CLXIII.—*Carboxylated β-Diketones.*

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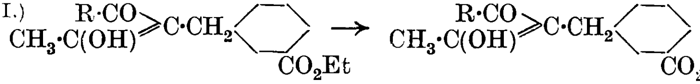
IN this communication we describe the synthesis of new β-diketones containing auxiliary carboxyl groups, these substances having been prepared with the object of facilitating the resolution of metallo-β-diketones into optically active enantiomerides.

Hitherto this separation has been effected only with such salts as [CoAc,2en]Cl_2 and [CoPr,2en]Cl_2, where Ac and Pr represent the univalent radicals of acetylacetone and propionylacetone respectively (Werner, Schwyzer, and Karrer, *Helv. Chim. Acta*, 1921, **4**, 113), but not with metallo-β-diketones such as [$BePr_2$] and [$CuPr_2$] or [$FeAc_3$] and [$CoAc_3$], where the metal is wholly combined with the organic radical. Even if the two foregoing pairs of metallo-β-diketones exist respectively in tetrahedral and octahedral forms, an experimental difficulty arises from the fact that these substances, being non-ionised inner metallic complexes, do not combine either with optically active acids or with alkaloids. Moreover, the examination of selected crystals has not in this series led to positive results.

An auxiliary acidic group has been conferred on acetylacetone by condensing the sodium salt of this β-diketone with *ethyl ω-chloro-*m-*toluate* (m-*carbethoxybenzyl chloride*), $CH_2Cl{\cdot}C_6H_4{\cdot}CO_2Et$, when 3-m-*carbethoxybenzylacetylacetone* (I; $R = CH_3$) was produced which by hydrolysis in concentrated sulphuric acid furnished 3-m-*carboxybenzylacetylacetone* (II: $R = CH_3$), a β-diketone containing two acidic functions, a chelate radical and the carboxyl substituent.

(I.)



(II.)

$R = CH_3$ or C_3H_7.

Cobaltic and chromic derivatives of the free carboxy-diketone were prepared but found to be unsuitable for resolutions with optically active alkaloids.

Homologues of the foregoing diketones with unsymmetrical chelate groups were prepared by a similar series of operations carried out on sodium butyrylacetone, when 3-m-*carbethoxybenzylbutyrylacetone* (I; $R = C_3H_7$) resulted, and this ester on hydrolysis yielded 3-m-*carboxybenzylbutyrylacetone* (II; $R = C_3H_7$).

The free carboxy-diketone (II; $R = C_3H_7$) gave a green dicupric salt convertible into a grey monocupric derivative the colour of which suggested (Morgan, Drew, and Porter, *Ber.*, 1925, **58**, 333) that the metal was held in the chelate group, but, although soluble in organic media, the monocupric compound rapidly decomposed in warm solutions into dicupric salt and carboxy-diketone.

A similar pair of beryllium derivatives was prepared, the monoberyllium compound being soluble in organic media, but crystallisation of this substance was impossible because of its rapid decomposition into ill-defined, insoluble products. Moreover, the alkaloidal salts of this monoberyllium derivative were also unsatisfactory and afforded no indication of any resolution.

Both carboxy-β-diketones exhibit keto-enol isomerism : specimens crystallised from non-hydroxylic solvents such as benzene or petroleum were more fusible and gave immediately with ferric chloride purple colorations, thus indicating the enolic variety, whereas preparations crystallised from alcohol were less fusible and developed the coloration only gradually, thereby suggesting a diketonic modification.

EXPERIMENTAL.

*Ethyl ω-chloro-*m*-toluate* (m*-carbethoxybenzyl chloride*) was prepared by a modification of the patented method (E.P. 29720/1910; D.R.-P. 234913; Friedländer's "Fortschritte," X, p. 117). *m*-Toluic acid (100 g.) was gradually warmed to 120° with 75 c.c. of thionyl chloride and thereby converted into *m*-toluoyl chloride, b. p. 105°/20 mm. Chlorine was passed into 112·5 g. of this chloride at 160—180° until its weight increased to 138 g. The resulting ω-chloro-*m*-toluoyl chloride was warmed gently with 50 c.c. of alcohol; a vigorous reaction set in with evolution of hydrogen chloride, the flask being finally heated to 140°. The ester was washed rapidly with dilute aqueous sodium carbonate and water, dried, and distilled under reduced pressure; 130 g. (= 89%) were obtained boiling at 140—150°/12 mm. (Found : Cl, 18·4. $C_{10}H_{11}O_2Cl$ requires Cl, 17·9%).

I. 3-m-*Carbethoxybenzylacetylacetone* (I; R = CH_3).—Eighty g. of sodium acetylacetone and 130 g. of the foregoing ester were heated together under reflux at 135—145° for 3 hours and finally at 160°. The cooled product was extracted with water and ether; the dried ethereal layer was distilled, yielding acetylacetone and 84 g. of a higher fraction, b. p. 175—215°/11 mm. The less volatile fraction dissolved in alcohol and was added to aqueous copper acetate containing an equivalent proportion of ammonia. After 2 or 3 days the copper derivative was collected, and washed with dilute acetic acid to dissolve copper hydroxide and with ether to remove liquid impurities. The ethereal washings were worked up again with further distillations of crude diketone.

Copper 3-m-*carbethoxybenzylacetylacetone*, a light grey, microcrystalline powder, was insoluble in water but soluble in organic solvents; it crystallised from benzene and melted at 173—176° (Found : C, 61·3; H, 5·6. $C_{30}H_{34}O_8Cu$ requires C, 61·6; H, 5·8%).

On extraction with dilute sulphuric acid and ether 67 g. of this copper salt yielded 42 g. (= 70%) of the liquid diketone, b. p. 209—215°/12 mm., which developed a reddish-purple coloration with alcoholic ferric chloride.

Acidic Hydrolysis of 3-m-*Carbethoxybenzylacetylacetone.*—The ester was not affected by boiling with 5*N*-sulphuric acid, 40% sulphuric acid, concentrated hydrochloric acid, or glacial acetic acid. Heating with syrupy phosphoric acid led to products giving no coloration with ferric chloride.

A solution of 1 or 2 g. of the ester in 3 or 4 volumes of concentrated sulphuric acid was heated on the water-bath; hydrolysis occurred and the cooled red liquid yielded a white solid when poured on to crushed ice. This product was crystallised from benzene or benzene–petroleum. The first mother-liquors contained unchanged carbethoxy-β-diketone, which was recovered and worked up in subsequent batches.

3-m-*Carboxybenzylacetylacetone* (II; R = CH_3), obtained by this hydrolysis in 50% yield, crystallised from alcohol in colourless needles, m. p. 130°, and from benzene in white needles, m. p. 115°. The change in melting point is reversible and is probably due to keto-enolic isomerism. A specimen crystallised from benzene gave with ferric chloride a purple coloration, whereas the preparation from alcohol developed this colour only after a time (Found : C, 67·1; H, 5·8. $C_{13}H_{14}O_4$ requires C, 66·7; H, 6·0%).

3-*m*-Carboxybenzylacetylacetone was fairly stable in acid solution but readily hydrolysed by alkalis (p. 1261). It was soluble in ordinary organic solvents except light petroleum and dissolved sparingly in water.

Copper Derivatives of 3-m-*Carboxybenzylacetylacetone.*—A bluish-green precipitate separated on adding excess of aqueous copper acetate to an acetone solution of 3-*m*-carboxybenzylacetylacetone. This dicupric salt containing copper attached both to carboxyl and chelate groups (Cu, 21·7. $C_{26}H_{24}O_8Cu_2$ requires Cu, 21·5%) was insoluble in the ordinary organic solvents excepting pyridine, in which it dissolved extremely readily. On concentrating the pyridine solution, a precipitate was formed which lost pyridine on drying and reverted to the original dicupric salt. This substance developed slowly a red ferric chloride coloration, decomposed to a brown paste at 250°, and lost half its copper on trituration with an equivalent proportion of *N*/10-sulphuric acid, yielding a light grey *monocupric* derivative (Cu, 11·9. $C_{26}H_{26}O_8Cu$ requires Cu, 12·0%), which decomposed at 235—240° to a brown paste. It was insoluble in all ordinary solvents, and with ferric chloride it developed a red coloration only after a few minutes. This slowness of reaction and the grey colour suggest that the copper of the monocupric salt is attached to the chelate group.

Other Metallic Derivatives.—Normal beryllium acetate added to an acetone solution of the 3-*m*-carboxybenzylacetylacetone produced a white precipitate of beryllium derivative insoluble in organic solvents. A portion of the beryllium could be removed by trituration with dilute sulphuric acid (one equivalent) and the residue was then soluble in organic media, but it could not be purified by crystallisation because it reverted to a mixture of free diketone-carboxylic acid and the diberyllium derivative of this acid.

The dark green chromium derivative, although soluble in chloroform, was transformed in the warm solution into an insoluble green vitreous mass.

II. 3-m-*Carbethoxybenzylbutyrylacetone* (I; R = C_3H_7).—Butyrylacetone prepared from methyl propyl ketone and ethyl acetate (Morgan and Drew, J., 1924, **125**, 737) was dissolved in 10 volumes of dry cold ether and converted into its sodium salt by the addition of sodium in thin slices. After collecting the separated sodium derivative, the mother-liquors were concentrated, the total yield being practically quantitative. A mixture of 110 g. of sodium butyrylacetone and 145 g. of 3-*m*-carbethoxybenzyl chloride was heated under reflux in an oil-bath. At 140—150°, the sodium salt dissolved to a clear liquid and sodium chloride separated. After an hour at 160°, the cooled product was extracted with ether and water. The ethereal layer was washed with dilute acetic acid and distilled under reduced pressure. Butyrylacetone passed over first, yielding 25 g. of its copper derivative, and a higher fraction was obtained boiling above 180°/10 mm. The less volatile portion, dissolved in alcohol, was treated with excess of aqueous copper acetate containing one equivalent proportion of ammonia. After a few days, the mixture was slightly acidified and the copper derivative collected and washed successively with light petroleum and ether. The grey copper derivative, when extracted with dilute sulphuric acid and ether, regenerated the *diketone*, b. p. 200—201°/6 mm. (yield 47 g. or 22%).

Copper 3-m-*carbethoxybenzylbutyrylacetone* was soluble in chloroform or benzene and crystallised from the latter as a light grey, microcrystalline powder, m. p. 168—170° (Found: C, 63·6; H, 6·6. $C_{34}H_{42}O_8Cu$ requires C, 63·6; H, 6·5%).

3-m-*Carboxybenzylbutyrylacetone* (II; R = C_3H_7).—The foregoing ester was hydrolysed in 1 to 2 g. lots by mixing with 3 or 4 volumes of concentrated sulphuric acid, the solution being stirred for 2 to 3 minutes on the water-bath. The cooled yellow solution was then poured on to crushed ice and the white solid crystallised as quickly as possible from carbon tetrachloride (yield 50%).

This diketonic acid was more soluble and less stable than its lower homologue from acetylacetone, the crude material being decomposed completely on boiling for more than a few minutes with solvents. It was readily soluble in these organic media and dissolved sparingly in water. When crystallised from aqueous alcohol, the diketo-acid separated in small plates sintering at 80° and melting indefinitely at 100—112°. The purple ferric coloration developed only slowly with this specimen. But a preparation crystallised from benzene–petroleum melted at 78—90° and gave the ferric coloration immediately (Found: C, 69·1; H, 6·9. $C_{15}H_{18}O_4$ requires C, 68·7; H, 6·8%).

Copper Derivatives of 3-m-*Carboxybenzylbutyrylacetone*.—*Dicupric* 3-m-*carboxybenzylbutyrylacetone* was obtained as a bluish-green precipitate by adding copper acetate to an acetone solution of the diketo-acid. On washing with acetone, a portion dissolved and monocupric derivative was recovered from this extract. The insoluble dicupric salt decomposed to a brown paste when heated above 225° (Found: Cu, 19·4, 19·8. $C_{30}H_{32}O_8Cu_2$ requires Cu, 19·6%).

Monocupric 3-m-*carboxybenzylbutyrylacetone*, prepared as a grey powder by triturating the foregoing copper compound with *N*/10-sulphuric acid, was soluble in alcohol or acetone, but crystallisation had to be effected as rapidly as possible because the substance decomposed on boiling the solution, with formation of the free diketo-acid and dicupric compound. The monocupric compound sintered at 173° and melted to a green liquid at 176—178° (Found: Cu, 11·1. $C_{30}H_{34}O_8Cu$ requires Cu, 10·9%).

Beryllium Derivatives of 3-m-*Carboxybenzylbutyrylacetone*.—On mixing an acetone solution of 3-*m*-carboxybenzylbutyrylacetone with aqueous normal beryllium acetate a copious white precipitate was obtained insoluble in water and the ordinary organic solvents, thus corresponding in properties with the foregoing dicupric salt. This insoluble beryllium compound was triturated with a very slight excess of 2*N*-sulphuric acid, and the mixture filtered. The filtrate contained beryllium; the precipitate was now soluble in organic media. This soluble beryllium derivative could not, however, be crystallised, as its solutions in benzene or other organic solvents rapidly underwent chemical change with the formation of a gelatinous white precipitate.

Numerous attempts were made to prepare the morphine, cinchonidine, brucine, and strychnine salts of the foregoing soluble beryllium derivative, but the products were ill-defined, uncrystallisable, vitreous, or oily substances from which no definite evidence as to resolution could be deduced.

III. m-*Carboxybenzylacetone* or ω-*Acetonyl*-m-*toluic Acid*, $CH_3{\cdot}CO{\cdot}CH_2{\cdot}CH_2{\cdot}C_6H_4{\cdot}CO_2H$.—On warming with dilute aqueous sodium hydroxide, *m*-carbethoxybenzylacetylacetone or *m*-carbethoxybenzylbutyrylacetone dissolved to a colourless solution from which acids precipitated a white solid soluble in ether. This product, which was also obtained by alkaline hydrolysis of *m*-carboxybenzylacetylacetone and *m*-carboxybenzylbutyrylacetone, was identified as m-*carboxybenzylacetone*. It was slightly soluble in water, but dissolved readily in organic media, crystallising therefrom on addition of light petroleum; it also separated from the latter solvent in lustrous plates, m. p. 77° (Found : C, 68·5; H, 6·4. $C_{11}H_{12}O_3$ requires C, 68·7; H, 6·2%). The equivalent weight by alkalimetry was 194; theory requires 192.

IV. 3-o-*Carbethoxybenzylacetylacetone*,

$$(CH_3\cdot CO)_2CH\cdot CH_2\cdot C_6H_4\cdot CO_2Et.$$

—*o*-Toluoyl chloride, obtained in practically quantitative yield from *o*-toluic acid and phosphorus trichloride at 120—170°, was subjected to a stream of chlorine at 160—180° without a catalyst until the calculated increase in weight had been attained. The resulting ω-chloro-*o*-toluoyl chloride boiled at 129—133°/12 mm.

When treated with a slight excess of warm alcohol, this chloride was esterified with loss of hydrogen chloride. The ethyl ω-chloro-*o*-toluate was washed with dilute aqueous sodium carbonate, dried, and distilled in small quantities, when the ester boiled at 139—143°/12 mm.

When larger quantities were distilled, after a portion of the ester had passed over, a solid product collected in the condenser which was identified as phthalide, m. p. 73° (Found : C, 71·9; H, 4·6. Calc. : C, 71·6; H, 4·5%).

Ethyl ω-chloro-*o*-toluate was condensed with sodium acetylacetone as in the case of the ω-chloro-*m*-toluate (p. 1258).

3-o-*Carbethoxybenzoylacetylacetone* was obtained by acidifying its grey *copper* derivative (m. p. 168—170°); it boiled at 196°/14 mm. and gave a reddish-purple coloration with ferric chloride (Found : C, 68·6; H, 7·1. $C_{15}H_{18}O_4$ requires C, 68·7; H, 6·9%).

In the distillation of the foregoing diketone, a solid (Found : C, 73·75; H, 5·15%) of higher boiling point came over after the diketone. This product was obtained crystalline by adding petroleum to its benzene solution.

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