1059. *The Base-catalysed Isomerisation of Some 3-Alkyldihydroanisoles.*

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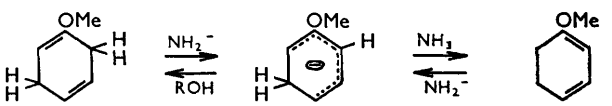
Isomerisation with sodamide in liquid ammonia of the 3-alkyldihydroanisoles (IV) containing unconjugated double bonds gives the exocyclic conjugated dienes (VI) as the final product if R′ = R″ = H or R′ = H, R″ = Me, but the endocyclic isomer (V) is obtained if R′ = R″ = Me. Reduction by sodium and propan-2-ol in liquid ammonia of 3,4-dimethylanisole (VII) and of 6-methoxy-1,2,3,4-tetrahydronaphthalene (IX), followed by similar isomerisation, gives the endocyclic dienes (VIII) and (X). The mechanisms involved are discussed.

Reduction of alkylanisoles with sodium and ethanol in liquid ammonia gives chiefly dihydroanisoles containing unconjugated double bonds as the result of kinetically controlled reactions.[1,2,3] In the presence of an alkali-metal amide in liquid ammonia, these dienes are converted into the more stable conjugated isomers, usually by turning of a double bond about the carbon atom bearing the methoxyl group. This has been shown [3,4] to be due to establishment of an equilibrium of the type shown below. Apart from their intrinsic interest, a study of such reactions is important in understanding the course of reductions by lithium and various amines, since such equilibrations are clearly involved and permit reduction to occur past the dihydro-stage.[2]



Because 2,5-dihydroanisole is converted into 2,3-dihydroanisole as above, it was expected that 2,5-dihydro-3-methylanisole (I) would give the homologue (II). In fact this is produced to some extent, as shown by the diene reaction with dimethyl acetylenedicarboxylate.[5] However, it was noted [6] that if the isomerisation proceeded for a long time, and in particular if the ammonia evaporated, a different product was obtained. This has now been shown to be the exocyclic diene (III) and it has been found that the endocyclic diene (II) cannot be prepared by this method in a state of purity because its rate of isomerisation to the diene (III) is comparable with its rate of formation.

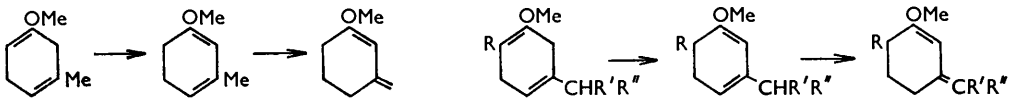
The courses of these and analogous reactions were followed by means of ultraviolet spectra. The unreduced alkylanisoles have twin peaks,[7] $\lambda_{max.}$ 270—279 and 277—288 mμ,

[1] Birch, *J.*, 1944, 430.
[2] Birch, *J.*, 1946, 593.
[3] Birch, *J.*, 1950, 1551.
[4] Birch, *J.*, 1947, 1642.
[5] Birch and Hextall, *Austral. J. Chem.*, 1955, **8**, 96.
[6] Birch, unpublished work.
[7] Burawoy and Chamberlain, *J.*, 1952, 2311.

whereas endocyclic and exocyclic dienes have single peaks, $\lambda_{max.}$ 267—270 and 244—250 mμ, respectively. Unconjugated dienes show only end absorption in the region 200—220 mμ. Similar differences between endo- and exo-cyclic dienes exist also in the steroid [8] and terpene [9] series, but the values observed here for the exocyclic (*trans*) dienes are higher than the calculated values [10] (*ca.* 230 mμ) probably owing to an extension of conjugation to the methoxyl group. In contrast, the endocyclic (*cis*) dienes show little evidence of such an effect.

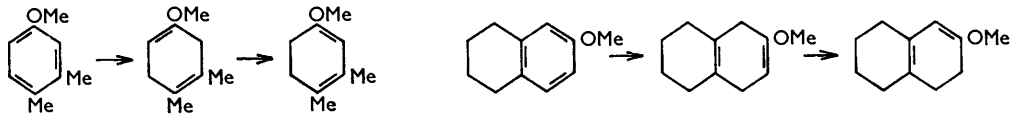
When the unconjugated diene (I) was isomerised for short periods (3 min. and 1 hr.), the product contained unchanged starting material together with the endo- and exo-cyclic dienes (II and III respectively), as shown by end absorption at 200—220 mμ and peaks at 268 and 244 mμ respectively. After 24 hours there was little end absorption and only one peak at 244 mμ, demonstrating complete conversion into the exocyclic diene (III). The infrared spectrum of the product showed a peak at 890 cm.$^{-1}$, probably due to the exocyclic methylene group, and the compound gave formaldehyde on ozonolysis.

By similar reactions, the unconjugated diene (IV; R = $CHMe_2$; R′ = R″ = H) obtained by reduction of 3-methoxy-*p*-cymene gave the corresponding exocyclic diene (VI), as did also the product (IV; R = R′ = H; R″ = Me) from 3-ethylanisole. On the other hand the compound (IV; R = R′ = R″ = Me), from 2-methoxy-*p*-cymene, gave only the corresponding endocyclic diene (V) and by use of more vigorous conditions,



(I) (II) (III) (IV) (V) (VI)

with lithium amide in boiling 1,2-diaminoethane, the same diene (V) was obtained together with some of the original aromatic compound. 3,4-Dimethylanisole (VII) and 1,2,3,4-tetrahydro-6-methoxynaphthalene (IX) also gave, finally, only the analogous dienes (VIII) and (X), respectively.

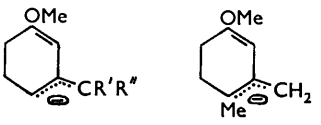


(VII) (VIII) (IX) (X)

The conversion of the endo- into the usually more stable (*transoid*) exo-cyclic diene presumably involves the production of intermediate salts of type (XI), and it has already been shown [4] that amide anion in liquid ammonia can cause isomerisation of some alkenes containing only one double bond. Failure of some endocyclic dienes to isomerise to the exocyclic isomers could be explained either by the greater stability of the former, which seems unlikely, or by inability to produce the appropriate anion. It has been shown [4] that the most readily isomerised alkenes are those containing the least number of alkyl substituents attached to the potential mesomeric system, a consequence, in part, of the inductive effect of the alkyl groups, but even more of steric inhibition of solvation of the anion. Such solvations clearly play a most important part in all reactions involving carbon anions, including reduction.[11] The favourable effect of liquid ammonia or related amines must be due largely to such solvation.

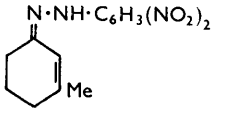
[8] Fieser and Fieser, " Steroids," Reinhold Publishing Corporation, New York, 1959, p. 16.
[9] O'Connor and Goldblatt, *Analyt. Chem.*, 1954, **26**, 1728.
[10] Woodward, *J. Amer. Chem. Soc.*, 1942, **64**, 72.
[11] Krapcho and Bothner-By, *J. Amer. Chem. Soc.*, 1959, **81**, 3658.

It appears therefore that an anion of type (XI) can be formed if R′ = R″ = H or R′ = H = R″ = Me but not if R′ = R″ = Me, in agreement with the above reasoning. The presence of an alkyl group at the other end of the potential mesomeric anion, as in system (XII), would explain the failure to isomerise in this case, although the endocyclic double bond might also be stabilised by the extra substitution. A similar explanation can be applied in the case of the hexahydromethoxynaphthalene.

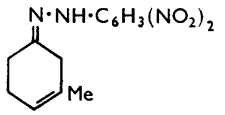


(XI)

(XII)



(XIII)



(XIV)

The 2,4-dinitrophenylhydrazones of the corresponding αβ- and βγ-unsaturated ketones, *e.g.*, (XIII) and (XIV), were prepared from the dihydroanisoles by known methods,[2,12] but attempts to prepare the pure 3-methylenecyclohexanone derivative from the exocyclic diene (III) failed, and this is obviously very readily isomerised to a 3-methylcyclohex-2-enone derivative.

Experimental

Ultraviolet spectra were recorded with a Unicam S.P. 500 spectrophotometer for ethanol solutions, except in the cases of the dinitrophenylhydrazones, which were dissolved in chloroform.

The alkyldihydroanisoles, conjugated and unconjugated, are colourless liquids with a characteristic odour. Since the yields, apart from distillation losses, were almost quantitative in both reduction and conjugation reactions, they are not given below.

Alkylanisoles.—Where not already available, these were prepared by methylation of the phenol with dimethyl sulphate. In the following Table known values are given in parentheses for comparison.

Table 1.

	B. p.	n_D	λ (mμ)	$\varepsilon_{max.}$
A. Anisole [a]			(270)	(1580)
			(277)	(1400)
B. 3-Methylanisole [a]			(272)	(1700)
			(278)	(1650)
C. 3-Ethylanisole	110°/62 mm.	1·5061/28°	272	1810
			279	1730
D. 3,4-Dimethylanisole	105°/32	1·5129/30°	278	1860
			284	1680
E. 3-Methoxy-*p*-cymene	94—95°/12	1·5050/23°	275	2450
			281	2360
F. 2-Methoxy-*p*-cymene	100°/12	1·5068/22°	274	2230
			280	2150
G. 6-Methoxytetralin	128—130°/13	1·5449/22°	279	2180
			288	2030

[a] Burawoy and Chamberlain.[7]

Reduction of Alkylanisoles.—The compound (10 g.) was dissolved in liquid ammonia (500 ml.) and absolute alcohol (twice the theoretical amount required by the sodium used), and the solution was stirred mechanically in a 1 l. 3-necked flask provided with a solid carbon dioxide–acetone reflux condenser closed by a potassium hydroxide drying tube. Sodium (6—10 atom-equiv. calc. on the alkylanisole) was added in small pieces during 30—45 min. through the third neck, which was stoppered to avoid free access of air except during the actual additions, since oxygen competes for the metal.[13] The blue colour, at first fugitive, remained during

[12] Wilds and Nelson, *J. Amer. Chem. Soc.*, 1953, **75**, 5360.
[13] Eastham and Larkin, *J. Amer. Chem. Soc.*, 1959, **81**, 3652.

stirring for at least 30 min. after all the sodium had been added. Compounds which were difficult to reduce required greater atomic ratios of sodium (up to 10 atom-equiv.), and it was advisable to add enough of it to ensure that the blue colour remained for 1½ hr. after the end of the addition. In these cases, it was also preferable to use propan-2-ol instead of ethanol.

When the blue colour had disappeared (which result was readily obtained, if desired, by removal of the stopper for a few minutes), the condenser was removed and water (250 ml.) was added cautiously from a tap funnel with continued stirring. The product was extracted three times with light petroleum (b. p. 40—60°), the extract dried (K_2CO_3) and evaporated, and the residue distilled under water-pump vacuum. The reduction was repeated, if necessary, with propan-2-ol and a greater ratio of sodium, until the distillate had absorption in the 270—290 mμ range sufficiently small to indicate that the amount of unreduced compound was negligible (<3%).

The unconjugated products (see Table 2) gave no red colour with a solution of *p*-benzoquinone in benzene, but a black precipitate of quinhydrone resulted on gentle warming of the solution.[11]

Isomerisation of Unconjugated Dienes.—The unconjugated diene (7 g.) was added to a suspension of sodamide (from 1·7 g. sodium) in liquid ammonia (400 ml.), and the deep red solution, protected from ingress of air by a Bunsen valve, was set aside for 24 hr., during which the ammonia evaporated completely. More ammonia (100 ml.) was then added, followed by dropwise addition, with shaking, during 20 min., of a mixture of absolute ethanol (5 ml.) and ether (20 ml.), that destroyed the red colour. Water (200 ml.) was then added cautiously and the product extracted three times with light petroleum (b. p. 40—60°). After drying of the extract (K_2CO_3), the solvent was evaporated and the residue distilled under water-pump

TABLE 2.

Cyclohexa-1,4-diene	Atom-equiv. of Na used	ROH	B. p./mm.	n_D	Found (%) C	Found (%) H	Formula	Reqd. (%) C	Reqd. (%) H
A. 1-Methoxy-[1]	6	EtOH	45—46°/15	1·4775/24°					
B. 1-Methoxy-5-methyl-[1]	6	EtOH	64°/16	1·4788/25°					
C. 1-*Methoxy*-5-*ethyl*- ...	10	Pr^{i}OH	104—108°/42	1·4762/30°	77·85	10·3	$C_9H_{14}O$	78·2	10·2
D. 1-*Methoxy*-4,5-*dimethyl*-	10	Pr^{i}OH	104—105°/40	1·4809/29°	78·3	10·3	,,	,,	,,
E. 1-*Isopropyl*-2-*methoxy*-4-*methyl*-	9	EtOH	90°/12	1·4780/21°	79·8	10·7	$C_{11}H_{18}O$	79·5	10·8
F. 1-*Isopropyl*-5-*methoxy*-4-*methyl*-	10	Pr^{i}OH	98—99°/16	1·4762/25°	79·4	10·7	,,	,,	,,
G. 1,2,3,4,5,8-Hexahydro-6-methoxynaphthalene [11]	10	Pr^{i}OH	121—122°/14	1·5132/20°					

TABLE 3.

	B. p./mm.	n_D	λ (mμ)	$\varepsilon_{max.}$	Formula		C (%)	H (%)
A. 1-Methoxycyclohexa-1,3-diene [4]	42°/14	1·4893/24°	268	4840				
B. 1-*Methoxy*-3-*methylene*-*cyclohexene*	62°/18	1·4929/23°	244	5910	$C_8H_{12}O$	Found	78·0	9·65
						Req.	77·4	9·7
C. 1-*Methoxy*-3-*ethylidene*-*cyclohexene*	118°/55	1·4902/26°	247	5260	$C_9H_{14}O$	Found	77·9	10·25
						Req.	78·2	10·2
D. 1-*Methoxy*-3,4-*dimethyl*-*cyclohexa*-1,3-*diene*	99—100°/38	1·4866/28°	271	3970	,,	Found	78·2	10·35
E. 3-*Isopropyl*-2-*methoxy*-6-*methylenecyclohexene*	86—88°/12	1·4857/21°	250	5050	$C_{11}H_{18}O$	Found	79·45	10·8
						Reqd.	79·5	10·8
F. 2-*Isopropyl*-4-*methoxy*-5-*methylcyclohexa*-1,3-*diene*	87—88°/12	1·4830/22°	267	4230	,,	Found	79·8	10·5
G. 1,2,3,4,5,6-*Hexahydro*-7-*methoxynaphthalene*	118—120°13	1·5143/25	270	2470	$C_{11}H_{16}O$	Found	80·3	10·0
						Reqd.	80·5	9·75

vacuum. The resulting conjugated dienes (see Table 3) (both endo- and exo-cyclic) gave a red colour with a solution of *p*-benzoquinone in benzene.[11]

Similar experiments were carried out with the unconjugated dihydro-derivative of 3-methylanisole (Table 2; B) except that the isomerisation was allowed to proceed for (*a*) 3 min. and (*b*)

1 hr., before being stopped by rapid addition of alcohol (5 ml. in *ca.* 20 sec.), with shaking, followed by water. The products, obtained as before, both showed end-absorption in the region 200—220 mμ due to the original unconjugated diene, and flattened peaks at *ca.* 244 and 268 mμ., having ε values of 820 and 910 respectively in case (*a*) and both of 3200 in case (*b*), showing that the endo- and the exo-cyclic conjugated diene were formed in roughly equal and increasing amounts after isomerisation for 3 min. and 1 hr. respectively.

An attempt was made to obtain the exocyclic conjugated diene from unconjugated dihydrocarvacrol methyl ether (Table 2; F) by using more vigorous conditions. This compound (5·5 g.) and diaminoethane (50 ml., redistilled from sodium) were added to a suspension of lithium amide (from 0·8 g. of lithium) in liquid ammonia (100 ml.), and the mixture was gradually heated under a reflux water condenser until all the ammonia had evaporated. The diaminoethane solution was then boiled under reflux for 1 hr. After cooling, a mixture of ethanol (10 ml.) and ether (10 ml.) was added dropwise with shaking, followed by water (200 ml.), and the product (3·3 g.) was obtained as before. It showed end absorption in the ultraviolet region (perhaps due to tetrahydro-compound formed by disproportionation), and also peaks at 268, 273, and 280 mμ., the first of these being due to the conjugated endocyclic diene (Table 3; F) and the last two to the original aromatic compound (Table 1; F).

Ozonolysis of 1-*Methoxy*-3-*methylenecyclohexene.*—The compound (0·80 g.) in ethyl acetate (110 ml.) was ozonised at −80° and the solution then hydrogenated (uptake 2H) at room temperature and pressure over Adams catalyst (0·26 g.). After the catalyst had been filtered off, the filtrate was distilled into an excess of a saturated solution of dimedone in 10% aqueous alcohol, until about half of it had distilled. The mixture was boiled, with stirring, until the vapour no longer smelled of ethyl acetate, the remaining solution was cooled in ice, and the product was filtered off and dried. The formaldehyde–dimedone adduct (0·26 g.) had m. p. and mixed m. p. 188°.

Preparation of 2,4-*Dinitrophenylhydrazones.*—These were obtained by the methods of Wilds and Nelson.[12] The αβ-unsaturated ketone derivatives were obtained on boiling the unconjugated or conjugated (endo- or exo-cyclic) dienes with the reagent, whereas the βγ-unsaturated compounds were obtained from the unconjugated dienes by careful treatment in ice-cold solution. They were crystallised from alcohol except where otherwise stated, though use of light petroleum (b. p. 60—80°) was sometimes advantageous with the βγ-isomers.

αβ-Unsaturated 2,4-dinitrophenylhydrazones were obtained from:

B. 3-Methylcyclohex-2-enone, deep red plates, m. p. 175° (Birch [4] gives m. p. 174—175°).

C. 3-*Ethylcyclohex*-2-*enone*, red needles, m. p. 165—166°, $\lambda_{max.}$ 388 mμ (ε 29,500) (Found: C, 55·25; H, 5·45; N, 18·3. $C_{14}H_{16}N_4O_4$ requires C, 55·25; H, 5·25; N, 18·4%).

D. 3,4-Dimethylcyclohex-2-enone, red needles, m. p. 149—150° (Birch [1] gives m. p. 146°), $\lambda_{max.}$ 389 mμ (ε 29,200) (Found: C, 55·5; H, 5·45; N, 18·35%).

E. 6-Isopropyl-3-methylcyclohex-2-enone (piperitone), orange-red needles, m. p. 116° (Birch and Mukherji [14] give m. p. 116°), $\lambda_{max.}$ 385 mμ (ε 28,200).

F. 3-Isopropyl-6-methylcyclohex-2-enone (carvenone), orange-red needles, m. p. 165° (Birch and Mukherji [14] give m. p. 165°).

βγ-Unsaturated 2,4-*dinitrophenylhydrazones* were obtained from:

B. 3-*Methylcyclohex*-3-*enone*, orange-red needles, m. p. 132—133°, $\lambda_{max.}$ 366 mμ (ε 24,000) (Found: C, 53·9; H, 4·8. $C_{13}H_{14}N_4O_4$ requires C, 53·8; H, 4·8%). This compound was reported by Lukes and Jizbu (*Chem. Listy*, 1952, **46**, 622) but the m. p. given (177—178°) shows that it was the αβ-unsaturated derivative.

D. 3,4-*Dimethylcyclohex*-3-*enone*, orange-yellow hair-like [from light petroleum (b. p. 60—80°)], m. p. 143—144°, $\lambda_{max.}$ 366 mμ (ε 24,000) (Found: C, 55·6; H, 5·3. $C_{14}H_{16}N_4O_4$ requires C, 55·25; H, 5·25%).

E. 6-*Isopropyl*-3-*methylcyclohex*-3-*enone*, orange-red needles, m. p. 119°, $\lambda_{max.}$ 368 mμ (ε 23,500) (Found: C, 58·1; H, 6·0; N, 16·9. $C_{16}H_{20}N_4O_4$ requires C, 57·8; H, 6·0; N, 16·7%).

F. 3-*Isopropyl*-6-*methylcyclohex*-3-*enone*, orange-red needles, m. p. 155°, $\lambda_{max.}$ 368 mμ (ε 24,000) (Found: C, 58·1; H, 6·15. $C_{16}H_{20}N_4O_4$ requires C, 57·8; H, 6·0%).

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[14] Birch and Mukherji, *J.*, 1949, 2531.