

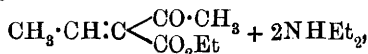
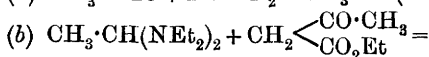
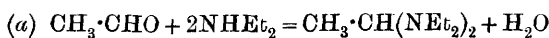
VII.—*Optically Active Esters of β -Ketonic and β -Aldehydic Acids. Part IV. Condensation of Aldehydes with Menthyl Acetoacetate.*

By ARCHIE CECIL OSBORN HANN and ARTHUR LAPWORTH.

THE only α -substituted derivatives of menthyl acetoacetate which have yet been described are the azo-compounds (Trans., 1903, 83, 1114), which have been isolated in a solid condition and found to exhibit mutarotation in a very marked degree. All attempts to prepare the ordinary α -alkyl substituted derivatives, on the other hand, have failed, probably because, as obtained by the ordinary methods, they are mixtures of fusible isomerides, that is to say, of the *l*-menthyl esters of the *d*- and *l*-alkylacetoacetates.

Many of the alkylidenediacetoacetates, however, may be isolated

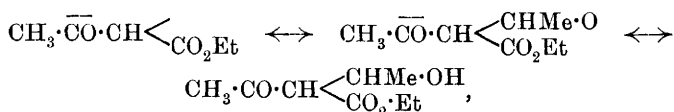
without difficulty in crystalline and apparently homogeneous forms. The method used in preparing them was usually that employed by Knoevenagel (*Annalen*, 1894, 281, 25; *Ber.*, 1894, 27, 2345, &c.), namely, by treating a mixture of the alkyl acetoacetate and an aldehyde with an organic base as a condensing agent. This synthesis has been shown by its discoverer to proceed in two stages, in the first of which condensation takes place between one molecule of the aldehyde and one of the ester, yielding the unsaturated alkylidenemonoacetoacetate, $\text{CR}:\text{C}(\text{CO}_2\cdot\text{Alk})\cdot\text{CO}\cdot\text{CH}_3$, whilst in the second stage the above product unites with another molecule of the original alkyl acetoacetate affording the alkylidenebisacetoacetate, having the constitution $\text{CHR} < \begin{smallmatrix} \text{CH}(\text{CO}_2\text{Alk})\cdot\text{CO}\cdot\text{CH}_3 \\ \text{CH}(\text{CO}_2\text{Alk})\cdot\text{CO}\cdot\text{CH}_3 \end{smallmatrix}$. The mechanism of the process is generally supposed to consist in the initial formation of a compound of the aldehyde and the base which, it is usually stated, may be a primary or secondary but not a tertiary base; this initial compound then reacts with the ketonic ester, as, for example:



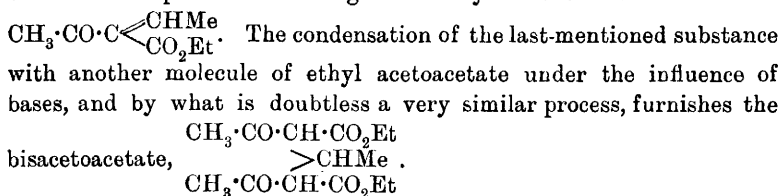
and Knoevenagel has isolated these supposed intermediate compounds and shown that they react with the acetoacetic esters in the manner represented in the foregoing equation (*Ber.*, 1898, 31, 2596).

The assumption that the condensation depends on the formation of such intermediate compounds is, however, entirely unnecessary, and the authors have found that, contrary to general belief, tertiary bases, if sufficiently powerful, are effective in bringing about the condensation, and there can be little or no doubt that the efficiency of a base depends mainly on its strength; thus, whilst pyridine scarcely acts at all, trimethylamine and tripropylamine in small quantities give good results, although they are not by any means so rapid in their action as the secondary bases, which are more powerful. In this and similar cases, the real effect of the bases is doubtless precisely similar to that which they exercise in bringing about the rapid attainment of equilibrium between the normal and *iso*-forms of tautomeric compounds, and in accelerating the union of hydrogen cyanide with carbonyl compounds, namely, by lowering the concentration of the hydrogen ions and thus increasing that of the negative ions of the acidic acetoacetic esters. The bases may be assumed to form small quantities of the ammonium derivatives exactly analogous to the metallic derivatives of the β -diketones or β -ketonic esters. The subsequent change may then be represented in the ordinary way as

the result of the addition of this ammonium compound to the carbonyl group of the aldehyde or more satisfactorily, we think, as the union of one of the ions* of the acetoacetic ester with the carbonyl group of the aldehyde, to form a complex ion of the same type as that of the cyanohydrins (Trans., 1903, 83, 1000), followed by the union of these negative ions to form the hydroxyl compound (analogous to the cyanohydrins), which is generally recognised to be the first step in condensations of the type; thus with acetaldehyde and ethyl acetate,

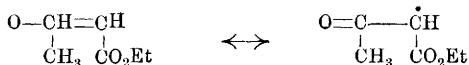


the latter compound then losing water to yield the unsaturated ester



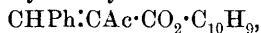
In the condensations of menthyl acetoacetate with aldehydes, the reactions appear to proceed more slowly than when the ethyl ester is used, and in many cases they are completed only after prolonged heating or by the addition of a small quantity of sodium hydroxide, which is very much more efficient than the comparatively weak organic bases.

* We have previously suggested (Trans., 1902, 81, 1512) as a modification of an ionic view of tautomeric change which we supposed to have been advanced for the first time by Brühl (*Ber.*, 1899, 32, 2329), that the change of internal structure occurs only in the ions, as, for example, in the above case:



Brühl's paper, unfortunately, contained no reference to previous suggestions of a similar nature put forward by Knorr (*Annalen*, 1896, 293, 38) and by Wislicenus (*Tautomerie, Ahrens-Sammlung*, 897, *et seq.*). The latter had assumed, also, that ionisation might precede isomeric change, pointing out that when this was the case the change of internal structure would take place "more readily" than when an intramolecular atomic or group migration was also involved. Wislicenus thus anticipated a most important point in the views which we have put forward; he does not, however, appear to suggest that the change in the ion is a reversible one and tending towards an equilibrium (compare, in this respect, Lander, Trans., 1903, 83, 420), or that the ketonic form itself may undergo ionisation. The statement of the above view in terms of an hypothesis which does not postulate ionisation becomes virtually identical with Lander's suggestion (*loc. cit.*, p. 421) that the metallic derivatives exist in desmotropic forms.

The intermediate unsaturated esters, unlike those from the ethyl ester, may be occasionally produced in large amount by working at the ordinary temperature, and there is no difficulty in thus obtaining excellent yields of menthyl benzylideneacetoacetate,

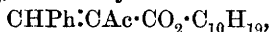


whilst in the preparation of the corresponding ethyl ester the temperature must be maintained below -5° for more than 20 hours. The same remark applies to the condensation with propaldehyde, which at the ordinary temperature yields first the crystalline menthyl propylideneacetoacetate, $\text{CHEt}:\text{CAc}\cdot\text{CO}_2\cdot\text{C}_{10}\text{H}_9$, although none of the corresponding derivatives of ethyl acetoacetate with fatty aldehydes appear to be obtainable in a similar way. The want of success experienced in attempting to prepare other examples of these intermediate compounds is probably attributable to the failure of the substances to crystallise in the absence of suitable nuclei before they undergo further condensation. It is noticeable with nearly all the compounds dealt with that they crystallise with extreme sluggishness, this being a characteristic of the derivatives of menthyl acetoacetate which has already been mentioned on more than one occasion (*Trans.*, 1902, 81, 1500, and 1903, 83, 1117). To this property also is doubtless due the failure which has attended all efforts to prepare crystalline condensation products from menthyl acetoacetate and formaldehyde. It is not our intention to discuss the moot question of the propriety of representing some of the alkylidenebisacetoacetates as derivatives of cyclohexanone, a contention which appears to involve the improbable assumption that the esters are more stable under the influence of hydrazine hydrate than under that of the trace of weak base which is usually employed in preparing them (compare Rabe and Elze, *Annalen*, 1902, 323, 83, and Knoevenagel, *Ber.*, 1903, 36, 2118). Moreover, the point has no very direct bearing on the interpretation of any of our observations.

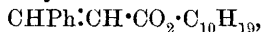
The menthyl esters of the alkylideneacetoacetic acids were not found to exhibit any very noteworthy mutarotation either in solvents or in the presence of traces of bases or acids. It is difficult to explain the reason for this apparent stability, more particularly as the specific rotatory powers of these esters are abnormally low, being in many cases not more than one-fourth of the value calculated from the observations of other workers on menthyl esters (*Tschugaëff*, *J. Russ. Phys. Chem. Soc.*, 1902, 34, 6069, and *Cohen and Briggs*, *Trans.*, 1903, 83, 1213). In the absence of all other data, the abnormally low rotatory powers might have been reasonably attributed to the presence of an asymmetric carbon atom which originates in the acidic part of the molecule during the synthesis (compare *Trans.*, 1903, 83, 1118), but the absence of any large amount of mutarotation,

such as was observed in the case of the azo-derivatives of menthyl acetoacetate, is difficult to reconcile with such a view.

Still more difficult to understand are the rotatory powers of the intermediate unsaturated alkylideneacetoacetates, which, if correctly represented by the formula $\text{CHR}:\text{CAc}\cdot\text{CO}_2\cdot\text{C}_{10}\text{H}_{19}$, contain no centre of asymmetry except that in the menthyl residue, nor, apart from the latter, is the molecule built up in an enantiomorphous way. Nevertheless, the rotatory powers of menthyl propylideneacetoacetate, $\text{CHEt}:\text{CAc}\cdot\text{CO}_2\cdot\text{C}_{10}\text{H}_{19}$, and benzylideneacetoacetate,



have the molecular rotations $[\text{M}]_D - 97\cdot70^\circ$ and $- 32\cdot80^\circ$, numbers which are respectively about two-thirds and one-fifth of the lowest usual values for the menthyl esters of monobasic acids, or, to look at the matter in another way, the latter of the two substances mentioned is apparently only the acetyl derivative of menthyl crotonate,



which has a rotatory power of about the normal value, namely, $[\text{M}]_D - 203\cdot1^\circ$ (*Annalen*, 1903, 327, 157). In view of these observations, Erlenmeyer may after all be correct in attributing an enantiomorphous character to one of the cinnamic acids (*Ber.*, 1903, 36, 2340. Compare also Sudborough and Thompson, *Trans.*, 1903, 83, 1167). The possibility still remains, however, that they may be re-

presented by the formula $\begin{array}{c} \text{O} \text{---} \text{CMe} \\ | \quad | \\ \text{CHPh}\cdot\text{C}\cdot\text{CO}_2\text{Et} \end{array}$, as, we believe, has already been suggested by Claisen.

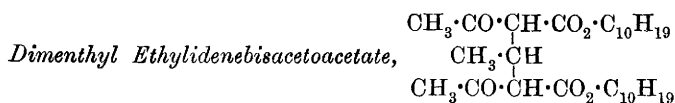
EXPERIMENTAL.

Methylene Derivatives.

When molecular proportions of menthyl acetoacetate and formaldehyde, together with a few drops of piperidine, are allowed to remain for about twenty-four hours, condensation occurs with rise of temperature, water separates, and a colourless oil is obtained, which solidifies in the course of a few days. All attempts to obtain this substance in the crystalline form have been unsuccessful.

Ethylidene Derivatives.

Numerous attempts were made to prepare *menthyl ethylideneacetoacetate* by condensing menthyl acetoacetate with aldehyde in alcoholic solution, but without success. The conditions were varied by using excess of the aldehyde and by keeping the mixture at 0° or -10° ; in each case, however, the dimenthyl ester alone was formed.



This compound is best prepared by mixing two molecular proportions of the ester with one of acetaldehyde in alcoholic solution, a few drops of piperidine, diethylamine, or tripropylamine being added at intervals. The oily liquid is then warmed on the water-bath for two or three days, by which time it has assumed a jelly-like consistency, and contains the condensation product in the form of excessively slender needles. The mother liquors from these crystals on treatment with a drop of strong aqueous sodium hydroxide furnish an additional supply of material.

Some difficulty was experienced in obtaining the substance in a satisfactory condition; it was eventually found preferable to dry the compound thoroughly on a porous plate, then to dissolve it in cold dry benzene and precipitate with light petroleum.

0.1969 gave 0.5120 CO_2 and 0.1745 H_2O . $\text{C} = 70.9$; $\text{H} = 9.8$.

$\text{C}_{30}\text{H}_{50}\text{O}_6$ requires $\text{C} = 71.1$; $\text{H} = 9.8$ per cent.

The compound is very readily soluble in all the usual media with the exception of water and light petroleum; it is obtained from a mixture of benzene and light petroleum in very slender, but well-formed, needles melting at 194 – 196° . The crystals have a weak double refraction; the extinction direction in polarised light is straight, and the directions of greatest elasticity and length are coincident. A solution of 0.4001 gram of the substance in 25 c.c. of benzene gave $[\alpha]_D = -24.9^\circ$, changing to -26.5° on the third day.

Experiments were also made in order to determine whether the rotatory power was altered by the addition of a trace of a base as an accelerator. For this purpose, an approximately one per cent. benzene solution was divided between two 2-dcm. tubes, and a trace of piperidine added to one; the rotation in both cases, however, gave the same value, no mutarotation being observed during twenty-four hours.

Propylidene Derivatives.

Menthyl Propylideneacetoacetate, $\text{CH}_3 \cdot \text{CH}_2\text{CH} : \text{C}(\text{CO} \cdot \text{CH}_3) \cdot \text{CO}_2 \cdot \text{C}_{10}\text{H}_{19}$

For the preparation of this compound, menthyl acetoacetate and propaldehyde in equivalent proportions were condensed with three or four drops of piperidine at the ordinary temperature. On the following day, the mixture formed a viscid, oily liquid containing drops of water, and was induced to solidify by the addition of a single drop of

concentrated aqueous sodium hydroxide, the flask containing the liquid being shaken vigorously from time to time. Condensation was also effected by allowing the reaction mixture to remain for some hours at 0° . In one experiment, two molecular proportions of menthyl acetoacetate were condensed with one of propaldehyde, the mono-menthyl ester being again formed. Another batch, prepared under the same conditions, yielded a compound melting at about 200° , which was subsequently shown to be the menthyl propylidenebisacetoacetate. Further condensations, however, whether effected with one or two molecular proportions of the menthyl ester only gave the unsaturated compound, the temperature at which the reaction proceeded being, apparently, immaterial.

0.2033 gave 0.5430 CO_2 and 0.1843 H_2O . $\text{C} = 72.8$; $\text{H} = 10.0$.

$\text{C}_{17}\text{H}_{28}\text{O}_3$ requires $\text{C} = 72.8$; $\text{H} = 10.0$ per cent.

The substance is easily soluble in benzene, chloroform, ether, or acetone, and when recrystallised from hot alcohol is obtained in the form of plates melting at $84\text{--}88^{\circ}$.

Conclusive evidence as to the nature of the compound under examination was afforded by its behaviour with warm sodium hydroxide solution, as a powerful odour of propaldehyde was evolved, and this decomposition is characteristic of the unsaturated alkylidene acetoacetates.

The crystals are rectangular, apparently orthorhombic plates which have straight extinction, the direction of greatest elasticity and length being coincident. The double refraction is strong. After melting between glass slips, this substance solidifies rapidly to fan-shaped masses which show aggregate extinction. Under the high power in convergent polarised light, the bisectrix of an interference figure of wide angle may be distinguished occasionally. The double refraction is positive, and the axial plane cuts the crystals in the directions of their greatest length.

The action of the substance on polarised light was investigated, 0.3980 gram being dissolved in benzene and made up to 25 c.c.; with this solution, a rotation corresponding with $[\alpha]_{\text{D}} = -34.9^{\circ}$ was obtained, and no alteration of this value was observed.



This ester is obtained by condensing the monomenthyl derivative with about an equal weight of menthyl acetoacetate and a few drops of piperidine and alcohol. The reaction is considerably hastened by

warming on the water-bath, a viscid, oily liquid being obtained, which, on cooling, usually became almost solid in fifteen minutes.

0.1976 gave 0.5183 CO_2 and 0.1797 H_2O . $\text{C} = 71.5$; $\text{H} = 10.0$.

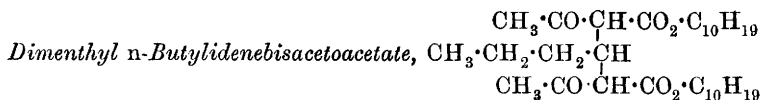
$\text{C}_{31}\text{H}_{52}\text{O}_6$ requires $\text{C} = 71.5$; $\text{H} = 10.0$ per cent.

The substance is easily soluble in benzene, chloroform, or hot ethyl acetate; very sparingly so in ether or light petroleum, and is almost insoluble in alcohol. On recrystallisation from acetone, it melts at $201\text{--}207^\circ$. The crystallographic characters of the compound are precisely similar to those of dimenthyl ethylidenebisacetoacetate.

A solution of 0.1301 gram in 25 c.c. of benzene had a constant rotation of $[\alpha]_D = -26.9^\circ$. Solutions in benzene in presence of a trace of piperidine were also observed in the polarimeter, but even here no mutarotation could be detected.

Normal Butylidene Derivatives.

All attempts to prepare menthyl *n*-butylideneacetoacetate were unsuccessful, the more complex ester being formed in each case.



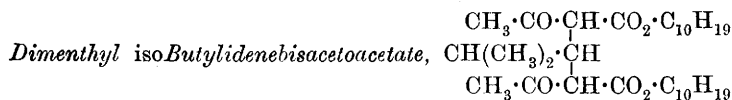
This substance is prepared by mixing *n*-butaldehyde with a molecular proportion of the menthyl ester in presence of a few drops of piperidine. The mixture soon forms an oily liquid at the ordinary temperature, and the product is obtained in the solid condition by the addition of alcohol and a small quantity of aqueous sodium hydroxide.

0.2023 gave 0.5339 CO_2 and 0.1853 H_2O . $\text{C} = 71.9$; $\text{H} = 10.1$.

$\text{C}_{32}\text{H}_{54}\text{O}_6$ requires $\text{C} = 71.9$; $\text{H} = 10.1$ per cent.

The compound separates from ethyl acetate in fine needles melting at 184° ; it is easily soluble in ether, benzene, and chloroform, less so in alcohol, acetone, and light petroleum. Crystallographically, it appears to be similar to the corresponding ethylidene derivative. A solution of 0.1857 gram in 25 c.c. of benzene gives $[\alpha]_D = -16.8^\circ$.

When this substance is treated in chloroform solution with hydrogen chloride, a viscid mass is obtained on evaporating the solvent; on triturating the substance with light petroleum and allowing the mixture to remain for some days, crystals are obtained melting at $136.5\text{--}137.5^\circ$, but this material was formed in such small quantity that it could not be subjected to detailed examination.

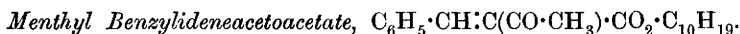
isoButylidene Derivatives.

This compound is obtained under conditions similar to those employed in the foregoing case, the addition of a drop of concentrated sodium hydroxide solution being used to hasten the condensation.

0.1647 gave 0.4331 CO_2 and 0.1500 H_2O . $\text{C} = 71.71$; $\text{H} = 10.1$.

$\text{C}_{32}\text{H}_{54}\text{O}_6$ requires $\text{C} = 71.9$; $\text{H} = 10.1$ per cent.

The substance crystallises from ethyl acetate in needles, which soften at 193° and melt completely at 202° . The ester is fairly soluble in the usual organic media; its crystals are slender needles, like those of the other alkylidenebisacetoacetates, but are always considerably larger and apparently somewhat better defined. A benzene solution of 0.2933 gram of the substance made up to 25 c.c. gave $[\alpha]_D = -42.6^\circ$; here a slight mutarotation was observed, the rotatory power assuming a constant value of $[\alpha]_D = -46.0^\circ$ at the end of a week.

Benzylidene Derivatives.

A mixture of menthyl acetoacetate and benzaldehyde in molecular proportion, together with a few drops of piperidine, was allowed to remain at the ordinary temperature for about 24 hours; a cloudiness, due to the separation of water, was noticed at the end of an hour, and a semi-solid mass was finally obtained. The crystalline substance which separated was freed from the remaining oil by filtration under pressure, and was then dried on a porous plate and recrystallised from hot spirit.

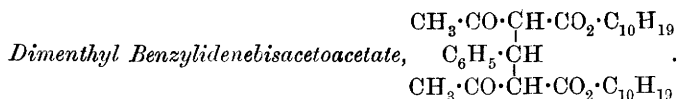
0.1960 gave 0.5491 CO_2 and 0.1487 H_2O . $\text{C} = 76.4$; $\text{H} = 8.4$.

$\text{C}_{21}\text{H}_{28}\text{O}_3$ requires $\text{C} = 76.8$; $\text{H} = 8.5$ per cent.

The compound is easily soluble in the usual organic media, although but sparingly so in light petroleum; it separates from alcohol in flattened, colourless needles, and melts sharply at $133\text{--}134^\circ$.

The crystals are well-formed, flat needles, or six-sided, elongated plates, which have straight extinction and are probably orthorhombic. The directions of greatest elasticity and length are coincident; the double refraction is moderate. When melted on a glass slip beneath

a cover-glass and then cooled, the compound solidifies fairly quickly in radiate masses of slender, flat needles, which are only distinguishable under a high power. A solution of 0.3995 gram of the substance in 25 c.c. of benzene gave $[\alpha]_D = -10.0^\circ$, no alteration in this value being noticed during three days.



This ester was obtained by condensing the benzylidene compound with one molecular proportion of menthyl acetoacetate in presence of a small quantity of alcohol and a few drops of piperidine; the mixture, when warmed on the water-bath, became considerably more viscous, and at the end of 12 hours was semi-solid and translucent. The product showed a great tendency to separate as a jelly from benzene, acetone, or ethyl acetate, but was obtained in the crystalline form by adding an equal bulk of light petroleum to its solution in cold chloroform; fine needles separated when the liquid evaporated at the ordinary temperature.

0.2077 gave 0.5612 CO_2 and 0.1720 H_2O . $\text{C} = 73.7$; $\text{H} = 9.2$.

$\text{C}_{35}\text{H}_{52}\text{O}_6$ requires $\text{C} = 73.9$; $\text{H} = 9.2$ per cent.

The compound is very sparingly soluble in alcohol, ether, and light petroleum, but dissolves fairly readily in benzene, acetone, or ethyl acetate. It softens at 203° and melts completely at 206° . Crystallographically, the substance resembles the corresponding ethylidene derivative. A solution of 0.1437 gram in benzene made up to 25 c.c. and observed in a 2-dcm. tube gave a value for $[\alpha]_D = -30.4^\circ$.

Addendum.—It has been mentioned in the preceding pages that not only alkaline hydroxides and powerful primary and secondary organic bases, but also tertiary bases bring about the condensation of aldehydes with menthyl acetoacetate. This is found to be equally true with ethyl acetoacetate, as the following observations show.

When ethyl acetoacetate and 40 per cent. formaldehyde are mixed with pyridine even in fairly large quantity, no noticeable rise of temperature occurs, and condensation does not appear to take place even after some weeks at the ordinary temperature. If, however, two or three drops of concentrated trimethylamine solution or pure tripropylamine are added to 5 c.c. of the mixture, the temperature rises very rapidly, and in a few minutes water separates; in fact, these bases act much in the same way as does diethylamine, but considerably less rapidly weight for weight. As the products were liquid in the foregoing case,

a similar experiment was performed with a mixture of acetaldehyde (1 mol.) and ethyl acetoacetate (2 mols.); with 10 c.c. of such a mixture, 5 c.c. of pyridine produced no appreciable effect, but 20 drops of tripropylamine caused the separation of water within a few minutes at the ordinary temperature, and after three days the mixture solidified to a mass of crystals identical with those obtained by using piperidine or diethylamine in small quantities.

On adding 2 grams of tripropylamine to a mixture of 5.3 grams of benzaldehyde and 14 grams of ethyl acetoacetate, both freshly distilled, a marked rise in temperature occurred at once, and after five days at the ordinary temperature the whole had solidified to a crystalline mass of diethyl benzylidenebisacetoacetate.

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