Total Synthesis of Analogues of the β-Lactam Antibiotics. Part 3.[1] 2-Ethoxycarbonyl Derivatives of Carbapen-1-em-3-*exo*-carboxylates and Carbapenam-3-*exo*-carboxylates[2]

Rajiv Sharma, Richard J. Stoodley,*† and Andrew Whiting
Department of Organic Chemistry, The University, Newcastle upon Tyne NE1 7RU

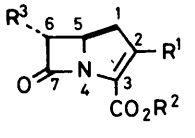
t-Butyl 2-ethoxycarbonylcarbapen-1-em-3-*exo*-carboxylate (**7a**) has been synthesised by a strategy involving final closure of the 1,2-bond using an intramolecular Wittig condensation. Hydroxyalkylation of the azetidinone nitrogen of 4-vinylazetidin-2-one with t-butyl α,α-dihydroxyacetate followed by treatment of the product (**12a**) with thionyl chloride–2,6-dimethylpyridine gave t-butyl α-chloro-α-(2-oxo-4-vinylazetidin-1-yl)acetate (**12b**) which underwent chlorine displacement with ethyl (triphenylphosphoranylidene)acetate (**10b**). The resultant phosphorane (**9a**) was converted into the carbapen-1-em (**7a**) by sequential treatment with trifluoroacetic acid, ozone, dimethyl sulphide, and potassium hydrogen carbonate. A similar reaction sequence was used to prepare *p*-nitrobenzyl 2-ethoxycarbonylcarbapen-1-em-3-*exo*-carboxylate (**7b**).

An attempt to deprotect the t-butyl ester moiety of compound (**7a**) with trifluoroacetic acid resulted in β-lactam cleavage to give α-[(2*SR*,5*RS*)-4-ethoxycarbonyl-5-t-butoxycarbonyl-1-trifluoroacetyl-2,5-dihydropyrrol-2-yl]acetic acid (**21a**). Hydrogenolysis of the carbapen-1-em (**7b**) in the presence of sodium hydrogen carbonate gave initially the sodium salt (**7c**) and then sodium 2-ethoxycarbonylcarbapenam-3-*exo*-carboxylate as a 1 : 2 mixture of 2-*endo*- (**24a**) and 2-*exo*-isomers (**25a**).

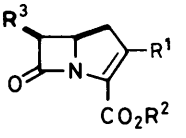
Whereas hydrogen added predominantly to the *endo*-face of the alkene moiety of the carbapen-1-em (**7a**) to give mainly compound (**25c**), diazomethane attacked largely from the *exo*-face to give mainly the cycloadduct (**32**). Under thermal conditions, the last-cited compound was transformed into t-butyl 2-ethoxycarbonyl-1-methylcarbapen-1-em-3-*exo*-carboxylate (**33**).

Under conditions in which the carbapen-1-em (**7a**) underwent complete deuterium exchange at position 3, the relative (**33**) underwent *ca.* 25% deuterium exchange at position 3.

The potent antibacterial activity of thienamycin (**1a**) and its relatives has provoked considerable interest[3] in the synthesis of carbapen-2-ems of types (**1**) and (**2**). By contrast, carbapen-1-ems of types (**3**) and (**4**) have received only scant study. At the outset of this work, such compounds had been described by the Merck[4,5] and Sankyo[6] groups. For example, treatment of compound (**5**) with bromine followed by a base provided the carbapenam (**6**) which was transformed into the carbapen-1-em (**3a**) by elimination of hydrogen bromide and replacement of a benzyloxycarbonyl group by hydrogen.[5] It had also been established that carbapenems of types (**1**; R^1 = SR) and (**3**; R^1 = SR) underwent equilibration under basic conditions; at equilibrium, compounds of the latter type were favoured.[4,5]

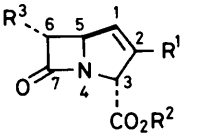


(**1**)



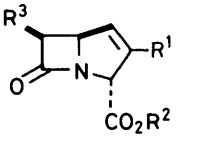
(**2**)

a ; R^1 = $SCH_2CH_2NH_2$, R^2 = H, R^3 = CH(OH)Me
b ; R^1 = H, R^2 = Na, R^3 = H
c ; R^1 = R^2 = H, R^3 = CH(OH)Me
d ; R^1 = CO_2Et, R^2 = Bu^t, R^3 = H
e ; R^1 = H, R^2 = $CH_2C_6H_4NO_2$-*p*, R^3 = H
f ; R^1 = Me, R^2 = $CH_2C_6H_4NO_2$-*p*, R^3 = H
g ; R^1 = H, R^2 = Me, R^3 = H



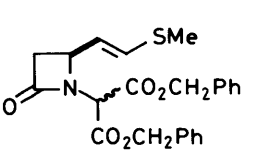
(**3**)

a ; R^1 = SMe, R^2 = CH_2Ph, R^3 = H
b ; R^1 = CO_2Me, R^2 = CH_2Ph, R^3 = H
c ; R^1 = CH_2OCOPh, R^2 = $CH_2C_6H_4NO_2$-*p*, R^3 = H
d ; R^1 = $SCH_2CH_2NH_2$, R^2 = H, R^3 = CH(OH)Me
e ; R^1 = H, R^2 = Me, R^3 = H

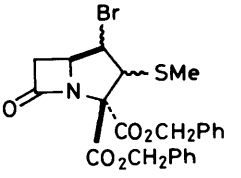


(**4**)

a ; R^1 = CO_2Me, R^2 = CH_2Ph, R^3 = $NHCOCH_2OPh$
b ; R^1 = CO_2Et, R^2 = Et, R^3 = $NHCOCH_2Ph$
c ; R^1 = CO_2Me, R^2 = H, R^3 = $NHCOCH_2Ph$



(**5**)



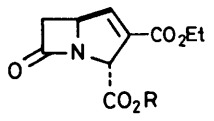
(**6**)

† *Present address:* Department of Chemistry, UMIST, P.O. Box 88, Manchester M60 1QD.

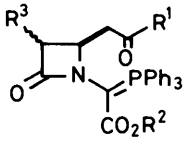
Our interest in carbapen-1-ems stemmed from the hope that they would be convertible into carbapen-2-ems by appropriate kinetically controlled reactions. In this paper, we describe the synthesis of carbapen-1-ems of type (7) and some attempts to effect their transformation into related carbapen-2-ems.

Results and Discussion

When we started this study, the power of the intramolecular Wittig condensation as a route to carbapen-2-ems of type (2) had been demonstrated;[7–10] ylides of type (8) had served as precursors. It was envisaged that this strategy could be used to prepare carbapen-1-ems of type (7), providing species of type (9; X = O) could be generated. The knowledge that stabilised phosphoranes are inert to ozone in the presence of trifluoroacetic acid[11] suggested that compounds of type (9; X = CH_2) would serve as precursors of compounds of type (9; X = O). The phosphorane (**10a**) undergoes alkylations with reactive halides[12] and, furthermore, its relative (**10b**) reacts with the iodide (**11a**) to give the ylide (**11b**).[13] Accordingly, it was hoped that compounds of type (9; X = CH_2) would be accessible from the reaction of the phosphorane (**10b**) with a chloride of type (**12**; X = Cl) derivable by a well-established procedure.[14]

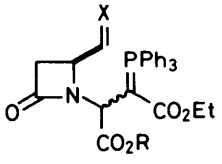


(7)



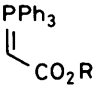
(8)

a ; R = Bu^t
b ; R = $CH_2C_6H_4NO_2$-*p*
c ; R = Na
d ; R = H
e ; R = Me



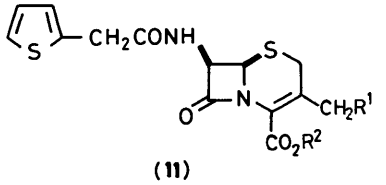
(9)

a ; X = CH_2, R = Bu^t
b ; X = CH_2, R = $CH_2C_6H_4NO_2$-*p*



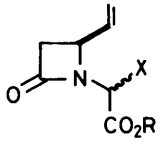
(10)

a ; R = Me
b ; R = Et



(11)

a ; R^1 = I, R^2 = Bu^t
b ; R^1 = C(:PPh_3)CO_2Et, R^2 = Bu^t
c ; R^1 = OAc, R^2 = H



(12)

a ; X = OH, R = Bu^t
b ; X = Cl, R = Bu^t
c ; X = OH, R = $CH_2C_6H_4NO_2$-*p*
d ; X = Cl, R = $CH_2C_6H_4NO_2$-*p*

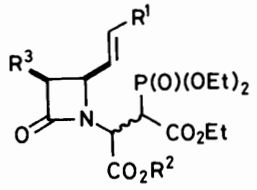
Treatment of 4-vinylazetidin-2-one[15] with t-butyl α,α-dihydroxyacetate[16] and triethylamine in tetrahydrofuran (THF) gave the carbinolamide (**12a**) in 84% yield after recrystallisation. The last-cited compound reacted with thionyl chloride and 2,6-dimethylpyridine in THF at −20 °C to give the chloride (**12b**) which was transformed into the ylide (**9a**) (*ca.* 57% yield after SiO_2 chromatography and crystallisation) by the action of the phosphorane (**10b**) (2 mol equiv.) in dichloromethane. The ylide (**9a**) was treated with trifluoroacetic acid (10 mol equiv.) followed by ozone in dichloromethane at −78 °C to give, after reduction (Me_2S) and neutralisation ($KHCO_3$), the crystalline carbapen-1-em (**7a**) (51% yield after SiO_2 chromatography).

The structure of the carbapen-1-em (**7a**) was established on the basis of its elemental composition and its spectroscopic properties. In particular, the material showed a strong i.r. absorption (KBr) at 1 785 cm^{-1} for the β-lactam carbonyl group, a u.v. band (EtOH) at 230 nm (ε 3 900) for the acrylate chromophore, and ^1H n.m.r. signals (300 MHz; $CDCl_3$) at δ 2.97 (dd, *J* 16 and 3 Hz) and 3.48 (dd, *J* 16 and 6 Hz) for the C-6 methylene protons, at δ 4.67 (m) and 5.22 (dd, *J* 3.5 and 1.5 Hz) for the C-5 and C-3 methine protons, and at δ 7.09 (t, *J* 1.5 and 1.5 Hz), for the C-1 vinylic proton. It has been noted previously that long-range coupling between 3- and 5-H of carbapen-1-em-3-carboxylates is observed when they bear an *anti*-relationship.[5]

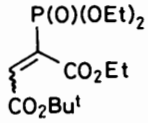
Using a similar sequence, the carbinolamide (**12c**), obtained as a syrup (80% yield after SiO_2 chromatography) from the reaction of 4-vinylazetidin-2-one with *p*-nitrobenzyl α-ethoxy-α-hydroxyacetate,[11] was transformed into the carbapen-1-em (**7b**). Thus the reaction of the carbinolamide (**12c**) with thionyl chloride–2,6-dimethylpyridine yielded the chloride (**12d**) which was treated with the phosphorane (**10b**) in ethyl acetate to give the ylide (**9b**) (*ca.* 54% yield after SiO_2 chromatography). Ozonolysis of the last-cited compound in the presence of trifluoroacetic acid and work-up with dimethyl sulphide and sodium hydrogen carbonate provided the carbapen-1-em (**7b**) (87% yield after SiO_2 chromatography).

Although isolated as a syrup, the carbapen-1-em (**7b**) was present as a single diastereoisomer on the basis of ^1H n.m.r. spectroscopy. Again, the observation that the 3-proton appeared as a double doublet (*J* 3 and 1.5 Hz) due to long-range coupling to both the 1- and 5-protons [which appeared, respectively, as a triplet (*J* 1.5 and 1.5 Hz) at δ 7.06 and a multiplet centred at δ 4.73], established the *exo*-orientation of the 3-carboxylate moiety.

During the course of and subsequent to these studies, the synthesis of carbapen-1-ems of types (**3**) and (**4**) has been reported by other groups. Thus Beecham workers[17] effected the transformation of carbapen-2-ems of types (**1**; R^1 = H) and (**2**; R^1 = H) into carbapen-1-ems of types (**3**; R^1 = SR) and (**4**; R^1 = SR) by sequential treatment with a thiol and iodobenzene dichloride. The intramolecular Wittig condensation has featured in syntheses developed by three groups. Durst and his co-workers[18] prepared compound (**13a**) by the Michael addition of 4-vinylazetidin-2-one to the vinyl phosphonate (**14**) and converted it into the carbapen-1-em (**7a**) by sequential reactions with ozone and sodium hydride. Branch and Pearson,[19] using an identical strategy to that reported herein, prepared the carbapen-1-ems (**3b**) and (**4a**); interestingly, unlike in the present study, the carbapen-2-ems (**15a**) and (**15b**) were also isolated. In Hakimelahi's synthesis[20] of the carbapen-1-em (**4b**), the phosphonate precursor (**13b**) was generated by the addition of triethyl phosphite to compound (**16**). A 1,2-bond closure, involving an intramolecular aldol condensation, was used by Sankyo workers[21] in the preparation of the carbapen-

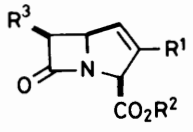


(13)



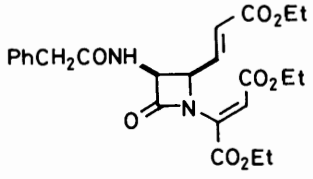
(14)

a ; $R^1 = R^3 = H$, $R^2 = Bu^t$
b ; $R^1 = Ph$, $R^2 = Et$, $R^3 = NHCOCH_2Ph$



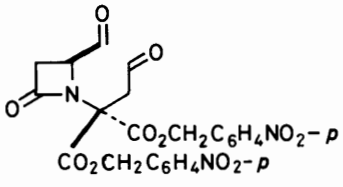
(15)

a ; $R^1 = CO_2Me$, $R^2 = CH_2Ph$, $R^3 = H$
b ; $R^1 = CO_2Me$, $R^2 = CH_2Ph$, $R^3 = NHCOCH_2OPh$
c ; $R^1 = CO_2Et$, $R^2 = Et$, $R^3 = NHCOCH_2Ph$

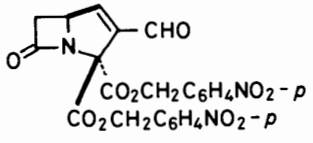


(16)

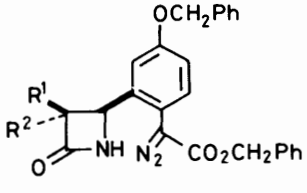
1-em (**3c**); thus treatment of the dialdehyde (**17**) with piperidinium acetate provided the bicycle (**18**) which was transformed into compound (**3c**) by reduction, benzoylation, and dealkoxycarbonylation steps. Finally, a 3,4-bond closure



(17)

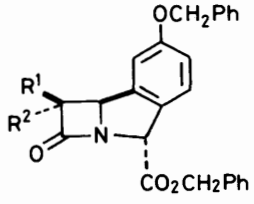


(18)



(19)

a ; $R^1 = NHCOCH_2OPh$, $R^2 = H$
b ; $R^1 = H$, $R^2 = CH(OSiMe_3)Me$



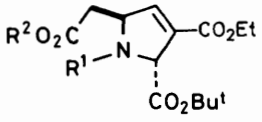
(20)

a ; $R^1 = NHCOCH_2OPh$, $R^2 = H$
b ; $R^1 = H$, $R^2 = CH(OSiMe_3)Me$

was employed by Merck workers[22] to prepare the carbapen-1-ems (**20a** and **b**); the cyclisation of the diazo precursors (**19a** and **b**) was achieved by the action of rhodium(II) acetate.

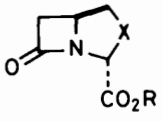
Structure–activity studies have established that the 2- and 6-substituents of thienamycin (**1a**) are not obligatory for antibacterial activity. Thus the salt (**1b**) inhibits the growth of a range of bacteria.[7] In the case of cephalosporins, it is well established that the double bond must be located at position 3, *e.g.* (**11c**), for bioactivity, the Δ^2-isomers being inactive.[23] By analogy therefore, carbapen-1-ems of type (**3**; R^2 = Na) might be expected to lack antibacterial properties. However, the claim in a patent that the Δ^1-isomer of thienamycin, *i.e.* (**3d**), was a bacteriocide[24] prompted efforts to prepare the salt (**7c**).

In the hope of deriving the acid (**7d**), the carbapen-1-em (**7a**) was treated in deuteriochloroform with trifluoroacetic acid. Although an acidic product was quickly formed, it lacked a β-lactam carbonyl absorption in the i.r. region; moreover, the product had retained the t-butyl ester moiety according to ^1H n.m.r. spectroscopy. The acid was formulated as the 2,5-dihydropyrrole (**21a**) on the basis of its spectroscopic properties



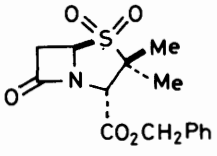
(21)

a ; $R^1 = COCF_3$, $R^2 = H$
b ; $R^1 = COCF_3$, $R^2 = Me$
c ; $R^1 = H$, $R^2 = COCF_3$



(22)

a ; X = O, R = Bu^t
b ; X = S, R = Bu^t
c ; X = SO_2, R = Bu^t
d ; X = CH_2, R = CH_2Ph



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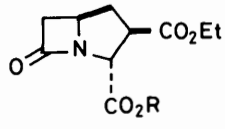


(24)

a ; R = Na
b ; R = Me
c ; R = Bu^t

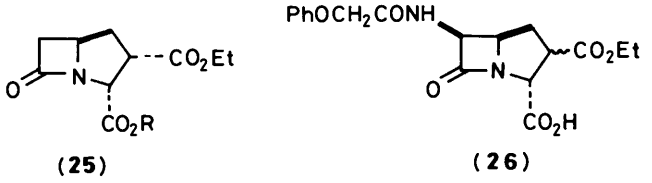
and, in particular, its mass spectrum featured a prominent ion at *m/z* 294, corresponding to $C_{11}H_{11}F_3NO_5$ (*i.e.* $M^+ - CO_2Bu^t$) by mass measurement. In accord with its structure, the acid (**21a**) was converted into the methyl ester (**21b**), isolated as a syrup in 70% yield after silica-gel chromatography, on brief treatment with diazomethane. The ester (**21b**) featured a base peak at *m/z* 308, corresponding to $C_{12}H_{13}F_3NO_5$ by mass measurement, in its mass spectrum; on the basis of ^1H n.m.r. spectroscopy (300 MHz; $CDCl_3$), compound (**21b**) was considered to be present as a 5:1 mixture of rotamers, arising from restricted rotation about the amide bond.

The acid (**21a**) probably arises from the mixed anhydride (**21c**) by an intramolecular *O*→*N* acyl transfer; in turn, the mixed anhydride is likely to be formed from the carbapen-1-em (**7a**) by a trifluoroacetolysis of its β-lactam linkage. Analogous reactions have been observed with isoclavams, *e.g.* (**22a**),[25] isopenams, *e.g.* (**22b**),[1] isopenam dioxides, *e.g.* (**22c**),[1] and sulbactam benzyl ester (**23**).[1] Clearly, the azetidinone linkage of the carbapen-1-em (**7a**) is endowed with high chemical reactivity.

Brief hydrogenolysis of the *p*-nitrobenzyl ester (**7b**) over palladium–charcoal in a water–ethanol–ethyl acetate mixture containing sodium hydrogen carbonate, gave the salt (**7c**) (73% yield) as an amorphous solid. The salt (**7c**) was characterised

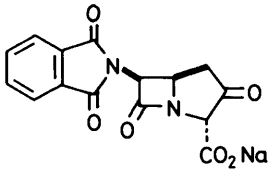
by its i.r. and ^{1}H n.m.r. spectroscopic properties and by its transformation into the methyl ester (**7e**) (90% yield after SiO_2 chromatography) by the action of iodomethane in *N,N*-dimethylformamide (DMF).

The salt (**7c**), which was stable in deuterium oxide over a 12-hour period according to ^{1}H n.m.r. spectroscopy, failed to inhibit the growth of a range of bacteria. Moreover, the activity claimed for compound (**3d**) has subsequently been reported to be of a low order and the material only inhibits the growth of *Staphylococcus aureus*.[26] Other carbapen-1-em-3-carboxylic acids have been prepared,[6,19,21,22,27] but only compound (**4c**),[19] which incorporates an *endo*-orientated acylamino group at position 6, is endowed with antibacterial properties.

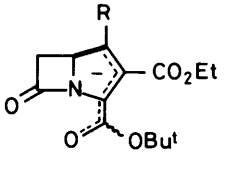


(**25**)
a; R = Na
b; R = Me
c; R = But

(**26**)



(**27**)



(**28**)
a; R = H
b; R = Me

It was of interest to attempt to prepare the salt (**24a**) and/or the salt (**25a**) for antibacterial evaluation. Although it had been claimed in a patent that the olefinic moiety of the carbapen-2-em (**1c**) was reduced by hydrogen over palladium oxide,[28] it was not clear whether the 3-carboxylic acid moiety was *exo*-or *endo*-orientated. Moreover, the finding that catalytic hydrogenolysis of a mixture of the carbapenem (**22d**) and its 3-epimer afforded a crude product which, although unstable, exhibited some antibacterial activity[5] provided an added incentive for the venture.

Hydrogenolysis of the *p*-nitrobenzyl ester (**7b**) as before, but for a longer period, afforded an amorphous solid in 66% yield. That the material was a carboxylic acid salt was suggested by the presence of an i.r. absorption at 1 615 cm^{-1} and by its solubility in water. Although the i.r. absorption at 1 735 cm^{-1} was somewhat low for a β-lactam carbonyl moiety, the lack of an olefinic signal in the ^{1}H n.m.r. spectrum was compatible with the structures (**24a**) and/or (**25a**). That the material was indeed a mixture of the salts (**24a**) and (**25a**) was established by its reaction with iodomethane in DMF; silica-gel fractionation of the product led to the isolation of the esters (**24b**) and (**25b**). The minor isomer, which was the chromatographically more-mobile material, was isolated as a syrup in 22% yield. Its diastereoisomer, which was also a syrup, was obtained in 46% yield.

The constitution of the esters, as $C_{11}H_{15}NO_5$, was established by high-resolution mass spectroscopy and both compounds featured strong i.r. absorptions at 1 775 cm^{-1} for the β-lactam carbonyl moieties. The 90 MHz ^{1}H n.m.r. spectra ($CDCl_3$) of the esters were characterised by the presence of one-proton doublets (*J* 7 Hz) at *ca.* δ 4.67 for the 3-protons; however, there were differences in the chemical shifts of other protons. In particular, the 6α-protons appeared as double doublets (*J* 16 and 5 Hz) at δ 3.28 in the minor isomer and at δ 3.36 in the major isomer; the 6β-protons resonated as doublet doublets (*J* 16 and 2 Hz) at δ 2.80 in the minor isomer and at δ 2.69 in the major isomer. On the basis of subsequent evidence, the minor and major esters were assigned the respective stereostructures (**24b**) and (**25b**).

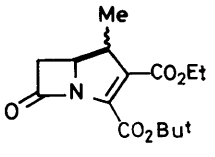
The salt, which was evidently a 1:2 mixture of compounds (**24a**) and (**25a**), was stable in deuterium oxide over a 24-hour period. It failed to inhibit the growth of a range of bacteria. Several other carbapenam-3-carboxylic acids or their salts have been described;[6,29–36] of these, only compounds (**26**)[35] and (**27**)[36] are claimed to inhibit bacterial growth.

When subjected to the action of hydrogen over palladium–charcoal in ethyl acetate, the carbapen-1-em (**7a**) was converted into a hydrogenation product (77% yield after SiO_2 chromatography) that was a 5:1 mixture of diastereoisomers on the basis of 300 MHz ^{1}H n.m.r. spectroscopy. Again, the 3-proton of both isomers appeared as doublets (*J* 7.5 Hz) at δ 4.63. However, the 6α-and 6β-protons were readily distinguished in the two isomers. The former appeared as a doublet of double doublets (*J* 16, 4.5, and 2.5 Hz) at δ 3.13 in the *minor* diastereoisomer and as a double doublet (*J* 16 and 4.5 Hz) at δ 3.37 in the major diastereoisomer; the latter appeared as double doublets (*J* 16 and 2.5 Hz) at δ 2.82 in the minor diastereoisomer and at δ 2.69 in the major diastereoisomer. On the basis of chemical-shift comparisons, it seems reasonable to conclude that the major diastereoisomer arising from the hydrogenation of the salt (**7c**) corresponds to the major diastereoisomer produced by hydrogenation of the t-butyl ester (**7a**).

On the basis of n.O.e.d. spectroscopy, the major diastereoisomer arising from the hydrogenation of compound (**7a**) was assigned a stereostructure (**25c**). Thus irradiation of the 3-proton caused a 17% enhancement of the 2-proton, revealing their *syn*-relationship. Evidently, the addition of hydrogen to the olefinic linkage of compound (**7a**) occurs predominantly from the *endo*-face; a similar, but less pronounced, diastereofacial reactivity is observed with the salt (**7c**). Presumably, addition to the *exo*-faces is impeded by the 3-*exo*-carboxylate moieties.

As already mentioned, carbapen-1-ems of type (**3**) can equilibrate with carbapen-2-ems of type (**1**) in the presence of a strong base. For example, a *ca.* 6:1 mixture of compounds (**1g**) and (**3e**) was produced in THF containing 1,5-diazabicyclo-[5.4.0]undec-5-ene.[27] In the hope of producing some of its double-bond isomer (**1d**), the carbapen-1-em (**7a**) was treated with 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) in deuteriochloroform. Although no change was noted, deuterium exchange of the 3-proton of compound (**7a**) occurred when the experiment was repeated in the presence of deuterium oxide; there was no detectable exchange of the 1-proton. Evidently, the carbapen-1-em (**7a**) is overwhelmingly preferred to the carbapen-2-em (**1d**) at equilibrium and, furthermore, the carbanionic intermediate (**28a**) shows a strong kinetic preference to protonate at position 3.

In the hope that it would isomerise to the carbapen-2-em (**29**) under basic conditions, the cyclopropane (**30**) was sought. The elimination of nitrogen from dihydropyrazoles usually provides a preparatively useful route to cyclopropanes[37] and, accordingly, the reaction of the carbapen-1-em (**7a**) with diazomethane was examined. In dichloromethane at 0 °C, two cycloadducts were produced which were separable by silica-gel chromatography. The minor cycloadduct, which was eluted first from the column, was obtained in 4% yield after recrystallisation. Its diastereoisomer, which was also crystalline, was isolated in 72% yield. The constitutions of the cycloadducts were established by elemental analysis and their structures by 300 MHz ^{1}H n.m.r. spectroscopy. In the minor diastereoisomer,



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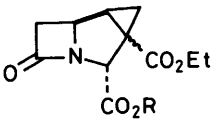

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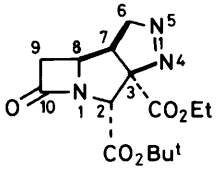

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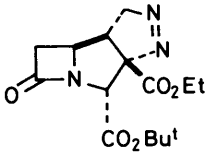


(32)

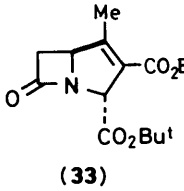
the β-lactam-associated hydrogen atoms appeared as a double doublet at δ 2.42 (*J* 16.4 and 2.8 Hz) (attributed to 9β-H), a double doublet at δ 3.15 (*J* 16.4 and 5.6 Hz) (ascribed to 9α-H), and a multiplet at *ca.* δ 4.15 (for 8-H); the corresponding protons of the major diastereoisomer absorbed at δ 2.83 (*J* 16 and 2.2 Hz), 3.40 (*J* 16 and 5 Hz), and 3.50.

On the basis of n.O.e.d. spectroscopy, the minor and major cycloadducts were assigned the stereostructures (**31**) and (**32**), respectively. In the case of the minor cycloadduct, irradiation of the 9β-hydrogen caused an 8% enhancement of the 6β-hydrogen; in the major cycloadduct, the 6α-hydrogen was enhanced by 3% when the 8-hydrogen was irradiated. Evidently, the addition of diazomethane to the olefinic linkage of compound (**7a**) occurs very largely from the *exo*-face. This stereochemical outcome contrasts with that observed in the addition of hydrogen.

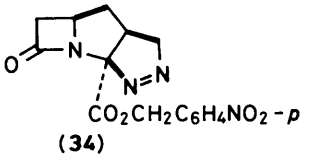
In boiling toluene, the major 4,5-dihydro-3*H*-pyrazole (**32**) was rapidly converted into a more-mobile product, isolated as a chromatographically homogeneous syrup in 81% yield after silica-gel purification. On the basis of spectroscopic evidence, the product was the carbapen-1-em (**33**) rather than the cyclopropane (**30**). As well as displaying a u.v. absorption (EtOH) at 221 nm (ε 6 300), the material showed a broad three-proton singlet at δ 2.20 ($CDCl_3$) for the vinylic methyl group.

It is noteworthy that Bateson *et al.*[38] observed that the carbapen-2-em (**1e**) reacted with diazomethane to give a *ca.* 1:3 mixture of the cycloadducts (**34**) and (**35**). Whereas the minor dihydropyrazole (**34**) was converted only into the cyclopropane (**36**) under thermal conditions, the major dihydropyrazole (**35**) afforded a *ca.* 4:1 mixture of the cyclopropane (**37**) and the carbapen-2-em (**1f**).

Having access to the carbapen-1-em (**33**), it was of interest to examine its reaction with DBN. Presumably, in the case of compounds (**7a**) and (**1d**), the former is preferred to the latter because, in part, the eclipsing of the 1-hydrogen atom and 2-ethoxycarbonyl moiety is less severe than the eclipsing of the 2-ethoxycarbonyl and 3-t-butoxycarbonyl groups. For compounds (**33**) and (**29**), the 1-methyl group may be expected to reduce their energy difference. In the event, under conditions in which compound (**7a**) underwent virtually complete deuterium exchange at position 3, compound (**33**) underwent only partial exchange (*ca.* 25%) of the 3-proton. Clearly, the carbanion (**28b**) is more difficult to generate than its counterpart (**28a**).



(33)



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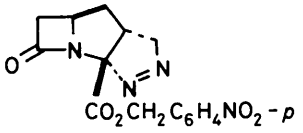

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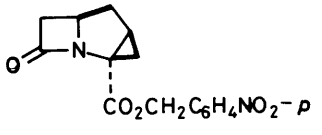

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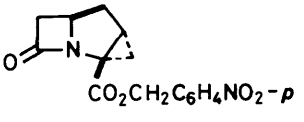

(37)

Experimental

Dry solvents, referred to in the ensuing experiments, were prepared as follows: dichloromethane was stored over anhydrous calcium chloride; DMF and ethyl acetate were stored over 4 A molecular seives; THF was dried over calcium chloride or lithium aluminium hydride and, immediately prior to use, was distilled; toluene was dried over anhydrous calcium chloride and then distilled from phosphorus pentaoxide. Light petroleum refers to that fraction boiling in the range 40—60 °C. Ethereal diazomethane was prepared[39] by adding a solution of 'Diazald' in diethyl ether to potassium hydroxide in aqueous ethanol at *ca.* 60 °C. 300 MHz ^{1}H N.m.r. spectra were measured on a Bruker WM-300 WB spectrometer. For chromatographic and other instrumental details, see Part 1.[25]

Reaction of 4-*Vinylazetidin*-2-*one with t-Butyl* α,α-*Dihydroxyacetate*.—To a stirred solution of 4-vinylazetidin-2-one[15] (2.77 g, 29 mmol) and triethylamine (4.31 cm^3, 31 mmol) in dry THF (50 cm^3) was added a solution of t-butyl α,α-dihydroxyacetate[16] (6.68 g, 38 mmol) in dry THF (50 cm^3). Evaporation of the reaction mixture, after 12 h, left a syrup which was dissolved in ethyl acetate and washed with brine (× 3). Evaporation of the dried ($MgSO_4$) organic layer and crystallisation of the residue from diethyl ether–light petroleum gave *t-butyl* α-*hydroxy*-α-(2-*oxo*-4-*vinylazetidin*-1-*yl*)*acetate* (**12a**) (5.43 g, 84% which possessed the following properties: m.p. 65—66 °C; $\nu_{max.}$(KBr) (*inter alia*) 3 300br (OH) and 1 740br cm^{-1} (β-lactam and ester C=O); $\lambda_{max.}$(EtOH) 213 nm (ε 700); δ (60 MHz; $CDCl_3$) 1.64br (9 H, s, CMe_3), 2.66 (1 H, dd, *J* 16 and 3 Hz, COC*H*HCH), 3.20 (1 H, dd, *J* 16 and 6 Hz, COCH*H*CH), 4.10—4.65 (2 H, m, $COCH_2CH$ and CHO*H*), and 4.95—6.00 (4 H, m, $CH{=}CH_2$ and C*H*OH); *m*/*z* (*inter alia*) 126 ($M^+ - C_5H_9O_2$, base peak) (Found: C, 58.1; H, 7.6; N, 6.1. $C_{11}H_{17}NO_4$ requires C, 58.1; H, 7.5; N, 6.2%).

Preparation of the Carbapenem (**7a**).—To a stirred, cooled (CCl_4–solid CO_2) solution of the carbinolamide (**12a**) (6.12 g, 27 mmol) in dry THF (100 cm^3) under nitrogen was added 2,6-dimethylpyridine (3.73 cm^3, 32 mmol) followed by thionyl chloride (2.33 cm^3, 32 mmol). After 40 min, the mixture was filtered through 'Hiflo' and the filtrate was evaporated. The resultant yellow syrup was dried *in vacuo* (over $CaCl_2$) and dissolved in dry dichloromethane (100 cm^3). To the solution was added the phosphorane (**10b**) (20.5 g, 59 mmol) and the mixture was left under nitrogen for 12 h. After having been washed with aqueous sodium hydrogen carbonate, the organic layer was dried ($MgSO_4$) and evaporated. Purification of the syrupy residue by silica-gel chromatography [light petroleum–EtOAc (1.5:1) as the eluant] gave a syrupy solid which was crystallised from diethyl ether. The resultant white solid (8.50 g,

ca. 57%) was considered to be predominantly 1-t-butyl 4-ethyl 2-(2-oxo-4-vinylazetidin-1-yl)-3-(triphenylphosphoranylidene)-succinate (**9a**) on the basis of the following properties: $\nu_{max.}$(KBr) (*inter alia*) 1 750 (β-lactam C=O), 1 735 (ester C=O), and 1 635 and 1 620 cm^{-1} (phosphorane ester C=O); *m/z* (*inter alia*) 557 (M^+), 456 ($M^+ - C_5H_9O_2$), 402, 303, and 262 ($C_{18}H_{15}P^+$), and 183 (Found: M^+, 557.2321. $C_{33}H_{36}NO_5P$ requires *M*, 557.2331).

The phosphorane (**9a**) (8.50 g, *ca.* 15 mmol) was treated with trifluoroacetic acid (11.5 cm^3, 149 mmol). After 1 h, the solution was diluted with dichloromethane (300 cm^3), cooled (Me_2CO–solid CO_2), and saturated with ozone. Excess ozone was removed by bubbling oxygen through the mixture which was then treated with dimethyl sulphide (5.6 cm^3, 76 mmol) and allowed to warm up to room temperature. After 1 h, the mixture was poured into aqueous saturated potassium hydrogen carbonate (500 cm^3) and vigorously stirred for 2 h. Evaporation of the dried ($MgSO_4$) organic phase and purification of the residue by silica-gel chromatography (light petroleum–EtOAc; gradient elution) gave *t-butyl 2-ethoxycarbonylcarbapen-1-em-3-exo-carboxylate* (**7a**) (2.19 g, 51%). A sample, recrystallised from diethyl ether–light petroleum, showed the following properties: m.p. 61—62 °C; $\nu_{max.}$(KBr) *inter alia* 1 785 (β-lactam C=O), 1 735br (ester C=O), and 1 630 cm^{-1} (C=C); $\lambda_{max.}$(EtOH) 230 nm (ε 3 900); δ (300 MHz; $CDCl_3$) 1.30 (3 H, t, *J* 7 Hz, CH_2*Me*), 1.46 (9 H, s, CMe_3), 2.97 (1 H, dd, *J* 16 and 3 Hz, 6β-H), 3.48 (1 H, dd, *J* 16 and 6 Hz, 6α-H), 4.24 (2 H, q, *J* 7 Hz, OCH_2Me), 4.65—4.68 (1 H, m, 5-H), 5.22 (1 H, dd, *J* 3.5 and 1.5 Hz, 3-H), and 7.09 (1 H, t, *J* 1.5 and 1.5 Hz, 1-H); *m/z* (*inter alia*) 238 ($M^+ - C_2H_3O$), 208, 181, 180 ($M^+ - C_4H_5O$), and 57 ($C_4H_9^+$, base peak) (Found: C, 60.1; H, 6.8; N, 4.9. $C_{14}H_{19}NO_5$ requires C, 59.8; H, 6.8; N, 5.0%).

Reaction of 4-Vinylacetidin-2-one with p-Nitrobenzyl α-Ethoxy-α-hydroxyacetate (with G. Richardson).—To a solution of 4-vinylazetidin-2-one[15] (7.50 g, 77 mmol) and triethylamine (12.4 cm^3, 89 mmol) in dry THF (30 cm^3) was added a solution of *p*-nitrobenzyl α-ethoxy-α-hydroxyacetate[11] (24.2 g, 96 mmol) in dry THF (50 cm^3). Evaporation, after 24 h, left a syrup which was dissolved in dichloromethane. The solution, after having been washed with dilute hydrochloric acid, was dried ($MgSO_4$) and evaporated. Purification of the product by silica-gel chromatography (light petroleum–EtOAc; gradient elution) gave p-*nitrobenzyl α-hydroxy-α-(2-oxo-4-vinylazetidin-1-yl)-acetate* (**12c**) (18.9 g, 80%) as a chromatographically homogeneous syrup with the following properties: $\nu_{max.}$(film) (*inter alia*) 3 400br (OH) and 1 750br cm^{-1} (β-lactam and ester C=O); $\lambda_{max.}$(EtOH) 213 (ε 3 600) and 264 nm (4 700); δ (60 MHz; $CDCl_3$) 2.73 (1 H, dd, *J* 15 and 3 Hz, COC*H*HCH), 3.23 (1 H, dd, *J* 15 and 5 Hz, COCH*H*CH), 4.10—4.40 (1 H, m, $COCH_2CH$), 4.5br (1 H, s, OH), 5.15—6.20 (6 H, m, $CH{=}CH_2$, *CH*OH, and $OCH_2C_6H_4$), and 7.50 and 8.20 (each 2 H, d, *J* 8 Hz, C_6H_4) (addition of D_2O caused the signal at δ 4.50 to disappear); *m/z* (*inter alia*) 136 ($C_7H_6NO_2^+$, base peak) and 126 ($M^+ - C_8H_6NO_4$) (Found: $M^+ - C_8H_6NO_4$, 126.0553. $C_8H_8NO_2$ requires *m/z* 126.0555).

Preparation of the Carbapenem (**7b**).—To a stirred, cooled (CCl_4–solid CO_2) solution of the carbinolamide (**12c**) (10.0 g, 33 mmol) in dry THF (80 cm^3) under argon was added 2,6-dimethylpyridine (4.2 cm^3, 36 mmol) followed by thionyl chloride (2.6 cm^3, 36 mmol). When the formation of the chloride (**12d**) was judged to be complete (t.l.c., *ca.* 30 min), the mixture was filtered through 'Hiflo' and the filtrate was evaporated. The residue was dissolved in dry ethyl acetate (30 cm^3) and to the stirred solution under argon was added, over 10 min, a solution of the phosphorane (**10b**) (26.0 g, 75 mmol) in dry ethyl acetate (500 cm^3). After 24 h, the mixture was filtered and the filtrate evaporated. Purification of the residue by silica-gel chromatography (light petroleum–EtOAc; gradient elution) gave a foam (11.5 g, *ca.* 55%) that was considered to be predominantly 1-(*p*-nitrobenzyl) 4-ethyl 2-(2-oxo-4-vinylazetidin-1-yl)-3-(triphenylphosphoranylidene)succinate (**9b**) on the basis of the following properties: $\nu_{max.}$(film) (*inter alia*) 1 745 (β-lactam and ester C=O) and 1 625 cm^{-1} (phosphorane ester C=O); *m/z* (*inter alia*) 636 (M^+) and 262 ($C_{18}H_{15}P^+$, base peak).

Trifluoroacetic acid (12.3 cm^3, 160 mmol) followed by dichloromethane (350 cm^3) were added to the phosphorane (**9b**) (10.0 g, *ca.* 16 mmol) and the cooled (Me_2CO–solid CO_2) solution was saturated with ozone. After removal of the excess of ozone with a stream of nitrogen, dimethyl sulphide (5.8 cm^3, 79 mmol) was added. The mixture was allowed to warm to room temperature and stirred with saturated aqueous sodium hydrogen carbonate (500 cm^3) for 2 h. Evaporation of the dried ($MgSO_4$) organic layer left a yellow syrup which was purified by silica-gel chromatography (light petroleum–EtOAc; gradient elution) to give p-*nitrobenzyl 2-ethoxycarbonylcarbapen-1-em-3-exo-carboxylate* (**7b**) (4.50 g, 80%) as a chromatographically homogeneous foam with the following properties: $\nu_{max.}$(film) (*inter alia*) 1 780 (β-lactam C=O), 1 750 (ester C=O), and 1 720 cm^{-1} (unsaturated ester C=O); δ (60 MHz; $CDCl_3$) 1.27 (3 H, t, *J* 7 Hz, CH_2*Me*), 3.10 (1 H, dd, *J* 16 and 3 Hz, 6β-H), 3.57 (1 H, dd, *J* 16 and 5 Hz, 6α-H), 4.23 (2 H, q, *J* 7 Hz, OCH_2Me), 4.65—4.80 (1 H, m, 5-H), 5.30 (2 H, s, $OCH_2C_6H_4$), 5.40 (1 H, dd, *J* 4 and 2 Hz, 3-H), 7.06 (1 H, t, *J* 2 and 2 Hz, 1-H), and 7.40 and 8.09 (each 2 H, d, *J* 8 Hz, C_6H_4); *m/z* (*inter alia*) 287 ($M^+ - C_3H_5O_2$) and 180 ($M^+ - C_8H_6NO_4$, base peak) (Found: $M^+ - C_8H_6NO_4$, 180.0647. $C_9H_{10}NO_3$ requires *m/z* 180.0661).

Reaction of the Carbapenem (**7a**) *with Trifluoroacetic Acid Followed by Diazomethane.*—To a solution of the carbapenem (**7a**) (0.050 g, 0.18 mmol) in deuteriochloroform (0.5 cm^3) was added trifluoroacetic acid (0.015 cm^3, 0.19 mmol). The reaction was monitored by ^1H n.m.r. spectroscopy and, when the starting material had disappeared (*ca.* 30 min), the mixture was concentrated. Toluene was added to the residue and the solution was re-evaporated to give α-[(2SR,5RS)-4-*ethoxycarbonyl-5-t-butoxycarbonyl-1-trifluoroacetyl-2,5-dihydropyrrol-2-yl*]*acetic acid* (**21a**) as a syrup which possessed the following properties: $\nu_{max.}$(film) (*inter alia*) 3 240br (OH), 1 730 and 1 715 (ester and acid C=O), 1 700 (amide C=O), and 1 655 cm^{-1} (C=C); δ (60 MHz; $CDCl_3$) 1.38 (3 H, t, *J* 8 Hz, CH_2*Me*), 1.45 (9 H, s, CMe_3), 2.60 (1 H, dd, *J* 16 and 8 Hz, COC*H*HCH), 3.40 (1 H, dd, *J* 16 and 3 Hz, COCH*H*CH), 4.27 (2 H, q, *J* 8 Hz, OCH_2Me), 5.20—5.60 (2 H, m, $COCH_2CH$ and $NCHCO_2CMe_3$), 6.90 (1 H, s, 3-H), and 9.75 (1 H, s, CO_2H) (addition of D_2O caused the signal at δ 9.75 to disappear); *m/z* (*inter alia*) 396 (MH^+), 340 ($MH^+ - C_4H_8$) 295, 294 ($M^+ - C_5H_9O_2$), 248, 236, and 57 ($C_4H_9^+$ base peak) (Found: $M^+ - C_5H_9O_2$, 294.0613. $C_{11}H_{11}F_3NO_5$ requires *m* 294.0589).

The afore-cited experiment was repeated and the acid (**21a**) [derived from the carbapenem (**7a**) (0.050 g, 0.18 mmol)] was dissolved in dichloromethane (5 cm^3) and treated at 0 °C with an excess of diazomethane in diethyl ether. Evaporation and purification of the product by silica-gel chromatography [light petroleum–EtOAc (9:1) as the eluant] gave *methyl α-[(2SR,5RS)-4-ethoxycarbonyl-5-t-butoxycarbonyl-1-trifluoroacetyl-2,5-dihydropyrrol-2-yl]acetate* (**21b**) (0.055 g, 76%) as a syrupy 5:1 mixture of rotamers with the following properties: $\nu_{max.}$(film) (*inter alia*) 1 740 (ester C=O), 1 700 (amide C=O), and 1 660 cm^{-1} (C=C); $\lambda_{max.}$(EtOH) 218 nm (ε 10 900); δ (300 MHz; $CDCl_3$) 1.32 and 1.34 (2.5 and 0.5 H, each t, *J* 7 Hz, together CH_2*Me*), 1.44 and 1.47 (7.5 and 1.5 H, each s, together $OCMe_3$), 2.62 and 2.63 (0.83 and 0.17 H, each dd, *J* 16.5 and 9 Hz, together COC*H*HCH), 2.99 and 3.30 (0.17 and 0.83 H, each dd, *J* 16.5 and 3.5 Hz, together COCH*H*CH), 3.70 and 3.72

(2.5 and 0.5 H, each s, together OMe), 4.18—4.36 (2 H, m, OCH_2Me), 5.25—5.26 and 5.47—5.49 (0.17 and 0.83 H, each m, together 5-H), 5.34—5.40 (1 H, m, 2-H), and 6.90 and 6.96 (0.83 and 0.17 H, each t, *J* 2 and 2 Hz, together 3-H); *m/z* (*inter alia*) 378 ($M^+ - CH_3O$), 308 ($M^+ - C_5H_9O_2$, base peak), 248 and 236 (Found: $M^+ - C_5H_9O_2$, 308.0764. $C_{12}H_{13}F_3NO_5$ requires *m/z* 308.0746).

Hydrogenolysis of the Carbapen-1-em (**7b**).—(*a*) To a solution of the carbapen-1-em (**7b**) (0.500 g, 1.4 mmol) in ethyl acetate (30 cm^3) and ethanol (3 cm^3) was added 10% palladium–charcoal (0.500 g, 1 mass equiv.) and a solution of sodium hydrogen carbonate (0.110 g, 1.3 mmol) in water (5 cm^3). The mixture was stirred under a hydrogen atmosphere for 30 min and filtered through 'Hiflo'. Evaporation of the solvent left a residue which was partitioned between water (15 cm^3) and ethyl acetate (30 cm^3). The aqueous layer was evaporated and the residue was dried (*in vacuo*; P_2O_5). The resultant solid (0.257 g, 75%) which was sodium 2-ethoxycarbonylcarbapen-1-em-3-*exo*-carboxylate (**7c**), possessed the following properties: $\nu_{max.}$(KBr) (*inter alia*) 1 770 (β-lactam C=O), 1 710 (unsaturated ester C=O), and 1 610 cm^{-1} (carboxylate C=O); δ (60 MHz; D_2O) 1.30 (3 H, t, *J* 7 Hz, CH_2Me), 3.13 (1 H, dd, *J* 16 and 3 Hz, 6β-H), 3.63 (1 H, dd, *J* 16 and 5 Hz, 6α-H), 4.30 (2 H, q, *J* 7 Hz, OCH_2Me), 5.10—5.20 (1 H, m, 3-H), and 7.2br (1 H, s, 1-H) (the 5-H, expected as a m at *ca.* δ 4.70, was obscured by the HOD signal) (the spectrum was unaltered after 12 h).

(*b*) The afore-cited experiment was repeated except that the time for the reduction was extended to 2 h. Work-up as before gave sodium 2-ethoxycarbonylcarbapenam-3-*exo*-carboxylate (**24a**)/(**25a**) (0.230 g, 66%) as a solid with the following properties: $\nu_{max.}$(KBr) (*inter alia*) 1 735br (β-lactam and ester C=O) and 1 615 cm^{-1} (carboxylate C=O); δ (60 MHz; D_2O) 1.30 (t, *J* 7 Hz, CH_2Me), 1.60—4.60 (m, 1- and 6-H_2, 2-, 3-, and 5-H, and CH_2Me) (the spectrum was unchanged over a 24-h period).

Reaction of the Salts (**7c**) *and* (**24a**)/(**25a**) *with Iodomethane.*—(*a*) To a stirred suspension of the salt (**7c**) (0.120 g, 0.49 mmol) in dry DMF (5 cm^3) was added iodomethane (0.06 cm^3, 0.96 mmol). After 24 h, the mixture was diluted with dichloromethane and washed (× 3) with brine. Evaporation of the dried organic layer and purification of the product by silica-gel chromatography (light petroleum–EtOAc; gradient elution) gave methyl 2-ethoxycarbonylcarbapen-1-em-3-*exo*-carboxylate (**7e**) (0.105 g, 90%) as a chromatographically homogeneous syrup; δ (60 MHz; $CDCl_3$) 1.30 (3 H, t, *J* 7 Hz, CH_2Me), 3.05 (1 H, dd, *J* 16 and 3 Hz, 6β-H), 3.57 (1 H, dd, *J* 16 and 5 Hz, 6α-H), 3.75 (3 H, s, OMe), 4.25 (2 H, q, *J* 7 Hz, OCH_2Me), 4.60—4.80 (1 H, m, 5-H), 5.35 (1 H, dd, *J* 3 and 2 Hz, 3-H), and 7.15 (1 H, t, *J* 2 and 2 Hz).

(*b*) To a stirred suspension of the sodium salt (**24a**)/(**25a**) (0.200 g, 0.8 mmol) in dry DMF (10 cm^3) was added iodomethane (0.07 cm^3, 1.1 mmol). After 24 h, the mixture was diluted with dichloromethane and washed (× 3) with brine. Evaporation of the dried ($MgSO_4$) organic layer and purification of the product by silica-gel chromatography (light petroleum–EtOAc; gradient elution) gave two fractions.

The first-eluted material, isolated as a chromatographically homogeneous syrup (0.050 g, 26%), was identified as *methyl* 2-exo-*ethoxycarbonylcarbapenam*-3-exo-*carboxylate* (**25b**). It possessed the following properties: $\nu_{max.}$(film) (*inter alia*) 1 775 (β-lactam C=O) and 1 745br cm^{-1} (ester C=O); δ (90 MHz; $CDCl_3$) 1.25 (3 H, t, *J* 7 Hz, CH_2Me), 1.69—2.04 and 2.42—2.71 (each 1 H, m, 1-H_2), 2.80 (1 H, dd, *J* 16 and 2 Hz, 6β-H), 3.28 (1 H, dd, *J* 16 and 5 Hz, 6α-H), 3.47—3.73 (1 H, m, 2-H), 3.74 (3 H, s, OMe), 3.78—4.00 (1 H, m, 5-H), 4.15 (2 H, q, *J* 7 Hz, OCH_2Me), and 4.66 (1 H, d, *J* 7 Hz, 3-H); *m/z* (*inter alia*) 241 (M^+) and 182 ($M^+ - C_3H_5O_2$, base peak).

The second-eluted fraction, also isolated as a chromatographically homogeneous syrup (0.090 g, 46%), was considered to be *methyl* 2-endo-*ethoxycarbonylcarbapenam*-3-exo-*carboxylate* (**24b**). It showed the following properties: $\nu_{max.}$(film) (*inter alia*) 1 775 (β-lactam C=O) and 1 740 cm^{-1} (ester C=O); δ (90 MHz; $CDCl_3$) 1.24 (3 H, t, *J* 7 Hz, CH_2Me), 1.80—2.12 and 2.44—2.67 (each 1 H, m, 1-H_2), 2.69 (1 H, dd, *J* 16 and 2 Hz, 6β-H), 3.36 (1 H, dd, *J* 16 and 5 Hz, 6α-H), 3.43—3.71 (1 H, m, 2-H), 3.71 (3 H, s, OMe), 3.99—4.24 (3 H, m, OCH_2Me and 5-H), and 4.68 (1 H, d, *J* 7 Hz, 3-H); *m/z* (*inter alia*) 241 (M^+), 213, 200, and 182 ($M^+ - C_3H_5O_2$, base peak) (Found: M^+, 241. 0943. $C_{11}H_{15}NO_5$ requires *M*, 241.0950).

Hydrogenation of the Carbapenem (**7a**).—A stirred mixture of the carbapenem (**7a**) (0.050 g, 0.18 mmol), ethyl acetate (10 cm^3), and 10% palladium–charcoal (0.100 g, 2 mass equiv.) was left under a hydrogen atmosphere for 4 h. The filtrate, obtained after passage of the mixture through 'Hiflo,' was evaporated and the residue purified by silica-gel chromatography (light petroleum–EtOAc, gradient elution) to give a chromatographically homogeneous syrup (0.039 g, 77%) that was a 5:1 mixture of *t-butyl* 2-exo-*ethoxycarbonylcarbapenam*-3-exo-*carboxylate* (**25c**) and its 2-endo-*diastereoisomer* (**24c**). The mixture possessed the following properties: $\nu_{max.}$(film) (*inter alia*) 1 775 (β-lactam C=O) and 1 720 cm^{-1} (ester C=O); $\lambda_{max.}$(EtOH) 231 nm (ε 900); δ (300 MHz; $CDCl_3$) 1.25 and 1.28 (0.5 and 2.5 H, each t, *J* 7 Hz, together CH_2Me), 1.44 and 1.47 (7.5 and 1.5 H, each s, together $OCMe_3$), 1.95—2.04 and 2.23 [0.83 H (7 lines) and 0.17 H (dt, *J* 12.5, 10, and 10 Hz), together 1-H], 2.34—2.42 and 2.55—2.65 (0.17 and 0.83 H, each 5 lines, together 1-H), 2.69 and 2.82 (0.83 and 0.17 H, each dd, *J* 16 and 2.5 Hz, 6β-H), 3.13 and 3.37 [0.17 H (ddd, *J* 16, 4.5, and 2.5 Hz) and 0.83 H (dd, *J* 16 and 4.5 Hz), together 6α-H], 3.44—3.52 and 3.52—3.59 (0.83 and 0.17 H, each apparent q, together 2-H), 3.70—3.76 and 4.03—4.57 (0.17 and 2.87 H, each m, together 5-H and OCH_2Me), and 4.63 (1 H, d, *J* 7.5 Hz, 3-H) (in an n.O.e.d. spectroscopic study, irradiation of the signal at δ 4.63 caused a 17% enhancement of the q centred at δ 3.48); *m/z* (*inter alia*) 283 (M^+), 255, 210, 199, 183, and 182 (base peak) (Found: $M^+ - C_5H_9O_2$, 182.0838. $C_9H_{12}NO_3$ requires *m/z* 182.0817).

Deuteriation of the Carbapenem (**7a**).—To a vigorously stirred solution of the carbapenem (**7a**) (0.200 g, 0.71 mmol) in dichloromethane (2 cm^3) was added DBN (0.20 cm^3, 1.6 mmol) followed by deuterium oxide (0.5 cm^3). After 18 h, the mixture was diluted with dichloromethane and washed with dilute hydrochloric acid (× 2) and aqueous sodium hydrogen carbonate. Evaporation of the dried ($MgSO_4$) organic layer left a syrupy solid (0.189 g) which was recrystallised from diethyl ether–light petroleum to give *t-butyl 2-ethoxycarbonyl*[3-endo-^{2}H]*carbapen*-1-*em*-3-exo-*carboxylate* (0.050 g, 25%) with the following properties: m.p. 70—73 °C; $\nu_{max.}$(KBr) (*inter alia*) 1 780 (β-lactam C=O), 1 730br (ester C=O), and 1 625 cm^{-1} (C=C); δ (60 MHz; $CDCl_3$) 1.27 (3 H, t, *J* 7 Hz, CH_2Me), 1.40 (9 H, s, $OCMe_3$), 2.88 (1 H, dd, *J* 16 and 3 Hz, 6α-H), 3.40 (1 H, dd, *J* 16 and 5 Hz, 6α-H), 4.13 (2 H, q, *J* 7 Hz, OCH_2Me), 4.45—4.65 (1 H, m, 5-H), and 6.92 (1 H, d, *J* 1.5 Hz, 1-H); *m/z* (*inter alia*) 239 ($M^+ - C_2H_3O$), 209, 182, 181 ($M^+ - C_4H_5O$), and 57 ($C_4H_9^+$, base peak) (Found: $M^+ - C_5H_9O_2$, 181.0721. $C_9H_9DNO_3$ requires *m/z* 181.0723).

Reaction of the Carbapenem (**7a**) *with Diazomethane.*—A solution of the carbapenem (**7a**) (0.300 g, 1.07 mmol) in dichloromethane (20 cm^3) at 0 °C was treated with an excess of ethereal diazomethane. After 2 h, the mixture was evaporated and the residue was subjected to silica-gel chromatography

[light petroleum–EtOAc (3:7) as the eluant] to give two materials.

The first-eluted material, isolated as a solid (0.027 g, 8%), was considered to be *t-butyl* [2RS,3RS,7RS,8RS]-3-*ethoxycarbonyl*-10-*oxo*-1,4,5-*triazatricyclo*[6.2.0.0^{3,7}]*dec*-4-*ene*-2-*carboxylate* (**31**). After recrystallisation from dichloromethane–diethyl ether, the material (0.015 g, 4%) showed the following properties: m.p. 94—97 °C; $\nu_{max.}$(KBr) (*inter alia*) 1 770 (β-lactam C=O) and 1 735 cm^{-1} (ester C=O); $\lambda_{max.}$(EtOH) 227 nm (ε 2 500) and 325 nm (200); δ (300 MHz; $CDCl_3$) 1.27 (3 H, t, *J* 7 Hz, CH_2*Me*), 1.48 (9 H, s, CMe_3), 2.42 (1 H, dd, *J* 16.4 and 2.8 Hz, 9β-H), 3.15 (1 H, dd, *J* 16.4 and 5.6 Hz, 9α-H), 3.30 (1 H, t, separation 8 Hz, 7-H), 4.04—4.26 (3 H, m, OCH_2Me and 8-H), 4.59 (1 H, dd, *J* 18 and 7.3 Hz, 6α-H), 5.14 (1 H, d, *J* 18 Hz, 6β-H), and 5.36 (1 H, s, 2-H) (in an n.O.e.d. spectroscopic study, irradiation of the signal at δ 2.42 caused a 27% enhancement of the signal at δ 3.15 and an 8% enhancement of the d at δ 5.14; irradiation of the signal at δ 3.30 caused a 13% enhancement of the signal at δ 4.61; irradiation of the signal at δ 4.54 caused a 35% enhancement of the signal at δ 5.14); *m/z* (*inter alia*) 222 ($M^+ - C_5H_9O_2$), 194 ($M^+ - C_5H_9N_2O_2$), and 57 ($C_4H_9^+$, base peak) (Found: C, 55.9; H, 6.5; N, 12.9. $C_{15}H_{22}N_3O_5$ requires C, 55.7; H, 6.5; N, 13.0%).

The second-eluted material, also isolated as a crystalline solid (0.319 g, 92%), was considered to be *t-butyl* [2SR,3SR,7SR,8SR]-3-*ethoxycarbonyl*-10-*oxo*-1,4,5-*triazatricyclo*[6.2.0.0^{3,7}]*dec*-4-*ene*-2-*carboxylate* (**32**). After having been recrystallised from dichloromethane–diethyl ether, the material (0.248 g, 72%) possessed the following properties: m.p. 140—143 °C; $\nu_{max.}$(KBr) (*inter alia*) 1 765 (β-lactam C=O) and 1 730 cm^{-1} (ester C=O); $\lambda_{max.}$(EtOH) 230 (ε 920) and 325 nm (210); δ (300 MHz; $CDCl_3$) 1.29 (3 H, t, *J* 7 Hz, CH_2*Me*), 1.47 (9 H, s, $OCMe_3$), 2.80 (1 H, ddd, *J* 8, 5, and 2 Hz, 7-H), 2.83 (1 H, dd, *J* 16 and 2 Hz, 9β-H), 3.40 (1 H, dd, *J* 16 and 5 Hz, 9α-H), 3.50 (1 H, dt, *J* 5, 5, and 2 Hz, 8-H), 4.24 (2 H, q, *J* 7 Hz, OCH_2Me), 4.54 (1 H, dd, *J* 18 and 8 Hz, 6β-H), 4.86 (1 H, dd, *J* 18 and 2 Hz, 6α-H), and 5.41 (1 H, s, 2-H) (in an n.O.e.d. spectroscopic study, irradiation of the signal at δ 3.50 caused a 3% enhancement of the dd at δ 4.86; no significant enhancements were observed when the signals at δ 4.86, 4.55, and 3.40 were irradiated); *m/z* (*inter alia*) 222 ($M^+ - C_5H_9O_2$), 194 ($M^+ - C_5H_9N_2O_2$), and 57 ($C_4H_9^+$, base peak) (Found: C, 55.7; H, 6.4; N, 13.1. $C_{15}H_{21}N_3O_5$ requires C, 55.7; H, 6.5; N, 13.0%).

Thermolysis of the Triazatricyclodecene (**32**).—A solution of the triazatricyclodecene (**32**) (0.340 g, 1.05 mmol) in dry toluene (20 cm^3) was heated under reflux for 2 h, when t.l.c. revealed the formation of a major more-mobile product. Evaporation and purification of the material by silica-gel chromatography (light petroleum–EtOAc; gradient elution) gave *t-butyl* 2-*ethoxycarbonyl*-1-*methylcarbapen*-1-*em*-3-exo-*carboxylate* (**33**) (0.250 g, 81%) as a chromatographically homogeneous syrup. The sample possessed the following properties: $\nu_{max.}$(film) (*inter alia*) 1 780 (β-lactam C=O), 1 725 ester C=O), and 1 640 cm^{-1} (C=C); $\lambda_{max.}$(EtOH) 221 nm (ε 6 300); δ (60 MHz; $CDCl_3$) 2.2 (3 H, br s, 1-Me), 2.85 (1 H, dd, *J* 16 and 3 Hz, 6β-H), 3.43 (1 H, dd, *J* 16 and 6 Hz, 6α-H), 4.17 (2 H, q, *J* 7 Hz, OCH_2Me), 4.35—4.50 (1 H, m, 5-H), and 5.05—5.15 (1 H, m, 3-H); *m/z* (*inter alia*) 252, 222 ($M^+ - C_3H_5O_2$), 194 ($M^+ - C_5H_9O_2$), and 57 ($C_4H_9^+$, base peak) (Found: $M^+ - C_5H_9O_2$, 194.0830. $C_{15}H_{21}NO_5$ requires *m/z* 194.0817).

Deuteriation of the Carbapenem (**33**).—To a vigorously stirred solution of the carbapenem (**33**) (0.250 g, 0.85 mmol) in dichloromethane (2 cm^3) was added DBN (0.26 cm^3, 1.02 mmol) followed by deuterium oxide (0.5 cm^3). After 12 h, the mixture was diluted with dichloromethane and washed with dilute hydrochloric acid (× 2) and aqueous sodium hydrogen carbonate. Evaporation of the dried ($MgSO_4$) organic layer left a syrup (0.179 g) which was purified by silica-gel chromatography [light petroleum–EtOAc (4:1) as the eluant] to give t-butyl 2-ethoxycarbonyl-1-methyl[3-*endo*-^{2}H]carbapen-1-em-3-*exo*-carboxylate (0.074 g, 30%) as a chromatographically homogeneous syrup. The ^{1}H n.m.r. spectrum (60 MHz; $CDCl_3$) of the sample was similar to that of compound (**33**) except that the signal at δ 2.2 was broader and the integral for the multiplet at δ 5.05—5.15 was reduced by *ca.* 25%.

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References

1 Part 2, P. H. Crackett, C. M. Pant, and R. J. Stoodley, *J. Chem. Soc., Perkin Trans. 1*, 1984, 2785.
2 Preliminary communication, R. Sharma and R. J. Stoodley, *Tetrahedron Lett.*, 1981, **22**, 2025.
3 R. D. G. Cooper in 'Topics in Antibiotic Chemistry,' ed. P. G. Sammes, Ellis Horwood Ltd., Chichester, vol. 3, 1979, p. 41; T. Kametani, *Heterocycles*, 1982, **17**, 463; W. Durckheimer, J. Blumbach, R. Lattrell, and K. H. Scheunemann, *Angew. Chem., Int. Ed. Engl.*, 1985, **24**, 180.
4 D. B. R. Johnson, S. M. Schmitt, F. A. Bouffard, and B. G. Christensen, *J. Am. Chem. Soc.*, 1978, **100**, 313.
5 S. M. Schmitt, D. B. R. Johnson, and B. G. Christensen, *J. Org. Chem.*, 1980, **45**, 1135 and 1142.
6 S. Oida, A. Yoshida, and E. Ohki, *Chem. Pharm. Bull.*, 1980, **28**, 3494.
7 L. D. Cama and B. G. Christensen, *J. Am. Chem. Soc.*, 1978, **100**, 8006; *Tetrahedron Lett.*, 1980, 2013.
8 A. J. G. Baxter, K. H. Dickinson, P. M. Roberts, T. C. Smale, and R. Southgate, *J. Chem. Soc., Chem. Commun.*, 1979, 236; R. J. Ponsford, P. M. Roberts, and R. Southgate, *ibid.*, 1979, 847; A. G. Baxter, R. J. Ponsford, and R. Southgate, *ibid.*, 1980, 429.
9 T. Kametani, S.-P. Huang, and M. Ihara, *Heterocycles*, 1979, **12**, 1189; T. Kametani, S.-P. Huang, S. Yokohama, Y. Suzuki, and M. Ihara, *J. Am. Chem. Soc.*, 1980, **102**, 2060.
10 H. Onoue, M. Narisada, S. Uyeo, H. Matsumura, K. Okada, T. Yano, and W. Nagata, *Tetrahedron Lett.*, 1979, 3867.
11 I. Ernest, J. Gosteli, C. W. Greengrass, W. Holick, D. E. Jackman, H. R. Pfaendler, and R. B. Woodward, *J. Am. Chem. Soc.*, 1978, **100**, 8214.
12 H. J. Bestmann and H. Schulz, *Chem. Ber.*, 1962, **95**, 2921.
13 A. H. Shingler and N. G. Weir in 'Recent Advances in the Chemistry of β-Lactam Antibiotics,' ed. J. Elks, Special Publication No. 28, The Chemical Society, London, 1977, p. 153.
14 R. Scartazzini, H. Peter, H. Bickel, H. Heusler, and R. B. Woodward, *Helv. Chim. Acta*, 1972, **55**, 408; J. Finkelstein, K. G. Holden, and C. D. Perchonock, *Tetrahedron Lett.*, 1978, 1629.
15 E. J. Moriconi and W. C. Meyer, *J. Org. Chem.*, 1971, **36**, 2841.
16 L. A. Carpino, *J. Org. Chem.*, 1984, **29**, 2820.
17 J. H. Bateson, R. I. Hickling, P. M. Roberts, T. C. Smale, and R. Southgate, *J. Chem. Soc., Chem. Commun.*, 1980, 1084; M. J. Basker, J. H. Bateson, A. J. G. Baxter, R. J. Ponsford, P. M. Roberts, R. Southgate, T. C. Smale, and J. Smith, *J. Antibiot.*, 1981, **34**, 1224.
18 B. Venugopalan, A. B. Hamlet, and T. Durst, *Tetrahedron Lett.*, 1981, **22**, 191.
19 C. L. Branch and M. J. Pearson, *J. Chem. Soc., Perkin Trans. 1*, 1982, 2123.
20 G. H. Hakimelahi, *Helv. Chim. Acta*, 1982, **65**, 1378.
21 K. Hirai, K. Fujimoto, Y. Iwano, T. Hiraoka, T. Hata, and C. Tamura, *Tetrahedron Lett.*, 1981, **22**, 1201.
22 J. V. Heck and B. G. Christensen, *Tetrahedron Lett.*, 1981, **22**, 5027;

J. V. Heck, M. J. Szymoifka, and B. G. Christensen, *ibid.*, 1982, **23**, 1519.
23 J. D. Cocker, S. Eardley, G. I. Gregory, M. E. Hall, and A. G. Long, *J. Chem. Soc. C*, 1966, 1142; R. M. Sweet and L. F. Dahl, *J. Am. Chem. Soc.*, 1970, **95**, 5489; N. C. Cohen, *J. Med. Chem.*, 1983, **26**, 259.
24 B. G. Christensen, R. W. Ratcliffe, and D. H. Shih, U.S.P. 4 146 633 (*Chem. Abstr.*, 1979, **91**, 5109).
25 J. Brennan, G. Richardson, and R. J. Stoodley, *J. Chem. Soc., Perkin Trans. 1*, 1983, 649.
26 D. H. Shih and R. W. Ratcliffe, *J. Med. Chem.*, 1981, **24**, 639.
27 H. R. Pfaendler, J. Gosteli, R. B. Woodward, and G. Rihs, *J. Am. Chem. Soc.*, 1981, **103**, 4526.
28 B. G. Christensen and D. H. Shih, Belg. 866 227 (*Chem. Abstr.*, 1979, **90**, 137673).
29 T. Haneishi, M. Nakajima, N. Serizawa, M. Inukai, Y. Takiguchi, M. Arai, S. Satoh, H. Kuwano, and C. Tamura, *J. Antibiot.*, 1983, **36**, 1581.
30 T. Yoshioka, A. Watanabe, I. Kojima, Y. Shimauchi, M. Okabe, Y. Fukagawa, and I. Ishikura, *J. Antibiot.*, 1984, **37**, 211.
31 M. Shibuya and S. Kubota, *Tetrahedron Lett.*, 1981, **24**, 3611.
32 M. Shiozaki, N. Ishida, H. Maruyama, T. Hiraoka, and S. Sugawara, *J. Antibiot.*, 1984, **33**, 57.
33 K. Fujimoto, Y. Iwano, and K. Hirai, *Tetrahedron Lett.*, 1984, **25**, 1151.
34 J. G. de Vries, G. Hauser, and G. Sigmund, *Tetrahedron Lett.*, 1984, **25**, 5989.
35 M. J. Pearson and C. L. Branch, Eur. Pat. Appl. EP 73 100 (*Chem. Abstr.*, 1983, **99**, 87915).
36 Jpn. Kokai Tokkyo Koho JP 58 174 382 (*Chem. Abstr.*, 1984, **100**, 138848).
37 R. J. Crawford and A. Mishra, *J. Am. Chem. Soc.*, 1966, **88**, 3963.
38 J. H. Bateson, R. Southgate, J. W. Tyler, and S. C. M. Fell, *J. Chem. Soc., Perkin Trans. 1*, 1986, 973.
39 A. I. Vogel, 'Practical Organic Chemistry,' 3rd edn., Longman, London, 1979, p. 771.

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