Tetrahedron Letters No. 44, pp 3979 - 3982, 1976. Pergamon Press. Printed in Great Britain.

SYNTHESIS OF A NOVEL CLASS OF PENICILLINS: DL-5,6-DEHYDROPENICILLINS

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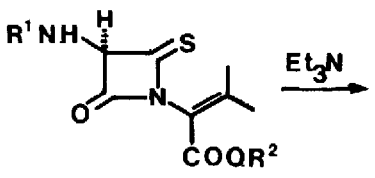
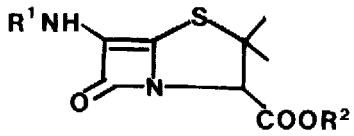
(Received in UK 30 March 1976; accepted for publication 16 September 1976)

In the foregoing paper[1] we described the synthesis of the 4-thioxo-2-azetidinones 1, 3 and the phenoxyacetamido analogue of 3 by irradiation of the corresponding 4-acylmethylthio-2-azetidinones. In the same paper we reported, furthermore, that alkylation of either 1a or the phenoxyacetamido analogue of 3 with Et_3N and excess methyl iodide affords the 1,2-seco-5,6-dehydropenicillin derivative 4. In the present communication we wish to report that derivatives 1 and 3, when treated with Et_3N alone, undergo an intramolecular alkylation to afford esters of DL-5,6-dehydropenicillins ("dehydropenicillins")(2)[2].



1

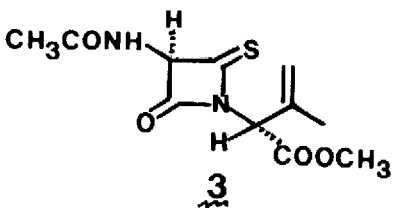
Et_3N



2

(DL-form)

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



3

Et_3N → [1d] → 2d

Derivatives 2 represent not only a novel class of penicillins but also the first examples of bicyclic 2-azetin-4-one derivatives, the few authentic 2-azetin-4-ones previously reported[1,3] being of the monocyclic type.

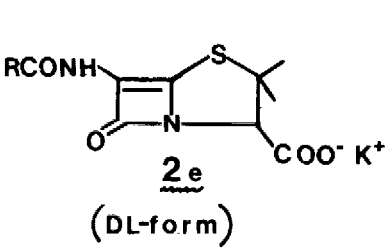
With one substrate of type 1 (1a), alternative cyclizations by silica gel or thermic treatment were also attempted, and shown to occur, but the yields of dehydropenicillin derivative (2a) were quite lower. On the other hand, when the two

latter cyclization procedures were applied to 3, practically no 2d was formed.

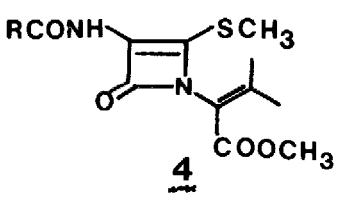
For the preparation of DL-dehydropenicillin esters 2 from the crude 4-thioxo-2-azetidinones 1[1] or 3[1] by Et_3N treatment a typical procedure was as follows. A solution of 1a (0.645 g) and Et_3N (0.08 ml) in CH_2Cl_2 (30 ml) was stirred under nitrogen and at room temperature until disappearance of 1a (~4 hr; ir monitoring: disappearance of the typical 1820 cm^{-1} band[1]). Concentration under vacuum, and silica gel chromatography (C_6H_6:EtOAc, 4:1) of the residue afforded pure (t.l.c) 2a (0.460 g, 71% yield) as a white amorphous solid which crystallized from Et_2O-petroleum ether: mp 138-139°; uv (EtOH) 220 (log ε 3.88), 245 (3.87), 328 nm (4.41); ir ($CHCl_3$) 1742 (ester CO), 1720[5] (unsat. β-lactam CO), 1630 cm^{-1} (amide CO); nmr[4] ($CDCl_3$) δ 1.47 (3H,s) and 1.73 (3H,s) $[C(CH_3)_2]$, 3.80 (3H,s, $COOCH_3$), 4.52 (1H,s, 3-H), 4.80[5] (2H,s, OCH_2CO), 6.80-7.50 (5H,m, aromatic), 7.85 (1H,br.s, NH); m/e 362,269,209,199,167,139,94,66[6]. Similarly were prepared the other DL-dehydropenicillin esters. Pure (t.l.c.) 2b was obtained from 1b (72.5% yield) as a white amorphous solid: mp 129-131° after crystallization from Et_2O-petroleum ether; ir practically matching the one of 2a; nmr ($CDCl_3$) δ 1.35 (3H,s) and 1.63 (3H,s) $[C(CH_3)_2]$, 4.50 (1H,s, 3-H), 4.80 (2H,s, OCH_2CO), 5.18 (2H,s, $COOCH_2$), 6.70-7.50 (10H,m, aromatic), 7.85 (1H,br.s, NH); m/e 439,438,345,303,209,94,91,66[6]. Pure (t.l.c.) 2c was obtained from 1c (23% yield after 24 hr reaction and neutral alumina chromatography eluting with C_6H_6) as a white, not very stable and not crystallizable, foamy product: ir ($CHCl_3$) 1750 (ester CO), 1730 cm^{-1} (unsat. β-lactam CO); nmr ($CDCl_3$) δ 1.35 (3H,s) and 1.72 (3H,s) $[C(CH_3)_2]$, 3.20 (1H,br.s, NH), 3.80 (3H,s, $COOCH_3$), 4.58 (1H,s, 3-H), 7.10-7.68 (15H,m, aromatic)[6]. Pure (t.l.c.) 2d was obtained from 1d (50% yield) or from 3 (32% yield) as a glass [isolation of the pure product was by silica gel chromatography (Et_2O:EtOAc, 2:1) when starting from 1d prepared from the corresponding 4-phenacylthio-2-azetidinone[1], and by prep. silica gel t.l.c. (Et_2O:EtOAc, 3:1) when starting from 3 or from the ~40% pure 1d prepared from the corresponding 4-acetonylthio-2-azetidinone[1]]: mp 98-100° after crystallization from Et_2O-petroleum ether; ir ($CHCl_3$) 1740 (ester CO), 1715 (unsat. β-lactam CO), 1630 cm^{-1} (amide CO); nmr ($CDCl_3$) δ 1.47 (3H,s) and 1.75 (3H,s) $[C(CH_3)_2]$, 2.20 (3H,s, CH_3CO), 3.80 (3H,s, $COOCH_3$), 4.48 (1H,s, 3-H), 7.60 (1H,br.s, NH); m/e 270,238,211,199,167,139,98,59[6].

Cyclization of the crude 1a (0.100 g) by stirring overnight at room temperature with silica gel (~5 g) in $CHCl_3$ (10 ml) or by heating at 90-100° for 10 hr in tetrachloroethylene (10 ml) gave, after concentration of the solution under vacuum and prep. silica gel t.l.c. (C_6H_6:EtOAc, 7:3), 2a in 38% yield.

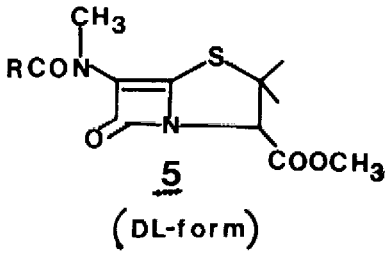
Benzyl ester 2b was converted to DL-dehydropenicillin V potassium salt (2e) as follows. A solution of 2b (0.438 g) in EtOH:EtOAc (4:1,20 ml) was hydrogenated for 70 min at 1 atm and with 10% Pd/C (0.87 g, added in two equal portions, the second being added after 30 min hydrogenation and removal of the first portion by filtration). Addition of stoichiometric 5% aq. $KHCO_3$ (to pH 7.8-8.0) to the filtered cooled (0°) solution, concentration under vacuum, treatment of the residue with EtOAc and final precipitation of the product by addition of Et_2O to the filtered EtOAc solution afforded 2e (0.330 g, 85% yield) as a white solid: ir (KBr) 1705[7] (unsat. β-lactam CO), 1620[7] (amide CO), 1602 cm^{-1} (br., carboxylate CO); nmr (CD_3OD) δ 1.51 (3H,s) and 1.76 (3H,s) $\left[C(CH_3)_2\right]$, 4.38 (1H,s, 3-H), 4.86 (2H,s, OCH_2CO), 6.85-7.40 (5H,m, aromatic). Derivative 2e gave, contrary to the "saturated" penicillins, a negative hydroxylamine test[8] and showed only a very weak antibacterial activity when tested against B. subtilis and Staph. aureus by the agar diffusion disc assay.



2e
(DL-form)



4



5
(DL-form)

R=$PhOCH_2$

When 2a was treated with methyl iodide and t-BuOK, the 1,2-secodehydropenicillin 4[1] and the DL-dehydropenicillin 5 were obtained in low yields as follows. To a stirred solution of 2a (0.362 g, 1.0 mmol) and CH_3I (0.070 ml, 1.1 mmol) in THF (20 ml) was added dropwise at 0° and under nitrogen a solution of t-BuOK (0.112 g, 1.0 mmol) in THF (16 ml). After 18 hr stirring at room temperature, the neutralized (AcOH diluted with THF) and filtered solution was concentrated under vacuum. Prep. silica gel t.l.c. (C_6H_6:EtOAc, 4:1) afforded unchanged 2a (0.120 g, 33% recovery), 2-methylthio-2-azetin-4-one 4 (0.028 g, 11% yield based on recovered 2a; identical in all respects to the product obtained previously[1] from 1a), and DL-dehydropenicillin 5 (0.025 g, 10% yield based on recovered 2a) as a white amorphous solid which crystallized from Et_2O-petroleum ether: mp 120-122°; ir ($CHCl_3$) 1746 (ester CO), 1720 (unsat. β-lactam CO), 1622 cm^{-1} (amide CO)(absence of the NH band); nmr ($CDCl_3$) δ 1.43 (3H,s), 1.65 (3H,s) $\left[C(CH_3)_2\right]$, 3.58 (3H,s, CH_3N), 3.83 (3H,s, $COOCH_3$), 4.10 (1H,s, 3-H), 4.90 (2H,s, OCH_2CO), 6.87-7.73 (5H,m, aromatic);

m/e 376,317,283,213,209,181[9]. When the reaction was repeated using a large excess of CH_3I (5 eq), the conversion of 2a was practically complete, the yield of isolated 5 was higher (~30%), and only traces of 4 (t.l.c.) were formed.

Acknowledgement. The authors wish to express their thanks to Mr. R. Di Battista for his technical assistance in this investigation. Thanks are due to Dr. E. Mantovani, Dr. A. Robertiello, and Dr. L. Settembri for the ir, mass, and nmr spectra, and to Mrs. E. Perricone for the antibacterial activity assays.

REFERENCES AND NOTES

(1) A. Brandt, L. Bassignani, L. Re, Tetrahedron Lett., preceding paper.

(2) The intermediacy of 1d in the Et_3N-catalyzed cyclization of 3 to 2d is in line with the well-known analogous double bond isomerization of other related 1,2-secopenicillin derivatives on Et_3N treatment, see for example M. Yoshimoto, S. Ishihara, E. Nakayama, E. Shoji, H. Kuwano, and N. Soma, Tetrahedron Lett., 4387 (1972).

(3) (a) K.E. Henery-Logan and J.V. Rodricks, J.Am.Chem.Soc. 85, 3524 (1963); (b) B.A. Arbuzov and N.N. Zobova, Dokl.Akad.Nauk SSSR, 172, 845 (1967); Chem. Abstr., 66, 94838s (1967); (c) K. Clauss and H. Jensen, Tetrahedron Lett., 119 (1970); (d) B.A. Arbuzov, N.N. Zobova, and F.B. Balabanova, Izv.Akad.Nauk SSSR, Ser.Khim., 1570 (1970); Chem.Abstr., 74, 76350n (1971); (e) B.A. Arbuzov, N.N. Zobova, and F.B. Balabanova, Izv.Akad.Nauk SSSR, Ser.Khim., 577 (1971); Chem. Abstr., 75, 76704b (1971).

(4) 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.

(5) For this value, the same arguments given in the accompanying paper for the corresponding value in derivative 6[1] can be set forth. The structure of 2a has been confirmed by high-resolution mass-spectrometry and ^{13}C nmr studies (to be published).

(6) Elemental analysis gave proper values.

(7) Same value as for 2a when the ir spectrum of the latter was taken in KBr.

(8) J.H. Ford, Ind. and Eng.Chem.(Analytical), 19, 1004 (1947).

(9) The structure of 5 has been confirmed by high-resolution mass-spectrometry (to be published).