Intramolecular Participation by Enolate Anions in the Cleavage of Aryl Esters of Mesitoic Acid; Carbon–Carbon Bond Formation in Aqueous and Alcoholic Solvents

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The mechanistic criteria which determine whether nucleophilic participation by the acetyl group in the cleavage of aryl esters of mesitoic acid will occur through oxygen or carbon are discussed. Participation through oxygen, which must be preceded by formation of a tetrahedral adduct at the carbonyl group is replaced by participation through carbon even in hydroxylic solvents, when formation of the adduct is prevented in the esters 2-acetylphenyl mesitoate (I) and 1-acetyl-2-naphthyl mesitoate (IV).

UNDER basic aqueous conditions, 2-acetylphenyl mesitoate (I) hydrolyses to yield mesitoic acid and 2-hydroxyacetophenone[1] (Scheme 1, route A). The reaction has been shown to proceed *via* intramolecular nucleophilic participation by the conjugate base of the solvated acetyl carbonyl group, both by the observation of a rate enhancement of 130 compared with the 4-isomer and by the isolation of the dimethyl acetal of 2-hydroxyacetophenone (II) when the reaction was repeated in anhydrous methanol (Scheme 1, route B). Under certain basic conditions, keto-substituted esters can also rearrange to β-diketones.[2] The reaction occurs *via* the enolate anion acting as a nucleophile through carbon at the ester carbonyl group in an intramolecular Claisen condensation. For example, ω-acylbutyric esters rearrange to cyclohexanediones in the presence of sodium ethoxide.[2,3] Attack by ethoxide ion at the ester carbonyl group merely regenerates starting ester while intramolecular participation by the adduct of the keto-group with ethoxide ion does not appear to be important.

Both 2-acetylphenyl mesitoate (I)[4] and 2-acetylphenyl benzoate[5] have been shown to isomerise to the corresponding β-diketones. In both cases the reactions were carried out under non-nucleophilic conditions using a strong base in an aprotic solvent (powdered sodium in dry ethyl formate[4] and potassium carbonate in toluene[5]).

Recently, Bowden and Last have examined the alkaline hydrolysis of methyl 8-acyl- and 8-aroyl-1-naphthoates.[6] They found that whereas with the 8-formyl and 8-(3- and 4-substituted benzoyl) esters the hydrolysis was catalysed by the neighbouring carbonyl group, with the 8-acetyl, 8-propionyl, and 8-isobutyryl esters catalysis occurred by the neighbouring carbon acid.

The most probable competitive reactions to intramolecular β-diketone formation in the treatment of acetyl substituted esters with base under protic conditions are intermolecular attack by nucleophile at the ester carbonyl group and nucleophilic addition to the keto-carbonyl group followed by intramolecular participation of the adduct. This paper describes two attempts to suppress these competing alternatives and

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[1] H. D. Burrows and R. M. Topping, *J. Chem. Soc.* (*B*), 1970, 1323.

[2] For examples see W. J. Hickinbottom, 'Reactions of Organic Compounds,' Longmans, London, 3rd edn., 1959, pp. 363—366.

[3] J. C. Bardhan, N. C. De, and B. B. Datta, *J. Chem. Soc.*, 1951, 3195.

[4] C. T. Davis and T. A. Geissman, *J. Amer. Chem. Soc.*, 1954, **76**, 3507.

[5] W. Baker, *J. Chem. Soc.*, 1933, 1381.

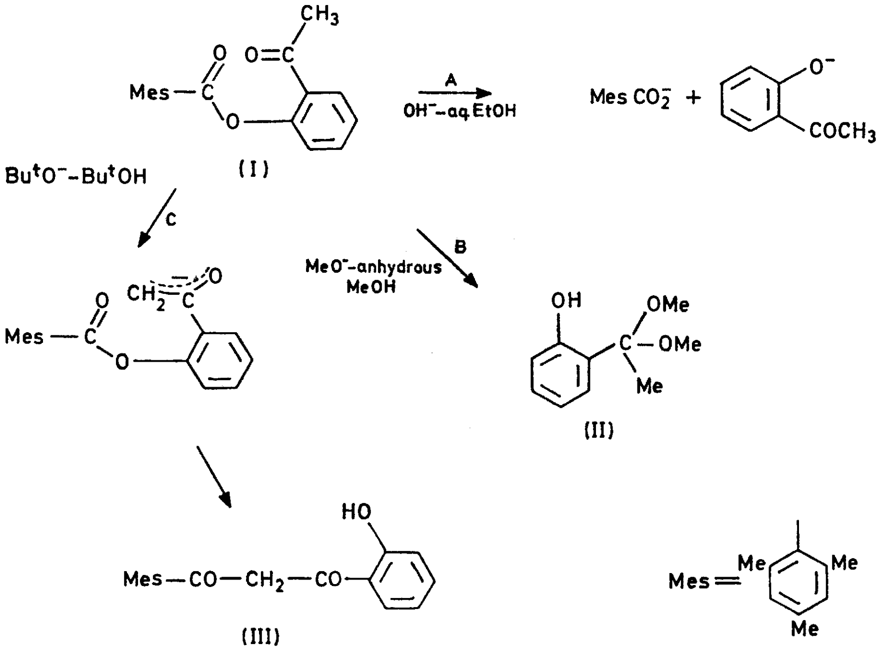
[6] K. Bowden and A. M. Last, *Chem. Comm.*, 1970, 1315 *J.C.S. Perkin II*, 1973, 345, 351, 358.

to allow participation of the acetyl group through its *enolate* form even in protic solvents.

RESULTS AND DISCUSSION

(a) *The Reaction of 2-Acetylphenyl Mesitoate with Potassium t-Butoxide in t-Butanol.*—The first attempt to stimulate nucleophilic participation of the acetyl group through carbon required the use of a strongly basic but weakly nucleophilic reagent. Potassium t-butoxide by virtue of its strong basicity,[7,8] bulky anion, and tendency to form ion pairs in solution[7] appeared to meet these criteria. Addition of a small amount of potassium t-butoxide to a solution of 2-acetylphenyl mesitoate (I) in t-butanol (10^{-4}M) at 30° resulted in a rapid change in the u.v. spectrum (complete within 10 min; isosbestic point at 285 nm). The final spectrum possessed strong absorption bands above 300 nm, suggesting the presence of a phenolic species. A preparative scale reaction of ester (I) with potassium t-butoxide in t-butanol gave, upon acidification, a yellow solid, m.p. 73—74°. The results of i.r., u.v., n.m.r., and mass spectral analysis all indicated that the product formed was the β-diketone (III) (lit.,[4] m.p. 73·5°). No indication of the formation of mesitoic acid (a product of intramolecular acetyl group participation through oxygen) was observed. Isolation of (III) clearly supports a mechanism in which the t-butoxide ion removes a proton from the acetyl group to give an enolate anion which then acts as a nucleophile, through carbon, at the ester carbonyl group (Scheme 1, route C). This process is mechanistically analogous to the rearrangement of 2-carbamoylphenyl mesitoate to *N*-salicoylmesitamide[9] and also to intramolecular nucleophilic attack by the carboxylate anion observed upon base catalysed methanolysis of 2-carboxyphenyl mesitoate.[10]

(b) *The Reaction of 1-Acetyl-2-naphthyl Mesitoate with Potassium Hydroxide in 47·5% Ethanol–Water.*—Nucleophilic participation of the acetyl group of ester (I) through oxygen must be preceded by formation of the tetrahedral adduct.[1] The second attempt to observe participation through carbon was based upon hindrance to formation of such an adduct. Nucleophilic attack at a carbonyl group occurs preferentially from a direction perpendicular to the plane containing the group.[11] In the ester 1-acetyl-2-naphthyl mesitoate (IV), the acetyl group is forced out of the plane of the aromatic nucleus by the adjacent *ortho*-substituents (the *peri*-hydrogen and the mesitoate ester group), making the addition of nucleophiles to the acetyl carbonyl group correspondingly difficult. The reaction of 1-acetyl-2-naphthyl mesitoate (IV) with potassium hydroxide was readily followed spectrophotometrically over the range 250—450 nm [ester (IV) (10^{-4}M), KOH (1·0M), 47·5% ethanol–water, μ = 1·0M, 30°, 10 mm cells, $t_{\frac{1}{2}}$ 10 min] and was found to follow good pseudo-first-order kinetics to >80% reaction. T.l.c. on the products (2% acetic acid–benzene) indicated the presence of three components. Components R_F 0·14 and 0·26 corresponded to mesitoic acid and 1-acetyl-2-naphthol respectively. The particular constitution of ester (IV) led us to expect the β-diketone (V) as the third com-



SCHEME 1

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[7] D. J. Cram, 'Fundamentals of Carbanion Chemistry,' Academic Press, New York, 1965, p. 37.

[8] L. F. Fieser and M. Fieser, 'Reagents for Organic Synthesis,' Wiley, New York, 1967, p. 911.

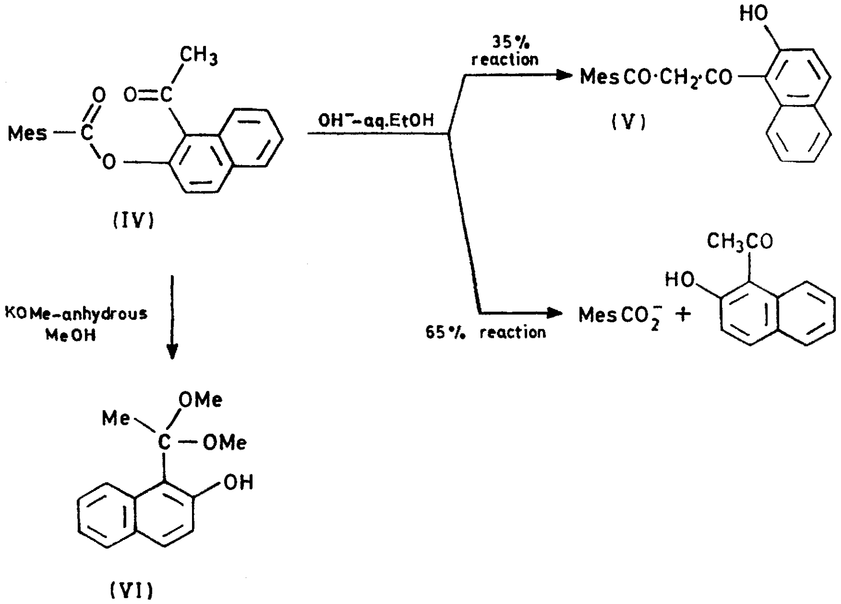
[9] R. M. Topping and D. E. Tutt, *J. Chem. Soc.* (*B*), 1967, 1346.

[10] H. D. Burrows and R. M. Topping, *Chem. Comm.*, 1970, 1389.

[11] M. L. Bender, *Chem. Rev.*, 1960, **60**, 60.

ponent even though the reaction had occurred under aqueous conditions. This result was verified by preparing the β-diketone (V) by an unambiguous route [reaction of ester (IV) with KOH in anhydrous pyridine] and by running a comparative t.l.c. Authentic β-diketone (V) gave a spot on t.l.c. of R_F value identical with that of the unknown component, both with 2% acetic acid–benzene (R_F 0·44) and 2% acetic acid–chloroform (R_F 0·90) as eluants.

Establishment of the identities of the three products of reaction of 1-acetyl-2-naphthyl mesitoate with potassium hydroxide in aqueous ethanol allowed optical matching of the final spectrum of the reaction with the spectrum of a mixture of mesitoic acid, 1-acetyl-2-naphthol and the β-diketone (V), under the appropriate conditions. A best fit was obtained corresponding to 65% products of hydrolysis and 35% product of isomerisation (Scheme 2).



SCHEME 2

Treatment of the formation of products as a case of parallel pseudo-first-order reactions resulted in apparent first-order rate constants for the hydrolysis of ester (IV) to 1-acetyl-2-naphthol and mesitoic acid (k_{obs}^{hydr} 6·2 × 10^{-4} s^{-1}) and for the isomerisation of ester (IV) to the β-diketone (V) (k_{obs}^{isom} 3·3 × 10^{-4} s^{-1}).

That at least some of the hydrolytic product in the solvolysis of ester (IV) arose *via* intramolecular participation by the conjugate base of the solvated acetyl group was indicated by the results of the reaction of the ester (IV) with potassium methoxide in anhydrous methanol. A principal product of this reaction, isolated by column chromatography, was the dimethyl acetal of 1-acetyl-2-naphthol (VI) (Scheme 2).

In the reaction of the less hindered ester 2-acetylphenyl mesitoate (I) with hydroxide ion in aqueous ethanol, mesitoic acid, and 2-hydroxyacetophenone accounted for 100% of the products.

EXPERIMENTAL

Treatment of Ester (I) *with Potassium t-Butoxide in t-Butanol. Preparation of* 1-(2-*Hydroxyphenyl*)-3-*mesityl-propane*-1,3-*dione* (III).—Potassium t-butoxide (0·5 g, 0·0045 mol) was added to a solution of ester (I) (0·112 g, 4·0 × 10^{-4} mol) in t-butanol (5 ml). The mixture was set aside for 0·5 h at room temperature, acidified with acetic acid mixed with crushed ice, and allowed to crystallise overnight. The solid was filtered off and washed with water. Recrystallisation from methanol gave yellow crystals (0·071 g, 63%), m.p. 73—74°, *m/e* 282 (M^+) and 147 (acylium ion), $\nu_{max.}$ (Nujol) 1620, 1610, and 1580 cm^{-1}.

These results suggested the product to be the β-diketone (III) (lit.,[4] m.p. 73·5—74°). The u.v. spectrum supported this, $\lambda_{max.}$ (47·5% ethanol–water) 318 (ε 13,900 l mol^{-1} cm^{-1}) and 348 nm (15,200), and altered on addition of base to give $\lambda_{max.}$ 350 nm (ε 20,000 l mol^{-1} cm^{-1}). The n.m.r. spectrum (CCl_4) showed bands at τ −1·93 (s), 2·3—3·4 (m), 3·80 (s), and 7·68 (s) in the ratio 1 : 6·2 : 1 : 8·9. The peak at τ −1·93 disappeared on adding D_2O. This spectrum appears to indicate keto–enol tautomerism as has been observed in other β-diketones, *e.g.* acetylacetone.[12]

Preparation of 1-*Acetyl*-2-*naphthyl Mesitoate* (IV).—Mesitoyl chloride (2·0 g, 0·011 mol) was added to 1-acetyl-2-naphthol (prepared by Fries rearrangement of 2-naphthyl acetate [13]) (2·6 g, 0·014 mol) in anhydrous pyridine (10 ml) and set aside at room temperature for 36 h. The mixture was acidified with HCl, extracted with ether, and the ether removed. Recrystallisation of the resulting solid from diethyl ketone–methanol–water gave yellow *crystals* (3·4 g, 95%), m.p. 178·5—180° (Found: C, 79·15; H, 6·15. $C_{22}H_{20}O_3$ requires C, 79·5; H, 6·0%), $\nu_{max.}$ (Nujol) 1740 and 1720 cm^{-1} (C=O), *m/e* 332 (M^+) and 147 (mesityl

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[12] See for example J. R. Dyer, 'Applications of Absorption Spectroscopy of Organic Compounds,' Prentice-Hall, Englewood Cliffs, 1965, p. 92.

[13] K. Fries, *Ber.*, 1921, **54**, 711.

acylium ion), τ ($CDCl_3$) 1·9—2·8 (m), 3·17 (s), 7·39 (s), 7·53 (s), and 7·68 (s) in the ratio 6 : 2 : 3 : 6 : 3.

Preparation of 1-(2-*Hydroxy*-1-*naphthyl*)-3-*mesitylpropane*-1,3-*dione* (V).—Ester (IV) (0·1 g, 3×10^{-4} mol) was heated under reflux for 25 h with potassium hydroxide (0·3 g, $5{\cdot}4 \times 10^{-3}$ mol) in anhydrous pyridine (3 ml). The mixture was acidified with ice-cold acetic acid. The resulting yellow solid was filtered, washed with dilute hydrochloric acid, and then with water before crystallisation from aqueous methanol. Recrystallisation from aqueous methanol gave a dark brown, microcrystalline *solid* (0·095 g, 95%), m.p. 177—178° (Found: C, 79·35; H, 6·35. $C_{22}H_{20}O_3$ requires C, 79·5; H, 6·05%), $\nu_{max.}$ (Nujol) 1625, 1610, and 1585 cm^{-1}, *m/e* 332 (M^+) and 147 (mesityl acylium ion), τ (CCl_4) −1·62 (s), 1·8—2·95 (m), 3·07 (s), 3·70 (s), 7·61 (s), and 7·71 (s) in the ratio 1 : 8·35 : 2·35 : 0·94 : 7·94 : 2·71. The peak at τ −1·62 disappeared on addition of D_2O. It was thought that in β-diketone (V) as in β-diketone (III) some keto–enol tautomerism was occurring.

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