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# REACTIONS AND PROPERTIES OF AZETIDIN-2-OXO-4-THIONES

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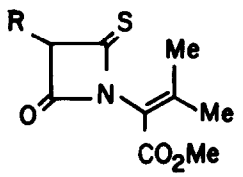
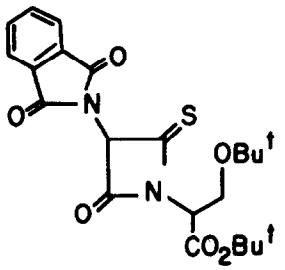
Azetidin-2-oxo-4-thiones, which are imides of substituted thiomalonic acid, have been recently discovered as a result of studies on compounds related to penicillins and cephalosporins pursued in this[1] and in two other laboratories.[2,3] We now describe some properties and reactions of two representatives of this novel class of compounds.

The azetidin-2-oxo-4-thiones 1a and 2 exhibit in their infrared spectra a strong band at 1830 $cm^{-1}$.[1] This frequency is 70-90 $cm^{-1}$ higher than the carbonyl frequency in non-fused β-lactams, and 40-60 $cm^{-1}$ higher than the corresponding frequency in the strained fused bicyclic β-lactam antibiotics.[4] The infrared carbonyl frequency of β-lactams has been taken as an indicator for the degree of resonance stabilization of the amide bond[5] and for its chemical activity.[6] A positive correlation was found between the rate constants of base hydrolysis and IR carbonyl frequencies in various β-lactams.[6] In agreement with this relationship the azetidin-2-oxo-4-thiones 1a and 2 proved to be highly susceptible to hydrolysis and alcoholysis.

Treatment of the thiomalonimide 1a with a suspension of silica gel in chloroform (2 days) gave the thiazoline 4 (quantitative), m.p. 147-8° (from methylene dichloride-hexane). NMR δ ($CDCl_3$) 1.38 (s, Me), 1.69 (s, Me), 3.80 (s, OMe), 4.74 br ($NCH_2$ and NCH), and 7.90 (m, aromatic); $\nu_{max}$ ($CHCl_3$) 1770, 1740, 1720 and 1610 $cm^{-1}$; mass spectrum m/e ($M^+$ 332). This transformation involves a silica gel catalyzed hydrolysis by the water present in the medium to the intermediate 3a which undergoes spontaneous decarboxylation and cyclization to the thiazoline 4 as shown by the arrows a. The same transformation occurred when the silica gel was replaced by triethylamine (0.1 equivalents $Et_3N$, 2 days). Under similar conditions the thiomalonimide 2 was converted into the thioamide 6a.[7] It has been reported[8] that a number of



1



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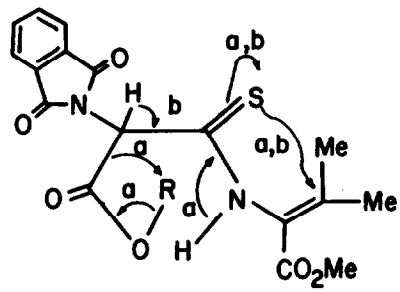

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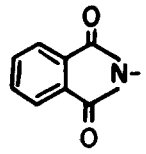
a; R = 

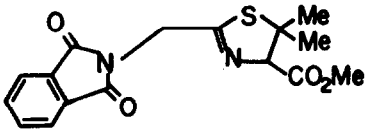
b; R = PhOCH$_2$CONH

a; R = H

b; R = Me

thiomalonimides of type 1 (e.g. 1b) are converted by treatment with silica gel or triethylamine into the corresponding dehydropenicillins to which structure 5 (e.g. 5b) was assigned. By analogy compound 1a should have been converted into 5a, in our hands however this transformation did not occur.

Treatment of the thiomalonimide 1a (165 mg) with triethylamine (2 drops) in absolute methanol (10 ml) for 5 min, afforded, after preparative t.l.c., two compounds of the same molecular weight [m/e 390 ($M^+$)]. Structure 7 was assigned to the less polar compound (m.p. 203°C, 61%): NMR δ ($CDCl_3$) 1.45 (s, Me), 1.68 (s, Me), 3.64 (s, OMe), 3.87 (s, OMe), 4.63 (s, $NCHCO_2$), 7.90 (m, aromatic H), and 8.60 br (NH)(disappears after addition of $D_2O$); $\nu_{max}$ ($CHCl_3$) 1780, 1745, 1720, and 1660 $cm^{-1}$; $\lambda_{max}$ ($CHCl_3$) 284 nm (ε 24800). Strcture 8a was attributed to the more polar compound (m.p. 152°C, 20%), NMR δ ($CDCl_3$) 1.50 (s, Me), 1.76 (s, Me), 3.84 (s, OMe), 3.92 (s, OMe), 4.61 (s, $NCHCO_2$), 7.60 (3H, m, aromatic H) and 7.90 (2H, m, aromatic and NH) (1H, m, after addition of $D_2O$); $\nu_{max}$ ($CHCl_3$), 1745 sh, 1730 sh, 1720, and 1620 $cm^{-1}$, $\lambda_{max}$ ($CHCl_3$), 361 nm (ε 27100). The major product 7 is thus obtained by a nucleophilic attack of methanol at C-2 to give 3b, which undergoes spontaneous ring closure to the thiazolidine 7 as shown by the arrows b. The formation of 8a requires a competitive methanolysis of the phthalimido group in 1a to the phthaleamic ester 9 which rearranges to the thiazolidylideneoxazolone 8a. A similar intramolecular



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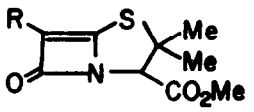

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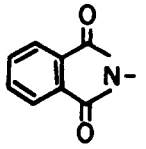
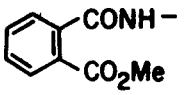
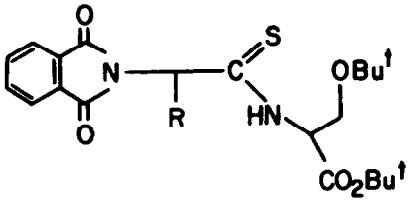
a;R= 

C;R= 

b;R=PhOCH$_2$CONH-



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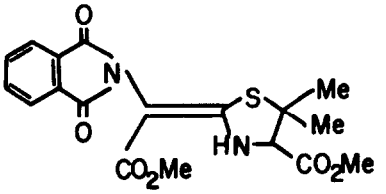
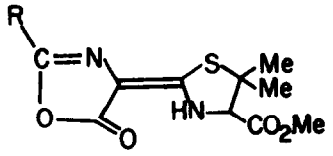


7

a; R=H

b; R=CO$_2$Me



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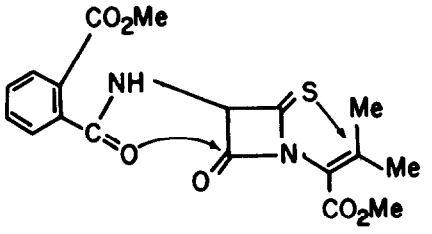

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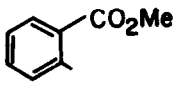
a;R= 

b;R=PhOCH$_2$-

rearrangement in which the azetidinone ring is cleaved by a neighbouring acylamino group occurs in many penicillins.[9]

The assignment of structure 8a to the more polar compound is corroborated by comparison of its UV spectrum with the spectra of other thiazolidylideneoxazolones of structure 8 prepared by a different route,[10] and with those of 4-(1-thioalkylidene)- and 4-(1-aminoalkylidene)oxazolones.[11] The three infrared absorption bands in the carbonyl region account for two esters and one oxazolone.[12] These spectral data are incompatible with the isomeric strained structure 5c which if existed would require a higher IR C=O frequency[5] as well as a shift to a shorter wave length in the UV region.[13] The spectral data of 8a are similar to those of the "dehydropenicillin" to which Re and co-workers[8] attributed the bicyclic unsaturated β-lactam structure 5b; we propose structure 8b for this last compound.

Methanolysis of 2 (MeOH, 0.1 equivalent $Et_3N$, 20 min) afforded the thioamide 6b.[7] The thiomalonimide 1a was not affected by heating up to 155°C ($CHCl_3$, sealed tube, 3 h). It is remarkably stable to acidic conditions. Thus, 1a was recovered unchanged after treatment with trifluoroacetic acid (30 min, room temperature) or with aqueous acetic acid (40 h, room temperature).

References and Notes

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4. For ir data on β-lactams see: P.V. Demarco and R. Nagarajan, "Cephalosporins and Penicillins. Chemistry and Biology", E.H. Flynn, Ed., Academic Press, New York, N.Y., 1972, p. 311.
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7. N.m.r., i.r., and mass spectra gave correct values.
8. A. Brandt, L. Bassignani and L. Re, Tetrahedron Letters, 3979 (1976).
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11. D.C. Cook and A. Lawson, J.Chem.Soc.,Perkin Trans 1, 465 (1973).
12. When no conjugated substituents are attached to the ring of $\Delta^2$-oxazolin-5-ones the C=O and C=N frequencies are found respectively at 1820 and 1670 $cm^{-1}$. These frequencies decrease on attachment of an exocyclic double bond at position 4 and may reach values as low as 1700 $cm^{-1}$ for the carbonyl and 1620 $cm^{-1}$ for the C=N grouping. See: E. Baltazzi, Quart. Rev., 150 (1955), and ref. 11.
13. Presumably the UV spectrum of a hypothetical 5c should be similar to that of 7.