Cyclohexadienones. Use of the Dienone–Phenol Rearrangement in Measuring Migratory Aptitudes of Alkyl Groups [1]

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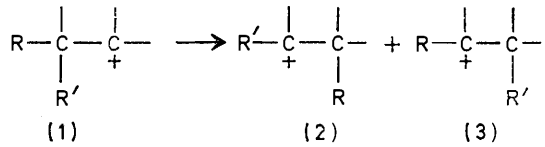
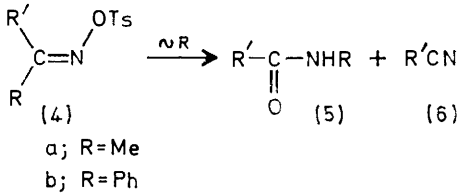
Kinetic and product studies of the rearrangements in aqueous sulphuric acid of selected cyclohexa-2,5-dienones are used to measure the migratory aptitudes in this carbonium-ion rearrangement of the methyl, ethyl, and n-propyl groups. The rearrangement of 4a-ethyl-5,6,7,8-tetrahydronaphthalen-2(4a*H*)-one in aqueous sulphuric acid has been reinvestigated. It is demonstrated that the lanthanide shifts brought about by Eu(fod)$_3$ on the n.m.r. spectra of isomeric alkylphenols have great value in structure determination.

THE knowledge that some groups R migrate more readily than others in rearrangements of carbonium ions led to the concept of the migratory aptitudes (m.a.)$_R$ of groups R. It was hoped that (m.a.)$_R$ might be an intrinsic property of the group, and that the product ratio (2)/(3) could be equated with the ratio (m.a.)$_R$/(m.a.)$_{R'}$.[2] Attempts to compare migratory aptitudes in the pinacol–pinacolone rearrangement of symmetrical and other pinacols have been reviewed,[3] and it is clear that the ratio of products from migration of R and R′ can also



(1) (2) (3)

depend on the stereochemistry [*meso*- or (±)-] of the pinacol, the conformational preferences in the transition state relative to the reactant molecules or cations, and on the rates of rotation about the central C–C bond relative to rearrangement.[4] A further problem is that a group R in (1) may migrate in preference to R′, not because R is an intrinsically better migrating group but because the group R′ left behind may be better able to stabilise the product cation (2). Such considerations suggest that valid experiments to measure migratory aptitudes of groups R should use a substrate (1) which fulfills the following requirements: (*a*) the rate of the migration step of the overall reaction should be accurately measurable; (*b*) the proportion of this rate which is due to migration of each migrating group R or R′ should be measurable (*e.g.* by product analysis); (*c*) only one group R should be varied, so that the effect of groups left behind will remain constant; (*d*) the rates for (1) ⟶ (2) when R is varied should be measured under the same conditions, so that effects due to solvent, *etc.* are constant; (*e*) the stereochemistry of (1) and (2) should be kept constant so that conformational problems are reduced. Ideally, however, the stereochemical disposition of the migrating group(s) should be fixed, to avoid rotation about the central C–C bond. Grob and his co-workers have given valuable results for the Beckmann rearrangement of the ketoximes (4) ⟶ (5); cleavage to (6) accompanies this reaction but product studies allowed the total rate to be partitioned between rearrangement and cleavage.[5] Earlier studies by Stiles and Meyer of the rearrangement of skeletally ^{13}C-labelled pinacols, for example (7), in aqueous sulphuric acid of one or two concentrations, were used to give migratory aptitudes



(4) (5) (6)

a; R = Me
b; R = Ph

for R = Me, Et, and Bu^t. This work [6] gave rate constants which had to be corrected for the fact that conversion into the protonated pinacols was incomplete; however, the protonation behaviour of the pinacols was not known and had to be guessed. It was also assumed that migration was the rate-determining step for all the

[1] A preliminary account of some of this work has been published: J. W. Pilkington and A. J. Waring, *Tetrahedron Letters*, 1973, 4345.

[2] W. E. Bachmann and F. H. Moser, *J. Amer. Chem. Soc.*, 1932, **54**, 1124; W. E. Bachmann and J. W. Ferguson, *ibid.*, 1934, **56**, 2081.

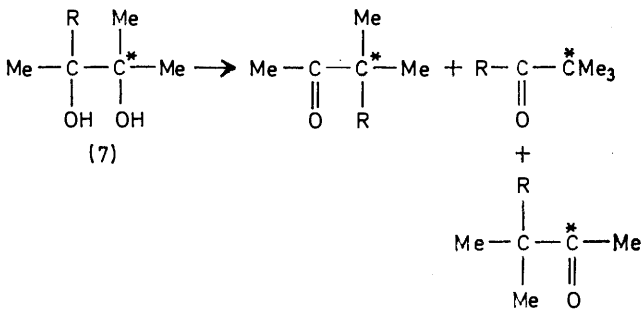
[3] C. J. Collins, *Quart. Rev.*, 1960, **14**, 357.

[4] B. M. Benjamin, H. J. Schaeffer, and C. J. Collins, *J. Amer. Chem. Soc.*, 1957, **79**, 6160; D. Y. Curtin and P. I. Pollack, *ibid.*, 1951, **73**, 992; D. Y. Curtin, E. E. Harris and P. I. Pollack, *ibid.*, p. 3453; D. Y. Curtin and M. C. Crew, *ibid.*, 1955, **77**, 354.

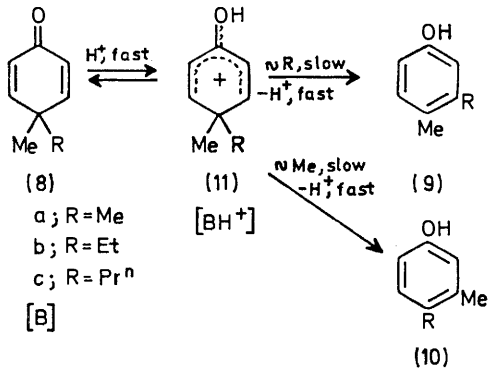
[5] C. A. Grob, H. P. Fischer, W. Raudenbusch, and J. Zergenyi, *Helv. Chim. Acta*, 1964, **47**, 1003.

[6] M. Stiles and R. P. Meyer, *J. Amer. Chem. Soc.*, 1959, **81**, 1497.

compounds studied; more recent evidence suggests that this is not the case, at least for R = Bu^t.[7]



We chose to use the dienone–phenol rearrangement of cyclohexa-2,5-dienones (8) ⟶ (9) and (10) in measuring migratory aptitudes. The mechanism of this reaction is well established for simple dienones [8–12] and migration of a group R or Me is rate-determining in all examples reported so far. The experimental data should allow deviations from this statement to be detected (see later).



The protonation equilibrium of each dienone, (8) ⇌ (11) is measured using u.v. spectroscopy (with acidity function methods to define the acidity of the media) and the rate of conversion of dienone into products, $k_{obs.}$, measured (most accurately by u.v. spectroscopy) in a series of acids of varying strengths. The kinetic data are then corrected using equation (1) to give the rate of rearrangement of the reactive dienone cation (11), k_1, at each acidity. Product studies at low extents of reaction allow the total rate to be partitioned between the paths (11) ⟶ (9) and (11) ⟶ (10), and any other reactions which may occur (*e.g.* fragmentations). Comparison of the appropriate rates for various groups R gives their relative migratory aptitudes which should be constant over the entire acidity range. If two dienones with different groups R have identical protonation behaviour, and both follow the same rearrangement mechanism throughout the range of acidity studied, with only the steps (8) ⟶ (9) and (10) operating with a constant m.a. ratio for the two groups R, then the two plots of log $k_{obs.}$ against acidity will be parallel and will give the m.a. ratio directly [when the product ratios (9)/(10) have been allowed for]. This is, in fact, the case for dienones (8a), (8b), and (8c), although their protonation behaviour was studied fully. In general, however, these simplifying factors should not be taken for granted.

$$\text{d[stoicheiometric dienone]}/\text{d}t = -k_{obs.}[\text{stoicheiometric dienone}]$$

$$\textit{i.e.}\ \text{d}[B + BH^+]/\text{d}t = -k_{obs.}[B + BH^+] = -k_1[BH^+]$$
$$\therefore k_1 = k_{obs.}\{1 + [B]/[BH^+]\} \quad (1)$$

Preparation of Dienones.—The dimethyl dienone (8a) has been studied previously; basicity, kinetic, and product data are taken from our earlier work.[8] The ethyl methyl dienone (8b) has been made before by a different route.[13] Since our work was completed it has also been made by selenium dioxide dehydrogenation of 4-ethyl-4-methylcyclohexanone.[14] We condensed the piperidine enamine of 2-methylbutanal with methyl vinyl ketone to give 4-ethyl-4-methylcyclohex-2-enone [15] which was dehydrogenated to the dienone using 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ). The n-propyl-dienone (8c) was made similarly from 4-methyl-4-n-propylcyclohex-2-enone, prepared by direct condensation of 2-methylpentanal with methyl vinyl ketone: the cyclohexenone has been previously made in inferior yield *via* the enamine route.[16]

Product Studies.—The sole product from the dimethyl dienone (8a) in sulphuric or perchloric acid at 25 °C is 3,4-dimethylphenol.[8] Earlier reports on rearrangements of ethyl methyl dienones are confused. Burnell treated (8b) with acetic anhydride and a little sulphuric acid, and then hydrolysed the acetate produced to give a phenol claimed to be identical with that obtained by low-temperature Fries rearrangement of 3-methylphenyl acetate followed by Clemmensen reduction (*i.e.* 4-ethyl-3-methylphenol).[13] However, the phenol is referred to only as '3-ethyl-4-methylphenol', but the structure drawn for it is 4-ethyl-3-methylphenol.[13] Reports give equal m.p.s for the 4-nitrobenzoates of the two isomers, and very similar m.p.s for other crystalline derivatives.[14,17] We found g.l.c. hardly distinguished between the two isomeric phenols; i.r. and n.m.r. spectra allowed marginal distinction, but not the accurate analysis of their mixtures. Suitable distinction was achieved using n.m.r. solvent shifts and, particularly, the n.m.r. shifts brought

[7] P. D. Bartlett and T. T. Tidwell, *J. Amer. Chem. Soc.*, 1968, **90**, 4421; S. Wold, *Acta Chem. Scand.*, 1969, **23**, 2978.
[8] K. L. Cook and A. J. Waring (*a*) *J.C.S. Perkin II*, 1973, 84; (*b*) *ibid.*, p. 88, and earlier papers quoted therein.
[9] M. J. Hughes and A. J. Waring, *J.C.S. Perkin II*, 1974, 1043.
[10] A. J. Waring, *Tetrahedron Letters*, 1975, 171.
[11] V. P. Vitullo, *J. Org. Chem.*, 1970, **35**, 3976.
[12] V. P. Vitullo and N. Grossman, *Tetrahedron Letters*, 1970, 1559; *J. Amer. Chem. Soc.*, 1972, **94**, 3844.
[13] R. H. Burnell, *J. Chem. Soc.*, 1958, 1307.
[14] J. N. Marx, J. C. Argyle, and L. R. Norman, *J. Amer. Chem. Soc.*, 1974, **96**, 2121.
[15] R. L. N. Harris, F. Komitsky, jun., and C. Djerassi, *J. Amer. Chem. Soc.*, 1967, **89**, 4765.
[16] S. Yamada, K. Hiroi, and K. Achiwa, *Tetrahedron Letters*, 1969, 4237.
[17] Beilstein's Handbook, Band VI, 3rd. Supplement, System No. 530, 3rd Part, p. 1818, and refs. 41 and 42 given later.

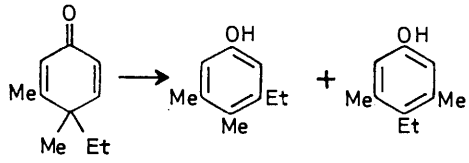
about on the addition of $Eu(fod)_3$.[18] At the time of this work it seemed to be believed that lanthanide shift reagents were hydrolysed by phenols, and therefore inapplicable,[19] but we have found no evidence of instability over periods of a few hours in the presence of the, admittedly weakly acidic, phenols we have studied. More recently $Eu(dpm)_3$ has been used successfully with a number of alkylphenols,[20] and $Eu(fod)_3$ has been applied to our problem in hand,[14] and to 2,4-dimethylphenol and a carboxylic acid.[21] The data we obtained for many alkylphenols are given in Table 1. It is clear that the downfield shift which occurs on addition of $Eu(fod)_3$ is largest for protons or alkyl groups *ortho* to the phenolic hydroxy-group, smaller for *meta*, and smallest for *para*-substituents. The method is used later to distinguish between 3-methyl-4-n-propylphenol and 4-methyl-3-n-propylphenol. Careful t.l.c. and paper chromatography also allowed the two ethyl methyl phenols to be separated and distinguished by R_F values and colour reactions. The rearrangement of the dienone (8b) in sulphuric acid, or in acetic anhydride–sulphuric acid followed by hydrolysis, is estimated to give (98 ± 1%) of 3-ethyl-4-methylphenol and (2 ± 1%) of 4-ethyl-3-methylphenol, proving predominant ethyl migration to occur. No other product was observed and, in particular, no 3- or 4-methylphenol which might arise by de-ethylation. This result agrees with a careful study of the rearrangement of 4-ethyl-4-methyl-1(4*H*)-naphthalenone.[22] However, because most analytical techniques allowed only a marginal distinction between phenols (9b) and (10b) we used a further method to confirm the important point that the ethyl group does migrate more readily than methyl. For this, 4-ethyl-3,4-dimethylcyclohexa-2,5-dienone (12) was prepared and rearranged. Ethyl migration would give 5-ethyl-3,4-dimethylphenol (13), a known compound [8b] which has been prepared by another route (see Experimental section) and which has clearly non-equivalent methyl peaks in the n.m.r. spectrum. Methyl migration would give 4-ethyl-3,5-dimethylphenol (14) whose methyl groups are equivalent. In fact the former product predominates (98—99%), confirming our point.

TABLE 1

$Eu(fod)_3$ shifts for alkylphenols in CCl_4 solution. All shifts are in p.p.m. downfield, for 1 : 1 molar ratio of $Eu(fod)_3$: phenol, scaled to give a shift of 1.00 p.p.m. for the 4-alkyl group

Compound	Position of substituent 2-	3-	4-	5-	6-	Shift of 4-alkyl group (p.p.m.)
2,4,6-Trimethylphenol	Me	H	Me	H	Me	
	3.84	2.26	1.00	2.26	3.84	0.42
3,4,5-Trimethylphenol	H	Me	Me	Me	H	
	6.86	1.30	1.00	1.30	6.86	1.26
3,4-Dimethylphenol	H	Me	Me	H	H	
	7.28	1.24	1.00	2.01	7.28	1.23
2,4,5-Trimethylphenol	Me	H	Me	Me	H	
	8.33	3.75	1.00	1.44	10.35	0.57
4-Ethyl-3-methylphenol	H	Me	$-CH_2$	H	H	
	6.78	1.19	1.00	2.09	7.00	1.22
			Me			
			0.79			
3-Ethyl-4-methylphenol [a,b]	H	$-CH_2-$	Me	H	H	
	6.97	1.29	1.00	1.97	6.78	1.30
		Me				
		0.94				
3-Methyl-4-n-propylphenol [a]	H	Me	$-CH_2Et$	H	H	
	7.28	1.19	1.00	1.93	7.42	1.51
			$-CH_2Me$			
			0.87			
			Me			
			0.66			
4-Methyl-3-n-propylphenol [b]	H	$-CH_2Et$	Me	H	H	
	6.29	1.18	1.00	1.76	6.67	1.86
		Me				
		1.01				

[a] From synthesis of authentic material. [b] From rearrangement.



(12) (13) (*ca.* 98%) (14) (*ca.* 2%)

Rearrangement in aqueous sulphuric acid of 4-methyl-4-n-propylcyclohexa-2,5-dienone (8c) gives two isomeric phenols in the ratio 98:2 (±1%), and no de-propylation products. The major product was identified as

[18] R. E. Rondeau and R. E. Sievers, *J. Amer. Chem. Soc.*, 1971, **93**, 1522.
[19] J. K. M. Sanders and D. H. Williams, *Chem. Comm.*, 1970, 422; 'N.M.R. Quarterly,' Perkin Elmer Ltd., No. 1, August 1971.
[20] N. Platzer and P. Demerseman, *Bull. Soc. chim. France*, 1972, 192.
[21] J. P. Shoffner, *J. Amer. Chem. Soc.*, 1974, **96**, 1599.
[22] R. B. Carlin and K. P. Sivaramakrishnan, *J. Org. Chem.*, 1970, **35**, 3368.

4-methyl-3-n-propylphenol (9c). The n.m.r. coupling pattern shows two adjacent protons and one isolated proton, and the high chemical-shift (τ 3.48) of the isolated, and one of the other protons (τ 3.53), which are placed *meta* to one another (J 2.9 Hz) show both to be either *ortho* or *para* to the hydroxy-group. This proves a 3,4- or 2,5-dialkylphenol structure. The use of $Eu(fod)_3$ shifts in the n.m.r. establishes it as a 3,4-dialkylphenol, and the larger shift for the ring-attached methylene group than for the ring-attached methyl proves it to be 4-methyl-3-n-propylphenol. The product has different g.l.c., n.m.r. spectroscopic and $Eu(fod)_3$-shift behaviour from an authentic sample of 3-methyl-4-n-propylphenol.[23] This last was made by Clemmensen reduction of 3-methyl-4-propionylphenol, the minor (and steam-involatile) product of low-temperature Fries rearrangement of *m*-tolyl propionate.[24] The major (steam volatile) product of the Fries rearrangement was 5-methyl-2-propionylphenol,[24,25] whose structure is confirmed by i.r. and n.m.r. spectroscopy: it was reduced to 5-methyl-2-n-propylphenol [26] which is also clearly different in g.l.c. and n.m.r. properties from the dienone–phenol product.

Basicity and Kinetic Studies.—The dienones were dissolved in aqueous sulphuric acid solutions of widely varied concentration, and the extents of protonation and rates of rearrangement examined by established methods.[8,9] Their protonation behaviours are given by equations (2) and (3), with the parameters shown in Table 2, and are identical within experimental error. All three dienones follow closely the amide acidity function,[27] H_A, and have thermodynamic pK values based on this function of (-2.37 ± 0.03), (-2.26 ± 0.10), and (-2.43 ± 0.12) for (8a), (8b), and (8c) respectively. The measured rate constants, $k_{obs.}$, for reaction at any acidity are corrected using equation (1) to give k_1 for the cations (11). Plots of log k_1 against

$$\log_{10}[BH^+]/[B] = m_A[(H_A)_{\frac{1}{2}} - H_A] \quad (2)$$

$$\log_{10}[BH^+]/[B] = m_O[(H_O)_{\frac{1}{2}} - H_O] \quad (3)$$

H_A or H_O,[28] and Bunnett and Olsen plots [29] are linear, according to equations (4), (5), and (6), with the parameters given in Table 3. The small differences between the gradients of these lines are due to the fact that the

$$\log k_1 = aH_A + b \quad (4)$$

$$\log k_1 = cH_O + d \quad (5)$$

$$\log k_1 = \phi\,(H_O + \log [H_2SO_{4\,stoich.}]) + \log k_1^0 \quad (6)$$

measured values of the indicator ratio, $[BH^+]/[B]$ are used in converting each $k_{obs.}$ into k_1, rather than the 'smoothed' value which accords with the indicator equations (2) and (3). The linearity in plots (4) and (5) has been discussed previously, and the conclusions drawn regarding transition-state acidity-function behaviour,[8] will apply here also. The rates for the ethyl- and propyl-dienones were multiplied by 0.98 to give the rates of ethyl or n-propyl migration. The rate for the dimethyl-dienone (8a) must be halved for comparisons of migratory aptitudes, to allow for the presence of two equivalent methyl groups: this factor will be discussed later. The migratory aptitudes calculated for methyl, ethyl, and n-propyl are then in the ratio 1.0 : 51 ± 3 : 43 ± 2, over the acidities studied.

TABLE 2

Basicity measurements at 25 °C

Compd.	Wavelengths [a]	$(H_A)_{\frac{1}{2}}$ [b]	m_A [c]	$(H_O)_{\frac{1}{2}}$ [d]	m_O [e]	pK'
(8a)	240,260	-2.37 ± 0.03	1.03 ± 0.01	-3.15 ± 0.05	0.53 ± 0.03	As (H_A)
(8b)	242,260	-2.26 ± 0.10	1.05 ± 0.10	-2.96 ± 0.10	0.65 ± 0.15	
(8c)	245,265	-2.43 ± 0.12	1.09 ± 0.10	-3.32 ± 0.24	0.54 ± 0.04	

[a] Wavelengths, in nm, used for the measurements. [b] Half-protonation acidity on amide acidity function, H_A, using scales of refs. 27. [c] See equation (2). [d] Half-protonation acidity on H_O acidity function, using scale of ref. 28. [e] See equation (3). [f] Best estimates of thermodynamic pK values.

TABLE 3

Kinetic relationships for rearrangements in aqueous H_2SO_4 at 25 °C

Compd.	$-a$ *	$-b$ *	$-c$ †	$-d$ †	$-\phi$ ‡	$-\log k_1^\circ$/ s^{-1} ‡
(8a)	0.534	5.55	0.267	5.09	0.30	4.97
(8b)	0.636	4.45	0.337	4.00	0.35	3.72
(8c)	0.559	4.29	0.30	3.89	0.26	3.42

* Values in equation (4). † Values in equation (5). ‡ Values in equation (6).

Because the three dienones just discussed have similar protonation behaviour a comparison of their rearrangement rates measured by $k_{obs.}$ will be as valid as k_1 values and, because $k_{obs.}$ incorporates no experimental scatter in the correcting factor ($1 + [B]/[BH^+]$) [see equation (1)], somewhat more accurate. We find that plots of log $k_{obs.}$ against acidity for (8a), (8b), and (8c) are accurately parallel, and believe that this parallelism proves the constancy of the migratory aptitudes, rearrangement mechanism, and protonation behaviour for all three compounds over the whole acidity range studied. The migratory aptitudes, after use of the factors 0.5, 0.98, 0.98, as above, are then in the ratio methyl, ethyl, and

[23] G. D. Parkes, *J. Chem. Soc.*, 1948, 2143.
[24] R. Baltzly, W. S. Ide, and A. P. Phillips, *J. Amer. Chem. Soc.*, 1955, **77**, 2522; R. Baltzly and A. Bass, *ibid.*, 1933, **55**, 4292.
[25] W. von Auwers, *Annalen*, 1924, **439**, 132.
[26] K. W. Rosenmund and W. Schnurr, *Annalen*, 1928, **460**, 56.
[27] K. Yates, J. B. Stevens, and A. R. Katritzky, *Canad. J. Chem.*, 1964, **42**, 1957; C. D. Johnson, A. R. Katritzky, and N. Shakir, *J. Chem. Soc.* (*B*), 1967, 1235.
[28] C. D. Johnson, A. R. Katritzky, and S. A. Shapiro, *J. Amer. Chem. Soc.*, 1969, **91**, 6654.
[29] J. F. Bunnett and F. P. Olsen, *Canad. J. Chem.*, 1966, **44**, 1917.

TABLE 4

Kinetics for compound (8b) in aqueous sulphuric acid at 25.0 °C; u.v. at 242 and 260 nm

Acid, wt. %	$-H_A$	$-H_0$	$-\log k_{obs.}$/ s^{-1} [a]	$-\log k_1$/ s^{-1} [b]
35.0	1.75	2.06	4.168	3.472 [c]
41.8	2.08	2.59	3.680	3.161 [c]
45.2	2.24	2.87	3.427	3.046
46.1	2.28	2.96	3.315	2.996
47.5	2.35	3.08	3.239	2.975
48.5	2.40	3.17	3.145	2.910
49.3	2.44	3.24	3.073	2.854
50.0	2.48	3.30	3.068	2.870
50.3	2.50	3.33	3.056	2.860
54.3	2.74	3.72	2.801	2.652
57.4	2.93	4.06	2.646	2.554
60.8	3.14	4.47	2.496	2.447
64.0	3.34	4.91	2.352	2.321
67.5	3.57	5.45	2.147	2.129
72.2	3.93	6.18	2.045	2.037

[a] Standard deviation 0.001—0.004. [b] Calculated using experimentally determined values of [B]/[BH$^+$] around the pK, and equation (2) at high and low acidities; standard deviation 0.004 to 0.06 at H_A −2.24. [c] Standard deviation ⩾0.08; not included in linear correlation by equations (4)—(6).

TABLE 5

Kinetics for compound (8c) in aqueous sulphuric acid at 25.0 °C; u.v. at 245 and 265 nm

Acid, wt. %	$-H_A$	$-H_0$	$-\log k_{obs.}$/ s^{-1} [a]	$-\log k_1$/ s^{-1} [b]
6.1	0.01	0.04	6.54	[c]
10.8	0.43	0.41	6.11	[c]
14.4	0.68	0.68	5.83	[c]
21.8	1.07	1.18	5.22	[c]
29.5	1.48	1.70	4.70	[c]
34.1	1.70	2.00	4.32	[c]
41.2	2.05	2.53	3.807	2.96
46.0	2.27	2.95	3.413	2.89
49.7	2.46	3.27	3.161	2.79
53.4	2.68	3.63	2.959	2.71
58.3	2.98	4.17	2.674	2.52
62.0	3.22	4.63	2.517	2.44
63.9	3.34	4.90	2.449	2.42
64.0	3.34	4.90	2.455	2.43
65.2	3.42	5.10	2.378	2.35
67.1	3.54	5.36	2.308	2.28
67.2	3.54	5.38	2.315	2.28
68.5	3.64	5.58	2.275	2.25
70.5	3.95	5.89	2.194	2.19

[a] Standard deviation 0.001—0.004. [b] Calculated using experimentally determined values of [B]/[BH$^+$] around the pK. and equation (2) at high and low acidities; standard deviation 0.004 to 0.06 at H_A −2.46. [c] Standard deviation ⩾0.08; not included in linear correlation by equations (4)—(6).

n-propyl = 1.0 : 49 ± 2 : 39 ± 2. Previous values for $(m.a.)_{Et}$ are 17,[6] and 60.[5] Our reasons for considering the former to be unreliable were presented earlier in this paper. The latter value may reflect an increase in m.a. of the migrating ethyl group as a rearranging cation becomes less electron deficient, but this is uncertain. Dubois and Bauer [30] report changes in the value of $(m.a.)_{Et}/(m.a.)_{Me}$ as the groups left behind in a rearrangement are changed from methyl to ethyl, but their values of $(m.a.)_{Et}/(m.a.)_{Me}$ are very small (1.2—5.0) and may not reliably be associated with a single rate-determining reaction step. Marx and his co-workers [14] report a value for ethyl of 55, measured on dienones (8b) and (8a) in trifluoroacetic acid at 38.5 °C. This value was derived after a correction was made for an assumed difference in basicity (and degree of protonation) between the dienones, based on their n.m.r. spectra in the single acid solution studied. Possible errors in this procedure were discussed,[14] which may lead to an error of *ca.* 20% in the m.a. ratio. The assumption of equal basicities for (8a) and (8b) gives $(m.a.)_{Et}/(m.a.)_{Me}$ as 45, and both values are gratifyingly close to our own. We do not know of a previous value for m.a. of the n-propyl group.

* This is for rearrangement in aqueous sulphuric acid. Our previous study of (15a) confirmed this ratio, with a value 78 : 22 at low extents of reaction.[9]

TABLE 6

Kinetic data for compound (15b) in aqueous sulphuric acid at 25.0 °C; u.v. at 267 and 307 nm

Acid, wt. %	$-H_A$	$-H_0$	$-\log k_{obs.}$/ s^{-1} [a]
76.5	4.28	6.89	4.04
78.2	4.42	7.18	4.02
79.6	4.54	7.40	3.94
82.0	4.74	7.80	3.905
83.6	4.88	8.07	3.84

[a] $k_{obs.} = k_1$; standard deviation 0.01—0.02. Linear correlations with acidity [equations (4) and (5)] give a = −0.336, b = −5.48, c = −0.171, d = −5.22.

TABLE 7

Kinetic data for compound (18b) in aqueous sulphuric acid at 25.0 °C; u.v. at 260 and 314 nm

Acid, wt. %	$-H_A$	$-H_0$	$-\log k_{obs.}$/ s^{-1} [a]
67.1	3.54	5.38	6.81
70.1	3.76	5.85	6.68
74.3	4.10	6.53	6.61
80.6	4.62	7.57	6.47

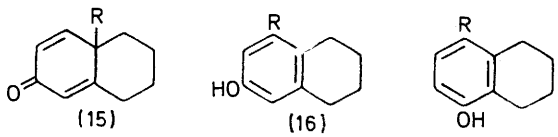
[a] $k_{obs.} = k_1$; standard deviation 0.09. Linear correlations with acidity give a = −0.296, b = −7.83 in equation (4) and c = −0.147, d = −7.57 in equation (5). These lines are virtually parallel to those for (15a) ⟶ (17) which proceeds *ca.* 1.6 times faster.

Studies of 4a-*Ethyl*-5,6,7,8-*tetrahydronaphthalen*-2(4aH)-*one* (15b).—In our preliminary communication of some of this work [1] we omitted the statistical factor of 0.5 applied to the rearrangement rate of dienone (8a), on the basis of conformational arguments which were not published and which we now believe to be invalid. To test this point we have compared the kinetic behaviour of the ethyl substituted bicyclic dienone (15b) with that of the methyl analogue (15a). We wished also to check a recent report [31] which states that, although the methyl dienone (15a) rearranges with methyl migration and ring migration in the rate ratio 86 : 14 [giving phenols (16a) and (17a) respectively],* the ethyl dienone (15b) gives ethyl- and ring-migration in the ratio 77 : 23 [giving products (16b) and (17b)]. This result seems to be inconsistent with the high ratio of $(m.a.)_{Et}/(m.a.)_{Me}$, unless the non-migrating groups R have an unusually large effect on the rates of formation of products (17). For the n-propyl dienone (15c) the published product

[30] J. E. Dubois and P. Bauer, *J. Amer. Chem. Soc.*, 1968, **90**, 4510 and 4511.

[31] H. J. Shine and C. E. Schoening, *J. Org. Chem.*, 1972, **37**, 2899.

ratio is more reasonable, with 98% of propyl migration product (16c) and 2% of ring-migration product (17c).[31] The dienone (15a) has been studied previously.[9] The ethyl analogue (15b) was made by a method analogous to

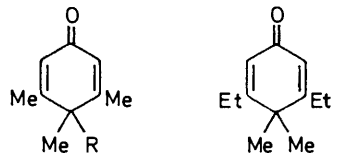


(15) (16) (17)

a; R = Me
b; R = Et
c; R = Pr^n

that used for (15a),[32] by condensation of acetone with 2-ethyl-2-formylcyclohexanone. The latter can be made from 2-formylcyclohexanone by ethylation of its sodio-derivative [33] or of its thallium(I) salt. The former method is known to give considerable amounts of 2-ethoxymethylenecyclohexanone.[33] Thallium salts of enolisable β-dicarbonyl compounds are highly praised for giving clean *C*-alkylation,[34] but our experiments gave considerable *O*-alkylation also (see Experimental section). The ethyl dienone (15b) was rearranged in sulphuric acid solutions which give complete (>99%) protonation, giving the rate data shown in Table 6. Aliquots taken from the rearrangement mixtures at 1.3 and 2.6 half lives contained only one (>99%) product. After 6.5 half-lives this is >95% of the total product, and other small g.l.c. peaks represent <5% in total. The major product was shown to be (16b), formed by ethyl migration. We take the rate of ethyl migration to be the same as the total rate: comparison with the rate of formation of (16a) from (15a) * then gives a ratio of $(m.a.)_{Et}/(m.a.)_{Me}$ of (60 ± 7). This result confirms the need for a statistical factor of 0.5 to be applied to the rate of rearrangement of (8a).† We assume that the unusually abundant minor product reported from the rearrangement of (15b) [31] may be formed by further reactions of the kinetically controlled product (16b). The reaction conditions reported, reaction for 2 days at 51.5 °C in 20.6N-H_2SO_4 (*i.e.* 65.1% H_2SO_4 by weight, H_0 — 5.09, H_A — 3.34) are very severe. The half-life of (15b) in this acid is *ca.* 4.7 h at 25 °C, so 2 days at 25 °C would be 10 half-lives. The rates for other dienone–phenol rearrangements, including a close analogue of (15a) and (15b), increased by 8—9 times between 25 and 40 °C; [9] if (15b) follows the same pattern, 2 days at 51.5 °C will represent over 300 half-lives. Slow isomerisations of phenols analogous to (16) and (17) have recently been found,[9,35] and it may be that (16b) rearranges similarly. The ' unexpected ' product (17b) was not isolated or characterised, but was assumed to correspond to an unidentified g.l.c. peak from the rearrangement mixture, and to have structure (17b) solely by analogy with that of the well authenticated analogue (17a).[31]

Studies of 4-*Ethyl*-3,4,5-*trimethylcyclohexa*-2,5-*dienone.* —It has been shown [8b] that a 4-methyl group in the tetramethyl-dienone (18a) migrates to the alkylated C-3 or C-5 position at least 7×10^4 times more slowly than the migration in 4,4-dimethylcyclohexa-2,5-dienone (8a). Because migration to an alkylated position is a normal reaction in bicyclic and steroidal dienones (see Scheme 1; for reviews see ref. 36) we wished to study a



(18) (19)

a; R = Me
b; R = Et

monocyclic model compound where such a migration proceeds at a measurable rate. The dienone (18b) was made for this purpose. The preparation was by successive conjugate methylations of the dienone (8b) to give 4-ethyl-4,5-dimethylcyclohex-2-enone then 4-ethyl-3,4,5-trimethylcyclohexanone (3- and 5-methyl groups *trans* ‡), bromination to the *cis*-2,6-dibromo-derivative,‡ and dehydrobromination to give (18b). Kinetic data for rearrangements in acids which give complete (>99%) protonation of the analogue (18a) are given in Table 7. Comparison of the rates of rearrangement for the dienone (18b), for 3,5-diethyl-4,4-dimethylcyclohexa-2,5-dienone (19),[8b] and for rearrangement *via* the spiran path in (15a) ⟶ (17) [9] [*cf.* (20) ⟶ (21)] shows all to be equal within a factor of two. The virtual identity of rates for (18b) and (19) supports our view [8b] that the first migration step is not rate-determining, although it is slow, and that the second migration (of an ethyl group in each case) is rate-limiting. This does not prove the second migration to be inherently difficult, but probably reflects a high value of k_r/k_f, or k_r'/k_f' combined with slow formation of cations (23) or (24). The rate of formation of product

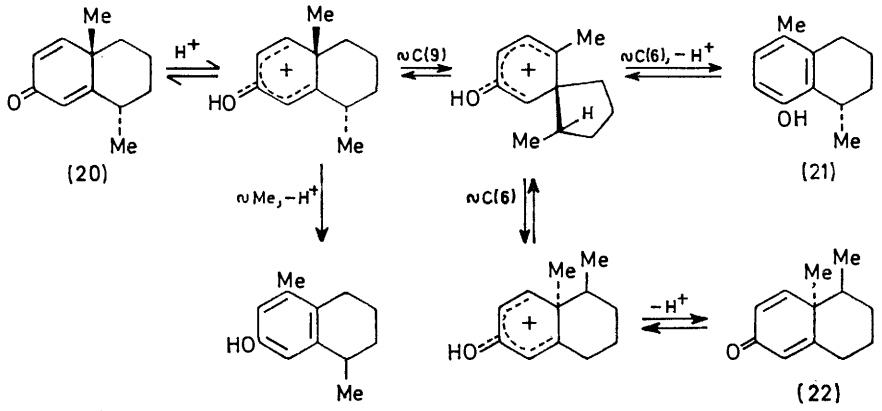
* The ratio of rate constants for (15b)/(15a) is (47 ± 5). For (15a) (78.5 ± 0.8)% of the total rate is due to formation of (16a), thus $(m.a.)_{Et}/(m.a.)_{Me}$ = (47 ± 5)100/(78.5 ± 0.8) = 60 ± 7.

† The range of values of $(m.a.)_{Et}/(m.a.)_{Me}$ derived here does not quite overlap the more accurate value derived from compounds (8a) and (8b). The results for (15a) and (15b) cover a relatively small range of acidity, the kinetics for (15a) are relatively slow and are subject to the largest potential error, and the partitioning of total rate between the paths leading to (16a) and (17a) introduces a further source of error.

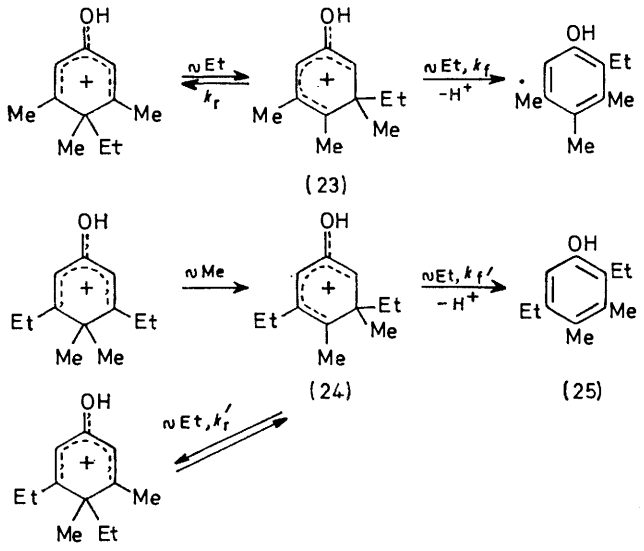
‡ The stereochemistry of these compounds is discussed in the Experimental section.

[32] R. B. Woodward and T. Singh, *J. Amer. Chem. Soc.*, 1950, **72**, 494; S. M. Bloom, *ibid.*, 1958, **80**, 6280.
[33] R. R. Agarwal and S. S. Deshapande, *J. Indian Chem. Soc.*, 1949, **26**, 483 (compare W. S. Johnson and H. Posvic, *J. Amer. Chem. Soc.*, 1947, **69**, 1361).
[34] E. C. Taylor, G. H. Hawks, and A. McKillop, *J. Amer. Chem. Soc.*, 1968, **90**, 2421.
[35] W. H. Hopff and A. S. Dreiding, *Angew. Chem. Internat. Edn.*, 1965, **4**, 690; J.-C. Jacquesy, R. Jacquesy, and Ung Hong Ly, *Tetrahedron Letters*, 1974, 2199.
[36] A. J. Waring, *Adv. Alicyclic Chem.*, 1966, **1**, 129; A. J. Waring, *Österr. Chem. -Ztg.*, 1967, **68**, 232; B. Miller in ' Mechanisms of Molecular Migration,' ed. B. S. Thyagaragan, Interscience, New York, 1968, p. 247.

(25) from (19) gives a minimum value for the rate of methyl migration to an alkylated centre of (1.67 ± 0.03) 10^{-7} s^{-1} in H_2SO_4 of H_0 − 5.80.[8b,*] Accordingly an ethyl or n-propyl group should migrate in (18b) ⟶ (23) or in (20) ⟶ (21) about 50/2 or 44/2 times faster, *i.e.* with minimum rate constants in this acid about 4.2 × 10^{-6}, and 3.7 × 10^{-6} s^{-1}, respectively.* The last value compares with a measured rate constant for (20) ⟶ (21) of (1.0 ± 0.15) 10^{-6} s^{-1}. The arguments employed here suggest that the dienone (20) should partly isomerise to (22),† and that (20) and (22) should both rearrange to (21) at roughly equal rates. These hypotheses are being tested.



SCHEME 1



SCHEME 2

EXPERIMENTAL

Basicity, Kinetic, and Spectroscopic Measurements.—The studies were performed using the methods and instruments as in ref. 9. N.m.r. spectra were measured on a Perkin-Elmer 100 MHz instrument, or model R12-B (60 MHz) with spin-decoupling. All n.m.r. integrations were consistent with the structures claimed. G.l.c. measurements were made using a Pye 104 instrument, with glass columns and silanised Supasorb (B.D.H.) as support for the stationary phases; a flame-ionisation detector was used throughout.

4-Ethyl-4-methylcyclohex-2-enone.—The Benzing [38] modification of Mannich and Davidsen's method was used to prepare the enamine, 1-piperidino-2-methylbut-1-ene, from 2-methylbutanal and piperidine. The procedure of Heyl and Herr [39] was also satisfactory. The enamine (30 g) was stirred with freshly distilled but-1-en-3-one (methyl vinyl ketone, 16.5 g) for 100 h at room temperature, then 18 h at 40—50° and 5 h further at room temperature; it was then treated with 15% aqueous hydrochloric acid and worked up according to the procedure of Djerrasi and his co-workers.[15,‡] The cyclohexenone (22.6 g), b.p. 49—51 °C at 1 mmHg, 61—62 °C at 2 mmHg, has $\nu_{max.}$ (film) 1 680 s and 3 015 w cm^{-1}, $\lambda_{max.}$ (EtOH) 228 nm (log ε 4.053); τ (CCl_4) 9.08 (t, *J*, 7.1 Hz, CH_2-*Me*), 8.92 (s, 4-Me), 8.55 (q, *J* 7.1 Hz, CH_2-Me), 4.28 (d, *J* 10 Hz, 2-H), 3.45 (d, *J* 10 Hz, 3-H) (Found: C, 78.1; H, 10.0. Calc. for $C_9H_{14}O$: C, 78.2; H, 10.2%).

4-Ethyl-4-methylcyclohexa-2,5-dienone.—The foregoing cyclohexenone (4.2 g) and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ, 7.1 g) were heated at 95—100 °C, under N_2, in purified dioxan (150 ml) for 50 h. Further DDQ (0.7 g) was added, and heating continued until the conversion into the dienone was >90% (judged by g.l.c. of aliquots on an NGS column at 160 °C). Work-up as described in Method C of ref. 40 for the preparation of 3,4,4-trimethylcyclohexa-2,5-dienone gave the dienone (4.06 g, 90% pure) which was purified by column chromatography on alumina (elution with light petroleum, b.p. 40—60 °C, then ether–light petroleum mixtures) or preparative g.l.c. (7 ft × ⅜ in column of 25% XF 1 150 at 165 °C) to ⩾99% purity. The dienone, a white solid, m.p. 26—28 °C, b.p. 60 °C at 1 mmHg, has $\nu_{max.}$ (CCl_4) 1 460m, 1 660m, 1 665—1 675s, 1 710w, 2 970m, and 3 040w cm^{-1}; $\lambda_{max.}$ (EtOH)

* Rate constants in 70% H_2SO_4, at 25 °C, which we have taken as standard conditions for comparisons of data.

† This assumes that C-6 has a greater migratory aptitude than C-9; studies of analogous dienones show an s-butyl group has m.a. *ca.* 600 times larger than an n-propyl.[37]

‡ Ref. 15 claims to use the enamine from 2-methylpropanal, clearly a misprint, and a reaction time of 4 days at room temperature which we found to give only partial reaction.

[37] L. E. Kendall and A. J. Waring, to be published.
[38] E. Benzing, *Angew. Chem.*, 1959, **71**, 521.
[39] F. W. Heyl and M. E. Herr, *J. Amer. Chem. Soc.*, 1953, **75**, 1918.
[40] K. L. Cook and A. J. Waring, *J.C.S. Perkin I*, 1973, 529.

237 nm (log ε 4.178), $\lambda_{max.}$ (iso-octane) 227 nm (log ε 4.142), $\lambda_{max.}$ (H_2O) 242 nm (log ε 4.185); τ (CCl_4) 9.22 (t, *J* 7.4 Hz, CH_2-*Me*), 8.74 (s, 4-Me), 8.33 (q, *J* 7.4 Hz, *CH*$_2$-Me), 3.88 (d, *J* 10·4 Hz, 2- and 6-H), 3.34 (d, *J* 10.4 Hz, 3- and 5-H); τ (C_6D_6) 9.51 (CH_2-*Me*), 9.20 (4-Me), 8.80 (*CH*$_2$-Me), 3.80 (2-, 3-, 5-, and 6-H) (Found: C, 79.3; H, 9.1%; *M*, 136. Calc. for $C_9H_{12}O$: C, 79.4; H, 8.9%; *M*, 136).

Preparative Rearrangement of 4-Ethyl-4-methylcyclohexa-2,5-dienone.—In aqueous sulphuric acid. The dienone (50.0 mg) mixed with aqueous sulphuric acid (10 ml of 48% by weight) was set aside at 25 °C for 140 min. After neutralisation with solid sodium hydrogen carbonate the mixture was extracted with ether, and the extract dried and evaporated to give an oil (49 mg), identified as 3-ethyl-4-methylphenol (*ca.* 99% of the total, shown by g.l.c. on 10% Apiezon at 142 °C).

In acetic anhydride.—The dienone (115 mg) was added with stirring to a solution of conc. sulphuric acid (1 drop) in acetic anhydride (0.4 ml); it was then set aside for 12 h at room temperature and worked-up as described by Burnell [13] to give a pale yellow oil (74 mg), identified as 3-ethyl-4-methylphenyl acetate, which showed a single peak (>98%) on g.l.c. (10% Apiezon at 160 °C) and has $\nu_{max.}$ (film) 1 215s, 1 370, 1 495m, 1 760—1 770s, 2 875, 2 935w, 2 960m, and 3 020w cm^{-1}; τ (CCl_4) 8.78 (t, *J* 7.7 Hz, CH_2-*Me*), 7.81 (s, 4-Me), 7.38 (q, *CH*$_2$-Me), 7.74 (s, O·CO·Me), 3.20 (s, 2-H), 3.25 (d, *J* 7.7 Hz, 6-H), and 2.95 (d, *J* 7.7 Hz, 5-H). Hydrolysis with 5% aqueous sodium hydroxide solution for 2 h at room temperature, then 4 h at 100 °C, neutralisation (dil. sulphuric acid), extraction with chloroform, and drying of the extracts and evaporation gave 3-ethyl-4-methylphenol (34 mg, *ca.* 99% of one material shown by g.l.c. on 10% Apiezon at 160 °C).

Authentic 3-Ethyl-4-methylphenol.—4-Methylphenol (33 g) mixed with anhydrous aluminium chloride (84 g) and bromoethane (33 g) at room temperature was stirred mechanically for 72 h.[41] The thick mixture was extracted with dichloromethane, and the extract treated with warm sodium hydroxide solution. The alkaline solution was subjected to steam distillation, the distillate rejected and the residue acidified and again steam distilled to give a mixtute of phenols. These were extracted into ether, dried, evaporated, and distilled. The fraction b.p. 58—61 °C at 0.3—0.5 mmHg is 3-ethyl-4-methylphenol, a white solid, m.p. 33—34 °C from pentane–hexane at −80 °C (lit.,[42] m.p. 35—36 °C), $\nu_{max.}$ (CCl_4) 880w, 925, 1 055, 1 125, 1 157s, 1 191, 1 270w, 1 293s, 1 320w, 1 465m, 2 875, 2 937, 2 968s, 3 020w, and 3 615s cm^{-1}. The i.r. spectrum is similar to that published for a solution in CS_2 [43] and agrees with data over a small frequency range for a solution in an unspecified solvent.[44] The phenol has τ (CCl_4) 8.85 (t, *J* 7.7 Hz, CH_2-*Me*), 7.82 (s, 4-Me), 7.47 (q, *CH*$_2$-Me), 3.55 (d of d, *J* 7.7 and 2.6 Hz, 6-H), 3.49 (d, *J* 2.6 Hz, 2-H), and 3.13 (d, *J* 7.7 Hz, 5-H); τ (C_6D_6) 8.98 (CH_2-*Me*), 7.95 (4-*Me*), 7.62 (*CH*$_2$-Me), 3.58 (2-H), 3.54 (6-H), and 3.10 (5-H); M^+ 136 (calc. for $C_9H_{12}O$, *M* 136).

4-Ethyl-3-methylphenol.—The acetate of 3-methylphenol, made by Chattaway's general method [45] (see later for details of the analogous preparation of the propionate) was subjected to Fries rearrangement.[24] The major product, 4-acetyl-3-methylphenol, was separated by its involatility in steam and has m.p. 128—129 °C (from aqueous ethanol) (lit.,[24] m.p. 126.5—128 °C), τ ([$^2H_6$]acetone) 7.56 (s, CH_3–CO and 3-Me), 3.25—3.37 (mult., 2- and 6-H), 2.30 (d, *J* 9 Hz, 5-H). Clemmensen reduction [23,26] gave 4-ethyl-3-methylphenol, b.p. 226—228 °C, identical with an authentic sample,* with $\nu_{max.}$ (CCl_4) 870w, 950m, 1 121m, 1 158s, 1 190s, 1 277w, 1 295s, 2 875, 2 930, 2 970, 3 020w, and 3 612s cm^{-1} similar to reported values [43,46]; τ (CCl_4) 8.83 (t, *J* 7.5 Hz, CH_2-*Me*), 7.76 (s, 3-Me), 7.45 (q, *J* 7 Hz, *CH*$_2$-Me), 3.50 (mult., 6-H), 3.45 (d, *J* 2.6 Hz, 2-H), 3.07 (d, *J* 8.6 Hz, 5-H); τ (C_6D_6) 8.95 (CH_2-*Me*), 7.95 (3-Me), 7.59 (*CH*$_2$-Me), 3.56 (2-H), 3.51 (6-H), and 3.10 (5-H).

Identification of the Rearrangement Products from 4-Ethyl-4-methylcyclohexa-2,5-dienone as 3-Ethyl-4-methylphenol, and their Distinction from 4-Ethyl-3-methylphenol.—The two authentic ethylmethylphenols prepared above were barely differentiated by g.l.c. on many columns (including 25% NGS at 160 °C, 10% E30 at 150 °C, and 10% Apiezon at 130 °C). The i.r. spectra allow a distinction at a low confidence level; n.m.r. spectra and solvent-shift data allow a more confident distinction. The isomers were resolved by t.l.c. on carefully activated plates spread with Merck " Kieselgel G nach Stahl ", development being with 97% methanol and 3% by volume of ammonia (*d* 0.880) or a 90 : 10 mixture of these, and by paper chromatography on Whatman 3MM paper using as developing solvent n-butanol : ethanol : aqueous ammonia (*d* 0.880) : water, 10 : 10 : 1 : 4 (v/v).[47] Chromatograms were sprayed with diazotised *p*-nitroaniline,[48] and with ferric chloride–potassium ferricyanide mixture [49] both of which gave spots of distinguishable colours for the two isomers. The i.r. and n.m.r. spectra showed that both rearrangement products were largely 3-ethyl-4-methylphenol; the chromatography showed that up to *ca.* 5% of 4-ethyl-3-methylphenol could be present in each. The use of $Eu(fod)_3$ shifts in the n.m.r. spectra (see earlier and Table 1) allowed full confirmation that the major rearrangement product is 3-ethyl-4-methylphenol, that the minor product is 4-ethyl-3-methylphenol, and that their yields are in the ratio *ca.* (98 ± 1) to (2 ± 1).

4-Ethyl-4,5-dimethylcyclohex-2-enone and 4-Ethyl-3,4,5-trimethylcyclohexanone.— 4-Ethyl-4-methylcyclohexa-2,5-dienone (2.0 g) in ether (30 ml) at 0 °C was added to a solution of lithium dimethylcuprate [from copper(I) iodide (3.34 g) and ethereal methyl-lithium] at 0 °C. After 30 min at 0 °C the mixture was added with vigorous stirring to saturated aqueous ammonium chloride (600 ml). The ether layer was separated, the aqueous layer extracted with ether (4 × 50 ml), and the combined ether extracts dried ($MgSO_4$) and evaporated to give crude 4-ethyl-4,5-dimethylcyclohex-2-enone. This was treated as above, with an excess of lithium dimethylcuprate [from copper(I) iodide (5.0 g)] and set aside for 15 min at 0 °C. Work-up as above gave the crude *4-ethyl-3,4,5-trimethylcyclohexanone* (1.50 g), purified by chromatography on an alumina column

* Provided by Midland-Yorkshire Tar Distillers Ltd.

[41] G. Baddeley, *J. Chem. Soc.*, 1944, 330.
[42] M. S. Newman and F. Bayerlein, *J. Org. Chem.*, 1963, **28**, 2804.
[43] D. D. Shrewsbury, *Spectrochim. Acta*, 1960, **16**, 1294.
[44] L. Irvine and T. J. Mitchell, *J. Appl. Chem.*, 1958, **8**, 425.
[45] F. D. Chattaway, *J. Chem. Soc.*, 1931, 2495.
[46] W. Beckering, C. M. Frost, and W. W. Fowkes, *Analyt. Chem.*, 1964, **35**, 2412.
[47] A. G. Long, J. R. Quayle, and R. J. Stedman, *J. Chem. Soc.*, 1951, 2197.
[48] H. G. Bray, W. V. Thorpe, and K. White, *Biochem. J.*, 1950, **46**, 271.
[49] G. N. Barton, R. S. Evans, and J. A. F. Gardner, *Nature*, 1952, **170**, 249.

(150 g of Brockman Grade II alumina) with light petroleum (b.p. 40—60 °C), then 1% ether in light petroleum and 2% ether in light petroleum. The pure *ketone*, a colourless liquid after distillation, has $\nu_{max.}$ (CCl_4) 1 385, 1 460, 1 720s, and 2 965s cm^{-1}; τ (CCl_4) 9.15 (d, 3-Me), 9.14 (d, *J* 5.1 Hz, 5-Me), 9.12 (t, CH_2-*Me*), 9.01 (4-Me), and 7.6—8.9 (complex) (Found: M^+, 168.148 ± 0.005. $C_{11}H_{20}O$ requires *M* 168.151 4).

2,6-*Dibromo*-4-*ethyl*-3,4,5-*trimethylcyclohexanone*.—To the foregoing ketone (0.551 g) in glacial acetic acid (5 ml), stirred at 10—12 °C, was added bromine (1.048 g) in acetic acid (15 ml) during 20 min. After 30 min further at 10—15 °C the mixture was added to cold water (40 ml) and extracted with ether (3 × 30 ml). The ether extracts, after washing with water, $NaHCO_3$ solution until neutral, and water, were dried and evaporated. Recrystallisation from boiling pentane (cooling to −78 °C) gave the *dibromo-ketone* (0.96 g, 90%), white needles, m.p. 145—146 °C, $\nu_{max.}$ (CCl_4) 1 390s, 1 465m, 1 758s, and 2 970s cm^{-1}; τ (CCl_4) 9.07 (t, *J* 7.1 Hz, CH_2-*Me*), 9.01 (s, 4-Me), 8.76 (d, *J* 6.4 Hz, 3- and 5-Me), 5.50 (d, *J* 11.4 Hz, 2-H axial), 4.82 (d, *J* 5.0 Hz, 6-H axial). The i.r. and chemical-shift data show both the 2- and 6-bromine atoms are equatorial, and the coupling shows H-3 is axial and H-5 equatorial (see the discussion in ref. 40); thus the two methyl groups at C-3 and C-5 are *trans*-related. This stereochemistry is consistent with *axial* approach of alkylating agent to the π-electron system of 4-ethyl-4,5-dimethylcyclohex-2-enone, in its 5-methyl *equatorial* conformation.

4-*Ethyl*-3,4,5-*trimethylcyclohexa*-2,5-*dienone*.—The foregoing dibromo-ketone (0.96 g) was heated at reflux in dry, redistilled dimethylformamide (10 ml) with dried powdered calcium carbonate (1.5 g) during 3 h. The cooled mixture was filtered and the solid washed with cold water (150 ml) and then pentane (50 ml); the washings were combined with the filtrate. The combined liquids were extracted with pentane (6 × 25 ml), and the pentane layers dried and evaporated to give the crude dienone (*ca.* 95% pure; 0.45 g). Purification by column chromatography on alumina, elution being with light petroleum and mixtures of ether in light petroleum, gave material *ca.* 98% pure. This was sublimed at 80—100 °C and 0.1 mmHg, and the product collected on a cold finger at −80 °C. The pure *dienone* (⩾99% pure as judged by g.l.c. on 25% NGS at 200 °C) is a colourless solid, m.p. 37.8—39.4 °C, $\nu_{max.}$ (CCl_4) 1 320, 1 385m, 1 618w, 1 635m, and 1 670s cm^{-1}; $\lambda_{max.}$ (hexane) 232 nm, (log ε 4.197), $\lambda_{max.}$ (H_2O) 237.5 nm (log ε 4.232); τ(CCl_4) 9.43 (t, *J* 7.4 Hz, 4-CH_2-*Me*), 8.75 (s, 4-Me), 8.33 (q, *J* 7.4 Hz, 4-*CH*$_2$-Me), 8.08 (d, *J* 0.5 Hz, 3- and 5-Me, coupled to 2-H and 6-H), 3.96 (mult., 2-H and 6-H); τ (C_6D_6) 9.71 (t, 4-CH_2-*Me*), 9.25 (s, 4-Me), 8.82 (q, 4-C*H*$_2$-Me), 8.58 (d, 3- and 5-Me), and 3.70 (2- and 6-H) (Found: C, 80.9; H, 9.9%; M^+ 164.120 ± 0.005. $C_{11}H_{16}O$ requires C, 80.5; H, 9.8%; *M* 164.118 1).

4-*Ethyl*-3,4-*dimethylcyclohexanone and* 2,6-*Dibromo*-4-*ethyl*-3,4-*dimethylcyclohexanone*.— 4-Ethyl-4-methylcyclohex-2-enone (2.0 g) was treated with lithium dimethylcuprate [2 mole equiv., from 5.7 g of copper(I) iodide] at 0 °C for 1 h as described above. Work-up as before gave 4-ethyl-3,4-dimethylcyclohexanone (1.92 g, 96%), pure to g.l.c. (25% NGS column at 150 °C), $\nu_{max.}$ (CCl_4) 1 382m, 1 430w, 1 463m, 1 710—1 720s, 2 875w, 2 930w, and 2 960s cm^{-1} [lit.,[15] (film) 1 730 cm^{-1}]; τ (CCl_4) 9.04 (s, 4-Me), 8.97—9.23 (complex), 8.03—8.77, and 7.64—7.92 (complex).

The ketone (1.92 g) in acetic acid (20 ml) was treated with bromine (3.94 g; 2 mole equiv.) in acetic acid (30 ml) at 12 °C, and the mixture worked-up as before to give the unstable *dibromo-ketone* (3.44 g, 90%), white crystals, m.p. 90—92 °C (from hexane), $\nu_{max.}$ (CCl_4) 1 387m, 1 463m, 1 740w, 1 758s, 2 875m, 2 935w, and 2 970s; τ (CCl_4) 9.09 (t, *J* 7.9 Hz, CH_2-*Me*), 8.85 (s, 4-Me), 8.81 (d, *J* 7.1 Hz, 3-Me), 8.6 to 7.8 (mult., 3- and 5-H), 5.40 (d, *J* 12.8 Hz, 2-H), 5.14 (d of d, $J_{ax,ax} + J_{ax,eq} = 20.0$ Hz, 6-H). These spectra show that the 2-H and 6-H atoms are *axial*, and the 3-methyl group is *equatorial*. In C_6D_6 the dibromo-ketone has τ 9.71 (s, 4-Me), 9.69 (t, *J* 7.9 Hz, CH_2-*Me*), 9.21 (d, *J* 7.1 Hz, 3-Me) 8.7—8.1 (mult., 3- and 5-H), 6.08 (d, $J_{ax,ax}$ 12.8 Hz, 2-H), 5.79 (d of d, $J_{ax,ax} + J_{ax,eq}$ 20.0 Hz, 6-H) (Found: C, 38.8; H, 5.3; M^+ on di-^{79}Br-isotope 309.957 9 ± 0.005. $C_{10}H_{16}Br_2O$ requires C, 38.5; H, 5.2%; *M* 309.956 8).

4-*Ethyl*-3,4-*dimethylcyclohexa*-2,5-*dienone*.—The preceding dibromo-ketone (3.2 g) was treated with calcium carbonate (8.0 g) in dimethylformamide (50 ml) for 1 h, as described in the preparation of 4-ethyl-3,4,5-trimethylcyclohexa-2,5-dienone, the product being extracted with light petroleum (b.p. 40—60 °C). The crude product (0.8 g) was >90% pure (g.l.c. on 10% NGS at 150 °C), and was purified by column chromatography on alumina, using light petroleum and light petroleum–ether mixtures, to >98% purity; $\nu_{max.}$ (film) 1 595w, 1 629w, and 1 655—1 665s cm^{-1} (lit.,[15] 1 655 cm^{-1}); $\lambda_{max.}$ (H_2O) 234.5 nm (log ε 4.017); τ (CCl_4) 9.38 (t, *J* 7.0 Hz, CH_2-*Me*), 8.80 (s, 4-Me), *ca.* 8.80 (q, *J* 7.0 Hz, C*H*$_2$-Me), 8.14 (d, *J* 1.1 Hz, 3-Me), 4.06 (d of d, *J* 1.1 and 1.5 Hz, 2-H), 4.00 (d of d, *J* 10.0 and 1.5 Hz, 6-H), and 3.59 (d, *J* 10.0 Hz, 5-H).

Preparative Rearrangement of 4-*Ethyl*-3,4-*dimethylcyclohexa*-2,5-*dienone*.—The above dienone (16 mg) in aqueous sulphuric acid (2.5 ml, 51.4% by weight) was kept at 25.0 °C for 28 h (7—8 half-lives). Dilution with water, neutralisation with sodium hydrogen carbonate, extraction with ether, and drying and evaporation of the ether extract gave an oil (16 mg). G.l.c. (10% NGS column at 180 °C) showed the presence of two products (97% of one, *ca.* 1½% of a second), and *ca.* 1½% of all other minor peaks. The major product had identical chromatographic behaviour and spectra to samples of 3-ethyl-4,5-dimethylphenol made by rearrangement of 3-ethyl-4,4-dimethylcyclohexa-2,5-dienone,[8b] and by the route given below; the n.m.r. spectrum, τ (CCl_4) 8.86 (t, *J* 7.3 Hz, CH_2-*Me*), 7.94 (s, 4-Me), 7.82 (s, 5-Me), 7.48 (q, *J* 7.3 Hz, C*H*$_2$-Me), 3.69 (2- and 6-H), differs slightly from that reported [8b] (Found: M^+ 150. $C_{10}H_{14}O$ requires *M*, 150).

3,4-*Dimethyl*-5-*ethylphenol*.—3,4-Dimethylphenol was ethylated using bromoethane and aluminium chloride, as described for the preparation of 3-ethyl-4-methylphenol. The residue after distillation up to 115 °C at 16 mmHg was crystallised from light petroleum (b.p. 40—60°), then water, to give the desired product (>99% pure, g.l.c. on 10% NGS at 180 °C), m.p. 76—78 °C.

2-*Ethyl*-2-*formylcyclohexanone*.— 2-Hydroxymethylenecyclohexanone [50] (21.75 g) was converted into its sodium salt using sodium ethoxide (from 3.6 g sodium) in ethanol, and treated with iodoethane (25.0 g).[33] The resulting oil was distilled at 3 mmHg to give fractions * b.p. 40—60 °C,

* The second fraction contains the desired compound (formyl group at τ 1.36 in the n.m.r. spectrum); the third fraction is mainly the vinylic ether, 2-ethoxymethylenecyclohexanone (τ 2.78), containing some formyl compound also.

[50] C. Ainsworth, *Org. Synth.*, Coll. Vol. IV, 1963, 536.

60—66 °C (major fraction) and 100—102 °C, none of which was pure: all gave a positive feric chloride test for an enol. To further 2-hydroxymethylene-cyclohexanone (12.6 g) dissolved in light petroleum (50 ml; b.p. 40—60 °C) thallous ethoxide (25.0 g) was added dropwise, with vigorous stirring. The resulting pale yellow solid thallium salt (28.7 g, 88%) was heated at reflux with redistilled iodoethane (90 ml) for 4.5 h. After cooling, the thallous iodide was removed by filtration and washed with carbon tetrachloride; the combined organic fractions were evaporated to a brown oil (14.1 g). This was found by g.l.c. (E30 at 125 °C) and n.m.r. to contain *ca.* 25% of the desired 2-ethyl-2-formylcyclohexanone.

4a-*Ethyl*-5,6,7,8-*tetrahydronaphthalen*-2-*one*.—The crude ethylation product from the thallium salt above (14.1 g) was dissolved in acetone (125 ml), and piperidine (8.2 g) then acetic acid (5.8 g) was added with stirring. The mixture was heated under reflux for 90 h, after which the acetone was removed by evaporation and ether (100 ml) was added. The solution was washed with hydrochloric acid (3 × 50 ml of 1.0M), water, sodium hydrogen carbonate solution, and water; it was then dried and evaporated to give a brown oil. To this was added methanol (120 ml) and then potassium hydroxide solution (7.0 g KOH in 7 ml water) after which the mixture was heated under reflux for 18 h. The residue after evaporation of the methanol was diluted with water (50 ml) and extracted with ether. The washed (H_2O) ether extract was dried and evaporated to give crude product (1.90 g), *ca.* 90% pure, which was purified by column chromatography on alumina or preparative t.l.c. on Merck silica, followed by distillation under vacuum, to >99% purity. The dienone, a pale yellow oil, has $\nu_{max.}$ (CCl_4) 1 625m, 1 660s, 1 710w, 2 860s, and 2 920—2 960 cm^{-1} (lit.,[31] 1 630 and 1 670 cm^{-1}); $\lambda_{max.}$ (EtOH) 243 nm (log ε 4.12); τ (CCl_4) 9.39 (t, *J* 7.3 Hz, CH_2-*Me*), 8.85—7.75 (mult., $-CH_2$-Me and 5-, 6-, 7-, and 8-H), 4.06 (d, $J_{1,3}$ 1.3 Hz, 1-H), 3.97 (d of d, $J_{1,3}$ 1.3 Hz, $J_{3,4}$ 9.5 Hz, 3-H), 3.61 (d, *J* 9.3 Hz, 4-H); τ (C_6D_6) 9.66 (t, CH_2-*Me*), 4.16 (4-H), 3.89 (1-H), and 3.79 (3-H) (coupling constants as in CCl_4) (Found: M^+ 176.116 4 ± 0.005. $C_{12}H_{16}O$ requires 176.120 1).

Preparative Rearrangements of 4a-*Ethyl*-5,6,7,8-*tetrahydronaphthalen*-2-*one*.—The foregoing dienone (5.0 mg) was mixed with aqueous sulphuric acid (1.0 ml, 82% by weight) at 25.0 °C, and then set aside at 25 °C. Aliquots of 0.1 ml were taken after 2 and 4 h, and each was diluted with iced water to ten times its volume and extracted repeatedly with ether; the remaining solution was similarly treated after 10 h (6.5 ± 0.8 half-lives). The ether extracts were examined by g.l.c. (10% E30 at 150 °C and 10% Carbowax 20M at 155 to 195 °C) and the 10 h sample extract washed with sodium hydrogen carbonate solution, dried, evaporated, and the product examined. A second dienone sample was treated similarly for 5.0 ± 0.6 half-lives, worked up, and the product was combined with the previous one for i.r. and n.m.r. examination, and isolation of the major product by preparative g.l.c. (10% E30 at 125 °C). G.l.c. of the 2 and 4 h samples showed the presence of unchanged dienone and only one product peak; the 10 h sample showed a trace of unchanged dienone, the same major product peak, and a number of small peaks equivalent in total to <5% of the major peak area. The isolated major product, 4-ethyl-5,6,7,8-tetrahydro-2-naphthol, has $\nu_{max.}$ (CCl_4) 1 570, 2 875, 2 950, and 3 630 cm^{-1}; τ (CCl_4) 8.88 (t, *J* 7 Hz, CH_2-*Me*), 8.22 (mult., 5- and 8-H), 7.46 (mult., 6- and 7-H), 3.81 (d, *J* 3 Hz, 1- or 3-H), 3.67 (d, *J* 3 Hz, 3- or 1-H, *meta* coupled) (lit.,[31] τ 3.8, 3.7) (Found: M^+ 176.119 ± 0.005. $C_{12}H_{16}O$ requires *M*, 176.120 1).

4-*Methyl*-4-*n*-*propylcyclohex*-2-*enone*.—To but-3-en-2-one (methyl vinyl ketone; 90% in water) (40.0 g) and 2-methylpentanal (Koch–Light Laboratories Ltd.) (50.0 g) was added water (46 ml) and methanol sufficient to render the mixture homogeneous (100 ml). This solution was added dropwise with stirring, during 1.0 h, to a solution of potassium hydroxide (1.85 g) in methanol (10 ml), initially at 45 °C. The temperature was then raised to 70 °C and separation into two layers occurred. Ether extraction, drying of the ether extract, and evaporation gave an oil which was distilled to give material, >86% pure, b.p. 94—165 °C at 14 mmHg, then at 91—93 °C at 3.5 mmHg or 78—80 °C at 1.8 mmHg to give the cyclohexenone (33.12 g, 43%) of >99% purity (lit.,[6] b.p. 101—103 °C at 14 mmHg, in 13% yield from a preparation *via* the enamine) (Found: C, 78.6; H, 10.4. Calc. for $C_{10}H_{16}O$: C, 78.9; H, 10.6%).

4-*Methyl*-4-*n*-*propylcyclohexa*-2,5-*dienone*.—The foregoing cyclohexenone (2.00 g) was treated with DDQ (3.10 g) at 95—100 °C in dry dioxan (120 ml), under nitrogen, for 85 h. The usual work-up gave crude dienone (1.42 g) of *ca.* 90% purity. A larger preparation using 5.00 g of the cyclohexenone gave 3.07 g of dienone. Purification by preparative g.l.c. (7 ft × ⅜ in column of 25% silicone XF1150 at 165—170 °C) gave the colourless liquid *dienone* (⩾99% pure, by g.l.c. on a 25% NGS column at 150 °C), $\nu_{max.}$ (film) 2 965s, 1 698w, 1 675—1 665s, 1 661m, 1 605w, and 1 401s cm^{-1}; $\lambda_{max.}$ (H_2O) 243 nm (log ε 4.17); τ (CCl_4) 9.5—8.7 (mult., n-propyl), 8.78 (s, 4-Me), 3.92 (d, *J* 10.0 Hz, 2- and 6-H), 3.40 (d, *J* 10.0 Hz, 3- and 5-H) (Found: C, 79.8; H, 9.5%; M^+, 150.105 9. $C_{10}H_{14}O$ requires C, 79.9; H, 9.4%; *M*, 150.104 4).

Preparative Rearrangement of 4-*Methyl*-4-*n*-*propylcyclohexa*-2,5-*dienone*.—The dienone (70.0 mg) was shaken with 10 ml of 6.07M-sulphuric acid (44.5% by weight) at 25 °C during 6.5 h. Work-up in the manner described for 4-ethyl-4-methylcyclohexa-2,5-dienone gave a mixture (70.0 mg) of *ca.* 19% unchanged dienone and 81% of a single product. The conversion, based on the kinetic data, should be higher but the dienone is incompletely soluble in the quantities used here. The mixture was added to 4M-aqueous sodium hydroxide (5 ml) and steam distilled to remove unchanged dienone; it was then acidified (dil. H_2SO_4), extracted with ether, and the dried ($CaSO_4$) extract evaporated to give 43.0 mg (61%) of 4-*methyl*-3-*n*-*propylphenol* (98 ± 1% pure by g.l.c. on NGS at 180 °C). A further rearrangement of 90 mg of dienone during 18 h gave 54 mg (60%) of the same product (99% pure). The phenol has $\nu_{max.}$ (CCl_4) 3 620s, 3 022w, 2 962s, 2 938m, 2 877m, 1 293m, 1 264m, 1 189s, and 1 154s cm^{-1}; τ (CCl_4) 9.01 (t, *J* 8.3 Hz, $-CH_2$-*Me*), 7.78 (s, 4-Me), 7.48 (t, *J* 7 Hz, 3-CH_2-Et), 3.53 (d of d, *J* 8.6 and 2.9 Hz, 6-H), 3.48 (d, *J* 2.9 Hz, 2-H), 3.10 (d, *J* 8.6 Hz, 5-H); τ (C_6D_6) 9.14 (CH_2-*Me*), 7.91 (4-Me), 7.60 (3-CH_2-Et), 3.54 (6-H), 3.49 (2-H), and 3.09 (5-H). N.m.r. shifts obtained on the addition of $Eu(fod)_3$ are recorded in Table 1. (Found: M^+ 150.107 4 ± 0.005. $C_{10}H_{14}O$ requires *M* 150.104 4). A sample purified by preparative g.l.c. (10% E30 column at 125 °C) had identical properties.

5-*Methyl*-2-*propionylphenol and* 3-*Methyl*-4-*propionylphenol*.—The general procedure of Chattaway [45] was used to make *m*-tolyl propionate. Sodium hydroxide (15.0 g) in water (100 ml) was added with stirring and cooling at 0 °C to 3-methylphenol (36.0 g). Crushed ice (100 g) and propio-

nic anhydride (45.0 g) were added successively, and the mixture was shaken for 3 min. After 10 min at room temperature the mixture was extracted with ether, and the ether extract washed (H_2O), dried, and evaporated. The *m*-tolyl propionate was >98% pure, and free of 3-methylphenol. It was subjected to a Fries rearrangement [24] in nitrobenzene for 5 days at 0 °C. Careful steam distillation allowed the nitrobenzene solvent to be collected, then (mainly) 5-methyl-2-propionylphenol which gives a deep violet colour on treatment with ferric chloride in ethanol–water (9 : 1). This isomer, m.p. 43—44 °C (from aqueous ethanol) (lit.,[25,51] m.p. 41.5—42.5, 43—46 °C) has $\nu_{max.}$ (CCl_4) 2 980w, 2 940w, 1 645s, and 1 577, 1 210 cm^{-1} (showing only a broad, diffuse peak from *ca.* 3 300—2 700 cm^{-1}, typical of a chelated OH group in an *ortho*-hydroxy ketone); τ ([$^2H_6$]acetone) 8.86 (t, *J* 7 0 Hz, CH_2-*Me*), 7.72 (s, 5-Me), 7.01 (q, *J* 7.0 Hz, *CH_2*-Me), 3.42 (complex, 4- and 6-H), 2.41 (d, *J* 8.4 Hz, 3-H), and −2.21 (sharp, s, OH, strongly chelated to the 2-propionyl group), confirming the structure established by Auwers.[25]

The residue from steam distillation gives no colour on treatment with ferric chloride solution. It was extracted with ether, from which it was subsequently extracted into 1.0M-aqueous sodium hydroxide solution; the alkaline solution was acidified (dil. hydrochloric acid) and extracted with ether. The dried ether extract was evaporated and the pale brown solid residue extracted continuously with light petroleum (b.p. 80—100 °C) in a Soxhlet extractor. The evaporated extract was 3-methyl-4-propionylphenol, m.p. 110—111 °C (from aqueous ethanol) (lit.,[25] 114—120 °C; lit.,[51] 114—115 °C), $\nu_{max.}$ (Nujol) 3 240s, 1 880, 1 740w, 1 647, 1 612, 1 573, 1 562, 1 555s, 1 310, 1 245, 1 220s, 880, and 802m cm^{-1}; τ ([$^2H_6$]acetone) 8.92 (t, *J* 7.0 Hz, CH_2*Me*), 7.57 (s, 3-Me), 7.14 (q, *J* 7.0 Hz, *CH_2*Me), 3.31—3.29 (mult., 2- and 6-H), 2.29 (d, *J* 9.3 Hz, 3-H). The coupling pattern, high chemical shifts of the 2- and 6-protons, and lack of intramolecular hydrogen-bonding of the phenolic group support the structure claimed.

3-Methyl-4-n-propylphenol.—The foregoing 3-methyl-4-propionylphenol (3.0 g) was subjected to Clemmensen reduction using the conditions described for another compound.[52] The reaction mixture was extracted with ether, the extract evaporated and the residue steam distilled. The distillate was extracted with ether and the dried ether extract evaporated and subjected to molecular distillation, to give 3-methyl-4-n-propylphenol, pure to g.l.c. (PEGA column at 190 °C), $\nu_{max.}$ (film) 3 340s, br., 3 020w, 2 956, 2 928, 2 868, 1 610, 1 588, 1 501, 1 460, 1 455, 1 263, 1 200, 1 160m, 1 120, 1 003, 954, 915, 820, and 800w cm^{-1}; τ (CCl_4) 9.08 (t, *J* 7.0 Hz, $-CH_2$*Me*), 8.48 (mult., *$-CH_2$*Me), 7.86 (s, 3-Me), 7.58 (t, *J* 7.0 Hz, *$-CH_2$*Et), 3.53 and 3.18 (AB pattern, *J* 9.3 Hz, 6- and 5-H), and 3.50 (s, 2-H). The compound is distinguished from the product of dienone–phenol rearrangement of 4-methyl-4-n-propylcyclohexa-2,5-dienone by its g.l.c. behaviour (PEGA column at 190 °C), n.m.r. (marginal distinction), and n.m.r. $Eu(fod)_3$ shifts given in Table 1.

5-Methyl-2-n-propylphenol.[26]—5-Methyl-2-propionylphenol (18.5 g) was subjected to Clemmensen reduction as described above to give 5-methyl-2-n-propylphenol (12.44 g) as a colourless oil, $\nu_{max.}$ (film) 3 400, 2 960, 2 910, 2 870s, 1 880w, 1 620, 1 584, 1 540, 1 120, 947s, 860m, 815, and 800s cm^{-1}; τ 9.11 (t, *J* 7.3 Hz, $-CH_2$*Me*), 8.44 (mult., *CH_2*Me), 7.86 (s, 5-Me), 7.55 (t, *J* 7.6 Hz, *$-CH_2$*Et), 4.73 (s, OH), 3.68 (s, 6-H), 3.54, and 3.20 (AB pattern, *J* 7.8 Hz, 4- and 3-H respectively). The peaks τ 3.68 and 3.54 are due to *meta*-coupled protons. This isomer is clearly different in g.l.c. and n.m.r properties from both methyl propylphenols described earlier.

We thank the University of Birmingham, and Professor M. Stacey, for a scholarship to J. W. P., and Midland-Yorkshire Tar Distillers Ltd. for a gift of 4-ethyl-3-methylphenol.

[5/1874 *Received* 29*th September*, 1975]

[51] Beilstein's Handbook, 3rd. Supplement, Band 8, p. 465.
[52] R. R. Read and J. Wood, jun., *Org. Synth.*, Coll. Vol. III. 1955, 444.