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FREE-RADICAL OXIDATIVE TRANSFORMATIONS OF ANDROST-4-ENE-3β,9α,17β-TRIOL 3,17-DIACETATE

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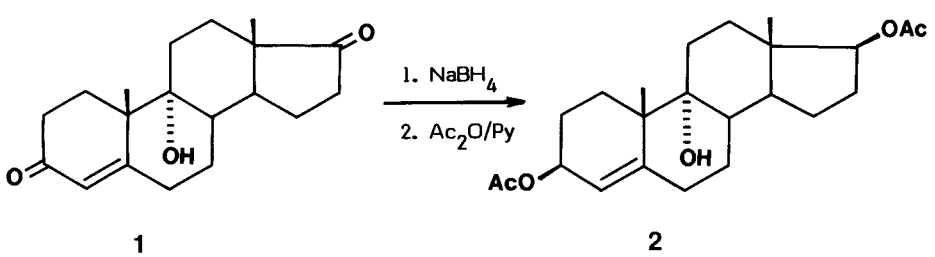
Abstract - The oxidation of androst-4-ene-3β,9α,17β-triol 3,17-diacetate (**2**) with lead tetraacetate resulted mainly in β-fragmentation of the C(9)-C(10) bond to give a mixture of 10α- and 10β-acetoxy-Δ^4-unsaturated 9,10-seco-steroidal ketones (**3a** and **3b**) as the minor components (in ~7% yield) and the rearranged 4β-acetoxy-$\Delta^{5(10)}$-unsaturated 9,10-seco-9-ketone (**4**) as the major product (in 61% yield). Unexpectedly, when the same substrate (**2**) was subjected to the mercuric oxide - iodine oxidation, it underwent predominantly α-epoxidation of the olefinic double bond to produce the 4α,5α-epoxy derivative (**5**) (in 58% yield).

It is well known that the oxidations in non-polar solvents of secondary and tertiary steroidal alcohols (in which the OH group is directly attached to the polycyclic system) with lead tetraacetate[1] or with hypoiodite-forming reagents (such as $Pb(OAc)_4$-I_2 and HgO-I_2)[2] can proceed along several different pathways, mainly involving: (i) intramolecular cyclization to tetrahydrofuran-type ethers, (ii) oxidative β-fragmentation to carbonyl-containing seco-steroidal products, and (iii) conversion to ketones and acetates. Which of these competing processes will prevail depends on the position of the hydroxy group and the structural features of the substrate.[3]

As part of our study concerning the structural factors which determine the course of the above oxidations, in this work oxidative transformations of the tertiary homoallylic steroidal alcohol, androst-4-ene-3β,9α,17β-triol 3,17-diacetate (**2**), induced by lead tetraacetate and mercuric oxide - iodine, respectively, have been investigated.

Compound (**2**) was prepared by sodium borohydride reduction of 9α-hydroxy-androst-4-ene-3,17-dione (**1**),[5] followed by acetylation of the newly formed hydroxy groups (Scheme 1).

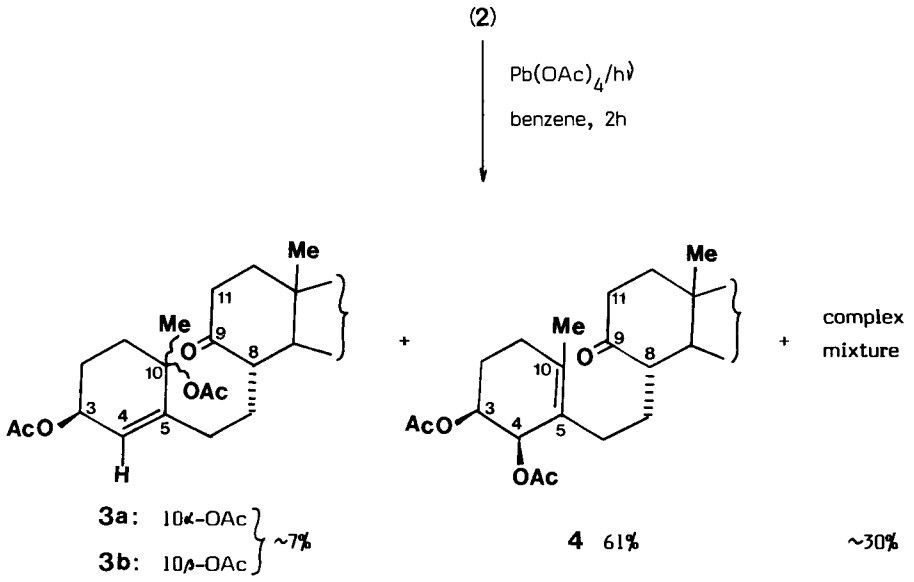


1 **2**

Scheme 1

RESULTS AND DISCUSSION

The lead tetraacetate oxidation of androst-4-ene-3β,9α,17β-triol 3,17-diacetate (**2**) was performed in benzene solution with 3 molar equivalents of $Pb(OAc)_4$, in the presence of $CaCO_3$, by irradiation with a high pressure mercury lamp TQ 150 Z2 at room temperature for 2 h (when practically all starting material was consumed). The separation of the reaction products by column chromatography afforded a mixture of epimeric 10α- and 10β-acetoxy-Δ^4-unsaturated 9,10-seco derivatives (**3a** and **3b**) as the minor components (in ~7% yield), and the 4β-acetoxy-$\Delta^{5(10)}$-unsaturated 9,10-seco-9-ketone (**4**) as the major product (in 61% yield) (Scheme 2), while the rest was a complex mixture which was not further investigated.

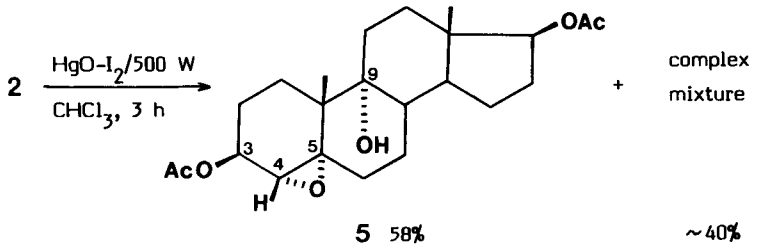


Scheme 2

Although the epimeric 10α- and 10β-acetoxy derivatives (**3a** and **3b**) could not be separated by the usual chromatographic methods, spectral data obtained for the mixture strongly indicated the proposed structures. Thus, they revealed the presence of a keto-carbonyl function (IR absorption at 1705 cm^{-1} and three ill-resolved multiplets between 2.2-2.5 ppm in the ^1H NMR spectrum assignable to the C(8) and C(11) protons α to the keto-carbonyl group) and an additional acetoxy group (parts of the two close singlets at 2.02 and 2.04 ppm in the ^1H NMR spectrum). On the other hand, elemental microanalysis ($C_{25}H_{36}O_7$) and spectral properties of the main product were consistent with structure (**4**). In this compound the configuration at C(4) was deduced from ^1H NMR data; namely, the coupling constant $J_{3\text{-H},\ 4\text{-H}}$ ~4.8 Hz for the H-C(4) doublet appearing at 5.38 ppm is compatible with a dihedral angle of about 50°,[6] thus implying the β-configuration of the acetoxy group.

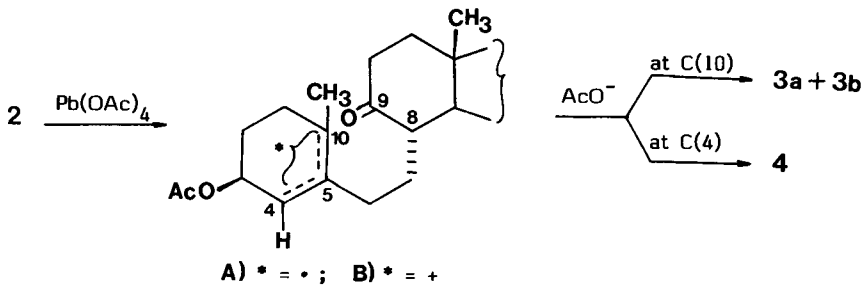
Oxidation of the same substrate (**2**) with mercuric oxide and iodine was carried out with a large excess of oxidant (about 5 molar equivalents) in chloroform solution, by irradiation with a 500 W lamp at room temperature for 3 h (i.e. until consumption of the substrate). Unexpectedly, with this oxidant the homoallylic 9α-alcohol (**2**) underwent mainly α-epoxidation of the olefinic double bond to afford the 4α,5α-epoxy derivative (**5**) (in 58% yield)[7] (Scheme 3). Similar results were obtained when the reaction was performed under nitrogen.

The structure (**5**) was deduced from elemental microanalysis ($C_{23}H_{34}O_6$) and spectral data (see Experimental), and confirmed by comparison with the compound obtained by epoxidation of androst-4--ene-3β,9α,17β-triol 3,17-diacetate (**2**) with m-chloroperbenzoic acid.



Scheme 3

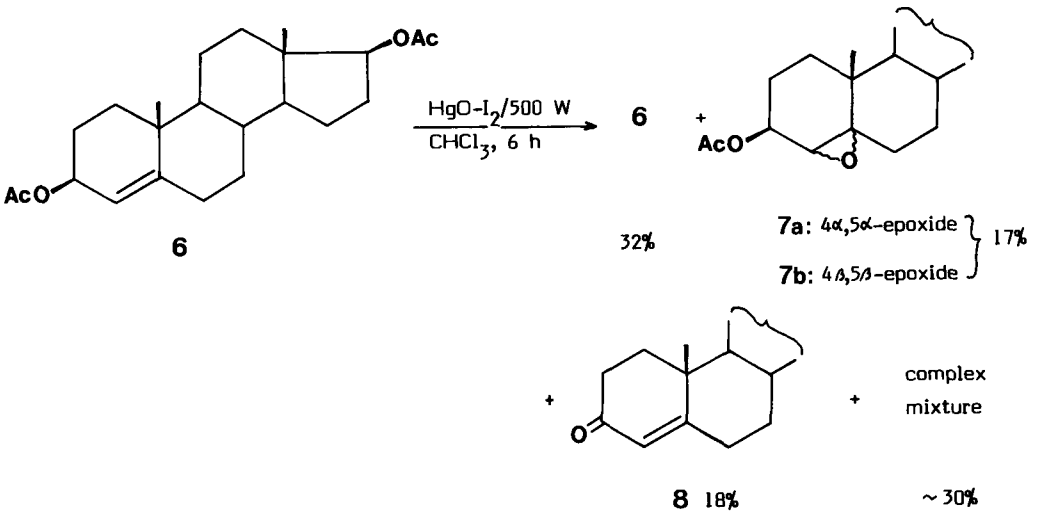
From these results it follows that the lead tetraacetate oxidation of alcohol (2) takes the expected β-fragmentation course. Namely, due to the absence of a sterically available δ-CH center for intramolecular cyclization, the alkoxy radical generated by homolysis of the Pb-O bond in the primarily formed lead(IV)-alkoxide undergoes preferential cleavage of the C(9)-C(10) bond to give the stable tertiary allylic carbon radical (A, Scheme 4). Upon one-electron oxidation, the resulting mesomeric carbocation (B) can undergo either non-stereospecific acetoxylation at C(10) to furnish the epimeric mixture (3a + 3b), or acetoxylation at the 4β position to produce the predominant seco-product (4).



Scheme 4

On the contrary, epoxidation of the olefinic double bond with the HgO-I_2 reagent has not been observed as yet. Therefore, in order to get more information concerning the way of oxygen addition to the Δ^4-double bond in alcohol (2) and particularly to explain the role of the 9α-OH group in the observed process (although, formally, this group does not participate in the reaction), a similar HgO-I_2 oxidation was performed with the corresponding 9α-desoxy analogue, i.e. androst-4-ene-3β,17β-diol diacetate (6).

From the results given in Scheme 5 it can be seen that the photochemically induced HgO-I_2 oxidation of the 9α-desoxy compound (6) takes place with decreased efficiency in comparison to the similar oxidation of the 9α-OH derivative (2), leaving after 6 h of irradiation 32% of the starting material unconsumed. Moreover, in the 9α-desoxy substrate (6) a non-stereospecific attack of oxygen at the Δ^4-double bond produces a ~1:1 mixture of 4α,5α- and 4β,5β-epoxides (7a + 7b) in not more than 17% yield, the only other isolable product being testosterone acetate (8) (formed in 18% yield).



Scheme 5

The observed difference in reactivity between the 9α-hydroxy derivative (2) and the 9α-desoxy compound (6) strongly indicates that the 9α-hydroxy group in (2) plays a crucial role in oxygen addition, affecting both the stereochemistry and the efficiency of epoxidation of the olefinic Δ^4-double bond in compound (2). It could suggest that the formation of a loose complex between the HgO-I_2 reagent (or some other reactive species derived from it) and the substrate molecule with participation of the 9α-OH group precedes the reaction.[8] However, on the basis of present evidence it is not possible to give a detailed mechanistic rationalization of the results obtained.

Further investigation is in progress in order to elucidate the mechanism of this unusual epoxidation process with the HgO-I_2 combination.

EXPERIMENTAL[9]

M. ps are uncorrected. IR spectra were measured on a Perkin-Elmer Spectrophotometer, Model 337. ^{1}H NMR spectra were recorded at 80 MHz on a Varian Spectrometer FT 80; solvent - $CDCl_3$, internal standard - TMS, room temp; chemical shifts are recorded in ppm as δ values. Mass spectra were obtained on a Finnigan MAT Mass Spectrometer Model 8230. Silica gel of 0.063-0.200 mm size was used for preparative column chromatography. Separation of products was monitored by thin-layer chromatography on silica gel G (Stahl) with benzene-ethyl acetate (7:3), detection being effected with 50% aqueous sulfuric acid. Light petroleum refers to the fraction boiling at 40-60° C.

Preparation of androst-4-ene-3β,9α,17β-triol 3,17-diacetate (2). - To a stirred solution of 9α-hydroxy--androst-4-ene-3,17-dione (1)[5] (5.00 g) in methanol (100 ml), maintained at room temperature, sodium borohydride (3 g) was added portionwise. The mixture was stirred for additional 30 min and then diluted with ice-water, acidified with 10% aqueous sulfuric acid and extracted with diethyl ether-ethyl acetate (1:1). The organic layer was washed with water, saturated aq. $NaHCO_3$ and water, dried over Na_2SO_4 and evaporated to dryness under reduced pressure, to give androst-4-ene-3β,9α,17β-triol (5.01 g, 99.5%). This product was acetylated with acetic anhydride (30 ml) in dry pyridine (80 ml) at room temperature for 16 h. The mixture was poured on crashed ice-water (about 100g) containing conc. HCl (10 ml), with vigorous stirring, the precipitate filtered off, thoroughly washed with water and air-dried, affording **androst-4-ene-3β,9α,17β-triol 3,17-diacetate** (2) (6.30 g, 98.0%), which was recrystallized from acetone (3.86 g, 60.1%), m.p. 159° C; $[\alpha]_D^{20}$ = -1.0° (c = 1.00, $CHCl_3$). IR(KBr): ν_{max} = 3510, 1740, 1720, 1250, 1235, 1020 cm^{-1}; ^{1}H NMR: δ = 0.82 (s, H_3C-18), 1.24 (s, H_3C-19), 2.01 and 2.04 (two s, AcO-3 and AcO-17), 4.65 (q, HC-17), 5.20 (m, HC-3), 5.48 (broad s, HC-4). MS: m/z = 330($M^{+\cdot}$ - 60), 312(330 - 18). (Found: C, 70.49; H, 9.03. Calc. for $C_{23}H_{34}O_5$ (390.52): C, 70.74; H, 8.78%).

Oxidation of androst-4-ene-3β,9α,17β-triol 3,17-diacetate (2) with lead tetraacetate. - To a solution of triol-diacetate (2) (2.00 g, 5.12 mmol) in anhydrous benzene (200 ml), placed in a quartz cylindric irradiation vessel, lead tetraacetate (7.47 g, 15.39 mmol + 10% excess) and dry calcium carbonate (2 g) were added. The vigorously stirred mixture was irradiated at room temperature with a high pressure mercury lamp (TQ 150 Z, Hanau), contained in a central water-cooled jacket. After 1 h the mixture was diluted with diethyl ether, filtered through a Celite mat and the inorganic salts thoroughly washed with diethyl ether. The combined filtrates were washed with water, saturated aq. $NaHCO_3$ and water, dried over Na_2SO_4 and evaporated to dryness under reduced pressure, to give a mixture (about 2.2 g) which was chromatographed on silica gel (60 g). Benzene-diethyl ether (98:2) eluted first a complex mixture (93 mg), which was not further investigated. The next benzene-diethyl ether (98:2) and (97:3) eluates contained a mixture of **3β,10α,17β-** and **3β,10β,17β-triacetoxy-9,10-seco-androst-4-en-9-one** (**3a** and **3b**) (158 mg, 6.9%), oil. IR (film): ν_{max} = 1730, 1704, 1240, 1020 cm^{-1}; ^1H NMR: δ = 1.10 (s, H_3C-18), 2.02 and 2.04 (parts of two s, AcO-10), 2.06 (two s, AcO-3 and AcO-17), 2.2 - 2.5 (three m, HC-8 and H_2C-11), 4.67 (t, HC-17), 5.25 (m, HC-3), 5.50 (broad d, HC-4).

Elution with benzene-diethyl ether (96:4) afforded **3β,4β,17β-triacetoxy-9,10-seco-androst-5(10)-en--9-one** (**4**) (1.39 g, 60.6%), which was recrystallized from acetone-light petroleum (1.05 g, 45.7%), m.p. 141° C; $|\alpha|_D^{20}$ = +59.6° (c = 0.50, $CHCl_3$). IR (KBr): ν_{max} = 1742, 1738, 1732, 1705, 1245, 1218, 1040, 1020 cm^{-1}; ^1H NMR: δ = 1.10 (s, H_3C-18), 1.76 (s, H_3C-19), 2.03, 2.06 and 2.09 (three s, AcO-3, AcO-4 and AcO-17), 2.2 - 2.5 (three m, HC-8 and H_2C-11), 4.69 (t, HC-17), 4.95 (d x d, J = 11.2, 4.8 Hz, HC-3), 5.38 (broad d, J = 4.8 Hz, HC-4). MS: m/z = 388($M^{+\cdot}$ - 60), 346 (388 - 42), 328 (388 - 60), 310(328 - 18), 286(346 - 60). (Found: C, 67.01; H, 8.28. Calc. for $C_{25}H_{36}O_7$ (448.56): C, 66.94; H, 8.09%).

Diethyl ether eluted a complex unresolvable mixture (509 mg).

Oxidation of androst-4-ene-3β,9α,17β-triol 3,17-diacetate (2) with mercuric oxide - iodine. - A mixture of the triol-diacetate (**2**) (2.16 g, 5.53 mmol), mercuric oxide (5.99 g, 27.65 mmol) and iodine (7.02 g, 27.65 mmol) in CCl_4 (400 ml) was stirred and irradiated for 3 h without heating with a 500 W tungsten lamp placed in a central water- and air-cooled jacket. It was then filtered, washed with 10% aq. $Na_2S_2O_3$, saturated aq. $NaHCO_3$ and water, dried over Na_2SO_4 and evaporated in vacuo to dryness. The residue (2.2 g) was recrystallized from acetone - methanol affording **4α,5-epoxy-5α-androstane-3β,9α,17β--triol 3,17-diacetate** (**5**) (1.296 g, 57.6%), m.p. 198° C (from acetone; 1.08 g, 48.1%); $|\alpha|_D^{20}$ = +31.1° (c = 1.00, $CHCl_3$). IR (KBr): ν_{max} = 3550, 1735, 1250, 1240, 1050, 900 cm^{-1}; ^1H NMR: δ = 0.82 (s, H_3C-18), 1.25 (s, H_3C-19), 2.03 and 2.08 (two s, AcO-3 and AcO-17), 2.75 (HO-C-9), 2.84 (s, HC-4), 4.65 (q, HC-17), 4.85 (m, HC-3). MS: m/z = 346($M^{+\cdot}$ - 60), 328(346 - 18), 310(328 - 18), 286(346 - 60). (Found: C, 67.86; H, 8.50. Calc. for $C_{23}H_{34}O_6$ (406.52): C, 67.95; H, 8.43%).

Epoxidation of androst-4-ene-3β,9α,17β-triol 3,17-diacetate (2). - To a stirred solution of the diol-diacetate (**2**) (100 mg) in dichloromethane (3 ml) cooled at 0° C, m-chloroperbenzoic acid (50 mg) in dichloromethane (2 ml) was added, and the mixture was stirred at 0 - 5° C for another 3 h. It was then diluted with ethyl acetate, the organic layer washed with 10% aq. $NaHSO_3$, water, saturated aq. $NaHCO_3$, water, dried over Na_2SO_4 and evaporated in vacuo to dryness to afford **4α,5-epoxy-5α-androstane-3β,9α,17β-triol 3,17-diacetate** (**5**) (100 mg, 96.1%), m.p. 198° C (from acetone) (undepressed by admixture with the sample obtained in the HgO-I_2 oxidation of **2**). IR and ^1H NMR spectra were identical to those of **5** obtained as described above.

Oxidation of androst-4-ene-3β,17β-diol diacetate (6) with mercuric oxide - iodine. - A mixture of the diol-diacetate (**6**) (1.00 g, 2.67 mmol), mercuric oxide (2.89 g, 13.35 mmol) and iodine (3.39 g, 13.35 mmol) in CCl_4 (400 ml) was stirred and irradiated for 6 h as described above. The usual work-up afforded an oily mixture (1.06 g) which was separated by column chromatography on silica gel (40 g), with light petroleum-ethyl acetate (85:15). The first eluates gave unchanged starting diol-diacetate (**6**) (320 mg, 32.0%), m.p. 107° C (from acetone-light petroleum) (lit.[6] m.p. 105-107° C). IR and ^1H NMR spectra were identical to those recorded on an authentic sample.

Further eluates contained **4α,5-epoxy-5α-androstane-3β,17β-diol diacetate** (**7a**) (72 mg, 6.9%), m.p. 176° C (from methanol; 54 mg, 5.2%) (lit.[10] m.p. 174° C). IR (KBr): ν_{max} = 1738, 1730, 1247,

1235, 1047 cm^{-1}; ^1H NMR: δ = 0.81 (s, H_3C-18), 1.12 (s, H_3C-19), 2.05 and 2.10 (two s, AcO-3 and AcO-17), 2.90 (s, HC-4), 4.60 (t, HC-17), 4.95 (m, HC-3).

The next fractions gave first a mixture of 4α,5α- and 4β,5β-epoxides (**7a** and **7b**) (58 mg, 5.6%) in a ratio of ~2:3 (estimated from the intensities of the HC-4 signals in the ^1H NMR spectrum obtained for this mixture), and then **4β,5-epoxy-5β-androstane-3β,17β-diol diacetate** (**7b**) (51 mg, 4.9%), m.p. 92° C (from acetone; 42 mg, 4.0%), (lit.[11] m.p. 93-95° C). IR (KBr): ν_{max} = 1738, 1730, 1240, 1040, 1020 cm^{-1}; ^1H NMR: δ = 0.81 (s, H_3C-18), 1.05 (s, H_3C-19), 2.05 and 2.12 (AcO-3 and AcO-17), 3.18 (d, HC-4), 4.60 (t, HC-17), 5.15 (m, HC-3).

Further fractions afforded **testosterone acetate** (**8**) (160 mg, 18.1%), m.p. 138° C (from acetone--methanol; 121 mg, 13.7%) (lit.[12] m.p. 137° C). IR (KBr): ν_{max} = 1730, 1670, 1245, 1040, 1020 cm^{-1}; ^1H NMR: δ = 0.83 (s, H_3C-18), 1.20 (s, H_3C-19), 2.05 (s, AcO-17), 4.62 (q, HC-17), 5.73 (s, HC-4).

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7. The yield refers to the crystalline product obtained by direct recrystallization of the crude reaction mixture. According to TLC, an additional amount of the product (**5**) was present in the mother liquor.
8. Since the HgO-I_2 oxidation of (**2**) performed under nitrogen gave the same α-epoxide (**5**) as the main reaction product and in comparable yield, it was concluded that the epoxide oxygen originates from the oxidant.
9. We wish to thank Dr. R. Tasovac (Microanalytical Laboratory, Faculty of Science, Belgrade) for carrying out elemental microanalyses. IR, ^1H NMR and mass spectra were recorded in the Laboratories for Instrumental Analysis, Faculty of Science, Belgrade (direction Prof. D. Jeremić).
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