REACTION OF 4-ALKYLIDENE-2,5-CYCLOHEXADIENONES WITH TRIETHYLAMMONIUM ACETATE IN ACETIC ACID

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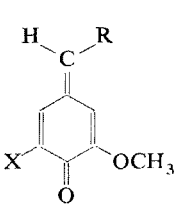
Methylene- and ethylidenecyclohexadienones *I*—*IV* react with triethylammonium acetate in acetic acid with the formation of phenolic benzyl acetates *V*—*VIII*. Under analogous conditions, isopropylidenecyclohexadienones *IX*—*XII* rearrange into isopropenylphenols *XIII*—*XVI* which are in two cases accompanied by dimers of the indane type *XVII* and *XVIII*. On the basis of experiments performed in deuterated acetic acid or with the deuterium-labelled phenol *XIV*, plausible mechanisms have been proposed for the isomerisation as well as the dimerisation.

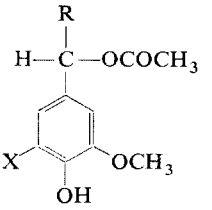
4-Alkylidene-2,5-cyclohexadienones (*p*-quinonemethides) are highly reactive compounds of an ambident character. Their carbonyl oxygen atom is basic enough to offer its electrons to electrophilic agents. On the contrary, the exocyclic carbon atom of the conjugated system is to such an extent electron-deficient that nucleophilic additions readily take place (Scheme 1). Unlike linear 2,4-hexadienones which undergo simultaneous 1,2-, 1,4-, and 1,6-additions[1], the quinonemethides are transformed by 1,6-additions only[2]. The total regioselectivity of these reactions may be obviously ascribed to the resonance energy released by transformation of the cyclic cross-conjugated system into an aromatic system.

One of the nucleophiles which is known to react readily with quinonemethides, is the acetate ion[3]. As observed in reexamination of this reaction, only those quinonemethides react with triethylammonium acetate in acetic acid in the manner shown in Scheme 1 when no methyl group or a single methyl group is attached to their exocyclic methine carbon atom. Thus *e.g.*, 4-methylene- and 4-ethylidenecyclohexadienones *I*—*IV* afford the corresponding benzyl acetates *V*—*VIII* in an almost quantitative yield (Table I). Under otherwise analogous conditions, the acetate ion is not added to quinonemethides *IX*—*XII*, the methide carbon atom of which is substituted by two methyl groups. In all these cases, the reaction products were the 4-isopropenylphenols *XIII*—*XVI*, *i.e.* compounds which are isomeric with the quinonemethides. In two cases (with quinonemethides *X* and *XI*), the isomers were accompanied by dimers *XVII* and *XVIII* of the indane type. Structures of all compounds were unequivocally determined from mass spectra and proton magnetic resonance spectra.

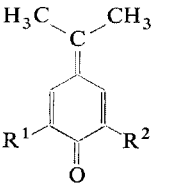
The isomerisation of alkylidenecyclohexadienones to isopropenylphenols is



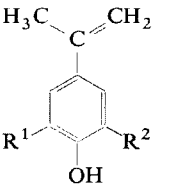
I—IV



V—VIII



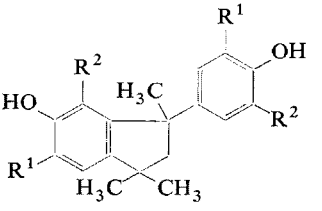
IX—XII



XIII—XVI

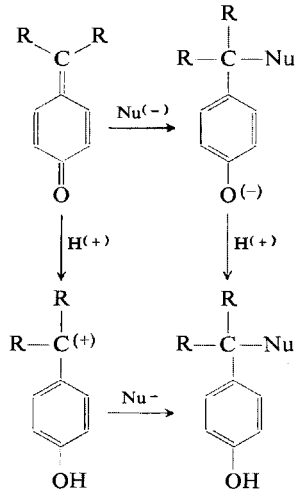
I, V; R = X = H
II, VI; R = H; X = Br
III, VII; R = CH_3; X = H
IV, VIII; R = CH_3; X = Br

IX, XIII; $R^1 = R^2 = H$
X, XIV; $R^1 = H$; $R^2 = OCH_3$
XI, XV; $R^1 = R^2 = OCH_3$
XII, XVI; R^1 = Br; $R^2 = OCH_3$



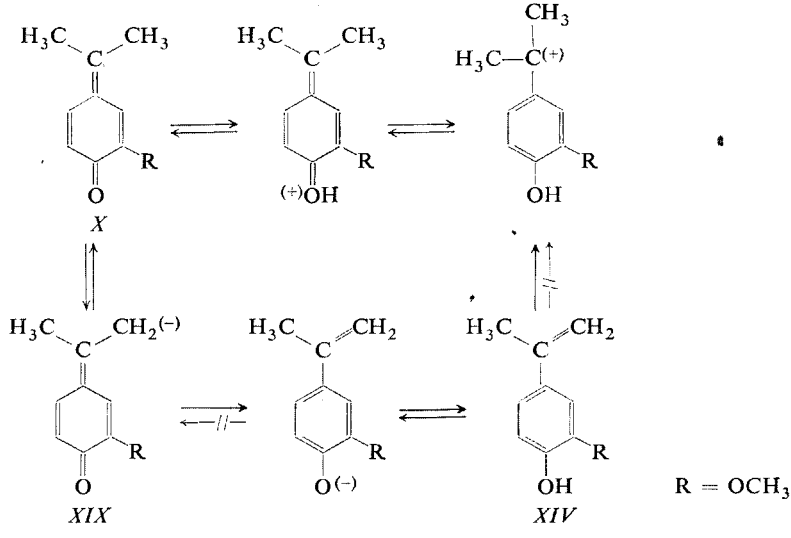
XVII; $R^1 = OCH_3$; $R^2 = H$
XVIII; $R^1 = R^2 = OCH_3$

somewhat similar to the enolisation of ketones. While the mechanism of the latter reaction has been examined in detail[4], almost nothing is known about the former reaction. In order to obtain further informations on the course of the isomerisation, the quinonemethide *X* was treated with triethylamine in [COO^2H]acetic acid. The isolated 4-isopropenyl-2-methoxyphenol (*XIV*) contained molecules with one to five deuterium atoms and the dimer *XVII* consisted of molecules with one to eleven deuterium atoms. In both compounds, deuterium was bound in C-methyl or C-methylene groups only. As observed however in a further experiment, no exchange of protons took place under similar conditions between the deuterated solvent and the side chain of the isopropenylphenol *XIV*. These experimental results may be interpreted as follows: *1*) The isomerisation reaction does not proceed by a concerted mechanism and *2*) the isomerisation reaction is irreversible and the possibility of the proton transfer by the keto–enol tautomerisation is thus excluded. Aromatisation of the cyclohexadienone system must be therefore preceded by another equilibrium reaction in which proton is removed from the isopropylidene group of the quinonemethide *X* by the action of a base with formation of the carbanion *XIX* (Scheme 2). Such a mechanism is favoured by the easy isomerisation of the quinonemethide *X* by triethylamine alone. Without a kinetic analysis of the reaction however, we cannot exclude a partial participation of an alternative mechanism initiated by protonation of the carbonyl group of the alkylidenecyclohexadienone.

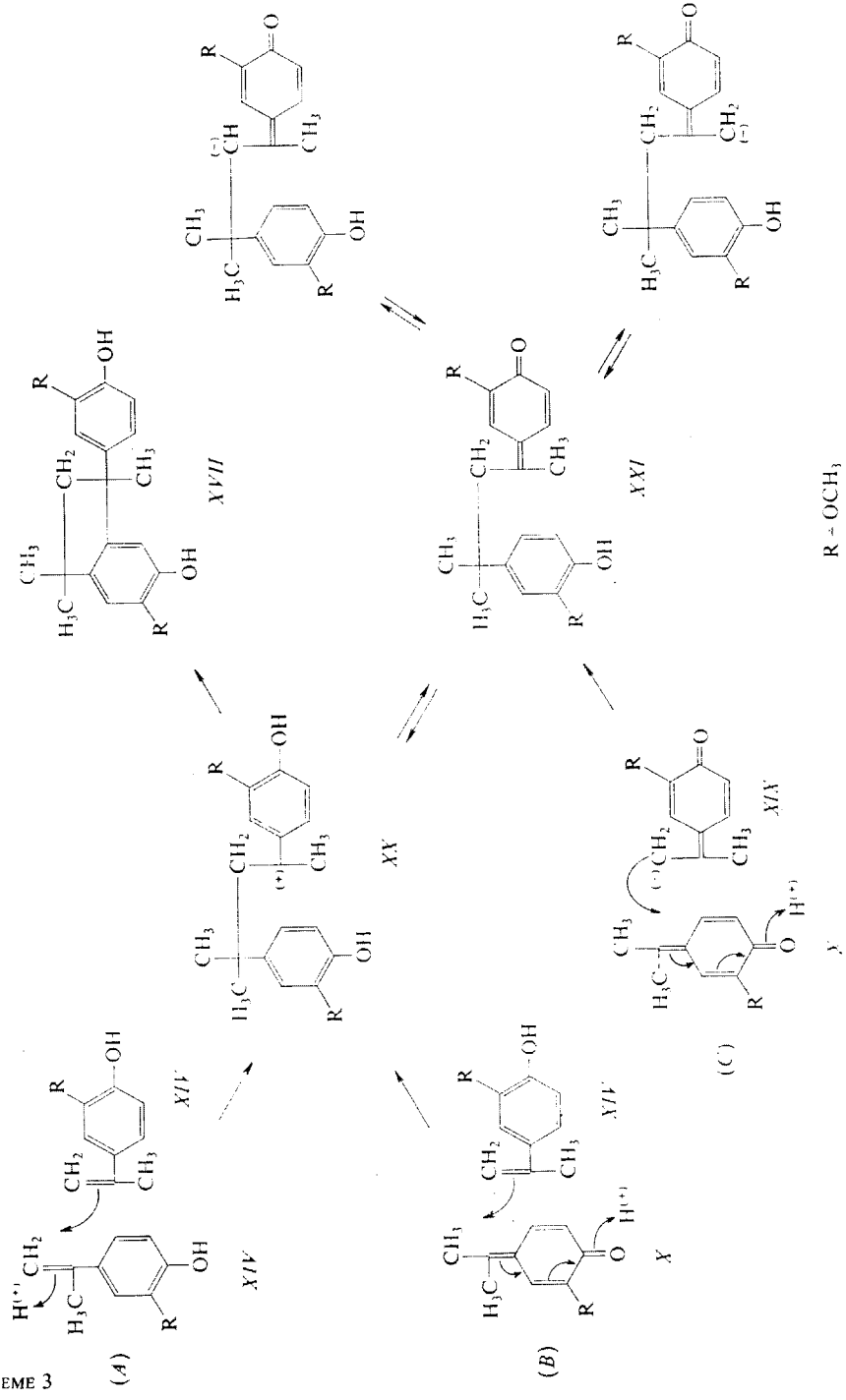


SCHEME 1

The indane compounds *XVII* and *XVIII* may arise by three paths (Scheme 3). One (*A*) of them is analogous to dimerisation of 4-isopropenylphenol *XIII* in weakly acidic media[5]. The second mechanism (*B*) is based on the observation that 2-alkylidene--3,5-cyclohexadienones (*ortho*-quinonemethides) afford chromanes with reactive dienophiles[6]. The dimerisation according to the third mechanism (*C*) represents a Michael addition of the vinylogous oxo-carbanion to the methide carbon atom of the quinonoid system. The latter mechanism is analogous to the addition of carbanions to quinonemethides[7].



SCHEME 2



SCHEME 3

The mechanism (*A*) was easily eliminated since no dimerisation of 4-isopropenyl-2-methoxyphenol (*XIV*) occurred in a solution of acetic acid and triehylamine. The acidity of the reaction medium is not obviously sufficient for the protonation of the double bond of the phenol *XIV*. The choice between mechanisms (*B*) and (*C*) was attempted by reaction of the quinonemethide *X* with the isopropenylphenol *XIV*, labelled with deuterium in the side chain (0·4% $^2H_0$, 3·5% $^2H_1$, 13·2% $^2H_2$, 30·0% $^2H_3$, 35·6% $^2H_4$, 17·3% $^2H_5$). The isolated dimer *XVII* contained exclusively molecules with at most two atoms of deuterium (13·0% $^2H_1$, 4·0% $^2H_2$). As proved by this result, the indane *XVII* is virtually formed by addition of the isopropenylphenol *XIV* to the quinonemethide *X* but the high percentage of nonlabelled molecules might indicate participation of the mechanism (*C*). The absence of molecules with more than two atoms of deuterium and increased content of monodeuterated particles in the product in contrast to the starting phenol *XIV* leads us to the idea that the noncyclic carbonium ion *XX* is readily transformed to the dimeric quinonemethide *XXI* (Scheme 3) which is capable of exchanging deuterium with the protic medium in a similar manner as the monomeric quinonemethide *X*.

EXPERIMENTAL

Melting points are uncorrected. Analytical samples were dried at room temperature for 8 h at 0·01 Torr. Purity of substances was checked by thin-layer chromatography on silica gel.

Reaction of Quinonemethides *I*—*IV* with Triethylammonium Acetate

To a solution of the appropriate quinonemethide (1 mmol) in chloroform (50 ml) there was added acetic acid (2 ml) and 0·01M solution of triethylamine in chloroform (0·01 ml). The mixture was

TABLE I
Acetates of Substituted Benzyl Alcohols

Acetate	M.p., °C	Yield, %	Formula (m.w.)	Calculated/Found		
				% C	% H	% Br
V	29—32	98	$C_{10}H_{12}O_4$ (196·2)	61·22 61·57	6·16 6·37	— —
VI	218—220	93	$C_{10}H_{11}BrO_4$ (275·1)	43·66 43·57	4·03 4·12	29·05 29·04
VII	74—75	95	$C_{11}H_{14}O_4$ (210·2)	62·84 62·82	6·71 6·77	— —
VIII	110—112	97	$C_{11}H_{13}BrO_4$ (289·1)	45·69 46·04	4·53 4·69	27·64 27·87

kept at room temperature until colourless, washed with water and saturated aqueous sodium hydrogen carbonate, dried over anhydrous magnesium sulfate, and evaporated under diminished pressure. The residual solid was recrystallised from a mixture of ether and light petroleum or ether and ethanol. In this manner, the quinonemethides *I*—*IV* were converted to the acetates *V*—*VIII* (Table I).

Isomerisation of Quinonemethides *IX* and *XII* with Triethylammonium Acetate

Reaction conditions were the same as in the preceding paragraph. The quinonemethide *IX* afforded 92% of 4-isopropenylphenol (*XIII*), m.p. 79—80°C; reported[8], m.p. 80·5°C. The quinonemethide *XII* yielded 95% of 2-bromo-4-isopropenyl-6-methoxyphenol (*XVI*) which crystallised with difficulty and was therefore converted in the usual manner to the benzoate, m.p. 74—75°C (ether–light petroleum). For $C_{17}H_{15}BrO_3$ (347·2) calculated: 58·80% C, 4·35% H, 23·01% Br; found: 58·25% C, 4·12% H, 22·98% Br. NMR spectrum: 2·13 (s, 3 H), 3·85 (s, 3 H), 5·13 (s, J = 1·3 Hz, 1 H), 5·35 (s, J = 1·3 Hz, 1 H), 7·01 (d, J = 2·0 Hz, 1 H), 7·29 (d, J = 2·0 Hz, 1 H), 7·35—7·75 (m, 3 H), 8·15—8·35 (m, 2 H).

Dimerisation of the Quinonemethide *X*

Reaction conditions were the same as in the preceding paragraph. In view of the difficult separability of the isomer *XIV* and dimer *XVII*, the mixture was benzoylated and the benzoates isolated by chromatography on silica gel in 6 : 1 light petroleum–ether. 4-Benzoyloxy-3-methoxy-1-isopropenylbenzene, m.p. 58—60°C (benzene–light petroleum). For $C_{17}H_{16}O_3$ (268·3) calculated: 76·10% C, 6·01% H; found: 76·22% C, 6·21% H. NMR spectrum: 2·15 (s, 3 H), 3·82 (s, 3 H), 5·10 (s, J = 1·4 Hz, 1 H), 5·35 (s, J = 1·4 Hz, 1 H), 7·8 (s, 3 H), 7·35—7·75 (m, 3 H), 8·15—8·30 (m, 2 H). 6-Benzoyloxy-1-(4-benzoyloxy-3-methoxyphenyl)-5-methoxy-1,3,3-trimethylindane, m.p. 146—148°C (ethanol). For $C_{34}H_{34}O_6$ (538·6) calculated: 75·81% C, 6·31% H; found: 76·22% C, 6·21% H. NMR spectrum: 1·09 (s, 3 H), 1·36 (s, 3 H), 1·675 (s, 3 H), 2·23 (d, J = 12·5 Hz, 1 H), 2·46 (d, J = 12·5 Hz, 1 H), 3·72 (s, 3 H), 3·83 (s, 3 H), 6·75—7·10 (m, 6 H), 7·30—7·70 (m, 6—7 H), 8·10—8·30 (m, 4 H).

Dimerisation of the Quinonemethide *XI*

Reaction conditions were the same as in the preceding paragraph. The mixture of the isomer *XV* and the dimer *XVIII* was separated by chromatography on silica gel in 5 : 1 light petroleum–ether. 4-Isopropenyl-2,6-dimethoxyphenol (*XV*), m.p. 27—28°C (light petroleum). For $C_{11}H_{14}O_3$ (194·2) calculated: 68·02% C, 7·26% H; found: 67·98% C, 7·22% H. 1-(4-Hydroxy-3,5-dimethoxyphenyl)-6-hydroxy-5,7-dimethoxy-1,3,3-trimethylindane (*XVIII*), m.p. 62—64°C (light petroleum). For $C_{22}H_{28}O_6$ (388·4) calculated: 68·02% C, 7·26% H; found: 68·22% C, 7·35% H. Mass spectrum: 388 (M^+), 373 (M^+-15), 219 (M^+-15-138).

Reaction of the Quinonemethide *X* with 2-(4-Hydroxy-3-methoxyphenyl)-1,1,3,3,3-pentadeuteriopropene

A solution of the quinonemethide *X* (90 mg) and the deuterated phenol *XIV* (0·4% $^2H_0$, 3·5% $^2H_1$, 13·2% $^2H_2$, 30·0% $^2H_3$, 35·6% $^2H_4$, 17·4% $^2H_5$) (90 mg) in chloroform was maintained at room temperature for 24 h. The dimer *XVII* was isolated as the benzoate, m.p. 146—147°C (undepressed on admixture with an authentic specimen) by chromatography on silica gel and contained 83·0% $^2H_0$, 13·0% $^2H_1$, and 4·0% $^2H_2$.

Isomerisation of Quinonemethides *IX*–*XII* with Triethylamine

A solution of the appropriate quinonemethide (1 mmol) in chloroform (20 ml) was treated with triethylamine (1 ml). The yellow reaction mixture was kept at room temperature until colourless and processed as usual to afford the corresponding isopropenylphenols *XIII*–*XVI* in an almost quantitative yield.

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REFERENCES

1. House H. O., Traficante D. D., Evans R. A.: J. Org. Chem. *28*, 348 (1963).
2. Hultzsch K.: *Chemie der Phenolharze*, p. 72. Springer, Berlin 1950.
3. Adler E., Björquist K. J.: Acta Chem. Scand. *7*, 561 (1953).
4. Forsén S., Nilsson M.: *The Chemistry of the Carbonyl Group* (J. Zabicky, Ed.), Vol. 2, p. 157. Interscience, London 1970.
5. Kahovec J.: Chem. listy *65*, 397 (1971).
6. Bolon D. A.: J. Org. Chem. *35*, 3666 (1970).
7. Becker H. D.: J. Org. Chem. *32*, 4093 (1967).
8. Vajser V. L., Rjabov N. D., Pirjatinskij B. M.: Dokl. Akad. Nauk SSSR *132*, 349 (1960).

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