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REACTIONS OF β-SUBSTITUTED AMINES—III

COMPLETE PRODUCT STUDY OF THE REACTIONS OF 3-CHLORO-1-ETHYLPIPERIDINE AND 2-CHLOROMETHYL-1-ETHYLPYRROLIDINE[1] WITH HYDROXIDE ION

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Abstract—A complete product study of the reaction of 3-chloro-1-ethylpiperidine (1) in aqueous sodium hydroxide showed the formation of three *bis*-(β-aminoethers), 2,2′-*bis*-(N-ethyl-2-pyrrolidinomethyl) ether (6), 3-(N′-ethyl-2′-pyrrolidinomethoxy)-N-ethylpiperidine (7) and 3,3′-*bis*-N-ethyl-3-piperidinyl ether (8) in addition to the two previously reported products. The structures of these three ethers are demonstrated and their formation is shown to be consistent with the previously suggested mechanism[1] of the reaction. Reactions of 2-chloromethyl-1-ethylpyrrolidine (2) are shown to proceed by the same mechanistic pathways with the formation of the same products. Reaction of 1 or 2 with two other nucleophiles, methoxide and ethoxide are also examined.

3-Chloro-1-ethylpiperidine (1) and 2-chloromethyl-1-ethylpyrrolidine (2) react with nucleophiles to give piperidine and 2-methylpyrrolidine derivatives.[1,4] The mechanism has been examined and the reaction has been shown to proceed through an aziridinium ion intermediate, 1-ethyl-1-azoniabicyclo[3.1.0] hexane (3), which has been isolated and synthesized independently.[1,4] A preliminary stereochemical study has shown the reaction to be 98 ± 5% stereospecific, at least for the formation of the pyrrolidine alcohol.[1,4] A subsequent investigation[5] has shown the reaction to be 100% stereospecific and will be reported separately.

DISCUSSION AND RESULTS

A complete product study was undertaken as a part of the mechanistic study because 35% of the product was not accounted for in the reaction of 1 with sodium hydroxide.[1,4] In the previous study,[6] the products of the reaction of 1 in 10% sodium hydroxide were separated by distillation *in vacuo* on a spinning band column. 1-Ethyl-2-hydroxymethylpyrrolidine (4a) and 1-ethyl-3-hydroxypiperidine (5a) were distilled and the remaining product (about 35%) polymerized in the pot.[1,6] In this study, the products were separated by GLC (12% Carbowax 20M on Anachrom ABS) and six components were observed. The first component to elute was an unidentified impurity (less than 1%) which is also found in the starting material, 1. The second and third fractions are 4a and 5a respectively, as shown by spectral comparison of collected fractions and retention times of authentic samples. The fourth, fifth and sixth fractions to elute are 2,2′-*bis*-(N-ethyl-2-pyrrolidinomethyl) ether (6), 3-(N′-ethyl-2′-pyrrolidinomethoxy)-N-ethylpiperidine (7) and 3,3′-*bis*-N-ethyl-3-piperidinyl ether (8) respectively. The structures of 6, 7 and 8 were assigned on the basis of spectral and physical evidence given below. The identification of these three ethers now accounts for 99% of the material balance of the reaction. Assuming the response of the flame ionization detector to be identical for all six components† the yields of 4a, 5a, 6, 7 and 8 were 22, 42, 16, 16 and 2% respectively.

If 1 is reacted with a stoichiometric amount of sodium hydroxide in 80% aqueous ethanol, two new products, 2-ethoxymethyl-1-ethylpyrrolidine (4c) and 3-ethoxy-1-ethylpiperidine (5b) are formed, while 6, 7 and 8 are not observed.

If the methanol solvate of 2-HCl (2-HCl : MeOH) is reacted in 25% aqueous sodium hydroxide, two methoxy ethers in addition to 4a, 5a, 6, 7 and 8 are formed. They are 1-ethyl-2-methoxymethylpyrrolidine (4c) and 1-ethyl-3-methoxypiperidine (5c).

The GLC retention times varied with conditions, but the order of elution was the same on three different columns (12% Carbowax 20M on Anachrom ABS, 10% OV-17 on Chromsorb-W and 25% Triton X-305 on Chromsorb-W). The order of elution was: 4c, 5c, 4b, 5b, 4a, 5a, 6, 7 and 8. In every case the pyrrolidine isomer eluted before its corresponding piperidine isomer. In the case of the *bis*-β-aminoethers, the pyrrolidine-pyrrolidine ether, 6, was eluted first, followed by the pyrrolidine-piperidine ether, 7, followed by the piperidine-piperidine ether, 8.

The ethoxyethers 4b and 5b, methoxy ethers 4c and 5c, and the *bis*-β-aminoethers 6, 7 and 8 each

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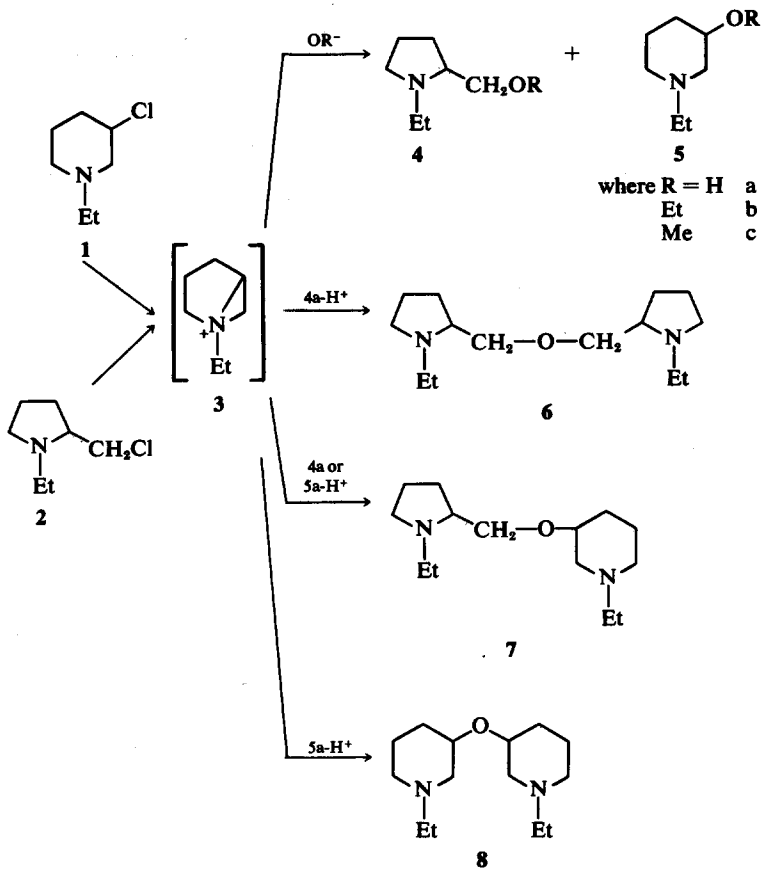
†The responses of the detector to 4a and 5a were identical to within experimental error and were used for calibration.



have characteristic strong bands in the 1100 to 1125 cm^{-1} region of the IR spectra of neat liquid films.* The neat liquid film IR spectra of the alcohols **4a** and **5a**, had broad bands for associated hydroxyl with maxima at 3400 cm^{-1} as well as strong bands at 1100 cm^{-1}, but not as intense as found in the spectra of the ethers.

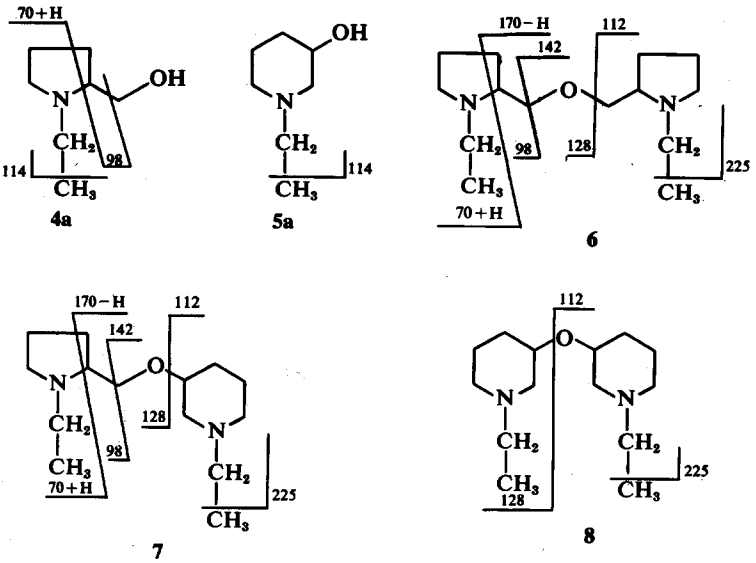
The IR spectra of the neat liquid films of the compounds agree with the observation of Talent and Siewers[7] in the 2500 cm^{-1} to 3000 cm^{-1} region. The 5-membered rings have two bands at 2940 cm^{-1} and 2975 cm^{-1} with the 2975 cm^{-1} band more intense than the 2940 cm^{-1} band. The 6-membered ring isomers have the same two bands, with the 2940 cm^{-1} band more intense than the 2975 cm^{-1} band. In agreement with its assigned structure, the pyrrolidine-piperidine ether, **7**, has two bands of equal intensities in the 2500 to 3000 cm^{-1} region of the IR spectrum as observed in the vapor phase spectra of **4b**, **5b**, **4c** and **5c**.

The mass spectra of **6**, **7** and **8** exhibit a strong parent less one (P − H) peak at *m/e* 239 and parent plus one (P + H) peak at *m/e* 241, typical of amines. Accurate mass measurement[8] of the parent ion at *m/e* 240 conclusively shows the molecular formulae of **6**, **7** and **8** to be $C_{14}H_{28}N_2O$, which is double the formulae of **4a** and **5a** with the loss of water. The elemental analyses also agree with the calculated percentages for $C_{14}H_{28}N_2O$ for the three ethers **6**, **7** and **8**.

Some of the peaks present in the mass spectra of **6**, **7** and **8** may be rationalized by comparison to the mass spectra of **4a**, **5a** and **5c**.

The 6-membered ring alcohol, **5a**, contains a small parent peak at *m/e* 129 with a base peak at 114 (P − CH_3) but only a small peak at *m/e* 98. The spectrum of **4a**, the 5-membered ring alcohol, has a small parent peak at *m/e* 129, a small 114 peak with the base peak at *m/e* 98, due to cleavage α to the primary OH group to give 1-ethylpyrrolidine ion and a CH_2OH radical, and a large peak at *m/e* 70, which may be due to further splitting of the 5-membered ring *m/e* 98 ion to form an aziridine ring and an ethylene group. The 6-membered ring ethoxy ether, **5c**, gives a spectrum similar to **5a** with a base peak at *m/e* 114, a small peak at *m/e* 98, and only a small peak at *m/e* 70.

*In a microsample IR spectrum of **8**, there was only a medium to weak band at 1090 cm^{-1}, but in the regular thin film spectrum of a larger sample, a medium to strong band at 1100 cm^{-1} was observed.



In the mass spectrum of the 5-membered ring *bis*-(β-aminoether), **6**, the base peak is at *m/e* 98 and a large peak at *m/e* 70, which appears to be characteristic of the 5-membered ring. A small peak at *m/e* 170 (P − 70) is also present. The spectrum of **7**, the ether with both the 5- and 6-membered rings, again shows a base peak at 98, a large peak at *m/e* 70 and a small peak at *m/e* 170. In the spectrum of the 6-membered ring ether, **8**, the base peak is at *m/e* 111 and the peak at *m/e* 70 is very small. No peak at *m/e* 170 was observed. The 111 peak in the spectra of **6**, **7** and **8** may be explained as initial loss of hydrogen from cleavage of a C—H bond α to the nitrogen to form the P − 1 moiety,[9] and then as the parent ion cleaves to form *the m/e* 112 peak, the P − 1 ion cleaves to form the *m/e* 111 peak.

The NMR spectra of all the compounds have Me triplets due to the N-Et group, centered at 0·9 to 1·08 ppm δ as indicated in Table 1. For any pair of isomers, the Me triplet of the piperidine isomer is always centered ~ 0·05 ppm upfield of that of the corresponding pyrrolidine isomers, except for **4b** and **5b**, which have NMR spectra that are complicated by the methyl triplet of the OEt group in the same region.

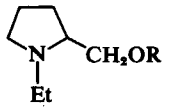
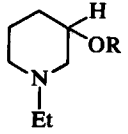
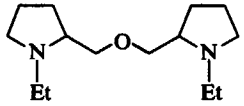
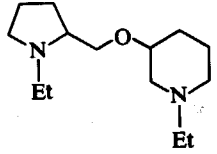
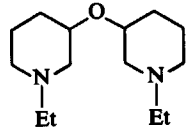
Compounds **4a** and **5a** have different splitting patterns for the N-Et group, **5a** having an A_2X_3 pattern consisting of a triplet at 1·0 ppm δ and a quartet at 2·3 ppm δ and **4a** having an ABX_3 pattern consisting of a triplet at 0·98 ppm δ and 4 sets (J_{AB} = 12 Hz) of quartets located at 271, 260, 210 and 198 Hz (2·65 and 2·04 ppm δ). The shifts of the latter two quartets, which are in the same region as some of the ring methylene group absorptions, could be assigned with certainty only after decoupling the Me group, which resulted in the collapse of the four sets of quartets into a typical AB quartet (J = 12 Hz). In addition, an 8 line AB part of an ABX-type spectrum for the methylene part of the hydroxymethyl group was observed at about 3·5 ppm δ (J_{AB} = 11, J_{AX} = 8·1, J_{BX} = 0·7 Hz).

In the NMR spectra of the *bis*-(β-aminoethers) **6**, **7** and **8**, the pyrrolidine-pyrrolidine ether, **6**, had a Me triplet with similar chemical shifts to the other pyrrolidines and the four quartets of the ABX_3 system of N—CH_2—CH_3 at 130·3, 141·6, 168·0 and 179·4 Hz at 60 MHz (2·88 and 2·28 ppm δ, J_{AB} = 11·3 Hz) along with the 8-line AB part of an ABX pattern at about 3·4 ppm δ, while the N—CH_2 quartet at 2·31 ppm δ that is typical of piperidines was absent. The piperidine-piperidine ether, **8**, has a Me triplet similar to the other piperidines and a large quartet at 2·31 ppm δ, but it lacks the 8 line AB part of the ABX pattern (N—CH—CH_2—O—) at 3·4 ppm δ. The pyrrolidine-piperidine ether, **7**, has two overlapping Me triplets centered about 0·05 ppm apart, a large quartet at 2·31 ppm δ and the 8 line AB part of the ABX pattern at 3·4 ppm δ. This latter spectrum was almost identical with a composite of the NMR spectra of **4a** and **5a** (minus the OH peaks). The NMR spectra of **6** and **8** are identical to the NMR spectra of the corresponding model methoxy ether compounds **4b** and **5b**, except for the OMe group absorption.

The NMR spectrum of the piperidine-piperidine ether **8** has a seven peak multiplet at 3·8 ppm δ for $(CH_2)_2$CH—O but it was absent in the pyrrolidine-pyrrolidine ether **6**. The multiplet is partially obscured by other peaks in the NMR spectrum of the pyrrolidine-piperidine ether **7** but can be seen. Thus the NMR spectra of **6**, **7** and **8** completely confirm the structures shown.

The *bis*-β-aminoethers are probably formed by

Table 1. Important PMR chemical shift data of compounds 4 through 8[a, b]

Compound	Number in text	CH_3CH_2N	CH_3CH_2N	CH_3O—	CH_3CH_2O—	CH_3CH_2O—	$NCHCH_2O$—	NCH_2CHO—
	R=H, 4a	1·00	2·65, 2·04	—	—	—	3·5	—
	R=Me, 4c	1·05	*c*	3·25	—	—	3·3	—
	R=H, 5a	0·95	2·30	—	—	—	—	3·8
	R=Me, 5c	1·00	2·30	3·25	—	—	—	3·37
	R=Et, 5b	1·08	2·46	—	1·20	3·59	—	*d*
	6	1·05	2·88, 2·28	—	—	—	3·38	—
	7	0·99, 1·07	*c*, 2·31	—	—	—	3·40	3·55
	8	0·99	2·31	—	—	—	—	3·55

[a]All spectra were recorded in benzene with tetramethylsilane as an internal standard.
[b]All chemicals are reported in ppm δ.
[c]The four quartets of the pyrrolidine NCH_2CH_3 were under other peaks and not specifically identified.
[d]Not identified.

the attack of the anion of **4a** or **5a** at position 2 or 3 of the intermediate, **3**. If the reaction of **2** with 25% aqueous sodium hydroxide is stopped before it is half completed, only starting material, **2**, and alcohols, **4a** and **5a**, are found as products. The ratio of the three *bis*-β- amino-ethers, **6**, **7** and **8** to alcohols, **4a** and **5a**, found in the product, is governed by the concentration of the base in the reaction mixture. It is found to vary from less than 10% *bis*-β-amino-ethers for reaction in dilute aqueous sodium hydroxide to about 60% for reaction in 25% aqueous sodium hydroxide.

The evidence cited above demonstrates the structures of the three previously unreported *bis*-β-aminoethers, **6**, **7**, and **8**, isolated from the reaction of **1** or **2** with aqueous sodium hydroxide. These products are not only consistent with the mechanism previously proposed[1,4] for the reactions of **1** and **2** with nucleophiles, but lend support to it.

EXPERIMENTAL

NMR spectra were recorded at 60 MHz on a Varian Associates A-60 spectrometer and/or at 90 MHz on a Brucker HX-90 spectrometer and/or at 100 MHz on a Varian Associates HA-100 spectrometer. All chemical shifts are reported in δ ppm and couplings in Hz. Medium resolution mass spectra were obtained on an AEI-MS 1201 mass spectrometer. IR spectra were taken on the neat liquid films with a Perkin-Elmer model 337 spectrometer. IR spectra of the vapor phase were determined on a Perkin-Elmer model 337 in a Carle Instruments "light pipe" cell attached to a stopped-flow gas chromatograph.*

Analytical GLC separations were done with a Barber-Coleman Model 5000 analytical gas chromatograph fitted with a 12 ft × ¼ inch copper column packed with 12% Carbowax 20 M on Anachrom ABS. The carrier gas was N_2 and the detector was a flame ionization detector operating off a 1:10 splitter. Collections were done by a hand-held "U" tube cooled with liquid N_2 and attached to the outlet of the splitter. Samples to be separated by preparative GLC were first examined on a Varian Aerograph Series 1200 gas chromatograph fitted with a 6 ft by 1/8 inch glass column packed with 10% OV-17 on 160 to 180 mesh Chromsorb-W, with N_2 as a carrier gas on a flame ionization detector. In all cases, temp programming was necessary because **4a**, **5a**, **4b**, **5b**, **4c**, and **5c** were not resolved at a temp high enough to elute **6**, **7** and **8** from the column. Preparative GLC separations were done on a Hewlett-Packard model 776 Prepmaster Jr. fitted with an 80 in by 3/8 in stainless steel column packed with 25% Triton X-305 on 60 to 80 mesh Chromsorb-W. A flame ionization detector was operated off a 1:9 splitter and N_2 was used as the carrier gas. The collectors, which were manually operated, were cooled in an ice bath. The separation of the mixture required several passes since the entire mixture of products could not be separated at one temp and it was not possible to temp program the preparative chromatograph. This was done by first crudely separating the low retention-time alcohols and alkyl ethers from the *bis*-β-aminoethers and then rechromatography of the two crude fractions.

*The stopped flow gas chromatograph was a system devised and built in this laboratory by C. F. Hammer, D. Korte and P. Rankin.

Microanalyses were performed through the courtesy of Dr. W. C. Alford of the National Institutes of Health's Microanalytical Laboratory.

3-Chloro-1-ethylpiperidine, (**1**). An aqueous soln of **1**·HCl (10·0 g in 200 ml) was covered with ether (200 ml) and $NaHCO_3$ (5 g) was slowly added to the magnetically stirred soln. The ether was separated and the water layer was extracted several times with ether. The combined ether extracts were dried over $MgSO_4$ and evaporated. The chloroamine (**1**) was distilled, b.p. 43–44° (3·7 mm), 5·9 g (74%) n_D^{25} 1·4663 [lit.[10] b.p. 74–76° (20 mm), n_D^{20} 1·4678].

2-Chloromethyl-1-ethylpyrrolidinium chloride, **2**·HCl was synthesized by reacting **4a** with thionyl chloride in chloroform by a previously reported procedure.[10] Pure **2**·HCl was obtained after decolorizing four times with charcoal (Norit A), recrystallization from MeOH and drying under vacuum (6 mm at room temp), m.p. 210–210·5° [lit.[10] m.p. 193·5–194°]. When the sample was air dried, a crystalline solvate of uncertain composition, approximately 1:1 (**2**·HCl):**MeOH**, was obtained.

3-Ethoxy-1-ethylpiperidine, (**5c**). To a N_2 purged slurry of sodamide (2·15 g, 0·055 mole) in toluene (30 ml, purified over Na wire), **5a** (7·0 g, 0·05 moles) was added over a 20 min period. The soln was gradually heated until the evolution of ammonia ceased. EtI (4·9 ml, 0·06 mole) was added and the soln was refluxed for 3 hr, cooled and allowed to stand overnight. The soln was filtered and the filtrate was extracted with 6 N HCl (5 × 10 ml). An excess of KOH was added to the combined acid extract and the soln was extracted with ether. The ether was dried over $MgSO_4$, filtered and evaporated. The residual oil was distilled, b.p. 88–89° (26–27 mm), 1·5 g (17%) [lit.[11] b.p. 80–82° (20 mm), 64% yield].

The reaction of **1** *with 10% aqueous sodium hydroxide.* NaOHaq (50 ml of 10% NaOH, 0·12 mole) was slowly added to freshly distilled **1** (7·2 g, 0·05 mole), the mixture was brought to a boil and refluxed for 5 hr. The mixture was cooled and extracted in a continuous extractor for 3 days with refluxing ether. The ether was dried over $MgSO_4$ and evaporated giving a yellow oil (4·0 g, 82%) that was separated by GLC on the 12% Carbowax 20 M column. The fractions were collected as described above and components identified as described in the text.

Reactions in 25% aqueous sodium hydroxide. **1**·HCl, **2**·HCl, and (**2**·HCl):**MeOH** were reacted with 25% NaOH-aq by adding the sample (usually about 0·1 mole) to 25% NaOHaq (50 ml) and refluxing overnight (about 14 hr). The mixture was then cooled and extracted with ether, the ether was dried and evaporated and the resulted oil mixture separated by preparative GLC. The separated components were further purified by molecular distillation before IR, NMR, refractive indices and elemental analyses were determined.

The GLC retention times, IR, NMR spectra and refractive indices of **4a** and **5a** were compared with authentic samples for identification.

The IR, NMR, mass spectra and refractive indices and elemental analyses were obtained for the *bis*-(β-amino-ethers), **6** and **7**. The spectra and elemental analysis were obtained for **8**, but there wasn't sufficient sample for refractive index determination. NMR, IR and MS spectral data are given in the text above.

6 n_D^{20} 1·4730. (Calc: C, 69·95; H, 11·74. Found: C, 69·84; H, 11·75%.)

7 n_D^{20} 1·4766. (Calc: C, 69·95; H, 11·74; N, 11·66. Found: C, 69·73; H, 11·41; N, 11·53%)

8 n_D^{20} (not determined). (Calc: C, 69·95; H, 11·74. Found: C, 69·73; H, 11·53%.)

Ethers **4b** and **5b** from the reaction of **(2-HCl):MeOH** in 25% NaOHaq were identified only by their IR and NMR spectra.

4b n_D^{20} 1·4434; **5b** n_D^{20} 1·4500

Reaction of **1** *in 80% aqueous ethanol.* NaOH (0·209 g, 0·005 mole) and freshly distilled **1** (0·404 g, 0·003 mole) were dissolved in 1 molar sodium perchlorate in 80% aqueous EtOH (25 ml). The temp was maintained at 45° with a constant temp bath for 22 hr. A NaCl ppt which had formed was filtered off and water (50 ml) was added. The soln was adjusted to pH 8 with $NaHCO_3$ and extracted with ether in a continuous extractor. The ether was dried and evaporated and the residual oil was separated by GLC on the Carbowax 20 M column. The product was shown to be the two ethoxy ethers **4c** and **5c** and the aminoalcohols **4a** and **5a** by their IR and NMR spectra and by comparison of the GLC retention times with authentic samples of **5a** and **5c**.

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