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THE STEREOCHEMISTRY OF 2-HYDROXY-3-AMINOBORNANES

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Abstract—The configuration of α-aminocamphor was determined from NMR studies, the mechanism for the syntheses of α- and β-aminoborneols elucidated, and 2-*exo*-hydroxy-3-*exo*-aminobornane, a new diastereoisomer of 2-hydroxy-3-aminobornane synthesized.

THERE are four possible diastereoisomers of 2-hydroxy-3-aminobornane i.e. IV, V, VII, VIII. Duden and Macintyre[1] synthesized α- and β-aminoborneol by reducing α-aminocamphor with sodium in ethanol and wet ether respectively. Catalytic reduction of α-aminocamphor with Adam's catalyst in xylene by van Tamelen and Judd[2] produced α-aminoborneol in greater purity (m.p. 191·8°) and reduction with LAH gave purer β-aminoborneol (m.p. 173°). From NMR studies, Tori *et al.*[3] confirmed the configuration of α- and β-aminoborneols, previously proposed by van Tamelen *et al.*,[4] as 2-*exo*-hydroxy-3-*endo*-aminobornane (V) and 2-*endo*-hydroxy-3-*endo*-aminobornane (IV) respectively. The assignment by Tori *et al.* was based on the coupling constants, which depend on the dihedral angles, between H(2) and H(3) of the two isomers.[5]

Because both IV and V were synthesized from α-aminocamphor and the latter has two diastereoisomers possible (Figs. 1; II, III) the configuration of α-aminocamphor is now determined to elucidate the mechanism of van Tamelen and Judd's syntheses.[2] This compound (as the hydrochloride salt in D_2O) obtained by reduction[6] of α-isonitrosocamphor with zinc dust in sodium hydroxide solution had NMR spectrum with a doublet H(3) at 5·94 τ with a coupling constant of 4·7 Hz to the C-4 bridgehead proton indicating[5] an *exo* position for H(3). There was no broadening of this signal by long-range coupling of H(3, *exo*) with H(5, *exo*) in agreement[7] that some *endo*-substituted bornanones do not exhibit this effect. Thus α-aminocamphor is assigned the 3-*endo*-aminobornan-2-one configuration. Since completion of this work, Cooper and Chittenden[8] in a preliminary communication reported that autoclaving[9] methylamine with bornan-2-3-dione gave 3-*endo*-methylaminobornan-2-one.

An attempt was made to synthesize 3-*exo*-aminobornan-2-one (II) by catalytic reduction of α-isonitrosocamphor[10] with Adam's catalyst in ethanol. Hydrogenation would be expected to proceed from the less hindered *endo* side of the molecule and produce the resulting *exo* amino derivative. The reduction was stopped when two moles of hydrogen was consumed, but the hydrochloride salt of the product gave IR and NMR spectra identical to those of III. The D_6-DMSO solution of the salt was basified with NaOD in D_2O and the NMR spectrum of the base showed a gradual disappearance of the H(3) doublet at 6·56 τ within 45 min, indicating enolization had taken place. In view of the steric interaction between the *exo* amino function of II

and the 8-CH_3 of the bridge, II would be expected to be the thermodynamically unstable epimer, and at equilibrium, III would be the predominant epimer as has been shown.

The stereochemical course of reduction of the carbonyl function of 3-*endo*-aminobornan-2-one (III) by LAH[2] can be expected to be influenced by the steric environment of its α-substituents. Due to the formation of the amino-aluminohydride anion complex at the *endo* position of III, it is not surprising that attack by the anion of LAH should occur predominantly from the *exo* side (see Fig. 1) which is comparatively

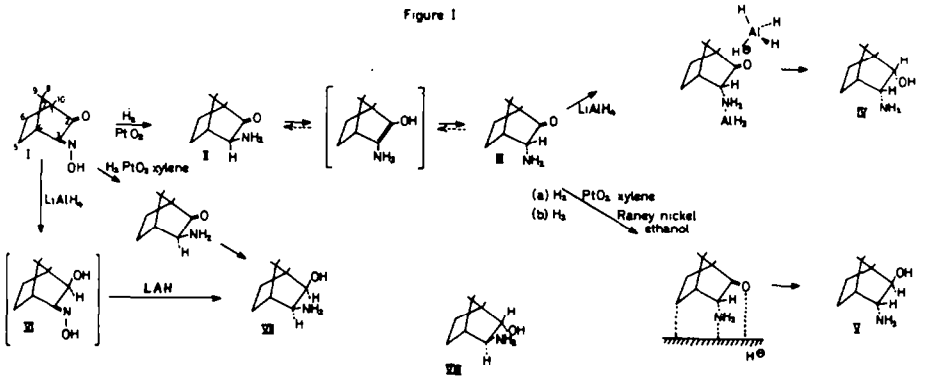

FIG. 1

less hindered, to produce 2-*endo*-hydroxy-3-*endo*-amino-bornan (IV). Catalytic reduction of III with Adam's catalyst in xylene[2] gave 2-*exo*-hydroxy-3-*endo*-aminobornane (V) which is not surprising as the bornane molecule would be adsorbed onto the catalyst surface via the less hindered and more polar *endo* side, and hydrogenation would take place from that direction.

The above reduction was repeated, using a protonic solvent (ethanol) instead of xylene. A white crystaline product, m.p. 179° was obtained but its NMR spectrum showed a mixture of two parts of V and three parts of IV. Solvation of the polar functions of III by the protonic solvent may have introduced a further complication to the steric environment, and hydrogenation from both *exo* and *endo* directions had taken place. When Raney nickel was used in place of Adam's catalyst, the predominant product was V, m.p. 192° with IR and NMR spectra identical to those of an authentic sample.[4] Probably the stronger Coulombic attraction between the electronegative amino and carbonyl functions and the nickel surface had overcome the solvation effect of ethanol and allowed the hydrogenation to be stereospecific. Furthermore, reduction of α-isonitrosocamphor (I) under the same condition also gave V, which is a convenient method to synthesize this compound. The oxime group was apparently first reduced, and II thus formed rapidly epimerized to the more stable III which is further reduced to V. This was confirmed by stopping the reduction when half of the calculated volume of hydrogen was consumed; III could be isolated from a sample of the reaction mixture.

If α-isonitrosocamphor were reduced in a non-polar solvent such as xylene with Adam's catalyst, it would be expected that epimerization as shown above would be

discouraged and the reduced product would be predominantly 2-*exo*-hydroxy-3-*exo*-aminobornane (VII), a hitherto unreported diastereoisomer of 2-hydroxy-3-aminobornane. This reduction was found to give the desired new isomer (VII).

The NMR spectrum of VII showed bands corresponding to H(2, *endo*) and H(3, *endo*) forming a symmetrical AB quartet. The coupling constant $J_{2N,3N}$ was 7·8 Hz indicating that the two protons are *cis* to each other.[5] That they are both *endo* is indicated by the absence of long range coupling with protons in C_6 and C_5.[5] The sharper doublet at 6·62 τ is tentatively assigned to H(2) and the slightly broader doublet at 6·96 τ was assigned to H(3) on account of its possible coupling with H(4) whose coupling constant is theoretically very small.

Reduction of α-isonitrosocamphor was also carried out using LAH to give a product which after recrystalization had identical IR and NMR spectra as those of VII. The NMR spectrum of the crude product however, showed the presence of about 10–15% of IV. The LAH anion apparently attacks the keto and hydroxyimino functions mainly from the less hindered *endo* side of the molecule though some attack from the *exo* side occurred to yield a small amount of IV. It is proposed that the keto function is reduced prior to reduction of the hydroxyimino group, since it has been previously observed[11] that the carbonyl function of a ketoaldoxime can be selectively reduced with a theoretical quantity of ethereal LAH.

The present work provides convenient synthetic routes for the preparation of three, i.e. IV, V and VII diastereoisomers of 2-hydroxy-3-aminobornane; it has not yet been possible to synthesize the fourth possible isomer VIII.

EXPERIMENTAL

α-Isonitrosocamphor, the starting material, was synthesized[10] from natural (+)-camphor, supplier: BDH. The NMR spectra were obtained on a 60 MHz Perkin Elmer R-10 instrument with TMS as internal standard. All chemical shifts are expressed in τ; d: doublet, s: sharp, b: broad, m: multiplet. The IR spectra were measured on a Unicum SP 200 spectrophotometer with Nujol mulls or KCl discs. M.ps were uncorrected. Micro-analysis by Dr. F. B. Strauss, Oxford, and Mr. G. S. Grouch, Brunswick Square, London.

(a) 2-exo-*Hydroxy*-3-exo-*aminobornane* (VII)

(i) 10 g of α-isonitrosocamphor[10] (I) (0·055 mole) was dissolved in 60 ml of dry zylene with some warming and was hydrogenated at atm press with 1 g PtO_2 as catalyst. The reduction was completed after 24–36 hr. The catalyst was filtered off and the base extracted from the xylene soln with dil HCl. The aqueous layer was shaken twice with 20 ml ether to remove traces of xylene. Basification of the acid soln with dil NaOH aq released the base which was extracted with 3 × 20 ml portions ether. The ether extract was dried overnight with Na_2SO_4, the ether removed under *vacuo* and the white solid that remained was recrystallized from light petroleum (60–80°) giving a crop of flake-like crystals, m.p. 196°, 5·2 g (56%), hydrochloride salt, m.p. 285–290° (char). (Found: hydrochloride salt; C, 58·5; H, 9·7; N, 6·6; Cl, 17·3; $C_{10}H_{20}ONCl$ requires C, 58·4; H, 9·8; N, 6·8; Cl, 17·2%); NMR $CDCl_3$, 9·06[a] (10-CH_3), 9·22 (9-CH_3), 8·93 (8-CH_3) 6·96[b,d] (3-H, 7·8 Hz), 6·62[d] (2-H, 7·8 Hz).

(ii) A soln of 10 g (0·055 mole) α-isonitrosocamphor[10] dissolved in 200 ml dry ether was added to a suspension of 7 g (0·18 mole) LAH in 400 ml dry ether over a period of 1 hr and the mixture was stirred overnight. The excess LAH was destroyed by dropwise addition of water while stirring vigorously. In rapid succession 15 ml of water, 17 ml of 10% NaOH and 24 ml water were added. The ether soln was decanted and the salts washed several times with fresh portions of ether. The base was extracted with dil HCl and treated as in (i). The cryde product, 8·5 g (92%) was recrystallized several times from light petroleum (60–80°) giving m.p. 195–196°. IR spectrum of its hydrochloride salt was identical with that of (i).

(b) 2-exo-*Hydroxy*-3-endo-*aminobornane* (V)

(i) 3 g α-isonitrosocamphor (0·016 mole) dissolved in 20 ml EtOH was hydrogenated at atm press with

2 g Raney Ni (W5). The reduction was completed after 24–30 hr, the catalyst filtered off, the EtOH removed under reduced press and the residue crystallized from light petroleum (60–80°) giving 2·1 g (75%) white crystals m.p. 192°; hydrochloride salt crystallized from EtOH and ether had m.p. 285–287° (dec). (Found: hydrochloride salt; C, 58·4; H, 9·7; N, 6·6; Cl, 17·2. Calc. for $C_{10}H_{20}ONCl$: C, 58·4; H, 9·8; N, 6·8; Cl, 17·2%).

(ii) 3-*endo*-Aminobornan-2-one (III) was reduced in the same procedure as (i), giving V, m.p. 192°.

(c) 3-endo-*Aminobornane-2-one* (III)

1 g α-isonitrosocamphor (0·005 mole) dissolved in 20 ml EtOH containing 0·5 ml HCl was hydrogenated at atm press with 100 mg PtO_2 as catalyst. The reduction was stopped when 250 ml H_2 was used up. The catalyst was filtered off, the filtrate concentrated, and the hydrochloride salt of the amine precipitated as fluffy crystal with addition of ether to the soln, yield: 0·8 g, 72%, m.p. 250·5°, IR and NMR spectra identical to III obtained by reduction of α-isonitrosocamphor with zinc dust in sodium hydroxide soln.[6] NMR: hydrochloride salt in D_2O, 9·04[s] (10-CH_3), 8·94 (9-CH_3), 9·05 (8-CH_3), 7·5[m] (4-H) 5·94[d] (3-H, 4·7 Hz); base, in $CDCl_3$, 9·08[s] (10-CH_3), 8·99 (9-CH_3) 9·12 (8-CH_3), 7·85[m] (4-H), 6·56[d] (3-H, 4·5 Hz).

(d) *Hydrogenation of* 3-endo-*aminobornan-2-one in ethanol with platinum oxide as catalyst*

2·4 g of III dissolved in 20 ml EtOH was hydrogenated with 400 mg PtO_2 as catalyst, and the product was isolated according procedure in (b), yielding 1·7 g white needle-shaped crystals, m.p. 179°. NMR spectrum showed the product contained two parts of V, and three parts of IV.

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