THE PARTITION PRINCIPLE AS APPLIED TO THE STRUCTURES OF ENOLIC SODIUM DERIVATIVES OF 1,3-DIKETONES AND BETA-KETO ESTERS

BY ARTHUR MICHAEL AND JOHN ROSS

The partition principle of Thomsen[1] was based upon the distribution of an insufficient amount of base for complete neutralization between two acids. This principle was extended to the course of organic reactions,[2] and was verified experimentally with a number of typical organic reactions.[3] Accordingly, the distribution of the sodium in a compound capable of reacting in more than one enolic form would be expected to follow the partition law, and the ratio of the amounts of the sodium enolates should stand to one another in a definite relation to the avidities of the corresponding enolic structures.

Geuther[4] represented the structures of acetoacetic ester and the sodium derivative by $CH_3C(OH)\!=\!CHCOOEt$ and $CH_3C(ONa)\!=\!CHCOOEt$ and although this conception was accepted by Claisen, Nef and other chemists, the commonly accepted view was that of Frankland[5] and J. Wislicenus[6] who considered the formulas CH_3COCH_2COOEt and $CH_3COCHNaCOOEt$, respectively, to represent these compounds. In 1888 it was shown,[7] theoretically and experimentally, that the chemical relations of these substances could be explained only from the keto structure $CH_3CO\text{-}CH_2COOEt$ for the ester and the enol structure $CH_3C(ONa)\!=\!CH\text{-}COOEt$ (I), for the sodium derivative. However, it was emphasized[8] that a solution of the sodium compound should also contain some of the isomeric derivative $CH_3COCH\!=\!C(ONa)OEt$ (II), since malonic ester yields an enolate, and the formula of acetoacetic ester may be derived from that of malonic ester by replacing one of the carbethoxy groups of the former by the more negative acetyl group; further, that the relative amount of (I) should largely exceed that of (II), since acetyl is a much more negative radical than carbethoxyl.

This view is supported by the fact that along with the main product

[1] Thomsen, *Pogg. Ann.*, **135**, 497 (1869).

[2] Michael, *J. prakt. Chem.*, **60**, 341 (1899); *Ber.*, **39**, 2138 (1906); THIS JOURNAL, **32**, 1005 (1910).

[3] Michael, *Ber.*, **39**, 2133–2156, 2569, 2786–2795 (1906); **40**, 140 (1907).

[4] Geuther, *Jahresb.*, 323 (1863); *Z. Chem.*, 652 (1868); *Ann.*, **219**, 123 (1883).

[5] Frankland, *ibid.*, **138**, 204, 328 (1866).

[6] J. Wislicenus, *ibid.*, **186**, 163 (1877).

[7] Michael, *J. prakt. Chem.*, **37**, 473 (1888); *Am. Chem. J.*, **10**, 158 (1888); **14**, 481 (1892).

[8] Michael, *J. prakt. Chem.*, **37**, 488 (1888).

of the action of chlorocarbonic ester upon the sodium enol acetoacetic ester, viz., $CH_3C(OCOOEt){=}CHCOOEt$ (III),[9] some of the isomeric CH_3-$COCH(COOEt)_2$ (IV) is formed.[10] Since it has not been possible to convert the O-carbethoxy ester (III) into the enolic sodium derivative of (IV),[12] it would appear that (III) and (IV) are formed from the corresponding sodium derivatives I and II.

A reagent that would react with equal velocity with each of the above sodium enol derivatives to give stable products derived from the structures of the corresponding enols could be used to demonstrate the existence of such sodium enolic compounds, and the relative amounts should be in direct relation to the avidities of the enol structures; but no reagent is known that entirely fulfils these ideal conditions. In certain reactions, such as the above example of the sodium enol derivatives of acetoacetic ester, chlorocarbonic ester is the best reagent available but the proportions even in this case can only be accepted qualitatively.

J. Wislicenus[13] showed that the time required for complete reaction in alcoholic solution with a series of alkyl iodides was greater for sodium enol acetoacetic ester than for the α-ethyl derivative, and much greater than for sodium enol malonic ester. A comparison of the rates of reaction at 25° of methyl iodide and ethyl bromide with sodium enol malonic ester and sodium enol acetoacetic ester is given in the curves. which very clearly show that the reaction velocity with both of these alkyl halides is much greater for sodium enol malonic ester than for sodium enol acetoacetic ester.

The alkyl halide was added to an alcoholic solution of the sodium enol malonic ester and sodium enol acetoacetic ester prepared by adding the esters to the alcoholic solution of sodium ethoxide. At certain intervals, samples of the reaction mixture were removed by a pipet, immediately added to an excess of cold dilute hydrochloric acid, and the excess of acid titrated with alkali. The error due to formation of neutral sodium salts of carboxylic acids was probably small under these conditions.

The above reactions were carried out with approximately 2 N solutions, this being the concentration usually employed for alkylation of sodium enol derivatives of this type. For comparison, the curve for the rate of reaction between the alkyl halides and sodium ethoxide in alcohol is placed alongside the curves for sodium enol acetoacetic and malonic esters. The reaction with methyl iodide in all cases proceeds very rapidly

[9] Michael, J. prakt. Chem., 37, 474 (1888); 45, 583 (1892).

[10] Nef [Ann., 266, 105 (1891); 276, 213 (1893)] stated that it is formed in considerable proportion, but Michael [Am. Chem. J., 14, 491 (1892)] showed that less than 10% is formed, which proportion was confirmed by Claisen.[11]

[11] Claisen, Ber., 25, 1761, 1767 (1892).

[12] Michael, ibid., 38, 2089 (1905).

[13] Wislicenus, Ann., 212, 239 (1882).

with these concentrations, and it was impossible in the case of malonic ester to prevent a small rise of temperature. With ethyl bromide the reaction velocity could be examined more accurately. It should be noticed that half the sodium had reacted with ethyl bromide within thirty minutes in the case of sodium enol malonic ester, and within eighteen hours in the case of sodium enol acetoacetic ester. The curves for the reactions between the alkyl halides and sodium ethoxide are of interest. With methyl iodide the reaction velocity of sodium ethoxide is less than for sodium enol acetoacetic ester, but with ethyl bromide the reverse relation exists. It is apparent, therefore, that using an alcoholic solution of sodium enol acetoacetate, a larger percentage yield of alkyl derivative will be obtainable with methyl iodide than with ethyl bromide.
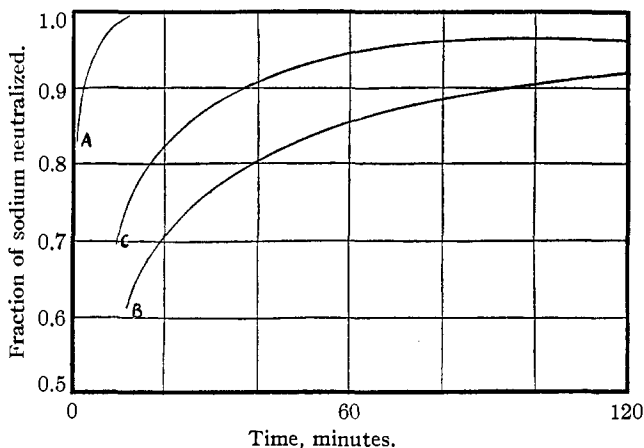

Fig. 1.—A, CH_3I + NaOEt + $CH_2(COOEt)_2$.
B, CH_3I + NaOEt + C_2H_5OH.
C, CH_3I + NaOEt + CH_3COCH_2COOEt.

When the reaction of methyl iodide (1 mole) with an alcoholic solution of equimolecular amounts of sodium ethoxide, acetoacetic and malonic esters was carried out at 0°, the product was found to consist of 6% methylmalonic ester and 70% methylacetoacetic ester. Under the same conditions using ethyl bromide, the product contained 30% ethylmalonic ester and only a trace of ethylacetoacetic ester. Therefore, using methyl iodide, the main reaction resulted in alkylation of acetoacetic ester, while with ethyl bromide, the main reaction was the alkylation of malonic ester.

These results and those of Wislicenus agree with the conclusion that the velocity relations in the action of alkyl halide upon the sodium derivatives of organic compounds depend upon the free positive chemical energy of the sodium in the respective compounds.[14]   Thus, while methyl

[14] See Michael, THIS JOURNAL, 32, 1003 (1910).

iodide replaces readily the sodium in sodium enol acetoacetic ester, by methyl, it does so with greater difficulty with sodium enol formylaceto-acetic ester;[15] it can substitute the sodium of the sodium derivative of the more acidic enol oxalacetic ester only at a higher temperature (100°), and then with a poor yield;[16] and the well neutralized sodium of sodium enol nitromethane, or that of any neutral organic salt, cannot be replaced by methyl in this way,
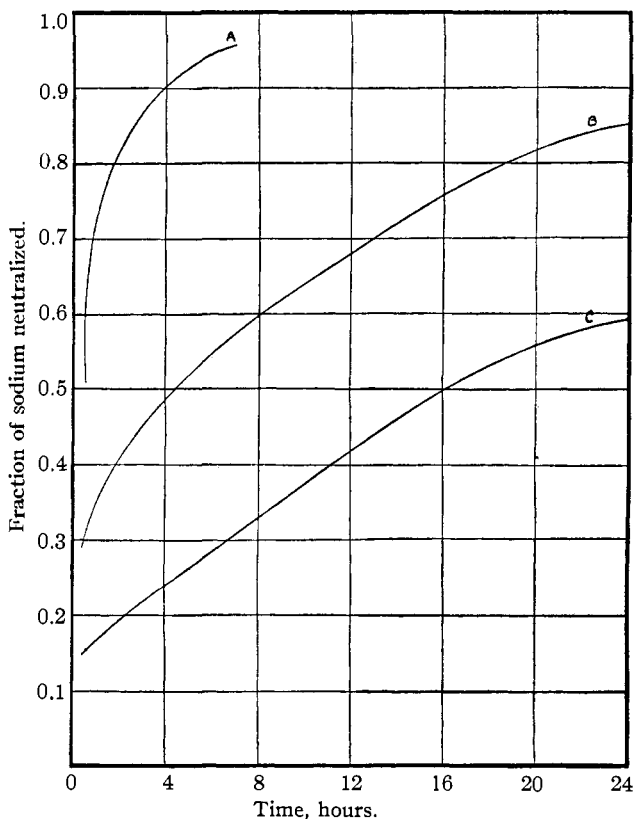

Fig. 2.—A, C_2H_5Br + NaOEt + $CH_2(COOEt)_2$.
B, C_2H_5Br + NaOEt + C_2H_5OH.
C, C_2H_5Br + NaOEt + CH_3COCH_2COOEt.

Since enol acetoacetic ester is decidedly more acidic than enol malonic ester, the distribution of the sodium in the above mixture must have been largely at the acetoacetic ester residue and, as there is a relatively small difference in the reaction velocity of methyl iodide toward the two sodium derivatives, the presence of the much larger mass of sodium enol aceto-

[15] Michael, *Ber.*, **38**, 2098 (1905).
[16] Wislicenus and Arnold, *Ann.*, **246**, 336 (1888).

acetic ester mainly determined the proportions of the reaction products. It follows from the greater percentage of ethylation of the malonic than of the acetoacetic enolate with the use of the much less reactive ethyl bromide, that a transference of sodium from sodium enol acetoacetic ester to malonic ester must occur during the reaction. This conclusion evidently conforms with the partition principle.

The methylation of α-acetyl-α'-carbethoxysuccinic ester (V) through its enolic sodium derivative was then examined to ascertain whether a partition of sodium among the possible enolic forms of this ester could be proved by use of methyl iodide as a reagent. The ester (V) should be capable of forming three structural sodium derivatives (VI), (VII) and (VIII). Upon alkylation (VI) and (VII) would give the same α-acetyl-α-methyl-α'-carbethoxysuccinic ester (IX), and the sodium derivative (VIII) would give the isomeric α-acetyl-α'-methyl-α'-carbethoxysuccinic ester (X).

$$
\begin{array}{ccccc}
CH_3C(ONa){=}CCOOEt & \longleftarrow & CH_3COCHCOOEt & \longrightarrow & CH_3COCHCOOEt \\
\quad | & & \quad | & & \quad \\
EtOOCCHCOOEt & & CH(COOEt)_2 & & EtOOC\ C{=}C(ONa)OE \\
\quad \downarrow\ VI & & V\ \downarrow & & VIII\ \downarrow \\
CH_3COC(CH_3)COOEt & & CH_3COC{=}C(ONa)OEt & & CH_3COCHCOOE \\
\quad | & \longleftarrow & \quad | & & \quad | \\
CH(COOEt)_2 & & EtOOCCHCOOEt & & CH_3C(COOEt)_2 \\
\quad IX & & VII & & X
\end{array}
$$
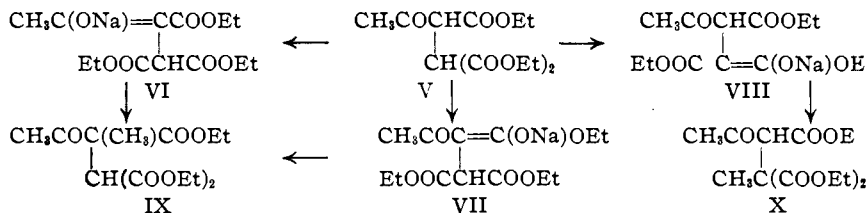
Treating the alcoholic solution of the sodium derivative of ester (V) with methyl iodide at $0°$ gave mainly α-acetyl-α'-methyl-α'-carbethoxysuccinic ester and no evidence of the formation of the isomeric ester (IX) could be obtained. Methylation therefore occurred at the malonic residue in preference to the acetoacetic residue, notwithstanding that there must have been a larger amount of sodium at the latter group in the original solution of sodium enolates. This result showed the much greater reactivity of the malonic enolate group compared with the acetoacetic enolate group.

In the original solution the sodium enol derivative (VI) should preponderate; there should also be a certain amount of the enolate (VII) together with a much smaller proportion of (VIII). In the structures (VI) and (VII) a greater neutralization of the sodium is realized, being directly derived from the enol forms of acetoacetic ester, as well as being indirectly under the influence of the negative malonic residue. In structure (VIII) the sodium is directly attached to the enolic malonic residue and is only under the indirect spatial influence of the enol acetoacetic residue. Evidently, the sodium atoms of Formulas (VI) and (VII) are relatively neutral compared with the sodium in (VIII). The experiment showed that the reaction occurred at the malonic enolate group, and that the enolates (VI) and (VII) are practically inert toward methyl iodide

under the experimental conditions. The entrance of the methyl group at the malonic residue proves that methyl iodide cannot be used to ascertain the position of the sodium in the sodium derivatives of esters of the mixed type (V).

The structure of the methylated ester (X) was determined by saponification with barium hydroxide, when a mixture of α-methyl-α-carboxy-succinate was obtained together with α-methyl-α-carboxy levulinate. There was also formed a small amount of the salt of 1,2-dimethylcyclo-penta-3,5-dione-1,2-dicarboxylic acid (XII). It was shown that ester (V) readily forms the sodium derivative of cyclopenta-3,5-dione-1,2-dicarboxylic ester (XI) when treated with sodium ethoxide. It is not possible, therefore, to state whether this acid arose through methylation of the cyclic diketo ester (XI) or by cyclization of the dimethylated ester (XIII).

$$
\begin{array}{ccc}
 & CH_3 & CH_3 \\
 & | & | \\
CH_2\!<\!\!\begin{array}{l}CO\!-\!CHCOOEt \\ CO\!-\!CHCOOEt\end{array} & CH_2\!<\!\!\begin{array}{l}CO\!-\!CCOOH \\ CO\!-\!CCOOH\end{array} & \begin{array}{l}CH_3COCCOOEt \\ EtOOCCCOOEt\end{array} \\
 & | & | \\
 & CH_3 & CH_3 \\
XI & XII & XIII
\end{array}
$$
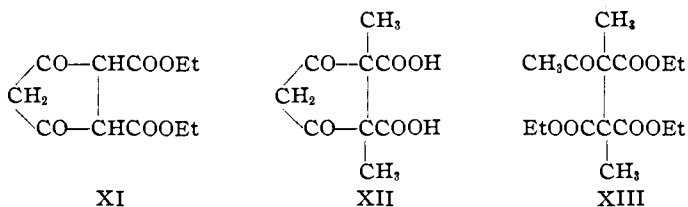
The formation of the pentacyclic keto ester (XI) from the open-chain keto ester (V) is analogous to the formation of 5-phenyldihydroresorcinol-4-carboxylic ester from the addition product of sodium enol acetoacetic ester to cinnamic ester[17] or from the addition product of sodium enol malonic ester to benzalacetone.[18] When ester (V) was treated in ether solution with alcoholic sodium ethoxide, two isomeric cyclic keto esters were obtained, a liquid and a solid, m. p. 86°. The liquid keto ester gave a deep blue color with alcoholic ferric chloride and was probably the mono enolic form of structure (XI). The solid isomer gave no coloration with ferric chloride, and may be derived by rearrangement of the di-enolic structure (XIV). This may be related to the phenomenon termed "intra-annular tautomerism," assumed in this type of compound by Farmer, Ingold and Thorpe,[19] in which case it would be represented by the structure (XV).

$$
\begin{array}{cc}
CH_2\!<\!\!\begin{array}{l}C(OH)\!=\!CCOOEt \\ C(OH)\!=\!CCOOEt\end{array} & CH_2\!<\!\!\begin{array}{l}C(OH)\!-\!CCOOEt \\ C(OH)\!-\!CCOOEt\end{array} \\
XIV & XV
\end{array}
$$

The structure of benzoylacetone has been in the past the subject of many physical and chemical investigations, but the direction of enolization
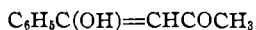
[17] Michael, Am. Chem. J., 9, 117 (1887); J. prakt. Chem., 35, 353 (1887).

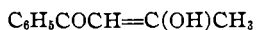[18] Vorländer, Ber., 27, 2053 (1894); Michael, ibid., 27, 2126 (1894).

[19] Farmer, Ingold and Thorpe, J. Chem. Soc., 118, 1362 (1920); 121, 128 (1922).

has not yet been decisively established. Since the results of earlier investigations upon the constitution of enols have been summarized by Scheiber and Herold,[20] only brief references that are relevant to the struc-ture of benzoylacetone need be made here.
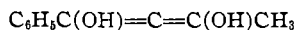
The magnetic rotation,[21,22] and molecular refraction[22] indicate that benzoylacetone has the enol structure (XVI).

$$C_6H_5C(OH){=}CHCOCH_3 \qquad C_6H_5COCH{=}C(OH)CH_3$$
$$XVI \qquad\qquad XVII$$
$$C_6H_5C(OH){=}C{=}C(OH)CH_3 \qquad C_6H_5COCH_2COCH_3$$
$$XVIII \qquad\qquad XIX$$

The parachor of benzoylacetone[23] is very close in value to a calculation based upon an open-chain diketone structure (XIX) and this agrees with the results obtained from examination of the reaction with tertiary amines.[24]

The bromine titration method of K. H. Meyer[25] led him to conclude that benzoylacetone in alcohol solution exists as 94–98% of a mono-enol in reversible equilibrium with the diketone. The method evidently cannot decide between structures (XVI) and (XVII), but Meyer favored the structure (XVI) since he considered that the physical investigations as well as the results of the bromine titration of keto–enols in general showed that the benzoyl group has a greater enolizing capacity than the acetyl. Scheiber and Herold found that ozonization of benzoylacetone gave chiefly benzoic acid (97.5% of the theoretical) and carbon dioxide, and the formation of some methylglyoxal was proved through the osazone. These chemical results therefore also point to the structure (XVI) for benzoylacetone, although they do not exclude the presence of the isomeric enol (XVII) and of the di-enol (XVIII). The ozone addition is a slow process, and if one of the mono-enolic isomers adds much faster than the other, and the isomers are in a state of rapid reversible equilibrium, then the process may proceed mainly in one direction. The results obtained by the method would not then express correctly the quantitative relations between the mono-enolic forms.

On the other hand, Claisen[26] considered that the fission of benzoyl-acetone by the action of alkali into acetophenone and acetate, and the

[20] Scheiber and Herold, *Ann.*, **405**, 295 (1914).

[21] Perkin, *J. Chem. Soc.*, **61**, 832 (1892).

[22] Smedley pointed out [Smedley, *ibid.*, **97**, 1486 (1910); Auwers and Jacobsen, *Ann.*, **426**, 161 (1922)] that when correction was made for exaltation in magnetic rotation common to cinnamyl derivatives, the value found agrees with the value calcu-lated for hydroxybenzylideneacetone and it is unnecessary to postulate the presence of a dienol (XVIII) form, which Perkin had suggested.

[23] Sugden, *J. Chem. Soc.*, 321 (1929).

[24] Michael and Smith, *Ann.*, **363**, 36 (1908).

[25] Meyer, *Ann.*, **380**, 242 (1911); *Ber.*, **45**, 2846 (1912).

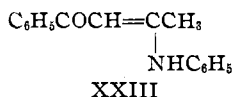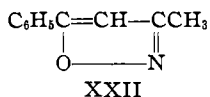[26] Claisen, *Ber.*, **59**, 144 (1926).

reactions of benzoylacetone with ammonia, aniline or hydroxylamine to give, respectively, $C_6H_5COCH=C(NH_2)CH_3$, $C_6H_5COCH=C(NHC_6-H_5)CH_3$ and 3,5-methylphenylisoxazole (XXII), indicated greater reactivity at the acetyl group, and consequently Claisen suggested structure (XVII) as possibly representing benzoylacetone.

It would be expected from the partition principle that a solution of sodium enol benzoylacetone would contain sodium derivatives (XX and XXI), corresponding to the enolic structures (XVI and XVII).

$$C_6H_5C(ONa)=CHCOCH_3 \qquad\qquad C_6H_5COCH=C(ONa)CH_3$$
$$\text{XX} \qquad\qquad\qquad\qquad\qquad \text{XXI}$$
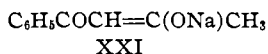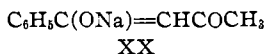
In the hope of obtaining some information regarding the structure of the sodium derivative, the action of chlorocarbonic ester upon sodium enol benzoylacetone was studied.
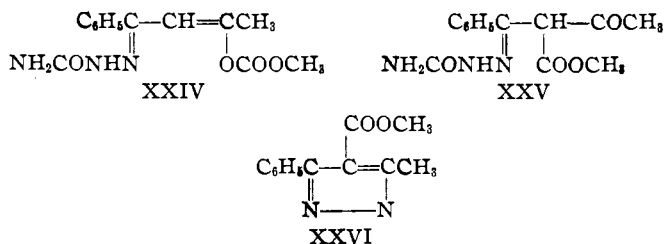
The sodium derivative was prepared by adding an ether solution of the benzoylacetone to an ether suspension of sodium ethoxide prepared by Brühl's method. Chlorocarbonic methyl ester was added gradually and the reaction allowed to proceed in the cold. Approximately 85% of a substitution product was obtained. This was found to consist of two isomeric O-carbomethoxy keto esters, one a crystalline solid, melting at 57°, and the other a liquid, boiling at 164° (2 mm.). The solid ester showed no sign of changing into the liquid isomer when heated slightly above its melting point for forty-eight hours; but, on fractionation of the liquid O-ester, varying amounts of the solid O-ester could be frozen out of the first and last fractions, although the liquid keto ester could be kept indefinitely at ordinary temperature without any indication of changing into the solid form. Each O-ester gave benzoylacetone when treated with aqueous ammonia or aqueous hydroxylamine in the cold. With hydroxylamine acetate in the cold, each gave some 3-methyl-5-phenylisoxazole (XXII) and, with aniline, in ether solution, theoretical yields of the anilido derivative (XXIII).

$$\begin{array}{cc} C_6H_5C{=}CH{-}CCH_3 & \qquad C_6H_5COCH{=}CCH_3 \\ \ \ |\qquad\quad \| & \qquad\qquad\quad | \\ O{-}\!\!-\!\!-\!\!-N & \qquad\qquad NHC_6H_5 \\ \text{XXII} & \qquad\qquad \text{XXIII} \end{array}$$

These reactions involving the elimination of the carbomethoxy group are of little value as evidence of the structures of the carbomethoxy compounds. It was found that benzoylacetone under like conditions gave the same products and there was no means of finding out whether condensation preceded or followed the elimination of the carbomethoxyl.
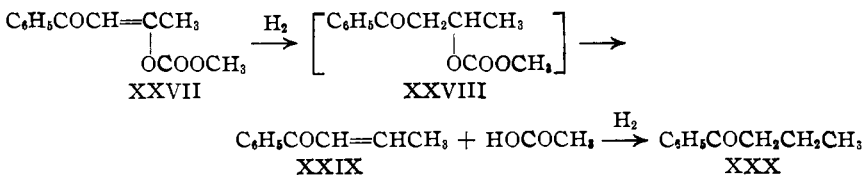
With semicarbazide acetate, the O-esters showed a difference in behavior. The solid ester gave in the cold a semicarbazone derivative of benzoyl-acetoacetate (XXV) together with a semicarbazone derivative of the O-ester (XXIV). The latter could be converted into (XXV) by treatment

with dilute acids when migration occurred of the —COOCH₃ group from the oxygen to the carbon atom

$$C_6H_5C-CH=CCH_3 \qquad\qquad C_6H_5C-CH-COCH_3$$
$$NH_2CONHN \qquad OCOOCH_3 \qquad NH_2CONHN \quad COOCH_3$$
$$XXIV \qquad\qquad\qquad XXV$$

$$COOCH_3$$
$$C_6H_5C-C=CCH_3$$
$$N---N$$
$$XXVI$$

The final product of the reaction in dilute acetic acid solution was the pyrazole derivative (XXVI). A definite product could not be isolated from the liquid O-ester upon similar treatment with the semicarbazide acetate solution.

When the solid O-ester was treated in methyl alcohol solution with hydrogen in the presence of platinum oxide catalyst,[27] it was found that two molecular equivalents of hydrogen were rapidly absorbed, producing *n*-propyl phenyl ketone. The addition must therefore proceed at the unsaturated carbon group and may be considered to take place as follows

$$C_6H_5COCH=CCH_3 \quad \xrightarrow{H_2} \quad \left[C_6H_5COCH_2CHCH_3 \right] \longrightarrow$$
$$OCOOCH_3 \qquad\qquad\qquad OCOOCH_3$$
$$XXVII \qquad\qquad\qquad XXVIII$$

$$C_6H_5COCH=CHCH_3 + HOCOCH_3 \xrightarrow{H_2} C_6H_5COCH_2CH_2CH_3$$
$$XXIX \qquad\qquad\qquad\qquad XXX$$

The rate of absorption did not show any marked decrease after the absorption of the first molecular equivalent of hydrogen, so that it may be supposed that the saturated carbonic ester derivative (XXVIII) was unstable and decomposed relatively rapidly to give phenyl propenyl ketone and acid carbonic methyl ester, The phenyl propenyl ketone (XXIX) would be reduced readily to the saturated ketone (XXX).

When treated with hydrogen under the same conditions, the liquid O-ester gave as readily phenyl *n*-propyl ketone in almost quantitative yield.

Benzoylacetone similarly treated was reduced to give 1-phenylbutane-1,3-diol (XXXI).

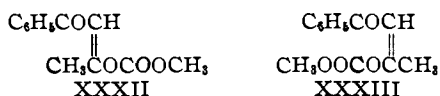$$C_6H_5CH(OH)CH_2CH(OH)CH_3$$
$$XXXI$$
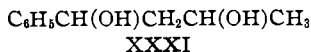
This was obtained as a liquid distilling at 130° (2 mm.) without decomposition. It gives a diacetate upon acetylation in pyridine. Franke and Kohn[28] obtained a 1-phenylbutane-1,3-diol melting at 73° by the action

[27] Adams, "Organic Syntheses," John Wiley and Sons, Inc., New York, 1928, Vol. VIII, p. 92.

[28] Franke and Kohn, *Monatsh.*, 27, 1115 (1906).

of phenylmagnesium iodide upon acetaldol melting at 73°. Bauer[28a] by the action of sodium and alcohol on benzoylacetone obtained some 1-phenylbutane-1,3-diol, a liquid of b. p. 168° (13 mm.), and Kubota and Hayashi[28b] by the action of hydrogen on benzoylacetone at 105° in the presence of copper catalyst, obtained, among other products, some of this diol. Whether our material is identical or stereomeric with the compounds obtained by these authors, can only be decided by further examination.

Since benzoylacetone is thus ruled out as a common intermediate in the reduction of the isomeric O-esters, and since each of the O-esters gives the same saturated ketone, it must be concluded that these two O-esters are related to one another as stereomers with configurations as follows

$$\begin{array}{cc} C_6H_5COCH & C_6H_5COCH \\ \parallel & \parallel \\ CH_3COCOOCH_3 & CH_3OOCOCCH_3 \\ XXXII & XXXIII \end{array}$$

It also follows that in this reaction with the chlorocarbonic ester, the sodium enol benzoylacetone reacts (at least to 85%) as though it had the structure (XXI) and that the enolate consisted of a mixture of stereomeric sodium compounds. Such a result agrees with the partition principle since the sodium compounds would be derived from stereomeric enols of different acidity. The above results also raise the question of the stereochemical homogeneity of the corresponding free mono-enol of benzoyl acetone.

In view of these results, it was of interest to examine the action of chlorocarbonic ester upon sodium enol dibenzoylmethane. When the sodium derivative was prepared, using an ether suspension of sodium methoxide as in the experiment with benzoylacetone, it was found that over 90% of the dibenzoylmethane was recovered unchanged after treatment with chlorocarbonic ester. Better results were obtained when the sodium derivative was prepared directly from pulverized sodium and dibenzoylmethane in ether solution. A yield of 7% of O-carbethoxy derivative (XXXV), together with some dibenzoylmethane, was obtained, but the main product was a thick sirup of undetermined composition that could not be distilled nor crystallized. It is possible that the method of preparing the sodium derivative resulted in a partial reduction of the dibenzoylmethane or produced some complex compound of high molecular weight.

$$\begin{array}{cc} C_6H_5COCH=C(ONa)C_6H_5 & C_6H_5COCH=CC_6H_5 \\ & | \\ & OCOOCH_3 \\ XXXIV & XXXV \end{array}$$
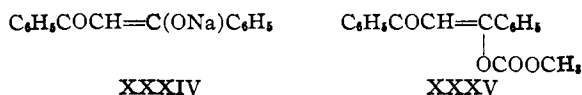
[28a] Bauer, *Compt. rend.*, **154**, 1093 (1911).

[28b] Kubota and Hayashi, *Bull. Chem. Soc. Japan*, 1, 14 (1926).

In another experiment the sodium derivative was prepared using an ether solution of dibenzoylmethane and finely powdered sodamide. The solid sodium derivative was filtered off and washed free of ammonia with ether, before the addition of the chlorocarbonic ester; 50% of dibenzoylmethane was recovered, and 30% of the O-ester melting at 90° together with 20% of liquid material which possibly contained a stereomeric O-ester was obtained.

These experiments show the greater difficulty of replacing by carbomethoxyl the sodium of an enol group adjacent to a phenyl than to the methyl group.

Since benzoyl is a more negative radical than acetyl (the dissociation values, K, of acetic and benzoic acids are 0.0063 and 0.0018, respectively), it is evident that the sodium in the structure $C_6H_5C(ONa)=CHCOCH_3$ should be better neutralized than in the structure $C_6H_5COCH=C(ONa)-CH_3$. The isomeric enolic benzoylacetones are definitely acidic compounds, and the sodium in the first derivative should be considerably better neutralized and therefore less reactive than the sodium in the second structure, a conclusion supported by the relative difficulty of obtaining an O-carbethoxy derivative of dibenzoylmethane. The facile action of chlorocarbonic ester upon sodium enol benzoylacetone and upon sodium enol acetylacetone[29] has proved the greater reactivity of the sodium in the $C_6H_5COCH=C(ONa)CH_3$ than in the $C_6H_5C(ONa)=CHCOCH_3$ structure. It has also shown that in the first structure the sodium is partitioned between the stereo structures (XXXVI) and (XXXVII), of which the latter enolate should preponderate.

$$C_6H_5COCH \qquad\qquad C_6H_5COCH$$
$$\| \qquad\qquad\qquad\qquad \|$$
$$CH_3C(ONa) \qquad\qquad (NaO)CCH_3$$
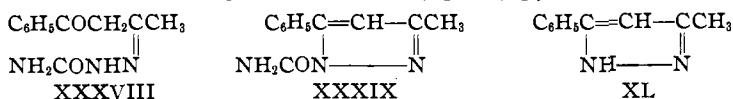$$\text{XXXVI} \qquad\qquad\qquad \text{XXXVII}$$

For comparison with the results of the experiments upon the action of semicarbazide acetate upon the keto esters above, the action of semicarbazide upon benzoylacetone was reëxamined. Posner[30] stated that semicarbazide does not react with benzoylacetone in the cold, but with molecular amounts of semicarbazide hydrochloride at 60°, sodium acetate and benzoylacetone, he obtained 3,5-methylphenylpyrazole-1-carboxamide (XXXIX).

Using semicarbazide or semicarbazide acetate in alcoholic solution at 0°, it was found that pyrazole ring formation could be avoided. The monosemicarbazone (XXXVIII) is readily formed and with excess of semicarbazide a disemicarbazone is formed. Treatment of the mono-semicarbazone in alcoholic solution with a small amount of acetic acid

[29] Claisen, *Ann.*, **277**, 176 (1893).
[30] Posner, *Ber.*, **34**, 3983 (1901).

or hydrochloric acid gave the 3,5-methylphenylpyrazole-1-carboxamide, which on warming or standing in acid solution readily hydrolyzed with loss of carbon dioxide to give the 3,5-methylphenylpyrazole (XL).

$$C_6H_5COCH_2CCH_3 \qquad C_6H_5C{=}CH{-}CCH_3 \qquad C_6H_5C{=}CH{-}CCH_3$$

$$NH_2CONHN \qquad\quad NH_2CON{-}{-}{-}N \qquad\quad NH{-}{-}{-}N$$

| XXXVIII | XXXIX | XL |

Accordingly, semicarbazide acetate in acid solution or semicarbazide hydrochloride with benzoylacetone gave directly mainly 3,5-methylphenyl-pyrazole together with some 3,5-methylphenylpyrazole-1-carboxamide.

The physical properties of benzoylacetone indicate that it exists mainly as $C_6H_5C(OH){=}CHCOCH_3$ (XVI). Since benzoyl is decidedly more negative than acetyl, the sodium derivative should consist largely of $C_6H_5C(ONa){=}CHCOCH_3$ (XX), yet the sodium derivative with chloro-carbonic methyl ester yields only stereomeric forms of $C_6H_5COCH{=}C(OCOOCH_3)CH_3$ which are formed from $C_6H_5COCH{=}C(ONa)CH_3$ (XXI), since benzoylacetone with alkali should give mainly a mixture containing much of (XX) and little of (XXI), and fluxing with it should result in a mixture of benzoate and acetone, with much less acetate and acetophenone. However, acetate and acetophenone are the sole or at least the main products of the decomposition. With typical carbonyl reagents, e. g., ammonia, hydroxylamine, phenylhydrazine and semicar-bazide, benzoylacetone yields primarily derivatives by replacement of the O-atoms of the carbonyl group of the acetyl radical,[31] and the introduced group then acts on the C-atoms of the $-C(OH){=}CH-$ group to form cyclic derivatives, or with a further quantity of the reagent yield products involving the enolic group. Physical investigation supports structure (XVI), while chemical investigation points unmistakably to $C_6H_5COCH{=}C(OH)CH_3$ (XVII). How may these opposing results be reconciled?

In sodium derivatives (XX) and (XXI), the metal in (XX) must be decidedly more neutralized than that in (XXI); sufficiently in the former that $ClCOOCH_3$ acted upon it slowly or not at all. The energetic reaction therefore extended only to (XXI), which is reformed progressively followed by introduction of the carbomethoxyl group. The course of alkali fission of (XX) and (XXI) depends upon the reaction mechanism of the

[31] This behavior led Claisen [Ber., 59, 146 (1926), footnote 10] to believe that the position of the enolic group in benzoylacetone is open to question, and Scheiber and Herold [Ann., 405, 318 (1914)] considered that the formation of acetophenone and ace-tate by alkali fission favors the structure $C_6H_5COCH{=}C(ONa)CH_3$ for the sodium derivative. The statement is not tenable that this view finds support in the easy syn-thesis of sodium enol benzoylacetate from acetophenone and ethyl acetate compared with the difficulty and poor yields encountered when it is attempted to prepare it from ethyl benzoate and acetone. The second reaction would depend upon the formation of sodium enol acetone, which appears in such small amount in the action of sodium upon acetone that its formation can hardly be considered as definitely established.

process. Carbonyl derivatives that do not form enolates with alkali react primarily by addition of the alkali to the carbonyl group to form the group —C(OM)OH—. The slightly neutralized energy of the alkali in this complex loosens the affinity of the C-atom to the directly attached C-atoms[32] and cleavage occurs between the C-atoms by hydrolysis. The rupture should take place at the carbon linkage which is most weakened by the positive influence of the alkali atom. In fluxing enolates (XX) and (XXI) with alkali, similar intermediate products should be formed by addition of water at the unsaturated carbon system and as the alkali atom in the addition product from (XXI) is decidedly less neutralized than in that from (XX), disruption of the carbon chain takes place with the (XXI) compound, thus

$$C_6H_5CO—CH=C(ONa)CH_3 + H_2O \rightarrow C_6H_5COCH_2C(ONa,OH)CH_3 \rightarrow C_6H_5COCH_3 + CH_3COONa$$
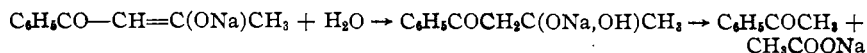
Finally, the course of the reaction of benzoylacetone with carbonyl reagents depends upon whether they add more facilely to the carbonyl or to the —C(OH)=C— group. This relationship may vary with the chemical character of the radicals in direct union with these groups. The course of the above reactions is therefore *prima facie* evidence that with the benzoylacetone structure (XVI) they act much more readily on the carbonyl than on the enolic group. Direct experimental confirmation of this is found in the action of hydroxylamine upon the isomeric keto ethers $C_6H_5COCH=C(OC_2H_5)CH_3$ and $C_6H_5C(OC_2H_5)=CHCOCH_3$ since in each case the O of the carbonyl group is replaced by the hydroxylamine residue.[33]

There is no doubt that the principles developed in the examination of the above reactions can be applied to problems concerning compounds of this or similar types where the partition principle is involved.

Experimental

A. **Reaction Velocity of Sodium Enolates with Methyl Iodide and Ethyl Bromide.**— To a solution of 2–3 g. of sodium in 50 cc. of absolute alcohol 13 g. of acetoacetic ester was added; 14.5 g. of methyl iodide was added to the cold solution of the enolate and after mixing thoroughly was placed in a thermostat at 25°. At known intervals 10 cc. of this mixture was removed with a pipet and run into 50 cc. of 0.5 N hydrochloric acid cooled in ice. The excess acid was then titrated with standard caustic soda using phenolphthalein as indicator. Thus as the reaction proceeded, it was possible to measure the amount of sodium that had been neutralized by the alkyl halide.

Similar experiments were made using (a) malonic ester, (b) an equal volume of alcohol in the place of the acetoacetic ester. Also a series of experiments was carried out using ethyl bromide in the place of methyl iodide. The results are summarized in Curves I and II.

Reaction between Alkyl Halide and a Mixture of NaOEt, CH₂(COOEt)₂ and CH₃-

[32] Michael, This Journal, 32, 997 (1910); Michael and Ross, *ibid.*, 52, 4601 (1930).

[33] Claisen, *Ber.*, 59, 148 (1926).

COCH₂COOEt in Alcohol Solution.—A mixture of 32.5 g. of acetoacetic ester with 40 g. of malonic ester was added to a solution of 5.75 g. of sodium in absolute alcohol. After standing for one hour, 36 g. of methyl iodide was added and the mixture stood in ice water for twelve hours. The product was then mixed with 500 cc. of water containing a small amount of acetic acid and the neutral esters extracted with ether, dried and the ether removed upon the water-bath.

The cold esters were then shaken with successive portions of 5% caustic potash (40 g. in 800 cc. of water). Toward the end of this extraction the amount of ester became so small that it was necessary to take it up in a small volume of ether. The ester that remained in ether solution was washed with water, dried, distilled and weighed as methyl malonic ester;[34] the yield was 2.5 g. or 6% of the possible yield calculated upon complete methylation of malonic ester.

The aqueous alcoholic extract was left overnight cooled in water in order to complete saponification. Using the procedure described by Michael and Wolgast,[35] the solution was acidified and after refluxing for two hours, the volatile ketones distilled off. The aqueous ketone distilled was saturated with salt and the ketones taken up in ether, separated, dried and distilled up an 8-inch Vigreux fractionating column. The fraction distilling at 76–77.5°, after separation from alcohol by the sodium bisulfite compound, was weighed as pure ethyl methyl ketone; yield, 12 g. (70%). The semicarbazone gave large prisms, melting at 148° without recrystallization.[36]

A similar experiment was carried out using ethyl bromide in the place of ethyl iodide, allowing the reaction mixture to stand for seven days and using the same method as above for the separation of the products: 12 g. of ethylmalonic ester (30%) and 3 g. of methyl propyl ketone (16%), b. p. 101–102°, were obtained. The semicarbazone melted at 110°.[37] These results may be summarized as follows

	Yield of alkylacetoacetic ester, %	Yield of alkylmalonic ester, %
CH₃I	70	6
C₂H₅Br[38]	trace	30

B. Methylation of Sodium Enol α-Acetyl-α'-carbethoxysuccinic Ester.—*α-Acetyl-α'-carbethoxysuccinic ester* was prepared by the action of sodium enol acetoacetic ester on chloromalonic ester[38a]: 33 g. of acetoacetic ester was added to 5.75 g. of pulverized so-

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[34] Michael, *J. prakt. Chem.*, **72**, 537 (1905).

[35] Michael and Wolgast, *Ber.*, **42**, 3176 (1909).

[36] Robinson, *J. Chem. Soc.*, **109**, 1044 (1916), gives m. p. 148°.

[37] Michael, THIS JOURNAL, **41**, 419 (1919).

[38] It is significant to note in comparison with this result that the products of complete reaction at 25 of 26 g. of acetoacetic ester, sodium ethoxide (from 4.6 g. of sodium in 100 cc. of alcohol), and 22 g. of ethyl bromide contain approximately 40% ethylacetoacetic ester and 10% di-ethylacetoacetic ester. It is apparent that when an alkyl halide acts upon a sodium enolate with equal or less velocity than it does upon alcoholic sodium ethoxide, it is evidently not advisable to carry out the reaction in alcoholic solution.

[38a] Gault and Klees [*Bull. soc. chim.*, **39**, 1000 (1926)] by the action of chloroacetoacetic ester upon sodium enol malonic ester obtained among other products a liquid of b. p. 170–175° (15 mm.), which they considered to be α-acetyl-α'-carbethoxy succinic ester. By the action of sodium enol acetoacetic ester upon chloromalonic ester they obtained a solid compound m. p. 34° which they regard as the keto form of α-acetyl-α'-carbethoxysuccinic ester. However, the solid they describe is very close in its properties to α,α'-di-aceto-succinic ester (α₃ form, m. p. 32°) and we propose to examine this point in another communication.

dium suspended in ether and the mixture allowed to stand overnight, when the formation of the sodium derivative was complete; 49 g. of chloromalonic ester was added and the mixture warmed gently on the water-bath for one hour. After cooling, the excess of alkali was neutralized by dilute acetic acid and the neutral product was washed with 10% sodium carbonate, dried and fractionated: 40 g. of material distilling at 60–120° (15 mm.) was apparently unchanged acetoacetic and chloromalonic esters; 20 g. distilling at 140–160° (5 mm.) consisted of α-acetyl-α-carbethoxysuccinic ester. A higher boiling fraction 160–200° (5 mm.) (10 g.) partially solidified; the solid was ethanetetra-carboxylic ester.[39]

The α-acetyl-α'-carbethoxysuccinic ester was refractionated and obtained as a color-less oil, b. p. 147° (5 mm.), which gave a deep red color with alcoholic ferric chloride; yield, 25%.

Anal. Calcd. for $C_{13}H_{20}O_7$: C, 54.16; H, 6.94. Found: C, 53.95; H, 6.79.

It readily gave a semicarbazone, m. p. 76°.

Anal. Calcd. for $C_{14}H_{23}O_6N_3$: C, 48.70; H, 6.67. Found: C, 48.53; H, 6.90.

Methylation.—To a cold solution of 2.3 g. of sodium in 30 cc. of ethyl alcohol, 28.8 g. of α-acetyl-α'-carbethoxysuccinic ester was added. After the mixture had stood for two hours, 18 g. of methyl iodide was added and the mixture left overnight cooled in ice water. The product was diluted with ether and washed with dilute acetic acid, then with aqueous sodium carbonate and dried and fractionated.

There was obtained 27 g. of ester, b. p. 144–152° (2 mm.), which gave a deep red color with alcoholic ferric chloride. Saponification with barium hydroxide showed that the product consisted almost entirely of α-acetyl-α'-methyl-α'-carboxysuccinic ester.

Anal. Calcd. for $C_{14}H_{22}O_7$: C, 55.62; H, 7.28. Found: C, 55.03; H, 7.40.

Saponification with Barium Hydroxide.—Five grams of the above methylated ester, b. p. 144–152° (5 mm.), was boiled for four hours with a slight excess of 8% barium hydroxide solution. The product was cooled and the precipitate of barium salts filtered off, washed with ether, decomposed with hydrochloric acid in the cold and the organic acid extracted with ether. A sirupy acid was obtained which from chloroform-ligroin solution slowly deposited crystals (m. p. 158°). This solid acid (0.7 g.) on recrystalliza-tion melted at 166° with decomposition and analysis indicated that it had the composi-tion $C_6H_8O_6$. The mixed melting point with a sample of α-methyl-α-carboxysuccinic acid (m. p. 170°) was not lowered. The latter acid was prepared from chloromalonic ester and sodium enol methylmalonic ester.[40] Moreover, upon heating a portion of this acid at 175° for fifteen minutes, methylsuccinic acid was obtained, melting at 111° after recrystallization, and shown to be identical, by mixed melting point, with methyl-succinic acid.

The remaining sirupy acid which could not be obtained in crystalline form was heated at 150° for fifteen minutes and a product obtained that distilled at 155° (5 mm.). This was then shown to be α-methyllevulinic acid by direct comparison and by a mixed melting point of the semicarbazone (m. p. 191°). No indication could be found of the presence of β-methyllevulinic acid in the decomposition product.

The filtrate from the insoluble barium salts was evaporated on the water-bath to a small bulk and the acid extracted with ether after acidifying. On concentration of the ether solution, the acid separated as glittering plates. It was recrystallized from ace-

[39] It seems probable that in the alcoholic solution some chloromalonic ester was reduced to malonic ester, from which the necessary sodium enol malonic ester was formed that reacted with unchanged chloro ester to give the tetracarboxylic ester.

[40] Bischoff and Kuhlberg, Ber., 23, 635 (1918); Blaise and Gault, Bull. soc. chim., [4] 9, 460 (1912).

tone and melted at 295–300° with sublimation. It gave no color with alcoholic ferric chloride. Analysis agrees with the formula of 4,5-dimethylcyclopentane-1,3-dione-4,5-dicarboxylic acid; yield, 0.5 g.

Anal. Calcd. for $C_9H_{10}O_6$: C, 50.47; H, 4.67. Found: C, 50.29; H, 4.63.

α-**Methyl-α-carboxylevulinic ester** was prepared by the condensation of bromoacetone with sodium enol methylmalonic ester in alcohol solution. A yield of 50% was obtained and the keto ester distilled at 133° (5 mm.).

Anal. Calcd. for $C_{11}H_{18}O_5$: C, 57.40; H, 7.83. Found: C, 57.15; H, 8.0.

This ester readily gave a semicarbazone, m. p. 102°.

Anal. Calcd. for $C_{12}H_{21}O_5N_3$: C, 50.18; H, 7.32. Found: C, 49.95; H, 7.47.

α-**Methyl-α-carboxylevulinic acid** was obtained as a sirup through saponification of the above ester with barium hydroxide. Upon distillation, it gave α-methyllevulinic acid, b. p. 160° (5 mm.), which was characterized by the semicarbazone, m. p. 191°.[41]

The Action of Sodium Ethoxide upon α-Acetyl-α-carbethoxysuccinic Ester.—To a suspension of sodium ethoxide prepared from 1.2 g. of pulverized sodium and 23 g. of ethyl alcohol in ether, 14 g. of the above ester was added and the mixture warmed for two hours upon the water-bath. The mixture was cooled and added to 40 cc. of water containing 4 g. of acetic acid, and extracted with ether. The ether solution was washed with sodium carbonate and a considerable amount of acid material removed. The acid fraction was acidified and the acid recovered as a thick sirup which, however, did not crystallize. The neutral ester was distilled and 9 g. of ester, b. p. 150–155° (2 mm.) was obtained which partially crystallized upon standing. The solid ester was filtered off and crystallized from ether–ligroin mixture. It melted at 86° and gave no coloration with alcoholic ferric chloride. It may have the bicyclic structure (XV).

Anal. Calcd. for $C_{11}H_{14}O_6$: C, 54.55; H, 5.79. Found: C, 54.91; H, 5.37.

The liquid ester, b. p. 149° (2 mm.), gave a deep blue color with alcoholic ferric chloride and because of this fact was tentatively ascribed the structure (XIV).

Anal. Calcd. for $C_{11}H_{14}O_6$: C, 54.55; H, 5.79. Found: C, 54.86; H, 5.60.

This liquid ester readily gave a di-semicarbazone melting at 220° and which crystallized in plates from dilute alcohol.

Anal. Calcd. for $C_{13}H_{20}O_6N_6$: C, 43.54; H, 5.62. Found: C, 43.84; H, 6.1.

With equimolecular quantities of semicarbazide acetate this ester gave a compound of m. p. 76°, crystallizing in large prisms from ether. From analysis it would appear to be a bicyclic pyrazole derivative.

Anal. Calcd. for $C_{11}H_{14}O_4N_2$: C, 52.39; H, 5.56. Found: C, 52.42; H, 6.10.

C. **Action of Chlorocarbonic Methyl Ester upon Sodium Derivatievs of Enol Benzoyl Acetone.**—Sodium methoxide was prepared by adding 8.0 g. of methyl alcohol to a suspension of 5.7 g. of pulverized sodium in ether, and standing for twelve hours at room temperature. An ether solution of 40.5 g. of benzoylacetone was added and to the sodium derivative thus obtained as a fine yellow suspension, 24 g. of methyl chlorocarbonate diluted with ether was gradually added to the cooled material. The mixture stood for twelve hours although most of the reaction was completed at the end of one hour. The ethereal mixture reacted slightly alkaline and was washed first with dilute acetic acid and then several times with 10% sodium carbonate, followed by water, and was dried with calcium chloride. The ether was removed on the water-bath and residue distilled up to 150° (3 mm.). A small quantity of unchanged benzoylacetone separated which had not been extracted by the sodium carbonate. On cooling 27 g. of solid keto ester, m. p. 57°, separated out as large needles, leaving 11.5 g. of a

[41] *Cf.* March, *Compt. rend.*, **134**, 180; *Ann. chim.*, [7] **26**, 323 (1902).

liquid keto ester which on redistillation boiled at 164° (2 mm.). Approximately 5.7 g. of benzoylacetone was recovered, so that the 85% of benzoylacetone that had reacted gave a ratio of nine parts of solid to four parts of liquid keto ester.

Solid Keto Ester.—This crystallized in long, colorless needles from a mixture of ether and ligroin, m. p. 57°. It gave no coloration with alcoholic ferric chloride.

Anal. Calcd. for $C_{12}H_{12}O_4$: C, 65.46; H, 5.45. Found: C, 65.30; H, 5.63.

Liquid Keto Ester.—This was purified by two fractional distillations and freezing out of the solid isomer. It was noticed that after distillation the solid isomer always appeared in the first and last fractions, which made it probable that the liquid ester was converted into the solid isomer upon heating to the boiling point temperature. A sample after keeping for six months at ordinary temperature showed no sign of changing into the solid form. The ester is a slightly yellow, highly refractive liquid which gave a deep red color with alcoholic ferric chloride, and boils at 164° (2 mm.).

Anal. Calcd. for $C_{12}H_{12}O_4$: C, 65.46; H, 5.45. Found: C, 65.60; H, 5.70.

Behavior Toward Semicarbazide and Salts

(a) **Solid Keto Ester.**—Using semicarbazide hydrochloride with an excess of sodium acetate in the cold gave the same results as free semicarbazide. An equivalent amount of the reagent in each case was added gradually to an alcoholic solution of the ester, cooling, and from 2.2 g. of the keto ester an immediate precipitation of 0.6 g. of a finely crystalline solid appeared, m. p. 166°. After several hours, large crystals of a slightly yellow solid, m. p. 183° (1.5 g.), were deposited, and after several days, 0.3 g. of a white solid, m. p. 202°.

Semicarbazone, m. p. 166°.—This recrystallized from aqueous alcohol as fine plates, which gave a deep blue color with alcoholic ferric chloride. This fact, with the analysis, suggests that it is a semicarbazone of benzoylacetoacetate of structure (XXV).

Anal. Calcd. for $C_{13}H_{15}O_4N_3$: C, 56.31; H, 5.54. Found: C, 56.35; H, 5.7.

Semicarbazone m. p. 183° crystallized in slightly yellow prisms from dilute alcohol. It was the main product of the reaction, gave no color with alcoholic ferric chloride and was apparently the semicarbazone of the O-carbomethoxy keto ester. An alcoholic solution of this semicarbazone containing a small amount of acetic acid when warmed to 50° for a few minutes becomes colorless and upon cooling quantitatively deposits the semicarbazone of benzoylacetoacetate. m. p. 166°. The small quantity of acetic acid apparently causes migration of the carbomethoxyl group from oxygen to the methylene carbon atom.

Anal. Calcd. for $C_{13}H_{15}O_4N_3$: C, 56.31; H, 5.54; Found: C, 56.42; H, 5.63.

Semicarbazone m. p. 202° crystallized in needles from dilute alcohol. The analysis pointed to a condensation product of keto ester with more than two molecules of semicarbazide.

Anal. Found: C, 34.7; H, 4.94.

Semicarbazide hydrochloride with an equivalent weight of sodium acetate in the cold reacted as follows: 2.2 g. of keto ester was mixed in the cold with an aqueous solution of 1.1 g. of semicarbazide hydrochloride and 1.3 g. of sodium acetate. There was an immediate precipitation of 0.6 g. of the solid semicarbazone of benzoylacetoacetate, m. p. 166°. None of the semicarbazone of the O-carbomethoxy keto ester, m. p. 183°, was formed. After seven days an oil separated which solidified on cooling. This crystallized from ligroin in large prisms, m. p. 62°. It gave no color with alcoholic ferric chloride. Analysis showed that it was 3,5-methylphenylpyrazole-4-carboxylic (methyl ester).

Anal. Calcd. for $C_{12}H_{12}O_2N_2$: C, 66.66; H, 5.55; N, 12.96. Found: C, 66.7; H, 5.28; N, 13.2.

(b) **On Liquid Keto Ester.**—No definite products could be isolated.

Action of Aqueous Ammonia.—This reagent added to an alcoholic solution of each of the isomeric O-esters caused decomposition in each case, benzoylacetone crystallizing out in about one hour.

Action of Hydroxylamine.—An aqueous solution of the free amine reacted on the solid keto ester in methyl alcohol solution in the same way as aqueous ammonia above. After half an hour, crystals of benzoylacetone were deposited. With hydroxylamine acetate, a 50% yield of 3-methyl-5-phenylisoxazole was obtained from the solid and also from the liquid carbomethoxy ester.

Action of Aniline.—To an ether solution of the solid ester, an equivalent quantity of freshly distilled aniline dissolved in ether was added. The anil of benzoylacetone $C_6H_5COCH=C(NHC_6H_5)CH_3$, m. p. 110°, crystallized out as deep yellow prisms after standing at room temperature for about three days. The isomeric esters gave the same product, the liquid O-ester apparently showing slightly greater reaction velocity. Benzoylacetone with aniline in ether solution after standing several days at room temperature gives the same product.[42]

Action of Potassium Carbonate.—To a solution of 8.8 g. of solid keto ester in methyl acetate, 4.0 g. of dry potassium carbonate was added, and the mixture boiled on the water-bath for four hours. The solution was filtered from the solid potassium carbonate, washed with water and dried. Upon concentration 7.0 g. of unchanged solid ester crystallized out. There remained a small amount of material in the mother liquor which proved to be benzoylacetone. A small amount of benzoylacetone was also obtained upon acidifying the potassium carbonate residue; 80% of the solid ester was recovered unchanged and approximately 15% of benzoylacetone was obtained. No indication of benzoylacetoacetic ester was found.

Reduction.—The method described by Adams[43] was used. A solution of 8.8 g. of the solid keto ester (m. p. 57°) in methyl alcohol, to which 0.2 g. of the platinum oxide catalyst was added, was shaken in an atmosphere of pure hydrogen. A total volume of 1750 cc. of hydrogen (1.8 molecular equivalents) was rapidly taken up and then absorption ceased. The absorption curve showed no significant change in the rate of absorption at the point where one molecular equivalent of hydrogen was taken up, so that it was necessary to proceed until hydrogenation was complete under the conditions used.

The solution was filtered, shaken with activated charcoal and the reaction product distilled after removal of the methyl alcohol. It boiled at 117° (8 mm.) as a colorless liquid with a characteristic odor.

Anal. Calcd. for $C_{10}H_{12}O$: C, 81.07; H, 8.11. Found: C, 80.72; H, 8.30.

This ketone readily gave a semicarbazone with alcoholic sodium acetate solution of semicarbazide hydrochloride, which crystallized in fine needles, melting at 188°.

Anal. Calcd. for $C_{11}H_{15}ON_3$: C, 64.39; H, 7.32. Found: C, 64.62; H, 7.50.

A mixed melting point showed this semicarbazone to be identical with the semicarbazone of *n*-propyl phenyl ketone, which was prepared from butyryl chloride and benzene.[44]

When similarly treated with hydrogen, the liquid keto ester also gave *n*-propyl

[42] Beyer, *Ber.*, **20**, 1770, 2180 (1887).

[43] Adams, "Organic Syntheses," John Wiley and Sons, Inc., New York, 1928, Vol. VIII, p. 92.

[44] (a) Burckev, *Ann. chim.*, [5] **26**, 467 (1882); (b) Sorge, *Ber.*, **35**, 1073 (1902).

phenyl ketone. The rate of absorption of hydrogen was slightly more rapid than with the solid keto ester. The saturated ketone was identified through the semicarbazone, m. p. 188°.[44b]

Catalytic Reduction of Benzoylacetone.—Benzoylacetone was carefully purified by recrystallization from methyl alcohol; 8.0 g. of benzoylacetone in 100 cc. of methyl alcohol was treated with hydrogen in the same manner as in preceding experiments; 1950 cc. of hydrogen was rapidly absorbed. The methyl alcohol was removed under reduced pressure and the product distilled. There was obtained 7.5 g. of 1-phenyl-butane-1,3-diol, b. p. 129–131° (2 mm.). It was a fragrant smelling oil which at this pressure distilled without decomposition, and gave no color with ferric chloride immediately, but upon standing the solution developed a red coloration, possibly due to oxidation to benzoylacetone.

Anal. Calcd. for $C_{10}H_{14}O_2$: C, 72.25; H, 8.43. Found: C, 71.96; H, 8.13.

Addition of acetyl chloride to a pyridine solution of the above diol gave a diacetate, b. p. 140° (2 mm.), a colorless oil.

Anal. Calcd. for $C_{14}H_{18}O_4$: C, 67.20; H, 7.20. Found: C, 67.53; H, 7.6.

D. Action of Chlorocarbonic Methyl Ester upon Sodium Enol Dibenzoylmethane.—To a suspension of 3.3 g. of pulverized sodium in ether, 32 g. of dibenzoylmethane in ethereal solution was gradually added, and the mixture left overnight cooled in ice water. To the fine yellow mass of the anhydrous sodium derivative, 13.5 g. of chlorocarbonate methyl ester, diluted with ether was gradually added. The mixture did not rise in temperature and so was left at room temperature for twelve hours. The product was washed with water, then with sodium carbonate solution, dried and the ether distilled off on the water-bath. As the product decomposed on distillation *in vacuo*, it was therefore heated at 100° (10 mm.) to remove any lower boiling substance. The residual sirup was dissolved in a mixture of ether and ligroin and permitted to crystallize by slow evaporation in a desiccator over paraffin wax. After some unchanged dibenzoylmethane (12 g.) crystallized out, a crystalline solid of m. p. 90° separated. This was recrystallized from a mixture of ether and ligroin. This solid gave no color with alcoholic ferric chloride and is the O-carbomethoxy derivative of dibenzoylmethane; yield, 3 g.

Anal. Calcd. for $C_{17}H_{14}O_4$: C, 72.35; H, 4.85. Found: C, 72.60; H, 5.04.

There remained 15 g. of sirup of undetermined composition. In another experiment the sodium derivative was prepared from powdered sodamide. The solid sodium enol dibenzoylmethane being filtered off and washed with dry ether, and treated as described above, a 30% yield of the O-carbomethoxy derivative, m. p. 90°, was obtained together with 20% of the sirupy liquid product.

E. Action of Semicarbazide and its Salts on Benzoylacetone

In the Presence of Excess Sodium Acetate.—An excess of semicarbazide hydrochloride (2.2 g.) was dissolved with 3.0 g. of sodium acetate in a minimum of cold water and the solution added to 3.2 g. of benzoylacetone dissolved in cold alcohol. After standing for an hour, at room temperature, large prisms were deposited but the reaction took about two days for completion. Upon recrystallization from dilute alcohol, the substance (3.8 g.) melted at 127–128° and was the monosemicarbazone of benzoylacetone. It gave a deep green color with alcoholic ferric chloride.

Anal. Calcd. for $C_{11}H_{13}O_2N_3$: C, 60.28; H, 6.12; N, 19.18. Found: C, 60.12; H, 6.04; N, 19.05.

Free Semicarbazide.—An equivalent quantity of 2.4 N caustic soda was added to a cold solution of semicarbazide hydrochloride, and this solution mixed in the

cold with an alcoholic solution of benzoylacetone. The above monosemicarbazone was obtained in almost the theoretical yield.

Semicarbazide Hydrochloride.—Two and two-tenths grams of semicarbazide hydrochloride dissolved in a minimum of water was added in the cold to 3.2 g. of benzoylacetone in alcohol. After several minutes the solution became warm, a few bubbles of gas were evolved, and it was therefore cooled in water. Some long needle-shaped crystals were deposited (0.1 g., melting at 161°) which proved to be 3,5-methylphenylpyrazole-1-carboxamide. Later a flocculent mass (1.3 g.) separated. Upon dilution of the reaction liquid, some unchanged benzoylacetone was obtained. The flocculent material crystallized from a mixture of ethyl acetate and ligroin as large prisms, melting at 121–122°. Analysis and reactions showed this to be 3,5-methylphenylpyrazole. It was found to be identical with a sample prepared from hydrazine and benzoylacetone.[45]

Anal. Calcd. for $C_{10}H_{10}N_2$: C, 75.95; H, 6.33; N, 17.72. Found: C, 75.72; H, 6.50; N, 18.0.

Action of Semicarbazide Acetate at 60°.—Two and two-tenths grams of semicarbazide hydrochloride was dissolved with 2.7 g. of sodium acetate in the minimum of water and the solution added to 3.2 g. of benzoylacetone in alcohol. The mixture was warmed in a water-bath at 60° for half an hour. The main product was 3,5-methylphenylpyrazole together with a small amount of 3,5-methylphenylpyrazole-1-carboxamide.

Action of Two Molecules of Semicarbazide on Benzoylacetone.—Two and two-tenths grams of semicarbazide hydrochloride was dissolved with 3.0 g. of sodium acetate in a minimum of water and the solution added to 1.6 g. of benzoylacetone in alcohol. On standing for one hour in the cold, fine needle crystals of the disemicarbazone were deposited, melting at 242°.

Anal. Calcd. for $C_{12}H_{16}O_2N_6$: N, 30.43. Found: N, 30.80.

Action of Acids on Benzoylacetone Monosemicarbazone.—The pure monosemicarbazone, m. p. 128°, can be recrystallized from boiling aqueous alcohol without showing any signs of change or decomposition. However, when warmed to 60° in the presence of acetic or of hydrochloric acids (equivalent quantity), it readily undergoes ring formation to give a mixture of 3,5-methylphenylpyrazole-1-carboxamide and 3,5-methylphenylpyrazole of varying proportions. The substances are easily separated, the carboxamide crystallizes out as long needles before the pyrazole is deposited. The 3,5-methylphenylpyrazole-1-carboxamide must be carefully freed from traces of acid before recrystallization, as otherwise it readily undergoes hydrolysis, losing carbon dioxide to give the 3,5-methylphenylpyrazole.

Anal. Calcd. for $C_{11}H_{11}ON_3$: C, 65.67; H, 5.47; N, 20.9. Found: C, 65.42; H, 5.63; N, 21.0.

Summary

1. The reaction velocities of sodium enol acetoacetic ester, sodium enol malonic ester and sodium ethoxide in alcohol solution with methyl iodide and ethyl bromide are compared.

2. The products of the reactions in alcoholic solution between sodium ethoxide, acetoacetic ester and malonic ester and (a) methyl iodide and (b) ethyl bromide are determined quantitatively and the course of the reactions explained.

⁴⁵ Sjollema, *Ann.*, **279**, 268 (1894); Posner, *Ber.*, **34**, 3983 (1901); and Moureu and Brachin. *Bull. soc. chim.*, [3] 31, 172 (1904), give m. p. 127°.

3. The results of the methylation of sodium enol α-acetyl-α'-carbethoxysuccinic ester is interpreted in the light of the above experiments.

4. The formation of carbomethoxy derivatives from chlorocarbonic methyl ester and sodium enol benzoylacetone in stereomeric forms is proved and its bearing upon the structure of sodium enol benzoylacetone discussed.

5. The products of the reaction between benzoylacetone and semicarbazide are described.

6. The structure of enol benzoylacetone is discussed and an explanation offered of the apparent discrepancy between the results of physical and chemical investigations.

7. The above experiments are interpreted in the light of the partition principle as applied to organic reactions, subject to the reaction velocities and reactivities of the groups involved.

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NOTES

Trichloromethylcyclopentanol-1.—The condensation of chloroform with ketones to give tertiary trichloro alcohols has been limited to acetone[1] and methyl ethyl ketone.[2] Other ketones have been tried but unsatisfactory results have been obtained in every case where a ketone of more than four carbon atoms was used.[3]

In view of the fact that this condensation reaction seemed to be limited to the two lowest members of the series of aliphatic ketones, it was decided to try two of the alicyclic type. Cyclopentanone and cyclohexanone were used and the procedure followed was essentially that described by Willgerodt.

Nine parts of cyclopentanone was mixed with thirteen parts of chloroform and six parts by weight of powdered potassium hydroxide was added over a period of several hours with constant stirring. A vigorous reaction sets in unless the mixture is kept well cooled by surrounding the reaction vessel with ice. When all of the potassium hydroxide had been added, it was allowed to stand for six days at 0–10°, being stirred occasionally. The residue was then filtered off and washed with ether. The combined filtrate and washings, after being neutralized with dilute hydrochloric acid, were washed with water and dried over anhydrous sodium sulfate. Distillation was carried out at atmospheric pressure until all of the ether, unreacted chloroform and cyclopentanone were removed. When the

[1] Willgerodt, *Ber.*, **14**, 2451 (1881).
[2] Ekeley and Klemme, THIS JOURNAL, **46**, 1252 (1924).
[3] Howard, *ibid.*, **48**, 774 (1926).