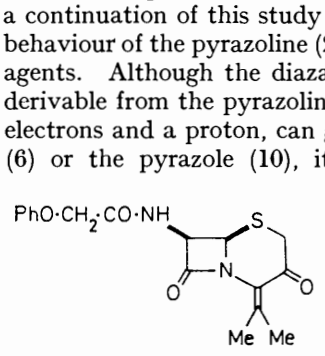
Studies Related to Penicillins. Part XIV.[1] Oxidations of (4*R*,5*R*)-11,11-Dimethyl-4-phenoxyacetamido-6-thia-2,9,10-triazatricyclo[6.3.0.0^{2,5}]-undec-8-en-3-one

By **Richard J. Stoodley** * and **Nigel S. Watson**, Department of Organic Chemistry, The University, Newcastle upon Tyne NE1 7RU

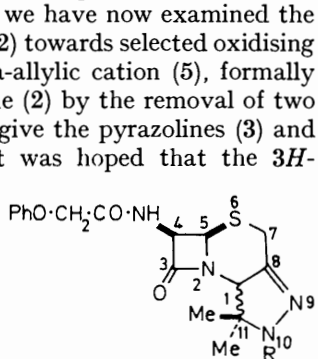
The adduct (13) [or (16)], obtained from the reaction of 4-isopropylidene-3-oxo-7β-phenoxyacetamidocepham (1) with hydrazine, readily undergoes dehydration to give the title pyrazoline (2). *N*-Bromosuccinimide converts the derivative (2) into the 8-bromo-pyrazoline (6), which is transformed into the 8-methoxy-pyrazoline (7) by silver(I) perchlorate in methanol. The 8-acetoxy-pyrazoline (8), formed by the action of lead tetra-acetate on the pyrazoline (2), affords the 8-hydroxy-pyrazoline (9) in the presence of methanolic triethylamine or potassium t-butoxide in tetrahydrofuran. With potassium t-butoxide in t-butyl alcohol, it yields the epimeric alcohol (16). Compounds (7)—(9) lose nitrogen when irradiated to give the cyclopropyl derivatives (18)—(20), respectively. Iron(III) chloride converts the cyclopropanol (20) into the carbinolamine (24).

The pyrazoline (2) reacts with mercury(II) acetate in acetic acid to give the pyrazolinylazetidine diacetate (28), which slowly decomposes with loss of nitrogen to the enone (29) at room temperature.

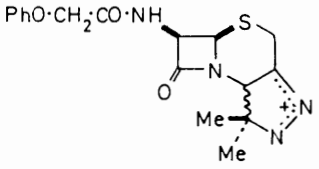
RECENTLY we have reported [2] some transformations of the cepham (1) which were directed towards its conversion into penicillin and cephalosporin analogues. In a continuation of this study we have now examined the behaviour of the pyrazoline (2) towards selected oxidising agents. Although the diaza-allylic cation (5), formally derivable from the pyrazoline (2) by the removal of two electrons and a proton, can give the pyrazolines (3) and (6) or the pyrazole (10), it was hoped that the 3*H*-pyrazole (11) would be formed preferentially. It was intended to examine the photolysis of the derivative (11) as a possible route to the diene (12); irradiation of 4,5,6,7-tetrahydro-3,3-dimethyl-3*H*-indazole is known [3] to yield 1-isopropenylcyclohexene.



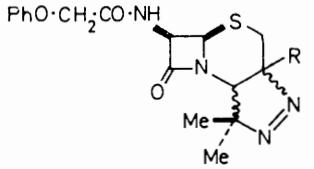
(1)



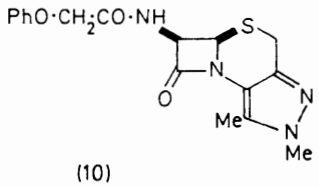
(2) R = H
(3) R = Br
(4) R = Ac



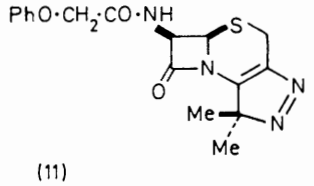
(5)



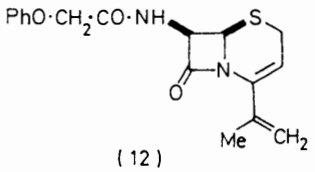
(6) R = Br
(7) R = OMe
(8) R = OAc
(9) R = OH



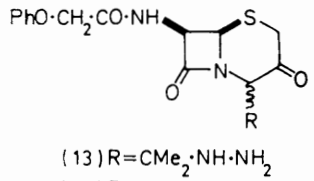
(10)



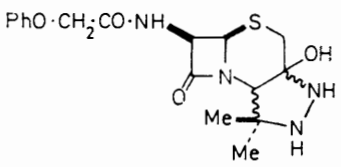
(11)



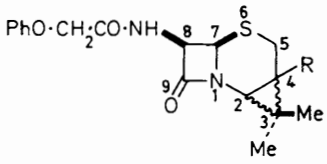
(12)



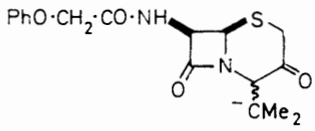
(13) R = $CMe_2 \cdot NH \cdot NH_2$
(14) R = $CHMe_2$
(15) R = $CMe_2 \cdot OH$



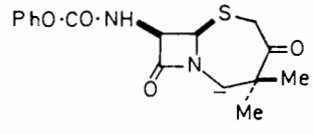
(16)



(17) R = Br
(18) R = OMe
(19) R = OAc
(20) R = OH



(21)



(22)

The addition of hydrazine to a solution of the cepham (1) in dichloromethane resulted in the precipitation of a hydrazine adduct. Spectroscopic considerations indicated that the material possessed either structure (13) or (16). When left in [$^2H_6$]dimethyl sulphoxide solution at 60° or heated in methanol or acetone, the adduct underwent dehydration to give the pyrazoline (2), which appeared to be a single isomer. In common with known Δ^2-pyrazolines,[4] the derivative (2) was *N*-acetylated by

[1] Part XIII, R. J. Stoodley and N. S. Watson, *J.C.S. Perkin I*, 1974, 252.
[2] R. J. Stoodley and N. S. Watson, *J.C.S. Perkin I*, 1973, 2105.
[3] G. L. Closs, W. A. Böll, H. Heyn, and V. Dev, *J. Amer. Chem. Soc.*, 1968, **90**, 173.
[4] T. L. Edwards in 'Heterocyclic Compounds,' ed. R. C. Elderfield, Wiley, New York, 1957, vol. 5, p. 45.

acetic anhydride–pyridine, affording the acetylpyrazoline (4).

When treated with *N*-bromosuccinimide in dichloromethane, the pyrazoline (2) was converted into a single monobromide. N.m.r. spectroscopy did not unambiguously distinguish between the structures (3) and (6); however, the latter was preferred on the basis of u.v. spectroscopy.

It is known that Δ^1-pyrazolines undergo thermal and photochemical decomposition to cyclopropanes;[4,5] consequently, attempts were made to transform the bromopyrazoline (6) into the cyclopropyl bromide (17). However, no identifiable product was isolated when the bromide (6) was heated in xylene at *ca.* 130° or irradiated in benzene at room temperature.

In the hope of forming the 3*H*-pyrazole (11), we treated the bromide (6) with silver(I) perchlorate. No reaction occurred in boiling acetone and mixtures of products were obtained in refluxing acetic acid or aqueous dioxan; however, in boiling methanol a methoxy-derivative was produced, which possessed a u.v. spectrum similar to that of the bromopyrazoline (6). Furthermore, the derivative lost nitrogen to give the methoxycyclopropane (18) when photolysed in benzene, indicating that it possessed the structure (7). This reaction affirmed the structure (6) for the bromopyrazoline.

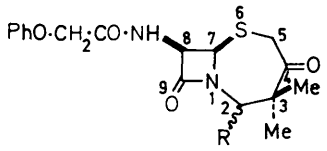
Attempts to eliminate hydrogen bromide from the bromopyrazoline (6) under basic conditions to give the 3*H*-pyrazole (11) were also unsuccessful. Complex mixtures of products were obtained when the bromide (6) was heated with 1,5-diazabicyclo[4.3.0]non-5-ene in deuteriochloroform or potassium t-butoxide in t-butyl alcohol.

When treated with lead tetra-acetate in boiling benzene, the pyrazoline (2) was converted into a single monoacetate, which possessed a u.v. spectrum similar to those of the bromo- (6) and the methoxy-pyrazoline (7). Moreover, when irradiated in benzene, the acetate lost nitrogen to give the cyclopropyl acetate (19), indicating that it possessed the structure (8). The foregoing results parallel those of Freeman, who has shown that 3-acetoxy-Δ^1-pyrazolines are produced by the oxidation of Δ^2-pyrazolines with lead tetra-acetate; pyrolysis of the derivatives affords cyclopropyl acetates.[6]

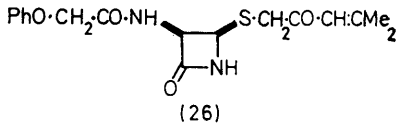
It is well known that cyclopropanols, which can be prepared from cyclopropyl acetates, readily undergo ring-opening reactions.[7] Formally, the cyclopropanol (20) is expected to yield either the carbanion (21) or (22) under basic conditions. Whereas the latter anion is expected to undergo protonation to give the derivative (23), the former species can give rise to either the ketone (14) or the enone (26), depending upon the ease of protonation *versus* β-elimination.

In order to assess the aforementioned reactivity, attempts were made to prepare the cyclopropanol (20). The results of treatment of the cyclopropyl acetate (19) with methanolic triethylamine and with methanolic sodium methoxide were unencouraging. However, the former reagent did convert the acetoxypyrazoline (8) into the alcohol (9), which afforded the cyclopropanol (20) when irradiated in dioxan. Acetylation of the derivative (20) with acetic anhydride–pyridine yielded the cyclopropyl acetate (19), identical with the material obtained by photolysis of the acetoxypyrazoline (8).

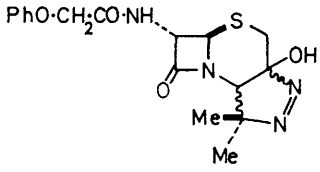
The conversion of the acetate (8) into the alcohol (9) was also accomplished by potassium t-butoxide in tetrahydrofuran. However, with potassium t-butoxide in t-butyl alcohol, an isomer of the alcohol (9) was produced. The coupling constant (1·5 Hz) of the β-lactam protons established that they were *trans* oriented,[8] in accord with the structure (27). Since the



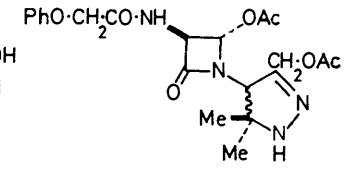
(23) R=H
(24) R=OH
(25) R=Cl



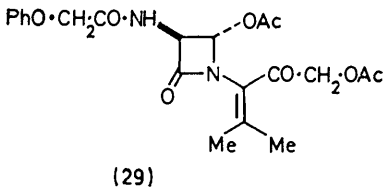
(26)



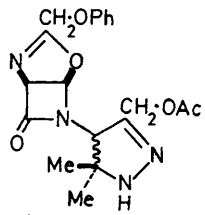
(27)



(28)



(29)



(30)

alcohol (9) was not converted into the isomer (27) under the reaction conditions, the epimerisation must have occurred prior to the deacetylation. Although the base-catalysed epimerisation of penam and cepham derivatives at positions 6 and 7, respectively, is well established,[9] the foregoing example provides a rare case in which the

[5] T. V. Van Auken and K. L. Rinehart, jun., *J. Amer. Chem. Soc.*, 1962, **84**, 3736; W. M. Jones, *ibid.*, 1958, **80**, 6687; 1959, **81**, 5133; 1960, **82**, 3136.
[6] J. P. Freeman, *J. Org. Chem.*, 1964, **29**, 1379.
[7] C. H. DePuy, *Accounts Chem. Res.*, 1968, **1**, 33.
[8] E. J. Corey and A. M. Felix, *J. Amer. Chem. Soc.*, 1965, **87**, 2518; I. McMillan and R. J. Stoodley, *Tetrahedron Letters*, 1966, 1205.
[9] R. J. Stoodley, *Progr. Org. Chem.*, 1973, **8**, 102, and references therein.

reaction occurs at a centre bearing an acylamino-substituent.*

A number of attempts were made to cleave selectively the cyclopropane ring of the derivative (20). The cyclopropanol (20) was unaffected at room temperature by potassium t-butoxide in t-butyl alcohol and by dilute hydrochloric acid; however, when heated with the reagents it decomposed to yield mixtures of non-β-lactam-containing products. With iron(III) chloride in tetrahydrofuran, the derivative (20) was transformed into a product which was considered to be the carbinolamine (24) on the basis of its spectroscopic properties. The *N*-substituent probably directs the opening of the three-membered ring in the foregoing example, since 4-chloro-4-methylpentan-2-one is produced when 1,2,2-trimethylcyclopropanol is treated with the reagent.[10] Presumably, the chloro-amine (25), the expected initial product, was converted into the carbinolamine (24) under the reaction conditions or during the isolation procedure.

In principle, the reaction of the alcohol (9) with a strong base could provide an alternative route to the anion (21). No reaction occurred when the alcohol (9) was treated with potassium t-butoxide in t-butyl alcohol at room temperature and non-β-lactam-containing products were formed at reflux temperature. A complex array of products was also obtained when the alcohol (9) was heated with dilute hydrochloric acid. Recently, Freeman and Rathjen have shown [11] that it is difficult to cleave 3-hydroxy-Δ^1-pyrazolines under acidic or basic conditions.

When treated with mercury(II) acetate in acetic acid, the pyrazoline (2) afforded a product which is formulated as the diacetate (28) on the basis of its analytical and spectroscopic properties. At room temperature the diacetate (28) was slowly transformed into a less polar material, which was isolated after preparative t.l.c.; spectroscopic analysis left little doubt that the product was the enone (29). The mercury(II)-induced conversion of the pyrazoline (2) into the diacetate (28) probably involves the intermediacy of the oxazoline (30), formed by a 5,6-bond cleavage. Penicillanic acid derivatives undergo similar reactions.[12]

EXPERIMENTAL

For general experimental details see Part I.[13] A Hanovia UVS 500/A lamp was used in the irradiation experiments.

Reaction of the Cepham (1) *with Hydrazine.*—Hydrazine hydrate (0·150 g, 3·0 mmol) was added to a stirred solution of the cepham (1) [14] (1·040 g, 3·0 mmol) in dichloromethane (40 ml). After 4 h the adduct (13) [or (16)] (1·040 g, 96%) was filtered off; m.p. 182—184°, $\nu_{max.}$ (KBr) 3320br (NH and OH), 1760 (β-lactam C=O), and 1680 cm^{-1} (amide C=O), τ [$(CD_3)_2SO$] 8·96 and 8·80 (each 3H, s, *gem*-Me_2), 7·10 (2H, ABq, *J* 14 Hz, CH_2·S), 6·25 (1H, s, CH·N), 5·39 (2H, s, CH_2·O), 5·08 (1H, d, *J* 4 Hz, β-lactam H), 4·69 (1H, dd, *J* 8 and 4 Hz, β-lactam H), 4·35br (1H, s, OH or NH), 3·21—2·59 (7H, m, aromatic H and 2 NH), and 1·00 (1H, d, *J* 8 Hz, CO·NH) [addition of D_2O caused the signal at τ 4·69 to collapse to a doublet (*J* 4 Hz) and those at 4·35 and 1·00 to disappear] (Found: C, 54·3; H, 5·6; N, 14·4. Calc. for $C_{17}H_{22}N_4O_4S$: C, 54·0; H, 5·8; N, 14·8%).

The adduct (13) [or (16)] (0·378 g, 1·0 mmol) was heated under reflux in methanol or acetone (100 ml) for 15 min. Evaporation left (4R,5R)-11,11-*dimethyl*-4-*phenoxyacetamido*-6-*thia*-2,9,10-*triazatricyclo*[6.3.0.$0^{2,5}$]*undec*-8-*en*-3-*one* (2) (0·355 g, 99%), m.p. 182—184° (from methanol), $[\alpha]_D$ +85° (0·1% in $CHCl_3$), $\nu_{max.}$ (KBr) 3400br (NH), 1760 (β-lactam C=O), and 1675 cm^{-1} (amide C=O), $\lambda_{max.}$ (EtOH) 221 (ε 12,800), 251 (6800), 263sh (6300), 270 (5500), and 276 nm (4000), τ [$(CD_3)_2SO$] 8·90 and 8·72 (each 3H, s, *gem*-Me_2), 6·28 (2H, ABq, *J* 14 Hz, 7-H_2), 5·50 (1H, s, 1-H), 5·31 (2H, s, CH_2·O), 4·91 (1H, d, *J* 4 Hz, 5-H), 4·62 (1H, dd, *J* 8 and 4 Hz, 4-H), 3·20br (1H, s, NH), 3·06—2·43 (5H, m, aromatic H), and 0·87 (1H, d, *J* 8 Hz, NH) [addition of D_2O caused the signal at τ 4·62 to collapse to a doublet (*J* 4 Hz) and those at 3·20 and 0·87 to disappear] (Found: C, 56·4; H, 5·4; N, 15·3%; M^+, 360. $C_{17}H_{20}N_4O_3S$ requires C, 56·7; H, 5·6; N, 15·6%; *M*, 360).

Reaction of the Pyrazoline (2) *with Acetic Anhydride.*—Acetic anhydride (0·076 g, 0·75 mmol) was added to a solution of the pyrazoline (2) (0·054 g, 0·15 mmol) in dry pyridine (5 ml). After 15 h the solution was diluted with water and extracted with chloroform. The organic layer was washed with dilute hydrochloric acid, followed by sodium hydrogen carbonate solution and water. Evaporation of the dried ($MgSO_4$) organic layer left a residue, which was purified by silica gel chromatography (chloroform as eluant) to give (4R,5R)-10-*acetyl*-11,11-*dimethyl*-4-*phenoxyacetamido*-6-*thia*-2,9,10-*triazatricyclo*[6.3.0.$0^{2,5}$]*undec*-8-*en*-3-*one* (4) (0·040 g, 66%), m.p. 100—102° (from chloroform–light petroleum), $[\alpha]_D$ +32° (0·13% in $CHCl_3$), $\nu_{max.}$ (KBr) 3340 (NH), 1760 (β-lactam C=O), and 1675 cm^{-1} (amide C=O), $\lambda_{max.}$ (EtOH) 218 (ε 9100), 255 (9600), 268sh (6300), and 275sh nm (3300), τ ($CDCl_3$) 8·48 and 8·27 (each 3H, s, *gem*-Me_2), 7·71 (3H, s, MeCO), 6·24 (2H, s, 7-H_2), 5·39 (2H, s, CH_2·O), 5·31 (1H, s, 1-H), 4·94 (1H, d, *J* 4 Hz, 5-H), 4·43 (1H, dd, *J* 9 and 4 Hz, 4-H), and 3·14—2·51 (6H, m, aromatic H and NH) [addition of D_2O caused the signal at τ 4·43 to collapse to a doublet (*J* 4 Hz)] (Found: C, 48·2; H, 4·7; N, 11·2%; M^+, 402. $C_{19}H_{22}N_4O_4S$,0·75$CHCl_3$ requires C, 48·2; H, 4·6; N, 11·4%; *M*, 402).

Reaction of the Pyrazoline (2) *with* N-*Bromosuccinimide.*—*N*-Bromosuccinimide (0·134 g, 0·75 mmol) was added to a solution of the pyrazoline (2) (0·280 g, 0·75 mmol) in chloroform (10 ml). After 90 min the mixture was diluted with chloroform and washed with water. Evaporation of the dried ($MgSO_4$) organic layer gave (4R,5R)-8-*bromo*-11,11-*dimethyl*-4-*phenoxyacetamido*-6-*thia*-2,9,10-*triazatricyclo*[6.3.0.$0^{2,5}$]*undec*-9-*en*-3-*one* (6) (0·344 g, 98%), m.p. 115—116° (decomp.) (from benzene–ether), $[\alpha]_D$ +332° (0·1% in $CHCl_3$), $\nu_{max.}$ (KBr) 3300 (NH), 1755 (β-lactam

* On the basis of n.m.r. spectroscopic evidence, the cepham (1), is considered to undergo epimerisation at position 7 in the presence of alkaline hydrogen peroxide (see ref. 2). Recently it has been reported that methyl phenoxymethylpenicillinate is epimerised at position 6 by lithium di-isopropylamide (G. A. Koppel, *Tetrahedron Letters*, 1973, 4233).

[10] H. L. Jones, unpublished work quoted in ref. 7.
[11] J. P. Freeman and C. P. Rathjen, *J. Org. Chem.*, 1972, **37**, 1686.
[12] R. J. Stoodley and N. R. Whitehouse, *J.C.S. Perkin I*, 1973, **32**; 1974, 181; *J.C.S. Chem. Comm.*, 1973, 477.
[13] I. McMillan and R. J. Stoodley, *J. Chem. Soc.* (*C*), 1968, 2533.
[14] B. G. Ramsay and R. J. Stoodley, *J. Chem. Soc.* (*C*), 1971, 3864.

C=O), and 1680 cm^{-1} (amide C=O), $\lambda_{max.}$ (EtOH) 220 (ε 14,000), 265 (2600), 271 (3200), 277 (3100), and 286 nm (1650), τ (CCl_4) 8·49 (6H, s, *gem*-Me_2), 6·37 (2H, ABq, *J* 14 Hz, 7-H_2), 5·58 (1H, s, 1-H), 5·49 (2H, s, CH_2·O), 5·41 (1H, d, *J* 5 Hz, 5-H), 4·71 (1H, dd, *J* 7 and 5 Hz, 4-H), 3·14—2·57 (5H, m, aromatic H), and 1·84br (1H, d, *J* 7 Hz, NH) [addition of D_2O caused the signal at τ 4·71 to collapse to a doublet (*J* 5 Hz) and that at 1·84 to disappear] (Found: C, 46·3; H, 4·2; N, 12·4%; M^+, 438. $C_{17}H_{19}BrN_4O_3S$ requires C, 46·6; H, 4·3; N, 12·8%; *M*, 438).

Reaction of the Bromopyrazoline (6) *with Silver*(I) *Perchlorate.*—(*a*) The bromopyrazoline (6) (0·044 g, 0·1 mmol) was heated under reflux with silver(I) perchlorate (0·021 g, 0·1 mmol) in acetone (15 ml). Work-up after 2 h afforded the starting material (0·039 g, 89%) (t.l.c. and n.m.r. spectroscopy).

(*b*) Experiment (*a*) was repeated with acetic acid and with 50% aqueous dioxan as solvents. Work-up after 5 h gave mixtures of products (t.l.c. and n.m.r. spectroscopy), which were not separable by silica gel chromatography.

(*c*) A solution of the bromopyrazoline (6) (0·093 g, 0·21 mmol) in methanol (20 ml) was heated under reflux with silver(I) perchlorate (0·044 g, 0·21 mmol). Work-up after 15 h yielded a syrup, which was fractionated by silica gel chromatography [benzene–ether (4 : 1) as eluant] to give (4R,5R)-8-*methoxy*-11,11-*dimethyl*-4-*phenoxyacetamido*-6-*thia*-2,9,10-*triazatricyclo*[6.3.0.$0^{2,5}$]*undec*-9-*en*-3-*one* (7) (0·036 g, 41%), m.p. 163—165° (from benzene–light petroleum), $[\alpha]_D$ +326° (0·1% in $CHCl_3$), $\nu_{max.}$ (KBr) 3320 (NH), 1750 (β-lactam C=O), and 1680 cm^{-1} (amide C=O), $\lambda_{max.}$ (EtOH) 217 (ε 12,100), 262 (1900), 268 (2300), and 274 nm (1900), τ ($CDCl_3$) 8·68 and 8·57 (each 3H, s, *gem*-Me_2), 6·91 (2H, ABq, *J* 14 Hz, 7-H_2), 6·50 (3H, s, MeO), 6·19 (1H, s, 1-H), 5·40 (2H, s, CH_2·O), 5·23 (1H, d, *J* 5 Hz, 5-H), 4·44 (1H, dd, *J* 8·5 and 5 Hz, 4-H), and 3·08—2·45 (6H, m, aromatic H and NH) [addition of D_2O caused the signal at τ 4·44 to collapse to a doublet (*J* 5 Hz)] (Found: C, 55·6; H, 5·5; N, 14·5%; M^+, 390. $C_{18}H_{22}N_4O_4S$ requires C, 55·4; H, 5·6; N, 14·4%; *M*, 390).

Irradiation of the Methoxypyrazoline (7).—A solution of the methoxypyrazoline (7) (0·078 g, 0·2 mmol) in dry benzene (20 ml) was irradiated in a Pyrex tube for 1 h. Evaporation left (7R,8R)-4-*methoxy*-3,3-*dimethyl*-8-*phenoxyacetamido*-6-*thia*-1-*azatricyclo*[5.2.0.$0^{2,4}$]*nonan*-9-*one* (18) (0·072 g, 99%), m.p. 153—155° (from ether–light petroleum), $[\alpha]_D$ +118° (0·1% in $CHCl_3$), $\nu_{max.}$ (KBr) 3420br (NH), 1760 (β-lactam C=O), and 1665 cm^{-1} (amide C=O), $\lambda_{max.}$ (EtOH) 218 (ε 7500), 263 (800), 269 (1000), and 276 nm (800), τ ($CDCl_3$) 8·94 and 8·78 (each 3H, s, *gem*-Me_2), 6·93 (1H, s, 2-H), 6·76 (2H, ABq, *J* 15 Hz, 5-H_2), 6·64 (3H, s, MeO), 5·44 (2H, s, CH_2·O), 5·17 (1H, d, *J* 4·5 Hz, 7-H), 4·32 (1H, dd, *J* 9·5 and 4·5 Hz, 8-H), and 3·17—2·49 (6H, m, aromatic H and NH) [addition of D_2O caused the signal at τ 4·32 to collapse to a doublet (*J* 4·5 Hz)] (Found: C, 59·5; H, 5·9; N, 7·8%; M^+, 362. $C_{18}H_{22}N_2O_4S$ requires C, 59·7; H, 6·1; N, 7·7%; *M*, 362).

Reaction of the Pyrazoline (2) *with Lead Tetra-acetate.*—Lead tetra-acetate (0·688 g, 1·5 mmol) was added to a solution of the pyrazoline (2) (0·540 g, 1·5 mmol) in dry boiling benzene (100 ml). After 10 min the mixture was diluted with chloroform and water. The organic layer was washed with sodium hydrogen carbonate solution followed by water, dried ($MgSO_4$), and evaporated to give (4R,5R)-8-*acetoxy*-11,11-*dimethyl*-4-*phenoxyacetamido*-6-*thia*-2,9,10-*triazatricyclo*[6.3.0.$0^{2,5}$]*undec*-9-*en*-3-*one* (8) (0·620 g, 99%) as a chromatographically homogeneous syrup, $[\alpha]_D$ +36° (0·1% in $CHCl_3$), $\nu_{max.}$ (film) 3280br (NH), 1770 (β-lactam C=O), and 1690 cm^{-1} (amide C=O), $\lambda_{max.}$ (EtOH) 217 (ε 9100), 261 (1600), 268 (1800), and 275 nm (1500), τ ($CDCl_3$) 8·65 and 8·40 (each 3H, s, *gem*-Me_2), 7·84 (3H, s, MeCO), 7·28 and 6·35 (each 1H, d, *J* 15 Hz, 7-H_2), 5·56 (1H, s, 1-H), 5·41 (2H, s, CH_2·O), 5·09 (1H, d, *J* 5 Hz, 5-H), 4·30 (1H, dd, *J* 9·5 and 5 Hz, 4-H), and 3·08—2·49 (6H, m, aromatic H and NH) [addition of D_2O caused the signal at τ 4·30 to collapse to a doublet (*J* 5 Hz)] (Found: M^+, 418·1301. $C_{19}H_{22}N_4O_5S$ requires *M*, 418·1311).

Irradiation of the Acetoxypyrazoline (8).—A solution of the acetoxypyrazoline (8) (0·293 g, 0·7 mmol) in dry benzene (20 ml) was irradiated in a Pyrex tube for 30 h. Evaporation left (7R,8R)-4-*acetoxy*-3,3-*dimethyl*-8-*phenoxyacetamido*-6-*thia*-1-*azatricyclo*[5.2.0.$0^{2,4}$]*nonan*-9-*one* (19) (0·160 g, 59%), m.p. 156—158° (from benzene–light petroleum), $[\alpha]_D$ +152° (0·1% in $CHCl_3$), $\nu_{max.}$ (KBr) 3380br (NH), 1760 (β-lactam C=O), 1745 (ester C=O), and 1665 cm^{-1} (amide C=O), $\lambda_{max.}$ (EtOH) 217 (ε 12,700), 261 (1200), 268 (1600), and 275 nm (1400), τ ($CDCl_3$) 8·91 and 8·84 (each 3H, s, *gem*-Me_2), 7·91 (3H, s, MeCO), 6·82 (1H, s, 2-H), 6·61 (2H, s, 5-H_2), 5·42 (2H, s, CH_2·O), 5·10 (1H, d, *J* 5 Hz, 7-H), 4·20 (1H, dd, *J* 8·5 and 5 Hz, 8-H), and 3·11—2·51 (6H, m, aromatic H and NH) [addition of D_2O caused the signal at τ 4·20 to collapse to a doublet (*J* 5 Hz)] (Found: C, 58·4; H, 5·6; N, 7·1%; M^+, 390. $C_{19}H_{22}N_2O_5S$ requires C, 58·5; H, 5·6; N, 7·2%; *M*, 390).

Reaction of the Acetoxypyrazoline (8) *with Bases.*—(*a*) Triethylamine (0·100 g, 1·0 mmol) was added to a solution of the acetoxypyrazoline (8) (0·420 g, 1·0 mmol) in methanol (30 ml). After 24 h the solution was diluted with chloroform, washed with dilute hydrochloric acid followed by water, and dried ($MgSO_4$). Evaporation gave (4R,5R)-8-*hydroxy*-11,11-*dimethyl*-4-*phenoxyacetamido*-6-*thia*-2,9,10-*triazatricyclo*[6.3.0.$0^{2,5}$]*undec*-9-*en*-3-*one* (9) (0·350 g, 93%), m.p. 226—227° (from chloroform–light petroleum), $[\alpha]_D$ +152° (0·1% in $CHCl_3$), $\nu_{max.}$ (KBr) 3400 and 3320 (NH and OH), 1770 (β-lactam C=O), and 1680 cm^{-1} (amide C=O), $\lambda_{max.}$ (EtOH) 217 (ε 8300), 262 (1100), 268 (1400), and 274 nm (1100), τ [$(CD_3)_2SO$] 8·67 (6H, s, *gem*-Me_2), 6·77 (2H, ABq, *J* 14 Hz, 7-H_2), 6·40 (1H, s, 1-H), 5·33 (2H, s, CH_2·O), 5·16 (1H, d, *J* 4 Hz, 5-H), 4·64 (1H, dd, *J* 9·5 and 4 Hz, 4-H), 3·08—2·50 (5H, m, aromatic H), and 0·89br (1H, d, *J* 9·5 Hz, NH) [addition of D_2O caused the signal at τ 4·64 to collapse to a doublet (*J* 4 Hz) and that at 0·89 to disappear] (Found: C, 54·6; H, 5·5; N, 14·7%; M^+, 376. $C_{17}H_{20}N_4O_4S$ requires C, 54·3; H, 5·3; N, 14·9%; *M*, 376).

(*b*) Potassium t-butoxide (0·034 g, 0·3 mmol) was added to a solution of the acetoxypyrazoline (8) (0·126 g, 0·3 mmol) in dry t-butyl alcohol (3 ml). After 2 h the mixture was diluted with chloroform and washed with dilute hydrochloric acid followed by water. Evaporation of the dried ($MgSO_4$) organic layer gave (4S,5R)-8-*hydroxy*-11,11-*dimethyl*-4-*phenoxyacetamido*-6-*thia*-2,9,10-*triazatricyclo*-[6.3.0.$0^{2,5}$]*undec*-9-*en*-3-*one* (27) (0·054 g, 48%), m.p. 101—103° (from ether–light petroleum), $[\alpha]_D$ +145° (0·2% in $CHCl_3$), $\nu_{max.}$ (KBr) 3370br (NH and OH), 1765 (β-lactam C=O), and 1680 cm^{-1} (amide C=O), $\lambda_{max.}$ (EtOH) 218 (ε 9400), 263 (1300), 270 (1700), and 276 nm (1500), τ ($CDCl_3$) 8·54 (6H, s, *gem*-Me_2), 6·85 (2H, ABq, *J* 14·5 Hz, 7-H_2), 6·18 (1H, s, 1-H), 5·54 (2H, s, CH_2·O), 5·33—5·16 (2H, m, 4-H and 5-H), 4·26br (1H, s, OH), 3·24—2·63 (5H, m, aromatic H), and 2·43br (1H, d, *J* 6·5 Hz, NH) [addition of D_2O caused the signal at τ 5·33—5·16 to collapse to two doublets

(each J 1·5 Hz) and those at 4·26 and 2·43 to disappear] (Found: M^+, 376·1198. $C_{19}H_{20}N_4O_4S$ requires M, 376·1205).

(*c*) A solution of the acetoxypyrazoline (8) (0·251 g, 0·6 mmol) in dry tetrahydrofuran (15 ml) was treated with 0·2M-potassium t-butoxide in t-butyl alcohol (2·0 ml, 0·4 mmol). Work-up after 15 min gave the hydroxypyrazoline (9) (0·184 g, 81%), m.p. 225—227° (from chloroform–light petroleum).

Irradiation of the Hydroxypyrazoline (9).—A solution of the hydroxypyrazoline (9) (0·278 g, 0·8 mmol) in dry dioxan (20 ml) was irradiated in a Pyrex tube for 4 h. The solution was diluted with chloroform, washed (3 times) with water, and dried ($MgSO_4$). Evaporation gave (7R,8R)-4-*hydroxy*-3,3-*dimethyl*-8-*phenoxyacetamido*-6-*thia*-1-*azatricyclo*[5.2.0.0^{2,4}]*nonan*-9-*one* (20) (0·250 g, 97%), m.p. 142—144° (from chloroform–ether), $[\alpha]_D$ +179° (0·18% in $CHCl_3$), $\nu_{max.}$ (KBr) 3460 and 3410 (NH and OH), 1755 (β-lactam C=O), and 1675 cm^{-1} (amide C=O), $\lambda_{max.}$ (EtOH) 220 (ε 12,300), 263 (1500), 270 (1600), and 276 nm (1400), τ ($CDCl_3$) 8·94 and 8·75 (each 3H, s, *gem*-Me_2), 7·01 (1H, s, 2-H), 6·72 (2H, s, 5-H_2), 5·47 (2H, s, CH_2·O), 5·15 (1H, d, J 5 Hz, 7-H), 4·26 (1H, dd, J 9 and 5 Hz, 8-H), and 3·11—2·39 (6H, m, aromatic H and NH) [addition of D_2O caused the signal at τ 4·26 to collapse to a doublet (J 5 Hz)] (Found: C, 58·4; H, 5·6; N, 7·9%; M^+, 348. $C_{17}H_{20}N_2O_4S$ requires C, 58·6; H, 5·8; N, 8·1%; M, 348).

Reaction of the Cyclopropanol (20) *with Acetic Anhydride*.—Acetic anhydride (0·076 g, 0·75 mmol) was added to a solution of the cyclopropanol (20) (0·052 g, 0·15 mmol) in dry pyridine (3 ml) and the mixture was heated under reflux. After 2 h the solution was diluted with water and extracted with chloroform. The organic layer was washed with dilute hydrochloric acid followed by water and dried ($MgSO_4$). Evaporation gave the cyclopropyl acetate (19) (0·053 g, 91%) (t.l.c. and n.m.r. spectroscopy).

Reaction of the Cyclopropanol (20) *with Iron*(III) *Chloride*.—Iron(III) chloride hexahydrate (0·074 g, 0·27 mmol) was added to a stirred solution of the cyclopropanol (20) (0·095 g, 0·27 mmol) in tetrahydrofuran (8 ml). Work-up after 30 min gave a residue, which was purified by silica gel chromatography [chloroform–ethyl acetate (9 : 1) as eluant] to give (7R,8R)-2-*hydroxy*-3,3-*dimethyl*-8-*phenoxyacetamido*-6-*thia*-1-*azabicyclo*[5.2.0]*nonane*-4,9-*dione* (24) (0·050 g, 50%) as a chromatographically homogeneous syrup, $[\alpha]_D$ −34° (0·49% in $CHCl_3$), $\nu_{max.}$ (film) 3400br (NH and OH), 1760 (β-lactam C=O), and 1690 cm^{-1} (amide C=O), $\lambda_{max.}$ (EtOH) 220 (ε 5700), 264 (1300), 270 (1500), and 277 nm (1300), τ [$(CD_3)_2SO$] 8·91 and 8·72 (each 3H, s, *gem*-Me_2), 6·51 (2H, ABq, J 14 Hz, 5-H_2), 5·44 (2H, s, CH_2·O), 5·14 (1H, d, J 4 Hz, 2-H), 4·90—4·66 (2H, m, 7- and 8-H), 3·39 (1H, d, J 4 Hz, OH), 3·21—2·64 (5H, m, aromatic H), and 0·93 (1H, d, J 8 Hz, NH) [addition of D_2O initially caused the doublet at τ 5·14 to collapse to a singlet and that at 3·39 to disappear; subsequently, the signal at 4·90—4·66 collapsed to two doublets (each J 4·5 Hz) and that at 0·93 disappeared] (Found: M^+, 364·1084. $C_{17}H_{20}N_2O_5S$ requires 364·1093).

Reaction of the Pyrazoline (2) *with Mercury*(II) *Acetate*.—The pyrazoline (2) (0·216 g, 0·6 mmol) was added to a stirred solution of mercury(II) acetate (0·382 g, 1·2 mmol) in acetic acid (20 ml). After 90 min the precipitated mercury(I) acetate was filtered off and the filtrate was saturated with hydrogen sulphide and refiltered. The solution was diluted with water, adjusted to *ca.* pH 5 with solid sodium hydrogen carbonate, and extracted with chloroform. After washing with sodium hydrogen carbonate solution and water, the organic layer was dried ($MgSO_4$) and evaporated to yield (3S,4S)-4-*acetoxy*-1-(3-*acetoxymethyl*-5,5-*dimethyl*-Δ^2-*pyrazolin*-4-*yl*)-3-*phenoxyacetamidoazetidin*-2-*one* (28) (0·259 g, 97%), m.p. 178—180° (from benzene–ether), $[\alpha]_D$ −119° (0·2% in $CHCl_3$), $\nu_{max.}$ (KBr) 3420br (NH), 1775 (β-lactam C=O), 1750 (ester C=O), and 1675 cm^{-1} (amide C=O), $\lambda_{max.}$ (EtOH) 220 (ε 8800), 257sh (4900), 263 (5000), 269 (4800), 276 (4000), 328 (3200), and 388sh nm (1700), τ ($CDCl_3$) 8·78 and 8·67 (each 3H, s, *gem*-Me_2), 7·93 (6H, s, 2 MeCO), 5·65 (1H, s, CH·N), 5·51 (2H, s, CH_2·O), 5·11 (1H, dd, J 8·5 and 0·5 Hz, 3-H), 5·05 (2H, ABq, J 14 Hz, CH_2·OAc), 3·78 (1H, d, J 0·5 Hz, 4-H), 3·20—2·56 (6H, m, aromatic H and NH), and 2·29br (1H, d, J 8·5 Hz, NH) [addition of D_2O caused the signal at τ 5·11 to collapse to a doublet (J 0·5 Hz) and that at 2·29 to disappear] (Found: C, 56·8; H, 5·7; N, 12·3%; M^+, 446. $C_{21}H_{26}N_4O_7$ requires C, 56·5; H, 5·8; N, 12·6%; M, 446).

(3S,4S)-4-*Acetoxy*-1-(3-*acetoxy*-1-*isopropylideneacetonyl*)-3-*phenoxyacetamidoazetidin*-2-*one* (29).—After 2 weeks at room temperature the azetidinone (28) (0·089 g, 0·2 mmol) had partially decomposed. The mixture was fractionated by preparative t.l.c. (chloroform as eluant) to give the *enone* (29) (0·030 g, 35%) as a chromatographically homogeneous syrup, $[\alpha]_D$ −32° (1·2% in $CHCl_3$), $\nu_{max.}$ (film) 3360 (NH), 1780 (β-lactam C=O), 1750 (ester C=O), 1700sh (unsat. C=O), and 1685 cm^{-1} (amide C=O), $\lambda_{max.}$ (EtOH) 219 (ε 9200), 250 (4800), 261sh (4000), 269 (3400), and 276 nm (2500), τ ($CDCl_3$) 7·95, 7·87, 7·85, and 7·83 (each 3H, s, *gem*-Me_2 and 2 MeCO), 5·41 (2H, s, CH_2·O), 5·23 (1H, dd, J 10 and 1 Hz, 3-H), 4·97 (2H, ABq, J 16·5 Hz, CH_2·OAc), 3·57 (1H, d, J 1 Hz, 4-H), and 3·09—2·44 (6H, m, aromatic H and NH) [addition of D_2O caused the signal at τ 5·23 to collapse to a doublet (J 1 Hz)] (Found: M^+, 432·1563. $C_{21}H_{24}N_2O_8$ requires M, 132·1533).

We thank Mr. P. Kelly for the mass spectral determinations and the Beecham Research Laboratories for financial support.

[4/232 *Received*, 6*th February*, 1974]