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BICYCLIC BASES[1]

SYNTHESIS AND NUCLEAR MAGNETIC RESONANCE INVESTIGATION OF SOME CHIRAL 2-OXA-5-AZABICYCLO[2.2.1]HEPTANE DERIVATIVES[2,3]

P. S. PORTOGHESE and J. G. TURCOTTE
Department of Medicinal Chemistry, College of Pharmacy, University of Minnesota, Minneapolis, Minnesota 55455

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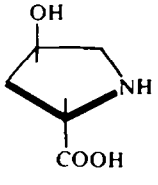
Abstract—The N-benzoyl derivatives of 2-oxa-5-azabicyclo[2.2.1]heptane (**7**) and of 2-oxa-5-azabicyclo [2.2.1]heptane-3-one (**8**) have been prepared from hydroxy-L-proline. The NMR spectra of these compounds have been analyzed with the aid of variable temperature studies. It was found that $\Delta G^{\ddagger}$ for N–CO rotation in **7** is ~2 Kcal/mole higher than for **8**. Possible explanations for the difference in $\Delta G^{\ddagger}$ are discussed.

IN PREVIOUS reports[1,4] we have described the synthesis and biological properties of chiral piperidine and piperazine derivatives. We now report on a synthesis of the 2-oxa-5-azabicyclo[2.2.1]heptane skeleton and studies utilizing this system as a model to investigate the influence of a proximal CO group on rotation of an amide N—CO bond. Information relating to the effect of a noncontiguous CO group on amide rotation has not been reported and would be particularly relevant to proteins where such dipoles have the potential for coulombic interaction.

The synthetic route utilized configurationally known *trans*-3-hydroxyproline (**1**) as starting material. The benzamide (**2**), prepared by a conventional benzoylation procedure, was treated with diazomethane to afford methyl ester **3**. Tosylation of **3** in pyridine afforded **4** which was selectively reduced with $LiBH_4$ to the primary alcohol (**5**). Cyclization to the desired bridged system (**7**) was effected in 90% yield



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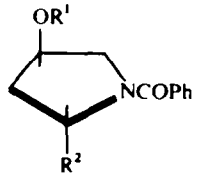
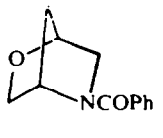


	R^1	R^2
2	H	COOH
3	H	COOMe
4	Ts	COOMe
5	Ts	CH_2OH
6	Ts	COOH

by refluxing a methanolic solution of **5** containing an equivalent of NaOMe. There was no evidence of base-catalyzed elimination or displacement of the tosyloxy group by methoxide.

Saponification of methyl ester **4** under controlled conditions gave the corresponding acid (**6**) which was converted to the lactone (**8**) according to the procedure of Patchett and Witkop.[5] The chiralities of **7** and **8** are as depicted since the starting material (**1**) for the synthetic possesses the (2*S*) configuration.



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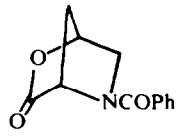

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Interpretation of the NMR spectrum of 7 was carried out on the 110° spectrum (Fig 1) because broadened signals were obtained at ambient temperature due to

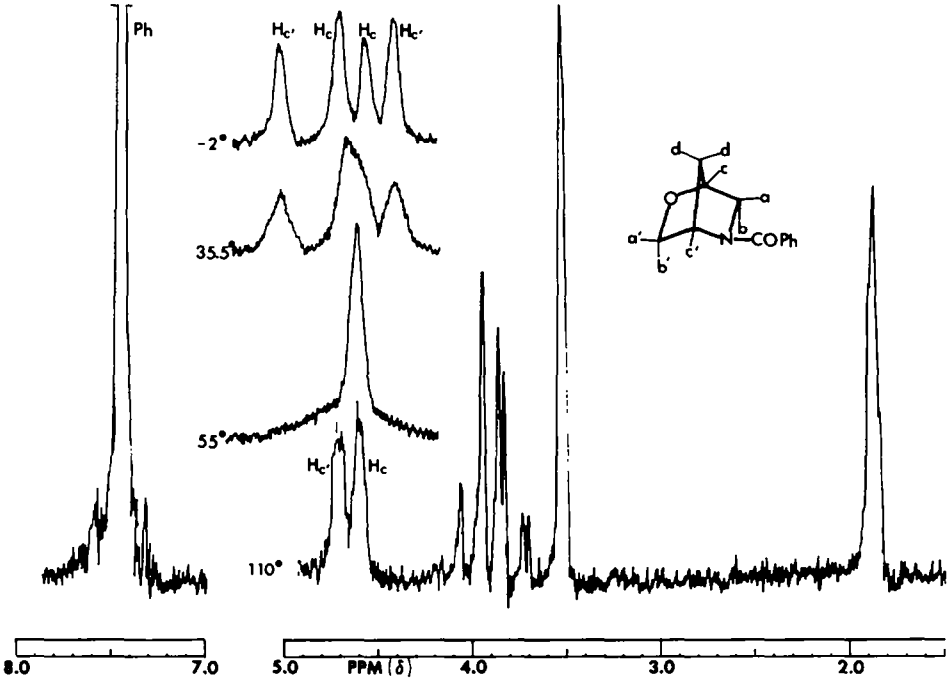


FIG 1. The variable temperature 60 MHz nuclear magnetic resonance spectrum of 2-oxa-5-azabicyclo[2.2.1]heptane (7) in $CDCl_3$

slow rotation of the amide linkage. Assignment of the bridgehead protons was based on the reasonable assumption that $H_{c'}$ should be more sensitive than H_c to temperature change, since the former is adjacent to the benzoyl group. It can be seen that the peak (110°) corresponding to $H_{c'}$ (δ 4·7) undergoes maximal broadening at $\sim$ 55° and forms two well-defined peaks of near-equal integrals at 36°. The signal corresponding to H_c (δ 4·6), on the other hand, is broadened to a lesser extent at its coalescence temperature (36°) because of the much smaller chemical shift difference between H_c in the rotational isomers. This is clearly indicated by the $-2°$ spectrum. The doublet at δ 3·93 (J_{ab} = 7·5 Hz) is assigned to H_b, as no coupling with H_c is predicted by the Karplus equation when the dihedral angle is approximately 90°.[6] The doublet of doublets centered at δ 3·78 has been assigned to H_a by virtue of its ability to couple with both H_c (J = 1·8 Hz) and H_a. A similar relationship has been reported for bornane and norbornane derivatives[7] and for 2,5-diazanorbornane.[1] The collapse

of the doublet of doublets to a doublet upon irradiation of H_c confirmed this assignment. The peak integrating for two protons at δ 3·51 corresponds to H_a and H_b. The bridge protons (H_d) are seen as a singlet at δ 1·87 which is in the region where bridge protons have been shown to absorb in heterobicyclo[2.2.1]heptane derivatives.[4, 8]

The ambient temperature (40°) NMR spectrum for the lactone (**8**) is shown in Fig. 2. The bridgehead protons were assigned from variable temperature studies. As the temperature was lowered the δ 4·73 resonance broadened and was clearly

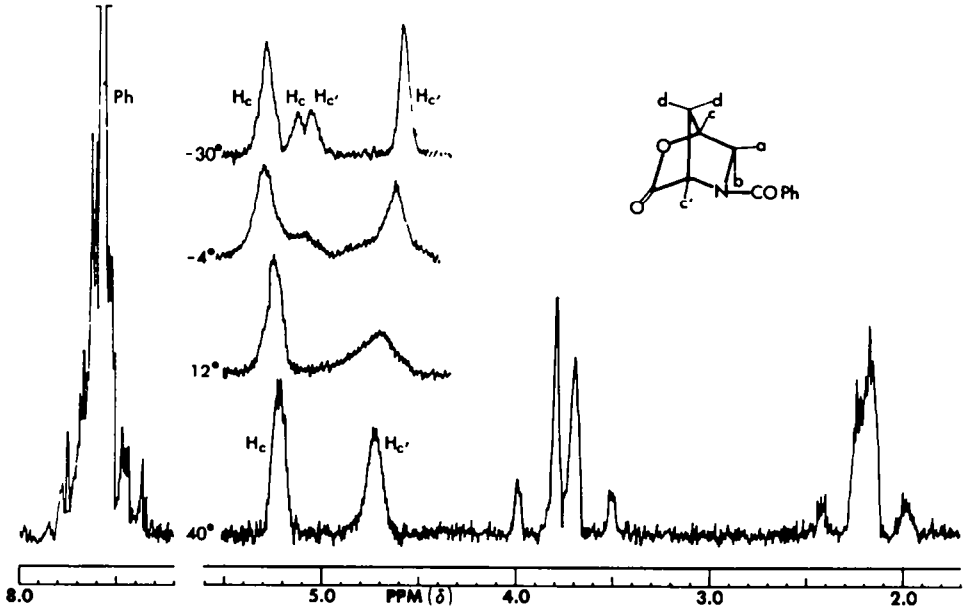
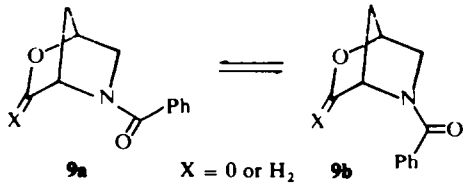


FIG 2. The variable temperature 60 MHz nuclear magnetic resonance spectrum of 2-oxa-5-azabicyclo[2.2.1]heptane-3-one (**8**) in $CDCl_3$

visible as two peaks at $-30°$. This also occurred with the singlet at δ 5·24 (40°) and it is evident that the chemical shift difference for the same proton in different conformers (at $-30°$) is considerably smaller than that observed for the two peaks derived from the δ 4·73 resonance. The above data indicates $H_{c'}$ to be associated with δ 4·73 signal and H_c with δ 5·24. The H_a and H_b chemical shifts (δ 3·88 and δ 3·68) are fairly close to those found for **7**. It can be noted that, while the 40° spectrum shows a doublet rather than a doublet of doublets for H_a, the peaks are broader ($W_{1/2}$ = 3·5 Hz) than the doublet corresponding to H_b ($W_{1/2}$ = 2·5 Hz). This is consistent with the assignment since, as in the case of **7**, H_a—H_c coupling should be greater than H_b—H_c coupling by virtue of the dihedral relationship.



9a X = 0 or H_2 **9b**

The mean lifetime for rotamers **9a** and **9b** were calculated according to the method of Gutowsky and Holm.[9] The $\Delta G^{\ddagger}$ values for the conformational interconversion were obtained from the Eyring equation.[10] The activation data disclose (Table 1) that interconversion occurs with greater facility for lactone **8**. The observed difference, $\Delta\Delta G^{\ddagger} \sim 2$ Kcal/mole, could be due to differences in $\Delta S^{\ddagger}$ and $\Delta H^{\ddagger}$, although it is more probable that the latter is primarily responsible since **7** and **8** both possess a rigid ring system.

TABLE 1. NMR[a] AND ACTIVATION DATA FOR CONFORMATIONAL INTERCONVERSION OF **7** AND **8**

Compound	Bridgehead protons	$\Delta\nu$ (Hz)[b]	Tc[c]	k (sec^{-1})	ΔG (KCal/mole)[d]
7	H_c	8[e]	35·5°[g]	18	16·3 ± 0·2
	$H_{c'}$	36[e]	55°[h]	80	16·9 ± 0·5
8	H_c	10[f]	−4°[i]	22	14·1 ± 0·5
	$H_{c'}$	29[f]	12°[i]	64	14·2 ± 0·3

[a] Determined at 60 MHz in $CDCl_3$

[b] Maximum peak separation

[c] Coalescence temperature

[d] Values are the mean of 5 determinations

[e] Obtained at −2°

[f] Obtained at −30°

[g] Obtained from direct observations of coalescence; thought to be correct within ±2°

[h] Obtained from maximum peak width at half-height; due to the broadness of this peak and interference by the H_c signal, T_c is thought to be correct within ±3°

[i] Obtained from maximum peak width at half-height; thought to be correct within ±2°

Factors which conceivably may alter interconversion rates **9a** ⇄ **9b** are:

(1) Change in the inductive effect on the nitrogen. It is possible that a −I effect of the lactone CO group in **8** would have an accelerating effect on amide rotation when compared to **7**.

(2) Subtle differences in the geometry of the bicyclic system due to the fact that C-3 is hybridized differently in **7** and **8**. It is difficult to predict to what extent this would affect amide rotation.

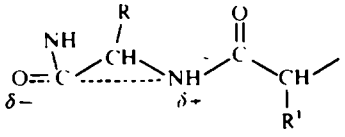
(3) Coulombic interaction between C=O dipoles. Since −4° spectrum of **8** shows two pairs of peaks corresponding to bridgehead protons in area ratios of ~0·3:1, this suggests the presence of a dipolar interaction. However, the direction and magnitude of an effect of this type on amide rotation is unknown.

(4) Interaction of the nitrogen lone pair with the lactone carbonyl carbon to form resonance contributor **10**. This is analogous to the delocalized resonance form of homoenolate ions proposed by Nickon, *et al.*[11] The normal resonance contributor

10 **11**

(11) would be reduced as a result of the decreased availability of the nitrogen lone pair, and this should result in a lower rotational barrier. The ether (7) would be incapable of entering into homoconjugation of this type and hence its rotational barrier would be higher. The higher amide CO stretching frequency (1625 cm^{-1}) for 8, when compared to that of 7 (1613 cm^{-1}) ($CHCl_3$ solvent), is consistent with this suggestion. A somewhat similar situation has been reported[12] for N-vinyl substituted amides in that the π orbitals of vinyl group overlap with the nitrogen lone pair, thereby lowering the energy barrier for N-CO rotation.

If orbital overlap of the type described in case 4 is responsible for the lower rotational barrier in 8, it is possible that a similar relationship exists among peptide residues of a protein in cases where a noncontinuous N atom and CO group adopt a conformation (12) approximating that found in the bicyclic system. Under these conditions a "stiff" peptide linkage might become more freely rotating.



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EXPERIMENTAL

M.ps were determined on a Thomas–Hoover capillary m.p. apparatus and are uncorrected. Standard IR spectra were obtained on a Perkin–Elmer 237B spectrophotometer and high resolution spectra were obtained with a Perkin–Elmer 521 spectrophotometer. Variable temp (accurate to $\pm 1°$) studies were carried out on an A-60D spectrometer. The chemical shift values are considered to be within δ $\pm$0·02 and the spin–spin coupling constants are within $\pm$0·02 Hz of the values reported. $CDCl_3$ containing 1% TMS and solute concentrations of 15% (w/v) were employed. Specific rotations were determined with a Perkin–Elmer 141 polarimeter.

N-Benzoylhydroxy-L-proline (2). To compound 1[13] (5·0 g, 0·038 mole) dissolved in cold 1 N NaOH (0·10 mole, 100 ml) was added freshly distilled benzoyl chloride (6·0 ml, 0·043 mole) in Et_2O (100 ml) and the mixture agitated on a mechanical shaker for about 24 hr. The ether layer was separated and the aqueous soln was washed with Et_2O, cooled in an ice-bath, and acidified with conc HCl. The solid was collected (filtration), washed with several portions of Et_2O to remove residual benzoic acid, and was dried to obtain 8·01 g (90%) of product. Recrystallization (twice) from H_2O gave dense crystals, m.p. 194–196°, $[\alpha]_D^{26}$ −131·9° (*c* 1·32, EtOH); λ_{max} 1630 (*tert*-amide CO), 1715 (COOH), and 3540 cm^{-1} (OH). (Found: C, 61·25; H, 5·68; N, 5·80. Calcd for $C_{12}H_{13}NO_4$: C, 61·27; H, 5·57; N, 5·95%).

N-Benzoylhydroxy-L-proline methyl ester (3). A cooled soln of 2 in 25 ml anhyd MeOH was treated with ethereal CH_2N_2 with stirring until a yellow color persisted. The mixture was heated on a steam bath, and the soln then was concentrated under reduced pressure to a small volume. Crystallization of the crude solid from EtOAc (twice) afforded 3 (5·20 g, 98%), m.p. 145–146°, $[\alpha]_D^{26}$ −139·2° (*c* 1·15, EtOH); λ_{max} 1615 (*tert*-amide CO), 1740 ($COOCH_3$), and 3540 cm^{-1} (OH). (Found: C, 62·80; H, 6·06; N, 5·67. Calcd for $C_{13}H_{15}NO_4$: C, 62·64; H, 6·06; N, 5·62%).

N-Benzoyl-O-tosylhydroxy-L-proline methyl ester (4). Compound 3 (5 g, 0·02 mole) was dissolved in anhydrous pyridine (10 ml) and the soln cooled in an ice-salt bath. Tosyl chloride (4·2 g, 0·002 mole) dissolved in pyridine (5 ml) was added to the cooled soln and the mixture was maintained at 5° for 60 hr. The mixture then was cooled and ice-cold 2 N HCl (85 ml) was added. The crude material which solidified after standing 8 hr at 5° was triturated, rinsed with cold water, and dried to yield 7·6 g (94%) of an amorphous solid. The product was crystallized from C_6H_6–Skelly B (8:2) to give crystals, m.p. 113–114·5°, $[\alpha]_D^{26}$ −61·8° (*c* 1·14, EtOH); λ_{max} (OSO_2), 1639 (*t*-amide CO), and 1748 cm^{-1} (COOMe). (Found: C, 59·41; H, 5·22; N, 3·31. Calcd for $C_{20}H_{21}NO_6S$: C, 59·54; H, 5·24; N, 3·47%).

N-Benzoyl-O-tosylhydroxy-L-prolinol (5). A soln of $LiBH_4$ (2·0 g, 0·092 mole) in anhyd 1,2-dimethoxyethane (75 ml) was added to 4 (8·9 g, 0·023 mole) in an equal volume of the same solvent. The mixture was

stirred at 0° for 2 hr and then at room temp for an additional 2 hr. After treatment with 25 ml HOAc the resulting soln was diluted with 65 ml H_2O and extracted twice with 100 ml portions EtOAc. Removal of solvent *in vacuo* gave a gummy residue which was treated with five successive portions of Et_2O, until solidification occurred. After each treatment with Et_2O, the solvent was removed *in vacuo* and the residue taken to dryness at about 60°. The solid, 7·60 g (93%), was crystallized from EtOAc-Skelly B (10:1) to give crystals, m.p. 97·5–99°, $[\alpha]_D^{26}$ −63·8 (*c* 1·17, EtOH); λ_{max} 1176 and 1182 (OSO_2), 1625 (t-amide CO), and 3540 cm^{-1} (OH). (Found: C, 61·05; H, 5·55; N, 3·70. Calcd for $C_{19}H_{21}NO_5S$: C, 60·78; H, 5·64; N, 3·73%).

N-*Benzoyl*-O-p-*toluenesulfonylhydroxy*-L-*proline* (**6**). To **4** (2·7 g, 0·006 mole) dissolved in cold, dry dioxan (5 ml) and MeOH (1 ml), NaOH (0·36 g, 0·009 mole) dissolved in MeOH (2 ml) was added. The mixture was maintained at 5° for 46 hr with intermittant swirling of the reaction flask. The mixture then was cooled, diluted with about 75 ml cold water and treated with 20 ml cold 2 N HCl. The white ppt was filtered off, rinsed with cold water, and dried. The yield of crude product was 2·57 g (98%). Crystallization from MeOH–H_2O* gave a crystalline product, m.p. 105–115°, $[\alpha]_D^{26}$ −52·3° (*c* 1·22, EtOH; λ_{max} 1730 (COOH), 1605 (t-amide CO) and at 1192 and 1176 cm^{-1} (O-tosyl). (Found: C, 56·28; H, 4·92. Calcd for $C_{19}H_{19}NO_6S \cdot H_2O$: C, 56·01; H, 5·22%).

(1S:4S)-N-*Benzoyl*-2-*oxa*-5-*azabicyclo*[2.2.1]*heptane* (**7**). Intermediate **5** (21·95 g, 0·058 mole), was dissolved in abs MeOH (900 ml) to which was added EtOH (145 ml) containing NaOMe (3·4 g). The soln was refluxed under anhyd conditions for 2 hr. The EtOH then was removed *in vacuo*, and the remaining slurry was dissolved in approximately 500 ml of sat K_2CO_3 aq. The soln was extracted in 5 portions with 500 ml EtOAc and the combined extracts were dried (Na_2SO_4), filtered, and the solvent removed *in vacuo* to give a yellow oil. After treatment with 100 ml Et_2O followed by evaporation *in vacuo*, solidification of the material occurred giving 10·5 g (90%) of product. The solid was twice recrystallized from Skelly B to give crystals, m.p. 76–78°, $[\alpha]_D^{26}$ +27·8° (*c* 1·56, EtOH); λ_{max} 813–819 (C—O—C), 1071–1098 (C—O—C), and 1613 cm^{-1} (t-amide CO). (Found: C, 71·21; H, 6·57; N, 6·74. Calcd for $C_{12}H_{13}NO_2$: C, 70·91; H, 6·45; N, 6·89%).

N-*Benzoylallohydroxy*-L-*proline lactone* (**8**). To **6** (6·95 g, 0·018 mole) dissolved in dry 2-butanone (1500 ml), (3·79 g, 0·036 mole) anhyd Na_2CO_3 was added. The soln was refluxed for 22 hr, $MgSO_4$ added and the mixture cooled and filtered. The solvent was removed *in vacuo* to give a solid which was crystallized from EtOAc-Skelly B to yield 2·86 g (70%) crystals, m.p. 131·5–133·5°, $[\alpha]_D^{26}$ +91·2° (*c* 1·25, EtOH); λ_{max} 1792 (γ-lactone) and at 1625 cm^{-1} (N-disubstituted amide). (Found: C, 66·61; H, 5·25; N, 6·35. Calcd for $C_{12}H_{11}O_3N$: C, 66·35; H, 5·15; N, 6·40%).

Acknowledgement—The authors express their appreciation to Dr. Vasant Telang for carrying out the decoupling experiments.

* Crystallization of the crude product from MeOH and water gave compounds having two m.p. ranges; 68–71° from dilute soln and 105–115° from more concentrated soln. The IR spectrum of each compound was identical when taken in chloroform. Crystallization of the acid from benzene gave one crystalline modification, m.p. 68–70°.

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