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# TRANSAMIDATION REACTIONS OF β-LACTAMS: A SYNTHESIS OF (±)-DIHYDROPERIPHYLLINE

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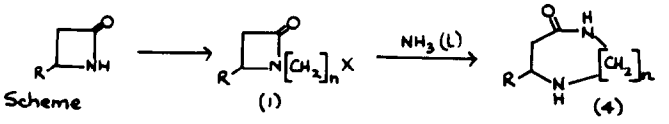
Summary: Whereas ammonolysis of N-(halogenoalkyl)azetidin-2-ones affords medium ring azalactams *via* transamidation, large or strained rings are not isolated, acyclic β-amino-amides being produced; two successive transamidative ring expansions from 4-phenylazetidin-2-one give a synthesis of (±)-dihydroperiphylline.

As part of a programme concerned with saturated heterocycles, including derivatives of the biologically important polyamines, we earlier reported a simple sequence for ring enlargement of azetidin-2-ones (β-lactams) to afford medium rings (Scheme).[1] This proceeds from N-(halogenoalkyl) derivatives (1) *via* intramolecular transamidation presumed to be driven by the strain energy of the four-membered ring. We now report an investigation of the scope of this transamidation, including attempts to extend it to large rings, which provides insight into the stability of lactams to ammonolysis. The incorporation of our sequence into a new synthesis of the spermidine alkaloid dihydroperiphylline is also reported.[2]

We have previously shown that treatment of N- ω-halogenoalkyl-β-lactams (1; n = 2, 3, or 4) with liquid ammonia in a sealed tube leads satisfactorily to seven-, eight-, and nine-membered azalactams, but insertion of an aminopentyl unit (n = 5) to provide a ten-membered ring was not successful, N-(5-aminopentyl) azetidin-2-one (2; n = 5) being the major product after 7 days at 65°C.[1] Reasoning that in a longer alkyl chain the unfavourable transannular interactions in the eight-membered transition state required for transamidation of (2; n = 5) might disappear, we prepared the N-(ω-bromoalkyl) derivatives

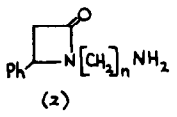



(1) X = Br or Cl

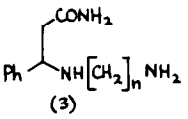
(1; R = Ph, X = Br, n = 8, 10, and 12)[3] from 4-phenylazetidin-2-one[4] and 1,8-dibromooctane, 1,10-dibromodecane, and 1,12-dibromododecane, respectively [powdered KOH, $Bu_4NHSO_4$/THF, 20°C;[5] 50%, 65%, and 74%]. Treatment of the bromide (1; R = Ph, X = Br, n = 12) with liquid ammonia in a sealed tube at 20°C for 7 days gave only the N-(ω-aminoalkyl)azetidinone (2; n = 12) whereas similar treatment of all three homologues (n = 8, 10, or 12), but at elevated temperature (70°C), for 28 days, afforded instead the acyclic amides (3; n = 8, 10, or 12) as the major products (99%, 97%, and 95%). Intermediate reaction conditions afforded various mixtures of the amines (2) and amides (3) and none of the ring expanded azalactams (4; R = Ph, n = 8, 10, or 12) was isolated. Our initial assumption that ring-opening arose from intermolecular transamidation of the aminoalkyl-β-lactams (2) by solvent ammonia was, however, challenged by the finding that N-propyl-4-phenylazetidin-2-one (from 4-phenylazetidin-2-one and 1-iodopropane, KOH, DMSO; 91%)[6] could be recovered unchanged from liquid ammonia at 70°C after periods of at least 28 days. This suggests that the amides (3) are derived from the azalactam products (4; R = Ph, n = 8, 10, and 12) of intramolecular transamidation which are formed transiently and undergo unexpectedly rapid ring opening *via* ammonolysis of the lactam bond. Another possible fate of the lactams (4; R = Ph, n = 8, 10, and 12) or of the amides (3) is to undergo β-elimination, and indeed in some cases traces of cinnamamides were observed in the crude product mixture by $^1H$ n.m.r. spectroscopy. The reasons for the apparently contrasting stabilities of these azalactams and the medium ring homologues under our reaction conditions are not yet clear.[7]

The surprising stability of the azetidinone moiety towards ammonolysis[8] could be overcome by the introduction of an electron-withdrawing substituent at nitrogen.[9] The N-acetyl-β-lactam (5a) (4-phenylazetidin-2-one, acetyl chloride, $Bu^nLi$, THF; 50%) was thus easily and efficiently converted into the amide (6a) by liquid ammonia in a sealed tube at 20°C (87%), and the N-(3-chloroethanoyl)- and N-(3-chloropropanoyl)-azetidinones, (5b) and (5c), respectively, were prepared and transformed into the corresponding diamides (6b) and (6c) under similar conditions.

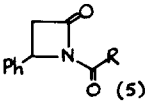
The N-(4-halobut-2-enyl)azetidinones (7a) and (7b) were prepared from 4-phenylazetidin-2-one and the corresponding 1,4-dihalobut-2-enes (KOH, $Bu_4NHSO_4$, THF; 61 and 76%) to probe the effect of a geometric constraint in the halogenoalkyl chain for the case of a four-carbon insertion. Heating of the *cis*-isomer (7a) with liquid ammonia (sealed tube, 70°C, 10 days) did indeed give the unsaturated nine-membered azalactam (8)[10] (57%); the *trans*-isomer (7b) on the other hand afforded, under the same conditions, only the acyclic amino-amide (9) of the type reported above. Taken with our observation (above) of the stability of azetidinones to ammonolysis, this suggests that expansion to the nine-membered ring does occur, but that the *trans*-double bond introduces strain sufficient to promote ring opening.



(2)

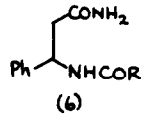


(3)



(5)

(5) a; R = Me
b; R = $CH_2Cl$
c; R = $[CH_2]_2Cl$



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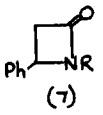

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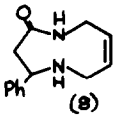
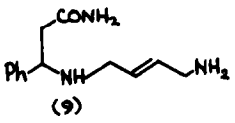


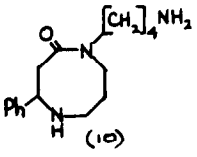
(8)

(6) a; R = Me
b; R = $CH_2NH_2$
c; R = $[CH_2]_2NH_2$

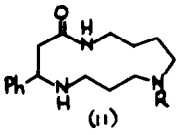
(7) a; R = $CH_2CH \overset{Z}{=} CHCH_2Cl$
b; R = $CH_2CH \overset{E}{=} CHCH_2Br$



(9)



(10)



(11)

(11) a; R = H
b; R = $COCH \overset{E}{=} CHPh$

Finally, the eight membered azalactam (4; R = Ph, n = 3), available in excellent yield from (1; R = Ph, n = 3) and already used by us in syntheses of the Homalium alkaloids,[11] was alkylated with 1-bromo-4-chlorobutane [$KN(SiMe_3)_2$), THF, 20°C, 88%] and the N-(4-chlorobutyl) derivative converted into the N-(4-aminobutyl)azalactam (10) (liquid ammonia, sealed tube, 20°C, 7 days; 94%). Intramolecular transamidation was accomplished with $KN(SiMe_3)_2$-THF to afford the 13-membered azalactam (11a) (21% conversion)[12] that was selectively acylated [PhCH=CHCOCl, 4-(dimethylamino)pyridine, $CH_2Cl_2$,-78°C; 69%] to complete a new synthesis of (±)-dihydroperiphylline (11b). Dihydroperiphylline is a natural product from Peripterygia marginata.[13]

We thank S.E.R.C. for support.

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3. New compounds gave spectra consistent with the assigned structure, and satisfactory combustion analysis or accurate mass measurement.

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5. D. Reuschling, H. Pietsch and A. Linkies, Tetrahedron Lett., 1978, 615.

6. R.A.W. Johnstone and M.E. Rose, Tetrahedron, 1979, 35, 2169.

7. Related acylic β-amino-amides have been isolated as by-products during expansions to eight- and nine-membered rings when alkylamines are used rather than ammonia (Ref.1).

8. Cf. A.K. Mukerjee and A.K. Singh, Synthesis, 1975, 547.

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12. Cf. U. Kramer, A. Guggisberg, and M. Hesse, Helv.Chim.Acta., 1979, 62, 2317, and refs. therein.

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