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REACTIONS OF 4-THIOXO-2-AZETIDINONES: SYNTHESIS OF A 2,4-AZETIDINEDIONE AND OF 4-ALKYLIDENE-2-AZETIDINONES

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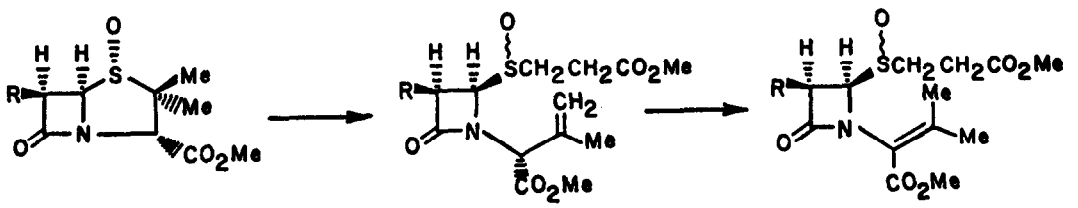
The synthesis[2-5] and some reactions[5-7] of 4-thioxo-2-azetidinones, a novel class of compounds, have been recently reported. The reactions hitherto described generally involve an initial attack of a nucleophile at the extremely sensitive amide bond, yielding products of ring cleavage. We have now found that some 1,3-dipolar reagents attack selectively at the thiocarbonyl functionality of the 4-thioxo-2-azetidinone 4, to afford compounds in which the four-membered ring remains intact. Thus, ozonolysis of 4 yields a 2,4-azetidinedione (malonimide) showing a novel substitution pattern, while its reaction with diazoalkanes provides a route to 4-alkylidene-2-azetidinones.

The phthalimidopenicillin sulfoxide 1 was heated in an excess of methyl acrylate to give the monocyclic sulfoxide 2 as a 2:1 (by NMR) mixture of isomers. Treatment of 2 with triethylamine caused migration of the double bond to afford the conjugated esters 3. Silica gel chromatography (toluene/ethyl acetate) yielded 60% (from 1) of the less polar isomer of 3, m.p. 135-136°,



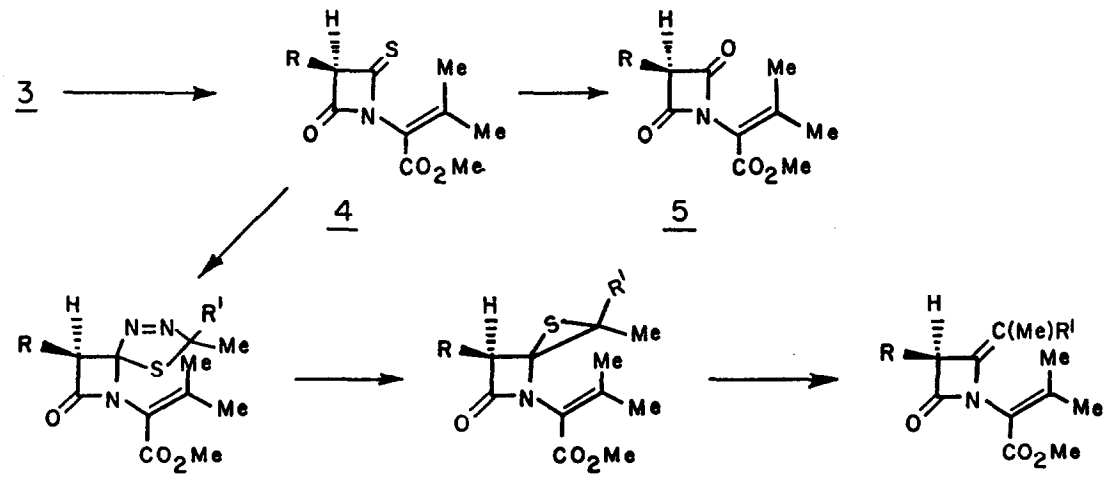
1 2 3

$[\alpha]_D$ +77.3° (c 1.0 $CHCl_3$). NMR δ ($CDCl_3$) 2.27 (3H, s) and 2.33 (3H, s) (Me_2C=C), 2.69-2.91 (4H, CH_2CH_2), 3.68 (3H, s, CH_2CO_2Me), 3.84 (3H, s, CO_2Me), 5.08 (1H, d, J=5 Hz, azetidinone 3-H), 5.88 (1H, d, J=5 Hz, azetidinone 4-H), 7.82 (4H, m, aromatic); ν_{max} ($CHCl_3$) 1780 (br) and 1720 (br) cm^{-1}. The more polar isomer of 3 accounts for 30% (from 1), m.p. 128-130°, $[\alpha]_D$ +30.3° (c 1.0 $CHCl_3$). NMR δ ($CDCl_3$) 2.31 (3H, s) and 2.39 (3H, s) (Me_2C=C), 2.74 (4H, s, CH_2CH_2), 3.42 (3H, s, CH_2CO_2Me), 3.81 (3H, s, CO_2Me), 5.14 (1H, d, J=5 Hz, azetidinone 3-H), 5.70 (1H, d, J=5 Hz, azetidinone 4-H), 7.83 (4H, m, aromatic); ν_{max}($CHCl_3$)1785 (br) and 1720 (br) cm^{-1}. Both isomers of the sulfoxide 3 were converted into the 4-thioxo-2-azetidinone 4[2,3] (80%) upon thermolysis in boiling benzene.

Ozonolysis of 4 (methanol, 0°) resulted in the formation of the 2,4-azetidinedione 5 (85%), m.p. 175-177°, $[\alpha]_D$ +3.1° (c 1.0 $CHCl_3$). NMR δ ($CDCl_3$) 2.21 (3H, s) and 2.38 (3H, s) (Me_2C=C),

3.80 (3H, s, CO_2Me), 5.93 (1H, s, azetidinedione H), 7.84 (4H, m, aromatic); ν_{max} ($CHCl_3$) 1885 (vw), 1755, and 1725 cm^{-1}; mass spectrum m/e 342 (M^+). The conversion of the 4-thioxo-2-azetidinone 4 into the 2,4-azetidinedione 5 could also be effected, albeit in a lower yield (25%), by m-chloroperbenzoic acid in dichloromethane at -50°. Compound 5 constitutes the first example of a malonimide bearing an imido group at C-3. 3-Acylaminomalonimides have been suggested as potential acylating agents capable of exerting antibacterial activity similar to that of the β-lactam antibiotics.[9] However, attempts to prepare compounds of this type via the known routes to 3-alkyl- or arylmalonimides have failed.[9]

The 1,3-addition of diazoalkanes to thioketones giving rise to thiadiazolines is well documented.[10] Thiadiazolines lose nitrogen, either spontaneously or upon heating, to give the corresponding thiirans.[10,11] It was anticipated that the thiocarbonyl group of the 4-thioxo-2-azetidinone 4 would react in a similar manner. Thus, addition of an ethereal solution of diazoethane to a solution of 4 in dichloromethane at 0° produced a mixture of the thiiran 8 and an unstable product, probably the thiadiazoline 6. Compound 8 m.p. 151-153°, was isolated (45%) as



R = Phthalimido

6 R' = H 8 R' = H 10 R' = H

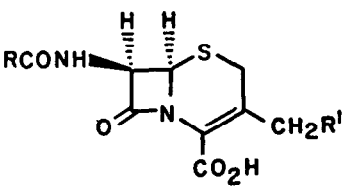
7 R' = Me 9 R' = Me 11 R' = Me

the sole product by means of thick layer chromatography. NMR δ ($CDCl_3$) 1.55 (1H, d, J=6 Hz, thiiran Me), 2.24 (3H, s) and 2.30 (3H, s) ($Me_2C=C$), 3.03 (1H, q, J=6 Hz, thiiran H), 3.79 (3H, s, CO_2Me), 5.69 (1H, s, azetidinone H), 7.81 (4H, m, aromatic); ν_{max} ($CHCl_3$) 1790, 1780, and 1730 cm^{-1}; mass spectrum m/e 386 (M^+). Treatment of the 4-thioxo-2-azetidinone 4 with an excess of 2-diazopropane (ether/dichloromethane, 0°) afforded 75% of a thiadiazoline, m.p. 104-108° (dec), to which structure 7 was assigned.[12] NMR δ ($CDCl_3$) 1.54 (3H, s) and 1.69 (3H, s) (two thiadiazoline Me), 2.19 (s) and 2.20 (s) (6H, $Me_2C=C$), 3.79 (3H, s, CO_2Me), 6.11 (1H, s, azetidinone H), 7.83 (4H, m, aromatic); ν_{max} ($CHCl_3$) 1790, 1780, and 1725 cm^{-1}; the elemental analysis corresponds to $C_{20}H_{20}N_4O_5S$. The thiadiazoline 7 is stable at 0° in the solid state;

when left in deuteriochloroform or benzene solution at ambient temperature during five days, it is quantitatively converted into the thiiran 9, m.p. 170-172°. NMR δ ($CDCl_3$) 1.60 (6H, s, two thiiran Me), 2.30 (s) and 2.32 (s) (6H, Me_2C=C), 3.78 (3H, s, CO_2Me), 5.69 (1H, s, azetidinone H), 7.80 (4H, m, aromatic); ν_{max} ($CHCl_3$) 1785, 1775, and 1725 cm^{-1}; mass spectrum m/e 400 (M^+).

Each of the thiirans 8 and 9 was heated in boiling benzene with 1.2 equ. of triphenylphosphine to yield the respective 4-alkylidene-2-azetidinones 10 (95%), m.p. 114-116°, $[\alpha]_D$ +39.1° (c 0.94 $CHCl_3$), and 11 (95%), m.p. 126°, $[\alpha]_D$ =+106.6° (c 1.1 $CHCl_3$). The azetidinone carbonyl of 10 absorbs in the IR($CHCl_3$)at 1810cm^{-1} and that of 11 at 1800cm^{-1}. NMR of 10 δ ($CDCl_3$) 1.52 (3H, d, J=7 Hz, MeCH=C), 2.18 (3H, s) and 2.31 (3H, s) (Me_2C=C), 3.77 (3H, s, CO_2Me), 4.69 (1H, dq, J=1.5 and 7 Hz, HC=C), 5.83 (1H, br, s, azetidinone H), 7.82 (4H, m, aromatic); mass spectrum m/e 354 (M^+). NMR of 11 δ ($CDCl_3$) 1.50 (s, 3H) and 1.57 (s, 3H) (Me_2C=CCH), 2.27 (3H, s) and 2.32 (3H, s) (Me_2C=CCO_2Me), 3.76 (3H, s, CO_2Me), 5.75 (1H, s, azetidinone H), 7.81 (4H, m, aromatic); mass spectrum m/e 368 (M^+).

The antibacterial activity of Δ^3-cephalosporins (12), in contradistinction to the inactivity of their Δ^2-isomers (13), has been attributed to the increased reactivity of their β-lactam amide bond. It has been suggested[13] that the lability of this bond is due to the decrease of



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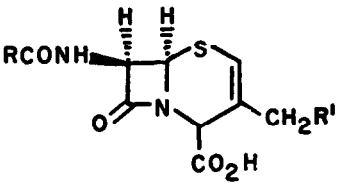

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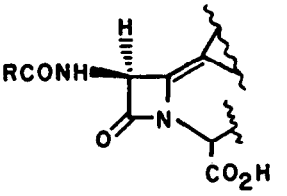

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the amide resonance resulting from the delocalization of the unshared electron pair on the nitrogen atom into the adjacent olefinic system. It is therefore of interest to examine the biological activity of 4-alkylidene-β-lactams of type 14 which comprise a similar, though differently oriented, enamine system. The synthesis of the β-lactams 10 and 11 offers a convenient access to this class of compounds.

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12. The isomeric Δ^2-1,2,3-thiadiazoline structure cannot be ruled out. It has, however, been shown[10] that reactions of some thioketones with diazo compounds yield Δ^3-1,3,4-thiadiazolines analogous to 7.

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