NEIGHBOURING GROUP PARTICIPATION IN NATURAL PRODUCTS CHEMISTRY

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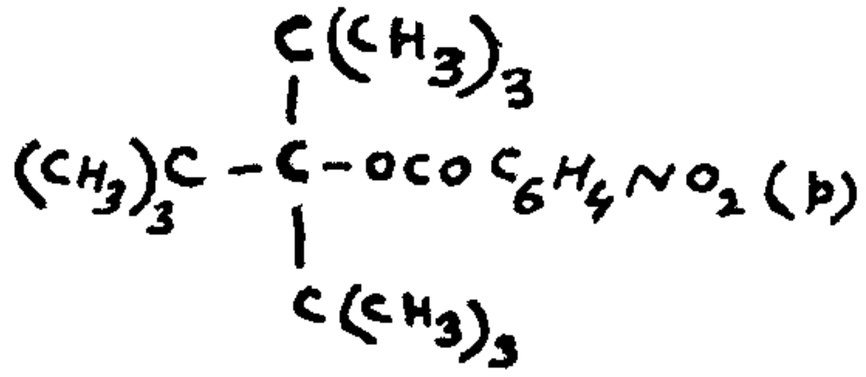
INTRODUCTION

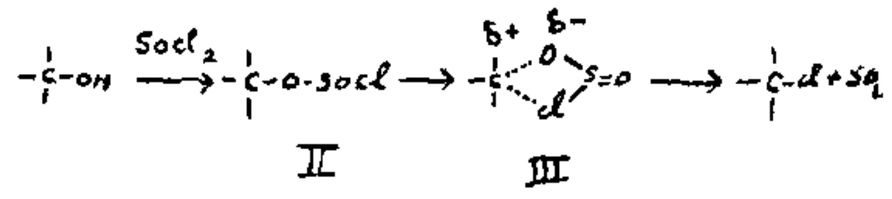
THE rate of reaction and the nature of the products formed when an organic molecule is involved depends to a very large extent on the main structure of the molecule and the groups present in it. These groups can alter the course of a reaction through the operation of inductive, resonance and steric effects individually or through combination. For example, higher dissociation constant of chloroacetic acid as compared to acetic acid is due to the inductive effect of chlorine.[1] *p*-Nitrophenol is about 600 times as strong an acid as phenol mainly because of resonance effect.[2] Those reactions in which there is a decrease in crowding in going from reactants to products are speeded up and the reactions in which crowding is increased are slowed down. For example the *p*-nitrobenzoate (I) undergoes solvolysis at a rate much faster than tert. butyl *p*-nitrobenzoate and this difference is primarily attributed to steric factor.[3] In all such cases the substituent makes the electrons move in one direction or the other and are not directly connected with the reaction centre. Recently considerable attention has been paid to those reactions in which the rate and the course are altered by a neighbouring group which gets directly involved with the reaction centre. This has been found to take place in nucleophilic and electrophilic substitutions as well as in free-radical reactions. The present discussion is however limited only to the first type as this class of reactions has been most extensively studied.



I

STERIC ASPECTS OF NUCLEOPHILIC SUBSTITUTION REACTIONS

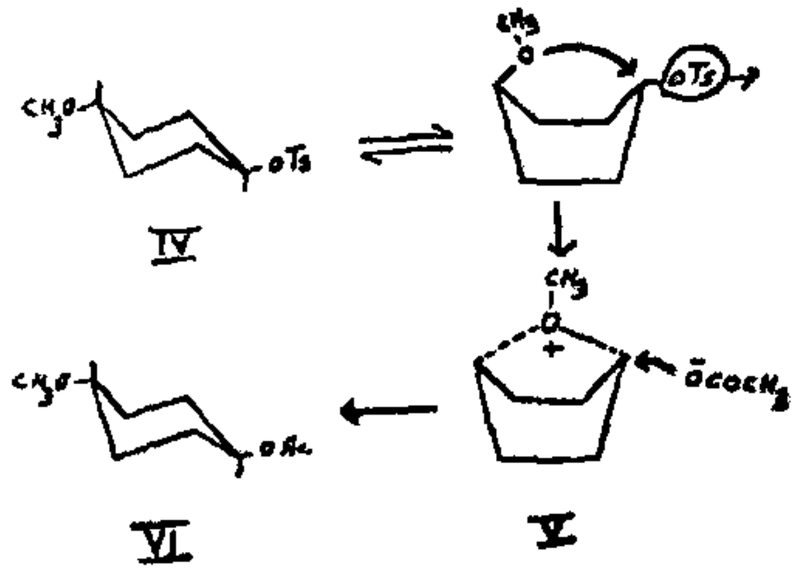
Substitution by nucleophilic reagents is known to proceed primarily through two pathways designated as S_N1 and S_N2. S_N2 reactions almost always give products with inversion of configuration and provide satisfactory explanation for Walden Inversion. On the other hand reactions proceeding through S_N1 mechanism normally give racemic products except in some special cases when products with retained configuration are formed. This retention of configuration can be due to two reasons. One reason is the operation of internal nucleophilic substitution mechanism designated as S_Ni. This is best illustrated by the formation of chlorides from optically active alcohols by thionyl chloride.[4,5] The reaction proceeds through the formation of alkyl chlorosulphite (II) which can be isolated and on heating gives the chloride of retained configuration arising from the cyclic intermediate (III).



II III

NEIGHBOURING GROUP PARTICIPATION[6-8]

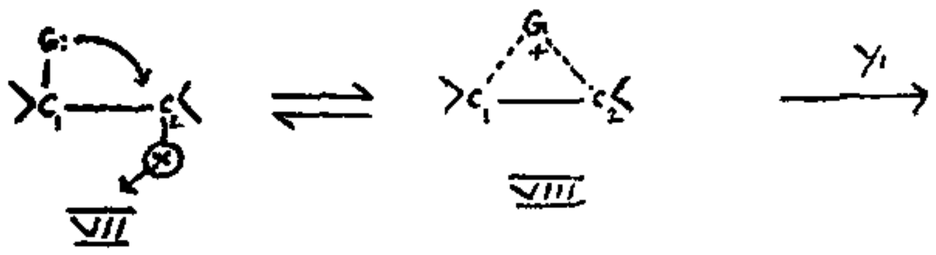
The other reason for the formation of products with retained configuration is the neighbouring group participation. It can be best explained by considering the following example. *trans* 4-Methoxycyclohexyl tosylate (IV) on acetolysis produces acetate with predominant retention of configuration (VI).[9] Participation by methoxyl group produces the cyclic structure (V) in the boat form which is considered to be responsible for the formation of the product with retained configuration as shown below.



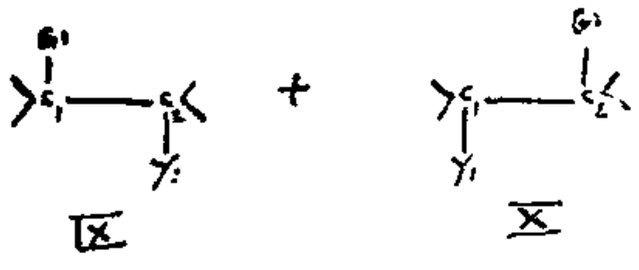
IV V VI

Neighbouring group participation is said to take place when the group gets partially or fully

bonded with the reaction centre in the transition state and this is intramolecular. Groups which have unshared electrons (*e.g.*, —OH, —O⁻, —OR, —SR, —NR_2, —COOR) or groups having π-electrons (*e.g.*, double bond, aryl group) can participate by attacking an electron-deficient centre from the rear, somewhat in the manner of substitution reactions proceeding by S_N2 mechanism. In most of the reactions of this type the neighbouring group is located behind the carbon atom undergoing substitution and is therefore better posed for attack than if it were a part of a different molecule. In a typical case like (VII) when the group G : participates in the elimination of group 'X' a cyclic transition state[10] (VIII) is obtained which is susceptible to attack at either C_1 or C_2, thus giving either the product with retained configuration (IX) or the rearranged product (X).



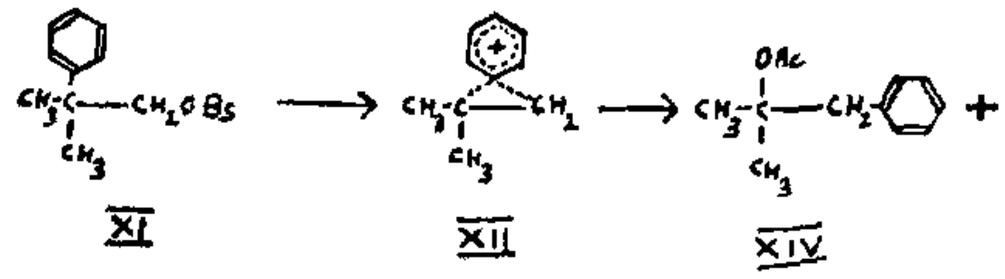
VII VIII



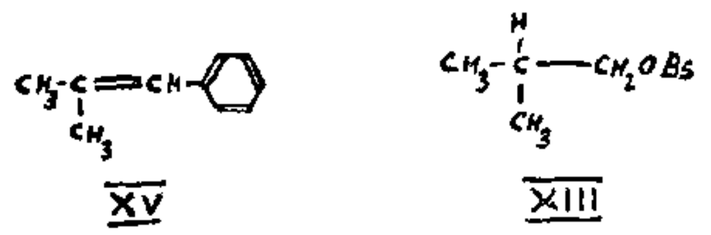
IX X

As a result of neighbouring group participation three principal types of results are obtained. Firstly, the rate of reaction is appreciably higher when participation takes place in the rate-determining step as compared to a similar reaction devoid of participation. In such cases the neighbouring group is said to provide 'anchimeric assistance'.[11] For example, acetolysis of 2-methyl-2-phenylpropyl brosylate* (XI) proceeds about 80 times faster than that of isobutyl brosylate (XIII) because of participation by the phenyl group to give phenonium ion[12] (XII). Sometimes the participation takes place after a rate-determining ionisation. In such cases no anchimeric assistance is observed.[13]

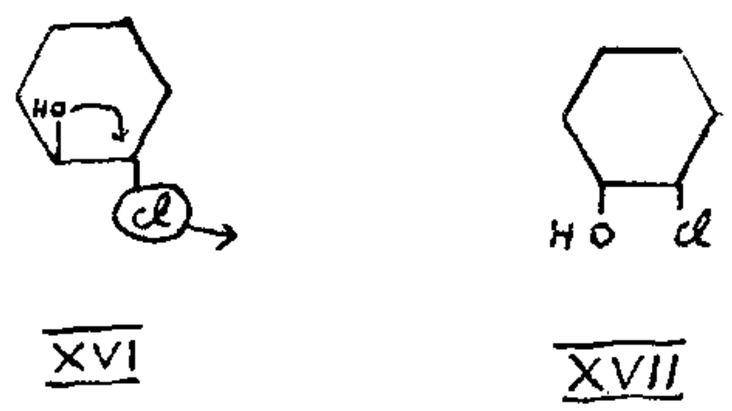
Secondly, neighbouring group participation usually has stereochemical consequences, such as the formation of products with retained configuration. This point has already been illustrated by the conversion of (IV) into (VI). Retention of configuration is normally due to attack of 'Y' at C_2 in (VIII). When there is effect of neighbouring group participation it can be inferred that the participating group is so located that it can approach the reaction centre from the rear and thus enable one to distinguish between different steric forms of a molecule. Of the two geometric isomers of 2-chlorocyclohexanol the *trans* isomer (XVI) can be distinguished from the *cis* isomer (XVII) because its rate of reaction with alkali which is about 100 times faster than that of the *cis* isomer.[14]



XI XII XIV



XV XIII



XVI XVII

Thirdly, neighbouring group participation quite frequently leads to molecular rearrangement when the participation is strong enough to form a covalent bond with the reaction centre. The rearranged product is formed because of the attack in the transition state by the entering nucleophile at a carbon atom other than the one which loses the substituent, *e.g.*, the attack of 'Y' at C_1 in (VIII). This can be exemplified by the conversion of the brosylate (XI) on acetolysis into the rearranged olefin (XV) and the acetate (XIV). Several rearrangements like pinacol-pinacolone rearrangement and Wagner-Meerwein rearrangement are considered to involve neighbouring group participation. Typical examples are discussed later on.

Role of Neighbouring Group Participation in the Chemistry of Natural Products

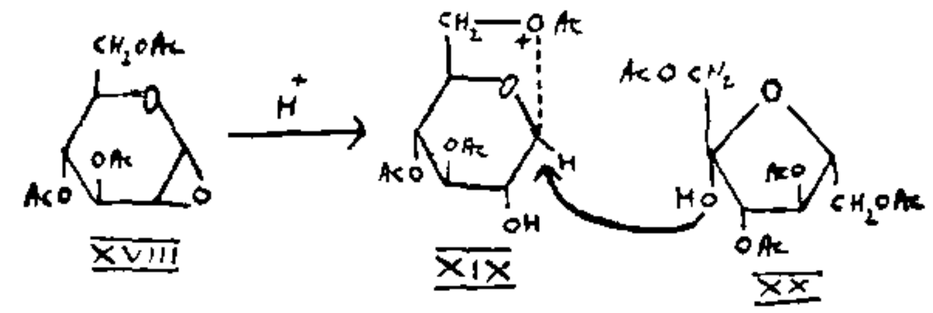
Most of the reactions in the chemistry of natural products have not been studied from the mechanistic point of view. It is therefore difficult to say precisely the mechanism followed but quite frequently analogies are drawn from the reactions

* Brosylate is the abbreviation for *p*-bromobenzenesulphonate.

of simpler compounds which are not of natural origin. Using analogies drawn from the neighbouring group participation reactions the chemistry of natural products can be provided a new approach. Some applications of this type of reactions to the different aspects of natural product chemistry, i.e., synthesis, biogenesis and rearrangements are discussed below.

Synthesis.—Synthesis of naturally occurring compounds involves two main difficulties. The first is the preparation of either the intermediate or the final compound in a particular steric configuration. This difficulty can be overcome by making use of the steric effects of the neighbouring groups as has been done in the synthesis of sucrose.

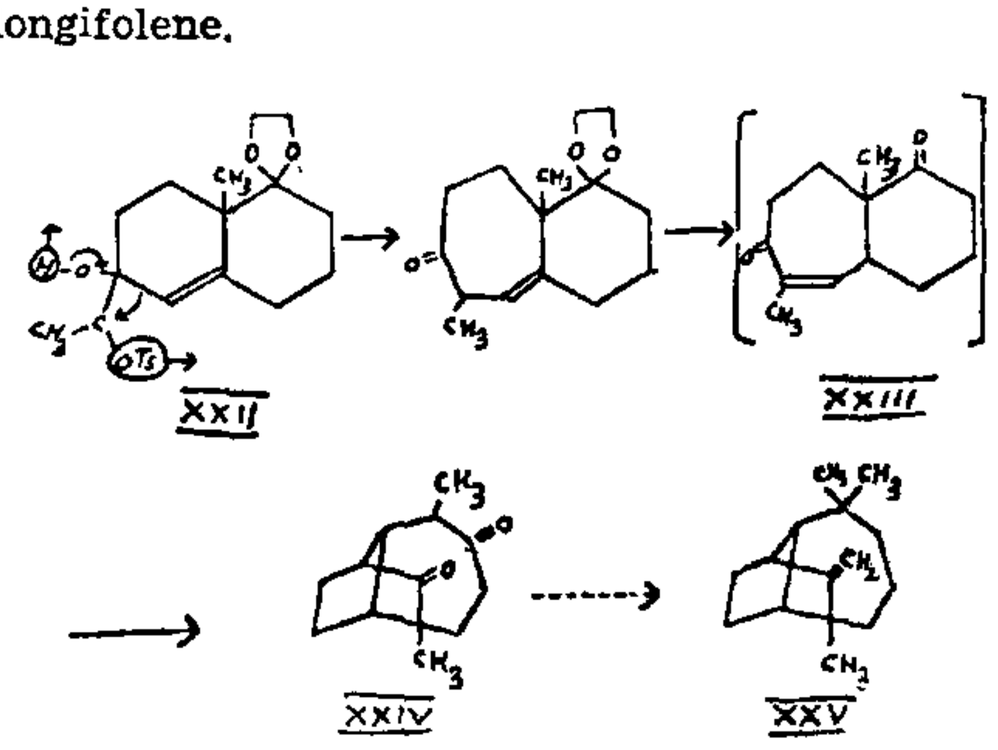
Sucrose.—Synthesis of sucrose remained a major problem for more than two decades after its structure was established in 1930. The main difficulty was to obtain $\alpha:\beta$-linking of glucose and fructose units. In ordinary methods of synthesis the opposite configuration is obtained; for example the condensation of the tetraacetyl anomers of glucose and fructose in presence of dehydrating agents yields only isosucrose octaacetate[15] ($\beta:\alpha$-isomer). Lemieux and Huber solved the problem by employing the principle of neighbouring group participation.[16] The important intermediate in the synthesis is the Brigl anhydride (XVIII) which is attacked



by alcohols at C_1 to give glucosides. Simpler alcohols, like methanol and ethanol, give β-glucosides, whereas higher alcohols, like menthol and cholesterol, give mixtures of α- and β-glucosides probably due to the fact that the approach of the higher alcohols to form β-glucosides is sterically hindered. Further, neighbouring group participation as shown in (XIX) also helps considerably in yielding the α-glucosides. Fructose tetraacetate (XX) being also a bulky molecule was expected to react in a way favourable to the formation of α-form. This was in fact realised and the condensation of Brigl anhydride with tetraacetyl fructofuranose gave sucrose octaacetate (XXI) in a yield of about 9%.

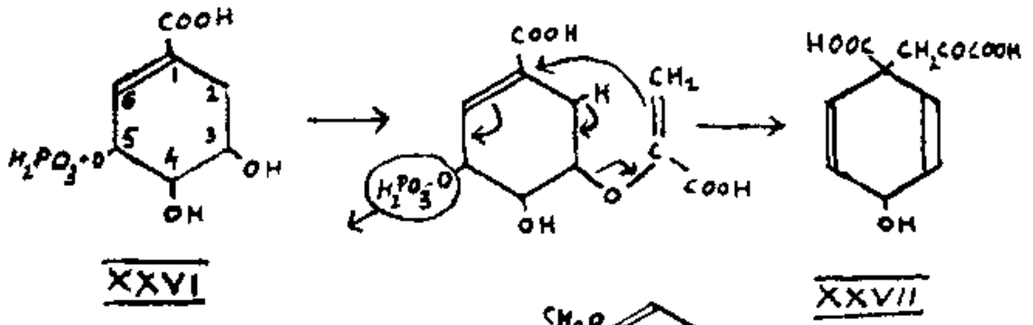
The second difficulty is the preparation of sterically strained products or intermediates. It can be overcome by making use of the driving force associated with neighbouring group participation. This is exemplified by the synthesis of cycloheptenone derivative (XXIII) in the total synthesis of longifolene.

Longifolene.—Though the tricyclic sesquiterpene, longifolene (XXV) was isolated as early as 1920, its structure was established only in 1953 by Moffett and Rogers using X-ray crystallography.[17] The synthesis of this substance also remained a difficult problem after its structural establishment. Of the several key intermediates envisaged by Corey and coworkers the cycloheptenone derivative (XXIII) was considered most suitable. It was synthesised from (XXII) by utilising intramolecular nucleophilic displacement involving π-electron participation.[18] The reaction was carried out by heating at 50° for 60 hours a solution of p-toluenesulphonate (XXII) in tetrahydrofuran saturated with lithium perchlorate containing suspended calcium carbonate. Lithium perchlorate in tetrahydrofuran solution facilitates the ionisation of the tosylate group and thus generates an electron-deficient carbon atom accompanied by the migration of the bond; calcium carbonate prevents the solution from becoming acidic. Under these conditions kinetically favoured cycloheptenone derivative is formed whereas under acidic conditions thermodynamically stable six-membered compounds would result. The cycloheptenone derivative (XXIII) when subjected to intramolecular michæl addition gave rise to ketone with the longifolene skeleton (XXIV) which could be converted into longifolene.



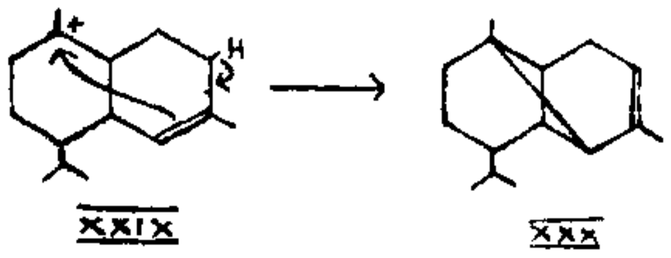
Biogenesis.—Nature produces with facility complex organic substances which are quite diffi-

cult to make in the laboratory. The mechanism followed in biosynthetic reactions is not always clearly known, but it is quite likely that neighbouring group participation plays an important role in some of the novel rearrangements encountered. Normally in the laboratory one uses *p*-toluenesulphonate, *p*-bromobenzenesulphonate, *p*-nitrobenzoate, chloride, etc., as the leaving groups but in natural processes phosphate and hydroxide can very effectively serve as the leaving groups[19] and generate an electron-deficient carbon atom which can then receive the intramolecular nucleophilic attack. Such a change probably takes place in the formation of the well-known precursor of C_9 compounds and units, prephenic acid (XXVII) from shikimic acid-5-phosphate (XXVI).[20–22] The condensation of pyruvic acid takes place in the enol form and involves neighbouring group participation. Here the π-electrons of $>C=CH_2$ act as nucleophile and the transition state also involves the endocyclic double bond. The carbon atom attacked is not the one suffering loss of phosphate as found in the previous cases but it is the C_1 which is in conjugation. A similar type of change has been shown to be involved in the biogenesis of thebaine (XXVIII) in *Papavar somniferum* plants.[23,24]



XXVI XXVII XXVIII

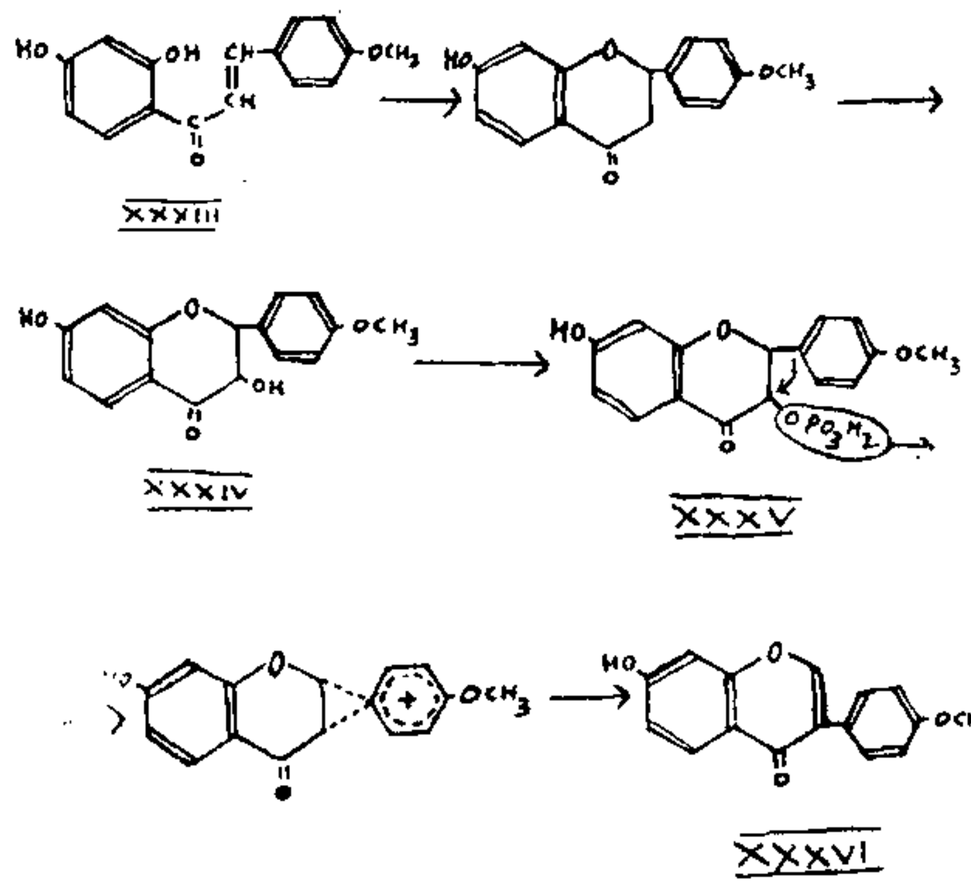
Biogenesis of terpenes.—Buchi *et al.* have indicated the possibility of formation of copæne



XXIX XXX XXXI XXXII

(XXX) from the ion (XXIX).[25] This conversion involves the participation by the double bond. Zierone (XXXII) has been suggested by Barton and co-workers to arise from the compound of the normal skeleton (XXXI) by the changes analogous to pinacol-pinacolone rearrangement.[26]

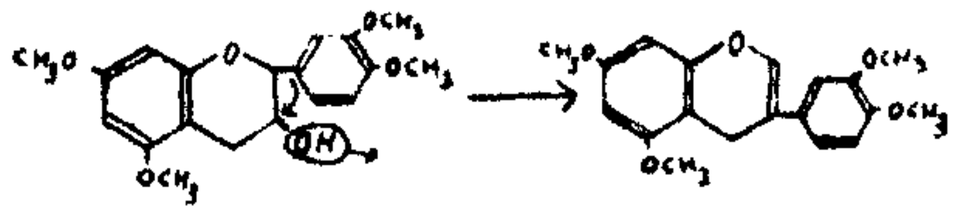
Biogenesis of isoflavones.—By using labelled precursors like phenylalanine it has been shown that the formation of isoflavone (XXXVI) from chalkone (XXXIII) involves phenyl migration.[27] The exact nature of the intermediates is not known but it is quite likely that a phosphorylated intermediate (XXXV) derived from the dihydroflavonol (XXXIV) which itself can be obtained easily from chalkone (XXXIII) as indicated below, undergoes the change.



XXXIII XXXIV XXXV XXXVI

Against the formation of isoflavones from the above hydroxyflavanone it may be argued that the creation of positive charge on carbon atom α- to the carbonyl group is not favoured and therefore such a change could not take place. However, in the change shown above from the phosphorylated intermediate, the transition state involves a non-classical carbonium ion in which the positive charge is spread over the aryl ring.

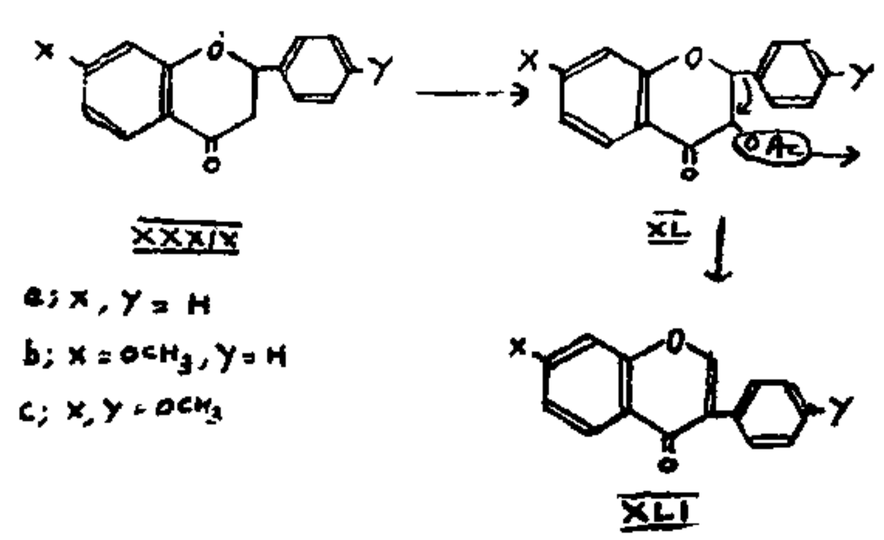
Similar type of migration has been found to take place in the conversion of tetra-o-methyl-catechin (XXXVII) into the isoflavene (XXXVIII).[28] This system differs from the



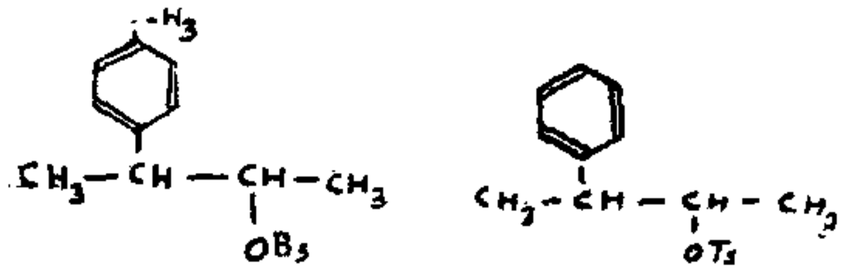
XXXVII XXXVIII

isoflavone system by the absence of the carbonyl group.

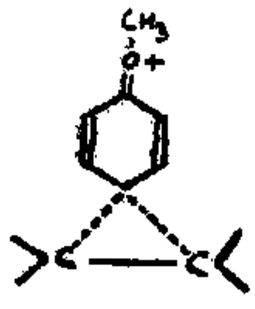
A more appropriate example is the formation of isoflavones in the reaction of flavanones with lead tetraacetate. Flavanone (XXXIX *a*), 7-methoxy flavanone (XXXIX *b*) and 7 : 4'-dimethoxy flavanone (XXXIX *c*) yield the corresponding isoflavones (XLI) along with other products on treatment with lead tetraacetate.[29] The first step seems to be the oxidation to form the 3-acetoxy derivative (XL) from which isoflavone seems to arise by aryl migration as shown below.



The view that the aryl migration in the above-mentioned cases probably involves neighbouring group participation mechanism is strongly supported by the fact that almost all the isoflavones isolated so far have oxygen functions like —OH, $-OCH_3$, $-O-CH_2-O-$, etc., in the ring B. These substituents are known, from the kinetic data and the study of products formed to strongly favour participation by the aryl group. Participation by the phenyl group as such is rather poor as the rate due to the anchimeric assistance by the phenyl group is opposed by its rate-retarding inductive effect.[11] Increased participation by the aryl groups carrying $-OCH_3$ groups is evident from the fact that 3-*p*-anisyl-2-butyl brosylate (XLII) suffers acetolysis about 300 times faster than 3-phenyl-2-butyl tosylate (XLIII).[30] This behaviour of oxygen function is attributed to the stabilisation of the 'phenonium ion' by helping to disperse the positive charge as shown in (XLIV).



XLII XLIII

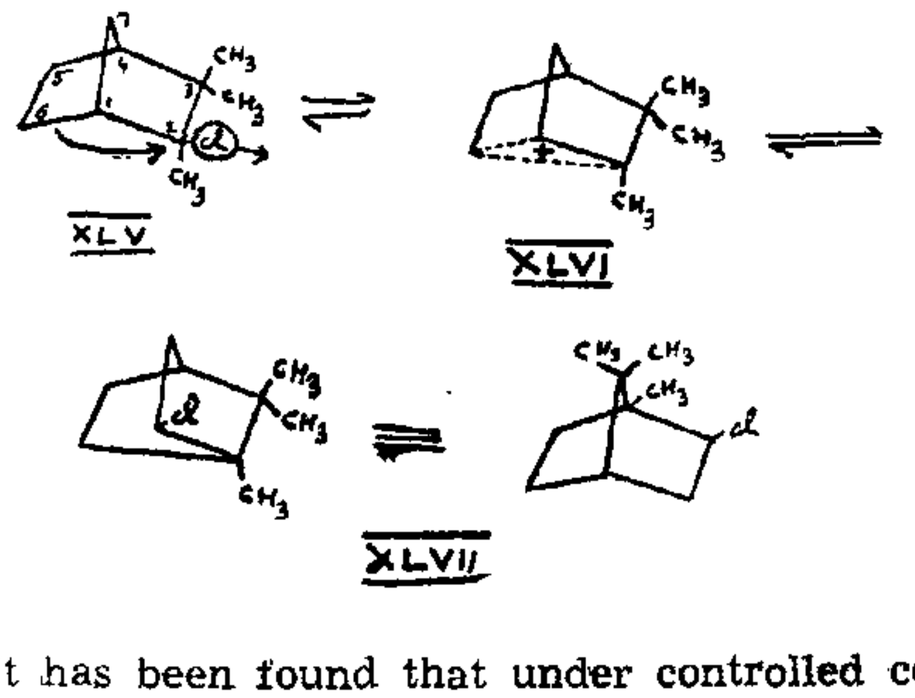


XLIV

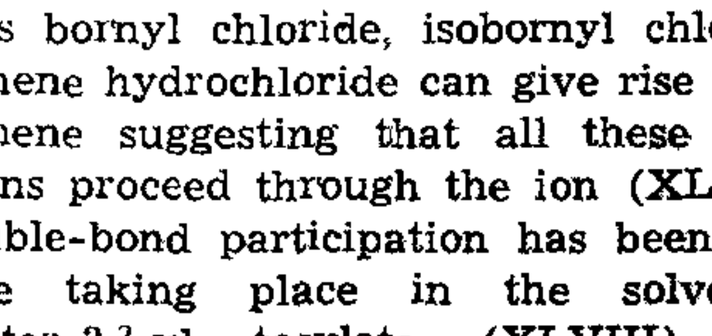
Some Typical Reactions of Naturally Occurring Compounds Involving Neighbouring Group Participation

Compounds of natural origin have been found to give rise to other products, which may or may not be naturally occurring by reactions involving neighbouring group participation. Besides being of preparative importance the participation reactions have also been utilised to acquire some insight into the stereochemistry of the compounds concerned. One comes across a large number of such reactions in the study of terpenoid compounds with the result that some of these reactions of terpenes have been studied in great detail from the mechanistic point of view.

The conversion of camphene hydrochloride (XLV) into isobornyl chloride (XLVII) is a classical example of Wagner-Meerwein rearrangement.[31] Rate of solvolysis of this chloride (XLV) is about 300-800 times faster than ordinary tertiary chlorides. This is attributed to the anchimeric assistance provided by the carbon atom at the 6 position to ionisation at the 2 position resulting in the formation of the non-classical carbonium ion (XLVI).



XLV XLVI

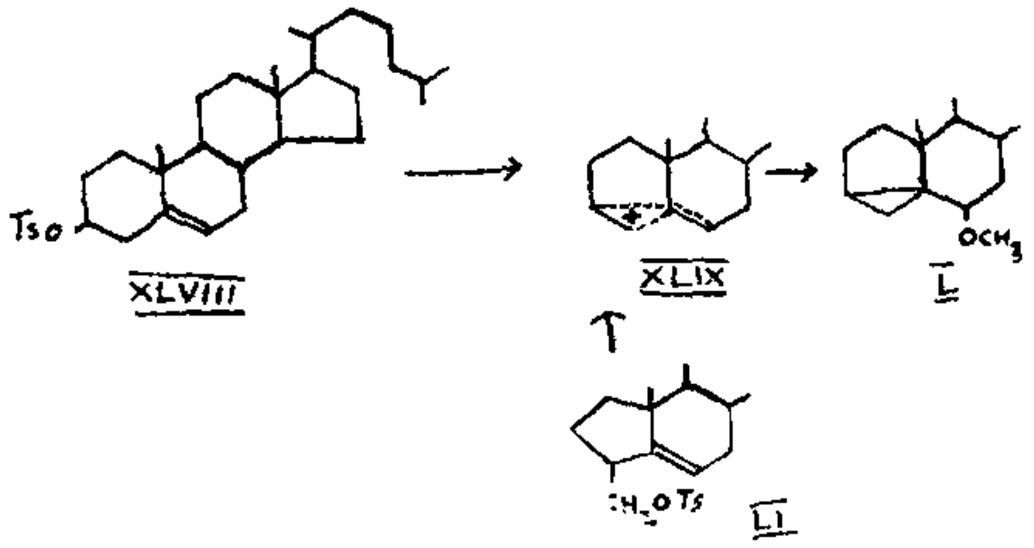


XLVII

It has been found that under controlled conditions bornyl chloride, isobornyl chloride and camphene hydrochloride can give rise to mainly camphene suggesting that all these interconversions proceed through the ion (XLVI).

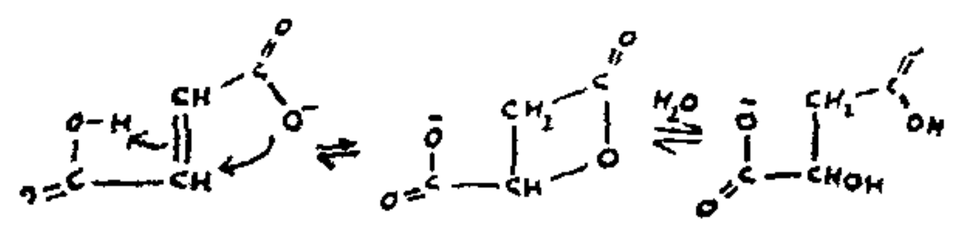
Double-bond participation has been reported to be taking place in the solvolysis of cholester-3β-yl tosylate (XLVIII) on the basis of the products formed and its rate of solvolysis which is more than a hundred times faster than the corresponding saturated

compound.[32,33] The tosylate (XLVIII) on methanolysis in presence of potassium acetate yields methyl ether of 3, 5-cyclocholestan-6-ol (L) (90%) and cholester-3 β-ol.[34] In this case the non-classical ion (XLIX) is suggested to be involved because tosylate of 3-hydroxymethyl-A-norcholest-5-ene (LI) can also give rise to the ion (XLIX) and has been found to yield the same solvolytic products.[35]



XLVIII XLIX L LI

Recent investigations have shown that simple conversion of fumaric acid (LII) into malic and (LIII) involves participation of the carboxy-



LII LIII

late group and the intermediate formation of the 6-lactone as shown above.[36]

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