4-Alkyl-thio- and -dithio-azetidinones from Penicillins

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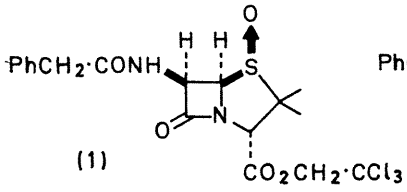
Summary Thiols react smoothly with penicillin sulphoxides to form 4-alkyldithioazetidinones which, by treatment with phosphites or reaction with nucleophiles and alkyl iodides, afford 4-alkylthioazetidinones; some related reactions are also reported.

THE electrophilic properties of the sulphenic acid intermediates produced on heating the penicillin sulphoxide (1) were recently established.[1] It has now been found that thiols also react smoothly with these sulphenic acid intermediates under mild conditions. Thus, heating the penicillin sulphoxide (1) under reflux in 2-methylpropane-1-thiol afforded the crystalline disulphide (2) (70%), m.p. 103—104° $[\alpha]_D^{24}$ + 3·0° (*c* 3·6, $CHCl_3$) in which the double bond had moved into conjugation. The disulphide adduct (2) was employed in either of two ways. By use of the recently developed pyrazoline route[2] the isopentenoyl function attached to the β-lactam nitrogen could be removed. This method consisted of adding diazomethane to give a mixture of the isomeric pyrazolines (3), followed by selective reduction with zinc dust in aqueous acetic acid to release the β-lactam (4), m.p. 72—78° $[\alpha]_D^{20}$ + 161° (*c* 1·0, dioxan). Alternatively, the disulphide (2) could be used to prepare *S*-alkyl derivatives. Thus, reaction of the disulphide (2) with triethyl phosphite (2 equiv.) in dry benzene at reflux for 10 min. followed by silica gel column chromatography of the products, afforded as the major component, the *S*-ethyl derivative (5) (29%), $[\alpha]_D^{22}$ + 4·3° (*c* 1·1, $CHCl_3$), ν_{max} 3350 (NH), 1760 (β-lactam), 1735 (ester), and 1690 cm^{-1}, (amide). The conversion of compound (5) into the β-lactam derivative (6) has already been reported.[2] In a similar manner, trimethyl phosphite reacted with the disulphide (2) to give the *S*-methyl derivative (7) (67%) $[\alpha]_D^{23}$ −3° (*c* 1·1, $CHCl_3$), ν_{max} 3400 (NH), 1765 (β-lactam), 1735 (ester), and 1680 cm^{-1} (amide).

Formation of the thioalkyl derivatives (5) and (7) must proceed by selective phosphorus attack on the disulphide (2) to form the salt (8), which is probably in equilibrium with the quinquecovalent intermediate derivative (9).[3] Alkyl exchange, in a Michaelis–Arbusov manner, proceeds in preference to attack of the thiolate anion on the side-chain phenylacetamido-groups. This is in contrast to the results of reduction of the sulphenic acid, derived from penicillin V sulphoxide, with trimethyl phosphite, which affords the thiazoline (10).[4]

The crystalline carbinolamine (12) (methanol solvate) m.p. 126—128°, $[\alpha]_D^{20}$ + 160° (*c* 0·75, tetrahydrofuran) has been prepared by acid hydrolysis[5] of the isocyanate from the Curtius rearrangement of penicillin G acid azide (*S*)-sulphoxide (11), $[\alpha]_D^{21}$ + 240° (*c* 1·0, tetrahydrofuran).



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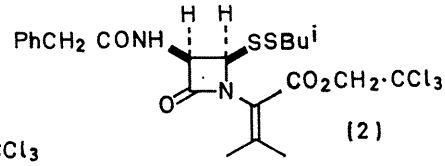

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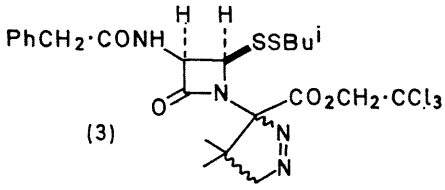

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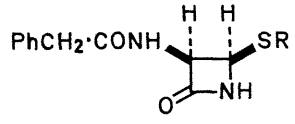
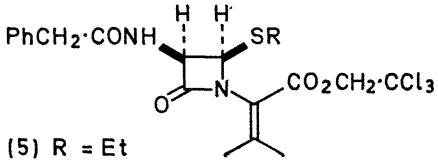
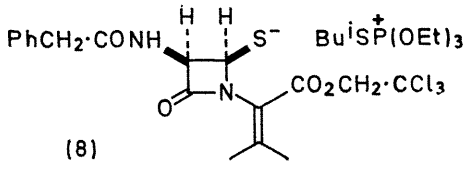


(4) R = SBu^i (14) R = SBu^n
(6) R = Et (21) R = SEt



(5) R = Et
(7) R = Me



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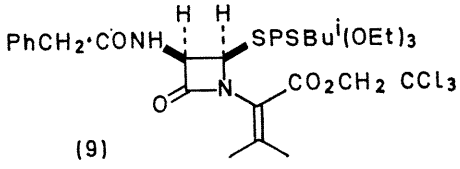

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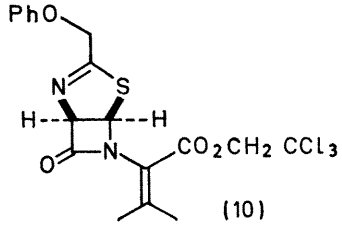
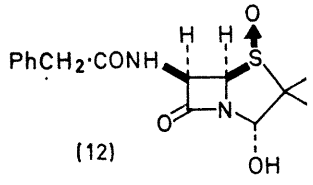


(10)

Heating this with 2-methylpropane-1-thiol afforded the disulphide (4) directly, by spontaneous loss of the isobutenyl substituent on the β-lactam nitrogen in (13). The corresponding crystalline n-butyl compound (14), m.p. 91—94°, $[\alpha]_D^{22}$ + 123·5° (*c* 0·86, tetrahydrofuran), has been similarly prepared. The thiolate anion produced by reaction of the disulphide (4) with tri-n-butylphosphine reacted with ethyl iodide in *NN*-dimethylformamide to form the *S*-ethyl derivative (6).

Heating the crystalline alcohol (15), m.p. 144—146°, $[\alpha]_D^{20}$ + 337° (*c* 1·0, H_2O), obtained by sodium borohydride reduction of the carbinolamine (12), with 2-methylpropane-1-thiol gave a new sulphide with the β-lactam protons coupled by a *J* value of 2·5 Hz, indicative of a *trans*-substituted β-lactam.[6] The latter sulphide was thus formulated as (3*R*,4*S*)-4-(2′-methylpropylthio)-3-phenylacetamidoazetidin-2-one (16), m.p. 116—120°, $[\alpha]_D^{22}$ − 32° (*c* 1·0, tetrahydrofuran), probably resulting from inter-



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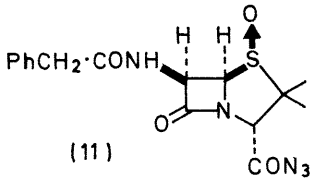

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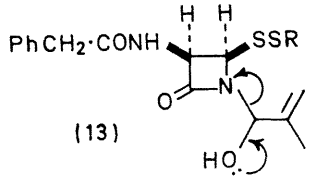

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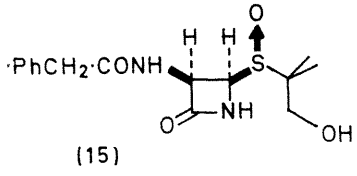

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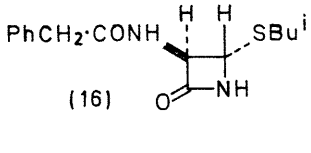

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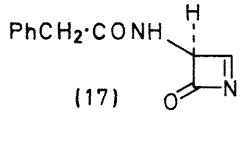

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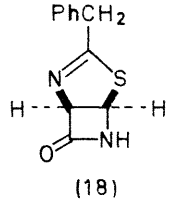

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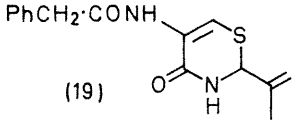

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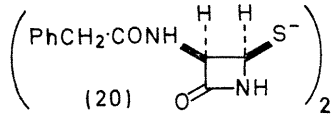

(20)

mediate elimination to an azetinone (17), with subsequent addition of thiol.

Reaction of the carbinolamine (12) with trimethyl phosphite[4] affords the crystalline thiazoline (18), m.p. 182—184° (dec.), $[\alpha]_D^{27}$ + 83° (*c* 1·0, tetrahydrofuran), formed by loss of the isobutenyl side-chain from the β-lactam nitrogen (*cf.* 13), and also the crystalline dihydrothiazinone (19), m.p. 150—152°, $[\alpha]_D^{21}$ ± 0° (*c* 1, tetrahydrofuran), λ_{max} (EtOH) 322 nm (ε 11,300).[7] Oxidation of the thiazoline, with either iodine or hydrogen peroxide in the presence of water, gave the crystalline symmetrical disulphide (20) m.p. 169—171°, $[\alpha]_D^{21}$ — 21° (*c* 1·0, dimethyl sulphxide). Nucleophilic cleavage of this disulphide with tri-n-butylphosphine in *NN*-dimethylformamide followed by alkylation of the generated anion with ethyl iodide gave the *S*-ethyl compound (6). If the phosphine was replaced by sodium sulphide, a mixture of thiolate and dithiolate anions was produced which on alkylation with ethyl iodide, afforded the *S*-ethyl compound (6) and the new disulphide (21) $[\alpha]_D^{20}$ + 125° (*c* 1·0, tetrahydrofuran), ν_{max} (Nujol) 3280 (NH), 1760 (β-lactam), 1670, and 1530 cm^{-1} (amide).

All new compounds gave correct microanalytical data and the expected spectral properties.

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