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9-OXO-6-OXA-1-AZABICYCLO[5.2.0]NON-4-ENES, BY-PRODUCTS ARISING IN THE TOTAL SYNTHESIS OF CLAVULANIC ACID ANALOGUES

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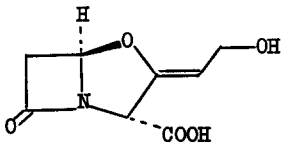
We have recently described[1] the total syntheses of the natural β-lactamase inhibitor, clavulanic acid (1)[2], and some of its analogues. We now wish to report the isolation of novel 9-oxo-6-oxa-1-azabicyclo[5.2.0]non-4-enes (4) during the course of similar reactions.

In one series of analogues, (3a) and its geometric isomer were synthesised by base-induced cyclisation of the chloroketone (2a)[1c]. In an extension of this series, the chloroketones (2b)[3] and (2c) were prepared by the general scheme A.[4] Cyclisation (K_2CO_3 - DMF) of (2b) gave the analogue (3b), as the only bicyclic product (77%), whereas (2c) gave, in addition to (3c) (11%), the novel bicyclononene (4c) in 41% yield. Clearly (4c), which was surprisingly stable considering the presence of the sensitive acylketene acetal functionality, arises via enolisation involving the ester carbonyl group in (2c). (4c) could be hydrogenolysed (THF, 10% Pd-C, 1 hr) to the lactone (5) (63%).

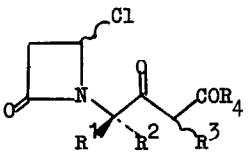
Bicyclononenes of type (4) had previously been encountered, less surprisingly, during the cyclisation of β-diketones such as (2d) and (2e) and the α,γ-diketo ester (2f), each prepared according to scheme A or B, by analogy.[4, 5] Treatment of (2d) with K_2CO_3 - DMF provided the desired analogue (3d) (13%),[6] together with the bicyclononene (4d) (5%). Similarly (2e) led to analogue (3e) (44%) and (4e) (9%), and (2f) gave (3f) (3%) and (4f) (8%). Supportive evidence for structures (4) and (5) comes from spectral data, some of which is presented in the Table. In addition the ^{13}C-n.m.r. spectrum of (4c) (in $CDCl_3$ with Me_4Si) had resonances at δ 23.4, 26.9 ($\underline{C}H_3$), 44.7 (C8), 66.5 (C2), 70.5 ($\underline{C}H_2O$), 80.2 (C7), 102.5 (C4), 126.7 - 136.6 ($\underline{C}_6H_5$), 162.9, 164.1 (C5, C9) and 195.9 ppm (C3).

Table

		(4c)	(4d)	(4e)	(4f)	(5)
λ max nm EtOH (ε)		279 (11240)	268 (11900)	282 (10270)	-	291 (8400)
ν $CHCl_3$ cm^{-1}	C=O (Lactam)	1773	1780	1772	1790	1769
	C=O (Other)	1640	1660	1675	1750, 1675	1739
	C=C	1565	1615	1645	1620	-
δ $CDCl_3$ ppm	C4-H	-	5.24 s	-	6.34 s	5.49 s
	C5-H	-	-	-	-	-
	C7-H	5.50 dd J 3.5, 1.5	5.47 dd J 3, 1.5	5.63 br	5.66 br	6.20 br
M^+ (Found)		363	167.0583	243.0899	211.0483	273.0994



(1)



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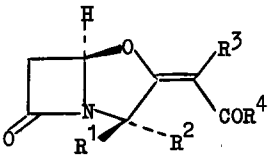

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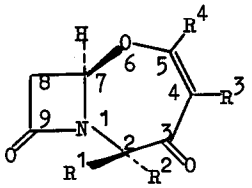

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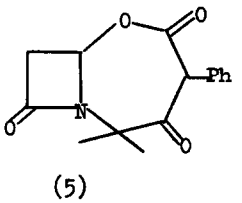
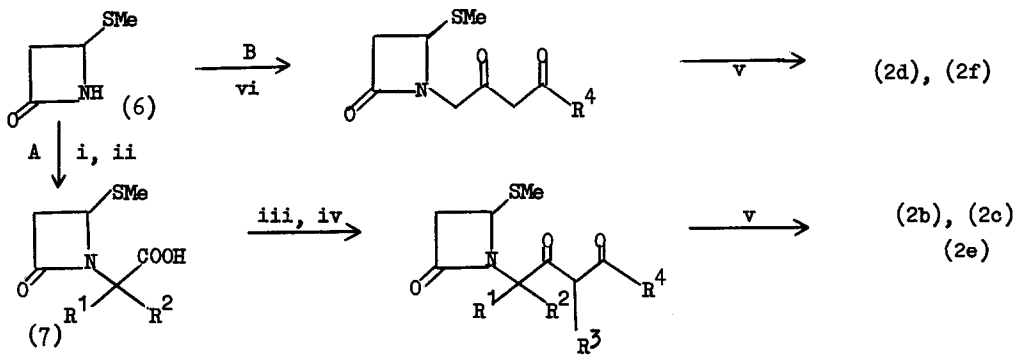


(5)

(2), (3) a; $R^1=R^2=R^3=H$, $R^4=OMe$
(2), (3) b; $R^1=R^2=H$, $R^3=Ph$, $R^4=OCH_2Ph$
(2), (3), (4) c; $R^1=R^2=Me$, $R^3=Ph$, $R^4=OCH_2Ph$
(2), (3), (4) d; $R^1=R^2=R^3=H$, $R^4=Me$
(2), (3), (4) e; $R^1=R^2=H$, $R^3=Me$, $R^4=Ph$
(2), (3), (4) f; $R^1=R^2=R^3=H$, $R^4=CO_2Me$

Schemes A and B



Reagents: i, NaH, $BrC(R^1R^2)CO_2Me$; ii, NaOH, MeOH; iii, $Ph_2P(O)Cl$, base
iv, $PhCH_2CO_2CH_2Ph$ or EtCOPh, $LiN(SiMe_3)_2$; v, Cl_2, CCl_4
vi, NaH, $BrCH_2COCH_2COR^4$.

References and Notes

1. (a) P.H. Bentley, P.D. Berry, G. Brooks, M.L. Gilpin, E. Hunt and I.I. Zomaya, J.C.S. Chem. Comm., 1977, 748; (b) P.H. Bentley, G. Brooks, M.L. Gilpin and E. Hunt, ibid, 1977, 905; (c) E. Hunt, P.H. Bentley, G. Brooks and M.L. Gilpin, ibid, 1977, 906; (d) P.H. Bentley and E. Hunt, ibid, 1978, 436 and 518.
2. T.T. Howarth, A.G. Brown and T.J. King, J.C.S. Chem. Comm., 1976, 266.
3. All new compounds had satisfactory spectral and analytical data.
4. Scheme A is based on an earlier successful route (ref. 1b) in which the methyl ester enolate of (7) ($R^1=R^2=H$) was acylated with various acid chlorides to generate the desired β-ketoesters. Here (7) is used to acylate ester and ketone enolates.
5. Scheme B is based on an earlier successful route (ref. 1c) in which azetidinone (6) was alkylated with methyl γ-bromoacetoacetate.
6. The geometric isomer of (3d) (2%) and a vinyl chloride (see ref. 1c) (5%) were also isolated.

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