CXLVIII.—*Optically Active Esters of β -Ketonic and β -Aldehydic Acids. Part II. Menthyl Acetoacetate.*

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IN continuation of researches on the tautomerism of β -ketonic esters, the study of an optically active ester of acetoacetic acid was undertaken, as little is yet known as to the mode in which interconversion of the enolic and ketonic forms of ethyl acetoacetate is brought about, for although it is already well established that bases in small quantities are effective in establishing equilibrium, the effect of acids has not been properly investigated.

After a number of attempts had been made to obtain the menthyl ester from menthyl acetate by the action of metallic sodium—a method which was found to afford the desired compound only in small quantity—the action of menthol on the ethyl ester in presence of hydrogen chloride was tried. A preliminary experiment indicated that alcohol was evolved in considerable amount before the hydrogen chloride was introduced, and we afterwards prepared some quantity of menthyl acetoacetate by the action of heat on a mixture of menthol and ethyl acetoacetate, a method which afforded excellent results. Shortly afterwards, we found that Cohn had obtained the compound by this process (*Monatsh.*, 1900, 21, 200), but as he shortly afterwards notified that he had abandoned the work (*Ber.*, 1900, 33, 734), with his concurrence we proceeded with the investigation.

The ease with which the ester is prepared renders it possible to produce large quantities of it in a short time, and we propose to employ the compound as the starting point in the preparation of a number of other active compounds which may possess interest from various standpoints.

Cohn does not state that he had formed any definite opinion as to the constitution of the solid ester which is obtained by this process. We are disposed to believe that it must be the ketonic form, and for the following reasons, which, it must be admitted, are not altogether conclusive.

The greater proportion of ethylacetoacetate at the ordinary temperature exists as the ketonic form (Trans., 1892, 61, 808). As a rule, compounds are stable in the enolic condition when they exhibit strongly acid properties, whereas the acidic properties of menthyl acetoacetate are exceeding weak, as is shown by the fact that it dissolves only very sparingly in cold alkalis, although these bring about equilibrium between the two forms very rapidly. Again, in the case of substituted acetoacetic esters, in which the substituent is not an acyl group, it is invariably the ketonic form which is the stable one. Lastly, there may be mentioned the behaviour of the compound towards ferric chloride, which indicates that the maximum quantity of enolic ester is not present at the first moment of dissolution in a solvent.

Menthyl acetoacetate exhibits mutarotation in non-oxygenated solvents, the change occurring with a speed which renders it easy to study the effects of agents with advantage.

It is interesting to observe that hitherto only those types of compounds which have been shown by independent chemical or physical methods to exhibit desmotropy or isodynamic isomerism possess the property of mutarotation, a fact which serves to support Lowry's conclusion (Trans., 1899, 75, 213) that the two phenomena are very closely related. Thus the compounds in which mutarotation has hitherto been observed with certainty are the aldoses and pentoses, nitro- and π -bromonitro-camphor, nitrocamphane, α -benzoylcamphor, camphorquinonephenylhydrazone, and menthyl acetoacetate, and in all these cases there is every reason to believe that isodynamic change is the cause. In the case of many other active menthyl esters obtained from the formylacetate and acetoacetate, no observable change of rotation occurs, and this was to be expected, as there is no sufficient reason to suppose them capable of desmotropic change, although in some instances their constitutions are capable of two modes of representation, differing only in the position of a hydrogen atom.

The most striking feature of the mutarotation of menthyl acetoacetate is the fact that traces of acids as well as of bases accelerate the change. The significance of this observation is referred to elsewhere (p. 1513) and need not again be discussed.

Menthyl acetoacetate has apparently all the chemical characters of the ethyl ester, but exhibits certain qualitative differences, inasmuch as its reactions are more sluggish, requiring in most cases much longer

periods for their completion. A similar sluggishness is observed in the crystallising power of the higher substituted menthyl acetoacetates which we have recently obtained, for where the ethyl esters crystallise very readily, the menthyl esters tend to form jellies, or remain liquid for many weeks.

EXPERIMENTAL.

Preparation and Properties of Menthyl Acetoacetate.—Cohn (*Monatsh.*, 1900, 21, 200) heated ethyl acetoacetate with menthol in a reflux apparatus at about 150° for 5 hours, and finally fractionated the product by distillation under diminished pressure. We prefer to heat the materials in a Wurtz flask over an Argand burner, allowing the alcohol produced to distil off as soon as it is formed, and, when the action becomes very slow, to boil off the unaltered menthol and ethyl acetoacetate under a pressure of about 15 mm., the distillation being interrupted when a thermometer immersed in the vapour indicates a temperature of about 160° . The residue is poured into a beaker, and on cooling it slowly sets to a nearly solid mass, which is ground into a paste, freed from most of the oily matter by the aid of the pump, and finally washed in the funnel with a very small quantity of ether. The product so obtained forms a white, crystalline mass. It may be recrystallised by dissolving it in dry ether and cooling the solution by a freezing mixture. A further quantity of the substance may be obtained from the lower boiling portions of the distillate and the attendant oil by refractionation or by conversion into the copper derivative.

By very slow crystallisation, the ester may be obtained in the form of large, transparent prisms, in which, however, there is very little tendency to the development of good end faces. Through some of the larger faces, which are usually very bright, a biaxial figure of very small angle may be observed in convergent polarised light, emerging obliquely to the field; the crystals appear to belong to the monoclinic system, in which case the bisectrix is in the plane of symmetry. The double refraction is positive in sign and weak.

The melting point of the compound is given by Cohn as $30-32^{\circ}$, which is the melting point we have usually observed, but on one or two occasions we have noticed that a small quantity of the material in a thin-walled capillary tube remained for a considerable time at $38-40^{\circ}$ without melting, and if the temperature were raised somewhat rapidly, fusion did not occur until a temperature of $43-45^{\circ}$ was reached. On cooling, no matter how long the material had been kept in the fused condition, rapid solidification always occurred, the whole setting to a mass of flat needles identical in crystalline character with the large prisms above described.

The solid substance is probably the ketonic form of the ester, for

when it is dissolved in anhydrous ether, benzene, or chloroform, and a drop of an ethereal solution of ferric chloride is added, no marked coloration is developed unless the liquid is boiled or is allowed to remain for some time; a coloration is at once developed in the cold, however, if a trace of an organic base, such as pyridine, is previously added.

Solutions in alcohol, immediately after preparation, gave with ferric chloride a faint coloration which rapidly deepened, whilst if the solution had been allowed to remain for a few minutes in the cold the maximum colour appeared to be produced at once. A violet coloration is also produced when a drop of alcohol is added to the nearly colourless solution of the ester in benzene or ether containing ferric chloride. In fact, the phenomena observed were very similar to those which we had noticed in the case of menthyl formylphenylacetate, and, as in that case, all attempts to prepare the desmotropic form of the ester were unsuccessful.

The specific rotation of the compound was determined in several solvents. In 1.5 per cent. solution in absolute alcohol, it had $[\alpha]_D -68.5^\circ$. In ethyl acetate, its rotation at 1.5 per cent. concentration was $[\alpha]_D -59.8^\circ$, and remained constant. In these liquids, no very marked alteration of the specific rotation with time was noticed.

Menthyl acetoacetate exhibits the phenomenon of mutarotation in non-oxygenated solvents in a much more marked manner than does the formylphenylacetate. The change, moreover, appears to be much more rapid, and the velocity is greatly affected by the presence of catalytic agents, and varies considerably with the degree of purity of the solvent. In the cases cited below, we have employed media which have been subjected to careful purification.

In chloroform, an initial rotation of about $[\alpha]_D -68.5^\circ$ was observed, and in the course of some hours this had attained a constant value of -70.7° . In light petroleum, the rotation was initially $[\alpha]_D 65.1^\circ$, and rapidly reached a maximum value of -74.4° . In benzene, with which we have made most of our experiments, the rotation changed from about $[\alpha]_D -61.5^\circ$ to -67.4° or -68.4° for concentrations between 1 and 2 per cent., the duration of measurable change varying from 20 minutes to 2 hours, depending, no doubt, on the purity of the specimen of solvent used.

The effect of catalytic agents on the change could be conveniently studied in this instance, and we made numerous experiments on the point. The mode of procedure was similar to that adopted in the case of camphorquinonehydrazone (this vol., p. 1517), a series of readings with three or more tubes containing the same solution being made simultaneously in every case.

It was observed that, as usual, traces of all bases, including even

weak tertiary bases, increase the velocity of change, and that traces of acids produce a similar effect. The acids tried included acetic, trichloroacetic, benzoic, salicylic, and crotonic acids, and were found to be effective even in minute quantities, particularly so in the case of the strongest one—trichloroacetic acid.

In this instance, too, it was found that marked acceleration was produced even by such weak bases as the monobromo- and mononitroanilines, although the effect was distinctly smaller than when more powerful bases were used in equivalent quantities. The effects of various other substances soluble in benzene were also examined, but hitherto only those compounds the effect of which might be ascribed to acidic or basic properties have been found effective when added in minute amount: certain compounds, such as alcohol, produce very marked acceleration, but only when present in comparatively large quantities.

As an instance of the sensitiveness of the compound toward acids, it may be mentioned that in one experiment four tubes were filled with the same solution of the ester in benzene; the initial rates of change of rotation in each were measured and found to be nearly the same. Into two of these tubes traces of trichloroacetic acid were introduced by touching a moist crystal of the acid with a platinum wire which was then dipped into the solutions. In the case of the two unopened tubes, the mutarotation continued to be observable for more than an hour, whilst in the two others the maximum rotation was reached in less than ten minutes.

Derivatives of Menthyl Acetoacetate.

With the exception of the copper compound, the metallic derivatives of the ester have not been obtained in characteristic forms. The compounds obtained by the action of amines and hydrazines on menthyl acetoacetate are, as a rule, easily isolated in a crystalline form. The phenylhydrazide has already been described by Cohn (*Ber.*, 1900, 33, 735.)

The *copper* derivative, $(C_{14}H_{23}O_3)_2Cu$, is precipitated as an oil on adding copper acetate dissolved in twenty times its weight of water to an alcoholic solution of the ester. When left in contact with the alcoholic liquid, it slowly becomes crystalline, and was purified by crystallisation from hot alcohol. It separates almost completely from cold 90 per cent. ethyl alcohol in dark green, transparent prisms, which contain alcohol of crystallisation; the latter is gradually lost when the substance is exposed to the air, the compound then forming a bluish-green powder. When heated rapidly, the crystals soften at $78-80^\circ$, but do not melt below 106° ; the dry substance, on the

other hand, melts sharply at $117-118^{\circ}$ and slowly decomposes. On analysis:

0.8139 gave 0.1173 CuO. $\text{Cu} = 11.5$.

$(\text{C}_{14}\text{H}_{23}\text{O}_3)_2\text{Cu}$ requires $\text{Cu} = 11.6$ per cent.

The *semicarbazide*, $\text{NH}_2 \cdot \text{CO} \cdot \text{N}_2\text{H}_2 \cdot \text{C}(\text{CH}_3) : \text{CH} \cdot \text{CO}_2 \cdot \text{C}_{10}\text{H}_{19}$, was made by adding semicarbazide hydrochloride dissolved in a little water to a solution of the ester in alcohol; on warming gently, the product separated rapidly as a paste of glistening, flat needles, and was crystallised from hot alcohol. On analysis:

0.1985 gave 0.4423 CO_2 and 0.1635 H_2O . $\text{C} = 60.7$; $\text{H} = 9.1$.

$\text{C}_{15}\text{H}_{27}\text{O}_3\text{N}_3$ requires $\text{C} = 60.6$; $\text{H} = 9.0$ per cent.

It dissolves readily in benzene, acetone, ethyl acetate, or hot alcohol, somewhat less readily in ether, and is nearly insoluble in light petroleum. It crystallises from alcohol in small, flat needles, from ether in elongated plates, and melts at $143-144^{\circ}$. A 1.5 per cent. solution in benzene had the rotation $[\alpha]_D - 56.1^{\circ}$ and no mutarotation was observed.

The crystals from ether are usually four-sided, rhomboidal plates, and on these the extinction directions in polarised light are inclined at varying angles to the longer sides; they frequently show a biaxial interference figure, the optic axis emerging nearly perpendicular to the field.

The *p-nitrophenylhydrazide*, $\text{NO}_2 \cdot \text{C}_6\text{H}_4 \cdot \text{N}_2\text{H}_2 \cdot \text{C}(\text{CH}_3) : \text{CH} \cdot \text{CO}_2 \cdot \text{C}_{10}\text{H}_{19}$, was prepared by heating together the requisite quantities of the ester and *p*-nitrophenylhydrazine in alcoholic solution for several hours on the water-bath and precipitating the product with water. The oily product, which did not show any sign of crystallising after some days, was fractionally extracted with cold light petroleum, when a considerable proportion was obtained, on evaporation of the solvent, in a crystalline form. It was purified by recrystallisation from alcohol:

0.2275 gave 0.5320 CO_2 and 0.1626 H_2O . $\text{C} = 63.8$; $\text{H} = 7.9$.

$\text{C}_{20}\text{H}_{29}\text{O}_4\text{N}_3$ requires $\text{C} = 64.0$; $\text{H} = 7.7$ per cent.

The hydrazide is readily soluble in warm alcohol and most of the usual media, but is only sparingly dissolved by light petroleum and is insoluble in water. It melts at $105-106^{\circ}$.

A solution of 0.3533 gram in 25 c.c. of benzene gave $[\alpha]_D - 42.5^{\circ}$, no mutarotation being observable, even after addition of an acid or a base.

The crystals from alcohol are transparent, brownish-yellow prisms or pyramids. When melted on a microscope slide beneath a cover-glass, the substance solidifies very slowly on cooling, forming small,

flat, isolated, four-sided plates, in which the extinction in polarised light is parallel to the smaller pair of sides. When the crystals are crushed and examined in convergent polarised light, many fragments show a biaxial interference figure of wide angle. The double refraction is unusually strong.

Menthyl β -Aminocrotonate, $\text{NH}_2 \cdot \text{C}(\text{CH}_3) : \text{CH} \cdot \text{CO}_2 \cdot \text{C}_{10}\text{H}_{19}$.—When ammonia is passed into menthyl acetoacetate at a temperature slightly above the melting point of the ester, it is only very slowly absorbed, and even after some days the action does not appear to be complete. If, however, a small quantity of ammonium acetate is introduced into the liquid, reaction occurs much more quickly, globules of water separate, and the whole finally sets to a semi-solid mass. In order to purify the product, it was spread on porous earthenware and then crystallised from hot alcohol. On analysis :

0.2006 gave 0.5179 CO_2 and 0.1906 H_2O . $\text{C} = 70.4$; $\text{H} = 10.6$.

$\text{C}_{14}\text{H}_{25}\text{O}_2\text{N}_2$ requires $\text{C} = 70.3$; $\text{H} = 10.5$ per cent.

The compound dissolves fairly readily in most of the usual organic media and separates from alcohol on spontaneous evaporation in large, brilliant, transparent prisms, with one good plane of cleavage. It melts at $88-89^\circ$, and after solidification melts once more at the same temperature.

A benzene solution containing 0.3895 gram of the substance in 25 c.c. of benzene was examined ; this gave $[\alpha]_D - 105.2^\circ$, and no alteration of this value was observed.

Small, elongated crystals of the compound are sometimes obtained ; these have straight extinction in polarised light, the directions of greatest length and elasticity being parallel. Crushed fragments of the crystals examined in convergent light frequently show a biaxial interference figure of moderate angle ; this figure is probably that corresponding with the acute bisectrix ; the dispersion is strong, the angle for red light being greater than that for blue.

Menthyl β -Benzylaminocrotonate,

—A mixture of menthyl acetoacetate and benzylamine in molecular proportion was warmed gently until the solid had disappeared and was then allowed to remain at the ordinary temperature for some time. A milkiness, due to separation of water, soon became noticeable and at the end of six hours the whole was solid. The mass was dissolved in a little hot absolute alcohol and the crystalline separation purified by recrystallisation from absolute alcohol. On analysis :

0.2006 gave 0.5638 CO_2 and 0.1732 H_2O . $\text{C} = 76.7$; $\text{H} = 9.6$

$\text{C}_{21}\text{H}_{31}\text{O}_2\text{N}$ requires $\text{C} = 76.6$; $\text{H} = 9.4$ per cent.

The substance dissolves readily in benzene, chloroform, carbon tetrachloride, ethyl acetate, acetone, or light petroleum, but is less readily dissolved by methyl or ethyl alcohol. It separates from hot absolute alcohol in flat needles and melts at 85—86°. A solution containing 0.4032 gram in 25 c.c. of benzene gave $[\alpha]_D -59.8^\circ$ and this value remained constant.

The crystals are elongated rectangular plates or flat needles, which show straight extinction in polarised light; the directions of greatest length and elasticity are parallel.

Menthyl β -Anilinocrotonate, $C_6H_5 \cdot NH \cdot C(CH_3) : CH \cdot CO_2 \cdot C_{10}H_{19}$.—This compound was made by the interaction of aniline and menthyl acetoacetate in molecular proportion in the cold; the action is complete in 24 hours, and the product, which is somewhat oily, may be drained on porous earthenware and finally crystallised several times from methyl alcohol. On analysis:

0.2022 gave 0.5670 CO_2 and 0.1679 H_2O . $C = 76.5$; $H = 9.2$.

$C_{20}H_{29}O_2N$ requires $C = 76.2$; $H = 9.2$ per cent.

It dissolves somewhat readily in most of the usual organic media and separates from methyl alcohol or absolute ethyl alcohol in thin plates or flat needles. It melts sharply at 89—90°, and after solidification fuses once more at the same temperature. A solution containing 0.4045 gram in 25 c.c. in benzene gave $[\alpha]_D -98.2^\circ$, and this value remained constant.

The crystals from absolute alcohol are usually flat, rectangular plates which probably belong to the monoclinic system; in polarised light, the extinction is straight and the directions of greatest length and elasticity are parallel. In convergent polarised light, the obtuse bisectrix of a bixial interference figure emerges through the larger face at an angle inclined to the perpendicular; the axial plane is coincident with the plane of symmetry and the double refraction is moderately strong and negative in sign. When the substance is melted on a glass slide beneath the cover-slip, it solidifies very slowly as the temperature falls, to masses of large, irregular plates identical in character with those above described.

Action of Acid Chlorides on Menthyl Acetoacetate and its Metallic Derivatives.—Acetyl chloride acts slowly on the ester, hydrogen chloride being evolved, but nothing of definite character could be isolated from the product; when, instead of the ester, the sodium or copper derivative is used, very rapid action occurs, but from the product nothing but the copper compound of the unaltered ester could be isolated. Unsatisfactory results were also obtained when attempts were made to prepare the O-acetyl derivative from the ester by treatment with a mixture of acetyl chloride and pyridine by Claisen's method.

More definite results were obtained by acting with benzoyl chloride on the sodium derivative of the ester suspended in ether. The action, which was apparently a slow one, was completed by the aid of heat and it should be mentioned that, even after several days' heating on the water-bath, no deposit of sodium chloride was observed, although the odour of the benzoyl chloride had entirely disappeared; we are unable to offer any explanation of the fact. The ethereal solution was finally shaken with ice-cold water to remove sodium chloride and was then extracted repeatedly with a solution of sodium carbonate. On evaporation, the residual ethereal solution gave an oil which resisted all attempts at purification. From the sodium carbonate solution, however, an oil was deposited on acidification; this was dissolved in alcohol and the solution treated with aqueous copper acetate, when a copious deposit of an insoluble copper derivative was obtained.

The *copper* compound crystallised from hot ethyl acetate in slender needles of a greenish-blue colour. On analysis :

0.5053 gave 0.0527 CuO. Cu = 8.4.

$(C_{21}H_{27}O_4)_2$ Cu requires Cu = 8.4 per cent.

The substance is sparingly soluble in alcohol or cold ethyl acetate or acetone, but dissolves somewhat readily in cold chloroform or benzene. When heated slowly, it darkens at 210° – 215° and melts and decomposes at 226° , but if heated suddenly to 230° it melts some degrees above this point.

In order to obtain the free ester, the copper compound was suspended in purified ether and shaken with dilute hydrochloric acid until the crystals had disappeared; on evaporation of the washed and dried ethereal solution, a substance, which formed a very thick oil at the ordinary temperature was obtained. This decomposed when distilled under the lowest pressures which we were able to obtain, and was therefore dried at 100° and analysed :

0.2375 gave 0.6358 CO_2 and 0.1802 H_2O . C = 73.0; H = 8.4.

$C_{21}H_{28}O_4$ requires C = 73.2; H = 8.1 per cent.

The compound has therefore the composition, as well as the general properties of menthyl benzoylacetoacetate, $COMe \cdot CHBz \cdot CO_2 \cdot C_{10}H_{19}$, and is, in all probability, a mixture of the enolic and ketonic forms of that substance; its alcoholic solution gave a deep brownish-purple solution with ethereal ferric chloride. A 25 per cent. solution of the compound in benzene gave $[\alpha]_D -44.3^{\circ}$ and this value remained constant during a week.

In order to prove that a benzoyl group was present in the substance, it was oxidised with boiling alkaline permanganate solution and a considerable quantity of benzoic acid was obtained; during the oxidation, a

powerful odour of menthol was observed. That the acetyl group was still present as well as the benzoyl group was evident from the strongly acidic properties of the compound, which dissolved readily in sodium carbonate solution.

Menthyl acetoacetate reacts only slowly, if at all, with phenyl-carbimide; a mixture of 1 mol. of the latter with 2 mols. of the former remained unaltered in appearance during several months, and even after further heating on the water-bath retained the odour of the carbimide.

The bromo-derivatives of the ester do not crystallise readily, nor do they appear to afford crystalline copper derivatives. The products obtained by the action of 1, 2 or 3 mols. of bromine on the ester were carefully examined, but in all cases they remained oily and afforded oily copper derivatives; no better results were obtained on attempting to prepare the γ -bromo-derivatives.

The products obtained by the action of aldehydes and of diazonium compounds on the ester are at present under examination. We propose also to extend this study of optically active esters to active esters of other β -ketonic and β -aldehydic acids, and also to derivatives of menthyl cyanoacetate.

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