Syntheses Based on 1,2-Secopenicillins. Part 4.[1] A New Tricyclic β-Lactam Derivative

By **Michael J. Pearson**, Beecham Pharmaceuticals, Research Division, Brockham Park, Betchworth, Surrey RH3 7AJ

Heating (3*R*,4*R*)-1-[azido-(t-butoxycarbonyl)methyl]-4-(prop-2-ynylthio)-3-(triphenylmethylamino)azetidin-2-one (4) in refluxing toluene resulted in smooth intramolecular cycloaddition of the azido-group to the acetylenic function to afford (5a*R*,6*R*,9ξ)-t-butyl 6,7-dihydro-7-oxo-6-triphenylmethylamino-4*H*,5a*H*-azeto[2,1-*b*]-*v*-triazolo[3,4-*e*][1,3,5]thiadiazepine-9-carboxylate (5).

SEVERAL fused tricyclic β-lactam derivatives have been described recently.[2-12] In most cases the compounds were obtained by modification of the thiazolidine or dihydrothiazine ring system already present in penicillins and cephalosphorins. Alkyl azides are known to react with activated acetylenes to afford *v*-triazoles,[13] and such a process has now been utilised in an intramolecular cycloaddition to provide a tricyclic β-lactam of novel structure.

The prop-2-ynylazetidinone (1) [14] was condensed with an excess of t-butyl glyoxylate in refluxing benzene to give the α-hydroxy-ester (2), which with thionyl chloride afforded the α-chloro-derivative (3), both products being mixtures of isomers. Treatment of (3) with tetramethylguanidinium azide in chloroform then gave the azidoacetylene (4). Although the product was homogeneous by t.l.c., its n.m.r. spectrum indicated a mixture of diastereoisomers. Signals at δ 5.08 and 5.34 are assigned to C*H*N_3. Trituration with ether provided one isomer (4a) as a white crystalline solid. Evaporation of the mother liquors gave an amorphous solid, consisting of (4a) (30%) and the other diastereoisomer (4b) (70%).

When (4a) was refluxed in toluene for 3 h, simultaneous disappearance of the characteristic azide and acetylene C–H i.r. bands was accompanied by formation of a single new product (t.l.c.; n.m.r.). Crystallisation from ethyl acetate–light petroleum gave an 80% yield of a crystalline solid assigned structure (5a) on the basis of molecular models (the orientation at C-9 has not been determined). It is known that the direction of this type of dipolar addition is governed by both electronic and steric factors.[13] In our case it was surmised that the latter consideration would be of major importance because of the inherent inflexibility of the β-lactam and triazole rings. The alternative mode of cycloaddition to give the triazole (6) was discounted, since the *trans*-double bond could not be accommodated in the rigid eight-membered ring.

Heating the mixture of isomers (4a and b) in toluene

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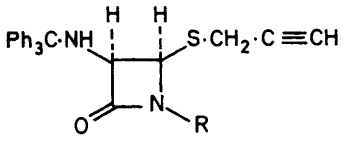
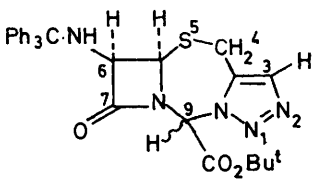
also afforded a cycloaddition product. N.m.r. spectroscopy indicated a mixture of triazoles (5a and b), consistent with the isomeric ratio in the starting azide (4).

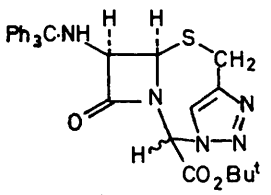
This acid-catalysed isomerisation was also evident in the preparation of the acylamino-derivative (8). Detritylation of either (5a) or (5b) with toluene-*p*-sulphonic



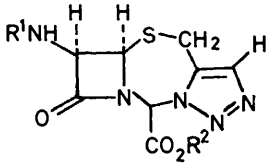
(1) R = H
(2) R = CH(OH)·CO_2Bu^t
(3) R = CHCl·CO_2Bu^t
(4) R = CHN_3·CO_2Bu^t



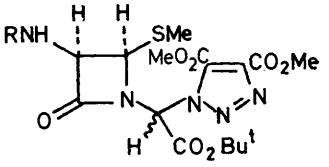
(5)



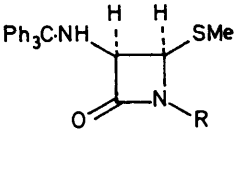
(6)



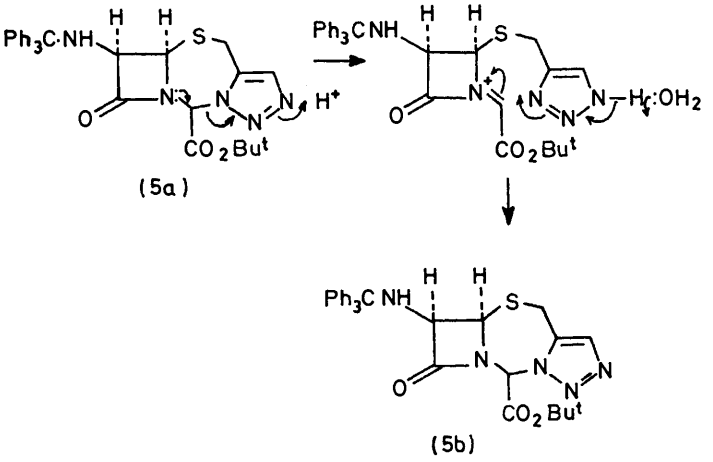
(7) R^1 = H, R^2 = Bu^t
(8) R^1 = PhO·CH_2·CO, R^2 = Bu^t
(9) R^1 = PhO·CH_2·CO, R^2 = H



(10) R = Ph_3C
(14) R = H



(11) R = CHN_3·CO_2Bu^t
(12) R = H
(13) R = CH(OH)·CO_2Bu^t



(5a)

(5b)

SCHEME

However, chromatography (Merck silica gel H) gave an amorphous product which consisted entirely of the triazole (5b). Indeed similar treatment of the crystalline triazole (5a) caused isomerisation to the amorphous (5b).

acid in methylene chloride–methanol gave the same free base (7). This was acylated with phenoxyacetyl chloride to provide the amide (8). The t-butyl group was removed by treatment with trifluoroacetic acid, to give

the free acid (9), which showed no antimicrobial activity.

The reason for this isomerisation is not clear, since Dreiding models indicate that there are no particularly unfavourable steric interactions in either isomer. However the phenomenon is not purely electronic, since the triazole (10), prepared by the reaction of dimethyl acetylenedicarboxylate with the azide (11) [prepared from the azetidinone (12) [15] *via* (13)] was obtained as a mixture of isomers, the ratio of which was unchanged by chromatography on silica gel. Furthermore the removal of the triphenylmethyl group by toluene-*p*-sulphonic acid afforded the free base (14), as a mixture of isomers in the same ratio. Thus it seems that steric factors are important in the tricyclic series, and although the isomerisation mechanism has not been studied a tentative suggestion is outlined in the Scheme.

EXPERIMENTAL

General experimental procedures were as outlined in Part 1.[15] (3R,4R)-1-[*Hydroxy-(t-butoxycarbonyl)methyl*]-4-*prop*-2-*ynylthio*-3-*triphenylmethylaminoazetidin*-2-*one* (2).—t-Butyl glyoxylate monohydrate (7.4 g, 10 equiv.) was refluxed in benzene (70 ml) for 0.5 h under a Dean–Stark head. The lactam (1) [14] (1.99 g) was then added and the solution was refluxed for 3½ h. The mixture was washed with water (5 × 20 ml), dried, and evaporated. Chromatography afforded the amorphous α-hydroxy-ester (2) as a mixture of isomers (1.72 g), $\nu_{max.}$ 3 500, 3 300, 1 772, and 1 738 cm^{-1}; δ 1.47 (9 H, s), 2.22 (1 H, t, *J* 2.5 Hz), 2.83—3.3 (3 H, m, 1 H exch.), 4.49 (1 H, m, becoming two d, 4.47 and 4.5, *J* 5 Hz, on D_2O exch.), 4.73 and 4.77 (1 H, two d, *J* 5 Hz), 5.27 (1 H, m, becoming two s, 5.2 and 5.35 on D_2O exch.), and 7.1—7.7 (15 H, m).

(3R,4R)-2-[*Azido-(t-butoxycarbonyl)methyl*]-4-*prop*-2-*ynylthio*-3-*triphenylmethylaminoazetidin*-2-*one* (4).—The alcohol (2) (2.99 g) was dissolved in dry tetrahydrofuran (100 ml) at −15 °C and 2,6-lutidine (1.97 ml) was added, followed dropwise by thionyl chloride (1.23 ml) in tetrahydrofuran (20 ml) over 15 min. The mixture was filtered and the filtrate evaporated; the residue was dissolved in toluene and the solution evaporated to afford the chloride (3) as an amorphous solid (3.01 g). This was dissolved in dry chloroform (40 ml) and tetramethylguanidinium azide (950 mg) added. After 15 min the solution was washed with dilute hydrochloric acid and brine, dried, and evaporated. Chromatography gave the azide (4) as a mixture of isomers (2.31 g). Trituration with ether provided one *isomer* as a crystalline solid (4a) (900 mg), m.p. 154—155 °C (from ethyl acetate–light petroleum), $\nu_{max.}$ (Nujol) 3 370, 3 270, 2 140, 1 780, and 1 762 cm^{-1}; δ 1.49 (9 H, s), 2.21 (1 H, t, *J* 2.5 Hz), 2.95 (2 H, t, *J* 2.5 Hz), 2.97 (1 H, d, *J* 9 Hz, exch.), 4.63 (1 H, m, collapsing to d, *J* 5 Hz, on D_2O exch.), 4.8 (1 H, d, *J* 5 Hz), 5.08 (1 H, s), and 7.1—7.8 (15 H, m) (Found: C, 67.3; H, 5.7; N, 12.7; S, 5.6. $C_{31}H_{31}N_5O_3S$ requires C, 67.2; H, 5.6; N, 12.7; S, 5.8%).

N.m.r. showed that the mother liquors from the crystallisation contained a further quantity (30%) of the crystalline isomer (4a), the remaining material being the other diastereoisomer (4b). No further enrichment in (4b) could be obtained since t.l.c. separation was not possible. The n.m.r. spectrum of (4b) was deduced from that of the mixture: δ 1.49 (9 H, s), 2.22 (1 H, t, *J* 2.5 Hz), 3.0 (1 H, m, exch.), 3.11 (2 H, t, *J* 2.5 Hz), 4.68 (1 H, m, collapses to d, *J* 5 Hz, on D_2O exch.), 4.95 (1 H, d, *J* 5 Hz), 5.34 (1 H, s), and 7.1—7.8 (15 H, m).

Cyclisation of the Crystalline Azide (4a).—The azide (4a) (346 mg) was refluxed in toluene (10 ml) for 3½ h. The solvent was evaporated off and the residue crystallised from ethyl acetate–light petroleum to give (5aR,6R,9ξ)-*t-butyl* 6,7-*dihydro*-7-*oxo*-6-*triphenylmethylamino*-4H,5aH-*azeto*-[2,1-b]-v-*triazolo*[3,4-e][1,3,5]*thiadiazepine*-9-*carboxylate* (5a) as white crystals (271 mg), m.p. 183 °C, $[\alpha]_D^{23}$ +148° (*c* 1.13 in $CHCl_3$), $\nu_{max.}$ (Nujol) 3 300, 1 787, and 1 761 cm^{-1}; δ 1.48 (9 H, s), 3.42 (1 H, d, *J* 10 Hz, exch.), 3.48 and 4.15 (2 H, ABq, *J* 15 Hz), 4.14 (1 H, m, collapses to d, *J* 5 Hz, on D_2O exch.), 4.58 (1 H, d, *J* 5 Hz), 6.14 (1 H, s), and 7.1—7.8 (15 H, m) (Found: C, 67.2; H, 5.8; N, 12.6; S, 5.9. $C_{31}H_{31}N_5O_3S$ requires C, 67.2; H, 5.6; N, 12.7; S, 5.8%).

Cyclisation of the Mainly Non-crystalline Azide (4b).—The azide (4) (159 mg) [consisting of (4b) and (4a) in the ratio 7 : 3] was refluxed in toluene (10 ml) for 2¼ h. The solvent was evaporated off and chromatography gave starting material (19 mg) and pure *triazole* (5b) as an amorphous solid (126 mg), $[\alpha]_D^{23}$ +55.6° (*c* 1.28 in $CHCl_3$); $\nu_{max.}$ 1 780 and 1 740 cm^{-1}; δ 1.40 (9 H, s), 2.98 (1 H, d, *J* 10 Hz, exch.), 3.95 (2 H, s), 4.80 (1 H, dd, *J* 5 and 10 Hz, collapsing to d, *J* 5 Hz, on D_2O exch.), 5.3 (1 H, d, *J* 5 Hz), 7.03 (1 H, s), and 7.1—7.8 (15 H, m) (Found: M^+, 553.2156. $C_{31}H_{31}N_5O_3S$ requires *M*, 553.2148).

Isomerisation of the Triazole (5a).—(*a*) The crystalline triazole (5a) (40 mg) was passed through a silica column (5 g; Merck silica gel H) (elution with chloroform). The n.m.r. spectrum of the recovered material indicated *ca.* 50% isomerisation to (5b).

(*b*) Treatment of the crystalline triazole (5a) (40 mg) in chloroform (2 ml) containing silica gel H (200 mg) for 2 h caused complete conversion into (5b), as judged by n.m.r. spectroscopy.

Detritylation of the Triazoles (5a *and* b).—(*a*) *Crystalline compound* (5a). The crystalline triazole (5a) (215 mg) was dissolved in methylene chloride (10 ml) and cooled to −15 °C. Toluene-*p*-sulphonic acid (81 mg) in the minimum volume of methanol was added over 1—2 min, and the solution kept at −5 °C for 16 h. The solvent was evaporated off and the residue dissolved in ethyl acetate. The solution was washed with dilute aqueous sodium hydrogen carbonate and brine, dried, and evaporated. Chromatography gave the *free base* (7) (90 mg), $\nu_{max.}$ 3 400, 3 350, 1 780, and 1 745 cm^{-1}; δ 1.5 (9 H, s), 1.84 (2 H, s, exch.), 4.11 (2 H, s), 4.85 (1 H, d, *J* 5 Hz), 5.68 (1 H, d, *J* 5 Hz), 7.12 (1 H, s) and 7.59 (1 H, s) (Found: M^+, 311.1075. $C_{12}H_{17}N_5O_3S$ requires *M*, 311.1052).

(b) *The amorphous triazole* (5b). Detritylation of the amorphous triazole (5b) as in (a) gave the same free base (7) (95 mg).

Acylation of the Free Base (7).—The free base (7) (58 mg) was dissolved in methylene chloride (5 ml) at −10 °C. Triethylamine (20 mg) was added, followed by phenoxyacetyl chloride (33 mg) in methylene chloride (0.5 ml). The solution was washed with dilute aqueous sodium hydrogen carbonate followed by brine, dried, and evaporated. Chromatography gave the acylamino-derivative (8) as an amorphous solid (63 mg), $\nu_{max.}$ 3 380, 1 785, 1 740, and 1 685 cm^{-1}; δ 1.47 (9 H, s), 4.04 (2 H, s), 4.55 (2 H, s), 5.71 (1 H, d,

[15] E. G. Brain, A. J. Eglington, J. H. C. Nayler, M. J. Pearson, and R. Southgate, *J.C.S. Perkin I*, 1976, 447.

J 5 Hz), 5.97 (1 H, dd, *J* 5 and 10 Hz), and 6.82—7.73 (7 H, m) (Found: C, 53.8; H, 5.0; N, 15.3; S, 7.6. $C_{20}H_{23}N_5O_5S$ requires C, 53.9; H, 5.2; N, 15.7; S, 7.2%).

Preparation of the Free Acid (9).—The acylated derivative (8) (118 mg) was dissolved in trifluoroacetic acid (3 ml). After 30 min the solvent was evaporated off, the residue treated with toluene, and the mixture evaporated; this procedure was repeated. Trituration with ether gave the free acid (9) as a white amorphous solid (90 mg), $\nu_{max.}$ (Nujol) 3 260br, 1 780, 1 745sh, and 1 680 cm^{-1}; δ [$CDCl_3$–$(CD_3)_2SO$] 4.07 (2 H, s), 4.53 (2 H, s), 5.75 (1 H, dd, *J* 5 and 9 Hz, collapsing to a d, *J* 5 Hz, on D_2O exch.), 5.98 (1 H, d, *J* 5 Hz), 6.75—7.6 (7 H, m, 1 H exch.), and 8.18 (1 H, d, *J* 9 Hz, exch.).

(3R,4R)-1-[*Hydroxy*-(*t-butoxycarbonyl*)*methyl*]-4-*methylthio*-3-*triphenylmethylaminoazetidin*-2-*one* (13).—Treatment of the azetidinone (12) [15] (5.6 g) with t-butyl glyoxylate (17.7 g) in refluxing benzene (120 ml) as described for the azetidinone (1) afforded the alcohol (13) as an amorphous solid (5.68 g), $\nu_{max.}$ 3 460, 3 250, 1 770, and 1 735 cm^{-1}, a mixture of isomers in the ratio *ca.* 5 : 3 [the two C*H*·OH signals appeared at δ 5.05 and 5.24 (after D_2O exch.)]; δ 1.48 (9 H, s), 1.69 and 1.90 (3 H, two s), 3.0 (1 H, d, *J* 10 Hz, exch.), 4.03br (1 H, s, exch.), 4.22—4.78 (2 H, m), 4.96—5.38 (1 H, m, collapses to two s, 5.05 and 5.24, on D_2O exch.), and 7.08—7.73 (15 H, m).

(3R,4R)-1-[*Azido*-(*t-butoxycarbonyl*)*methyl*]-4-*methylthio*-3-*triphenylmethylaminoazetidin*-2-*one* (11).—The alcohol (13) (5.6 g) was converted into the azide (11) by the procedure for the preparation of (4). The product was an amorphous solid (4 g), $\nu_{max.}$ 3 280, 2 120, 1 770, and 1 745 cm^{-1}; δ 1.4 (9 H, s), 1.7 and 1.87 (3 H, two s), 2.93 (1 H, d, *J* 10 Hz, exch.), 4.27—4.67 (2 H, m), 5.1 and 5.23 (1 H, two s, methine protons of major and minor isomers, respectively), and 7.13—7.87 (15 H, m). The material was a mixture of isomers in a ratio consistent with that in the starting alcohol (13). The two isomers could not be crystallised and were inseparable by t.l.c.

Dimethyl 1-[2-*Methylthio*-4-*oxo*-3-*triphenylmethylaminoazetidin*-1-*yl*-(*t-butoxycarbonyl*)*methyl*]-1,2,3-*triazole*-4,5-*dicarboxylate* (10).—The azide (11) (529 mg) was refluxed in toluene (5 ml) containing dimethyl acetylenedicarboxylate (284 mg) for 1 h. The solvent was evaporated off and the residue chromatographed on silica to give the amorphous triazole (10) (490 mg), $\nu_{max.}$ 1 775 and 1 750 cm^{-1}; δ 1.43 (9 H, s), 1.72 and 1.78 (3 H, two s), 3.0br (1 H, s, exch.), 3.97 (6 H, s), 4.33—5.07 (2 H, m), 6.83 and 6.97 (1 H, two s), and 7.2—7.92 (15 H, m). The isomer ratio, as judged by the relative intensities of the methine singlets at δ 6.83 and 6.97, was identical with that of the starting azide (11).

Dimethyl 1-[3-*Amino*-2-*methylthio*-4-*oxoazetidin*-1-*yl*-(*t-butoxycarbonyl*)*methyl*]-1,2,3-*triazole*-4,5-*dicarboxylate* (14).—Detritylation of the triazole (10) (355 mg) with toluene-*p*-sulphonic acid (105 mg) as described for (5) afforded the free base (14) as a gummy foam (176 mg), $\nu_{max.}$ 3 450, 3 330, 1 780, 1 750, and 1 740sh cm^{-1}; δ 1.45 (9 H, s), 1.75 (2 H, s, exch.), 2.07 and 2.12 (3 H, two s), 3.98 (6 H, s), 4.65 (1 H, d, *J* 5 Hz), 5.18 and 5.48 (1 H, two d, *J* 5 Hz), and 6.88 and 7.03 (1 H, two s, methine proton of each isomer). The product, homogeneous by t.l.c., was again a mixture of isomers, the ratio being identical with that of the starting azide (11).

I thank my colleagues at Beecham Pharmaceuticals for advice and encouragement.

[6/1382 *Received*, 15*th July*, 1976]