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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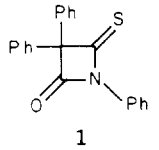
Received November 6, 1979

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



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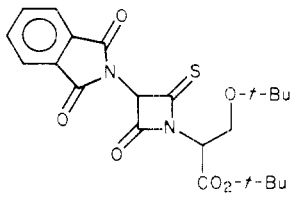

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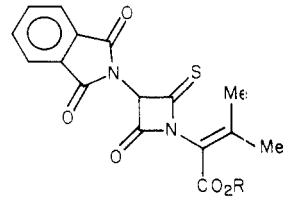

3, R = Me
4, R = $CHPh_2$

(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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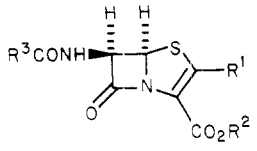
detailed and comprehensive treatment is given in the present paper.

4-Thioxo-2-azetidinones exhibit in their infrared spectra an intense carbonyl absorption band within the range of 1815–1830 cm^{-1}. This is considerably higher than that of the carbonyl stretching band of nonfused β-lactams and of the bicyclic penicillins and cephalosporins.[8] It is even higher than the corresponding frequency of penems **5**



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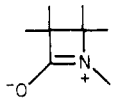

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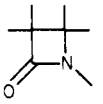
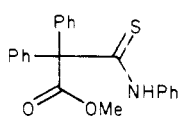


7

which absorb in the range of 1795–1805 cm^{-1}.[9] An increase in the infrared carbonyl frequency of β-lactams has been correlated with a decrease in the degree of resonance stabilization of the amide bond, namely, with a decrease in the contribution of the mesomeric form **6** relative to **7**.[10] The destabilization of β-lactam systems, which may result from steric or electronic factors[10] or both, as in the penems,[9] is reflected in their enhanced reactivity toward nucleophilic reagents. Indeed, a positive correlation was found between the rate constants of base hydrolysis and the infrared carbonyl frequencies of β-lactams.[11] In agreement with this relationship, 4-thioxo-2-azetidinones appear to be highly susceptible to hydrolysis and alcoholysis. It is, however, worth noting that these compounds withstand treatment (24 h at room temperature) with trifluoroacetic acid and are stable to heat (e.g., compound **3** was recovered unchanged after being warmed at 155 °C for 3 h).

Methanolysis of the 4-thioxo-2-azetidinones **1** and **2** in the presence of triethylamine occurred exclusively at the C-2 carbonyl group, yielding the corresponding thioamides **8** (quantitative) and **9** (70%). Methanolysis of **3** under



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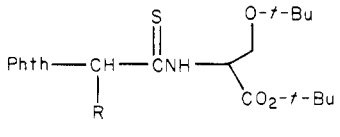
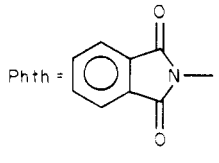
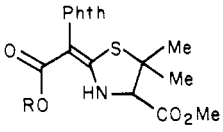


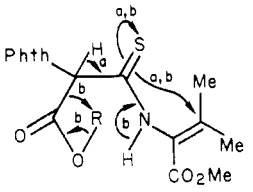
9, R = CO_2Me
10, R = CO_2H
11, R = H



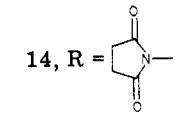
the same conditions gave two compounds. The major product **12** (61%) results from a nucleophilic attack of the alcohol at C-2. Presumably the primary product **15** rearranges as shown by the arrows a to the thiazolidine **12**. The minor product which was obtained in 19% yield was assigned structure **17**. The formation of this oxazolone is explained by a competitive methanolysis of the phthalimido group in **3** leading to the phthaleamic ester **19**, which spontaneously rearranges as shown by the arrows. The



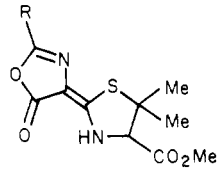
12, R = Me
13, R = *t*-Bu

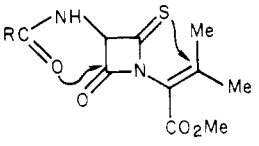


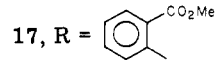
15, R = Me
16, R = H



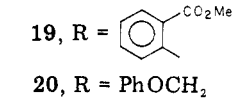
14, R =







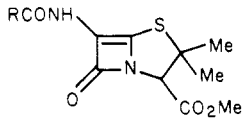
17, R =

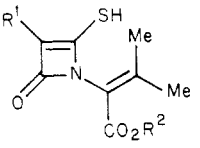


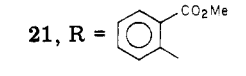
19, R =

18, R = $PhOCH_2$

20, R = $PhOCH_2$



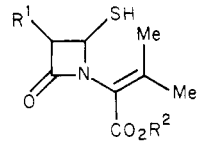


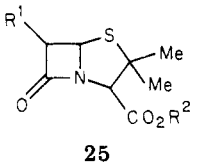


21, R =

23

22, R = $PhOCH_2$





24

25

thiazolidinylideneoxazolone **17** is isomeric with the thiazolidine **12** as well as with the hypothetical 5,6-dehydropenicillin **21**. A 5,6-dehydropenicillin structure was attributed by Re and co-workers[6] to rearrangement products of some 4-thioxo-2-azetidinones. For example, it was claimed that treatment of the 4-thioxo-2-azetidinone **20** with triethylamine resulted in the formation of the 5,6-dehydropenicillin **22**. However, the reported spectral data for Re's compound are very similar to those of the compound to which we assign the oxazolone structure **17**. The formation of oxazolones by an intramolecular attack of an acylamino group on the carbonyl function of 2-azetidinones is well-known in penicillin chemistry.[12] The same type of reaction occurs also in the transformation of α-acylaminocarboxylic acid derivatives into Δ^2-oxazolin-5-ones.[13] On the other hand, the formation of a 5,6-dehydropenicillin system which would require the intermediacy of a thioenolic form **23** seems very unlikely. It has been reported that attempts to perform a similar intramolecular Michael addition of 4-mercapto-β-lactams of type **24** to penam systems **25** were unsuccessful.[14-17] These failures have

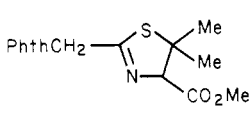
(6) Brandt, A.; Bassignani, L.; Re, L. *Tetrahedron Lett.* **1976**, 3979.
(7) Brandt, A.; Bassignani, L.; Re, L. *Tetrahedron Lett.* **1977**, 3159.
(8) For infrared data of β-lactams see: DeMarco, P. V.; Nagarajan, R. In "Cephalosporins and Penicillins"; Flynn, E. H., Ed.; Academic Press: New York and London, 1972; p 311.
(9) Ernest, I.; Gosteli, J.; Greengrass, C. W.; Holick, W.; Jackman, D. E.; Pfaendler, H. R.; Woodward, R. B. *J. Am. Chem. Soc.* **1978**, *100*, 8214.
(10) Sweet, R. M. In "Cephalosporins and Penicillins"; Flynn, E. H., Ed.; Academic Press: New York and London, 1972; p 280.
(11) Indelicato, J. M.; Norvilas, T. T.; Pfeiffer, R. R.; Wheeler, W. J.; Wilham, W. L. *J. Med. Chem.* **1974**, *17*, 523 and references cited therein.
(12) Doyle, F. P.; Nayler, J. H. C. In "Advances in Drug Research"; Harper, N. J., Simmonds, A. B., Eds.; Academic Press: London and New York, 1964; Vol. 1, p 1.
(13) Steglich, W. *Fortsch. Chem. Forsch.* **1969**, *12*, 77.

been rationalized by Baldwin[16a] on stereoelectonic grounds. The same kind of mechanistic constraints would exist also in the annelation of the thioenolates **23**. Furthermore, the resulting 5,6-dehydropenicillin system would be of an energy content higher than that of the considerably less strained penams **25**. We therefore suggest structure **17** for the compound obtained from **3** and structure **18** for the rearrangement product of **20**. These assignments are corroborated by comparing the UV and IR spectra of these compounds with those of other thiazolidinylidene-oxazolones as well as with those of 4-(1-thioalkylidene)- and 4-(1-aminoalkylidene)oxazolones.[18,19] The C=O and C=N absorptions of nonconjugated Δ^2-oxazolin-5-ones appear at 1820 and 1670 cm^{-1}, respectively. However, attachment of an exocyclic double bond at C-4 results in a fall of these frequencies which may reach values as low as 1700 cm^{-1} for the C=O and 1620 cm^{-1} for the C=N group.[19,20] Thus, the three absorption bands of **17** in the region 1720–1745 cm^{-1} account for two ester and one oxazolone carbonyl groups, whereas the peak at 1620 cm^{-1} accounts for the oxazolone carbon to nitrogen double bond.

Triethylamine-catalyzed alcoholysis of the 4-thioxo-2-azetidinone **3** with *tert*-butyl alcohol and *N*-hydroxysuccinimide afforded the esters **13** (47%) and **14** (81%), respectively. Reduction of the olefinic linkage in compounds **12–14** would give products that might function as intermediates in a synthesis of penicillins according to Sheehan's classical method.[21] However, attempts to reduce the tetrasubstituted double bond in these compounds by catalytic hydrogenation (Pd/C, PtO_2, various solvents) and by sodium cyanoborohydride (in the presence of varying amounts of acid)[22] were unsuccessful.

The high reactivity of the amide bond of the 4-thioxo-2-azetidinones **2** and **3** is also reflected in their ready hydrolysis which occurred on treatment with a suspension of silica gel in chloroform. The reaction of **2** with the water present in the medium gave the carboxylic acid **10** which spontaneously lost carbon dioxide to give the thioamide **11** (quantitative). Compound **3** was hydrolyzed under the same conditions to give quantitatively the thiazoline **26**, evidently through the intermediacy of the acid **16** which underwent decarboxylation and cyclization as shown by the arrows b.

As part of a program concerned with the synthesis of β-lactam antibiotics and nuclear analogues thereof,[23] we became interested in the elaboration of a synthetic route to fused β-lactams of type **27**. These compounds were designed for testing the possibility of activating the β-lactam amide bond by conjugation of the nitrogen atom's unshared electron pair to a double bond which is situated at the bridgehead, and not α to the carboxyl group as in the antibacterially active 1-dethiacarbacephalotin **28** and the cephalosporins.[24,25] This activation may also be



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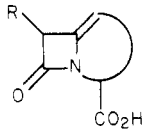

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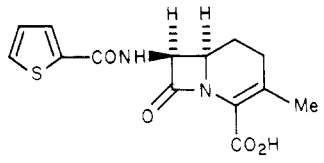

28

manifested in antibiotic activity of compounds of this type.[26] Suitably substituted 4-thioxo-2-azetidinones are suggested as potential synthons for the synthesis of β-lactams of type **27**. As preparatory work for a projected synthesis of these compounds, we now describe the conversion of 4-thioxo-2-azetidinones into 4-alkylidene-2-azetidinones.

In view of the softer character of the thiocarbonyl as compared to the carbonyl group,[27] it was anticipated that 4-thioxo-2-azetidinones would react with the soft diazoalkanes at the C=S in preference to the C=O linkage.[28] The reaction between thiones and diazo compounds constitutes the first step in an olefin synthesis by a twofold extrusion process.[29] This methodology has now been extended to the preparation of 4-alkylidene-2-azetidinones.

Treatment of **3** at 0 °C with 2-diazopropane resulted in the immediate formation of the thiadiazoline **29** (75%).[30] This compound was relatively stable in the solid state at 0 °C but in solution it lost nitrogen, slowly at room temperature and within 30 min at 70 °C, to give quantitatively the episulfide **31**. The 4-thioxo-2-azetidinone **4** was likewise converted into the episulfide **32** (63%). The episulfides **31** and **32** were smoothly desulfurized with triphenylphosphine in boiling benzene to afford the corresponding 4-isopropylidene-2-azetidinones **35** (83%) and **36** (85%).

Diphenyldiazomethane failed to react with the 4-thioxo-2-azetidinone **3** by a 1,3-dipolar mechanism (boiling THF). However, treatment of **3** at 60 °C with diphenyldiazomethane and a catalytic amount of $Rh(OAc)_2$, which promotes carbene formation,[31] afforded the episulfide **33** (65%). Sulfur extrusion from **33** with triphenylphosphine gave the 4-diphenylmethylidene-2-azetidinone **37** (85%). The reaction of **3** with ethyl diazomalonate in the presence of the rhodium catalyst required a large excess of the diazomalonate and gave directly the alkylideneazetidinone **38** (58%). Evidently the reactive carbene intermediate reacted faster with the initially formed episulfide **34** than

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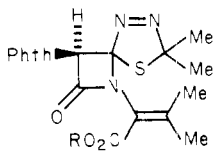
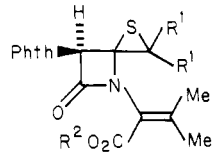
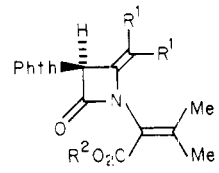
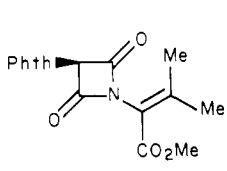


29, R = Me
30, R = $CHPh_2$



31, $R^1 = R^2$ = Me
32, R^1 = Me; $R^2 = CHPh_2$
33, R^1 = Ph; R^2 = Me
34, $R^1 = CO_2Et$; R^2 = Me





35, $R^1 = R^2$ = Me
36, R^1 = Me; $R^2 = CHPh_2$
37, R^1 = Ph; R^2 = Me
38, $R^1 = CO_2Et$; R^2 = Me

with the starting material. Sulfur extrusion from episulfides by carbenes has been previously reported.[32]

The infrared carbonyl absorptions of the 4-alkylidene-2-azetidinones **35–37** appear in the range 1800–1810 cm^{-1} whereas **38** absorbs at 1830 cm^{-1}. These figures reflect the delocalization of the nitrogen atom's unshared pair of electrons which is extended by the electron-withdrawing alkoxycarbonyl group.

Controlled ozonolysis of **3** took place regiospecifically at the thiocarbonyl group, leaving the olefinic linkage intact. The 2,4-azetidinedione **39** thus formed (80%) could also be obtained, albeit in lower yield (25%), by the oxidation of **3** with *m*-chloroperbenzoic acid.

Potentially useful pharmacological properties were attributed to some 2,4-azetidinediones.[33] The traditional methods for their preparation were based on the cycloaddition of ketenes and isocyanates or on the cyclization of malonic acid derivatives.[33] Two new syntheses of 2,4-azetidinediones by photochemical reactions have been recently reported.[34,35] The method described in the present paper offers an access to 2,4-azetidinediones with diversified substitution patterns.

Experimental Section

For general experimental details and preparation of starting materials see the preceding paper.[1]

Methanolysis of the 4-Thioxo-2-azetidinone 1. To a solution of 4-thioxo-2-azetidinone **1** (20 mg, 0.06 mmol) in methanol (2 mL) was added a drop of triethylamine. After 16 h the solution was evaporated to give the thioamide **8** (22 mg, quantitative): IR ($CHCl_3$) 1730, 1700, and 1590 cm^{-1}; NMR (60 MHz, $CDCl_3$) δ 3.80 (s, OMe), 7.3–7.8 (aromatic); high-resolution mass spectrum, calcd for $C_{22}H_{19}NO_2S$ 361.1136, found 361.1133; *m/e* 361 (M^+), 226, 194, and 167.

Methanolysis of the (±)-4-Thioxo-2-azetidinone 2. To a solution of (±)-4-thioxo-2-azetidinone **2** (85 mg, 0.19 mmol) in chloroform (1 mL) and methanol (5 mL) was added triethylamine (1 drop). After 20 min the solvent was evaporated and the residue was chromatographed on silica gel (toluene–ethyl acetate) to afford the thioamide **9** (64 mg, 70%) as a mixture of two isomers: IR ($CHCl_3$) 1770 and 1715 cm^{-1}; NMR (90 MHz, $CDCl_3$) δ 1.14 (s, *t*-Bu), 1.18 (s, *t*-Bu), 1.44 (s, *t*-Bu), 1.50 (s, *t*-Bu), 3.81 (m, OMe and CH_2O), 5.13 (m, $NCHCO_2$), 5.79 (s, CO_2CHCS), 5.83 (s, CO_2CHCS), 7.85 (m, Phth), 10.15 (m, NH); mass spectrum, *m/e* 478 (M^+), 366, 262, 203, and 204.

Alcoholysis of the (±)-4-Thioxo-2-azetidinone 3. A. Methanolysis. To a solution of (±)-4-thioxo-2-azetidinone **3** (165 mg, 0.46 mmol) in methanol (10 mL) was added triethylamine (2 drops). After 10 min the solvent was evaporated and the residue was chromatographed on silica gel (toluene–ethyl acetate) to afford first the thiazolidine **12** (110 mg, 61%): mp 203 °C (from toluene); IR ($CHCl_3$) 1780, 1745, 1720, and 1660; UV ($CHCl_3$) λ_{max} 284 nm (ϵ 24 800); NMR (60 MHz, $CDCl_3$) δ 1.45 (s, CMe), 1.68 (s, CMe), 3.64 (s, OMe), 3.87 (s, OMe), 4.63 (s, $NCHCO_2$), 7.90 (m, Phth), 8.60 (br s, NH); high-resolution mass spectrum, calcd for $C_{18}H_{18}N_2O_6S$ 390.0881, found 390.0873; *m/e* 390 (M^+), 359, 331, 299, and 271. The next fraction consisted of the thiazolidine **17** (35 mg, 19%): mp 152 °C (from benzene); IR ($CHCl_3$) 1745, 1730, 1720, and 1620 cm^{-1}; UV ($CHCl_3$) λ_{max} 361 nm (ϵ 27 100); NMR (60 MHz, $CDCl_3$) δ 1.50 (s, CMe), 1.76 (s, CMe), 3.84 (s, OMe), 3.92 (s, OMe), 4.61 (s, $NCHCO_2$), 7.60 (m, aromatic), 7.90 (br s, NH); high-resolution mass spectrum, calcd for $C_{18}H_{18}N_2O_6S$ 390.0881, found 390.0891; *m/e* 390 (M^+) and 163.

B. Reaction with *tert*-Butyl Alcohol. To a solution of (±)-4-thioxo-2-azetidinone **3** (222 mg, 0.62 mmol) in *t*-BuOH (5 mL) was added triethylamine (2 drops). After 20 h the excess of *t*-BuOH was evaporated and the residue was chromatographed on silica gel (toluene–ethyl acetate) to afford the thiazolidine **13** (125 mg, 47%): IR ($CHCl_3$) 1770 and 1720 cm^{-1}; UV ($CHCl_3$) λ_{max} 284 nm (ϵ 12 300); NMR (60 MHz, $CDCl_3$) δ 1.37 (s, *t*-Bu), 1.45 (s, CMe), 1.67 (s, CMe), 3.87 (s, OMe), 4.61 (s, $NCHCO_2$), 7.90 (m, Phth), 8.63 (br s, NH); mass spectrum, *m/e* 432 (M^+), 376, 332, 299, and 273.

C. Reaction with *N*-Hydroxysuccinimide. (±)-4-Thioxo-2-azetidinone **3** (330 mg, 0.92 mmol) in THF (5 mL) was treated with *N*-hydroxysuccinimide (150 mg, 1.3 mmol) and triethylamine (2 drops) for 40 min. The solvent was evaporated and the residue was triturated consecutively with water and ether to give the thiazolidine **14** (352 mg, 81%): mp 250–254 °C; IR ($CHCl_3$) 1780, 1735, and 1555 cm^{-1}; UV ($CHCl_3$) λ_{max} 291 nm (ϵ 26 200); NMR (60 MHz, $CDCl_3$) δ 1.46 (s, CMe), 1.72 (s, CMe), 2.80 (s, CH_2CH_2), 3.89 (s, OMe), 4.73 (s, $NCHCO_2$), 7.95 (m, Phth), 8.45 (br s, NH); mass spectrum, *m/e* 473 (M^+), 359, 299, and 190.

Hydrolysis of the (±)-4-Thioxo-2-azetidinone 2. A mixture of (±)-4-thioxo-2-azetidinone **2** and silica gel in chloroform was stirred for 40 h, and then filtered and evaporated to give the thioamide **11** (quantitative): IR ($CHCl_3$) 1765 and 1715 cm^{-1}; NMR (60 MHz, $CDCl_3$) δ 1.10 (s, *t*-Bu), 1.45 (s, *t*-Bu), 3.81 (d, J = 3 Hz, CH_2O), 4.77 (s, CH_2CS), 5.17 (m, $NCHCO_2$), 7.90 (m, Phth), 8.38 (m, NH); high-resolution mass spectrum, calcd for $C_{21}H_{28}N_2O_5S$ 420.1719, found 420.1729; *m/e* 420 (M^+), 204, 203, and 160.

Hydrolysis of the (±)-4-Thioxo-2-azetidinone 3. The (±)-4-thioxo-2-azetidinone **3** (120 mg, 0.33 mmol) was added to a suspension of silica gel in chloroform. The mixture was stirred for 2 days, filtered, and evaporated to afford the thiazoline **26** (110 mg, 99%): mp 147–148 °C (CH_2Cl_2–hexane); IR ($CHCl_3$) 1770, 1740, 1720, and 1610 cm^{-1}; NMR (60 MHz, $CDCl_3$) δ 1.38 (s, CMe), 1.69 (s, CMe), 3.80 (s, OMe), 4.74 (s, $PhthCH_2$ and $NCHCO_2$), 7.90 (m, Phth); high-resolution mass spectrum, calcd for $C_{16}H_{16}N_2O_4S$ 332.0831, found 332.0840; *m/e* 332 (M^+), 273, 258, 243, and 160.

(3*R*)-4-Isopropylidene-1-(1-(methoxycarbonyl)-2-methylprop-1-enyl)-3-phthalimido-2-azetidinone (35). A. Reaction of (3*R*)-3-Phthalimido-4-thioxo-2-azetidinone 3 with 2-Diazopropane. A solution of (3*R*)-3-phthalimido-4-thioxo-2-azetidinone **3** (1.0 g, 2.8 mmol) in CH_2Cl_2 (50 mL) was treated at 0 °C with an excess of ethereal 2-diazopropane. The excess of diazopropane was removed by a stream of argon, and the solvent was evaporated. The residue was chromatographed on silica gel (acetone–hexane) to give the thiadiazoline **29** (897 mg, 75%): mp 104–108 °C dec (CH_2Cl_2–hexane); IR ($CHCl_3$) 1790, 1780, and 1725 cm^{-1}; NMR (90 MHz, $CDCl_3$) δ 1.54 (s, CMe), 1.69 (s, CMe), 2.19 (s, C=CMe), 2.20 (s, C=CMe), 3.79 (s, OMe), 6.11 (s, azetidine H), 7.83 (m, Phth); mass spectrum, *m/e* 400 ($M^+ - N_2$), 372, 368, and 213. Anal. Calcd for $C_{20}H_{20}N_4O_5S$: C, 56.07; H, 4.71; N, 13.08. Found: C, 56.14; H, 4.74; N, 13.00.

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B. Nitrogen Extrusion from the Thiadiazoline 29. A solution of **29** (100 mg, 0.23 mmol) in benzene (2 mL) was heated at 70 °C during 30 min. Removal of the solvent followed by crystallization of the residue afforded the episulfide **31** (85 mg, 91%): mp 170–172 °C (ether–hexane); IR ($CHCl_3$) 1785, 1775, and 1725 cm^{-1}; NMR (90 MHz, $CDCl_3$) δ 1.60 (s, CMe_2), 2.30 (s, C=CMe), 2.32 (s, C=CMe), 3.78 (s, OMe), 5.69 (s, azetidine H), 7.80 (m, Phth); high-resolution mass spectrum, calcd for $C_{20}H_{20}N_2O_5S$ 400.1093, found 400.1057; *m/e* 400 (M^+), 372, 368, and 213.

Alternatively, a solution of the thiadiazoline **29** in $CHCl_3$ was kept for 5 days at room temperature. The solvent was evaporated to give the episulfide **31** (quantitative).

C. Sulfur Extrusion from the Episulfide 31. A solution of the episulfide **31** (150 mg, 0.37 mmol) and triphenylphosphine (118 mg, 0.45 mmol) in benzene (7 mL) was refluxed under argon for 24 h. The solvent was evaporated and the residue was chromatographed on preparative silica gel plates (hexane–acetone) to give **35** (130 mg, 94%): mp 126 °C (from ether–hexane); $[\alpha]^{26}_D$ +106.6° (*c* 1.1, $CHCl_3$); IR ($CHCl_3$) 1810, 1780, and 1720 cm^{-1}; NMR (90 MHz, $CDCl_3$) δ 1.50 (s) and 1.57 (s) (Me_2C=CCH), 2.27 (s) and 2.32 (s) (Me_2C=CCO_2), 3.76 (s, OMe), 5.75 (s, azetidine H), 7.81 (m, Phth); high-resolution mass spectrum, calcd for $C_{20}H_{20}N_2O_5$ 368.1371, found 368.1383; *m/e* 368 (M^+), 340, and 213.

(3*S*)-1-(1-(Diphenylmethoxy)carbonyl-2-methylprop-1-enyl)-4-isopropylidene-3-phthalimido-2-azetidinone (36). A. Reaction of (3*R*)-3-Phthalimido-4-thioxo-2-azetidinone 4 with 2-Diazopropane. (3*R*)-3-Phthalimido-4-thioxo-2-azetidinone **4** (2.5 g, 4.9 mmol) was treated with 2-diazopropane as described above for the preparation of **31** from **3**. The residue obtained after evaporation was dissolved in benzene and heated for 15 min at 70 °C to give the episulfide **32** (1.7 g, 63%): mp 156–159 °C (CH_2Cl_2–hexane); IR ($CHCl_3$) 1785, 1775, and 1720 cm^{-1}; NMR (90 MHz, $CDCl_3$) δ 1.13 (s, CMe), 1.25 (s, CMe), 2.31 (s, C=CMe), 2.33 (s, C=CMe), 5.57 (s, azetidine H), 6.89 (s, $CHPh_2$), 7.32–7.38 (m) and 7.41 (s) ($CHPh_2$), 7.80 (m, Phth); high-resolution mass spectrum, calcd for $C_{32}H_{28}N_2O_5$ 520.1998, found 520.2029 (M^+ – S); *m/e* 552 (M^+), 520, 420, 353, and 309.

B. Sulfur Extrusion from the Episulfide 32. A solution of the episulfide **32** (1.18 g, 2.1 mmol) and triphenylphosphine (688 mg, 2.6 mmol) in benzene (25 mL) was refluxed for 24 h. The residue obtained after evaporation of the solvent was chromatographed on silica gel (hexane–acetone) to give the 4-isopropylideneazetidinone **36** as a foam (920 mg, 83%): $[\alpha]^{26}_D$ +51.5° (*c* 1.0, $CHCl_3$); IR ($CHCl_3$) 1800 and 1715 cm^{-1}; NMR (90 MHz, $CDCl_3$) δ 1.31 (s) and 1.36 (s) (CHC=CMe_2), 2.28 (s) and 2.33 (s) (Me_2C=CCO_2), 5.68 (br s, azetidine H), 6.92 (s, $CHPh_2$), 7.30 (s, Ph), 7.33 (s, Ph), 7.80 (m, Phth); high-resolution mass spectrum, calcd for $C_{32}H_{28}N_2O_5$ 520.1998, found 520.1962; *m/e* 520 (M^+), 353, 309, and 213.

(3*S*)-4-Diphenylmethylidene-1-(1-(methoxycarbonyl)-2-methylprop-1-enyl)-3-phthalimido-2-azetidinone (37). A. Reaction of (3*R*)-3-Phthalimido-4-thioxo-2-azetidinone 3 with Diphenyldiazomethane. To a stirred solution of (3*R*)-3-phthalimido-4-thioxo-2-azetidinone **3** (140 mg, 0.39 mmol) and $Rh(OAc)_2$ (15 mg) in benzene (20 mL) was added at 70 °C a solution of diphenyldiazomethane (390 mg, 2.0 mmol) in benzene (20 mL) during 1.5 h. A vigorous nitrogen evolution was observed. The residue obtained after evaporation of the solvent was purified by chromatography on preparative silica gel plates (toluene–ethyl acetate) followed by trituration with ether to give the episulfide **33** (133 mg, 65%): mp 187 °C; $[\alpha]^{26}_D$ –120.2° (*c* 1.0, $CHCl_3$); IR ($CHCl_3$) 1790, 1780, and 1725 cm^{-1}; NMR (90 MHz, $CDCl_3$) δ 2.01 (s, C=CMe), 2.32 (s, C=CMe), 3.51 (s, OMe), 6.05 (s, azetidine H), 7.09–7.54 (m, CPh_2), 7.69 (m, Phth); high-resolution mass spectrum, calcd for $C_{30}H_{24}N_2O_5S$ 524.1405, found 524.1402; *m/e* 524 (M^+), 492, 369, 368, 337, and 187.

B. Sulfur Extrusion from the Episulfide 33. A solution of the episulfide **33** (10 mg, 0.02 mmol) and triphenylphosphine (6 mg, 0.02 mmol) in benzene (1 mL) was refluxed under an argon atmosphere for 8 h. Evaporation of the solvent followed by chromatography of the residue on a preparative silica gel plate (toluene–ethyl acetate) gave the azetidinone **37** (8 mg, 85%): IR ($CHCl_3$) 1805, 1785, 1730, and 1680 cm^{-1}; NMR (80 MHz, $CDCl_3$) δ 2.02 (s, C=CMe), 2.23 (s, C=CMe), 3.54 (s, OMe), 6.26 (s, azetidine H), 7.01–7.51 (m, CPh_2), 7.69 (m, Phth). Anal. Calcd for $C_{30}H_{24}N_2O_5$: C, 73.16; H, 4.91; N, 5.69. Found: C, 73.37; H, 4.89; N, 5.55.

(3*S*)-4-(Bis(ethoxycarbonyl)methylidene)-1-(1-(methoxycarbonyl)-2-methylprop-1-enyl)-3-phthalimido-2-azetidinone (38). To a solution of (3*R*)-3-phthalimido-4-thioxo-2-azetidinone **3** (1.0 g, 2.8 mmol) and $Rh(OAc)_2$ (50 mg) in benzene (50 mL) was added at 65 °C a solution of ethyl diazomalonate (2.1 g, 11.2 mmol) in benzene (50 mL) during 1 h. A vigorous evolution of nitrogen was observed. The solvent was evaporated and the residue was chromatographed on silica gel (toluene–ethyl acetate) to give the title compound **38** (785 mg, 58%): mp 127–128 °C (from methanol); $[\alpha]^{26}_D$ +132.2° (*c* 1.0, $CHCl_3$); IR ($CHCl_3$) 1830, 1780, 1730, and 1660 cm^{-1}; NMR (90 MHz, $CDCl_3$) δ 1.07 (t, J = 7 Hz, OCH_2CH_3), 1.24 (t, J = 7 Hz, OCH_2CH_3), 2.25 (s, C=CMe), 2.38 (s, C=CMe), 3.74 (s, OMe), 4.02 (q, J = 7 Hz, OCH_2CH_3), 4.10 (q, J = 7 Hz, OCH_2CH_3), 6.27 (s, azetidine H), 7.78 (m, Phth); high-resolution mass spectrum, calcd for $C_{24}H_{24}N_2O_9$ 484.1482, found 484.1530; *m/e* 484 (M^+), 397, and 379.

1-(2-(Methoxycarbonyl)-2-methylprop-1-enyl)-3-phthalimido-2,4-azetidinedione (39). A. Oxidation with *m*-Chloroperbenzoic Acid. To a stirred solution of the thiomalonimide **3** (250 mg, 0.70 mmol) in CH_2Cl_2 (50 mL) was added a solution of *m*-chloroperbenzoic acid (150 mg, 80%, 0.70 mmol) in CH_2Cl_2 (25 mL) at –50 °C during 0.5 h. After an additional 1 h the solution was washed with 5% $NaHCO_3$ and water, dried, and evaporated. The residue was chromatographed on silica gel (toluene–ethyl acetate) to give the malonimide **39** (50 mg, 21%).

B. Oxidation with Ozone. Ozone was passed through an ice-cold solution of the thiomalonimide **3** (500 mg, 1.4 mmol) in methanol (10 mL) while a white solid precipitated. After the consumption of the starting material (monitored by TLC), the excess of ozone was removed by a stream of nitrogen. The reaction mixture was concentrated, and the precipitate was filtered and recrystallized from methanol to give the malonimide **39** (380 mg, 80%): mp 175–177 °C; IR ($CHCl_3$) 1885 (vw), 1755, and 1725 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 2.21 (s, C=CMe), 2.38 (s, C=CMe), 3.80 (s, OMe), 5.93 (s, azetidine H), 7.84 (m, Phth); ^{13}C NMR ($CDCl_3$) δ 22.0 and 23.5 (Me_2C=C), 52.4 (OMe), 60.6 (CHN), 116.0 and 162.3 (C=C), 124.2, 131.5 and 135.0 (aromatic), 159.1 and 165.6 (phthalimide and malonimide carbonyls), 166.1 (CO_2); high-resolution mass spectrum, calcd for $C_{17}H_{14}N_2O_6$ 342.0851, found 342.0816; *m/e* 342 (M^+), 187, and 155.

Registry No. **1**, 72726-92-2; **2**, 61222-75-1; (±)-**3**, 72777-02-7; (3*R*)-**3**, 61256-95-9; (3*R*)-**4**, 72726-95-5; **8**, 72727-35-6; **9**, isomer 1, 72727-36-7; **9**, isomer 2, 72727-37-8; **11**, 65223-00-9; **12**, 72727-38-9; **13**, 72727-39-0; **14**, 72727-40-3; **17**, 72727-41-4; **26**, 72727-42-5; **29**, 69939-43-1; **31**, 69939-44-2; **32**, 72727-43-6; **33**, 72727-44-7; (3*S*)-**35**, 69939-46-4; (3*S*)-**36**, 72727-45-8; (3*S*)-**37**, 72727-46-9; (3*S*)-**38**, 72727-47-0; **39**, 69939-41-9; 2-diazopropane, 2684-60-8; diphenyldiazomethane, 883-40-9; ethyl diazomalonate, 5256-74-6; *N*-hydroxysuccinimide, 6066-82-6.