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Synthetic Methods for Cyclohexa-1,3-dienes

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The review gives a systematic account of the methods of synthesis of cyclohexa-1,3-diene, its homologues, and derivatives with functional groups. The purity of the preparations obtained by each method is considered on the basis of modern data. The bibliography includes 221 references

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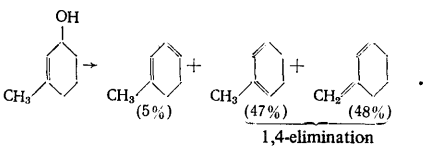
I. INTRODUCTION

Substituted cyclohexa-1,3-dienes are important intermediates in the synthesis of many physiologically active compounds, including terpenes, carotenoids, and steroids. Cyclohexa-1,3-diene (I) itself has been used as the starting material in one of the schemes for the stereoselective synthesis of 11-deoxyprostaglandines[1]. It is a promising monomer for the manufacture of aromatisable polymers. Both the diene (I) itself and the vast majority of its derivatives (with the possible exception of α-terpinene and α-phellandrene) are obtained solely by synthesis. Despite the importance of this class of compounds, there is no review literature on the methods of their synthesis. The aim of the present review is to fill this gap†. The methods of synthesis of the diene (I), its homologues, and derivatives with functional groups are relatively varied. The principal methods can be divided into five groups in the majority of which the starting material contains the cyclohexane ring. The synthesis of the diene (I) and in the first place its homologues and derivatives involves certain experimental difficulties. Many of the synthetic methods result in the formation of side products, including isomeric dienes. The high reactivity of cyclohexadienes, particularly their tendency to dimerise, polymerise, aromatise, and oxidise, may also be the cause of the reduced yield of the desired products and the appearance of impurities. The principal causes of the possible inhomogeneity of cyclohexa-1,3-dienes are considered below.

II. THE AMBIGUITY OF THE REACTIONS AND THE PRINCIPAL SIDE PROCESSES

1. The Mode of Elimination and the Admixture of 3-Methylenecyclohexenes

The formation of the second double bond in the cyclohexadiene ring is usually achieved with the aid of elimination reactions (the elimination of hydrogen halides, water, alcohol, etc.) which can occur via different pathways even under mild conditions: via 1,2- and 1,4-elimination mechanisms[2]. The 1,4-elimination product can predominate, which is confirmed by the data in Tables 1 and 2 (see below). The dehydration of substituted cyclohex-2-en-1-ols leads as a rule to mixtures of two dienes with endocyclic double bonds and, in the presence of an alkyl group in the 1- and 3-positions, is accompanied by the formation of an admixture of 3-methylenecyclohex-1-enes. The amount of the latter in the mixtures can be very considerable (in excess of 40%), for example[3]:



The elimination of two water molecules (from cyclohexanediols) or two hydrogen halide molecules (from dibromocyclohexanes) evidently proceeds with intermediate formation of the allyl system and hence should also obey the rule mentioned above.

2. Admixture of Cyclohexa-1,4-dienes

When two water molecules are split off from cyclohexane-1,3-diols or cyclohexane-1,4-diols, cyclohexa-1,4-diene is formed as a side product in an amount of 20% and above (see below). It is reasonable to suppose that isomers with isolated double bonds can also be present in the dehydrobromination products of 1,3- and 1,4-dibromocyclohexanes (particularly the latter). Cyclohexa-1,4-dienes can also be formed as the products of the isomerisation of the corresponding 1,3-dienes in an alkaline medium.

3. Isomerisation

The isomerisation of cyclohexa-1,3-dienes can occur as a result of a 1,5-shift of hydrogen (above 250 °C), a 1,5-shift of substituents (400–500 °C), and a change in the nature of the substituent (500–600 °C).[4] The processes lead to the formation of a mixture of isomers with different positions of the double bonds and under the conditions of pyrolysis complex mixtures of skeletal isomers are produced.

In the presence of strong bases (for example, solutions of alkali metal alkoxides in the corresponding alcohols or dimethyl sulphoxide, (DMSO), cyclohexa-1,3-diene itself is partly converted into the 1,4-isomer (see, for example, Refs.5–8). The amount of the latter in the mixtures formed depends greatly on the nature of the base, the solvent, and other isomerisation conditions, varying in the range 0–34%;

† The literature up to 1945 is excluded from consideration.

cyclohexa-1,4-dienes is capable of isomerising quantitatively to the corresponding conjugated dienes under the influence of the same bases in ammonia, amines, and other solvents.

4. Aromatisation

A specific feature of the cyclohexa-1,3-diene derivatives is the ease with which they are aromatised. The conversion of dienes of the above series into benzene derivatives takes place as a result of two related reactions—dehydrogenation and disproportionation—with the simultaneous formation of cyclohexenes.

Cyclohexa-1,3-dienes can be dehydrogenated on heating in the liquid or gaseous phase with substances capable of absorbing hydrogen or with oxidants; the most thoroughly investigated hydrogen absorbing agents are palladium on charcoal[9–15] and elemental sulphur[16,17]. In the vapour phase above 400 °C, the dehydrogenation of cyclohexa-1,3-diene takes place in the absence of catalysts with evolution of molecular hydrogen[2,18–20]. The degree of conversion is then considerable (approximately 50%) only at 500 °C. Thermal aromatisation of the 5,5-disubstituted cyclohexa-1,3-dienes takes place via dealkylation (with evolution of a gaseous alkane) at 550 °C [21,22] and above.

It is generally known that the disproportionation of cyclohexa-1,3-dienes can occur as a heterogeneous process—as a result of contact with catalysts: palladium, platinum, nickel, and iron at 50–100 °C or alumina at 250–400 °C.[23] Homogeneous disproportionation takes place when dienes interact with strong bases under exceptionally mild conditions. Thus, when cyclohexadienes come into contact with a solution of potassium t-butoxide in DMSO (55 °C, 24 h) [7] or t-butyl alcohol (60°, 3h),[24] the dienes are quantitatively converted into a mixture of equal amounts of aromatic and mono-olefinic compounds. Sodium amide in liquid ammonia in the presence of a proton donor (for example, ammonium chloride) exhibits a powerful disproportionating activity[8]. Thermal disproportionation of the diene (I) takes place when it is heated for a long time at 150–200 °C in the absence of a solvent or catalyst during dimerisation[25] or polymerisation[26–28], the overall yield of benzene or cyclohexene reaching 20%.

5. Dimerisation and Polymerisation

Dimerisation via the diene condensation mechanism (see, for example, Refs.25, and 29–31) and thermal polymerisation (see, for example, Refs.27, 28, 32, and 33) take place as parallel reactions on heating cyclohexa-1,3-diene at 170 to 200 °C; the process is completed by the complete disappearance of the monomer in the course of approximately 10 h. The polymerisation of the diene (I) is catalysed by Lewis acids and takes place even at −80 °C in the presence of titanium tetrachloride[34–39], tin tetrachloride[34], or boron trifluoride[38,39]. On treatment with n-butyl-lithium, the polymerisation takes place at 30–60 °C.[36,37,40].

6. Oxidation

Cyclohexa-1,3-diene[41,42] and its derivatives[42] are oxidised by oxygen, particularly readily in the light, to endoperoxides even at room temperature; under the same conditions, not only the oxidation but also the aromatisation of dienes is observed[43].

7. Practical Recommendations

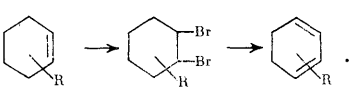
The foregoing shows that, in selecting a scheme for the synthesis of a substituted cyclohexa-1,3-diene, one must take into account many factors which can be reflected in the purity of the preparation. In the synthesis of cyclohexa-1,3-dienes, prolonged heating at 170 °C and above is undesirable (dimerisation, polymerisation, and disproportionation) and even brief heating at 250 °C can be damaging (isomerisation), while temperatures of 400 °C and above (dehydrogenation) must be completely ruled out. In synthetic methods the use of Lewis acids is inadmissable (polymerisation) and contact with strong bases (isomerisation and disproportionation), alumina, particularly at an elevated temperature (disproportionation), and atmospheric oxygen (oxidation and dehydrogenation) can have undesirable consequences.

The number of specimens of substituted cyclohexa-1,3-dienes described in the literature is very large but the purity and isomeric composition of the preparations have been checked only in studies during the last two decades. Analysis of the early literature data shows that the vast majority of the cyclohexadiene specimens could not have been homogeneous and hence the employment of these data in synthetic practice requires a preliminary aasessment of their reliability.

III. SYNTHESIS OF CYCLOHEXA-1,3-DIENES

1. Synthesis from Cyclohexenes

(a) *Bromination–dehydrobromination.* The most frequently employed scheme for the synthesis of cyclohexadienes from cyclohexenes involves bromination–dehydrobromination:



The bromination of cyclohexene (II) or its homologues is carried out at −5–0 °C in chloroform[32], carbon tetrachloride[44], or glacial acetic acid[45]; in all cases the reaction leads to the corresponding 1,2-dibromo-derivatives in yields of 80–85%. In the method ensuring the maximum yield of the dibromo-derivative (95%),[46] carbon tetrachloride with added absolute ethanol was used as the solvent.

Quinoline at the boiling point was widely used in early studies as the dehydrobromating reagent; the dienes were isolated from the reaction mixture by distillation (yield 45 to 65%). It has been shown by Raman[47] and ultraviolet[48] spectroscopy and also by gas-liquid chromatography (GLC) [35] that the composition of the preparation obtained by this method incorporates 40–50% of the diene (I), 40–50% of cyclohexene (II), and approximately 20% of benzene. It is extremely difficult to separate these compounds (b.p. 80.5°, 83°, and 80 °C respectively) by fractional distillation. The isolation of the pure diene (I) via its complex with silver nitrate[49] is suitable only for small batches of the diene.

The above method was used in early studies to obtain cyclohexadienes from 1-methyl-, 5-methyl-, 1,3-dimethyl-, and 1,4-dimethyl-cyclohexenes. The compositions of the dienes enumerated above were not monitored but it was shown by ultraviolet spectroscopy[50] that "5-methyl-cyclohexa-1,3-diene" obtained by this method contains 58% of toluene. According to Domnin's data[51], the dehydrobromination of 1,2-dibromo-1-chlorocyclohexane by quinoline led to chlorocyclohexadiene considerably contaminated by chlorocyclohexene and chlorobenzene. From the above, all the preparations of substituted cyclohexadienes obtained by the method described

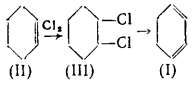
should contain not more than 50% of the main substance. Furthermore, as a result of the different pathways followed in the elimination of the second molecule of hydrogen bromide, there is a possibility of the formation of mixtures of isomers.

It has been suggested that 1,2-dibromocyclohexane be dehydrobrominated[44] by the readily available sodium alkoxide derived from ethylene glycol (at 220–230 °C) with the distillation of the reaction products; the yield of the hydrocarbon fraction is then 60%; according to infrared spectroscopic data, the resulting mixture contains 81% of the diene (I), 4% of the benzene, and 15% of cyclohexene (II). Despite the only slight increase of the yield and purity of the preparation obtained, this method has an advantage over that described above, since the expensive quinoline is replaced by the readily available sodium hydroxide and ethylene glycol. It is known[52] that, when sodium hydroxide is replaced by potassium hydroxide, the yield of the diene (I) increases to 71%, but its purity was not estimated. Presumably the specimen obtained is also not free from benzene and cyclohexene as impurities.

It has been suggested that a solution of sodium isopropoxide in aprotic solvents (for example, in the dimethyl ether of triethylene glycol) be used as the dehydrobrominating agent at 110–115 °C with distillation of the products *in vacuo*[53]. The yield of the diene (I) is then 35–40%. It is known[53] that an increase of the reaction temperature leads to the contamination of the product by benzene and cyclohexene. It has been established[54] that the application of a similar method (involving the use of sodium methoxide), for the synthesis of substituted cyclohexadiene leads to extremely complex mixtures of products.

Thus a change in the nature of the dehydrobrominating agent has still not permitted the synthesis of individual cyclohexadienes by means of the scheme described.

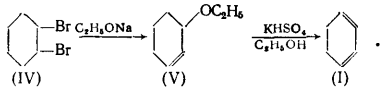
(b) *Chlorination–dehydrochlorination.* A scheme based on the chlorination of cyclohexene with subsequent thermal[55] or catalytic[56] dehydrochlorination of the resulting 1,2-dichlorocyclohexane (II) has been considered as a method of industrial synthesis of the diene (I):



(II) (III) (I)

The addition of chlorine to cyclohexene takes place readily in both liquid and gas phases. According to patent data[57,58], the dehydrochlorination of the dichloro-derivative (III) can be achieved in 89% yield when it is treated with sodium hydroxide in poly(ethylene glycol); the preparation obtained is contaminated by an admixture of 3-chlorocyclohexene[57]; the similarity of the dehydrohalogenation method to that described above suggests that the preparation should contain also benzene and cyclohexene. In order to achieve a continuous process, it has been suggested[56] that the vapour of the dichloro-derivative (III) be passed over alumina and silica gel, deposited on activated charcoal, at 300 °C and a pressure of 100 mmHg. The yield of the diene (I) is 33%, but, according to GLC data, the preparation is contaminated by benzene (10%), methylcyclopentadienes (7%), and methylcyclopentenes (3.5%). A patent has been taken out[55] for the pyrolytic (230–480 °C) dehydrochlorination of the dichloro-derivative (III), which results in a 34% yield of the diene (I) together with 7% of benzene and small amounts of cyclohexene and cyclohexa-1,4-diene. Thus the scheme described requires extensive further elaboration for its practical realisation.

(c) *The Hofmann–Damm method.* The scheme proposed by Hofmann and Damm[32] for the dehydrobromination of 1,2-dibromocyclohexane is extremely widely used:

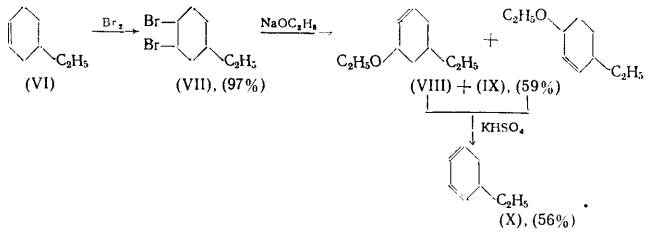


(IV) (V) (I)

Treatment of the dibromo-derivative (IV) with a boiling alcoholic solution of sodium ethoxide leads to a 40–70% yield of 3-ethoxycyclohexene (V) accompanied by the formation of 15–30% of the diene (I). Distillation of the ether (V) from sodium bisulphate makes it possible to split off an alcohol molecule which gives rise to a 60–90% yield of the diene (I). The formation of a mixture of the ether (V) and the diene (I) on treatment of the dibromo-derivative (IV) with sodium ethoxide constitutes a definite disadvantage of the scheme, since this mixture requires separation which inevitably entails losses. The method has been frequently tried and improved[59]. According to Raman spectroscopic data, the preparation obtained is free of admixtures of benzene and cyclohexene.

In one of the versions of this scheme, it has been suggested[60] that sodium ethoxide be replaced by the methoxide (the yield of 3-methoxycyclohexene is 69%) and that methanol be split off by heating (155–160 °C) with orthophosphoric acid in triethylene glycol. The yield of the diene (I) in the last stage is 82%. According to the data of Zupancic and Wucherpfennig[60], the diene (I) formed is chromatographically homogeneous. Sodium isopentoxide has been suggested for the same purpose. A considerable acceleration of the reaction (IV) → (V) (at 130 °C it is almost instantaneous) and the easier elimination of isopentyl alcohol in the second stage have been pointed out as advantages of the above reagent. However, the diene (I) formed under these conditions contains an appreciable amount of cyclohexene as an impurity.

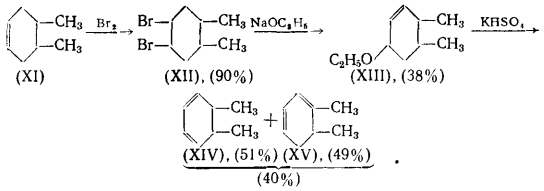
Using the Hofmann–Damm method[32], 1-methyl-,[54] 4-methyl-,[54] 1-ethyl-, 3-ethyl-, and 4-ethyl-,[61] 1-n-propyl-, 1-isopropyl-, 1-n-butyl-, 1,4-dimethyl-, and 4,4-dimethyl-,[21] 4,5-dimethyl,[61] 4-ethyl-4-methyl-,[62] and 1-phenyl- and 1,2-dibromo-cyclohexenes[63] have been converted into substituted cyclohexadienes. The reaction conditions and the yields at different stages reproduce fairly closely those described above for the diene (I) itself. The structure of the preparations of substituted cyclohexadienes obtained was established only in a small number of instances. It is known[61] that the reaction applied to 4-ethylcyclohexene (VI) leads to a fairly homogeneous (approximately 98%) 5-ethylcyclohexa-1,3-diene (X), i.e. there is virtually no migration of the double bonds under the elimination conditions:



(VI) (VII), (97%) (VIII) + (IX), (59%) (X), (56%)

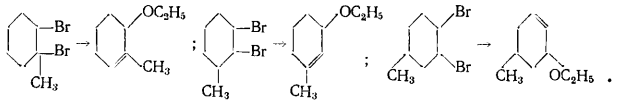
On the other hand[61], under analogous conditions, a mixture of approximately equal amounts of the isomeric dienes (XIV) and (XV), which correspond to different elimination

pathways, is formed from 4,5-dimethylcyclohexene (XI):



(XI) (XII), (90%) (XIII), (38%) (XIV), (51%) (XV), (49%) (40%)

It was later established reliably by GLC and ^{1}H NMR [64] that the interaction of the methyl-substituted dibromocyclohexenes (XVI)–(XVIII) with sodium ethoxide proceeds via one of the two possible pathways with a selectivity of 95–97%:

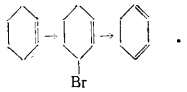


(XVI) (XIX), (51%) (XVII) (XX), (43%) (XVIII) (XXI), (62%)

On the other hand[64], heating of the ethers (XIX)–(XXI) with potassium hydrogen sulphate at 100 °C leads to extremely complex mixtures of hydrocarbons and, apart from the two possible elimination pathways, the mixture composition is complicated also as a result of the isomerisation of the dienes formed. The results of the above study[64] were subsequently reproduced[65].

Thus the above procedure for the synthesis of substituted cyclohexa-1,3-dienes can be of interest only when the starting materials are 4-substituted or 4,4-disubstituted cyclohexenes, since only then do both reaction pathways lead to the same diene. Consequently among the preparations enumerated above, only the 5-methyl-, 5-ethyl-,[61] 5,5-dimethyl-,[21] and 5-ethyl-5-methyl-cyclohexadienes[62] can be relatively homogeneous.

(d) *The Ziegler method.* Cyclohexenes were converted into cyclohexadienes in accordance with the following scheme[66]:



(II) (XXII) (I)

The bromination of cyclohexene with *N*-bromosuccinimide in carbon tetrachloride leads to a 70–85% yield of 3-bromocyclohexene (XXII), whose dehydrobromination with the aid of quinoline at 190 °C results in a 50–70% yield of the diene (I); this method has been frequently employed. According to GLC data[35,40], the preparation obtained is not less than 99% pure and contains only traces of cyclohexene, which appears doubtful on the basis of the comparison with the data presented above. A mixture of 1- and 2-chlorocyclohexa-1,3-dienes was obtained in the same way from 1-chlorocyclohexene[67] and a mixture of 1-methoxycarbonyl-2-methyl- and 1-methoxycarbonyl-6-methyl-cyclohexa-1,3-dienes was obtained from 4-methoxycarbonyl-3-methylcyclohexene[68]. The diene has been synthesised analogously from the nitrile of cyclohexene-1-carboxylic acid[69]. Collidine[49], triethylamine[68], sodium methoxide[69], and potassium t-butoxide[70] have also been used as dehydrobrominating agents, but in all the instances indicated above a decrease of the yield of the desired product was observed.

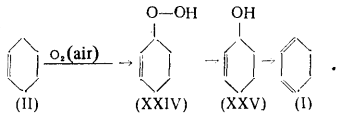
Thus one can assume that the method has no advantages over that discussed above, particularly as regards the synthesis of substituted cyclohexadienes, since the formation of mixtures of isomers from the individual substituted cyclohexene has been demonstrated experimentally in this instance [67,68]. Thus "2-cyanocyclohexa-1,3-diene" [69] and "5-methylcyclohexa-1,3-diene" [71] obtained in this way are most probably mixtures of isomers.

A version of the given scheme is the allyl chlorination of cyclohexene[72] by t-butyl hypochlorite in the presence of benzoyl peroxide (yield 77%) with subsequent dehydrochlorination of 3-chlorocyclohexene by dimethylaniline at 180 °C; the yield of the diene (I) is 80%, but the purity of the preparation has not been established. However, it forms an adduct with maleic anhydride in 93% yield. Bearing in mind that the dehydrochlorination of chlorocyclohexene proceeds much more readily than that of dichlorocyclohexane, this process can be regarded as the most likely industrial scheme for the synthesis of the diene (I) using the high-temperature allyl chlorination of cyclohexene in the first stage (by analogy with the thoroughly investigated propene chlorination process). However, this question has not so far been investigated.

(e) *The allyl oxidation.* The oxidation of cyclohexene with selenium dioxide in acetic anhydride leads to a 50% yield of 1-acetoxycyclohex-2-ene (XXIII). Two distillations of the acetate (XXIII) from potassium hydrogen sulphate at 145 to 155 °C give rise to a 60–70% yield of the diene (I), whose relative homogeneity has been confirmed by the fairly satisfactory agreement of its constants with those of a preparation known to be pure.

In order to convert acetates of type (XXIII) into cyclohexadienes, they were pyrolysed at 420 °C;[73] however, it has been shown for 3-methoxycarbonylcyclohex-1-en-2-yl acetate that the reaction product is a mixture of the possible isomers of methoxycarbonylcyclohexadiene, which is apparently contaminated by the corresponding aromatic compounds, i.e. this method cannot be recommended.

One of the most promising schemes for the industrial application of the syntheses of the diene (I) is[74]



(II) (XXIV) (XXV) (I)

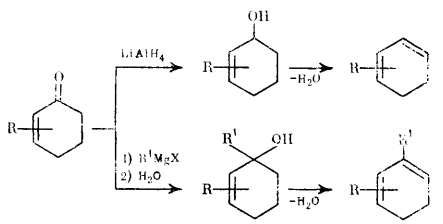
Cyclohexene is usually oxidised by atmospheric oxygen at 150 °C and 25–75 atm. This reaction is known to be autocatalytic[74–77]. The employment of cumenyl hydroperoxide as the catalyst[78] makes it possible to carry out the process under milder conditions (90–100 °C, 6–10 atm). As a rule[75,76,77], the degree of conversion is not high (15–30%) and the unreacted cyclohexene is readily separated by distillation and can be reused. The decomposition of the cyclohexenyl hydroperoxide (XXIV) may entail the formation of cyclohex-2-en-1-one and epoxycyclohexane; their minimal amount (3 to 10%) is obtained when the oxidation product is treated with 1 *N* NaOH at 40 °C [76] or with iron sulphate in alcohol[77]. The conditions for the dehydration of cyclohex-2-en-1-ol, are described below.

Thus the application of the schemes described in this section to the synthesis of cyclohexa-1,3-diene derivatives is undesirable in view of the formation of complex mixtures of isomers. On the other hand, cyclohexene is the most readily available starting material for the synthesis of the diene (I) itself. Among the methods discussed above, the Hofmann–Damm method can yield the purest preparation of cyclohexa-1,3-diene. However, the simplest procedure involving bromination–dehydrobromination with the aid of quinoline or the more readily available alkoxide derived from ethylene glycol

has not lost its importance despite the low purity of the diene obtained, since the impurities do not interfere with many reactions (for example, the diene condensation). The oxidation of cyclohexene and the dehydration of the resulting enol (XXV) are apparently beyond competition at the present time as regards their application on an industrial scale.

2. Synthesis from Cyclohex-2-en-1-ones

Cyclohexenones, which are relatively readily available as a result of a wide variety of condensation and cyclisation reactions, are the most common and apparently some of the most promising starting materials in the synthesis of substituted cyclohexa-1,3-dienes. The main schemes of such syntheses are as follows:



The frequent use of these schemes is due to the fact that their main disadvantage (inhomogeneity of the dienes obtained) was discovered only towards the beginning of the 1960's after the development of the chromotographic and spectroscopic analytical techniques.

(a) *Synthesis via secondary alcohols.* The literature data on the reduction of cyclohexenones and the dehydration of the unsaturated alcohols formed are presented in Table 1. The reductant employed is mainly lithium tetrahydroaluminate in boiling ether[2,21,80,82,85]; the yield of alcohols is 70–90%. The allyl alcohols formed are thermally stable and are readily purified by distillation.

The main method for the industrial dehydration of the enol (XXV) itself considered in the literature involves the passage of its vapour over alumina[23,86–88] and the optimum yield of the diene (I) (up to 85%) can be achieved at 270 °C. It has been established[86] that the reaction is accompanied by the formation of cyclohexene, cyclohexane, and benzene, the latter being absent from the first portions of the catalytic reaction mixture[23]; the amount of impurities is 2–5% and increases with contact time. In order to diminish the role of side processes, it has been suggested[88] that the vapour of compound (XXV) be diluted with water; for the optimum molar component ratio of 2 : 1 respectively, the degree of conversion is 77% and the purity of the product is 99%. According to patent data[89,90], when a specially prepared catalyst based on alumina is used, it is possible to achieve a yield of 94% combined with a purity of diene (I) of 96.5% (the rest is cyclohexene).

It has been reported[91,92] that calcium and magnesium phosphates are effective catalysts of the vapour-phase dehydration of compound (XXV); at 250–280 °C and for a contact time of 18–30 s, the diene (I) can be obtained in 70–85% yield with a purity of 97–99% according to refractometric data, which is doubtful. The application of an aluminium boride catalyst for this purpose in a fluidised bed at 250–280 °C has been described[93] (yield up to 93%, purity according to GLC 99.3%, the residue consisting of 0.6% of benzene and 0.1% of cyclohexene).

The dehydration of substituted cyclohexenols over alumina at 300 °C [21] or 350 °C [85] has been described (yield approximately 60%); it must be supposed that the dienes formed under these conditions are contaminated by their disproportionaton products.

Table 1. Synthesis of cyclohexadienes via the reduction-dehydration of cyclohexen-1-ones.

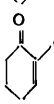
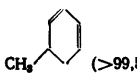
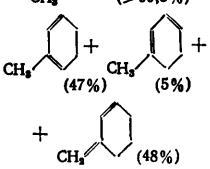
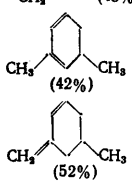
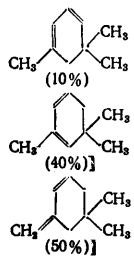
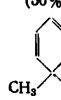
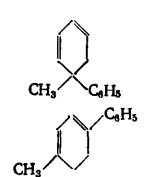
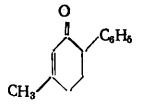
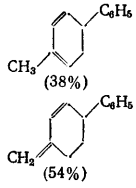
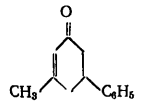
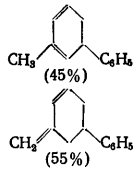
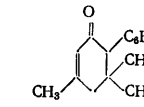
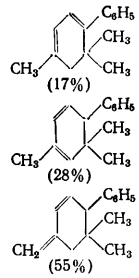
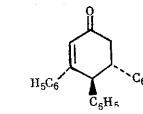
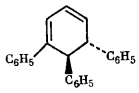
Initial ketone	Yield of alcohol, %	Dehydration conditions	Yield of hydrocarbon fraction, %	Composition of hydrocarbon fraction	References
	—	C	78		[79]
	89	*A*	80	(96%)	[2]
	66	*A*	80	 (>99,5%)	[2]
	70	*A*	77	 (47%) (5%) (48%)	[2]
	—	C	—	 (42%) (52%)	[80]
	—	B	—	 (10%) (40%)] (50%)]	[80, 81]
	—	C	63		[79]
	—	C	58		[79]
	—	*A*	—	 (8%)	[82]

Table 1 (contd.)

Initial ketone	Yield of alcohol, %	Dehydration conditions	Yield of hydrocarbon fraction, %	Composition of hydrocarbon fraction.	Refs.
	—	B	—	 (38%) (54%)	[80]
	—	B	—	 (45%) (55%)	[80]
	—	B	—	 (17%) (28%) (55%)	[79, 83]
	—	D	65		[84]

* A = *p*-$CH_3C_6H_4SO_3H$; B = $CuSO_4$; C = $[(C_6H_3O)_3PCH_3]^+I^-$; D = $KHSO_4$.

Distillation of cyclohexenols in the presence of catalytic amounts of toluene-*p*-sulphonic acid[2,82], potassium hydrogen sulphate[94], magnesium chloride[75], or iodine[78] or refluxing with anhydrous copper or magnesium sulphate[95] has been widely used in laboratory practice for this purpose (Table 1). According to GLC data[2,80], the cyclohexadienes obtained by these methods are free of disproportionation products. The relatively low reaction temperature in this instance apparently makes it possible also to prevent the thermal isomerisation of the cyclohexa-1,3-dienes formed[2,80].

For the dehydration of cyclohexenols itself and 5,5-disubstituted cyclohexenols, it has recently been suggested[79,96] that the secondary alcohol be heated briefly at 50 °C with methyl triphenoxyphosphonium iodide in hexamethylphosphoramide; the dienes formed under these conditions in yields of 60–80% are free from impurities. However, in those cases where there is a possibility of different pathways in the elimination process, the reactions were not investigated.

Table 1 demonstrates the existence of different pathways in the dehydration of substituted cyclohexenols; in many cases the preferred reaction pathway is 1,4-elimination, which in the presence of an alkyl substituent in the 3-position leads to the formation of considerable (up to 40%) amounts of dienes with an exocyclic double bond. Homogeneous preparations can be obtained as a result of this reaction in only two cases:

(1) If any of the dehydration pathways leads to the same substance (this happens in the presence of one substituent in the 2-position or of two substituents in the 5-position, or of two identical substituents in the 2- and 5-positions).

(2) On geminal substitution in the 4,4- and 6,6-positions whereupon there is a possibility of only one reaction pathway.

Thus, despite its simplicity and convenience, this method of synthesis of substituted cyclohexadienes leads as a rule to mixtures of dienes (in the general case three-component mixtures) which are difficult to separate.

(b) *Synthesis via tertiary alcohols.* The interaction of cyclohexenones with organomagnesium and organolithium compounds followed by the dehydration of the tertiary unsaturated alcohols is apparently the most frequently employed method of synthesis of cyclohexadienes. The literature data on the application of this scheme are presented in Tables 2 and 3. In all the studies mentioned in the above tables, the organomagnesium compounds were synthesised and made to react with ketones in ether under standard conditions.

Attention should be drawn to the fact that the interaction of a Grignard reagent with cyclohexenones may be complicated by 1,4-addition which leads to saturated ketones[2,97]. This reaction lowers the yield of the dienes, sometimes to a considerable extent. With increase of the bulk of the substituent introduced into the molecule, the contribution of 1,4-addition increases sharply and can reach 70%;[97] copper(I) chloride catalyses this side reaction[97,124].

The tertiary alcohols formed as a result of the main reaction are as a rule unstable and are readily dehydrated, particularly in an acid medium. When the reaction mixture remaining after the organomagnesium synthesis is treated with acids (for example, with 6–10% sulphuric acid), the above alcohols cannot be isolated and the reaction products are diene hydrocarbons[104]. Traditional treatment of the reaction mixture with ammonium chloride also does not permit the isolation of the alcohols in many instances. Treatment with water makes it possible to isolate the alcohols only if the reaction mixture is poured into an ice–water mixture; the reverse order of mixing leads directly to the dienes[125]. The instability of the alcohols obtained complicates their purification and makes it desirable to dehydrate the residue after removing the ether from the hydrolysis products of the organomagnesium compounds (without drying the extract).

The dehydration of unsaturated tertiary alcohols can be achieved by their simple distillation (at 80–120 °C).[2] The addition of acid catalysts (oxalic[11] and toluene-*p*-sulphonic acids[2] and potassium hydrogen sulphate[118]) greatly accelerates the process, but the yield of dienes is then somewhat reduced. The composition of the dehydration products on distillation in a neutral medium and in the presence of toluene-*p*-sulphonic acid is virtually the same[2]. The application of phosphoryl chloride in pyridine for this purpose has been described[103] (yield 62%). The use of severe conditions, such as passing the vapour of the tertiary alcohol over alumina at 300 °C,[121] is evidently superfluous.

The composition of the mixtures of dienes obtained by the above procedure has been established reliably in an extremely limited number of cases[2,21,104,125]. In a number of studies the inhomogeneity of the product (the presence of an admixture of a diene with an exocyclic double bond) was suggested tentatively[106,109,117,118]. It has been postulated[109] that in some reactions the "transoid" dienes predominate in the mixtures produced. As a rule, the dienes obtained were regarded as homogeneous substances.

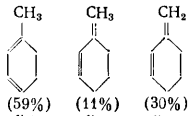
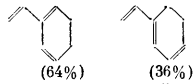
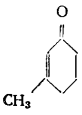
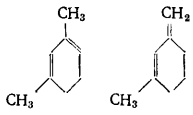
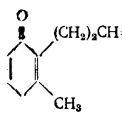
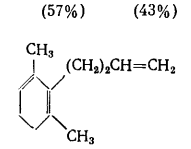
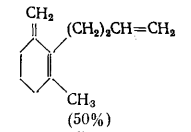
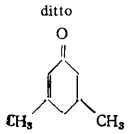
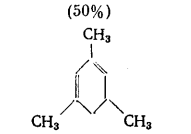
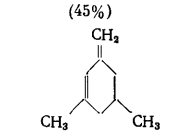
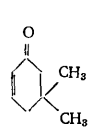
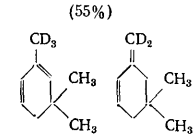
The data presented in Table 2 show that, when a methyl group is introduced by the given procedure into the molecule,

exceeds 30%. If a secondary alkyl group is introduced, such dienes are present in the mixture in still greater amounts. The presence of an alkyl substituent in the 3-position in the initial ketone increases the yield of the "transoid" diene to 45–55%.[3,21,104,125]. If the substituents in the 1- and 3-positions of the diene formed differ, the formation of two isomeric dienes with an exocyclic double bond is to be expected.

Finally, 1,4-elimination can lead to the appearance in the reaction products of a cyclohexadiene with a different disposition of the double bonds than would be expected from a formal inspection of the reaction scheme. This has been observed, for example, by Mironov et al.[2]

Thus the above reaction involving cyclohexadienes leads to complex mixtures of products and the literature data on this question contain numerous errors.

Table 2. Synthesis of cyclohexadienes from cyclohex-2-en-1-ones via organomagnesium and organolithium compounds (the composition of the reaction products has been established reliably).

Initial ketone	Reagent	Dehydration conditions	Yield, %	Mixture composition	Refs.
	CH_3MgI	*A*	69	 (59%) (11%) (30%)	[2,83, 97]
ditto	CH_3MgI	B	62	ditto (59%) ditto (12%) ditto (29%)	[2]
	$CH_2=CHMgBr$	*A*	—	 (64%) (36%)	[96]
ditto	$CH_2=CHMgBr$	C	<15	ditto (60%) ditto (40%)	[96]
	CH_3MgI	*A*	40	 (57%) (43%)	[98–103]
	CH_3MgI	*A*	—	 (50%)	[104]
				 (50%) ditto (50%) ditto (50%)	
ditto 	CH_3Li	*A*	—	ditto (50%)	[104]
	CH_3MgI	D	77	 (45%)  (55%)	[21, 105–107]
	CD_3MgI	D	—	 (~50%) (~50%)	[80]

* A = distillation; B = p-$CH_3C_6H_4SO_3H$; C = $[(C_6H_5O).P(CH_3)_3]^+I^-$; D = $CuSO_4$.

Table 3. Synthesis of cyclohexadienes from cyclohex-2-en-1-ones via organomagnesium and organolithium compounds (the composition of the reaction products was postulated on the basis of the synthetic scheme).

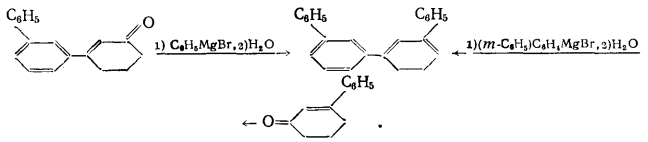
Substitution in initial ketone	Reagent	Dehydration conditions*	Yield, %	Refs.
Unsubstituted	C_6H_5MgBr	E	96	[13]
ditto	C_3F_7MgBr	E	43	[108]
3-Methyl-	C_2H_5MgBr	A	50	[109]
ditto	n-C_3H_7MgBr	A	50	[109]
ditto	iso-C_3H_7MgBr	A	19	[109]
ditto	n-C_4H_9MgBr	A	50	[109]
3-Ethyl-	C_2H_5MgBr	E	69	[110]
3-n-Butyl-	C_2H_5MgBr	E	83	[110]
ditto	n-C_4H_9MgBr	E	80	[110]
3-t-Butyl-	n-C_4H_9MgBr	E	80	[110]
4-Isopropyl-	CH_3MgI	F	70	[111]
4-(1,5-Dimethylhexyl)-	CH_3MgI	G	60	[112]
2-Phenyl-	C_6H_5Li	A	70	[113]
3-Phenyl-	$C_6H_{11}MgBr$	B	40	[114]
ditto	C_6H_5MgBr	E	~100	[14, 114]
ditto	p-$CH_3C_6H_4MgBr$	E	~50	[11]
ditto	$C_6H_5C_6H_4Li$**	E	~50	[115]
4-($CH_3C_6H_4$)-**	CH_3MgI	E	~50	[12]
3-(m-$C_6H_5C_6H_4$)-	C_6H_5Li	E	~50	[11]
ditto	m-$C_6H_5C_6H_4MgBr$	E	~50	[116]
3-(p-$C_6H_5C_6H_4$)-	m-$C_6H_5C_6H_4MgBr$	E	~50	[116]
5-Ethyl-3-methyl-	CH_3MgI	D	62	[106]
3-Methyl-5-n-propyl-	CH_3MgI	D	62	[117]
5-Isopropyl-3-methyl-	CH_3MgI	D	62	[117]
3,5-Diphenyl-	C_6H_5MgBr	E	80	[15, 115]
ditto	$CH_3C_6H_4MgBr$**	E	80	[15]
ditto	p-$C_6H_5C_6H_4Li$	E	—	[115]
5-Phenyl-3-m-tolyl-	p-$CH_3C_6H_4MgBr$	E	~80	[15]
5-Phenyl-3-p-tolyl-	p-$CH_3C_6H_4MgBr$	E	~80	[15, 102, 118–120]
ditto	C_2H_5MgBr	H	60	[121]
ditto	C_3H_7MgBr	H	60	[121]
ditto	$CH_2=CHMgBr$	A	70	[122]
ditto	$CH_3CH=CHMgBr$	A	70	[122]
3,4,6-Trimethyl-	CH_3MgI	A	70	[123]

*A = distillation; B = p-$CH_3C_6H_4SO_3H$; C = $[(C_6H_5O).P(CH_3)_3]^+I^-$; D = $CuSO_4$; E = 10% H_2SO_4; F = $(COOH)_2$; G = $POCl_3$ in C_5H_5N; H = $KHSO_4$.

** o-, m-, and p-isomers.

The isolation of the individual cyclohexadienes from the mixtures obtained requires the application of preparative GLC. 1,3-Diphenylcyclohexa-1,3-diene[14] (homogeneous according to the method of synthesis) and other polyphenylcyclohexadienes[11,12,115,116], which can be readily purified by crystallisation, are apparently and exception. However, one should bear in mind that in this case too it is difficult to predict unambiguously the positions of the double bonds in the diene obtained. For example, it is known[116] that the application of the above scheme in the examples quoted yields the same substance (the second isomer may be lost in the course

of the purification by crystallisation):



Furthermore, in analogous schemes[11], when one of the substituents is p-$C_6H_5C_6H_4$ and the other is C_6H_5, dienes with identical melting points are formed.

Thus, despite its wide-scale application, the method described is suitable only in a limited number of instances.

Table 4. Synthesis of cyclohexadienes via the tosyl hydrazones of substituted cyclohex-2-en-1-ones.

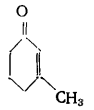
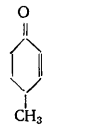
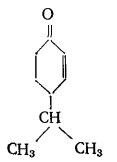
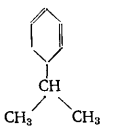
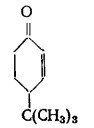
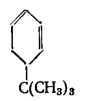
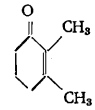
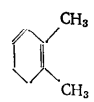
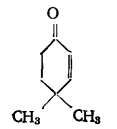
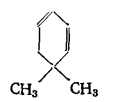
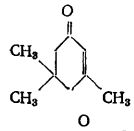
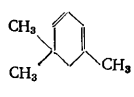
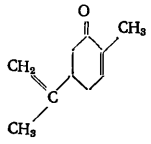
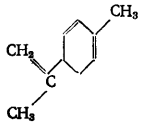
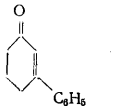
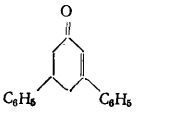
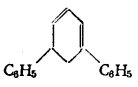
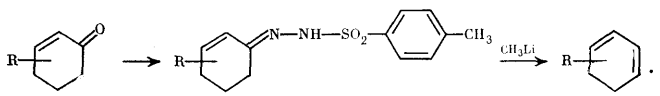
Initial ketone	Diene obtained	Yield, %	References
		50	[127]
		40	[127]
		—	[128]
		—	[128]
		—	[128]
		87	[126]
		85	[64, 126]
		~100	[126, 129]
		80	[126]

Table 4 (contd.)

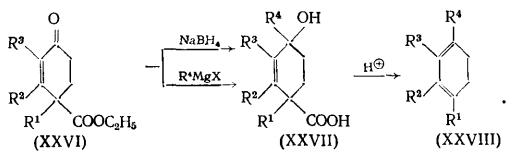
Initial ketone	Diene obtained	Yield, %	References
		40	[126]
		55	[126, 130—132]

(c) *Dauben's method.* In 1968 Dauben et al.[126] suggested that cyclohexenones be converted into cyclohexadienes by the reaction of the tosyl hydrazones of these ketones with methyl-lithium in a benzene–ether mixture; the literature data on this method are compiled in Table 4.



It has been reported[129] that in this process methyl-lithium can be replaced by n-butyl-lithium, but, according to Dauben et al.[126], such replacement results in a decrease in the yield of the diene and in addition the use of *n*-butyl-lithium results in the contamination of the diene produced by mono-olefinic compounds. A considerable advantage of the method under discussion is that hydrogen is eliminated exclusively from the α-position relative to the hydrazone group. In combination with the low temperature of the experiment, this makes it possible to obtain cyclohexadienes having a specified structure with a high degree of purity.

(d) *Plieninger's method.* A relatively convenient method of synthesis of substituted cyclohexadienes (XXVIII) involves the coupled dehydration–decarboxylation of 1-hydroxy-cyclohex-2-ene-4-carboxylic acids (XXIV):



(XXVI) (XXVII) (XXVIII)

The hydroxyacids (XXVII) are synthesised by the reduction of the relatively readily available ketoacid esters[16,133] with sodium tetrahydroborate in ethanol[16]; the dehydration-decarboxylation (as a rule without the isolation of the hydroxy-acids) is achieved on treatment of the acids with 4–5 *N* sulphuric acid at 20 °C. The overall yield of the dienes[16] is 14–60%. It has been suggested[134] that zinc tetrahydroborate in benzene be used as the reductant in the above scheme (yield of hydroxyacid 60–90%) and that the dineopentyl acetal of dimethylformamide be employed as the dehydrating agent at 20–70 °C in a non-polar solvent (α-methylnaphthalene), serving simultaneously as a "cushion" in the distillation of the diene. This procedure made it possible to increase the yield of dienes in the last stage to 50–85%. It is striking that this scheme yields dienes with a homogeneous isomeric composition free from extraneous impurities, which has been

shown convincingly[134]. The known instances of the application of this scheme are presented in Table 5. This is undoubtedly one of the promising methods of synthesis of substituted cyclohexadienes, but the conditions for the dehydration-decarboxylation of the hydroxyacids (XXVII) require further improvement; in particular the dehydrating agent (dineopentyl acetal of dimethylformamide) should be replaced by one more readily available.

Table 5. Synthesis of cyclohexa-1,3-dienes by the dehydration-decarboxylation of 1-hydroxycyclohex-2-ene-4-carboxylic acids.

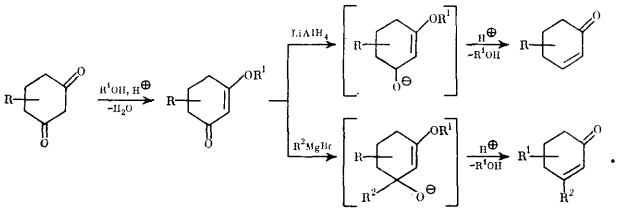
Substitution in initial ester (XXVI) (R^1–R^3) and in the diene (XXVIII) obtained				Reduction conditions	Yield of hydroxy-acids, %	Reaction conditions*	Yield of diene, %	References
R^1	R^2	R^3	R^4					
CH_3	H	H	H	$NaBH_4$	—	*A*	14**	[16]
CH_3	H	H	H	$Zn(BH_4)_2$	63	B	51	[134]
H	CH_3	H	H	$NaBH_4$	—	*A*	14**	[16]
H	CH_3	H	H	$Zn(BH_4)_2$	60	B	50	[134]
CH_3	CH_3	H	H	$NaBH_4$	86	*A*	85	[16]
CH_3	H	H	CH_3	CH_3MgI	64	B	54	[134]
H	CH_3	CH_3	H	$Zn(BH_4)_2$	94	B	84	]134]

* A = 5 *N* H_2SO_4, 20 °C; B = dineopentyl acetal of dimethylformamide.

** For two stages.

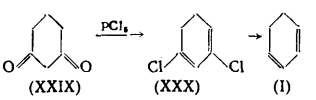
3. Synthesis from Cyclohexanediones and Cyclohexanediols

(a) *Starting materials.* The relatively readily available cyclohexane-1,3-diones in many instances serve as the starting materials for the synthesis of cyclohex-2-en-1-ones in accordance with the mechanisms (see, for example, Gannon and House[135]):



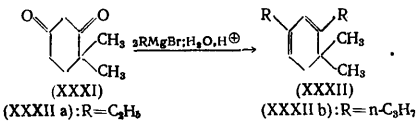
Cyclohexane-1,3-diols and cyclohexane-1,4-diols can be prepared by hydrogenating the corresponding diones or the available aromatic diols. Cyclohexane-1,2-diols are formed on oxidation of the corresponding cyclohexenes.

(b) *The substitution reaction.* When cyclohexane-1,3-dione is treated with phosphorus pentachloride in chloroform, it is possible to obtain 1,3-dichlorocyclohexa-1,3-diene (XXX) in approximately 60% yield, whose reduction with sodium in moist ether gives rise to the corresponding hydrocarbon containing an admixture of cyclohexene:



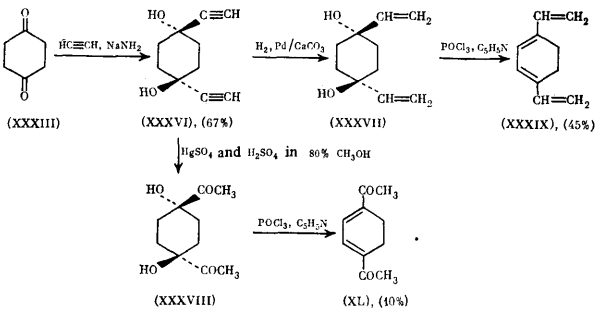
This reaction has also been described for 2-methyl-,[136] 5,5-dimethyl-, 5-phenyl-, and 2-methyl-5-phenyl-cyclohexane-1,3-diones. The yield of dichlorocyclohexadienes is 50–80%, but their purity has not been estimated.

(c) *Synthesis via tertiary alcoholds.* The interaction of hexanediones with two equivalents of a Grignard reagent followed by the dehydration of the resulting dione[137] leads to the diene fraction (XXXII) in approximately 50% yield;



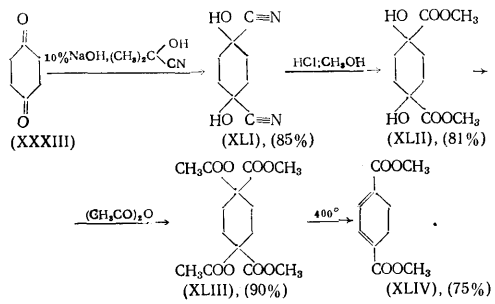
According to GLC data, the dienes formed are inhomogeneous, but the stretching vibration frequencies of the double bonds in the Raman spectra suggest that 1,3-dienes predominate in the mixtures. The synthesis of diphenylcyclohexadiene from cyclohexane-1,4-dione (XXXIII) has been achieved using an analogous scheme; organomagnesium synthesis under standard conditions led to a mixture of *cis*- and *trans*-1,4-diphenylcyclohexane-1,4-diols, whose dehydration with 20% sulphuric acid gave a 55% yield of 1,4-diphenylcyclohexa-1,3-diene (XXXIV), which was homogeneous according to the authors[138]. However, subsequent data[139] showed that the specimen contained 1,4-diphenylcyclohexa-1,4-diene (XXXV) (from 25 to 75% depending on the time of contact between the mixture of diols and the acid). Such mixtures are not susceptible to separation[139], but their treatment with potassium t-butoxide in t-butyl alcohol and subsequent crystallisation permit the isolation of the individual diene (XXXIV).

(d) *Synthesis via interaction with acetylides.* The interaction of dione (XXXIII) with sodium acetylide in liquid ammonia, leading to *trans*-1,4-diethynylcyclohexane-1,4-diol (XXXVI), from which divinylcyclohexa-1,3-diene (XXXIX) and diacetylcyclohexa-1,3-diene (XL) were obtained by means of the standard methods illustrated in the scheme below, has been described[140]:



1,4-Bis(2-phenylethyl)cyclohexadiene has been synthesised in accordance with an analogous scheme using phenylacetylene[141]. The positions of the double bonds in the dienes and also their homogeneity, which is particularly important for liquid divinylcyclohexadiene, have not been determined; it must be supposed that the preparations were not free from 1,4-isomers.

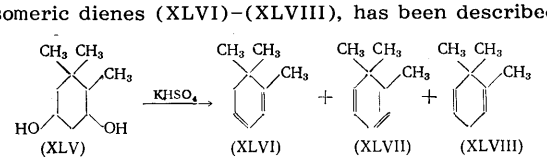
A related scheme has been used[142] to obtain dimethyl cyclohexadiene-1,4-dicarboxylate (XLIV):



A deficiency of this scheme is the use in the last pyrolytic stage of the diacetate (XLIII) at 400 °C, which is accompanied by a partial (18%) dehydrogenation of the substance. The homogeneity of the diene obtained relative to the positions of the double bonds has been confirmed by GLC data and the preparation of the adduct of the diene (XLIV) with maleic anhydride in a high yield. Evidently the given isomer predominates in the corresponding equilibrium mixture. The schemes presented above are not general and it is desirable to employ cyclohexanediones mainly for the synthesis of other starting materials—principally cyclohexenones.

(e) *Dehydration of cyclohexane-1,2-diols.* It has been shown by a large series of studies (see, for example, Refs. 143–145) that the dehydration of cyclohexane-1,2-diol cannot serve as a method of synthesis of cyclohexadiene, since its main products are cyclohexanone and formylcyclopentane. The synthesis of cyclohexane-1,2-diyl diacetate and its pyrolysis (540–660 °C) have been described[146] as a method of synthesis of cyclohexadiene, the yield in the last stage amounting to 84% according to the data presented[146]. However, the cyclohexadiene formed must be greatly contaminated by benzene. It is known that the products of the pyrolysis of 1-methylcyclohexane-1,2-diyl diacetate, obtained from 1-methylcyclohexene, contain a large amount of 3-methylenecyclohexene. Furthermore, the diene obtained should undergo isomerisation and aromatisation under the experimental conditions. Evidently the application of this extremely widely used scheme for the synthesis of dienes from monoolefinic compounds to the synthesis of cyclohexadienes is undesirable.

(f) *Dehydration of cyclohexane-1,3-diol.* The dehydration of cyclohexane-1,3-diol by 80% sulphuric acid gives rise to a mixture of cyclohexa-1,3-diene and cyclohexa-1,4-diene in proportions of approximately 5:1. The dehydration of *cis*-5,5-dimethylcyclohexane-1,3-diol[149,150] on distillation from phthalic anhydride leads to a 50% yield of 5,5-dimethylcyclohexa-1,3-diene, containing, according to GLC data, 8% of 3,3-dimethylcyclohexene and 8% of 4,4-dimethylcyclohexene, which can be readily removed by fractional distillation. Under the same conditions, *trans*-2,2-dimethylcyclohexane-1,3-diol[150] yields a complex mixture of products, which contains less than 10% of cyclohexadiene hydrocarbons. The dehydration of 5,5,6-trimethylcyclohexane-1,3-diol (XLV) on distillation with potassium hydrogen sulphate and resulting, according to Raman spectroscopic data, in a mixture of the isomeric dienes (XLVI)–(XLVIII), has been described[120]:



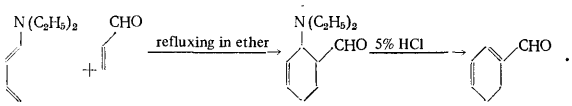
(g) *The elimination of water from cyclohexane-1,4-diol.* The elimination of water from cyclohexane-1,4-diol on treatment with 80% sulphuric acid gives a 44% yield of a mixture of cyclohexa-1,3-diene and cyclohexa-1,4-diene in proportions of 1:4. When the 1,4-diol is distilled from potassium hydrogen sulphate, the 1,4-isomer also predominates in the resulting mixture of dienes. The employment of anhydrous magnesium sulphate as the dehydrating agent[106] makes it possible to obtain a 40% yield of a mixture of dienes, in which the amount of the diene (I) is much greater. When cyclohexane-1,4-diol is distilled with phthalic anhydride (at 200 °C),[19] it is possible to obtain an 88% yield of a mixture consisting of 66% of the diene (I) and 34% of its 1,4-isomer according to GLC data. These mixtures can be readily separated by fractional distillation. Dehydration of cyclohexane-1,4-diol in a mixture with methanol in the vapour phase over alumina at 240–250 °C has been described[151]; the yield of the mixture of hydrocarbons was 48%. The main mixture component is apparently the diene (I), which has been isolated by column distillation and forms an adduct with maleic anhydride in a satisfactory yield.

The replacement of the dehydration of cyclohexane-1,4-diols by their conversion into diacetates with subsequent pyrolysis must be regarded as undesirable, since aromatisation takes place to a considerable extent (up to 28%) under the experimental conditions (450–500 °C).[152]

The data presented show that the synthesis of cyclohexa-1,3-dienes from cyclohexanediols leads as a rule to mixtures of the dienes and their 1,4-isomers.

4. Condensation and Cyclisation Reactions

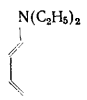
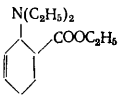
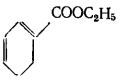
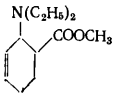
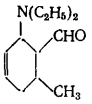
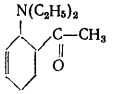
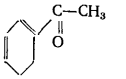
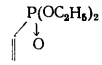
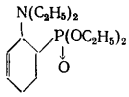
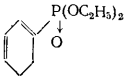
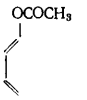
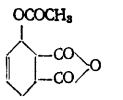
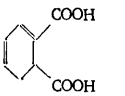
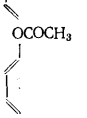
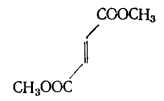
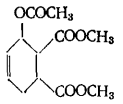
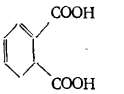
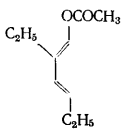
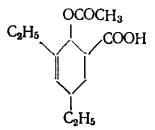
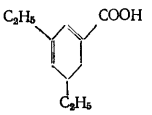
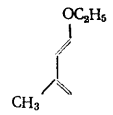
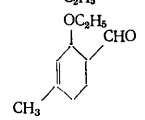
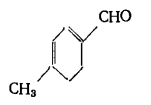
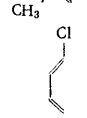
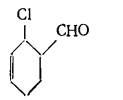
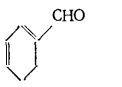
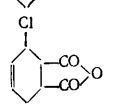
(a) *Diene condensation.* One of the preparatively important reactions for the formation of the cyclohexadiene ring is the diene condensation of acyclic dienes with dienophiles of the ethylene series when one of the addends (the diene or dienophile) contains a substituent which can be subsequently readily eliminated, for example[153]:



Examples of the employment of this scheme are compiled in Table 6. Dialkylamino-, acetoxy-, and alkoxy-groups, as well as the chlorine atom have been used as the substituents to be eliminated. The specific features of the diene condensation reaction limit the scope of the above scheme solely to the synthesis of cyclohexadienes containing electron-accepting groups, mainly carbonyl and carboxy-groups. The purity and the isomeric composition of the dienes obtained, described in Table 6, were in the vast majority of cases not determined. However, presumably the elimination took place preferentially via the pathway represented, since it corresponds to the elimination of the most mobile hydrogen atom from the α-position relative to the electron-accepting group, whereas the isomerisation of the dienes under the experimental conditions is unlikely.

It has been recently reported[168] that the diene condensation of 1-acetoxybuta-1,3-diene and its homologues with derivatives of acrylic and fumaric acids results in the formation of acetoxycyclohexene-carboxylic or dicarboxylic acids, which can be converted into the corresponding cyclohexa-1,3-dienes in 69–87% yield as a result of the elimination of

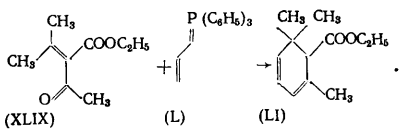
Table 6. Synthesis of cyclohexadienes via diene condensation-elimination.

Diene	Dienophile	Adduct	Eliminated molecule	Elimination conditions	Yield, %	Cyclodiene	References
			$HN(C_2H_5)_2$	5% HCl	40		[153]
ditto			ditto	HCl in C_2H_5OH	58		[154—158]
ditto			ditto	ditto	42		[159]
ditto			ditto	10% HCl	16		[153]
ditto			ditto	heating	<20		[153]
ditto			ditto	NaH	~30		[160]
			CH_3COOH	HCl	~60		[161—163]
			ditto	4% KOH	<20		[162]
			ditto	heating	30		[164]
			C_2H_5OH	heating	80		[165]
	ditto		HCl	heating	~80		[166]
ditto			ditto	KOH in CH_3OH	—		[167]
			»	$(CH_3)_3COK$	—		[24]

acetic acid and decarboxylation:

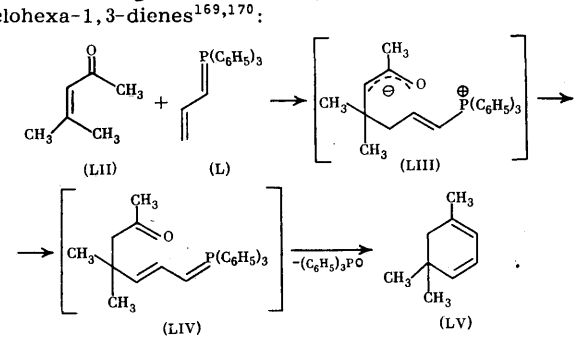
Unfortunately specific methods are not described in the above communication[168]: nor are there any data concerning the positions of the double bonds in the dienes formed.

(b) *Intramolecular Wittig reaction.* It has been observed [169] that, instead of the expected product of the Wittig condensation, the interaction of allylidenetriphenylphosphorane (L) with the ketoester (XLIX) gives rise to a 60% yield of compound (LI) with a cyclohexadiene ring:



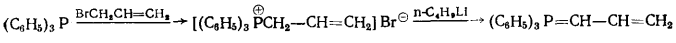
(XLIX) (L) (LI)

This method is general for the synthesis of substituted cyclohexa-1,3-dienes[169,170]:



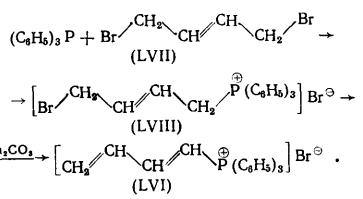
(LII) (L) (LIII) (LIV) (LV)

This reaction[170] involves the addition of the ylide (L) to the β-position of the unsaturated ketone (LII) with formation of a structure of type (LIII). Proton transfer leads to the ylide (LIV), which is capable of undergoing the intramolecular Wittig condensation. The reaction proceeds under mild conditions and makes it possible to obtain dienes in 30–60% yield. The initial ylide of type (L) is synthesised by the reduction of the corresponding phosphonium bromide with n-butyl-lithium:



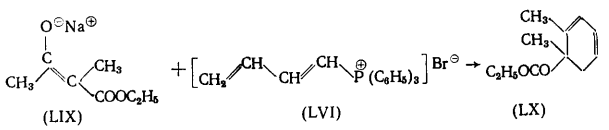
According to Büchi and Wüest[169] and Dauben et al.[170], the reaction is not accompanied by any side processes and makes it possible to obtain homogeneous preparations of cyclohexa-1,3-dienes. Examples of the application of this reaction are presented in Table 7.

The condensation of *trans*-1-butadienylphenylphosphonium bromide (LVI) with the enolates of carbonyl compounds is a convenient method of synthesis of cyclohexadienes[171–173]. The salt (LVI) can be obtained in a high yield (92%) on interaction of triphenylphosphine with *trans*-1,4-dibromobut-2-ene (LVII) in benzene with subsequent dehydrobromination of the resulting *trans*-4-bromobut-2-enyltriphenylphosphonium bromide (LVIII) by anhydrous sodium carbonate in chloroform:



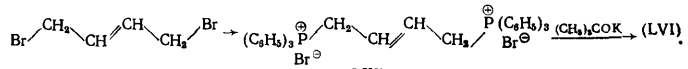
(LVII) (LVIII) (LVI)

When the salt (LVI) is refluxed with carbonyl compounds in the form of enolates (LIX) in tetrahydrofuran, cyclohexa-1,3-dienes (LX) are formed:



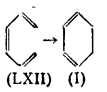
(LIX) (LVI) (LX)

Examples of the use of this reaction are presented in Table 8. The method under discussion leads to highly pure dienes. The interaction of the diphosphonium salt (LXI) with potassium t-butoxide in ether also leads to the salt (LVI), which condenses with carbonyl compounds under the experimental conditions giving rise to cyclohexadienes in high yields[171]:



(LVII) (LXI)

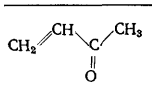
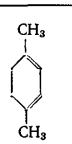
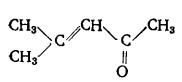
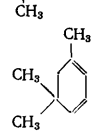
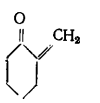
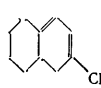
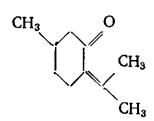
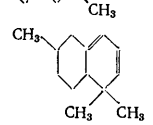
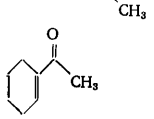
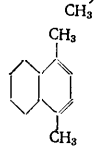
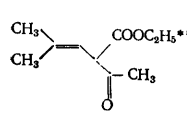
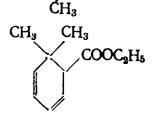
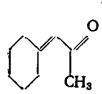
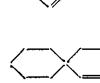
(c) *Electrocyclisation of hexa-1, 3, 5-trienes.* It is known that the thermal cyclisation of 3-*cis*-hexa-1,3,5-trienes leads to compounds of the cyclohexadiene series:



(LXII) (I)

The literature data for this reaction are compiled in Table 9. The reaction is typical electrocyclisation which proceeds strictly stereoselectively[185–187] via a disrotatory pathway. Only the 3-*cis*-trienes undergo the cyclisation reaction below 230 °C; their 3-*trans*-isomers are thermally stable below this temperature[184–188]. The potential barrier to the conversion of 3-*trans*-trienes into the *cis*-isomers is 41–51 kcal mol^{-1}.[188,189]

Table 7. Synthesis of cyclohexadienes by the condensation of α, β-unsaturated ketones with allylidenephosphoranes[170].

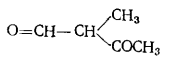
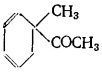
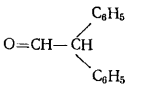
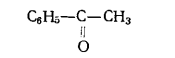
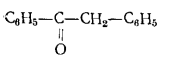
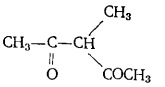
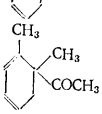
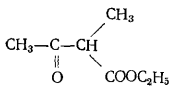
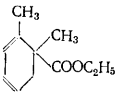
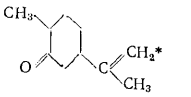
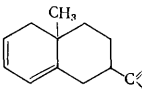
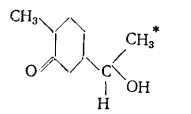
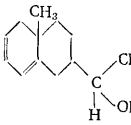
Unsaturated ketone	Yield*	Diene obtained	Reaction conditions	Yield, %
	B		ether, 25° 30 h	62
	A		ether, 25°, 30 h	55
	B		THF, 25°, 18 h	25
	A		THF, 25°, 16 h	41
	B		THF, refluxing, 30 h	25
	A		ether, 25°, 14 h	60
	A		ether, 25°, 12 h	32

* A = CH_2=CH–CH=$P(C_6H_5)_3$; B = CH_3–CH=CH–CH=$P(C_6H_5)_3$.

** See Büchi and Wüest[169].

Under mild conditions (100–170 °C), the reaction is not accompanied by the formation of side products. However, despite the simplicity with which it can be carried out, the cyclisation of *cis*-hexa-1,3,5-trienes has no preparative value at the present time because of the low availability of the pure 3-*cis*-trienes, whose synthesis usually leads to their mixtures with the *trans*-isomers. The employment of such mixtures precludes the preparation of homogeneous cyclohexa-1,3-dienes.

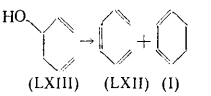
Table 8. Synthesis of cyclohexadienes by the reaction of the enolates of carbonyl compounds with *trans*-1-butadienyltriphenylphosphine bromide[171].

Initial ketone or aldehyde	Reaction product	Yield, %
		35
		35
		45
		57
		40
		57
		85
		73

* See Büchi and Pawlak[172].

It has been reported[190,191] that the cyclisation reaction of hexa-1,3,5-trienes is catalysed by alumina, but the use of this catalyst cannot be regarded as desirable, since the reaction products are inevitably contaminated by aromatic compounds.

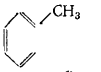
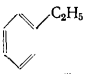
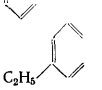
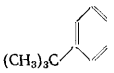
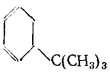
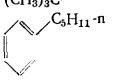
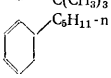
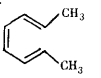
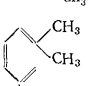
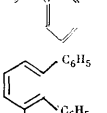
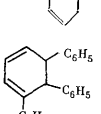
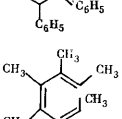
Many synthetic methods designed to obtain hexa-1,3,5-trienes lead directly to cyclohexadienes. Thus the dehydration of hexa-1,5-dien-3-ol (LXII) with phthalic anhydride results in the formation of the diene (I) (30%) together with the hexatriene (LXII) (70%):



(LXIII) (LXII) (I)

The cyclodehydration of substituted hexa-3,5-dien-2-ols also takes place under the influence of alumina at 200–500 °C. However, the cyclohexadienes obtained under such conditions[9,179,180,192,193] undergo aromatisation to a large extent (up to 80%)[179].

Table 9. Thermal cyclisation of hexa-1,3,5-trienes.

Initial triene	*t*, °C	Product	Yield, %	Thermodynamic parameters		Refs.
				$\Delta H^{\neq}$, kcal mol^{-1}	$\Delta S^{\neq}$, e.u.	
	120—190		100	29.3	—7.3	[174—178]
	100—150		—	28.9	—4.9	[179—181]
	100—150		—	26.1	—12.4	[179—181]
	100—150		100	27.0	—6.2	[181]
	100—150		100	26.0	—11.3	[181]
	75—125		100	26.7	—11.3	[181]
	110—150		100	27.8	—7.9	[182]
	132		100	29.4	—7.0	[183]
	120—170		100	31.8	—13.8	[184]
	84—122		100	22.0	—13.8	[96]
	150		65	—	—	[84]
	210		98	27.4	—19.0	[185]

Thus, among the numerous condensation and cyclisation reactions leading to compounds of the cyclohexa-1,3-diene series, the synthesis via organophosphorus compounds and

the diene condensation of acyclic compounds with subsequent elimination of a substituent may be of preparative value. The latter reaction cannot, however, be regarded as a general method of synthesis of cyclohexa-1,3-dienes.

5. Other Methods

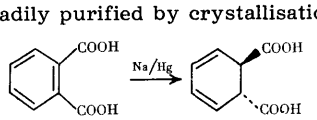
Among the numerous other reactions whose products are cyclohexa-1,3-dienes, only a few are of preparative importance. The isomerisation of cyclohexa-1,4-dienes, the synthesis of acids of the cyclohexadiene series, and also the transformation of substituents in the complete cyclohexa-1,3-diene ring can be included among them.

(a) *Isomerisation of cyclohexa-1,4-dienes.* Cyclohexa-1,4-dienes are obtained by the reduction of aromatic compounds with an alkali metal (usually sodium) and alcohol in liquid ammonia; despite the large bibliography on this reaction, we shall confine ourselves to mentioning only the first communication[194] and two reviews[195,196]. The most convenient recipe for the preparation of cyclohexa-1,4-diene itself was given by Wibaut and Hoak[197]. Cyclohexa-1,4-dienes containing electron-accepting groups (for example, the carbonyl or carboxy-groups) are available as a result of the diene condensation of buta-1,3-dienes with acetylenic dienophiles (see, for example, Onishchenko[198]).

It has been reported that the transformation of cyclohexa-1,4-diene into the 1,3-isomer (I) is possible on treatment with alkali metal alkoxides (in liquid ammonia[199,200] or in dimethylformamide[201]) or with potassium amide[202]. However, one should bear in mind that this transformation is reversible and that the ratio of the dienes in the resulting mixture depends significantly on the nature of the base and the solvent as well as other reaction conditions (see, for example, Mironov et al.[8]). One cannot rule out the possibility that the isomerisation of cyclohexa-1,4-diene in the presence of sodium ethoxide in liquid ammonia (in the absence of a proton donor from the reaction mixture) can serve as the basis of the industrial manufacture of the diene (I), provided that the admixture of the 1,4-isomer and benzene do not interfere with its subsequent employment.

The reduction of aromatic compounds with subsequent isomerisation of the resulting cyclohexa-1,4-diene has been described as a method of synthesis of substituted cyclohexa-1,3-dienes in relation to toluene[202,203], *p*-xylene[203], anisole [204–206], 1-methoxy-3,4-dimethylbenzene[205], 1-dimethylamino-4-methylbenzene[207], and biphenyl[208]. The isomerisation reaction has been carried out mainly under the influence of sodium amide in liquid ammonia and the yield has been as a rule high, but in some instances[206] the reversibility of the reaction has been noted.

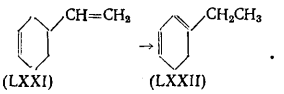
(b) *The Baeyer method.* Among the transformations of aromatic compounds into cyclohexa-1,3-dienes, one of the most convenient involves the reduction of phthalic acid (LXIX) (more precisely its sodium salt) with 3% sodium amalgam by the Baeyer method, which leads to a 60% yield of *trans*-cyclohexa-3,5-diene-1,2-dicarboxylic acid (LXX), which can be readily purified by crystallisation:



(LXIX) (LXX)

It has been reported[209] that the transformation of compound (LXIX) into compound (LXX) can be achieved by electrochemical reduction at a lead cathode in 99% yield. One should bear in mind that, on being refluxed in aqueous solution, the acid (LXX) isomerises quantitatively to cyclohexa-2,4-diene-1,2-dicarboxylic acid[210,211].

(c) *Isomerisation of 4-vinylcyclohexene.* The isomerisation of the readily available 4-vinylcyclohex-1-ene (LXXI) (dimer of buta-1,3-diene) has been used as a method of synthesis of 1-ethylcyclohexa-1,3-diene (LXXII):

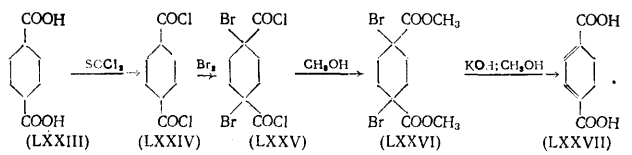


(LXXI) (LXXII)

When the diene (LXXI) is passed over alumina at 350 °C, the yield of the diene (LXXII) is 60% [212,213]; according to GLC data, the substance contains a large number of small amounts of side products. However, it is extremely unlikely that the diene (LXXII) obtained under these conditions did not contain considerable admixtures of ethylbenzene and the 2-isomer.

Cobaltocene has been used as the catalyst of this reaction [214] (15 h at 185 °C). Presumably, under these fairly mild conditions, the substance obtained is more homogeneous, but its yield is low (23%).

(d) *Synthesis of cyclohexa-1,5-diene-1,4-dicarboxylic acid.* The following scheme has been widely used to synthesise cyclohexa-1,3-diene-1,4-dicarboxylic acid (LXXVII)[210, 215–217]:



(LXXIII) (LXXIV) (LXXV) (LXXVI) (LXXVII)

The interaction of the acid (LXXIII) with thionyl chloride at its boiling point leads to the acid dichloride ((LXXIV). Bromination of the latter (without isolation in a pure form) at room temperature and subsequent refluxing with methanol give rise to a mixture of the *cis*- and *trans*-isomers of the dibromoester (LXXVI). Crystallisation makes it possible to isolate in 44% yield the homogeneous *trans*-isomer of compound (LXXVI)#.[217] The dehydrobromination of the *trans*-dibromoester (LXXVI) by refluxing it with a solution of potassium hydroxide in methanol leads to an almost quantitative yield of the acid (LXXVII), which can be readily purified by crystallisation. Despite the large number of stages, the required product can be obtained in a satisfactory yield.

(e) *Transformation of substituents in the cyclohexa-1,3-diene ring.* The transformation of substituents in the complete cyclohexa-1,3-diene ring is represented by a limited number of examples and standard synthetic methods are used as a rule: esterification of carboxylic acids[210,215,217,218] (yield 70–80%), hydrolysis of the acid esters[219], conversion of cyclohexa-3,5-diene-1,2-dicarboxylic acid into the corresponding anhydride[163], and the reduction of esters of substituted cyclohexa-1,3,5-diene-1,2-dicarboxylic acid with lithium tetrahydroaluminate to the corresponding diols (yield 70 to 80%); [220,221] by reduction with lithium tetrahydroaluminate, the diols were re-reduced with lithium tetrahydroaluminate

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The isolation of the residual reaction products[215] is apparently undesirable, since the resulting mixture contains dimethyl terephthalate.

via their toluene-p-sulphonates or methanesulphonates into hydrocarbons with two methyl groups in yields up to 80% [220, 221]. Thus the majority of the reactive groups in cyclohexa-1,3-dienes can be transformed without affecting the diene ring.

IV. CONCLUSION

Inspection of the synthetic methods described above for cyclohexa-1,3-dienes reveals the following features.

The method involving the bromination-dehydrobromination of cyclohexene is most convenient for the laboratory synthesis of cyclohexa-1,3-diene itself. The Hofmann–Damm method makes it possible to obtain a fairly homogeneous preparation. The much simpler method involving the dehydrobromination of dibromocyclohexane with quinoline or alkoxides can be recommended in those cases where the presence of cyclohexene and benzene in the resulting preparation does not interfere with subsequent reactions.

The majority of the methods of synthesis of substituted cyclohexadienes described in the literature must be regarded as satisfactory. Thus the commonest schemes in which the starting materials are cyclohexenes, cyclohexanediones, cyclohexenones, and cyclohexanediols as a rule give rise to complex mixtures of hydrocarbons where the diene which should be formally the product of the given reaction may be present in only insignificant amounts.

Among the general methods of preparative synthesis of pure substituted cyclohexadienes, the most important are as follows:

(a) Interaction of cyclohexenone tosylhydrazones with lithium alkyls.

(b) The coupled dehydration-carboxylation of 1-hydroxycyclohex-2-ene-4-carboxylic acids.

(c) The condensation of organophosphorus compounds with unsaturated ketones or the enolates of saturated ketones.

Cyclohexadienes containing electron-accepting groups can be most readily obtained by the diene condensation of acyclic dienes followed by the elimination of the functional group present in the diene or the dienophile. Many of the other methods described make it possible to obtain in specific individual instances substituted cyclohexa-1,3-dienes in satisfactory yields and with a high purity, but such instances constitute an exception rather than the rule for the schemes considered.

The method involving the oxidation of cyclohexene by atmospheric oxygen and the dehydration of the resulting cyclohexenol is at present most completely prepared for industrial application. Despite the relatively low yield of the oxidation product in a single cycle (15–30%), the possibility of the ready regeneration of the unreacted cyclohexene permits the attainment of its conversion into cyclohexenol up to 70%. The conditions for the dehydration of the latter have been fairly thoroughly determined. This and the other stage can serve as the basis of a continuous process. One cannot rule out the possibility that the chlorination of cyclohexene and the subsequent dehydrochlorination of dichlorocyclohexene or 3-chlorohexene may prove economically more effective but this method has been less thoroughly investigated compared with that described above.

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