

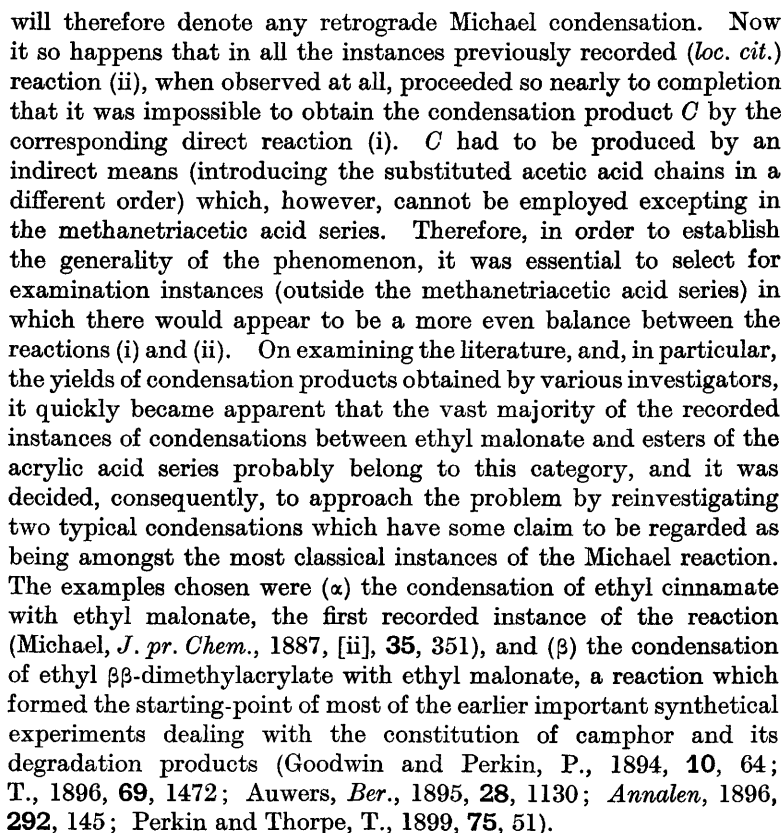
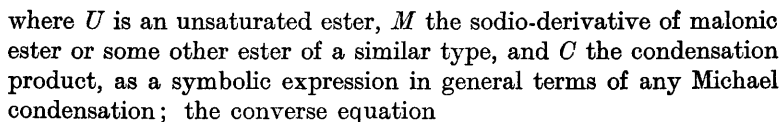
CCXXVI.—*The Reversibility of the Michael Reaction.*

By CHRISTOPHER KELK INGOLD and WALTER JAMES POWELL.

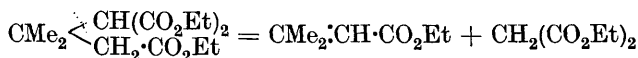
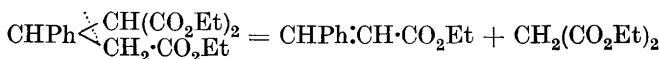
ALTHOUGH the condensation of $\alpha\beta$ -unsaturated esters with sodium derivatives of compounds of the type of ethyl malonate, generally known as the Michael reaction, is one of the most valuable methods of synthesis in the hands of the organic chemist, its mechanism and controlling conditions appear to have received singularly little attention. This is particularly remarkable when it is recalled that the mechanism of the acetoacetic ester condensation, of the Perkin reaction, and indeed of most of the important synthetical processes, has been the subject of protracted controversies.

During the course of an inquiry into the reason why certain attempts to produce derivatives of methanetriacetic acid by means of the Michael reaction met with no success, facts were discovered (Ingold and Perren, this vol., p. 1865) which strongly suggested that the Michael condensation is a reversible process, at least in the particular series of compounds dealt with. Therefore it seemed of

(a) It is convenient to adopt the equation



In the first place, it was necessary to show that the retrograde reaction could be realised in these instances. This presented no difficulty, for when the pure condensation products (ethyl β -phenylpropane- $\alpha\alpha\gamma$ -tricarboxylate and ethyl $\beta\beta$ -dimethylpropane- $\alpha\alpha\gamma$ -tricarboxylate) were dissolved in alcoholic solutions containing equivalent quantities of sodium ethoxide, and heated at 100° under the conditions usually employed in carrying out ordinary Michael reactions, fission occurred to the extent of approximately 60 per cent. in the sense of the following equations :



From this result the attainment of equilibria appears to follow as a necessary corollary. Moreover, it rapidly became clear in the course of the experimental investigation that essentially *the same* equilibrium is invariably attained, no matter whether it be approached by the direct or by the retrograde process; no matter, therefore, whether the starting-point be the pure product *C*, or a mixture of equivalent amounts of the constituent esters *U* and *M*, or any mixture of this mixture with the ester *C*, always provided that sufficient time be allowed for the equilibrium to be reached.

(b) It would be a matter of the greatest interest to obtain a collection of accurate values for the equilibria with ethyl malonate at different temperatures and concentrations of a series of α - and β -substituted acrylic esters. Unfortunately, the method of separating by fractional distillation the three esters present at equilibrium is a cumbersome and inaccurate way of estimating their relative proportions, but for lack of suitable analytical processes this has been the method employed in the present investigation. However, where similar experimental conditions have been used, the yields obtained are in moderately close agreement with those recorded by previous workers (*loc. cit.* *Vide* also Michael, *Ber.*, 1900, **33**, 3748; Perkin, T., 1896, **69**, 1467), and the following table is probably a not very inaccurate statement of the equilibria which can be reached under the customary experimental conditions (Solvent : 99.8 per cent. ethyl alcohol. Concentration : 300 grams of alcohol for gram-molecular quantities of the reactants).

Condensation Product (<i>C</i>).	Yield of <i>C</i> (per cent.).	
	Temp. 100° .	Temp. 25° .
Ethyl β -methylpropane- $\alpha\alpha\gamma$ -tricarboxylate	65	?
„ β -phenylpropane- $\alpha\alpha\gamma$ -tricarboxylate	35	70
„ $\beta\beta$ -dimethylpropane- $\alpha\alpha\gamma$ -tricarboxylate ...	30	50
„ $\alpha\beta\beta$ -trimethylpropane- $\alpha\alpha\gamma$ -tricarboxylate ...	trace ?	?

The effect on ring closure of the *gem*-dimethyl group, and in general of substituents of considerable atomic or molecular volume, has been emphasised in two recent communications (Ingold, this vol., pp. 305, 951). It has been proved, for instance, that derivatives of $\beta\beta$ -dimethylglutaric acid pass, by the interaction of substituents attached to the two acetic acid chains, into cyclic compounds more readily than do similar derivatives of glutaric acid. There is much evidence tending to show that the acetic acid residues are in closer proximity in the former case than in the latter. It seems, therefore, very reasonable to suppose, for instance, that the acetic and malonic ester chains in ethyl $\beta\beta$ -dimethylpropane- $\alpha\gamma$ -tricarboxylate are in closer proximity than those in ethyl β -methylpropane- $\alpha\gamma$ -tricarboxylate; further, because the accumulation of bulky groups in a restricted space is invariably a condition of instability, it must follow that the convergence of these chains caused by the groups attached to the β -carbon atom of the glutaric acid derivative must determine its tendency towards decomposition into smaller molecules. It is obvious from the table that this tendency towards disruption is greater in the case of the $\beta\beta$ -dimethyl compound than with the β -methyl analogue. The single phenyl group occupies a position intermediate between the single methyl group and the *gem*-dimethyl group, whilst the remarkable effect of introducing a substituent into the acetic acid chain, an effect so noticeable in the methanetriacetic acid series (*loc. cit.*), is again observed in the case of the trimethyl compound.*

We have, therefore, a method of considerable potential value for determining the effect of substitution on the stability of a carbon chain, but it is unfortunate that in this field, in which certain thermal and thermochemical determinations would be of the greatest service, very few measurements have been made. It would appear, however, that the heat of a reaction of type (i) is usually positive, and that, as follows from the formula $d \log_e K/dT = -QR^{-1}T^{-2}$, the equilibrium moves in the direction which favours the product *C* when the temperature is reduced. Moreover, the same formula shows that *Q* must be greater for the condensation between ethyl malonate and ethyl cinnamate than for that between ethyl malonate and ethyl dimethylacrylate, although no direct experimental

* The effect of the electrochemical character of substituent groups is also easily appreciable, as many instances, which lie without the scope of this paper, show. The larger yields of condensation products obtained when ethyl malonate is replaced by ethyl cyanoacetate (compare, for instance, Perkin and Thorpe, T., 1899, **75**, 52) may be attributed in part to the more intense polar character of the CN-group, but here again the difference is in the sense which accords with the relation between the molecular volumes of the groups concerned.

determinations have as yet been made. As Nernst (*Wied. Annalen*, 1894, **53**, 57), Bödlander (*Zeitsch. physikal. Chem.*, 1898, **27**, 55), and others have shown, Q and the osmotic work A do not differ by much if no gaseous substances take part in the equilibrium, and it is the common value towards which Q and A converge which is the true measure of the stability of the molecule.

(c) The above considerations show that if it be desired to prepare the compound C by means of reaction (i), there are certain factors by adjusting which the equilibrium may be caused to move in the direction favouring the production of that substance. Thus the equilibrium may be disturbed by some further change, either physical or chemical. To take a single instance of the effect of concentration, if two-thirds of the theoretical quantity of ethyl cinnamate be used in the preparation of ethyl β -phenylpropane- $\alpha\alpha\gamma$ -tricarboxylate, the yield obtained on allowing the reaction to take place at 25° (other conditions being as indicated on p. 1978) is more than 80 per cent. of the theoretical, calculated on the ethyl cinnamate employed.

The table on p. 1978 shows in a very clear manner the effect of lower temperatures on the equilibrium quantities of the condensation products. It is curious that none of the investigators previously referred to, for whom the preparation of ethyl $\beta\beta$ -dimethylpropane- $\alpha\alpha\gamma$ -tricarboxylate was the starting-point of their synthetical experiments, appears to have tried the effect of lower temperatures with a view to improve the yields, which, under the conditions they employed, were always poor. Michael, on the other hand, was fully aware that better yields of ethyl β -phenylpropane- $\alpha\alpha\gamma$ -tricarboxylate could be obtained by conducting the reaction in the cold, but he did not appreciate the fact that the cause of this lay in the simultaneous occurrence of the retrograde process.

EXPERIMENTAL.

The general plan of these experiments, as well as the results obtained, has been fully described above, and only a few minor details need be added here, since the method of conducting Michael condensations is well known.

Identity and Purity Criteria.

The ethyl malonate and ethyl cinnamate employed were carefully purified by distillation, and the ethyl β -phenylpropane- $\alpha\alpha\gamma$ -tricarboxylate required for the experiments on the retrograde reaction was prepared from the other two esters by condensation at a low temperature. It was purified by distillation (b. p. 220 — 224° /

25 mm.), and its purity controlled by analysis (Found : C = 63.9; H = 7.3. Calc., C = 64.3; H = 7.1 per cent.).

The products of the retrograde reaction (type ii) were separated by fractional distillation. The ethyl cinnamate was identified by its boiling point (270—274°), by analysis (Found : C = 74.6; H = 6.9. Calc., C = 75.0; H = 6.8 per cent.), and by hydrolysis to cinnamic acid, and the ethyl malonate by its boiling point (195°) and by conversion into malonamide.

Ethyl dimethylacrylate was prepared from ethyl α -bromoisovalerate and quinoline (Perkin, *loc. cit.*) and was so distilled as to remove the trace of volatile impurity that often causes the freshly-distilled ester to turn pink. The ethyl $\beta\beta$ -dimethylpropane- $\alpha\alpha\gamma$ -tricarboxylate, prepared from ethyl dimethylacrylate and ethyl malonate by condensation at 35°, was purified by distillation (b. p. 181°/28 mm.), and its purity checked by analysis (Found : C = 58.4; H = 8.4. Calc., C = 58.3; H = 8.3 per cent.).

The ethyl dimethylacrylate isolated from the retrograde reaction (type ii) was identified by its boiling point (155°), by analysis (Found : C = 65.3; H = 9.3. Calc., C = 65.6; H = 9.4 per cent.), and by hydrolysis to dimethylacrylic acid. The ethyl malonate was identified as in the previous instance.

Times Required to Attain Equilibria.

Equilibrium is attained more rapidly between ethyl malonate, ethyl cinnamate, and ethyl β -phenylpropane- $\alpha\alpha\gamma$ -tricarboxylate than between ethyl malonate, ethyl $\beta\beta$ -dimethylacrylate, and ethyl $\beta\beta$ -dimethylpropane- $\alpha\alpha\gamma$ -tricarboxylate. In the former case, heating for six hours at 100° or for one week at 25° suffices for the approximate attainment of the equilibria characteristic of these temperatures, whilst in the latter it is better to heat the mixture for about twenty-four hours at 100° or for two weeks at 35°.

Method of Conducting Retrograde Reactions (Type ii). Example :

Decomposition of Ethyl β -Phenylpropane- $\alpha\alpha\gamma$ -tricarboxylate into Ethyl Cinnamate and Ethyl Malonate.

The following instance illustrates the method employed. Ethyl β -phenylpropane- $\alpha\alpha\gamma$ -tricarboxylate (100 grams) was added to a solution of sodium (6.8 grams) in absolute ethyl alcohol (89 grams), and the mixture heated at 110° in a closed vessel for seven hours. It was then cooled as quickly as possible, poured into dilute hydrochloric acid, and the esters isolated by extraction with ether in the usual manner. On distilling the product under diminished pressure, 30 grams (30 per cent.) of ethyl β -phenylpropane- $\alpha\alpha\gamma$ -tricarboxylate

were recovered (b. p. 220—224°/25 mm.), together with a more volatile fraction, which, on refractionating at the ordinary pressure, yielded 31 grams (60 per cent.) of ethyl cinnamate (b. p. 270—274°), and a quantity of ethyl malonate. Malonic acid also was recovered from the aqueous liquors. Ten per cent. of the material remained to be accounted for as experimental losses.

We gratefully acknowledge our indebtedness to Professor J. F. Thorpe for his interest in this investigation. Part of the cost was defrayed from a grant made by the Chemical Society, to whom also we wish to record our thanks.

IMPERIAL COLLEGE OF SCIENCE AND TECHNOLOGY,

SOUTH KENSINGTON, S.W.7.

[Received, October 14th, 1921.]
