463. *Fries Reaction. Part I. Isomerisation of Thymyl Acetate.*

By Á. Furka and T. Széll.

The Fries reaction of thymyl acetate, catalysed by aluminium chloride, was studied in homogeneous nitrobenzene solution by kinetic methods. It was found that the rate of isomerisation increased with the molar ratio catalyst : ester (suddenly between values of 1·0 and 1·5 for this ratio), with acetyl chloride concentration, and with temperature, and decreased on addition of thymol or methyl thymyl ketone. The rate of formation of this ketone was found to conform closely to a first-order reaction. The rate of the Friedel–Crafts reaction of thymol with acetyl chloride was found to be much higher than that of the corresponding Fries reaction, but the rate of reaction of acetylthymyl acetate with thymol was the same as that of the Fries reaction. These reactions afforded identical end-products.

Some of our results are similar to those obtained by Cullinane *et al.*[1] for different esters and catalysts.

Although the mechanism of the Fries reaction had been studied by several authors since its discovery,[2] it has not been satisfactorily elucidated. Some workers [3] claimed the process to be intramolecular, but others [4] thought it was intermolecular. Still others [5] regard the reaction as a compromise between these two types.

It seemed that application of physicochemical methods might help to solve the problem. Hitherto, only those Fries reactions catalysed by boron trifluoride [6] and by titanium tetrachloride and aluminium chloride [1] have been studied kinetically.*

In the present work the rearrangement of thymyl acetate in homogeneous nitrobenzene solution in the presence of anhydrous aluminium chloride was studied kinetically.

* In the course of our present work, a personal communication from Dr. N. M. Cullinane (Cardiff) informed us that his group is engaged in the kinetic investigation of Fries reactions catalysed by aluminium chloride.

[1] ($TiCl_4$) Cullinane, Evans, and Lloyd, *J.*, 1956, 2222; Cullinane and Edwards, *J.*, 1957, 3016; ($AlCl_3$) Cullinane and Bailey-Wood, *Rec. Trav. chim.*, 1959, **78**, 440; Edwards, Ph.D. Thesis, University of Wales, 1958.

[2] Fries and Finck, *Ber.*, 1908, **41**, 4271.

[3] Fries and Ehlers, *Ber.*, 1923, **56**, 1304; Witt and Braun, *Ber.*, 1914, **47**, 3216; von Auwers and Mauss, *Annalen*, 1928, 464, 293; Illari, *Gazzetta*, 1947, **77**, 339, 492.

[4] Skraup and Poller, *Ber.*, 1924, **57**, 2033; Rosenmund and Schnurr, *Annalen*, 1928, **460**, 56; Cox, *J. Amer. Chem. Soc.*, 1930, **52**, 352; Ralston, McCorkle, and Segebrecht, *J. Org. Chem.*, 1941, **6**, 750; Schönberg and Mustafa, *J.*, 1943, 79; Hauser and Mann, *J. Org. Chem.*, 1952, **17**, 390; Tarbell and Fanta, *J. Amer. Chem. Soc.*, 1943, **65**, 2169; Bisanz, *Roczniki Chem.*, 1956, **30**, 87 (*Chem. Abs.*, 1957, **51**, 323*b*)

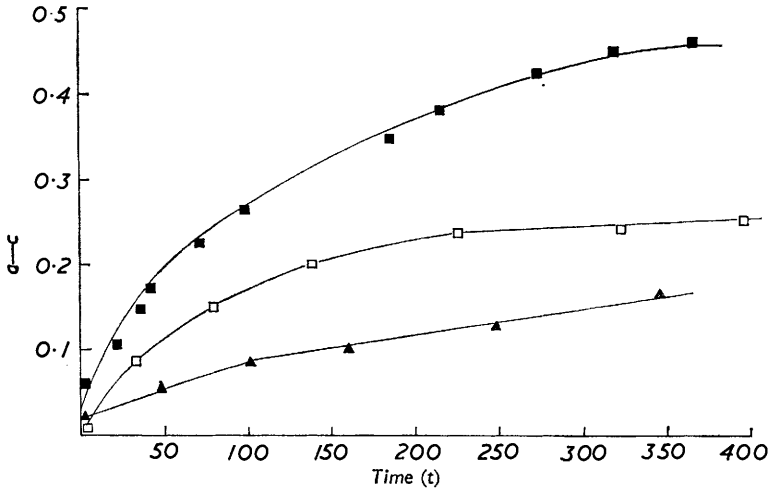
[5] Gershzon, *Zhur. obshchei Khim.*, 1943, **16**, 82; Klamann, *Annalen*, 1954, **583**, 63; Baltzly, Ide, and Phillips, *J. Amer. Chem. Soc.*, 1955, **77**, 2522; Gerecs, Széll, and Windholz, *Acta Chim. Acad. Sci. Hung.*, 1953, **3**, 459; Gerecs and Windholz, *Naturwiss.*, 1955, **24***b*, 414; Cullinane, Evans, and Lloyd, *J.*, 1945, 2222; Cullinane and Edwards, *J.*, 1957, 3016.

[6] Kästner, Thesis, Marburg, 1937, in " Newer Methods of Preparative Organic Chemistry," 1st American edn., Interscience Publ., Inc., New York, 1948, pp. 284—291.

Results and Discussion

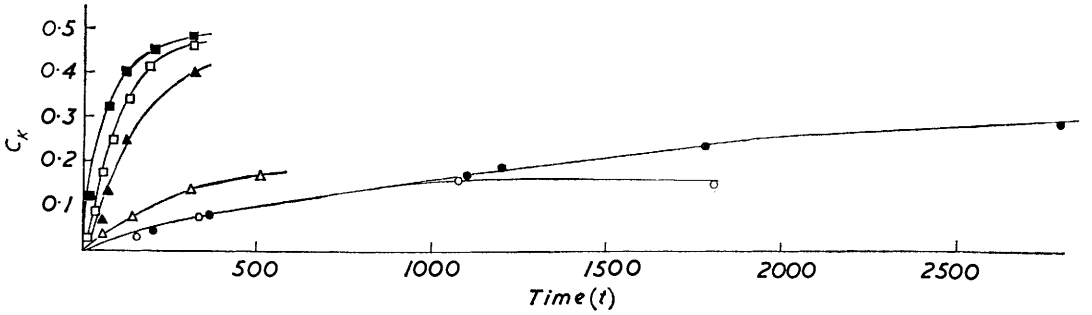
Symbols.—*a*, *b*, C_{AcCl}, C_T, C_K, and $C_{K,Ac}$ are the initial concentrations respectively of thymyl acetate, aluminium chloride, acetyl chloride, thymol, acetylthymol, and the acetate of this ketone; *c* and *x* are, respectively, the concentrations of thymyl acetate and of acetylthymol at time *t* (in min.). Concentrations are in terms of moles/l. and *T* is the temperature (in °K).

Fig. 1. *Rate of disappearance of thymyl acetate at different concentrations at* 40°.



□, $a = 0{\cdot}2475$, $b = 0{\cdot}75$; ■, $a = 0{\cdot}4966$, $b = 0{\cdot}75$; ▲, $a = 0{\cdot}7443$, $b = 0{\cdot}75$.
Times (t) *in all Figures are in minutes.*

Fig. 2. *Rate of formation of acetylthymol at different concentrations of aluminium chloride at* 40°.



○, $a = 0{\cdot}4953$, $b = 0{\cdot}25$; △, $a = 0{\cdot}4985$, $b = 0{\cdot}625$; □, $a = 0{\cdot}4963$, $b = 1{\cdot}00$; ●, $a = 0{\cdot}4967$, $b = 0{\cdot}50$; ▲, $a = 0{\cdot}4966$, $b = 0{\cdot}75$; ■, $a = 0{\cdot}4966$, $b = 1{\cdot}25$.

Rate of Disappearance of the Ester at Different Initial Concentrations.—Experiments were carried out with solutions containing identical concentrations of aluminium chloride and increasing concentrations of ester in order to study the rate of disappearance of thymyl acetate. The results in Fig. 1 show that the rate of disappearance of the ester at first increases with increasing ester concentration, but later decreases rapidly, becoming very slow just when it would be expected to be highest, *i.e.*, at a ratio of 1 : 1. Two conclusions can be drawn from this fact: (1) The disappearance of thymyl acetate cannot be attributed to the bimolecular reaction between ester and aluminium chloride; presumably an ester–aluminium chloride complex is formed, the rate of disappearance of which is dependent on its aluminium chloride content. (2) This complex is formed immediately, as shown by the

fact that the decrease in rate caused by increasing the initial concentration of ester is evident from the beginning of the reaction.

Effect of the Initial Aluminium Chloride Concentration on the Rate of Disappearance of Ester and on the Formation of the Ketone.—When the initial concentration (a) of the ester

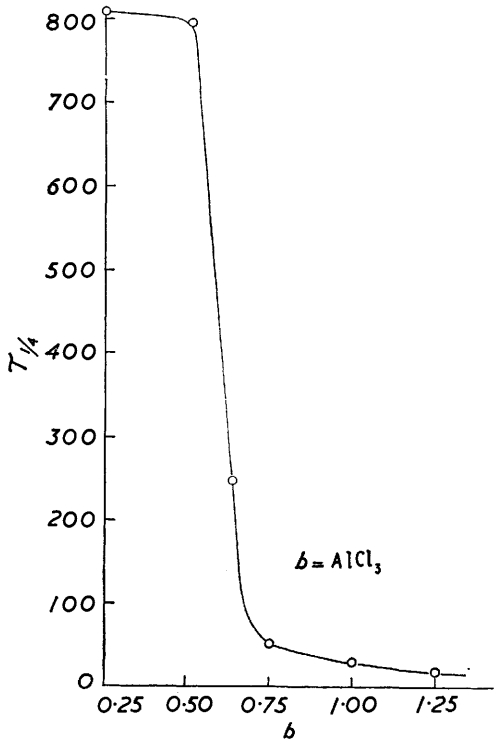
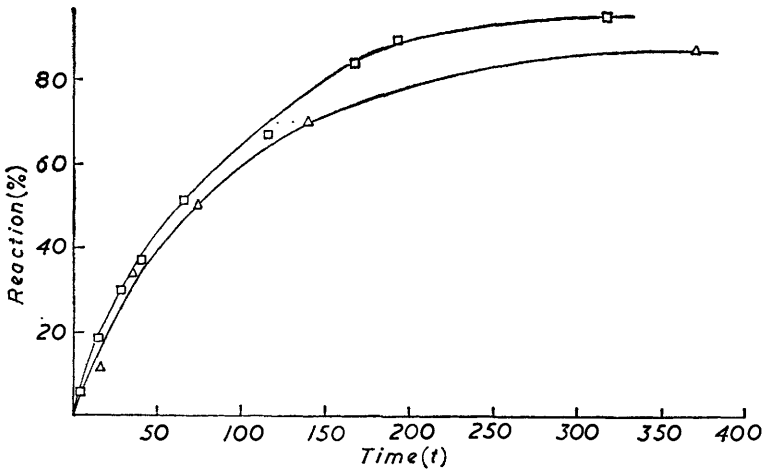


FIG. 3. *Dependence of quarter-life ($\tau_{\frac{1}{4}}$) on the concentration of aluminium chloride.*

FIG. 4. *Dependence of formation of acetylthymol on dilution.*



□, $a = 0{\cdot}4963$, $b = 1{\cdot}00$; △, $a = 0{\cdot}2418$, $b = 0{\cdot}50$.

was kept constant at 0·5, and that of aluminium chloride was varied from 0·25 to 1·25, the rates of disappearance of ester and of formation of ketone were found to vary within wide limits (see Fig. 2). The effect of the initial concentration of aluminium chloride is shown

even more markedly in Fig. 3, where the quarter-lives are plotted against the initial concentration of aluminium chloride: below a catalyst : ester ratio of 1 and above a ratio of 1·5 the increase in the initial concentration of aluminium chloride does not cause substantial decrease in the quarter-lives. There is, however a sudden, marked change in the rate of disappearance just within the limits of these two molar ratios (*i.e.*, $b = 0{\cdot}5$ and 0·75). This phenomenon may be attributed to the structure of the activated ester–aluminium chloride complex, for the determination of which further experiments are

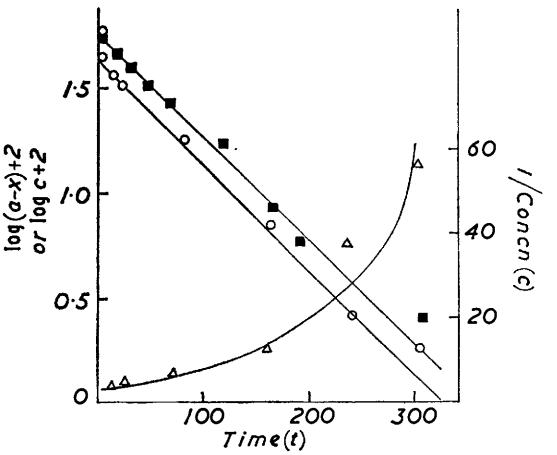


FIG. 5. *Plots for obtaining order of reaction.*

■, log $(a - x)$; ○, log c; △, $1/c$.

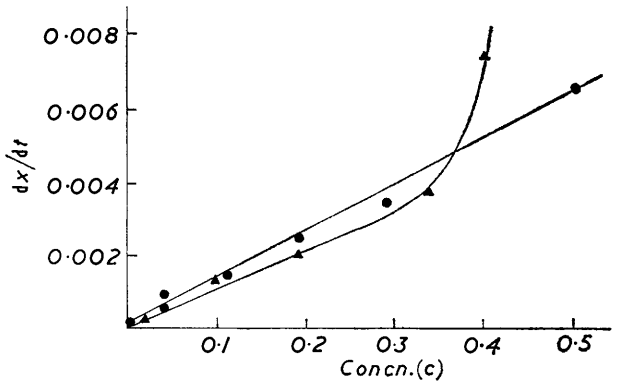


FIG. 6. *Graphic application of first-order equation.*

▲, thymyl acetate; ●, methyl thymyl ketone.

needed. In agreement with the results reported by Cullinane *et al.*,[1] it was found that at the beginning of the reaction the ester decomposed exceeded the ketone formed. Presumably, thymoxide ions or the thymyloxyaluminium dichloride and acyl cations or their aluminium chloride complex is formed from this excess. The fact, however, that part of the ester decomposes nearly instantaneously at an ester : catalyst ratio of, *e.g.*, 1 : 2, but that this scission becomes measurable at a later stage, suggests that an equilibrium becomes set up between scission products and unchanged ester–catalyst complex.

Determination of the Order of Reaction.—A 2-fold dilution results in a distinct though slight decrease in the rate of formation of the ketone and in that of disappearance of the ester (Fig. 4). This indicates that the rearrangement is not quite a first-order process. On the other hand, determination of the order by different methods (Fig. 5), including van't Hoff's differential method, shows that the rate of formation of the ketone approximates to a first-order reaction (actually of order 1·05). Direct graphical application of the first-order rate equation (Fig. 6) confirms this for the formation of ketone but not for disappearance of the ester, the relevant plot deviating considerably from a straight

line. Hence the two processes do not seem to be concurrent. We suggest, therefore, that the ketone is not formed through the scission products of the ester–aluminium chloride complex (which is formed instantaneously on mixing) but directly from this complex.

Table 1 contains the velocity constants, k, calculated from the first-order equation for the disappearance of the ester, and Table 2 summarises those determined numerically and graphically for the ketone formation, also according to first order.

Effect of Temperature on the Rearrangement.—The rearrangement of thymyl acetate was investigated for a catalyst : ester ratio of 1 : 2 at 33°, 40°, and 47°. It was found that change in temperature has a marked effect on both the rate of disappearance of ester and

TABLE 1. *Decomposition of ester at* 40°. ($a = 0{\cdot}4960$; $b = 1{\cdot}00$.)

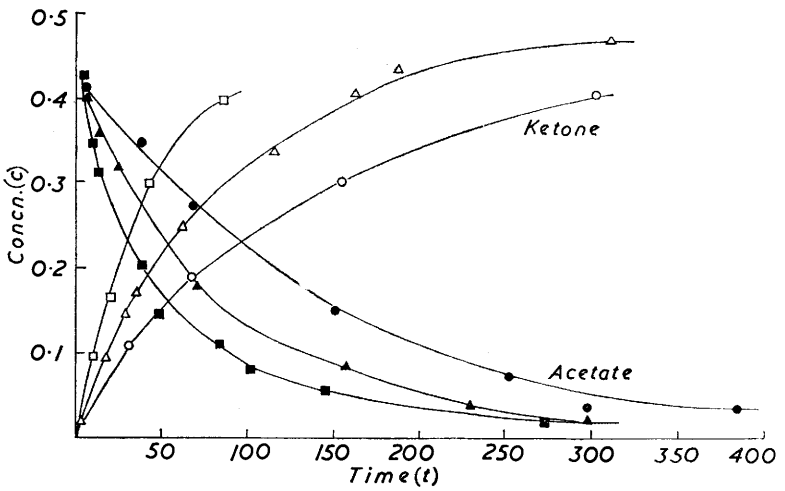
t (min.)	11·7	22·2	72·7	161·8	237·0	307·0
c	0·348	0·318	0·190	0·084	0·027	0·018
10^2k (min.$^{-1}$)	3·14	2·00	1·30	1·10	1·20	1·08

TABLE 2. *Formation of ketone at* 40°. ($a = 0{\cdot}4960$; $b = 1{\cdot}00$.)

t (min.)	x	10^2k (min.$^{-1}$)	t (min.)	x	10^2k (min.$^{-1}$)
13·9	0·0879	1·44	163·0	0·4133	1·10
27·8	0·1426	1·34	188·3	0·4542	1·12
37·7	0·1768	1·17	313·3	0·4703	0·96
64·8	0·2496	1·08	From $\tau_{\frac{1}{2}}$		1·19
65·5	0·2491	1·06	From $\tau_{\frac{1}{2}}$		1·07
113·3	0·3266	0·95	From Fig. 6		1·15

that of formation of ketone (see Figs. 7 and 8 and Table 3). The latter is to be considered as a process of first order even for a catalyst : ester ratio of 1 : 1, though at 47° the deviation is already substantial.

FIG. 7. *Rate of disappearance of thymyl acetate and of formation of acetylthymol at different temperatures.*



33°; $a = 0{\cdot}4967$, $b = 1{\cdot}00$; ● thymyl acetate, ○ methyl thymyl ketone
40°; $a = 0{\cdot}4963$, $b = 1{\cdot}00$; ▲ ,, ,, △ ,, ,,
47°; $a = 0{\cdot}4967$, $b = 1{\cdot}00$; ■ ,, ,, □ ,, ,,

We defer consideration of activation energies until we have obtained results for a wider temperature range and with different solvents and catalysts.

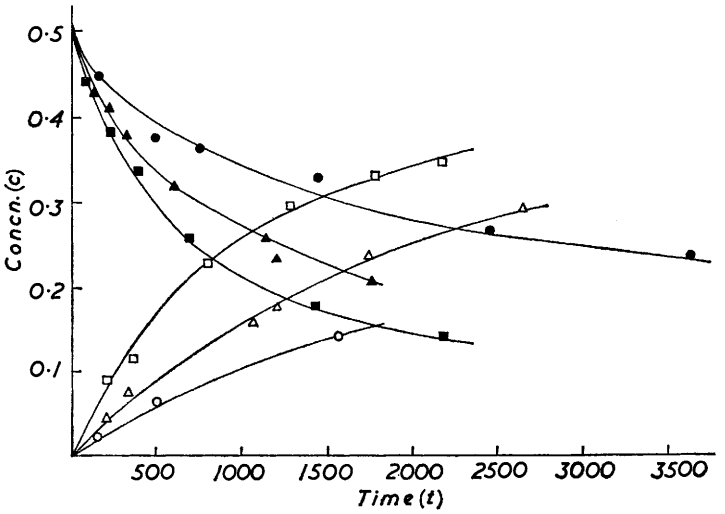
Effect of Aluminium Chloride on Methyl Thymyl Ketone.—A nitrobenzene solution

TABLE 3. *Effect of temperature on rate of formation of ketone.*

Catalyst/ester	2	2	2	1	1	1
T (°c)	33	40	47	33	40	47
10^2k (min.$^{-1}$)	0·670	1·150	2·200	0·018	0·033	0·056

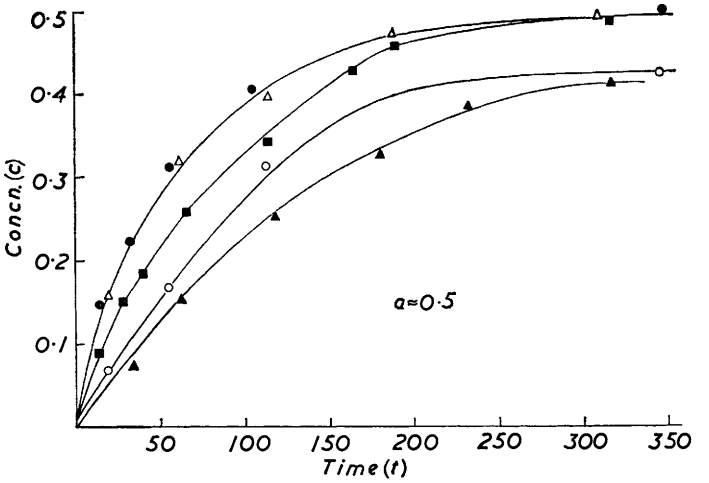
containing ketone and catalyst in a ratio of 1 : 2 was kept for 20 hr. at 40°, and the weight of recovered ketone showed negligible reaction; moreover, no hydrogen chloride was evolved. Similarly, during the Fries reactions hydrogen chloride was not evolved.

FIG. 8. *Rate of disappearance of thymyl acetate and of formation of acetylthymol at different temperatures.*



33°; $a = 0{\cdot}4954$, $b = 0{\cdot}50$; 40°; $a = 0{\cdot}4967$, $b = 0{\cdot}50$; 47°; $a = 0{\cdot}4952$, $b = 0{\cdot}50$.
(Symbols as for Fig. 7.)

FIG. 9. *Effect of thymol on the formation of acetylthymol at* 40°.



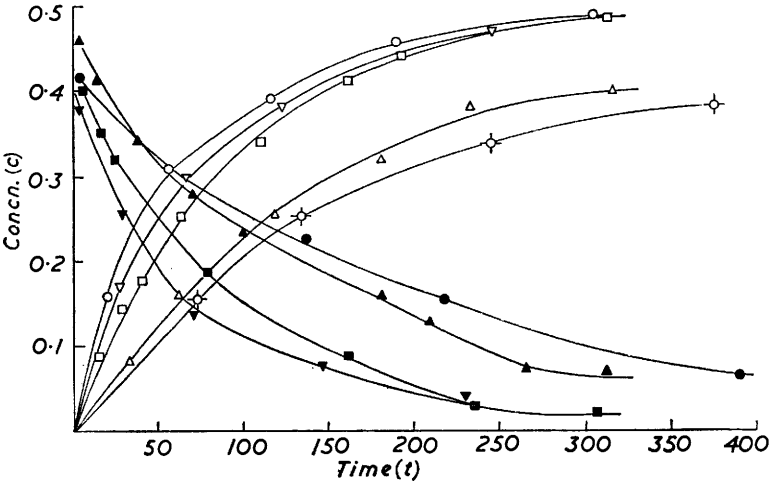
▲, $a = 0{\cdot}4966$, $b = 0{\cdot}75$; ■, $a = 0{\cdot}4963$, $b = 1{\cdot}00$; △, $a = 0{\cdot}4966$, $b = 1{\cdot}25$; ○, $a = 0{\cdot}4954$, $b = 1{\cdot}00$, $C_T = 0{\cdot}3278$; ●, $a = 0{\cdot}4965$, $b = 1{\cdot}25$, $C_T = 0{\cdot}3278$.

Hence, the methyl thymyl ketone formed in the Fries reaction upon thymyl acetate remains substantially unaffected by the aluminium chloride; further, it is neither converted completely into its aluminium dichloride derivative nor reconverted into ester.

Effect of Thymol on Rate of Formation of Ketone.—Thymol added to the system at the beginning of the reaction may decrease the rate of the conversion (Fig. 9). At a thymol concentration of 0·3 this decelerating effect is somewhat less than that which would have

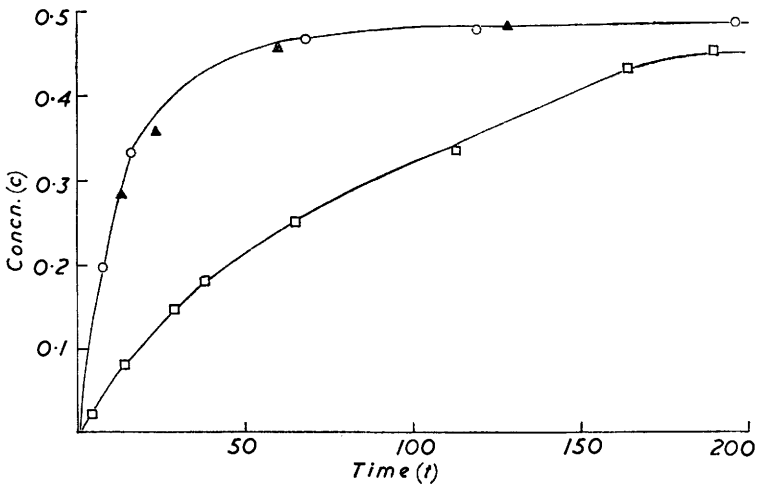
been caused by a similar decrease of 0·3 in the concentration of aluminium chloride. This effect of thymol is attributed to its ability to react with aluminium chloride, probably by a reversible reaction; and one can also conclude that one of the scission products of the ester may react with aluminium chloride.

FIG. 10. *Effect of acetylthymol on disappearance of thymyl acetate and on formation of the ketone.*



a = 0·4945, b = 1·00, C_K = 0·2480; ●, thymyl acetate; ·⊙·, acetylthymol.
a = 0·4986, b = 1·50, C_K = 0·2487; ▼, thymyl acetate; ▽, acetylthymol.
a = 0·4966, b = 0·75; ▲, thymyl acetate; Δ, acetylthymol.
a = 0·4963, b = 1·00; ■, thymyl acetate; □, acetylthymol.
a = 0·4966, b = 1·25; ○, acetylthymol.

FIG. 11. *Effect of acetyl chloride on formation of acetylthymol at* 40°.



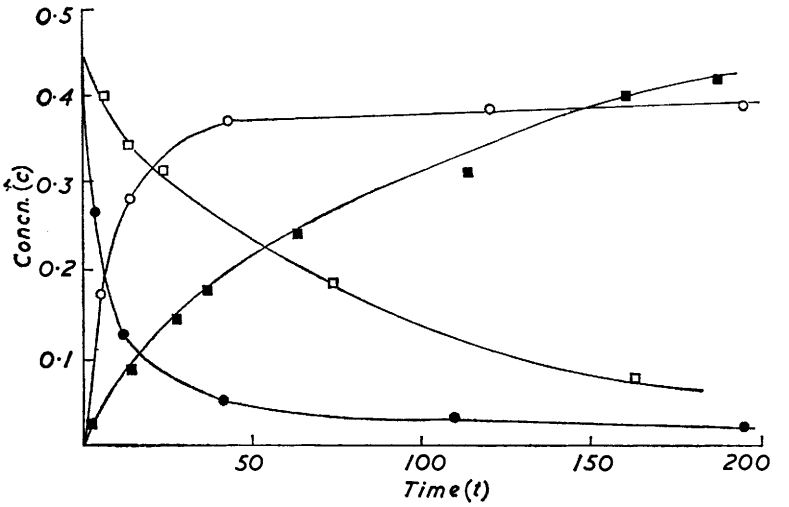
□, a = 0·4963, b = 1·00; ▲, a = 0·4957, b = 1·00, C_{AcCl} = 0·2352; ○, a = 0·4963, b = 1·25, C_{AcCl} = 0·2352.

Effect of Acetylthymol on the Rearrangement.—Initial addition of the ketone to the reaction system decreases the rate of both disappearance of the ester and formation of the ketone (Fig. 10). Although this effect is well known, it has not been studied quantitatively. The rate of formation of ketone is repressed as much by 0·25 mole of ketone per l. as by a reduction of 0·25—0·50 mole per l. in the initial aluminium chloride concentration. This

effect cannot be attributed to the reversible process discussed above (p. 2318), but may be due to the fact that nearly 2 moles of aluminium chloride are attached to the end-product of the Fries reaction. Also, nitrobenzene may be able to bind aluminium chloride. Hence it seems possible that the aluminium chloride is distributed during the Fries reaction between the ester, the scission products, the end-product, and the solvent.

Effect of Acetyl Chloride on Rate of Formation of Ketone.—When acetyl chloride is present in the reaction mixture, the rate of formation of the ketone is increased substantially (Fig. 11); two causes may be suggested for this effect. (i) A direct acylation of the ester nucleus may occur independently of, and faster than, the Fries reaction, or (ii) a ketonic ester may be formed which, together with the previous reaction, produces hydrogen chloride which also accelerates the process (see Part II, following paper).

FIG. 12. *Reaction between thymol and acetyl chloride in presence of aluminium chloride at* 40°.



$a = 0{\cdot}4963$, $b = 1{\cdot}00$; □, ester; ■, acetylthymol.
$C_T = 0{\cdot}5020$, $b = 1{\cdot}00$; $C_{AcCl} = 0{\cdot}4950$; ●, ester; ○, acetylthymol.

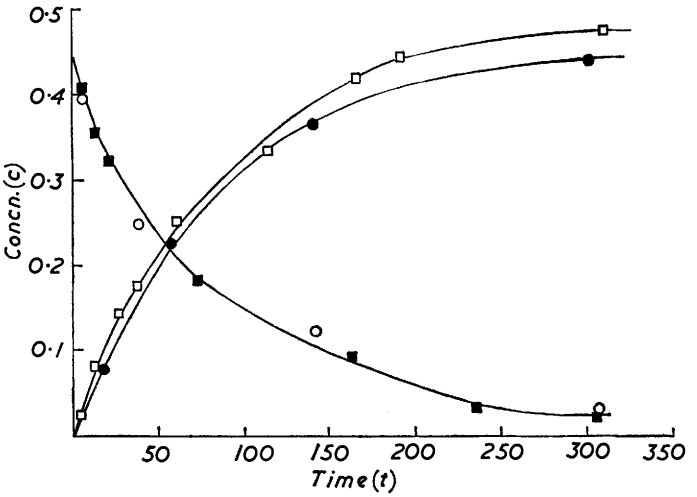
Friedel–Crafts Reaction of Thymol.—The Friedel–Crafts reaction between thymol and acetyl chloride in presence of aluminium chloride was studied for comparison with the Fries reaction (see Fig. 12). From the results of these investigations, the following points can be made: (1) The products of the Friedel–Crafts reaction between thymol and acetyl chloride and of the Fries rearrangement of thymyl acetate are identical. (2) The concentration of aluminium chloride has a marked influence on the rate of the Friedel–Crafts reaction. (3) In the Friedel–Crafts reaction, ester is formed, which decomposes subsequently in the same way as in the Fries reaction. (4) The rate of the Friedel–Crafts reaction is considerably higher than that of the corresponding Fries reaction of thymyl acetate under analogous conditions.

The high reaction rate can be explained by the fact that the hydrogen chloride liberated by ester formation accelerates the conversion of the ester into ketone (see Part II). Direct acylation of the thymol nucleus cannot, of course, be excluded.

Reaction of Thymyloxyaluminium Dichloride with Acetyl Chloride.—Loss of hydrogen chloride from the solution of thymol and aluminium chloride in nitrobenzene suggests that part of the thymol was converted into thymyloxyaluminium dichloride. On reaction of the mixture with acetyl chloride, acetylthymol was obtained; from its quantity and from the alkali equivalent of the hydrogen chloride evolved, it was evident that the thymyloxyaluminium dichloride was converted into ketone.

Reaction of Thymol with Acetylthymyl Acetate in Presence of Aluminium Chloride.—By means of Fig. 13, the reaction between thymol and ketone acetate may be compared with the corresponding Fries reaction.* It is seen that there is no substantial difference between the two reactions in regard to the rate of disappearance of ester and the rate of formation of ketone, and the end-products of the two reactions are also identical. This may be explained by the fact that thymol and ketone ester are rapidly converted into thymyl

FIG. 13. *Reaction between thymol and acetylthymyl acetate in presence of aluminium chloride at 40°.*



$a = 0{\cdot}4963$, $b = 1{\cdot}00$; ■, ester; □, acetylthymol.
$C_T = 0{\cdot}2501$, $b = 1{\cdot}00$; $C_{K,Ac} = 0{\cdot}2474$; ○ ester; ●, acetylthymol.

acetate and ketone, and subsequently the former undergoes the Fries reaction. The mechanism of the Fries reaction is still being investigated.

EXPERIMENTAL

Materials.—Thymyl acetate. This was prepared as described by Spasov,[7] and had b. p. 243·5—245·5°/760 mm. (purity, by saponification, 99·14%).

Thymol and acetyl chloride. Analytical-grade substances.

Acetylthymyl acetate. Prepared by use of acetic anhydride from the ketone obtained by Fries rearrangement of thymyl acetate, this had m. p. 49—51° (uncorrected).

Anhydrous aluminium chloride. V.E.B. Feinchemie, Eisenach (" for synth."), and B.D.H. preparations were used. Their catalytic effect on the rearrangement was found to be identical.

Isomerisation of Thymyl Acetate.—An appropriate quantity of thymyl acetate was weighed (to ±0·1 mg.) into a 25-ml. measuring flask provided with a ground-in glass stopper, and the flask was stoppered. Other reagents (*e.g.*, thymol, ketone, or ketone ester, as required) were then weighed in. In another flask a weighed quantity of aluminium chloride was dissolved in nitrobenzene (15—20 ml.), with shaking, and the flask was stoppered. (Acetyl chloride was included with the nitrobenzene when it was desired to study its effect.) The ester, the aluminium chloride solution, and a further flask containing nitrobenzene were kept in a thermostat at the required temperature until they had attained temperature equilibrium. The aluminium chloride solution was then poured into the flask containing the ester, which was filled to the

* As concentrations in the Fries reaction are double those of thymol and ketone acetate, the concentrations of ester and ketone as determined were doubled, and plotted after subtracting from the measured ketone concentrations the quantity equivalent to the initial ketone ester.

[7] Spasov, *Ann. Univ. Sofia* II, *Faculte Phys.-math.* II, 1938—39, **35**, 289 (*Chem. Abs.*, 1940, **34**, 2343 [6]).

mark with nitrobenzene. The moment of half-addition was taken as the time zero. Samples were then withdrawn at definite periods, and their ester or ketone content was determined.

Friedel–Crafts Reaction of Thymol with Acetyl Chloride.—The reaction was started by mixing solutions of thymol, aluminium chloride, and acetyl chloride in nitrobenzene at the required temperature. Intense evolution of gas started immediately and lasted for about 15 mins. Samples were taken and analysed.

Reaction of Thymyloxyaluminium Dichloride with Acetyl Chloride.—Thymol (1 mol.) and aluminium chloride (2 mol.) were dissolved in nitrobenzene, and dry air was bubbled through the solution at room temperature and 30 mm. The evolved hydrogen chloride was determined by absorption in alkali. After addition of acetyl chloride, the flask was placed in a thermostat at 40°, and samples were taken for determination of the acetylthymol content.

Determination of ester content. 2 Ml. of the reaction mixture were pipetted into 2 ml. of ethanol (or, in Friedel–Crafts reactions, into 2 ml. of water). The moment of half-addition was considered as the end of the reaction. The aluminium chloride was then converted by aqueous sodium fluoride solution into a soluble complex, and the ester content was determined in presence of ethanol by alkalimetry.[8] Corrections were applied for the solution adhering to the wall of the pipette and for the alkali consumption of the acetylthymol present (not more than 5%).

Determination of acetylthymol content. The sample, similarly taken and treated with sodium fluoride, was boiled with sodium hydroxide and made up with water to a known volume, and nitrobenzene was left to separate. A known volume of the supernatant clear liquid was acidified, and the crystals precipitated at 0° were filtered off. Ketone remaining in solution was determined and results were corrected accordingly.[9] The reactions gave identical products, m. p. 122·5—125° (Found: C, 74·95; H, 8·1. Calc. for $C_{12}H_{16}O_2$: C, 75·0; H, 8·4%).

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[8] Furka and Széll, *Acta Phys. Chem. Szeged*, 1959, **5**, 66.
[9] Széll and Furka, *Nature*, 1959, **184**, 117.