# (±)-Dinorpenicillin-2-spirocycloalkane

By JACQUES LECLERCQ,* ERIC COSSEMENT, ROLAND BOYDENS, LUDOVIC A. M. RODRIGUEZ, LÉON BROUWERS,† FRANÇOISE DE LAVELEYE,† and WALBURGIS LIBERT†

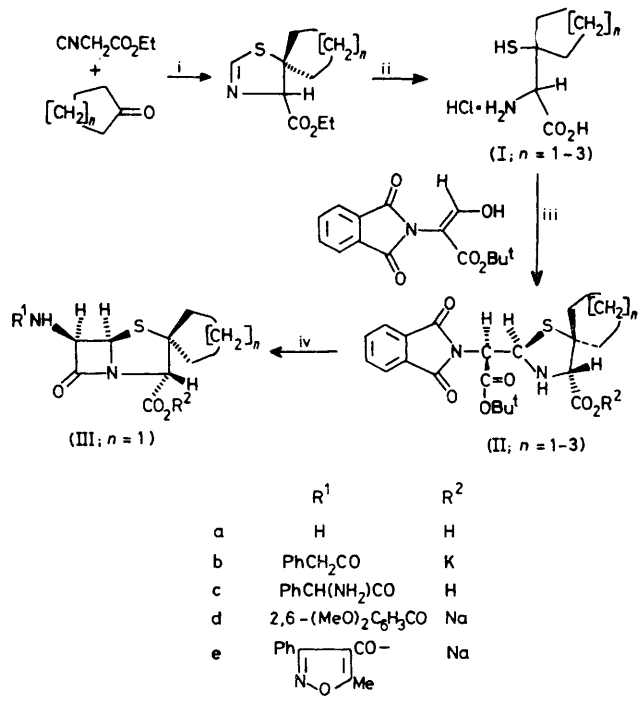
(*Department of Chemistry and †Department of Microbiology, U.C.B., Pharmaceutical Division, 68, rue Berkendael, B-1060 Brussels, Belgium*)

*Summary* (±)-Dinorpenicillin-2-spirocycloalkanes have been synthesized, and no change in inhibitory activity of *Staphylococcus aureus* transpeptidase has been observed; decrease in antibacterial activity occurring with larger spirocycles is interpreted in terms of unsuitable lipophilicity, impairing penetrability through the bacterial cell wall.

RECENT reports have described the synthesis of nuclear analogues of cephalosporins and penicillins;[1] the (±)-dinorpenicillin-2-spirocyclopentane skeleton, substituted at C-6 by an azido-function, has also been reported,[2] and Vanderhaeghe *et al.*[3] have independently reported the synthesis of (±)-dinor-2-spirocyclobutane and -2-spirocyclopentane analogues of penicillanic acid. These reports prompt us to report the first synthesis of the (±)-dinorpenicillin-2-spirocycloalkane nucleus substituted at C-6 by a free amino group and by acylamino side chains,[4] *e.g.*, compounds (IIIa—e).

The size of the spirocycloalkane was varied in order to check the effects of variation in strain within the penicillin on bactericidal activity. It was also expected that more information would be obtained on the steric requirements at the C-2 position for biological activity.

The classical Sheehan synthesis[5] was used, starting with the modified (±) penicillamines (I), readily available by the thiazoline synthesis of Schöllkopf *et al.*,[6] and subsequent hydrolysis in boiling 4N-hydrochloric acid (Scheme). The penicillin analogues so obtained consist of racemic mixtures [(3*S*,5*R*,6*R*) + (3*R*,5*S*,6*S*)], only the biologically active (3*S*,5*R*,6*R*)-enantiomer being shown in formulae (III).‡ Enantiomeric mixtures of benzylpenicillins have also been




| | $R^1$ | $R^2$ |
|---|---|---|
| a | H | H |
| b | $PhCH_2CO$ | K |
| c | $PhCH(NH_2)CO$ | H |
| d | 2,6-$(MeO)_2C_6H_3CO$ | Na |
| e |  | Na |

SCHEME. Reagents: i, NaH–tetrahydrofuran; $P_4S_{10}$–$C_6H_6$; ii, 4N-HCl, reflux; iii, AcONa–EtOH–$H_2O$; epimerisation; iv, $PhCH_2Br$–$NEt_3$–dimethylformamide; $NH_2NH_2$–dimethylformamide; HCl gas–$MeNO_2$; $Ph_3CCl$–$Et_3N$–$CH_2Cl_2$; dicyclohexylcarbodi-imide–$MeNO_2$; *p*-$MeC_6H_4SO_3H$–$Me_2CO$; $H_2$–Pd/C–$NEt_3$; R'COCl–$NEt_3$.

‡ Structural assignments are supported by analytical and spectroscopic data. *E.g.*, compound (IIIb; $n = 3$) shows $\gamma_{max}$ (KBr) 1762 $cm^{-1}$ (β-lactam); δ ($D_2O$; $Me_3Si[CH_2]_3SO_3^-Na^+$) 4·23 (s, 3-H), 5·36 (d, *J* 4·0 Hz, 5-H), and 5·48 (d, *J* 4·0 Hz, 6-H).

synthesized in order to prove the expected lack of activity of the (3*R*,5*S*,6*S*)-enantiomer in the biological tests mentioned below.

Specific activity at the level of bacterial cell wall biosynthesis was maintained, as shown by typical morphological changes of the cell wall and by inhibition of *Staphylococcus aureus* transpeptidase. A bulky spirocyclohexane substituent at C-2 does not impair transpeptidase inhibition, which is also unaffected by decreasing the size of the spirocycle.

However, whereas compound (IIIb; $n = 3$) is half as active (based on natural enantiomer) as benzylpenicillin against *Staphylococcus Aureus*, the analogues (IIIb; $n = 1$ or 2) with smaller rings are twice as active. The same holds true for the derivatives (IIIa; n = 2 or 3) which are twice as active as 6-aminopenicillanic acid on a strain of *Staphylococcus aureus*.

Consequently, the lower activity of the penicillin analogues (IIIb; $n = 3$) is interpreted in terms of the unsuitable lipophilicity of the whole molecule, causing a lower penetrability of the bacterial cell wall. This assumption is substantiated by the improved potency of (±)-dinorpenicillin-2-spirocycloalkanes in which the spirocycle has been made more hydrophilic,[7] which we are currently investigating.

(*Received, 15th August* 1977; *Com.* 852.)

[1] Bristol Meyers Canada Ltd. Belg. P. 837,265, 840,453 (*Chem. Abs.*, 1977, **86**, 140,060v); Ciba-Geigy A.-G., Ger. Offen. 2,153,554 (1972) (*Chem. Abs.*, 1972, **77**, 126,700m); Smith, Kline, and French, Belg. P. 841,243, 845,540; U.S.P. 4,000; Queen's Univ., Kingston Ont., Fr.P. 2,246, 547 (*Chem. Abs.*, 1975, **83**, 206,236d); U.S.P. 3,950,352; Ger. Offen. 2,356,862 (1975) (*Chem. Abs.* 1975; **83**, 114,394a); Belg. P. 832,174 (*Chem. Abs.*, 1977, **86**, 19,080y); Merck and Co., Inc., Ger. Offen. 2,355,209 (1974) (*Chem. Abs.*, **81**, 1974, 37,560f); B.P. 1,458,410 (*Chem. Abs.*, 1975, **82**, 31,314c); Shionogi K. K., Belg. P. 848,288; Lilly and Co., B.P. 1,314,628; Fujisawa Pharmaceutical Co., Ltd., B.P. 1,455,693 (*Chem. Abs.*, 1974, **81**, 49,674j); E. R. Squibb and Sons, Inc.: U.S.P. 3,971,776 (1976) (*Chem. Abs.*, 1977, **86**, 16,662d); P. J. Claes, J. Hoogmartens, G. Janssen, and H. Vanderhaeghe, *European J. Medicin Chem. Chim. Ther.*, 1975, **10**, 573, P. J. Claes and H. Vanderhaeghe, *ibid.*, 1976, **11**, 359.

[2] M. D. Bachi, N. Frydman, S. Sassan, C. Stern, and J. Vaya, *Tetrahedron Letters*, 1977, 641.

[3] P. J. Claes, G. Janssen, and H. Vanderhaeghe, personal communication; submitted for publication to *European J. Medicin Chem. Chim. Ther.*

[4] U.C.B. Dipha B.P. appl. 21,624, 21,625/76, May 1976.

[5] J. C. Sheehan, and K. R. Henery-Logan, *J. Amer. Chem. Soc.*, 1962, **84**, 2983.

[6] U. Schöllkopf, F. Gerhart, and R. Schroder, *Angew. Chem. Internat. Edn.* 1969, **8**, 672; U. Schöllkopf and D. Hoppe, *ibid.*, 1973, **12**, 1006.

[7] U.C.B.—Dipha, B.P. appl. 1905, 1906/77, January 1977.