the primary amino-ketone (**12**) favours the azabicycle (**13**); the situation is reversed in the case of the secondary amino-ketone (**19**) which is now preferred over the bicyclic (**20**) [c.f. physoperuvine, which has been estimated[1] to exist almost entirely as the bicyclic tautomer (98%)]. Some preliminary studies of the variation with temperature are shown in the schemes but solvent effects have not yet been investigated. Incorporation of a double bond into the amino-ketone system in (**17**) disturbs the balance marginally towards the bicyclic tautomer (**18**) (42% at 218 K compared with 34% of (**20**) at 223 K) but the effect here is less pronounced than for the hydroxy-ketones. The results to date suggest the operation of a delicate balance of structural and environmental factors and do not allow for easy rationalisation at present.

We thank the SERC for a studentship to C.S. and the SERC Mass Spectrometry service at Swansea for high-resolution mass spectra.

References.

1. A.B. Ray, Y. Oshima, H. Hikino and C. Kabuto, *Heterocycles*, **1982**, *19*, 1233. The physoperuvine structure was shown by these authors to be based on the 4-aminocycloheptanone ring system rather than 3-aminocycloheptanone as originally proposed. See also A.T. MacPhail and A.R. Pinder, *Tetrahedron*, **1984**, *40*, 1661.

2. P.-H. Ducrot and J.Y. Lallemand, *Tetrahedron Lett.*, **1990**, *31*, 3879; P.-H. Ducrot, J. Beauhaire and J.Y. Lallemand, *ibid*, 3883.

3. Y. Kayama, M. Oda and Y. Kitahara, *Chem. Lett.*, **1974**, 345.

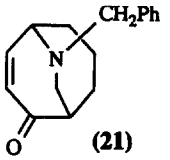
4. C.f. M. Barrelle and M. Apparu, *Bull. Soc. Chim. France*, **1972**, 2016.

5. The O-methyl derivative of (**8**) was also formed as a major product when methanol was used as solvent.

6. The unsaturated amido-ketone (**15**) was prepared from the amido-alcohol [see preceding paper, compound (**7**)] by treatment with $BaMnO_4$ in CH_2Cl_2 (80% yield).

7. The saturated analogue of (**15**) was obtained by Jones oxidation of the amido-alcohol [see preceding paper, compound (**8**) and Scheme 3].

8. Attempted deprotection using titanium tetrachloride led, unexpectedly, to formation of the rearranged bicyclic amine (**21**). This structure followed from a full NMR spectroscopic analysis which will be reported later.



(**21**)

Selected spectroscopic data.

The signals shown in italics for each tautomeric pair actually overlapped to give complex multiplets; they are quoted separately for reasons of clarity.

9. ^{1}H NMR (300 MHz, $CDCl_3$, 300 K): (**7**) δ *1.3-2.6* (complex, 12H), *3.2* (br.s, OH), 3.83 (dddd J ≈ 8.4, ~4.8, ~4.8, ~4.5 Hz, 1H); (**8**) δ *1.3-2.6* (complex 12H), 4.52 (dddd J = 8.4, 6.9, ~2, ~2 Hz, 1H), *3.2* (brs, OH). ^{13}C NMR (75 MHz, $CDCl_3$, 300 K): (**7**) δ 21.9(t), 28.7(t), 30.5(t), 33.6(t), 39.5(t), 40.2(t), 70.7(d), 217.0(s); (**8**) δ 23.3(t), 23.8(t), 31.2(t), 36.4(t), 37.1(t), 41.7(t), 76.0(d), 108.3(s).

10. ^{1}H NMR (300 MHz, $CDCl_3$, 300 K): (**9**) δ *1.4-1.7* (m, 6H), 2.53 (vbr.dd J = 13.2, 6.3 Hz, 1H), 2.74 (ddd J = 13.2, 11.8, 6.9 Hz, 1H), 3.97 (br.s, OH), 5.20 (vbr.m, 1H), 6.03 (ddd J = 12.7, 1.9, 1.9 Hz, 1H), 6.38 (dd J = 12.7, 5.5 Hz, 1H); (**10**) δ *1.4-1.7* (m, 5H), 1.85-2.02 (m, 3H), 4.26 (s, OH), 4.96 (dd J = 6.3, 1.2 Hz, 1H), 5.78 (dd J = 5.8, 1.2 Hz, 1H), 5.96 (dd J= 5.8, 1.9 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): (**9**) δ 22.2(t), 23.0(t), 33.6(t), 42.1(t), 69.2(d), 131.5(d), 148.8(d), 202.0(s); (**10**) δ 23.1(t), 23.7(t), 33.4(t), 39.3(t), 81.3(d), 111.5(s), 132.7(d), 133.8(d).

11. ^{1}H NMR (300 MHz, $CDCl_3$): (**17**) δ *1.2-2.1* (complex, 6H), 2.53 (m, 1H), 2.78 (m, 1H), 3.72, 3.90 (AB J = 12.7 Hz, 2H), 4.23 (m, 1H), 6.25 (br.d J = 12.4 Hz, 1H), 6.40 (br.dd J= 12.4, 6.2 Hz, 1H), *7.2-7.7* (m, 5H); (**18**) δ *1.2-2.1* (complex, 8H), 3.80 (br, 1H), 4.12, (AB J = 14.6 Hz, 2H), 5.93 (s, 2H), *7.2-7.7* (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$): (**17**) δ 22.7(t), 22.8(t), 31.1(t), 42.1(t), 52.1(t), 55.3(d), 127.2(d), 128.3(d), 128.5(d), 134.8(d), 138.8(s), 149.9(d), 203.3(s); (**18**) δ 21.4(t), 23.0(t), 28.7(t), 36.3(t), 45.7(t), 60.1(d), 94.7(s), 126.4(d), 127.9(d), 128.1(d), 133.2(d), 137.4(d), 140.6(s). ^{m}/z calc. for $C_{15}H_{19}NO$: 229.1467; found: 229.147.

12. ^{1}H NMR (300 MHz, $CDCl_3$, 233 K): (**19**) δ *1.2-2.5* (complex, 12H), 2.73 (br.m, 1H), 3.76 (AB J = 13.4 Hz, 2H), *7.2-7.5* (m, 5H); (**20**) δ *1.2-2.5* (complex, 12H), 3.31 (br.m, 1H), 4.03 (AB J = 14.2 Hz, 2H), *7.2-7.5* (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$, 233 K): (**19**) δ 22.7(t), 28.1(t), 28.5(t), 30.1(t), 40.0(t), 40.7(t), 51.0(t), 56.1(d), 126.9(d), 128.0(d), 128.4(d), 139.8(s), 218.6(s); (**20**) δ 22.6(t), 23.5(t), 26.0(t), 32.0(t), 38.2(t), 40.9(t), 45.7(t) 54.2(d), 92.2(s), 126.4(d), 127.8(d), 128.1(d), 140.8. ^{m}/z calc. for $C_{15}H_{21}NO$: 231.1623; found: 231.162.

(Received in UK 21 October 1991)