THE PARTITION PRINCIPLE AS APPLIED TO THE STRUCTURE OF ENOLIC SODIUM DERIVATIVES OF 1,3-DIKETONES AND BETA-KETO ESTERS. II[1]

BY ARTHUR MICHAEL AND JOHN ROSS
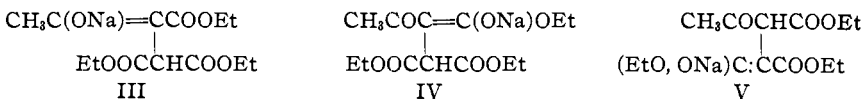
In a wide number of cases the sodium enolates of β-keto esters and 1,3-diketones react with chlorocarbonic ester to give mainly, or even entirely, the O-carbethoxy derivative. The sodium enolates of the keto esters, e. g., acetoacetic,[2] acetomalonic,[3] α-alkyl acetoacetic[4] and of the diketones, e. g., acetylacetone,[5] benzoylacetone[6] belong to the type RC-(ONa)=C(X, Y) in which the formation of an α-carbon derivative is the only alternative to the formation of an O-carbethoxyl derivative. With the sodium enolate of α-aceto-α'-carbethoxysuccinic ester (I) it should be possible to obtain C-derivatives at the α- and α'-carbon atoms as well as the O-carbethoxyl derivative.

In a recent communication,[7] it was shown that upon treating the sodium enol derivative of (I) with methyl iodide, methylation occurred entirely upon the malonic residue, giving the compound (II).

$$\begin{array}{cc} CH_3COCHCOOEt & CH_3COCHCOOEt \\ | & | \\ CH(COOEt)_2 & CH_3C(COOEt)_2 \\ I & II \end{array}$$
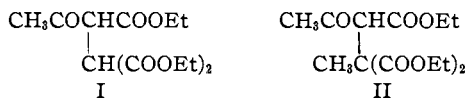
This result was interpreted as indicating the greater reaction velocity of the malonic enolate group with methyl iodide, as compared with that of the acetoacetic enolate group. From a consideration of the relative degree of neutralization of the sodium in the possible sodium enolates III, IV and V, it was concluded that the sodium in III was neutralized to such a degree as to be almost inactive toward methyl iodide in the cold.

$$\begin{array}{ccc} CH_3C(ONa)=CCOOEt & CH_3COC=C(ONa)OEt & CH_3COCHCOOEt \\ | & | & | \\ EtOOCCHCOOEt & EtOOCCHCOOEt & (EtO, ONa)C:CCOOEt \\ III & IV & V \end{array}$$

Toward sodium enolates, chlorocarbonic ester is a much more reactive compound than methyl iodide. With sodium enol malonic ester, chlorocarbonic ester yields methanetricarboxylic ester and the study of the

[1] Part I of this series of investigations appeared in THIS JOURNAL, **53**, 2394 (1931).

[2] Michael, *J. prakt. Chem.*, **37**, 474 (1888); **45**, 583 (1892); *Am. Chem. J.*, **14**, 491 (1892).

[3] Auwers and Auffenberg, *Ber.*, **51**, 1101 (1918).

[4] Michael, *Am. Chem. J.*, **14**, 491 (1892).

[5] Claisen, *Ann.*, **277**, 176 (1893).

[6] Michael and Ross, THIS JOURNAL, **53**, 2401 (1931).

[7] Michael and Ross, *ibid.*, **53**, 2394 (1931).

products of reaction with chlorocarbonic ester on the sodium derivative of enol-α-acetyl α'-carbethoxysuccinic ester (I) is therefore of interest as affording information whether the more reactive chlorocarbonic ester would form an O-carbethoxyl derivative in preference to a C-derivative at the acetoacetic or malonic residue, or a mixture of these derivatives.

α-Acetyl-α'-carbethoxysuccinic ester (I) was previously prepared by Gault and Klees[8] by the action of α-chloroacetoacetic ester upon sodium enol malonic ester in toluene. A number of other products were formed, among these a liquid ester, b. p. 170–175,° which they regarded as the corresponding enol form (VI). It gave a red color with alcoholic ferric chloride, and an acetyl derivative upon treatment with acetic anhydride, but it gave no reaction with phenylhydrazine, semicarbazide acetate or hydroxylamine. It was also noted that the ester did not add bromine, but this was thought to be due to rearrangement to the keto form by the catalytic action of the bromine.[9]

$$CH_3C(OH)\!\!=\!\!CCOOEt$$
$$\underset{\displaystyle CH(COOEt)_2}{|} \qquad VI$$
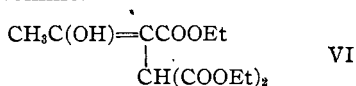
In a second paper,[10] these authors examined the action of chloromalonic ester upon sodium enol acetoacetic ester and in this reaction they obtained a much more satisfactory yield of α-acetyl-α'-carbethoxyl succinic ester (I) and the product crystallized, m. p. 34°. This solid was regarded as the keto form of the liquid ester first obtained, since it gave a semicarbazone, a phenylhydrazone, but no color with alcoholic ferric chloride. The solid ester disssolved in alkali, and, upon acidifying the alkali solution, a mixture of the solid and a liquid ester was obtained. The latter was regarded as the enol form (VI) since when treated with hydrogen bromide it gave the solid ester.

Previously,[6] we have described α-aceto-α'-carbethoxy succinic ester as a liquid, b. p. 147° (2 mm.), which gave a red color with alcoholic ferric chloride and a semicarbazone, m. p. 76°, with semicarbazide acetate. It has been possible by long cooling of the liquid ester to obtain the solid form, m. p. 34°, and, once obtained, no difficulty was experienced in crystallizing out this form from the liquid product. The ester, obtained pure by several crystallizations from ligroin, gave a purplish-red color a few seconds after mixing with alcoholic ferric chloride. Bromine titration by the Meyer indirect method indicated the presence of 0.3% enol in a methyl alcohol solution. Titration of a sample immediately after distillation from a Pyrex glass flask gave a value of 1.6% enol content. An attempt was made to liberate the enol from the sodium salt at −10°; a solid ester, m. p. 34° and

[8] Gault and Klees, *Bull. soc. chim.*, **39**, 883 (1926).

[9] Ref. 8, p. 904.

[10] Gault and Klees, *Bull. soc. chim.*, **39**, 1000 (1926).

also a liquid ester were obtained, but each of these products showed only 0.3% enol content by the bromine titration. We have therefore concluded, in agreement with Gault and Klees, that the solid, m. p. 34°, is the almost homogeneous ketonic form of the compound. However, from our experiments, the liquid obtained from this solid by melting, or by liberation from the sodium enolate under the conditions described, also appears to be mainly the ketonic form, i. e., an equilibrium mixture consisting of 99.7% keto and 0.3% enol. In its behavior toward bromine, ferric chloride, phenylhydrazine and semicarbazide acetate, the liquid product shows identical reactions as the solid ester. This is contrary to the observations of Gault and Klees, who stated that their liquid enol form did not react with phenylhydrazine or semicarbazide acetate. Such behavior would be unusual in compounds of this enolic type, and we have not been able to confirm their statement.

Claisen[11] concluded from experimental results obtained from a study of desmotropes that the "tendency towards formation of the hydroxyl form increases with the negativity and the number of the acyl radicals that are adjoined to the methane carbon." As a salient example of the rule, the increase in enolization on passing from tribenzoyl- to dibenzoylacetyl- and then to benzoyldiacetyl-methane was emphasized. This rule was generally accepted until Michael[12] called attention to the curious mistake of Claisen in accepting, contrary to the true relationship, a greater relative negativity for acetyl than for benzoyl. It was also pointed out that the increased stability of the keto form in passing from dibenzoyl- to tribenzoylmethane, and other facts, showed that, in general, the phenomenon with reference to positive and negative influence at the central carbon atom is of a periodic character. The later results of K. H. Meyer[13] and Dieckmann[14] confirmed the view that the rule, in the form stated by Claisen, is not tenable.[15] However, Auwers and Jacobsen[16] observed that the enol content of a number of mono-acylmalonic esters increased in a direct relation to the dissociation constants (K) of the aliphatic acids corresponding to the acyl radicals. This is the only group of desmotropes known in which the "Claisen rule" has been shown to be valid, and the connection here is to be attributed to the strictly comparable structures of the members of the group, and the very slight changes in the relative negativity of the acyl groups.

The extent of enolization in acetosuccinic ester compared with those of

[11] Claisen, *Ann.*, **291**, 37 (1898); *Ber.*, **36**, 3674 (1903).

[12] Michael, *Ann.*, **363**, 241 (1908).

[13] Meyer, *Ber.*, **45**, 2849 (1912).

[14] Dieckmann, *ibid.*, **55**, 2470 (1922).

[15] Notwithstanding, it is still quoted as valid in some recent textbooks; *e. g.*, Schmidt. "Lehrbuch der organische Chemie," 1929, p. 259.
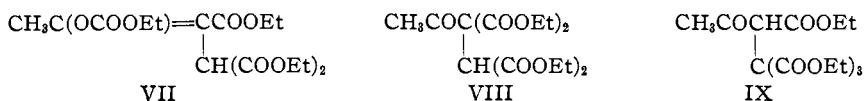
[16] Auwers and Jacobsen. *Ann.*, **426**, 179 (1921).

structurally analogous compounds may serve as a further contribution to this problem:
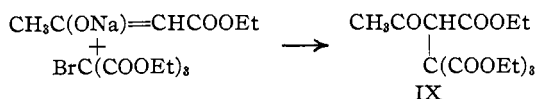
% of enol content

$$
\text{I} \begin{cases} \text{Acetoacetic ester} \dots \dots \dots \dots \dots \dots \dots \dots \dots \dots \dots \dots \dots \dots \dots \dots & 7.7 \\ \text{Acetosuccinic ester[13]} \dots \dots \dots \dots \dots \dots \dots \dots \dots \dots \dots \dots & 3.6 \\ \alpha\text{-Aceto-}\alpha'\text{-carbethoxysuccinic ester} \dots \dots \dots \dots \dots \dots \dots & 0.3 \\ \alpha\text{-Aceto-}\alpha',\alpha'\text{-dicarbethoxy succinic ester} \dots \dots \dots \dots \dots & 0.0 \end{cases}
$$

$$
\text{II} \begin{cases} \alpha\text{-Methyl acetoacetic ester} \dots \dots \dots \dots \dots \dots \dots \dots \dots \dots & 4.1 \\ \alpha\text{-Ethyl acetoacetic ester[13]} \dots \dots \dots \dots \dots \dots \dots \dots \dots & 3.0 \end{cases}
$$

From the table it is apparent that the equilibrium relations in the acetosuccinic series do not support the "Claisen rule." Actually, with increasing substitution of α-H by the weakly negative COOEt group, the proportion of the enol form is lowered, instead of increased, as it should be from the "Claisen rule." Since it is also true from II that substitution of H by positive alkyl groups affects the equilibrium in the same direction, it may be concluded that the rule may even be untenable among members with closely comparable chemical structures.
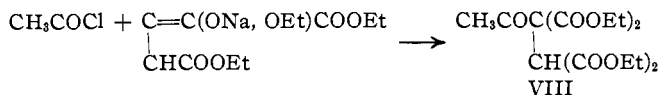
The sodium enolates (III), (IV) and (V) with chlorocarbonic ester should give the carbethoxyl derivatives (VII), (VIII) and (IX), respectively.
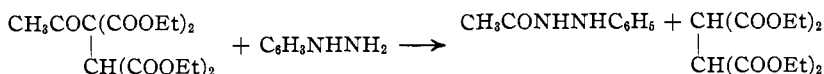
$$
\begin{array}{ccc}
CH_3C(OCOOEt){=}CCOOEt & CH_3COC(COOEt)_2 & CH_3COCHCOOEt \\
\quad | & | & | \\
\quad CH(COOEt)_2 & CH(COOEt)_2 & C(COOEt)_3 \\
\text{VII} & \text{VIII} & \text{IX}
\end{array}
$$

Treatment of the sodium derivative of α-aceto-α-carbethoxysuccinic ester (I) in alcoholic solution with chlorocarbonic ester gave a liquid ester that corresponded to structure (IX) in its reactions. With phenylhydrazine in ether solution it gave a phenylhydrazone identical with the phenylhydrazone of α-aceto-α',α'-dicarboxysuccinic ester. α-Aceto-α',α'-dicarbethoxysuccinic ester was also prepared by the action of bromomethanetricarboxylic ester upon sodium enol acetoacetic ester
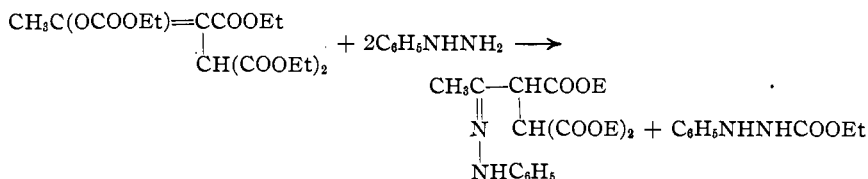
$$
\begin{array}{ccc}
CH_3C(ONa){=}CHCOOEt & & CH_3COCHCOOEt \\
\quad + & \longrightarrow & | \\
BrC(COOEt)_3 & & C(COOEt)_3 \\
& & \text{IX}
\end{array}
$$

For comparison, α-acetyl-α,α'-dicarbethoxysuccinic ester (VIII) was prepared by the action of acetyl chloride upon sodium enol ethanetetracarboxylic ester

$$
\begin{array}{ccc}
CH_3COCl + C{=}C(ONa, OEt)COOEt & & CH_3COC(COOEt)_2 \\
\qquad\qquad | & \longrightarrow & | \\
\qquad\qquad CHCOOEt & & CH(COOEt)_2 \\
& & \text{VIII}
\end{array}
$$

When the ester (VIII) was treated with phenylhydrazine in ether solution, it reacted immediately to give β-acetylphenylhydrazide and ethanetetracarboxylic ester in quantitative yield

$$CH_3COC(COOEt)_2$$
$$|$$
$$CH(COOEt)_2$$

$$+ C_6H_5NHNH_2 \longrightarrow$$

$$CH_3CONHNHC_6H_5 + CH(COOEt)_2$$
$$|$$
$$CH(COOEt)_2$$

Auwers and Auffenberg[3] found that acetylmalonic ester in pyridine solution when treated with chlorocarbonic ester gave a good yield of the O-carbethoxyl derivative. Using the same conditions, α-aceto-α'-carbethoxysuccinic ester (I) in pyridine solution with chlorocarbonic ester gave a liquid product, b. p. 182–184° (2 mm.), which was apparently a mixture of the O-derivative (VII) with the C-derivative (IX) of the ester in about equal proportion. Upon treatment in ether solution with phenylhydrazine, there were obtained the phenylhydrazones of α-aceto-α'-carbethoxysuccinic ester and of α-aceto-α',α'-dicarbethoxysuccinic ester, together with some β-phenylhydrazine carboxylic ester. O-carbethoxy-α-acetyl-α'-carbethoxysuccinic ester (VII) should be reacted upon by phenylhydrazine as follows:

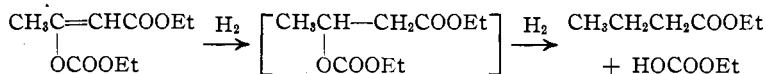$$CH_3C(OCOOEt){=}CCOOEt$$
$$|$$
$$CH(COOEt)_2$$

$$+ 2C_6H_5NHNH_2 \longrightarrow$$

$$CH_3C{-}CHCOOE$$
$$\parallel \quad |$$
$$N \quad CH(COOE)_2 + C_6H_5NHNHCOOEt$$
$$|$$
$$NHC_6H_5$$

It has been shown[6] that the methylation of sodium enolate of α-aceto-α'-carbethoxysuccinic ester proceeded entirely at the malonic group, although in the enolate mixture the product derived from the acetyl group (III) must be present in much larger proportion. Sodium enol benzoylacetone must also consist of two structural enolates, yet chlorocarbonic ester reacts exclusively on the sodium enol acetyl derivative, notwithstanding that according to the partition principle the latter must be present in less amount than the isomeric sodium enol benzoyl derivative. Although chlorocarbonic ester is decidedly more reactive toward enolates than methyl iodide, the ester behaves in the same manner toward the sodium derivatives of (I), substitution occurring only at the malonic enolate group. In all these reactions the greater degree of neutralization of the sodium derivative of the more acidic enolic group gives relative protection to the metal in these positions from replacement under the experimental conditions.

It has been proved[6] that the stereomeric O-carbethoxyl derivatives of benzoylacetone are readily reduced by hydrogen in the presence of platinum oxide catalyst to form propiophenone, thus showing that the CH_3C-$(OCOOCH_3){=}CH{-}$ group added hydrogen while the C_6H_5CO radical resisted hydrogenation. Further, under the same conditions, it was shown that benzoylacetone was reduced to $C_6H_5CH(OH)CH_2CH(OH)CH_3$. These results indicated that in the catalytic hydrogenation both enol groups

$C_6H_5C(OH)$=$CHCOCH_3$ and C_6H_5COCH=$C(OH)CH_3$ in benzoylacetone undergo reductions to isomeric keto-carbinols and these are further reduced to the glycol derivative. It seemed of interest to examine the behavior of other O-acyl ester derivatives toward this catalytic reduction. Since these experiments were made, the results obtained with several compounds of this character have been published by Roll and Adams.[17] Using acetic acid as a solvent, these chemists showed that O-acetoacetoacetic ester (β-acetoxycrotonic ester) by catalytic reduction with platinum oxide and hydrogen gave butyric ester, and that O-acetylbenzoylacetone yielded phenyl propyl ketone. This course of reduction with the O-acetyl compounds corresponds with that of O-carbethoxylbenzoylacetone.

We found that with O-carbethoxyacetoacetic ester in methyl alcohol, one molecular equivalent of hydrogen was rapidly absorbed and then about one-half a molecular equivalent of gas was more slowly absorbed. A product was obtained which upon examination proved to be butyric ester. The course of reaction would appear to be analogous to the reduction, under similar conditions, of O-carbethoxybenzoylacetone

$$CH_3C\text{=}CHCOOEt \xrightarrow{H_2} \left[CH_3CH\text{---}CH_2COOEt \right] \xrightarrow{H_2} CH_3CH_2CH_2COOEt$$
$$\qquad | \qquad\qquad\qquad\qquad\qquad | \qquad\qquad\qquad\qquad\qquad\qquad + HOCOOEt$$
$$\quad OCOOEt \qquad\qquad\qquad\quad OCOOEt$$

Liberation of carbon dioxide as gas from the decomposition of the acid carbonic ester would make the apparent volume of absorption less than two molecular equivalents of hydrogen.

The so-called diacetomalonic ester, shown by Michael[18] and later also by Auwers and Auffenberg,[19] to be O-aceto-enol-acetomalonic ester, or β-acetoxy-ethylidenemalonic ester, by analogy to the behavior of the O-carbethoxyl- and the O-acetylacetoacetic esters toward reduction, should lead to ethylidene or to ethylmalonic esters, respectively. Experiment showed, however, that this ester in methyl alcohol solution underwent no reduction by molecular hydrogen in the presence of platinum oxide. O-Carbethoxyacetomalonic ester, prepared by the action of chlorocarbonic ester upon sodium enol acetomalonic ester, gave indications of a slow reduction under these conditions. Scholl and Egerer[20] obtained an acetyl derivative by the action of acetyl chloride upon sodium enol methanetricarboxylic ester, to which they ascribed the C-acetyl formula, and the conclusion was verified by Auwers and Auffenberg.[21] We noticed no reduction of this keto derivative under the conditions described above. Likewise, methanetetracarboxylic ester[20] underwent no change.

[17] Roll and Adams, THIS JOURNAL, **53**, 3469 (1931).

[18] Michael, *Am. Chem. J.*, **14**, 495 (1892); *Ber.*, **38**, 2086 (1905).

[19] Auwers and Auffenberg, *ibid.*, **50**, 929 (1917).

[20] Scholl and Egerer, *Ann.*, **397**, 301 (1913).

[21] Auwers and Auffenberg, *Ber.*, **51**, 1087 (1918).

This catalytic hydrogenation, therefore, is not a general test to distinguish between O- and C-acyl derivatives.   The protection of the —C(OCOOEt)- =C— group of O-carbethoxyacetomalonic ester, in contrast to the facile reduction of the group in O-carbethoxyacetoacetic ester, must be ascribed to the accumulation of the influence of negative groups at the ethylenic carbon atoms.   It results, in the first compound, from the introduction of the negative carbethoxyl group in the place of an H atom of the O-carbethoxyacetoacetic ester.   The facility of reduction depends mainly on the free chemical energy at the unsaturated carbons and their affinity for hydrogen.   The first condition should be increased by negative influence, while the second should be decreased.   Negative chemical influence, therefore, lowers the affinity between the unsaturated C and the H and increases the free chemical energy at the carbon, and, up to a certain balance between these energy factors, the facility of reduction increases; beyond this it begins to fall off.   The negative influence, as in O-aceto-enol-acetomalonic ester, may become so great that the unsaturated carbons are protected against a mild reducing agent.   Positive alkyl groups in the place of an H joined to the unsaturated C of an ethylenic compound depresses both the above energy factors.   Hence, the facility of catalytic reduction is progressively lowered with increment of this positive influence at the unsaturated carbon group.   For example, Vavon and Kleiner[22] showed that the facility of catalytic reduction (using platinum black) of the following heptenes decreased in the order

n-C$_3$H$_7$CH=CHC$_2$H$_5$ CH$_3$CH=C(C$_2$H$_5$)$_2$ (CH$_3$)$_2$C=CHCH(CH$_3$)$_2$
$$(CH_3)_2C=C(CH_3)C_2H_5$$
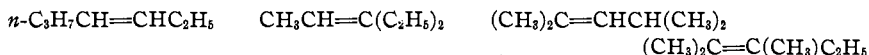
This order of reducibility corresponds to the extent of positive influence at the unsaturated carbon atoms.[23]   There can be no doubt that a close relation between the facility of reduction, the structures of the unsaturated derivatives and the chemical potential of the unsaturated carbon atoms for hydrogen, can be established.   In a later communication, with the use of a method of catalytic reduction, we hope to prove such a relation experimentally.

Experimental

α-Acetyl-α'-carbethoxysuccinic Ester.—The preparation of this ester from chloro-malonic and sodium enol-acetoacetic esters as a liquid has been described previously.[7,8] Upon keeping for a day at −10°, the liquid, b. p. 147° (5 mm.), solidified to a solid mass which was recrystallized from ligroin.   Needles, m. p. 34°, were obtained, un-doubtedly identical with the solid substance described by Gault and Klees.[10]   Crystal-lization of the crude product from ligroin is a ready method of purifying the ester from the cyclic and other keto esters which are also formed in the reaction.

Anal.   Calcd. for C$_{13}$H$_{20}$O$_7$: C, 54.16; H, 6.94.   Found: C, 53.98; H, 7.10.

[22] Vavon and Kleiner, Compt. rend., 177, 401 (1923).
[23] Michael, J. prakt. Chem., [2] 60, 432 (1899).

A determination of the enol content in methyl alcohol solution by the indirect bromine titration method[24] indicated the presence of 0.3% of enol. After fractional distillation, in the presence of a small amount of phthalic acid, from a Pyrex glass vessel, the enol content rose to 1.6% as the maximum in the fractions. These results confirm the observations of Gault and Klees upon the very small extent of bromine addition shown by this ester.

A solution of 8.7 g. of ester in excess caustic soda (1.5 times the theoretical of 5% solution) at $-10°$ was slowly acidified with the theoretical amount of cold, dilute sulfuric acid (5%). After several minutes, large needle-like crystals (5.0 g.) separated, which were found to be identical with the original ester. The filtrate was rapidly extracted with ether and the solvent removed in a vacuum desiccator. A liquid residue (2.5 g.) was obtained which was proved by titration to be 0.3% enolic. Upon cooling and seeding, it solidified to the solid ester.

The solid ester, m. p. 34°, with alcoholic ferric chloride after several seconds gives a reddish-purple color which fades within a few minutes.

It is evident from these experiments that the ester exists almost entirely in the ketonic form and that the pure enolic form is an exceedingly labile compound, even at temperatures below zero.

An ether solution of 2.8 g. of the ester and 1.1 g. of phenylhydrazine, after standing for two days, gave the phenylhydrazone. This crystallized from ethyl acetate as large needles, m. p. 91° (Gault and Klees[10] gave m. p. 89°).

Anal. Calcd. for $C_{19}H_{26}O_6N_2$: C, 60.31; H, 6.88. Found: C, 59.95; H, 7.06.

Action of Chlorocarbonic Ester upon Sodium Enol-α-acetyl-α'-carbethoxysuccinic Ester.—To a cold solution of 2.3 g. of sodium in 35 cc. of absolute alcohol, 28.8 g. of ester was added, and then, after thirty minutes, 11 g. of chlorocarbonic ester diluted with ether. After standing for four hours, the mixture was acidified with dilute acetic acid, extracted with ether, the extract washed with aqueous sodium carbonate, dried and the neutral ester distilled under reduced pressure. Some lower boiling liquid was obtained (unchanged ester) but the main product (10 g.) distilled at 182° (2 mm.). The compound gave no color with alcoholic ferric chloride. The analysis indicated that it was a carbethoxyl derivative of α-acetyl-α'-carbethoxysuccinic ester.

Anal. Calcd. for $C_{16}H_{24}O_9$: C, 53.34; H, 6.67. Found: C, 53.18; H, 6.9.

When the reaction was carried out in ether solution, a better yield (60%) of this ester was obtained.

An ether solution of 3.6 g. of the ester and 1.1 g. of phenylhydrazine, after standing for several days, gave the phenylhydrazone of α-acetyl-α',α'-dicarbethoxysuccinic ester, m. p. 104°. Identity was shown by direct comparison and mixed melting point.

Anal. Calcd. for $C_{22}H_{30}O_8N_2$: C, 58.67; H, 6.66. Found: C, 58.35; H, 6.92.

Action of Chlorocarbonic Ester upon α-Acetyl-α'-carbethoxysuccinic Ester in Presence of Pyridine.—To a solution of 14.4 g. of α-acetyl-α'-carbethoxysuccinic ester in 10 g. of pyridine, cooled in ice water, 6 g. of chlorocarbonic ester was slowly added with rapid shaking. After standing for twelve hours in the cold, ether was added to the semi-solid mass and the pyridine hydrochloride filtered off. After removal of the ether, the residue was distilled under reduced pressure and, besides the lower-boiling fraction (about 4 g.) of unchanged ester, the main fraction (10 g.), b. p. 182–184° (2 mm.), distilled as a colorless liquid.

Anal. Calcd. for $C_{16}H_{24}O_9$: C, 53.34; H, 6.67. Found: C, 53.22; H, 6.71.

Action of Phenylhydrazine.—To an ethereal solution of this ester, 2.2 g. of phenylhydrazine was added. After standing for two days, large needle-like crystals (1.5 g.)

[24] Meyer and Kappelmeier, *Ber.*, **44**, 2718 (1911).

of the phenylhydrazone of α-acetyl-α'-carbethoxysuccinic ester (m. p. 91°) had separated, which were filtered off and washed with ligroin. The mother liquor was evaporated in a vacuum desiccator and the residue rubbed with carbon disulfide. The deposit of crystals of the phenylhydrazone (m. p. 104°) of α-acetyl-α',α'-dicarbethoxysuccinic ester (1.0 g.) was filtered off and washed with ligroin and carbon disulfide. The residue in the mother liquor on evaporation in the desiccator and rubbing with ligroin slowly crystallized. The crystals (m. p. 80°) were shown to be identical with β-phenylhydrazinecarboxylic ester.

α-Acetyl-α,α'-dicarbethoxysuccinic Ester (Acetyl-sym.-ethanetetracarboxylic Ester).—To a suspension in ether of 2.3 g. of pulverized sodium, an ether solution of 32 g. of sym.-ethanetetracarboxylic ester was added and the mixture heated on a water-bath until all the sodium had been converted into the sodium derivative. To the cooled mixture, 10 g. of acetyl chloride was added and, after reaction had ceased, it was warmed for an hour. The ether solution was then cooled, washed with dilute acetic acid, followed by aqueous sodium carbonate, dried and fractionated. Two main fractions were obtained: (a) b. p. 160–165° (2 mm.) (17 g.) solidified on cooling and was unchanged ethanetetracarboxylic ester; (b) b. p. 175° (2 mm.) (17 g.) remained a thick liquid and was the mono-acetyl derivative of ethanetetracarboxylic ester. It gave no color with alcoholic ferric chloride and was not reduced by hydrogen in presence of platinum oxide.

Anal. Calcd. for $C_{16}H_{24}O_9$: C, 53.34; H, 6.67. Found: C, 53.48; H, 6.46.

Action of Phenylhydrazine.—To an ether solution of 1.8 g. of the ester, 0.55 g. of phenylhydrazine was added. There was an immediate reaction and crystals of flat needles separated. After several hours, the mixture was filtered and the crystals washed with ether. They melted at 131° and proved to be acetylphenylhydrazide. The filtrate upon concentration gave crystals of ethanetetracarboxylic ester (m. p. 76°). The amounts obtained of the product showed that the reaction proceeded approximately quantitatively.

α-Acetyl-α',α'-dicarbethoxysuccinic ester was prepared by the action of bromomethanetricarboxylic ester upon sodium enolacetoacetic ester.

To 4.6 g. of pulverized sodium, covered with ether, 26 g. of acetoacetic ester was added. When the formation of sodium enol acetoacetic ester was complete, 62 g. of bromomethanetricarboxylic ester, b. p. 147° (2 mm.),[25] was added and the mixture left to stand for twelve hours. The gelatinous mass was then acidified with dilute acetic acid, and the ether solution washed with aqueous sodium carbonate, dried and the neutral ester fractionally distilled under reduced pressure. A large fraction, boiling up to 150° (2 mm.), contained mainly unchanged material. The fraction boiling between 170–190° (2 mm.) was redistilled and 15 g. of colorless liquid, b. p. 182–184° (2 mm.), was obtained.

Anal. Calcd. for $C_{16}H_{24}O_9$: C, 53.34; H, 6.67. Found: C, 53.16; H, 6.82.

This ester slowly gave a faint purple color with alcoholic ferric chloride which faded after several minutes. Indirect titration in methyl alcohol solution with bromine gave no indication of the presence of the enol compound.

Action of Phenylhydrazine.—An ether solution of 3.6 g. of the ester with 1.1 g. of phenylhydrazine was permitted to stand for two days. No solid separated so the solution was evaporated in a desiccator and the residue rubbed with carbon disulfide. A fine crystalline powder was formed which was filtered off (2.0 g.). This phenylhydrazone derivative was recrystallized from a mixture of carbon disulfide and methyl acetate and separated as fine needles, m. p. 104°.

Anal. Calcd. for $C_{22}H_{30}O_8N_2$: C, 58.67; H, 6.66. Found: C, 58.45; H, 6.76.

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[25] Wheeler and Johnson, THIS JOURNAL, **24**, 687 (1902).

Reduction Experiments with Hydrogen in the Presence of Platinum Oxide. (a) O-Carbethoxyacetoacetic Ester.—To a solution of 2.0 g. of this ester, b. p. 140° (2 mm.), in 50 cc. of methyl alcohol, 0.05 g. of platinum oxide catalyst was added and the mixture shaken in an atmosphere of hydrogen; 230 cc. of hydrogen (N. T. P.) was first absorbed at an average rate of 30 cc. per minute, and then a further 130 cc. of gas were taken up during one hour. The solution was filtered, shaken with activated charcoal and distilled. The product from an experiment using 8.2 g. of ester in 50 cc. of methyl alcohol was combined with the above material. The alcohol solution of the ester produced was distilled up a 20-cm. Vigreux fractionating column. It was found that the ester had completely volatilized in the methyl alcohol. Therefore, the distillate was mixed with 25 cc. of 10% caustic soda and the alcohol slowly distilled off, leaving the aqueous solution of sodium salt. The acid obtained upon acidifying the sodium salt was converted into the acid chloride by treating with thionyl chloride, and this when treated with aniline, gave an anilide, m. p. 96°, which was found to be identical with butyric anilide.

(b) O-Carbethoxylacetomalonic ester was prepared by the action of chlorocarbonic ester upon acetomalonic ester in the presence of pyridine, as described by Auwers and Auffenberg.[8] The acetomalonic ester was prepared by action of chlorocarbonic ester upon copper acetoacetic ester.[26] A methyl alcohol solution (50 cc.) of 2.7 g. of this ester with 0.1 g. of platinum oxide absorbed 50 cc. of hydrogen in three hours. (Theory requires 233 cc. for one molecular equivalent of hydrogen.)

(c) O-Acetylacetomalonic ester was prepared by method of Michael[18] by the action of acetyl chloride upon sodium enol acetomalonic ester in ether.

(d) Acetylmethanetricarboxylic ester was prepared by the method of Scholl and Egerer[20] by the action of acetyl chloride upon sodium enolmethane tricarboxylic ester.

(e) Methanetetracarboxylic ester was prepared by the action of chlorocarbonic ester upon sodium enol-methanetricarboxylic ester.[20]

These last three compounds were treated similarly in methyl alcohol solution with hydrogen in presence of the platinum oxide catalyst, but in no case did absorption of hydrogen occur.

Summary

1. The action of chlorocarbonic ester upon sodium enol α-aceto-α′-carbethoxy succinic ester has been examined.

2. The results further demonstrated the greater reaction velocity of the sodium enol malonic ester group as compared with the sodium enol acetoacetic ester group, which again is shown to be a function of the degree of neutralization of the reactive element (sodium) in that group.

3. The enol contents of α-aceto-α′-carbethoxysuccinic and α-acetyl-α,′α′-dicarbethoxysuccinic esters have been determined and the variation in enolization in these, and in similarly constituted, esters is shown to be opposed to the "Claisen rule."

4. The action of hydrogen in the presence of platinum oxide catalyst upon O-carbethoxyacetoacetic ester, O-carbethoxyacetomalonic ester, O-acetylacetomalonic ester, acetylmethanetricarboxylic ester and methanetetracarboxylic ester has been studied, and it has been found that with increase in the number of the acyl groups about the ethylenic carbon atoms, reduction proceeds with difficulty or not at all.

[26] Nef, *Ann.*, **266**, 105 (1891).

5. The facility of catalytic reduction of ethylenic compounds with reference to chemical structure is discussed.

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NOTES

Identity of Neonicotine and the Alkaloid Anabasine.—In a recent article[1] Orechoff and Menschikoff reported the results of a study of the alkaloids of *Anabasis aphylla* L. (Fam. Chenopodiaceae). The alkaloids isolated and identified were lupinine and anabasine. Anabasine was shown to be β-pyridyl-α'-piperidine. They considered it to be different from nicotimine, an alkaloid associated with nicotine in the tobacco plant, to which Pictet had erroneously assigned this structure.

The writer obtained a sample of "anabasine sulfate" through the courtesy of the Amtorg Trading Corporation and made an examination of the alkaloids. Anabasine was separated and purified. It was found to be identical with neonicotine, the isolation of which the writer reported at the 79th meeting of the Society on April 8, 1930. The report was published on January 12, 1931.[2] Anabasine differs from neonicotine in being levorotatory, whereas synthetic neonicotine is inactive.

The writer isolated neonicotine from the reaction products of sodium, pyridine and oxygen, while he was attempting to separate the insecticidal substance (neonicotine) from the comparatively non-toxic dipyridyls. Although previous workers had reported the presence of isonicotine (γ-pyridyl-γ'-piperidine) in the products of the sodium–pyridine reaction, the writer has been unable to find that any pyridylpiperidine other than neonicotine or β-pyridyl-α'-piperidine[2] is produced in his modified procedure. It is interesting that out of nine compounds theoretically possible, the particular pyridylpiperidine which most closely resembles nicotine should be found in nature. It represents the first dipyridyl alkaloid. It is also interesting to note that this is a rare instance of the synthesis of an alkaloid preceding its isolation from a plant.

In addition to neonicotine the writer found considerable methylneonicotine (methylanabasine) in his sample of anabasine sulfate. Orechoff and Menschikoff do not report this alkaloid as one of the constituents of the *Anabasis aphylld*. When the total mixed alkaloids are dissolved in water and extracted with ether, the anabasine remains in the water, and the methylanabasine is extracted. Its presence was immediately suspected because the ether fraction when evaporated was found to be more soluble in cold water than in hot water, which is generally true of all N-methylpyridylpiperidines.

¹ Orechoff and Menschikoff, *Ber.*, **64**, 266 (1931)
² C. R. Smith, THIS JOURNAL, **53**, 277 (1931).