Dehydrative Decarboxylation of Clavulanic Acid. A Ready Synthesis of 7-Oxo-3-vinyl-4-oxa-1-azabicyclo[3.2.0]hept-2-ene

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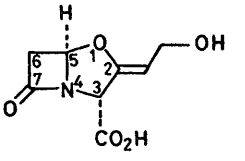
Summary Clavulanic acid (**1**) is converted by an efficient one-step process into the conjugated diene (**3**), which has been used in the preparation of novel analogues of (**1**), such as (**4**), (**6**), and (**7**).

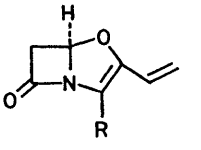
RECENT reports have described the preparation[1] of the conjugated dienoic esters (**2**) and their use[1b,2] in the synthesis of derivatives of the natural β-lactamase inhibitor clavulanic acid (**1**).[3] As part of a programme concerned with the preparation of analogues of (**1**) which lack the C-3 carboxy-group,[4] we were interested in preparing the conjugated diene (**3**) and investigating its use as a source of novel β-lactam compounds.

When a solution of (**1**) in tetrahydrofuran (THF) was treated with *NN*-dimethylformamide dimethyl acetal (1·1 equiv.) at room temperature, rapid dehydrative decarboxylation[5] occurred to give the conjugated diene (**3**) in 80% yield. This diene, which rapidly polymerises when freed of solvent or in concentrated solution, was characterised by its spectral properties: λ_{max} (EtOH) 277·5 nm; ν_{max} ($CHCl_3$) 1797, 1670, and 1640 cm^{-1}.† Compound (**3**) was also produced in good yield by reaction of (**1**) with triphenylphosphine (1 equiv.) and diethyl azodicarboxylate[6] (1 equiv.) in THF at 0 °C.

Further characterisation of (**3**) was provided by its ready formation of Diels–Alder adducts with a number of the more reactive dienophiles. For example, (**3**) reacted with

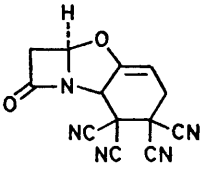


(**1**)

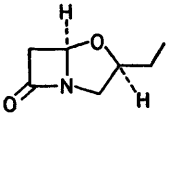


(**2**); R = CO_2CH_2Ph or $CO_2CH_2C_6H_4NO_2$-*p*

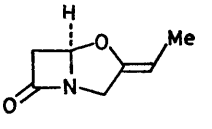
(**3**); R = H



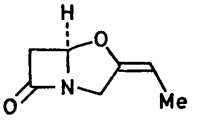
(**4**)



(**5**)



(**6**)



(**7**)

† The ^1H n.m.r. spectrum was also in accordance with the proposed structure.

tetracyanoethylene in toluene at room temperature to give, after 1 h, a 90% yield of the tricyclic adduct (**4**):‡ m.p. 203—204 °C; $[\alpha]_D$ + 268·5° (dimethylformamide).

Hydrogenation of (**3**) in THF over 10% palladium on charcoal gave a mixture of hydrogenation products from which the tetrahydro derivative (**5**)‡ (27% yield) and the two dihydro derivatives (**6**)‡ (28%) and (**7**)‡ (12%) were obtained pure by chromatography.§

Compounds (**3**), (**6**), and (**7**) were all potent inhibitors of a number of β-lactamase enzymes and were able to synergistically enhance the antibacterial activity of ampicillin against several β-lactamase-producing bacteria.

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‡ Spectral properties and analytical data or accurate mass measurement were in accordance with the proposed structure.

§ Stereochemical assignments for (**5**), (**6**), and (**7**) are based on comparisons of their n.m.r. spectral properties with those of related compounds of known stereochemistry; details will be published elsewhere.

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