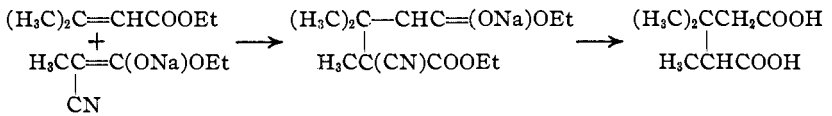
[CONTRIBUTION FROM CONVERSE MEMORIAL LABORATORY, HARVARD UNIVERSITY]

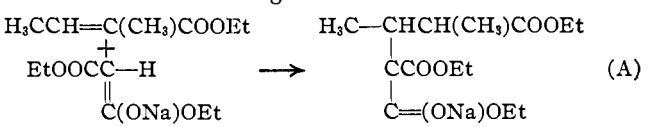
The Course of Addition of the Sodium Enolates of Malonic and Methylmalonic Esters to Benzalacetophenone and to Crotonic Ester

BY ARTHUR MICHAEL AND JOHN ROSS[1]

J. F. Thorpe[2] found that the addition product from sodium enol α-cyanopropionic ester and β,β-dimethylacrylic ester gave α,β,β-trimethylglutaric acid upon complete acid hydrolysis. From this result, he concluded that the methyl, not the sodium, of the addendum migrated in the reaction. This conclusion was not proved experimentally; the same glutaric derivative would be formed if the sodium had migrated to the α-Δ-carbon of the substituted acrylic ester, or to the Δ-oxygen of the adjacent carbethoxyl, with corresponding changes in the positions of unsaturation



With a normal course of addition, the free ester from the addition product of sodium enol methylmalonic ester and crotonic ester, and that formed by methylation of sodium enol α-carbethoxy-β-methylglutaric ester, should be identical. Examination of the reactions[3] showed that isomeric compounds are formed. This anomalous isomerism was explained by Michael and Ross[4] by the synthesis of the enolate of the first compound from sodium enol malonic and tiglic esters

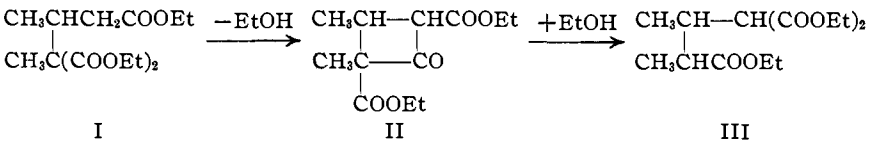


The synthesis of enolate A from sodium enol methylmalonic and crotonic esters could take place directly only by migration of the methyl of the former, but an isomer of A might be formed by that of its carbethoxyl, which might rearrange to A. It was concluded that the methyl shifted. Corresponding results were noted with analogous enolates and with other α,β,Δ-esters.[5]

Holden and Lapworth[6] have recently advanced a different interpretation of the course of the methylmalonic enolate–crotonic ester reaction. They assumed that Na— and —$C(CH_3)(COOEt)_2$ functioned as addendum

(1) A preliminary communication appeared in THIS JOURNAL, **54**, 408 (1932).
(2) Thorpe, *J. Chem. Soc.*, **77**, 923 (1900).
(3) Michael, *Ber.*, **33**, 3731 (1900).
(4) Michael and Ross, THIS JOURNAL, **52**, 4598 (1930).
(5) Michael and Ross, *ibid.*, **53**, 1150 (1931).
(6) Holden and Lapworth, *J. Chem. Soc.*, 2368 (1931).

parts. Without implication of the sodium, they represented the course of reaction after the primary normal addition phase (I), as follows



I II III

Experiment and theory combine to make this view improbable. It had been shown that methylmalonic ester forms I when it reacts with crotonic ester in the presence of a little sodium ethoxide[7] and that I is also formed[8] by methylating the sodium enolate of β-methyl-γ-carbethoxyglutaric ester; further, on treatment with sodium ethoxide, that I undergoes almost quantitative fission into sodium enol methylmalonic and crotonic esters. Under these conditions, according to the interpretation of Holden and Lapworth, I should be converted into the sodium enolate of the tetracyclic ketone II and then into that of the open-chain ester III. The latter should undergo retrogression with sodium ethoxide to a considerable extent, with formation of tiglic not crotonic ester, but in the reaction in question the appearance of crotonic ester only was detected, nor was tiglic ester formed on refluxing I in ether solution with sodium ethoxide for several hours.

It has been shown experimentally, in agreement with the law of chemical neutralization, that such additions can take place only with degradation of free chemical energy. In these reactions, this is determined by the magnitude of neutralization of the positive chemical energy of the metallic atom of the enolate and, hence, addition is possible only when the energy of the metal is better neutralized in the addition product than in the original enolate. In the great majority of these reactions, the migration of the metal of the enolate would result in an increase of its free chemical energy. In agreement, it has been proved experimentally[9] that the hydrogen, not the sodium, of the —CONa—CH— group in the enolate migrates in such additions, provided a better neutralization of the metal is thereby obtained.[10]

Holden and Lapworth assumed that the metal of sodium enol methylmalonic ester united with the α-Δ-carbon of crotonic ester, or with the Δ-oxygen of the adjacent carbethoxyl, with positional rearrangement of unsaturation and the residual radical of the enolate united with the β-Δ-carbon to form IV. Intramolecular condensation of the Dieckmann type was now accepted and the reaction proceeded with elimination of

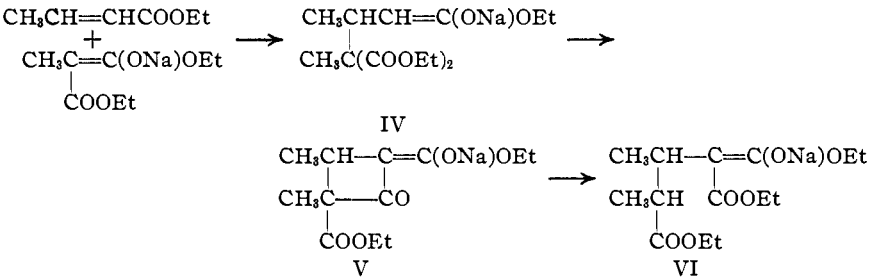
(7) Michael and Ross, THIS JOURNAL, **52**, 4601 (1930).

(8) Michael, *ibid.*, **52**, 3749 (1930).

(9) For literature on the subject, see Michael, *ibid.*, **52**, 4599 (1930); **53**, 1150 (1931).

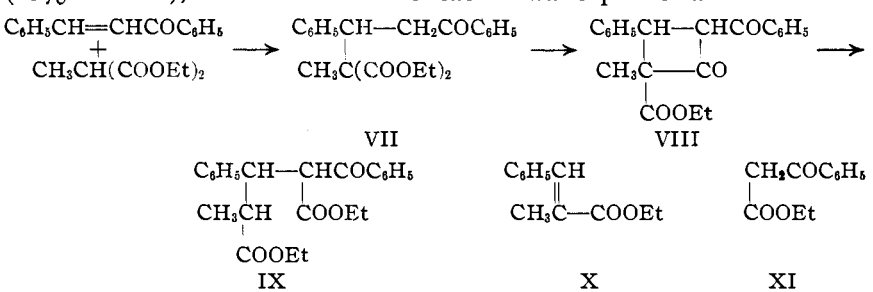
(10) From the formation of α,γ-dimethyl-γ-cyanoglutaric ester upon methylation of the addition product from sodium enol cyanoacetic and α-methylacrylic esters, Thorpe[2] concluded that the α-hydrogen, not the sodium, of the enolate migrated in the reaction. The conclusion was not proved conclusively by the result of this experiment. If the sodium had migrated, an enolate of a monocarbethoxy group would have been formed, which would have rearranged spontaneously to the enolate of the cyanocarbethoxy group and this derivative would give the α,γ-dimethyl ester obtained by Thorpe.

alcohol to form the tetracyclic structure V, followed by addition of alcohol to form the open-chain enolate VI:



The intermediate production of IV would mean that the sodium would leave its original position in the enolate of the dicarboxylic ester group of methylmalonic ester to form the enolate of a monocarboxylic ester group. Such a change is impossible, since it would imply an increase in the chemical energy of the sodium and the addition could not proceed with degradation of chemical energy. Again, there is experimental evidence[11] that an enolate with the structure of IV would retrograde spontaneously into crotonic and sodium enol methylmalonic esters. In the conversion of IV to V, an intramolecular condensation to a tetracyclic derivative was assumed, although all attempts to realize a tetracyclic enolate synthesis have been without success. Further, V should rearrange mainly to the intramolecularly, better neutralized enolate, in which the sodium is located at the γ-carbonyl group. This compound could not give VI by addition of alcohol, since the free chemical energy of the sodium would become thereby decidedly less neutralized. Even the conversion by alcohol addition of V to VI is theoretically improbable, since the free chemical energy of its sodium would become much less neutralized than in the stable enolate of V.

Holden and Lapworth support their interpretations by an examination of the reaction between sodium enol methylmalonic ester and benzalacetophenone (chalcone) in boiling benzene solution. Only products connected with retrogression, benzoylacetic (XI) and α-methylcinnamic (X) esters (45% of calcd.), were isolated. The reaction was expressed as

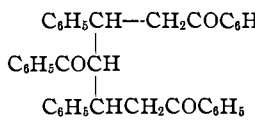


(11) Michael and Ross, THIS JOURNAL, **52**, 4602 (1930).

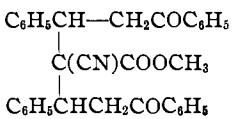
It was considered that the sodium derivative of the normal addition product (VII) would be formed in the first instance and that there would then occur indirectly an exchange of a γ-COOEt for an α-hydrogen, yielding ester IX, with possibly the ketonic ester VIII as the intermediate step. The experimental results were regarded as conclusive evidence of an indirect exchange of position of a carbethoxy group of VII with an α-hydrogen and as demonstrating that the proof offered by Michael and Ross for the mechanism of the sodium enol methylmalonic–crotonic esters addition is "fallacious."

We have found that in the presence of piperidine, or of a small amount (0.1 mole) of sodium ethoxide, methylmalonic ester adds readily to chalcone to give approximately an 80% yield of VII, α-methyl-α-carbethoxy-β-phenyl-γ-benzoylbutyric ester. However, the action of sodium ethoxide (1 mole) or of metallic sodium (1 mole) on ester VII causes almost complete retrogression in the cold to give sodium enol methylmalonic ester (90%) and chalcone, perhaps with a trace of benzoylacetic ester, as the product gives a slight color reaction with ferric chloride. Evidently, this result is directly opposed to the interpretation of Holden and Lapworth, but agrees with our previous observations that enolates of compounds of the type of α,β-dimethyl-α-carbethoxyglutaric ester (I) undergo retrogression to the original additive components.

Holden and Lapworth have not taken into consideration the extraordinary tendency of chalcone to form addition compounds involving two of its molecules with one of an addendum. Kostanecki and Tambor[12] obtained compound XII by the addition of acetophenone to chalcone.



XII



XIII

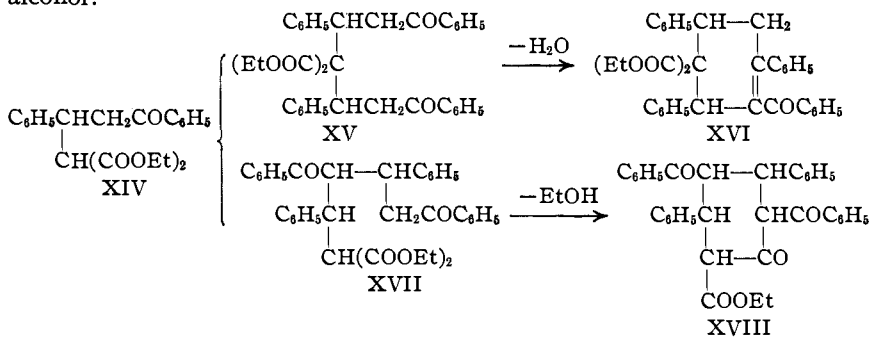
Kohler, Graustein and Merrill[13] found that it was difficult to prevent the formation of the "trimolecular" compound XIII in the addition of cyanoacetic methyl ester to chalcone, even when sodium ethoxide was used in small amount.

Dieckmann and Kron,[14] through the action of one mole of sodium enol malonic ester on two moles of chalcone, obtained a crystalline compound to which they assigned the hexacyclic structure XVIII.

α-Carbethoxy-β-phenyl-γ-benzoylbutyric ester (XIV), formed by the addition of malonic ester to chalcone,[15] may add to the latter in two ways, to give compounds XV and XVII, respectively. In the presence of sodium

(12) Kostanecki and Tambor, *Ber.*, **29**, 1495 (1896).
(13) Kohler, Graustein and Merrill, THIS JOURNAL, **44**, 2536 (1922).
(14) Dieckmann and Kron, *Ber.*, **41**, 1277 (1908).
(15) Kohler, *Am. Chem. J.*, **46**, 482 (1911).

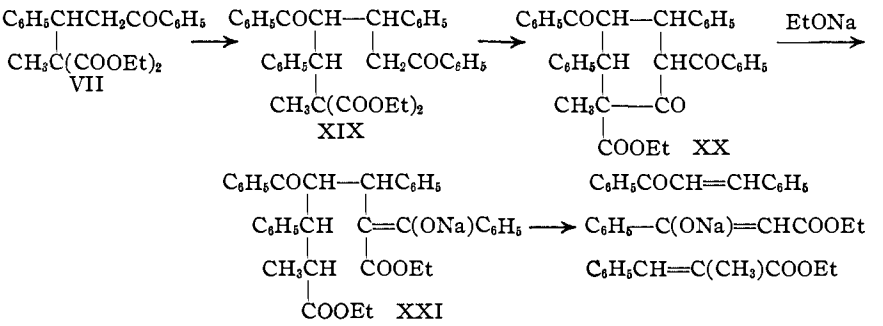
ethoxide, each of these may undergo condensation to a hexacyclic derivative; thus XV, by elimination of water, to give XVI, and the sodium enolate of XVII, to give the sodium enolate of XVIII by the elimination of alcohol:



We have reëxamined the action of sodium enol malonic ester on chalcone and have found that the compounds XVI, XVIII and XVII can be readily obtained. The formation of XVI, 1,3,5-triphenyl-2-benzoyl-4,4-dicarbethoxycyclohexene-1, is favored by an excess of sodium ethoxide and the absence of alcohol. The enolate of XVIII, 1,5-diphenyl-2,6-dibenzoyl-4-carbethoxycyclohexanone-3, is formed in the action of chalcone on XIV in the presence of slightly less than one equivalent of sodium ethoxide. To obtain XVII strict attention must be paid to the purity of the reagents and to the concentration of the sodium ethoxide. This open-chain ester (XVII) is partially converted by sodium ethoxide into the enolate of the cyclic keto ester XVIII and, conversely, ester XVIII, upon treatment with sodium ethoxide, passes over to a very considerable extent into the sodium enolate of XVII. In these introconversion reactions, a small amount of the neutral, cyclic, compound XVI is also formed.

Ester VII can form only compound XIX with a second molecule of chalcone. In the presence of sodium ethoxide, this open-chain derivative may be expected to yield a mixture of the two possible enolates of the cyclic ketone XX. According to the results of Dieckmann[16] on the point of rupture between carbon atoms in analogously constituted enolates, ring-fission of the enolates of XX by alcohol should lead to enolate XXI, and this upon retrogression should give a mixture of chalcone, α-methyl cinnamic and sodium enol benzoylacetic esters. These are the products obtained by Holden and Lapworth from sodium enol methylmalonic ester and chalcone in boiling benzene solution. The intermediate cyclic enolate formed in this reaction must be an extremely labile substance, for, as stated below, practically the same amounts of the retrogression products are formed on standing of the mixture in cold ether as in boiling benzene. The above reactions are represented in the following scheme

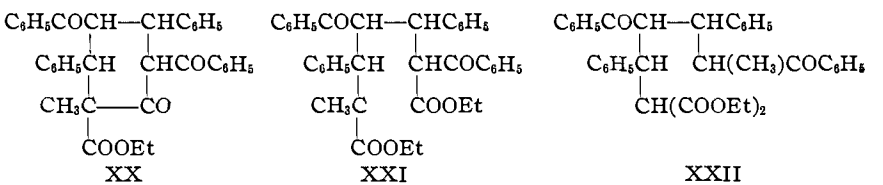
(16) Dieckmann, *Ber.*, **33**, 2670 (1900).

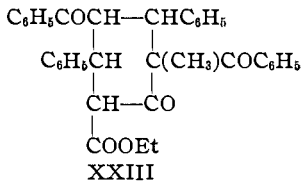


Attempts were made to prepare compounds XIX and XX, in order to examine their behavior toward sodium ethoxide. The products obtained by the action of sodium enol methylmalonic ester upon chalcone in cold ether solution were sodium enol benzoylacetic and α-methylcinnamic esters (50% approx.) and about 30% of a sirupy material of high molecular weight. From this sirup, a very small quantity of a crystalline solid was isolated which analyzed approximately for ester XIX, but it was obtained in too small an amount for further examination. Addition of chalcone to ester VII, using sodium ethoxide, gave similar results and no increase of the supposed ester XIX. In the presence of piperidine, or of a small amount of sodium ethoxide, methylmalonic ester and two molecules of chalcone gave only the primary addition compound VII.

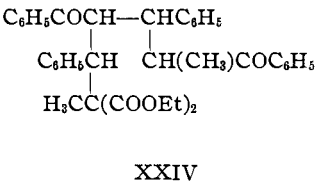
Resort was therefore made to the methylation of the sodium enolate of the cyclic derivative XVIII and that of the open-chain compound XVII. The latter can give only one enolate, involving the malonic ester group, and the former may give three enolates. However, as stated above, the enolates of the open-chain (XVII) and the cyclic (XVIII) compounds are intraconvertible and give a mixture in which that of XVII predominates. Evidently, XVII and XVIII should give the same products of methylation, which was confirmed by experiment. The reactions gave only a moderate yield of the methyl derivatives, probably due in part to polymerization of the mother substances. However, in accord with theory, the yield of the open-chain methyl derivatives was decidedly greater than that of the cyclic products.

Besides the cyclic 2- and 6-methyl derivatives (XX and XXIII, respectively), there were obtained the open-chain ϵ-methyl (XXII) and the α,ϵ-dimethyl (XXIV) products.



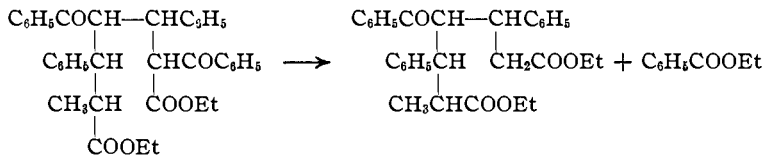


XXIII



XXIV

Upon addition to an ether–alcohol solution of sodium ethoxide, the cyclic 2-methyl keto ester (XX) dissolves immediately, with ring-fission by ethylate addition, to give the enolates of two apparently stereomeric[17] forms of XXI, and which upon warming in ether solution with ethylate undergo decomposition to form benzoic ester and α-methyl-β,β'-diphenyl-γ-benzoylpimelic ester (XXV)



XXI XXV

Upon treatment, in ether solution in the cold, with sodium ethoxide, the ester XXII was converted into an enolate of an isomer, and when heated in ether solution with sodium ethoxide it gave the sodium derivative of the cyclic ketone XXIII.

The structures attributed to the cyclic methyl derivatives XX and XXIII, and to the open-chain XXI and XXII, are based upon their behavior toward alcoholic ferric chloride. Ester XXII could enolize only at the malonic ester radical, but this group is always indifferent toward the reagent and the indifference of XXII conforms to the advanced structure. The cyclic XXIII contains the group RCOCHRCOOEt, which always shows the iron test and, accordingly, XXIII exhibits the enolic reaction. Theoretically, XX, and the two isomers XXI, formed from XX by addition of alcohol, should be susceptible to the reagent, since

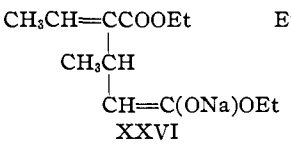
(17) The behavior of the isomeric esters XXIII and XX, and of XXII, toward sodium ethylate is without analogy in stereochemical reactions. No precedent is known for the conversion of XXII, before addition of alcohol, into the enolate of another form to yield finally the enolate of the cyclic XXIII; nor that XX should first give, by addition of ethylate, a mixture of the two open-chain enolates of XXI. It seems reasonable to suppose that XX, like XXIII, is converted into a mixture of its own and the enolate of a stereomer, and that the two stereomeric enolates of XXI are formed by addition of alcohol to the enolate mixture. It has recently been shown that an enolate may occur in stereomeric forms [Michael and Ross, THIS JOURNAL, **53**, 2401 (1931)].

Stereoisomerism is here used in the sense that certain organic compounds can find no expression in structural formulas and that the phenomenon in question is due to the spatial arrangements of the atoms in the molecules. This does not imply that the number and the configurations of the stereomers can always be coördinated with, or expressed in terms of, van't Hoff's views on spatial chemical isomerism. It has long been known that many organic isomers, stereomeric in the above sense, cannot be incorporated into the van't Hoff theoretical system, and that its space representations of the relations between saturated and unsaturated compounds are untenable. It is therefore difficult to understand that Lewis should have thought tenable spatial representations of the above relations from the octet viewpoint were obtained by changing from a conception of the carbon atom as a cube to that of a modified tetrahedron.—A. M.

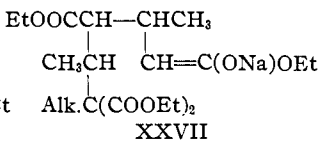
they contain the enolizable $C_6H_5COCHRCO$— group. It has been found, however, that certain compounds with similarly constituted groups, *i. e.*, $C_6H_5COCH(COOEt)CH(C_6H_5)CH_2COC_6H_5$, do not give the color test and structures assigned to XX and XXI therefore agree with their behavior toward ferric chloride.

That ester XX upon treatment with sodium ethoxide should give benzoic ester and the pimelic ester derivative XXV, instead of the possible retrogression products, may be due to an unfavorable configuration of the primarily formed XXI. Similar to the behavior of XXII, this may undergo stereomerization and the product undergo decomposition instead of retrogression. It is also possible that the use of sodium ethoxide, instead of sodium enol methylmalonic ester, may be the determinative chemical factor. Clearly there is a qualitative difference in the reactivity of sodium ethoxide and sodium enol methylmalonic ester, but had the latter been used as the reagent, there would have resulted an ambiguity in the interpretation of the results. Although retrogression of ester XXI in the presence of sodium ethoxide could not be experimentally demonstrated, it must still be considered as a possible reaction by which benzoylacetic enolate and α-methylcinnamic esters could be produced in the reaction between sodium enol methylmalonic ester and chalcone.

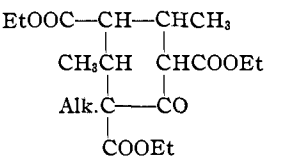
It has been shown that crotonic ester under the influence of sodium ethylate,[18] or of metallic sodium,[19] is converted, with polymerization of two molecules of the ester, into the sodium derivative of α-ethylidene-β-methylglutaric ester (XXVI). In the reaction between sodium enol alkyl malonic and crotonic esters, a hexacyclic derivative might be formed by the union of alkyl malonic ester with enolate XXVII to form enolate XXVII, which with loss of alcohol might form the enolate of the hexacyclic XXVIII.



XXVI



XXVII



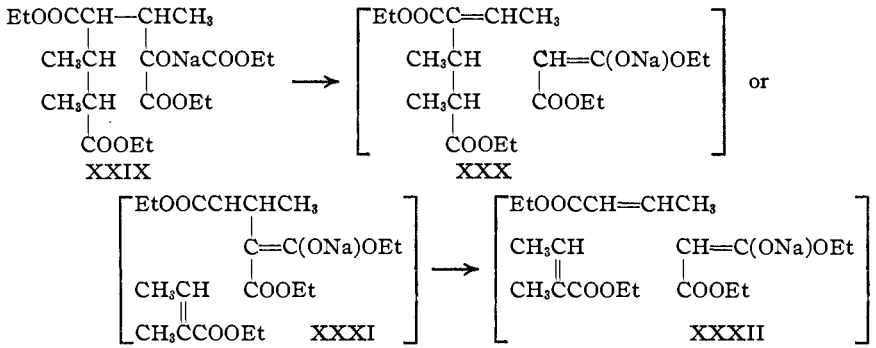
XXVIII

In a previous paper,[20] it was shown that in the action of sodium enol ethylmalonic ester on crotonic ester a considerable quantity of XXVI, the enolate of the polymerization product of crotonic ester, and comparatively little of the addition product (XXVII, alk. = C_2H_5), appeared. However, with sodium enol methylmalonic ester none of enolate XXVI was formed, nor was it formed in the action of sodium enol α-cyanopropionic ester, although there was obtained in this reaction a very small

(18) V. Pechmann, *Ber.*, **33**, 3340 (1900).
(19) Michael, *ibid.*, **33**, 3760 (1900).
(20) Michael and Ross, THIS JOURNAL, **53**, 1154 (1931).

amount of a keto ester, which may have had a hexacyclic structure corresponding to XXVIII.

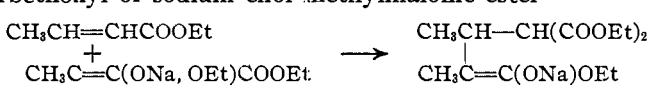
Fission of ester XXVIII (alk. = CH_3) by alcoholic ethoxide should give primarily the enolate of the open-chain ester XXIX, which upon retrogression should give the products designated under XXX, XXXI or XXXII, or a mixture of these, namely, crotonic, tiglic, α-carbethoxy-β-methylglutaric esters and the enolates of malonic and α,β-dimethyl-γ-ethylideneglutaric esters.



From these possible retrogression products the enolate of α,β-dimethyl-γ-carbethoxyglutaric ester (B) could be formed only by the union of sodium enol malonic and tiglic esters. But it has been shown[20] that the ease of addition and the relative yield of the addition product is much smaller from sodium enol malonic ester and tiglic than from crotonic ester. Therefore, among the possible retrogression products, the enolate of malonic ester would add to crotonic ester in a much larger proportion than to tiglic ester, and the final retrogression products should be a mixture of tiglic with a relatively small amount of crotonic ester and the sodium enolates of β-methyl-α-carbethoxyglutaric and malonic esters.

Since the main product of the action of sodium enol methylmalonic ester on crotonic ester was enolate B, and no tiglic ester, the hexacyclic structure XXVIII cannot be considered as a possible intermediate in the formation of B from sodium enol methylmalonic and crotonic esters.

Besides through the migration of methyl, the formation of an enolate addition product may be considered as occurring by the direct migration of the carbethoxyl of sodium enol methylmalonic ester



This interpretation seemed so improbable that it was not discussed previously. It implies the formation of a sodium enolate addition product in which the metal is less neutralized than in the employed enolate of methylmalonic ester. This course of migration would be contrary, therefore, to

the law of chemical neutralization and it is also to our knowledge of the nature of such addition reactions.

In conclusion, the arguments advanced above may be summarized as follows. It has been shown that the formation of the cyclobutanone structures II and VIII of Holden and Lapworth is theoretically extremely improbable, and experimentally not possible with the use of such reagents as sodium ethoxide and sodium. Sodium enol benzoylacetic and α-methylcinnamic esters, as products of the action of sodium enol methylmalonic ester on chalcone, may be retrogression products of a hexacyclic enolate, formed by the union of two molecules of chalcone and one molecule of the methylmalonic ester enolate. It has been shown that hexacyclic structures are formed under the conditions of the reaction, but it has not been possible to complete experimentally the chain of steps intermediate to the formation of benzoylacetic enolate and α-methylcinnamic esters. However, it has been shown that the enolate of α,β-dimethyl-α-carbethoxyglutaric ester (B), obtained by addition of sodium enol methylmalonic to crotonic esters, could not have been formed through retrogression from a hexacyclic structure of a similar type.

Experimental

Addition of Malonic Ester to Benzalacetophenone.—α-Carbethoxy-β-phenyl-γ-benzoylbutyric ester was obtained as a solid melting at 71°, as described by Kohler,[15] by addition of malonic ester to one molecular equivalent of chalcone in ether solution, in the presence of a small amount of sodium ethoxide (0.1 mole), or a few drops of piperidine. The ester crystallized in fine needles from a mixture of ether and ligroin.[21]

α-Carbethoxy-β-phenyl-γ-benzoylbutyric acid was obtained from the above ester by saponification with alcoholic potash. Upon acidifying a sirupy product was obtained, which crystallized from an ether–ligroin mixture in fine needles, melting at 165° with decomposition.

Anal. Calcd. for $C_{18}H_{16}O_5$: C, 69.23; H. 5.57. Found: C, 69.05; H, 5.65.

From the mother liquor, or by slow crystallization, larger needle-like crystals were obtained, melting at 145°.[22]

Anal. Found: C, 69.12; H, 5.7.

The higher-melting acid was slowly converted into the lower-melting form upon standing in the air, or by slow recrystallization, but the higher-melting form was stable in a desiccator.

Action of One Mole of Sodium Enol Malonic Ester on Two Moles of Benzalacetophenone.—To a suspension of 1.2 g. of pulverized sodium in ether, 8 g. of malonic ester was added. When the reaction was complete (twelve hours) a solution of 20.8 g. of chalcone in ether was added and then ether until the total volume was 300 cc. The mixture, cooled in ice water, was left for twenty-four hours, and an excess of acetic acid was slowly added with vigorous shaking. The ether solution was washed with

(21) Barat [*J. Indian Chem. Soc.*, **7**, 333 (1930)] described a compound, m. p. 150°, obtained by addition of malonic ester to benzalacetophenone, which upon saponification with caustic potash, gave an acid, m. p. 152–154°, and the latter when heated gave a "lactol," m. p. 158°. The appearance of the compound of m. p. 150°, which Barat considered to be α-carbethoxy-β-phenyl-γ-benzoylbutyric ester (VII), we are unable to explain. In no experiment did we obtain a pure compound that would correspond to a substance of this melting point and analysis.

(22) Vorländer and Knotzsch [*Ann.*, **294**, 332 (1897)] first obtained this acid.

aqueous sodium carbonate, then with water and the neutral solution dried and concentrated to about 100 cc. Cooling, or addition of ligroin, caused separation of crystals in the following order: very fine needles of the hexacyclic keto ester (XVI), m. p. 235°; large hexagonal prisms of the hexacyclic keto ester (XVIII), m. p. 187°; large needles of the open-chain keto ester (XVII), m. p. 197°;[23] and, finally, fine needles of α-carbethoxy-β-phenyl-γ-benzoylbutyric ester (XIV), m. p. 71°.

1,3,5-Triphenyl-2-benzoyl-4,4-dicarbethoxycyclohexene-(1) (XVI).—When two moles of sodium ethoxide are used with one mole of malonic ester and two moles of chalcone then the main product (70%) is ester XVI. Experiments indicated that the formation of this compound is favored by an excess of sodium ethoxide and prolonged time of reaction. It crystallizes from chloroform in fine needles, m. p. 235°.

Anal. Calcd. for $C_{37}H_{34}O_6$: C, 79.57; H, 6.09. Found: C, 79.55; H, 5.85.

When warmed with alcoholic potash, it dissolved and after a few minutes a neutral, yellow oil was liberated. The aqueous extract when acidified gave α-carbethoxy-β-phenyl-γ-benzoylbutyric acid, m. p. 165°. The neutral, yellow oil, which did not crystallize, was probably a condensation, or a polymerized, product of chalcone.

Addition of Malonic Ester to Two Moles of Benzalacetophenone.—A solution of 8 g. of malonic ester and 20.8 g. of chalcone in 200 cc. of ether was added to a sodium ethoxide solution from 0.2 g. sodium in 4 cc. of alcohol and the mixture allowed to stand at room temperature for six weeks. Upon examination it was found that 0.5 g. of the hexacyclic keto ester XVIII and 17 g. of ester XIV were formed.

1,5-Diphenyl-2,6-dibenzoyl-4-carbethoxycyclohexanone-3 (XVIII).—After preliminary experiments, the following conditions were found to give the best yield: 0.5 g. of sodium was dissolved in 8 cc. of absolute alcohol and 100 cc. of dry ether added, when solution was complete. A solution of 104 g. of chalcone and 40 g. of malonic ester in 500 cc. of dry ether was then cooled to 0° and quickly added to the solution of sodium ethoxide. After a few minutes, it was necessary to cool the mixture in ice water and it then stood for twenty-four hours. A solution of 4.5 g. of sodium in 70 cc. of absolute alcohol was prepared, diluted with 100 cc. of ether and cooled to 0°. To this solution the above mixture was added with stirring and, after diluting with ether to one liter, the mixture was left to react for twenty-four hours.

The solution was acidified with acetic acid, washed with water and the acid and neutral products separated by extracting with 10% sodium carbonate solution. After drying, the ether solution of the neutral products was reduced to one-half of its volume by distilling off ether. Upon standing (sometimes before concentrating) the cyclic ketonic ester XVIII separated as large highly refractive prisms. A further quantity was obtained by addition of petroleum ether to the mother liquor, but this second crop contained some of the open-chain ester XVII, m. p. 197°. The material in the mother liquor consisted of chalcone and ester XIV. By treatment with a further quantity of sodium ethoxide in the preceding manner (using less than one equivalent of sodium ethoxide) a further quantity of the hexacyclic keto ester XVIII was obtained.

Anal. Calcd. for $C_{35}H_{30}O_5$: C, 79.23; H, 5.53. Found: C, 79.13; H, 5.7.

A solution of this compound in acetic ester was added to an equivalent of sodium ethoxide in alcoholic solution and the mixture allowed to stand at room temperature for four hours. The neutral product of reaction consisted mainly (60%) of α-carbethoxy-β,δ-diphenyl-γ,ε-dibenzoylcaproic ester (XVII), approximately 30% of the unchanged cyclic ketonic ester and a small amount (10%) of ester XVI.

(23) Dieckmann and Kron [*Ber.*, **41**, 1277 (1908)] in this reaction obtained a 20–30% yield of a crystalline compound, which melted at 197° and analyzed for the cyclohexene derivative XVI. We found that the compound corresponding to this analysis had m. p. 235°; the ester melting at 197° gave figures on analysis in agreement with the open-chain structure XVII. Moreover, the conversion of XVII into XVIII confirms the structure we have ascribed to this ester.

α-Carbethoxy-β,δ-diphenyl-γ,ε-dibenzoylcaproic Ester (XVII) crystallizes from a mixture of ether and chloroform in long needles and melts at 197°. It gives no color with ferric chloride in alcoholic solution.

Anal. Calcd. for $C_{37}H_{36}O_6$: C, 77.10; H, 6.25. Found: C, 77.29; H, 6.1.

When treated in acetic ester solution with two equivalents of sodium ethoxide in the cold, it is almost entirely converted into the enolate of the hexacyclic ketonic ester XVIII.

Upon methylation of the sodium enolate of XVII in acetic ester solution with methyl iodide, the same products were formed as by methylation of the sodium enolate of the hexacyclic ketonic ester XVIII.

Methylation of 1,5-diphenyl-2,6-dibenzoyl-4-carbethoxycyclohexanone-3 (XVIII).—To a solution of 0.9 g. of sodium in 15 cc. of absolute alcohol 21 g. of XVIII dissolved in 400 cc. absolute, cold acetic ester was added with stirring. After a few minutes, an excess of methyl iodide (40 cc.) was added and the mixture allowed to stand at room temperature for twelve hours. It was then heated on the water-bath for six hours, when the solution was neutral to litmus. After distilling off the excess of solvent and reagent, the solution was cooled, washed with dilute mineral acid, then with aqueous soda and dried. The last traces of acetic ester were removed by heating in a vacuum, with the distilling flask in a water-bath. The residual sirup was then taken up in ether and the following compounds in turn crystallized out

(a) Ester XVII, m. p. 197°, 3 g.
(b) Ester XXII, m. p. 237°, 2 g.
(c) Ester XX, m. p. 170°, 1 g.
(d) Ester XXIII, m. p. 210°, 1 g.

There were also obtained small amounts of esters XXV and XX and there remained a considerable amount of unresolved material as a sirupy mixture.

α-Carbethoxy-β,δ-diphenyl-γ,ε-dibenzoyl-ε-methylcaproic Ester (XXII).—This compound crystallizes from chloroform–ether solution in large rhombic prisms, melting at 237°. It gives no color with alcoholic ferric chloride.

Anal. Calcd. for $C_{38}H_{38}O_6$: C, 77.29; H, 6.44. Found: C, 77.54; H, 6.36.

One gram of the ester was powdered and added to a solution of 0.05 g. of sodium in 2 cc. of alcohol and the mixture diluted with ether. On shaking for about five minutes all the ester dissolved to form a yellow solution from which separated a small amount of a solid sodium derivative. After standing overnight, the mixture was acidified and flat needles, melting at 192°, gradually separated. This compound gives no color with alcoholic ferric chloride and according to the analysis it is isomeric or stereomeric with the original ester.

Anal. Calcd. for $C_{38}H_{38}O_6$: C, 77.29; H, 6.44. Found: C, 77.05; H, 6.20.

1,5-Diphenyl-2-methyl-2,6-dibenzoyl-4-carbethoxycyclohexanone-3-one (XXIII).—One gram of ester XXII was powdered, added to a solution of 0.05 g. of sodium in 2 cc. of alcohol and the mixture diluted with ether. After twelve hours it was heated with a reflux condenser on a water-bath for six hours. After cooling and acidifying, there was obtained 0.7 g. of ester XXIII, melting at 175° and crystallizing as large needles from chloroform–ether solution. It gives a deep red color with alcoholic ferric chloride.

Anal. Calcd. for $C_{36}H_{32}O_5$: C, 79.41; H, 5.93. Found: C, 79.33; H, 6.0.

1,5-Diphenyl-2,6-dibenzoyl-4-methyl-4-carbethoxycyclohexanone-3 (XX).—This compound, formed in the methylation of the sodium enolate of XVIII, crystallizes in fine needles from a chloroform–ether mixture, melting at 170°. It gives no color with alcoholic ferric chloride.

Anal. Calcd. for $C_{36}H_{32}O_5$: C, 79.41; H, 5.93. Found: C, 79.30; H, 5.90.

Two grams of ester XX was brought into a solution of 0.1 g. of sodium in 3 cc. of absolute alcohol and ether added. The ester dissolved immediately, forming a deep red solution. In an hour, a small amount of a solid sodium derivative separated. After twelve hours, the mixture was acidified and there was obtained 1.7 g. of a mixture of esters, which were separated by fractional crystallization into two products. One is an ester, melting at 188°, crystallizing in large regular cubes. Analysis agrees with the open-chain structure XIX. It gives no color with alcoholic ferric chloride.

Anal. Calcd. for $C_{38}H_{38}O_6$: C, 77.29; H, 6.44. Found: C, 77.42; H, 6.24.

The other product is an ester, melting at 210°, crystallizing in fine needles or nodular groups of needles. It gives no color with alcoholic ferric chloride. It is apparently a stereomer of XIX.

Anal. Calcd. for $C_{38}H_{38}O_6$: C, 77.29; H, 6.44. Found: C, 77.25; H, 6.30.

Two grams of the cyclic ester XX was added to a solution of 0.1 g. of sodium in 3 cc. of absolute alcohol and dry ether added. The solution of the enolate was heated with a reflux condenser for six hours. After cooling, it was acidified, the solution washed with aqueous soda and dried. On standing a neutral compound gradually crystallized out. There was obtained 1.0 g. of ester XXV, which crystallized as fine needles from ether–chloroform and melted at 154°. It gave no color with ferric chloride in alcoholic solution.

Anal. Calcd. for $C_{31}H_{34}O_5$: C, 76.53; H, 7.0. Found: C, 76.60; H, 6.80.

From the mother liquor, upon vacuum distillation in an oil-bath heated to 150°, a small amount (0.1 g.) of benzoic ester was obtained, which was identified by conversion into benzoic acid. The residue, after removal of the benzoic ester, contained a mixture of the open-chain, stereomeric ester XXI.

From the soda extract, 0.3 g. of material was obtained consisting of benzoic acid. It was purified by sublimation and identified by a mixed melting point.

α-Carbethoxy-α,ε-dimethyl-β,δ-diphenyl-γ,ε-dibenzoylcaproic Ester (XXIV).—This substance, melting at 210°, was obtained by methylation of the sodium enolate of XVIII. It crystallizes in flat needles or nodules and gives no color with ferric chloride.

Anal. Calcd. for $C_{39}H_{40}O_6$: C, 77.49; H, 6.62. Found: C, 77.37; H, 6.4.

It is not soluble in alcoholic sodium ethoxide and is acted upon only slowly by this reagent.

Addition of Methylmalonic Ester to Benzalacetophenone.—α-Carbethoxy-β-phenyl-γ-benzoyl-α-methylbutyric ester (VII) is obtained by addition of methylmalonic ester to one molecular equivalent of chalcone in ether solution, in the presence of a small amount of sodium (0.1 mole), or of a few drops of piperidine. The yield is about 80%. It crystallizes in large needles from a mixture of ether and ligroin and melts at 95°.

Anal. Calcd. for $C_{23}H_{26}O_5$: C, 72.21; H, 6.86. Found: C, 72.05; H, 6.6.

Upon treatment, in ether solution, with phenylhydrazine, it gives a phenylhydrazone, crystallizing in needles and melting at 130°.

Anal. Calcd. for $C_{29}H_{34}O_4N_2$: C, 73.41; H, 7.17. Found: C, 73.20; H, 7.3.

Upon warming with alcoholic potash, a vigorous reaction occurred with liberation of a yellow oil. This consisted, probably, mainly of chalcone; methylmalonic acid was isolated after acidifying the alkaline solution.

A solution of 9.5 g. of the ester in dry ether was allowed to react in the cold with 0.6 g. of powdered sodium. After twenty-four hours, most of the sodium had dissolved with slow evolution of a gas. From the neutral product of the reaction there was obtained 3.5 g. of methylmalonic ester, b. p. 80–90° (5 mm.), and 5.0 g. of a sirup which could not be distilled without decomposition, nor could it be obtained in a crystalline form.

An ether solution of 9.5 g. of the ester was mixed with sodium ethoxide, prepared by Brühl's method from 0.6 g. of granulated sodium. After twenty-four hours the mixture was acidified. From the neutral product there was obtained 3.8 g. of methylmalonic ester, and 5.0 g. of a sirup which crystallized on long standing and proved to be chalcone.

In the above two experiments no isolable amount of benzoylacetic or α-methylcinnamic esters was obtained. After removal of the methylmalonic ester, the residual sirup gave a faint red coloration with alcoholic ferric chloride, which might have indicated the presence of a very little of a β-keto ester (benzoylacetic ester).

Addition of Methylmalonic Ester (1 Mole) to Benzalacetophenone (2 Moles).—8.7 grams of methylmalonic ester was added to a solution of 21 g. of chalcone in ether and the mixture united with a solution of 0.1 g. of sodium in 3 cc. of absolute alcohol. After twenty-one days the solution was acidified and the reaction product worked up. It was found to consist of α-methyl-α-carbethoxy-β-phenyl-γ-benzoylbutyric ester (16 g.), methylmalonic ester (1.5 g.), chalcone (10 g.) and traces of benzoylacetic and cinnamic esters.

When piperidine was used instead of sodium ethoxide, the products were the butyric ester derivative and unchanged chalcone.

Addition of Sodium Enol Methylmalonic Ester to Benzalacetophenone.—8.7 grams of methylmalonic ester in ether solution was treated with 1.2 g. of pulverized sodium. When the reaction was complete, a solution of 20.8 g. of chalcone in dry ether was added and the volume made up to 300 cc. by further addition of ether. The mixture, cooled in ice water, was left for twenty-four hours, and it was then acidified with acetic acid. The neutral part of the reaction product was heated in an oil-bath up to 150° in a vacuum, and the distillate fractionated. There were obtained 2.5 g. of methylmalonic ester, b. p. 75–90° (2 mm.), 7.5 g. of α-methylcinnamic and benzoylacetic esters, b. p. 120–140° (2 mm.). The residue, consisting mainly of chalcone with products of polymerization, was dissolved in ether and ligroin added. On standing, a small amount (0.5 g.) of a solid was obtained, which was separated by fractional crystallization from chloroform–ether into two compounds, melting approximately at 185° and 235°, respectively. Owing to the small amount a further examination was impossible.

Action of Benzalacetophenone on α-Methyl-α-carbethoxy-β-phenyl-γ-benzoylbutyric Ester in Presence of Sodium Ethoxide.—Sodium ethoxide, prepared by the method of Brühl from 1.2 g. of granulated sodium, was suspended in dry ether and an ether solution of 19.2 g. of the butyric ester derivative and 10.8 g. of chalcone added. The mixture stood in the cold for twenty-four hours. Upon working up, as in the preceding experiment, there were obtained 5 g. of methylmalonic ester, 3 g. of a mixture of α-methylcinnamic and benzoylacetic esters, b. p. 120–140° (2 mm.), 0.5 g. of unchanged butyric derivative and a sirupy residue consisting of chalcone and amorphous products.

Summary

1. The action of sodium enol malonic ester on benzalacetophenone has been investigated, and the conditions for the two modes of addition of the latter to α-carbethoxy-β-phenyl-γ-benzoylbutyric ester determined.

2. It has been shown that one molecule of sodium enol malonic ester reacts readily with two molecules of benzalacetophenone to form two hexacyclic derivatives.

3. The addition of methylmalonic ester, and of sodium enol methylmalonic ester, to benzalacetophenone has been examined, the mechanism of the latter reaction discussed and Holden and Lapworth's interpretation shown to be impossible.

4. Contrary to the assumption of Holden and Lapworth, the production of benzoylacetic enolate and α-methylcinnamic esters in the action of sodium enol methylmalonic ester on benzalacetophenone, has no theoretical connection with the formation of sodium enol α,β-dimethyl-γ-carbethoxyglutaric ester in the union of sodium enol methylmalonic and crotonic esters.

5. It has been shown that α-methyl-α-carbethoxy-β-phenyl-γ-benzoylbutyric ester, and α-carbethoxy-α,β-dimethylglutaric ester, do not form cyclobutanone structures when treated with sodium ethoxide or sodium, but undergo almost complete retrogression. These esters, or their enolates, therefore, cannot be intermediates in the addition reactions discussed above and for this reason alone the interpretations of Holden and Lapworth are untenable.

6. Certain difficulties arising from the assumptions of Holden and Lapworth have been discussed and it has been shown that the only explanation of the formation of the enolate of α,β-dimethyl-γ-carbethoxyglutaric ester from sodium enol methylmalonic ester, consistent with experiment and theory, is the migration of methyl during the addition process.

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The Action of Bleaching Powder on Ketones and on Ethyl Acetoacetate

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In contrast to the general familiarity of the reaction between acetone and bleaching powder, very little is known of the action of bleaching powder on other ketones. Three substances each containing a CH_3CO- group were selected for study, namely, ethyl methyl ketone, furfuralacetone and ethyl acetoacetate.

Ethyl methyl ketone was selected to see if the reaction would yield chloroform and calcium propionate or ethylidene chloride and calcium acetate. Only the first of these two possibilities was realized. This provides a convenient source of propionic acid. Furfuralacetone, similarly studied, was found to be an excellent starting material for furylacrylic acid. Since furfuralacetone is readily prepared from furfural and acetone this method for the synthesis of furylacrylic acid is preferable to the Perkin reaction[2] which employs furfural, acetic anhydride and potassium acetate as reagents.

(1) Holder of a Quaker Oats Fellowship (1929–1930) administered through the Miner Laboratories, Chicago.

(2) Baeyer, *Ber.*, **10**, 357 (1877).