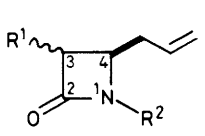
Olivanic Acid Analogues. Part 3.[1] Total Synthesis of C(6α)-Methoxy-substituted 7-Oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylates

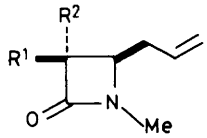
Terence C. Smale * and Robert Southgate
Beecham Pharmaceuticals, Research Division, Brockham Park, Betchworth, Surrey, RH3 7AJ

The reaction of the dianion of 4-allylazetidin-2-one with oxygen gave hydroxylation at the C(3)-position. This intermediate has been converted *via* the phosphorane (**9**) into the 6α-methoxyazabicycloheptene (**13**), which was subsequently functionalised with a C(3)-ethylthio substituent. Since the sodium salt corresponding to ester (**14**) is unstable, the biologically hydrolysable phthalidyl ester (**15**) was prepared.

Since the discovery of the olivanic acids and thienamycin,[2] much effort has been directed towards syntheses of analogues of these potent antibiotics. Papers from these laboratories[3] have shown that 4-allylazetidin-2-one (**1**) is a good synthon for making the 1-azabicyclo[3.2.0]hept-2-ene ring system, and that C(3) sulphur substituents could subsequently be introduced.[4] It has been found for penicillins and cephalosporins that introduction of a 6α(7α)-methoxy group can improve the stability of the molecule to β-lactamases.[5] Therefore we have now prepared 6α-methoxy compounds in the olivanic acid series utilising compound (**1**) as the starting material. Earlier papers from Glaxo[6] and Abbott[7] groups have described alternative methodologies for obtaining 6β-methoxy systems lacking a C(3) substituent.



(**1**) $R^1 = R^2 = H$



(**5**) $R^1 = H$, $R^2 = OMe$

(**2**) $R^1 = H$, $R^2 = SiMe_2Bu^t$

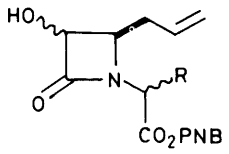
(**6**) $R^1 = OMe$, $R^2 = H$

(**3**) $R^1 = trans-OH$, $R^2 = SiMe_2Bu^t$

(**4**) $R^1 = OH$, $R^2 = H$

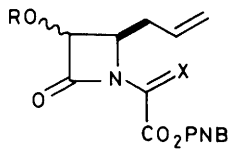
Wasserman and Lipshutz[8] have demonstrated that lithium enolates derived from amides react with molecular oxygen to give α-hydroperoxides which can be reduced to α-hydroxy amides. Our first attempt to apply this reaction to a β-lactam was on the *N*-protected azetidinone (**2**). The C(3) anion was formed at −78 °C and was then caused to react with oxygen at 0 °C for periods of time from 10 min to 2 h. However, only 1—2% of the hydroxy compound (**3**) could be isolated after sodium sulphite reduction of the intermediate hydroperoxide. It was reasoned that the N(1),C(3) dianion derived from unprotected 4-allylazetidin-2-one (**1**) should be more reactive. This hypothesis was tested by firstly treating compound (**1**) with butyl-lithium at 0 °C for 1 h, then bubbling oxygen through the solution for 2 h, and finally adding aqueous sodium sulphite. Chromatography gave recovered compound (**1**) (48%) and a 1:1 mixture of *cis* and *trans* isomers of the 3-hydroxyazetidinone (**4**) (26%).

It was hoped that the hydroxy compound (**4**) could be *O*-methylated to provide the target C(3) substituent. However, the methylation conditions tried, such as 1 equiv. of sodium hydride followed by iodomethane, tended to give recovered starting material plus dimethylated compounds (**5**) and (**6**). Therefore the synthesis was continued with the free hydroxy group and compound (**4**) condensed with *p*-nitrobenzyl glyoxylate to give diol (**7**) as a mixture of diastereoisomers. The commonly used condensation conditions involving refluxing in benzene with azeotropic water removal gave poor yields of (**7**), but a room-temperature method under base catalysis with molecular sieves to remove water was more satisfactory.



(**7**) R = OH

(**8**) R = Cl

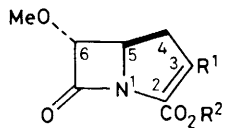


(**9**) R = H, X = PPh_3

(**10**) R = H, X = CH_2

(**11**) R = Me, X = PPh_3

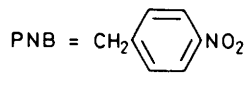
(**12**) R = Me, X = CH_2

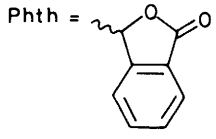


(**13**) $R^1 = H$, $R^2 = PNB$

(**14**) $R^1 = SEt$, $R^2 = PNB$

(**15**) R = SEt, $R^2 = Phth$

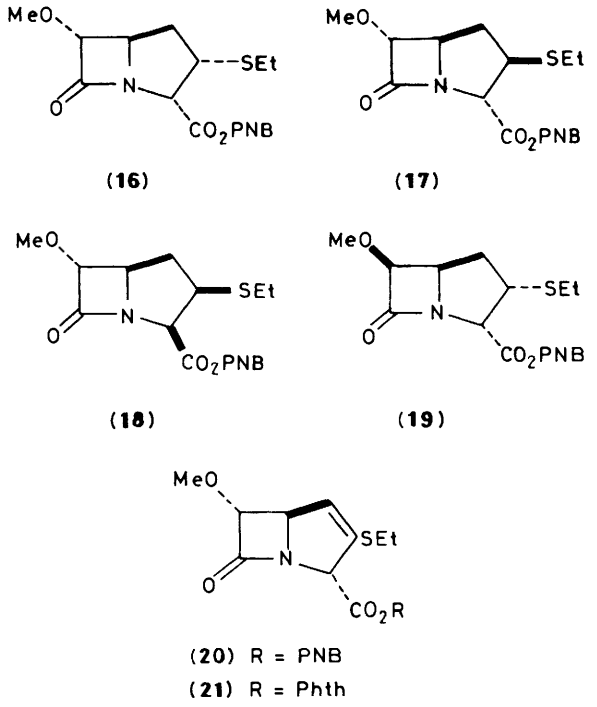




The next stage (chloride formation) required differentiation between the two hydroxy groups in compound (**7**). This was achieved by reaction with thionyl chloride and 2,6-lutidine at low temperature (−20 °C) for only 10 min to give the chloro compounds (**8**) with minimal effect on the C(3) hydroxy group. Treatment of unpurified chlorides (**8**) with triphenylphosphine and 2,6-lutidine then produced the phosphoranes (**9**) in 52% yield from the diol. Such phosphoranes give poor n.m.r. spectra, therefore compounds (**9**) were characterised by reaction with formaldehyde to give the acrylates (**10**), which showed that the material was still a 1:1 *cis–trans* mixture. Purdie methylation of hydroxy phosphoranes (**9**) provided a 93% yield of a *cis–trans* mixture of methoxy derivatives (**11**), which were also characterised by conversion into acrylates (**12**).

The phosphorane function in (**11**) was protected as a phosphonium salt by dissolution in a trifluoroacetic acid–ethyl acetate mixture. Ozonolysis then produced an aldehyde which spontaneously cyclised to the azabicycloheptene after regeneration of the Wittig reagent with sodium hydrogen carbonate. However, only the *trans*-substituted compound (**13**) could be

isolated (47%), the *cis* material being lost during the reaction and chromatography sequence. A 1,4-addition of ethanethiol to (**13**), catalysed by potassium carbonate, in *N*,*N*-dimethylformamide (DMF) gave a mixture of three diastereoisomers (**16**) (58%), (**17**) (6%), and (**18**) (18%). The 2β-isomer (**18**) could be isomerised to the 2α-isomer (**17**) using 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in ethyl acetate. The stereochemistries were assigned by analogy with the compounds reported in our earlier communication.[4a] In one experiment, the unchromatographed crude product from the ozonolysis was immediately treated with ethanethiol to give, in addition to the above adducts, a C(5)–C(6) *cis* compound (**19**) in low yield. This compound was partly decomposed by chromatography, thus supporting the supposed reduced stability of the *cis* series.



Re-introduction of the double bond was achieved by oxidation of compounds (**16**) and (**17**), or mixtures of the two compounds, with iodobenzene dichloride(dichloroiodobenzene)–pyridine[4b] to form mainly the Δ^3 isomer (**20**) (58%) together with a little of the Δ^2 isomer (**14**) (8%). Under the influence of DBU, the double bond in the Δ^3 compound (**20**) isomerised to form an equilibrium mixture from which compounds (**14**) (44%) and (**20**) (31%) were recovered, the latter compound being recycled. The acid-protecting group in compound (**14**) was removed by atmospheric-pressure hydrogenation, but although there was some initial evidence for formation of a sodium salt, it was too unstable to isolate, characterise, or test biologically. This reduction in chemical stability of the olivanic acid ring system which is produced by introduction of a 6α-methoxy group has also been found by other workers in the 6β series.[6]

A biologically labile ester was made by hydrogenation of the Δ^3 compound (**20**) to a sodium salt, which was then esterified with 3-bromophthalide in DMF to produce (**21**) in 64% overall yield. The base-induced double-bond isomerisation resulted in 42% recovery of compound (**21**) and a 23% yield of the required phthalide ester (**15**). Compound (**15**) did not exhibit any antibacterial activity, even when tested in the presence of mouse blood plasma, which should enzymatically cleave such esters.[9]

Experimental

M.p.s were determined with a Kofler hot-stage apparatus. I.r. spectra were recorded for 5% solutions in chloroform, on a Perkin-Elmer 197 spectrophotometer. U.v. spectra were obtained on a Perkin-Elmer 554 spectrophotometer. ^{1}H N.m.r. spectra were obtained using $CDCl_3$ solutions incorporating tetramethylsilane as internal standard, on Varian CFT 20 (80 MHz), Perkin-Elmer R32 (90 MHz), or Bruker WM 250 (250 MHz) instruments. Mass spectra were recorded on a VG 7070 spectrometer operating in the electron-impact (e.i.) mode except where stated (c.i. refers to chemical ionisation mode). The homogeneity of all compounds was tested by t.l.c. on plastic sheets pre-coated with a 0.2 mm thickness of silica gel 60 F_{254} (Merck 5735). Preparative chromatography was carried out using a 'flash' technique[10] on silica gel 60 (finer than 230 mesh ASTM) (Merck 7729) with increased pressure provided by a Medcalf HyFlo pump. Solutions were dried with sodium sulphate, and solvents were evaporated under reduced pressure and below 30 °C on a Büchi rotary evaporator. All compounds prepared are racemic.

(3RS,4RS)-4-*Allyl*-1-[*dimethyl*(*t-butyl*)*silyl*]-3-*hydroxyazetidin*-2-*one* (**3**).—A solution of lithium *N*-isopropylcyclohexylamide was prepared from *N*-isopropylcyclohexylamine (0.38 g) and 2M-butyl-lithium solution (1.35 ml) in dry tetrahydrofuran (THF) (10 ml). This solution was stirred under argon at −78 °C and a solution of (*RS*)-4-allyl-1-[dimethyl-(t-butyl)silyl]azetidin-2-one (**2**)[1] (0.50 g) in dry THF (5 ml) added. After a period of 10 min the reaction flask was transferred to an ice-bath and oxygen was bubbled through the solution for 3 h. The product was reduced in a stirred solution of sodium sulphite (0.32 g) in water (2 ml) and the organic solvent was then evaporated off. The aqueous residue was extracted with ethyl acetate, and the organic phase was washed with brine, dried, and chromatographed on silica gel with ethyl acetate–hexane (3:7 ⟶ 1:0) as eluant to give the hydroxyazetidinone (**3**) as a gum (0.004 g, 1%), $\nu_{max.}$ 3 300, 2 920, 2 860, 1 725, and 1 640 cm^{-1}; δ_H (80 MHz) 0.23 and 0.25 (6 H, 2 s, $SiMe_2$), 0.96 (9 H, s, Bu^t), 1.9—2.8 (2 H, m, 4-CH_2), 3.55 (1 H, ddd, *J* 9, 4, and 2 Hz, 4-H), 4.46 (1 H, d, *J* 2 Hz, 3-H), 5.0—5.3 (2 H, m, =CH_2), and 5.82 (1 H, ddt, *J* 17, 9, and 6 Hz, –CH=); *m*/*z* (NH_3, c.i.) 242 (MH^+); (e.i.) 184 ($M - C_4H_9$).

(3RS,4RS)- *and* (3RS,4SR)-4-*Allyl*-3-*hydroxyazetidin*-2-*one* (**4**).—A solution of (*RS*)-4-allylazetidin-2-one (**1**)[3b] (5.00 g) in dry THF (250 ml) was stirred at 0 °C in an atmosphere of argon and butyl-lithium (75 ml of a 2M solution in hexane) was added during 5 min. A period of 1 h was allowed for dianion formation and dry oxygen was then bubbled through the solution *via* a sintered inlet for 2 h. The product was neutralised with acetic acid (8.9 g) and then reduced by being stirred with a solution of sodium sulphite (5.7 g) in water (20 ml) for 0.5 h. The organic phase was decanted, the solvent was distilled off, and the residue was dissolved in ethyl acetate and dried. Filtration and evaporation followed by chromatography of the residue on a column of silica gel (12 × 4 cm) eluted with chloroform–ethanol (19:1 ⟶ 9:1) gave, firstly, recovered starting material (**1**) (2.40 g, 48%) and then the 1:1 diastereoisomeric mixture of *hydroxyazetidinones* (**4**) as a gum (1.47 g, 26%), (Found: MH^+, 128.0715. $C_6H_9NO_2$ requires *M*H, 128.0711; $\nu_{max.}$ 3 370, 3 280, 2 980, 2 910, 1 745, and 1 640 cm^{-1}; δ_H (90 MHz) 2.1—2.7 (2 H, m, 4-CH_2), 3.5—3.9 (1 H, m, 4-H), 4.44 (0.5 H, t, *J* 2 Hz, *trans* 3-H), 4.91 (0.5 H, dd, *J* 5 and 2 Hz, *cis* 3-H), 4.9—5.3 (3 H, m, =CH_2 and OH), 5.5—6.1 (1 H, m, =CH–), and 6.85 (1 H, br s, NH); *m*/*z* 84 (HOCH=$CHCH_2CH$=CH_2).

4-*Allyl*-3-*methoxy*-1-*methylazetidin*-2-*ones* (**5**) *and* (**6**).—The mixture of hydroxyazetidinones (**4**) (0.031 g) was stirred in dry

THF (2 ml) at 0 °C and 50% sodium hydride dispersion (0.012 g) was added, followed after 20 min by iodomethane (0.2 ml). The cooling bath was removed and the reaction continued for 4 h at room temperature. The solvent was then removed, the residue was dissolved in ethyl acetate, and the solution was washed with brine, dried, and concentrated. Chromatography on silica gel with ethyl acetate–hexane (1:1 ⟶ 6:4) as eluant gave, firstly, the *trans* (3RS,4RS)-*methoxyazetidinone* (**5**) as a gum (0.007 g, 19%) (Found: MH^+, 156.1013. $C_8H_{13}NO_2$ requires *M*H, 156.1024); $\nu_{max.}$ 2 980, 2 920, 2 820, 1 745, and 1 640 cm^{-1}; δ_H (80 MHz) 2.0—2.7 (2 H, m, 4-CH_2), 2.82 (3 H, s, NCH_3), 3.48 (3 H, s, OCH_3), 3.4—3.6 (1 H, m, 4-H), 4.16 (1 H, br s, 3-H), 5.0—5.3 (2 H, m, $=CH_2$), and 5.78 (1 H, ddt, *J* 17, 9, and 6 Hz, –CH=); *m/z* 98 (100%, $MeOCH{=}CHCH_2CH{=}CH_2$).

Next was eluted the *cis* (3*RS*,4*SR*)-methoxyazetidinone (**6**), also as a gum (0.003 g, 8%), $\nu_{max.}$ 2 990, 2 910, 2 820, 1 745, and 1 640 cm^{-1}; δ_H (80 MHz) 2.40 (2 H, t, *J* 6 Hz with fine coupling, 4-CH_2), 2.78 (3 H, s, NCH_3), 3.52 (3 H, s, OCH_3), 3.65 (1 H, td, *J* 6 and 5 Hz, 4-H), 4.44 (1 H, d, *J* 5 Hz, 3-H), 5.0—5.3 (2 H, m, $=CH_2$), and 5.85 (1 H, ddt, *J* 17, 10, and 6 Hz, –CH=). Continued elution provided recovered starting material (**4**) (0.003 g, 10%).

p-*Nitrobenzyl* (4-*Allyl*-3-*hydroxy*-2-*oxoazetidin*-1-*yl*)-*hydroxyacetates* (**7**).—The mixture of hydroxyazetidinones (**4**) (0.100 g) was dissolved in dry THF (5 ml) and treated with *p*-nitrobenzyl glyoxylate (0.268 g), triethylamine (0.008 g), and calcined 3A molecular sieves (0.3 g). The mixture was stirred at room temperature for 20 h and then filtered and concentrated. The residue was chromatographed on silica gel with ethyl acetate–hexane (6:4 ⟶ 4:1) as eluant to give the product (**7**) as a gummy mixture of four diastereoisomers (0.137 g, 52%), $\nu_{max.}$ 3 320, 3 000, 2 920, 1 750, 1 640, 1 610, 1 525, and 1 350 cm^{-1}; δ_H (90 MHz) 2.1—2.7 (2 H, m, 4-CH_2), 3.5—5.4 (7 H, complex m), 5.32 (2 H, s, CH_2Ar), 5.4—6.0 (1 H, m, –CH=), 7.53 (2 H, d, *J* 9 Hz, ArH), and 8.18 and 8.20 (2 H, 2 d, *J* 9 Hz, ArH).

p-*Nitrobenzyl* (4-*Allyl*-3-*hydroxy*-2-*oxoazetidin*-1-*yl*)(*triphenylphosphoranylidene*)*acetates* (**9**).—An argon-blanketed solution of the glycolate (**7**) (0.127 g) in dry THF (8 ml) was cooled to −20 °C and 2,6-lutidine (0.095 ml) was added, followed by thionyl chloride (0.060 ml). After being stirred for 10 min, the reaction mixture was rapidly filtered and the filtrate was concentrated. The crude chloride (**8**) was evaporated twice from toluene and then kept under high vacuum for 15 min. A solution of this material in dry dioxane (8 ml) was treated with triphenylphosphine (0.210 g) and 2,6-lutidine (0.095 ml) and stirred in an atmosphere of argon at room temperature for 2 days. The reaction mixture was concentrated, the residue was dissolved in ethyl acetate, and the solution was washed with brine, dried, and evaporated. The residue was chromatographed on silica gel employing gradient elution with ethyl acetate–hexane (7:3 ⟶ 1:0) and then ethyl acetate–ethanol (1:0 ⟶ 19:1). The early fractions provided an unidentified sulphur-containing phosphorane (0.025 g) and later fractions gave a *cis–trans* mixture of the title phosphoranes (**9**) as a foam (0.113 g, 52%), $\nu_{max.}$ 3 320, 3 000, 1 740, 1 620, 1 610, 1 525, and 1 355 cm^{-1}.

p-*Nitrobenzyl* 2-(4-*Allyl*-3-*hydroxy*-2-*oxoazetidin*-1-*yl*)*acrylates* (**10**).—The mixture of phosphoranes (**9**) (0.070 g) was stirred in dioxane (4 ml) at room temperature and 40% aqueous formaldehyde (0.5 ml) was added. After 18 h the solution was concentrated and the residue was chromatographed on silica gel with ethyl acetate–hexane (1:1) as eluant to give a 1:1 mixture of the cis- *and* trans-*acrylate* (**10**) as a gum (0.031 g, 77%) (Found: M^+, 332.1034. $C_{16}H_{16}N_2O_6$ requires *M*, 332.1005); $\nu_{max.}$ 3 330, 3 000, 1 750, 1 730, 1 610, 1 525, and 1 350 cm^{-1}; δ_H (90 MHz; $CDCl_3$ + D_2O) 2.1—2.7 (2 H, m, 4-CH_2), 4.20 (0.5 H, ddd, *J* 7, 5, and 2 Hz, *trans* 4-H), 4.47 (0.5 H, q, *J* 6 Hz, *cis* 4-H), 4.56 (0.5 H, d, *J* 2 Hz, *trans* 3-H), 4.8—5.2 (2.5 H, m, *cis* 3-H and allyl $=CH_2$), 5.31 (2 H, s, CH_2Ar), 5.5—5.9 (1 H, m, –CH=), 5.94, 6.01, 6.06, and 6.13 (2 H, 4 s, acrylate $=CH_2$), and 7.53 and 8.22 (4 H, 2 d, *J* 9 Hz, ArH).

p-*Nitrobenzyl* (4-*Allyl*-3-*methoxy*-2-*oxoazetidin*-1-*yl*) (*Triphenylphosphoranylidene*)*acetate* (**11**).—A stirred solution of the hydroxy phosphorane mixture (**9**) (0.330 g) in iodomethane (10 ml) was treated with silver oxide (0.165 g) and heated under reflux for 2 h. The solid was filtered from the solution, which was then concentrated and the residue was chromatographed on silica gel with ethyl acetate as eluant to give a *cis–trans* mixture of methoxy phosphoranes (**11**) as a foam (0.314 g, 93%), $\nu_{max.}$ 3 000, 2 930, 1 745, 1 620, 1 520, and 1 350 cm^{-1}.

p-*Nitrobenzyl* 2-(4-*Allyl*-3-*methoxy*-2-*oxoazetidin*-1-*yl*)*acrylates* (**12**).—To a solution of methoxy phosphoranes (**11**) (0.044 g) in dioxane (3 ml) was added 40% aqueous formaldehyde (0.4 ml). The solution was stirred at room temperature for 18 h and then evaporated and the residue was chromatographed on silica gel with ethyl acetate–hexane (1:1) as eluant to produce a *ca.* 1:1 mixture of *cis* and *trans* isomers of the acrylate (**12**) as a gum (0.023 g, 90%), $\nu_{max.}$ 3 000, 2 940, 2 840, 1 755, 1 730, 1 640, 1 610, 1 525, and 1 350 cm^{-1}; δ_H (90 MHz) 2.0—2.7 (2 H, m, 4-CH_2), 3.48 and 3.54 (3 H, 2 s, OCH_3), 4.1—4.8 (2 H, m, 3- and 4-H), 4.8—5.3 (2 H, m, allyl $=CH_2$), 5.30 and 5.32 (2 H, 2 s, CH_2Ar), 5.73 (1 H, ddt, *J* 16, 10, and 7 Hz, –CH=), 6.00, 6.02, 6.05, and 6.16 (2 H, 4 s, acrylate $=CH_2$), and 7.54 and 8.24 (4 H, 2 d, *J* 9 Hz, ArH).

p-*Nitrobenzyl* (5RS,6RS)-6-*Methoxy*-7-*oxo*-1-*azabicyclo*-[3.2.0]*hept*-2-*ene*-2-*carboxylate* (**13**).—A solution of the methoxy phosphorane mixture (**11**) (0.200 g) in ethyl acetate (10 ml) at 10 °C was treated with trifluoroacetic acid (1 ml). After a period of 10 min the solution was cooled to −70 °C and ozonolysed oxygen bubbled through the mixture until it just became blue. Excess of ozone was blown out with a stream of argon and a solution of triphenylphosphine (0.088 g) in ethyl acetate (2 ml) was added. The reaction flask was transferred to an ice-bath after 0.5 h and saturated aqueous sodium hydrogen carbonate (30 ml) was added to the vigorously stirred mixture. The organic layer was separated, washed with brine, dried, and evaporated. Chromatography of the residue on silica gel using ethyl acetate–hexane (1:1) as eluant provided the *bicyclic azetidinone* (**13**) (0.050 g, 47%), m.p. 130—135 °C (from chloroform–ethyl acetate–hexane) (Found: C, 56.6; H, 4.5; N, 8.6. $C_{15}H_{14}N_2O_6$ requires C, 56.6; H, 4.4; N, 8.8%); $\nu_{max.}$ 3 000, 2 950, 2 840, 1 780, 1 730, 1 610, 1 525, and 1 355 cm^{-1}; $\lambda_{max.}$(EtOH) 265 nm (ε 17 200 dm^3 mol^{-1} cm^{-1}); δ_H (90 MHz) 2.78 (1 H, ddd, *J* 19, 9, and 3 Hz, 4-H), 3.02 (1 H, ddd, *J* 19, 9, and 3 Hz, 4-H), 3.52 (3 H, s, OCH_3), 4.31 (1 H, td, *J* 9 and 3 Hz, 5-H), 4.53 (1 H, d, *J* 3 Hz, 6-H), 5.25 and 5.47 (2 H, ABq, *J* 14 Hz, CH_2Ar), 6.45 (1 H, t, *J* 3 Hz, 3-H), and 7.61 and 8.21 (4 H, 2 d, *J* 8 Hz, ArH).

p-*Nitrobenzyl* 3-(*Ethylthio*)-6-*methoxy*-7-*oxo*-1-*azabicyclo*-[3.2.0]*heptane*-2-*carboxylates* (**16**), (**17**), *and* (**18**).—The bicyclic compound (**13**) (0.108 g) was stirred in dry DMF (2 ml) at room temperature and ethanethiol (0.05 ml) and powdered potassium carbonate (0.023 g) were added. After 0.5 h the solvent was removed under high vacuum, the residue was dissolved in ethyl acetate, and the solution was washed with brine, dried, and evaporated. The crude product contained three isomers of the thiol adduct which could be separated by very careful chromatography on silica gel with ethyl acetate–hexane (3:7 ⟶ 4:6) as eluant. The compounds in order of increasing polarity were the (2RS,3RS,5SR,6SR)-*isomer* (**16**) (0.075 g,

58%), m.p. 91—94 °C (from ethyl acetate–hexane) (Found: C, 53.7; H, 5.3; N, 7.3. $C_{17}H_{20}N_2O_6S$ requires C, 53.7; H, 5.3; N, 7.4%); $\nu_{max.}$ 2 940, 1 760, 1 750sh, 1 610, 1 525, and 1 350 cm^{-1}; δ_H (90 MHz) 1.19 (3 H, t, *J* 7 Hz, SCH_2CH_3), 1.9—2.4 (2 H, m, 4-H_2), 2.57 (2 H, q, *J* 7 Hz, SCH_2), 3.40 (1 H, dt, *J* 5 and 7 Hz, 3-H), 3.48 (3 H, s, OCH_3), 4.12 (1 H, dt, *J* 7 and 3 Hz, 5-H), 4.32 (1 H, d, *J* 3 Hz, 6-H), 4.79 (1 H, d, *J* 7 Hz, 2-H), 5.26 (2 H, s, CH_2Ar), and 7.55 and 8.23 (4 H, 2 d, *J* 9 Hz, ArH).

The medium-polarity adduct was the (2RS,3SR,5SR,6SR)-*isomer* (**17**) which was a gum (0.008 g, 6%) (Found: M^+, 380.1039. $C_{17}H_{20}N_2O_6S$ requires 380.1042); $\nu_{max.}$ 2 940, 1 770, 1 750sh, 1 610, 1 525, and 1 355 cm^{-1}; δ_H (90 MHz) 1.23 (3 H, t, *J* 7 Hz, SCH_2CH_3), 1.73 (1 H, dt, *J* 14 and 5 Hz, 4-H), 2.55 (1 H, dt, *J* 14 and 7 Hz, 4-H), 2.57 (2 H, q, *J* 7 Hz, SCH_2), 3.49 (3 H, s, OCH_3), 3.73 (1 H, ddd, *J* 7, 5, and 4 Hz, 3-H), 3.94 (1 H, ddd, *J* 7, 5, and 2 Hz, 5-H), 4.46 (1 H, d, *J* 2 Hz, 6-H), 4.47 (1 H, d, *J* 4 Hz, 2-H), 5.25 (2 H, s, CH_2Ar), and 7.51 and 8.24 (4 H, 2 d, *J* 9 Hz, ArH).

The most polar compound was the (2RS,3RS,5RS,6RS)-*isomer* (**18**) which was also a gum (0.023 g, 18%) (Found: M^+ 380.1038. $C_{17}H_{20}N_2O_6S$ requires 380.1042); $\nu_{max.}$ 2 940, 1 770, 1 745, 1 610, 1 525, and 1 355 cm^{-1}; δ_H (90 MHz) 1.19 (3 H, t, *J* 7 Hz, SCH_2CH_3), 1.87 (1 H, td, *J* 12 and 10 Hz, 4-H), 2.32 (1 H, dt, *J* 12 and 6 Hz, 4-H), 2.57 (2 H, q, *J* 7 Hz, SCH_2), 3.47 (3 H, s, OCH_3), 3.6—4.0 (2 H, m, 3- and 5-H), 4.20 (1 H, d, *J* 7 Hz, 2-H), 4.40 (1 H, d, *J* 2 Hz, 6-H), 5.30 (2 H, s, CH_2Ar), and 7.58 and 8.23 (4 H, 2 d, *J* 9 Hz, ArH).

C(2)-*Isomerisation of Sulphide* (**18**).—A solution of the (2*RS*,3*RS*,5*RS*,6*RS*)-sulphide (**18**) (0.068 g) in ethyl acetate (5 ml) was treated with DBU (0.008 g) and kept at room temperature for 6 h. The reaction product was concentrated and chromatographed on silica gel with ethyl acetate–hexane (3:7) as eluant to isolate the (2*RS*,3*SR*,5*SR*,6*SR*)-sulphide (**17**) (0.040 g, 59%). This was identical with compound (**17**) isolated from the previous experiment (i.r., n.m.r., t.l.c.).

p-*Nitrobenzyl* (2RS,3RS,5SR,6RS)-3-(*Ethylthio*)-6-*methoxy*-7-*oxo*-1-*azabicyclo*[3.2.0]*heptane*-2-*carboxylate* (**19**).—A solution of the mixed methoxy phosphoranes (**11**) (0.632 g) in ethyl acetate (30 ml) was ozonolysed as described in the preparation of compound (**13**) above. The crude product was not chromatographed but was immediately dissolved in dry DMF (6 ml), and ethanethiol (0.16 ml) and potassium carbonate (0.073 g) were added. After 0.5 h the reaction mixture was worked up as described in the thiol addition reaction above. The first thiol adduct to be eluted from the column was the C(5)–C(6) cis-*isomer* (**19**) as a gum (0.024 g, 6%). This product was rechromatographed to improve its purity but this procedure gave a low recovery of compound (0.004 g) (Found: M^+, 380.1026. $C_{17}H_{20}N_2O_6S$ requires *M*, 380.1042); $\nu_{max.}$ 2 950, 2 920, 2 820, 1 770, 1 750, 1 605, 1 525, and 1 350 cm^{-1}; δ_H (250 MHz) 1.20 (3 H, t, *J* 7 Hz, SCH_2CH_3), 1.96 (1 H, dt, *J* 14 and 8 Hz, 4-H), 2.49 (1 H, ddd, *J* 14, 8, and 5 Hz, 4-H), 7.58 (2 H, q, *J* 7 Hz, SCH_2), 3.53 (3 H, s, OCH_3), 3.4—3.6 (1 H, m, 3-H), 4.24 (1 H, dt, *J* 8 and 5 Hz, 5-H), 4.67 (1 H, d, *J* 5 Hz, 6-H), 4.79 (1 H, d, *J* 7 Hz, 2-H), 5.26 (2 H, s, CH_2Ar), and 7.55 and 8.23 (4 H, 2 d, *J* 9 Hz, ArH). Continued elution of the first column provided the previously described C(5)–C(6) *trans*-isomers (total 0.127 g, 31%).

p-*Nitrobenzyl* (2RS,5SR,6SR)-3-(*Ethylthio*)-6-*methoxy*-7-*oxo*-1-*azabicyclo*[3.2.0]*hept*-3-*ene*-2-*carboxylate* (**20**).—The sulphide (**16**) (0.078 g) was dissolved in dry benzene (2 ml) in an atmosphere of argon and dry pyridine (0.035 g) was added. The solution was cooled to 5 °C and iodobenzene dichloride [(dichloroiodo)benzene] (0.062 g) was added. Reaction was allowed to proceed for 2 h at 5 °C and then the solution was partially concentrated and applied to a column of silica gel. Elution with ethyl acetate–hexane (3:7) gave the Δ^3-*compound* (**20**) as a gum (0.045 g, 58%) (Found: M^+, 378.0896. $C_{17}H_{18}N_2O_6S$ requires *M*, 378.0885); $\nu_{max.}$ 3 000, 2 930, 1 775, 1 755sh, 1 610, 1 575, 1 525, and 1 355 cm^{-1}; δ_H (90 MHz) 1.28 (3 H, t, *J* 7 Hz, SCH_2CH_3), 2.81 (2 H, q, *J* 7 Hz, SCH_2), 3.50 (3 H, s, OCH_3), 4.28 (1 H, d, *J* 2 Hz, 6-H), 4.61 (1 H, dt, *J* 3.5 and 2 Hz, 5-H), 5.12 (1 H, dd, *J* 3.5 and 2 Hz, 2-H), 5.26 (2 H, s, CH_2Ar), 5.75 (1 H, t, *J* 2 Hz, 4-H), and 7.53 and 8.21 (4 H, 2 d, *J* 8 Hz, ArH). Continued elution gave a little of the Δ^2-isomer (**14**) (0.006 g, 8%).

p-*Nitrobenzyl* (5RS,6RS)-3-(*Ethylthio*)-6-*methoxy*-7-*oxo*-1-*azabicyclo*[3.2.0]*hept*-2-*ene*-2-*carboxylate* (**14**).—A solution of the Δ^3-compound (**20**) (0.055 g) in dry dichloromethane (5 ml) was stirred at room temperature under argon with DBU (0.006 g) for 2 h. The solution was then evaporated and the residue was chromatographed on silica gel with ethyl acetate–hexane (3:7 ⟶ 1:1) as eluant. This gave recovered starting material (**20**) (0.017 g, 31%) and then the Δ^2-*compound* (**14**) (0.024 g, 44%), m.p. 142—145 °C (from acetone–hexane) (Found: C, 53.7; H, 4.8; N, 7.3. $C_{17}H_{18}N_2O_6S$ requires C, 54.0; H, 4.8; N, 7.4%); $\nu_{max.}$ 3 000, 2 930, 1 780, 1 700, 1 610, 1 550, 1 525, and 1 355 cm^{-1}; $\lambda_{max.}$ (EtOH) (ε/dm^3 mol^{-1} cm^{-1}) 267 (10 300) and 323 nm (12 000); δ_H (250 MHz) 2.34 (3 H, t, *J* 8 Hz, SCH_2CH_3), 2.7—3.0 (2 H, m, SCH_2), 3.10 (1 H, dd, *J* 18 and 9 Hz, 4-H), 3.28 (1 H, dd, *J* 18 and 9 Hz, 4-H), 3.57 (3 H, s, OCH_3), 4.29 (1 H, td, *J* 9 and 2 Hz, 5-H), 4.55 (1 H, d, *J* 2 Hz, 6-H), 5.28 and 5.50 (2 H, ABq, *J* 14 Hz, CH_2Ar), and 7.68 and 8.23 (4 H, 2 d, *J* 9 Hz, ArH).

Attempted Hydrogenolysis of Ester (**14**).—A solution of the *p*-nitrobenzyl ester (**14**) (0.024 g) in dioxane (5 ml) was added to a prehydrogenated suspension of 5% palladium–carbon catalyst (0.036 g) in a mixture of dioxane (5 ml) and water (2.5 ml). The compound was hydrogenated at atmospheric pressure for 3 h, when t.l.c. indicated complete loss of compound (**14**). A solution of sodium hydrogen carbonate (0.0053 g) in water (0.5 ml) was added and the catalyst was then filtered off. The filtrate was washed with ethyl acetate (2 × 5 ml) and then chromatographed on a column of 'Biogel P-2' (200—400 mesh) with water as eluant. The fractions showing the expected extinction at 305 nm were combined and on the basis of the extinction coefficient (ε 8 000 dm^3 mol^{-1} cm^{-1}) were estimated to contain 0.005 g of the sodium salt corresponding to compound (**14**). However, no characterisation was obtained because lyophilisation resulted in decomposition and a 300 μg ml^{-1} aqueous solution lost the required u.v. chromophore on storage at 5 °C for 18 h.

Phthalidyl (2RS,5SR,6SR)-3-(*Ethylthio*)-6-*methoxy*-7-*oxo*-1-*azabicyclo*[3.2.0]*hept*-3-*ene*-2-*carboxylate* (**21**).—5% Palladium–carbon catalyst (0.066 g) in a mixture of dioxane (10 ml) and water (5 ml) was prehydrogenated for 0.5 h. A solution of the *p*-nitrobenzyl ester (**20**) (0.066 g) in dioxane (10 ml) was added, followed by a solution of sodium hydrogen carbonate (0.0147 g) in water (0.5 ml). The mixture was hydrogenated at atmospheric pressure for 1.5 h, then more catalyst (0.030 g) was added and reaction was complete in a further 0.5 h. The reaction mixture was filtered and the filtrate was evaporated to small bulk. Water (10 ml) was added and the aqueous solution was washed with ethyl acetate (2 × 20 ml). The aqueous solution was evaporated to dryness and then re-evaporated three times from toluene and kept under vacuum for 1 h to give the crude sodium salt (0.042 g). This was dissolved in DMF (5 ml) and 3-bromophthalide (0.037 g) was added. After the mixture had been stirred for 1 h at ambient temperature the solvent was removed under high vacuum, the residue was taken up in ethyl acetate, and the solution was washed with brine and dried, and

chromatographed on silica gel with hexane–ethyl acetate (6:4) as eluant. This gave the *phthalidyl ester* (**21**), which was a 1:1 mixture of isomers about the phthalide chiral carbon atom, as a gum (0.042 g, 64%) (Found: M^+, 375.0778. $C_{18}H_{17}NO_6S$ requires M, 375.0777); $\nu_{max.}$ 3 000, 2 920, 1 780, 1 605, 1 570, and 985 cm^{-1}; δ_H (250 MHz) 1.29 and 1.32 (3 H, 2 t, J 7.5 Hz, SCH_2CH_3), 2.7—3.0 (2 H, m, SCH_2), 3.52 and 3.53 (3 H, 2 s, OCH_3), 4.30 and 4.31 (1 H, 2 d, J 2 Hz, 6-H), 4.62 and 4.66 (1 H, 2 dt, J 4 and 2 Hz, 5-H), 5.13 and 5.14 (1 H, 2 dd, J 4 and 2 Hz, 2-H), 5.76 and 5.78 (1 H, 2 t, J 2 Hz, 4-H), 7.41 and 7.42 (1 H, 2 s, OCHO), and 7.5—8.0 (4 H, m, ArH).

Phthalidyl (5RS,6RS)-3-(*Ethylthio*)-6-*methoxy*-7-*oxo*-1-*aza*-*bicyclo*[3.2.0]*hept*-2-*ene*-2-*carboxylate* (**15**).—A solution of the phthalidyl ester (**21**) (0.027 g) in dichloromethane (5 ml) was treated with DBU (0.004 g) and stirred at room temperature for 3 h to establish the Δ^2—Δ^3 equilibrium. The solution was concentrated and rapidly chromatographed on silica gel with ethyl acetate–hexane (1:1 ⟶ 6:4) as eluant to yield recovered Δ^3 ester (**21**) (0.0113 g, 42%) and then the required Δ^2-bicycloheptene (**15**) as a gum (0.0062 g, 23%), $\nu_{max.}$ 3 000, 1 785, 1 720, 1 605, 1 545, and 980 cm^{-1}; $\lambda_{max.}$ 229 and 331 nm; δ_H (250 MHz) 1.32 and 1.37 (3 H, 2 t, J 8 Hz, SCH_2CH_3), 2.7—3.0 (2 H, m, SCH_2), 3.09 and 3.11 (1 H, 2 dd, J 18 and 8.5 Hz, 4-H), 3.28 and 3.30 (1 H, 2 dd, J 18 and 10 Hz, 4-H), 3.50 and 3.52 (3 H, 2 s, OCH_3), 4.23 and 4.24 (1 H, 2 ddd, J 10, 8.5, and 2 Hz, 5-H), 4.50 and 4.51 (1 H, 2 d, J 2 Hz, 6-H), 7.47 and 7.53 (1 H, 2 s, OCHO), and 7.6—8.0 (4 H, m, ArH); M^+ absent, m/z 347.0841 [Calc. for (M − CO): m/z, 347.0827].

Acknowledgements

We thank Mr J. V. H. Syms for large-scale preparation of the phosphorane (**11**).

References

1 Part 2, J. H. Bateson, A. M. Quinn, T. C. Smale, and R. Southgate, *J. Chem. Soc., Perkin Trans. 1*, preceding paper.
2 For a review see A. G. Brown, *J. Antimicrob. Chemother.*, 1981, **7**, 15.
3 (*a*) A. J. G. Baxter, K. H. Dickinson, P. M. Roberts, T. C. Smale, and R. Southgate, *J. Chem. Soc., Chem. Commun.*, 1979, 236; (*b*) J. H. Bateson, A. J. G. Baxter, P. M. Roberts, T. C. Smale, and R. Southgate, *J. Chem. Soc., Perkin Trans. 1*, 1981, 3242.
4 (*a*) J. H. Bateson, P. M. Roberts, T. C. Smale, and R. Southgate, *J. Chem. Soc., Chem. Commun.*, 1980, 185; (*b*) J. H. Bateson, R. I. Hickling, P. M. Roberts, T. C. Smale, and R. Southgate, *ibid.*, p. 1084.
5 For a recent review see E. M. Gordon and R. B. Sykes, in 'Chemistry and Biology of β-Lactam Antibiotics,' eds. R. B. Morin and M. Gorman, Academic Press, 1982, vol. 1, pp. 199—370.
6 M. W. Foxton, R. C. Mearman, C. E. Newall, and P. Ward, *Tetrahedron Lett.*, 1981, **22**, 2497.
7 D. T. W. Chu, J. E. Hangeveld, and D. Lester, *Tetrahedron Lett.*, 1983, **24**, 139.
8 H. H. Wasserman and B. H. Lipshutz, *Tetrahedron Lett.*, 1975, 1731.
9 J. P. Clayton, M. Cole, S. W. Elson, H. Ferres, J. C. Hanson, L. W. Mizen, and R. Sutherland, *J. Med. Chem.*, 1976, **19**, 1385.
10 B. J. Hunt and W. Rigby, *Chem. Ind. (London)*, 1967, 1868.

Received 27*th February* 1985; *Paper* 5/329