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A FACILE METHOD FOR THE PREPARATION OF 6-EPI-PENICILLINS

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Base-catalysed epimerization of penicillanic derivatives has been reported recently (1-5). The epimerization failed for penicillins containing a secondary amide side chain. It has been suggested (3) that the first proton to be removed by base is that of the amide function and that the proximity of the resulting negative charge prevents the loss of a second proton from C-6. The present paper reports a novel procedure for epimerization of penicillins containing a secondary amide side chain. The method consists in silylating the amide function of penicillin esters with N,O-bis-(trimethylsilyl)-acetamide (BSA), before treatment with base.

A solution of phenoxymethylpenicillin benzylester 1 (m.p. 75-76°C) $[\alpha]_D^{25}$ +144° (c 1, acetone) (6) in methylene chloride or dimethyl-formamide (DMF) was silylated with BSA and treated with triethylamine at room temperature. After 24 h the reaction mixture consisted of two compounds (in a ratio 1:1), which were separated on the basis of their solubility in dry ether. The insoluble compound was crystallized from CH_2Cl_2-dry ether: m.p. 140-140.5°C, $[\alpha]_D^{25}$ -225° (c 1, acetone), m/e = 440, UV (methanol) λ max. 315 mμ (ε : 7806), 258 mμ (ε : 6956), IR (KBr) ν max. 3365 (amine), 3315, 1665, 1535 (amide), 1742, 1220 (ester), 1630 (unsat. thiolactone), and 1568 (C = C) cm^{-1}, NMR ($CDCl_3$) δ 4.33 (d, J 6 cps, 3-H), 6.62 (br.s, NH), 8.01 (d, J 8 cps, 5-H), 8.45 (s, amide) (doublets at 4.33 and 8.01 collapsed to singlets when D_2O was added). These data suggested a benzyl-2,2-dimethyl-7-oxo-6-phenoxymethyl acetamido-2,3,4,5-tetrahydro-1,4-thiazepine-3-carboxylate (2) structure for this compound. Parent 1,4-thiazepines were reported as side products of base-catalysed epimerization of penicillanic acid derivatives (7,8). The ether soluble compound (amorphous), m.p. 41-46°C, $[\alpha]_D^{25}$ +172° (c 1, acetone), m/e = 440, IR (KBr) ν max. 1778 (β-lactam), 1745 (ester) cm^{-1}, NMR ($CDCl_3$) δ 5.17 (dd, J 1.5, and 9 cps, 6-H), 5.22 (d, J 1.5 cps, 5-H) 7.64 (br.d, J 9 cps, NH), was the 6-epi-phenoxymethyl-penicillin benzylester 3 which was identical in all respects to the benzylester obtained by reduction of the 6-epi-phenoxymethylpenicillin sulfoxide benzylester 4, m.p. 158-159°C, $[\alpha]_D^{25}$ +220° (c 0.5, acetone), with PBr_3 in DMF (9). The latter was obtained by epimerization of 5, m.p. 128-129°C, $[\alpha]_D^{25}$ +142° (c 0.5, acetone), with BSA according to Gutowski (10). It has been reported that rearrangement (5) to 1,4-thiazepines can be suppressed by using 1,5-diazabicyclo-

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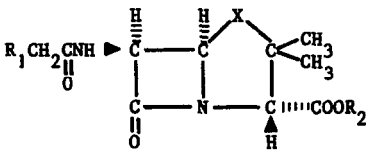
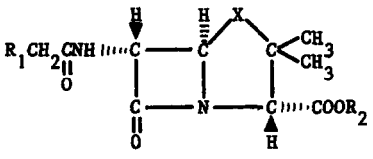
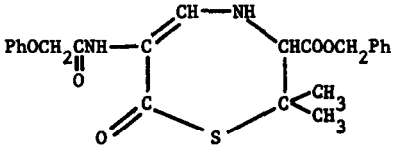
[4,3,0]-non-5-ene (DBN) as epimerization catalyst. This was also the case for treatment of 1 with BSA and DBN in methylene chloride. NMR spectrometry showed that 75 % of the starting material was epimerized to 3 and that no rearrangement to a 1,4-thiazepine occurred. The mixture of the two epimers can be differentiated (TLC) by conversion into their corresponding sulfoxides 4 and 5 (m-chloroperbenzoic acid/CH_2Cl_2) (11). These were separated by fractional crystallization from methanol. The former was identical to the compound obtained by the procedure of Gutowski (10).



	R_1	R_2	X
1	PhO-	$PhCH_2$-	S
5	PhO-	$PhCH_2$-	SO
6	PhO-	H	S
7	Ph-	H	S



	R_1	R_2	X		R_1	R_2	X
3	PhO-	$PhCH_2$-	S	11	PhO-	$-CH_3$	SO
4	PhO-	$PhCH_2$-	SO	12	Ph-	H	S
8	PhO-	H	S	13	Ph-	$-CH_3$	S
9	PhO-	H	SO	14	Ph-	$-CH_3$	SO
10	PhO-	$-CH_3$	S				



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The novel method can also be extended to the epimerization of the free acids of phenoxymethylpenicillin 6 and benzylpenicillin 7. Both amide and carboxylic functions of 6 were silylated in methylene chloride with an excess of BSA. Addition of DBN afforded a mixture of the starting penicillin 6 and its epimer 8 in a ratio 1:4 (estimated from the NMR spectrum). Reaction products were converted into their potassium salts and separated on the basis of the solubility of 8 (K-salt) in dry acetone. The epimer 8 (K-salt) was obtained in a 70 % yield, m.p. 166.5-169.5°C, $[\alpha]_D^{25}$ +195° (c 0.5, water), IR (KBr) ν max. 3740-3100 (hydrate), 3220, 1615, 1530 (amide), 1760 (β-lactam), 1600, 1395 (COO^-) cm^{-1}, NMR (D_2O) δ 1.52 and 1.59 (s, gem. dimethyl), 4.34 (s, 3-H), 4.54 (s, $-CH_2-$), 4.88 (d, J 1.5 cps, 6-H), 5.30 (d, J 1.5 cps, 5-H), and 6.82-7.51 (m, phenyl). It exhibits negligible antimicrobial activity against standard test organisms. Purity assayed by iodometric titration was 91 % (based on a consumption of 9 equiv./mole). Compound 8 was also prepared by another procedure consisting of: epimerization of 5 with BSA, followed by catalytic debenzylation to 9 m.p. 158-160°C, $[\alpha]_D^{25}$ +264° (c 1, acetone) .

Reduction of the sulfoxide 9 with PBr_3 in DMF (9) afforded 8 (23 % yield based on 5), which was identical to the compound prepared by the novel method. Further characterization of 8 was obtained by conversion into its methylester (10) with diazomethane, m.p. 84.5-87°C, $[\alpha]_D^{20}$ +187.5° (c 0.5, acetone), m/e = 364, IR (KBr) ν max. 3350, 1675, 1525 (amide), 1780 (-lactam), 1745 and 1212 (ester) cm^{-1}, NMR ($CDCl_3$) δ 1.44 and 1.59 (s, gem. dimethyl), 3.77 (s, $-OCH_3$), 4.52 (s, 3-H and $-CH_2-$), 5.20 (d.d, J 1.8 and 8 cps, 6-H), 5.29 (d, J 1.8 cps, 5-H), 6.82-7.35 (m, phenyl), 7.67 (br.d, J 8 cps, NH). The melting point was not in agreement with the value reported for 10 as obtained by total synthesis (12). Oxidation of 10 with m-chloroperbenzoic acid (11) yielded (72 %) the crystalline sulfoxide 11, m.p. 125-127°C, $[\alpha]_D^{20}$ +235° (c 0.5, acetone), m/e = 380. The crystalline K-salt of 6-epi-benzylpenicillin 12, m.p. 153-154°C, $[\alpha]_D^{20}$ +197° (c 0.5, water), was obtained in a 70 % yield by BSA-DBN treatment of 7. Physical and spectral data were in agreement with those reported by Johnson et al. (2). Iodometric assay showed a purity of 87 % (based on a consumption of 9 equiv./mole). Esterification with diazomethane yielded the corresponding methylester 13, m.p. 107-108°C, $[\alpha]_D^{20}$ +196° (c 0.5, $CHCl_3$), +191° (c 0.5, acetone), m/e = 348. Johnson et al. (2) found m.p. 116°C and $[\alpha]_D^{25}$ +119.1° (c 1, $CHCl_3$). Treatment of 13 with m-chloroperbenzoic acid afforded the crystalline sulfoxide 14, m.p. 110-112°C, $[\alpha]_D^{20}$ +238° (c 0.5, acetone). The present procedure permits epimerization of penicillins containing a secondary amide chain in high yield. Both esters and free acids can be used as starting material.

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