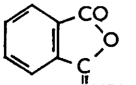
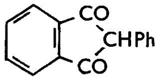
411. *The Rearrangement of Benzylidenephthalide to 2-Phenylindane-1,3-dione.*

By L. K. Creamer, A. Fischer, and J. Vaughan.

The above alkoxide-induced rearrangement has been examined. It is concluded that Eskola's assumption of the pseudo-ester (V) or (VI) as the key intermediate is incorrect and that the phthalide rearranges *via* the normal ester.

From studies[1-3] on the methoxide-catalyzed rearrangement of benzylidenephthalide (I) to 2-phenylindane-1,3-dione (II), Eskola concluded that the reaction proceeds, not through the anion (IV) of methyl *o*-phenylacetylbenzoate (III), but through the anion of the pseudo-ester (V), which was the only product he isolated from an acid-quenched reaction mixture. He showed also that, contrary to an earlier assumption,[4] the pseudo-ester is the main product of Fischer–Speier esterification of *o*-phenylacetylbenzoic acid and that its conversion into the indanedione (II) by methoxide ion yields the same rate constants and Arrhenius parameters as the phthalide rearrangement. These findings, however, neither preclude the choice of the ion (IV) * as the fruitful intermediate, nor establish the pseudo-ester anion in this role. In fact, other indirect evidence[7,8] accords with a rearrangement scheme involving methoxide attack at the carbonyl carbon of the phthalide


(I)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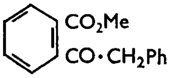
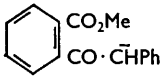
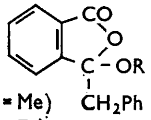

(III)


(IV)


(V: R = Me)
(VI: R = Et)

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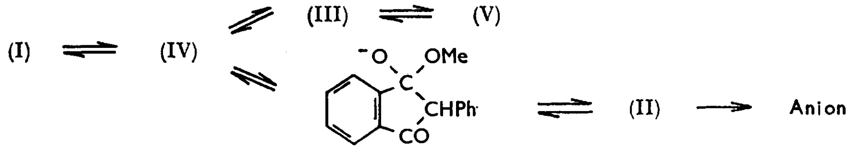
* An intermediate recently assumed by Shapiro *et al.*,[5] and similar to that suggested by Awad and Aly[6] for the rearrangement of benzylidenenaphthalide.

[1] Eskola, *Suomen Kem.*, 1947, **20***B*, 21.
[2] Eskola, *Suomen Kem.*, 1957, **30***B*, 12.
[3] Eskola, *Suomen Kem.*, 1957, **30***B*, 57.
[4] Nathanson, *Ber.*, 1893, **26**, 2576.
[5] Shapiro, Geiger, and Freedman, *J. Org. Chem.*, 1960, **25**, 1860.
[6] Awad and Aly, *J. Org. Chem.*, 1960, **25**, 1873.
[7] Siegel and Moran, *J. Amer. Chem. Soc.*, 1947, **69**, 1457; Filler and Hebron, *ibid.*, 1959, **81**, 391; Kenyon and Thaker, *J.*, 1957, 2531; Filler and Novar, *J. Org. Chem.*, 1960, **25**, 662.
[8] Black and Lutz, *J. Amer. Chem. Soc.*, 1953, **75**, 5995.

(I). Eskola's isolation of a pseudo-ester (V) from the reaction mixture may then be accounted for on the basis of a side-equilibrium involving (III) and (V):



The likely driving force is the ionization of the diketone (II); it is known[9] that if the indanedione is not stabilized by ionization, such reactions may be reversed.

Our first concern was with the apparent absence of an ion (IV) in the reaction mixture, indicated by Eskola's failure to isolate its conjugate acid (III). This ester, previously unknown, has been prepared readily from the parent acid and diazomethane, and its infrared spectrum and that of the pseudo-ester revealed the known characteristic differences. The spectra enabled us to determine one ester in the presence of the other, and to detect the presence of the phthalide (I). We thus found that the phthalide is immediately converted into the normal ester (III), whose concentration then decreases while that of the pseudo-ester (V) is built up quite rapidly to yield finally an equilibrium mixture of 4 : 1 in favour of the latter. We also examined the Fischer–Speier esterification of *o*-phenylacetylbenzoic acid; apart from the major product (V), a pure normal ester was isolated by fractional crystallization: as is often the case for normal and pseudo-ester pairs, the former is rather more soluble than the latter in alcohol[10] and that is why Eskola isolated only the pseudo-ester (V).

If it is the ion (IV) which rearranges to the diketone (II), then the normal ester should yield the diketone on treatment with pyridine. Further, if in the alkoxide–alcohol system the pseudo-ester is in equilibrium with the ion (IV) throught he normal ester and can rearrange to the diketone only by first being converted into the normal ester, then treatment of the pseudo-ester (V) with pyridine should not lead to the diketone (II). Both expectations were realized in practice. In addition, it was found that the phthalide did not rearrange with pyridine as the added base; thus the phthalide rearrangement as a whole is not subject to general base-catalysis.

We followed the kinetics of methoxide-catalyzed reactions at 20°, and found that the compounds (I), (V), and (III) yielded the same rate constants. Such equivalence was also found for the series in which the benzyl (or benzylidene) group carries a *p*-methoxy- or a *m*-chloro-substituent. These results support the suggestion of a side-equilibrium involving (III) and (V), the rate of interconversion being fast compared with that of rearrangement of the normal ester (III) to the diketone (II). The possibility that phthalide is present in measurable equilibrium with the esters appears to be ruled out by absence of characteristic phthalide peaks from the spectrum of the quenched reaction mixture. The major product of reaction of the normal ester (III) with pyridine is the phthalide rather than the diketone (II); this suggests that conversion of the ion (IV) into the phthalide does occur. Presumably the effect of this reversion is negligible, in alcohol, by comparison with the much faster forward reaction.

We then followed the kinetics of rearrangement of a number of phthalides carrying substituents in the *meta*- or *para*-position of the benzylidene group. The Hammett line was determined by the *meta*-substituents, with Taft's[11] σ^0-values. Such values also provided a good fit for *para*-substituents, except for the $-M$ substituents *p*-NO_2 and 3,4-benzo (Fig. 1). These two groups required exalted σ-values and the implication is that

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[9] Nazarov, Zav'yalov, and Burmistrova, *Bull. Acad. Sci. U.S.S.R.*, 1956, 197; Zalukajevs, *Latvijas P.S.R. Zinātnu Akad. Vēstis.*, 1952, No. 11, 129 (*Chem. Abs.*, 1955, **49**, 261); Zalukajevs and Vanags, *ibid.*, 1956, No. 3, 109 (*Chem. Abs.*, 1957, **51**, 4335).

[10] Egerer and Meyer, *Monatsh.*, 1913, **34**, 69.

[11] Taft, *J. Phys. Chem.*, 1960, **64**, 1805.

the rate-determining step involves a structure close to (IV), with a negative centre adjacent to the phenyl group. The positive reaction constant ($\rho + 1{\cdot}9$) reflects the influence of the ionization step producing (IV) but does not exclude cyclization as the rate-determining step.

Kinetic studies on ethoxide-catalyzed reactions in ethanol yielded interesting results. The rate constant for the rearrangement of the phthalide (I) was higher (8-fold) than that for the methoxide-catalyzed reaction, and both this compound and the pseudo-ester (VI) gave the same rate constant. However, the phthalide gave a high initial rate, which became steady; the pseudo-ester gave a low initial rate which changed to the same steady value. The normal ester (III) gave kinetic results (Fig. 2) similar to those obtained with the phthalide (I).

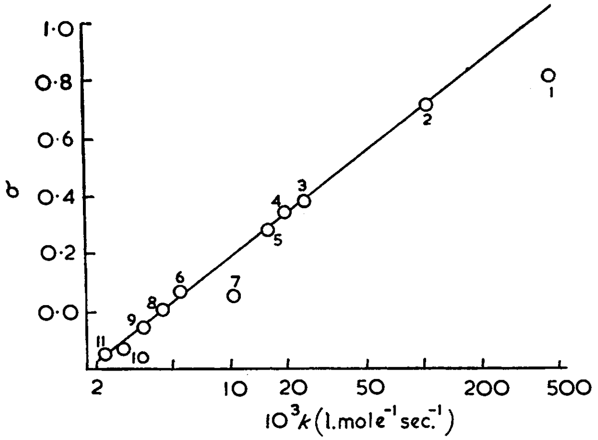
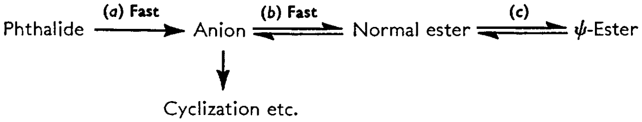


FIG. 1. Hammett plot for phthalide rearrangement in methanol.

1, *p*-NO_2. 2, *m*-NO_2. 3, *m*-Cl. 4, *m*-F. 5, *p*-Cl. 6, *m*-OMe. 7, 3,4-Benzo. 8, H. 9, *m*-Me. 10, *p*-Me. 11, *p*-OMe.

Although these deviations from linearity could not be observed with the methoxide-catalyzed reactions, they may be explained on the basis of the proposed reaction scheme:



If it is assumed that steps (*a*) and (*b*) are fast, that step (*c*) is slower, and that the rate-determining step is either deprotonation of the normal ester or cyclization of its anion, then phthalide gives normal ester very rapidly but gives pseudo-ester less fast and indanedione slowly. Starting with phthalide (or normal ester) there is an initially high concentration of normal ester (resulting in a high initial rate) which is reduced as the normal–pseudo equilibrium is set up. Phthalide, normal ester, and pseudo-ester all yield the same rate constant, but only after equilibrium (*c*) has been established. But if step $\psi \longrightarrow$ n (—*c*) is slow enough to influence rate measurements, then with pseudo-ester as starting material the initial rate should be low by comparison, not only with the initial phthalide rate, but also with the steady rate observed for all three cases.

Thus the difference in kinetics between ethoxide- and methoxide-catalyzed reactions is attributed to a relatively slow equilibration of normal and pseudo-esters when ethoxide is used. This assumption was supported in quenching experiments at the same temperature (20°) as that adopted for the rate measurements. In one series of experiments the phthalide (I) was the starting material; in the other it was the pseudo-ester (VI); mole fractions of normal ester obtained were plotted against time, and Fig. 3 shows that, unlike the methoxide case, the equilibration may readily be followed. When allowance is made for the concentration differences between these quenching experiments and the earlier kinetic runs, the time at which steady equilibrium is attained accords with that at which the steady rearrangement rate constant is reached. If the above argument is correct, then under our conditions there is a larger rate difference, with methoxide, between rearrangement and ester conversion. This appears to be reasonable, because the lower basicity of methoxide [12] leads to a lower concentration of normal ester anion and hence to less rapid rearrangement than with ethoxide. In the kinetic work, the rates with ethoxide were within a measurable range with much lower concentration of alkoxide. The greater concentration of methoxide used would lead to more rapid equilibration of normal and pseudo-esters.

Identification of the rate-determining step as cyclization rather than deprotonation is supported by other observations. In the reaction of *p*-nitrobenzylidenephthalide, a transitory red colour developed which was similar to that produced by dissolving *p*-nitrobenzyl phenyl ketone in sodium alkoxide solution; this colour may therefore be linked with the production of the anion (IV). Then the fact that a measurable quantity of anion is produced is in accord only with the assumption that the rate-determining step occurs later than the production of the anion (IV). It may also be noted that, with methoxide–methanol, the reaction was too rapid under our adopted conditions to allow the variation in colour intensity to be followed; with ethoxide–ethanol it proved quite possible to make such measurements.

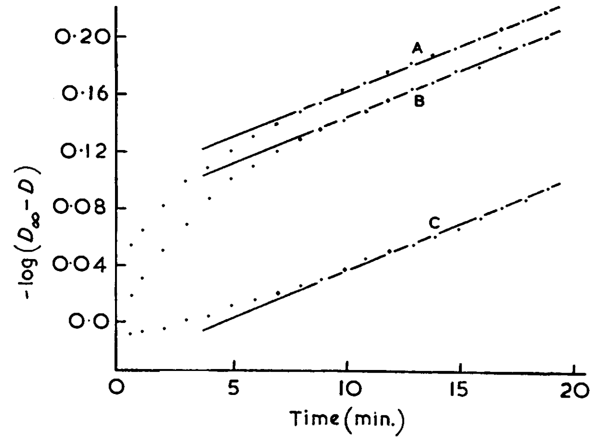


FIG. 2. Reaction of sodium ethoxide in ethanol with A (III), B (I), C (VI).

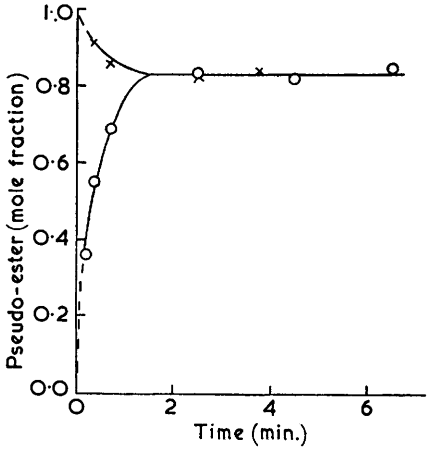


FIG. 3. Composition of quenched reaction mixture (ethanol solvent).
○, starting material = (I); ×, starting material = (VI).

Finally, cyclization appears likely to be the rate-determining step by analogy with the ethoxide-catalyzed Dieckmann condensation of diethyl *o*-phenylenediacetate for which Carrick and Fry [13] have shown that ring closure of the anion, rather than deprotonation of the diester, is rate-determining.

EXPERIMENTAL

Substituted Benzylidenephthalides.—The following *arylidenephthalides* were prepared by condensation of the appropriate substituted phenylacetic acids with phthalic anhydride, with

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[12] Hine and Hine, *J. Amer. Chem. Soc.*, 1952, **74**, 5268.
[13] Carrick and Fry, *J. Amer. Chem. Soc.*, 1955, **77**, 4384.

sodium acetate as catalyst: benzylidene-,[14] m. p. 100°; 3-*chlorobenzylidene-*, m. p. 158·5° (Found: C, 70·0; H, 4·0; Cl, 13·9. $C_{15}H_9ClO_2$ requires C, 70·2; H, 3·5; Cl, 13·8%); 4-chlorobenzylidene-,[15] m. p. 154°; 3-*methoxybenzylidene-*, m. p. 123° (Found: C, 75·9; H, 5·1. $C_{16}H_{12}O_3$ requires C, 76·2; H, 4·8%); 4-methoxybenzylidene-,[16] m. p. 147°; 3-methylbenzylidene-,[17] m. p. 155·5°; 4-methylbenzylidene-,[18] m. p. 153°; 3-nitrobenzylidene-, m. p. 244° (Found: C, 67·5; H, 3·5; N, 5·5. $C_{15}H_9NO_4$ requires C, 67·4; H, 3·4; N, 5·2%); 4-nitrobenzylidene-,[19] m. p. 222°; and 1-naphthylmethylene-,[16] m. p. 174°.

Pseudo-esters.—Benzylidenephthalide (20 g.) was dissolved in boiling methanol (125 ml.), and the solution was saturated with dry hydrogen chloride. The mixture was heated under reflux for 15 hr., cooled, and filtered; after 15 hr. at -10°, the filtrate had deposited 3-benzyl-3-methoxyphthalide (7 g., 30%), m. p. 111—112°. After two recrystallizations from methanol, the pseudo-ester had m. p. 113° unchanged by addition of a sample prepared by esterification of *o*-phenylacetylbenzoic acid.[4] The material remaining in the mother-liquor was fractionally recrystallized from methanol, yielding finally a small amount of crystals identified, by m. p. and mixed m. p., as the ketone (III). Similarly were obtained 3-3′-*chlorobenzyl*-3-*methoxyphthalide*, m. p. 110° (Found: C, 66·3; H, 4·6; Cl, 12·2. $C_{16}H_{13}ClO_3$ requires C, 66·6; H, 4·5; Cl, 12·3%); 3-*methoxy*-3-4′-*methoxybenzylphthalide*, m. p. 103·5° (Found: C, 72·2; H, 5·8. $C_{17}H_{16}O_4$ requires C, 71·8; H, 5·7%); and 3-benzyl-3-ethoxyphthalide,[2] m. p. 85·5°.

Normal Esters.—These were prepared by reaction of the corresponding phenylacetylbenzoic acid with diazomethane in ether. The esters were recrystallized at $\not> 20$° from methanol. The acids were obtained by boiling a suspension of the appropriate benzylidenephthalide with alkali.[20] These procedures gave *methyl* o-*phenylacetylbenzoate*, m. p. 39° (Found: C, 75·5; H, 5·7. $C_{16}H_{14}O_3$ requires C, 75·9; H, 5·2%), o-m-*chlorophenylacetylbenzoate*, m. p. 39° (Found: C, 66·8; H, 4·8; Cl, 11·9. $C_{16}H_{13}ClO_3$ requires C, 66·6; H, 4·5; Cl, 12·3%), and o-p-*methoxyphenylacetylbenzoate*, m. p. 74° (Found: C, 72·1; H, 5·9. $C_{17}H_{16}O_4$ requires C, 71·8; H, 5·7%).

Solvents.—Methanol was purified by distillation from 12N-sulphuric acid (2%), dried with magnesium, and fractionated. Ethanol was treated in the same manner. "AnalaR" pyridine was dried over potassium hydroxide and distilled. Sodium methoxide solutions (*ca.* 0·5M) were prepared by dissolving methanol-washed sodium in anhydrous methanol free from carbon dioxide. After standardization with hydrochloric acid, the solutions were diluted to the required concentrations.

Infrared Spectra.—Spectra were measured on a Perkin–Elmer 221C spectrophotometer with sodium chloride optics. The spectrum of the ester (III) (in CCl_4) shows a carbonyl peak at 1728 cm.$^{-1}$ (ester) with a shoulder at 1713 cm.$^{-1}$ (C=O).[21] The pseudo-ester has a single carbonyl peak at 1782 cm.$^{-1}$, characteristic of a 3-alkoxyphthalide.[22] In the 850—925 cm.$^{-1}$ region the normal ester is transparent whereas the pseudo-ester has peaks at 856, 885, and 895 cm.$^{-1}$. The phthalide (I) has a carbonyl peak at 1780 cm.$^{-1}$ and a double-bond stretching peak at 1664 cm.$^{-1}$, the latter characteristic for the phthalide in admixture with the esters. The phthalide also absorbs in the 850—925 cm.$^{-1}$ region, with peaks at 860, 868, and 917 cm.$^{-1}$.

Formation of Esters in the Rearrangement of Benzylidenephthalide.—0·5M-Sodium methoxide (25 ml.) at 0° was added to benzylidenephthalide (1 g.) in anhydrous methanol (150 ml.), also at 0°. After 5 sec., the solution was poured into 0·1M-hydrochloric acid (1 l.). The mixture was extracted with ether (2 × 100 ml.) and the combined ether extracts were washed with dilute sodium hydrogen carbonate solution until the washings were colourless. After drying ($MgSO_4$), the ether was removed in an air-stream at room temperature. The infrared spectrum of the residue (75% recovery) (in CCl_4) showed only those peaks which occurred in the spectra of the normal and pseudo-esters. In particular the 1664 cm.$^{-1}$ peak of benzylidenephthalide was absent.

By the base-line technique, the optical densities of the carbonyl peaks at 1782 cm.$^{-1}$ were

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[14] Weiss, *Org. Synth.*, 1943, Coll. Vol. II, p. 61.

[15] Walther and Wetzlich, *J. prakt. Chem.*, 1900, **61**, 195.

[16] Bergmann, *J. Org. Chem.*, 1956, **21**, 462.

[17] Heilmann, *Ber.*, 1890, **23**, 3158.

[18] Ruhemann, *Ber.*, 1891, **24**, 3965.

[19] Leupold, *Ber.*, 1901, **34**, 2837.

[20] Gabriel and Michael, *Ber.*, 1878, **11**, 1017.

[21] Bellamy, "The Infra-red Spectra of Complex Molecules," Methuen, London, 1958, pp. 137, 179.

[22] Wheeler, Young, and Erley, *J. Org. Chem.*, 1957, **22**, 547.

measured and, by the use of standard solutions, the concentrations of both species were calculated. Results were:

Reaction time (min.)	0·1 min.	2 min.	20 min.
Mole fraction of normal ester	0·69	0·17	0·21

The rapid consumption of benzylidenephthalide was confirmed from ultraviolet spectra. Even with phthalide and methoxide concentrations $<10^{-4}$M, the phthalide half-life was <1 min.

The reaction in ethanol was carried out at 20°, the solution being 5×10^{-4}M in phthalide and 0·03M in ethoxide. The infrared spectrum of the quenched product was measured in the ranges 850—925 and 1650—1900 cm.$^{-1}$. It was assumed that the carbonyl peaks of the normal ethyl and methyl esters had the same extinction coefficient, and the mole fraction of normal ester was evaluated as before. The mole fraction was also evaluated by using the pseudo-ester peaks in the 850—925 cm.$^{-1}$ range, and the same results were obtained. Similar experiments were carried out starting from the ethyl pseudo-ester. Results of both sets of experiments are shown in Fig. 3.

Reaction in Pyridine.—The substrate (30 mg.) in pyridine (50 ml.) was heated under reflux (drying tube) for 5 hr. The ultraviolet spectra of the solutions, obtained before and after heating, are reproduced in Fig. 4. Only the normal ester reacts under these conditions. The results suggest that ring closure on oxygen [to give phthalide (I)] in the mesomeric anion (IV) is *ca.* 20 times as fast as ring closure on carbon [to give normal ester (III)].

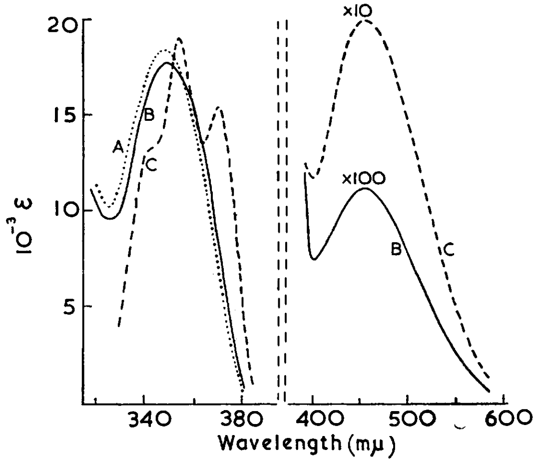

Fig. 4. Spectra in pyridine. A, Phthalide (I) before and after refluxing; B, normal ester (III) after refluxing; C, diketone (II). The normal ester before refluxing, and the pseudo-ester (V) before and after refluxing, showed no significant absorption in either region. Magnifications of the intensity scale are as marked.

Rate Measurements.—Runs were followed by measuring the optical density of the product anion. Aliquot parts (10 ml.) of solutions of the phthalide (10^{-3}M) and alkoxide (0·007—0·9M), heated at 20·1° ± 0·1°, were mixed and placed in an optical cell (1 or 3 cm. path length), and the cell was stoppered and placed in a water-jacketed cell-holder fitting into a "Spekker" absorptiometer and maintained at 20·1°. Fifteen readings of the optical density were made at measured time intervals, runs being followed to 60—90% reaction. The optical density was also measured after ten half-lives to obtain the infinity value.

The second order rate equation is $dx/dt = k''$ [normal ester][OMe]; hence

$$dx/dt = k'[\text{total ester}][\text{OMe}] = k[A - x][B - x],$$

where x is the concentration of anion, A is the initial total ester concentration, *i.e.*, the initial phthalide concentration, since this is converted into the esters very rapidly, B is the initial methoxide concentration, k' is $k''/(1 + K)$, K being the equilibrium constant for conversion of normal into pseudo-ester.

On integration and substitution of the optical density expression for x, we obtain

$$k' = \frac{2{\cdot}3}{(B - A)t} \log \frac{D_\infty - (A/B)D}{D_\infty - D}.$$

For the less reactive compounds, $B \gg A$ and the pseudo-first-order form was used, namely, $k' = (2{\cdot}3/Bt) \log [D_\infty/(D_\infty - D)]$. The rate constants calculated from the above expressions increased slightly with increasing methoxide concentration. This was attributed to an ionic-strength effect and the rate constants were corrected to zero ionic strength by means of the expression $\log k = \log k' + \alpha I$. A satisfactory linear correlation was then obtained, the value of α being $-0{\cdot}6$.

At least four runs were followed with each compound. Mean rate constants (Table 1) are estimated to be accurate to $\pm 5\%$, except that for the very reactive 4-nitrobenzylidenephthalide (half-life *ca.* 5 min.) the accuracy is probably $\not> 10\%$.

TABLE 1.

Substituted benzylidenephthalides, methyl *o*-phenylacetylbenzoates, and 3-methoxy-3-benzylphthalides in methanol at 20·1°.

Subst.:	H	*m*-Cl	*p*-Cl	*m*-F	*m*-OMe	*p*-OMe
Phthalides	3·98	23·1	15·2	18·3	5·05	2·13
Normal esters	4·02	25·0	—	—	—	2·12
Pseudo-esters	4·04	24·6	—	—	—	2·03

Subst.:	*m*-Me	*p*-Me	*m*-NO_2	*p*-NO_2	3,4-Benzo
Phthalides	3·47	2·75	101	429	10·1

In ethanol, benzylidenephthalide ($k = 31{\cdot}6 \times 10^{-3}$ l. mole^{-1} sec.$^{-1}$) rearranged *ca.* eight times as fast as in methanol. Similar rate increases were observed for 3- and 4-nitrobenzylidenephthalide. As may be seen from Fig. 2, compounds (I), (III), and (VI) rearranged at the same rate in ethanol, after the initial, rather slow, equilibration.

Hammett Relation.—The reaction constant was derived [23] by using rate and σ^0 data for those aryl substituents included in Taft's select list, *i.e.*, for substitution by (H), Cl, F, Me, NO_2. The ρ-value obtained was 1·91, and $\log k_0 = -2{\cdot}35$. Effective σ-values for all the substituted phenyl groups were then calculated (Table 2).

TABLE 2.

σ-Values for substituents.

	H	*m*-Cl	*p*-Cl	*m*-F	*m*-OMe	*p*-OMe	*m*-Me	*p*-Me	*m*-NO_2	*p*-NO_2	3,4-Benzo
$\bar{\sigma}$	$-0{\cdot}02$	$+0{\cdot}38$	$+0{\cdot}28$	$+0{\cdot}32$	$+0{\cdot}03$	$-0{\cdot}17$	$-0{\cdot}06$	$-0{\cdot}11$	$+0{\cdot}72$	1·05	$+0{\cdot}19$
$\bar{\sigma} - \sigma^\circ$	$-0{\cdot}02$	$+0{\cdot}01$	$+0{\cdot}01$	$-0{\cdot}03$	$-0{\cdot}03$	$-0{\cdot}01$	$+0{\cdot}01$	$+0{\cdot}04$	$+0{\cdot}02$	$+0{\cdot}23$	$+0{\cdot}15$ [25]

Data for all except *p*-nitrophenyl and 2-naphthyl groups were found to correlate with σ^0-values within the precision of the latter ($\pm 0{\cdot}03$). By following Taft and Lewis's recommended procedure,[24] ρ was recalculated from the data for all phthalides except 4-nitrobenzylidene- and 2-naphthylmethylene-phthalide, a ρ-value of 1·89 being obtained; the correlation coefficient, r, was 0·997; and the intercept of the regression line with the ordinate, $\log k_0$, was $-2{\cdot}35$. The effective σ-values calculated were, of course, identical with those found above(Table 2). Since the measured rate constant $k' = k''/(1 + K)$, the measured ρ-value should not be independent of σ. However, since $K_0 \approx 4$ and ρ for this reaction, ester interchange, should be very small, $1 + K \approx 1 + K_0$. Thus the measured ρ is that for condensation of the normal ester.

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UNIVERSITY OF CANTERBURY, CHRISTCHURCH, NEW ZEALAND. [*Received, November 1st*, 1961.]

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[23] Jaffé, *Chem. Rev.*, 1953, **53**, 253.

[24] Taft and Lewis, *J. Amer. Chem. Soc.*, 1959, **81**, 5343.

[25] σ° was taken as $+0{\cdot}04$; cf. Fischer, Packer, Vaughan, Wilson, and Wong, *J. Org. Chem.*, 1959, **24**, 155.