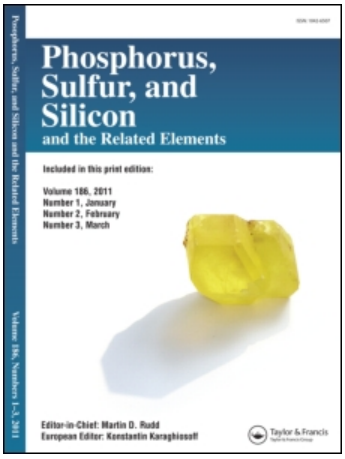

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THE MANNICH CONDENSATION WITH 1-HETERA-4-CYCLOHEXANONES. THE NOVEL FORMATION OF 7-BENZYL-3-HETERA-7-AZABICYCLO[3.3.1]NONAN-9-ONES, 3,6-DIBENZYL-HEXAHYDRO-8a-METHOXY *5H*-4a,8-(METHANO-HETERAMETHANO)-*2H*-PYRIDO[3,4-*e*]-1,3-OXAZINES, AND 2,4,10,12-TETRABENZYL-2,4,10,12-TETRAAZA-15-HETERADISPIRO[5.1.5.3]HEXADECAN-7-ONES. SINGLE CRYSTAL X-RAY DIFFRACTION ANALYSES OF 3,6-DIBENZYLHEXAHYDRO-8a-METHOXY-*5H*-4a,8-(METHANOTHIOMETHANO)-2*H*-PYRIDO[3,4-*e*]-1,3-OXAZINE AND 2,4,10,12-TETRABENZYL-2,4,10,12-TETRAAZA-15-THIADISPIRO[5.1.5.3]HEXADECAN-7-ONE

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THE MANNICH CONDENSATION WITH 1-HETERA-4-CYCLOHEXANONES. THE NOVEL FORMATION OF 7-BENZYL-3-HETERA-7-AZABICYCLO[3.3.1]NONAN-9-ONES, 3,6-DIBENZYLHEXAHYDRO-8a-METHOXY 5*H*-4a,8-(METHANOHETERAMETHANO)-2*H*-PYRIDO[3,4-*e*]-1,3-OXAZINES, AND 2,4,10,12-TETRABENZYL-2,4,10,12-TETRAAZA-15-HETERADISPIRO[5.1.5.3]HEXADECAN-7-ONES. SINGLE CRYSTAL X-RAY DIFFRACTION ANALYSES OF 3,6-DIBENZYLHEXAHYDRO-8a-METHOXY-5*H*-4a,8-(METHANOTHIOMETHANO)-2*H*-PYRIDO[3,4-*e*]-1,3-OXAZINE AND 2,4,10,12-TETRABENZYL-2,4,10,12-TETRAAZA-15-THIADISPIRO[5.1.5.3]HEXADECAN-7-ONE.

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We report for the first time the formation of unusual multicyclic products from the condensation of 1-hetera-4-cyclohexanones in a Mannich reaction with benzylamine, formaldehyde, and acetic acid in methanol. In addition to the expected ketones, namely 7-benzyl-3-hetera-7-azabicyclo[3.3.1]nonan-9-ones, there were obtained from 4-thianone and 4-selenanone the following systems. Repeated Mannich condensations produced 3,6-dibenzylhexahydro-8a-(methoxy-5*H*-4a,8-(methanothiomethano)-2*H*-pyrido[3,4-*e*]-1,3-oxazine, 3,6-dibenzylhexahydro-8a-methoxy-5*H*-4a,8-(methanoselenomethano)-2*H*-pyrido[3,4-*e*]-1,3-oxazine, 2,4,10,12-tetrabenzyl-2,4,10,12-tetraaza-15-thiadispiro[5.1.5.3]-hexadecan-7-one, and 2,4,10,12-tetrabenzyl-2,4,10,12-tetraza-15-selenadispiro[5.1.5.3]hexadecan-7-one. Single crystal X-ray diffraction analysis confirmed the structures of the first three solids. Using tetrahydro-4*H*-pyran-4-one, it was possible to obtain 7-benzyl-3-oxa-7-azabicyclo[3.3.1]nonan-9-one and 2,4,10,12-tetrabenzyl-2,4,10,12-tetraaza-15-oxadispiro[5.1.5.3]hexadecan-7-one. To the best of our knowledge, these systems have not been previously recorded, and the method reported herein is a one-step approach. NMR analyses, including ^{1}H, ^{13}C, and ^{15}N analyses, were completed and support all of the structures described herein. A mechanism is briefly outlined to explain the formation of these novel polycyclic heterocycles.

Key words: Mannich reaction; 1-hetera-4-cyclohexanones; 3,6-dibenzylhexahydro-8a-(methoxy-5*H*-4a,8-(methanoheteromethano)-2*H*-pyrido-[3,4-*e*]-1,3-oxazine; 2,4,10,12-tetrabenzyl-2,4,10,12-tetraaza-15-heteradispiro[5.1.5.3]hexadecan-7-one; 7-benzyl-3-hetera-7-azabicyclo[3.3.1]nonan-9-ones; selenium and sulfur derivatives.

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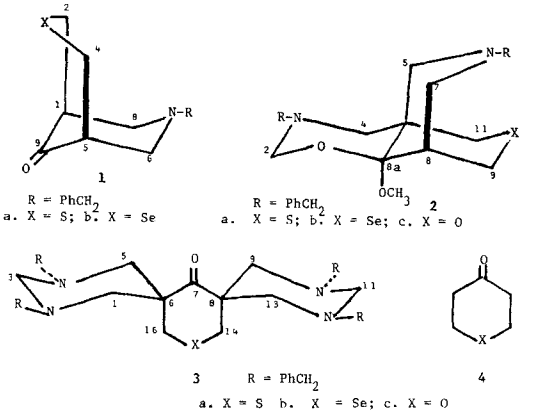
INTRODUCTION

Condensations of cyclic ketones in the Mannich reaction are known[3] including those in which 1-hetera-4-cyclohexanones participate[4,5] as well as carbocyclic analogues.[6] All mechanisms considered as viable to explain the Mannich reaction commonly include the initial formation of an iminium ion of the type $R\overset{+}{N}H{=}CH_2$.[3,4,5,7] We report herein the isolation and identification of two novel multicyclic systems from several related ions. To the best of our knowledge, the families of the title compounds have not been reported in the literature. The basic structure in the oxazine portion in one system is reminiscent of that found in the morphine framework, and thus the synthetic strategy outlined represents a potential novel entry into these heterocyclic analogues of opiates.

RESULTS AND DISCUSSION

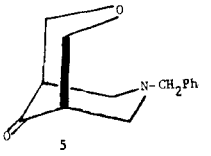
In the synthetic approach to 3-hetera-7-azabicyclo[3.3.1]nonan-9-ones **1**,[5a,f,g] it has now been discovered that two additional products are formed, namely **2** and **3**, the quantities of which appear to depend upon the ratio of starting materials.



For the sulfur derivatives the initial reaction mixture consisted of 4-thianone (**4a**, one equivalent), benzylamine (1 equivalent), acetic acid (1.5 equivalent), paraformaldehyde (8 equivalents), and methanol. It was possible to isolate both **1a** and **2a** (ratio 5.7:1), respectively. With two equivalents of benzylamine and a very slight excess of acetic acid, the yields of **2a** were somewhat variable but commonly from 40–45%. The spiro compound **3a** was also obtained in varying yields but the maximum return was obtained when **4a** (one equivalent, added dropwise to the other components), benzylamine (2 equivalents), paraformaldehyde (2.2 equivalents), acetic acid (2.2 equivalents) and methanol were heated at reflux [**1a**:**2a**:**3a** = 5.5:1.3:1]. In similar fashion, 4-selenanone (**4b**, one equivalent) with benzylamine (1 equivalent), acetic acid (1 equivalent), and a large excess of paraformaldehyde in methanol were allowed to react under nearly identical conditions. Spiro ketone **3b** precipitated from the initial reaction mixture in low yield. Partitioning the reaction mixture between ether and water afforded

both ketones **1b** and **2b** [≈2:1]. Other ratios of reagents gave varying amounts of these products along with a complex mixture.

The ketone **5** (R = $PhCH_2$) is suspected[5j] to be a chair–chair form and is generated under conditions in which benzylamine and acetic acid (one equivalent each) are heated with an excess of paraformaldehyde (8 equivalents) and one equivalent of tetrahydro-4*H*-pyran-4-one (**4c**) in methanol. By changing the ratio of benzylamine, acetic acid, and **4c** to 2:2:1, **5** was formed while **3c** precipitated from the cooled reaction mixture in modest yield. The residual mixture and all other mixtures were extremely complex regardless of the conditions employed. Both ^1H and ^{13}C NMR analyses of these mixtures strongly suggested the presence of **2c** but it has not been possible to isolate the system. A primary side product in these reactions was the hexahydrotriazine **6**. In the *absence* of a ketone, **6** is a known product[3,8] from this type of reaction using aqueous formaldehyde. With methanol as solvent, we have been able to obtain **6** in slightly higher yield.



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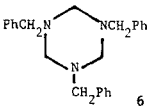

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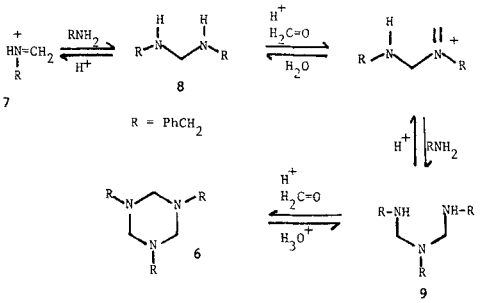
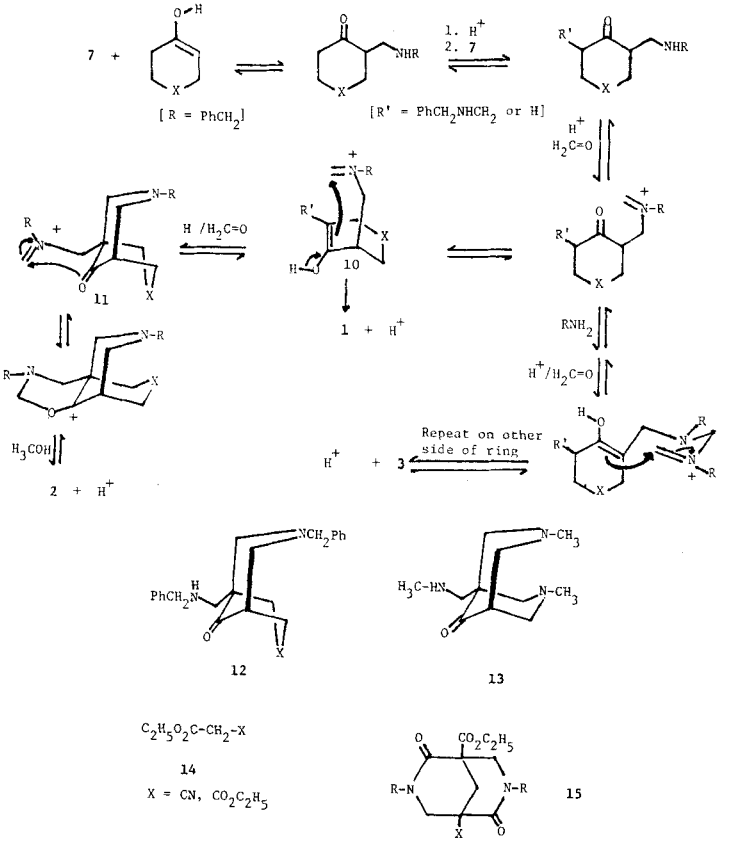
Assuming that $PhCH_2\overset{+}{N}H{=}CH_2$ is the initial intermediate formed in our reactions, the following Schemes can explain the formation of **6** and **1–3**. Amines like **6**, **8**, and **9** have been suggested to form via the Mannich reaction under *basic* conditions but are reportedly unstable under acidic conditions.[3,10] Consequently,



7 8 6 9

the reversible formation of the iminium ions shown in the Scheme is reasonable. Presumably, all three iminium species are present to some extent in the equilibrium. It is noted that in the conversion of intermediate **10** to **11**, ketone **12** would be the precursor of **11** (R = $PhCH_2$). Ketone **12** is very similar to **13** isolated and reported by Smissman and Reunitz when *N*-methylpiperidin-4-one, methylamine, acetic acid, and paraformaldehyde were allowed to react.[9] It is our assumption that the chair-boat form prevails in **12** when X = S or Se although this may not be the case in which X = O (or NR). Both **1a**[5f] and **1b**[5a] are known to be chair-boat forms in the solid state and a derivative of **5** is known to be a chair-chair form in the solid state[5j] and all are close analogues of **12** and **13**, respectively, which we believe are members of the family which include the precursors of **3**. Interestingly, it has been reported recently that 1,3,5-trialkylhexahydro-1,3,5-triazines and members of **14** under mild acidic conditions yield



3,7-diazabicyclo[3.3.1]nonan-2,6-diones (**15**).[21] The authors noted that the reaction proceeded either with stoichiometric or catalytic amounts of acid.

A search of the literature has *not* revealed any members of the families of **2** or **3**. Both ^{1}H and ^{13}C NMR analyses (fully decoupled and off resonance) were extremely helpful in the structure elucidation but HETCOR 2-D plots proved indispensable for the interpretation and assignment of signals in the spectra. Both HETCOR 2-D plots are shown in Figures 1 and 2 while the ^{1}H and ^{13}C signals are summarized in Tables I and II for **2a** and **2b**, respectively. Since the analyses are rather involved, the selenium system **2b** will serve to illustrate the rationale for the assignments. The off-resonance ^{13}C singlet for C(9) in models **16** and **17** occurred at 95.6 and 95.1 ppm, respectively, while in **2a** and **2b** the signals appeared at 96.9 and 97.6 ppm, respectively, and were assigned to the counterpart C(8a) in each case. Correspondingly, in **2b** the quartet centered at 46.5 ppm was assigned to CH_3O (which occurred at 46.9 ppm in **16**). The extreme downfield peak at 78.8 ppm in **2b** was presumed to be from C(2) which is bonded to both oxygen and nitrogen. Signals at 20.1 and 25.1 ppm were assigned to C(9) and C(11), respectively, and correlate well with that at 21.1 ppm in model system **18** for C(2,4).[5a] It is interesting that the ^{13}C signal at 20.1 ppm correlated with an *AB* quartet for an upfield ^{1}H doublet at δ 2.53 and a downfield doublet that was part of complex pattern centered at δ 3.50. A careful analysis of the coupling

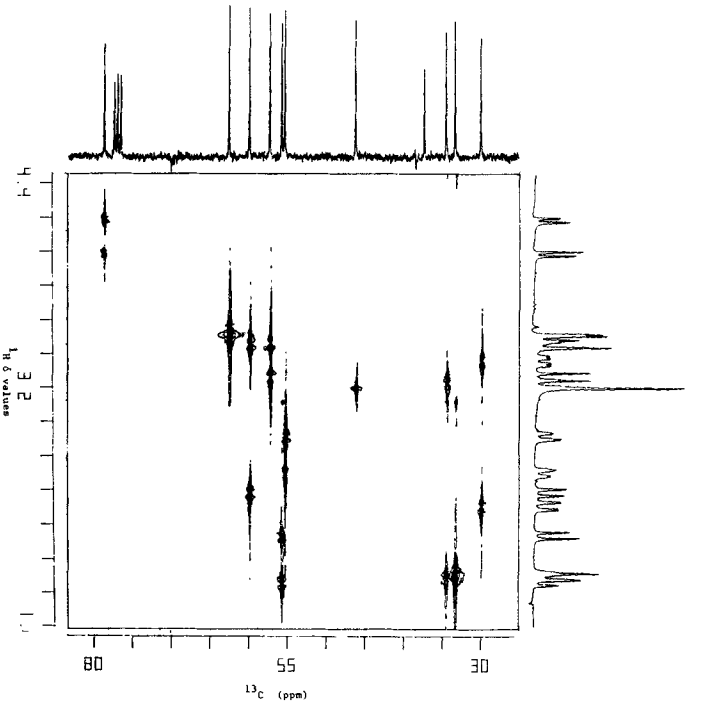


FIGURE 1 HETCOR 2-D plot for **2a**.

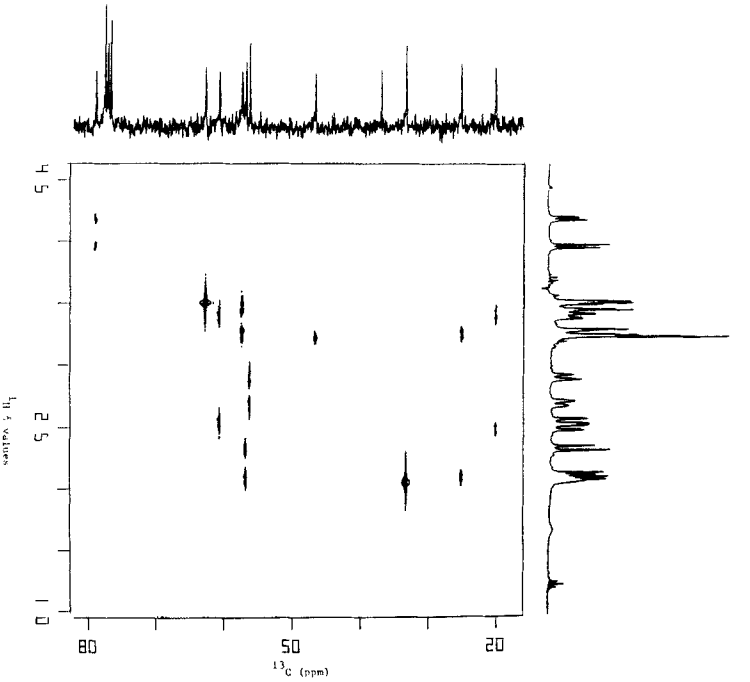
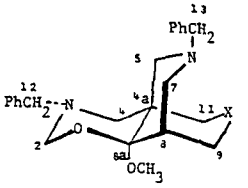


FIGURE 2 HETCOR 2-D plot for **2b**.

TABLE I

^{1}H NMR chemical shifts[a] of **2a,b**



2a. X = S
b. X = Se

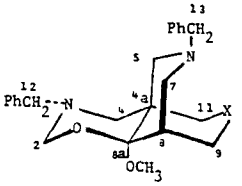
	2a	**2b**
H(2)ax	4.02	3.97
H(2)eq	4.18	4.21
H(4)ax	2.74	2.72
H(4)eq	2.95	2.93
H(5)ax	2.12	2.11
H(5)eq	2.37	2.37
H(7)ax	3.31	3.29
H(7)eq	3.50	3.51
H(8)	2.13	2.09
H(9)ax	2.54	2.53
H(9)eq	3.39	3.47
H(11)ax	2.08	2.13
H(11)eq	3.25	3.29
H(12)	2.62	2.58
H(12)	3.49	3.44
H(13)	3.55	3.53
H(13)	—	—
CH_3O	3.22	3.25
Ar–H	7.22–7.38 7.58	7.26–7.64

[a] Proton NMR assignments as based on HETCOR spectrum. **2a,b** run in $DCCl_3$.

constant (^2J = 11 Hz) of the upfield doublet with various peaks in the downfield multiplet permitted an assignment for the shift (δ 3.47) of the downfield doublet for H(9)eq. A similar treatment of the proton AB quartet associated with the peak at 25.1 ppm allowed assignment of the ^{1}H signals at δ 2.13 and 3.29 to protons attached to C(9, 11). It was presumed that axial protons of a methylene group would be upfield of the equatorial proton. This is supported by the observation that H(11) is *gauche* to both C(8a)–O and to C(4a)–C(4) while H(9) axial is *gauche* to only C(8a)–O. However, H(11) equatorial has two similar interactions [*gauche* to both C(4a)–C(5) and to C(4a)–C(4)] while H(9) equatorial has one [*gauche* to C(7)–C(8)]. The ^{1}H shift for the axial proton (δ 2.13) correlated with the ^{13}C signal at 25.1 ppm and the former is at higher field than that (δ 2.53) which correlated with the ^{13}C signal at 20.1 ppm. The same was true for the equatorial protons (δ 3.29 and 3.47) associated with these carbons. Thus, the axial proton upfield was assigned to H(11) axial, the upfield equatorial proton to H(11) equatorial, and the carbon peak at 25.1 ppm to C(11). As a result, the signals at δ 2.53 and 3.47 were assigned to H(9) axial and H(9) equatorial, respectively, with the carbon peak at 20.1 ppm being assigned to C(9) in **2b**.

TABLE II

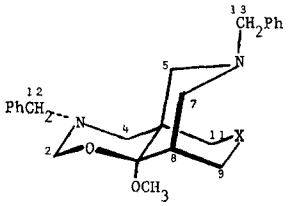
^{13}C NMR chemical shifts[a,b] for **2a,b**

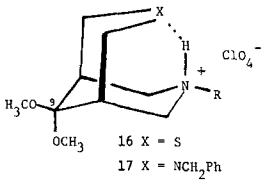


2a. X = S
2b. X = Se

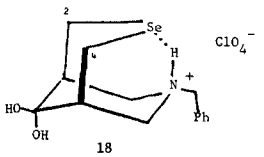
	2a	**2b**
C(2)	78.8 (t)	78.7 (t)
C(4)	55.4 (t)	56.1 (t)
C(4a)	37.4 (s)	36.8 (s)
C(5)	55.8 (t)	56.7 (t)
C(7)	57.3 (t)	57.3 (t)
C(8)	33.4 (d)	33.2 (d)
C(8a)	96.9 (s)	97.7 (s)
C(9)	30.1 (t)	20.1 (t)
C(11)	34.6 (t)	25.1 (t)
C(12)	59.9 (t)[c]	60.5 (t)
C(13)	62.6 (t)[c]	62.6 (t)
CH_3O	46.3 (q)	46.5 (q)

[a] In ppm from $(CH_3)_4Si$. **2a,b** run in $DCCl_3$. Aliphatic carbons only.
[b] Letters in parentheses indicate off-resonance multiplicities: s = singlet, d = doublet, t = triplet, q = quartet.
[c] Assignment may be reversed.





16 X = S
17 X = NCH_2Ph



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The five remaining ^{13}C signals (56.1, 56.3, 56.7, 60.5, and 62.6 ppm) were assigned to carbons alpha to nitrogen [C(4, 5, 7, 12, 13)]. The signals at 60.5 and 62.6 ppm were easily assigned to the benzylic carbons in **2b** but it was not possible to distinguish between C(12) and C(13) and therefore the assignments in Table II must be considered tentative. In addition, the signal at 56.1 ppm was tentatively assigned to C(4) since it is *gauche* to two C–O bonds, namely C(8a)–O and C(8a)–OCH_3. In contrast, C(5) and C(7) are each *gauche* to one C–C bond [C(8a)–C(8) vs C(8a)–C(4a)] and to one C–O bond [C(8a)–O in both cases]. The assignments for C(5) and C(7) were made from similar criteria as used with *C(9)*

TABLE III

^1H and ^{13}C NMR spectral data for **3a**, **3b**, and **3c** in ppm

Positions	3a(S) ^1H	3a(S) ^{13}C	3b(Se) ^1H	3b(Se) ^{13}C	3c(O) ^1H	3c(O) ^{13}C
1, 5	2.17(ax)	57.6	2.27(ax)	58.4	2.14(ax)	56.4
	2.77(eq)		2.77(eq)		2.71(eq)	
3, 11	2.50(ax)	76.6	2.55(ax)	75.8	2.46(ax)	75.7
	3.62(eq)		3.54(eq)		3.58(eq)	
6, 8		51.3		51.1		49.7
7		211.7		211.8		210.1
9, 13	2.17(ax)	57.6	2.27(ax)	58.4	2.14(ax)	56.4
	2.77(eq)		2.77(eq)		2.71(eq)	
14, 16	3.15	36.4	3.17	26.7	4.18	56.4
$PhCH_2$	3.33	59.6	3.34	59.6	3.38	59.6
$PhCH_2$	3.49	59.6	3.50	59.6	3.38	59.6
Ar–C		127.1		126.9		126.9
Ar–H	7.20–7.30	128.2	7.20–7.30	128.0	7.10–7.35	128.0
		128.6		128.5		128.3
		137.8		137.7		137.5

and C(11). Since the relative stereochemistry was presumed similar in **2a**, the assignments paralleled those of **2b**. However, it was *not* possible to deduce the stereochemistry regarding the orientation of the methoxy group relative to the selenane or thiane ring systems and an X-ray diffraction analysis was required. Such data would also clearly establish the structures for future reference of other family members of related systems.

Members **3a–c** had relatively simple ^1H and ^{13}C NMR spectra as seen in Table III. Assuming the attached spiro rings containing nitrogen are near chair forms, the axial proton signals for H(1, 5, 9, 13) occurred at δ 2.17, 2.27, and 2.14 in **3a**, **3b**, and **3c**, respectively, while the equatorial counterparts were at δ 2.77, 2.77, and 2.71. Likewise, the ^1H signals for H(3, 11) axial appeared at δ 2.50, 2.55, and 2.46 and the equatorial protons at 3.62, 3.54, and 3.58, respectively. A broad singlet was observed at δ 3.15, 3.17 and 4.18 for each H(14, 16) in these analogues. The remaining signals were for benzylic or aromatic protons.

The ^{13}C NMR analysis followed rather logically and that for **3b** will be discussed in detail for illustrative purposes. Fully decoupled and off-resonance spectra were taken and revealed C(1, 5, 9, 13) at 58.4 ppm and C(3, 11) at 75.8 ppm. The small signals (no NOE) at 51.1 ppm were assigned to C(6,8) while C(14, 16) occurred at 26.7 ppm which is more deshielded than in 4-selenanone (**4b**, 19.3 ppm).[11] Again in view of the lack of members of this family, an X-ray crystallographic analysis was deemed necessary.

The crystallographic data, final parameters for non-hydrogen atoms and bond distances and bond angles for **2a**, are given in Tables IV–VI. A view of the molecule is shown in Figure 3. The molecule is composed of three heterocyclic six-membered rings: (A) 1,3 oxazine, (B) thiacyclohexane (thiane), and (C) piperidine, and two benzyl groups attached to rings A and C (see Figure 4). All three heterocyclic rings are joined by a bridge, namely the C(4a)–C(8a) bond, while B and C also share the C(8)–C(8a) bond. All three rings are in the chair

TABLE IV

Crystal data for **2a**

Formula	$C_{24}H_{30}N_2O_2S$
F.W.	410.6 g/mol
Crystal system	Monoclinic
Space group	$P2_1/a$
Cell	at 138 K
a	17.395(6) Å
b	7.596(3) Å
c	16.959(7) Å
β	106.87(2)°
V	2144.4 Å^3
Unique data	4406 reflections
Observed data	2995 reflections
R	0.0450
R_w	0.0450
Radiation	MoKα
2θ limits	0.50–26.50°
Z	4
D_c	1.27 g/cm^3

TABLE V

Atomic parameters. Final parameters for non-hydrogen atoms for **2a**. E.S.D.'s for last digit in parentheses

Atom	x	y	z	u_{eq} (Å^2)
O(1)	0.08377(8)	0.2645(2)	0.27029(9)	0.0220(5)
C(2)	0.0408(1)	0.1195(4)	0.2248(1)	0.0257(8)
N(3)	0.0902(1)	0.0245(3)	0.1831(1)	0.0231(6)
C(4)	0.1615(1)	−0.0452(3)	0.2451(1)	0.0198(8)
C(4a)	0.2100(1)	0.1061(3)	0.2960(1)	0.0174(7)
C(5)	0.2394(1)	0.2267(3)	0.2379(1)	0.0187(7)
N(6)	0.2774(1)	0.3890(2)	0.2763(1)	0.0194(6)
C(7)	0.2232(1)	0.4876(4)	0.3115(1)	0.0239(8)
C(8)	0.1963(1)	0.3779(3)	0.3742(1)	0.0220(8)
C(8a)	0.1536(1)	0.2111(3)	0.3337(1)	0.0190(7)
C(9)	0.2636(1)	0.3278(4)	0.4524(1)	0.0275(8)
S(10)	0.34030(4)	0.1772(1)	0.43854(3)	0.0275(2)
C(11)	0.2792(1)	0.0244(3)	0.3636(1)	0.0212(8)
C(12)	0.13220(9)	0.0982(2)	0.39037(9)	0.0219(5)
C(13)	0.0769(2)	0.1694(4)	0.4303(2)	0.0284(9)
C(14)	0.0443(1)	−0.1180(4)	0.1324(2)	0.0318(9)
C(15)	0.0878(1)	−0.1951(1)	0.0755(1)	0.0296(8)
C(16)	0.1319(2)	−0.0897(5)	0.0380(2)	0.040(1)
C(17)	0.1703(2)	−0.1605(2)	−0.0160(2)	0.051(1)
C(18)	0.1648(2)	−0.3381(6)	−0.0333(2)	0.052(1)
C(19)	0.1218(2)	−0.4445(5)	0.0037(2)	0.050(1)
C(20)	0.0842(2)	−0.3739(4)	0.0586(2)	0.040(1)
C(21)	0.3029(1)	0.4932(4)	0.2169(1)	0.0246(8)
C(22)	0.3607(1)	0.6394(3)	0.2546(3)	0.0214(8)
C(23)	0.3684(1)	0.7843(4)	0.2073(1)	0.0277(9)
C(24)	0.4258(2)	0.9125(4)	0.2389(2)	0.034(1)
C(25)	0.4751(1)	0.9004(4)	0.3188(2)	0.034(1)
C(26)	0.4672(1)	0.7581(4)	0.3672(2)	0.0315(9)
C(27)	0.4106(1)	0.6282(4)	0.3351(1)	0.0255(8)

TABLE VI

Bond distances (Å) and bond angle (°) for **2a**

Bond distances			
O(1)–C(2)	1.426(3)	S(10)–C(11)	1.819(2)
O(1)–C(8a)	1.427(2)	O(12)–C(13)	1.433(3)
C(2)–N(3)	1.454(3)	C(14)–C(15)	1.509(3)
N(3)–C(4)	1.473(3)	C(15)–C(16)	1.384(4)
N(3)–C(14)	1.466(3)	C(15)–C(20)	1.386(4)
C(4)–C(4a)	1.534(3)	C(16)–C(17)	1.388(4)
C(4a)–C(5)	1.538(3)	C(17)–C(18)	1.378(6)
C(4a)–C(8a)	1.540(3)	C(18)–C(19)	1.372(5)
C(4a)–C(11)	1.532(3)	C(19)–C(20)	1.392(4)
C(5)–N(6)	1.459(3)	C(21)–C(22)	1.510(3)
N(6)–C(7)	1.460(3)	C(22)–C(23)	1.391(3)
N(6)–C(21)	1.450(3)	C(22)–C(27)	1.392(3)
C(7)–C(8)	1.527(3)	C(23)–C(24)	1.387(4)
C(8)–C(8a)	1.528(3)	C(24)–C(25)	1.380(3)
C(8)–C(9)	1.540(3)	C(25)–C(26)	1.388(4)
C(8a)–O(12)	1.416(2)	C(26)–C(27)	1.390(4)
C(9)–S(10)	1.824(3)		
Bond angles			
O(1)–C(2)–N(3)	110.8(2)	C(7)–C(8)–C(8a)	110.3(1)
O(1)–C(8a)–C(4a)	109.9(1)	C(7)–C(8)–C(9)	115.2(2)
O(1)–C(8a)–C(8)	107.5(2)	C(8)–C(8a)–O(12)	112.7(1)
O(1)–C(8a)–O(12)	110.5(2)	C(8)–C(9)–S(10)	116.4(1)
C(2)–O(1)–C(8a)	112.7(2)	C(8a)–C(4a)–C(11)	110.9(1)
C(2)–N(3)–C(4)	109.0(1)	C(8a)–C(8)–C(9)	109.4(2)
C(2)–N(3)–C(14)	110.6(2)	C(8a)–O(12)–C(13)	115.4(2)
N(3)–C(4)–C(4a)	110.1(2)	C(9)–S(10)–C(11)	100.9(1)
N(3)–C(14)–C(15)	111.8(2)	C(14)–C(15)–C(16)	121.2(3)
C(4)–N(3)–C(14)	110.8(2)	C(14)–C(15)–C(20)	120.8(2)
C(4)–C(4a)–C(5)	108.5(1)	C(15)–C(16)–C(17)	121.0(3)
C(4)–C(4a)–C(8a)	108.0(2)	C(15)–C(20)–C(19)	120.9(3)
C(4)–C(4a)–C(11)	107.5(2)	C(16)–C(15)–C(20)	118.0(2)
C(4a)–C(5)–N(6)	114.1(1)	C(16)–C(17)–C(18)	120.2(3)
C(4a)–C(8a)–C(8)	109.3(2)	C(17)–C(18)–C(19)	119.5(3)
C(4a)–C(8a)–O(12)	107.0(2)	C(18)–C(19)–C(20)	120.3(3)
C(4a)–C(11)–S(10)	115.9(2)	C(21)–C(22)–C(23)	120.1(2)
C(5)–C(4a)–C(8a)	109.1(2)	C(21)–C(22)–C(27)	121.3(2)
C(5)–C(4a)–C(11)	112.7(2)	C(22)–C(23)–C(24)	120.8(2)
C(5)–N(6)–C(7)	110.7(2)	C(22)–C(27)–C(26)	120.7(2)
C(5)–N(6)–C(21)	109.9(1)	C(23)–C(22)–C(27)	118.5(2)
N(6)–C(7)–C(8)	111.6(2)	C(23)–C(24)–C(25)	120.4(2)
N(6)–C(21)–C(22)	114.1(1)	C(24)–C(25)–C(26)	119.5(2)
C(7)–N(6)–C(21)	111.6(2)	C(25)–C(26)–C(27)	120.1(2)

conformation with A/B *trans*-fused and A/C are *cis*-fused. The B and C rings form a bicyclo[3.3.1]nonane ring system. The dihedral angle between rings A and D is $74.46 \pm 0.06°$, while the dihedral angle between rings B and E is $67.19 \pm 0.06°$. In compound **2a**, the benzyl group is attached equatorially to the nitrogen of the oxazine ring, while in a similar compound it is attached axially.[12] The second benzyl group is also equatorial and substituted on the nitrogen of the piperidine ring. The distortion of the thiane ring is probably due to the presence of a sulfur atom which causes bond lengthening, and consequently flattens the

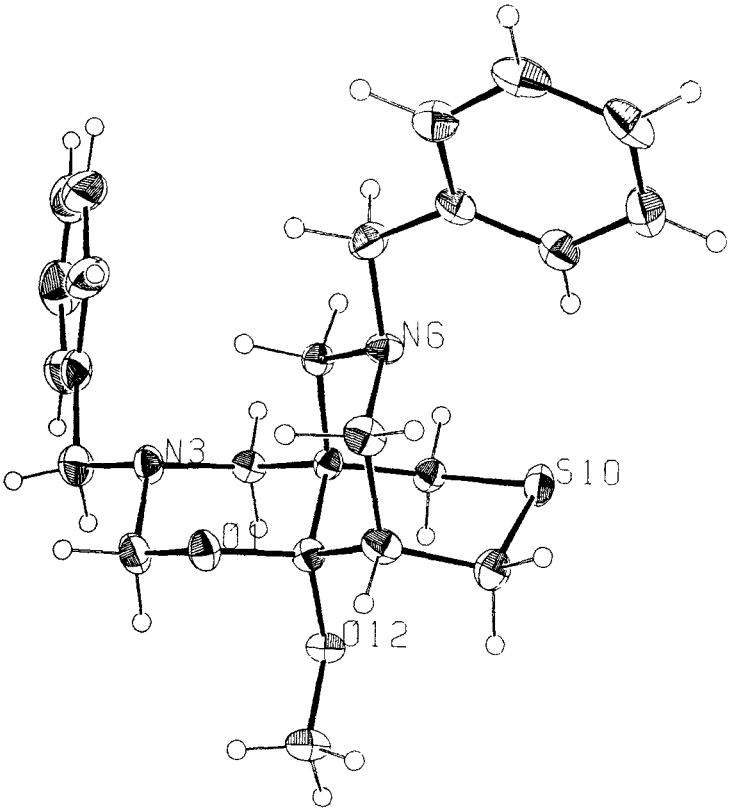


FIGURE 3 A perspective view of **2a**. The thermal ellipsoids enclose 50% probability.

ring at that end. The torsion angles around the sulfur are: C(8)–C(9)–S(10)–C(11), −40.1° and C(4a)–C(11)–S(10)–C(9), 39.1°. This is a large deviation from the ideal torsion angle of 56° but such has been observed previously in other thiane rings.[13] The two C–S bond lengths [C(9)–S(10) = 1.824(3)Å and C(11)–S(10) = 1.819(2) Å] are comparable to 1.817(5) Å given by Sutton as the mean distance for paraffinic C—S bonds[14] and is within the range (1.811–1.840 Å) found in several sulfur-containing, six-membered ring systems which have been studied.[15–17]

The bond angle C(9)–S(10)–C(11) is 100.9°; similar values for the same angle in different thiane ring structures have been previously reported.[13,15] The C(2)–N(3)–C(4), O(1)–C(2)–N(3), and C(2)–O(1)–C(8a) bond angles of the oxazine ring are not significantly different from the same angles found in similar 1,3-oxazine ring systems in which the oxazine ring is fused to other six-membered rings.[12,18] The N(6)–S(10) interatomic distance is 3.099 Å.

Tricyclic system **2b**, $C_{24}H_{30}N_2O_2Se$, exists with three, six-membered, heterocyclic rings fused together and is isomorphous with **2a**. Crystallographic data, bond lengths, bond angles, and dihedral angles may be obtained upon request. The corresponding rings A, B and C are in chair conformations.

Dispiro ketone **3a**, $C_{39}H_{44}N_4SO$, crystallizes (crystal data in Table VII) with the

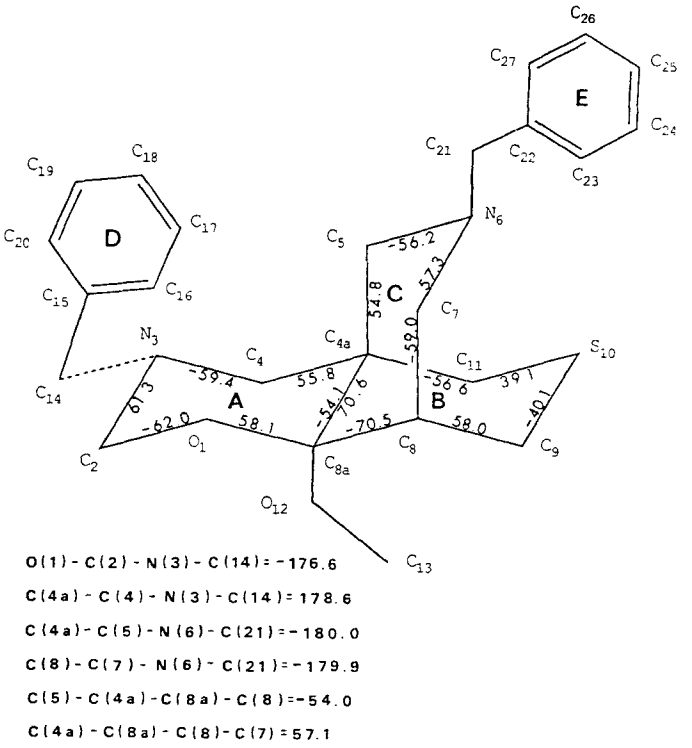


FIGURE 4 Numbering scheme and torsion angles (°) of the heterocyclic rings in **2a**. The torsion angles listed along the bonds shared by rings B and C are for ring B. Those angles for ring C are given in those listed below.

TABLE VII

Crystal data for $C_{39}H_{44}N_4OS$ (**3a**)

Formula	$C_{39}H_{44}N_4OS$
MWT	616.86
a	15.144(7) Å
b	11.613(5) Å
c	19.652(6) Å
α	90.0°
β	99.29(3)
γ	90.0
V	3410.7(25) Å^3
F(000)	1320
μMoK	1.243 cm^{-1}
λMoK	0.71069 Å
D_{calc}	1.201 g cm^{-3}
Z	4
Meas refl.	2368
Obs. refl.	1156
R	8.2%
R_w	10.4%
G.O.F.	0.42
Space group	$P2_1/n$
Octants meas	±h, +k, +l

sulfur-containing ring a half chair conformation. Dihedral angles C(16)–C(6)–C(7)–C(8) of −4.4° and C(14)–C(8)–C(7)–C(6) of 6.4° and the coplanarity of C(16), C(6), C(7), C(8) and C(14) (std. dev. 0.02) confirm the flattening of the carbonyl end of the ring. The sulfur atom is displaced from the plane by 0.98 Å. Bond lengths, bond angles, and related dihedral angles are in Table VIII.

TABLE VIII

Bond angles (°) and distances (Å) for $C_{39}H_{44}N_4SO$ (**3a**)

C(1)–N(2)	1.45 (2)	C(1)–N(2)–C(3)	110.0(12)
N(2)–C(3)	1.46 (2)	N(2)–C(3)–N(4)	110.2(12)
C(3)–C(4)	1.46 (2)	C(3)–N(4)–C(5)	109.4(12)
N(4)–C(5)	1.47 (3)	N(4)–C(5)–C(6)	112.2(15)
C(5)–C(6)	1.53 (2)	C(5)–C(6)–C(1)	109.0(14)
C(6)–C(1)	1.54 (2)	C(6)–C(1)–N(2)	109.6(12)
C(6)–C(7)	1.52 (3)	C(5)–C(6)–C(7)	106.2(14)
C(6)–C(16)	1.52 (2)	C(5)–C(6)–C(16)	108.3(12)
C(7)–O(1)	1.20 (2)	C(1)–C(6)–C(16)	110.3(14)
C(7)–C(8)	1.53 (3)	C(1)–C(6)–C(7)	109.0(13)
C(8)–C(9)	1.55 (2)	C(7)–C(6)–C(16)	114.3(14)
C(8)–C(13)	1.51 (2)	C(6)–C(7)–O(1)	117.0(18)
C(8)–C(14)	1.53 (2)	C(6)–C(7)–C(8)	127.2(13)
C(9)–N(10)	1.45 (3)	C(8)–C(7)–O(1)	116.0(18)
N(10)–C(11)	1.42 (2)	C(7)–C(8)–C(9)	105.4(14)
C(11)–N(12)	1.48 (2)	C(7)–C(8)–C(13)	109.2(15)
N(12)–C(13)	1.44 (3)	C(7)–C(8)–C(14)	114.4(15)
C(14)–S(15)	1.81 (2)	C(9)–C(8)–C(13)	108.5(16)
N(2)–C(17)	1.43 (2)	C(9)–C(8)–C(14)	111.4(14)
N(4)–C(18)	1.45 (2)	C(13)–C(8)–C(14)	108.0(13)
N(10)–C(19)	1.49 (2)	C(8)–C(9)–N(10)	108.5(13)
N(12)–C(20)	1.46 (2)	C(9)–N(10)–C(11)	114.0(13)
C(17)–C(21)	1.49 (2)	N(10)–C(11)–N(12)	110.1(14)
C(21)–C(22)	1.47	C(11)–N(12)–C(13)	110.3(1)
C(22)–C(23)	1.43	N(12)–C(13)–C(8)	110.5(14)
C(23)–C(24)	1.38	C(8)–C(14)–S(15)	114.0(11)
C(24)–C(25)	1.29	C(14)–S(15)–C(16)	94.0(7)
C(25)–C(26)	1.52	S(15)–C(16)–C(6)	116.0(12)
C(26)–C(21)	1.40		
C(18)–C(27)	1.47		
C(27)–C(28)	1.44		
C(28)–C(29)	1.42		
C(29)–C(30)	1.44		
C(30)–C(31)	1.35		
C(31)–C(32)	1.39		
C(32)–C(27)	1.48		
C(19)–C(33)	1.51		
C(33)–C(34)	1.40		
C(34)–C(35)	1.42		
C(35)–C(36)	1.42		
C(36)–C(37)	1.43		
C(37)–C(38)	1.42		
C(38)–C(33)	1.39		
C(20)–C(39)	1.55		
C(39)–C(40)	1.49		
C(40)–C(41)	1.36		
C(41)–C(42)	1.40		
C(42)–C(43)	1.32		
C(43)–C(44)	1.45		
C(44)–C(39)	1.41		

(*continued*)

TABLE VIII—(*continued*)

Dihedral angles

C(7)–C(6)–C(16)–S(15)	38.8(17)	C(8)–C(9)–N(10)–C(11)	−59.3(16)
C(7)–C(8)–C(14)–S(15)	−41.8(18)	C(9)–N(10)–C(11)–N(12)	59.5(16)
C(8)–C(14)–S(15)–C(16)	64.7(14)	N(10)–C(11)–N(12)–C(13)	−59.9(16)
C(6)–C(16)–S(15)–C(14)	−63.4(12)	C(11)–N(12)–C(13)–C(8)	59.4(17)
C(16)–C(6)–C(7)–C(8)	−4.4(23)	N(12)–C(3)–C(8)–C(9)	57.4(17)
C(14)–C(8)–C(7)–C(6)	6.4(23)	C(13)–C(8)–C(9)–N(10)	−54.0(17)
O(1)–C(7)–C(6)–C(1)	48.0(18)		
O(1)–C(7)–C(6)–C(5)	−69.0(18)		
O(1)–C(7)–C(8)–C(9)	67.8(17)		
O(1)–C(7)–C(8)–C(9)	−48.6(19)		
O(1)–C(7)–C(8)–C(13)	−79.4(16)		
S(15)–C(16)–C(6)–C(5)	161.4(11)		
S(15)–C(16)–C(6)–C(1)	−163.5(14)		
S(15)–C(14)–C(8)–C(13)	77.6(18)		
S(15)–C(14)–C(8)–C(9)	−54.0(16)		
C(5)–C(6)–C(1)–N(2)	60.8(15)		
C(6)–C(1)–N(2)–C(3)	−65.0(14)		
C(1)–N(2)–C(3)–N(4)	61.4(15)		
N(2)–C(3)–N(4)–C(5)	−56.2(16)		
C(3)–N(4)–C(5)–C(6)	52.4(16)		
N(4)–C(5)–C(6)–C(1)	57.1(17)		

The carbon atoms attached to the carbonyl carbon are the points of attachment of spiro six-membered diaza-ring systems (Figure 5) which display chair conformations (dihedral angles within diaza-ring systems, 52.4–65.0°). The chair conformation is slightly distorted by the opening of the angles at the spiro carbons within the planar five-membered ring, [C(16)–C(6)–C(7), 114.3(14)°, and C(14)–C(8)–C(7), 114.4(15)°] which results in smaller dihedral angles within the diaza-ring [N(2)–C(1)–C(6)–C(5), −54.0(16)°; N(4)–C(5)–C(6)–C(1), 52.4(16)°; N(10)–C(9)–C(8)–C(13), −54.0(17)° and C(9)–C(8)–C(13)–N(12); 57.4(17)°].

The diaza-ring systems display equatorial extrannular bonds to the carbonyl carbon and to the benzyl methylene carbons while unshared pairs of electrons on nitrogen atoms and bonds to sulfur from adjacent methylene carbons occupy axial positions. The closeness to the theoretical value of the dihedral angles involving the nitrogen atoms indicates relatively little distortion in these parts of the rings, and thus the unshared pair positions may be viewed as truly axial.

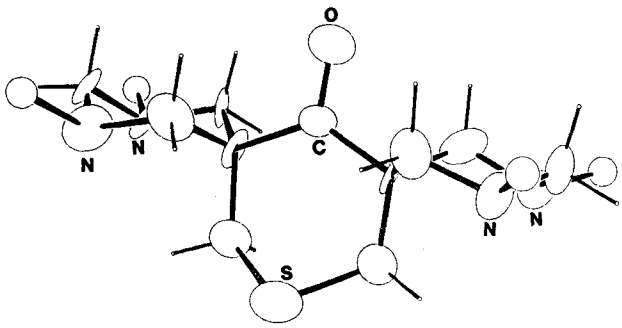
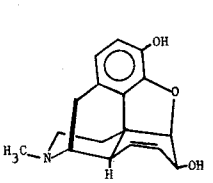


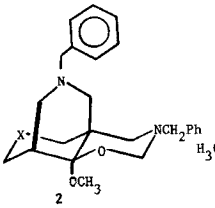
FIGURE 5 A perspective view of **3a**.

The three ring system in **3a** displays approximate two-fold symmetry about the S...C=O line. This symmetry does not extend to the positions of the benzyl groups which appear feathered about the triannular nucleus. There is no evidence that these rings are frozen in the feathered conformation observed in the crystalline solid.

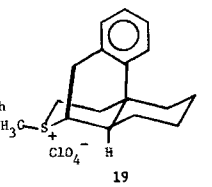
Examination of the dihedral angles involving the carbonyl group in **3a** reveals that this group is *not* symmetrically disposed with respect to the substituents at the adjacent spiro carbons, showing one smaller dihedral angle with a spiro ring member on each side; O(1)—C(7)—C(6)—C(1), 48.0(18)° and O(1)—C(7)—C(8)—C(13), −48.6(19)° and one larger one; O(1)—C(7)—C(6)—C(5), −69.0(18)° and O(1)—C(7)—C(8)—C(9), 67.8(17)°.



Morphine



2



19

In summary, we have isolated and identified two novel heterocyclic systems **2** and **3** from a Mannich reaction using 1-hetera-4-cyclohexanones, benzylamine and acetic acid. Interestingly, members of **2** (redrawn below) bear resemblance to morphine and a few opiates isosteres **19** which have been examined recently for analgesic activity.[19] Thus, access to heterocyclic mimics might be gained through proper manipulation of the chemistry described herein.

EXPERIMENTAL

All reactions were performed under N_2 with magnetic stirring unless otherwise specified. Melting points were taken on a Thomas Hoover capillary apparatus and are uncorrected. IR spectra were recorded on a Perkin Elmer 681 unit. High resolution mass spectral data were acquired on a CEC model 21-110B HR spectrometer. Both ^1H and ^{13}C NMR spectra were taken at 299.94 MHz and 75.43 MHz, respectively, on a Varian XL-300 HR spectrometer. Some ^{13}C spectra were recorded at 25.20 MHz on an XL-100(15) spectrometer. The ^{15}N and ^{77}Se spectra were collected at 30.41 and 57.22 MHz on the XL-300 spectrometer. Chemical shifts for ^1H and ^{13}C are in parts per million (ppm) downfield from TMS. The ^{15}N signals are downfield from NH_3 (*l*, 25°C, 0 ppm) using $^{15}NH_4NO_3$ (8.0 *M*, 19.73 ppm) or formamide (neat, 112.4 ppm) as external secondary standards. With ^{17}Se, the signals were downfield from $(H_3C)_2Se$ (0 ppm) using $(C_6H_5)_2Se_2$ (481 ppm) as an external secondary standard. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, TN. Ketone **4b** was prepared as reported previously[11] as was diol **18**.[5a]

7-Benzyl-3-thia-7-azabicyclo[3.3.1]nonan-9-one(**1a**), *3,6-Dibenzylhexahydro-8a-methoxy-5H-4a,8-(methanothiomethano)-2H-pyrido[3,4-e]1,3-oxazine* (**2a**) *and 2,4,10,12-Tetrabenzyl-2,4,10,12-tetraaza-15-thiadispiro[5.1.5.3]hexadecan-7-one* (**3a**).

Method A: 1.0 Equivalent benzylamine.

The general method described[5f] was utilized, but the relatively large scale employed required modifications in the procedure. A 1000 mL flask was charged with benzylamine (21.43 g, 0.20 mol), paraformaldehyde (48.04 g, 1.60 mol), acetic acid (18.02 g, 0.30 mol) and methanol (750 mL). The apparatus was thoroughly flushed with N_2, and the mixture was heated to reflux with stirring. Ketone **4a** (23.24 g, 0.20 mol) was then added in one portion. The solution immediately developed a yellow color, changing to red as the reaction proceeded and the paraformaldehyde slowly dissolved. On cooling to RT, no solid precipitate was noted. The workup of the reaction mixture was as described

previously. The red oil, afforded by removal of the solvent, was suspended in water (1500 mL), and this suspension was washed with ether. The aqueous layer was set aside. The combined ether layers were partially dried (K_2CO_3, 1 h, vigorous stirring) and filtered. Standing at RT for 3 days resulted in the formation of white crystals in the ether solution. Recrystallization (95% ethanol) afforded **2a** (2.43 g, 5.92%), mp 147–149°C.

The aqueous phase was extracted with H_2CCl_2 and the combined organic extracts were dried ($MgSO_4$, overnight). Filtration, followed by evaporation, afforded a brown oil, which was digested in boiling Skelly B (1 liter) for thirty minutes. The hot supernatant was decanted from the brown residue and evaporated to afford a yellow oil. The residue was treated twice again in this manner and then once with 500 mL of Skelly B, each time combining the supernatant with the oil (22.5 g) from the previous digestion process. The resulting oil solidified on standing and was sublimed (104°C/0.04 mm Hg) to afford **1a** (16.69 g, 33.73%), mp 92–93°C (lit[5f] 90–91°C) and a residual yellow oil that did not sublime. In a similar experiment, it was found that this residual oil consists primarily of **1a**. Further efforts at distillation and sublimation (90–150°C, 5×10^{-4} mm Hg, diffusion pump) of the oily residue failed to give significant quantities of **1a**.

Method B: 2.0 Equivalents benzylamine.

A 50 mL flask was charged with paraformaldehyde (1.20 g, 40.0 mmol), benzylamine (1.07 g, 10.0 mmol), glacial acetic acid (0.66 g, 11.0 mmol), and methanol (20 mL). The apparatus was flushed with N_2 and the mixture was boiled with stirring for 15 min. To the mixture was added in one portion a solution of ketone **4a** (0.58 g, 5.0 mmol) in methanol (10 mL), and the resulting mixture was heated at reflux for 9 h during which time the paraformaldehyde slowly dissolved and the solution turned yellow. After cooling to RT, the solution was allowed to stir an additional 10 h. Removal of the solvent afforded a yellow oil which was partitioned between ether (50 mL) and water (50 mL). The layers were separated and the pale yellow ether layer was allowed to stand for 24 h at −10°C. A white crystalline solid precipitated from this ether solution. This was filtered and set aside. The filtrate was concentrated to half of the previous volume and allowed to stand for 3 h. A second crop of the white solid was precipitated. This was filtered, combined with the first crop, and recrystallized (95% ethanol, 30 mL) to afford **2a** (0.93 g, 45%) as white needles: mp 147.2–148.8°C.

The aqueous phase was cooled in an ice bath and made alkaline by the addition of NaOH pellets (0.50 g, 12 mmol) and extracted with ether. The combined ether extracts from this last step were dried (Na_2SO_4, overnight) and were evaporated to afford a yellow oil. This oil was digested in boiling Skelly B for 30 min. The supernatant was decanted from the brown residue and evaporated to afford crude **1a** as a yellow oil (0.50 g) that did not solidify.

Method C: Dropwise addition.

A 50 mL flask was charged with a slurry of paraformaldehyde (1.20 g, 40.0 mmol) in methanol (20 mL) and was heated at reflux under N_2 for 15 min. To this boiling mixture was added *dropwise* over 3.5 h a solution of ketone **4a** (0.58 g, 5.0 mmol), benzylamine (1.07 g, 10.0 mmol), and glacial acetic acid (0.66 g, 11.0 mmol) in methanol (10 mL). During the addition, the paraformaldehyde slowly dissolved and the solution turned to an orange-red color. The solution was heated at reflux for an additional 3.5 h and then allowed to stir at RT for 48 h. A white solid precipitated and was filtered, washed with methanol (5 mL) and recrystallized (2-propanol, 30 mL) to afford **3a** (0.2610 g, 8.5% relative to the amount of benzylamine used) as white needles: mp 172.5–173.5°C. The reaction mixture filtrate was evaporated to an orange-red oil which was partitioned between ether (50 mL) and water (50 mL). The ether layer was treated as before to afford, after recrystallization (ethanol, 25 mL), **2a** [0.2112 g, 10%; mp 146.5–148.0°C] the ^{13}C NMR spectrum of which was identical to that given previously. The pink aqueous suspension was made alkaline by the addition of NaOH pellets (0.50 g, 12.5 mmol) to give a yellow suspension. This suspension was extracted with ether and the combined ether extracts were dried (Na_2SO_4, overnight). The dry ethereal solution was filtered and evaporated, and the resulting yellow oil was digested in boiling Skelly B (200 mL) for 30 min. The hot supernatant was decanted from the brown residue and evaporated (aspirator followed by vacuum pump) to leave a pale yellow oil (0.59 g, ~47%). The ^{13}C NMR spectrum of this oil indicated that it was mostly ketone **1a** with a small amount of **2a** present as an impurity.

Analytical data

The ^{13}C NMR, ^{15}N NMR and IR spectral data for **1a** have been previously reported.[5f] A HETCOR 2-D NMR spectrum of this compound permitted a reinterpretation and correction of the aliphatic portion of the ^1H NMR spectrum ($DCCl_3$): δ 2.71[dd, ^2J = 11.2 Hz, ^3J = 5.0 Hz, 2 H, H(6, 8)ax], 2.80[m, 2 H, H(1, 5)], 3.08[dd, ^2J = 11.2 Hz, ^3J = 1.3 Hz, 2 H, H(6, 8)eq], 3.12[dd, ^2J = 13.5 Hz, ^3J = 7.3 Hz, 2 H, H(2, 4)ax], 3.23[dd, ^2J = 13.5 Hz, ^3J = 4.0 Hz, 2 H, H(2, 4)eq], 3.57[s, 2 H, H(10)], 7.26–7.34[m, 5 H, Ar*H*].

The spectral data for **2a** were: IR (KBr) cm^{-1} 3030, 2940, 2830, 1365, 1358, 1104, 1067, 740, 704. NMR ($DCCl_3$): the ^1H and ^{13}C NMR data are in Tables I and II. ^{15}N NMR ($DCCl_3$) ppm 35.9 [N(6)], 46.4 [N(3)]. Anal. of **2a** calcd. for $C_{24}H_{30}N_2O_2S$: C, 70.21; H, 7.37; N, 6.82; S, 7.81. Found: C, 69.99; H, 7.51; N, 6.64; S, 7.97.

The spectral data for **3a** were: IR (KBr) cm^{-1} 3065, 3030, 2950, 2920, 2895, 2830, 2800, 1680 (C=O), 1500, 1457, 1097, 748, 736, 703. NMR ($DCCl_3$) the ^1H and ^{13}C NMR data are in Table III. Anal. of **3a** calcd. for $C_{39}H_{44}N_4SO$: C, 75.94; H, 7.19; N, 9.08; S, 5.20. Found: C, 75.73; H, 7.33; N, 9.10; S, 5.20.

Since members of **2** were essentially unknown, a derivative was made. A flask was charged with a solution of ketal **2a** (1.00 g, 2.44 mmol) in benzene (20 mL). To this solution was added dropwise over 15 min a solution of $HClO_4$ (60%, 1.00 g, 5.97 mmol) in 2-propanol (5 mL) with vigorous stirring. The salt precipitated as a white powdery solid, and additional 2-propanol (10 mL) was added to prevent caking of the precipitate. The mixture was stirred (1 h, RT), and the salt was filtered, recrystallized (ethanol, 25 mL), and dried (Abderhalden, P_2O_5, 77°C, vacuum pump, 12 h) to afford 3,6-dibenzylhexahydro-8a-methoxy-5*H*-4a,8-(methanothiomethano)-2*H*-pyrido[3,4-*e*]-1,3-oxazine dihydroperchlorate (0.60 g, 40%) as white crystals: mp 160–162°C (dec); IR (KBr) cm^{-1} 2760–2845 (N—H), 1080 (Cl—O). ^1H NMR (DMSO-d_6) δ 2.17 [d, $J = 11.7$ Hz, 1 H, H(4)ax], 2.35 [d, $J = 11.7$ Hz, 1 H, H(4)eq], 2.43 [d, $J = 13.0$ Hz, 1 H, H(11)ax], 2.64 [br, s, 1 H, H(8)], 2.76 [d, $J = 13.6$ Hz, 1 H, H(9)ax], 3.00 [d, $J = 13.0$ Hz, H(11)eq], 3.18 [s, 3 H, CH_3O], 3.22 [m, 2 H, H(9)eq and $PhCH_2$], 3.32 [d, $J = 13.6$ Hz, 1 H, H(5)ax], 3.46 [d, $J = 12.0$ Hz, H(7)ax], 3.57 [d, $J = 13.6$ Hz, 1 H, H(5)eq], 3.79 [d, $J = 12.0$ Hz, H(7)eq], 4.00 [d, $J = 7.3$ Hz, 1 H, H(2)ax], 4.19 [d, $J = 12.0$ Hz, 1 H, $PhCH_2$] 4.24 [d, $J = 7.3$ Hz, 1 H, H(2)eq], 4.40 [dd, $J = 12.6$, 5.9 Hz, $PhCH_2$], 4.54 [dd, $J = 12.6$, 3.9 Hz, 1 H, $PhCH_2$], 7.25–7.39 [m, 5 H, Ar*H*], 7.49–7.64 [m, 5 H, Ar*H*], 9.53 [br s, 1 H, N—*H*]; ^{13}C NMR (DMSO-d_6) ppm 28.3 [t, C(9)], 31.3 [d, C(8)], 31.8 [t, C(11)], 37.4 [s, C(4a)], 46.4 [q, CH_3O], 52.3 [t, C(4)], 54.2 [t, C(7)], 55.4 [t, C(5)], 56.2 [t, $PhCH_2$], 60.2 [t, $PhCH_2$], 78.0 [t, C(2)], 93.8 [s, C(8a)], 127.1, 128.3, 129.1, 129.7, 130.6, 137.0 [Ar*C*]. Anal. Calcd. for $C_{24}H_{30}N_2O_2S2{\cdot}HClO_4$: C, 47.14; H, 5.27; Cl, 11.59; N, 4.58; S, 5.24. Found: C, 47.22; H, 5.14; Cl, 11.38; N, 4.44; S, 5.47.

7-Benzyl-3-selena-7-azabicyclo[3.3.1]nonan-9-one (**1b**), *3,6-Dibenzylhexahydro-8a-methoxy-5H-4a,8-(methanoselenomethano)-2H-pyrido[3,4-e]-1,3-oxazine* (**2b**) *and 2,4,10,12-tetrabenzyl-2,4,10,12-tetraaza-15-selenadispiro[5.3.5.1]hexadecan-7-one* (**3b**).

Method A: 1.0 Equivalent of benzylamine.

The reaction was modified from that described.[5a] Ketone **4b** (0.58 g, 3.7 mmol) was treated with benzylamine (0.40 g, 3.7 mmol), acetic acid (0.23 g, 3.8 mmol), and paraformaldehyde (0.90 g, 29.9 mmol) in methanol (25 mL). The mixture was heated at reflux for 5 h and was stirred at RT for an additional 1 h. No precipitate was noted in the red solution. After removal of the solvent, the resulting red oil was partitioned between ether and water. The ether layer was treated as described above to afford, after recrystallization (95% alcohol), ketal **2b** (0.1001 g, 11.8% relative to the amount of benzylamine) mp 161–162°C. The aqueous layer was cooled to 0°C and was made alkaline by the addition of KOH pellets (85%, 0.70 g, 12.5 mmol); the resulting suspension extracted with ether (6 × 30 mL). The combined ether extracts were dried (K_2CO_3). Filtration, followed by evaporation, afforded a yellow oil, the spectrum of which was essentially identical to **1b** (0.24 g, 22% relative to 4-selenanone, **4b**).

Method B: 2.0 Equivalents benzylamine.

Using the apparatus and procedure described for Method A, ketone **4b** (0.83 g, 5.0 mmol) was treated with benzylamine (1.07 g, 10.0 mmol), glacial acetic acid (0.62 g, 10.3 mmol), paraformaldehyde (1.20 g, 40.0 mmol), and methanol (25 mL). The apparatus was flushed with N_2, and the mixture was heated at reflux with stirring for 15 min. Ketone **4b** (0.83 g, 5.0 mmol) was then added in one portion and the mixture was heated at reflux. The supernatant turned yellow upon addition of 4-selenanone. Continued heating resulted in the slow dissolution of the paraformaldehyde and the development of a brilliant pink color in the supernatant. After 3 h, the formation of a white precipitate was noted. After 5 h, the reaction mixture was cooled to RT and stirred an additional 13 h. The white solid was filtered from the reaction mixture, washed with methanol (5 mL) and recrystallized (95% 2-propanol) to give **3b** (57.6 mg, 1.9%) as white crystals: mp 165–166°C.

The filtrate from the reaction mixture was evaporated to leave a pink oil which was partitioned between ethyl ether and water. The colorless ether layer was separated and treated as before to afford, after recrystallization (95% ethanol), **2b** (0.2030 g, 8.8%), mp 159–160°C.

The pink aqueous suspension from the partitioning was made alkaline by the addition of KOH pellets (85%, 2.00 g, 30.3 mmol) to give an oily yellow suspension. Ether extraction, drying (K_2CO_3, overnight), and digestion in Skelly B as previously described resulted in a yellow oil. This oil was dissolved in hot 95% ethanol (30 mL), decolorized with carbon, and evaporated to 10 mL. Upon standing at −10°C for 1 day, while needles precipitated. These were filtered and air dried to afford ketone **1b** (0.38 g, 25.8%), mp 91–92°C.[5a] This mp had been erroneously reported[5a] in the Experimental Section as 157.5–157°C for **1b** which mp is now known to be for crude **2b**.

Method C: 1.4 equivalents benzylamine.

A 50 mL flask was charged with benzylamine (0.67 g, 6.2 mmol), glacial acetic acid (0.38 g, 6.8 mmol),

paraformaldehyde (1.50 g, 50.0 mmol), and methanol (30 mL). The apparatus was flushed with N_2 and the mixture heated to reflux with stirring. After 0.5 h, the mixture was cooled to RT and 4-selenanone[11] (**4b**, 0.75 g, 4.6 mmol) was added in one portion. The mixture was again heated at reflux for 5 h during which time all solids dissolved and the resulting solution turned yellow. The solution was then cooled to RT and allowed to stir overnight. Evaporation of the solvent resulted in a yellow oil, which was partitioned between water (50 mL) and ethyl ether (50 mL). The layers were separated and the ether layer was allowed to stand for two days at RT during which a white solid precipitate formed in the solution. This was filtered and recrystallized (95% ethanol, 25 mL) to afford **2b** (0.25 g) as white needles: mp 160.0–160.5°C.

The aqueous layer was cooled (ice bath) and was made alkaline by the addition of KOH pellets (85%, 1.20 g, 21.4 mmol). The resulting suspension was extracted (ether) and the combined extracts were dried (K_2CO_3, overnight). Filtration, followed by evaporation, afforded a yellow oil which was digested in Skelly B for 0.5 h on a steam bath. The hot supernatant was decanted and evaporated to give another yellow oil. This was dissolved in hot 95% ethanol (10 mL) which, upon cooling, precipitated additional **2b** (67.0 mg, 22% total), mp 159–160°C.

Analytical data

The IR, ^{13}C NMR, ^{15}N NMR, and ^{77}Se NMR spectra for **1b** have been previously reported.[5a] The ^1H NMR ($DCCl_3$) assignments have been modified in light of a HETCOR 2-D NMR spectrum: δ 2.71 [d, $J = 9$ Hz, 2 H, H(6, 8)ax], 2.73 [br s, 2 H, H(1, 5)], 3.10 [d, $J = 9$ Hz, 2 H, H(6, 8)eq], 3.23 [m, 4 H, H(2, 4)], 3.58 [s, 2 H, PhCH_2], 7.24–7.32 [m, 5 H, ArH].

The spectroscopic data for **2b** were: IR (KBr) cm^{-1} 2840, 1370, 1362, 1108, 1062, 1055, 762, 706; the ^1H and ^{13}C NMR data are in Tables I and II. ^{15}N NMR ($DCCl_3$) ppm 36.2 [N(12)], 47.0 [N(3)]; ^{77}Se NMR ppm 126.6 [Se(8)]. Anal. calcd. for $C_{24}H_{30}N_2O_2Se$: C, 63.01; H, 6.61; N, 6.12; Se, 17.26. Found: C, 62.88; H, 6.83; N, 6.02; Se, 16.91.

The spectral data for **3b** were: IR (KBr) cm^{-1} 3062, 3032, 2910, 2820, 2792, 1675, 1494, 1453, 1086, 1068, 741, 729, 697; NMR ($DCCl_3$) the ^1H and ^{13}C NMR data are in Tables I and II. ^{15}N NMR ($DCCl_3$) ppm 43.6; ^{77}Se NMR ($DCCl_3$) ppm 51.4. Anal. calcd. for $C_{39}H_{44}OSe$: C, 70.57; H, 6.68. Found: C, 70.42 H, 6.86.

7-Benzyl-3-oxa-7-azabicyclo[3.3.1]nonan-9-one (**5**) *and 2,4,10,12-Tetrabenzyl-2,4,10,12-tetraaza-15-oxadispiro[5.1.5.3]hexadecan-7-one* (**3c**). In a procedure similar to that used to obtain **3a**, benzylamine (2.14 g, 20.0 mmol), tetrahydro-4*H*-pyran-4-one (**4c**, 1.00 g, 10.0 mmol), paraformaldehyde (1.50 g, 50 mmol), glacial acetic acid (1.32 g, 22 mmol) and methanol (20 mL) were allowed to react for 23 h. Upon cooling to room temperature, crude **3c** precipitated, and, after recrystallization (2-propanol), was converted to a white solid, 0.0736 g (1.2%), mp 158.5–159.0°C. The ^1H and ^{13}C NMR data are in Table III. Anal. of **3c**, calcd. for $C_{39}H_{44}N_4O_2$: C, 78.00; H, 7.38; N, 9.33. Found: C, 77.67; H, 7.51; N, 0.40.

Evaporation of the residual solution gave an oil. Both ^1H and ^{13}C NMR spectra of the crude oil possessed peaks resminiscent of those found for **3a** and **3b**. Repeated chromatography of the oil on alumina (neutral) with 1:1 hexane:ethyl acetate removed many impurities (as evidenced by TLC analysis) and gave a clear yellow oil, 1.26 g (54%). The spectral properties of this oil were identical with the known **5**.[6f] All other attempts to separate the components have been unsuccessful.

1,3,5-Tribenzylhexahydro-1,3,5-triazine (**6**). A 100-mL flask was charged with benzylamine (10.72 g, 0.10 mol) and the apparatus was flushed with N_2. Formaldehyde (37%, aq.) 12.17 g, 0.15 mol) was added in a dropwise manner over 30 min. An exothermic reaction ensued, and the product separated (upper layer) from the reaction mixture as a viscous oil. Upon completion of the addition, the reaction mixture was heated at reflux for an additional 3 h to ensure completion. After cooling to RT, the mixture was diluted with NaCl solution (sat'd, 50 mL), extracted (ether, 5 × 50 mL), and the combined extracts were dried (K_2CO_3, 5 h). Evaporation afforded a colorless oil. This oil was passed through a column [neutral alumina, hexane/ethyl acetate [5:1)] and afforded the triamine (R_f 0.64) as the first band. Evaporation of the solvent gave **6** as a colorless oil (11.09 g, 93.1%) that solidified on standing: mp 43.5–45.5°C (lit[8] 46°C); IR (film) cm^{-1} 3058, 3024, 2905, 2804, 1600, 1570, 740, 700; ^1H NMR ($DCCl_3$) δ 3.40 (s, 6 H, ring CH_2), 3.63 (s, 6 H, PhCH_2), 7.17–7.32 (m, ArH); ^{13}C NMR ($DCCl_3$) ppm 56.9 (t, PhCH_2), 73.6 (t, ring CH_2), 126.7 (d, *p*-Ar*C*), 127.9 (d, *o*- or *m*-Ar*C*), 128.6 (d, *m*- or *o*-ArC), 138.2 (s, *i*-Ar*C*); ^{15}N NMR ($DCCl_3$) ppm 49.2. Mass spectral m/e for **6** calcd. for $C_{24}H_{27}N_3$: 357 (M^+). Found: 357. Repetition of the reaction under identical conditions similar to those of method B in the preparation of **1a** or **1b** gave **6** in a yield of 57.3%.

7-Benzyl-9,9-dimethoxy-3-thia-7-azabicyclo[3.3.1]nonane Hydroperchlorate (**16**). Caution: the use of shields, protective goggles and gloves is *very strongly recommended* when performing this experiment. The formation of explosive methyl perchlorate is a likely side reaction in this experiment.

No difficulty was noted in when the reaction was performed as described, but this may have been fortuitous. A 100-mL flask was fitted with a Soxhlet containing 3A molecular sieve (30 g), a condenser, a heating mantle, a magnetic stirrer, and a heating mantle. The effective cycling volume of the Soxhlet was approximately 15 mL. The flask was charged with a solution of ketone **1a** (1.00 g, 4.04 mmol) in methanol (20 mL) and benzene (20 mL). To this solution was added $HClO_4$ (60%, 2.03 g, 12.1 mmol) in one portion. The apparatus was flushed with N_2 and the pale yellow solution was heated at reflux with stirring and cycling through the Soxhlet for 24 h. After cooling the solution to RT and concentrating to about 5 mL, ethyl ether (20 mL) was added, thus precipitating the salt as a powder. This was filtered, washed with ether (5 mL), and dissolved in hot methanol (20 mL, decolorizing carbon). Trituration with ether (25 mL), followed by standing for 24 h, afforded **16** (0.7345 g, 46.2%) as small white crystals: mp 193–194°C (dec); IR (KBr) cm^{-1} 2800–2600 (1090 (Cl—O); ^1H NMR (DMSO-d_6) δ 2.58 [br s, 2 H, H(1, 5)], 2.75 [d, J = 14 Hz, 2 H H (2, 4)ax], 3.15–3.18 [m, 8 H, H(2,4)eq, CH_3O], 3.38 [dd or b, t, J = 12 Hz, 2 H, H (6, 8)ax], 3.60 [d, J = 12 Hz, H(6, 8)eq], 4.33 [d, J = 5 Hz, 2 H, $PhCH_2$], 7.49–7.62 [m, 5 H, Ar*H*], 9.28 [br s, 1 H, N—*H*]; ^{13}C NMR (DMSO-d_6) ppm 28.8 [t, C(2, 4)], 32.2 [d, C(1, 5)], 46.6 [q, CH_3O], 47.0 [q, CH_3O], 54.5 [t, C(6, 8)], 60.2 [t, $PhCH_2$], 95.1 [s, C(9)], 129.0 [d, *o*- or *m*-ArC], 129.5 [s, *i*-Ar*C*], 130.1 [d, *p*-Ar*C*], 130.2 [d, *m*- or *o*-Ar*C*]; ^{15}N NMR (DMSO-d_6) ppm 53.5 [N(7)]. Anal. calcd. for $C_{26}H_{24}ClNO_6S$: C, 48.79; H, 6.14; Cl, 9.00; N, 3.56; S, 8.14. Found: C, 48.73; H, 6.09; Cl, 9.39; N, 3.54; S, 8.40.

N,N'-Dibenzyl-9,9-dimethoxy-3,7-diazabicyclo[3.3.1]nonane hydroperchlorate (**17**). Caution: The use of shields, protective goggles and gloves is *very strongly recommended* when performing this reaction. The formation of explosive methyl perchlorate is a possible side reaction in this experiment. No difficulty was noted in when the experiment was performed as described. A 100-mL flask was equipped as outlined for **16**. The effective cycling volume of the Soxhlet was approximately 20 mL. The flask was charged with a solution of *N,N'*-dibenzyl-3,7-diazabicyclo[3.3.1]nonan-9-one[20] (1.00 g, 3.12 mmol) in CH_3OH (25 mL) and C_6H_6 (25 mL) to which was added $HClO_4$ (60%, 1.50 g, 8.96 mmol) in one portion. The apparatus was flushed with N_2 and the colorless solution was heated to reflux with cycling through the Soxhlet. After 24 h, the now pale yellow solution was cooled to RT and concentrated to about 5 mL. Upon standing for a few minutes, a product precipitated as a white solid which was filtered, washed with C_6H_6, and recrystallized (CH_3OH) to afford the monoperchlorate **17** (0.9103 g) as small white crystals, mp 223.6–224.0°C (dec.). The mother liquor was concentrated to approximately 10 mL. Upon cooling at −10°C overnight, a second crop of **17** was obtained (89.4 mg, 68.6% total), mp 223.6–224°C (dec). The spectral data were as follows: IR (KBr) cm^{-1} 2800–2600 ($\overset{+}{N}$—H), 1100 (Cl—O); ^1H NMR (DMSO-d_6) δ 2.35 [br s, 2 H, H(1, 5)], 2.90 [d, J = 13 Hz, 4 H, H(2, 4, 6, 8)ax], 3.08 [d, J = 13, 4 H, H(2, 4, 6, 8)eq], 3.14 [s, 6 H, CH_3O], 3.88 [s, 4 H, $PhCH_2$], 7.38–7.54 [m, 10 H, Ar*H*], 9.84 [br s, 1 H, $\overset{+}{N}$—*H*]; ^{13}C NMR (DMSO-d_6) ppm 33.0 [d, C(1, 5)], 47.0 [q, CH_3O], 53.8 [t, C(2, 4, 6, 8)], 59.6 [t, $PhCH_2$], 95.4 [s, C(9)], 128.2 [d, *p*-Ar*C*], 128.4 [d, *o*- or *m*-Ar*C*], 129.6 [d, *m*- or *o*-Ar*C*], 133.5 [s, *i*-Ar*C*]; ^{15}N NMR (DMSO-d_6) ppm 52.9 [N(3, 7)]. Anal. calcd. for $C_{23}H_{31}ClN_2O_6$: C, 59.16: H, 6.69; Cl, 7.59; N, 6.00. Found: C, 58.98; H, 6.81; Cl, 7.86; N, 6.28.

Crystal data

A thin rectangular plate-like crystal of 3,6-dibenzyl-hexahydro-8a-methoxy-5*H*-4a,8-(methanothiomethano)-2*H*-pyrido[3,4,*e*]-1,3-oxazine (**2a**) was used for all X-ray measurements. Preliminary diffraction studies indicated the crystal to be monoclinic. The space group $P2_1/a$ was determined from systematic absences: 0k0, $k = 2n + 1$; h0l, $h = 2n + 1$. The cell parameters were determined by least-squares fit to $\pm 2\theta$ values of 40 reflections measured at 138K using $MoKa_1$ radiation ($\lambda = 0.70926$).

Intensities of all unique reflections with $2\theta \leq 53°$ were collected at 138 ± 2K using $MoK\bar{\alpha}$ radiation (graphite monochromator) on an Enraf–Nonius CAD-4 automatic diffractometer fitted with a liquid-N_2 low temperature device. A θ–2θ scan was employed using a variable scan width, $(0.9° + 0.2 \tan \theta)$, and a variable scan speed. The maximum scan time for a reflection was 60 seconds. The intensities of three standard reflections, monitored every 7200 seconds of X-ray exposure, showed a maximum variation of 5%. The orientation of the crystal was checked after every 200 measurements. Of the total 4406 reflections measured, 2995 were considered observed on the basis of $I \geq 2\sigma(I)$. Intensities were corrected for Lorentz and polarization factors, but no absorption correction was made. Each structure amplitude was assigned an experimental weight, $\omega_F = 1/\sigma_F^2$ where σ_F was obtained from counting statistics. The structure was determined by using the direct methods program MULTAN[21] and was refined by full-matrix least-squares routines[22] using anisotropic thermal parameters for the non-hydrogen atoms. All of the hydrogen atoms were located from a difference Fourier map and were refined isotropically. The refinement converged to a final R of 0.045, $R_\omega = 0.045$, $S = 1.303$, $(\Delta/\sigma)_{max} = 0.037$ for 2995 observed reflections. The final difference map was featureless with maximum peak heights of ± 0.26 ē/Å^3.

A crystal of $C_{39}H_{44}N_4SO$ (**3a**) was mounted on a Syntex P3 automated diffractometer. Unit cell dimensions (Table IX) were determined by least squares refinement of the best angular positions for fifteen independent reflections ($2\theta > 15°$) during normal alignment procedures using molybdenum radiation ($\lambda = 0.71069$ Å). Data (2368 points) were collected at room temperature using a variable scan rate, a θ–2θ scan mode and a scan width of 1.2° below $K\alpha_1$ and 1.2° above $K\alpha_2$ to a maximum 2θ value of 45.0°. Backgrounds were measured at each side of the scan for a combined time equal to the total scan time. The intensities of three standard reflections were remeasured after every 97 reflections and as the intensities of these reflections showed less than 6% variation, corrections for decomposition were deemed unnecessary. Data were corrected for Lorentz, polarization and background effects. After removal of redundant and space group forbidden data, observed data, (1156 points) ($I > 3.0\sigma(I)$) were used for solution and refinement. The structure was solved using direct methods[23] for positions of nonhydrogen atoms. Least squares refinement[24] converged with anisotropic thermal parameters. A difference Fourier synthesis did not allow location of all hydrogen positions therefore all hydrogen positions were calculated using a C–H distance of 0.97 Å and appropriate geometry. All hydrogen atoms were included in the final refinement with isotropic thermal parameters but their positional and thermal parameters were held fixed. Because of the scarcity of observed data, attention was directed toward obtaining the greatest amount of structural information about the hetero rings at the expense of precision of refinement of the phenyl rings. While the temperature parameters for all atoms were converted to anisotropic form, the positional and anisotropic thermal values for carbons of phenyl rings were refined for two cycles and then held invariant while positional and anisotropic thermal parameters for atoms of the hetero rings and aliphatic benzyl carbons were refined to convergence. Therefore bond angles and distances involving atoms of the phenyl rings are reported without error. A difference Fourier revealed no electron density of intepretable level. Scattering factors were taken from Cromer and Mann.[25]

The final cycle of refinement—[function minimized $\sum (|F_o| - |F_c|)^2$], led to final agreement factor, $R = 8.2\%$, $R = (\sum ||F_o| - |F_c|| / \sum |F_o|) \times 100$. A weight equal to $1/F$ was introduced in the final cycles of refinement: $R_w = 10.4\%$.

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