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CONTRASTING THERMAL BEHAVIOUR OF DIASTEREOISOMERIC 4-ACETYLTHIO-3-ACYLAMINO-1-(α-TRIPHENYLPHOSPHORANYLIDENE)ALKOXYCARBONYLMETHYLAZETIDIN-2-ONES

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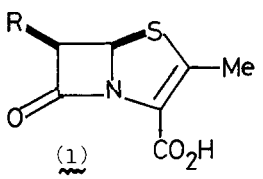
Summary: Under conditions in which cis isomers of the title compounds are converted into 6β-acylamino-2-methylpenem-3-carboxylates, trans isomers afford thiazole-4-carboxylates and 2-alkyloxazolin-5-ones.

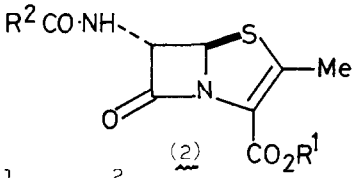
The demonstration that compound (1a) is endowed with potent antibacterial activity[1] has provoked much interest in the synthesis of penem-2-carboxylic acid derivatives. However, following the earlier report[2] that acid (1b) was too reactive chemically (although it showed weak antibacterial activity), 6-acylaminopenems have been relatively neglected.[3-6] The chemical reactivity of penem (1b) may reasonably be attributed to cleavage of its β-lactam linkage,[7] promoted by attack of an external nucleophile at the 7-carbonyl group from the least-hindered exo face. In the hope that the relocation of the acylamino group at the 6α-site would hinder such nucleophilic attack and provide less-reactive entities, we have been interested in the synthesis of penems of types (2) and (3).



(1)

a; R = H

b; R = NH·CO·CH_2·OPh

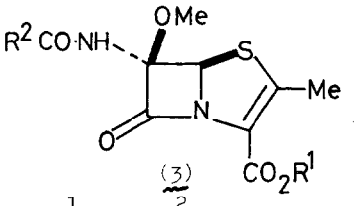


(2)

a; R^1 = Me, R^2 = CH_2Ph

b; R^1 = CH_2·C_6H_4·NO_2-p, R^2 = CH_2·OPh

c; R^1 = CH_2·C_6H_4·NO_2-p, R^2 = CH_2Ph



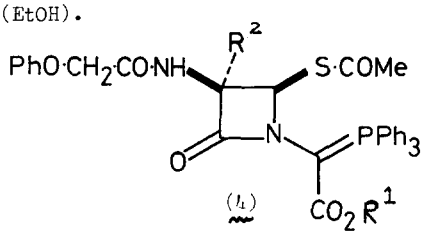
(3)

a; R^1 = Me, R^2 = CH_2·OPh

Woodward and his co-workers had shown that, under thermal conditions, phosphorane (4a) was converted into penem (5a) and triphenylphosphine oxide.[2] Moreover, we had observed[6] that phosphorane (4b) reacted analogously to give penem (5b) and triphenylphosphine oxide. Accordingly, it was expected that penems of types (2) and (3) would be available from precursors of types (6) and (7). We now report the synthesis of two phosphoranes of type (6), i.e. (6a,b), and one phosphorane of type (7), i.e. (7a), and show that the compounds do not react in the anticipated manner.

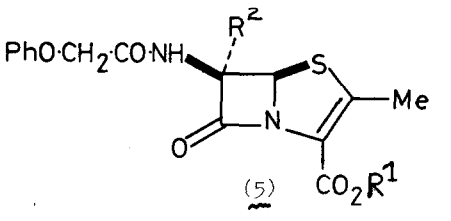
Reductive ozonolysis (O_3 in CH_2Cl_2 at -78°C, $MeCO_2H$-Zn) of butenoate (8a)[8] gave the carbinolamide (9a) (71% yield), as a 1:1 mixture of diastereoisomers. Treatment of compound (9a) with 2,6-lutidine (1.2 mol. equiv.) and thionyl chloride (1.1 mol. equiv.) in tetrahydrofuran (-30°C → 0°C, filtration, evaporation) followed with triphenylphosphine (2 mol. equiv.)

and silica gel (10 mass equiv.) in tetrahydrofuran was followed by evaporation. After 15 h the mixture was loaded onto a silica-gel column; elution gave phosphorane (6a) (66% yield), $[\alpha]_D$+21° (EtOH).



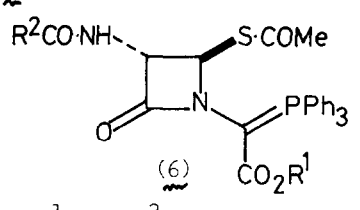
(4)

a; $R^1 = CH_2 \cdot C_6H_4 \cdot NO_2$-p, R^2 = H
b; $R^1 = CH_2 \cdot C_6H_4 \cdot NO_2$-p, R^2 = OMe
c; R^1 = Me, R^2 = OMe



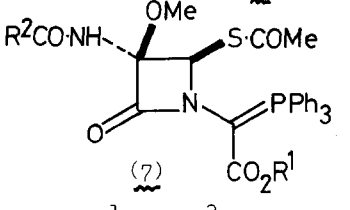
(5)

a; $R^1 = CH_2 \cdot C_6H_4 \cdot NO_2$-p, R^2 = H
b; $R^1 = CH_2 \cdot C_6H_4 \cdot NO_2$-p, R^2 = OMe
c; R^1 = Me, R^2 = OMe



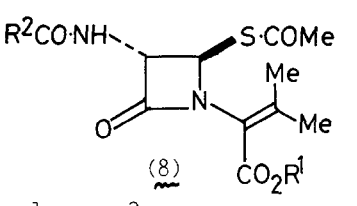
(6)

a; R^1 = Me, $R^2 = CH_2Ph$
b; $R^1 = CH_2 \cdot C_6H_4 \cdot NO_2$-p, $R^2 = CH_2 \cdot OPh$



(7)

a; R^1 = Me, $R^2 = CH_2 \cdot OPh$



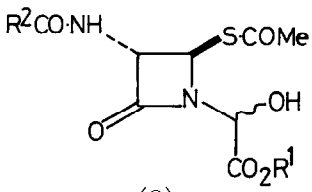
(8)

a; R^1 = Me, $R^2 = CH_2Ph$
b; $R^1 = CH_2 \cdot C_6H_4 \cdot NO_2$-p, $R^2 = CH_2 \cdot OPh$

Butenoate (8b)[8] reacted with ozone (CH_2Cl_2, -78°C) and methanol to give azetidinone (10) (36% yield), m.p. 156-157°C, $[\alpha]_D$ +67° (MeOH). Carbinolamide (9b), obtained as a 1:1 mixture of diastereoisomers by treatment of azetidinone (10) with p-nitrobenzyl glyoxylate and triethylamine in dioxan, was converted into phosphorane (6b) [57% yield based upon (10)] as described for the (9a) → (6a) transformation.

When reacted in dichloromethane with thionyl chloride followed by t-butyl alcohol, sulphinic acid (11a)[9] afforded sulphinate (11b) (54% yield after SiO_2 chromatography), as a 1:1 mixture of diastereoisomers. Methoxylation of the azetidinone (11b), using the Koppel-Koehler procedure,[10] was achieved in tetrahydrofuran-methanol at -78°C by adding t-butyl hypochlorite (1.3 mol. equiv.) followed by methanolic lithium methoxide (3.5 mol. equiv.). After a reductive work-up ($MeCO_2H$-Zn) and silica-gel chromatography, two fractions were isolated. The first-eluted material (31% yield) was a 1.5 : 1 mixture of methoxyazetidinones (12a), whose structure was established by conversion into thioester (12b)[6] (55% yield after SiO_2 chromatography), $[\alpha]_D$ +53° ($CHCl_3$), by sequential reactions involving neat thionyl chloride, thioacetic acid (3 mol. equiv.) in dichloromethane at -10°C, and triphenylphosphine (2 mol. equiv.) in dichloromethane. The second-eluted fraction (20% yield) was methoxyazetidinone (11c), apparently as a single diastereoisomer. Sequential reactions of the last-mentioned compound with thionyl chloride, thioacetic acid and triphenylphosphine gave thioester (11d) (45% yield after SiO_2 chromatography), $[\alpha]_D$ -6° ($CHCl_3$). By the procedure used to effect the (8a) → (6a) transformation, thioester (11d) was converted into phosphorane (7a) (54% yield), $[\alpha]_D$ -27° ($CHCl_3$).

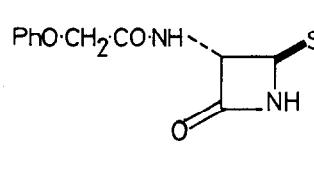
There are three features of note in the transformation of sulphinate (11b) into thioesters (11d) and (12b). First, and most welcome in the present context, was the finding that the methoxylation process was not subject to high diastereocontrol.[11] Second, the reaction of t-butyl sulphinate esters with thionyl chloride provides a useful route to sulphinyl chlorides when sensitive substrates are involved.[12] Third, the reductive acetylation procedure was highly diastereocontrolled, implicating intermediates (11e) and (12c).[8]



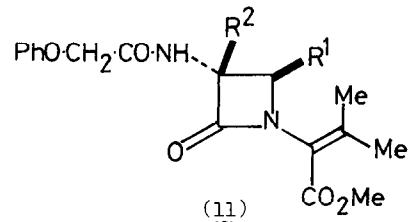
(9)

a; R^1 = Me, R^2 = CH_2Ph

b; R^1 = $CH_2 \cdot C_6H_4 \cdot NO_2$-p, R^2 = $CH_2 \cdot OPh$



(10)



(11)

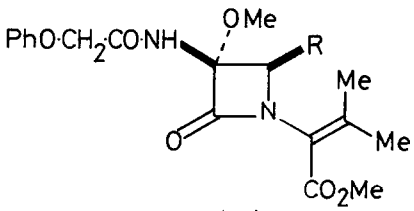
a; R^1 = SO_2H, R^2 = H

b; R^1 = $SO \cdot OBu^t$, R^2 = H

c; R^1 = $SO \cdot OBu^t$, R^2 = OMe

d; R^1 = S·COMe, R^2 = OMe

e; R^1 = $S^-P^+(Ph)_3S \cdot COMe$, R^2 = OMe

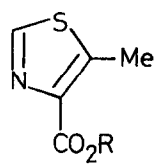


(12)

a; R = $SO \cdot OBu^t$

b; R = S·COMe

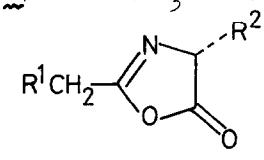
c; R = $S^-P^+(Ph)_3S \cdot COMe$



(13)

a; R = Me

b; R = $CH_2 \cdot C_6H_4 \cdot NO_2$-p



(14)

a; R^1 = Ph, R^2 = H

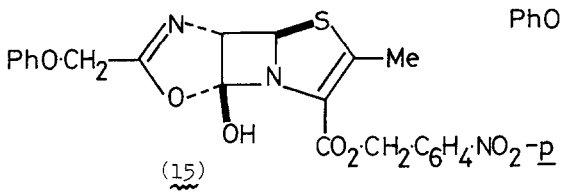
b; R^1 = OPh, R^2 = H

c; R^1 = OPh, R^2 = OMe

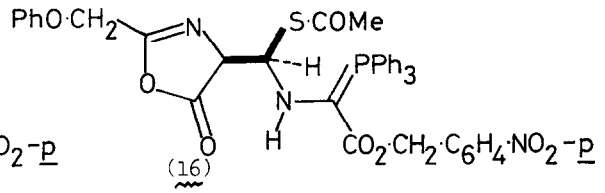
When heated (ca. 80°C, 2 days) in toluene containing hydroquinone under nitrogen, phosphorane (6a) was converted into three new products. Following silica-gel chromatography, two of these were isolated and shown to be thiazole (13a) (75% yield) and triphenylphosphine oxide. That oxazolinone (14a) was a component of the original mixture was inferred by t.l.c. and i.r. spectroscopy ($\nu_{max.}$ 1 825 cm^{-1}).[13] Thermolysis of phosphorane (6b) (ca. 80°C, 3.5 days) gave thiazole (13b) (56% after SiO_2 chromatography), m.p. 125-126°C, and triphenylphosphine oxide. The presence of oxazolinone (14b) in the crude thermolysate was suggested by the i.r. absorption at 1 830 cm^{-1}. Thermolysis of phosphorane (7a) (ca. 80°C, 4 days) gave thiazole (13a) (70% after SiO_2 chromatography). Although the final thermolysate showed no i.r. absorption attributable to oxazolinone (14c), a shoulder at 1 810 cm^{-1} was apparent after 16 h which disappeared after 44 h.

The thermal behaviour of phosphoranes (6b) and (7a) contrasts sharply with that of their diastereoisomers (4a) and (4c), which are reported[2,6] to give penems (5a) and (5c) in yields of

70% and 52% within 4.5 days and 4 h at ca. 80°C, respectively. We suggest that phosphoranes (6a,b) and (7a) undergo the intramolecular Wittig condensation to give penems (2a,b) and (3a), which are thermally unstable with respect to thiazoles (13a,b) and oxazolinones (14a-c). To account for the dramatic difference in the thermal reactivity of the diastereoisomeric penems, we postulate that participation by the amide side-chain plays a significant role in the fragmentations.[14] Thus the transition state leading, for example, from penem (2b) to intermediate (15) is much less congested than that of its diastereoisomeric counterpart. The alternative possibility, that phosphoranes (6a,b) and (7a) react to give β-lactam-cleaved intermediates, e.g. (16), which serve as precursors of the products, cannot, however, be discounted.



(15)



(16)

It is noteworthy that Kitchin and his collaborators have recently reported the synthesis of the enantiomer of penem (2c) by a 1,5 bond-forming strategy, which was conducted at ambient temperature.[5]

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References and Footnotes

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11 We are aware of only one other report in which the methoxylation of a monocyclic azetidinone was examined (S. Uyeo, I. Kikkawa, Y. Hamashima, H. Ona, Y. Nishitani, K. Okada, T. Kubota, K. Ishikura, Y. Ide, K. Nakano, and W. Nagata, J.Am.Chem.Soc., 1979, 101, 4403); in this example, high diastereocontrol was observed.

12 Analogous reactions of aromatic sulphinic esters have been reported (H.F. Herbrandson, R.T. Dickerson, Jr., and J. Weinstein, J.Am.Chem.Soc., 1956, 78, 2576).

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14 Woodward and his co-workers (see ref. 2) mentioned that 6β-acylaminopenem-3-carboxylates underwent partial decomposition to thiazole-4-carboxylates under thermal conditions and tentatively suggested the operation of a [2+2] cycloreversion pathway.

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