This issue is specially devoted to Professor C. R. Kanekar in whose memory the articles have been contributed by various authors. The papers except the Memorial Lecture have been communicated by Prof. P. T. Narasimhan, F.N.A.

SISIR KUMAR MITRA MEMORIAL LECTURE—1972

REACTIONS IN HIGH BOILING SOLVENTS

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(*Delivered on 31 December 1972*)

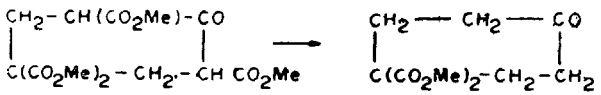
In organic chemical reactions at high temperatures one often comes across a number of difficulties. A major difficulty is the maintenance of uniformity of temperature throughout the entire mass of solid reactants. Though use of suitable solvents is very much helpful and these are extensively used, in special cases mixtures of metallic powders with the reactants are found convenient for the purpose. There are also the reactions at high pressures. These may be mainly divided into two groups, (*a*) reactions where pressure is extremely important on the basis of *Le Chatelier's principle,* and (*b*) reactions where pressure is necessary to keep volatile reactants in the liquid state for carrying out such reactions well above their boiling points. In this latter group, in most instances, the condition is achieved by the use of a 'sealed tube' as in the Carius method for determination of halogens and sulphur in organic compounds.

Such sealed tube reactions are usually carried out by having the reactants in a thick walled glass tube of good quality closed at one end. After introduction of the reactants the other end is also closed properly by melting the glass and sealing. The tube, closed at both ends, is then heated to the desired temperature mostly around 180–200°C, in a bomb furnace. There is a possibility of the tube bursting. Such explosions are not at all rare, specially when the tube is sealed by inexpert hands and in such a case it is usually shattered to pieces. For working with larger quantities, sometimes these are carried out in special pear shaped, pressure and heat resistant glass bottles. The very old type soda-water bottles were previously used in the laboratory. In such cases also there is considerable chance for explosion and protective measures are essential. Of course, now a days all kinds of autoclaves are there for carrying out reactions, specially on a large scale, at high temperatures and high pressures, but these also have their limitations.

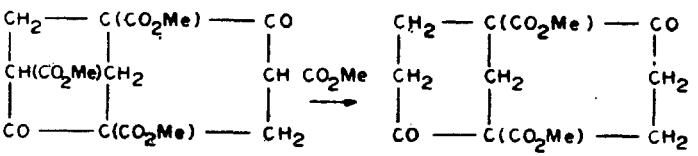
In the first instance, preferential hydrolysis of an ester group, having a keto group in β-position, by heating with water in a sealed tube at 180–200°C may be cited. The method was developed by Meerwein (1913). It works in β-keto ester system with possibility for enolisation, that is in the presence of an ionizable proton. Thus methyl cyclohexanone-2, 4, 4, 6-tetracarboxylate yields methyl cyclohexanone-4, 4-dicarboxylate, and methyl bicyclo-(3, 3, 1) -nonane-2, 6-dione-1, 3, 5, 7-tetracarboxylate yields methyl bicyclo-(3, 3, 1)-nonane-2, 6-dione-1, 5-dicarboxylate (Meerwein and Schürmann 1913; cf. Connor and Adkins 1932).

Toivonen (1922, 1940, 1947) and Toivonen *et al.* (1927, 1935, 1947, 1948) modified this method by heating the β-keto ester in glycerol with some water at

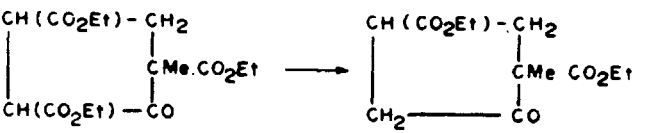
170-200°C. Thus ethyl 2-methylcyclopentan-1-one-2, 4, 5-tricarboxylate is converted into ethyl 2-methylcyclopentan-1-one-2, 4-dicarboxylate. In this case it is not necessary to carry out the heating in a sealed tube, as it is quite convenient to carry out the reaction by heating in an open flask provided with an upright tube as an air condenser. In all such cases, only those ester groups, which are attached to a carbon atom with an attached hydrogen atom and a β-keto group, are hydrolysed. Of course there is simultaneous loss of carbon dioxide from the carboxy group so formed due to the presence of the keto group in the β-position



Methyl Cyclohexanone-2,4,4,6-tetracarboxylate — Methyl Cyclohexanone-4,4-dicarboxylate



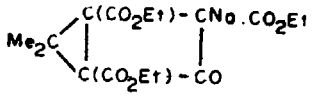
Methyl Bicyclo-(3,3,1)-nonane-2,6-dione-1,3,5,7-tetracarboxylate — Methyl Bicyclo-(3,3,1)-nonane-2,6-dione-1,5-dicarboxylate



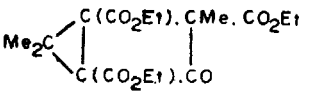
Ethyl 2-Methylcyclopentan-1-one-2,4,5-tricarboxylate — Ethyl 2-Methylcyclopentan-1-one-2,4-dicarboxylate

It is interesting to mention in this connection that Perkin and Thorpe (1901) carried out considerable volume of work on the formation and reactions of an interesting yellow sodium compound obtained by the action of ethyl α, α′, -dibromo-β, β-dimethylglutarate and ethyl malonate in presence of ethanolic sodium ethoxide. It was observed to be a sodium compound of a bicyclopentane derivative. It is quite a stable product, very sparingly soluble in water, and in methanolic solution it gives an intense red colouration with ferric chloride. On heating in ethanolic solution with methyl iodide the sodium is replaced by methyl group giving the methylated product (Perkin *et al.* 1901). Beesley *et al.* (1915), Ingold and Thorpe (1919), Ingold *et al.* (1923) and Grimwood *et al.* (1923) subsequently published a series of papers on the stability of such bicyclo-pentane rings and obtained other derivatives, e.g., with *spiro*-cyclohexane ring and *spiro*-cyclopentane ring in place of the *gem*-dimethyl group. However, according to Toivonen and

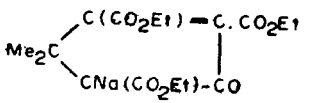
co-workers and Chakravarti (1943, 1944) the yellow sodium compound and the methylated product should be represented as cyclopentene derivatives in view of the fact that this methylated product on saturation of the double bond yielded ethyl 5-keto-1, 2, 2-trimethyl-1, 3, 4-tricarboxylate, which on hydrolysis by heating with glycerol and water gave ethyl 5-ketocamphorate. The structure of the latter was established by its straightforward conversion into camphoric acid. This is the third synthesis of camphoric acid. The previous two syntheses of camphoric acid are by Komppa (1903) and Perkin and Thorpe (1904, 1906).



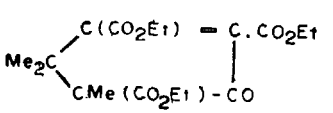
Sodium Compound of Bicyclopentane Derivative—Perkin and Thorpe (Yellow Sodium Compound)



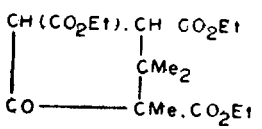
Methylated Product—Perkin and Thorpe



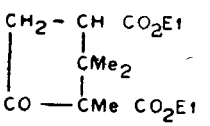
Yellow Sodium Compound Corrected Cyclopentene Structure—Toivonen



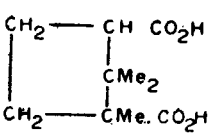
Methylated Product of Yellow Sodium Compound—Toivonen



Ethyl 5-Keto-1, 2, 2-trimethyl-1, 3, 4-tricarboxylate



Ethyl 5-Ketocamphorate



Camphoric Acid

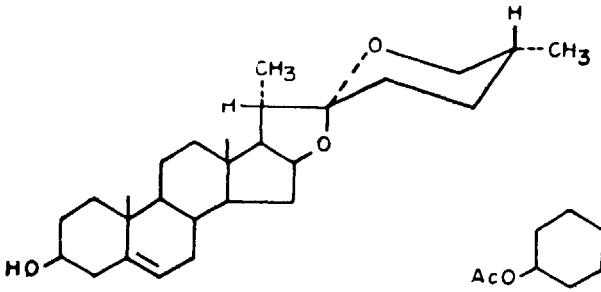
Kishner (1911) observed that by adding slowly a hydrazone to hot potassium hydroxide mixed with some platinized porous plate the corresponding methylene compound may be obtained. Wolff (1912), on the other hand, carried out the same reaction, i.e., conversion of a : CO to a : CH_2, by heating the semicarbazone or the hydrazone of the keto compound with sodium ethoxide in a sealed tube to about 180°C. This latter method is known as the Wolff-Kishner reduction. Kishner's original method, for various reasons, is not regarded as a useful one though it is

suitable for carrying out in an open flask, and over a considerable period the sealed tube heating was universally adopted. Ruzicka and Goldberg (1935) carried out the reduction successfully using a high boiling solvent like benzyl alcohol. For this purpose they heated the semicarbazone in an open flask with benzyl alcohol and some sodium. Sherk *et al.* (1945) and Soffer *et al.* (1945) used one of the high boiling solvents like octyl alcohol, triethanolamine and the ethylene glycols along with hydrazine hydrate and sodium. The simplest of the modifications is the Huang-Minlon (1946, 1948) procedure. In this the carbonyl compound is heated to 180–200°C with diethylene or triethylene glycol and sodium or potassium hydroxide in an open flask. It is no longer necessary to carry out this reduction in a sealed tube.

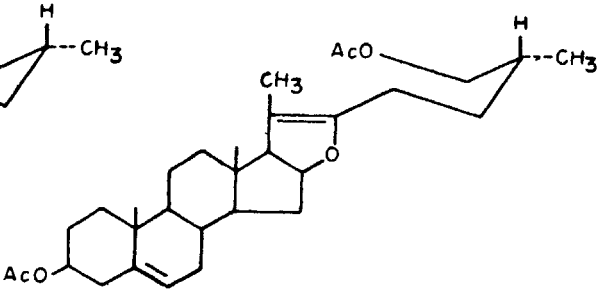
Conversion of the steroid sapogenins into pseudosapogenins constitutes the first step in the preparation of the useful hormones from these sapogenins. Marker *et al.* (1940) carried out the reaction by heating the sapogenin with five times its weight of acetic anhydride in a sealed tube at about 200°C. Several attempts have been made for developing methods for carrying out the conversion avoiding the use of a sealed tube. Butyric anhydride (b.p.198°C) was thus successfully used (Marker and Rohrman 1940) under reflux condition instead of acetic anhydride. Similarly, heating a steroid sapogenin with *n*-octanoic acid (b.p.238°C) with or without addition of a little *n*-octanoic anhydride or acetic anhydride yields the corresponding pseudosapogenin (Cameron *et al.* 1955). In case any of these anhydrides is not used in this method, azeotropic distillation of the water formed is found to be useful. There are a number of modifications in which the conversion is carried out at a much lower temperature under the catalytic influence of hydrogen ion. These do not involve use of sealed tube or high boiling solvents/reagents (Gould *et al.* 1952; Rust 1952; Dauben *et al.*, 1953, 1954).

Chakravarti *et al.* (1957, 1961) found it quite convenient to use glycerol triacetate (triacetin, b. p. 259°C) as a high boiling solvent for this conversion. According to this procedure diosgenin is heated at 192°C with some glycerol triacetate and a much smaller amount of acetic anhydride (1.5 times instead of 5 times weight of diosgenin) than is required in the usual method of Marker *et al.* (1940). The reaction is suitable for carrying out in an open flask under reflux condition using an air condenser. Yield of pseudodiosgenin diacetate is good and the product is smoothly obtained in the pure state. This method gives equally satisfactory results in the cases of preparation of the pseudogenins of tigogenin, sarsasapogenin, *epi*-smilagenin (Chakravarti *et al.* 1960), etc. and the yields are nearly quantitative. In the case of hecogenin a higher temperature (240°C) is helpful for the conversion. In all these cases, after the reaction the product separates out on dilution with water. From the pseudogenin diacetates the pseudogenins are obtained by alkaline hydrolysis. However, smilagenone by this method gave an oily product. This case is comparable to that of pseudo—Δ^4-tigogenone (Marker *et al.* 1940).

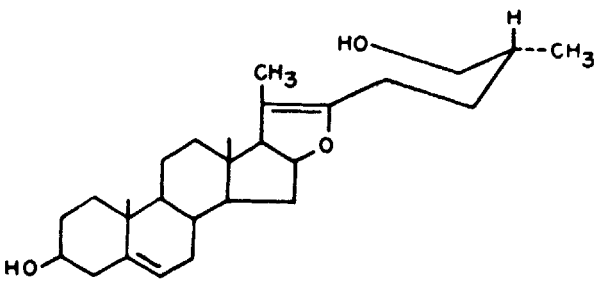
Chakravarti and Robinson (1945-47, 1947) carried out an interesting study on the action of Raney nickel catalyst on the strychnos bases in boiling xylene solution.



DIOSGENIN



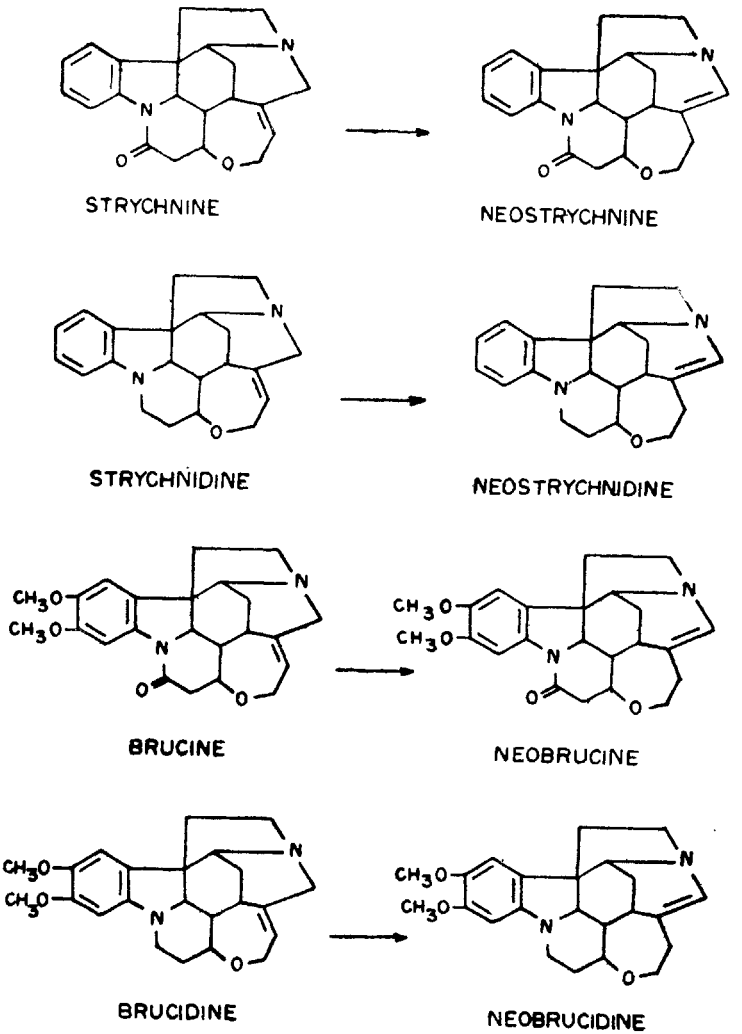
PSEUDODIOSGENIN DIACETATE



PSEUDODIOSGENIN

Under these conditions strychnine gave neostrychnine by a shift of the isolated double bond one step nearer to the basic nitrogen. i.e., from 21 (22) to 20-position. In this way, strychnidine gave neostrychnidine, brucine gave neobrucine and brucidine gave neobrucidine, all in quantitative yields. In recent years Chakravarti and co-workers made a comprehensive study of the action of Raney nickel catalyst on various steroids and triterpenoids in high boiling solvents.

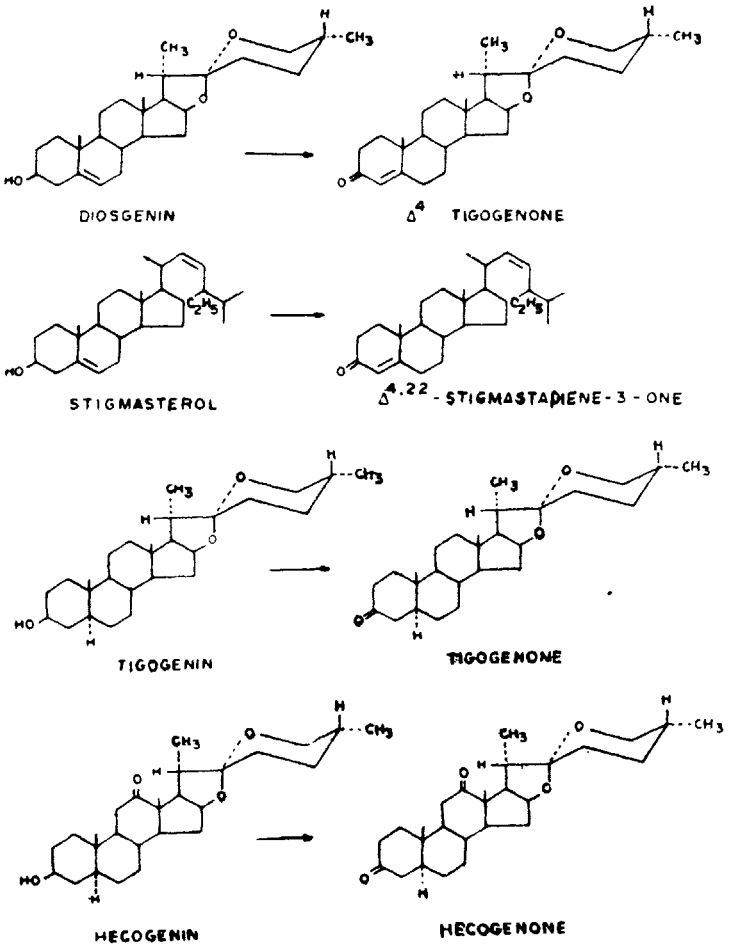
As available from a special report (Kleiderer 1945), Ruschig carried out the catalytic conversion of pregnenolone to progesterone in presence of cyclohexanone as a hydrogen acceptor. Kleiderer and Kornfeld (1948) determined the general applicability of this oxidation and also studied the possibility of using it in the reverse sense, i.e., as a reductive method in presence of a hydrogen donor, more or less similar to the use of aluminium alkoxides. A number of secondary alcohols, e.g., cholesterol and cholestanol, were oxidised to the related ketones, Δ^4-cholestenone and cholestanone respectively with Raney nickel in presence of cyclohexanone as a hydrogen acceptor. For catalytic reductions they used various types of hydrogen donors like ethanol, isopropanol and cyclohexanol. Subsequently, Romo (1952) prepared a number of 3-keto-Δ^4-steroids by oxidation of 3-hydroxy-Δ^4-steroids with Raney nickel in presence of acetone or methyl ethyl ketone as the hydrogen acceptor. According to a patent taken out by Sondheimer *et al.* (1959), steroids containing a double bond α : β to a secondary alcoholic group on treatment with



Raney nickel and a hydrogen acceptor like acetone are oxidised, the secondary alcoholic group being converted into a ketonic group.

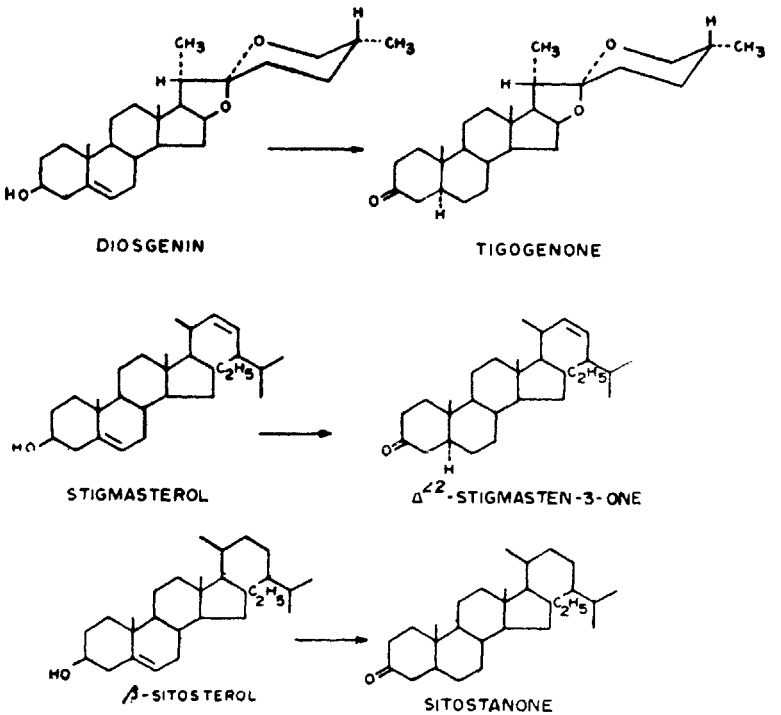
It is important to note that in all the above cases involving oxidation/reduction with Raney nickel a hydrogen acceptor/donor was invariably used, whereas in the conversion of the strychnos bases into the neo-isomers one part of the molecule acts as the acceptor and another part as the donor and no separate reagent is necessary for any such purpose. Along this line an investigation was taken up by Chakravarti *et al.* (1962, 1963, 1964) and Banerjee (1968) on the action of Raney nickel on steroids avoiding use of a separate reagent as hydrogen acceptor/donor. In the first

instance, the reaction was carried out in boiling xylene, as in the case of the strychnos bases, with diosgenin as the steroid, but most of the diosgenin was recovered unchanged. The reaction thus appeared to be very slow at the temperature of boiling xylene. Accordingly, the reaction was repeated in *p*-cymene (b. p. 177°C) solution under boiling condition. The product isolated in this case was Δ^4-tigogenone. In a similar manner stigmasterol gave $\Delta^{4,22}$-stigmastadiene-3-one, tigogenin gave tigogenone and hecogenin gave hecogenone.



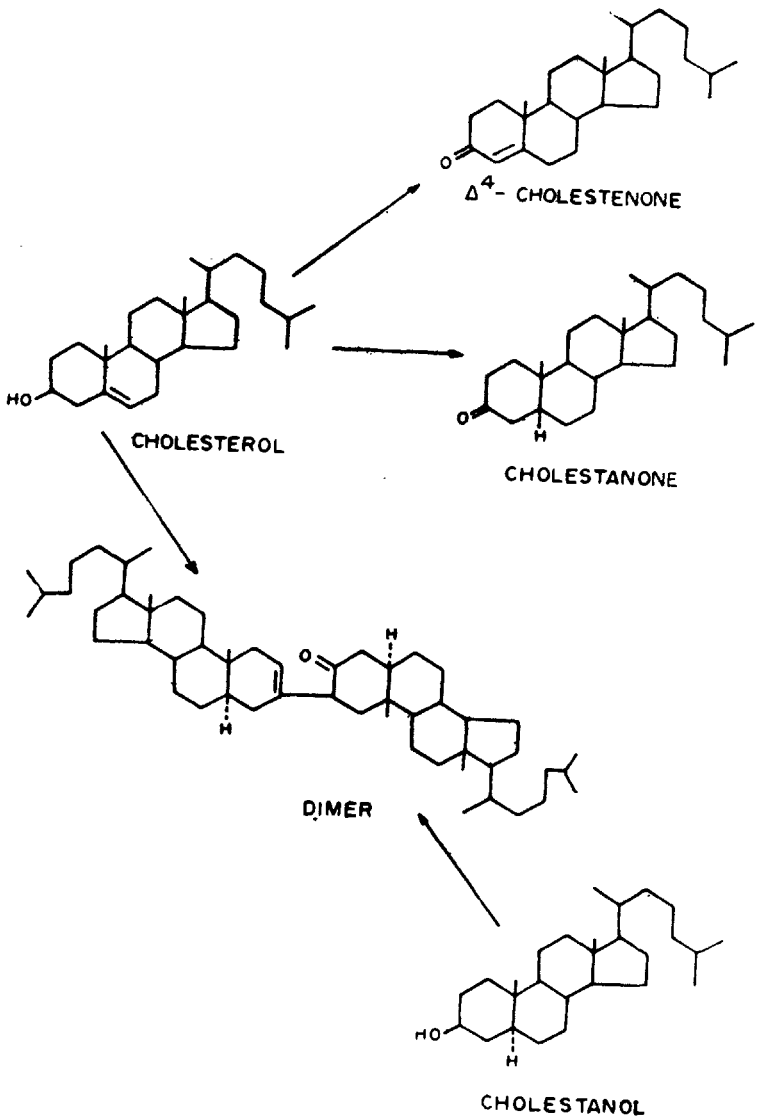
Using large excess of the catalyst, however, under the same conditions diosgenin gave tigogenone with saturation of the double bond. Similarly, stigmasterol gave Δ^{22}-stigmasten-3-one and β-sitosterol gave sitostanone.

The case of cholesterol was studied more exhaustively. In this case the normal product was Δ^4-cholestenone. With excess of the catalyst the major product was cholestanone, whereas with very large excess of the catalyst a dimer was



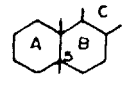
obtained. From a study of the I. R., N. M. R. and mass spectra of this dimer, its identity with the dimer of Corey and Young (1955) was established. The dimer was also obtained from cholestanol using a very large excess of the catalyst. With very large excess of the catalyst, the dimer is the only product that could be isolated.

It was observed that in these reactions where there was a saturation of 5 : 6-double bond, the configuration of A/B ring fusion of the product isolated was invariably *trans*. To confirm this finding regarding the stereospecificity of the effect of Raney nickel in high boiling solvents, steroids having *cis* configuration in A/B ring fusion were subjected to the above reaction with Raney nickel. Thus smilagenone, when heated under reflux condition with Raney nickel in *p*-cymene solution gave tigogenone having A/B *trans* configuration with 5 α-H in place of 5β-H. Tigogenone was also obtained in a similar manner from epismilagenin.

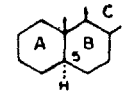


Under similar conditions coprostanone gave cholestanone and sarsasapogenin gave neotigogenone. The action of Raney nickel on cholic acid in boiling *p*-cymene appeared to be rather complex. Methyl cholate, however, gave a small yield of methyl 7α, 12α—dihydroxy-3-oxo-5α-cholanoate under similar expeimental conditions. In all these cases a 5 α-steroid is converted into 5 β-steroid.

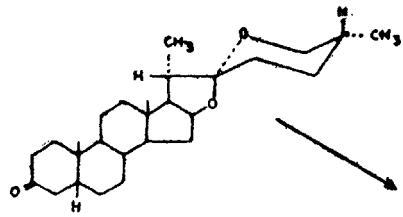
The androgenic activities of 5 β-androstanes are much weaker than those of the 5 α-isomers. In this respect it is interesting to note that in a similar manner



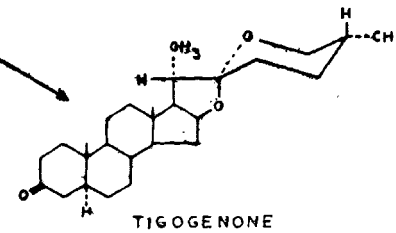
Cis A/B
(5β-H)



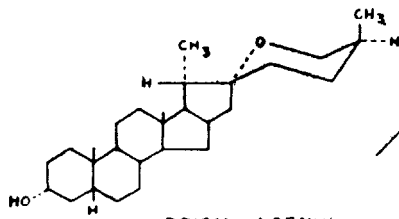
Trans A/B
(5α-H)



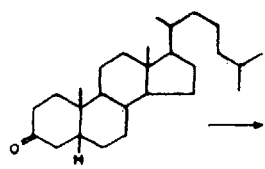
SMILAGENONE



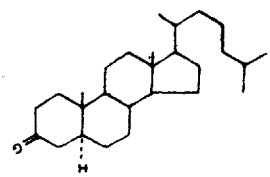
TIGOGENONE



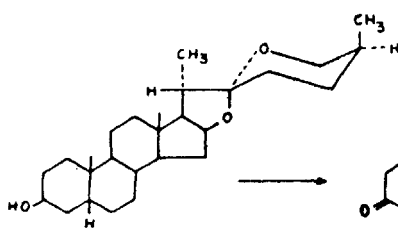
EPISMILAGENIN



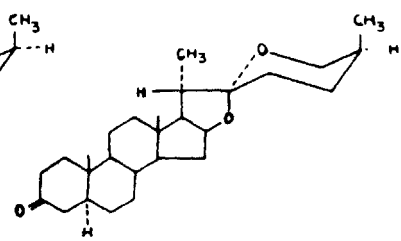
COPROSTANONE



CHOLESTANONE



SARSASAPOGENIN



NEOTIGOGENONE

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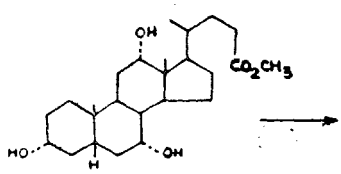
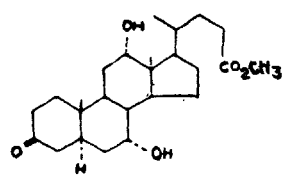
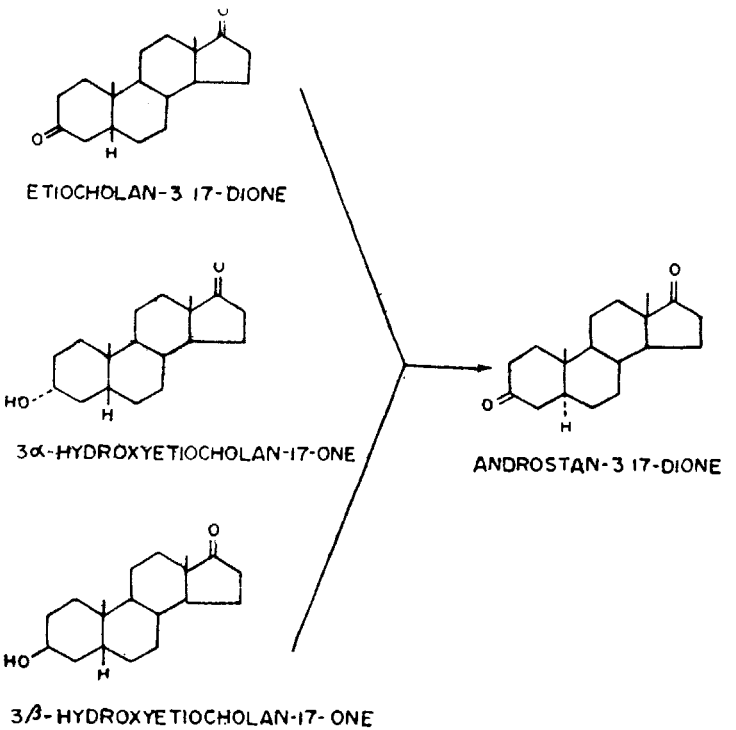


METHYL CHOLATE



METHYL 7α,12α-DIHYDROXY-3-OXO-5β-CHOLANOATE

the biologically inactive 3 α-hydroxy-etiocholan-17-one, 3β-hydroxyetiocholan-17-one and etiocholan-3, 17-dione were all smoothly converted into androstan-3 17-dione having considerable androgenic activity. Work in this line on esters of bile acids have been followed up by Ziller *et al.* (1967) and Mitra and Elliot (1968) (cf. Danielsson *et al.* 1963).



In place of *p*-cymene (b.p. 177°C) other similar high boiling solvents *e.g.*, pseudocumene (b.p. 168°C) may be used, but in such a case, at the lower temperature the saturation of the 5 : 6-double bond becomes difficult. In other words, in boiling pseudocumene solution cholesterol yields Δ^4-cholestenone but not cholestanone.

The effect of Raney nickel on steroids in boiling *p*-cymene solution thus involves four different types of reactions as summarised below :

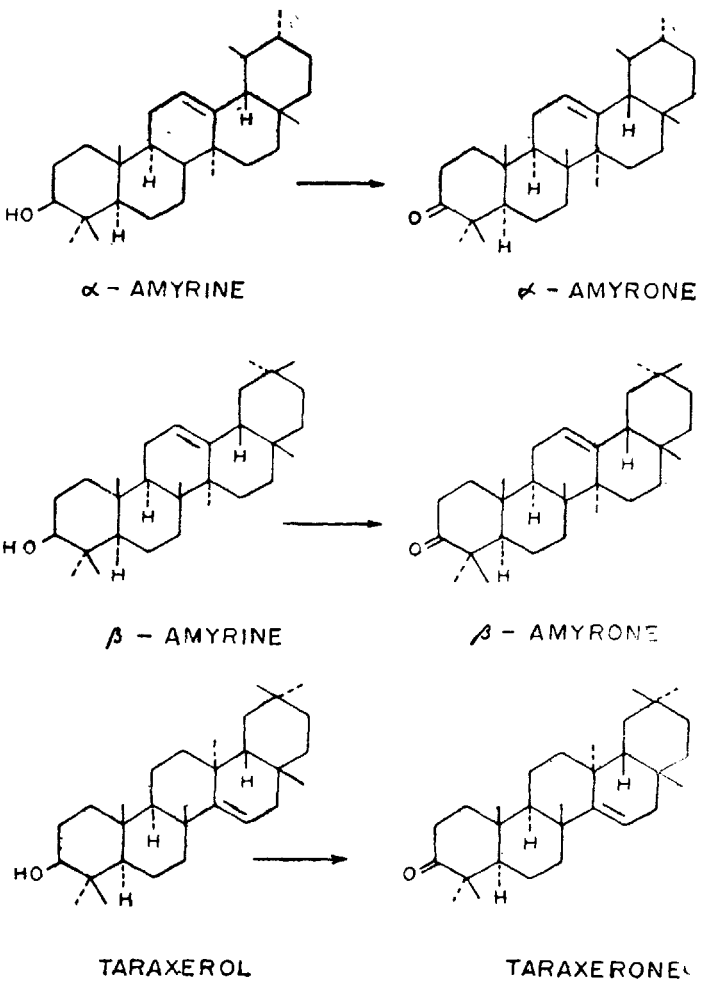
Type A—dehydrogenation (oxidation) of the 3α—or 3 β-OH group;

Type B—hydrogenation of 5 : 6-double bond;

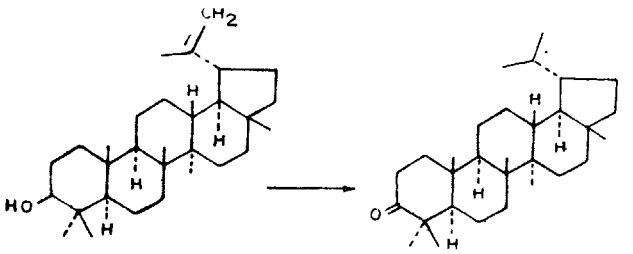
Type C—isomerization of 5 β-hydrogen to 5α—(*i.e.* cis-A/B to trans-A/B) ;

Type D—dimerization.

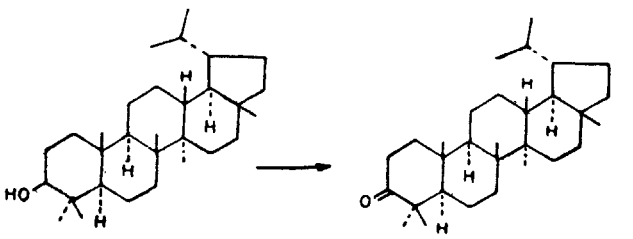
The reaction was extended (cf. Banerjee *et al.* 1965; and Mahato *et al.* 1968, 1971) to a number of triterpenes. α-Amyrin on refluxing with Raney nickel in *p*-cymene solution gave α-amyrone. Similarly, β-amyrin gave β-amyrone and taraxerol gave taraxerone. But lupeol gave lupanone with saturation of the double bond. In this case, with smaller amount of the catalyst, instead of formation of lupenone considerable amount of lupeol was recovered unchanged. Lupanone was also obtained from the saturated alcohol, dihydrolupeol in a similar manner.



The action of Raney nickel on ursolic acid and betulinic acid in boiling *p*-cymene solution appeared to be rather complex, but methyl ursolate gave methyl ursonate and methyl betulate gave the saturated keto-ester, methyl dihydrobetulonate. Epifriedelinol, a saturated pentacyclic triterpene alcohol, when refluxed with Raney nickel in *p*-cymene solution afforded friedelin, and germanicol on similar treatment gave germanicone.

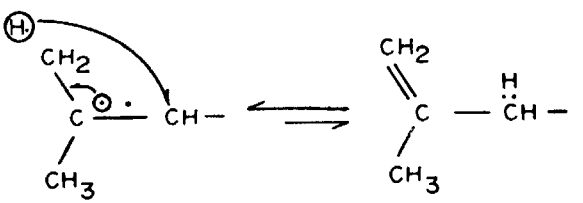


LUPEOL LUPANONE



DIHYDROLUPEOL LUPANONE

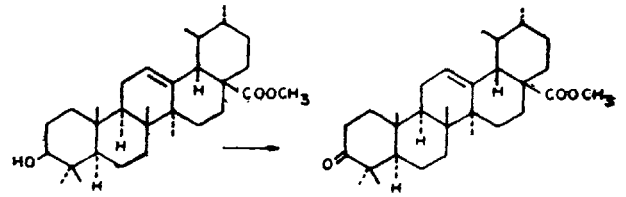
When cycloartenol was heated with a small amount of the catalyst in *p*-cymene solution, besides a small amount of the saturated ketone, cycloartanone, two isomeric unsaturated ketones were obtained, cycloartenone and a new ketone isocycloartenone. The last one was converted into the corresponding alcohol, isocycloartenol, and the latter on treatment with Raney nickel catalyst in boiling *p*-cymene yielded a mixture of cycloartenone, isocycloartenone and cycloartanone. Isocycloartenone is less stable than its isomer, cycloartenone from thermodynamic consideration and therefore, its formation requires absorption of energy, evidently supplied by the reaction. Isocycloartenone appears to be formed by a free-radical mechanism, first knocking out an allylic H atom which then adds to the olifinic carbon (Fig 1).



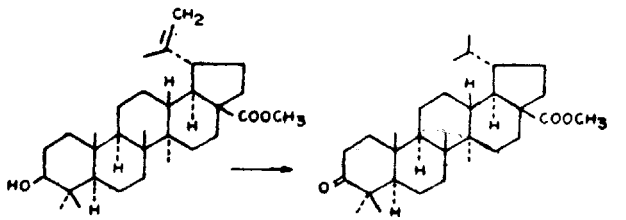
Isopropylidene Isopropenyl

FIG. 1

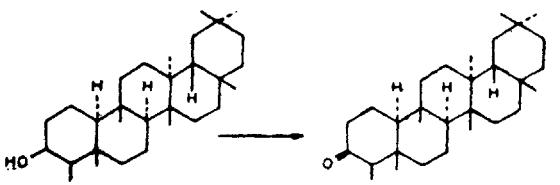
When cycloartenol (a 3 β-alcohol) was heated with an excess of the catalyst in a similar manner, the product obtained was the saturated ketone, cycloartanone. Cycloarten-3-α-ol when heated with moderately large amount of Raney nickel in *p*-cymene solution also yielded the saturated ketone, cycloartanone.



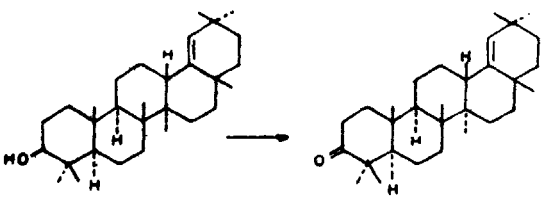
METHYL URSOLATE METHYL URSONATE



METHYL BETULATE METHYL DIHYDRO-BETULONATE



EPIFRIEDELINOL FRIEDELIN



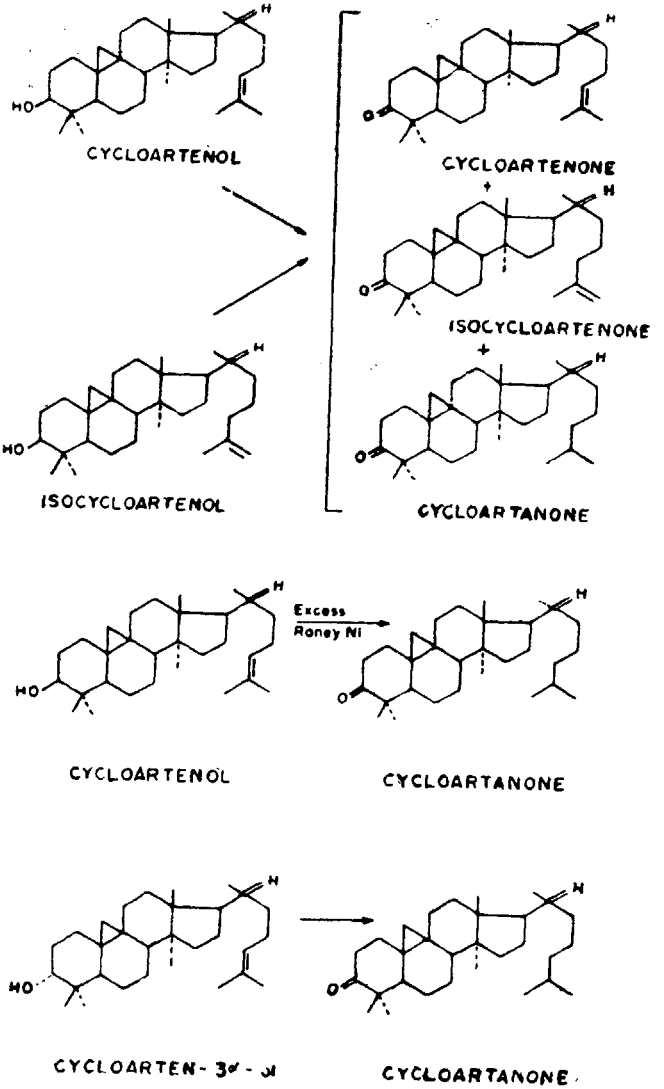
GERMANICOL GERMANICONE

When $\Delta^{9(11)}$-lanostenol was heated with the catalyst in a similar manner the product was $\Delta^{9(11)}$-lanostenone irrespective of the amount of catalyst used. Lupeol hydrochloride under similar conditions gave a ketone. 18-iso-β-amyranone. The latter product was also obtained when the reaction was carried out with 18-iso-α—amyranol. From this it is evident that under the conditions Raney nickel may bring about hydrogenolysis of triterpene chlorides.

The effect of Raney nickel on triterpenoids in boiling *p*-cymene solution thus mainly involves the following three types of reactions :

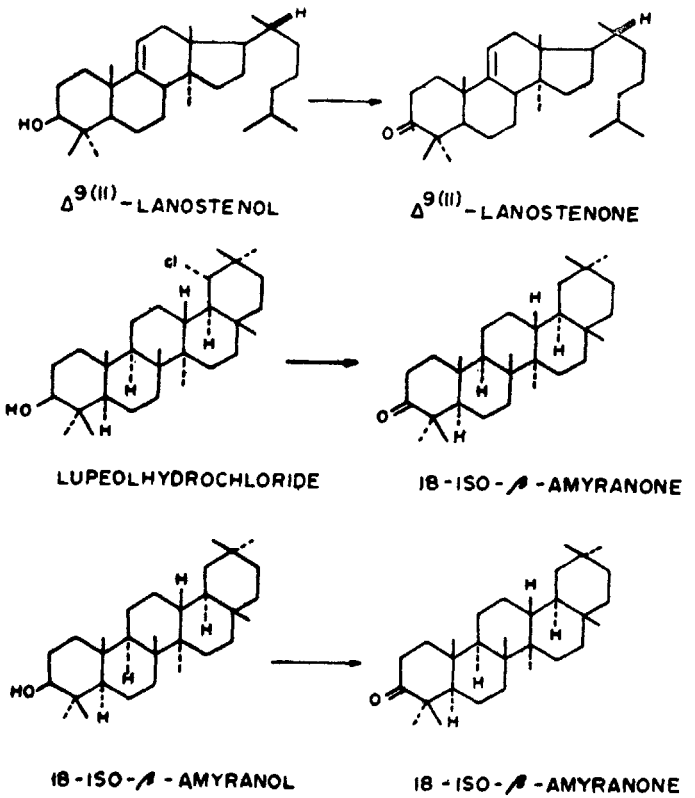
Type I—dehydrogenation (oxidation) of the 3α- or 3β-OH group;

Type II—saturation of the easily reducible double bond ;



Type III—shifting of the double bond to an adjacent position as in an allylic shift.

In addition to these different types of reactions of Raney nickel catalyst on steroids and triterpenoids in boiling *p*-cymene solution an interesting observation was made by Chakravarti and Datta (1964) in the case of yuccagenin. Under these conditions, using a large excess of the catalyst, it gave tigogenone. It seems that yuccagenin with the hydroxy group in 3 α-position is first changed to the corresponding 5 : 6-dihydro-3-keto compound, and the latter by allylic fission loses the 2 α-hydroxy group giving tigogenone. In line with this it was observed that both gitogenin and 3-dehydrogitogenin under these conditions also yield tigogenone.

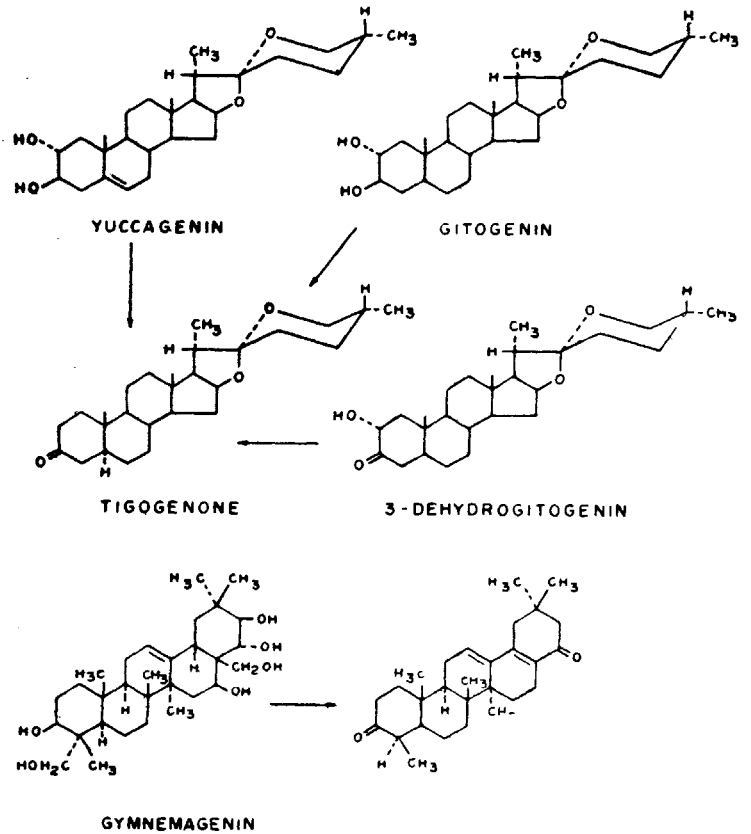


This type of allylic fission is another type of reaction (cf. hydrogenolysis in case of lupeol hydrochloride mentioned earlier) in case of both steroids and triterpenoids. An interesting example in the case of triterpenoids is the action of the catalyst under these conditions on gymnemagenin (Chakravarti and Debnath 1972). In this case the major product is a diketone formed by loss of four oxygen atoms out of six hydroxy groups of gymnemagenin as also two carbon atoms. The allylic fission type reaction is operative in this case also.

This reaction is also applicable to other classes of terpenes. For example, menthol yields nearly quantitative yield of menthone (Chakravarti and Debnath 1972).

The Raney nickel reaction appears essentially to be a hydrogenation *cum* dehydrogenation process, possibly involving a free radical intermediate. When a conjugated steroid ketone like cholest-4-en-3-one was heated with Raney Ni in *p*-cymene no reduction of the double bond took place and the ketone could be recovered unchanged. It was thought that the double bond in conjugation with the carbonyl group, being stabler than isolated double bond, where no delocalization of the π-orbitals is possible, might have resisted the hydrogenation under the

conditions. Hence the reaction was carried out with a few triterpene ketones with easily reducible isolated double bond like cycloartenone, lupenone, methyl keto-betulate, etc. In these cases also no saturation of the double bond occurred and



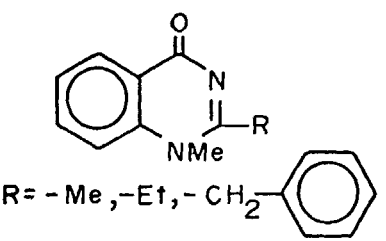
the ketones were recovered unchanged. Even unsaturated acetates like cholesteryl acetate and cycloartenyl acetate were unaffected by this recation. But unsaturated 3-hydroxy steroids or terpenoids smoothly furnished the saturated ketones on treatment with Raney Ni in boiling *p*-cymene solution. Thus the hydrogen necessary for the reduction of the double bond appears to be supplied from the reacting molecules and not necessarily from the Raney Ni itself. The hydrogen evolved on dehydrogenation of the alcohols actually brings about the saturation of the double bond in presence of the catalyst. The solvent may perhaps consume some amount of this liberated hydrogen.

The fact that for the formation of a saturated ketone larger amount of the catalyst is necessary, seems to suggest that with the increase in the amount of the catalyst, the availability of the surface, where reduction of the double bond with the liberated hydrogen takes place, increases—thus increasing the availability of hydrogen for reduction of the dehydrogenated product, possibly in the free

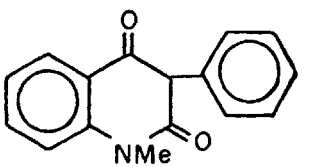
radical state, on the surface of the catalyst. These hold good in the case of steroids also.

One interesting point to note in this connection is that triterpene alcohols with a reducible double bond on heating with Raney Ni in *p*-cymene yield in most cases the saturated ketone, whilst in the case of steroids with 5 : 6-double bond both unsaturated and saturated ketones are obtained. This may be explained as follows. Dehydrogenation of 3-OH group of steroids having 5 : 6-double bond promotes a shift of the double bond to 4 : 5-position to attain stabilization by delocalising the π-orbitals. With triterpenes hydrogenation of the isolated double bond involving the breaking of the π-bond is much easier than the hydrogenation of the more stable conjugated steroid ketone. Although the solvent *p*-cymene is quite stable, it probably consumes an appreciable amount of the liberated hydrogen because here the lower reactivity is compensated by a higher probability of successful collision on account of the quantity of the solvent used.

A parallel case of a neutral alkaloidal product is that of aegeline studied by Banerjee and Chakravarti (1965). Each one of aegeline, dihydroaegeline and

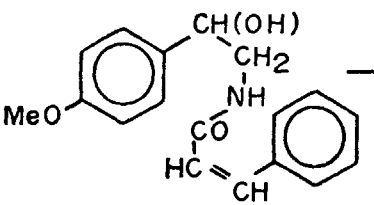


(Arborine)

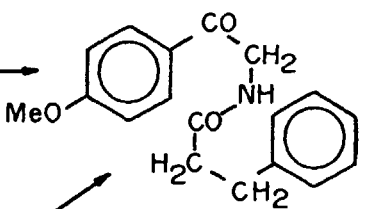


Arboricine

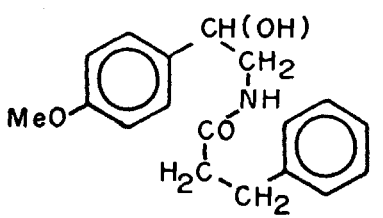
(1-Methyl-3-phenyl-carbostyril)



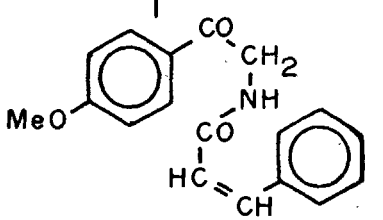
Aegeline



Dihydroaegelone



Dihydroaegeline



Aegelone

aegelone, when heated with Raney nickel in boiling *p*-cymene, afforded dihydroaegelone in good yields.

In some synthetic reactions, which are usually carried out at high temperatures by direct heating of the reactants, the yields become much better if the heating is carried out using nonreactive solvent having the desired high boiling point. For instance, 1 2-dimethyl-4-quinazolone, 2-ethyl-1-methyl-4-quinazolone and the alkaloid arborine were previously synthesised by Chakravarti and his collaborators (Chakravarti *et al.* 1953; Chakravarti *et al.* 1961; and Chakravarti, 1963) by first acylating N-methylanthranilamide with acetic anhydride, propionic anhydride and phenylacetyl chloride respectively and then heating the acylated product to 190°C. The yields are much improved when the reaction is carried out by heating the reactants in boiling *p*-cymene (Chakravarti and Adhya 1963). So also is the case of synthesis of arboricine (1-methyl-3-phenylcarbostyril), a product formed from arborine by heating with alkali solution. It was previously synthesised by Chakravarti and his collaborators in 14 per cent yield by heating a mixture of methylaniline and ethyl phenylmalonate to 210-220°C. In the modified method of Chakravarti *et al.* (1961) and Adhya *et al.* (1960) by heating the mixture in boiling *p*-cymene the yield is as high as 75 per cent.

There are cases of avoiding a high pressure reaction making use of alternative reagents suitable for the purpose and this holds good even where *Le Chatelier's* principle is important. For instance, the conversion of : CO to : $CH(NH_2)$ with hydrogen and ammonia at an elevated temperature may sometimes be replaced with advantage (Leuckart 1885) by adopting an old method by heating the keto compound with formamide. This method was found to work smoothly in the case of conversion of *l*-diethylamino-*n*-pentan-4-one (Novalketone) into *l*-diethylamino-4-amino-*n*-pentane (Novaldiamine) (Bardhan and Chakravarti 1940).

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