1700, 1640, 1595 cm^{-1}; NMR (Me_2SO-d_6) δ 1.18 (3 H, t, CH_2CH_3), 2.20 (3 H, s, CH_3), 2.70 (2 H, q, CH_2CH_3), 6.95 (1 H, s, C5-H), 7.42 (5 H, s, C_6H_5). Anal. Calcd for $C_{13}H_{15}N_3O_2S$: C, 56.30; H, 5.45; N, 15.15. Found: C, 56.33; H, 5.53; N, 15.16.

B. With Acetyl Chloride. Acetyl chloride (0.5 g, 6.3 mmol) was added to a mixture of **4m** (0.5 g, 2.1 mmol), pyridine (4.5 mL), and acetone (2.5 mL) at 0 °C. After being stirred at room temperature for 2 h, the mixture was poured into ice–water. The resulting precipitate was collected by filtration and recrystallized from ethanol to give 108 mg (18.3%) of colorless crystals. The IR and NMR spectra of this compound were identical with those of the compound prepared by method A.

2-(Benzamido)-4-benzoyl-phenyl-Δ^2-1,3,4-thiadiazoline (3n). Benzoyl chloride (6.27 g, 44.6 mmol) was added dropwise to a stirring mixture of **2a** (2 g, 11.2 mmol), pyridine (1.8 mL), and tetrahydrofuran (20 mL). After the solution was refluxed for 6 h, the resulting precipitate was collected by filtration and recrystallized from ethanol to give 3.11 g (72%) of **3n**: mp 198–199 °C; IR (KBr) 3150, 1665, 1615 cm^{-1}; NMR (Me_2SO-d_6) δ 7.15 (1 H, s, C_5-H), 7.42 (5 H, s, C_6H_5), 7.20–8.10 (10 H, m, C_6H_5), 12.06 (1 H, s, NH). Anal. Calcd for $C_{22}H_{17}O_2N_3S$: C, 68.20; H, 4.42; N, 10.85. Found: C, 68.36; H, 4.38; N, 10.82.

Registry No. 2a, 1627-73-2; **2b**, 5470-48-4; **2c**, 5706-80-9; **2d**, 4334-74-1; **2e**, 2929-81-9; **2f**, 3608-75-1; **2g**, 555-90-8; **2h**, 1200-00-6; **2i**, 2302-95-6; **2k**, 1752-30-3; **2l**, 2302-93-4; **3a**, 62236-01-5; **3b**, 62236-05-9; **3c**, 62236-06-0; **3d**, 62236-07-1; **3e**, 62236-08-2; **3f**, 62236-02-6; **3g**, 62236-02-6; **3h**, 62236-04-8; **3i**, 72938-21-7; **3j**, 72926-22-8; **3k**, 72926-23-9; **3l**, 72926-24-0; **3m**, 72926-25-1; **3n**, 72926-26-2; **4a**, 62236-09-3; **4c**, 72926-27-3; **4d**, 72938-22-8; **4e**, 72926-28-4; **4f**, 72926-29-5; **4g**, 72926-30-8; **4h**, 72926-31-9; **4i**, 72926-03-5; **4j**, 72926-04-6; **4k**, 72926-05-7; **4l**, 72926-06-8; **4m**, 72926-07-9; **5**, 28898-88-6; **6**, 2002-03-1; **7**, 72926-08-0; **8**, 72926-09-1; **9**, 2613-12-9; **10**, 72926-10-4; **11**, 14537-59-8; **12**, 3357-38-8; acetic anhydride, 108-24-7; acetyl chloride, 75-36-5; formalin, 50-00-0; thiosemicarbazide, 79-19-6; propionyl chloride, 79-03-8; methyl iodide, 74-88-4; propionic anhydride, 123-62-6; 2-(acetylamino)-5-phenyl-4-propionyl-Δ^2-1,3,4-thiadiazoline, 72926-11-5; benzoyl chloride, 98-88-4.

Supplementary Material Available: NMR data for compounds **3** and **4** (2 pages). Ordering information is given on any current masthead page.

Synthesis of 4-Thioxo-2-azetidinones

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Received November 6, 1979

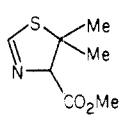
4-Thioxo-2-azetidinones, which are C- and N-substituted imides of monothionomalonic acid, have been prepared by a thermal rearrangement of 4-(2-methoxycarbonylethylsulfinyl)-2-azetidinones through the intermediacy of β-lactam 4-sulfenic acids. The 4-sulfinyl-2-azetidinones have been obtained by total synthesis, or from penicillin sulfoxides. The former approach, which allows the choice of variegated arrays of substituents, was employed in the synthesis of (±)-1-(1-(methoxycarbonyl)-2-methylprop-1-enyl)-3-phthalimido-4-thioxo-2-azetidinone (**8**) (a didehydrovaline derivative), (±)-1-(1-(*tert*-butoxycarbonyl)-2-*tert*-butoxyethyl)-3-phthalimido-4-thioxo-2-azetidinone (**19**) (a serine derivative), and 1,3,3-triphenyl-4-thioxo-2-azetidinone (**20**). Compound **27**, which is the levorotatory enantiomer of the racemic **8**, has been obtained by the degradation of methyl 6-(β-phthalimido)penicillanate sulfoxide (**21**).

4-Thioxo-2-azetidinones are formally derived from the imide of monothionomalonic acid. This class of compounds was unknown until 1976 when the syntheses of a few C- and N-substituted thiomalonimides were independently reported from this[1] and two other laboratories.[2,3] In the present paper we describe in detail a general method for the preparation of these compounds by total synthesis as well as by the degradation of sulfoxides of phthalimidopenicillanates.[4] The former approach provides an access to thioxoazetidinones bearing a varied array of substituents, and may be valuable for the synthesis of more elaborate systems including nuclear analogues of β-lactam antibiotics.[6] Some of the properties and reactions of 4-thioxo-2-azetidinones are described in the accompanying paper.[7]

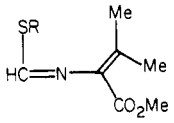
Within the framework of a project on the synthesis of β-lactams structurally related to penicillins,[8] we were interested in the generation of the β-lactam sulfenic acid **6**. A plausible route to this acid was based on the thermal elimination of methyl acrylate from the β-lactam sulfoxide **5**. The (methoxycarbonyl)ethyl group in **5** was chosen since the enhanced acidity of its two α-hydrogen atoms, which are β to the sulfinyl group, was expected to facilitate the formation of the sulfenic acid **6**.[9,10] Indeed thermolysis of **5** in the presence of dihydropyran as a trapping agent and an aluminum halide as catalyst[11] afforded the dihydropyranyl derivative **7** as the major product, thus indicating the intermediacy of the sulfenic acid **6**. It was noticed, however, that **7** was accompanied by traces of a product, exhibiting in its IR spectrum an absorption band

(1) Bachi, M. D.; Vaya, J. *J. Am. Chem. Soc.* **1976**, *98*, 7825.
(2) Chou, T. S.; Koppel, G. A.; Dorman, D. E.; Paschal, J. W. *J. Am. Chem. Soc.* **1976**, *98*, 7864.
(3) Brandt, A.; Bassignani, L.; Re, L. *Tetrahedron Lett.* **1976**, 3975.
(4) For preliminary communications on the totally synthetic method see ref 1, and on degradative methods see ref 2, 3, and 5.
(5) Bachi, M. D.; Goldberg, O.; Gross, A. *Tetrahedron Lett.* **1978**, 4167.
(6) For example, the thioxo group may function as a handle for the attachment of an alkylidene appendage at position 4 of the β-lactam ring; see ref 5 and 7.
(7) Bachi, M. D.; Goldberg, O.; Gross, A.; Vaya, J. *J. Org. Chem.*, following paper in this issue.
(8) Bachi, M. D.; Breiman, R. *J. Chem. Soc., Perkin Trans. 1* **1980**, 11.
(9) Baxter, A. G. W.; Kitchin, J.; Stoodley, R. J.; Wilkins, R. B. *J. Chem. Soc., Chem. Commun.* **1973**, 285. Stoodley, R. J.; Wilkins, R. B. *J. Chem. Soc., Perkin Trans. 1* **1974**, 1572.
(10) Shelton, J. R.; Davis, K. E. *Int. J. Sulfur Chem.* **1973**, *8*, 197.
(11) Ager, I.; Barton, D. H. R.; Greig, D. G. T.; Lucente, G.; Sammes, P. G.; Taylor, M. V.; Hewitt, G. H.; Looker, B. E.; Mowatt, A.; Robson, C. A.; Underwood, E. *J. Chem. Soc., Perkin Trans. 1* **1973**, 1187.

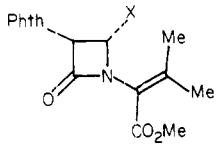
0022-3263/80/1945-1477$01.00/0

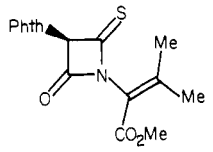


1



2, R = Me
3, R = $CH_2CH_2CO_2Me$

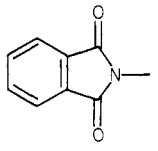




4, X = $SCH_2CH_2CO_2Me$
5, X = $(SO)CH_2CH_2CO_2Me$
6, X = SOH

8

7, X = 

Phth = 

at 1830 cm^{-1}, to which structure **8** was subsequently assigned. Additional studies which stemmed from this fortuitous observation resulted in the methodology for the preparation of 4-thioxo-2-azetidinones based on the pyrolysis of (methoxycarbonyl)ethylsulfinyl β-lactams.

Treatment of the thiazoline **1**[12] with sodium hydride and methyl iodide resulted in ring opening and S-alkylation to give the methyl thioformimidate **2**. On warming compound **2** with an excess of methyl 3-mercaptopropionate, methyl mercaptan was evolved and the (methoxycarbonyl)ethyl thioformimidate **3** was formed. The β-lactam **4** was obtained in 56% yield by the interaction of the thioformimidate **3** with phthaloylglycyl chloride and triethylamine. Oxidation of **4** with 1 equiv of *m*-chloroperbenzoic acid at −35 °C gave the sulfoxide **5** (88%). Pyrolysis of **5** in benzene, chloroform, or carbon tetrachloride in a sealed tube at 80–100 °C gave the 4-thioxo-2-azetidinone **8** (80%).

The potentially wide applicability of the method is illustrated by the syntheses of the thiomalonimides **19** and **20**. Condensation of *O-tert*-butyl-DL-serine *tert*-butyl ester with ethyl thionoformate gave the thioformamide **9** (97%)

HCSNHR

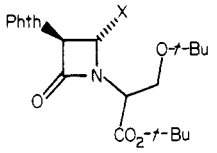
9, R = $CH(CO_2\text{-}t\text{-}Bu)CH_2O\text{-}t\text{-}Bu$
10, R = Ph

which was S-alkylated with methyl iodide and sodium hydride in toluene to the methyl thioformimidate **11**. On

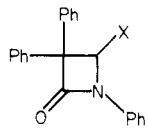
$HC(SR^1)=NR^2$

11, R^1 = Me, R^2 = $CH(CO_2\text{-}t\text{-}Bu)CH_2O\text{-}t\text{-}Bu$
12, R^1 = $CH_2CH_2CO_2Me$, R^2 = $CH(CO_2\text{-}t\text{-}Bu)CH_2O\text{-}t\text{-}Bu$
13, R^1 = Me, R^2 = Ph
14, R^1 = $CH_2CH_2CO_2Me$, R^2 = Ph

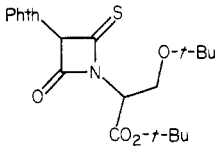
warming **11** with methyl 3-mercaptopropionate, the thioformimidate **12** was obtained. Treatment of **12** with phthaloylglycyl chloride and triethylamine produced the β-lactam **15** (51%, based on **9**) as a 1:1 mixture of two diastereoisomers. The β-lactam **17** was obtained in 48% yield from thioformanilide (**10**) in a similar sequence of reactions involving the intermediacy of the thioformimidates **13** and **14**; the latter was reacted with diphenylketene in the β-lactam-forming step. Oxidation of the (methoxycarbonyl)ethyl thio-β-lactams **15** and **17** with *m*-chloroperbenzoic acid afforded the corresponding sulfoxides **16** (85%) and **18** (71%). Thermolysis (105 °C for 24 h) of **16** afforded the thiomalonimide derivative of serine (**19**). Conversion of the sulfoxide **18** into the trisubstituted thioxoazetidinone **20** (80%) required a slightly higher temperature (140 °C for 24 h).



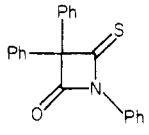
15, X = $SCH_2CH_2CO_2Me$
16, X = $(SO)CH_2CH_2CO_2Me$



17, X = $SCH_2CH_2CO_2Me$
18, X = $(SO)CH_2CH_2CO_2Me$

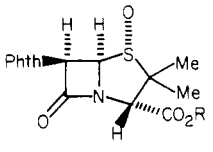


19

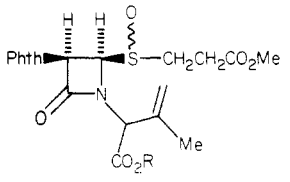


20

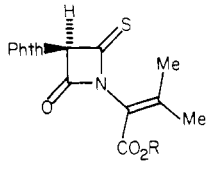
Penicillins and penicillin sulfoxides have been used as starting materials for the preparation of 4-thioxo-2-azetidinones which, like compound **8**, are built on the nitrogen atom of didehydrovaline.[2,3] In a preliminary communication we reported a most convenient route for the conversion of phthalimidopenicillanate sulfoxides into thiomalonimides.[5] Thus, heating the penicillin sulfoxide **21** in methyl acrylate generated a sulfenic acid which added to the unsaturated ester to give a mixture of two isomeric sulfoxides (**23**). Treatment of **23** with triethylamine caused migration of the double bond to give the conjugated ester **25** (89% from **21**). The isomeric sulfoxides were separated by chromatography. Thermolysis of these cis-β-lactams, as described before for the pyrolysis of the trans-β-lactam **5**, gave the levorotatory thioxomalonimide **27**. Compound **27** is identical in all its physical data, except for the optical activity, with the racemic compound **8**. In a similar way the diphenylmethyl penicillanate sulfoxide **22** was converted into the thiomalonimide **28** through the intermediacy of the β-lactam sulfoxides **24** and **26**.



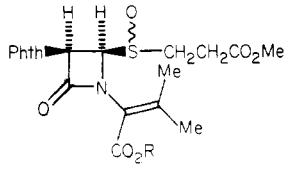
21, R = Me
22, R = $CHPh_2$



23, R = Me
24, R = $CHPh_2$



27, R = Me
28, R = $CHPh_2$



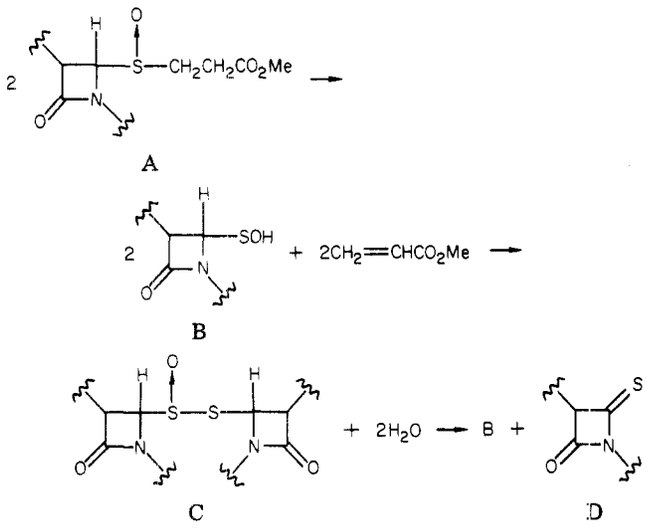
25, R = Me
26, R = $CHPh_2$

The formation of the 4-thioxo-2-azetidinones seems to involve the sequence shown in Scheme I.[13] Methyl acrylate is eliminated from the methoxycarbonylethyl

(12) Bachi, M. D.; Goldberg, O. *J. Chem. Soc., Perkin Trans. 1* **1974**, 1184.

(13) For similar thermolyses of sulfoxides and thiosulfinate esters, see: (a) Shelton, J. R.; Davis, K. E. *J. Am. Chem. Soc.* **1967**, *89*, 718. (b) Block, E. *Ibid.* **1972**, *94*, 642.

Scheme I



sulfoxide A with concomitant formation of the sulfenic acid B which undergoes self-condensation to the thiolsulfinate ester C. Fragmentation of C results in the formation of the thioxoazetidinone D and the sulfenic acid B which is recycled. A thiolsulfinate ester of type C was isolated by Chou et al. and subsequently converted into a thiomalonimide of type D.[2]

Experimental Section

IR spectra were recorded with a Perkin-Elmer 237 spectrometer. Proton NMR data were usually determined with a Varian A-60 spectrometer; the 90-MHz spectra and the 80-MHz spectra were taken, respectively, with Bruker FT-HFX-10 and Varian FT-80A instruments. The ^{13}C NMR spectra were taken on a Bruker HFX machine at 22.63 MHz. Low- and high-resolution mass spectra were recorded on a Varian MAT-731 spectrometer. Optical rotations were measured with a Perkin-Elmer 141 polarimeter. Melting points were measured using a Büchi apparatus and are uncorrected. All reactions were performed in dry solvents under argon. Organic solutions were dried over $MgSO_4$.

(±)-4-(2-(Methoxycarbonyl)ethylthio)-1-(1-(methoxycarbonyl)-2-methylprop-1-enyl)-3-phthalimido-2-azetidinone (4). A solution of the thiazoline **1** (1.0 g, 5.8 mmol) in dimethoxyethane (30 mL) was added at 0 °C to a stirred suspension of NaH (0.77 g, 50% in paraffin, 16 mmol) in dimethoxyethane (30 mL). After 10 min methyl iodide (1.8 g, 12.7 mmol) was added in one portion. The cooling bath was removed and after 90 min the mixture was filtered through Celite and evaporated. The residue was treated with ether, insoluble material was filtered off, and the solution was evaporated to give an oil. Distillation (80–90 °C at 0.3 mmHg) afforded the methyl thioimidate **2** (920 mg, 85%): IR ($CHCl_3$) 1715, 1615, and 1580 cm^{-1}; NMR ($CDCl_3$) δ 1.92 (s, 2 Me), 2.40 (s, SMe), 3.76 (s, OMe), 8.27 (s, HC=N). To the methylthioimidate **2** (860 mg, 4.6 mmol) was added methyl 3-mercaptopropionate (1.72 mL) and argon was bubbled through the solution during 50 h. The excess of methyl 3-mercaptopropionate was distilled off (40–45 °C at 0.4 mmHg) to give the thioformimidate **3** (960 mg, 81%): IR ($CHCl_3$) 1720, 1590, 1570 cm^{-1}; NMR ($CDCl_3$) δ 1.90 (s, 2 Me), 2.5–3.5 ($SCH_2CH_2CO_2$), 3.69 (s, OMe), 3.75 (s, OMe), and 8.20 (s, HC=N). To a stirred solution of freshly prepared thioformimidate **3** (0.9 g, 3.5 mmol) and triethylamine (0.5 g, 4.9 mmol) in toluene (40 mL) was added phthaloylglycyl chloride (1.07 g, 4.8 mmol) in toluene (40 mL) during 2 h. After an additional 18 h the precipitated triethylammonium chloride was filtered off and the filtrate was evaporated. The residue was chromatographed on silica gel (toluene–ethyl acetate) to give the title compound **4** (872 mg, 56%): mp 92–3 °C (from hexane–CH_2Cl_2); IR ($CHCl_3$) 1790, 1770, 1720 cm^{-1}; NMR ($CDCl_3$) δ 2.09 (s, Me), 2.22 (s, Me), 2.55–2.9 ($SCH_2CH_2CO_2$), 3.63 (s, OMe), 3.84 (s, OMe), 5.36 (d, J = 2.5 Hz, azetidine H), 5.58 (d, J = 2.5 Hz, azetidine H), and 7.85 (m, Phth); mass spectrum, m/e 446 (M^+). Anal. Calcd for $C_{21}H_{22}N_2O_7S$: C, 56.50; H, 4.97; N, 6.28; S, 7.18. Found: C, 56.68; H, 5.08; N, 6.48; S, 7.64.

(±)-4-(2-(Methoxycarbonyl)ethylsulfinyl)-1-(1-(methoxycarbonyl)-2-methylprop-1-enyl)-3-phthalimido-2-azetidinone (5). To a stirred solution of the sulfide **4** (2.4 g, 5.4 mmol) in $CHCl_3$ (300 mL) was added *m*-chloroperbenzoic acid (1.04 g, 90%, 5.4 mmol) in $CHCl_3$ (300 mL) at −35 °C during 3 h. The solution was washed with 5% aqueous $NaHCO_3$ and water, dried, and evaporated. Chromatography of the residue on silica gel (toluene–ethyl acetate) gave the sulfoxide **5** (2.20 g, 88%): mp 156–7 °C (from hexane–CH_2Cl_2); IR ($CHCl_3$) 1790, 1775, 1735, and 1725 cm^{-1}; NMR ($CDCl_3$) δ 2.10 (s, Me), 2.31 (s, Me), 2.55–2.95 ($SCH_2CH_2CO_2$), 3.65 (s, OMe), 3.87 (s, OMe), 5.42 (d, J = 2.5 Hz, azetidine H), 6.05 (d, J = 2.5 Hz, azetidine H), and 7.88 (m, Phth); mass spectrum, m/e 376 ($M^+ - CH_2{=}CHCO_2Me$), 358 ($M^+ - CH_2{=}CHCO_2Me - H_2O$). Anal. Calcd for $C_{21}H_{22}N_2O_8S$: C, 54.54; H, 4.80; N, 6.06; S, 6.93. Found: C, 54.20; H, 5.02; N, 6.11; S, 6.98.

(±)-4-(3,4-Dihydro-2*H*-pyran-5-ylthio)-1-(1-(methoxycarbonyl)-2-methylprop-1-enyl)-3-phthalimido-2-azetidinone (7). A mixture of the sulfoxide **5** (0.2 g, 0.43 mmol) and $AlBr_3$ (1 mg) in freshly distilled dihydropyran (5 mL) was heated at 80–85 °C during 21 h in a sealed tube, filtered, and evaporated. The residue was chromatographed on silica gel (thick plate, toluene–ethyl acetate) to give recovered starting material (0.12 g) and the pyranyl derivative **7** (56 mg, 73% based on reacted **5**): mp 97–98 °C (from CH_2Cl_2–hexane–ether); IR ($CHCl_3$) 1785, 1765, 1730, 1720, and 1220 cm^{-1}; NMR ($CDCl_3$) δ 1.5–2.0 (CH_2-CH_2), 2.08 (s, Me), 2.30 (s, Me), 3.8–4.1 (OCH_2), 3.83 (s, OMe), 5.40 (d, J = 3 Hz, azetidine H), 5.51 (d, J = 3 Hz, azetidine H), 6.75 (br s, =CH), and 7.8–8.0 (Phth). Anal. Calcd for $C_{22}H_{22}N_2O_6S$: C, 59.72; H, 5.01. Found: C, 59.50; H, 5.06.

(±)-1-(1-(Methoxycarbonyl)-2-methylprop-1-enyl)-3-phthalimido-4-thioxo-2-azetidinone (8). A solution of the sulfoxide **5** (230 mg, 0.5 mmol) in CCl_4 (10 mL) was heated in a sealed tube at 100 °C for 17 h. The solvent was evaporated and the residue was triturated with methanol to give the title compound **8** (143 mg, 80%): mp 164–167 °C (from hexane–CH_2Cl_2); IR ($CHCl_3$) 1830, 1780, 1740, and 1730 cm^{-1}; NMR ($CDCl_3$) δ 2.20 (s, Me), 2.44 (s, Me), 3.80 (s, OMe), 5.97 (s, azetidine H), and 7.90 (m, Phth); mass spectrum, m/e 358 (M^+), 330, 315, 299, 271, 203, 187, and 132. Anal. Calcd for $C_{17}H_{14}N_2O_5S$: C, 56.98; H, 3.94; N, 7.82; S, 8.95. Found: C, 56.50; H, 4.14; N, 7.70; S, 8.48.

***O*-*tert*-Butyl-*N*-thioformyl-DL-serine *tert*-Butyl Ester (9).** H_2S was bubbled through a solution of *O*-*tert*-butyl-DL-serine *tert*-butyl ester (16.2 g, 75 mmol) and *O*-ethyl thionoformate[14] (11.3 g, 0.11 mol) in $CHCl_3$ (100 mL) at 0 °C for 30 min. After an additional 14 h at room temperature, the solution was evaporated and the residue was dissolved in chloroform and washed with 0.1 N hydrochloric acid and water. The organic solution was dried and evaporated to give the title compound **9** (18.9 g, 97%): mp 68 °C (from CH_2Cl_2–hexane); IR ($CHCl_3$) 1740 cm^{-1}; NMR ($CDCl_3$) δ 1.15 (s, *t*-Bu), 1.50 (s, *t*-Bu), 3.86 (d, J = 3 Hz, CH_2O), 5.32 (m, $NCHCO_2$), 8.35 (br, NH), 9.50 (d, J = 6 Hz, HCS); mass spectrum, m/e 261 (M^+). Anal. Calcd for $C_{12}H_{23}NO_3S$: C, 55.15; H, 8.87; N, 5.36; S, 12.27. Found: C, 55.22; H, 9.02; N, 5.30; S, 12.40.

(±)-4-(2-(Methoxycarbonyl)ethylthio)-1-(1-(*tert*-butoxycarbonyl)-2-*tert*-butoxyethyl)-3-phthalimido-2-azetidinone (15). A solution of the thioformamide **9** (18.6 g, 71 mmol) in toluene (150 mL) was added during 30 min to an ice-cold stirred suspension of NaH (3.8 g, 50% in paraffin, 79 mmol) in toluene (100 mL). After an additional 30 min, methyl iodide (19.5 g, 0.14 mol) in toluene (10 mL) was added. The mixture was stirred for an additional 1 h, filtered through Celite, and evaporated to give the methyl thioformimidate **11**: IR ($CHCl_3$) 1725 and 1590 cm^{-1}; NMR ($CDCl_3$) δ 1.16 (s, *t*-Bu), 1.45 (s, *t*-Bu), 2.40 (s, SMe), 3.35–4.25 ($NCHCH_2O$), 8.42 (s, HC=N). Compound **11** was mixed immediately without further purification with methyl 3-mercaptopropionate (25 mL) and heated at 45 °C for 18 h. The excess of methyl 3-mercaptopropionate was distilled off (40–45 °C at 0.4 mmHg) to give the thioformimidate **12**: IR ($CHCl_3$) 1730 and 1600 cm^{-1}; NMR ($CDCl_3$) δ 1.16 (s, *t*-Bu), 1.47 (s, *t*-Bu), 2.8

(14) Mayer, R.; Berthold, H. *Z. Chem.* **1963**, *3*, 310.

(m) and 3.2 (m) ($SCH_2CH_2CO_2$), 3.45–3.95 ($NCHCH_2O$), 3.71 (s, OMe), 8.31 (s, HC=N). To a stirred solution of crude **12** and triethylamine (18 g, 0.18 mol) in toluene (400 mL) was added a solution of phthaloylglycyl chloride (27 g, 0.12 mol) in toluene (500 mL) during 2 h. After an additional 12 h, the mixture was concentrated under reduced pressure to a volume of 500 mL and a second portion of triethylamine (10.8 g, 0.11 mol) was added, followed by the dropwise addition (3 h) of a second portion of phthaloylglycyl chloride (15 g, 67 mmol) in toluene (400 mL). The mixture was stirred for an additional 12 h, filtered, and evaporated. Chromatography of the residue on a silica gel column (hexane–acetone) gave the title compound **15** (19.5 g, 51% based on **9**) as a 1:1 mixture of two diastereoisomers: IR (film) 1785, 1775, 1740, and 1725 cm^{-1}; NMR (90 MHz, C_6D_6) δ 1.15 (s, O-*t*-Bu), 1.19 (s, O-*t*-Bu), 1.48 (s, O-*t*-Bu), 1.50 (s, O-*t*-Bu), 2.49 (m) and 2.86 (m) ($SCH_2CH_2CO_2$), 3.33 (s, OMe), 3.34 (s, OMe), 4.0–4.4 ($NCHCH_2O$), and 5.4–5.45 (azetidine 2 H of two isomers). High-resolution mass spectrum, calcd for $C_{26}H_{34}N_2O_8S$ 534.2036, found 534.2069; *m/e* 534, 348, 292, 291, 236, 188, 187, and 160.

4-(2-Methoxycarbonylethylthio)-1,3,3-triphenyl-2-azetidinone (17). A solution of thioformanilide[14] (**10**) (680 mg, 5.0 mmol) in THF (30 mL) was added during 30 min to a stirred suspension of NaH (200 mg, 8.3 mmol) in THF (5 mL). Methyl iodide (1 g, 7.0 mmol) in THF (10 mL) was added during 15 min and the mixture was filtered through Celite and evaporated to give the thioformimidate **13** (720 mg): IR ($CHCl_3$) 1580 cm^{-1}; NMR ($CDCl_3$) δ 2.35 (s, SMe), 6.8–7.3 (aromatic), 8.35 (s, HC=N). The thioformimidate **13** (720 mg, 4.8 mmol) was mixed with 2 mL of methyl 3-mercaptopropionate and a slow stream of argon was passed through the solution during 20 h. Removal of the excess of mercaptan (40–45 °C at 0.4 mmHg) afforded the thioformimidate **14** (1.0 g): IR ($CHCl_3$) 1730 and 1570 cm^{-1}; NMR ($CDCl_3$) δ 2.6–3.5 ($SCH_2CH_2CO_2$), 3.60 (s, OMe), 6.9–7.45 (aromatic), 8.40 (s, HC=N). To a solution of the crude thioimidate **14** (1.0 g, ~4.5 mmol) in toluene (150 mL) was added diphenylketene (950 mg, 4.9 mmol) in toluene (100 mL) during 3 h. The mixture was kept overnight at room temperature and for 2 h at 70 °C and evaporated. Chromatography of the residue on silica gel (CH_2Cl_2–hexane) gave the β-lactam **17** (990 mg, 48% based on **10**): mp 179–180 °C (from CH_2Cl_2–hexane); IR ($CHCl_3$) 1750 (br) cm^{-1}; NMR ($CDCl_3$) δ 2.0–2.5 ($SCH_2CH_2CO_2$), 3.60 (s, OMe), 5.85 (s, azetidine H), and 7.2–7.8 (aromatic); mass spectrum, *m/e* 417 (M^+), 298, 287, 223, 194, 152, and 120. Anal. Calcd for $C_{25}H_{23}NO_3S$: C, 71.93; H, 5.55; N, 3.36; S, 7.67. Found: C, 71.77; H, 5.50; N, 3.54; S, 7.84.

(±)-4-(2-(Methoxycarbonyl)ethylsulfinyl)-1-(1-(*tert*-butoxycarbonyl)-2-*tert*-butoxyethyl)-3-phthalimido-2-azetidinone (16). To a stirred solution of the sulfide **15** (two isomers, 1 g, 1.87 mmol) in CH_2Cl_2 (80 mL) at −40 °C was added a solution of *m*-chloroperbenzoic acid (0.33 g, 90%, 1.72 mmol) in CH_2Cl_2 (80 mL) during 1 h. The mixture was washed with 5% aqueous $NaHCO_3$ and water, dried, and evaporated. Chromatography on a silica gel column (toluene–ethyl acetate) gave the title compound **16** (810 mg, 85%) as a 1:1 mixture of two isomers which were separated by a second chromatography to give the following: (A) The less polar isomer **16**: IR ($CHCl_3$) 1775 and 1725 cm^{-1}; NMR ($CDCl_3$) δ 1.21 (s, *t*-Bu), 1.54 (s, *t*-Bu), 2.86 (m, $SOCH_2CH_2CO_2$), 3.62 (s, OMe), 3.76 (m, CH_2O), 4.76 (m, $NCHCO_2$), 5.49 (d, J = 2.5 Hz, azetidine H), 6.02 (d, J = 2.5 Hz, azetidine H), and 7.85 (m, Phth); mass spectrum, *m/e* 446 ($M^+ - CH_2{=}CHCO_2CH_3 - H_2O$), 390, 334, 289, 203, and 187. Anal. Calcd for $C_{26}H_{34}N_2O_9S$: C, 56.71; H, 6.22; N, 5.09. Found: C, 56.33; H, 5.93; N, 5.26. (B) The more polar isomer **16**: IR ($CHCl_3$) 1775 and 1720 cm^{-1}; NMR ($CDCl_3$) δ 1.21 (s, *t*-Bu), 1.54 (s, *t*-Bu), 2.87 (m, $SOCH_2CH_2CO_2$), 3.60 (s, OMe), 4.10 (d, J = 2.5 Hz, CH_2O), 4.79 (t, J = 2.5 Hz, $NCHCO_2$), 5.30 (d, J = 2 Hz, azetidine H), 6.15 (d, J = 2 Hz, azetidine H), and 7.9 (m, Phth); mass spectrum, *m/e* 446 ($M^+ - CH_2{=}CHCO_2Me - H_2O$), 390, 334, 289, 203, and 187. Anal. Calcd for $C_{26}H_{34}N_2O_9S$: C, 56.71; H, 6.22; N, 5.09. Found: C, 56.81; H, 6.33; N, 5.04.

4-(2-(Methoxycarbonyl)ethylsulfinyl)-1,3,3-triphenyl-2-azetidinone (18). To a stirred solution of the β-lactam **17** (1.63 g, 3.9 mmol) in CH_2Cl_2 (50 mL) at −45 °C was added a solution of *m*-chloroperbenzoic acid (690 mg, 4.0 mmol) in CH_2Cl_2 (50 mL) during 0.5 h. The solution was washed with 5% aqueous $NaHCO_3$ and water, dried, and evaporated. The residue was chromatographed on silica gel (toluene–ethyl acetate) to give the sulfoxide **18** (1.2 g, 71%) as a 5:3 mixture of two isomers. The major isomer **18** was separated from the mixture by crystallization from ether: mp 135 °C; IR ($CHCl_3$) 1765 and 1735 cm^{-1}; NMR ($CDCl_3$) δ 2.0–2.8 ($SCH_2CH_2CO_2$), 3.60 (s, OMe), 5.95 (s, azetidine H), 7.2–8.0 (aromatic); NMR (90 MHz, C_6D_6) δ 2.0–2.8 ($SCH_2CH_2CO_2$), 3.25 (s, OMe), 5.85 (s, azetidine H), and 6.9–8.3 (aromatic). Anal. Calcd for $C_{25}H_{23}NO_4S$: C, 69.27; H, 5.35; N, 3.23; S, 7.40. Found: C, 69.10; H, 5.43; N, 3.29; S, 7.67. Evaporation of the mother liquor followed by chromatography on silica gel preparative thick plates (toluene–ethyl acetate) afforded the minor isomer of **18**; NMR in $CDCl_3$ and IR spectra were identical with those of the major isomer; NMR (90 MHz, C_6D_6) δ 2.0–2.4 ($SCH_2CH_2CO_2$), 3.10 (s, OMe), 5.80 (s, azetidine H), and 6.9–8.2 (aromatic). Anal. Calcd for $C_{25}H_{23}NO_4S$: C, 69.27; H, 5.35; N, 3.23; S, 7.40. Found: C, 69.11; H, 5.37; N, 3.27; S, 7.25.

(±)-1-(1-(*tert*-Butoxycarbonyl)-2-*tert*-butoxyethyl)-3-phthalimido-4-thioxo-2-azetidinone (19). A solution of the sulfoxide **16** (450 mg, 0.82 mmol) in CCl_4 (20 mL) was heated in a sealed tube at 105 °C for 24 h. The solvent was evaporated and the residue was rapidly chromatographed on a silica gel column (toluene–ethyl acetate) to give recovered starting material (310 mg, 69%) and the title compound **19** (70 mg, 62% based on reacted starting material): IR ($CHCl_3$) 1830, 1785, and 1730 cm^{-1}; NMR ($CDCl_3$) δ 1.18 (s, O-*t*-Bu), 1.51 (s, O-*t*-Bu), 3.85–4.25 (CH_2O-*t*-Bu), 4.85 (m, $NCHCO_2$), 5.90 (s, azetidine H), and 7.88 (m, Phth); mass spectrum, *m/e* 446 (M^+), 390, 334, 289, 203, and 187.

1,3,3-Triphenyl-4-thioxo-2-azetidinone (20). A solution of the sulfoxide **18** (225 mg, 0.52 mmol, mixture of two isomers) in xylene (5 mL) was heated at 140 °C in a sealed tube during 24 h. The solvent was evaporated and the residue was chromatographed on silica gel (hexane–acetone) to give the thiomalonimide **20** (136 mg, 80%): IR ($CHCl_3$) 1815 and 1790 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.3–7.8 (13 H, aromatic) and 8.1–8.4 (2 H, aromatic); ^{13}C NMR ($CDCl_3$) δ 205.2 (C=S), 170.6 (C=O); high-resolution mass spectrum, calcd for $C_{14}H_{10}S$ 210.0504, found 210.0534; *m/e* 329 (M^+, <0.1%), 210 (M^+ − PhNCO), 194, and 165.

(3*R*,4*R*)-4-(2-(Methoxycarbonyl)ethylsulfinyl)-1-(1-(methoxycarbonyl)-2-methylprop-1-enyl)-3-phthalimido-2-azetidinone (25). A solution of the phthalimidopenicillanate sulfoxide **21**[15] (1.5 g, 4.0 mmol) in freshly distilled methyl acrylate (50 mL) was heated at 80 °C during 5 h. The excess of acrylate was evaporated and the residue was chromatographed on silica gel (ethyl acetate–toluene) to give recovered starting material (100 mg, 7%) and the sulfoxide **23** (1.6 g, 87%) as a 2:1 mixture of two isomers: IR ($CHCl_3$) 1790 and 1730 cm^{-1}; NMR (1:1 v/v $CDCl_3$–C_6D_6) δ 2.00 (br s, C=CMe), 2.25 (m, $SCH_2CH_2CO_2$, minor isomer), 2.45–2.75 ($SCH_2CH_2CO_2$, major isomer), 3.10 (s) and 3.71 (s) (two OMe of minor isomer), 3.43 (s) and 3.56 (s) (two OMe of major isomer), 5.0–5.4 ($C{=}CH_2$, azetidine H, and $NCHCO_2$), 5.60 (d, J = 5 Hz, azetidine H of minor isomer), 5.81 (d, J = 5 Hz, azetidine H of major isomer), and 7.0–7.75 (Phth). To the mixture of the two isomers of **23** (1.0 g, 2.2 mmol) in chloroform (40 mL) was added a drop of triethylamine. After 15 min the solution was evaporated and the residue was chromatographed on silica gel (ethyl acetate–toluene) to give the following: (A) The less polar isomer **25** (640 mg, 64%): mp 135–136 °C (from CH_2Cl_2–hexane); $[\alpha]^{26}_D$ +77.3° (*c* 1.0, $CHCl_3$); IR ($CHCl_3$) 1780 (br) and 1720 (br) cm^{-1}; NMR (90 MHz, $CDCl_3$) δ 2.27 (s, C=CMe), 2.33 (s, C=CMe), 2.69–2.91 ($SCH_2CH_2CO_2$), 3.68 (s, OMe), 3.84 (s, OMe), 5.08 (d, J = 5 Hz, azetidine H), 5.88 (d, J = 5 Hz, azetidine H), and 7.82 (m, Phth); mass spectrum, *m/e* 376 ($M^+ - CH_2{=}CHCO_2CH_3$), 358 ($M^+ - CH_2{=}CHCO_2CH_3 - H_2O$), 343, 299, 203, 187, 132, and 104. Anal. Calcd for $C_{21}H_{22}N_2O_8S$: C, 54.54; H, 4.80; N, 6.06. Found: C, 54.78; H, 4.82; N, 6.18. (B) The more polar isomer **25** (250 mg, 25%): mp 128–130 °C (from CH_2Cl_2–hexane); $[\alpha]^{26}_D$ +30.3° (*c* 1.0, $CHCl_3$); IR ($CHCl_3$) 1785 (br) and 1720 (br) cm^{-1}; NMR (90 MHz, $CDCl_3$) δ 2.31 (s, C=CMe), 2.39 (s, C=CMe), 2.74 (s, $SCH_2CH_2CO_2$), 3.42 (s, OMe), 3.81 (s, OMe), 5.14 (d, J = 5 Hz, azetidine H), 5.70 (d, J = 5 Hz, azetidine H), and 7.83 (m, Phth); mass spectrum, *m/e* 358 ($M^+ - CH_2{=}CHCO_2CH_3 - H_2O$), 343, 299, 187, 132, and 104. Anal.

(15) Cooper, R. D. G.; DeMarco, P. V.; Spry, D. O. *J. Am. Chem. Soc.* **1969**, *91*, 1528.

Calcd for $C_{21}H_{22}N_2O_8S$: C, 54.54; H, 4.80; N, 6.06. Found: C, 54.89; H, 4.90; N, 6.24.

(3*R*)-1-(1-(Methoxycarbonyl)-2-methylprop-1-enyl)-3-phthalimido-4-thioxo-2-azetidinone (27). A mixture of the two isomers of **25** (150 mg, 0.32 mmol, from a 2:1 mixture of **23**) in CCl_4 was heated at 100 °C in a sealed tube for 48 h. Evaporation of the solvent gave a yellowish foam which was triturated with methanol to afford the thiomalonimide **27** (98 mg, 84%). IR, NMR, and mass spectra were identical with those of compound **8**; $[\alpha]^{26}_D$ -15.2° (*c* 1.0, $CHCl_3$).

(3*R*,4*R*)-1-(1-((Diphenylmethoxy)carbonyl)-2-methylprop-2-enyl)-4-(2-(methoxycarbonyl)ethylsulfinyl)-3-phthalimido-2-azetidinone (24). The sulfoxide **22** (2.3 g, 4.4 mmol) was thermolyzed as described for the preparation of **23** to give two isomeric sulfoxides: (A) A less polar isomer **24** (1.3 g, 49%) as a colorless oil: $[\alpha]^{26}_D$ -56.4° (*c* 1.0, $CHCl_3$); IR ($CHCl_3$) 1775 (br) and 1725 (br) cm^{-1}; NMR (80 MHz, $CDCl_3$) δ 2.03 (s, C=CMe), 2.3-2.8 ($SCH_2CH_2CO_2$), 3.63 (s, OMe), 4.79 (s, $NCHCO_2$), 5.05-5.3 (C=CH_2 and azetidine H), 5.76 (d, J = 5.2 Hz, azetidine H), 6.97 (s, $CHPh_2$), 7.33 (s, Ph), 7.36 (s, Ph), and 7.79 (m, Phth). Anal. Calcd for $C_{33}H_{30}N_2O_8S$: C, 64.49; H, 4.92; N, 4.56; S, 5.22. Found: C, 64.59; H, 4.86; N, 4.88; S, 5.44. (B) A more polar isomer of **24** (1.0 g, 37%): mp 127 °C (CH_2Cl_2-hexane); $[\alpha]^{26}_D$ -69.3° (*c* 0.9, $CHCl_3$); IR ($CHCl_3$) 1780, 1775 (sh) and 1725 (br) cm^{-1}; NMR (80 MHz, $CDCl_3$) δ 2.01 (s, C=CMe), 2.70 (s, $SCH_2CH_2CO_2$), 3.39 (s, OMe), 4.89 (s, $NCHCO_2$), 5.1-5.2 (m, C=CH_2 and azetidine H), 5.62 (d, J = 5.2 Hz, azetidine H), 6.98 (s, $CHPh_2$), 7.34 (s, CPh_2), and 7.85 (m, Phth). Anal. Calcd for $C_{33}H_{30}N_2O_8S$: C, 64.49; H, 4.92; N, 4.56; S, 5.21. Found: C, 64.42; H, 4.96; N, 4.50; S, 5.40.

(3*R*,4*R*)-1-(1-(Diphenylmethoxy)carbonyl-2-methylprop-1-enyl)-4-(2-(methoxycarbonyl)ethylsulfinyl)-3-phthalimido-2-azetidinones (26). A solution of the less polar isomer of **24** in chloroform was treated for 15 min with a drop of triethylamine to give one isomer of **26**: foam; $[\alpha]^{26}_D$ +15.5° (*c* 1.0, $CHCl_3$); IR ($CHCl_3$) 1790, 1780, and 1730 cm^{-1}; NMR (80 MHz, $CDCl_3$) δ 2.28 (s, C=CMe), 2.34 (s, C=CMe), 2.4-2.8 ($SCH_2CH_2CO_2$), 3.64 (s, OMe), 4.85 (d, J = 5.2 Hz, azetidine H), 5.76 (d, J = 5.2 Hz, azetidine H), 7.00 (s, $CHPh_2$), 7.33 (s, Ph), 7.39 (s, Ph), and 7.81 (m, Phth). Anal. Calcd for $C_{33}H_{30}N_2O_8S$: C, 64.49; H, 4.92; N, 4.56; S, 5.22. Found: C, 64.65; H, 5.04; N, 4.82; S, 5.54. Similarly the more polar isomer of **24** gave a second isomer of **26**: foam; $[\alpha]^{26}_D$ -7.3° (*c* 1.1, $CHCl_3$); IR ($CHCl_3$) 1785 (br) and 1730 cm^{-1}; NMR (80 MHz, $CDCl_3$) δ 2.33 (s, C=CMe), 2.40 (s, C=CMe), 2.55 (m, $SCH_2CH_2CO_2$), 3.41 (s, OMe), 4.89 (d, J = 5.2 Hz, azetidine H), 5.54 (d, J = 5.2 Hz, azetidine H), 6.97 (s, $CHPh_2$), 7.32 (s, Ph), 7.37 (s, Ph), and 7.82 (m, Phth). Anal. Calcd for $C_{33}H_{30}N_2O_8S$: C, 64.49; H, 4.92; N, 4.56; S, 5.22. Found: C, 64.61; H, 4.92; N, 4.81; S, 5.41.

(3*R*)-1-(1-(Diphenylmethoxy)carbonyl-2-methylprop-1-enyl)-3-phthalimido-4-thioxo-2-azetidinone (28). A mixture of the two isomers **26** (100 mg, 0.16 mmol) was heated in CCl_4 (80 °C) in a sealed tube during 24 h. Evaporation of the solvent gave **28** as a yellow foam (79 mg, 95%) which was triturated with absolute methanol to give a yellow crystalline compound: mp 189-191 °C; $[\alpha]^{26}_D$ -31.3° (*c* 1.0, $CHCl_3$); IR ($CHCl_3$) 1835, 1785, and 1730 cm^{-1}; NMR (90 MHz, $CDCl_3$) δ 2.20 (s, C=CMe), 2.41 (s, C=CMe), 5.75 (s, azetidine H), 6.86 (s, $CHPh_2$), 7.30 (s, CPh_2), and 7.83 (m, Phth); high-resolution mass spectrum, calcd for $C_{15}H_{12}N_2O_3S$ 300.0608, found 300.0562 [$M^+ - CO_2C(C_6H_5)_2$], 203.0040 ($C_{10}H_5NO_2S$), and 187.0270 ($C_{10}H_5NO_3$).

Registry No. **1**, 50896-32-7; **2**, 35859-85-9; **3**, 61222-65-9; **4**, 72726-84-2; **5**, 72777-01-6; **7**, 72726-85-3; **8**, 72777-02-7; **9**, 61222-67-1; **10**, 637-51-4; **11**, 72726-86-4; **12**, 72726-87-5; **13**, 54150-53-7; **14**, 72726-88-6; **15**, isomer I, 72777-03-8; **15**, isomer II, 72777-04-9; **16**, isomer I, 72777-05-0; **16**, isomer II, 72777-06-1; **17**, 72726-89-7; **18**, isomer I, 72726-90-0; **18**, isomer II, 72726-91-1; **19**, 61222-75-1; **20**, 72726-92-2; **21**, 23236-46-6; **22**, 72777-07-2; **23**, isomer I, 70004-70-5; **23**, isomer II, 69980-47-8; **24**, isomer I, 72726-93-3; **24**, isomer II, 72777-08-3; **25**, isomer I, 70004-01-2; **25**, isomer II, 70004-00-1; **26**, isomer I, 72726-94-4; **26**, isomer II, 72777-09-4; **27**, 61256-95-9; **28**, 72726-95-5; methyl 3-mercaptopropionate, 2935-90-2; phthaloylglycyl chloride, 6780-38-7; *O*-*tert*-butyl-DL-serine *tert*-butyl ester, 17083-22-6; *O*-ethyl thionoformate, 29392-46-9; diphenylketene, 525-06-4.

Properties and Reactions of 4-Thioxo-2-azetidinones

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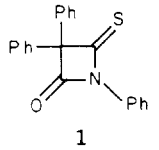
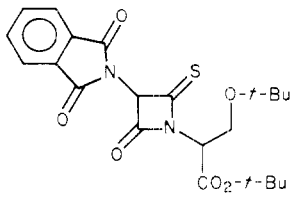
Received November 6, 1979

4-Thioxo-2-azetidinones represented by compounds 1-4 appear to be suitable substrates for contrasting the chemistry of the C=O and C=S linkages. Hydrolysis and alcoholysis occur selectively at the carbonyl bond while 1,3-dipolar reagents like diazoalkanes and ozone, as well as carbenes, attack exclusively at the thiocarbonyl function. The 4-alkylidene-2-azetidinones **35-38** have been obtained from the 4-thioxo-2-azetidinones **3** or **4** and 2-diazopropane, diphenyldiazomethane, or ethyl diazomalonate. The reactions with 2-diazopropane involved the formation of thiadiazolines from which the sulfur and nitrogen elements were extruded. The reactions with the last two reagents which were performed in the presence of $Rh(OAc)_2$ involved carbene intermediates.

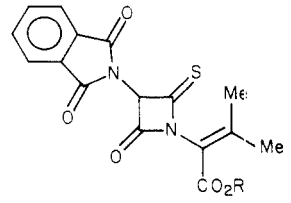
The preparation of the 4-thioxo-2-azetidinones **1-4** has been described in the preceding paper.[1] Compounds of this class appear to be suitable substrates for contrasting the chemistry of the C=O and C=S linkages as well as potential synthons for the preparation of other heterocycles. The value of the 4-thioxo-2-azetidinones as synthons stems from their availability by a synthetic method[1] which allows flexibility in the selection of varied appendages, as well as from the intrinsic properties of the highly functionalized strained system. Only a few reactions of 4-thioxo-2-azetidinones have been reported in short communications from this[3,4] and another laboratory.[5-7] A more



1



2



3, R = Me
4, R = $CHPh_2$

(1) Bachi, M. D.; Goldberg, O.; Gross, A.; Vaya, J. *J. Org. Chem.*, preceding paper in this issue.
(2) For a recent review on nonclassical β-lactam antibiotics, see: Cama, L. D.; Christensen, B. G. *Annu. Rep. Med. Chem.* **1978**, *13*, 149.
(3) Bachi, M. D.; Vaya, J. *Tetrahedron Lett.* **1977**, 2209.
(4) Bachi, M. D.; Goldberg, O.; Gross, A. *Tetrahedron Lett.* **1978**, 4167.
(5) Brandt, A.; Bassignani, L.; Re, L. *Tetrahedron Lett.* **1976**, 3975.

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