7.9 (1 H, br s), 7.3 (5 H, s), 4.81 (2 H, d, J = 5.3), 2.84 (1 H, dd, J = 7.8, 9.5), 2.70 (2 H, m), 2.59 (1 H, m), 1.95 (3 H, s), 1.92 (2 H, m), 1.33 (3 H, s), 0.84 (3 H, s); ^{13}C NMR δ 207.7, 203.9, 136.4, 128.9, 128.3, 128.0, 54.2, 50.2, 47.8, 43.6, 41.7, 30.3, 30.1, 23.1, 17.6. Anal. Calcd for $C_{17}H_{23}NSO$: C, 70.55; H, 8.01. Found: C, 70.52; H, 8.06.

***N*-Methyl-6-methoxy-6-oxothiohexanamide (7ha)**: light yellow oil; 86% yield from **6ha**; IR ν 3330, 2935, 1740, 1544, 1433, 1378, 1196, 1090, 1010 cm^{-1}; ^{1}H NMR δ 8.3 (1 H, br s), 3.68 (3 H, s), 3.17 (3 H, d, J = 4.7), 2.70 (2 H, t, J = 7.3), 2.37 (2 H, t, J = 7.2), 1.83 (2 H, m), 1.65 (2 H, m); ^{13}C NMR δ 205.0, 173.8, 51.2, 45.4, 33.3, 32.5, 28.2, 23.5. Anal. Calcd for $C_8H_{15}NO_2S$: C, 50.77; H, 7.99. Found: C, 50.54; H, 7.89.

***N*-Methyl-6-(diethylamino)-6-oxothiohexanamide (7ia)**: light yellow oil; 22% overall yield from **3i** using a neutral hydrolysis of unpurified **6ia**; IR ν 3248, 3076, 2975, 2935, 2874, 1619, 1560, 1463, 1381, 1267, 1218, 1097, 914, 730, 645 cm^{-1}; ^{1}H NMR δ 3.36 (2 H, q, J = 7.1), 3.32 (2 H, q, J = 7.1), 3.16 (3 H, d, J = 4.7), 2.75 (2 H, t, J = 7.0), 2.35 (2 H, t, J = 6.9), 1.81 (2 H, m), 1.68 (2 H, m), 1.18 (3 H, t, J = 7.1), 1.11 (3 H, t, J = 7.1); ^{13}C NMR δ 205.1, 172.2, 45.4, 42.0, 40.2, 32.7, 32.5, 28.4, 23.9, 14.1, 12.9. Anal. Calcd for $C_{11}H_{22}N_2OS$: C, 57.35; H. 9.63. Found: C, 57.36; H. 9.45.

Control Experiment. By the general procedure given above, **6fb** was hydrolyzed in aqueous THF for 2 days at room temperature. Workup of one-third of the reaction mixture produced an oil which was shown by ^{1}H NMR to consist of carboxamide **9fb** and thioamide **7fb** in a 56:44 molar ratio. After an additional 2 days (4 days total) workup of half of the remaining reaction mixture and subsequent ^{1}H NMR analysis showed no change in the molar ratio. At this point, pure thioamide **7fb** was added to the remaining reaction mixture and stirred an additional 2 days at room temperature. Subsequent analysis after workup indicated that none of the excess thioamide **7fb** was converted to amide **9fb**.

Acknowledgment. This work was supported by a Biomedical Research Support Grant from Colorado State University. We would like to thank Cynthia Baker for her assistance in obtaining the ^{31}P NMR spectra.

Registry No. **1g**, 61826-55-9; **1h**, 627-91-8; **1i**, 91017-35-5; **2a**, 74-89-5; **2b**, 100-46-9; **2c**, 107-11-9; **3a**, 75-36-5; **3b**, 79-03-8; **3c**, 98-88-4; **3d**, 7065-46-5; **3e**, 104-97-2; **3f**, 3350-78-5; **3g**, 130062-20-3; **3h**, 35444-44-1; **3i**, 64792-78-5; **4a**, 31464-99-0; **4b**, 130012-35-0; **4c**, 36592-38-8; **5aa**, 130012-36-1; **5ba**, 130012-37-2; **5bb**, 130012-38-3; **5ca**, 123269-09-0; **5cb**, 130012-39-4; **5cc**, 130012-40-7; **5da**, 130012-41-8; **5ea**, 130012-42-9; **5fa**, 130012-43-0; **5fb**, 130012-44-1; **5ga**, 130012-45-2; **5gb**, 130012-46-3; **5ha**, 130012-47-4; **5ia**, 130012-48-5; **6aa**, 130012-49-6; **6ba**, 130012-50-9; **6bb**, 130012-51-0; **6ca**, 123269-11-4; **6cb**, 130012-52-1; **6cc**, 130012-53-2; **6da**, 130012-54-3; **6ea**, 130012-55-4; **6fa**, 130012-56-5; **6fb**, 130012-57-6; **6ga**, 130012-58-7; **6gb**, 130012-59-8; **6ha**, 130012-60-1; **6ia**, 130012-61-2; **7aa**, 5310-10-1; **7ba**, 2955-71-7; **7bb**, 63418-53-1; **7ca**, 5310-14-5; **7cb**, 14309-89-8; **7cc**, 130012-62-3; **7da**, 130012-63-4; **7ea**, 130012-64-5; **7fa**, 130012-65-6; **7fb**, 130012-66-7; **7ga**, 130012-67-8; **7gb**, 130012-68-9; **7ha**, 130012-69-0; **7ia**, 130031-61-7; $(MeO)_2P(S)Cl$, 2524-03-0.

Intra- and Intermolecular α-Sulfamidoalkylation Reactions

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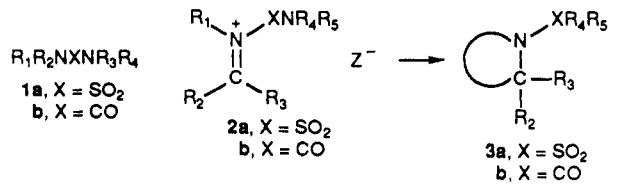
The utility of α-sulfamidoalkylation processes for the generation of sulfamides has been examined. Select aryl-substituted sulfamides were prepared and then treated with acid. Both intra- and intermolecular α-sulfamidoalkylation transformations were observed to proceed in moderate to good yields. The pathways for these reactions are discussed. The generality of these processes has been demonstrated using *N*,*N*′-di(aryl-substituted)sulfamides, and the utility of these reactions was examined for the preparation of cyclic sulfamides of novel structure.

In recent years an increasing number of articles has appeared describing the synthesis, properties, and biological activities of substituted sulfamides **1a**.[1] These compounds are the sulfonyl analogues of ureas **1b**. Previously, we have demonstrated that intramolecular α-ureidoalkylation transformations proceeding through the intermediacy of an iminium ion (i.e., **2b**) provide an expeditious route for the preparation of N,N-cycloalkylated ureas (i.e., **3b**).[2] In the present study, we report on the use of the corresponding α-sulfamidoalkylation process (i.e., **2a** → **3a**) for the generation of sulfamides of novel structure.



Results and Discussion

α-Sulfamidoalkylation Reactions of Sulfamide and *N*-Mono(aryl-substituted)sulfamides. The utility of the proposed α-sulfamidoalkylation transformation **2a** → **3a** was assessed by using sulfamide **4** and the aryl-substituted sulfamides **5** in which the number of methylene units separating the aromatic ring from the sulfamide moiety was systematically varied from zero to four. The starting sulfamides **5a–e** were prepared according to established synthetic protocols.[3] Iminium ion formation was

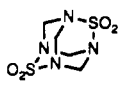
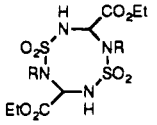
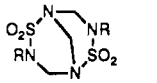
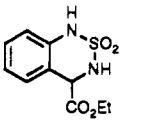
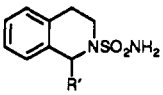
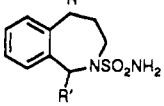
† Present Address: Department of Chemistry, Won Kwang University, Iri, Chun-Buck, Korea.

(1) (a) Lee, C. H.; Korp, J. D.; Kohn, H. *J. Org. Chem.* **1989**, *54*, 3077. (b) Timberlake, J. W.; Ray, W. J.; Stevens, E. D. *Ibid.* **1989**, *54*, 5024. (c) Muller, G. W.; DuBois, G. E. *Ibid.* **1989**, *54*, 4471. (d) Unterhalt, B.; Hanewacker, G.-A. *Arch. Pharm. (Weinheim)* **1988**, *321*, 375. (e) Patzold, F.; Niclas, H.-J.; Forster, H.-J. *Z. Chem.* **1989**, *29*, 203. (f) Giraldes, A.; Nieves, R.; Ochoa, C.; Vara de Rey, C.; Cenarruzabeitia, E.; Lasheras, B. *Eur. J. Med. Chem.* **1989**, *24*, 497. (g) Elguero, J.; Joya, P.; Martinez, A. *Heterocycles* **1989**, *29*, 245. (h) Lee, C. H.; Kohn, H. *J. Pharm. Sci.*, in press, and references therein.

(2) (a) Liao, Z.-K.; Kohn, H. *J. Org. Chem.* **1985**, *50*, 1884. (b) Liao, Z.-K.; Kohn, H. *Ibid.* **1984**, *49*, 4745. (c) Liao, Z.-K.; Kohn, H. *Ibid.* **1984**, *49*, 3812. (d) Liao, Z.-K.; Kohn, H. *Ibid.* **1982**, *47*, 2787.

0022-3263/90/1955-6098$02.50/0

Table I. Major Products and Yields for α-Sulfamidoalkylation Reactions of Sulfamide and *N*-Mono(aryl-substituted)sulfamides

sulfamide	acetal	major product	cmpd no.	yield, %
4	6		8	95
4	7		9, R = H	75
5b, *n* = 1	7		13, R = CH_2Ph	74
5a, *n* = 0	6		10, R = Ph	46
5b, *n* = 1	6		12, R = CH_2Ph	72
5e, *n* = 4	6		18, R = $(CH_2)_4Ph$	56
5a, *n* = 0	7		11	56
5c, *n* = 2	6		14, R′ = H	88
5c, *n* = 2	7		15, R′ = CO_2Et	80
5d, *n* = 3	6		16, R′ = H	85
5d, *n* = 3	7		17, R′ = CO_2Et	11

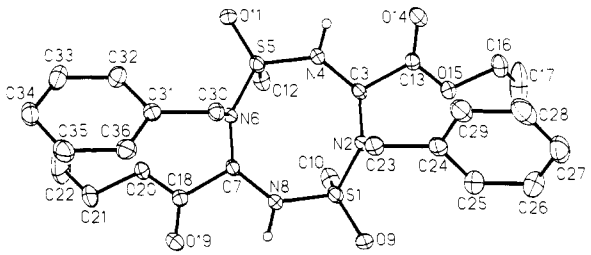
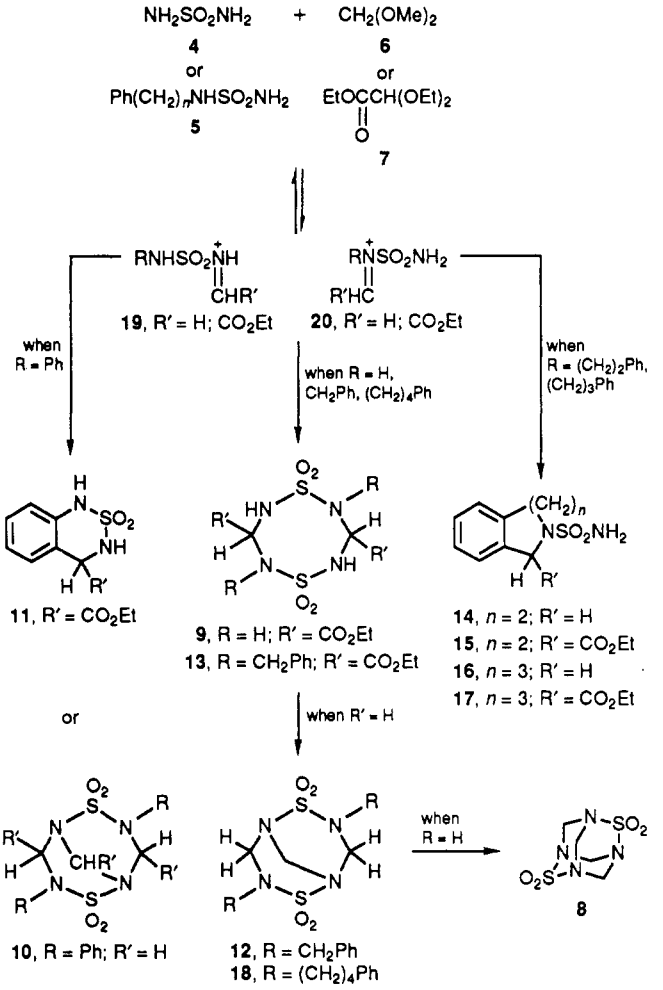


Figure 1. ORTEP view of compound **13**, with atom labeling scheme. The thermal ellipsoids are 30% equiprobability envelopes, with the two sulfamide hydrogens as spheres of arbitrary diameter.

accomplished by treatment of **4** and **5** with either of the two acetals dimethoxymethane (**6**) or ethyl diethoxyacetate (**7**) in trifluoroacetic acid at room temperature.

In Table I, the major adduct isolated from each reaction is listed along with the purified yield. Treatment of **5e** with **7** led to a complex reaction mixture (TLC analysis), which did not permit the isolation of any individual products. Identification of compounds **8–12** and **14–18** was accomplished with the aid of infrared, ^1H and ^{13}C NMR, and mass spectroscopy coupled with elemental analysis. Diagnostic signals were observed in the ^1H (δ 4.25–5.59) and ^{13}C (47.62–70.92 ppm) NMR spectra for these compounds for either the methylene or ethoxycarbonylmethine unit furnished by the acetal. In those cases where annelation of the benzene ring occurred, six discrete resonances in the ^{13}C NMR aromatic region were generally detected. Our inability to conclusively identify the eight-membered ring product **13** obtained from N-benzylsulfamide (**5b**) and

Scheme I. Summary of Competing α-Sulfamidoalkylation Transformations



ethyl diethoxyacetate (**7**) led us to secure the single-crystal X-ray structure of this adduct (Figure 1). An ORTEP drawing of **13** (Figure 1) shows that the ring adopts a staggered conformation in the solid state similar to the structure obtained for 3,7-dicarbethoxyperhydro-1,5,2,4,6,8-dithiatetrazocine 1,1,5,5-tetraoxide (**9**) and the corresponding permethylated derivative, 3,7-dicarbethoxy-2,4,6,8-tetramethylperhydro-1,5,2,4,6,8-dithiatetrazocine 1,1,5,5-tetraoxide.[4] Of particular note, the orientations of the approximately planar nitrogens in **13** are significantly different. At N(2) and N(6) the benzyl substituents occupy essentially axial sites, whereas the hydrogens at N(4) and N(8) are situated in equatorial positions. This compares well with the nonequivalent orientations for the ring nitrogens previously observed in this series of compounds.[4] The preference of the *N*-benzyl groups for the axial sites in **13** may result (in part) from the occupancy of the neighboring equatorial-like positions by the ethoxycarbonyl units.

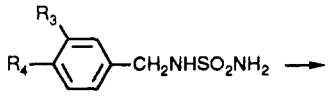
Correlation of the reaction products with the structure of the starting materials permits us to propose a unifying mechanism for these sulfamide-based processes (see Scheme I). Treatment of **4** or **5** with acetals (i.e., **6** or **7**) under acidic conditions is believed to generate an initial mixture of iminium ions **19** and **20**. These species can undergo either intra- or intermolecular α-sulfamidoalkylation transformations depending on the nature of the sulfamide substituent (i.e., R group) and the reaction

(3) (a) Vandi, A.; Moeller, T.; Audrieth, L. F. *J. Org. Chem.* **1961**, *26*, 1136. (b) Appel, R.; Berger, G. *Chem. Ber.* **1958**, *91*, 1339. (c) Ziegler, E.; Ruf, W. *Z. Naturforsch.* **1975**, *30B*, 951. (d) Davis, F. A.; Gangiordano, M. A.; Starmer, W. E. *Tetrahedron Lett.* **1986**, *27*, 3957. (e) Graf, R. *Chem. Ber.* **1959**, *92*, 509. (f) CIBA Ltd. Belg. Patent 640,160, May 19, 1964; *Chem. Abstr.* **1965**, *62*, 16134e. (g) Lafferty, J. J.; Loev, B. U.S. Patent 3,143,549, Aug. 4, 1964; *Chem. Abstr.* **1965**, *62*, 489e. (h) DuBois, G. E.; Stephenson, R. A. *J. Org. Chem.* **1980**, *45*, 5371. (i) Catt, J. D.; Matier, W. L. *Ibid.* **1974**, *39*, 566. (j) Helterich, V. B.; Wiehle, D. J. *Prakt. Chem.* **1961**, *4*, 177. (k) Aeberli, P.; Gogerty, J.; Houlihan, W. J. *J. Med. Chem.* **1967**, *10*, 636.

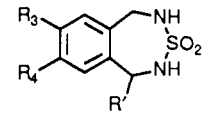
(4) Lee, C.-H.; Kohn, H. *Heterocycles* **1988**, *27*, 2581.

conditions. In those cases where α-sulfamidoalkylation of the aromatic ring in **19** or **20** can proceed by a 6-*Endo*- or 7-*Endo-Trig* process,[5] cyclization generally occurred to give the benzo-annelated products (i.e., **11**, **14–17**).[6] Correspondingly, when the aromatic moiety in the sulfamide is sufficiently removed from the newly generated iminium ion (i.e., **5e**), or when no aromatic ring existed (i.e., **4**), intermolecular dimerization[7] of **19** (**20**) ensued to furnish the eight-membered ring perhydro-1,5,2,4,6,8-dithiatetrazocine 1,1,5,5-tetraoxide (i.e., **9**, **13**). This adduct can then react with **6** (**7**) under the employed conditions to yield **10**, **12**, **18**, and **8**.[8]

Several exceptions to this proposed pathway were observed. First, the dimeric product **10** was isolated from the reaction of **5a** and **6** rather than the cyclic 6-*Endo-Trig* product. Second, treatment of the parent compound, *N*-benzylsulfamide (**5b**) with either dimethoxymethane (**6**) or ethyl diethoxyacetate (**7**) in trifluoroacetic acid yielded the dimeric products **12** and **13**, respectively. In these transformations, intermolecular dimerization processes proceeded more efficiently than the intramolecular α-sulfamidoalkylation reaction leading to the 7-*Endo-Trig* products **21a** and **21b**. This reactivity pattern, however,

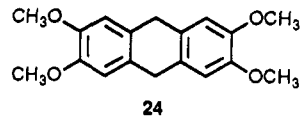


5b, R_3, R_4 = H
22, R_3 = OCH_3; R_4 = H
23, R_3, R_4 = OCH_3

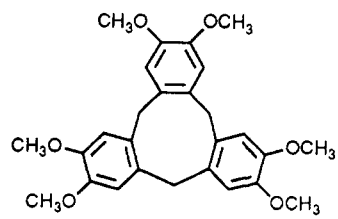


21a, R', R_3, R_4 = H
b, R' = C(O)OEt; R_3, R_4 = H
c, R' = H; R_3 = OCH_3; R_4 = H
d, R' = C(O)OEt; R_3 = OCH_3; R_4 = H
e, R' = H; R_3, R_4 = OCH_3
f, R' = C(O)OEt; R_3, R_4 = OCH_3

was reversed upon activation of the aromatic nucleus by the placement of electron-releasing methoxy substituents on the ring. Addition of **6** and **7** to **22** furnished the cyclized adducts **21c** and **21d**, respectively, in high yields. Correspondingly, treatment of (3,4-dimethoxybenzyl)-sulfamide (**23**) with **6** and **7** in acetic acid–methanesulfonic acid gave **21e** and **21f**, respectively. Use of trifluoroacetic acid with **23** and **7** led only to **9**, **24**,[9] and **25**.[10] Both **24** and **25** were observed when ethyl diethoxyacetate (**7**) was omitted from the reaction, indicating that *N*-(3,4-dimethoxybenzyl)sulfamide (**23**) underwent rapid ionization in trifluoroacetic acid to generate **24** and **25**.



24



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The structural identity of the 7-*Endo-Trig* product **21d** was verified by conversion of this adduct of the *N*,*N*'-dimethyl derivative **26**. Analysis of **26** by X-ray crystallography confirmed the proposed benzo-annelated thia-

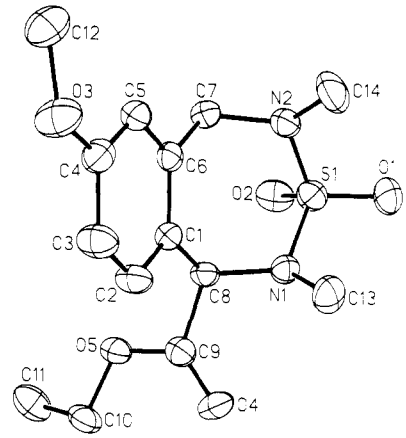
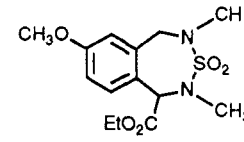


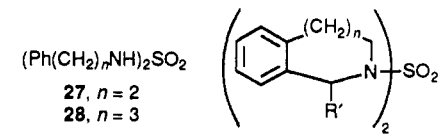
Figure 2. ORTEP view of compound **26**, with atom labeling scheme. The thermal ellipsoids are 40% equiprobability envelopes, with hydrogens omitted for clarity.

diazepine 3,3-dioxide ring structure (Figure 2). In the crystal structure the ring adopts a seven-membered chair-like conformation. Significant delocalization of the electron pair on both nitrogens is indicated by the sum of the torsion angles (346–350°) around each of these atoms.



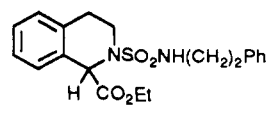
26

α-Sulfamidoalkylation Reactions of *N*,*N*'-Bis(phenylalkyl)sulfamides. The observation that both phenethylsulfamide (**5c**) and phenpropylsulfamide (**5d**) underwent facile intramolecular α-sulfamidoalkylation processes with **6** and **7** prompted our examination of the reactivity of the corresponding bis-substituted sulfamides **27** and **28** with acetals in trifluoroacetic acid. Both **27** and **28** were prepared by treatment of sulfamide **4** with excess arylamine at elevated temperatures. Treatment of **27** with **6** and **7** furnished the novel sulfamides **29a** and **29b**, respectively. An excess of acetal was needed for the formation of **29b**. Employment of lower amounts of **7** led to the monocyclized adduct **30**. Similarly, the reaction of



27, *n* = 2
28, *n* = 3

29a, *n* = 1; R' = H
b, *n* = 1; R' = C(O)OEt
c, *n* = 2; R' = H

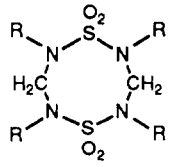


30

28 with **6** gave **29c**. Formation of **29c** required the use of dilute methylene chloride solutions. Addition of **6** to a concentrated trifluoroacetic acid–methylene chloride solution yielded only the dimeric product **31**.

Synthetic Utility of α-Sulfamidoalkylation Transformations. Preliminary experiments have been conducted to assess the utility of the annelated carbethoxy derivatives (i.e., **11**, **15**, **17**) for the preparation of sulfamides of more elaborate structures. Addition of sodium methoxide to **15** led to the generation of the tricyclic

(5) Baldwin, J. *J. Chem. Soc., Chem. Commun.* **1976**, 734.
(6) These results compare favorably with those reported for α-ureidoalkylation transformations proceeding through acyl-substituted iminium ions.[2b,d]
(7) (a) Dusenmund, J.; Schurreit, T. *Arch. Pharm. (Weinheim)* **1986**, *319*, 826. (b) Dusenmund, J. *Ibid.* **1974**, *307*, 881. (c) Dusenmund, J. *Ibid.* **1977**, *310*, 404. (d) Dusenmund, J. *Ibid.* **1977**, *310*, 600.
(8) Petersen, H. *Synthesis* **1973**, 243.
(9) Rabideau, P. W. *J. Org. Chem.* **1971**, *36*, 2723.
(10) Lindsey, A. S. *J. Chem. Soc.* **1965**, 1685.



31, R = $(CH_3)_3Ph$

sulfamide **32**. Support for the proposed structure was achieved by the preparation of **32** by an α-ureidoalkylation procedure (Scheme II). Treatment of the disodium salt of 1,2,5-thiadiazolidine-3,4-dione 1,1-dioxide[11] (**33**) with phenethyl *p*-toluenesulfonate[12] gave **34**, which upon reduction with sodium borohydride (0.75 equiv) afforded the monohydroxy adduct **35**. Dissolution of **35** in trifluoroacetic acid yielded **32**. Reduction of the carbonyl group in **32** with borane–methyl sulfide complex[13] led to the novel sulfamide **36**.

Conclusions

The synthetic potential of α-sulfamidoalkylation transformations for the generation of cyclic sulfamides has been documented. This methodology has permitted the synthesis of sulfamides of novel structure. The success achieved with arylsulfamides **5**, **27**, and **28** suggests that the corresponding alkenyl and acetylenic sulfamides should serve as suitable starting materials for the construction of alicyclic based sulfamides.[2c]

Experimental Section

General Methods. Infrared spectra (IR) were calibrated against the 1601-cm^{-1} band of polystyrene. ^1H and ^{13}C NMR spectra were taken at 300 and 75 MHz, respectively. The low-resolution electron-impact mass spectral data (MS) were obtained at an ionizing voltage of 70 eV. Microanalyses were obtained from Spang Microanalytical Laboratory, Eagle Harbor, MI.

All glassware was dried before use. The solvents and reactants were of the best commercial grade available and were used without further purification. Thin- and thick-layer chromatography were run on precoated silica gel GHLF microscope slides (2.5 × 10 cm; Analtech No. 21521) or silica gel GHLF (20 × 20 cm; Analtech No. 11187).

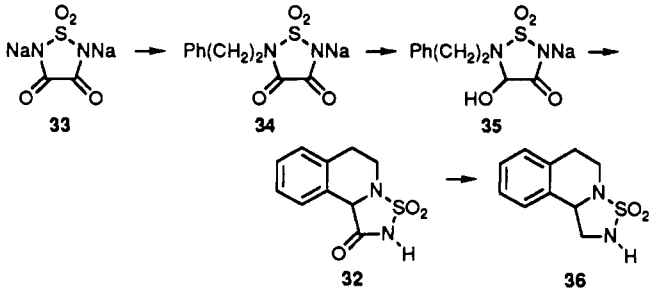
General Procedure for the Preparation of *N*-Mono(aryl-substituted)sulfamides 5 and 23. The mixture of **4** (10 mmol), amine (10 mmol), and H_2O (10 mL) was heated to reflux (5 h). The solution was cooled to room temperature and acidified (pH 2) with an aqueous 1 N HCl solution. The mixture was permitted to stand at 0–5 °C. The solid that formed was filtered and then washed with H_2O to give the desired substituted sulfamide.

***N*-Benzylsulfamide (5b)**: yield 1.25 g (67%); mp 106–107 °C (lit.[3e] mp 106–107 °C); ^1H NMR (DMSO-d_6) δ 4.07 (d, 2 H, J = 7.4 Hz), 6.64 (s, 2 H), 7.06 (t, 1 H, J = 7.4 Hz), 7.22–7.41 (m, 5 H).

***N*-Phenethylsulfamide (5c)**: yield 1.48 g (72%); mp 67–68 °C (lit.[3f] mp 68 °C); ^1H NMR (DMSO-d_6) δ 2.79 (t, 2 H, J = 7.3 Hz), 3.07–3.14 (m, 2 H) 6.56 (s, 2 H), 6.59 (t, 1 H, J = 6.6 Hz), 7.19–7.41 (m, 5 H); ^{13}C NMR (DMSO-d_6) 35.25, 44.26, 126.15, 128.35, 128.66, 139.37 ppm.

***N*-(3-Phenyl-*n*-propyl)sulfamide (5d)**: yield 1.54 g (71%); mp 64–65 °C (lit.[3f] mp 65–67 °C); ^1H NMR (DMSO-d_6) δ 1.72–1.81 (m, 2 H), 2.61 (t, 2 H, J = 7.6 Hz), 2.86–2.93 (m, 2 H), 6.48–6.52 (m, 3 H), 7.15–7.30 (m, 5 H): ^{13}C NMR (DMSO-d_6) 30.78, 32.45, 45.12, 126.66, 128.26, 141.72 ppm. The remaining aromatic peak was not detected and is presumed to be accidentally equivalent with one of the other observed signals.

Scheme II. α-Ureidoalkylation Procedure for the Preparation of Compound 32



33 **34** **35** **32** **36**

***N*-(4-Phenyl-*n*-butyl)sulfamide (5e)**: yield 1.40 g (75%); mp 81–82 °C; IR (KBr) 3380, 1370, 1110 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.55–1.70 (m, 4 H), 2.59–2.64 (m, 2 H), 3.04–3.10 (m, 2 H), 5.36 (t, 1 H, J = 5.4 Hz), 5.48 (s, 2 H), 7.15–7.27 (m, 5 H); ^{13}C NMR ($CDCl_3$) 28.21, 28.71, 35.07, 42.97, 125.45, 127.49, 128.09, 141.80 ppm; MS, m/e (rel intensity) 228 (4), 147 (37), 131 (100), 119 (18), 109 (54), 104 (50), 91 (97).

Anal. Calcd for $C_{10}H_{16}N_2O_2S$: C, 52.60; H, 7.06; N, 12.27. Found: C, 52.47; H, 7.10; N, 12.27.

***N*-(3,4-Dimethoxybenzyl)sulfamide (23)**: yield 1.64 g (72%); mp 118–119 °C; IR (KBr) 3300, 3200, 1330, 1150 cm^{-1}; ^1H NMR (DMSO-d_6) δ 3.73 (s, 3 H), 3.75 (s, 3 H), 4.01 (d, 2 H, J = 5.9 Hz), 6.61–6.63 (m, 2 H), 6.92 (br s, 4 H); ^{13}C NMR (DMSO-d_6) 46.00, 55.46, 55.59, 111.62, 111.75, 119.85, 130.94, 147.90, 148.61 ppm; MS, m/e (rel intensity) 246 (100), 165 (78), 151 (99), 136 (20), 107 (25).

Anal. Calcd for $C_9H_{14}N_2O_4S$: C, 43.89; H, 5.73; N, 11.30. Found: C, 43.97; H, 5.74; N, 11.32.

***N*-(3-Methoxybenzyl)sulfamide (22).** Utilizing the general procedure described for the preparation of *N*-mono(aryl-substituted)sulfamides **5**, **4** (0.96 g, 10 mmol) was treated with 3-methoxybenzylamine (1.37 g, 10 mmol) in H_2O (10 mL). After acidification, the mixture was extracted with Et_2O (2 × 50 mL). The Et_2O solution was washed with H_2O, dried (Na_2SO_4), and concentrated in vacuo to give 1.44 g (66%) of **22**: mp 45–46 °C; IR (KBr) 3230, 1320, 1155 cm^{-1}; ^1H NMR (DMSO-d_6) δ 3.74 (s, 3 H), 4.06 (d, 2 H, J = 6.0 Hz), 6.64 (s, 2 H), 6.80–6.93 (m, 3 H), 7.05 (t, 1 H, J = 6.0 Hz), 7.20–7.26 (m, 1 H); ^{13}C NMR (DMSO-d_6) 46.04, 55.00, 112.41, 113.17, 119.82, 129.19, 140.29, 159.24 ppm; MS, m/e (rel intensity) 216 (83), 149 (37), 134 (100), 121 (37), 105 (43).

Anal. Calcd for $C_8H_{12}N_2O_3S$: C, 44.43; H, 5.60; N, 12.96. Found: C, 44.35; H, 5.55; N, 12.84.

***N*-Phenylsulfamide (5a).**[3b,e] To a benzene solution (50 mL, dried over CaH_2) containing chlorosulfonyl isocyanate (8.46 g, 60 mmol) was added formic acid (2.76 g, 60 mmol, dried over boron oxide) dropwise at 0–5 °C. The mixture was kept at room temperature (16 h) and then heated at 40 °C, until a clear solution resulted. Aniline (11.2 g, 120 mmol) was added dropwise at 0–5 °C and then an aqueous 1 N NaOH solution (60 mL) was added. The mixture was permitted to stand at 0–5 °C and then the solid that precipitated was filtered and recrystallized with H_2O to give 3.82 g (37%) of **5a**: mp 105–107 °C (lit.[3e] mp 102–103 °C); ^1H NMR (CD_3CN) δ 5.46 (br s, 2 H), 7.10–7.37 (m, 5 H), 7.50 (s, 1 H); ^{13}C NMR (CD_3CN) 121.06, 125.01, 130.16, 139.37 ppm.

Tetramethylenedisulfotetramine (8).[7a,b,14] A mixture of **4** (96 mg, 1 mmol), **6** (152 mg, 2 mmol), and trifluoroacetic acid (5 mL) was stirred at room temperature (6 h). The solid that formed was filtered and dried to give 126 mg (96%) of **8**: mp 252–254 °C (lit.[7] mp 255–260 °C); IR (KBr) 1350, 1140 cm^{-1}; ^1H NMR (DMSO-d_6) δ 5.56 (s); ^{13}C NMR (DMSO-d_6) 70.92 ppm. [*Caution*:[8] *Tetramethylenedisulfotetramine has extraordinarily high toxicity and is five times more active than strychnine as a poison attacking the central nervous system.*]

Diethyl Perhydro-1,5,2,4,6,8-dithiatetrazocine-3,7-dicarboxylate 1,1,5,5-Tetraoxide (9). Compound **4** (96 mg, 1 mmol) and **7** (176 mg, 1 mmol) in trifluoroacetic acid (5 mL) were stirred at room temperature (16 h). The mixture was concentrated in vacuo and then the residue was triturated with diethyl eth-

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er–hexane (1:1). The white solid was filtered to afford 292 mg (81%) of **9**: mp 202–203 °C (lit.[4] mp 203–205 °C).

3,7-Diphenyl-2,6,1,3,5,7-dithiatetraazabicyclo[3.3.1]nonane (10). Compound **5a** (172 mg, 1 mmol) and **6** (152 mg, 2 mmol) in trifluoroacetic acid (5 mL) were stirred at −20 °C (4 h) and then at room temperature (16 h). The solution was concentrated in vacuo and the residue was purified by flash chromatography ($CHCl_3$) to give 170 mg (46%) of **10**: mp 220 °C dec; IR (KBr) 1350, 1120 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.08 (d, 2 H, J = 13.2 Hz), 5.16 (d, 2 H, J = 13.2 Hz), 5.59 (s, 2 H), 7.34–7.42 (m, 10 H); ^{13}C NMR ($CDCl_3$) 68.59, 69.55, 126.31, 128.18, 129.84, 138.09 ppm; MS (+FAB) 381 $[M + 1]^{+1}$.

Anal. Calcd for $C_{15}H_{16}N_4O_4S_2$: C, 47.35; H, 4.24; N, 14.73. Found: C, 47.58; H, 4.20; N, 14.53.

Ethyl 3,4-Dihydro-1*H*-2,1,3-benzothiadiazine-4-carboxylate 2,2-Dioxide (11). A solution of compounds **5a** (256 mg, 1 mmol) and **7** (176 mg, 1 mmol) was stirred in trifluoroacetic acid (10 mL) at room temperature (2 days) and then concentrated to dryness in vacuo. The major product **11** was isolated by preparative TLC (5% acetone–chloroform) in 56% yield (143 mg): R_f 0.25 (5% acetone–chloroform); mp 111–112 °C; IR (KBr) 3270, 3200, 1720, 1330, 1160 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.21 (t, 3 H, J = 7.0 Hz), 4.16 (q, 2 H, J = 7.0 Hz), 5.35 (d, 1 H, J = 7.7 Hz), 6.76 (d, 1 H, J = 7.9 Hz), 6.94–6.99 (m, 1 H), 7.21–7.26 (m, 2 H), 7.90 (d, 1 H, J = 7.7 Hz), 10.35 (s, 1 H); ^{13}C NMR (DMSO-d_6) 13.70, 58.64, 60.89, 116.59, 116.86, 120.88, 128.23, 128.60, 138.39, 168.55 ppm; MS, m/e (rel intensity) 256 (6), 183 (100), 143 (9), 119 (70), 92 (48).

Anal. Calcd for $C_{10}H_{12}N_2O_4S$: C, 46.86; H, 4.72; N, 10.93. Found: C, 46.90: H, 4.86; N, 10.81.

3,7-Dibenzyl-2,6,1,3,5,7-dithiatetraazabicyclo[3.3.1]nonane 2,2,6,6-Tetraoxide (12). A trifluoroacetic acid (10 mL) solution containing **5b** (180 mg, 1 mmol) and **6** (76 mg, 1 mmol) was stirred at room temperature (2 days) and then concentrated to dryness in vacuo. The residue was purified by flash chromatography ($CHCl_3$) to give **12** (R_f 0.65, $CHCl_3$) in 72% yield (94 mg): mp 105–106 °C (lit.[7a] mp 104 °C); IR (KBr) 1370, 1150 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.27 (d, 2 H, J = 14.6 Hz), 4.55 (d, 2 H, J = 14.6 Hz), 4.50 (d, 2 H, J = 13.3 Hz), 4.74 (d, 2 H, J = 13.3 Hz), 5.30 (s, 2 H), 7.31–7.42 (m, 10 H); ^{13}C NMR ($CDCl_3$) 52.62, 64.94, 69.49, 128.50, 128.76, 128.92, 134.06 ppm.

Diethyl 2,6-Dibenzylperhydro-1,5,2,4,6,8-Dithiatetrazocine-3,7-dicarboxylate 1,1,5,5-Tetraoxide (13). Method A. A trifluoroacetic acid (30 mL) solution containing **5b** (930 mg, 5 mmol) and **7** (970 mg, 5.5 mmol) was stirred at room temperature (16 h). The solid that precipitated was filtered, washed with trifluoroacetic acid, and dried in vacuo to give 1.02 g (74%) of **13**: mp 216–218 °C dec; IR (KBr) 3260, 1725, 1360, 1160 cm^{-1}; ^1H NMR (DMSO-d_6) δ 0.92 (t, 3 H, J = 7.0 Hz), 3.20–3.28 (m, 1 H), 3.60–3.71 (m, 1 H), 4.35 (d, 1 H, J = 16.7 Hz), 4.79 (d, 1 H, J = 16.7 Hz), 5.98 (d, 1 H, J = 10.0 Hz), 7.25–7.35 (m, 5 H), 9.52 (d, 1 H, J = 10.0 Hz); ^{13}C NMR (DMSO-d_6) 13.20, 44.66, 61.81, 66.76, 127.18, 127.81, 136.18, 164.99 ppm. One of the aromatic peaks was not detected and is presumed to be accidentally equivalent with one of the other observed signals. MS (-FAB) 539 $[M - 1]^{-1}$.

Anal. Calcd for $C_{11}H_{14}N_2O_4S$: C, 48.88; H, 5.22; N, 10.37. Found: C, 48.88; H, 5.19; N, 10.36.

Method B. An acetic acid (15 mL) solution containing **5b** (1.86 g, 10 mmol), **7** (1.84 g, 11 mmol), and methanesulfonic acid (1 mL) was stirred at room temperature (1 day). The solid that formed was filtered, washed with acetic acid, and dried in vacuo to give 0.86 g (32%) of **13**: mp 216–218 °C dec.

2-Sulfamido-1,2,3,4-tetrahydroisoquinoline (14). Utilizing the procedure described for **12**, **5c** (196 mg, 1 mmol) was treated with **6** (76 mg, 1 mmol) in trifluoroacetic acid (10 mL). After concentration, the residue was purified by flash chromatography ($CHCl_3$) to give 187 mg (88%) of **14**: R_f 0.22 ($CHCl_3$); mp 155–156 °C (lit.[3k] mp 157–159 °C); IR (KBr) 3290, 3200, 1320, 1110 cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.90 (t, 2 H, J = 5.7 Hz), 3.26 (t, 2 H, J = 5.7 Hz), 4.20 (s, 2 H), 6.94 (s, 2 H), 7.13–7.16 (m, 4 H); ^{13}C NMR (DMSO-d_6) 28.12, 43.72, 47.62, 126.03, 126.44, 126.51, 128.62, 132.43, 133.30 ppm; MS, m/e (rel intensity) 212 (11), 132 (29), 131 (86), 129 (2), 104 (100).

Anal. Calcd for $C_9H_{12}N_2O_2S$: C, 50.92; H, 5.70; N, 13.20. Found: C, 50.92; H, 5.71; N, 13.21.

Ethyl 2-Sulfamido-1,2,3,4-tetrahydroisoquinoline-1-carboxylate (15). A trifluoroacetic acid (30 mL) solution containing **5c** (1.98 g, 10 mmol) and **7** (2.00 g, 11.4 mmol) was stirred at room temperature (2 days). The solution was concentrated in vacuo and then the residue was purified by flash chromatography (5% acetone–chloroform) to give 2.26 g (80%) of **15**: R_f 0.35 (5% acetone–chloroform); mp 93–94 °C; IR (KBr) 3320, 3240, 1710, 1325, 1135 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.15 (t, 3 H, J = 7.0 Hz), 2.84–3.00 (m, 2 H), 3.34–3.47 (m, 1 H), 3.65–3.73 (m, 1 H), 4.08 (q, 2 H, J = 7.0 Hz), 5.33 (s, 1 H), 6.94 (s, 2 H), 7.20–7.38 (m, 4 H); ^{13}C NMR (DMSO-d_6) 13.86, 27.60, 41.29, 58.09, 60.92, 126.42, 127.10, 127.34, 128.78, 130.48, 134.84, 170.86 ppm; MS, m/e (rel intensity) 211 (M − CO_2Et, 100), 132 (52), 131 (21), 130 (33), 103 (13).

Anal. Calcd for $C_{12}H_{16}N_2O_4S$: C, 50.69; H, 5.67; N, 9.85. Found: C, 50.77; H, 5.71; N, 9.73.

2-Sulfamido-2,3,4,5-tetrahydro-1*H*-2-benzazepine (16). The procedure described for the preparation of **12** was employed using **5d** (214 mg, 1 mmol), **6** (76 mg, 1 mmol), and trifluoroacetic acid (10 mL). After workup and flash chromatography ($CHCl_3$), **16** was isolated in 85% yield (192 mg): R_f 0.30 ($CHCl_3$); mp 126–127 °C; IR (KBr) 3310, 3240, 1315, 1140 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.76–1.79 (m, 2 H), 2.88–2.92 (m, 2 H), 3.45 (t, 2 H, J = 5.0 Hz), 4.26 (s, 2 H), 6.71 (s, 2 H), 7.15–7.16 (m, 4 H); ^{13}C NMR (DMSO-d_6), 27.55, 33.94, 51.92, 53.30, 126.07, 127.54, 128.80, 129.08, 138.02, 142.14 ppm; MS, m/e (rel intensity) 226 (26), 146 (31), 130 (69), 117 (100), 109 (50), 91 (65).

Anal. Calcd for $C_{10}H_{14}N_2O_2S$: C, 53.08; H, 6.24; N, 12.38. Found: C, 52.78: H, 6.39; N, 12.18.

Ethyl 2-Sulfamido-2,3,4,5-tetrahydro-1*H*-2-benzazepine-1-carboxylate (17). A trifluoroacetic acid (100 mL) solution containing **5d** (2.14 g, 10 mmol) and **7** (2.00 g, 11.4 mmol) was stirred at room temperature (7 days) and then concentrated to dryness in vacuo. The residue was dissolved in hot MeOH (10 mL) and the solution was permitted to stand at 0–5 °C (16 h). The solid that formed was filtered, washed with cold MeOH, and dried to give 0.34 g (11%) of **17**: mp 149–150 °C; IR (KBr) 3340, 3230, 1720, 1350, 1160 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.13 (t, 3 H, J = 7.0 Hz), 1.71–1.80 (m, 2 H), 2.71–2.76 (m, 1 H), 2.94–3.33 (m, 1 H), 3.30–3.42 (m, 2 H), 4.06–4.17 (m, 2 H), 5.52 (s, 1 H), 6.86 (s, 2 H), 7.10–7.23 (m, 4 H); ^{13}C NMR (DMSO-d_6) 13.92, 26.47, 31.33, 44.84, 60.90, 64.72, 126.33, 128.43, 129.68, 130.42, 134.71, 140.01, 169.85 ppm; MS, m/e (rel intensity) 225 (M − CO_2Et, 100), 146 (50), 144 (41), 129 (29), 117 (59).

Anal. Calcd for $C_{13}H_{18}N_2O_4S$: C, 52.33; H, 6.08; N, 9.39. Found: C, 52.27; H, 6.20; N, 9.28.

3,7-Bis(4-phenyl-*n*-butyl)-2,6,1,3,5,7-dithiatetraazabicyclo[3.3.1]nonane 2,2,6,6-Tetraoxide (18). Using the same procedure described for the preparation of **12**, **5e** (210 mg, 1 mmol) and **6** (104 mg, 1.5 mmol) were stirred in trifluoroacetic acid (10 mL). After workup and preparative TLC, **18** was obtained in 56% yield (248 mg): R_f 0.70 ($CHCl_3$); IR ($CHCl_3$) 1340, 1145 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.55–1.65 (m, 8 H), 2.58–2.63 (m, 4 H), 3.13–3.20 (m, 2 H), 3.22–3.29 (m, 2 H), 4.25 (d, 2 H, J = 13.3 Hz), 4.71 (d, 2 H, J = 13.3 Hz), 5.29 (s, 2 H), 7.14–7.29 (m, 10 H); ^{13}C NMR ($CDCl_3$) 27.83, 28.27, 35.21, 49.13, 65.60, 69.42, 125.91, 128.29, 128.35, 141.47 ppm; MS m/e (rel intensity) 492 (1), 282 (4), 268 (11), 253 (100), 239 (5), 216 (4), 189 (9), 160 (68).

Anal. Calcd for $C_{23}H_{32}N_4O_4S_2$: C, 56.11; H, 6.55; N, 11.38. Found: C, 56.16; H, 6.62; N, 11.23.

7-Methoxy-1,2,4,5-tetrahydro-3,2,4-benzothiadiazepine 3,3-Dioxide (21c). Compound **22** (500 mg, 2.3 mmol) and **6** (75 mg, 2.3 mmol) in trifluoroacetic acid (30 mL) were stirred at room temperature (3 h). The solid that formed was filtered, washed with acetone, and dried to give 420 mg (80%) of **21c**: mp 230–232 °C dec; IR (KBr) 3260, 1330, 1140 cm^{-1}; ^1H NMR (DMSO-d_6) δ 3.74 (s, 3 H), 4.11–4.16 (m, 4 H), 6.80–6.83 (m, 2 H), 6.99 (t, 1 H, J = 7.0 Hz), 7.06 (t, 1 H, J = 6.3 Hz), 7.20 (d, 1 H, J = 8.3 Hz); ^{13}C NMR (DMSO-d_6) 45.85, 46.66, 55.20, 112.03, 115.07, 130.36, 131.07, 140.39, 158.53 ppm; MS, m/e (rel intensity) 228 (66), 163 (27), 146 (100), 134 (20).

Anal. Calcd for $C_9H_{12}N_2O_3S$: C, 47.35; H, 5.30; N, 12.27. Found: C, 47.21; H, 5.39; N, 12.11.

Ethyl 7-Methoxy-1,2,4,5-tetrahydro-3,2,4-benzothiadiazepine-1-carboxylate 3,3-Dioxide (21d). A solution of **22** (432 mg, 2 mmol), **7** (390 mg, 2.2 mmol), and trifluoroacetic

acid (20 mL) was stirred at room temperature (3 days) and then concentrated to dryness in vacuo. MeOH (15 mL) was added to the residue and the mixture was stirred at room temperature (2 h). The insoluble materials were filtered, washed with MeOH, and dried to give 400 mg (67%) of **21d**: mp 225 °C dec; IR (KBr) 3250, 1725, 1335, 1150 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.26 (t, 3 H, J = 7.0 Hz), 3.76 (s, 3 H), 4.10 (d, 1 H, J = 14.8 Hz), 4.23–4.35 (m, 3 H), 5.16 (d, 1 H, J = 10.1 Hz), 6.85–7.04 (m, 4 H), 7.50 (d, 1 H, J = 10.1 Hz); ^{13}C NMR (DMSO-d_6) 13.97, 46.54, 55.26, 57.46, 61.19, 112.20, 116.01, 127.83, 129.21, 140.28, 158.77, 169.32 ppm; MS, m/e (rel intensity) 300 (1), 227 (100), 173 (7), 148 (35).

Anal. Calcd for $C_{12}H_{16}N_2O_5S$: C, 47.99; H, 5.37; N, 9.33. Found: C, 47.82; H, 5.49; N, 9.19.

7,8-Dimethoxy-1,2,4,5-tetrahydro-3,2,4-benzothiadiazepine 3,3-Dioxide (21e). An acetic acid (10 mL) solution containing **23** (224 mg, 1 mmol), **6** (76 mg, 1 mmol), and methanesulfonic acid (1 mL) was stirred at room temperature (16 h). The solid that precipitated was filtered, washed with EtOH, and then dried to give 170 mg (72%) of **21e**: mp 240–241 °C; IR (KBr) 1320, 1110 cm^{-1}; ^1H NMR (DMSO-d_6) δ 3.74 (s, 6 H), 4.12 (d, 4 H, J = 3.1 Hz), 6.93 (s, 2 H), 6.99 (t, 2 H, J = 3.1 Hz); ^{13}C NMR (DMSO-d_6) 46.16, 55.73, 113.45, 131.35, 147.45 ppm; MS, m/e (rel intensity) 258 (85), 193 (24), 178 (73), 177 (44), 176 (100).

Anal. Calcd for $C_{10}H_{14}N_2O_4S$: C, 46.49; H, 5.46; N, 10.85. Found: C, 46.61; H, 5.40; N, 10.69.

Ethyl 7,8-Dimethoxy-1,2,4,5-tetrahydro-3,2,4-benzothiadiazepine-1-carboxylate 3,3-Dioxide (21f). Compound **23** (1.18 g, 5 mmol), **7** (0.88 g, 5 mmol), and methanesulfonic acid (1 mL) in acetic acid (50 mL) were stirred at 50 °C (4 days). The precipitate that formed was filtered, washed with acetic acid, and then dried in vacuo to give 0.59 g (32%) of **21f**: mp 230 °C dec; IR (KBr) 3240, 3220, 1720, 1325, 1150 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.15 (t, 3 H, J = 7.0 Hz), 3.70 (s, 3 H), 3.77 (s, 3 H), 4.11 (d, 1 H, J = 6.8 Hz), 4.22–4.38 (m, 3 H), 5.15 (d, 1 H, J = 9.9 Hz), 6.56 (s, 1 H), 6.97 (br s, 1 H), 7.03 (s, 1 H), 7.20 (d, 1 H, J = 9.9 Hz); ^{13}C NMR (DMSO-d_6) 13.99, 46.05, 55.72 (2 C), 57.76, 61.13, 111.15, 114.29, 129.90, 131.60, 147.44, 148.03, 169.21 ppm; MS, m/e (rel intensity) 330 (9), 257 (100), 204 (2), 178 (45), 163 (4), 147 (5).

Anal. Calcd for $C_{13}H_{18}N_2O_6S$: C, 47.26; H, 5.49; N, 8.48. Found: C, 47.17; H, 5.60; N, 8.57.

Reaction of *N*-(3,4-Dimethoxybenzyl)sulfamide (23) with Ethyl Diethoxyacetate (7) in Trifluoroacetic Acid. A trifluoroacetic acid (30 mL) solution containing **23** (1.23 g, 5 mmol) and **7** (0.99 g, 5.5 mmol) was stirred at room temperature (16 h) and then concentrated to dryness in vacuo. The residue was triturated with $CHCl_3$ (20 mL) and the insoluble materials were filtered to give 0.47 g (52%) of **9**: mp 203–204 °C dec (lit.[4] mp 203–205 °C dec); ^1H NMR (DMSO-d_6) δ 1.24 (t, 6 H, J = 7.0 Hz), 4.17 (q, 4 H, J = 7.0 Hz), 5.33 (t, 2 H, J = 9.7 Hz), 8.12 (d, 4 H, J = 9.7 Hz); ^{13}C NMR (DMSO-d_6) 13.84, 61.99, 64.55, 165.86 ppm.

The filtrate was concentrated in vacuo and the residue was separated by preparative TLC (chloroform/acetone = 60:1) to give 0.20 g (65%) of **24** (R_f 0.50, 10% acetone–chloroform; mp 229–230 °C (lit.[9] mp ~230 °C)) and 0.07 g (16%) of **25** (R_f 0.52, 10% acetone–chloroform; mp 234–235 °C (lit.[10] mp 233–234 °C)).

Reaction of *N*-(3,4-Dimethoxybenzyl)sulfamide (23) in Trifluoroacetic Acid. A solution of *N*-(3,4-dimethoxybenzyl)sulfamide (**23**) (0.62 g, 2.5 mmol) and trifluoroacetic acid (10 mL) was stirred at room temperature (3 h). The solid that formed was filtered, washed with trifluoroacetic acid, and then dried in vacuo to give 0.26 g of a binary mixture of **24** and **25**. The filtrate was concentrated in vacuo and the residue was triturated with $CHCl_3$ (10 mL). The insoluble materials were filtered, washed, and dried to give 0.21 g (89%) of sulfamide **4** (lit.[15] mp 90–91 °C). The mixture of **24** and **25** was separated by preparative TLC (2% acetone–chloroform) to give 0.12 g (66%) of **24** (mp 229–230 °C (lit.[9] mp ~230 °C)) and 0.04 g (14%) of **25** (mp 234–235 °C (lit.[10] mp 233–234 °C)).

Ethyl 7-Methoxy-2,4-dimethyl-1,2,4,5-tetrahydro-3,2,4-thiadiazepine-1-carboxylate 3,3-Dioxide (26). A mixture of methyl iodide (1.30 g, 6 mmol), **21c** (0.30 g, 1 mmol), K_2CO_3 (1.38 g, 10 mmol), and acetone (30 mL) was stirred at room temperature (2 days). The mixture was filtered and the filtrate was concentrated in vacuo. The residue was purified by flash column chromatography ($CHCl_3$) to give 0.31 g (90%) of **26**: mp 114–115 °C; IR (KBr) 1740, 1360, 1150 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.28 (t, 3 H, J = 7.5 Hz), 2.66 (s, 3 H), 2.75 (s, 3 H), 3.82 (s, 3 H), 3.84 (d, 1 H, J = 15.6 Hz), 4.26 (q, 2 H, J = 7.5 Hz), 4.87 (d, 1 H, J = 15.6 Hz), 5.77 (s, 1 H), 6.84–6.88 (m, 2 H), 7.07–7.09 (m, 1 H); ^{13}C NMR ($CDCl_3$) 14.03, 32.64, 36.38, 54.14, 55.35, 61.25, 61.59, 112.45, 117.65, 126.32, 129.87, 137.26, 159.62, 168.72 ppm.

Anal. Calcd for $C_{14}H_{20}N_2O_5S$: C, 51.47; H, 6.17; N, 8.53. Found: C, 51.20; N, 6.14; N, 8.53.

General Procedure for the Preparation of *N,N'*-Bis(phenylalkyl)sulfamides 27 and 28. A mixture of **4** (10 mmol), phenylalkylamine (20 mol), and anhydrous pyridine (10 mL) was heated to reflux (16 h) and then the solution was concentrated in vacuo. The residue was recrystallized with EtOH to give the desired product.

***N,N'*-Diphenethylsulfamide (27)**: yield 2.64 g (87%); mp 100–101 °C; IR (KBr) 3240, 1325, 1120 cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.68 (t, 4 H, J = 7.4 Hz), 2.95–3.02 (m, 4 H), 6.93 (t, 2 H, J = 7.3 Hz), 7.23–7.38 (m, 10 H); ^{13}C NMR (DMSO-d_6) 35.37. 44.38, 126.18, 128.42, 128.70, 139.41 ppm; MS, m/e (rel intensity) 304 (3), 213 (100), 184 (25), 119 (14), 105 (23), 91 (61).

Anal. Calcd for $C_{16}H_{18}N_2O_2S$: C, 63.13; H, 6.62; N, 9.20. Found: C, 63.25; H, 6.70; N, 9.20.

***N,N'*-Bis(3-phenyl-*n*-propyl)sulfamide (28)**: yield 3.03 g (92%); mp 124–125 °C; IR (KBr) 3280, 1320, 1115 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.72–1.74 (m, 4 H), 2.71 (t, 4 H, J = 7.6 Hz), 2.84–2.94 (m, 4 H), 6.50 (t, 2 H, J = 7.4 Hz), 7.22–7.34 (m, 10 H); ^{13}C NMR (DMSO-d_6) 31.25, 33.42, 39.50, 42.61, 125.59, 129.87, 142.39 ppm; MS, m/e (rel intensity) 332 (30), 132 (21), 118 (100), 104 (37), 91 (62).

Anal. Calcd for $C_{18}H_{24}N_2O_2S$: C, 65.03; H, 7.28; N, 8.43. Found: C, 65.02; H, 7.24; N, 8.50.

Bis[2-(1,2,3,4-tetrahydroisoquinolinyl)] Sulfone (29a). A CH_2Cl_2 (30 mL) solution containing **27** (610 mg, 2 mmol), **6** (320 mg, 4 mmol), and trifluoroacetic acid (5 mL) was stirred at room temperature (2 days), and then the solution was concentrated to dryness in vacuo. The residue was purified by flash chromatography using $CHCl_3$ as the eluent to give 500 mg (76%) of **29a**: R_f 0.55 ($CHCl_3$); mp 175–176 °C; IR (KBr) 1325, 1135 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.92 (t, 4 H, J = 5.8 Hz), 3.54 (t, 4 H, J = 5.8 Hz), 4.45 (s, 4 H), 7.03–7.19 (m, 8 H); ^{13}C NMR ($CDCl_3$) 28.81, 43.89, 47.70, 126.27, 126.70, 128.88, 132.14, 133.22 ppm. The remaining aromatic peak was not detected and is presumed to be accidentally equivalent with one of the other observed signals. MS, m/e (rel intensity) 328 (6), 133 (17), 132 (100), 131 (11), 105 (16), 104 (36).

Anal. Calcd for $C_{18}H_{20}N_2O_2S$: C, 65.83; H, 6.14; N, 8.53. Found: C, 65.93; H, 6.25; N, 8.44.

Ethyl 2-[(Phenethylamino)sulfonyl]-1,2,3,4-tetrahydroisoquinoline-1-carboxylate (30). Compound **27** (0.16 g, 2 mmol) and **7** (0.77 g, 4 mmol) in trifluoroacetic acid (15 mL) were stirred at room temperature (3 days) and then concentrated to dryness in vacuo. Pure **30** was isolated by preparative TLC (20% hexane–chloroform) as a liquid in 56% yield (0.43 g): R_f 0.35 (20% hexane–chloroform); IR (KBr) 3320, 1730, 1330, 1150 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.24 (t, 3 H, J = 7.0 Hz), 2.84 (t, 2 H, J = 6.6 Hz), 2.90–2.95 (m, 2 H), 3.26–3.33 (m, 2 H), 3.68–3.72 (m, 2 H), 4.12–4.20 (m, 2 H), 4.57 (t, 1 H, J = 6.0 Hz), 5.44 (s, 1 H), 7.15–7.45 (m, 9 H); ^{13}C NMR ($CDCl_3$) 13.97, 28.42, 35.82, 41.26, 44.17, 58.69, 61.80, 126.65, 126.39, 127.34, 128.62, 128.76, 128.99, 129.88, 134.13, 138.00, 171.17 ppm. The remaining aromatic peak was not detected and is presumed to be accidentally equivalent with one of the other observed signals. MS, m/e (rel intensity) 315 (M - CO_2Et, 100), 223 (18), 132 (59), 104 (34).

Anal. Calcd for $C_{20}H_{24}N_2O_4S$: C, 61.83; H, 6.23; N, 7.21. Found: C, 61.92; H, 6.31; H, 7.16.

Bis[2-[(1-ethoxycarbonyl))-1,2,3,4-tetrahydroisoquinolinyl]] Sulfone (29b). Compound **27** (305 mg, 1 mmol) and **7** (880 mg, 5 mmol) were added to trifluoroacetic acid (5 mL), and the solution was stirred at room temperature (3 days) and then concentrated in vacuo to dryness. The residue was purified by flash chromatography ($CHCl_3$) to give 311 mg (68%) of **29b** as a 1:1 diastereomeric mixture: R_f 0.42 ($CHCl_3$); IR (KBr) 1725, 1320, 1135 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.19–1.26 (m, 6 H), 2.83–3.03 (m, 4 H), 3.76–3.87 (m, 4 H), 4.07–4.26 (m, 4 H), 4.48 (s, 1 H),

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4.50 (s, 1 H), 7.25–7.34 (m, 6 H), 7.43–7.45 (m, 2 H); ^{13}C NMR ($CDCl_3$) 13.82, 28.04, 28.27, 41.17, 41.42, 58.24, 58.39, 61.43, 126.30, 127.45, 127.49, 127.71, 128.85, 129.89, 130.01, 134.14, 170.60, 170.65 ppm. Two upfield (13–62 ppm) and four downfield (126–135 ppm) peaks were not detected and are presumed to be accidentally equivalent with the other observed signals. MS, *m/e* (rel intensity) 399 (M – CO_2Et, 28), 398 (100), 239 (20), 211 (29), 132 (29), 131 (17), 130 (30).

Anal. Calcd for $C_{24}H_{28}N_2O_6S$: C, 61.00; H, 5.97; N, 5.93. Found: C, 60.90; H, 5.85; N, 6.03.

Bis[2-(2,3,4,5-tetrahydro-1*H*-2-benzazepinyl)] Sulfone (29c). The procedure described for the preparation of **29a** was employed using **28** (660 mg, 2 mmol), **6** (320 mg, 4 mmol), and trifluoroacetic acid (5 mL) in CH_2Cl_2 (30 mL). After flash chromatography **29c** was obtained in 82% yield (292 mg): R_f 0.60 ($CHCl_3$); mp 180–181 °C; IR (KBr) 1330, 1140 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.67–1.72 (m, 4 H), 2.86–2.90 (m, 4 H), 3.41 (t, 4 H, J = 5.1 Hz), 4.28 (s, 4 H), 7.00–7.19 (m, 8 H); ^{13}C NMR ($CDCl_3$) 27.92, 34.73, 51.77, 53.39, 126.27, 127.78, 129.00, 129.25, 137.90, 141.71 ppm; MS, *m/e* (rel intensity) 356 (15), 146 (100), 130 (16), 118 (22), 115 (12), 91 (34).

Anal. Calcd for $C_{20}H_{24}N_2O_2S$: C, 67.38; H, 6.79; N, 7.86. Found: C, 67.43; H, 6.68; N, 7.89.

2,4,6,8-Tetrakis(3-phenyl-*n*-propyl)perhydro-1,5,2,4,6,8-dithiatetrazocine 1,1,5,5-Tetraoxide (31). A CH_2Cl_2 (5 mL) solution containing **28** (0.66 g, 2 mmol), **6** (0.32 g, 4 mmol), and trifluoroacetic acid (1 mL) was stirred at room temperature (2 days) and then concentrated in vacuo. The residue was triturated with MeOH (10 mL) and the solid that formed was filtered to give 0.62 g (89%) of **31**: R_f 0.62 ($CHCl_3$); mp 117–118 °C; IR (KBr) 1340, 1120 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.79–1.84 (m, 8 H), 2.57 (t, 8 H, J = 7.2 Hz), 3.04–3.10 (m, 8 H), 4.40–4.90 (br s, 4 H), 7.12–7.30 (m, 20 H); ^{13}C NMR ($CDCl_3$) 29.78, 32.59, 48.32, 62.01, 126.15, 128.12, 128.47, 140.69 ppm; MS, *m/e* (rel intensity) 583 (M – $C_6H_5(CH_2)_2$, 2), 490 (27), 478 (18), 357 (72), 345 (100), 280 (11), 239 (84), 148 (69), 132 (30), 118 (99).

Anal. Calcd for $C_{38}H_{48}N_4O_4S_2$: C, 66.25; H, 7.02; N, 8.13. Found: C, 66.31; H, 7.14; N, 8.26.

5,6-Benzo-1,2,9-thiadiazabicyclo[4.3.0]nonan-3-one 1,1-Dioxide (32). Method A. A NaOMe solution was prepared by adding NaH (60% dispersion in mineral oil, 90 mg, 2 mmol) to MeOH (30 mL). Compound **15** (540 mg, 1.9 mmol) was added to the NaOMe–MeOH solution and the reaction was stirred at room temperature (24 h). The solution was concentrated to dryness in vacuo and the residue was dissolved in H_2O (20 mL). The aqueous solution was acidified with aqueous concentrated HCl and the precipitate that formed was filtered and recrystallized with H_2O to give 350 mg (77%) of **32**: mp 162–163 °C; IR (KBr) 3250, 1710, 1330, 1155 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 2.70–2.76 (m, 1 H), 2.99–3.01 (m, 1 H), 3.33–3.42 (m, 1 H), 3.58–3.66 (m, 1 H), 5.57 (s, 1 H), 7.21–7.54 (m, 4 H), 10.50 (br s, 1 H); ^{13}C NMR (DMSO-d_6) 26.00, 40.79, 61.90, 126.39, 127.11, 127.47, 127.66, 128.79, 133.67, 169.29 ppm; MS (-FAB) 237 [M – 1]$^-$.

Anal. Calcd for $C_{10}H_{10}N_2O_3S$: C, 50.41; H, 4.23; N, 11.77. Found: C, 50.47; H, 4.28; N, 11.82.

Method B. Compound **35** (2.78 g, 10 mmol) was dissolved in trifluoroacetic acid (20 mL) and stirred at room temperature (1 day). The solution was concentrated to dryness in vacuo, and the residue was purified by flash chromatography (5:3:1 acetone/chloroform/methanol) to give 1.92 g (80%) of **32**: R_f 0.35 (5:3:1 acetone/chloroform/methanol); one spot (R_f 0.35 (5:3:1 acetone/chloroform/methanol)) was observed in the TLC of co-spot of **32** obtained from methods A and B; mp 164–165 °C; mmp (with method A product) 162–164 °C; ^{1}H NMR (acetone-d_6 + DMSO-d_6) δ 2.66–2.72 (m, 1 H), 3.16–3.28 (m, 1 H), 3.30–3.39 (m, 1 H), 3.69–3.75 (m, 1 H), 4.82 (s, 1 H), 5.72 (br s, 1 H), 7.17–7.26 (m, 3 H), 7.67–7.69 (m, 1 H).

Disodium Salt of 1,2,5-Thiadiazolidine-3,4-dione 1,1-Dioxide (33).[11] A NaOMe solution was prepared by adding Na (3.40 g, 150 mmol) to MeOH (60 mL). Sulfamide (**4**) (7.20 g, 75 mmol) in MeOH (60 mL) was added dropwise with vigorous mechanical stirring to give a white suspension. Diethyl oxalate (11.00 g, 75 mmol) was added dropwise with stirring and then the resulting suspension was heated to reflux (16 h). After cooling, the white solid that formed was filtered, washed with MeOH, and dried under vacuum to give 12.20 g (95%) of **33**. The product was then further purified by recrystallization from H_2O and then dried at 100 °C in vacuo: mp ~360 °C dec (lit.[11] mp ~360 °C dec).

2-Phenethyl-1,2,5-thiadiazolidine-3,4-dione 1,1-Dioxide Sodium Salt (34). A DMSO (freshly distilled from CaH_2, 40 mL) suspension containing 1,2,5-thiadiazolidine-3,4-dione 1,1-dioxide disodium salt (**33**) (3.40 g, 20 mmol) and phenethyl *p*-toluenesulfonate[12] (5.52 g, 20 mmol) was stirred at room temperature (3 days). The solution was concentrated in vacuo (80 °C, 5 Torr) and then the residue was triturated with acetone (20 mL). The insoluble materials were filtered, and the filtrate was slowly added to Et_2O (100 mL). The solid that formed was filtered and dried in vacuo to give 4.20 g (76%) of **34**: R_f 0.75 (5:3:1 acetone/chloroform/methanol); mp 300 °C dec; IR (KBr) 1720, 1630, 1340, 1165 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 2.95 (t, 2 H, J = 7.5 Hz), 3.69 (t, 2 H, J = 7.5 Hz), 7.21–7.32 (m, 5 H); ^{13}C NMR (DMSO-d_6) 33.51, 40.79, 123.44, 128.41, 128.71, 138.24, 158.77, 161.77 ppm; MS (-FAB) 253 [M – 23]$^-$.

Anal. Calcd for $C_{10}H_9N_2O_4SNa$: C, 42.40; H, 3.20; N, 9.89. Found: C, 42.04; H, 3.47; N, 9.96.

5-Phenethyl-4-hydroxy-1,2,5-thiadiazolidin-3-one 1,1-Dioxide Sodium Salt (35). To a THF (120 mL) solution containing **34** (2.76 g, 10 mmol) was added $NaBH_4$ (0.27 g, 7.1 mmol) in increments at 0–5 °C (4 h). The solution was stirred at room temperature and then neutralized (pH 7.0) with concentrated aqueous HCl. The mixture was filtered and the filtrate was concentrated in vacuo. The residue was purified by flash chromatography (5:3:1 acetone/chloroform/methanol) to give 1.73 g (62%) of **35**: R_f 0.30 (5:3:1 acetone/chloroform/methanol); ^{1}H NMR (DMSO-d_6) δ 2.46–2.58 (m, 2 H), 2.68–2.86 (m, 2 H), 4.22 (d, 1 H, J = 7.1 Hz), 5.84 (d, 1 H, J = 7.1 Hz), 6.76–6.88 (m, 5 H); ^{13}C NMR (DMSO-d_6) 34.31, 44.24, 85.46, 126.01, 128.28, 128.58, 139.77, 173.62 ppm.

5,6-Benzo-1,2,9-thiadiazabicyclo[4.3.0]nonane 1,1-Dioxide (36). Compound **32** (0.48 g, 2 mmol) was dissolved in dried THF (10 mL) and then cooled in an ice bath. Borane–methyl sulfide complex (2 M THF solution, 0.45 g, 6 mmol) was added dropwise (1 min) and the solution was stirred at room temperature (3 days). The solution was concentrated and the residue was dissolved in EtOAc (20 mL). An aqueous 1 N HCl solution was then added to the EtOAc solution leading to the vigorous evolution of gas. The EtOAc layer was separated, and the organic layer was washed with H_2O, dried ($MgSO_4$), and then concentrated to dryness in vacuo. The residue was purified by flash chromatography (20% EtOAc–$CHCl_3$) to give 0.23 g (85%) of **36**: R_f 0.65 (20% EtOAc–$CHCl_3$); mp 81–82 °C; IR ($CHCl_3$) 3240, 1310, 1160 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.85 (dd, 1 H, J = 16.0 Hz, 3.0 Hz), 3.04–3.14 (m, 1 H), 3.21–3.35 (m, 2 H), 3.62–3.65 (m, 1 H), 3.89–3.95 (m, 1 H), 4.74 (br s, 1 H), 4.92–4.97 (m, 1 H), 7.04–7.25 (m, 4 H): ^{13}C NMR ($CDCl_3$) 28.16, 40.93, 49.40, 58.47, 125.02, 126.99, 127.61, 129.18, 132.75, 133.69 ppm; MS, *m/e* (rel intensity) 224 (1), 223 (4), 159 (8), 135 (15), 131 (100), 130 (74), 117 (5), 104 (35).

Anal. Calcd for $C_{10}H_{12}N_2O_2S$: C, 53.55; H, 5.40; N, 12.49. Found: C, 53.41; H, 5.40; N, 12.49.

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Supplementary Material Available: Experimental procedure for the X-ray analyses of compounds **13** and **26**, Table 2 listing the final cell constants, as well as other information pertinent to data collection and refinement, and Tables 3–6 and 7–9 giving a complete listing of atomic coordinates and equivalent isotropic displacement parameters, bond lengths, bond angles, and hydrogen-bonding parameters where appropriate for compounds **13** and **26** (9 pages). Ordering information is given on any current masthead page.