the product bands were eluted from the silica gel with tetrahydrofuran. In the case of **5d**, a 28% yield of 8-bromo-*N*-2′,3′,5′-tetraacetylguanosine (**7**) was also obtained. Compound **7** could be converted to **5d** in 55% yield using the above procedure. Results and properties are listed in Tables I and II.

**8-Hydroxyadenosine (6a) and 8-Hydroxyguanosine (6b).**—Compound **5** was dissolved in a mixture of pyridine and ammonium hydroxide (1:3, 20 ml/mmol) and the solution was stirred at room temperature for 3 to 7 days. The solvents were removed at reduced pressure and the product was crystallized from water (Tables I and II).

**8-Hydroxypurine 2′,3′-Carbonates (1a and 1b).**—Compound **6** (1 mmol), diphenyl carbonate (1.3 mmol), and sodium bicarbonate (6 mg) were heated in dimethylformamide (6 ml) at 150° for 30 min. The products were separated by thick layer chromatography using THF for the adenosine derivative and chloroform–ethanol (7:3) for the guanosine derivative (Tables I and II).

**Purine 2′,3′-Carbonates (8 and 9).**—Compounds **8** and **9** were prepared from guanosine and adenosine respectively in the same manner as **1** above. The products were isolated by thick layer chromatography using THF. Compound **8** crystallized from ethanol (Tables I and II).

**Attempted Synthesis of 8,2′-*O*-Anhydronucleosides.**—Several attempts were made to convert **1a** and **1b** to their respective 8,2′-*O*-anhydro derivatives. Both compounds were subjected to each of the following sets of conditions: (A) nucleoside, sodium bicarbonate, and dimethylformamide at 150° for 30 min; (B) nucleoside, sodium benzoate, and dimethylformamide at 150° for 30 min; (C) nucleoside, potassium *tert*-butoxide, and dimethylformamide at 150° for 30 min; (D) nucleoside, potassium *tert*-butoxide, and *tert*-butyl alcohol at 80° for 30 min. In all cases 10 mg of either **1a** or **1b** was used, the volume of solvent was 0.5 ml, and 1 mg of the base catalyst was used. Products were identified by paper chromatography. In all cases only unreacted starting material and **6** were detected. No other nucleoside material was detected in any of these experiments.

**Registry No.**—**1a**, 29851-53-4; **1b**, 29851-54-5; **5c**, 29851-55-6; **5d**, 29851-56-7; **6a**, 29851-57-8; **6b**, 29851-58-9; **7**, 29851-59-0; **8**, 29842-76-0.

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## Synthesis of 19-Hydroxy-19a-methyl-5-ene Steroids *via* the 6β,19-Epoxy Derivatives

YUMI WATANABE AND YUTAKA MIZUHARA*[1]

*Chemical Laboratory, School of Medicine, Keio University, Hiyoshi, Yokohama, Japan*

MICHIO SHIOTA

*Chemical Laboratory, Ochanomizu University, Oisuka, Tokyo, Japan*

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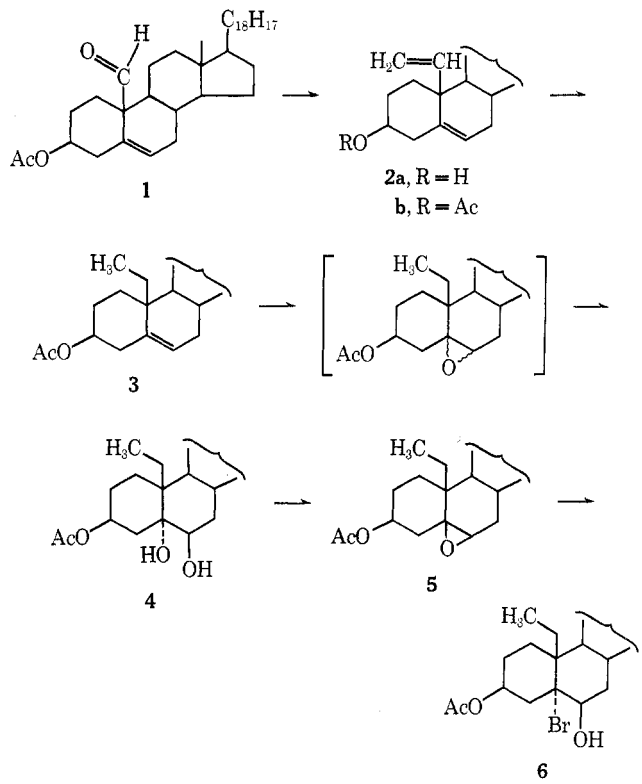
The reaction of methyllithium with steroidal 19-aldehydes has been reported by Caspi to give 19-hydroxy-19a-methyl-5-enes, and it has also been shown that only 19*R* alcohols are formed by this reaction.[2,3] The isomeric 19*S* alcohol was obtained by reduction of the 19a-methyl-19-oxo compound with lithium aluminium hydride.[4] We examined the reaction of lead tetraacetate with 3β-acetoxy-5α-bromo-6β-hydroxy-19a-methylcholestane to determine the stereochemistry of the formation of the ethers, 3β-acetoxy-5α-bromo-6β,19-epoxy-19a-methylcholestanes, and found that the resulting ethers could be reduced to the 19-hydroxy-19a-methyl-5-enes. This paper deals with the stereochemistry of the formation of the 6β,19-epoxides and the synthesis of 19-hydroxy-19a-methylcholest-5-enes from them.

The starting material **6** for the synthesis of the 6β,19-epoxides was prepared by the way summarized in Scheme I. The Wittig reaction on 3β-acetoxy-19-oxocholest-5-ene (**1**)[5] with methylene–triphenylphosphorane in ether gave the 19a-methylene derivative **2a** in good yield and its acetate **2b** was partially hydrogenated to the 19a-methyl-5-ene **3** with platinum catalyst in ethanol. The epoxidation of **3** with monoperphthalic acid gave a mixture of 5,6-epoxides, which consisted of 90% of α oxide and 10% of β isomer. The mixture of the epoxides was transformed into the 5α,6β-dihydroxy derivative **4** and then the diol was converted to the 5β,6β-epoxide **5** in the usual way.[6,7] Treatment of **5** with an equimolar amount of hydrobromic acid in acetic acid yielded the compound **6**.

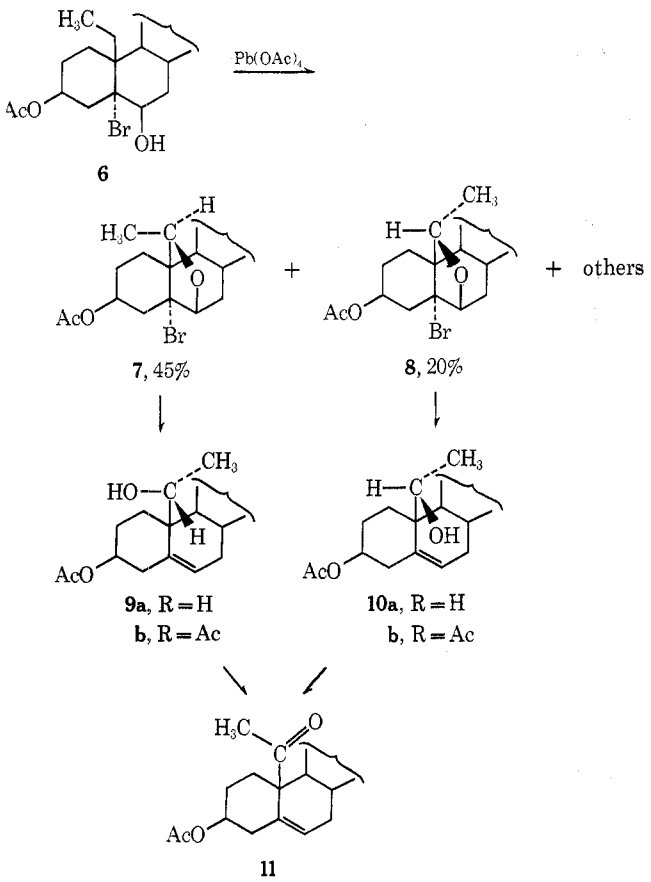
SCHEME I




The 6β-hydroxy-19a-methyl compound **6** was treated with lead tetraacetate in cyclohexane in the presence of iodine, and the two main products, 45% of **7** and 20% of **8**, were obtained by column chromatography. Reduction of **7** and **8** with zinc in acetic acid afforded quantitatively the 19-hydroxy compounds, **9** and **10**, respectively. The results are summarized in Scheme II. The stereochemistry at C-19 of **7** and **8** was assigned in

(1) To whom all correspondences should be addressed.
(2) E. Caspi and J. Wicha, *Chem. Commun.*, 209 (1966).
(3) J. Wicha and E. Caspi, *J. Chem. Soc. C*, 1740 (1968).
(4) J. Wicha and E. Caspi, *ibid.*, 947 (1969).
(5) M. Akhtar and D. H. R. Barton, *J. Amer. Chem. Soc.*, **86**, 1528 (1964).
(6) M. Davis and V. Petrow, *J. Chem. Soc.*, 2536 (1949).
(7) C. W. Shoppee and R. Lake, *ibid.*, 4864 (1960).

SCHEME II




relation to that of the 19-hydroxy compounds **9** and **10**. On reduction, the stereochemistry at C-19 could be maintained, and therefore **7** and **8** have the same configuration at C-19 as that of **9** and **10**, respectively. Oxidation of **9** and **10** gave the same product, the 19a-methyl-19-oxo compound **11**, synthesis of which by a different route was previously reported,[8] and the dehydration of **9** and **10** also gave the same product **2**. The above chemical evidence indicates that the compound **9** is the epimer of **10** at C-19 or that **7** is the epimer of **8**. On the stereochemistry of 19-hydroxy-19a-methyl steroids, Caspi reported that treatment of an aldehyde of the type **1** with methyllithium gave a single product in an almost quantitative yield, and the resulting alcohol had the 19*R* configuration. In our experiments, the aldehyde **1** with methyllithium gave the diol **9a** as the main product, which was therefore concluded to have the 19*R* configuration according to the finding by Caspi. On the other hand, reduction of the 19-oxo compound **11** with lithium aluminium hydride yielded the diol **10a** as the main product. Examination of Dreiding model for the process of reduction suggests that the resulting alcohol **10a** will have 19*S* configuration and this deduction is in agreement with the result reported by Caspi.[4] From the above result, the alcohol **9** has been shown to have the 19*R* configuration while **10** to have the 19*S* stereochemistry.

The above results indicated that the oxidation of **6** with lead tetraacetate gave two isomeric 6*β*,19-epoxides as the main products and that the ratio of the 19*R* and 19*S* isomers was about 7:3. The formation of ether ring will occur preferably with a conformer, in which the bulky 19a-methyl group will be located at the rear of the molecule, and therefore the oxidation would yield the 19*R* isomer as the major product.

Comparison of infrared spectra of the 19*R* alcohol **9b** and the 19*S* one **10b** showed some differences in absorption bands due to the 19-hydroxy groups. The ir spectrum of **9b** in dilute carbon tetrachloride solution showed a band at 3627 $cm^{-1}$ due to the free hydroxyl group accompanied with a very weak shoulder at 3595 $cm^{-1}$ due to the intramolecular hydrogen-bonded hydroxyl group, while that of the 19*S* one at 3633 and 3540 $cm^{-1}$. As reported by Caspi,[3] it was apparent from models that C-2, C-4, C-8, and C-11 axial protons would restrict rotation around the C-10–C-19 bond of the 19-hydroxy-19a-methyl-5-enes. Consequently, in usual circumstances, the 19*R* and 19*S* alcohols will remain in reasonably fixed positions with the hydroxyl group. The difference in the ir spectra of the two isomers indicated that rotation around C-10–C-19 bond would be partially restricted. The 19*R* and 19*S* alcohols will perhaps remain with the hydroxyl group over ring A and B, respectively, and therefore the hydroxyl group of the 19*S* alcohol will be hydrogen bonded with the $\pi$ electrons of the 5,6 double bond more strongly than that of the 19*R* one.

## Experimental Section[9]

**3*β*-Acetoxy-19a-methylenecholest-5-ene (2b).**—To an ethereal solution of *n*-butyllithium (containing 0.01 mol, about 30 ml), triphenylmethylphosphonium bromide (3.57 g, 0.01 mol) was added over a 5-min period. A gentle flow of nitrogen was maintained throughout the reaction. The solution was stirred for 4 hr at room temperature. An ethereal solution of 2.1 g (0.005 mol) of 3*β*-acetoxy-19-oxocholest-5-ene (**1**) was added to the red solution of the phosphorane; the solution became almost colorless and a white precipitate separated. The mixture was heated under reflux overnight under nitrogen. After cooling, the mixture was diluted with ether and the precipitate was removed by filtration. The filtrate was washed with water until neutral, dried, and evaporated. The residue was acetylated with pyridine–acetic anhydride. The product was chromatographed on alumina and eluted with *n*-hexane to afford 1.5 g of **2b**, which was recrystallized from methanol: mp 89.5–90°; $[\alpha]^{27}D$ −95° (*c* 1.739, $CHCl_3$); ir (KBr) 1750, 1628, 1245, 920 $cm^{-1}$; nmr ($CDCl_3$) $\delta$ 2.00 (3-OAc), 4.9–5.7 (10-vinyl), 5.65 (6-H).

*Anal.* Calcd for $C_{30}H_{48}O_2$: C, 81.76; H, 10.98. Found: C, 81.83; H, 10.81.

**3*β*-Acetoxy-19a-methylcholest-5-ene (3).**—A solution of 1.0 g of **2b** in 100 ml of ethanol was hydrogenated with 200 mg of prereduced platinum oxide under atmospheric pressure at room temperature for 2 hr. After the catalyst was removed by filtration, the filtrate was concentrated *in vacuo*. Recrystallization of the residue from methanol gave 800 mg of **3**: mp 104–104.5°; $[\alpha]^{25}D$ −23° (*c* 1.108, $CHCl_3$); ir (KBr) 1745, 1242 $cm^{-1}$; nmr ($CDCl_3$) $\delta$ 0.91 (19a-$CH_3$, t, $J$ = 3 cps), 2.03 (3-OAc), 5.6 (6-H).

*Anal.* Calcd for $C_{30}H_{50}O_2$: C, 81.39; H, 11.38. Found: C, 81.26; H, 11.20.

**3*β*-Acetoxy-5*α*,6*β*-dihydroxy-19a-methylcholestane (4).**—A solution of 1.0 g of **3** in ether containing an excess amount of monoperphthalic acid was allowed to stand at room temperature overnight. The crude product (1.0 g) in 30 ml of acetone was treated with 1.5 ml of 1.5 *N* perchloric acid at room temperature overnight. The product was recrystallized from ether–*n*-hexane and 780 mg of **4** was obtained: mp 185°; $[\alpha]^{25}D$ −26° (*c* 0.631, $CHCl_3$); ir (KBr) 3540, 1720, 1255, 1045, 1035, 870 $cm^{-1}$.

*Anal.* Calcd for $C_{30}H_{52}O_4$: C, 75.58; H, 11.00. Found: C, 75.52; H, 10.83.

(8) Y. Watanabe, Y. Mizuhara, and M. Shiota, *Chem. Commun.*, 984 (1969).

(9) All melting points are uncorrected. Nmr spectra were determined at 60 Mc, using $CDCl_3$ as solvent with tetramethylsilane as internal standard. Optical rotations were obtained in a 0.1-dm cell with a DIP-SL Nippon-Bunko polarimeter.

**3β-Acetoxy-5β,6β-epoxy-19a-methylcholestane (5).**—A suspension of 1.0 g of the diol **4** and 300 mg of *p*-toluenesulfonic acid in 50 ml of acetic anhydride was heated at 110° for 30 min. After cooling, the mixture was poured onto ice and extracted with ether. The ethereal extract was washed with sodium bicarbonate solution and water until neutral, dried, and evaporated *in vacuo*. The residue in 50 ml of ethanol was heated under reflux with 1.5 g of potassium hydroxide for 30 min, and the resulting epoxide was acetylated with pyridine and acetic anhydride. The crude product was chromatographed on alumina and elution with *n*-hexane–chloroform afforded 850 mg of the β-oxide **5**, which was recrystallized from methanol: mp 68°; $[\alpha]^{25}D$ −9° (*c* 0.439, $CHCl_3$); ir (KBr) 1745, 1239, 1040, 820 $cm^{-1}$; nmr ($CDCl_3$) δ 1.22 (19a-$CH_3$, t, $J$ = 4 cps), 2.05 (3-OAc), 2.95 (6-H).

*Anal.* Calcd for $C_{30}H_{50}O_3$: C, 78.55; H, 10.99. Found: C, 78.75; H, 11.06.

**3β-Acetoxy-5α-bromo-6β-hydroxy-19a-methylcholestane (6).**—A solution of 700 mg of **5** in 70 ml of acetic acid and 0.21 ml of 47% hydrobromic acid was allowed to stand at room temperature for 30 min. The solution was diluted with water and then extracted with ether. The ether layer was washed with sodium bicarbonate solution and water, dried, and evaporated *in vacuo* below 30°. The residue was recrystallized from *n*-hexane–ether, and 550 mg of **6** was obtained: mp 134–135° dec; ir (KBr) 3490, 1725, 1260, 1040, 760 $cm^{-1}$.

*Anal.* Calcd for $C_{30}H_{51}O_3Br$: C, 66.77; H, 9.53. Found: C, 66.57; H, 9.75.

**Oxidation of 6 with Lead Tetraacetate.**—A suspension of 2.0 g of lead tetraacetate and 950 mg of calcium carbonate in 40 ml of cyclohexane was stirred and heated to 80°; then 350 mg of **6** and 400 mg of iodine was added. The mixture was irradiated with a 500-W lamp under reflux with vigorous agitation for 45 min. After the solution had become colorless, it was filtered, and the filtrate was washed with a 10% sodium thiosulfate solution and water. After evaporation of the solvent, the residue was chromatographed on alumina, and elution with *n*-hexane–chloroform (40:1) gave 70 mg of **8**. Further elution with the same solvent gave 159 mg of **7**. The products were recrystallized from methanol.

**3β-Acetoxy-5α-bromo-6β,19*R*-epoxy-19a-methylcholestane (7):** mp 124–125°; $[\alpha]^{25}D$ −3.0° (*c* 0.330, $CHCl_3$); ir (KBr) 1743, 1235, 1035, 790 $cm^{-1}$; nmr ($CDCl_3$) δ 1.47 (19a-$CH_3$, d, $J$ = 7.5 cps), 2.05 (3-OAc), 4.1 (6-H), 4.58 (19-H, q, $J$ = 7.5 cps), 5.2 (3-H).

*Anal.* Calcd for $C_{30}H_{49}O_3Br$: C, 67.00; H, 9.19. Found: C, 67.05; H, 9.49.

**3β-Acetoxy-5α-bromo-6β,19*S*-epoxy-19a-methylcholestane (8):** mp 146°; $[\alpha]^{25}D$ +17° (*c* 0.215, $CHCl_3$); ir (KBr) 1747, 1238, 1040, 920, 790 $cm^{-1}$; nmr ($CDCl_3$) δ 1.44 (19a-$CH_3$, d, $J$ = 7 cps), 2.02 (3-OAc), 4.05 (6-H), 4.4 (19-H, q, $J$ = 7 cps), 5.35 (3-H).

*Anal.* Calcd for $C_{30}H_{49}O_3Br$: C, 67.00; H, 9.19. Found: C, 66.79; H, 8.89.

**3β-Acetoxy-19*R*-hydroxy-19a-methylcholest-5-ene (9b).**—A solution of 150 mg of **7** in 5 ml of acetic acid and 0.2 ml of water was treated with 900 mg of zinc dust at 50° under vigorous stirring. The usual work-up gave crude **9b** and recrystallization from methanol afforded a pure sample (120 mg): mp 93–94°; $[\alpha]^{25}D$ −30° (*c* 0.266, $CHCl_3$); ir (KBr) 3520, 1745, 1240, 1035, 910 $cm^{-1}$; nmr ($CDCl_3$) δ 1.35 (19a-$CH_3$, d, $J$ = 7.5 cps), 2.00 (3-OAc), 4.2 (19-H, q, $J$ = 7.5 cps), 4.5 (3-H), 5.6 (6-H).

*Anal.* Calcd for $C_{30}H_{50}O_3$: C, 78.55; H, 10.99. Found: C, 78.32; H, 10.85.

**3β-Acetoxy-19*S*-hydroxy-19a-methylcholest-5-ene (10b).**—Reduction of 60 mg of **8** in the same way followed by recrystallization from methanol gave 40 mg of pure **10b**: mp 89°; $[\alpha]^{25}D$ −37° (*c* 0.784, $CHCl_3$); ir (KBr) 3510, 1740, 1245, 1040, 910 $cm^{-1}$; nmr ($CDCl_3$) δ 1.36 (19a-$CH_3$, d, $J$ = 7 cps), 2.02 (3-OAc), 4.28 (19-H, q, $J$ = 7 cps), 4.6 (3-H), 5.6 (6-H).

*Anal.* Calcd for $C_{30}H_{50}O_3$: C, 78.55; H, 10.99. Found: C, 78.24; H, 10.88.

**3β-Acetoxy-19a-methyl-19-oxocholest-5-ene (11). Oxidation of 9b and 10b with Chromic Acid.**—A solution of 125 mg of **9b** in 10 ml of acetone was treated with 0.1 ml of 8 *N* chromic sulfuric acid solution at 0° for 30 min. Treatment in the usual way gave the 19-oxo compound **11**, and its ir spectrum was identical with that of an authentic sample synthesized by another route and a mixture melting point was not depressed. Oxidation of **10b** in the same way also gave the same 19-oxo compound: mp 127–128°; $[\alpha]^{25}D$ −115° (*c* 0.665, $CHCl_3$); ir (KBr); 1742, 1705, 1240 $cm^{-1}$; nmr ($CDCl_3$) δ 2.00 (3-OAc), 2.18 (10-acetyl), 5.8 (6-H).

*Anal.* Calcd for $C_{30}H_{48}O_3$: C, 78.89; H, 10.59. Found: C, 78.81; H, 10.25.

**Dehydration of 9b and 10b with Phosphorus Oxychloride.**—A solution of 20 mg of **9b** in 0.5 ml of pyridine was treated with 0.05 ml of phosphorous oxychloride at room temperature overnight. Recrystallization of the crude product (18 mg) gave the pure 19a-methylene compound **2**, which was identical with an authentic sample prepared by the Wittig reaction. Dehydration of **10b** yielded the same compound **2** as that of **9b**.

**Registry No.**—**2b**, 24183-24-2; **3**, 29751-52-8; **4**, 29751-53-9; **5**, 29751-54-0; **6**, 29751-55-1; **7**, 29875-95-4; **8**, 29875-96-5; **9b**, 29875-97-6; **10b**, 29751-56-2; **11**, 24177-47-7.

## Stereochemistry of the Isolongifolene Ketone Epimers

L. K. LALA

*International Flavors and Fragrances Research Laboratories, Union Beach, New Jersey 07735*

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Recently Dev[1] has reported that $BF_3$ etherate treatment of an isolongifolene epoxide[2] gives rise to a ketone to which he has assigned the stereochemistry as depicted in structure II. Epimerization of this ketone gives rise to a new ketone to which structure IV has been assigned. However, Eschinasi and coworkers[3] have assigned the opposite stereochemistry of these two ketones at the C-7 position. Described here is chemical evidence which supports Dev's assignment of the stereochemistry of these two epimeric ketones.

We have previously reported that acid treatment of isolongifolene epoxide I gave, among other products, rearranged alcohol III and ketone II.[4] Subsequent treatment of ketone II with base gave a more stable ketone IV. In order to establish the relative stereochemistry of these ketones at the C-7 position, the following approach was taken.

The lithium aluminum hydride reduction of ketone II gave alcohol V, which was refluxed with lead tetraacetate in benzene to give a cyclic ether VI in 60% yield. In contrast to this behavior, no detectable amount of cyclic ether was obtained by a similar lead tetraacetate treatment of alcohol VII which was obtained by the lithium aluminum hydride reduction of ketone IV (Scheme I).

When the stereochemistry of the hydroxyl group with regard to hydrogen at the C-7 position is cis, Dreiding models reveal that a cyclic ether cannot arise from VII; and, indeed, this was found to be the case. The possibility of the hydroxyl group having the opposite configuration is ruled out as Dreiding models indicate that a cyclic ether could be obtained from a compound with such structure. The assigned cis stereochemistry of the

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