tion of the corresponding ethane with nitrobenzene. A small sample was dried for 3 days at 110° and analyzed before moisture could be regained.

Anal. Calcd. for $C_{30}H_{20}N_8$: C, 73.2; H, 4.10; N, 22.8. Found: C, 73.6, 73.7; H, 3.70, 3.80; N, 22.3, 22.5.

Chlorination of tetra-2-benzimidazolylethylene with sulfuryl chloride. Fifty g. (0.098 mole) of tetra-2-benzimidazolylethylene was finely ground and suspended in 650 ml. of trichlorobenzene. One g. of iodine was added, the mixture was heated to 150° and maintained at 150–155° while 200 ml. (2.47 moles) of sulfuryl chloride was added over 4 hr. The mixture was held at 155° for an additional 30 min., cooled, and poured into 2 l. of water. The product was filtered, washed with alcohol, and dried. The yield of crude material was 85 g. This was ground and extracted for 7 hr. in a Soxhlet extractor with benzene. The residue was then extracted twice with 500-ml. portions of nitrobenzene at 90°, washed free of nitrobenzene with alcohol, and dried. The yield was 59.5 g. (69.3%) of bright orange solid.

Anal. Found: C, 40.1, 40.6; H, 1.60, 1.70; N, 12.7, 12.7; Cl, 42.3, 42.4.

This corresponds to a mixture of monohydrates with an average content of 10.6 chlorine atoms.

This product can be further chlorinated to a chlorine content of 53.4% by autoclaving at 150° for 10 hr. with excess sulfuryl chloride.

Bromination of tetra-2-benzimidazolylethylene. A mixture of 10.5 g. (0.065 mole) of bromine and 10.5 g. (0.077 mole) of sulfuryl chloride was slowly added to a suspension of 4 g. (0.008 mole) of tetra-2-benzimidazolylethylene in 100 ml. of trichlorobenzene. The temperature rose to 31°. The mixture was heated to 80°, held one hour, then heated to 130° and held one hour. After cooling, the mixture was filtered and the filter cake washed with alcohol. The dry product weighed 8 g., was insoluble in nitrobenzene, and contained 70.2% bromine, corresponding to 14 bromine atoms. No chlorine was found.

Sulfonation of tetra-2-benzimidazolylethylene. A mixture of 93 ml. of 100% sulfuric acid and 8 ml. of 65% oleum was cooled to 19°. Ten g. (0.203 mole) of finely ground tetra-2-benzimidazolylethylene was added slowly at 20–25°. The mixture was heated at 70° until a drop was just soluble in dilute sodium hydroxide (45 min.). The solution was then cooled and poured slowly into 200 ml. of water. Fifty ml. of 30% sodium hydroxide was added and, after filtration to remove any insoluble material, the filtrate was mixed with 150 ml. of 30% sodium hydroxide. After cooling again to room temperature, the product was filtered, redissolved in 400 ml. of water, and reprecipitated with 7 g. of potassium chloride. The product weighed 35 g. when dry.

Anal. Found: N, 4.63, 4.39; Organic S, 2.04, 2.04. This corresponds to a mixture of sulfonated derivatives averaging 1.5 sulfonic acid groups admixed with sodium and potassium salts.

This product dyes wool from a weakly acidic dyebath in red-yellow shades.

WILMINGTON, DEL.

[CONTRIBUTION FROM THE RESEARCH DIVISION, BRISTOL LABORATORIES, INC.]

Dialkylaminoalkyl Ethers of Some 2,6-Dialkylphenols

WILLIAM B. WHEATLEY AND CHARLES T. HOLDREGE

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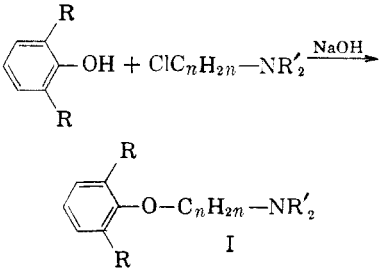
A number of dialkylaminoalkyl ethers of some 2,6-dialkylphenols, particularly 2,6-diisopropylphenol, have been prepared in good yields by the Williamson synthesis using dialkylaminoalkyl chlorides. Attempts to prepare other ethers, *e.g.*, β-hydroxyethyl and β-haloethyl ethers, were almost completely unsuccessful, probably because of steric hindrance.

2,6-Dialkylphenols have recently become available on a scale such that their use as intermediates is now feasible.[1] Because of the fact that certain basic ethers of substituted phenols have shown utility as therapeutic agents, we set out to prepare some dialkylaminoalkyl ethers of these 2,6-dialkylphenols. This particular type of compound has received little attention, due in part to the previous accessibility of only the simpler dialkylphenols such as 2,6-xylenol, and of the 2,4,6-trialkylphenols.

The majority of compounds to be described are ethers of 2,6-diisopropylphenol (DIP), and most of the discussion which follows refers to this phenol. The presence of two branched ortho substituents causes this phenol to be cryptophenolic, being insoluble in aqueous alkali, but soluble in Claisen's alkali. It does form a sodium salt quite readily on treatment in boiling toluene with either sodium hydride or sodium hydroxide.[2] This sodium 2,6-diisopropylphenoxide is not typical, however, since it participates in the Williamson ether synthesis in widely varying degrees, depending on the nature of the halide used as the other reactant.



I

With dialkylaminoalkyl chlorides, the desired basic ethers (I) were obtained in quite acceptable yields. With other halides, the results were often negative. All attempts to prepare β-hydroxyethyl 2,6-diisopropyl ether were unsuccessful; neither ethylene chlorohydrin nor ethylene carbonate[3] could be caused to react with DIP under a variety

(1) A. J. Kolka, J. P. Napolitano, A. H. Filbey, and G. G. Ecke, *J. Org. Chem.*, **22**, 642 (1957).

(2) T. H. Coffield, A. H. Filbey, G. G. Ecke, and A. J. Kolka, *J. Am. Chem. Soc.*, **79**, 5019 (1957).

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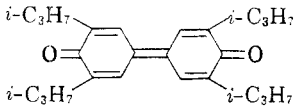
of conditions. Ethyl chloroacetate also failed to react with the sodium salt of DIP.

An alternate synthesis of basic ethers would involve the preparation of an ω-haloalkyl ether and subsequent reaction of this halide with an amine. The only successful preparation was that of the β-chloroethyl ether, from DIP and β-chloroethyl *p*-toluenesulfonate, although in only 26% yield. Because of the low yield, this approach was not investigated further. Neither ethylene dibromide or ethylene chlorobromide reacted with DIP in the presence of sodium hydroxide.

The facile conversion of DIP to its sodium salt in nonaqueous medium and the inconsistent reactivity of this sodium salt toward alkylating agents pose an interesting question. The answer probably includes both polar and steric factors. The fact that DIP is more difficult to etherify than other phenols not having large alkyl groups in the 2 and 6 positions suggests steric hindrance. A polar effect is indicated in that the only really good reactions observed are those with basic alkyl chlorides, in which cyclic quaternary imonium ions are known to be involved.[4]

In order to ascertain the effect of groups in the 4-position, a few 4-substituted-2,6-dialkylphenols were prepared. The 4-bromo- and 4-chloro-2,6-diisopropylphenol were prepared easily and in high yield by halogenation with bromine and sulfuryl chloride, respectively. Friedel-Crafts reactions of DIP with benzyl alcohol and phenylmethylcarbinol yielded the 4-benzyl- and 4-α-methylbenzyl-2,6-diisopropylphenols. An attempted nitration of DIP apparently resulted in oxidation to a diphenoquinone (II), a reaction which has been recorded for analagous 2,6-dialkyl-phenols with a variety of oxidizing agents.[5]



II

A few basic ethers of phenols having *t*-butyl groups in the ortho positions were made, using 2-methyl-6-*t*-butylphenol, 2,6-di-*t*-butylphenol (DTB), and 2,6-di-*t*-butyl-p-cresol (DBPC). Under the experimental conditions used, we could detect no noticeable difference in reactivity. This is interesting in relation to the work of Stillson, Sawyer, and Hunt,[6] who studied the properties of hindered phenols containing ortho *t*-alkyl groups. These workers found that DBPC and 2,4,6-tri-*t*-butylphenol were insoluble in both aqueous and alcoholic alkali, and failed to form sodium salts on refluxing with sodium in ether or petroleum ether. We likewise found DTB to be insoluble in Claisen's alkali, but it must form a sodium salt in the course of the conversion to the basic ether. As with DIP, DTB failed to react with ethylene carbonate.

A recent paper by Coffield, Filbey, Ecke, and Kolka[2] discusses further reactions of these 2,6-dialkylphenols.

EXPERIMENTAL[7]

Basic ethers. In a typical experiment, 0.3 mole of the 2,6-dialkylphenol, 0.4 mole of the dialkylaminoalkyl chloride hydrochloride, and 0.8 mole of flake sodium hydroxide were stirred together for 24 hr. in refluxing toluene. After treatment of the cooled reaction mixture with water to dissolve inorganic material, the toluene solution was extracted three times with dilute hydrochloric acid. Basification of the acid extracts and ether extraction, followed by distillation of the dried ether solution yielded the basic ether I. As noted in Table I, most of these were converted to crystalline acid addition salts for ease in pharmacological evaluation.

In working up a significant number of experiments, it was found that extraction with dilute acid failed to transfer the basic ether from the toluene to the aqueous phase. If this occurred, the toluene layer was concentrated to an oil under reduced pressure. This residual oil was taken up in Skellysolve B and extracted with acid. Basification and ether extraction of the acid aqueous extracts then yielded the basic ether as described above. This modification is noted in Table I.

2,6-Diethylphenol. Diazotization and hydrolysis of 2,6-diethylaniline afforded 2,6-diethylphenol in 88% yield, b.p. 100–105° at 8 mm. The concomitant hydrolysis and steam distillation as described by Lambooy[8] proved highly effective in this instance.

4-Chloro-2,6-diisopropylphenol. A total of 2.5 moles of sulfuryl chloride was added to 2.0 moles of 2,6-diisopropylphenol in two equal portions. After 4 hr. on the steam bath, the mixture was distilled to give 370 g. (89% yield) of pale orange liquid, b.p. 94–97° at 1 mm.,[1] n_D^{25} 1.5279.

4-Bromo-2,6-diisopropylphenol. To a solution of 357 g. (2.0 moles) of 2,6-diisopropylphenol in 300 ml. of carbon tetrachloride was added dropwise 320 g. (2.0 moles) of bromine, maintaining the temperature at 15–20° by occasional cooling. Hydrogen bromide was evolved copiously. The solution was stirred for one hour at room temperature, then heated on the steam bath to drive off solvent and remaining hydrogen bromide. Distillation gave 498 g. (97% yield) of liquid, b.p. 101–107° at 1 mm., n_D^{25} 1.5465.

Anal. Calcd. for $C_{12}H_{17}BrO$: C, 56.1; H, 6.7. Found: C, 55.9; H, 6.8.

4-Benzyl-2,6-diisopropylphenol. Aluminum chloride (67 g. 0.5 mole) was added portionwise over a two-hour period to a stirred solution of 222 g. (1.25 moles) of 2,6-diisopropylphenol and 108 g. (1.0 mole) of benzyl alcohol in 200 ml. of Skellysolve B, keeping the temperature at 30–35° by cooling as needed. After standing overnight at room temperature, the dark red reaction mixture, which contained much oily solid, was hydrolyzed with ice–hydrochloric acid. The Skellysolve layer was separated and the aqueous layer extracted three times with ether. After evaporation of the solvent from the dried organic extracts, distillation gave 112 g. of recovered DIP, followed by 91.5 g. (34% yield) of 4-benzyl-2,6-diisopropylphenol, b.p. 156–162° at 1 mm., n_D^{25} 1.5553.

Anal. Calcd. for $C_{19}H_{24}O$: C, 85.0; H, 9.0. Found: C, 85.4; H, 9.0.

2,6-Diisopropyl-4-(α-methylbenzyl)phenol. Similarly, 2,6-diisopropylphenol and phenylmethylcarbinol gave 2,6-diisopropyl-4-(α-methylbenzyl)phenol in 67% yield, b.p. 158–163° at 1 mm., n_D^{25} 1.5496.

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(7) Melting points and boiling points are uncorrected. Analytical data were obtained by Mr. R. M. Downing.

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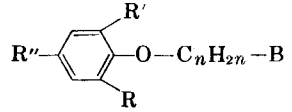
TABLE I

DIALKYLAMINOALKYL ETHERS OF 2,6-DIALKYLPHENOLS



R	R′	R″	C_nH_{2n}	B[a]	% Yield	BP. °C./mm.	n_D^{25}	M.P. of salt	Recrystallization Solvent[n]	Formula	Analyses: Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
CH_3	CH_3	H	$-CH_2CH_2-$	$N(CH_3)_2$	74	116–120/8	1.4972[b]	191.0–195.0	iPrOH	$C_{12}H_{19}NO\cdot HCl$	62.7	63.2	8.8	8.2
CH_3	t-C_4H_9	H	$-CH_2CH_2-$	$N(CH_3)_2$	82	122–127/1.5	1.4994[c]	128.5–130.5	iPrOH	$C_{15}H_{25}NO\cdot C_6H_8O_7$[e]	59.0	59.1	7.8	7.9
CH_3	t-C_4H_9	H	$-CH_2CH_2-$	$N(iC_3H_7)_2$	84	137–140/1.4	1.4904	[d]		$C_{19}H_{33}NO$	78.3	78.2	11.4	10.9
C_2H_5	C_2H_5	H	$-CH_2CH_2-$	$N(CH_3)_2$	70	129–133/9	1.4960	135.0–137.0	MIBK	$C_{14}H_{23}NO\cdot HCl$	65.2	65.4	9.4	9.1
iC_3H_7	iC_3H_7	H	$-CH_2CH_2-$	$N(CH_3)_2$	88	110–113/0.6	1.4908[f]	203.0–205.0	MEK	$C_{16}H_{27}NO\cdot HCl$	67.2	67.8	9.9	9.9
iC_3H_7	iC_3H_7	H	$-CH_2CH_2-$	$N(C_2H_5)_2$	86	130–140/1	1.4866	149.0–151.0	MIBK	$C_{18}H_{31}NO\cdot HCl$	69.1	69.3	10.3	10.4
iC_3H_7	iC_3H_7	H	$-CH_2CH_2-$	NC_4H_8	74	[g]		210.0–213.0	MIBK	$C_{18}H_{29}NO\cdot HCl$	69.3	69.3	9.7	9.7
iC_3H_7	iC_3H_7	H	$-CH_2CH_2-$	NC_5H_{10}	75	[g,h]		212.0–215.0	MIBK	$C_{19}H_{31}NO\cdot HCl$	70.0	70.2	9.9	10.1
iC_3H_7	iC_3H_7	H	$-CH_2CH_2-$	$N(iC_3H_7)_2$	78	123–126/1		154.0–156.0	Benzene-Skellysolve	$C_{20}H_{35}NO\cdot HCl$	70.2	70.6	10.6	10.5
iC_3H_7	iC_3H_7	H	$-CH_2CH_2-$	NC_4H_8O	24[m]	[g]		198.0–200.0	MIBK	$C_{18}H_{29}NO_2\cdot HCl$	65.8	66.0	9.2	9.3
iC_3H_7	iC_3H_7	H	$-CH_2CH_2CH_2-$	$N(CH_3)_2$	78	146–151/8	1.4884[i]	80–157[k]	MIBK	$C_{17}H_{29}NO\cdot HCl$	68.1	68.3	10.1	10.1
iC_3H_7	iC_3H_7	H	$-CH_2C(CH_3)_2CH_2-$	NC_5H_{10}	49[m]	174–180/1		206.0–210.0	MIBK	$C_{22}H_{37}NO\cdot HCl$	71.7	71.9	10.4	10.4
iC_3H_7	iC_3H_7	$C_6H_5CH_2$	$-CH_2CH_2-$	$N(CH_3)_2$	59[m]	[g]		206.0–209.0	iPrOH	$C_{23}H_{33}NO\cdot HCl$	73.4	73.6	9.1	9.3
iC_3H_7	iC_3H_7	$C_6H_5CH(CH_3)-$	$-CH_2CH_2-$	$N(CH_3)_2$	74[m]	162–166/0.5	1.5265	[d]		$C_{24}H_{35}NO$	81.5	81.7	10.0	9.8
iC_3H_7	iC_3H_7	Cl	$-CH_2CH_2-$	$N(CH_3)_2$	62	154–160/8	1.5060	223.0–226.0	MIBK	$C_{16}H_{26}ClNO\cdot HCl$	60.1	60.2	8.5	8.6
iC_3H_7	iC_3H_7	Cl	$-CH_2CH_2CH_2-$	$N(CH_3)_2$	70	144–148/1	1.5028	205.0–208.0	nBuOH	$C_{17}H_{28}ClNO\cdot HCl$	61.1	60.7	8.7	8.6
iC_3H_7	iC_3H_7	Br	$-CH_2CH_2-$	$N(CH_3)_2$	78	133–140/1	1.5238	230.0–232.0	nBuOH	$C_{16}H_{26}BrNO\cdot HCl$	52.7	52.3	7.4	7.2
iC_3H_7	iC_3H_7	Br	$-CH_2CH_2CH_2-$	$N(CH_3)_2$	85	144–154/1	1.5204	205.0–208.0	nBuOH	$C_{17}H_{28}BrNO\cdot HCl$	53.8	53.7	7.7	7.7
tC_4H_9	tC_4H_9	H	$-CH_2CH_2-$	$N(CH_3)_2$	80	[g]		169.0–171.0	MeOH	$C_{18}H_{31}NO\cdot C_6H_8O_7$	61.4	61.8	8.4	8.6
tC_4H_9	tC_4H_9	CH_3	$-CH_2CH_2-$	$N(CH_3)_2$	52[m]	130–137/0.6	1.4990[l]	171.5–172.5	MeOH	$C_{19}H_{33}NO\cdot C_6H_8O_7$	62.1	62.4	8.6	8.5

[a] NC_4H_8 = 1-pyrrolidino; NC_5H_{10} = 1-piperidino; N C_4H_8O = 4-morpholino. [b] Base prepared by Hey and Willey [*Brit. J. Pharmacol*, 9, 471 (1954)] from 2-(2,6-xylyloxyl)ethyl bromide and dimethylamine. [c] Base: Calcd. for $C_{15}H_{25}NO$: C, 76.5; H, 10.7; Found: C, 76.5; H, 10.5. [d] Crystalline salt not obtained; analysis for base given in table. [e] $C_6H_8O_7$ = citric acid. [f] Base: Calcd. for $C_{16}H_{27}NO$: C, 77.1; H, 10.9. Found: C, 76.5; H, 11.1. [g] Base not distilled; yield is that of crude salt. [h] Hydrochloride crystallized out on extraction with dilute hydrochloric acid. [i] Base: m.p. 44.5–47.0° (dilute ethanol): Calcd. for $C_{20}H_{25}NO$: C, 78.6; H, 11.6. Found: C, 79.0; H, 11.3. [j] Base: Calcd. for $C_{17}H_{29}NO$: C, 77.5; H, 11.1. Found: C, 77.9; H, 11.1. [k] In spite of repeated recrystallizations, this wide melting range persisted. [l] Base: Calcd. for $C_{19}H_{33}NO$: C, 78.3; H, 11.4. Found: C, 78.4; 11.3. [m] The modified working up procedure involving evaporation of the toluene and subsequent acid extraction from Skellysolve solution was used; see Experimental. [n] MIBK = methyl isobutyl ketone; MEK = methyl ethyl ketone.

Anal. Calcd. for $C_{20}H_{26}O$: C, 85.1; H, 9.3. Found: C, 85.4; H, 9.1.

2-(2,6-Diisopropylphenoxy)ethyl chloride. A solution of 53.5 g. (0.3 mole) of 2,6-diisopropylphenol in 300 ml. of toluene was added dropwise to a stirred suspension of 7.1 g. (0.3 mole) of sodium hydride in 150 ml. of toluene. The mixture was then stirred at reflux for one hour. To this thick suspension was added in five portions 70.7 g. (0.31 mole) of β-chloroethyl-*p*-toluenesulfonate. After refluxing overnight, the reaction mixture was treated while hot with 25 ml. of 20% sodium hydroxide, and when cool, with 200 ml. of water. The toluene layer was separated, dried, and distilled. A fraction boiling at 130–140° at 8 mm. appeared to be essentially the desired product: 18.7 g. (26% yield) was obtained, n_D^{25} 1.5070. A considerable amount of DIP was recovered as forerun.

Anal. Calcd. for $C_{14}H_{21}ClO$: C, 69.8; H, 8.8. Found: C, 70.1; H, 8.8.

3,3',5,5'-Tetraisopropyldiphenoquinone (II). To a stirred solution of 220 g. (1.23 moles) of 2,6-diisopropylphenol in 450 ml. of benzene and 320 ml. of glacial acetic acid, held at 0–5°, was added dropwise 90 ml. of concentrated nitric acid. Some brown fumes were evolved during the addition and appeared to have ceased at the end. After standing overnight at room temperature, the reaction mixture was poured into one liter of water, shaken well, and the aqueous layer discarded. The benzene layer was extracted in turn with 10% urea solution and saturated sodium bicarbonate solution. Evaporation of the solvent from the dried benzene solution left a semisolid residue, which on trituration with 250 ml. of cold methanol gave 55.1 g. of purplish red solid, m.p. 185–198°. Three recrystallizations from isopropyl alcohol gave material melting at 199–203°: red plates with a purple luster (lit.[1] m.p. 196–198°).

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SYRACUSE 1, N. Y.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE OHIO STATE UNIVERSITY]

Synthesis of Amino Compounds in the Sugar Series by Phenylhydrazone Reduction[1,2]

M. L. WOLFROM, F. SHAFIZADEH, J. O. WEHRMÜLLER, AND R. K. ARMSTRONG

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It has been shown that the reduction of the phenylhydrazone function provides a convenient method for the synthesis of a variety of amino compounds in the sugar series. These include: the 1-amino-1-deoxy derivatives of D-arabinitol, D-galactitol, D-glucitol, D-gulitol, and D-xylitol; the diaminodideoxyalditols 1,4-diamino-1,4-dideoxy-2,3-*O*-isopropylidene-D-threitol, 1,4-diamino-1,4-dideoxy-D-threitol, 1,2-diamino-1,2-dideoxy-D-glucitol, and 1,2-diamino-1,2-dideoxy-D-mannitol; and 5-amino-5-deoxy-1,2-*O*-isopropylidene-α-D-xylofuranose. All of these compounds have been isolated as crystalline salicylaldehyde Schiff bases and some of them have been further characterized as their hydrobromide and *N*-(2,4-dinitrophenyl) derivatives.

Reduction of the condensation products of carbohydrates with nitrogen bases provides a general route for the synthesis of a variety of amino sugars. Thus, many of the 1-amino-1-deoxyalditols have been prepared through the sodium amalgam reduction of the corresponding oximes.[3] These compounds can also be prepared by the reduction of the aldoses in the presence of ammonia[4,5] or by the hydrogenation of glycosylamines[6] and of 1-deoxy-1-benzylaminoalditols.[5] Other methods are based on the reduction of the aldonamides with lithium aluminum hydride[7] and the reduction of hydrazine derivatives. The latter method was employed by Fischer and Groh[8] for converting the phenylhydrazones of certain keto acids to the corresponding amino acids, a process which has been employed for the identification and estimation of the keto acids in plant products.[9] Emil Fischer also prepared (as the acetate salt) 1-amino-1-deoxy-D-fructose, "isoglucosamine," by the reduction of D-glucose phenylosazone with zinc and acetic acid.[10] Maurer and Schiedt[11] increased the yield in this reaction to 60% through employment of catalytic

(1) Carried out in part under contracts DA-33-019-ord-2042 (Office of Ordnance Research) and DA-33-019-ord-2025 (Aberdeen Proving Ground) between the U. S. Army Ordnance Corps (technical supervising agency, Ballistic Research Laboratories, Aberdeen Proving Ground, Md.) and The Ohio State University Research Foundation (Projects 679 and 675).

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