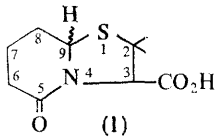
The Synthesis of Analogues of Penicillin. Part II [1]

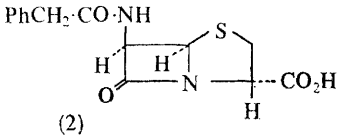
By **D. Todd,* R. J. Cornell,** and **R. T. Wester,** Department of Chemistry, Worcester Polytechnic Institute, Worcester, Massachusetts
T. Wittstruck, *Worcester Foundation for Experimental Biology, Shrewsbury, Massachusetts*

The synthesis of two δ-lactam analogues of benzylpencillin is described.

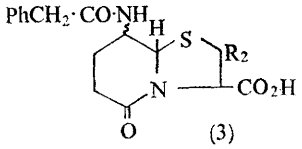
We have reported [1] the synthesis of the model compound (1) in which the β-lactam ring of penicillin G (2) is enlarged to a six-membered ring, and in which the side-chain nitrogen function is absent. We have now prepared a (±)-stereoisomer of the analogue (3b) of penicillin G in which the phenylacetamido-side-chain is in the correct position with respect to the sulphur of the thiazolidine ring. We have also prepared the simpler analogue without the methyl groups (3a).



(1)

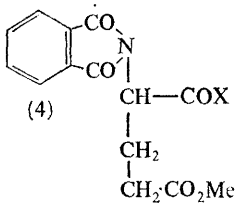


(2)



(3)

a; R = H
b; R = Me



(4)

a; X = OH
b; X = Cl
c; X = H

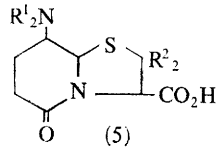
The synthetic scheme involves, as in the earlier work, the condensation of the appropriate *N*-protected aldehyde with (−)-L-cysteine [or (±)-penicillamine], followed by removal of the protective group and phenylacetylation of the resulting free amine.

L-Glutamic acid was converted into (±)-*N*-phthaloylglutamic anhydride, and this into the known γ-methyl hydrogen *N*-phthaloylglutamate (4a). The acid was converted by Rosenmund reduction of the acid chloride (4b) into the aldehyde (4c) (69—79%). The aldehyde was condensed in aqueous ethanol with L-cysteine to give (62—67%) the bicyclic thiazolidine lactam (5a). The n.m.r. spectrum of this compound has a split doublet, assigned to the C-9 proton, at δ 5·65, which shows the presence of two isomers in almost equal amounts. The phthaloyl group of (5a) was removed by hydrazinolysis in hot ethanol. After removal of the bulk of the phthalohydrazide formed, the isolation of the lactam amino-acid (5c) was difficult unless all the excess of hydrazine was removed by the addition of benzaldehyde and extraction of the benzaldehyde azine formed with ether. The product then crystallized readily from water. The n.m.r. spectrum of (5c) indicates that it is one pure isomer. Phenylacetylation of the amino-acid by both the Schotten-Baumann and the mixed anhydride methods consistently gave the desired product (3a), double m.p. 112—114° and 184—186°.

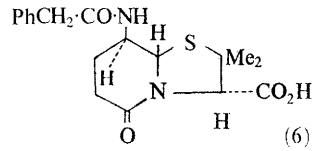
We repeated the above sequence with (±)-penicillamine instead of (−)-L-cysteine in the condensation with γ-methyl *N*-phthaloylglutamaldehydate. The dimethyl phthaloyl compound (5b) so obtained is apparently a mixture (*ca.* 7 : 3) of two isomers, (the n.m.r. spectrum clearly shows a split C-9 proton doublet at δ 5·80 and two sharp singlets, assigned to the C-3 proton of the isomers, at δ 4·30 and 4·62) and by hydrazinolysis was converted into the amino-acid (5d), isolated as one isomer only. Phenylacetylation of (5d) gave the desired homologue [(±)-(3b)].

[1] Part I, D. Todd and S. Teich, *J. Amer. Chem. Soc.*, 1953, **75**, 1895.

It was mentioned above that (5a) and (5b) each consisted of a pair of isomers. In the n.m.r. spectrum of (5a) a split doublet at δ 5·65 is assigned to the C-9 proton. (In penicillin itself, the proton at this position resonates



(5)



(6)

a; R_2^1 = Phthaloyl, R^2 = H
b; R_2^1 = Phthaloyl, R^2 = Me
c; R^1 = H, R^2 = H
d; R^1 = H, R^2 = Me

at δ 5·55.[2]) In the n.m.r. spectrum of the free amine (5c) the doublet assigned to the C-9 proton has $J_{8,9}$ 9 c./sec. and in the phenylacetylated final product (3a) the analogous J value is 10 c./sec. This large J value indicates that the protons at C-8 and C-9 are *trans* axial–axial. Similarly in the dimethyl series, the C-9 proton J values are 9, 9, and 10, which indicates that in both series only *trans* axial–axial isomers are formed.

Furthermore, the stereochemistry at C-3 relative to that at C-9 can be deduced as a result of the recent n.m.r. study of the absolute stereochemistry of thiazolidines derived from D-penicillamine and aldehydes.[3] It was deduced that in the case of isomer pairs of 5,5-dimethylthiazolidine-4-carboxylic acids (or esters), possessing a tertiary proton at C-2, that isomer in which the C-4 proton resonates at lower field is the *trans*-isomer. It was also found that in the two recorded condensations of aldehydes with penicillamine, the 2,4-*cis*-isomer predominated. The product of the condensation of the aldehyde (4c) with DL-penicillamine consists of a 7 : 3 mixture of two isomers, the C-3 (corresponding to C-4 in the simple model thiazolidine) protons of which resonate at 4·30 and 4·62 respectively. Thus the major product is probably the 3,9-*cis*-compound. Since hydrazinolysis of this mixture gave one pure amine in 46% yield, the latter must also be 3,9-*cis*, as is the final phenylacetylated material. The complete stereochemistry of the final (±)-product is represented by (6) (the mirror image containing the D-penicillamine moiety is shown). The stereochemistry is the reverse of that of penicillin at C-9 (only).*

Bioassays on compounds (1), (5a), and (5b) showed that none of these materials possessed penicillin activity.

EXPERIMENTAL

I.r. spectra were taken for solutions in chloroform or for potassium bromide pellets. N.m.r. spectra were determined with a Varian A-60 instrument, with tetramethylsilane as internal standard; compounds (5a), (5b), (3a), and (3b) were run in dimethyl sulphoxide and compounds (3a) and (3b) were in deuterium oxide. Analyses were performed by Weiler and Strauss, Oxford. M.p.s were determined with a Fischer-Johns apparatus.

(±)-*γ-Methyl Hydrogen* N-*Phthaloylglutamate* (4a).—(+)-L-Glutamic acid was converted into (±)-*N*-phthaloylglutamic anhydride (89%),[4] m.p. 201—204°, which, when boiled in methanol gave the γ-methyl ester (93%), m.p. 118—120° (lit.,[4] 119·5—120·5°). Fischer esterification of the γ-methyl ester gave (±)-*dimethyl* N-*phthaloylglutamate*, as cuboids, m.p. 50·0—51·5° (from benzene–heptane) (Found: C, 59·2; H, 5·0; N, 4·7. $C_{15}H_{15}NO_6$ requires C, 59·0; H, 5·0; N, 4·6%).

(±)-*γ-Methyl* N-*Phthaloylglutamate Acid Chloride* (4b).—A solution in benzene of ester (4a) (20 g.) and freshly purified thionyl chloride (21·3 g.) was heated under reflux for 4 hr. on a steam-bath, benzene and excess of thionyl chloride were removed *in vacuo*, and the solid product gave the *acid chloride* (14·2 g., 67%), m.p. 82—84° (from benzene–pentane) (Found: C, 54·3; H, 3·8; N, 4·4. $C_{14}H_{12}ClNO_5$ requires C, 54·4; H, 3·8; N, 4·5%).

The acid chloride (2 g.) was stirred with aniline (2·0 ml.) in benzene (10 ml.); work-up gave the anilide, m.p. 144—145° (lit.,[4] 144—145°) of (±)-(4a).

(±)-*Methyl* 5-*Oxo*-4-*phthalimidopentanoate* (4c).—To a solution of the acid chloride (4b) (17·3 g., 0·056 mole) in dry xylene (200 ml.) was added 5% palladium–barium sulphate (2·0 g.) and catalyst poison (0·2 ml.).[5] While the suspension was heated under reflux and stirred (mercury-seal stirrer), dry hydrogen was passed through for *ca.* 12 hr. (until cessation of hydrogen chloride evolution). About 94% of the expected amount of hydrogen chloride was evolved. The product was the *aldehyde* (4c) (10·7 g., 69%), m.p. 77·5—79° (from benzene–pentane) (Found: C, 60·9; H, 4·8; N, 5·3. $C_{14}H_{13}NO_5$ requires C, 61·1; H, 4·7; N, 5·1%); *semicarbazone*, m.p. 188·0—189·5° (Found: N, 16·9. $C_{15}H_{16}N_4O_5$ requires N, 16·9%).

8-*Phthalimidoperhydrothiazolo*[3,2-a]*pyridine*-3-*carboxylic Acid* (5a).—To a warm solution of the aldehyde (4c) (2·0 g.) in ethanol (15 ml.) was added a solution of L-cysteine hydrochloride hydrate (1·28 g.) and sodium acetate trihydrate (0·99 g.) in water (20 ml.). The filtered solution after 3 days deposited *needles* (1·7 g., 67%), m.p. 254—263° (decomp.) (from ethanol). (Other preparations of this isomer mixture have shown decomposition points from 248 to 274°) (Found: C, 55·7, 55·3; H, 3·9, 4·2; N, 8·2, 8·4; S, 9·2. $C_{16}H_{14}N_2O_5S$ requires C, 55·5; H, 4·1; N, 8·1; S, 9·3%).

This material could be partially hydrolysed under mild conditions; presumably the phthaloyl ring is opened. The phthalimido-compound (5a) (1·0 g., 2·9 mmoles) was titrated at 0° with N-sodium hydroxide; it consumed 5·8 mmoles of base (phenolphthalein indicator). Acidification gave a *compound*, m.p. 210—220° (from water), which resolidified and remelted at 245—260° (decomp.) [conversion into (5a)] (Found: C, 53·2; H, 4·3; N, 7·8. $C_{16}H_{16}N_2O_6S$ requires C, 53·0; H, 4·5; N, 7·7%).

8-*Aminoperhydrothiazolo*[3,2-a]*pyridine*-3-*carboxylic Acid* (5c).—A mixture of 85% hydrazine hydrate (0·20 g.), acid

* The spectra reported by McMillan and Stoodley [3] were determined for solutions in pyridine, while our spectra were determined in dimethyl sulphoxide or deuterium oxide. While the chemical shifts of the 3-protons might be expected to show some solvent dependency, it seems unlikely that a cross-over effect, in the case of the C-3,C-9-*cis*,*trans*-isomers, exists.

[2] G. F. H. Green, J. E. Page, and S. E. Staniforth, *Chem. Comm.*, 1966, 597.
[3] I. McMillan and R. J. Stoodley, *Chem. Comm.*, 1968, 11.
[4] J. C. Sheehan and W. A. Bolhofer, *J. Amer. Chem. Soc.*, 1950, **72**, 2469.
[5] R. Mossetig, *Org. Reactions*, 1948, **4**, 368.

(5a) (0·60 g.), and absolute ethanol (20 ml.) was heated under reflux for 4 hr., and evaporated to dryness *in vacuo*. Extraction of the residue with water (20 ml.) left a precipitate of phthalohydrazide (0·22 g., 78%). To the extract was added water (20 ml.) and benzaldehyde (1·0 g.); the solution was stirred for 20 min. and extracted with ether (3 × 30 ml.). The aqueous phase was reduced to 3 ml. *in vacuo* and treated with methanol (40 ml.) to give a precipitate (0·16 g., 44%) of the *amino-acid*, m.p. 270—290° (decomp.) (Found: C, 44·2; H, 5·7; N, 12·9. $C_8H_{12}SO_3N_2$ requires C, 44·4; H, 5·6; N, 13·0%).

8-*Phenylacetamidoperhydrothiazolo*[3,2-a]*pyridine*-3-*carboxylic Acid* (3a).—(a) *Schotten-Baumann procedure*. To a solution of the amino-acid (5c) (0·216 g.) and sodium hydroxide (0·12 g.) in water (15 ml.) at 0° phenylacetyl chloride (0·154 g.) was added in portions with shaking, with portions of 2N-sodium hydroxide as needed to keep the solution alkaline during 20 min. After 2 hr. more at 0° the solution was brought to 25° and acidified with hydrochloric acid; the oil that initially formed soon solidified (0·15 g.), m.p. 112—114° (from water) (other preparations have m.p.s 112—120°). This material did not give a correct analysis (Found: C, 55·6, 55·2; H, 5·5, 5·7; N, 8·4, 8·2%; Equiv. 364. $C_{16}H_{18}N_2O_4S$ requires C, 57·6; H, 5·4; N, 8·4; S, 9·6%; Equiv. 334). When the material was dried at 140° for 36 hr. at 0·1 mm. the m.p. was raised to 185—186° (This material on crystallization from water gave the low-melting form, which resolidified at 120° and remelted at 184—186°) (Found: C, 57·8; H, 5·4; N, 8·4; S, 9·9%) $\nu_{max.}$ (KBr) 1720 (acid C=O), 1642 (C=O of $PhCH_2$·CO), 1605 (δ-lactam C=O),* 1530 (amide II, NH deformation), 1498 and 1405 (aromatic), and 1460 and 1450 (CH_2) cm.$^{-1}$, δ [$^2H_6$]dimethyl sulphoxide 1·9 (1H, m) and 2·47 (1H, m) (6-CH_2), 3·41 (2H, s, $PhCH_2$), 4·0 (1H, m, 8-H), 4·83 (1H, d, *J* 10 c./sec., 9-H), 4·67 (1H) and 4·98 (1H) (octet, J_{AB} 12, J_{AX} 4·5, J_{BX} 7·0 c./sec., 2-CH_2), 5·04 (1H, q, J_{AX} 4·5, J_{BX} 7·0 c./sec., 3-H), 7·28 (5H, s, aromatic), and 8·43 (1H, d, *J* 10 c./sec., NH).

(b) *Mixed anhydride method*. Ethyl chloroformate (0·05 ml.) was added to an ice-cold solution of phenylacetic acid (0·068 g.) and triethylamine (0·08 ml.) in dry acetone (6 ml.). After 5 min. at 0° the mixture was cooled to −50° and to it was rapidly added, with vigorous stirring, a cold solution of the amino-acid (5c) (0·108 g.) in 3% sodium hydrogen carbonate solution (6 ml.). The solution was stirred for ½ hr. as it attained room temperature and extracted with ether, and the aqueous phase was brought to pH 2 with hydrochloric acid and ice-cooled. The crystals, m.p. 112—114°, which separated were identical with those formed by the Schotten-Baumann route.

2,2-*Dimethyl*-8-*phthalimidoperhydrothiazolo*[3,2-a]*pyridine*-3-*carboxylic Acid* (5b).—A solution of DL-penicillamine acetonide hydrochloride (5·8 g., 26 mmoles) and sodium acetate (2·1 g., 26 mmoles) in water (80 ml.) was added to a solution of the aldehyde (4c) (7·2 g., 26 mmoles) in ethanol (60 ml.). After 3 days at room temperature the product (3·0 g., 31%) separated and gave the *thiazolidine* as needles, m.p. 262—265° (decomp.) (from ethanol) (Found: C, 57·6; H, 5·3; N, 7·2. $C_{18}H_{18}N_2O_5S$ requires C, 57·9; H, 4·8; N, 7·5%).

8-*Amino*-2,2-*dimethylperhydrothiazolo*[3,2-a]*pyridine*-3-*carboxylic Acid* (5d).—A mixture of acid (5b) (1·0 g.), 85% hydrazine hydrate (0·32 g.), and absolute ethanol (30 ml.) was heated under reflux for 4 hr. The solvent was removed *in vacuo*, and the residual solid was extracted with water. After treatment with benzaldehyde (1 g.) as before, the *product* (0·30 g., 46%) was obtained by crystallization from methanol; m.p. 300° (decomp.) (Found: C, 49·0; H, 6·5; N, 11·4. $C_{10}H_{16}N_2O_3S$ requires C, 49·1; H, 6·6; N, 11·5%).

2,2-*Dimethyl*-8-*phenylacetamidoperhydrothiazolo*[3,2-a]-*pyridine*-3-*carboxylic Acid* (3b).—The amino-acid (5d) (0·5 g.) was treated as described earlier with phenylacetyl chloride (0·31 g.) and alkali to give the *acid* (3b) (0·2 g., 27%), double m.p. 188—190° and 268—270° (from water) (Found: C, 59·5; H, 5·8; N, 7·7; S, 8·9. $C_{18}H_{22}N_2O_4S$ requires C, 59·7; H, 6·1; N, 7·7; S, 8·9%), $\nu_{max.}$ (KBr) 3330 (NH), 1750 (acid C=O), 1650, 1630, 1530 (amide C=O), 1450 (CH_2), 1410 (aromatic), 1170, and 1135 (CMe_2) cm.$^{-1}$, δ [$^2H_6$]dimethyl sulphoxide 1·41 and 1·50 (each 3H, s, Me), 1·9 (1H, m) and 2·5 (1H, m) (6-CH_2), 3·42 (2H, s, $PhCH_2$), 4·0 (1H, m, 8-H), 4·52 (1H, s, 3-H), 5·16 (1H, d, *J* 10 c./sec., 9-H), 7·28 (5H, s, aromatic), and 8·43 (1H, d, *J* 10 c./sec., N–H).

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* In a study of a number of fused thiazolidine δ-lactams we have consistently found this band to be present.