Rearrangements during the Synthesis of Substituted 1-Benzylpyrrolidines and 3-Substituted 1-Benzylpiperidines

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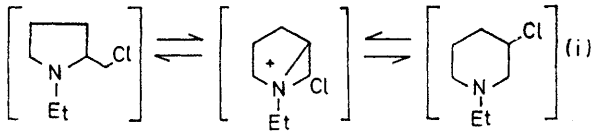
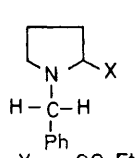
The preparation and interconversion of some 2-substituted 1-benzylpyrrolidines and 3-substituted 1-benzylpiperidines through intermediate aziridines is described. Reduction of a mixture of 2-azidomethyl-1-benzylpyrrolidine and 3-azido-1-benzylpiperidine, prepared either from 2-chloromethyl-1-benzylpyrrolidine or 3-chloro-1-benzylpiperidine, afforded a 50:50 mixture of 2-aminomethyl-1-benzylpyrrolidine and 3-amino-1-benzylpiperidine.

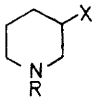
RING expansion of a pyrrolidine to a piperidine and contraction of the latter to the former can occur during replacement reactions leading to an aziridinium ion intermediate; *e.g.* 2-chloromethyl-1-ethylpyrrolidine cannot be isolated in a pure state by neutralisation of its salts, since ring expansion occurs and the product is contaminated with the isomeric 3-chloro-1-ethylpiperidine.[1] The inverse reaction occurs when 3-chloro-1-ethylpiperidine is subjected to nucleophilic displacement reactions.[2] Hammer *et al.*[3] carried out synthetic, kinetic, and stereochemical studies with these compounds and with the ionic intermediate 1-ethyl-1-azoniabicyclo [3.1.0] hexane[4] (as its perchlorate), and showed the existence of the equilibrium (i).



During the preparation of 2-aminomethyl-1-benzylpyrrolidine and 3-amino-1-benzylpiperidine, we encountered interconversion which could be easily followed by ^{1}H n.m.r. spectroscopy in the region δ 2.8—4.5. A



(1) X = CO_2Et
(2) X = CH_2·OH
(3a) X = CH_2Cl
(4a) X = CH_2N_3
(5) X = CH_2·NH_2
(7) X = CO_2H
(8) X = CO·NH_2



(3b) R = CH_2·Ph, X = Cl
(4b) R = CH_2·Ph, X = N_3
(6) R = CH_2·Ph, X = NH_2
(9) R = H, X = NHAc
(10) R = CH_2Ph, X = NHAc

mixture of the amines (5) and (6) was obtained by the following method. *N*-Benzylproline ethyl ester (1) was obtained by benzylation of DL-proline ethyl ester and reduced to give 1-benzyl-2-hydroxymethylpyrrolidine (2). Chlorination with thionyl chloride in an anhydrous medium then gave 1-benzyl-2-chloromethylpyrrolidine (3a), isolated as its hydrochloride. This salt melted at 151—152 °C, solidified, and remelted at 190—192 °C, the m.p. of 1-benzyl-3-chloropiperidine hydrochloride. Mixtures of the two salts did not show m.p. depression. Fuson and Zirkle[1] reported that 2-chloromethyl-1-ethylpyrrolidine hydrochloride undergoes a similar ring expansion on heating. Treatment of either 1-benzyl-2-chloromethylpyrrolidine (3a) or 1-benzyl-3-chloropiperidine (3b) with sodium azide in aqueous alcohol gave a mixture of the azides (4a and b), which on reduction with lithium aluminium hydride gave a mixture of the amines (5) and (6). This mixture could not be separated by distillation or by thin-layer or column chromatography, nor were we able to find easily crystallisable salts.

The two pure amines (5) and (6) were prepared by two different routes not involving intermediate aziridinium ions. *N*-Benzylproline ethyl ester (1) was hydrolysed to *N*-benzylproline (7),[5,6] which was converted into *N*-benzylprolinamide (8); reduction with lithium aluminium hydride then gave pure 2-aminomethyl-1-benzylpyrrolidine (5). Pure 3-amino-1-benzylpiperidine (6) was prepared by catalytic reduction of 3-acetamidopyridine to 3-acetamidopiperidine (9)[7] followed by benzylation, and acidic hydrolysis of the resulting 3-acetamido-1-benzylpiperidine (10).

The ^{1}H n.m.r. spectra in the region δ 2.8—4.5 of the amines (5) and (6) and of the mixture obtained by reduction of the mixed azides (4a and b) facilitated determination of the composition of the mixture. The chemical shifts of the peaks correspond to those expected for the group N–CH_2·C_6H_5. The singlet at δ 3.41 can be assigned to the benzylic protons of the piperidine (6), whereas the benzylic protons of 2-aminomethyl-1-benzylpyrrolidine produce two doublets centred at 3.20 and 3.93 (J_{AB} 13.2 Hz). This AB system results from magnetic non-equivalence of the two benzylic protons, caused by interaction of the exocyclic amino-group with these protons;[8] presumably in the case of 3-substituted piperidines the environment of the two protons is not suffici-

[1] R. C. Fuson and C. L. Zirkle, *J. Amer. Chem. Soc.*, 1948, **70**, 2760.
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[3] C. F. Hammer, S. R. Heller, and J. H. Craig, *Tetrahedron*, 1972, **28**, 239.
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[6] I. P. Yakovlev and V. I. Maksimov, *Izvest. Akad. Nauk S.S.S.R., otdel. Khim. Nauk*, 1963, 877.
[7] J. W. Cusic and E. Le Von (G. D. Searle & Co.), U.S.P. 3 101 341/1963 (*Chem. Abs.*, 1964, **60**, 2908f).
[8] P. L. Southwick, J. A. Fitzgerald, and G. E. Milliman, *Tetrahedron Letters*, 1965, 1247.

ently different to allow resolution. Values in the region δ 2.8—4.5 for the intermediate benzyl-pyrrolidines and -piperidines are shown in the Table.

^{1}H N.m.r. data ($CDCl_3$) of benzylic protons (δ values)

Compd.	CH_2	H_a *	H_b *	J/Hz
(1)		3.99	3.48	13.2
(2)		3.98	3.33	13.2
(3a + 3b)	3.45	3.98	3.21	13.2
(3b)	3.47			
(4a + 4b)	3.45	3.96	3.00	13.2
(5)		3.93	3.20	13.2
(6)	3.41			
(7)		Insoluble in $CDCl_3$		
(8)		4.01	3.48	13.2
(10)	3.46			

* Centre of doublet.

The δ value of the doublet centred at 3.93 varies only between 4.01 [for the amide (8)] and 3.93 [for the amine (5)]. The δ value of the doublet at lower field varies considerably, depending on the type of substituent on the α-carbon atom, from 3.48 for the ester and amide to 3.00 for the azide. On the other hand, compounds (6), (3b), and (10), having a benzylic methylene group which is hardly influenced magnetically by the group in the 3-position of the piperidine nucleus,[9] show only a singlet, which varies between δ 3.41 for the amine (6) and δ 3.47 for the chloro-compound (3b).

When either chloro-compound (3a or b) was treated with sodium azide, a 50 : 50 mixture of the azides (4a and b) was obtained, as shown by n.m.r. analysis of the mixture of amines (5) and (6) resulting from reduction with lithium aluminium hydride.

As in the case of 2-chloromethyl-1-ethylpyrrolidine hydrochloride, addition of alkali (at temperatures between 0 and 20 °C) to solutions of 1-benzyl-2-chloromethylpyrrolidine hydrochloride gave mixtures containing the pyrrolidine base and the corresponding 1-benzyl-3-chloropiperidine. With these benzyl compounds, the presence of the latter compound in the mixture was easily detected by n.m.r. spectroscopy. When the hydrochloride of 1-benzyl-3-chloropiperidine was treated with alkali under the same conditions, the resulting base did not contain the corresponding 1-benzyl-2-chloromethylpyrrolidine.[1]

EXPERIMENTAL

M.p.s. were determined for samples in open capilliary tubes with an Electrothermal apparatus. The purity of the compounds was determined by t.l.c. on silica gel in three solvent systems. I.r. specta were obtained with a Perkin-Elmer 257 apparatus, and n.m.r. spectra with a Hitachi Perkin-Elmer R-24 spectrometer (Me_4Si as internal standard). Analyses (C, H, and N) were carried out with a Perkin-Elmer 240 elemental analyser.

N-Benzylproline Ethyl Ester (1).—To a suspension of sodium hydrogen carbonate (4.7 g, 0.056 mol) in dry toluene (50 ml) was added DL-proline ethyl ester (7.2 g, 0.050 mol), followed by benzyl chloride (7 g, 6.3 ml, 0.055 mol). A crystal of potassium iodide was added and the mixture was heated under reflux during 12 h. After cooling, the precipitate was filtered off and the filtrate concentrated *in vacuo* to leave an oil, which was distilled *in vacuo* to give the *ester* (1) (9.5 g, 82%), b.p. 108—109° at 0.1 mmHg, n_D^{18} 1.5194 (Found: C, 72.0; H, 8.15; N, 5.95. $C_{14}H_{19}NO_2$ requires C, 72.05; H, 8.2; N, 6.0%), $\nu_{max.}$ (film) 2 800 (CH_2Ph), 1 720 (C=O), and 1 275 cm^{-1} (C–O).

1-Benzyl-2-hydroxymethylpyrrolidine (2).—To a suspension of lithium aluminium hydride (4.9 g, 0.128 mol) in anhydrous ether (50 ml) under gentle reflux was added, dropwise, the ester (1) (30 g, 0.128 mol) dissolved in anhydrous ether (100 ml). After the addition was complete, the mixture was refluxed during 2 h, the excess of lithium aluminium hydride was decomposed and the ether layer was separated, dried (Na_2SO_4), decolourised, and concentrated. The resultant oil was distilled *in vacuo* to give the *product* (2) (21 g, 85.6%), b.p. 109—112° at 0.11 mmHg (Found: C, 75.2; H, 8.8; N, 7.25. $C_{12}H_{17}NO$ requires C, 75.35; H, 8.95; N, 7.3%), $\nu_{max.}$ (film) 3 370 (OH) and 2 800 cm^{-1} (CH_2Ph).

1-Benzyl-2-chloromethylpyrrolidine (3a) *Hydrochloride.*—To a solution of thionyl chloride (8.7 ml, 0.12 mol) in chloroform (40 ml) was slowly added the alcohol (2) (21 g, 0.109 mol) dissolved in chloroform (25 ml). The mixture was maintained at room temperature for 2 h and then heated under reflux for a further 2 h. The solvent was evaporated off to leave a solid which was triturated with acetone and filtered off. Crystallisation from ethanol gave the *hydrochloride* (19 g, 77.2%), m.p. 151—152° (resolidifies and remelts at 190—192°) (Found: C, 58.2; H, 7.1; Cl, 28.9; N, 5.5. $C_{12}H_{17}Cl_2N$ requires C, 58.55; H, 6.95; Cl, 28.8; N, 5.7%), $\nu_{max.}$ (KBr) 2 600—2 350 cm^{-1} (N^+H).

Mixture of 2-Azidomethyl-1-benzylpyrrolidine and 3-Azido-1-benzylpiperidine (4a *and* b).—To a solution of the chloromethyl derivative (3a) hydrochloride (14.1 g, 0.057 mol) in ethanol (25 ml) was added a solution of sodium hydroxide (2.3 g, 0.057 mol) in water (10 ml) and ethanol (25 ml). To the solution was slowly added, at room temperature, sodium azide (3.7 g, 0.057 mol) in water (20 ml), and the mixture was heated under reflux during 7 h. The excess of alcohol was removed *in vacuo* and the aqueous mixture extracted with ether several times. The combined extracts were dried (Na_2SO_4), decolourised, and evaporated to yield an oil (12 g, 97.5%) which was used without further purification for the next stage; $\nu_{max.}$ (film) 2 790 (CH_2Ph) and 2 090 cm^{-1} (N_3). The mixture of (4a and b) was also obtained in a similar yield by the same procedure from 1-benzyl-3-chloropiperidine (3b) hydrochloride.

Mixture of 2-Aminomethyl-1-benzylpyrrolidine and 3-Amino-1-benzylpiperidine [(5) *and* (6)].—To a suspension of lithium aluminium hydride (2.1 g, 0.055 mol) in anhydrous ether (25 ml) under gentle reflux was slowly added the foregoing mixture of azides (12 g, 0.055 mol) dissolved in anhydrous ether (75 ml). The mixture was then heated under reflux during 2 h. The excess of lithium aluminium hydride was hydrolysed and the ethereal phase was separated, dried (Na_2SO_4), decolourised, and concentrated. The resultant oil was distilled *in vacuo* to give the mixture of (5) and (6) (7.5 g, 71.7%), b.p. 92—94° at 0.08 mmHg, $\nu_{max.}$ (film) 3 345 and 3 250 (NH_2) and 2 780 cm^{-1} (CH_2Ph).

N-Benzylproline (7).—The ester (1) (20.6 g, 0.088 mol) was treated with 8N-sodium hydroxide (100 ml) containing methanol (25 ml), and the mixture was refluxed for 1 h. After removal of the methanol by distillation *in vacuo*, the aqueous solution was brought to pH 6.5 with concentrated hydrochloric acid. The aqueous solution was then evaporated, and concentrated to dryness *in vacuo*, with care to remove the last traces of water. The residual solid was

[9] R. K. Hill and Tak-Hang Chan, *Tetrahedron*, 1965, **21**, 2015.

extracted with absolute ethanol at the b.p. and the extracts were decolourised and concentrated to give a paste which was crystallised from acetone. The product (7) separated as a crystalline solid (16 g, 88.4%), m.p. 176—178° (lit.,[5] 102°; lit.,[6] 170—170.5°) (Found: C, 70.0; H, 7.25; N, 6.7. $C_{12}H_{15}NO_2$ requires C, 70.2; H, 7.35; N, 6.8%), $\nu_{max.}$ (KBr) 2 810 (CH_2Ph) and 1 640 cm^{-1} (CO_2^-).

N-Benzylprolinamide (8).—*N*-Benzylproline (7) (10.3 g, 0.05 mol) was dissolved in tetrahydrofuran (300 ml) and triethylamine (7.0 ml, 5.0 g, 0.05 mol) was added. The mixture was cooled to −5 °C and ethyl chloroformate (4.8 ml, *ca.* 5.4 g, 0.05 mol) was added. After cooling to −30 °C the mixture was treated with liquid ammonia (6.0 ml) and slowly allowed to reach room temperature. The mixture was stirred for 12 h at this temperature and the precipitate was filtered off. The filtrate was concentrated to dryness and the residue dissolved in chloroform. The solution was washed with water, dried (Na_2SO_4), decolourised, and concentrated to dryness to give an oil which slowly solidified. Crystallization from ether–hexane gave the *product* (8) (9 g, 88.2%), m.p. 68—70° (Found: C, 70.4; H, 7.85; N, 13.65. $C_{12}H_{16}N_2O$ requires C, 70.55; H, 7.9; N, 13.7%), $\nu_{max.}$ (KBr) 3 370 and 3 180 (NH_2), 2 800 (CH_2Ph), and 1 635 cm^{-1} (C=O).

2-Aminomethyl-1-benzylpyrrolidine (5).—To a suspension of lithium aluminium hydride (4.0 g, 0.1 mol) in anhydrous tetrahydrofuran (50 ml) was added a solution of the amide (8) (9.0 g 0.05 mol) in anhydrous tetrahydrofuran (50 ml), and the mixture was heated under reflux during 3 h. The excess of lithium aluminium hydride was hydrolysed, the mixture was filtered, and the filtrate concentrated to dryness to give the *product* (5) as an oil (7.5 g, 76.8%), b.p. 104—106° at 0.08 mmHg, n_D^{18} 1.5453 (Found: C, 75.55; H, 9.35; N, 14.6. $C_{12}H_{18}N_2$ requires C, 75.75; H, 9.55; N, 14.7%). $\nu_{max.}$ (film) 3 350 3 250 (NH_2) and 2 795 cm^1 (CH_2Ph).

3-Acetamidopiperidine (9) *Hydrochloride*.—3-Acetamidopyridine [7] (8.2 g, 0.06 mol) was dissolved in N-hydrochloric acid (70 ml) and hydrogenated (40 lb in^{-2}) at room temperature over platinum oxide (0.3 g) for 60 h. The catalyst was filtered off and the filtrate concentrated to dryness. The residue was distilled with ethanol several times to remove the last traces of water and triturated with ethyl methyl ketone, and the solid was filtered off and crystallized from ethanol–ether to give the piperidine (9) hydrochloride (8.8 g, 82.2%), m.p. 160—162° (lit.,[7] 165—169°) (Found: C, 46.95; H, 8.5; Cl, 19.7; N, 15.55. $C_7H_{15}ClN_2O$ requires C, 47.05; H, 8.45; Cl, 19.85; N, 15.7%), $\nu_{max.}$ (KBr) 3 320 (NH), 2 840—2 550 (N^+H), and 1 660 cm^{-1} (C=O).

3-Acetamido-1-benzylpiperidine (10).—To a solution of compound (9) (7 g, 0.05 mol) in benzene (30 ml) was added triethylamine (5 g, *ca.* 7 ml, 0.05 mol), followed by benzyl bromide (8.9 g, *ca.* 6.2 ml, 0.05 mol) dissolved in benzene (10 ml), and the mixture was heated under reflux during 12 h. The precipitate was filtered off and the filtrate evaporated to dryness *in vacuo*. The residue was dissolved in chloroform (75 ml) and the solution washed with water (3 × 50 ml), dried (Na_2SO_4), decolourized, and concentrated to dryness giving *compound* (10) as a solid, which was crystallized from ethanol–ethyl ether; yield 8 g (69.5%), m.p. 100—102° (Found: C, 72.5; H, 8.45; N, 11.9. $C_{14}H_{20}N_2O$ requires C, 72.4; H, 8.7; N, 12.05%), $\nu_{max.}$ (KBr) 3 280 (NH), 2 795 (CH_2Ph), and 1 650 cm^{-1} (C=O).

3-Amino-1-benzylpiperidine (6).—Compound (10) (5 g, 0.022 mol) and 2N-hydrochloric acid (50 ml) were heated under reflux during 4 h. The mixture was evaporated to dryness *in vacuo*, made alkaline, and extracted with chloroform. The extracts were dried (Na_2SO_4), decolourised, and concentrated to dryness to give *compound* (6) as an oil (4 g, 95%), b.p. 80—82° at 0.01 mmHg, n_D^{22} 1.5444 (Found: C, 75.6; H, 9.35; N, 14.6. $C_{12}H_{18}N_2$ requires C, 75.55; H, 9.55; N, 14.7%), $\nu_{max.}$ (film) 3 340 and 3 240 (NH_2) and 2 790 cm^{-1} (CH_2Ph).

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