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The Favorskii Rearrangement

A.A.Akhrem, T.K.Ustynyuk, and Yu.A.Titov

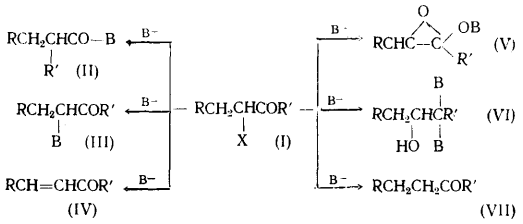
The skeletal rearrangement of α-halogeno-ketones, which is known as the Favorskii rearrangement, is met most frequently in aliphatic monocyclic, and polycyclic halogenated ketones. This molecular rearrangement is used in the synthesis of branched carboxylic acids and *cis*-αβ-unsaturated acids and for obtaining smaller rings in alicyclic and to a less extent heterocyclic compounds. The sterochemistry and the mechanism of the Favorskii rearrangement are also considered, these being of great interest for theoretical organic chemistry. A list of 261 references is included.

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I. INTRODUCTION

The rearrangement of the carbon skeleton of α-halogeno-ketones (I) (here and subsequently X denotes a halogen and B^- the anion of a base), which occurs under the influence of bases, is termed the Favorskii rearrangement. Various derivatives of carboxylic acids (II) containing the same number of carbon atoms as in the initial ketone can be formed depending on the base used and the number of halogen atoms in the ketone. The α-halogeno-ketones are extremely reactive compounds, and in the presence of bases they yield also products in which the halogen has been replaced (III) or eliminated (IV), oxides (V), α-hydroxy-acetals (VI), saturated ketones (VII), etc. Which reaction occurs depends on the structure of the initial ketone and the conditions.



The rearrangement of the carbon skeleton of α-halogeno-ketones was described for the first time as a general reaction by Favorskii[1-3] in 1892, although isolated examples of such rearrangements had been known earlier[4-6]. There have been several reviews[7-12] of the Favorskii rearrangement, covering the literature up to 1959.

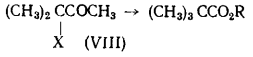
II. THE FAVORSKII REARRANGEMENT AS A SYNTHETIC METHOD

The chief synthetic uses of the Favorskii rearrangement are the preparation of branched carboxylic acids, the stereospecific synthesis of *cis*-αβ-unsaturated acids, ring contraction in alicyclic and heterocyclic compounds, and the modification of steroids.

The Favorskii rearrangement is usually effected by adding the halogeno-ketone to a solution or a suspension of the base. Hydroxides of alkali or alkaline-earth metals, alkoxides, alkali-metal carbonates and hydrogen carbonates, ammonia, and amines are used as the bases. The first two groups are strong bases, and the latter two weak bases. The solvents used can be divided into protic (water, alcohols) and aprotic (ether, dioxan, dimethoxyethane). The course of the reaction depends primarily on the structure of the initial halogeno-ketone; hence no general recommendations can be given on the choice of optimum conditions for the reaction: they must be chosen separately for each type of ketone.

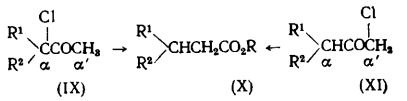
1. Aliphatic Halogeno-ketones

This is the most numerous group of halogeno-ketones. Favorskii's first work on α-monochloro-ketones was done as early as 1901[13]. The principal synthetic application of these compounds is to the preparation of branched aliphatic acids, which can be illustrated by the preparation of derivatives of αα-dimethylpropionic acid from the ketone (VIII: X = Br, Cl). Sodium methoxide in ether, the prop-2-oxide, and the phenoxide give yields of 61%, 64%, and 47% of the corresponding esters[14,15]. The free acid can be obtained in 30–40% yield by reaction of the ketone (VIII) with alkalis[16,17]:



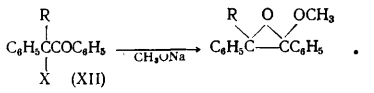
Increasing the degree of substitution at the α-carbon atom (to which the halogen is attached) usually favours the Favorskii rearrangement by lowering the rate of side-reactions, whereas substitution on the α′-atom hinders rearrangement[14,18-20]. Nevertheless, these principles are structurally equivalent: i.e. independently of the position of the halogen relative to the keto-group in compounds (IX) and (XI), the action of bases on them leads to derivatives of the same acid (X). Thus when $R^1 = R^2 = C_6H_5$, the action of sodium ethoxide on the ketone (IX) yields the acid (X: $R = C_2H_5$) in 85% yield, and on ketone (XI) in 69% yield[21]. Similar results are obtained with ketones of the types (IX) and (XI) when $R^1 = C_6H_5$, $C_6H_5CH_2$, Alk and $R^2 = H$[19,22-25]. In this case substitution of the halogen (Cl by Br) has no significant effect on the yield of the acid (X).[26,27] The equivalence of the α- and α′-positions is important in the synthetic application of the Favorskii rearrangement: it enables ketones to be brominated directly and the resulting mixture of α-bromo- and α′-bromo-isomers to be subjected to rearrangement

without separation, with the formation of a single reaction product[20].



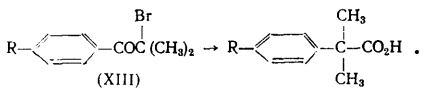
(IX) (X) (XI)

In the case of the ketones (VIII), (IX), and (XI) it has been shown that the Favorskii rearrangement takes place with both alkylated and arylated ketones. However, when aryl substituents are present on both α- and α'-carbon atoms (XII: X = Cl, Br; R = H, Alk, Ar), rearrangement is replaced by formation of the corresponding alkoxy-oxides[26,28-32]:



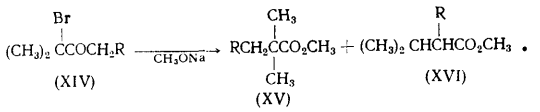
(XII)

In the above examples the α-halogeno-ketones contained an α'-hydrogen atom. However, cases are known in which rearrangement takes place in ketones containing no α'-hydrogen, e.g. in compounds of the type (XIII: R = H, C_6H_5):[33-35]



(XIII)

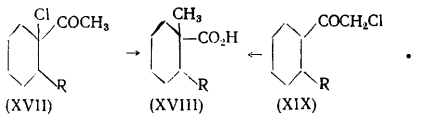
Sometimes the Favorskii rearrangement of monohalogeno-ketones yields a mixture of structural isomers. Thus ketones of the type (XIV) gave a mixture of the esters (XV) and (XVI), the proportion of the latter ester increasing from 16% to 80% with increase in the bulk of the alkyl radical R from methyl to isopropyl[36]:



(XIV) (XV) (XVI)

Possible reasons for this are discussed in Section III.

Many halogenated ketones undergoing the Favorskii rearrangement contained the keto-group in a side-chain attached to a cyclic residue. An example is the rearrangement of compounds of the type (XVII: R = H, CH_3) to the corresponding acids (XVIII)[15,37,38]. In conformity with the above equivalence of the α- and α'-positions the same acids are formed from isomeric ketones of the type (XIX: R = H, CH_3)[39,40] (see, however, Ref. 41):

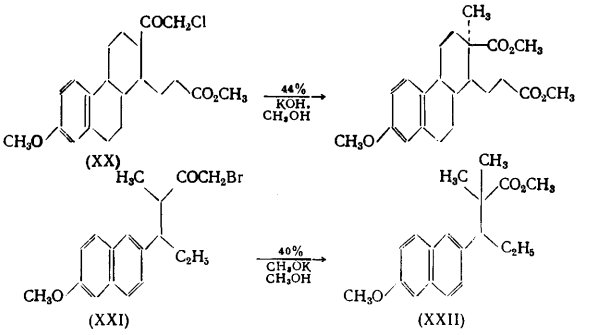


(XVII) (XVIII) (XIX)

Replacement of the chlorine atom in (XIX) by bromine favours the Favorskii rearrangement but not side-reactions[39]. Other results indicate[37] that brominated ketones of the type (XIX) form only hydrolysis products with bases.

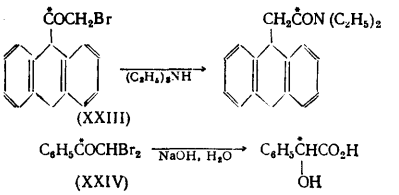
When R = CH_3, two isomeric acids (XVIII) can be formed from (XVII). It was shown initially that with sodium benzyloxide in ether the rearrangement proceeds strictly stereospecifically, with inversion of configuration at the carbon atom to which the halogen is attached[42]. Later, however, it appeared that this stereospecificity (which was not altogether exact) is observed only in aprotic solvents such as dimethyoxyethane and dimethyl sulphoxide, whereas in methanol or water a mixture of approximately equal quantities of the two possible isomers (XVIII) is formed; the proportions of the latter depend also on the concentration of the base[43-45]. Rearrangement of the isomeric chloro-ketone (XIX: R = CH_3) yields approximately equal quantities of the isomeric acids (XVIII: R = CH_3) in both protic and aprotic solvents[40].

Rearrangement of the ketones (XVII) and XIX) is of interest primarily as a method for synthesising angularly methylated tertiary acids. Such structures are present in abietic, marrianolic, and allenolic acids, and therefore the Favorskii rearrangement may prove useful for their synthesis. An example of its application to marrianolic acids is the rearrangement of the chloro-ketone (XX).[46] The resulting diester on Dieckmann cyclisation gave an isomer of oestrone ("oestrone-c"). Application of the Favorskii rearrangement to the synthesis of allenolic acids is illustrated by the conversion of the bromo-ketone (XXI) into the methyl ester (XXII).[47]



(XX) (XXI) (XXII)

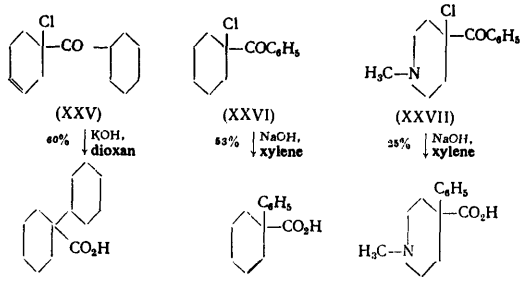
On rearrangement of the bromo-ketone (XXIII) in which the carbonyl group is labelled, in the presence of diethylamine as base, the tracer passes into the carbamoyl group, which demonstrates unambiguously that the carbon skeleton has undergone rearrangement[48]. These results are especially valuable, since only skeletal changes should be included in the range of Favorskii rearrangements. Therefore numerous examples of the reactions of α-halogeno-aldehydes with bases, for example should not be termed Favorskii rearrangements, since the carbon skeleton is not reorganised in this case, the analogy being purely formal. A tracer technique has shown that the carbon skeleton undergoes no rearrangement when the dibromo-ketone (XXIV) is converted into the corresponding hydroxy-acid[49]. Hence caution must be exercised in including reactions of dibromo-ketones of the types (XXXVII) and (XLV) in the range of the Favorskii rearrangement.



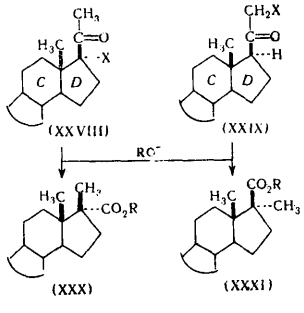
(XXIII) (XXIV)

Ketones containing cyclohexyl groups (XXV)[50-52] and aryl groups (XXVI and XXVII)[53-57] undergo Favorskii rearrangement when boiled with alkalis in aprotic solvents, to form cyclic acids which are difficult to obtain by other methods. The reaction of piperidine chloro-ketones of the type (XXVII) has found application for the synthesis of the analgesics demerol and β-pethidine[54,56,58]. In optically active compounds of the types (XXVI) and (XXVII)

the Favorskii rearrangement is accompanied by racemisation [54-57]. Replacement of chlorine by bromine in the ketone (XXVI) lowers the yield of the corresponding acid [59].

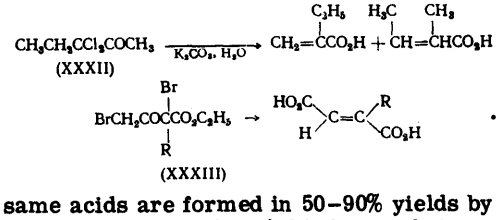


The keto-group is present in the side-chain also in 20-oxosteroids containing a halogen atom at $C_{(17)}$ (XXVIII) and $C_{(21)}$ (XXIX). In conformity with the principle of the equivalence of α- and α'-positions, rearrangement of both ketones gave good yields of a mixture of the epimeric 17ξ-methyletianic acids (XXX) and (XXXI). [60-63] The composition of the mixture depends on the structure of the initial steroid, the nature of the halogen, and the conditions of reaction. In most cases the isomer (XXXI) is formed predominantly, with maintenance of the configuration at $C_{(17)}$, both from (XXVIII: X = Br) [64-66] and from (XXIX: X = F, Cl, Br) [64,67-70]. The nature of the solvent is probably the decisive factor in the stereochemistry of the rearrangement. For example, 17α-bromopregnenolone acetate forms almost pure isomer (XXX) with sodium methoxide in dimethoxyethane, but almost pure isomer (XXXI) in aqueous potash [71].



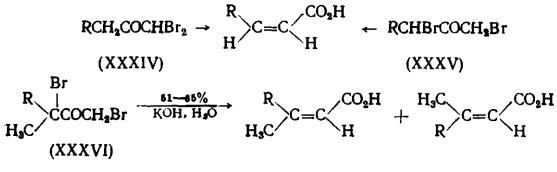
By using the product (XXXI) of the Favorskii rearrangement as starting material it was possible to accomplish a transition to highly active analogues of gestagens [63,72] and corticosteroids [70,73,74] containing a 17α-methyl group.

Di- and poly-halogeno-ketones, as well as monohalogeno-ketones, can undergo the Favorskii rearrangement. Derivatives of acrylic acids are formed from dihalogeno-ketones, an example being provided by the reactions of compounds (XXXII) [2,75,76] and (XXXIII: R = H, $CH_2COOC_2H_5$) [4,6,77]:



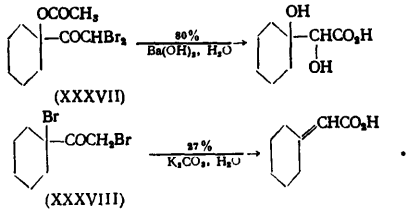
The same acids are formed in 50–90% yields by the action of bases on $\alpha\alpha$- and $\alpha\alpha'$-dihalogeno-ketones (XXXIV and XXXV: R = Alk, cycloalkyl): i.e. the equivalence of α- and α'-positions is observed here [78-82].

Therefore dibromination of ketones followed by Favorskii rearrangement (without separation of the isomers) provides a method for synthesising $\alpha\beta$-unsaturated acids [83]. The rearrangement of ketones of the type (XXXIV) and (XXXV) usually proceeds stereospecifically to yield *cis*-isomers of substituted acrylic acids. In the presence of bases, however, they readily isomerise to the more stable *trans*-isomers, which may distort the stereochemical picture of the reaction [78,80].

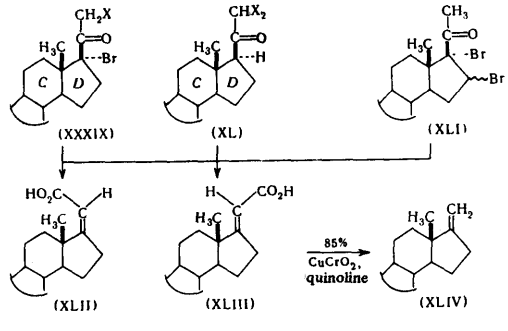


With branched dibromo-ketones of the type (XXXVI: R = Alk) the stereospecificity of the rearrangement disappears, and approximately equal quantities of the two possible isomers are formed [84,85].

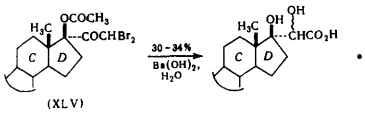
Dibromo-ketones involving a side-chain attached to a six-membered ring have also been subjected to the Favorskii rearrangement. Examples are given below for $\alpha\alpha$-dibromo-ketones of type (XXXVII) [86,87] and $\alpha\alpha'$-dibromo-ketones of type (XXXVII) [85,88,89]:



Examples of dihalogeno-ketones in which the side-chain is attached to a five-membered ring are the steroid $\alpha\alpha'$-, $\alpha\alpha$-, and $\alpha\beta$-disubstituted ketones—(XXXIX: X = Br, I) [62,68,88,90-93], (XL: X = F, Br) [67,94], and (XLI) [95] respectively—all three types giving high yields (up to theoretical) of mixtures of the isomeric acids (XLII) and (XLIII), in which the latter isomer probably predominates [96]. These acids are used to build up a corticoid side-chain [97,98], and their decarboxylation yields a 17-methylene-steroid (XLIV) [93]. Compounds similar to (XLIV) can be obtained also by the Favorskii rearrangement of 17α-bromo-20-oxo-steroids (XXVIII) under oxidising conditions capable of detaching the carbonyl group from the intermediate cyclopropanone derivative [99].

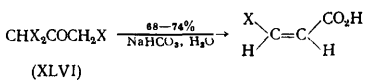


Dibromo-ketones like (XLV) containing a 17α-side-chain yield on rearrangement mixtures of diastereoisomeric 17β,20ξ-dihydroxy-acids[100,101], which are readily interconvertible under mild conditions:



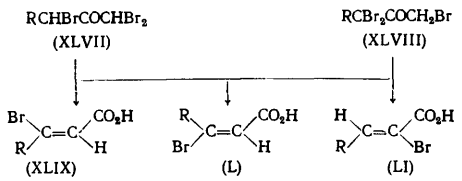
(XLV)

The Favorskii rearrangement of trihalogeno-ketones produces halogenated acrylic acids. With the simplest example, a 1,1,3-trihalogenoacetone (XLVI: X = Cl, Br), the only product is the *cis*-β-halogenoacrylic acid[102]:



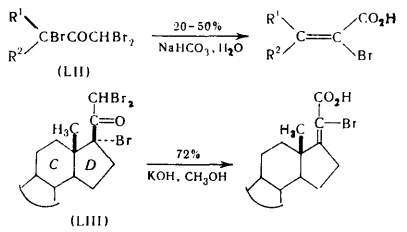
(XLVI)

With the higher homologues—e.g. the ketones (XLVII) and (XLVIII)—structural and steric specificity is usually lost, a mixture of β- and α-halogenoacrylic acids (XLIX)–(LI) being formed, the proportions of which depend both on the bulk of the alkyl radical R and on the reaction conditions[103,104]. Replacement of one or two bromine atoms in (XLVII) or (XLVIII) by chlorine yields predominantly β-chloro-analogues of the acids (XLIX) and (L), which indicates that bromine is more readily eliminated than chlorine under the conditions of the Favorskii rearrangement[104,105].



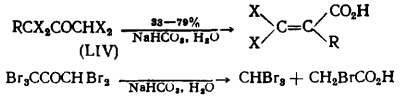
(XLVII) (XLVIII) (XLIX) (L) (LI)

Only α-halogenoacrylic acids are formed by rearrangement of tribromo-ketones of type (LII) containing a branched carbon chain. When $R^1 \neq R^2$, a mixture of roughly equal quantities of geometric isomers is formed[103,106]. The analogous steroid tribromo-ketones of type (LIII) yield α-bromo-acids on treatment with alkalis[96,106-108].



(LII) (LIII)

Tetrahalogeno-ketones (LIV: R = H, Alk; X = Cl, Br) undergo a Favorskii rearrangement with the formation of $\beta\beta$-dihalogenated acrylic acids[109,110]. Under the conditions of the rearrangement penta- and hexa-halogeno-ketones are cleaved by a halogenoform reaction, as indicated below for pentabromoacetone[111,112].

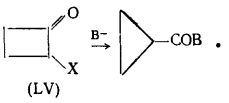


(LIV)

2. Monocyclic Halogeno-ketones

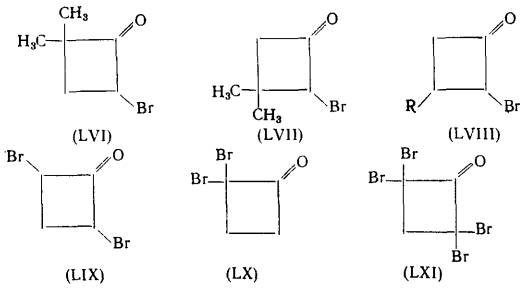
The Favorskii rearrangement has been widely applied to monocyclic halogeno-ketones to prepare compounds containing one less atom in the ring. The reaction is applicable to alicyclic and heterocyclic compounds containing 4–13 atoms in the ring.

Rearrangement of cyclobutane derivatives yields cyclopropanecarboxylic acids. An example is the reaction of the 2-halogenocyclobutanones (LV), which occurs extremely readily when X = Br and rather less readily when X = Cl[113-116]:



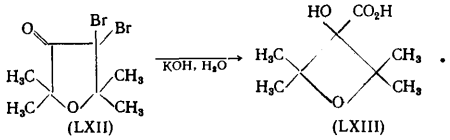
(LV)

The substituted cyclobutanones (LVI), (LVII), (LVIII: R = CH_3, OC_6H_5), and (LIX) react similarly to (LV)[115,117-119]. The reactions of the disubstituted ketones (LVIII) and (LIX) occur stereospecifically with formation of the *cis*-isomers of the monosubstituted cyclopropanecarboxylic acids. The $\alpha\alpha'$-disubstituted ketone (LIX) undergoes a Favorskii rearrangement, whereas $\alpha\alpha$-substituted ketones (LX) and (LXI) undergo ring cleavage in the presence of bases with the formation of $\gamma\gamma$-di- and $\alpha\alpha\gamma\gamma$-tetra-bromobutyric acids[115]. It has not proved possible to obtain benzocyclopropene derivatives by a Favorskii type of rearrangement[120].



(LVI) (LVII) (LVIII) (LIX) (LX) (LXI)

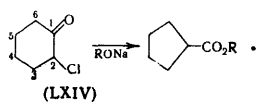
α-Halogenated cyclopentanones do not undergo the Favorskii rearrangement, but form products of polycondensation, substitution, or dehalogenation depending on the conditions[121-126]. However, condensed bromo-ketones of the type (CIX) (see below) yield the cubane system: i.e. five-membered rings are converted into four-membered rings. A similar transformation may occur when the dibromo-oxofuran (LXII) is treated with alkalis[126]:



(LXII) (LXIII)

However, the structure of the product (LXIII) cannot be regarded as completely proved.

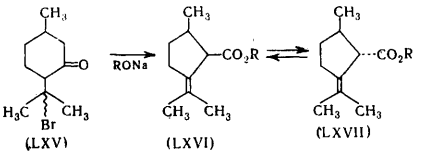
The Favorskii rearrangement of α-halogeno-ketones containing a six-membered ring has been the most thoroughly studied. A typical representative, 2-chlorocyclohexanone (LXIV), forms derivatives of cyclopentanecarboxylic acid:



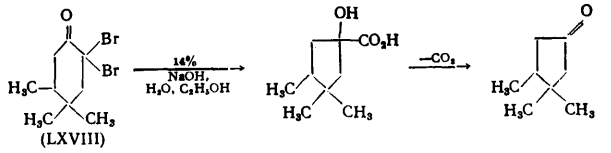
(LXIV)

A comparative study of the activity of various bases (alkalis[121,124], alkoxides[127-133], and alkyl sulphides[131,132,134-136]) has shown aliphatic branched-chain alkoxides to be the most efficient. The 2-bromo- and 2-fluoro-analogues of (LXIV) give smaller yields of the reaction products[67,137]. Alkyl homologues of (LXIV) containing substituents in positions 3–6 also undergo the Favorskii rearrangement[34,124,138-144], whereas 2-chloro-2-methylcyclohexanone does not undergo rearrangement[42,145].

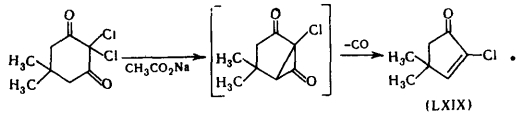
Dibromo-ketones containing a six-membered ring have been studied in especial detail in the case of pulegone dibromide (LXV)[146-153]. The pulegenic acid formed by its rearrangement can be used as a valuable intermediate for the synthesis of cyclopentanoid terpenes, which occur widely in plants and in insects. Both *cis*- and *trans*-isomers of pulegenic acid (LXVI) and (LXVII) can be obtained[154]. An attempt was made to use the stereospecificity of the reaction to establish the mechanism of the Favorskii rearrangement[155]. However, it was shown that the ratio of the isomeric pulegenic acids (LXVI and LXVII: R = H) is not a result of the rearrangement itself but depends on their ease of mutual isomerisation under the influence of bases (the equilibrium mixture contains 26% of the *cis*- and 74% of the *trans*-isomer) and on the slower rate of hydrolysis of the sterically hindered *cis*-ester (LXVI: R = CH_3, C_2H_5) in comparison with the *trans*-ester (LXVII: R = CH_3, C_2H_5). In several cases, therefore, the *trans*-acid, corresponding to the more readily hydrolysed ester (LXVII), is formed exclusively[156,157].



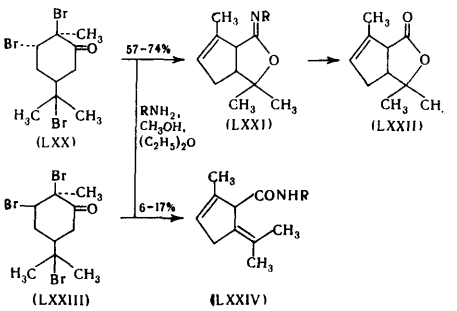
2,2-Dibromocyclohexanones of type (LXVIII) react with alkalis to form 2-hydroxy-acids, decarboxylation of which provides an easy route to the corresponding cyclopentanones[158,159]. Here, as with the ketones (LXII), (LXXVIII), and (LXXXI), it is entirely possible that the reaction may not be a Favorskii rearrangement but involve hydrolysis of (LXVIII) with formation of the 1,2-dione, which then undergoes a benzilic acid rearrangement.



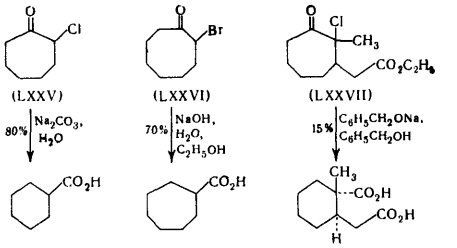
Ring contraction occurs also in the reaction of 2,2-dichlorodimedone with sodium acetate. Formation of the unsaturated chloro-ketone (LXIX) was explained by decarbonylation of the intermediate cyclopropanone derivative[160]:



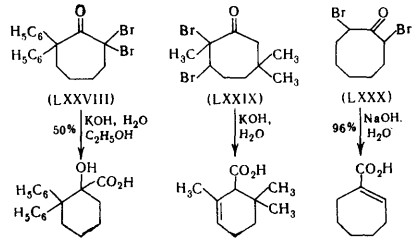
The individual tribromo-ketone isomers (LXX) and (LXXIII) or their mixtures undergo the Favorskii rearrangement under the influence of ammonia or an amine to form an iminolactone (LXXI) contaminated with an unsaturated amide (LXXIV). Hydrolysis of (LXXI) yields carvenolide (LXXII), which is the starting material for the synthesis of various iridolactones[161,162].



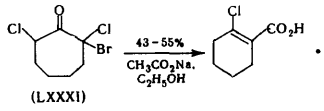
α-Halogeno-ketones containing a seven- or an eight-membered ring react with bases similarly to their six-membered analogues, forming in the Favorskii rearrangement acids containing respectively a six-membered or a seven-membered ring. Examples are the reactions of 2-chlorocycloheptanone (LXXV)[121,163,164] and of 2-bromocyclo-octanone (LXXVI)[165,166]. The α-chloro-ketones (LXXVII) gave a low yield of a compound which was a fragment of the structure of marrianolic acids[42].



Dibromo-ketones containing the halogen atoms in the αα-, αβ-, and αα′-positions—(LXXVIII)[167,168], (LXXIX)[169,170], and (LXXX)[166]—react with bases to form the corresponding unsaturated acids or hydroxy-acids containing contracted rings:



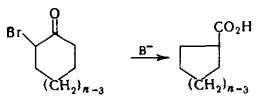
Rearrangement of the trihalogeno-ketone (LXXXI) gives a chlorinated unsaturated acid:



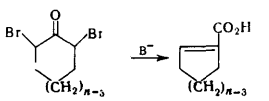
which indicates that bromine is more easily detached than is chlorine[171]. Tribromocyclo-octanone reacts similarly[166].

The Favorskii rearrangement has found application also for contracting rings of moderate size, examples being the reactions with bases of monobromo-ketones of the type

(LXXXII: $n = 10, 12$)[172,173] and dibromo-ketones of the type (LXXXIII: $n = 10–12$)[172–174]:



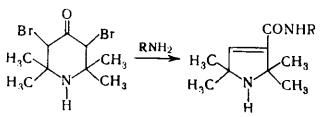
(LXXXII)



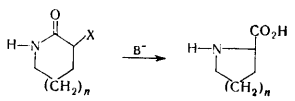
(LXXXIII)

the yields of the acids reaching 65–75%.

The Favorskii rearrangement has been accomplished also with heterocyclic α-halogeno-ketones. Thus the reaction of dibromopiperidone (LXXXIV) with ammonia or an amine yields the corresponding amide[175,176]. Analogues of proline are formed by the reaction of α-halogeno-lactams of the type (LXXXV: X = Cl, Br; $n = 3$, 7–11) with barium hydroxide[177–179] or with potassium t-butoxide[180]. In this case the resulting α-imino-acids may be formed by hydrolysis of (LXXXV) followed by recyclisation.



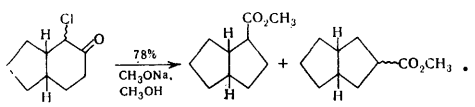
(LXXXIV)



(LXXXV)

3. Dicyclic and Polycyclic Halogeno-ketones

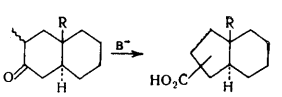
α-Halogeno-ketones containing the oxo-group in a fused carbocyclic system also undergo the Favorskii rearrangement, which provides a method for obtaining fused systems containing a smaller number of carbon atoms in the ring. The simplest example is the chloro-derivative of *cis*-perhydroindanone (LXXXVI), which under the influence of bases forms a mixture of *cis*-bicyclo[3,3,0]octanecarboxylic esters:



(LXXXVI)

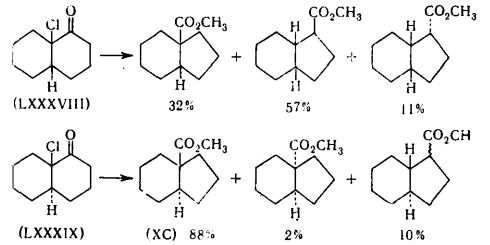
The corresponding *trans*-derivative does not undergo Favorskii rearrangement, perhaps owing to the steric strain in the *trans*-bicyclo[3,3,0]octane system[181–184].

The most widely investigated dicyclic halogeno-ketones are *trans*-decal-2-one derivatives of the type (LXXXVII: X = Cl, Br; R = H, CH_3), rearrangement of which yields a mixture of isomeric perhydroindanecarboxylic acids[142,185–189]:



(LXXXVII)

cis- and *trans*-9-Chlorodecal-1-ones (LXXXVIII) and (LXXXIX) react with sodium methoxide in dimethoxyethane to form products which almost completely retain the initial configuration at $C_{(9)}$:

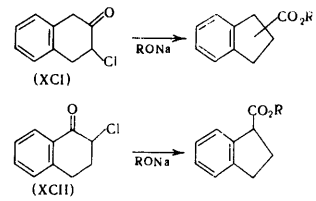


(LXXXVIII) 32% 57% 11%

(LXXXIX) (XC) 88% 2% 10%

The yields of the products are indicated below the formulae. Especially interesting is the stereospecific synthesis of the *trans*-perhydroindane derivative (XC) with a methoxycarbonyl group between the rings[190].

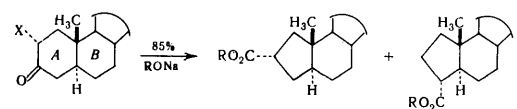
The chlorotetralone (XCI) reacts with alkoxides to form the corresponding esters[140,191]. Its isomer (XCII) also forms products of the Favorskii rearrangement according to some results[140,191], but only alkoxy-oxides of type (V) according to other results[192].



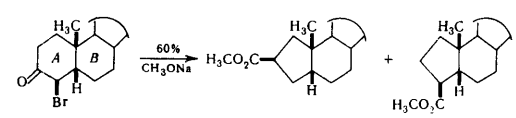
(XCI)

(XCII)

Application of the Favorskii reaction to halogenated steroid ketones, which are structurally related to decalone derivatives, enables modified steroids to be obtained in which A or B is a five-membered ring. The reactions of bases with halogenated cholestan-3-ones have been studied in greatest detail. Compounds in which the relative orientation of rings A and B is *trans* (XCIII) form a mixture of 2- and 3-alkoxycarbonyl isomers (XCIV) and (XCV). Some results[193,194] indicate that the former isomer (XCIV) predominates strongly, whereas others[195–198] show approximately equal quantities of the two isomers. The rate of the reaction depends on the nature of the halogen, decreasing in the sequence I > Br > Cl[143,144,199]. Compounds in which the orientation of rings A and B is *cis* (XCVI) also form a mixture of isomeric esters (XCVII) and (XCVIII)[194,200].



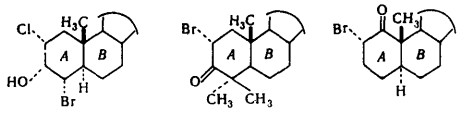
(XCIII) (XCIV) (XCV)



(XCVI) (XCVII) (XCVIII)

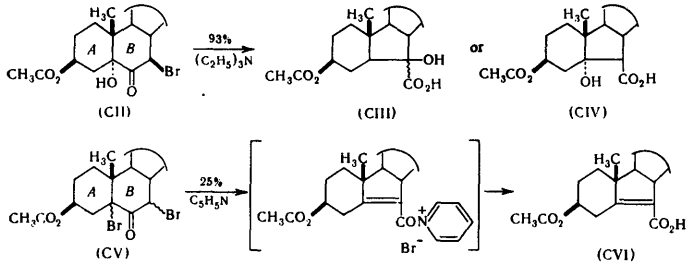
The dihalogenated hydroxy-compound (XCIX) also reacts with a base to produce a mixture of (XCIV) and (XCV)[201]. This probably involves initial dehydrohalogenation with formation of the ketone (XCIII). Yet the bromo-ketones

(C) and CI) do not undergo Favorskii rearrangement, but form only hydrolysis or substitution products with bases[202].



(XCIX) (C) (CI)

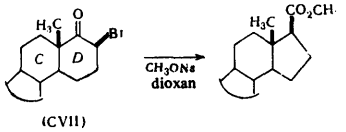
Examples of the contraction of ring B are provided by Favorskii rearrangement involving cholestane derivatives (CII) and (CV). The structure (CIII) was ascribed to the product in the former case[203]. It has been pointed out[204] that the structure (CIV), in which the hydroxyl remains at its previous position, must be regarded as more probable. When the dibromocholestanone (CV) was boiled with pyridine, dehydrobromination products were accompanied by the B-nor-acid (CVI), probably formed via the corresponding acylpyridinium bromide[205,206].



(CII) (CIII) (CIV)

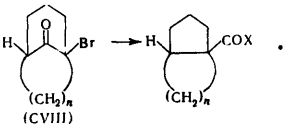
(CV) (CVI)

Contraction of the six-membered ring D by rearrangement of the D-homoandrostane derivative (CVII) could be accomplished only in very low yield[194,200,207]:



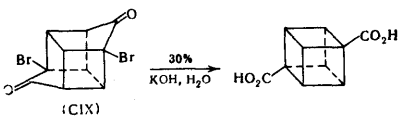
(CVII)

An interesting example of the Favorskii rearrangement involving bridged bicyclic systems is provided by the reactions of bromo-ketones of the type (CVIII: $n = 5–8$) with alkoxides, sodamide, silver nitrate, and mercury(II) acetate, when *cis*-isomers of derivatives of the corresponding acids (X = OH, OR, NH_2) are formed in 70–94% yield[35,208,209]:



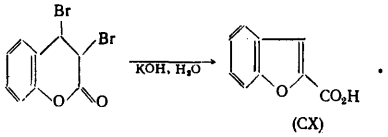
(CVIII)

The Favorskii rearrangement is applied also in the synthesis of cubane derivatives[210–212]. An example is the reaction of the dibromo-dione (CIX) with boiling aqueous alkali[213]:



(CIX)

The only example known of the Favorskii rearrangement of a bicyclic heterocycle is the reaction of mono- and di-bromocoumarins with alkalis to give acids of the type (CX)[214–218]:



(CX)

The formation of these acids can equally well be explained by opening of the pyran ring followed by recyclisation.

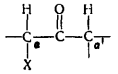
The results surveyed in this Section enable us to discuss the part played by the conformation of the halogen in the Favorskii rearrangement. Conformationally rigid structures (LXXXVII), (XCIII), and (XCVI), containing equatorial halogen, readily undergo rearrangement in good yield. Nevertheless, derivatives of the ketone (LXXXVII) and the chloro-ketone (LXXXIX)[219] (in protic solvents), containing axial halogen, did not undergo Favorskii rearrangement. It was therefore concluded[188] that an equatorial conformation of the halogen is necessary for this reaction to occur. However, this conclusion is disproved by other results[220], according to which the ketone (LXXXIX) containing an axial chlorine atom rearranges in aprotic solvents in high yield. Monocyclic tribromo-ketones (LXX) and (LXXIII)[162], as well as *cis*-2-chloro-4-t-butylcyclohexanone[143], also undergo Favorskii rearrangement. The presence in these compounds of a bulky 1-bromo-1-methylethyl or t-butyl substituent confers great rigidity on the axial conformation of their α-halogeno-substituents. All this indicates that the conformation of the halogen can have no significant effect on the possibility or the course of the Favorskii rearrangement.

III. MECHANISM OF THE FAVORSKII REARRANGEMENT

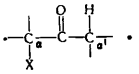
A considerable number of papers on the mechanism of the Favorskii rearrangement have been summarised in several reviews[11,204,221–223]. Nevertheless, no mechanism has yet been suggested which would be suitable for all structural types of α-halogeno-ketones and would explain unambiguously the features of the reaction. Most workers therefore assume that the rearrangement may occur by different mechanisms depending on the structure of the initial ketone and even on the conditions.

The α-halogeno-ketones undergoing the Favorskii rearrangement, which have been discussed in the preceding sections, can be divided into four structural types (A–D) distinguished by the presence or absence of hydrogen atoms in the α- and α′-positions:

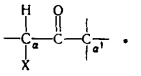
Hydrogen atoms attached to α- and α′-carbon atoms—(XI), (XIX)–(XXI), (XXIII), (XXIX), (XXXIV), (XXXV), (XL), (XLVI), (XLVII), (LV), (LVII)–(LIX), (LXIV), (LXXV), (LXXVI), (LXXX), (LXXXII)–(LXXXIV), (LXXXVI), (LXXXVII), (XCI), (XCIII), (XCVI)

A 

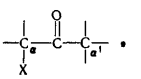
Hydrogen attached only to α′-carbon atom–(VIII), (IX), (XIV), (XVII), (XXV), (XXVIII), (XXXII), (XXXIII), (XXXVI), (XXXVIII), (XXXIX), (XLI), (XLVIII), (LII)–(LIV), (LXV), (LXX), (LXXIII), (LXXVII), (LXXIX), (LXXXI), (LXXXVIII), (LXXXIX), (CVIII), (CIX)

B 

Hydrogen attached only to α-carbon atom—(XXXVII), (XLV), (LVI), (LXVIII), (XCII), (CII), (CV), (CVII)

C 

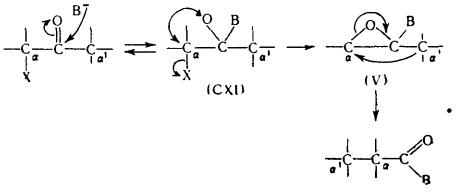
No hydrogen attached to α- and α'-carbon atoms—(XIII), (XXVI), (XXVII), (LXIII), (LXXVIII),

D 

The equivalence of the α- and α'-positions in the Favorskii rearrangement, many examples of which have been quoted for the different structural types of ketones in subsections 1–3 of Section II, is extremely significant for the mechanism. It is convenient to divide the mechanisms which have been suggested into two groups according to whether they are able to explain this equivalence ("symmetrical" mechanisms) or require additional postulates for such explanation ("unsymmetrical" mechanisms).

1. "Unsymmetrical" Mechanisms

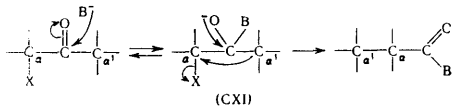
The first unsymmetrical mechanism to be considered is the oxide–ester mechanism suggested by Favorskii in 1894[2,13,224], according to which the base attacks the carbonyl group to form as the first step the anion (CXI), which is converted with loss of halogen into the intermediate oxide (V), further rearrangement of which yields the final product:



(CXI) (V)

The Favorskii mechanism is applicable to all structural types of halogeno-ketones. It was considered to be supported by the isolation of oxide–ethers of the type (V: B = OR) in certain rearrangements[225,226]. However, these oxide–ethers could not be converted into the final products[227,228], and their formation is therefore a secondary process, unrelated to the main reaction.

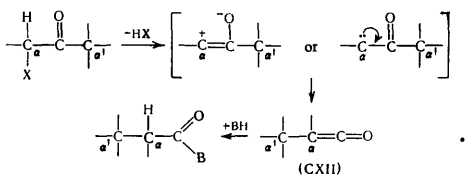
The semibenzilic mechanism[53], so called from its resemblance to the mechanism of the benzilic rearrangement, is more soundly based. It also involves initial formation of the anion (CXI), but this then undergoes direct rearrangement with migration of the α'-atom, the oxide stage being bypassed:



(CXI)

The semibenzilic mechanism is also applicable to ketones of types A–D. A modified (push–pull) form of this mechanism was suggested[35] for rearrangements occurring under the influence of silver(I) and mercury(II) salts. It is noteworthy that these cations are electrophilic—not nucleophilic—reagents, and therefore cannot be regarded as usual catalysts for the Favorskii rearrangement. The semibenzilic mechanism and its push–pull modification are normally applied to ketones with which the formation of symmetrical intermediates is impossible or difficult for structural reasons. The limits of the possible applicability of the semibenzilic mechanism will be examined later in discussing symmetrical mechanisms.

According to the keten mechanism, suggested by Richard in 1938[229], the first stage in the rearrangement is the elimination of hydrogen halide from the α-atom of the initial ketone[48] (or detachment of a proton from the enolic form followed by removal of halogen[229]). The resulting dipolar or diradical (carbene) intermediates undergo direct rearrangement into a keten (CXII), which reacts with the base to form the final product:



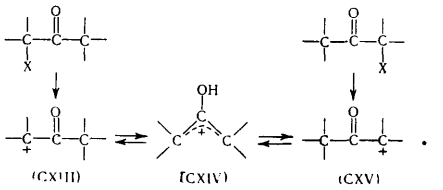
(CXII)

The keten mechanism is obviously applicable only to ketones of types A and C, containing hydrogen attached to the α-carbon atom. This mechanism is considered[118,119] to be inconsistent with data on the stereochemistry of the Favorskii rearrangement.

In all unsymmetrical mechanisms the carboxyl in the product should be attached to the α-carbon atom (with which the halogen was combined in the initial ketone). This leads to the conclusion that the α- and α'-positions are not equivalent with respect to the structure of the products, which is inconsistent with numerous experimental results. In order to avoid this difficulty, it was suggested that halogen migrated from α- to α'-positions, which would have explained the observed equivalence of these positions[64,65,230]. When this hypothesis was tested on acyclic[25,231] and cyclic[48] ketones, it was found that such migration of the halogen does not take place under the conditions of the Favorskii rearrangement. Therefore some "symmetrising" stage in the reaction must be postulated to explain the equivalence of α- and α'-positions.

2. "Symmetrical" Mechanisms

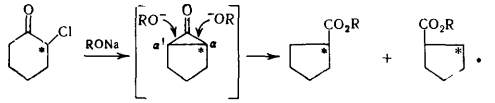
The first "symmetrical" mechanism was put forward by McPhee and Klingsberg in 1944[22]. The symmetrising stage in this mechanism is tautomeric equilibrium between the carbonium ions (CXIII) and (CXV) formed in the first stage, through a common enolic form (CXIV), which undergoes rearrangement into the final products:



(CXIII) (CXIV) (CXV)

The principal defect of the above mechanism is that it does not explain the part played by the base in the reaction. According to this mechanism the rate of elimination of halogen should be independent of the concentration of the base, whereas experiment indicates kinetics of the first order with respect to B^-.[23,144] A somewhat modified form of this mechanism suggested recently is also inconsistent with experimental results[25].

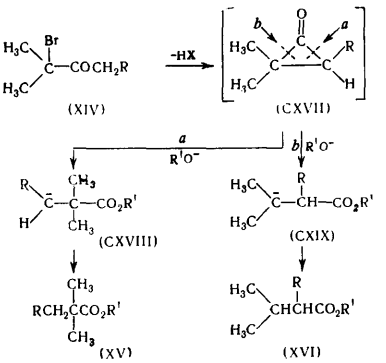
The cyclopropanone mechanism put forward by Loftfield in 1950[48,232] is free from these defects†. The rearrangement of 2-chlorocyclohexanone labelled with carbon-14 at the point of chlorination yielded a mixture of cyclopentanecarboxylic esters in which the tracer was equally distributed between the α- and β-carbon atoms (relative to the carboxyl). This was explained by the intermediate formation of a substituted cyclopropanone (CXVI), in which the α- and α'-carbon atoms were formally equivalent as a consequence of symmetry, and cleavage of the three-membered ring could occur with equal probability at the two bonds:



(CXVI)

At the present time the cyclopropanone mechanism is generally accepted for the Favorskii rearrangement. It is supported by the isolation of cyclopropanone intermediate products in the reactions of monohalogeno-ketones with bases[238] and of cyclopropenone derivatives in those of $\alpha\alpha'$-dihalogeno-ketones[239,240]. Direct evidence has also been obtained that already formed cyclopropanones[241,242] and cyclopropenones[243,244] react with strong bases in conformity with the Favorskii rearrangement to form acid derivatives. Compounds in which the cyclopropane ring is separated from the keto-group by a double bond also react in similar fashion[245]. Cyclopropanone intermediates have also been isolated and identified in reactions with dienes and with methanol[246-250].

The cyclopropanone mechanism explains quite well the structural selectivity of the reaction. It is supposed that cleavage of the intermediate cyclopropanone yields the more stable of the two possible carbanions. The stability of non-conjugated carbanions increases in the sequence: tertiary < secondary < primary < benzyl[11]. In conformity with this the intermediate dimethylcyclopropanone (CXVII: R = H) formed from halogeno-ketones of the type (XIV: R = H), for example, is cleaved with the formation of derivatives of $\alpha\alpha$-dimethylpropionic acid (XV: R = H)—not of β-methylbutyric acid (XVI: R = H)—since the former are produced via the primary anion (CXVIII: R = H), and the latter via the less stable tertiary anion (CXIX: R = H). It is interesting that fission of the specially prepared dimethylcyclopropanone (CXVII: R = H) occurs in the same way under the influence of bases[242].

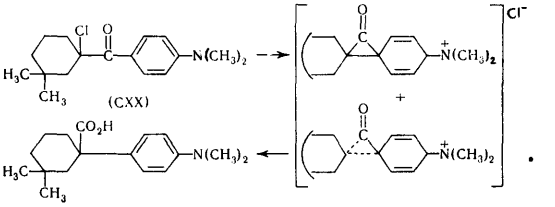


(XIV) (CXVII) (CXVIII) (CXIX) (XV) (XVI)

† A mechanism involving cyclopropanone intermediates was suggested as early as the 1890s[2,77,233,234]. It unites the Favorskii rearrangement with similar rearrangements of α-halogeno-sulphones[235], α-halogeno-amides[236], halogenated diazoethers[237], etc.

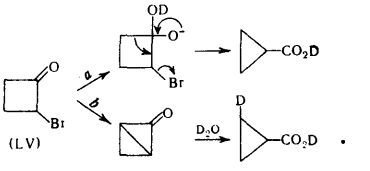
The above considerations are sufficient to explain the structural selectivity in the large majority of examples of the Favorskii rearrangement which have been studied. Recently however, results have been obtained which require more detailed account to be taken of possible operative factors[36]. Rearrangement of ketones of the type (XIV: R = Alk) is found to yield a mixture of the two possible products in which the proportion of (XVI), which is formed via the less stable tertiary carbanion (CXIX), increases with increase in the bulk of the alkyl radical R. This indicates that the course of the reaction is controlled not only by the stability of the intermediate carbanions but also by steric factors. With the ketone (XIV: R = H) these two factors act in the same direction: the intermediate product (CXVII: R = H) is attacked on the sterically less hindered side to form the more stable primary carbanion (CXVIII). In the case of ketones (XIV: R = Alk), however, these factors oppose one another, which results in the formation of a mixture of isomers. It should also be noted that the proportion of (XV: R = CH_3) in the reaction products is smaller when rearrangement is effected by sodium methoxide than with sodium ethoxide, and especially with potassium t-butoxide. This indicates that the part played by steric factors involving the base must be taken into account in addition to the influence of the bulk of the alkyl group of the alkoxide[36].

In its classic form the cyclopropanone mechanism is applicable only to ketones of types A and B, which contain the α'-hydrogen atom necessary for closure of the three-membered ring. With ketones of type C and D the semibenzilic mechanism is usually assumed without proof, their reactions being combined under the name Favorskii quasi-rearrangement, which emphasises this difference in mechanism. For several examples of the rearrangement of ketones of type D containing aryl substituents, however, the cyclopropanone mechanism can be applied in a somewhat modified form. Thus rearrangement of the ketone (CXX) and its heterocyclic analogues, which is accompanied by racemisation at the reactive centre, cannot be explained by a semibenzilic mechanism, but requires the acceptance of a "racemising" stage—assumed to be the formation of cyclopropanone intermediates[54-57]:



(CXX)

The semibenzilic and cyclopropanone mechanisms can be more reliably distinguished by investigating the incorporation of deuterium into the final product when the reaction is conducted in a deuteriated solvent. The difference between these mechanisms can be conveniently explained with the rearrangement of 2-bromocyclobutanone (LV) in heavy water as example:



(LV)

According to the semibenzilic mechanism (*a*) the resulting cyclopropanecarboxylic acid should not contain deuterium

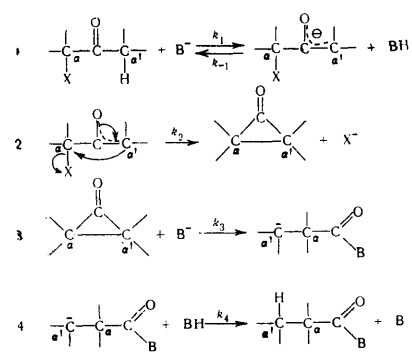
in the ring, whereas the cyclopropanone mechanism (*b*) leads to a deuteriated product. The undeuteriated acid obtained experimentally indicated that this reaction had a semibenzilic mechanism[119,251]. A more exact interpretation of the process requires that the exchange of deuterium between ketone and heavy water, unconnected with the Favorskii rearrangement, should be taken into account. According to the unsymmetrical scheme (*a*) the α- and β-carbon atoms (with respect to the carboxyl) should have different degrees of deuteriation, but according to the symmetrical scheme (*b*) they should be the same. Investigations on this basis confirmed the semibenzilic mechanism of the Favorskii rearrangement for the ketone (LV)[252].

Nevertheless, the rearrangement of 17α-bromo-20-oxo-steroids of the type (XXVIII) in deuteriated solvents (D_2O, CH_3OD) yielded predominantly the products (XXX) and (XXXI) containing one deuterium atom in the 17-methyl group. This is evidence of the cyclopropanone mechanism of this reaction (exchange of deuterium between the ketone and the medium is negligible here)[66].

As a third example we can consider the mechanism of the Favorskii rearrangement of ketones of the type (CVIII: $n = 6-8$), determined from the entry of deuterium into the reaction products[209]. When $n = 6$, the ketone (CVIII) reacts by the semibenzilic mechanism both with $NaOD-C_2H_5OD$ and with $t\text{-}C_4H_9OK-t\text{-}C_4H_9OD$. When $n = 7$, the semibenzilic mechanism operates with NaOD, but the cyclopropanone mechanism with $t\text{-}C_4H_9OK$. Finally, when $n = 8$, the Favorskii rearrangement takes place by the cyclopropanone mechanism in both cases, as is confirmed by the racemisation of the optically active ketone (CVIII: $n = 8$) during the reaction. Thus with compounds of type (CVIII) the mechanism of the rearrangement may depend not only on the structure of the initial ketone but also on the reaction conditions.

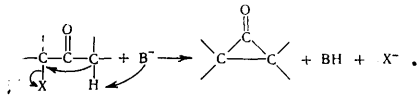
The kinetics and stereochemistry of the Favorskii rearrangement are usually explained in terms of the cyclopropanone mechanism. The elementary form of this mechanism outlined above becomes inadequate to explain all the kinetic and stereochemical results. We must therefore examine in detail existing views on the sequence of stages in the rearrangement, the significance of each of them, and also the nature of the transition state. The most probable variant of the cyclopropanone mechanism can be represented in its complete form by the four-stage scheme 1.

Scheme 1



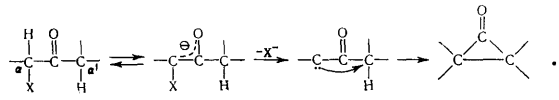
The first stage in the Favorskii rearrangement according to this scheme consists in enolisation of the ketone with loss of the α'-proton. In the second stage the resulting enolate splits off halogen as the anion and gives a cyclopropanone intermediate. This is followed by opening of the cyclopropanone by the anion of the base (third stage) and reaction of the resulting carbanion with the base to yield the final product (fourth stage). Stages 3 and 4 are supposed to occur so rapidly that they have no effect on the overall rate of the process.

The above scheme of the Favorskii rearrangement has been partly modified by many authors. Thus it has been suggested that stages 1 and 2 occur synchronously and that 1,3-elimination of the hydrogen halide to form the cyclopropanone[39] takes place in a single step:



This hypothesis, however, sharply contradicts the stereochemistry of many cases of the Favorskii rearrangement which have been studied, especially among the steroids[223].

As an alternative to the above four-stage mechanism it has been suggested also that formation of the anion may involve the α-hydrogen atom—not the α'-atom—after which chlorine is detached from the same atom and the resulting carbene is converted into a cyclopropanone[221]. An argument in favour of this possibility was the ease of enolisation of the initial halogeno-ketone at the α-atom. This peculiar combination of carbene and cyclopropanone mechanisms imposes additional structural limitations on the initial ketone, and is applicable only to halogeno-ketones of type A, containing hydrogen on both α- and α'-carbon atoms:



Neither of the above modifications of the main scheme is consistent with the kinetic and stereochemical data[23,25], and is therefore rejected by most authors at the present time. The kinetics and the stereochemistry of the Favorskii rearrangement are usually interpreted in terms of a four-stage scheme. The rate-determining stage in the reaction is established by study of deuterium exchange between the ketone and the medium and of the effect of the nature of the halogen.

Enolisation at the α'-atom as the first stage in the Favorskii rearrangement is proved by the occurrence of deuterium exchange between this position in the halogeno-ketone and the medium or by conducting the reaction in a deuteriated solvent or with a deuteriated halogeno-ketone. Such exchange is observed to some extent with most halogeno-ketones—both acyclic ketones of types (IX), (XI), and (XVII)[23,25,40,253-255] and 2-halogenocyclohexanones and their derivatives[144,256]—and also with 2α-halogeno-3-oxo-steroids[143,144,199]. Yet it is negligible with 17α-bromo-20-oxo-steroids (XXVIII)[66] and 9-chloro-*trans*-decal-1-one (LXXXIX)[219]. The occurrence of stage 1 explains also the catalytic effect of certain salts (lithium chloride, lithium iodide, sodium iodide) on the Favorskii rearrangement[25,38,44]. It was assumed that these salts associate with the base formed in stage 1 (BH—methanol in the present example), thereby shifting the equilibrium in this stage to the right and increasing the concentration of the enolate.

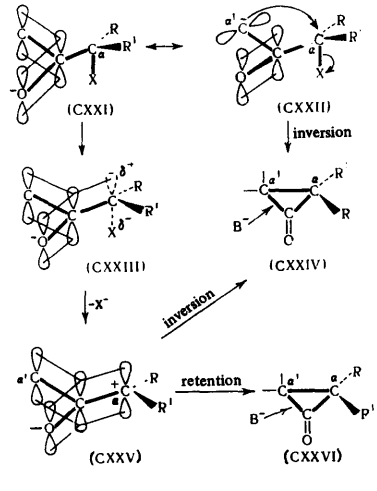
The degree of deuterium exchange, which depends primarily on the structure of the halogeno-ketone, is of

fundamental importance for comparing stages 1 and 2. We can cite as example ketones of the types $ArCH_2COCH_2X$ and $ArCH_2COCHXCH_3$, which differ only in the presence of a methyl group in the latter[25,38]. Whereas ketones of the first type exchange ~ 80% of the α'-hydrogen for deuterium before the reaction, the degree of deuterium exchange in ketones of the second type does not exceed 5%. Hence stage 1 is rapid ($k_{-1} > k_2$) in the first case: i.e. the rate of rearrangement is determined by the stage in which halogen is eliminated. In the second case, however, the presence of the methyl group increases the rate of solvolysis of the enolate and makes $k_2 > k_{-1}$. Deuterium exchange is therefore poor, and the reaction velocity is determined by the first stage—enolisation of the initial ketone.

With 4,4-disubstituted 2-halogenocyclohexanones and steroid ketones of the type (XCIII) deuterium exchange depends on the nature of the halogen[143,144,199]. In the α'-position deuterium exchange is considerably more facile with chloro-ketones than with bromo-ketones. In the first case, therefore, the rate of the reaction is determined by stage 2 ($k_2 < k_1$) and in the second case by stage 1 ($k_1 < k_2$). The group which is eliminated also has quite considerable effects in these examples: $k_{Br}/k_{Cl} = 6-116$ (according to various results). Thus, depending on the structure of the initial halogeno-ketone, the rate of the Favorskii rearrangement may be determined by either stage 1, stage 2, or both.

The electronic interpretation of the second stage in the Favorskii rearrangement, which is associated with the explanation of its stereochemistry, has also been the subject of prolonged controversy. Scheme 2 shows the chief possibilities for the occurrence of this stage.

Scheme 2



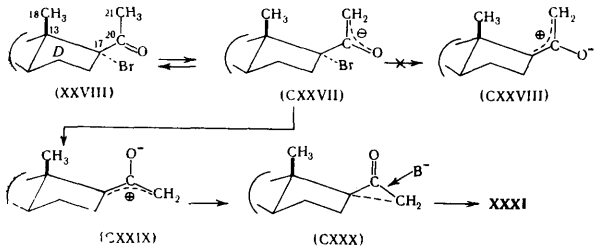
The anion produced in stage 1 in the form (CXXI) or (CXXII) can be further converted into cyclopropanone in two ways. Intramolecular substitution of S_N2 type—(CXXII)→ (CXXIV)—involves inversion of configuration at the reaction centre (the α-carbon atom). This results in stereospecific formation of the cyclopropanone (CXXIV), which is opened by the base at stages 3 and 4 to give a final product having a configuration at the α-atom‡ which is the inverse of the initial configuration.

Attainment of the configuration necessary for S_N2 substitution requires considerable distortion of the normal geometry of the enolate anion (CXXI) on passing to the carbanion (CXXII), which should result in a considerable energy barrier. It was therefore suggested[257-259] that a halogeno-enolate (CXXI) first loses the anion X^- to form the delocalised intermediate (CXXIII), which gives rise to the zwitterion (CXXV). Calculations by the LCAO-MO method indicate that the change (CXXI) → (CXXV) is accompanied by an increase in the delocalisation energy, this increase being regarded as the driving force of the process. The zwitterion (CXXV) can undergo direct cyclisation of the disrotatory type into the cyclopropanone[260]. In the transition state (CXXIII) during detachment of the X^- anion the C–X bond is highly ionic in character. A considerable positive charge appears on the α-carbon atom, which can be balanced by the supply of electrons from substituents attached to the α'-atom and especially from those on the α-atom. Therefore the stage of detachment of X^- is accelerated on α'-substitution by electron-donor groups (this is reflected in the high negative value of the Hammett ρ-coefficient, from −2.4 to −5.0, in halogeno-ketones of the type $ArCHClCOCH_3$ and $ArCH_2COCH_2Cl$[23,25]) and especially by the introduction of a donor methyl group in the α-position[255]. All these results support the possibility that the reaction may occur via the zwitterion (CXXV). The planar intermediate state (CXXV), in which the centre of asymmetry has disappeared, can obviously yield on cyclisation both the cyclopropanone (CXXIV) and the cyclopropanone (CXXVI), ring-opening of which will give final products with inversion and retention of the initial configuration at the α-centre (Scheme 2).

It is now accepted that the Favorskii rearrangement may occur by both the routes considered—through (CXXII) and through (CXXV)—and the stereochemistry of the reaction is interpreted on this basis. As shown in Section II, the Favorskii rearrangement is not characterised by any definite stereochemical requirements: depending on the structure of the halogeno-ketone, the type of base, and even the concentration of the latter, it occurs with either complete retention or complete inversion of configuration, or even with formation of a mixture of isomers. However, the most thoroughly studied examples of the rearrangement of ketones of type (XVII) and (XVIII) indicate that in aprotic solvents (ether, dimethoxyethane) the reaction involves inversion of configuration, whereas in protic solvents (methanol, water) either a mixture of isomers or one isomer with retention of the initial configuration is formed. The influence of the solvent on the fate of the anion formed in stage 1 has been discussed[43,45,241]. In aprotic solvents this anion is slightly if at all solvated, and therefore its "free" negative charge may enter the reaction as the carbanion (CXXII), forming products with inversion of configuration (CXXIV). Solvation of the anion in protic solvents confers on it an enolic structure and directs the reaction through the zwitterion (CXXV) to the product (CXXIV) or (CXXVI). The relative proportions of these isomers are determined primarily by steric factors. With 17α-bromo-20-oxo-steroids (XXVIII), for example, it has been shown that, in the detachment of Br^- from the intermediate enolate (CXXVII), steric hindrance

‡ The same stereochemical course of the reaction should be characteristic also of the concerted 1,3-elimination mentioned above.

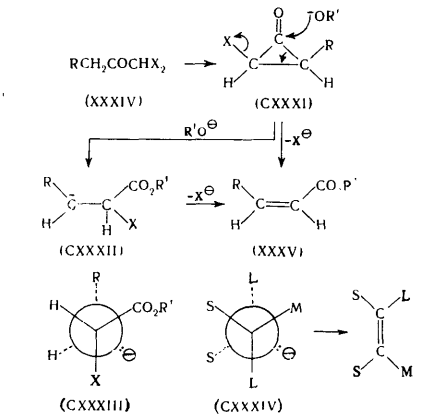
by the angular methyl group $C_{(18)}$, tending to prevent rotation about the $C_{(17)}$–$C_{(20)}$ bond, will ensure formation predominantly of the zwitterion (CXXIX), not of (CXXVIII). Cyclisation of (CXXIX) will lead to the corresponding cyclopropanone (CXXX), ring-opening of which by bases should yield a reaction product in which the initial configuration at the α-atom is retained (XXXI). Such stereochemistry is observed in protic solvents[66,71,223].



Various explanations of the stereochemistry of the Favorskii rearrangement have also been based on the intermediate formation of the cyclopropanones (stages 3 and 4)[42,43], but they are not so generally applicable, and are to some extent inconsistent with kinetic data.

The stereospecific formation of *cis*-acids of acrylic type in the Favorskii rearrangement of di- and tri-halogeno-ketones, e.g. (XXXIV), is explained on a different basis. The formation of *cis*-acids (XXXV) can be regarded[80,81] as resulting from concerted *trans*-antiparallel 1,3-elimination with formation of a *cis*-2-alkyl-3-halogenocyclopropanone (CXXXI). This product is then opened by the base into the acid (XXXV), also by a concerted process of elimination of the halide anion with preservation of the configuration.

Scheme 3



A more probable form of explanation is that the stereochemistry of the reaction is determined at the stage of elimination of halogen from the anion (CXXXII) formed when the cyclopropanone (CXXXI) is opened by the base[261]. Analysis of possible conformations of this anion indicates that the most probable type of conformation will be (CXXXIII), detachment of X^- from which will give the *cis*-acid (XXXV) stereospecifically. This conformation can be written more generally as (CXXXIV), where L denotes a large substituent, M a medium substituent, and S a small substituent (the sizes of the substituents are arbitrarily assumed to form the sequence X > R ≫ COOR > H). This hypothesis explains most of the known facts on the stereochemistry of the rearrangement of acyclic polyhalogeno-ketones[261] (Scheme 3).

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