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UNEXPECTED 7-METHYLATION OF OXINDOLES

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Abstract − A unique, regioselective 7-methylation reaction has been discovered during the reductive 3-alkylation of isatin with *i*-BuOH at 230 °C, in the presence of Raney nickel, under hydrogen atmosphere. Based on this observation, a synthetic method has been elaborated for the preparation of 3-alkyl-7-methyloxindoles.

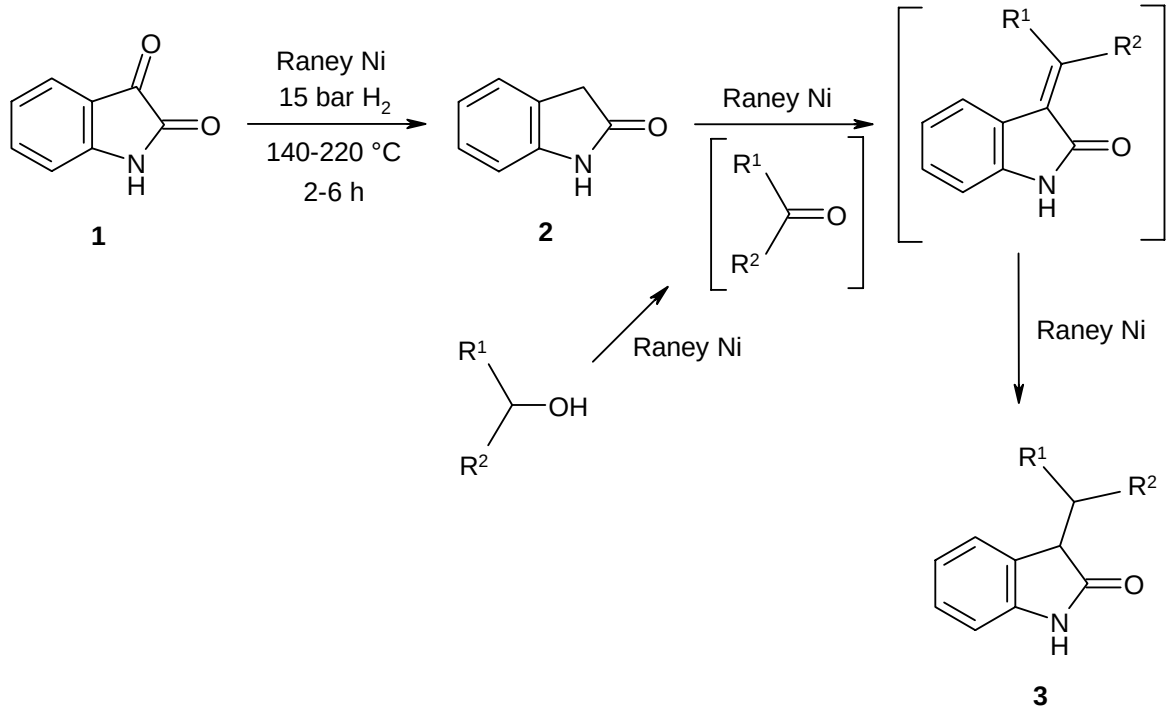
INTRODUCTION

Owing to the outstanding biological importance of oxindoles, which is demonstrated by marketed drugs[1a-b] and new drug candidates[1c-f] containing this skeleton, selective substitution reactions of oxindoles deserve special attention. Recently, we have disclosed the expeditious synthesis of 3-alkyl- and 3-(ω-hydroxyalkyl)oxindoles (**3**) by treatment of oxindole (**2**) with alcohols and diols in the presence of Raney nickel in an autoclave.[2] The complex reaction sequence (**2** → **3**) is shown in Scheme 1. Afterwards, the reaction has been extended to the 3-alkylation and 3-(ω-hydroxy)alkylation of isatin (**1**) with alcohols and diols in the presence of Raney nickel (**1** → **3**).[3] However, the one-pot reaction had to be carried out under hydrogen atmosphere in this latter case, in order that the introductory step of the reaction sequence, *i.e.* the reduction of isatin (**1**) to oxindole (**2**), is accelerated.[4]

RESULTS AND DISCUSSION

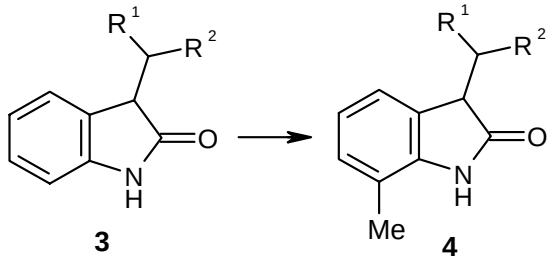
The alkylation of isatin (**1**) with 2-methyl-1-propanol (*i*-BuOH) in the presence of Raney nickel (200 °C, 3 h) afforded the expected 3-isobutyloxindole (**3a**, Scheme 2) in 89 % yield (Table 1, Entry 1).[3] In the course of the optimization of this reaction we observed that after a longer reaction time (200 °C, 6 h) the crude product mixture contained 5 % of a by-product, 3-isobutyl-7-methyloxindole (**4a**, Scheme 2). When treating isatin (**1**) with 2-methyl-1-propanol at more elevated temperatures (230 °C) for 8 h, in the presence of Raney nickel, the 7-methylated product (**4a**) could be isolated as the sole product in 64 %

yield after recrystallization (Entry 2). The structure of the 7-methylated compound (**4a**) was confirmed by NMR spectral experiments. Similarly, heating of oxindole (**2**) in 2-methyl-1-propanol with Raney nickel for 8 h at 230 ºC resulted in the formation of 3-isobutyl-7-methyloxindole (**4a**) in 59 % yield (Entry 3).



Scheme 1

3, 4	R^1	R^2
a	*i*-Pr	H
b	Me	H
c	Et	H
d	Pr	H



Scheme 2

To elucidate all details of the successive introduction of the isobutyl group in the 3-position and then the methyl group in the 7-position would require more scrutiny. Since the elaboration of 7-methylation of 3-alkyloxindoles has proved to be a worthwhile synthetic object itself, we preferred to focus our efforts on this problem for the moment. Drug candidates exhibiting an oxindole skeleton with a methyl group,[5] or carbon-based functional group[6] at the 7-position, or containing an additional ring between the 7-carbon and the oxindole nitrogen atom[7] indicate the synthetic usefulness of this method.

Table 1. Conditions and yields of 7-methylation reactions

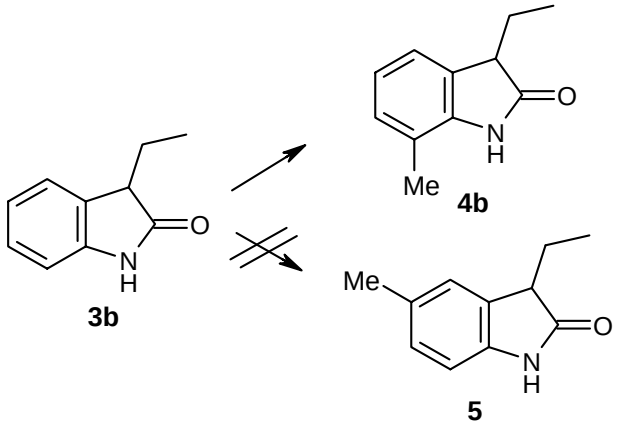
Entry	Starting material	Reaction conditions	Temperature (°C)	Reaction time (h)	Product	Prepared yield (%)
1	**1**	Raney Ni, 15 bar H_2, *i*-BuOH	200	3	**3a**	89[a]
2	**1**	Raney Ni, 15 bar H_2, *i*-BuOH	230	6	**4a**	64[b]
3	**2**	Raney Ni, *i*-BuOH	230	8	**4a**	59[b]
4	**3b**	Raney Ni, *i*-BuOH	220	9	**4b**	57[c]
5	**3b**	Raney Ni, BuOH	230	6	**4b**	49[c]
6	**3b**	Raney Ni, 10 eq. *i*-BuOH, diglyme	230	5	**4b**	65[c]
7	**3b**	Raney Ni, 10 eq. PrOH, diglyme	230	5	**4b**	58[c]
8	**3b**	Raney Ni, diglyme	230	8	**4b**	60[c,d]
9	**3c**	Raney Ni, diglyme	230	8	**4c**	55[d,e]
10	**3d**	Raney Ni, diglyme	230	8	**4d**	58[d,e]

[a] No recrystallization needed. [b] Recrystallized from a mixture of water and ethanol. [c] Recrystallized from a mixture of hexane and ethyl acetate. [d] Prepared according to the general procedure (see EXPERIMENTAL). [e] Recrystallized from hexane.

3-Ethyloxindole (**3b**) has been chosen as the starting material for the detailed study of the 7-methylation reaction step. The reaction of 3-ethyloxindole (**3b**) with 2-methyl-1-propanol at 220 °C for 9 h in the presence of Raney nickel afforded 3-ethyl-7-methyloxindole (**4b**) in 57 % yield (Table 1, Entry 4). The structure of compound (**4b**) was also confirmed by single crystal X-Ray diffraction.[8] A similar result was obtained using 1-butanol (Entry 5) instead of 2-methyl-1-propanol. In order to decrease pressure in the autoclave, we decided to use bis(2-methoxyethyl) ether (diglyme) as solvent. The reaction of compound (**3b**) with 4 equiv. of 2-methyl-1-propanol or 1-propanol in diglyme gave the 7-methylated product (**4b**) in 65 % and 58 % yields, respectively (Entries 6 and 7).

The formation of the 7-methylated product with various alcohols can be rationalized by supposing the presence of a common C-1 reagent in the reaction mixtures, most probably formaldehyde. It is known from the literature that various alcohols undergo cracking reactions on metal surfaces at elevated temperatures, resulting in formaldehyde, among other oxidized products.[9] We inquired whether diglyme itself can also serve as the source of the formaldehyde under the applied reaction conditions. Indeed, heating of compound (**3b**) in diglyme at 230 °C for 8 h in the presence of Raney nickel gave 7-methylated product (**4b**) in 60 % yield (Table 1, Entry 8). These are the best reaction conditions for the new 7-methylation reaction of 3-alkyloxindoles so far. The use of diglyme instead of alcohols is advantageous because of the decreased pressure in the autoclave. Using this procedure, 3-propyl- (**3c**) and 3-butyloxindoles (**3d**) have also been 7-methylated to compounds (**4c** and **4d**) (Entries 9 and 10).

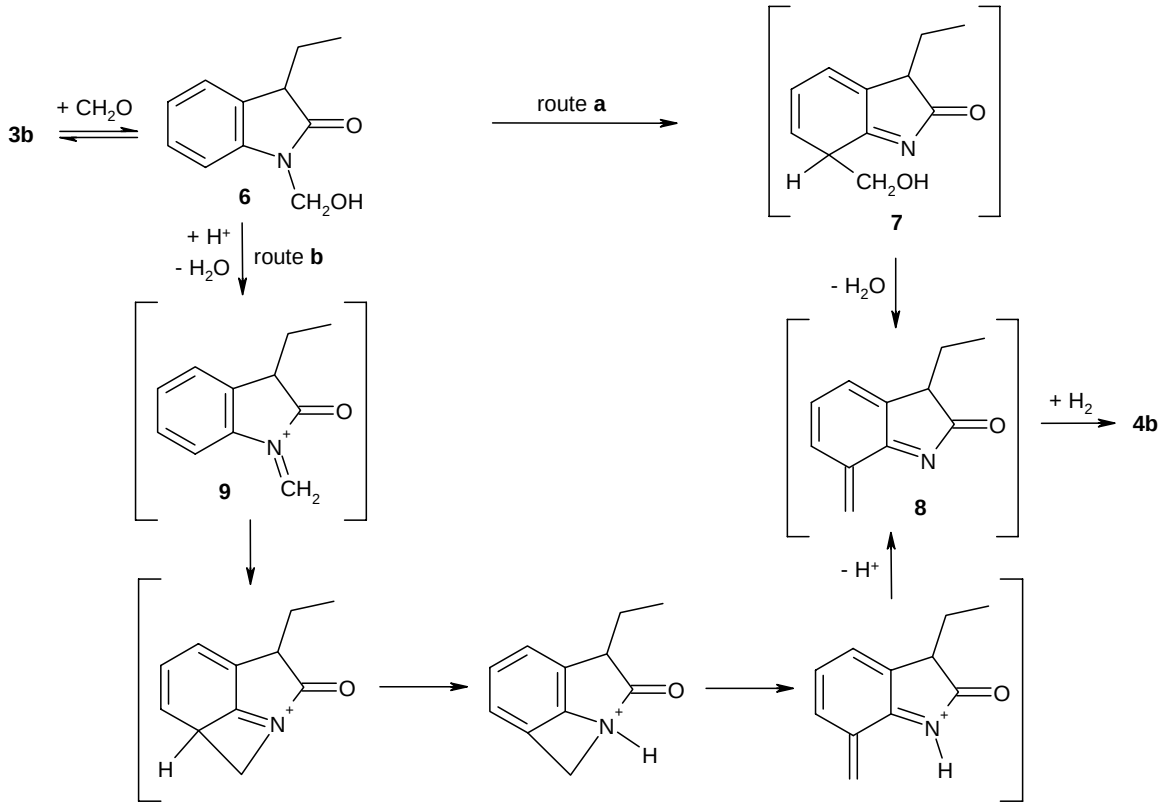
In order to get some insight into the mechanism of the 7-methylation reaction, further studies have been conducted. (i) Support in favour of the role of formaldehyde as methylating agent was obtained by treating 3-ethyloxindole (**3b**) with 10 equiv. of paraformaldehyde in inert solvents. In decalin and xylene (Raney Ni, 220 °C, 5 h), the product mixture contained 37 % and 40 % of 3-ethyl-7-methyloxindole (**4b**), respectively, in addition to the starting material (**3b**). (ii) An authentic sample of 3-ethyl-5-methyloxindole (**5**, Scheme 3) has been synthesised by the 3-ethylation of 5-methylisatin.[3] Crude product mixtures obtained in the 7-methylation reactions have been analyzed by ^{1}H NMR spectra and GC, however, the formation of the 5-methylated product (**5**) could not be detected, which demonstrates the regioselectivity of the methylation reaction.



Scheme 3

The regioselectivity observed suggests the intermediacy of *N*-hydroxymethyl derivative (**6,** Scheme 4).[10] Several pathways can be proposed for the transformation of the *N*-hydroxymethyl derivative (**6**) to the 7-methylated product (**4b**). An obvious possibility on the analogy of Fries rearrangement[11a] is the electrophilic rearrangement of derivative (**6**) to the 7-hydroxymethyl intermediate (**7**, route **a**), which undergoes irreversible thermal dehydration, and **8** can then be easily reduced[12] to the 7-methylated compound (**4b**) under the applied reaction conditions.

Related electrophilic rearrangements[11b] of *N*-nitro-[11c] and *N*-nitrosoanilines[11d] are reported in the literature. Cobalt chloride catalyzed transformation of *N*-alkylanilines to *o*- and *p*-alkylanilines[11e] and uncatalyzed rearrangement of benzyl phenyl ethers to *o*- and *p*-benzylphenols[13] are also precedented. The predominance of the *ortho* substituted products (i.e. [1,3] shift) was observed in the majority of these transformations. It is also known that under certain conditions phenols can be selectively hydroxymethylated[14] at the 2-position with formaldehyde. Other authors disclosed that aminomethylation of 2-methoxyphenol also takes place adjacent to the hydroxy group.[15]



Scheme 4

Another possible reaction pathway, which also explains the regioselectivity of the 7-methylation reaction, can be obtained as a sequence of electrocyclic reactions (Scheme 4, route **b**). The azabutadiene-type cationic species (**9**) can be derived from the *N*-hydroxymethyl derivative (**6**) by acid-catalyzed water elimination.[16] The final step of this pathway is the reduction of azabutadiene (**8**) to 3-ethyl-7-methyloxidole (**4b**). Transformations similar to the individual steps of the proposed reaction sequence are mentioned in the literature.[17-19] Finally, it is also of interest that the common intermediate of both postulated pathways (**8**), as a latent Michael acceptor, might be under different reaction conditions an open door to further functionalization.

CONCLUSION

An unexpected regioselective 7-methylation reaction has been observed during the 3-alkylation of isatin and oxindole with 2-methyl-1-propanol in the presence of Raney nickel. It is interesting to note the remarkably wide variety of elementary reaction steps taking place during this one-pot reaction. To the best of our knowledge, such a direct substitution of oxindoles and isatins (unsubstituted in the benzene ring) at the 7-position is unprecedented. Based on the above observation, a regioselective process has

been elaborated for the 7-methylation of 3-alkyloxindoles. Alternative syntheses of 3,7-disubstituted oxindoles in the literature involve complicated multistep procedures.

EXPERIMENTAL

All melting points were determined on a Büchi 535 capillary melting point apparatus and are uncorrected. IR spectra were obtained on a Bruker IFS-113v FT spectrometer in KBr pellets. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ on a Varian Unity Inova 500 spectrophotometer (500 and 125 MHz for ^{1}H and ^{13}C NMR spectra, respectively) using TMS as internal standard. Chemical shifts (δ) and coupling constants (J) are given in ppm and in Hz, respectively. Elemental analyses were performed on a Perkin-Elmer 2400 analyzer. The 7-methylation reactions were carried out in autoclaves (volume: 70 or 250 mL, depending on the amount of reagents used), which were equipped with a temperature controller, a manometer (60 bar), a valve for gas inlet and a magnetic stirrer. All reactions were followed by TLC on silica gel 60 F_{254} (eluent: hexane-ethyl acetate 1:1). Fluka's Raney nickel catalyst in water was used in the reactions.

3-Isobutyl-7-methyl-1,3-dihydro-2*H*-indol-2-one (4a)

Method A: Isatin (**1**, 7.35 g, 50 mmol), 2-methyl-1-propanol (110 mL) and Raney nickel (2.0 g, *ca.* 34 mmol) was stirred in an autoclave under hydrogen atmosphere (15 bar) for 6 h at 230 ºC. The mixture was then stirred with charcoal, filtered and the solvent was evaporated. The solid residue was recrystallized from a mixture of water and ethanol to give 6.50 g (64 %) of the title compound as colourless crystals.

Method B: Oxindole (**2**, 1.33 g, 10 mmol), 2-methyl-1-propanol (20 mL) and Raney nickel (1.0 g, *ca.* 17 mmol) was stirred in an autoclave for 8 h at 230 ºC. The mixture was then stirred with charcoal, filtered and the solvent was evaporated. The solid residue was recrystallized from a mixture of water and ethanol to give 1.19 g (59 %) of the title compound as colourless crystals.

mp 115-117 °C. IR (KBr): 3179, 1701 (C=O) cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.96 (d, $^{3}J_{H,H}$ = 6.6 Hz, 3 H, CHC*H*$_3$), 1.01 (d, $^{3}J_{H,H}$ = 6.6 Hz, 3 H, CHC*H*$_3$), 1.68-1.72 (m, 1 H, C*H*H), 1.84-1.89 (m, 1 H, CH*H*), 2.03-2.06 (m, 1 H, C*H*CH$_3$), 2.32 (s, 3 H, ArCH$_3$), 3.49 [t, $^{3}J_{H,H}$ = 7.2 Hz, 1 H, C(3)-H], 6.93 [t, $^{3}J_{H,H}$ = 7.5 Hz, 1 H, C(5)-H], 7.03 [d, $^{3}J_{H,H}$ = 7.8 Hz, 1 H, C(6)-H], 7.06 [d, $^{3}J_{H,H}$ = 7.4 Hz, 1 H, C(4)-H], 9.80 (br s, 1 H, NH) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 16.5 (ArCH$_3$), 22.1 (CH*C*H$_3$), 23.0 (CH*C*H$_3$), 25.2 (*C*HCH$_3$), 40.0 (CH$_2$), 44.7 [C(3)], 119.4 [C(7)], 121.6 [C(4)], 121.9 [C(5)], 129.0 [C(6)], 129.9 [C(3a)], 140.5 [C(7a)], 181.9 [C(2)] ppm. Anal. Calcd for $C_{13}H_{17}NO$: C, 76.81; H, 8.43; N, 6.89. Found: C, 76.69; H, 8.45; N, 6.82.

7-Methylation of 3-Alkyloxindoles, General Procedure

The appropriate 3-alkyloxindole (**3**, 5 mmol), diglyme (20 mL) and Raney nickel (0.5 g, *ca.* 8 mmol) was stirred in an autoclave at 230 ºC. The mixture was stirred with charcoal, filtered and the solvent was evaporated. The solid residue was recrystallized to give the title compounds as colourless crystals. For reaction times, recrystallization solvents and yields, see Table 1. Spectroscopic data for **4b-d** prepared according to the general procedure are given below.

3-Ethyl-7-methyl-1,3-dihydro-2*H*-indol-2-one (4b): mp, IR, ^{1}H and ^{13}C NMR spectra are in agreement with published data.[3] X-Ray crystallographic data of **4b** can be obtained from Cambridge Crystallographic Data Centre.[8]

7-Methyl-3-propyl-1,3-dihydro-2*H*-indol-2-one (4c): Yield: 55 %; mp 121-122 °C (hexane). IR (KBr): 3155, 2957, 1700 (C=O) cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.93 (t, $^{3}J_{H,H}$ = 7.3 Hz, 3 H, CH_2CH_3), 1.35-1.51 (m, 2 H, CH_2CH_3), 1.90-1.97 (m, 2 H $CHCH_2$), 2.32 (s, 3 H, $ArCH_3$), 3.48 [t, $^{3}J_{H,H}$ = 6.0 Hz, 1 H, C(3)-H], 6.94 [t, $^{3}J_{H,H}$ = 7.5 Hz, 1 H, C(5)-H], 7.03 [d, $^{3}J_{H,H}$ = 7.7 Hz, 1 H, C(6)-H], 7.07 [d, $^{3}J_{H,H}$ = 6.7 Hz, 1 H, C(4)-H], 9.61 (br s, 1 H, NH) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.0 (CH_2CH_3), 16.5 ($ArCH_3$), 19.2 (CH_2CH_3), 32.8 ($CHCH_2$), 46.5 [C(3)], 119.2 [C(7)], 121.4 [C(4)], 122.0 [C(5)], 129.0 [C(6)], 129.6 [C(3a)], 140.6 [C(7a)], 181.5 [C(2)] ppm. Anal. Calcd for $C_{12}H_{15}NO$: C, 76.16; H, 7.99; N, 7.40. Found: C, 75.96; H, 8.21; N, 7.24.

3-Butyl-7-methyl-1,3-dihydro-2*H*-indol-2-one (4d): Yield: 58 %; mp 104-105 °C (hexane). IR (KBr): 2958, 1701 (C=O) cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.87 (t, $^{3}J_{H,H}$ = 6.8 Hz, 3 H, CH_2CH_3), 1.32-1.42 (m, 4 H, 2 × CH_2), 1.89-1.99 (m, 2 H, $CHCH_2$), 2.32 (s, 3 H, $ArCH_3$), 3.48 [t, $^{3}J_{H,H}$ = 5.8 Hz, 1 H, C(3)-H], 6.94 [t, $^{3}J_{H,H}$ = 7.5 Hz, 1 H, C(5)-H], 7.03 [d, $^{3}J_{H,H}$ = 7.3 Hz, 1 H, C(6)-H], 7.07 [d, $^{3}J_{H,H}$ = 7.3 Hz, 1 H, C(4)-H], 9.70 (br s, 1 H, NH) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 13.8 ($ArCH_3$), 16.5 (CH_2CH_3), 22.7 (CH_2CH_3), 27.8 ($CHCH_2CH_2$), 30.4 ($CHCH_2$), 46.5 [C(3)], 119.2 [C(7)], 121.4 [C(4)], 122.0 [C(5)], 129.0 [C(6)], 129.5 [C(3a)], 140.7 [C(7a)], 181.5 [C(2)] ppm. Anal. Calcd for $C_{13}H_{17}NO$: C, 76.81; H, 8.43; N, 6.89. Found: C, 76.54; H, 8.49; N, 6.95.

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