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CYCLIZATION OF ENOLESTERS OF *o*-ACYLOXYPHENYL ALKYL KETONES—II[1]

A CONTRIBUTION TO THE MECHANISM OF THE REACTION

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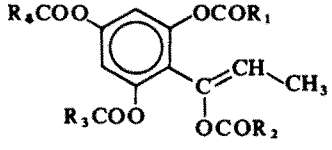
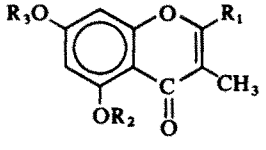
Abstract—The base catalysed cyclization of the enolesters of *o*-acyloxyphenyl alkyl ketones[1] probably involves the Baker–Venkataraman type[2] reaction only and the simultaneous occurrence of a Claisen–Haase rearrangement[3] is unlikely. In the presence of aqueous alkali the enolacetate gives a carbanion and the latter reacts with the neighbouring ester group resulting in ring closure to a γ-pyrone.

IN a recent publication,[1] we reported the base-catalysed cyclization of enolesters of *o*-acyloxyphenyl alkyl ketones (e.g. 1a → IIa) and suggested that the mechanism of the process is similar to that of the Baker–Venkataraman reaction.

In order to establish whether the *o*-acyloxy group or the acyl group of the enolester takes part in the cyclization, since a Claisen–Haase rearrangement[3] would give the same intermediate β-diketone as the Baker–Venkataraman transposition, esters containing different kinds of acyl groups were cyclized and the products identified. The cyclization of 2-(α-acetoxypropenyl)benzene-1,3,5-triol tripropionate (Ic) gave 2-ethyl-3-methyl-5,7-dihydroxychromone (IIb). As the m.p.[4] of this compound, is only 8–10° lower than that of 2,3-dimethyl-5,7-dihydroxychromone (IIa, the product of a possible Claisen–Haase reaction) and since no definite depression of the m.p. could be observed on admixture of the two chromones (IIa and IIb), the Claisen–Haase reaction could not be excluded.





I a: $R_1 = R_2 = R_3 = R_4 = CH_3$
b: $R_1 = R_2 = R_3 = R_4 = C^{14}H_3$
c: $R_1 = R_3 = R_4 = C_2H_5$, $R_2 = CH_3$
d: $R_1 = R_3 = R_4 = CH_3$, $R_2 = C^{14}H_3$
e: $R_1 = R_3 = R_4 = C_2H_5$, $R_2 = C^{14}H_3$
f: $R_1 = C_6H_5$, $R_2 = R_3 = R_4 = CH_3$

IIa: $R_1 = CH_3$, $R_2 = R_3 = H$
b: $R_1 = C_2H_5$, $R_2 = R_3 = H$
c: $R_1 = C^{14}H_3$, $R_2 = R_3 = H$
d: $R_1 = C_6H_5$, $R_2 = R_3 = H$
e: $R_1 = CH_3$, $R_2 = H$, $R_3 = CH_3CO$
f: $R_1 = CH_3$, $R_2 = R_3 = CH_3CO$

Similarly, the evidence obtained from the cyclization of a compound in which the carbonyl group had been esterified with labelled acetic acid (Id) was indefinite. If the reaction were solely of the Baker–Venkataraman type, no radioactivity should be present in the cyclization product obtained from Id. The experiment showed, however,

that the resulting chromone was radioactive, although the activity was considerably lower than the initial ester.[4] This result may indicate: (1) that both reactions occurred, or (2) that during the conversion of phloropropiophenone-triacetate (III) into the enolacetate, the inactive acetyl groups present in the molecule exchanged, in part, with the labelled acetyl groups.

A more definite result was obtained by the cyclization of 2-(α^{14}-CH_3-acetoxypropenyl)benzene-1,3,5-triol tripropionate (Ie) which yielded a product with the same m.p. as 2-ethyl-3-methyl-5,7-dihydroxychromone (IIb). If the acyl group of the hydroxyl was involved in ring formation, the chromone would be radioactive, and have the same m.p. as IIa. Although this experiment provided evidence for the participation of the *o*-acyl group, the radioactivity of the product (6·6–39·5%, based on the activity of the labelled initial enol acetate) rendered the result ambiguous. Again, the concurrence of the Baker–Venkataraman and Claisen–Haase mechanisms was indicated, but the possibility of an acyl exchange reaction giving rise to radioactive impurities such as IIc in the chromone could not be excluded IIb. The latter became more probable, when after prolonged reaction between phloropropiophenone triacetate and radioactive acetic anhydride, a higher radioactivity was found in the resulting ester and chromone. This fact supported the Baker–Venktataraman mechanism and an experiment in which If yielded a mixture of IIa and IId, did not contradict this mechanism since the formation of IIa is of no consequence, but that of the flavone, IId, could only be explained by the Baker–Venkataraman mechanism.

The enolacetate of desoxybenzoin hydrolysed under the conditions of the above cyclization without giving evidence of the Claisen–Haase reaction having taken place. This is in agreement with Wheeler's earlier observations[3] and with the view that the cyclization of the enol esters of *o*-acyloxyphenyl alkyl ketones is not accompanied by a Claisen–Haase reaction.

All these results support the Baker–Venkataraman mechanism.

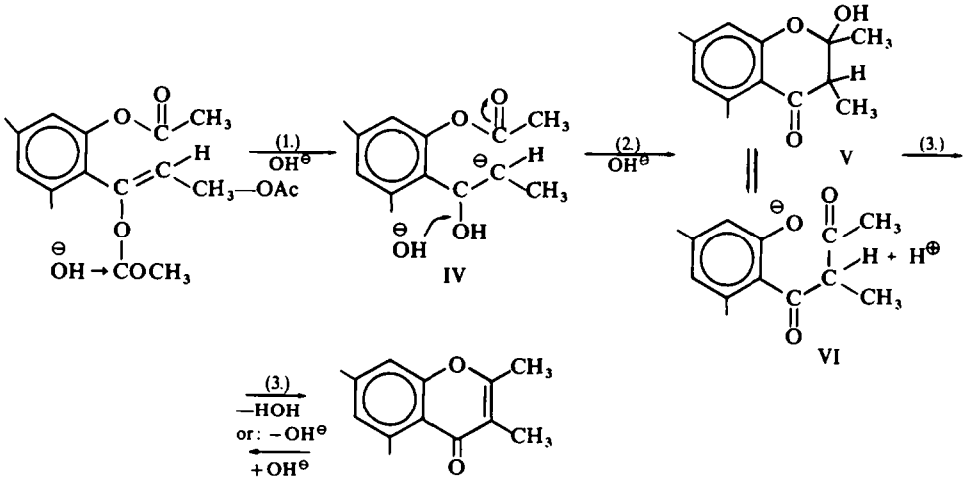
The cyclization of 2-(α-acetoxypropenyl)benzene-1,3,5-triol triacetate (Ia), used as a model, occurs in aqueous and non-aqueous media with a variety of bases. In the absence of water, the strength of the base determines its activity. The weakest base tried was pyridine, which was ineffective when heated under reflux either alone or in the presence of acetic anhydride; but the cyclization could be achieved by heating (in a sealed tube) at 160° for 2–3 hr but the chromone suffered partial deacetylation to IIe. A similar result was obtained using triethanolamine as base. In the presence of triethylamine or guanidine, at 155–160°, only IIa was formed, but if the enol acetate was fused with sodium acetate at 190° for 2 hrs, the product was IIe.

In aqueous medium, the reaction takes place more readily and always yielded IIa. A 2M solution of sodium hydroxide in aqueous ethanol converted a 0·05M solution of Ia into IIa in 2–3 min giving an over 80% yield. Lithium hydroxide proved even more effective, a 0·1 molar concentration producing the same yield in the same time.

In order to determine whether the enolester structure is a prerequisite of cyclization, 2,4,6-triacetoxypropiophenone (III), which does not contain the enol ester structure, was compared with the corresponding enolacetate (Ia). The former compound underwent a Baker–Venkataraman reaction in anhydrous medium, e.g. in pyridine in the presence of potassium hydroxide at the boiling point, or with pyridine alone in a sealed tube heated to 155–165° for 3 hr. The product suffered partial deacetylation, and a mixture of IIa and IIe was obtained. If IIf is an intermediate in the reaction

this would account for the deacetylation, since it was proved that IIf undergoes partial deacetylation under identical conditions. Using triethylamine as the better base to effect the Baker–Venkataraman reaction, or KOH, it was found that in aqueous alkaline medium hydrolysis occurred and at room temperature phloropropiophenone was obtained, whereas elevated temperatures caused further decomposition to phloroglucinol and propionic acid. As under similar conditions the enol acetate (Ia) cyclized to the chromone giving an excellent yield, there is no doubt that ring closure to chromones in aqueous alkaline medium requires the presence of the enolic ester structure.

These experimental results may be interpreted as follows: In the case of 2,4,6-triacetoxypropiophenone (III) the attack of the hydroxyl ion preferably at the sites of the phenolacetate groups instead of the α-hydrogen atom, resulted in hydrolysis instead of formation of a carbanion. In the case of Ia, however, the attack was at the site of the enolacetate, giving rise to the carbanion (IV; Step 1). The *trans* form of the latter then reacted directly with the neighbouring phenol acetate group (Step 2) to give the γ-pyrone ring *via* a hemiketal.



The sequence whether the hemiketal (V) is formed first or the diketone (VI) (or rather its tautomeric enol form), cannot be decided on the basis of the facts known at present. Rama Rao *et al.*[5] have suggested that in flavone syntheses by the Baker–Venkataraman method, compounds similar to phloropropiophenone give directly the hemiketal, which is converted into a carbanion by the loss of the C-3 proton, and this product is in equilibrium with the diketone. The carbanion gives the end product by E_1 elimination of the hydroxyl ion. In our experiments the diketone could not be isolated, and its presence was only concluded from the yellow colour appearing immediately and simultaneously with cyclization. However, the diketone which may give rise to such a yellow colour may also be formed as a secondary decomposition product of the chromone. Thus, alkaline treatment of IIa yields slowly phloropropiophenone and phloroglucinol, this process being also accompanied by the appearance of a yellow colour.

The mechanism proposed here deviates only slightly from the classical pattern of the Baker–Venkataraman reaction, in the manner in which the carbanion is generated. According to the classical view[8] a proton affixed to the α-carbon atom is eliminated to give the carbanion, whereas in our case the latter is directly formed from the enolic structure.

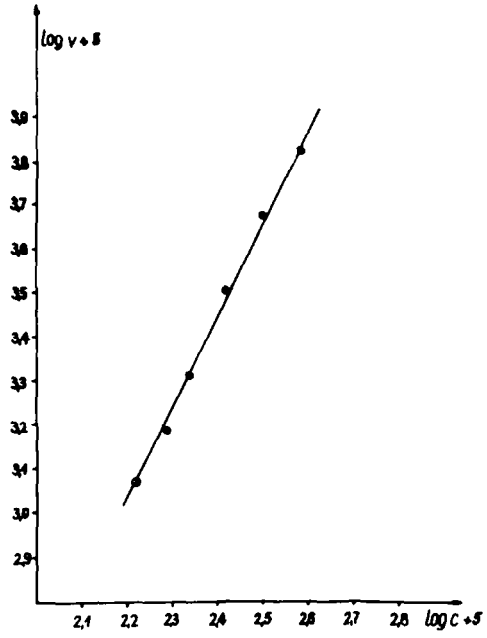


FIG. 1 Dependence of the rate of disappearance of Ia (v) on the concentration of Ia (van't Hoff's differential method applied to a run carried out at 30°).
[Ia] = 8·55 mole.l^{-1}.10^{-3}; [LiOH] = 9·0 mole.l^{-1}.10^{-3}
Solvent: CH_3OH—H_2O (1:1)

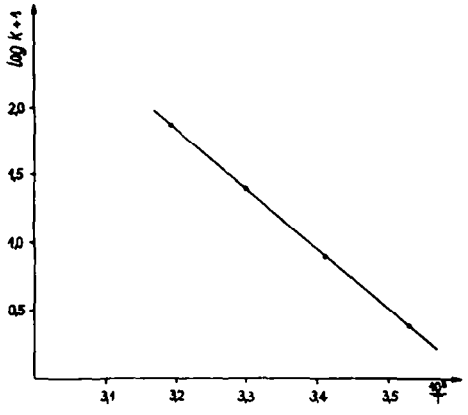
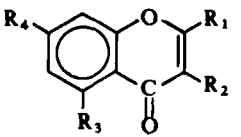


FIG. 2 Plots for obtaining the activation energy k = rate constant, T = absolute temperature.

TABLE 1. CHROMONES PREPARED FROM ENOL ESTERS



R_1	R_2	R_3	R_4	M.p. °C		Formula (M.w)		Found		Required	
				Found	Lit.			C	H	C	H
Me	Et	H	OH	244–245	238[6]	$C_{12}H_{12}O_3$	(204·2)	70·9	5·8	70·6	5·9
Me	Et	H	OAc	81–82		$C_{14}H_{14}O_4$	(246·3)	68·2	5·7	68·2	5·7
Me	Et	H	OPr	74–75		$C_{15}H_{16}O_4$	(260·3)	68·9	6·0	69·2	6·2
Et	Et	H	OH	208	208[7]	$C_{13}H_{14}O_3$	(218·3)	71·6	6·4	71·5	6·5
Et	Et	H	OAc	49–50		$C_{15}H_{16}O_4$	(260·3)	69·2	6·1	69·2	6·2
Et	Et	H	OPr	76–78		$C_{16}H_{18}O_4$	(274·3)	70·0	6·6	70·1	6·6
Pr	Me	OH	OH	192–193		$C_{13}H_{14}O_4$	(234·3)	67·0	5·8	66·7	6·0
Pr	Me	OAc	OAc	77		$C_{17}H_{18}O_6$	(318·3)	64·1	5·7	64·1	5·7
Pr	Et	OH	OH	165–166		$C_{14}H_{16}O_4$	(248·3)	67·6	6·4	67·7	6·5
Pr	Et	OAc	OAc	72–73		$C_{18}H_{20}O_6$	(332·3)	65·2	6·2	65·1	6·1

Polarographic measurement made during the cyclization are consistent with the above conception. Though there was some uncertainty in following the very rapid cyclization of Ia, it could be established that the overall reaction was of second order, the partial orders being 1 for the enolester as well as for the base used. A rate constant of 30·4 mole^{-1} min^{-1} (at 30°) and an energy of activation of about 19·5 kcal mole^{-1}

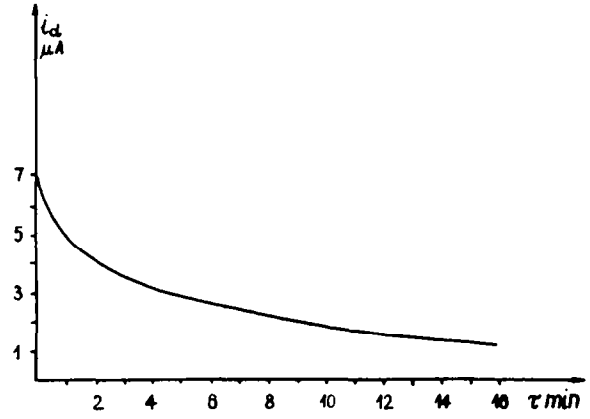


FIG. 3 Current intensity (i) *vs.* time (τ) at 30°.

were found (cf. Figs 1 and 2). The rate expression of the cyclization was found to be:

$$\text{d(chromone)}/\text{d}t = k[\text{enolacetate}]\,[\text{LiOH}]$$

Several further cyclizations of enolesters were made, some of which gave new chromones. These are shown in Table 1.

EXPERIMENTAL

M.ps were determined on a Koffler block and are uncorrected.

The *mixed esters* were prepared by heating the triacyloxyphenyl alkyl ketone ester with the corresponding acid anhydride under reflux for 15–18 min, in the presence of pyridine. The cyclizations were effected in NaOH aq. Details of both methods have been reported earlier.[1] If was prepared in oily form from 2-benzoyloxy-propiophenone[9] by refluxing it with Ac_2O for 3·5 hr in the presence of pyridine.

The C^{14}-labelled compounds were obtained as described in a previous publication.[4] The radioactivity of the enol esters and the cyclization products prepared from them are shown in Table 2.

The Baker–Venkataraman reactions

The compound (either III or Ia; 0·43 mmole) was heated in a base (pyridine, triethanolamine, triethylamine or guanidine, 1–3 ml) at 155–160° for 3 hr in a sealed tube of 8 ml. Water (10 ml) was added to the soln and the product was allowed to crystallize in a refrigerator.

Fusion with NaOAc was carried out by heating a pulverized homogeneous mixture of Ia (1·5 g, 4·3 mmole) and NaOAc (1·5 g) for 130 min at 190° in an ampoule of 5–10 ml, placed in an oil bath. After cooling the melt was treated with water (15 ml). The crystalline product (80%), m.p. 127–131°, recrystallized from EtOH as pure IIe, m.p. 141–142°, $FeCl_3$-test reddish-violet. (Found: C, 63·1; H, 4·7. $C_{13}H_{12}O_5$ (248·2) requires: C, 62·9; H, 4·9%).

Mixtures were examined and identified by TLC (Kieselgel G, benzene–$CHCl_3$–EtOH 50:48:2).

The product could be deacetylated to IIa in dry EtOH containing HCl, or a small quantity of NaOH; acylation gave the known compound IIf (cf. Canter[6]). The structure of IIe was proved by its positive $FeCl_3$ colour reaction, analysis, and by the IR and NMR spectra.

When the fusion was carried out with NaOAc at 200–210° for 4–4·5 hr, the product was IIa.

TABLE 2*

No.	Enol ester	M.p. °	imp/min mmole	Chromone obtained	M.p. °	imp/min mole
1	Ib (reflux time: 18 minutes)	97–98	1,367·000 (421%)	IIc	215–217	322·690 (102·7%)
2	Ie (reflux time: 15 minutes)	89–91	314·100 (96·9%)	IIb + (IIc)	203–204	21·359 (6·6%)
3	Ie (reflux time: 18 minutes)	88–91	324·100 (100·0%)	IIb + (IIc)	203–204	47·027 (14·5%)
4	Ie (reflux time: 210 minutes)	92–94	598·004 (184·5%)	IIb + (IIc)	203–207	128·003 (39·5%)

* The m.p. of pure IIc is 99–100°[1] and that of IIb 205–206°.[1] An activity of 324·100 imp/min was regarded as equivalent to the incorporation of one labelled C atom per mmole, based on the results of experiments Nos. 1, 2, 3. This was taken as 100%. The data were reproducible within ±5%. Radioactivity was measured with a Packard Tri-CARD liquid scintillation counter.

The action of aqueous alkali hydroxide on 2,4,6-*triacetoxypropiophenone* (III)

A soln of III (0·2 g; 0·65 mmole) in EtOH (1 ml) was mixed at 20° with 2N NaOH (7 ml). The mixture was allowed to stand for 18 min, acidified with 5N HCl, extracted with EtOAc, and the solvent evaporated.

Crude phloropropiophenone (0·15 g) was obtained, m.p. 162–174°, which showed no m.p. depression with an authentic sample.

If the reaction time was extended to 1 hr at 100°, phloroglucinol was produced. Under similar conditions, phloropropiophenone also gives phloroglucinol.

The action of aqueous alkalihydroxide on 2-(α-*acetoxypropenyl*)-*benzene*-1,3,5-*triol triacetate* (Ia)

The treatment of Ia with alkali in the same manner described for III, gave IIa in 72% yield. The product separated on acidification of the reaction mixture. Extraction of the mother liquor gave phloroglucinol. Prolonged treatment with alkali gave larger amounts of phloroglucinol, with a consequent decrease in the yield of the chromone.

Polarographic measurements

A Heyrovsky-type light recorder polarograph was used, with mercury bottom anode and dropping mercury cathode. The half-wave potential of Ia was −1·52 V, and that of IIa −1·82 V. The inert electrolyte used in the cell was 0·05M LiOH (1–6 ml); to this, solvent was added so that the final volume, after addition of the enol, was 20 ml in each case. The soln and the cell were deoxygenated by the passage of N_2 for 10 min. The voltage was adjusted to the potential corresponding to the section of the limiting current of the enol acetate (−1·575 V) and the required quantity of Ia was added as a 0·051M solution. A typical *i*-τ diagram is shown in Fig. 3.

The cyclization of the enol esters (Table 1) was accomplished in the manner described in our earlier experiments.[1]

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