lowest field because it experiences not only the α-OH effect but also two β-OH effects. Carbon 3 has the same three influences, which are slightly offset by the upfield γ-gauche effect of the axial 1-hydroxyl group. The C_3 resonance coincides with that of C_4, which is subject only to the effects of one α- and one β-hydroxyl. The resonance of C_1 is at the highest field. Apparently the α effect of sulfur in this context is smaller than or of opposite sign to the β effect of OH (C_1 experiences one α-OH, one β-OH, and one α-S effect).

Summary and Conclusions

5-Thio-D-glucopyranose exists primarily as the α anomer in D_2O and in Me_2SO/D_2O. The ^1H spectrum shows that the α/β ratio in D_2O is stable at about 85/15. Analysis of the ^1H spectrum of the α anomer shows that the ring is puckered in comparison with that of D-glucopyranose. The smaller C–S–C bond angles deform the ring in such a way that the various carbons are lifted further from the average plane. The deformation appears to be general throughout the ring, since all the ring vicinal coupling constants show this effect. Complete assignments were made for both the ^1H and the ^{13}C spectra, but the latter yielded no useful conformational information.

Experimental Section

5-Thio-D-glucopyranose was obtained from Pfanstiehl Laboratories. Proton spectra (0.3 Hz/point) were obtained at 360 MHz on a Nicolet NT-360 at the Purdue University Biochemical Magnetic Resonance Laboratory.[11] Solvent suppression was accomplished by strong irradiation at the appropriate frequency. Carbon-13 spectra were obtained at 20 MHz on a Varian CFT-20 and at 90 MHz on an NT-360.[10] Selective ^1H decoupling experiments were carried out on both instruments. Second-order spectral analyses were carried out with the software package of the CFT-20.

Acknowledgment. We thank Professor Roy L. Whistler of Purdue University for assistance in this research.

Registry No. 1α, 10227-19-7; 1β, 37850-98-9.

(11) This facility is supported by the National Institutes of Health, Division of Research Resources (Grant No. RR01077).

Syntheses and a Conformational Study of Certain Selected 3-Oxa-7-azabicyclo[3.3.1]nonan-9-ones. Single-Crystal X-ray Diffraction Analysis of 6,8-Bis(2-chlorophenyl)-3-oxa-7-azabicyclo[3.3.1]nonan-9-one

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Received February 10, 1981

Isomers of 2,4,6,8-tetraphenyl-3-oxa-7-azabicyclo[3.3.1]nonan-9-ones, 6,8-bis(2-chlorophenyl)-3-oxa-7-azabicyclo[3.3.1]nonan-9-one, and *N*-benzyl-3-oxa-7-azabicyclo[3.3.1]nonan-9-one have been prepared by Mannich-type cyclocondensations with appropriate tetrahydro-4*H*-pyran-4-ones. The carbonyl group in *N*-benzyl-3-oxa-7-azabicyclo[3.3.1]nonan-9-one was reduced to a CH_2 group under modified Wolff–Kishner conditions. Nucleophilic additions ($NaBH_4$, C_6H_5MgBr) to this same ketone produced isomeric alcohols. IR and ^1H and ^{13}C NMR spectral data indicate that these bicyclic ketones preferred a chair–chair conformation. A single-crystal X-ray diffraction analysis of 6,8-bis(2-chlorophenyl)-3-oxa-7-azabicyclo[3.3.1]nonan-9-one (a = 9.353 (4), b = 7.733 (4), c = 23.03 (2) Å; space group *Pnam*) was completed to confirm a chair–chair conformation for the ketone in the solid state. The O(3)–N(7) contact distance of 2.776 (3) Å is less than the sum of the van der Waals radii. Consequently the oxygen-containing ring is slightly flattened, and the nitrogen-containing ring is somewhat more puckered than the ideal system.

3,7-Diheterabicyclo[3.3.1]nonanes are of considerable interest both from a theoretical point of view as well as for potential biological activity.[1-4] Nitrogen analogues of bicyclo[3.3.1]nonan-9-ones[5-8] have been studied, but work on other hetero (O, S, P, etc.) analogues has been quite limited. To date, only a few 3-oxa-7-azabicyclo[3.3.1]nonan-9-ones have been recorded.[9] Herein we report the syntheses and conformational analyses of certain 3-oxa-7-azabicyclo[3.3.1]nonan-9-ones (1) and their derivatives.

Results and Discussion

Syntheses of derivatives of 1 were approached via two routes: (1) Mannich condensations of tetrahydro-4*H*-pyran-4-ones with appropriate aldehydes and amines and

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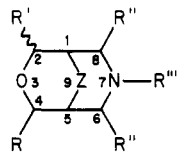


1a, R = R′ = R″ = H; R‴ = $CH_2C_6H_5$; Z = C=O
b, R = R′ = R″ = H; R‴ = $CH_2C_6H_5$; Z = CH(OH)
c, R = R′ = R″ = H; R‴ = $CH_2C_6H_5$; Z = C_6H_5COH
d, R = R′ = R″ = H; R‴ = $CH_2C_6H_5$; Z = CH_2
e, R = R′ = R‴ = H; R″ = 2-ClC_6H_4; Z = C=O
f, R = R′ = R‴ = H; R″ = 2-ClC_6H_4; Z = CH(OH)
g, R = R″ = C_6H_5; R′ = *cis*-C_6H_5;[a] R‴ = H; Z = C=O
h, R = R″ = C_6H_5; R′ = *trans*-C_6H_5;[b] R‴ = H; Z = C=O

[a] This C-C_6H_5 bond is syn to all other C-C_6H_5 bonds.
[b] This C-C_6H_5 bond is anti to all other C-C_6H_5 bonds.

(2) the addition of amines to 3,5-dibenzylidenetetrahydro-4*H*-pyran-4-one. The first route was productive, but the second route failed to give the expected products, and usually starting material was recovered.

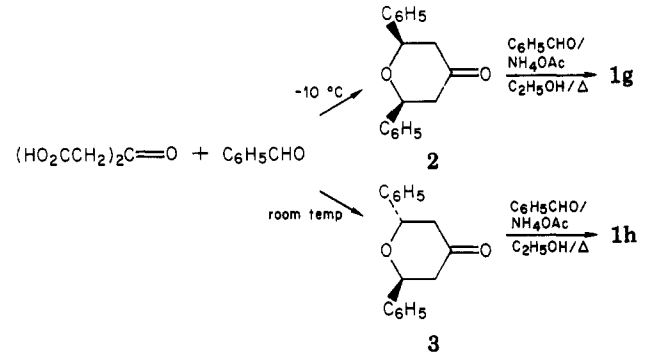
The *cis*- and *trans*-2,6-diphenyltetrahydro-4*H*-pyran-4-ones (**2** and **3**, respectively)[10] were prepared (Scheme I) by the acid-catalyzed condensation of acetonedicarboxylic acid with excess benzaldehyde at −10 °C and at room temperature (25 °C), respectively. Baliah and co-workers[9] have reported the syntheses of *cis*- and *trans*-2,4-diphenyl-6,8-diphenyl-3-oxa-7-azabicyclo[3.3.1]nonan-9-ones (**1g** and **1h**, respectively) starting from the corresponding monocyclic ketones **2** and **3**. We were unable to reproduce their results under the conditions given. However, ketones **1g** and **1f** were obtained via a modified procedure.

Mannich condensation of tetrahydro-4*H*-pyran-4-one (**4**) with 2-chlorobenzaldehyde and ammonium acetate in ethanol produced 6,8-bis(2-chlorophenyl)-3-oxa-7-azabicyclo[3.3.1]nonan-9-one (**1e**). Benzaldehyde failed to give the expected bicyclic ketone (Scheme II) under the same conditions. Also, attempts to prepare bicyclic ketones from the condensation of benzaldehyde and benzylamine failed, the dibenzylidene compound **5** being obtained quantitatively.

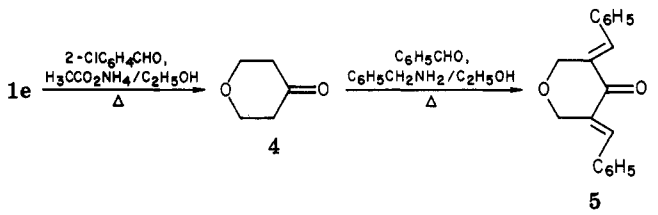
N-Benzyl-3-oxa-7-azabicyclo[3.3.1]nonan-9-one (**1a**) was prepared by a double Mannich condensation of ketone **4** with formaldehyde and benzylamine. Certain 3-oxa analogues of **1a** have been reported via a Mannich condensation of an appropriate 4-heteracyclohexanone with formaldehyde and benzylamine.[5-8] The recorded methods involve long reaction times (30 days), and the products were invariably used in crude form. It was possible to obtain a good yield (72%) in a short reaction time (6 h) of amino ketone **1a** which was completely characterized. Treatment of amino ketone **1a** with 60% $HClO_4$ produced perchlorate **6** as a monohydrate in good yield (83%). *N*-Benzyl-3-oxa-7-azabicyclo[3.3.1]nonane (**1d**) was obtained quantitatively by reducing the amino ketone **1a** under modified Wolff–Kishner conditions (Scheme III).[7,8] Amine **1d** was a clear liquid and was characterized via formation of its perchlorate **7**. An X-ray investigation of perchlorates **6** and **7** is in progress. Surprisingly, treatment of pure **5**[11] with amines or ammonium acetate under a variety of conditions did not produce any expected products (Scheme IV). Thus, it is suggested that free dienones like **5** may not be intermediates in the formation of the bicyclic compounds discussed previously.

Reduction of **1a** with $NaBH_4$ in 2-propanol (at room temperature) gave what appeared to be two isomers (ca. 1:1 ratio) of *N*-benzyl-3-oxa-7-azabicyclo[3.3.1]nonan-9-ol (**1b′,b″**). Also, the addition of C_6H_5MgBr in ether (at room temperature) gave two isomers (ca. 1:1.2 ratio) of *N*-benzyl-9-phenyl-3-oxa-7-azabicyclo[3.3.1]nonan-9-ol (**1c′,c″**). Separation of the two isomers of **1b** was possible via chromatography on Florisil, but only one isomer of **1c** could be obtained pure via the same technique because of decomposition of the other isomer on the column. The near unity ratio of products in the above nucleophilic ($NaBH_4$ and C_6H_5MgBr) additions may indicate that a CC

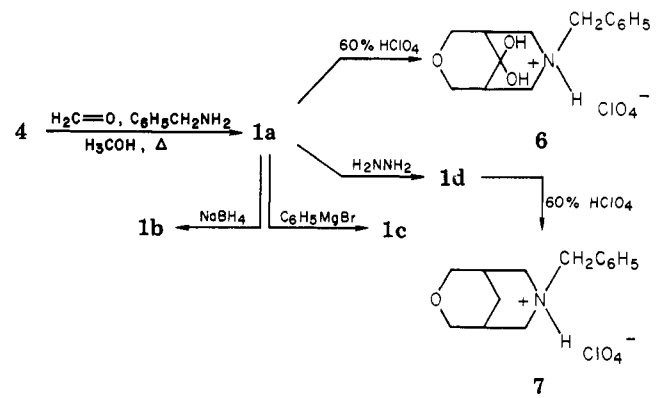
Scheme I

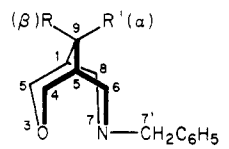


Scheme II



Scheme III





1b′, R = OH; R′ = H
b″, R = H; R′ = OH
c′, R = C_6H_5; R′ = OH
c″, R = OH; R′ = C_6H_5

Scheme IV

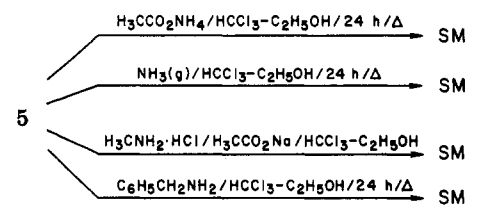


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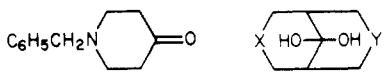
Table I. ^{13}C NMR Chemical Shifts[a] for Compounds 1a-e, 6, and 7

compd	carbon (signal pattern)					
	C(1,5)	C(2,4)	C(6,8)	C(9)	Ar CH_2	aromatic ring
1a	49.5	73.3	57.5	211.5	61.1	137.7, 128.4, 128.0, 126.9
1b''	37.9	72.1 (t)	52.2	67.0 (d)	63.3	131.2, 130.9, 130.3, 129.7, 129.3, 129.1
1c'	39.2	70.6	54.4	70.6	63.2	142.8, 130.8, 130.7, 129.8, 129.7, 129.6, 129.5, 129.2, 126.7, 126.9
1d	30.2 (m)	70.6	57.6	30.2	63.1	131.8, 131.1, 130.3, 130.1
1e	52.5	69.9 (t)	60.3 (d)	209.7		137.0, 132.4, 129.8, 128.9, 128.7, 126.8
6	39.0	55.5	61.8	92.9	70.2	131.8, 131.1, 130.8, 130.2
7	29.9 (d)	58.1	62.5	30.4 (t)	72.9	131.8, 131.1, 130.3, 130.1

[a] Chemical shifts are in parts per million (at 37 °C) downfield from internal tetramethylsilane; solvent: 0.5 mL of $DCCl_3$ with 100 mg of 1a,d,e; 0.5 mL of H_3COD saturated with 6 or 7; 0.5 mL D_3COD with 50 mg of 1c' and with 20 mg of 1b''. For multiplicities: d = doublet; m = multiplet; t = triplet.

conformation is highly probable for the ketone **1a** in the solvents employed.

^1H NMR Analysis. ^1H NMR analysis of compounds **1a–h**, **6**, and **7** proved interesting and instructive to a degree. Chemical shifts of H(1,5), H(2,4), and H(6,8) were assigned partially on the basis of electronegativity effects of the heteroatoms on the chemical shift of the α-protons and upon extensive proton-decoupling studies. The ^1H NMR spectra of **4** and *N*-benzyl-4-piperidone (**8**)[12] were



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used as model compounds in the above assignments. Chemical shifts for **1a–d** were found to be in the following order: $\delta_{H(1,5)} < \delta_{H(6,8)} < \delta_{H(CH_2C_6H_5)} < \delta_{H(2,4)} < \delta_{H(aromatic)}$. However, for the perchlorates **6** and **7**, the chemical shifts were found to be in the following order: $\delta_{H(1,5)} < \delta_{H(2,4)} < \delta_{H(6,8)} < \delta_{H(CH_2C_6H_5)} < \delta_{H(aromatic\ ring)}$. This was expected because of the protonation of N(7). The protonated form of the latter atom is known to exert a large deshielding effect on the α-protons [H(6,8) and $H(CH_2C_6H_5)$].[12] Also, chemical shifts of $H_a(2,4)$ and $H_a(6,8)$ are thought to be at higher field than those of $H_e(2,4)$ and $H_e(6,8)$, respectively. Such a chemical shift difference between the axial and equatorial protons has been observed in the ^1N NMR spectra of simple pentamethylene heterocycles and has been explained in terms of diamagnetic anistropic effects.[13] Several recent studies on 3,7-diazabispidinones support this explanation.[5,7,8,14] The multiplet signals observed for H(6,8) and H(2,4) in **1a–f** constituted an AB part of an ABX pattern except for H(6,8) in **1a** which was found to be the AM part of an AMX pattern. A second-order analysis yielded the $\delta_{H_a(2,4)}$, $\delta_{H_e(2,4)}$, $\delta_{H_a(6,8)}$, and $\delta_{H_e(6,8)}$ values (in **1a–f**) except for H(6,8) in **1a** where a first-order analysis (i.e., the mid point of each doublet) was adequate to obtain $\delta_{H_a(6,8)}$ and $\delta_{H_e(6,8)}$.[15] The geminal proton coupling constants for OCH_2 and NCH_2 (in **1a–f**) were found to be in the range of 10–12 Hz which is near the range one would expect for a methylene group having tetrahedral geometry.[16]

The vicinal coupling constants [$^3J_{H(1,5),H_a(2,4)}$, $^3J_{H(1,5),H_e(2,4)}$, $^3J_{H(1,5),H_a(6,8)}$, and $^3J_{H(1,5),H_e(6,8)}$ (in **1a** and **1d**)] were found to be ca. 2–4 Hz. This was informative because of the relationship between the dihedral angle HCCH and $^3J_{HH}$.[17] It has been shown in bicyclo[3.3.1]nonane that the $^3J_{HH}$ value for the boat–chair (or chair–boat) conformation ($^3J_{HH}$ is expected to be ca. 10–12 Hz) is greater than that value for a chair–chair conformation (ca. 2–4 Hz).[17] In compounds **1a** and **1d**, $^3J_{HH}$ was found to be ca. 2–4 Hz, and in compounds **1b,c,e–h** the coupling was apparently unresolvable at 100 MHz (below 0.5 Hz) or absent entirely.

^{13}C NMR Analysis. ^{13}C NMR chemical shifts for compounds **1a–f** are listed in Table I. These shifts for **1a–f** were assigned by using model compounds **4** and **8**.[18] Off-resonance ^{13}C spectra were recorded (for **1b'',d,e** and **7**) in order to differentiate between methine and methylene carbons. As expected, ^{13}C chemical shifts were found to be dependent upon steric effects as well as upon the electron density changes imposed by the substituents.[19–21] The ^{13}C NMR spectrum of perchlorate **6** was somewhat novel and did *not* show the expected signal for a C=O group (a signal at 211 ppm was observed for the C=O group in **1a**), but a ^{13}C signal appeared at 92.9 ppm (Table I). This shift was reminiscent of that for a carbon with *gem*-dioxy groups.[22] IR analysis of **6** also did not reveal an absorption band for C=O ($\nu_{C=O}$ 1730 cm^{-1} was observed for **1a**), but a broad, intense absorption occurred at 3300–3500 cm^{-1}. Elemental analysis of **6** indicated a molecular formula for $C_{14}H_{20}ClNO_7$ which corresponded to a monohydrate of **6**. This suggested that the perchlorate **6** existed as a hydrate such as **9**. Carbonyl hydration in quaternary salts of certain piperidin-4-ones[22] and phosphorinan-4-one[23] have been reported where the hydrated carbon has a ^{13}C NMR resonance at 101.7 and 94.4 ppm, respectively.

Conformational Study. Certain tentative conclusions about the conformation of the bispidinones **1a–h** described herein can be deduced from the spectral data gathered. Before proceeding, a brief discussion on general conformational features of the 3-oxa-7-azabicyclo[3.3.1]nonan-9-one system is in order. Derivatives of **1** can exist in four reasonable conformations **10–13**. All four conformations

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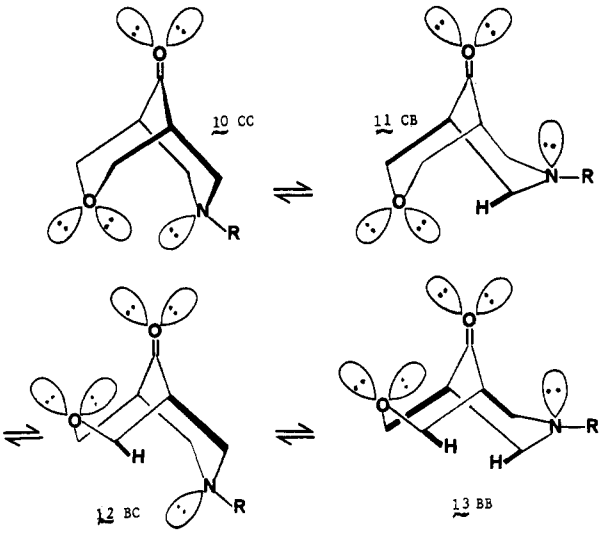
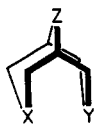
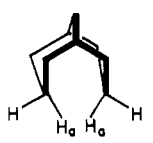


have potentially strong destabilizing interactions between certain nonbonded atoms. If destabilization, as a result of nonbonded interactions between the heteroatoms, is sufficiently large in 3,7-diheterabicyclo[3.3.1]nonane systems, conformers like 11–13 are possible.[4,24] Such destabilization may be due to one or all of the following factors:[4,25-27] (1) steric repulsion of the heteroatoms, (2) dipole repulsion, (3) lone-pair orbital repulsion. Because of such factors, both rings in **10** may be distorted substantially. Distortion has been found in related model compounds **14–16** (via X-ray analysis)[28-30] which have CC



14, X = Z = CH_2; Y = $^+NH_2Br^-$
15, X = O; Y = C=O; Z = NCH_3
16, X = O; Y = Z = S
17, X = Y = NCH_3; Z = CH_2

conformations in the solid state. Analysis of ^1H NMR spectral data and dipole moment studies of **17**[5] favored a CC conformation which was also supported by a LCAO–MO calculations.[31] Recently, a variable-temperature ^{13}C NMR study revealed a boat–chair ⇄ chair–boat equilibrium in a 3,7-diazabicyclo[3.3.1]nonan-9-one system.[32] Indeed, the parent carbocyclic compound bicyclo[3.3.1]-nonane (**18**) appears to have a flattened "wing" compared



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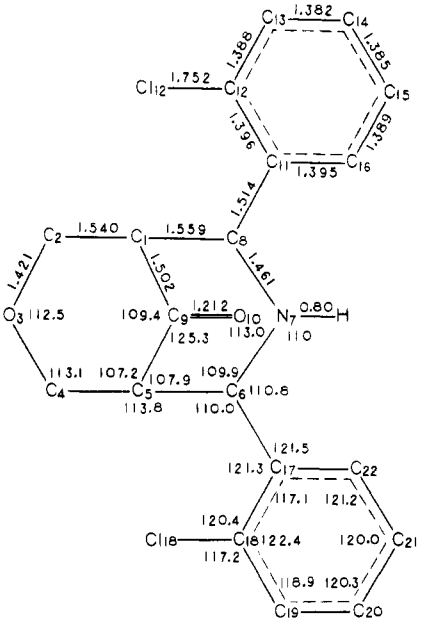

Figure 1. Schematic diagram of the molecule showing the numbering scheme, bond distances, and angles. N(7), HN(7), O(3), C(9), and O(10) lie on a minor plane; the unique distances and angles are presented. The standard deviations of bond distances and angles involving nonhydrogen atoms are 0.002–0.003 Å and 0.2°, respectively. For bonds to hydrogen atoms, the ranges are 0.02–0.04 Å and 1.2–1.4°.

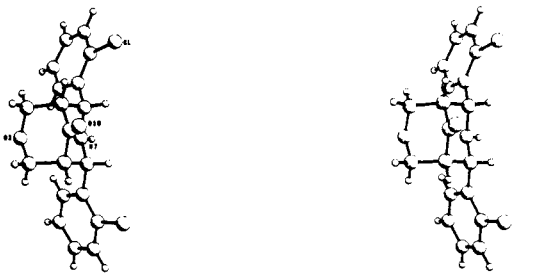

Figure 2. PLUTO drawing of a single molecule of 6,8-bis(2-chlorophenyl)-3-oxa-7-azabicyclo[3.3.1]nonan-9-one (**1e**).

to simple cyclohexane systems.[4,24] Conformation **10** might also be more favored on the basis of enthalpy considerations which have been deduced for **18** from theoretical as well as experimental investigations.[4] It should be mentioned that the "extra" signals in the ^{13}C NMR spectrum of **1b″** and **1c′** appear to be due to a nonequivalence in the rings carbons of the aryl group rather than to the presence of other conformers since no other ^{13}C signal was doubled nor did extraneous signals arise.

Analysis of the ^1H NMR spectra of compounds **1a–h** showed that the vicinal coupling constants ($^3J_{H(1,5),H_a(2,4)}$, $^3J_{H(1,5),H_e(2,4)}$, $^3J_{H(1,5),H_a(6,8)}$, $^3J_{H(1,5),H_e(6,8)}$) were small (ca. 2–4 Hz). These data can be explained only by the conformation **10**.[17] For conformations **11–13**, at least one of the $^3J_{HH}$ coupling values ($^3J_{H(1,5),H_a(6,8)}$ in **11**, $^3J_{H(1,5),H_a(6,8)}$ and $^3J_{H(1,5),H_e(2,4)}$ in **13**) should be fairly large (ca. 10–12 Hz),[17] and this was not observed for any member of **1**. Consequently, on the basis of our ^1H NMR spectral data ($^3J_{HH}$ values) for **1a–h** and on comparison with related compounds **14–17** of known configuration, conformation **10** (possibly with ring flattening) is tentatively assigned as the probable conformer for the 3-oxa-7-azabicyclo[3.3.1]-nonan-9-ones in solution.

Single-Crystal Analysis of 1e. Figure 1 gives the numbering scheme, bond distances, and angles. Note that atoms N(7), HN(7), O(3), C(9), and O(10) lie on a crystallographic mirror plane and that C(1) and C(5), C(8) and

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Table II. Selected Torsion Angles[a]

Nitrogen-Containing Ring	
C(1)-C(8)-N(7)-C(6)	57.5 (2)
C(9)-C(1)-C(8)-N(7)	-58.5 (2)
C(5)-C(9)-C(1)-C(8)	62.2 (2)
Oxygen-Containing Ring	
C(1)-C(2)-O(3)-C(4)	-54.4 (2)
C(9)-C(1)-C(2)-O(3)	57.2 (2)
C(5)-C(9)-C(1)-C(2)	-60.7 (2)
Eight-Membered Ring	
C(2)-C(1)-C(8)-N(7)	60.4 (2)
O(3)-C(2)-C(1)-C(8)	-62.1 (2)
Carbonyl	
C(8)-C(1)-C(9)-O(10)	-119.0 (3)
C(2)-C(1)-C(9)-O(10)	118.0 (3)
Chlorophenyl Group	
N(7)-C(8)-C(11)-C(12)	155.4 (2)
C(1)-C(8)-C(11)-C(16)	94.3 (2)

[a] The angles given are the unique torsion angles; angles related by the mirror operation have the same magnitude but the opposite sign.

C(6), C(2) and C(4), and the atoms of the chlorophenyl substituents are related by this symmetry operation.

The molecule was found to be in the chair–chair conformation as shown in the PLUTO[33] drawing (Figure 2). The chair conformation of the nitrogen-containing ring is required to accomodate the bulky 2-chlorophenyl groups [at atom positions C(6) and C(8)] which would be in energetically unfavorable axial positions in the boat conformation. As the oxygen-containing ring assumes the chair conformation in the absence of restrictive substitutions, it is likely that the double-chair conformer would predominate in the absence of the 2-chlorophenyl substituents. For the parent compound, bicyclononane, it has been calculated that the double-chair conformation is about 2.7–3.7 kcal/mol more stable than the chair–boat,[17a] and it is to be expected that steric repulsion and overlap of lone pair electrons, forces which favor the chair–boat conformation in molecules with more bulky heteroatoms at positions 3 and 7,[30] would be less significant in the present case.

N(7) is essentially tetrahedral, with the hydrogen atom directed away from O(3). The N(7)–O(3) contact distance, 2.776 (3) Å, is less than the sum of the van der Waals radii and is comparable to the N(3)—C(7)=O distances found for 1,5-dinitro-3-methyl-3-azabicyclo[3.3.1]nonan-7-one (2.76 and 2.69 Å).[29] In a recent study of a number of bicyclo[3.3.1]nonane systems, Bhattacharjee and Chacko reported four compounds having methylene carbons at positions 3 and 7, with an average C(3)–C(7) contact distance of 3.11 Å.[34]

Torsion angles of interest are given in Table II. Ideal geometry for a cyclohexane ring would have all the torsion angles with an absolute magnitude of 56°. The observed angles indicate a slight flattening of the oxygen-containing ring at the ether linkage. The nitrogen-containing ring is more puckered than the ideal system. The slight flattening of the oxygen-containing ring relative to the nitrogen-containing ring can be seen in Figure 3, which gives the interplanar angles for selected planes of the molecule.

The angle between the least-squares plane of the phenyl ring and the plane defined by atoms C(8), N(7), and C(6)

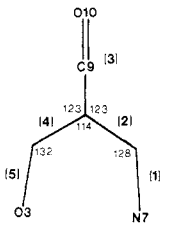

Figure 3. Angles between selected planes of the molecule in degrees. The atoms used in calculating the planes are: [1] C(8), N(7), and C(6); [2] C(1), C(8), C(6), and C(5); [3] C(1), C(5), C(9), and O(10); [4] C(1), C(5), C(2), and C(4); [5] C(2), O(3), and C(4). Positions of symmetry-related atoms are generated by $x' = x$, $y' = y$, and $z' = 0.5 - z$.

Table III. ^{1}H NMR Chemical Shifts (δ) of $H_a(2,4)$ and $H_e(2,4)$ in 1b-d

	compd			
hydrogen	**1b′** (D_3COD)	**1b″** (D_3COD)	**1c′** (D_3COD)	**1d** ($DCCl_3$)
$H_a(2,4)$	3.80	3.70	3.72	3.76
$H_e(2,4)$	4.16	3.80	3.94	3.92

is 27°. Torsion angles about the C(8)–C(11) bond are given in Table II. The chlorine atom deviates from the plane of the phenyl ring by 0.06 Å; the root-mean-square deviation of the atoms defining this plane is 0.009 Å.

In the related compound 1,5-dinitro-3-methyl-3-azabicyclo[3.3.1]nonan-7-one,[29] in which a carbonyl replaces the O(3) ether group, an interaction between N(3) and the carbonyl resulted in a deviation of the carbonyl carbon from the plane defined by C(2), C(3)=O, and C(4). In the present structure, the carbonyl at C(9) is distant from N(7) due to the chair conformation, and the carbonyl does not deviate significantly from planarity.

Only one weak hydrogen bond occurs in the structure, between N(7) and O(3) of the molecule at $-^1/_2 + x$, $-^1/_2 - y$, z. The N(7) to O(3) distance is 3.114 Å, and the H[N(7)] to O(3) distance is 2.36 Å.

Configuration at C(9) in Alcohols 1b and 1c. Two isomers of alcohol **1b** were obtained by reduction ($NaBH_4$) of the amino ketone **1a**. Since the $^3J_{HH}$ values were small [ca. 2–4 Hz, obtained by measuring the width at half-height ($W_{1/2}$) of the multiplet signals obtained for H(2,4) and H(6,8)],[1] the isomeric alcohols probably have a CC conformation.[17,35] Moreover, the IR spectrum (CCl_4) of alcohol **1f** (mixture of isomers) was taken at three different concentrations (1.2×10^{-2}, 6.0×10^{-3}, and 3.0×10^{-3} M), and only a sharp absorption band with a $\nu_{max} = 3614$ cm^{-1} was found at all three concentrations. This indicates a *free OH group*. From these observations, it can be concluded that a solution of **1f** exhibited only an intermolecular hydrogen bonded OH group at high concentrations.[36] Since the solution was fairly dilute, the alcohol (mixture of isomers) **1f** existed as a monomer (without any significant intermolecular association via an H bonded OH group), and the free OH group absorbed sharply at 3614 cm^{-1}. If an intramolecular H bonded OH group existed in the solution of **1f**, the ν_{OH} should be *below 3500 cm^{-1} as a broadened signal*, and this was not observed.[36] These spectral observations, therefore, favor a *CC conformation* for the alcohols **1b,c,f**.

The configuration at C(9) for isomers of alcohol **1b** and of **1c** is tentatively assigned by analyzing ^{1}H NMR spectral data. For comparison purposes, the ^{1}H NMR spectral data

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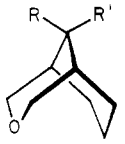
of a series of 3-oxabicyclo[3.3.1]nonan-9-ols (**19a–d**)[37] were



19a, R = OH; R′ = H
b, R = H; R′ = OH
c, R = C_6H_5; R′ = OH
d, R = OH; R′ = C_6H_5

examined. Analysis of ^1H NMR spectral data (Table III) of the alcohols **1b′** (isomer with R_f 0.65) and **1b″** (isomer with R_f 0.35) showed that $H_a(2,4)$ in alcohol **1b′** experienced a deshielding (ca. 0.04 ppm) effect imposed by the OH group when compared with that of **1d**. In contrast, $H_a(2,4)$ in **1b″** experienced a shielding effect (ca. 0.06 ppm). If the shielding effect of the OH group is the same as in model compounds **19a** and **19b**,[37] then the OH group should be β (i.e., OH is syn to the pyran ring) in **1b′** and α (i.e., OH is anti to the pyran ring) in **1b″**. In the case of alcohol **1c**, only one isomer **1c′** (R_f 0.84) was separable from the reaction mixture by column chromatography, and presumably the second isomer **1c″** was degraded during the chromatographic process as indicated by ^1H NMR analysis of the mixture stripped from the column. Analysis of the ^1H NMR spectrum of **1c′** showed that $H_a(2,4)$ experienced a small shielding effect when compared to the counterpart in **1d**. Using the model compound **19c**,[37] we tentatively conclude that the OH group in **1c′** should be α. Consequently, it follows that in the much less stable isomer **1c″**, the OH group should have the β configuration.[37]

Experimental Section

Materials and Methods. Melting points were obtained on a Thomas-Hoover melting point apparatus and were uncorrected. The ^1H and ^{13}C NMR data were obtained on a Varian XL-100(15) NMR spectrometer equipped with a Nicolet TT-100 PFT accessory operating at 100.1 MHz for ^1H and 25.2 MHz for ^{13}C NMR with Me_4Si as an internal standard in both cases. Infrared spectral data were obtained on a Beckmann IR-5A unit. Mass spectral data were gathered on a CEC Model 21-110B HR mass spectrometer. Elemental analyses were performed by Galbraith Laboratories.

1,3-Acetonedicarboxylic acid (Aldrich, mp 133 °C dec), benzaldehyde (analytical reagent, Mallinckrodt), ammonium acetate (analytical reagent, Mallinckrodt), tetrahydro-4*H*-pyran-4-one (Aldrich, 99%, bp 166–166.5 °C), D_2O (Aldrich, 99.8% D), triethylene glycol (Aldrich), hydrazine hydrate (Fisher Scientific Co.), $NaBH_4$ (Ventron), and Mg (Mallinckrodt, analytical reagent) were purchased and used as obtained. 2-Chlorobenzaldehyde [Eastman, bp 86–90 °C (10 mm)] and bromobenzene [Aldrich, bp 40 °C (>5 mm)] were distilled prior to use. Neutral Al_2O_3 (Brinkmann, activity stage I) and Florisil (Research specialties Co.) were used as packing material for the chromatographic operations, and plastic sheets precoated with neutral Al_2O_3 (F_{245}, Type E, Brinkmann) were used in TLC experiments. Organic solvents were distilled before use. All organic extracts were dried over Na_2SO_4. Ketones **2** [mp 70–72 °C (lit.[10] mp 69–70 °C), 25 g (35%)] and **3** [mp 133–135 °C (lit.[10] mp 131 °C), 16 g (21%)] were prepared by acid-catalyzed condensation of 1,3-acetonedicarboxylic acid (42 g, 287 mmol) with benzaldehyde (125 g, 1.18 mol) at −10 °C and at room temperature, respectively.[10] The dibenzylidene compound **5** [mp 186–87 °C (lit.[12] mp 185 °C), 1.5 g (53%)] was obtained by a base-catalyzed condensation of ketone **4** (1.0 g, 10 mmol) and benzaldehyde (2.1 g, 20 mmol).[11]

6,8-Diphenyl-*cis*-2,4-diphenyl-3-oxa-7-azabicyclo[3.3.1]nonan-9-one (1g). A mixture of ketone **2** (1.26 g, 5.0 mmol), benzaldehyde (1.1 g, 10 mmol), ammonium acetate (1.2 g, 15 mmol), and anhydrous ethanol (10 mL) was placed in a 50 mL, round-bottomed flask and was heated (oil bath, 55–60 °C) with stirring (magnetic) under N_2. After 30 min, a clear yellow solution was obtained. A white solid began to form after 1.5 h. This reaction mixture was heated under the same conditions (2 h) and was allowed to cool to room temperature. After the mixture was allowed to stand overnight in a refrigerator, a white solid was filtered off (suction), was washed well with ether (4 × 10 mL), and was dried (suction). Recrystallization (C_6H_6) gave 0.4 g (18%) of **1g** as a white powder: mp 254–256 °C dec (lit.[9] mp 242–244 °C dec); IR (KBr) ν_{max} 1715 (C=O), 1000–1100 (C–O–C), 3278 cm^{-1} (NH); ^1H NMR ($DCCl_3$) δ 1.55 (1 H, br s, NH), 3.06 [2 H, br s, H(1,5), $W_{1/2}$ = 4 Hz], 4.52 [2 H, br s, H(6,8), $W_{1/2}$ = 4 Hz], 5.06 [2 H, br s, H(2,4), $W_{1/2}$ = 4 Hz], 6.64–6.8 (5 H, m, Ar H), 7.0–7.08 (5 H, m, Ar H), 7.3–7.7 (10 H, m, Ar H); mass spectrum, *m/e* calcd for $C_{31}H_{27}NO_2$ (M^+) 445.2042, found (M^+) 445.2042.

6,8-Diphenyl-*trans*-2,4-diphenyl-3-oxa-7-azabicyclo[3.3.1]nonan-9-one (1h). This condensation was carried out as in the preparation of **1g** by using ketone **3** (1.25 g, 5 mmol), benzaldehyde (1.1 g, 10 mmol), ammonium acetate (1.2 g, 15 mmol), and anhydrous ethanol (15 mL). Recrystallization (C_6H_6) gave 0.37 g (16%) of **1h** as a white powder: mp 266–268 °C dec (lit.[9] mp 245–247 °C dec); IR (KBr) ν_{max} 1715 (C=O), 1000–1100 (C–O–C), 3279 cm^{-1} (NH); ^1H NMR ($DCCl_3$) δ 2.14 (1 H, br s, NH), 2.88 [2 H, br s, H(1,5), $W_{1/2}$ = 4 Hz], 4.36 [2 H, br s, H(6,8), $W_{1/2}$ = 4 Hz], 4.7 [2 H, br s, H(2,4), $W_{1/2}$ = 4 Hz], 6.62–6.8 (5 H, m, Ar H), 6.96–7.06 (5 H, m, Ar H), 7.34–7.64 (10 H, m, Ar H); mass spectrum, *m/e* calcd for $C_{31}H_{27}NO_2$ (M^+) 445.2042, found (M^+) 445.2035.

6,8-Bis(2-chlorophenyl)-3-oxa-7-azabicyclo[3.3.1]nonan-9-one (1e). A mixture of ketone **4** (0.5 g, 5 mmol), 2-chlorobenzaldehyde (1.4 g, 10 mmol), ammonium acetate (0.4 g, 5 mmol), and anhydrous ethanol (10 mL) was placed in an Erlenmeyer flask and *was heated slowly* (hot plate, 60 °C) with constant stirring (magnetic). After 15 min, a clear pale yellow solution was obtained, heating was continued on additional 30 min, and the reaction mixture was allowed to cool to room temperature. Removal of the solvent resulted in a brown syrup which, upon trituration (ether), gave a white solid. Recrystallization (2-propanol) gave 0.140 g (8%) of **1e** as white flakes: mp 212–214 °C dec; IR (KBr) ν_{max} 1715 (C=O), 1000–1100 (C–O–C) 3278 cm^{-1} (NH); ^1H NMR ($DCCl_3$) δ 2.31 (1 H, br s, NH), 2.71 [2 H, br s, H(1,5), $W_{1/2}$ = 5 Hz], 2.73 [2 H, d, $H_a(2,4)$, J = 12 Hz], 4.11 [2 H, d, $H_e(2,4)$, J = 12 Hz], 4.96 [2 H, br s, H(6,8), $W_{1/2}$ = 10 Hz], 7.22–7.5 (6 H, m, Ar H), 8.02 (2 H, d, Ar H, $^2J_{HH}$ = 8 Hz); ^{13}C NMR; see Table I; mass spectrum, *m/e* calcd for $C_{19}H_{17}Cl_2NO_2$ (M^+) 361.0636, found (M^+) 361.0628. Anal. Calcd for $C_{19}H_{17}Cl_2NO_2$: C, 63.00; H, 4.73; Cl, 19.57; N, 3.87. Found: C, 62.95; H, 4.73; Cl, 19.55; N, 3.78.

7-Benzyl-3-oxa-7-azabicyclo[3.3.1]nonan-9-one (1a). Benzylamine (1.1 g, 10 mmol) was neutralized carefully with glacial H_3CCO_2H (0.6 g, 10 mmol), and the resulting white solid was dissolved in anhydrous H_3COH (40 mL) by being stirred (magnetic) under N_2. Paraformaldehyde (2.4 g, 80 mmol) was suspended in the above solution. Heating (oil bath) and stirring (magnetic) were begun with the simultaneous addition of the ketone **4** (1.0 g, 10 mmol) in small portions. This reaction mixture (brown) was then heated under reflux (6 h), was allowed to cool (room temperature), and was stirred (magnetic) overnight at room temperature. Evaporation of methanol gave a brown oil which was shaken with ether (50 mL) and water (50 mL). The ether layer was discarded. After being washed with ether (2 × 50 mL), the aqueous layer was cooled (ice) and was made basic (ca. pH 10) by addition of NaOH pellets. The resulting suspension was extracted with $HCCl_3$ (3 × 25 mL). Evaporation of the dried organic extracts gave a brown oil which, upon distillation (vacuum), yielded **1a** (0.9 g, 39%) as a clear liquid: bp 118–120 °C (1 mm; oil bath, 200–210 °C); IR (neat liquid) ν_{max} 1730 (C=O) 1000–1100 cm^{-1} (C–O–C); ^1H NMR ($DCCl_3$) δ 2.5 [2 H, br s, H(1,5) $W_{1/2}$ = 10 Hz], 2.9 [2 H, dd, $H_e(6,8)$, $^2J_{HH}$ = 11 Hz, $^3J_{HH}$ = 4 Hz], 3.1 [2 H, dd, $H_e(6,8)$, $^2J_{HH}$ = 11 Hz, $^3J_{HH}$ = 4 Hz], 3.52 [2 H, s, H(7′)], 3.82 [2 H, dd, $H_a(2,4)$, $^2J_{HH}$ = 11 Hz, $^3J_{HH}$ = 3 Hz], 4.16 [2 H, br d, $H_e(2,4)$, $^2J_{HH}$ = 11 Hz, $W_{1/2}$ = 4 Hz], 7.28 (5 H, br s, Ar H); ^{13}C NMR, see Table I; mass spectrum, *m/e* calcd for $C_{14}H_{17}NO_2$ (M^+) 231.1259, found (M^+) 231.1263.

(37) Bucci, P.; Lippi, G.; Macchia, B. *J. Org. Chem.* **1970**, *35*, 913.

Amino ketone **1a** was prepared as before by using benzylamine (5.5 g, 50 mmol), H_3CCO_2H (3.0 g, 50 mmol), paraformaldehyde (12.0 g, 400 mmol), ketone **4** (5.0 g, 50 mmol), and H_3COH (200 mL). The crude **1a** (11.1 g, 48 mmol, 96%) was dissolved in dry ether (20 mL) and was cooled (ice), and a solution of 60% aqueous $HClO_4$ (8.4 g, 48 mmol) in ether (10 mL) was added dropwise. The pale yellow precipitate obtained was washed with ether (3 × 20 mL), was filtered, and was dried (suction). The crude perchlorate **6** (15.35 g, 96.4%) was treated in a certain manner. C_2H_5OH (95%, 50 mL) was added to increase the solubility of **6** in water. The above suspension was made strongly alkaline (to litmus) by adding aqueous NaOH solution (15%). A pale yellow oil separated and was extracted with $HCCl_3$ (4 × 30 mL). Evaporation of the dried $HCCl_3$ solution gave **1a** (8.3 g, 72%) as a brown oil. IR and ^1H NMR spectral data confirmed the identity of the product as **1a** as obtained previously.

Perchlorate of *N*-Benzyl-3-oxa-7-azabicyclo[3.3.1]nonan-9-one (6). Amino ketone **1a** (0.400 g, 1.7 mmol) was dissolved in anhydrous ether (ca. 20 mL), and the solution was cooled (ice). To the cold solution was added aqueous $HClO_4$ (60%, 0.290 g, 1.7 mmol), and a white solid separated out which was filtered, was washed with anhydrous ether (4 × 25 mL), and was dried (aspirator). Recrystallization (H_3CCN–$H_3CCO_2C_2H_5$, 1:2) gave **6** (0.460 g, 82.6%) as a pure white solid: mp 182–85 °C (softening), 201–202 °C dec; IR (KBr) ν_{max} 3350 (OH), 1070–1120 (ClO_4), 1000–1200 cm^{-1} (C–O–C); ^1H NMR [D_2O, $(H_3C)_3SiCD_2CD_2CO_2Na$ (TSP)] δ 2.1 [2 H, br s, H(1,5)], 3.66 [4 H, br s, H(2,4)], 4.08 [4 H, br s, H(6,8)], 4.36 (2 H, br s, H(7′)], 7.56 (5 H, s, Ar H); ^{13}C NMR, see Table I. Anal. Calcd for $C_{14}H_{18}ClNO_6{=}H_2O$: C, 48.08; H, 5.76; N, 4.01. Found: C, 48.14; H, 5.90; N, 4.01.

***N*-Benzyl-3-oxa-7-azabicyclo[3.3.1]nonane (1d).** A magnetically stirred solution of amino ketone **1a** (2.3 g, 9.9 mmol), hydrazine hydrate (85% solution, 2.93 g, 49.7 mmol) and triethylene glycol (30 mL), maintained under N_2, was heated to 60 °C, and 85% KOH (pellets; 3.69 g, 55.9 mmol) was added. The yellow solution was boiled under reflux (internal solution temperature 145 °C, oil bath 150–155 °C) for 4 h; then a Dean–Stark trap was inserted, and the distillate was removed until the temperature of the reaction solution reached 200 °C. The cooled contents of reaction flask were poured into water (30 mL), and the suspension was extracted with ether (4 × 25 mL). The ether extract was washed with aqueous NaOH (0.1 N, 2 × 25 mL). Evaporation of the dried ether layer gave **1d** (2.2 g, 100%) as a clear liquid: IR (neat) ν_{max} 3000–3010 (aromatic) 2750–3000 (Bohlmann bonds), 1000–1100 cm^{-1} (C–O–C); ^1H NMR ($DCCl_3$) δ 1.48–1.84 [4 H, m, H(1,5,9)], 2.3 [2 H, br d, H_a(6,8) $^2J_{HH}$ = 11 Hz], 2.92 [2 H, br d, H_e(6,8), $^2J_{HH}$ = 11 Hz], 3.48 [2 H, s, H(7′)], 3.76 [2 H, br d, H_a(2,4), $^2J_{HH}$ = 10 Hz], 3.92 [2 H, br d, H_e(2,4), $^2J_{HH}$ = 10 Hz], 7.2–7.4 (5 H, m, Ar H); ^{13}C NMR, see Table I; mass spectrum, m/e calcd for $C_{14}H_{19}NO$ (M^+) 217.1467, found (M^+) 217.1466. This sample of **1d** was converted to perchlorate **7** for final characterization.

Perchlorate of *N*-Benzyl-3-oxa-7-azabicyclo[3.3.1]nonane (7). Crude amine **1d** (1.0 g, 4.6 mmol) was dissolved in dry ether (20 mL), and the solution was cooled (ice). A solution of 60% aqueous $HClO_4$ (0.0 g, 4.6 mmol) in dry ether (5 mL) was added dropwise (30 min). The white precipitate, which separated out immediately, was washed with dry ether (3 × 10 mL), was filtered, and was dried (aspirator). Recrystallization (H_3CCN–ether, 1:5) gave 1.45 g (99.2%) of **7** as a pure white solid: mp 191–192.5 °C dec; IR (KBr) ν_{max} 1070–1120 (ClO_4), 1000–1120 cm^{-1} (C–O–C); ^1H NMR [D_2O, $(CH_3)_3SiCD_2CD_2CO_2Na$ (TSP)] δ 1.90–2.20 [4 H, br m, H(1,5,9)], 3.20–4.20 [8 H, m, H(2,4,6,8)], 4.34 [2 H, s, H(7′)], 7.54 (5 H, s, Ar H); ^{13}C NMR, see Table I. Anal. Calcd for $C_{14}H_{20}ClNO_5$: C, 52.92; H, 6.34; N, 4.41. Found: C, 53.01; H, 6.40; N, 4.46.

***N*-Benzyl-3-oxa-7-azabicyclo[3.3.1]nonan-9-ols (1b′,b″).** To a solution of the amino ketone **1a** (0.6 g, 2.6 mmol) in 2-propanol (10 mL) were added $NaBH_4$ powder (0.6 g, 16 mmol) and water (5 mL), and the reaction mixture was stirred overnight. A clear solution was obtained which, upon acidification with aqueous HCl (10%, 25 mL) followed by basification with aqueous NaOH (10%, 15 mL), gave a suspension. The suspension was extracted with $HCCl_3$ (3 × 50 mL), and the extracts were dried. Upon evaporation, the dried organic extract yielded 0.6 g of crude **1b** as a brown oil which was found to be a mixture of two components, **1b′** and **1b″** (Scheme III), via TLC analysis [neutral alumina, $HCCl_3$–H_3COH (40:1); R_f 0.65 and 0.35]. This brown oil was chromatographed on a column (neutral alumina, ca. 60 g) with a 100-mL total portion of each of the following as eluants in order: petroleum ether (bp 37–60 °C); petroleum ether–C_6H_6 (3:1, 1:1, and 1:3); C_6H_6; C_6H_6–ether (3:1, 1:1, and 1:3); ether; ether–$H_3CCO_2C_2H_5$ (3:1), 1:1, and 1:3); $H_3CCO_2C_2H_5$; ether–$HCCl_3$ (3:1, 1:1, and 1:3); $HCCl_3$; $HCCl_3$–H_3COH (40:1). However, only mixtures of isomers of **1b** (0.4 g) were obtained by using $HCCl_3$–H_3COH (1:40, 100 mL). A portion of the isomeric mixture (0.250 g) was rechromatographed on a Florisil (4 g) column by using *n*-C_6H_{14} (100 mL) $HCCl_3$ (100 mL) and $HCCl_3$–H_3COH (40:1), 100 mL) as eluants in the order given. Two isomers (**1b′** with R_f 0.65, 0.100 g; **1b″** with R_f 0.35, 0.100 g; mixture of **1b′** and **1b″**, 0.050 g) were separated by using $HCCl_3$–H_3COH (40:1, 100 mL) as eluants. The isomer **1b″** (R_f 0.35) was found to have the following characteristics: mp 200–201 °C dec; IR (KBr) ν_{max} 3350–3450 (OH), 1000–1200 cm^{-1} (C–O–C); ^1H NMR ($DCCl_3$) δ 2.2 [2 H, dd, H_a(6,8), $^2J_{HH}$ = 11 Hz, $^3J_{HH}$ = 4 Hz], 3.15 [2 H, br t, H_e(6,8), $^2J_{HH}$ = 11 Hz], 3.4 [1 H, br s, OH, D_2O exchanged], 3.48 [2 H, s, H(7′)], 3.70 [2H, br dd, H_a(2,4), $^2J_{HH}$ = 11 Hz], 3.74 [1 H, br s, H(9)], 3.80 [2 H, br dd, H_e(2,4), $^2J_{HH}$ = 11 Hz], 7.25 (5 H, m, Ar H); ^{13}C NMR (D_3COD), see Table I; mass spectrum, m/e calcd for $C_{14}H_{17}NO_2$ (M^+) 233.1416, found (M^+) 233.1416. Analysis of the ^1H NMR spectrum of the other isomer **1b′** (R_f 0.65) indicated the presence of ^1H NMR signals at δ 1.5 which were not expected for **1b′** (and might be due to some impurity). Therefore, the isomers **1b′** was rechromatographed on a Florisil column (4 g) with *n*-C_6H_{14} (100 mL), $HCCl_3$ (100 mL), and $HCCl_3$–H_3COH (40:1, 100 mL) in that order. Isomer **1b′** (0.050) was separated by using $HCCl_3$–H_3COH (40:1, 100 mL) and was analyzed: mp 150–155 °C dec; IR (KBr) ν_{max} 3350–3450 (OH), 1000–1200 cm^{-1} (C–O–C); ^1H NMR ($DCCl_3$) δ 1.9 [2 H, br d, H(1,5)], 2.5 [2 H, br dd, H_a(6,8), $^3J_{HH}$ = 10 Hz], 3.1 [2 H, br dd, H_e(6,8), $^3J_{HH}$ = 10 Hz], 3.42 [1 H, br s, OH, exchanged in D_2O], 3.6 [2 H, br s, H(7′)], 3.8 [3 H, br dd, H_a(2,4) and H(9)], 4.16 [2 H, br dd, H_e(2,4)], 7.3 [5 H, br s, Ar H]; mass spectrum, m/e calcd for $C_{14}H_{17}NO_2$ (M^+) 233.1416, found (M^+) 233.1425. TLC analysis ($HCCl_3$–CH_3OH, 40:1) of **1b′** showed only one spot, but the ^1H NMR analysis indicated trace amounts of an impurity.

***N*-Benzyl-9-phenyl-3-oxa-7-azabicyclo[3.3.1]nonan-9-ols (1c′ and 1c″).** The addition of a solution of ketone **1a** (0.56 g, 2.4 mmol) in dry ether (20 mL) to an ethereal solution of C_6H_5MgBr [prepared from Mg (90 mg, 3.6 mmol) and bromobenzene (freshly distilled; 0.57 g, 3.6 mmol) in dry ether (10 mL)] resulted in the immediate separation of a white precipitate. The resulting suspension was stirred (magnetic) overnight under an N_2 atmosphere. The addition complex was decomposed by adding ice-cold, saturated, aqueous NH_4Cl (100 mL) to obtain a clear aqueous and ether layer. The ether layer was separated, and the aqueous layer was extracted with ether (2 × 50 mL). These ether extracts were combined and were dried. Evaporation of the solvent gave a semisolid. Upon trituration of the semisolid with Skelly B (5 mL), a white solid (0.415 g) was obtained. Recrystallization (Skelly B) gave 0.271 g (36.2%) of alcohol **1c** as a white powder, mp 91–95 °C. TLC [neutral alumina, $HCCl_3$–H_3COH (40:1, 20 mL)] analysis indicated the presence of two components (R_f 0.84 and 0.51). This isomeric mixture (0.200 g) was chromatographed on a Florisil (20 g) column with *n*-C_6H_{14} (100 mL), $HCCl_3$ (100 mL), and $HCCl_3$–H_3COH (100 mL) of each of 40:1, 20:1, and 10:1 mixtures). Unfortunately only a mixture of compounds was eluted with all of the above eluants. The column was then stripped with H_3COH (200 mL), and the original mixture (0.150 g) was recovered after evaporation of the solvent. This mixture was rechromatographed on a Florisil (15 g) column by using *n*-C_6H_{14} (100 mL), $HCCl_3$ (100 mL), and $HCCl_3$–H_3COH (40:1, 200 mL). One isomer (**1c′**, Scheme III, R_f 0.84, 0.020 g) was separated by using $HCCl_3$–H_3COH (40:1, 200 mL) and was found to possess the following physical and spectral characteristics: mp 157–159 °C dec; IR (KBr) ν_{max} 3300–3350 (OH), 1000–1200 cm^{-1} (C–O–C); ^1H NMR (D_3COD) δ 2.62 [2 H, br s, H(1,5)], 3.20 [2 H, br dd, H_a(6,8), ^2J = 11 Hz], 3.4 [2 H, br dd, H_e(6,8), $^3J_{HH}$ = 11 Hz], 3.6 [2 H, br s, Ar CH_2], 3.72 [2 H, br dd, H_a(2,4), $^3J_{HH}$ = 11 Hz], 3.84 [1 H, br s, H(9)], 3.94 [2 H, br dd, H_e(2,4), $^3J_{HH}$ = 11 Hz], 7.88 [10 H, m, Ar H]; ^{13}C NMR (D_3COD), see Table I; mass spectrum, m/e calcd for $C_{27}H_{23}NO_2$ (M^+) 309.1739, found 309.1741. The chromatographic

eluation was continued by using $HCCl_3$–H_3COH (100 mL of each of 40:1, 20:1, and 10:1 mixtures) as eluant, and only a mixture was obtained. The column was stripped with H_3COH (200 mL), and a mixture (0.100 g) was recovered by evaporation of the solvent. This new mixture was rechromatographed on a Florisil (10 g) column with n-C_6H_{14} (100 mL), $HCCl_3$ (100 mL), and $HCCl_3$–CH_3OH (100 mL of each 40:1, 20:1, 10:1, 3:1, 1:1, and 1:3 mixtures) as eluants. Again only a mixture (TLC; R_f 0.84 and 0.50) was obtained initially, but in the last stage [using $HCCl_3$–H_3COH (1:3), 200 mL] a single component (R_f 0.52, 0.015 g) was separated and was found to possess the following characteristics: mp 270–275 °C dec; IR (KBr) ν_{max} 2960, 2920, 1730, 1450, 1260, 1100–1200 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.9 (6 H, br t) 1.42 (10 H, br m), 4.2 (2 H, br d) 7.2–7.7 (2 H, br m, Ar H). The above data did not correspond to the expected second isomer **1c**″ (Scheme III) which might have been altered or degraded on the column during the repeated eluation.

6,8-Bis(2-chlorophenyl)-3-oxa-7-azabicyclo[3.3.1]nonan-9-ol (1f). Ketone **1e** (0.100 g, 0.3 mmol) was suspended in anhydrous methanol (10 mL), and $NaBH_4$ powder (0.060 g, 1.6 mmol) was added in one portion; the reaction mixture was stirred (magnetic) overnight. A clear solution was obtained which, upon acidification with aqueous HCl (10%, 20 mL) followed by basification with aqueous NaOH (10%, 30 mL), gave a white solid. The white solid was filtered (suction), was washed with ice-cold water (5 × 20 mL), and was dried (aspirator). This mixture of isomers (0.097 g, 97%) was evaluated as such: mp 130–140 °C; IR (KBr) ν_{max} 3500 (OH), 1000–1200 cm^{-1} (C–O–C); ^1H NMR ($DCCl_3$) δ 2.0 [2 H, br s, H(1,5), $W_{1/2}$ = 8 Hz], 1.6–2.2 (2 H, br s, NH, exchanged with D_2O), 3.5 [2 H, br t, H(9)], 3.8 [2 H, br t, H_a(2,4)], 4.4 [2 H, br m, H_e(2,4)], 5.3 [2 H, br s, H_a(6,8), $W_{1/2}$ = 6 Hz], 7.3 (6 H, m, Ar H), 7.9 (2 H, br d, Ar H); mass spectrum, m/e calcd for $C_{19}H_{19}Cl_2NO_2$ (M^+) 363.0793, found, (M^+) 363.0790; TLC [neutral alumina, $HCCl_3$–H_3COH (40:1)] R_f 0.85 and 0.70.

IR (CCl_4) spectral analysis [0.05 mm calibrated, sealed, liquid cell (NaCl) Beckmann] were recorded for this isomeric mixture on three different (1.2×10^{-2}, 6.0×10^{-3} and 3.0×10^{-3} M) concentrations to differentiate between an intra- and an intermolecular hydrogen bonded OH group. Only a sharp absorption band at 3614 cm^{-1} was detected at all three concentrations.

Attempted Synthesis of 6,8-Diphenyl-3-oxa-7-azabicyclo[3.3.1]nonan-9-one. Method I. A mixture of ketone **5** (0.1 g, 0.4 mmol), ammonium acetate (0.03 g, 0.4 mmol), and anhydrous ethanol (20 mL) was boiled (oil bath, 85 °C) with stirring (magnetic) under N_2 for 24 h. Upon cooling (overnight, refrigerator), the reaction mixture yielded a yellow solid (0.08 g, mp 180–183 °C dec) which was identified as **5**.

Method II. Into a solution of ketone **5** (0.100 g, 0.4 mmol) in C_2H_5OH (20 mL) was passed ammonia (gas), and the solution was heated (oil bath, 60 °C) with stirring (magnetic) under N_2 for 10 h. When the reaction mixture cooled, starting material **5** (0.09 g, mp 183–186 °C dec) precipitated. Changing the solvent [95% C_2H_5OH, $(CH_3)_2CHOH$, $HCCl_3$–C_2H_5OH (1:1)] and reaction time (12 to 24 h) did not result in conversion of the starting material **5** to a product.

6,8-Diphenyl-7-methyl-3-oxa-7-azabicyclo[3.3.1]nonan-9-one. A mixture of ketone **5** (0.1 g, 0.4 mmol), methylamine hydrochloride (0.05 g, 0.7 mmol), sodium acetate (0.1 g, 0.7 mmol), and C_2H_5OH–$HCCl_3$ (1:1, 10 mL) was heated (oil bath, 60 °C) with stirring (magnetic) under N_2 for 12 h. When the reaction mixture cooled, the starting material **5** (0.085 g, mp 183–85 °C dec) precipitated.

6,8-Diphenyl-7-benzyl-3-oxa-7-azabicyclo[3.3.1]nonan-9-one. Freshly distilled benzylamine (1.1 g, 10 mmol) and glacial H_3CCO_2H (0.6 g, 10 mmol) were mixed to form a white solid which was dissolved in ethanol (20 mL) by stirring (magnetic). Benzaldehyde (2.2 g, 20 mmol) and ketone **4** (1 g, 10 mmol) were added to the above solution, and the resulting solution was heated (oil bath, 60 °C) under N_2. The solution became yellow (0.5 h), and a solid began to separate out (1.5 h). Upon continued heating of the mixture, a large amount of solid separated out, and the reaction mixture was allowed to cool (room temperature) and was then filtered (suction) to obtain a yellow solid (1.2 g): mp 185–187 °C; the ^1H NMR and IR spectra were found to be identical with those of **5**. A mixture of **5** (0.1 g, 0.4 mmol) and benzylamine (0.05 g, 0.4 mmol) in C_2H_5OH–$HCCl_3$ (1:1, 10 mL) was boiled for 24 h and then was allowed to cool. A yellow solid (0.07 g, mp 180–183 °C dec) precipitated and was identified as the starting material **5**.

Table IV. Summary of Crystallographic Data for 6,8-Bis(2-chlorophenyl)-3-oxa-7-azabicyclo[3.3.1]nonan-9-one (1e)

molecular formula	$C_{19}H_{17}NO_2Cl_2$	
molecular weight	362.3 g mol^{-1}	
linear abs coeff	36 cm^{-1} (Cu K$\bar{\alpha}$)	
space group	*Pnam*	
cell dimens	at −135 °C	room temp
a, Å	9.353 (4)	9.4790 (9)
b, Å	7.733 (4)	7.7822 (10)
c, Å	23.03 (2)	23.150 (5)
V, Å^3	1665.7	1707.7 (Z = 4)
density calcd (room temp)	1.409 g cm^{-3}	
density obsd (flotation in KI solution)	1.395 g cm^{-3}	
crystal size	0.27 × 0.25 × 0.12 mm	
no. of rflctns measd	1763	
no. of rflctns obsd ($I > 2\sigma(I)$)	1505	
final R, obsd rflctns	0.037	
final R_w, obsd rflctns	0.041	

Crystallographic Experimental Data. Bispidinone **1e** was recrystallized from 2-propanol as thick plates, the plate faces being (001). Weissenberg and precession photographs showed the crystal to be orthorhombic, space group $Pna2_1$ or *Pnam*. The unit cell dimensions (see Table IV) and intensity data were measured at 138 ± 2 K with an Enraf-Nonius CAD-4 diffractometer fitted with a low-temperature apparatus.

The cell parameters (Table IV) were obtained by a least-squares fit of the 2θ values of 48 reflections both at room temperature and at 138 ± 2 K by using Cu Kα_1 radiation (λ = 1.5405 Å). The intensities of all reflections with $1° \le 2\theta \le 150°$ were measured with Cu K$\bar{\alpha}$ radiation (λ = 1.5418 Å) by using the θ–2θ scan technique. The angular scan width was variable and taken to be $(0.9 + 0.14 \tan \theta)°$. A receiving aperture with a variable width of $(3.5 + 0.86 \tan \theta)$ mm and a constant height of 4 mm was located at a distance of 173 mm from the crystal. The maximum scan time for a reflection was 60 s, with two-thirds of the time spent scanning the peak and the remaining one-third divided equally between the high- and low-θ backgrounds. The intensities of three standard reflections measured after every 120 min of X-ray exposure time indicated no appreciable decomposition of the crystal during the course of the data collection. A total of 1763 unique reflections were measured of which 258 were considered unobserved [$I < 2\sigma(I)$]. All intensity data were corrected for Lorentz and polarization factors, and numerical absorption corrections were applied (μ = 36.0 cm^{-1}).

The structure was determined by application of the program MULTAN 78,[38] with the space group assumed to be $Pna2_1$. An E map, calculated by using 250 reflections ($E \ge 1.49$), with the highest combined figure of merit (2.46) gave the positions of all 24 nonhydrogen atoms in the first 30 peaks. An apparent mirror plant bisecting the molecule was consistent with the centrosymmetric distribution of the E's, and the structure was refined in the space group *Pnam*, a nonstandard setting of *Pnma*.

The structure was completed and refined by using the SHELX[39] programs. Following initial refinement of the nonhydrogen atoms, the hydrogen atoms were located in a difference map. Refinement was by full-matrix least-squares methods with anisotropic thermal parameters for the nonhydrogen atoms and istropic thermal parameters for the hydrogen atoms. Each structure amplitude was assigned an experimental weight, w_F, based on counting statistics.[40] In the final cycles of refinement, the quantity minimized was $\sum w_F(|kF_o| - |F_c|)^2$. The maximum parameter shift

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on the final cycle of refinement was 2% of its estimated standard deviation. In the final difference Fourier synthesis, there were peaks of +0.3 and -0.3 e/Å^3 around the Cl atom and a peak of 0.4 e/Å^3 in the middle of the C(1)-C(9) bond. Final parameters are given in Tables V-VII and may be obtained as supplementary material.

Acknowledgment. We gratefully acknowledge support of this work by the College of Arts and Sciences of the Oklahoma State University in the form of salary (to K.D.B.) and the USPHS, National Cancer Institute, in the form of a grant (to D.v.d.H.; No. CA 17562).

Registry No. 1a, 77716-01-9; **1b'**, 77716-02-0; **1b''**, 77716-03-1; **1c'**, 77716-04-2; **1c''**, 77716-05-3; **1d**, 77716-06-4; **1e**, 77716-07-5; **1f** (isomer 1), 77716-08-6; **1f** (isomer 2), 77716-09-7; **1g**, 77743-50-1; **1h**, 77789-89-0; **2**, 18458-71-4; **3**, 18458-72-5; **4**, 29943-42-8; **5**, 62513-33-1; **6**, 77727-42-5; **7**, 77716-10-0; benzaldehyde, 100-52-7; 2-chlorobenzaldehyde, 89-98-5; paraformaldehyde, 30525-89-4; benzylamine, 100-46-9; bromobenzene, 108-86-1.

Supplementary Material Available: Table V (fractional coordinates of the unique atoms in **1e**), Table VI (hydrogen atom parameters), and Table VII (anisotropic thermal parameters) (3 pages). Ordering information is given on any current masthead page.

Syntheses of Four Thiol-Substituted Crown Ethers

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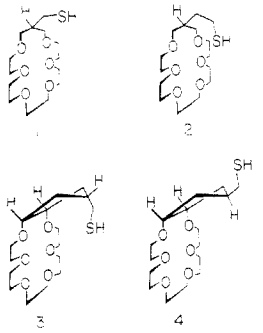
Received February 4, 1981

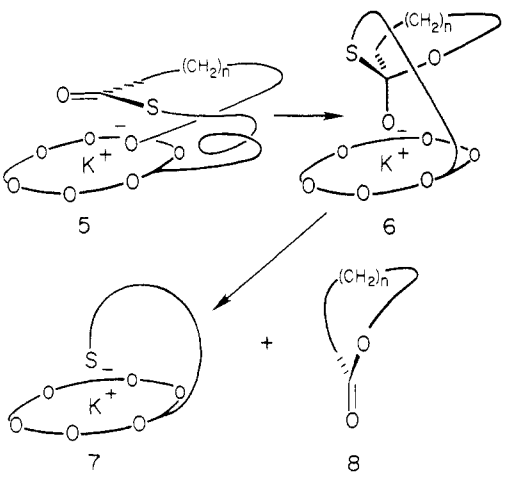
Approaches to thiol-substituted crown ethers of the 18-crown-6 and 19-crown-6 classes are described. Different modes of covalent attachment of the thiol to the crown ether provide variations in the spatial relationship of the thiol to the crown ether binding site.

Interactions of polyether ionophores with a broad range of cations have been extensively examined.[2] The nature of the host-guest[3] interaction is governed by the number, spacing, and identity of the donor atoms which make up the host binding site. Variations in substituents proximate to the binding sites have been used to alter binding specificity and/or chemical reactivity of the ionophores toward substrate ion pairs.[4] Herein we describe the synthesis of the crown ether series **1-4** in which the spatial relationship

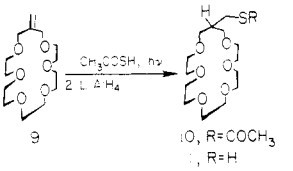


between the thiol and the binding site is varied through changes in the appendage between thiol and crown ether. The accompanying paper[5] describes the syntheses of potassium ω-alkoxy thioesters (e.g., **5**, Scheme I) from thiols **1-4** and discusses the effect of ionophore structure on the conversion of these reactive intermediates into macrocyclic lactones (macrolides) as depicted schematically in structures **5** → **6** → **7** + **8**.

Scheme I



Scheme II



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