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CONDENSATION OF VINYLCYCLENOLS WITH CYCLIC 1,3-DIKETONES

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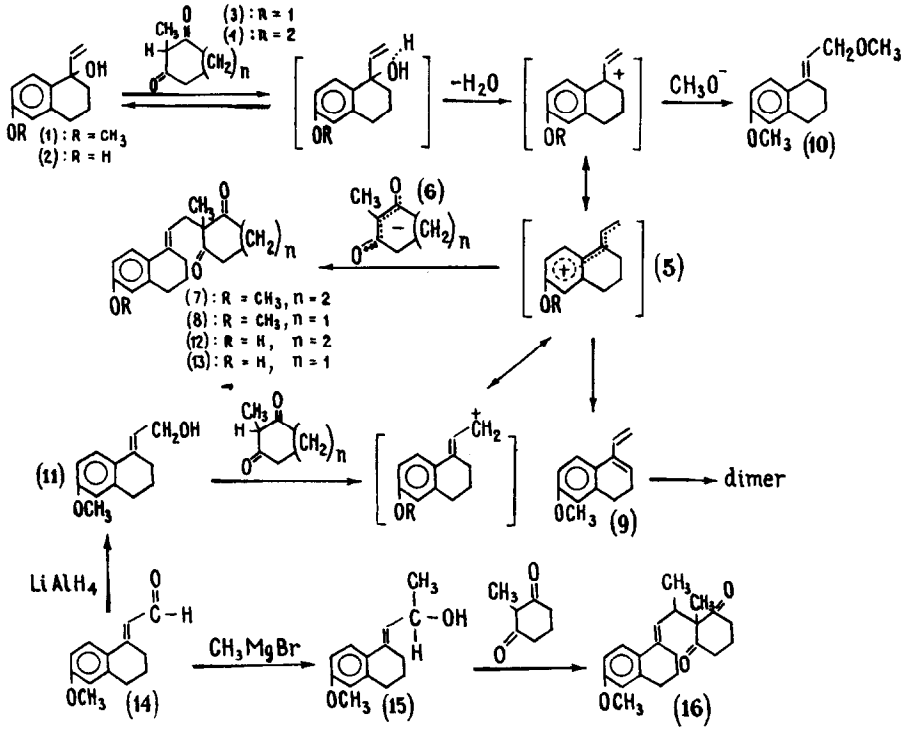
Some years ago[1-3] we described a new reaction, the condensation of the vinylcyclenols (1) and (2) with the cyclic 1,3-diketones (3) and (4) widely used by us and by others in the total synthesis of estrone, D-homo-estrone and their analogs[2-9]. However the scope and limits of application of the reaction remained unclear, although we have on several occasions discussed a probable mechanism[10].



Recent interest in this point[11] prompts us to set out our own findings, which we believe fully confirm our earlier suggestion. Initially the β-diketone, being a weak acid, protonates the carbinol (1); loss of water then occurs to produce the resonance-stabilised cation (5), which reacts with the β-diketone enolate anion (6), possibly via an intermediate 6-membered transition state, to yield the 8,14-seco-diketone (7) or (8).

In support of this view, we have found that the reaction is inhibited by an excess of base, a result also reported by Kuo et al[12]; presumably protonation of the carbinol cannot then occur. Mechanisms involving vinylogous displacement of the hydroxyl group by the β-diketone anion are therefore unacceptable. The most favourable conditions for the reaction are clearly those in which the concentration of the cation (5) is comparable with that of the β-diketone anion (6). Hence, although the carbinol (1) will react directly with diketones (3) or (4) in methanol, better results can be obtained by the addition of some base, which increases the concentration of (6) by buffering the dione, and reduces the formation of by-products from the excess of (5) which tends to be present under the more acidic conditions.

On the other hand, the more acidic the dione, the greater will be its degree of dissociation under the conditions of the condensation. Thus with the more acidic 2-methylcyclopentanedione-1,3 (3) the reaction is complete in 2 hrs., while with 2-methylcyclohexanedione-1,3 (4) it proceeds for 10-15 hrs. at 20°C, or 2 hrs. on boiling. This difference in reaction rates was observed in methanol, tert-butanol or p-xylene.

Further evidence in support of the cation (5) as an intermediate is the isolation of 1-vinyl-6-methoxy-3,4-dihydronaphthalene (9), and of dimers derived from it, when the compound (1) is condensed with β-diketones in non-polar solvents such as xylene. It presumably arises by deprotonation of (5). If the reaction is carried out in methanol, however, the main side-reaction appears to be the formation of 1-(β-methoxyethylidene)-6-methoxytetralin (10), n_D^{20} 1,5412 by addition of methanol to the intermediate (5). The structure of this by-product was confirmed spectrometrically: IR spectrum

1610, 1572 (aromatic ring) cm^{-1}. NMR spectrum: 3,23 (OCH_3); 3,63 (OCH_3); 3,9 and 4 ($-OCH_2-$); 5,7; 5,8; 5,9 (vinyl proton, triplet) ppm. Mass spectrum: (m/e) 218 (M^+); 187 ($M^+ -OCH_3$); 186 ($M^+ -CH_3OH$).

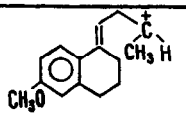
We have also shown that the diene (9), produced as a by-product above, is not an intermediate in the condensation. Similarly β-(6-methoxytetralidene-1)-ethanol (11) is not a intermediate; it does indeed react with β-diketones (3) and (4) in methanol, tert-butanol and xylene, but 2-3 times more slowly than the tertiary benzylic carbinol (1). Presumably the requisite carbonium ion (5) is less readily formed from the primary carbinol (11), because of the lower mobility of the hydroxyl group.

In this connection it is worth noting that the condensation of 1-vinyl--6-hydroxytetralol-1[13] (2) with β-diketones proceeds much faster than that of the 6-methoxy carbinol (1), the seco-diketones (12) and (13) being produced. We may imagine here that the possibility of anion formation at the 6-position greatly assists the departure of the 1-hydroxy group.

Finally, the action of methyl magnesium bromide on 6-methoxy-1-tetralideneacetaldehyde (14) gave β-(6-methoxytetralidene-1)-isopropanol (15), m.p. 82-84°. λ_{max} 265 mμ (log ε 4,3). IR spectrum 3290(OH), 1615 cm^{-1}. This compound also reacted with 2-methylcyclohexanedione-1,3 (4) on boiling in methanol (with or without added alkali) to yield 3-methoxy-$\Delta^{1,3,5(10),9(11)}$-12-methyl-8,14-seco-D-homoestratetraenedione-14,17a (16), m.p.107-8°. λ_{max} 264 mμ (log ε 4,3). IR spectrum 1724, 1692 (β-diketone), 1608 cm^{-1}. Mass spectrum: (m/e) 326 (M^+), 201*.

The by-product β-(6-methoxytetralidene-1)-isopropanol methyl ether was isolated as an oil. IR spectrum 1610, 1500 cm^{-1}. NMR spectrum: 1,3 ($-CH_3$), 3,25 ($-OCH_3$), 3,85 ($-OCH_3$), 5,72, 5,85 (vinyl protons, doublet) ppm. Mass spectrum: (m/e) 232 (M^+), 200 ($M^+ -CH_3OH$).

The condensation of carbinol (15) with β-diketones appears also to proceed by the mechanism we have discussed above.

* m/e. 201-fragment 

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