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Rapid Separation of Organic Mixtures by Formation of Metal Complexes

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A convenient and efficient technique for resolving alcohol mixtures by preferential complexation by calcium chloride or manganese chloride with one alcohol of the mixture is reported. Isolation of the complex formed and regeneration of the alcohol allows purification of certain alcohols. Catalytic amounts of ethanol enhance the complexing ability of the metal halides. The separation of commercial mixtures of *cis-* and *trans-*4-*tert*-butylcyclohexanol, technical geraniol, and contrived mixtures of cyclododecanol–cyclododecanone were investigated and optimum conditions for these systems were determined.

Often the most difficult and time-consuming aspect of a synthetic procedure is the process of separating the desired compound from a crude product mixture containing similar compounds. The rapid pace at which modern synthetic chemistry is advancing is in large measure due to the development of powerful chromatographic methods for resolving mixtures. However, chromatographic procedures work best on a small scale and become exceedingly difficult to perform as the quantity of materials to be separated increases.

By contrast, the classical chemical methods for separation are not as limited by scale; these methods usually involve making a derivative of a functional group which can be separated from impurities by nonchromatographic means (e.g., recrystallization). Derivative formation requires an extra step and once purified the derivative is often difficult to decompose.

We have for several years been purifying mixtures of organic alcohols by complex formation with calcium chloride and other anhydrous metal halides. The literature contains only isolated reports on the use of such complexes to purify mixtures.[1] The original procedure of Jones and Woods for purification of commercial geraniol exemplifies the simplicity of the general method.

The geraniol–citronellol[2] mixture (~60:40) is dissolved in hexane and stirred with finely ground anhydrous calcium chloride. Although calcium chloride is completely insoluble in hexane, it is quickly digested by the alcohol to form a solid complex. The complex is filtered, washed with hexane, and dissolved in water, whereupon essentially pure geraniol is liberated. The whole procedure is easily carried out in several hours on a kilogram scale if necessary. Although only 35% of the geraniol is recovered in this way, it is difficult to imagine a more convenient means of isolating it from this mixture.

We have now established that this separation technique is applicable to many alcohol mixtures. A large number of mixtures containing other coordinating functional groups (e.g., amines, amides, esters, epoxide, ketones, aldehydes, acids, and nitriles) were also examined. However, for unknown reasons, the various metal complexing agents were generally less effective in separating mixtures containing functional groups other than alcohols. Before elaborating on specific applications, it will be helpful to discuss the properties of the complexes which are formed with alcohols.

Chart I

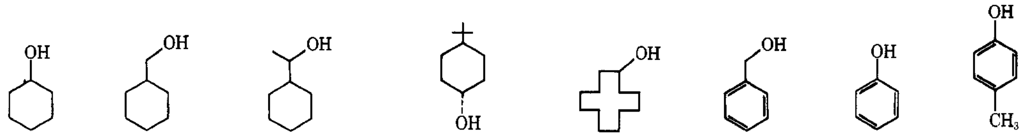
Salt	Alcohol	Alcohol/salt
$CaCl_2$	Geraniol	1.9
$CaCl_2$	α-Phenethyl alcohol	1.3
$CaBr_2$	Menthol	2.2
$MnCl_2$	Menthol	1.0
$MnCl_2$	α-Phenethyl alcohol	1.4

Nature of Alcoholates. The formation of alcoholates of anhydrous metal halides is well precedented and the stoichiometry $MX_2(ROH)_2$ is common for divalent metal ions (e.g., Mn, Ni, Ca, Zn, and Mg).[3] Since these complexes were of only small alcohols (i.e., MeOH, EtOH), we prepared and analyzed several larger complexes. As shown in Chart I, the stoichiometry of the complexes varies between one and two alcohols. These complexes were formed in the presence of a large excess of the alcohol.

An early clue about the course of complex formation and the reason for its specificity was provided by the observation that the hexane filtrate obtained during isolation of the solid complexes contained dissolved calcium chloride. In fact, alcohols such as oleoyl alcohol and citronellol, which did not form solid complexes with $CaCl_2$, dissolved large quantities of the salt in hexane. Similarly, complex mixtures of alcohols which, when pure, formed solid complexes in the standard procedure (i.e., stirred in hexane with the anhydrous salt) resulted in complete dissolution of the anhydrous salt in the hexane. Thus, although most alcohols form complexes, some crystallize more readily than others from the nonpolar solvents employed.

Another important aspect of complex formation is that the alcohols in the solid complexes stirring in hexane exchange rapidly with the alcohols in solution. This exchange process was demonstrated by isolating the $CaCl_2$ complex of 1-decanol and then stirring it in a hexane solution containing cyclohexanol (ca. 1.5 equiv). After stirring for 0.5 hr

Table I
Competitions between Pairs of Alcohols for Complex Formation with $MnCl_2$ in Hexane[a]



	1	2	3	4	5	6	7	8	1-Hexadecanol 9
Mp, °C	25	−43		81	80	−15	43	35	49
	1	1[b]	1	1	1, 5	1	1	1	1
		2	2, 3[b]	4, 2	5	6			
			3	4,[c] 3	5	6			
				4	4, 5			4	9
					5				5
						6			
							7		
								8	
									9

[a] Each of the competitions was carried out by stirring overnight an equimolar mixture of the two alcohols dissolved in hexane with 1.5 molar equiv (based on total alcohol) of finely ground anhydrous $MnCl_2$. A catalytic amount of ethanol (0.05 equiv) was added in each case. The complexes were isolated by filtration and the alcohols were released by addition of water. The ratio of alcohols in the complex was then determined by GLC. This work was done several years ago and recently we have found that the above conditions are not optimum. [b] A single entry means ~100% selection of that alcohol. A double entry means about equal selection. [c] Alcohol was favored but not selected 100%.

the solid complex contained only cyclohexanol. Whatever the cause of this facile exchange of ligands, in what appears to be a heterogeneous system, it is obviously of paramount importance to selective complex formation. The system simply equilibrates until it has optimized whatever thermodynamic factors favor solid complex formation. These features probably explain why this purification technique is capable of some of the subtle discriminations described later.

Some alcohols, especially large and/or hindered ones, when stirred with anhydrous $CaCl_2$ in hexane formed complexes very slowly. This was not surprising considering the heterogeneous nature of the process. Having already noted that an alcohol in solution could rapidly displace a weaker complexing alcohol from the solid complex (see above), it seemed likely that a small alcohol might catalyze complex formation in slower cases by aiding in digestion of the $CaCl_2$. In support of this concept we have found that catalytic quantities (1–10%) of *n*-aliphatic alcohols dramatically accelerate the rate of complex formations, especially in difficult cases. Although we now use anhydrous ethanol as the catalyst, propanol and butanol work equally well. In addition to reducing the time required for complex formation, this effect enables one to form complexes of many alcohols which fail to form any complex at all in the absence of the catalyst. For example, *l*-menthol readily formed a solid complex with anhydrous manganous chloride when 5% ethanol was present; in the absence of ethanol, under otherwise identical conditions, no complex was formed. Interestingly, *l*-menthol failed to form a complex with calcium chloride even when ethanol catalysis was employed. As will be seen later, the amount of ethanol catalyst is best kept to about 1–2% or less, since in certain sensitive separations the selectivity falls off as the amount of ethanol increases.

Factors Which Affect the Selectivity of Complex Formation. Our current understanding of the factors which determine selectivity is very limited. In general one must simply try this purification technique on the alcohol mixture in question to learn what the outcome will be. The empirical nature of this method should diminish as its use increases. In any case, we have observed certain effects which are worth pointing out. While discussing these factors individually, it is important to realize that although trends can be discerned for isolated factors, the actual effect on the selectivity is a complex function of all the factors. Thus, most of the following statements should be prefaced by the phrase "other things being equal".

The highest melting ligand is preferentially selected, as revealed in Table I, for various pairs of alcohols competing for complexation with manganous chloride ($MnCl_2$). However, exceptions are easy to find. Cyclohexanol was superior to all contenders, and phenols formed poorer complexes, probably because they are weaker bases, than alcohols of comparable melting point.

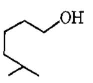
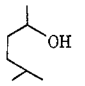
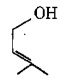
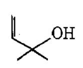
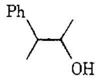
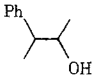
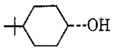
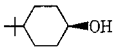
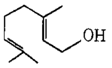
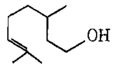
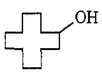
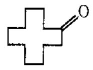
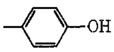
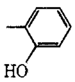
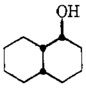
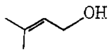
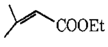
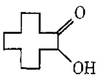
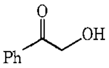
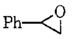
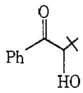
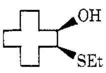
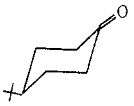
In competitions between two alcohols, both of which form solid complexes, the major component has the advantage. However, when one alcohol forms much better complexes than the other it tends to be selected even when it is the minor component. In these and other respects this purification procedure resembles fractional crystallization.

For a given carbon skeleton one generally finds that complexing ability decreases in the order primary > secondary > tertiary alcohol. Thus, 1-decanol is vastly superior to its 2, 3, 4, and 5 isomers.[5]

Actual Applications and Optimization of Variables. In addition to the separation of the contrived mixtures outlined in Table I, we have found that these purification techniques were successful in separating a variety of mixtures which arose during the course of other research problems (see Table II). Most all of the examples in Table II were carried out in a very crude manner; an undetermined amount (usually a large excess, 2+ molar equiv) of anhydrous calcium chloride was used and a "squirt" of anhydrous ethanol was added as catalyst. It is to the credit of this method of separation that even this qualitative approach was usually successful on the first try. In Table III are listed some of the mixtures for which no or only partial purification was observed. In general we have found this method to be effective on better than 50% of the alcohol-containing mixtures to which it has been applied.

More recently we have sought to establish an optimum set of reaction conditions to be tried first on any new mixture. The factors to be optimized are, of course, selectivity[6] and recovery—the product of these two determines the yield of the desired component isolated from the mixture. Unfortunately, this has not been easy, since each mixture seems to respond differently to the controllable variables.

Table II
Isolation of Alcohols from Mixtures by Means of Metal Complexes[a]

	Component which complexed	Component(s) which did not complex
		
		
	 erythro	 threo
a		
b		
c		
		
		The other three decahydro-1-naphthols
		
		
		
		PhCHO
		
		
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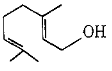
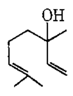
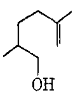
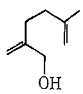
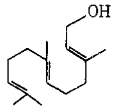
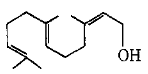
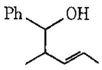
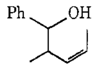
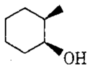
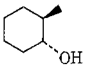
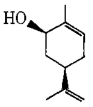
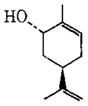
		

[a] These separations were carried out under variable conditions. Generally, an undetermined amount (usually a large excess, 2+ molar equiv) of anhydrous calcium chloride was used, along with a variable but small amount of ethanol as catalyst. Hexane was used as solvent.

Table III
Alcohol Mixtures Not Successfully Purified by $CaCl_2$ Complexation

	
	
	
	
	
Commercial oleyl alcohol	

In approximate order of decreasing importance these variables are (1) mole ratio of anhydrous salt to alcohol; (2) percent of anhydrous ethanol catalyst; (3) anhydrous salt ($CaCl_2$, $CaBr_2$, $MnCl_2$, $CoCl_2$, etc.); (4) length of time stirred at room temperature; (5) solvent (hexane, CH_2Cl_2). The first two variables are the most important and we have studied in detail the effect of these variables on three cases (a, b, and c) from Table II. As can be seen from examination of the data presented in Table IV, these three mixtures (a, b, and c) respond differently to variables 1 and 2. Case a (*trans*-4-*tert*-butylcyclohexanol–*cis*-4-*tert*-butylcyclohexanol) is quite sensitive to both the mole ratio of anhydrous salt to alcohol and to the amount of ethanol catalyst used, whereas case b (geraniol–citronellol) is quite insensitive to these same two variables. Fortunately, most of the alcohol mixtures we have studied resemble case b more than case a. Case c (cyclododecanol–cyclododecanone) is even less sensitive to the above-mentioned variables than is case b. In fact, we have found this type of separation (of an alcohol from a nonalcohol) to be one of the most reliable applications of this purification procedure.

The results in Table IV reveal that only case a is very sensitive to the $CaCl_2$/alcohol ratio and to the amount of ethanol catalyst. The optimum selectivity[6] is obtained when 0.5 mol of $CaCl_2$ is used per mole of *trans*-4-*tert*-butylcyclohexanol in the starting mixture and when only 1% of ethanol catalyst is present. The use of 10% ethanol catalyst increases the recovery and rate of complex formation but at great expense to the selectivity. When no ethanol is present the selectivity is very high but the yields are low. Fortunately, most alcohol mixtures we have encountered resemble the geraniol purification (case b) in sensitivity to conditions. However, since the best procedure for case a also gives reasonable yields for case b, we recommend that it be adopted as the *optimum procedure: use 0.5 mol of finely ground anhydrous* $CaCl_2$ *per mole of alcohol to be complexed in the starting mixture and 1% (based on total moles of mixture) of absolute ethanol catalyst; these ingredients are then vigorously stirred in hexane or* CH_2Cl_2 *solution (~0.6 M based on moles of mixture) for 4–12 hr.*

In the case of more hindered alcohols, where the ratio of metal salt to alcohol in the complex approaches 1 (see Chart I), it may be better to employ up to 1 mol of $CaCl_2$ per mole of alcohol to be complexed. As already pointed out, in most cases this concern over the $CaCl_2$/alcohol ratio is unnecessary and in much of our earlier work we used a large excess of $CaCl_2$ and still obtained good results. Of course, as the amount of $CaCl_2$ employed approaches the stoichiometric value it becomes necessary to ensure strictly anhydrous conditions. Thus, it may be desirable to use excess $CaCl_2$ when possible to avoid these difficulties.

On the other hand, when one is dealing with mixtures of an alcohol and other components containing weaker ligands (e.g., ketones, esters, epoxides) such as in case c of

Table IV[a]

Case a (4-*tert*-Butylcyclohexanols)

Molar equiv[b] $CaCl_2$	Ethanol,[c] %	Selectivity,[d] % trans isomer	Yield,[e] % trans isomer	Time, hr
0.35	1	>99	84	10
0.5	1	91	84	10
0.7	1	88	85	10
0.35	0	>99	15	10
0.35	1	>99	84	10
0.35	2	97	90	7
0.35	10	90	81	10

Case b (Geraniol + Impurities)

Molar equiv[b] $CaCl_2$	Ethanol,[c] %	Selectivity,[d] % geraniol	Yield,[e] % geraniol	Time, hr
0.35	1	97	48	9.5
1.0	1	96	59	10.5
2.0	1	96	56	10
0.35	10	96	48	10.5
0.7	10	93	51	11

Case c (Cyclododecanol + Cyclodecanone)

Molar equiv[b] $CaCl_2$	Ethanol,[f] %	Selectivity,[d] % alcohol	Yield,[e] % alcohol	Time, hr
0.25	1	>99	34	5
0.5	1	>99	51	5
1.0	1	>99	64	5
2.0	1	>99	71	5
4.0	1	>99	69	5
0.5	1	>99	51	5
0.5	10	>99	54	5

[a] All reactions were performed with vigorous magnetic stirring in hexane as solvent (60 ml) on 5 g of the mixtures. The 4-*tert*-butylcyclohexanol (case a) used was 70% trans and 30% cis; the technical grade geraniol (case b) contained 65% geraniol, 30% citronellol, and 5% of other impurities; the cyclododecanol–cyclododecanone (case c) consisted of an equimolar mixture of the alcohol and the ketone. [b] This figure is based on total alcohol available and thus the first entry of 0.35 means that there was enough $CaCl_2$ available to complex with all the *trans*-4-*tert*-butylcyclohexanol in the mixture (70%) if two molecules of the trans alcohol are bound to each calcium ion. In case c this figure is based on total alcohol and ketone available. [c] Based on total alcohol. [d] See ref 6. [e] See ref 8. [f] Based on total alcohol and ketone.

Table IV, it appears that the yield can be increased by going to high $CaCl_2$/alcohol ratios with little loss in selectivity. It also appears that the rate of complex formation can be increased in these instances (case c) by using more (5–10%) of ethanol catalyst without a deleterious effect on selectivity.

At this point it is worth discussing briefly the other three variables (3, 4, and 5) mentioned above. We have explored a variety of anhydrous alkaline earth and transition metal halides, but $CaCl_2$ seems to be the best general reagent and also the least expensive.

The length of time required for complex formation varies dramatically depending on the alcohol involved, the efficiency of stirring (since the reactions are heterogeneous), and the amount of ethanol catalyst employed (the more ethanol the faster the complex formation). The only solvents we have used are hexane and CH_2Cl_2. For a given mixture both solvents afford similar selectivities but hexane seems to result in better recoveries; the calcium chloride alcoholates are probably more soluble in CH_2Cl_2 than in hexane.

As an example of the preparative utility of these purification procedures 100 g of commercial 4-*tert*-butylcyclohexanol (67% trans, 33% cis) afforded 56.1 g (83% yield based on trans alcohol available) of 99% pure *trans*-4-*tert*-butylcyclohexanol. The literature procedure[4] for purifying the same quantity of a sample of this alcohol slightly richer in the trans isomer (~75% trans, 25% cis) involves formation and two recrystallizations of the acid phthalate followed by saponification to give 29.8 g (~40%) of the pure trans alcohol. Thus the $CaCl_2$ method proceeds in one step, requires no time-consuming recrystallizations, and affords twice the yield of the classical derivatization approach.

As already mentioned, the purification of the epimeric 4-*tert*-butylcyclohexanols by this procedure is more sensitive to conditions than any other mixture in our experience. Although yields of 75–85% were reproducible on a small scale (5 g of crude alcohol), the yields on the larger scale (100 g) varied between 65 and 85%. The responsible variable was found to be the stirring. Surprisingly, too vigorous stirring in this case was deleterious. Thus, stirring in a Morton flask for 20 hr gave only 84% selectivity[6] for the trans epimer but the yield remained high at 81%. The optimum conditions for this case appeared to be stirring for 10 hr in a normal flask. Stirring for shorter periods gave lower yields although the selectivity remained high, whereas with longer stirring the selectivity began to fall off rapidly. This dependence of selectivity on time was noticed only in the 4-*tert*-butylcyclohexanol system.

Since we have recently found that $MnCl_2$ also works quite well for this purification, it would be interesting to see if its selectivity also exhibited this time dependence. If it did not, then $MnCl_2$ would clearly be preferred over $CaCl_2$ in this instance.

In conclusion, it should be emphasized that although we feel we have established reasonable guidelines for the purification of alcohol mixtures by formation of metal complexes, the technique is clearly still highly empirical. Each new mixture will probably require optimization of the variables, especially if one is concerned about yields and not just rapid access to a pure component. This method of purifying alcohol mixtures by formation of metal complexes has already served us well in many research problems. We feel that through wider use many new applications will be discovered.

One would hope that this concept could be extended to purification of mixtures containing other functional groups capable of coordination as Lewis bases. We have had some success in separating mixtures of ketones and esters using stronger Lewis acids (e.g., $ZrCl_4$ and $FeCl_3$) in CCl_4.[5] We were surprised to find that even $CaCl_2$ forms complexes with esters, aldehydes, and ketones as evidenced by the shifts in the carbonyl absorption of the derived complexes shown in Table V;[5] unfortunately, in the presence of

Table V[a]
Shift of Carbonyl Absorption upon Complexing with $CaCl_2$

Ligand	Metal halide	Ir shift cm^{-1}
Methyl nonyl ketone	$CaCl_2$	−95
Cyclohexanone	$CaCl_2$	−90
Methyl laurate	$CaCl_2$	−115
Lauraldehyde	$CaCl_2$	−110
trans-Decalin-1,5-dione	$CaCl_2$	−95

[a] The complexes were obtained by stirring anhydrous $CaCl_2$ with the appropriate carbonyl compound in hexane. Ir spectra of the solid complexes were obtained as Nujol mulls.

mixtures of such carbonyl compounds the $CaCl_2$ complexes which form are also mixtures and show little selectivity in choice of ligand. Other functional groups which $CaCl_2$ complexed with but failed to purify mixtures containing such moieties include amides, acids, nitriles, epoxides, and amines. Thus, among the numerous mixtures containing polar functional groups, alcohol mixtures appear to be unique in their tendency to form selective complexes with $CaCl_2$ and related Lewis acids. This is perhaps due to a favorable balance between the stability of such alcoholates and their rates of exchange with free alcohols in solution. Understanding of this useful purification phenomenon might be facilitated if structures of the complexes could be determined. In this regard it is interesting that when competitions for $CaCl_2$ complexation were performed[5] between various pairs of straight-chain alcohols ranging from 1-butanol to 1-eicosanol the alcohol with the longer chain was clearly favored, and the degree of selection increased as the difference in the length of the competing alcohols increased. Thus these complexes have no trouble incorporating large hydrocarbon residues and it would probably be very informative to learn why this is so.

Experimental Section

General. Commercial samples of all reagents were employed. 4-*tert*-Butylcyclohexanol, cyclododecanol, cyclododecanone, and 1-dodecanol were obtained from Aldrich Chemical Co. Technical grade geraniol and 1-decanol were obtained from Eastman Organic Chemicals. The anhydrous calcium chloride (8 mesh) used was obtained from Mallinckrodt Chemical Works, anhydrous calcium bromide (powder) was obtained from Merck and Co., Inc., and anhydrous manganese(II) chloride was obtained from Ventron Corp., Alfa products. The technical grade geraniol was found to contain approximately 65% geraniol, 30% citronellol, and 5% other impurities.

The commercial 4-*tert*-butylcyclohexanol consisted of a mixture of isomers, with the trans isomer generally ranging from 67 to 80% of the total mixture. Pure samples of the cis and trans isomers, for comparison purposes, were obtained by column chromatography of 1.5 g of the commercial sample on 140 g of silica gel packed in a 3.2 cm diameter column. The axial (cis) isomer was eluted with 10% EtOAc in hexane and the equatorial (trans) isomer was eluted with 20% EtOAc in hexane.

All GLC analyses were performed on a Perkin-Elmer 990 instrument using either 3% FFAP on Gas-Chrom Q (80/100 mesh) packed in a 6 ft × 0.125 in. glass column, or 3% OV-17 on Gas-Chrom Q (80/100 mesh) packed in a 6 ft × 0.125 in. glass column. On 3% FFAP, retention times were as follows: *cis*-4-*tert*-butylcyclohexanol, 4.5 min (105°); *trans*-4-*tert*-butylcyclohexanol, 5.6 min (105°); 4-*tert*-butylcyclohexanone, 3.4 min (105°); cyclododecanol, 5.6 min (145°); cyclododecanone, 2.8 min (145°). On 3% OV-17, retention times were as follows: geraniol, 5.8 min (115°); citronellol, 4.6 min (115°); 1-dodecanol, 7.5 min (130°); 1-decanol, 2.7 min (130°).

All organic solutions were dried with anhydrous magnesium sulfate unless otherwise indicated.

I. Separation of *trans*-4-*tert*-Butylcyclohexanol from the Commercial Alcohol. A. Large Scale (Optimum Conditions). Commercial 4-*tert*-butylcyclohexanol (100 g, 640 mmol) (67% trans, 33% cis), ethanol (0.29 g, 0.37 ml, 6.4 mmol), and 1 l. of hexane were placed in a 2-l. three-necked flask fitted with a mechanical stirrer and a gas inlet tube. A stream of nitrogen was slowly passed through the apparatus. The freshly powdered anhydrous calcium chloride (23.8 g, 214 mmol) was added to the stirred solution all at once, and vigorous stirring was continued at 25° for 10 hr. The heterogeneous reaction mixture was filtered and the residue was washed with pentane (3 × 200 ml). The complex was then added to a separatory funnel containing 400 ml of ice-cold water and 400 ml of ether, and shaken vigorously until it dissolved. Some heat was evolved during this process. The ether layer was separated and the aqueous layer was washed with 200 ml of ether. The combined ether extracts were washed with 300 ml of water and then dried and concentrated to give 56.1 g (83%)[8] of alcohol. Analysis by GLC showed the regenerated alcohol to contain 99% of *trans*- and 1% of *cis*-4-*tert*-butylcyclohexanol.

B. Small Scale (Optimum Conditions). To a solution of 4-*tert*-butylcyclohexanol (5.0 g, 32 mmol) (70% trans, 30% cis) and a catalytic amount of ethanol (14.7 mg, 18.6 μl, 0.32 mmol) in 50 ml of hexane was added anhydrous calcium chloride (1.25 g, 11.2 mmol) which was freshly powdered in a mortar and pestle. After the resulting mixture had been stirred at 25° for 10 hr, the solvent was filtered off and the solid complex was washed with pentane (2 × 15 ml). The white complex was shaken in a separatory funnel containing 70 ml of water and 70 ml of ether until it dissolved. The ether layer was separated and the aqueous layer was washed once with 70 ml of ether. The combined ether extracts were dried and concentrated to give 2.91 g (84%)[8] of alcohol. This alcohol was shown by GLC to contain 99.5% *trans*- and 0.5% *cis*-4-*tert*-butylcyclohexanol.

C. Methylene Chloride as Solvent. Procedure B with 50 ml of methylene chloride instead of hexane afforded 1.70 g (42%)[8] of alcohol. Analysis by GLC showed the alcohol to contain 99.5% *trans*- and 0.5% *cis*-4-*tert*-butylcyclohexanol.

D. Calcium Bromide as Complexing Agent. Procedure B with anhydrous calcium bromide (2.24 g, 11.2 mmol) powder instead of calcium chloride afforded 3.83 g (67%)[8] of alcohol. The alcohol was shown by GLC to contain 87% *trans*- and 13% *cis*-4-*tert*-butylcyclohexanol.

E. Manganous Chloride as Complexing Agent. Procedure B with anhydrous manganous chloride (1.61 g, 12.8 mmol) instead of calcium chloride afforded 3.18 g (80%)[8] of alcohol. The alcohol was shown by GLC to contain greater than 99% *trans*-4-*tert*-butylcyclohexanol.

II. Separation of *trans*-4-*tert*-Butylcyclohexanol from 4-*tert*-Butylcyclohexanone. To a solution of *trans*-4-*tert*-butylcyclohexanol (2.34 g, 15 mmol), 4-*tert*-butylcyclohexanone (2.33 g, 15 mmol), and a catalytic amount of ethanol (13.8 mg, 17.5 μl, 0.3 mmol) in 50 ml of hexane was added anhydrous calcium chloride (1.67 g, 15 mmol) which was freshly powdered in a mortar and pestle. After stirring at 25° for 10 hr, the solvent was filtered off and the white complex was washed with pentane (3 × 15 ml). The complex was then added to a separatory funnel containing 70 ml of water and 70 ml of ether, and it was shaken until the complex dissolved. The ether layer was separated and the aqueous layer was washed with 70 ml of ether. The combined ether extracts were dried and concentrated to yield 2.09 g (89%)[8] of a white solid. The solid was shown by GLC analysis to contain 99.2% alcohol and 0.8% ketone.

III. Purification of Technical Geraniol. A. Via $CaCl_2$ Complex. To a solution of technical geraniol (3.08 g, 20 mmol) and a catalytic amount of ethanol (9.2 mg, 11.6 μl, 0.2 mmol) in 70 ml of hexane was added calcium chloride (3.33 g, 30 mmol) which was freshly powdered in a mortar and pestle. After the heterogeneous mixture was stirred at 25° for 10 hr, the solvent was filtered off and the white complex was washed with pentane (2 × 25 ml). The complex was then added to a separatory funnel containing 70 ml of water and 70 ml of ether and it was shaken until the solid dissolved. The ether layer was separated and the aqueous layer was washed once with 70 ml of ether. The combined ether extracts were dried and concentrated to give 1.21 g (60%)[8] of colorless oil. The oil was shown by GLC to contain 96% geraniol and 4% citronellol.

B. Via $MnCl_2$ Complex. Procedure A with anhydrous manganous chloride (2.52 g, 20 mmol) instead of calcium chloride afforded 1.32 g (58%) of colorless oil. The oil was shown by GLC to contain 90% geraniol and 10% citronellol.

IV. Separation of Cyclododecanol from Cyclododecanone. To a solution of cyclododecanol (2.76 g, 15 mmol), cyclododecanone (2.74 g, 15 mmol), and a catalytic amount of ethanol (13.8 mg, 17.5 μl, 0.3 mmol) in 70 ml of hexane was added freshly powdered anhydrous calcium chloride (6.68 g, 60 mmol). After stirring at 25° for 5 hr, the solvent was filtered off and the white complex was washed with pentane (3 × 25 ml). The complexed alcohol was regenerated by shaking the complex in a separatory funnel containing 70 ml of water and 70 ml of ether. The ether layer was separated and the aqueous layer was washed once with 70 ml of ether. The combined ether extracts were dried and concentrated to give 1.95 g (71%)[8] of white solid. This solid was shown by GLC to contain 99.8% alcohol and 0.2% ketone.

V. Separation of 1-Dodecanol from a 70:30 Mixture of 1-Dodecanol and 1-Decanol. To a solution of 1-dodecanol (3.92 g, 21 mmol), 1-decanol (1.43 g, 9 mmol), and a catalytic amount of ethanol (13.8 mg, 17.5 μl, 0.3 mmol) in 100 ml of hexane was added freshly powdered anhydrous calcium chloride (3.34 g, 30 mmol). After stirring at 25° for 13 hr, the solvent was filtered off and the white complex was washed with pentane (3 × 30 ml). The complex was then shaken in a separatory funnel containing 70 ml of water and 70 ml of ether until it dissolved. The ether layer was separated and the aqueous layer was washed once with 70 ml of ether. The combined ether extracts were dried and concentrated to yield 3.34 g (80%)[8] of colorless oil. Analysis by GLC showed the oil to contain 94% 1-dodecanol and 6% 1-decanol.

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Registry No.—*cis*-4-*tert*-butylcyclohexanol, 937-05-3; *trans*-4-*tert*-butylcyclohexanol, 21862-63-5; geraniol, 106-24-1; citronellol, 106-22-9; cyclododecanol, 1724-39-6; cyclododecanone, 830-13-7; 1-dodecanol, 112-53-8; 1-decanol, 112-30-1; calcium chloride, 10043-52-4; calcium bromide, 7789-41-5; manganous chloride, 7773-01-5; 4-*tert*-butylcyclohexanone, 98-53-3.

References and Notes

(1) (a) Purification of geraniol: E. Gilderneister and F. Hoffman, "Die Aetherischen Oele", Springer-Verlag, West Berlin, 1899, p 192; H. A. Jones and J. W. Woods, *Ind. Eng. Chem.*, **34**, 488 (1942). (b) Purification of sterols and wool fat alcohols: E. V. Truter, "Wool Wax. Chemistry and Technology", Wiley-Interscience, New York, N.Y., 1956. (c) Purification of phytosterols: M. V. Vasileva and A. M. Khaletskii, *Zh. Obshch. Khim.*, **34**, 1400 (1964).

(2) The contaminant in commercial geraniol was long believed by us, and apparently by many others, to be nerol. However, we have recently shown that the minor (~40%) component is citronellol.

(3) R. C. Osthoff and R. C. West, *J. Am. Chem. Soc.*, **76**, 4732 (1954).

(4) S. Winstein and N. J. Holness, *J. Am. Chem. Soc.*, **77**, 5562 (1955).

(5) K. B. Sharpless and J. A. Scott, unpublished results.

(6) Our use of the word "selectivity" is not in the conventional sense. Rather, we use the word here and subsequently to represent the percent of desired alcohol in the mixture obtained from decomposition of the complex.

(7) Camille and Henry Dreyfus Teacher–Scholar Grant recipient; Alfred P. Sloan Fellow, 1973–1975.

(8) The percent yield given is based on original amount available of desired alcohol. For example, in case IA, the amount of *trans*-4-*tert*-butylcyclohexanol available is 3.5 g (70% of 5.0 g). The yield of the purified trans epimer is 2.91 g or 84% of 3.5 g.

Diborane as a Reducing Agent. The Novel Reduction of *N*-Formylindoles and Electrophilic Substitution in Indoles

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Attempted reduction of *N*-formyl-3-methylindole (**1a**) and 2,3-dimethyl-*N*-formylindole (**1b**) with complex metal hydrides leads to skatole and 2,3-dimethylindole, respectively. Diborane reduction of indole derivatives has furnished interesting results.[1,2] Further studies with this reagent are now reported. Diborane reduction of **1a** gives 1,3-dimethylindole (**4a**, 49.4%) and 1,3-dimethyl-3-(3′-methylindolyl-1′-methyl)indoline (**6a**, 35.8%). Similarly, reduction of **1b** with diorane affords 1,2,3-trimethylindole (**4b**, 52.4%) and two diastereoisomeric 1,2,3-trimethyl-3-(2′,3′-dimethylindolyl-1′-methyl)indolines (**6b**, 36.7%, and **6c**, 6.8%). This appears to be the first report on the successful reduction of an *N*-acylindole to the corresponding *N*-alkyl derivative. The formation of the indolylmethylindolines (6) in the diborane reduction of *N*-formylindoles (1) implies that electrophilic substitution takes place primarily at the 3 position of 3-substituted indoles. These results are discussed in the light of the mechanisms of diborane reduction and electrophilic substitution in 3-substituted indoles.

Indoles,[3] oxindoles,[3d,4,5] isatins,[5] indole-2-, and indole-3-carbonyl derivatives[3a,d,6-10] including indole-3-glyoxamides,[3a,f,9,11] and their *N*-methyl analogs have been reduced with diborane. However, to our knowledge, there is no report in the literature on the reduction of *N*-acylindoles with any reducing agent.[12] In the present communication a simple method is presented for the reduction of *N*-formylindoles with diborane, partly from an interest in its synthetic implications and partly to compare the reducing properties of diborane with those of lithium aluminum hydride ($LiAlH_4$).

Jackson and his coworkers demonstrated that electrophilic substitution takes place primarily at the 3 position of 3-substituted indoles.[10,13] However, recently Wolinsky and Sundeen[14] and Casnati, Dossena, and Pochini[15] claimed to have obtained evidence in favor of direct electrophilic substitution at the 2 position of 3-alkylindoles. The work reported in the present communication was undertaken also with a view to throwing further light on this subject.

It has been observed that complex metal hydrides are unsuitable for the reduction of *N*-acylindoles,[12] presumably because of the tendency of the acyl groups of the latter to undergo cleavage under basic conditions.[12a,c,16] However, *N*-acylindoles are generally more stable in acidic than in basic media (cf. preparations of 1 by Vilsmeier–Haack method[17]). These facts and the pronounced aldehydic character of the *N*-formyl groups of 1[17] led us to assume that diborane would be the reagent of choice for their reduction, particularly because the danger of hydrolytic cleavage would be minimum, since the reaction medium would be acidic because of the Lewis acid character of both diborane and boron trifluoride (BF_3).[18]

While attempted reduction of the *N*-formylindoles (1) with $LiAlH_4$ or potassium borohydride (KBH_4) under a variety of conditions always resulted in the formation of skatole and 2,3-dimethylindole, respectively,[12a] reduction of **1a** with diborane afforded 1,3-dimethylindole (**4a**) and 1,3-dimethyl-3-(3′-methylindolyl-1′-methyl)indoline (**6a**) (Scheme I). Similarly, diborane reduction of **1b** gave 1,2,3-trimethylindole (**4b**) together with two diastereoisomeric 1,2,3-trimethyl-3-(2′,3′-dimethylindolyl-1′-methyl)indolines (**6b** and **6c**). In this connection, it may be pointed out that this appears to be the first report on the successful reduction of an *N*-acylindole.[12]

The origin of both the mono- and dimeric products in the diborane reduction of 1 may be rationalized by assuming that the intermediate (3) may undergo further reduction with excess diborane to give 4 (Scheme I). 3 may also undergo nucleophilic attack by the initially formed indoles (4) to afford the indoleninium cation (5), which is then reduced by excess diborane to the dimers (6).

The major dimeric product was assigned the trans configuration (**6b**) on the assumption that reduction of 5 by the addition of a hydride ion at the 2 position takes place