zation from acetic acid gave **12** (0.71 g, 57%) as yellow prisms, identical by TLC with an authentic sample: mp 300–302 °C (lit.[3] 300–303 °C); mass spectrum (70 eV) *m/e* (rel intensity) 228 (33, M^+), 226 (100, M^+), 225 (0.6, $C_8H_4ClN_3O_3$).

3- and 1-Benzyl-8-methylthioimidazo[4,5-*g*]quinazoline-*1*-^{15}N (2 and 3). These compounds were prepared from **12** via the sequence described in the text, using the experimental procedures which were reported previously.[3] Intermediates were characterized at each step by melting point, uv, and TLC comparison with authentic samples. The overall yield for the six-step sequence was ~19% for each isomer: **2**, ^1H NMR [$(CD_3)_2SO$/TFA] δ 5.84 (s, 2, CH_2), 9.66 d, 1, J = 6.5 Hz, 2-H); **3**, ^1H NMR [$(CD_3)_2SO$/TFA] δ 5.92 (d, 2, J = 1.2 Hz, CH_2), 9.69 (d, 1, J = 6.5 Hz, 2-H).

3-Benzyladenine-*3*-^{15}N (9) and 7-Benzyladenine-*3*-^{15}N (10). The ^{15}N label was incorporated via nitration of 4-bromoimidazole with nitric acid-^{15}N in the sequence previously described for the preparation of (unlabeled) 7-benzyladenine.[7a] Debenzylation of 7-benzyladenine-*3*-^{15}N with sodium/liquid ammonia[7b] provided adenine-*3*-^{15}N which was converted to **9** by the conventional procedure.[8] **10**: ^1H NMR [$(CD_3)_2SO$] δ 8.18 (d, 1, J = 15 Hz, 2-H).

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Registry No.—**1** ($^{15}N^1$), 59710-62-2; **2**, 59710-63-3; **3**, 59710-64-4; **9**, 59710-65-5; **10**, 59710-66-6; **11**, 31374-18-2; **12**, 59710-67-7; nitric acid-^{15}N, 43625-06-5; 4-bromoimidazole, 2302-25-2; benzyl bromide, 100-39-0.

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Dihydro-1,4-dithiin Annelation

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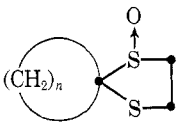
Synthetic methods available for the construction of rings fused to heterocyclic molecules are limited owing to the vulnerability of the heteroatom to the well-established conditions often employed in carbocyclic chemistry.[1] As part of our studies on the reactivity and synthetic uses of monosulfoxides of 1,3-dithiolane,[2] we now report a method for constructing carbocyclic fused dihydro-1,4-dithiins under mild conditions. This new heterocyclic annelation reaction is outlined in the following starting from the corresponding cyclic ketones **1**.

Dithiolation of **1** was accomplished in the usual manner.[3] Selective oxidation of the spiro-1,3-dithiolane **2** using *m*-chloroperbenzoic acid (MCPBA) in cold methylene chloride afforded the desired monosulfoxide **3** in good yields (Table I). Azeotropic distillation of the latter in benzene in the presence of a catalytic amount (ca. 10%) of *p*-toluenesulfonic acid (PTSA) smoothly transformed the spiro-1,3-dithiolane 1-oxide **3** by loss of H_2O to the dithiin **4** in essentially quantitative yield.

Table I[5]



Registry no.	*n*	Bp (mp), °C	% yield
59796-89-3	3	59–60 (10–12 μ)	64[a]
59796-90-5	4	53.5 (8 μ)	64[b,c]
59796-91-7	5	(82.8)	75[a]
59796-92-8	6	(59.2)	64[a]
59796-93-9	11	(107.2)	88[a]
59796-94-0	14	(88.9)	87[b]

[a] Based on the corresponding ketone **1**. [b] Based on pure spiro-1,3-dithiolane **2**. [c] Prepared by $NaIO_4$ oxidation in methanol and water.

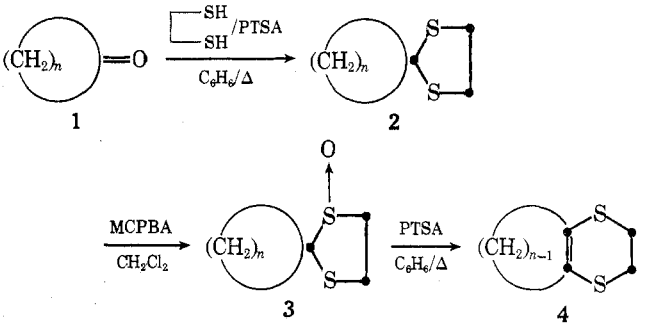
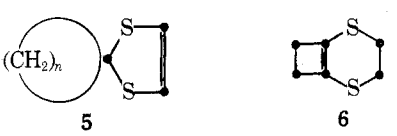
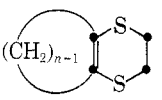


Table II lists yields of these ring expansion reaction products **4**. The absence of absorptions in the olefinic region of the NMR spectra of **4** and the appearance of a singlet at around δ 3.0 ppm for the ring protons of the dihydro-1,4-dithiin system[2] excludes the presence of isomeric 1,3-dithiole **5**, which would be expected to form under the normal Pummerer rearrangement conditions.[4] Attempts to prepare the cyclobutene derivative **6** were unsuccessful. While under the normal



experimental conditions (10% PTSA, PhH reflux, 30 h), the starting monosulfoxide **3** (n = 3) was found to be unreactive, under more strenuous conditions (e.g., 50% PTSA, PhH, re-

Table II[5]



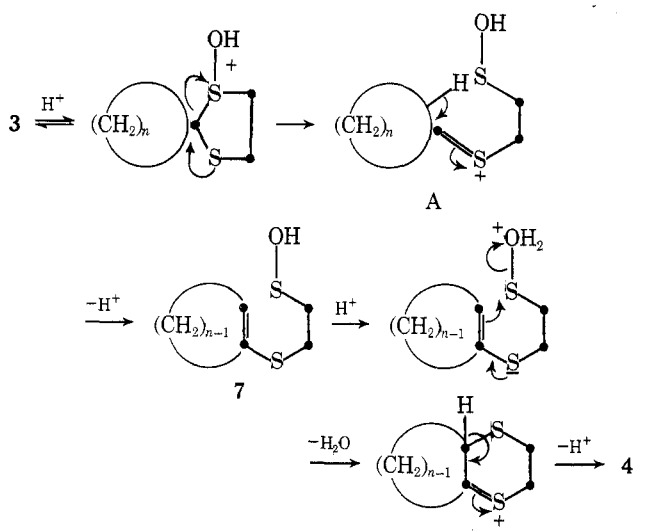
Registry no.	*n*	Bp, °C (mm)	% yield[a]
35756-14-0	4	71–72 (0.4)	96
23285-17-8	5	109–110 (1.4)[b]	93
59796-95-1	6	88–89 (0.3)	95
59796-96-2	11	169–170 (1.1)	96
59796-97-3	14	186–189 (0.8–0.9)	85

[a] Yield of pure product based on **3**. [b] Lit. bp 90–98 °C (1.0 mm): L. Levine and L. Jackson, U. S. Patent 3 439 051 (1969).

flux, 5 days), considerable tar formation prevailed and no **6** was detected. Isolation of the eight-membered monosulfoxide **3** (n = 7) has also been unsuccessful owing to its lability at room temperature such that even in the absence of acid catalyst, ring transformation occurred slowly giving usually a mixture of products including **4** (n = 7) as shown by mass spectrometric analysis[5] (m/e 200 M^+ for $C_{10}H_{16}S_2$) for the crude sulfoxide **3** (n = 7) (m/e 218 M^+ for $C_{10}H_{18}OS_2$).

A possible mechanism for this interesting ring expansion reaction of spiro-1,3-dithiolane 1-oxides **3** *under acid-catalyzed condition* is shown in Scheme I. Heterolytic cleavage

Scheme I



of the C(2)–S bond following initial protonation of the sulfoxide moiety would generate a sulfur stabilized carbonium ion A, which on loss of proton followed by acid-catalyzed ring closure of the sulfenic acid **7** affords the annelated 5,6-dihydro-1,4-dithiins **4** as shown. Similar intermediates of structure A have been proposed in the acid hydrolysis of 2,2-diphenyl-1,3-dithiolane 1-oxide,[6] and oxidative cleavage of 1,3-dithian[7,8] and dithiolane[9] derivatives in the synthesis of ketones.

Experimental Section[5]

The following experiments are illustrative of the general synthetic procedures.

2,2-Undecamethylene-1,3-dithiolane (2, n = 11). A mixture of 46.5 g of cyclododecanone, 24.1 g of 1,2-ethanedithiol, and 0.75 g of PTSA·H_2O in 200 ml of benzene was subjected to azeotropic distillation until the theoretical amount of water (4.6 ml) was collected. The benzene solution was concentrated in vacuo to give a solid, crude **2** (n = 11), which was suitable for use in subsequent reactions.

2,2-Undecamethylene-1,3-dithiolane 1-Oxide (3, n = 11). To an ice-cooled solution of 15 g of crude **2** in 100 ml of methylene chloride, a solution of 11.2 g of MCPBA (ca. 90% active) in 200 ml of methylene chloride was added dropwise over a 2-h period. The reaction mixture was quenched by addition of aqueous sodium carbonate and extracted twice with methylene chloride. The latter was dried ($MgSO_4$) and concentrated in vacuo to give a white solid which was recrystallized from hexanes to give 14 g (88%) of essentially pure **3** (n = 11). An analytical sample (mp 107.2 °C) was obtained by further recrystallization (Table I).

2,3-Decamethylene-5,6-dihydro-1,4-dithiin (4, n = 11). A mixture of 2 g of **3** (n = 11) and 0.2 g of PTSA·H_2O in 50 ml of benzene was subjected to azeotropic distillation via a Dean-Stark receiver for 18 h. The darkened benzene solution was taken up in ether and washed with sodium bicarbonate. The organic layer was separated, dried ($MgSO_4$), and concentrated to give a brown oil which was purified by short path distillation, affording 1.76 g (96%) of pure **4** (n = 11) (Table II): mass spectrum m/e 246 (M^+); NMR δ 1.0–2.0 (m, 16, carbocyclic ring protons), 2.2 (t, 4, allylic), and 3.0 ppm (s, 4, $-SCH_2CH_2S-$).

Registry No.—**2** (n = 3), 380-90-5; **2** (n = 4), 176-39-6; **2** (n = 5), 177-16-2; **2** (n = 6), 184-32-7; **2** (n = 11), 16775-67-0; **2** (n = 14), 59796-98-4.

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Preparation and Stereochemical Analysis of 5-Epibenzylpenicillin (*S*)- and (*R*)-Sulfoxide Esters

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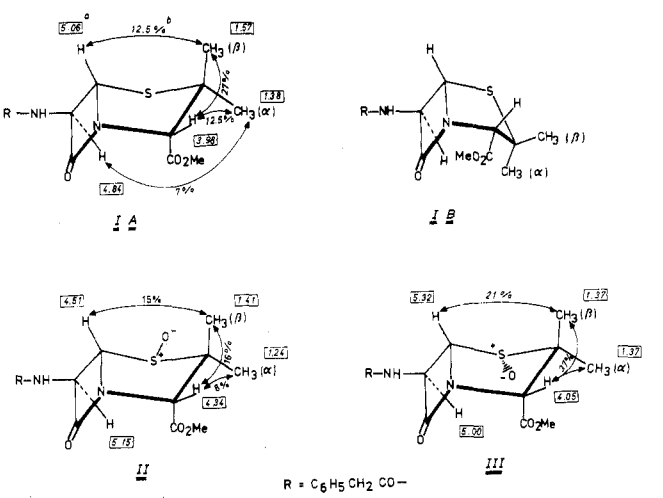
Oxidation of the 5 epimer of benzylpenicillin methyl ester[1] (I) with *m*-chloroperbenzoic acid yielded the (*S*)- and (*R*)-sulfoxide II and III in a ratio of 2:1. The isomers were isolated by column chromatography and crystallized from dry benzene. Apparently, steric control is the major directing influence in the oxidation of the 5 epimer, since neither sulfoxide configuration is likely to be stabilized by an internal hydrogen bond with the side chain amide proton,[2] as the two interacting atoms are manifestly too distant. It should be noted that natural or 6-epiphenoxymethyl- and benzylpenicillin esters yielded only the (*S*)-sulfoxide using this reagent.[2,3]

Thiazolidine ring conformation and sulfoxide configuration



[a] Chemical shifts in parts per million downfield from Me_4Si, for 5-H, 6-H, 3-H, 2 α-Me, and 2 β-Me, measured in dimethyl sulfoxide-d_6. [b] NOE values determined in dimethyl sulfoxide-d_6.