# Approaches to the Synthesis of Fused Bicyclic *N*-Acylaminoazetidin-2-ones

By PETER Y. JOHNSON,* CHARLES E. HATCH III, and NORMAN R. SCHMUFF
(*Department of Chemistry, The Johns Hopkins University, Baltimore, Maryland*, 21218)

*Summary* *N*-Acetamidoperhydrobenz[*c*]azetidin-2-one, a nuclear analogue of cephalosporin, has been prepared by two independent routes which should be potentially useful for the preparation of other analogues.

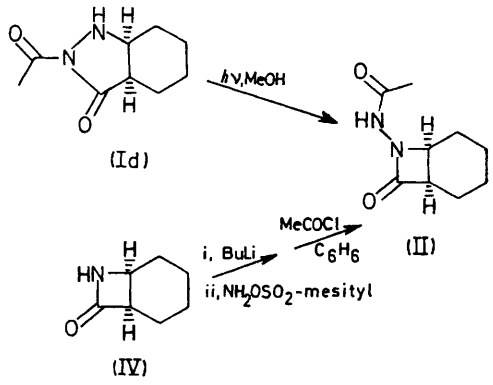
As part of our interest in the syntheses of nuclear analogues of cephalosporin[1] we have prepared *N*-acetamidoperhydrobenz[*c*]azetidin-2-one (II) by two independent routes. The first involved photochemical rearrangement of 2-acetylindazolidin-3-one (Id) and the second an amination–acetylation sequence applied to the perhydrobenz[*c*]azetidin-2-one system (IV).

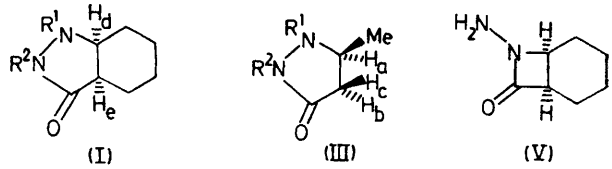
Our first approach to the synthesis of (II) was based on earlier work in which we reported the photochemical transformation of a monocyclic 1-unsubstituted 2-acylpyrazolidin-3-one to give an *N*-acylamino azetidin-2-one in good yield.[2] Synthesis of a photo precursor for (II) started with construction of the *cis*-ring-fused pyrazolidin-3-one (Ia). Although many monocyclic pyrazolidin-3-ones have been reported from the condensation of hydrazine with various

alicyclic $\alpha\beta$-unsaturated esters, we found no literature examples of an *N*-unsubstituted pyrazolidin-3-one ring fused to another ring. Condensation of hydrazine with ethoxycarbonylcyclohex-1-ene (1 : 1) at 110 °C for 6 h gave, after cooling, a gum. Purification by column chromatography (silica–$Et_2O$-EtOH) gave a small amount of (Ia)† as an oil. N.m.r. analysis indicated that this was predominantly the *cis* isomer containing a small amount of the *trans* isomer. Reaction of (Ia) with 1 equiv. of 2,2,2-trichloroethoxycarbonyl chloride (TrOC-Cl)[3] under Schotten Baumann conditions gave the 1,2-diacylhydrazide (Ib), m.p. 173·5—175·5 °C, in good yield. Treatment of (Ib) with MeCOCl and $Et_3N$ gave (Ic) which upon stirring at 25 °C with Zn dust in $MeCO_2H$ gave (Id), m.p. 84—86 °C, in high yield. Irradiation of a nitrogen-degassed 1% methanolic solution of (Id) with a Hanovia 450 W immersion lamp equipped with a Vycor filter gave the desired perhydrobenz[*c*]-azetidin-2-one (II), oil, 40—50% after chromatography.

The stereochemistry of molecules (Ib–d) and (II) was determined by comparison of their $^1H$ n.m.r. spectra with the corresponding molecules in the series based on 5-methylpyrazolidin-3-one (IIIa). For example, in the n.m.r. spectrum of (IIIb) one observes absorptions for the two protons on the side of the ring opposite the Me group ($H_a$ and $H_b$) in the same place as absorptions for the two bridgehead protons ($H_d$ and $H_e$) of (Ib) after correction for the methine *vs* methylene difference. However, the absorption for $H_c$, the ring proton of (IIIb) which is on the same side as the Me group, is significantly upfield from the $H_a$ and $H_b$ absorptions and in that region of the spectrum of (Ib) there is no absorption. Molecule (Ib) was therefore assigned the *cis* structure. Structures of (Ic), (Id), and (II) were assigned similarly.

Our second approach to the synthesis of (I) was based on initial construction of the azetidin-2-one ring followed by functionalization. Perhydrobenz[*c*]azetidin-2-one[4] (IV), formed by addition of chlorosulphonyl isocyanate to cyclohexene, followed by removal of the chlorosulphonyl group using $Na_2SO_3$-NaOH, was aminated by treatment at 0 °C with 1 equiv. of BuLi in glyme to give an anion which was




| | $R^1$ | $R^2$ |
|---|---|---|
| (a) | H | H |
| (b) | TrOC | H |
| (c) | TrOC | MeCO |
| (d) | H | MeCO |

further treated with 1 equiv. of *O*-mesitylene sulphonylhydroxylamine[5] to give *N*-aminoperhydrobenz[*c*]azetidin-2-one (V). The hydrazide (V) was readily acetylated with MeCOCl and $Et_3N$ (1 : 1) in benzene to give (II) which was identical (i.r., n.m.r., and mass spectra) with the photoproduct of (Id).

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† Structural assignments are based on i.r., n.m.r., and mass spectral and microanalytical data.

[1] Recent reports indicate that some nuclear analogues of cephalosporin are active antibiotics; see L. B. Cama and B. G. Christensen, *J. Amer. Chem. Soc.*, 1974, **96**, 7582.
[2] C. E. Hatch and P. Y. Johnson, *Tetrahedron Letters*, 1974, 2719; P. Y. Johnson and C. E. Hatch, *J. Org. Chem.* 1975, **40**, 909.
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[4] H. Bestian, H. Biener, K. Clauss, and H. Heyn, *Annalen*, 1968, **718**, 94.
[5] Y. Tamura, J. Minamikawa, K. Sumoto, S. Fujii, and M. Ikeda, *J. Org. Chem.*, 1973, **38**, 1239.