Tetrahedron Letters No. 44, pp 3975 - 3978, 1976. Pergamon Press. Printed in Great Britain.

SYNTHESIS OF A NOVEL CLASS OF 2-AZETIDINONES: 4-THIOXO-2-AZETIDINONES. CONVERSION TO A 1,2-SECO-5,6-DEHYDROPENICILLIN

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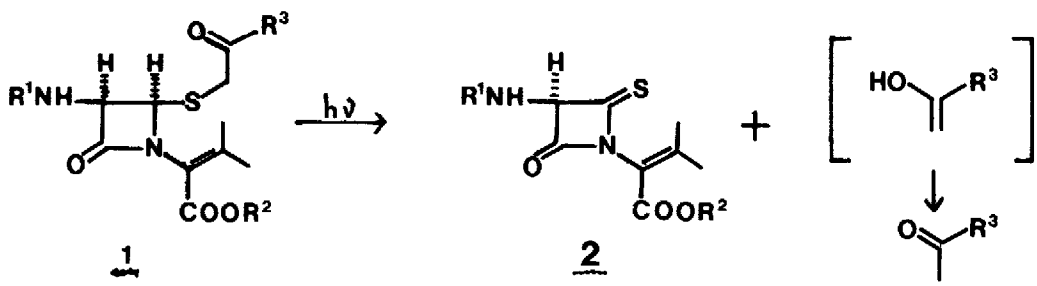
(Received in UK 30 March 1976; accepted for publication 16 September 1976)

In the present communication we report the synthesis of the 4-thioxo-2-azetidinones 2 and 4, the first examples of 2-azetidinones carrying a 4-thioxo group. The conversion of two of these derivatives (2a and 4a) to a 1,2-seco-5,6-dehydropenicillin (6) is also reported, and it represents the first route to 1,2-secopenicillins with an unsaturated β-lactam structure. Derivatives of type 2 and 4 are also, as reported in the accompanying paper[1], the direct synthetic precursor of the novel DL-5,6-dehydropenicillins.

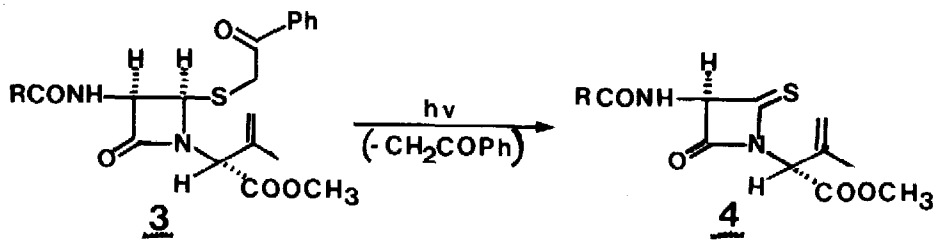
The 4-thioxo-2-azetidinones 2 and 4 were obtained, by a Norrish type II photoelimination reaction, on irradiation of the corresponding 4-acylmethylthio-2-azetidinones 1 and 3 with uv light.



1 2

a: R^1= $PhOCH_2CO$; R^2= CH_3; R^3= Ph
b: R^1= $PhOCH_2CO$; R^2= CH_2Ph; R^3= Ph
c: R^1= Ph_3C; R^2= CH_3; R^3= Ph
d: R^1= CH_3CO; R^2= CH_3; R^3= Ph
e: R^1= CH_3CO; R^2= CH_3; R^3= CH_3

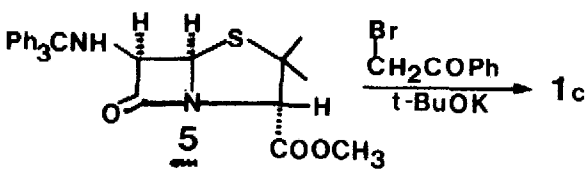
a: R^1= $PhOCH_2CO$; R^2= CH_3
b: R^1= $PhOCH_2CO$; R^2= CH_2Ph
c: R^1= Ph_3C; R^2= CH_3
d: R^1= CH_3CO; R^2= CH_3

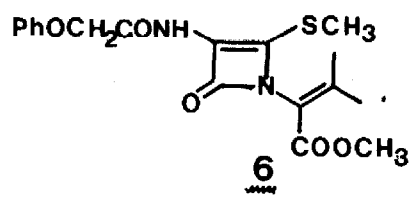


a: R = $PhOCH_2$

b: R = CH_3

Derivatives of type 1, except when substituted as in 1c (R^1 = acyl with R^3 = aryl), and the ones of type 3 have been prepared from esters of penicillins[2], penicillin sulfoxides[3] or 6β-triphenylmethylaminopenicillanic acid[4] or from substituted 4-thia-2,6-diazabicyclo[3.2.0]hept-2-en-7-ones[5] or by total synthesis[5a]. For the synthesis of 1c we developed an original, one-step, procedure from methyl 6β-triphenylmethylaminopenicillanate (5)[6]: To a stirred solution of 5 (3.78 g, 8.0 mmol) and phenacyl bromide (1.75 g, 8.8 mmol) in THF (30 ml) was added over a 30 min period, at -40° and under nitrogen, a solution of t-BuOK (0.898 g, 8.0 mmol) in THF (40 ml). After





additional 5 hr stirring at -40°, the neutralized (AcOH diluted with THF) and filtered solution was concentrated under vacuum, and the residue separated by silica gel chromatography (C_6H_6:EtOAc, 20:1) into unchanged 5 (1.71 g, 45% recovery) and pure (t.l.c.) 4-phenacylthio-2-azetidinone 1c (white foam, 1.52 g, 59% yield based on recovered 5): ir ($CHCl_3$) 1760 (β-lactam CO), 1720 (ester CO), 1673 (phenacyl CO), 1625 cm^{-1} (C=C); nmr[7] ($CDCl_3$) δ 1.83 (3H,s) and 2.03 (3H,s) [$C=C(CH_3)_2$], 3.00 (1H,d, J=8Hz, NH), 3.42 (2H,q, J=14Hz, SCH_2), 3.80 (3H,s, $COOCH_3$) 4.60 (1H, q, J=4 and 8Hz, 3-H), 4.92 (1H,d, J=4Hz, 4-H), 6.90-7.90(20 H,m, aromatic); m/e 590, 485,347,243,228,155,105,77,68[8].

For the preparation of the 4-thioxo-2-azetidinones 2 and 4 from the corresponding 4-acylmethylthio-2-azetidinones 1 and 3 a typical procedure was as follows. A deoxygenated stirred solution of 1a[9] (0.965 g) in CH_3CN (150 ml) was ir-

radiated, at room temperature and under nitrogen, with a Hanovia 500-W medium-pressure mercury lamp through a Pyrex filter for 45 min. Removal under vacuum of the solvent and of the formed acetophenone (0.1 mm, room temperature) afforded glassy 2a (0.645 g, 89% yield) contaminated with ~10% starting material. The product[10], not crystallizable and unstable on chromatography, was sufficiently pure for the next step and for its spectrometric characterization: ir ($CHCl_3$) 1820 (β-lactam CO), 1720 (ester CO), 1682 (amide CO), 1635 cm^{-1} (sh, C=C); nmr ($CDCl_3$) δ 2.06 (3H,s) and 2.28 (3H,s) [$C=C(CH_3)_2$], 3.80 (3H,s $COOCH_3$), 4.36 (2H,s, OCH_2CO), 4.91 (1H,d, J=8Hz, 3-H), 6.60-7.60 (5H,m, aromatic), 7.94 (1H,d, J=8Hz, NH). Similarly were prepared the other thioxo derivatives. Derivative 2b was obtained from 1b[9] (86% yield) as a glass: ir practically matching the one of 2a; nmr ($CDCl_3$) δ 2.06 (3H,s) and 2.28 (3H,s) [$C=C(CH_3)_2$], 4.33 (2H,s, OCH_2CO), 4.91 (1H,d, J=8Hz, 3-H), 5.17 (2H,s, $COOCH_2$), 6.60-7.60 (10 H,m, aromatic), 7.94 (1H,d, J=8Hz, NH). Derivative 2c was obtained from 1c (81% yield) as a foam, and was the only thioxo compound that could be purified (prep. silica gel t.l.c. eluting with C_6H_6:EtOAc, 20:1), giving in low yield a white foam: ir ($CHCl_3$) 1810 (β-lactam CO), 1720 (ester CO), 1620 cm^{-1} (sh, C=C); nmr ($CDCl_3$) δ 1.81 (3H,s) and 2.26 (3H,s) [$C=C(CH_3)_2$], 2.80 (1H,d, J=8Hz, NH), 3.67 (3H,s, $COOCH_3$), 4.75 (1H,d, J=8Hz, 3-H), 7.10-7.70 (15H,m, aromatic); $[\alpha]_D^{25}$ -1.4° (c= 1.00, $CHCl_3$)[8]. Derivative 2d was obtained from 1d[9] (85% yield) as a glass: ir ($CHCl_3$) 1820 (β-lactam CO), 1722 (ester CO), 1675 (amide CO), 1635 cm^{-1} (C=C); nmr ($CDCl_3$) δ 2.00 (3H,s) and 2.32 (3H,s) [$C=C(CH_3)_2$], 2.08 (3H,s, CH_3CO), 3.73 (3H,s, $COOCH_3$), 4.93 (1H,d, J=8Hz, 3-H), 7.53 (1H,d, J=8Hz, NH). Derivative 2d was obtained also from 1e[11] (using a Corex filter and irradiating for 4 hr) but in this case the crude, gummy, product was of low purity (~40% pure as judged by ir and nmr; yield corrected for pure 2d: ~37%); partial purification of the latter by repeated precipitations from Et_2O-petroleum ether afforded, in very low yield, a gummy poduct whose structure 2d was confirmed by comparing its ir and nmr spectra to the ones of the product obtained from 1d. Derivative 4a was obtained from 3a[9] (80% yield) as a glass: ir ($CHCl_3$) 1820 (β-lactam CO), 1740 (ester CO), 1680 cm^{-1} (amide CO); nmr ($CDCl_3$) δ 1.85 (3H,s, $C=CCH_3$), 3.75 (3H,s, $COOCH_3$), 4.48 (2H,s, OCH_2CO), 5.06-5.60 (4H,m, $CH_2=C$, 3-H, and CHCOO), 6.70-7.90 (5H,m, aromatic), 8.05 (1H,d, J=8Hz, NH). Derivative 4b was obtained from 3b[9] (78.5% yield) as a glass: ir ($CHCl_3$) 1818 (β-lactam CO), 1740 (ester CO), 1670 cm^{-1} (amide CO); nmr ($CDCl_3$) δ 1.88 (3H,s, $C=CCH_3$), 2.07 (3H,s, CH_3CO), 3.80 (3H,s, $COOCH_3$), 4.90-5.25 (4H,m, $CH_2=C$, 3-H, and CHCOO), 7.50 (1H,d, J=8Hz, NH).

The possibility of converting a derivative of type 2 or 4 to a 1,2-seco-5,6-

dehydropenicillin was demonstrated on substrates 2a and 4a which, on treatment with Et_3N and excess methyl iodide, gave the seco derivative 6 as follows. A solution of the crude 2a or 4a (0.181 g, 0.5 mmol) in CH_2Cl_2 (10 ml) was treated at room temperature and under nitrogen for 3 hr with CH_3I (0.156 ml, 2.5 mmol) and Et_3N (0.07 ml, 0.5 mmol). Prep. silica gel t.l.c. (C_6H_6:EtOAc, 4:1) of the residue obtained on concentration under vacuum gave pure 2-methylthio-2-azetin-4-one derivative 6 (0.098 g, 52% yield from 2a; 0.050 g, 26.5% yield from 4a) as a white amorphous solid which cristallized from Et_2O: mp 86-87.5°; ir ($CHCl_3$) 1715 (v. br., ester and unsat. β-lactam CO), 1635 (sh, C=C), 1622 cm^{-1}(amide CO);[12] nmr ($CDCl_3$) δ 1.91 (3H,s) and 2.25 (3H,s) [C=C(CH_3)$_2$], 2.75 (3H,s, SCH_3), 3.70 (3H,s, $COOCH_3$), 4.85[13] (2H,s,OCH_2CO), 7.00-8.00 (6H,m, aromatic and NH); m/e 376,283,235,223,193,181,94[8,14].

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(5) (a) R. Lattrell, Justus Liebigs Ann. Chem., 1361 (1974); (b) Glaxo Laboratories Ltd., Ger. Offen., 2,138,320 (1972); Chem. Abstr., 77, 61987p (1972).
(6) J.C. Sheehan and K.R. Henery-Logan, J.Am.Chem.Soc., 84, 2983 (1962).
(7) The 60-MHz nmr spectra were recorded on a Varian T-60 using TMS as internal standard. The mass spectra were obtained using a Varian Mat 111 instrument.
(8) Elemental analysis gave proper values.
(9) Prepared in ~70% yield from the corresponding substituted 4-thia-2,6-diazabicyclo [3.2.0.] hept-2-en-7-one and phenacyl bromide in analogy to the procedures described under ref.5.
(10) All the thioxo derivatives synthesized gave, contrary to their immediate precursors, an instantaneous reaction in the iodine-azide spot test for thiocarbonyl compounds (F. Feigl, "Spot Tests in Organic Analysis", 7th engl. ed, Elsevier, Amsterdam, 1966, pp 219-222).
(11) Prepared in four steps and in ~20% overall yield starting from 5 and prop-2-ynyl bromide, in analogy to the procedure described under ref. 4 for the preparation of an analogue.
(12) Ir (KBr) 1720 (ester CO), 1689 (unsat. β-lactam CO), 1630 (sh, C=C) 1618 cm^{-1} (amide CO). A shift of the β-lactam carbonyl stretching vibration at lower wavelenght following the introduction of a double bond in the β-lactam ring has already been reported (see refs. 3d and 3e cited in the accompanying paper[1]). The larger shift found here from the value observed for a saturated β-lactam analogue [J.P. Clayton, J.H.C. Nayler, R. Southgate, and P. Tolliday, Chem.Comm. 590 (1971)] is attributed to a stronger conjugative effect.
(13) This higher value as compared to the one observed by Clayton et al. (see ref. cited under note 12) for a saturated β-lactam analogue is in line with the presence of the double bond in the β-lactam ring of 6: compare the CH_3 resonance of $PhCH_2CH(NHCOCH_3)COOH$ and $PhCH{=}C(NHCOCH_3)COOH$ found at δ 1.89 (Aldrich Library of NMR Spectra, Vol.VII, 4C) and 2.05 [T.P. Dang, J.-C. Poulin, and H.B. Kagan, J.Organometal.Chem., 91, 105 (1975)] respectively.
(14) The structure of 6 has been confirmed by high-resolution mass-spectrometry and ^{13}C nmr studies (to be published).