Transformations of Penicillins: Reactions of Secopenicillanic Acid Derivatives with Ethyl *N*-Chloro-*N*-sodiocarbamate [1]

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3β-Acetamido-4-(methylthio)azetidin-2-one (1) did not react with ethyl *N*-chloro-*N*-sodiocarbamate, in contrast with its ready reaction with *N*-chloro-*N*-sodiotoluene-*p*-sulphonamide. The 4-(methylsulphinyl)azetidin-2-ones (2) reacted with the former reagent to give 3,3-bis(ethoxyformamido)-4-(methylsulphinyl)azetidin-2-ones (5), whereas the 4-(methylsulphinimidoyl)azetidin-2-ones (3), gave 3,3-bis(ethoxyformamido)-products (8) together with 3β-acetamido-3α-ethoxyformamido-products (9). The sulphimides (8) and (9) were transformed into new 1-ethoxyformamido-4-oxa-2,6-diazabicyclo[3.2.0]hept-2-en-7-ones (11) and (13).

INVESTIGATIONS [2] of the reactions of penicillanic and secopenicillanic acid derivatives with *N*-halogeno-*N*-metallo-reagents such as chloramine T and *N*-chloro-*N*-sodiocarbamates have led to new methods of modifying the penam nucleus without disruption of the β-lactam ring. We have demonstrated, for example, that 3β-amidoazetidin-2-ones (1) react with chloramine T to give sulphoxides (2a and b) or sulphimides (3a and b), and that new routes to oxazolinoazetidinones can thus be derived. These studies have been extended, and this paper describes the reactions of ethyl *N*-chloro-*N*-sodiocarbamate (4) with the acetamidoazetidin-2-one (1) and with the corresponding azetidin-2-one sulphoxides (2a and b) and sulphimides (3a and b).

Unexpectedly, when the azetidin-2-one (1) was treated with an excess of the carbamate (4) in acetonitrile or other non-protic solvents, no reaction occurred. The corresponding 3β-phenoxyacetamido- and 3β-phthalimido-azetidin-2-ones were also unreactive. This was in marked contrast to the ready reactions afforded by chloramine T, reflecting differences in the behaviour of these reagents as sources of ' chloronium ' ion and of *N*-anions. The reactivity of the related 4-sulphoxides (2a and b), in which H-3 was expected to be more reactive, was therefore studied. An inseparable diastereoisomeric mixture of the sulphoxides (2a and b) reacted readily with an excess of the carbamate (4), affording two isomeric products ($C_{22}H_{29}N_3O_9S$) which were separated chromatographically. The n.m.r. spectrum of each exhibited signals for a single uncoupled β-lactam proton and two non-equivalent ethoxyformamido-groups. The 3β-acetamido-side chain was absent in each case. Structures (5a and b), differing in sulphoxide stereochemistry, were assigned. [$^2H_6$]Dimethyl sulphoxide-induced chemical shift studies [3] showed that the less polar isomer contained an intramolecular hydrogen bond between the 3β-amide and the 4β-sulphoxide systems. The more polar isomer contained no intramolecular hydrogen bond. Molecular models showed that because of methyl

^{1}H N.m.r. data (δ values)

	SOMe	3α-N*H*·CO_2Et	3β-N*H*·CO_2Et
(5a) (less polar isomer)	2.85	6.67	8.04
(5b) (more polar) isomer)	2.51	6.12	6.38

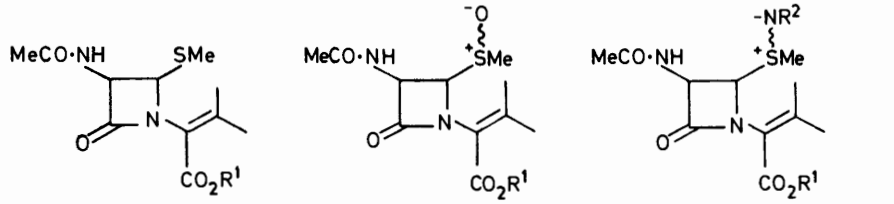
[1] Preliminary communication, D. H. Bremner, M. M. Campbell, and G. Johnson, *Tetrahedron Letters*, 1975, 3331.

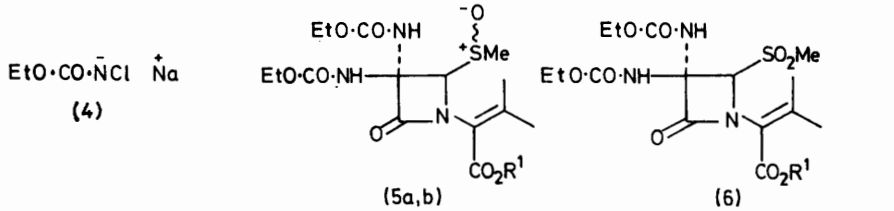
[2] M. M. Campbell, G. Johnson, A. F. Cameron, and I. R. Cameron, *J.C.S. Perkin I*, 1975, 1208; M. M. Campbell and G. Johnson, *ibid.*, pp. 1077, 1212, 1932; *J.C.S. Chem. Comm.*, 1975, 479; D. H. Bremner, M. M. Campbell, and G. Johnson, *ibid.*, 1976, 293; *Tetrahedron Letters*, 1975, 2955.

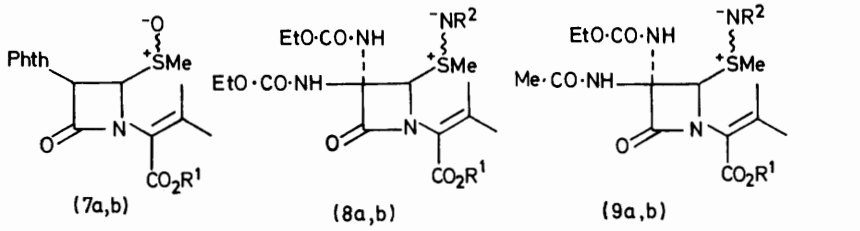
[3] R. D. G. Cooper, P. V. DeMarco, J. C. Cheng, and N. D. Jones, *J. Amer. Chem. Soc.*, 1969, **91**, 1408.

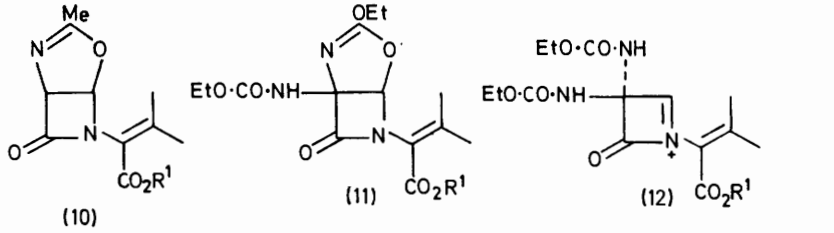
sulphoxide–dehydrovalinate steric interactions, intramolecular hydrogen bonding was possible only in the (*R*)-sulphoxide. Oxidation of each sulphoxide to a common sulphone (6) confirmed their diastereoisomeric nature.

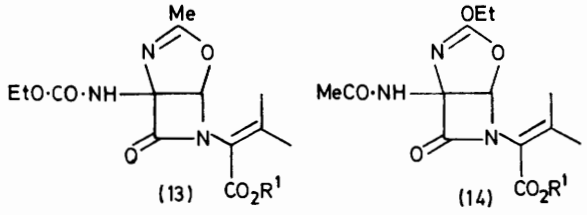
were separated with difficulty and identified as the 3,3-disubstituted azetidin-2-ones (8a and b). Also obtained, as an inseparable diastereoisomeric mixture, were the 3β-acetamido-3α-ethoxyformamidoazetidin-2-ones (9a and b). It is assumed that these products stem from an











$R^1 = CH_2Ph$ $R^2 = p\text{-}MeC_6H_4\cdot SO_2$
Phth = phthalimido

The 3β-phthalimidoazetidin-2-one sulphoxides (7a and b) did not react with the carbamate (4).

When the diastereoisomeric mixture of the sulphimides (3a and b) was similarly treated with an excess of the carbamate (4), two products were obtained, which intermediate 3-imine, with incoming amidate anion attacking from the less hindered α-face. Apparently the sulphimide group does not activate H-3 to quite the same extent as the sulphoxide group in these reactions.

We had previously shown [2] that certain reactions of

3β-amido-4β-sulphinimidoylazetidin-2-ones led to intramolecular displacement of the sulphimide and formation of oxazolinoazetidinones (10). The products (8) and (9) were therefore potential precursors of bridgehead-substituted oxazolinoazetidinones, an unusual class of bicyclic heterocycle.[4] Thus, the 3,3-disubstituted diastereoisomers (8a and b) were treated with *m*-chloroperbenzoic acid to give the 4-oxa-2,6-diazabicyclo[3.2.0]-hept-2-en-7-one (11), $[\alpha]_D^{22}$ 0°. The product (11) is probably racemic, indicating the possible intermediacy of the symmetrical azetinone (12).

The monoethoxyformamidoazetidin-2-one sulphimides (9a and b) afforded the corresponding product (13), $[\alpha]_D^{22}$ +28° (*c* 1.00 in $CHCl_3$). The i.r. spectrum showed loss of the secondary amide function, and the n.m.r. spectrum a marked change in the chemical shift of the acetamido-CH_3 group relative to the 3β-acetamides. Furthermore, the chemical shift of the 3-methyl group in (13) was identical with that of the corresponding group in compound (10),[2] establishing structure (13) rather than the alternative (14).

New reactions of the secopenicillanates, complementing those uncovered in related studies with chloramine T, have therefore emerged, and novel bridgehead-substituted oxazolinoazetidinones have been prepared. In addition, differences in activation requirements for H-6 in penicillanates [2] and penicillanate *S*-oxides,[2] and H-3 in secopenicillanates have been observed.

EXPERIMENTAL

General details are as reported in previous papers.[2]

Reaction of (3R,4R)-3-*Acetamido*-1-(1-*benzyloxycarbonyl*-2-*methylprop*-1-*enyl*)-4-[(R)- *and* (S)-*methylsulphinyl*]*azetidin*-2-*ones* (2a *and* b) *with Ethyl* N-*Chloro*-N-*sodiocarbamate* (4).—To the mixture of (2a and b) (0.30 g, 0.80 mmol) in acetonitrile (10 ml) was added the carbamate (4) (0.50 g, 3.40 mmol). The suspension was stirred until t.l.c. indicated complete reaction, diluted with ethyl acetate, washed twice with water, and dried ($MgSO_4$). Evaporation *in vacuo*, followed by chromatography, gave the major product (4R)-1-(1-*benzyloxycarbonyl*-2-*methylprop*-1-*enyl*)-3,3-*bis*(*ethoxyformamido*)-4-[(R)-*methylsulphinyl*]*azetidin*-2-*one* (5a) (0.14 g, 40%) as an amorphous solid, $[\alpha]_D^{22}$ −183° (*c* 1.23 in $CHCl_3$), $\nu_{max.}$ (film) 3 270 (amide NH), 1 792 (β-lactam C=O), 1 725 (ester and carbamate C=O), and 1050 cm^{-1} (S=O), δ ($CDCl_3$) 1.23 and 1.25 (each 3 H, t, *J* 7 Hz, O·CH_2·CH_3), 2.12, 2.28, and 2.85 (each 3 H, s, 3 × Me), 4.10 and 4.12 (each 2 H, q, *J* 7 Hz, O·CH_2·CH_3), 4.95 (1 H, s, 4-H), 5.06 and 5.30 (each 1 H, d, *J* 12 Hz, PhC$H_a$$H_b$ and PhC$H_a$$H_b$), 6.67 (1 H, s, NH), 7.32 (5 H, s, Ph), and 8.04 (1 H, s, NH) (Found: C, 53.3; H, 6.1; N, 8.5; S, 6.3. $C_{22}H_{29}N_3O_8S$ requires C, 53.5; H, 5.9; N, 8.5; S, 6.5%). The minor product (0.05 g, 18%), the (S)-S-*oxide* (5b), was also obtained as an amorphous solid (0.05 g, 20%), $[\alpha]_D^{22}$ +31.4° (*c* 1.5 in $CHCl_3$), $\nu_{max.}$ (film) 3 310 (amide NH), 1 792 (β-lactam C=O), 1 726 (ester and carbamate C=O), and 1 052 cm^{-1} (S=O), δ($CDCl_3$) 8.23 and 8.25 (each 3 H, t, *J* 7 Hz, O·CH_2·CH_3), 2.20, 2.25 and 2.51 (each 3 H, s, 3 × Me), 4.08 and 4.12 (each 2 H, q, *J* 7 Hz, O·CH_2·CH_3), 4.97 (1 H, s, 4-H), 5.05 and 5.32 (each 1 H, d, *J*, 12 Hz, PhC$H_a$$H_b$ and PhC$H_a$$H_b$), 6.12br and 6.38br (each 1 H, d, 2 × NH), and 2.67 (5 H, s, *Ph*CH_2) (Found: C, 53.5; H, 6.0; N, 8.5; S, 6.3%).

Oxidation of the S-*Oxides* (5a *and* b) *to the* SS-*Dioxide* (6).—The isomer (5a) (0.05 g, 0.1 mmol) in methylene chloride was treated dropwise with a solution of *m*-chloroperbenzoic acid until t.l.c. indicated complete reaction. The solution was then washed with aqueous sodium hydrogen carbonate and water, dried ($MgSO_4$), and evaporated *in vacuo* to give (4R)-1-(1-*benzyloxycarbonyl*-2-*methylprop*-1-*enyl*)-3,3-*bis*-(*ethoxyformamido*)-4-(*methylsulphonyl*)*azetidin*-2-*one* (6) (0.048 g, 93%) as an amorphous solid, $[\alpha]_D^{22}$ −76° (*c* 2.74 in $CHCl_3$), $\nu_{max.}$ (film) 3 330 (amide NH), 1 796 (β-lactam C=O), and 1 725 cm^{-1} (ester and carbamate C=O), δ($CDCl_3$) 2.25 (6 H, t, *J* 7 Hz, 2 × O·CH_2·CH_3), 2.10, 2.28, and 2.99 (each 3 H, s, 3 × Me), 4.1 and 4.15 (each 2 H, q, *J* 7 Hz, O·CH_2·CH_3), 5.07 and 5.35 (each 1 H, d, *J* 13 Hz, PhC$H_a$$H_b$ and PhC$H_a$$H_b$), 5.35 (1 H, s, 4-H), 6.53br and 6.65br (each 1 H, s, 2 × NH), and 7.33 (5 H, s, Ph) (Found: M^+, 511.1617. $C_{22}H_{29}N_3O_9S$ requires *M*, 511.1624). The 1-oxide (5b) was similarly converted into (6) (90%).

Reaction of (3R,4R)-3-*Acetamido*-1-(1-*benzyloxycarbonyl*-2-*methylprop*-1-*enyl*)-4-[(R)- *and* (S)-*methylsulphinimidoyl*]-*azetidin*-2-*one* (3a *and* b) *with the Carbamate* (4).—To a solution of the diastereoisomeric sulphimides (3a and b) (0.79 g, 1.49 mmol) in acetonitrile (12 ml) was added the carbamate (4) (0.44 g, 2.96 mmol). When t.l.c. indicated complete reaction, the suspension was diluted with ethyl acetate and washed twice with water; the organic phase was dried ($MgSO_4$) and concentrated *in vacuo*. The resultant oil was chromatographed, yielding as an amorphous solid (4R)-1-(1-*benzyloxycarbonyl*-2-*methylprop*-1-*enyl*)-3,3-*bis*(*ethoxyformamido*)-4-[(R)-N-(p-*tolylsulphonyl*)*methylsulphinimidoyl*]-*azetidin*-2-*one* (8a) (0.20 g, 20%) as an amorphous solid, $[\alpha]_D^{22}$ −2.5° (*c* 1.20 in $CHCl_3$), $\nu_{max.}$ (film) 3 310 (amide NH), 1 800 (β-lactam C=O), 1 725 (ester and carbamate C=O), 1 145 and 1 090 (SO_2) and 1 000 cm^{-1} (S=N), δ($CDCl_3$) 2.25 (6 H, t, *J* 7 Hz, 2 × O·CH_2·CH_3), 1.06, 1.20, 1.37, and 1.61 (each 3 H, s, 4 × Me), 4.14 (4 H, q, *J* 7 Hz, 2 × O·CH_2·CH_3), 5.24 (2 H, s, PhCH_2), 5.58 (1 H, s, 4-H), 6.45br (1 H, s, NH), and 7.10—8.00 (10 H, m, aromatic and NH) (Found: C, 54.6; H, 5.9; N, 8.9. $C_{29}H_{36}N_4S_2O_9$ requires C, 54.7; H, 5.6; N, 8.6%). Further elution gave the diastereoisomer (8b) (0.20 g, 20%), as an amorphous solid, slightly contaminated by (8a), $\nu_{max.}$ (film) 3 290 (amide NH), 1 800 (β-lactam C=O), 1 725 (ester and carbamate C=O), 1 140 and 1 087 (SO_2) and 990 cm^{-1} (S=N), δ($CDCl_3$) 2.22 (6 H, t, *J* 7 Hz, 2 × O·CH_2·CH_3), 1.95, 2.07, 2.35, and 2.80 (each 3 H, s, 5 × Me), 4.05 and 4.18 (each 2 H, q, *J* 7 Hz, 2 × O·CH_2·CH_3), 5.20 (2 H, s, PhCH_2), 5.69 (1 H, s, 4-H), 6.04br and 6.30br (each 1 H, s, 2 × NH), and 7.00—8.90 (9 H, m, aromatic). The final product eluted was an inseparable diastereoisomeric mixture of (4*R*)-3-acetamido-1-(1-benzyloxycarbonyl-2-methylprop-1-enyl)-3-ethoxyformamido-4-[*N*-(*p*-tolysulphonyl)methylsulphinimidoyl]azetidin-2-ones (9a and b) (0.21 g, 23%), obtained as an amorphous solid, $\nu_{max.}$ (mixture; film) 3 280 (amide NH), 1 790 (β-lactam C=O), 1 725 (ester and carbamate C=O), 1 690 (amide C=O), 1 135 and 1 085 (SO_2), and 990 cm^{-1} (S=N), δ($CDCl_3$) (isomer a) 1.25 (3 H, t, *J* 7 Hz, O·CH_2·CH_3), 2.05 (6 H, s, 2 × Me), 2.15, 2.35, and 2.66 (each 3 H, s, 3 × Me), 4.05 (2 H, q, *J* 7 Hz, O·CH_2·CH_3), 5.18 (2 H, s, PhCH_2), 5.60 (1 H, s, 4-H), 6.54br (1 H, s, NH), and 7.10—7.90 (10 H, m, aromatic and NH); (isomer b) 1.20 (3 H, t, O·CH_2·CH_3), 2.07 (9 H, m, 3 × Me), 2.35 (6 H, s, 2 × Me), 4.10 (2 H, q, *J* 7 Hz, O·CH_2·CH_3), 6.20br (3 H, s, 4-H and PhCH_2), and 7.10—7.90 (11 H, m, aromatic and 2 × NH).

[4] S.-I. Nakatsuka, H. Tanino, and Y. Kishi, *J. Amer. Chem. Soc.*, 1975, **97**, 5008.

Formation of the Oxazolinoazetidinone (11).—To a solution of the sulphimide (8a) (0.23 g, 0.35 mmol) in methylene chloride (14 ml) at 0 °C was added dropwise a solution of *m*-chloroperbenzoic acid in methylene chloride until t.l.c. indicated complete consumption of starting material. The solution was washed with aqueous sodium hydrogen carbonate and then with water, dried ($MgSO_4$), and evaporated *in vacuo*. The resultant green oil was chromatographed, giving as the major product (1R,5R)-6-(1-*benzyloxycarbonyl*-2-*methylprop*-1-*enyl*)-3-*ethoxy*-1-*ethoxyformamido*-4-*oxa*-2,6-*diazabicyclo*[3.2.0]*hept*-2-*en*-7-*one* (11) (0.11 g, 69%) as a colourless oil, $[\alpha]_D^{22}$ 0.0° (*c* 1.05 in $CHCl_3$), $\nu_{max.}$ (film) 3 310 (amide NH), 1 795 (β-lactam C=O), and 1 725 cm^{-1} (ester C=O), δ($CDCl_3$) 1.25 (3 H, t, *J* 7.5 Hz, O·CH_2·CH_3), 1.99 and 2.27 (each 3 H, s, CMe_2), 4.15 (2 H, q, *J* 7.5 Hz, O·CH_2·CH_3), 5.05 and 5.35 (each 1 H, d, *J* 13 Hz, PhC$H_a$$H_b$ and PhC$H_a$$H_b$) 5.82br (1 H, s, NH), 6.09 (1 H, s, 5-H), and 7.36 (5 H, s, Ph) (Found: M^+, 431.1685. $C_{21}H_{25}N_3O_7$ requires *M*, 431.1692).

Formation of the Oxazolinoazetidinone (13).—In a similar preparation, the diastereoisomers (9a and b) yielded (1R,5R)-6-(1-*benzyloxycarbonyl*)-2-*methylprop*-1-*enyl*)-1-*ethoxyformamido*-3-*methyl*-4-*oxa*-2,6-*diazabicyclo*[3.2.0]*hept*-2-*en*-7-*one* (13) (53%) as a clear oil, $[\alpha]_D^{22}$ +20.8° (*c* 1.92 in $CHCl_3$), $\nu_{max.}$ (film) 3 300 (amide NH), 1 795 (β-lactam C=O), and 1725 cm^{-1} (ester C=O), δ($CDCl_3$) 1.25 (3 H, t, *J* 7 Hz, O·CH_2·CH_3), 1.84 and 1.99 (each 3 H, s, CMe_2), 2.27 (3 H, s, 3-Me), 4.14 (2 H, q, *J* 7 Hz, O·CH_2·CH_3), 5.19 (2 H, s, PhCH_2), 5.90br (1 H, s, NH), 6.05 (1 H, s, 5-H), and 7.32 (5 H, s, aromatic) (Found: M^+ + H, 402.1670. $C_{20}H_{24}N_3O_6$ requires *M* + H, 402.1665).

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