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THE SYNTHESIS AND RING CLEAVAGE OF EPIMERS OF 1-t-BUTYL AND 1-ADAMANTYL-3-BIS-NORCHOLANYL-AZIRIDINONE. MECHANISTIC CONSIDERATIONS

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In 1963, Baumgarten and coworkers[1a] prepared an optically active 1-t-butyl-3-phenylaziridinone from optically active α-chloro-N-t-butyl-phenylacetamide by way of a base-induced, 1,3-elimination reaction originally proposed by Sarel and coworkers[2]. The product was of undetermined optical purity and of uncertain configuration.

We report the synthesis of three optically pure steroidal α-lactams, (R)-(III), (S)-(III), (R)-(IV) and one of undetermined purity (S)-(IV) from the corresponding optically pure α-bromocholanamides, (23S), (23R)-N-t-butyl- and (23R), (23S)-N-adamantyl-bromocholanamide (S)-(I), (R)-(I), (S)-(II) and (R)-(II)[3], and the assignment of their absolute configuration. They are the first representatives of high melting steroidal α-lactams that have two β-hydrogens in the alkyl group on C-3 and, nevertheless, display considerable thermal and chemical stability[1b]. They represent also the first optically pure α-lactams of determined configuration, the synthesis of which has a bearing on both the stereochemistry and mechanism of the cyclisation reaction (I-II) → (III-IV). As shown later in the communication, it was possible also to ascertain the stereochemistry and mechanism of the two modes of α-lactam ring-openings.

Each (1.2 mmoles) of the following α-haloamides: N-t-butyl-(23R)-, (23S)-bromocholanamide[3] (R)-(I) and (S)-(I); N-adamantyl-(23R)-, and (23S)-bromocholanamide[3], (R)-(II) and (S)-(II), in dry toluene (25 ml) were exposed to the action of freshly sublimed potassium t-butoxide (2.4 mmoles) in dry toluene (40 ml) at -20° for 10-20 min., the solvent removed in vacuo, and the residues subjected to fractional crystallizations from petroleum-ether (30-40). The yields, the physical and spectroscopic properties of the α-lactams thus obtained are assembled in the Table.

Although the α-haloamide → α-lactam conversions occur rapidly, the reactions were not complete even after 30 min. of exposure, and in each case the starting α-haloamides could be recovered from the reaction mixtures with no change in configuration.

The c.d. spectra of (R)-(III), (S)-III) and (R)-(IV) (see Table) display a strong optically active band at 252.5 mμ, and in addition, a much weaker ellipticity band of opposite sign at shorter wavelength (below 220 mμ). The u.v. spectra of these compounds in n-hexane are characterized by a hitherto unobserved, well-defined maximum of high intensity near 210 mμ and another maximum of low intensity near 250 mμ, both of which are solvent-dependent and thus correspond to $n \rightarrow \pi^*$ transitions[4].

The record in the literature shows that the o.r.d. and c.d. curves of (R)-α-amino-acids and derivatives normally exhibit a strong negative Cotton effect, whereas those of (S)-configuration are characterized by their strong positive effect[5]. Consequently, we assign (R)-configuration to (R)-(III) and (R)-(IV), which show a strong dichroic band at 252.5 mμ, and in turn, (S)-configuration to (S)-(III), since its c.d. curve is a mirror image of (R)-(III).

Characteristically, the C-18 methyl resonances of the (S)-α-lactams [(S)-(III) and (S)-(IV)] are more shielded than in (R)-α-lactams [(R)-(III) and (R)-(IV)], in parallel to respective (S) and (R) 23-bromoamides [(S),(I)-(S)-(II)] and (R)-(II)[3].

For the ring proton (C-23) resonances the case is the opposite; they are more shielded in the (R) than in the (S)-α-lactams (see Table).

The configurational assignments for (R)-(III)-(S)-(III) and (R)-(IV) were borne out in a study aimed at correlating the stereochemistry of products arising from nucleophilic ring-openings of the α-lactams.

If a stirred suspension of (R)-(III) (40 mg) in dry methanol (20 ml) is allowed to stand at 20° for 18 hrs., spectroscopic and t.l.c. analysis have shown that the residue left after removal of solvent comprised a mixture of an amide (90%) and an ester (10%). The predominant product was isolated and assigned the N-t-butyl (23R)-methoxycholanamide structure (V) since it manifests a negative c.d. band at 230 mμ (see Table).

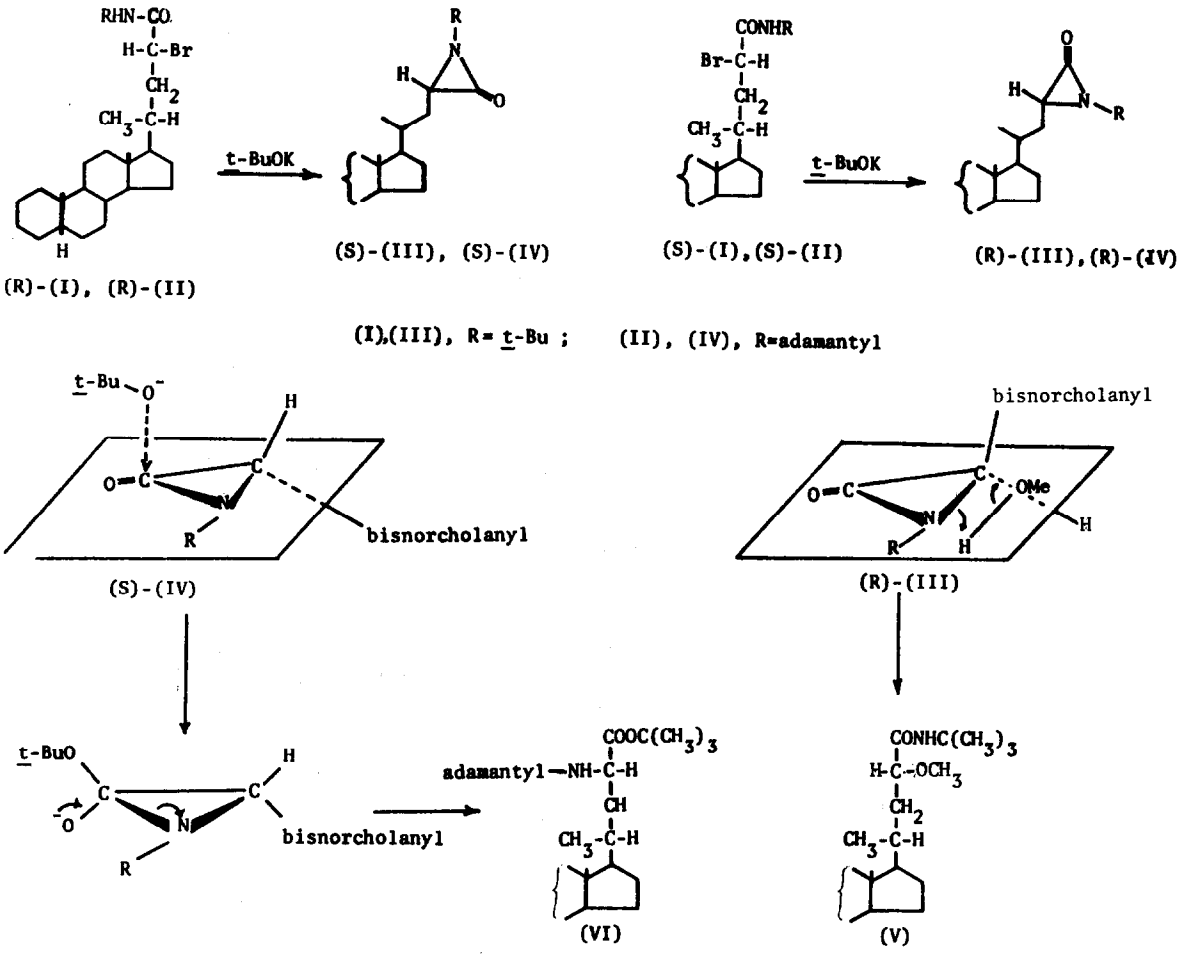
Treatment of (R)-(IV) with potassium t-butoxide in dry t-butanol yielded an optically pure (by t.l.c.) α-aminoacid ester, to which we assigned the t-butyl (23R)-adamantylamino-cholanate (VII) structure, on the basis of its strong negative c.d. band at 222.5 mμ (see Table). Its optically pure epimer, t-butyl (23S)-adamantyl-aminocholanate (VI) was similarly derived from the reaction of an impure form of (S)-(IV) with potassium t-butoxide, followed by t.l.c., and was characterized by a well-defined positive c.d. band at 220 mμ, as expected.

TABLE

Compd.[a]	Yield %	M.P. °C	$[\alpha]_D^{27}$[b]	ν(C=O)[c] cm^{-1}	Chemical Shifts in Hz[d] C-18 (3H,s)	Chemical Shifts in Hz[d] C-23 (1H,d)	UV Spectra in Hexane λmax mμ	UV Spectra in Hexane ε	CD in Dioxane λmax	CD in Dioxane [θ]max
(R)-(III)	90	143-145	-65.4°	1840	40.2	159 (J 7.0)	207.5 251	1140 215	207.5 252.5	+ 1680 -20120
(S)-(III)	80	108-110	+100°	1840	39	162 (J 7.5)	211 252	711 194	205 252.5	- 3234 +31460
(R)-(IV)	60	148-151	+ 3.5°	1840	39	162 (J 7.0)	212 240	913 255	217.5 252.5	- 2310 -27720
(S)-(IV)	45	semi-solid	-	1840	37	166 (J 7.5)	-	-	-	-
(V)	90	semi-solid	+ 6.1°	3350 1675 1510	39.5	212 (d.d)	211.5 225	1388 sh.	230	- 3870
(VI)	80	125-128	+ 25.6°	1730	37	204 (m)	207 222	1226 643	220	+ 2930
(VII)	80	146-149	+ 31.0°	1730	39.5	194 (m)	207 222	1130 518	222.5	- 8330

[a]All compounds listed gave the correct elemental analysis; [b]In $CHCl_3$, 1%; [c]In KBr; [d]On 60 MHz instrument in $CDCl_3$, downfield Me_4Si; [e]Measurements were taken on Cary Model 60 Spectropolarimeter with a 6001 CD accessory.

The data presented above clearly indicates that both the formation of α-lactams from the respective α-haloamides, and the two modes of ring-cleavages (the carbon-nitrogen bond fissions) occur stereospecifically. The α-haloamide → α-lactam cyclisation occurs with inversion of configuration and can therefore be depicted as following an S_Ni type mechanism. Significantly, the two modes of ring-opening by nucleophiles of various basicity occur with retention of configuration. This can be explained in terms of orientational differences inherent in the basicity of the attacking nucleophile on the small-ring carbons. Apparently the stronger base



approaches the carbonyl carbon from a direction perpendicular to the plane of the α-lactam, followed by cleavage of the carbonyl-nitrogen bond. In the case of methanolysis, the solvent orients itself coplanar with the carbon-nitrogen bond of the α-lactam, inducing ring-cleavage with concomitant formation of a new carbon-oxygen bond, resulting in retention of configuration, as delineated in the Chart.

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