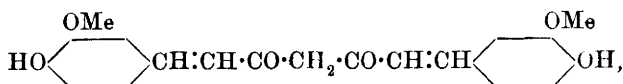


XXX.—*Curcumin*.

By PRAPHULLA CHANDRA GHOSH.

THE work described in this paper was in progress, and in fact completed, before an account of the synthesis of curcumin by Lampe (*Ber.*, 1918, **51**, 1347) appeared.

A portion of the work was devoted to proving the presence of the $\text{CO}\cdot\text{CH}_2\cdot\text{CO}\cdot$ group, which in any case is now clear from the synthesis, confirming the formula,



previously put forward by Milobendzki, Kostanecki, and Lampe (*Ber.*, 1910, **43**, 2163). The results bearing on this point are therefore given in an exceedingly abbreviated form.

With benzaldehyde, curcumin forms a benzylidene derivative, and it also forms a condensation product with nitrosodimethylaniline.

The action of bromine on curcumin and some of its derivatives was also studied with the object of testing the presence of two double bonds.

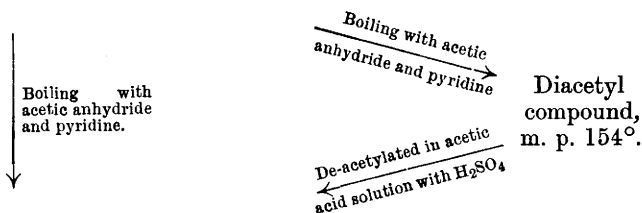
There were obtained *monobromocurcumin*, $\text{C}_{21}\text{H}_{19}\text{O}_6\text{Br}$, *monobromodicarbethoxycurcumin*, $\text{C}_{21}\text{H}_{17}\text{O}_4\text{Br}(\text{O}\cdot\text{CO}_2\text{Et})_2$, *monobromodicarbethoxycurcumin tetrabromide*, $\text{C}_{21}\text{H}_{17}\text{O}_4\text{Br}_5(\text{O}\cdot\text{CO}_2\text{Et})_2$, *dibromodicarbethoxycurcumin tetrabromide*, $\text{C}_{21}\text{H}_{16}\text{O}_4\text{Br}_6(\text{O}\cdot\text{CO}_2\text{Et})_2$, *monobromodiacetylcurcumin*, $\text{C}_{21}\text{H}_{17}\text{O}_4\text{Br}(\text{OAc})_2$, *dibromodiacetylcurcumin tetrabromide*, $\text{C}_{21}\text{H}_{16}\text{O}_4\text{Br}_6(\text{OAc})_2$, *monobromodimethylcurcumin*, $\text{C}_{21}\text{H}_{17}\text{O}_4\text{Br}(\text{OMe})_2$, and *dibromodimethylcurcumin tetrabromide*, $\text{C}_{21}\text{H}_{16}\text{O}_4\text{Br}_6(\text{OMe})_2$.

In the course of this investigation, it was discovered that dicarbethoxycurcumin could be converted into dicarbethoxyisocurcumin simply by boiling with acetic anhydride and pyridine. This led to the view that one of the two known diacetyl derivatives of curcumin was probably diacetylisocurcumin. Ciamician and Silber described a diacetylcurcumin melting at $169\text{--}170^\circ$, whilst Jackson prepared an isomeric substance melting at 154° by acetylating curcumin with acetic anhydride and sodium acetate. It was suspected that the latter was probably diacetylisocurcumin, and this suspicion was found to be correct.

Jackson's compound, which can also be formed by acetylating curcumin with acetic anhydride and pyridine, gives Heller's *iso*-curcumin (*Ber.*, 1918, **47**, 887) on hydrolysis. It is therefore quite

easy to convert curcumin into *isocurcumin*. These reactions can be represented graphically, thus:

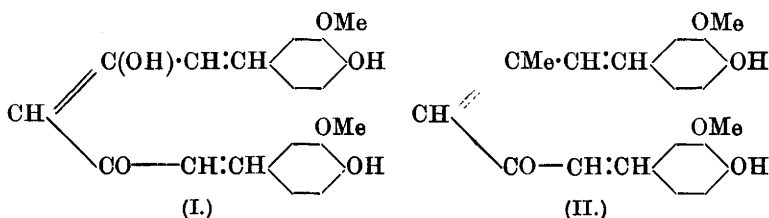
Dicarbethoxycurcumin \leftarrow Curcumin



Dicarbethoxy*isocurcumin* \leftarrow *isocurcumin*.

This simple conversion of curcumin into *isocurcumin* confirms Heller's view that the two substances are geometrical isomerides.

From the ferric chloride reaction, Heller considers that curcumin exists in the enolic form (I), and as there is considerable



resemblance between this formula and that of *divanillylidene-mesityl oxide* (II), the latter has been prepared in the course of this investigation by condensing two molecular proportions of vanillin with one of mesityl oxide by means of hydrochloric acid, and it is intended to compare the absorption spectra of this substance with that of curcumin; similarity of absorption spectra would speak in favour of similarity of molecular configuration.

The condensation of mesityl oxide with some other aromatic aldehydes has been studied, and *p-hydroxybenzylidenemesityl oxide*, *o-hydroxybenzylidenemesityl oxide*, *piperonylidenemesityl oxide*, and *cinnamylidenemesityl oxide* have been isolated.

In connexion with the geometrical isomerism of curcumin and *isocurcumin*, there is some evidence that *cinnamylidenemesityl oxide* and *piperonylidenemesityl oxide* exist in two forms.

Most of the compounds examined in the course of this investigation are fluorescent. They are arranged in the following list in the order of their intensity of fluorescence:

Substances arranged in gradually diminishing order of fluorescence.						Solvent in which the greatest intensity is observed.
Curcumin	Chloroform.
Benzylidenecurcumin,	$\text{CHPh}:\text{C}(\text{CO}\cdot\text{CH}:\text{CH}\cdot\text{C}_6\text{H}_3[\text{OMe}]\cdot\text{OH})_2$					Acetone.
<i>p</i> -Hydroxybenzylidenemesityl oxide,	$\text{OH}\cdot\text{C}_6\text{H}_4:\text{CH}:\text{CH}\cdot\text{CO}\cdot\text{CH}:\text{CMe}_2$					Toluene
<i>o</i> -Hydroxybenzylidenemesityl oxide					Toluene.
Dicarbethoxycurcumin,	$\text{CH}_2(\text{CO}\cdot\text{CH}:\text{CH}\cdot\text{C}_6\text{H}_3[\text{OMe}]\cdot\text{O}\cdot\text{CO}_2\text{Et})_2$					Acetone.
Diacetylcureumin,	$\text{CH}_2(\text{CO}\cdot\text{CH}:\text{CH}\cdot\text{C}_6\text{H}_3[\text{OMe}]\cdot\text{OAc})_2$					Acetone.
Divanillylidenemesityl oxide					Acetone.
Monobromocurcumin,	$\text{CHBr}(\text{CO}\cdot\text{CH}:\text{CH}\cdot\text{C}_6\text{H}_3[\text{OMe}]\cdot\text{OH})_2$					Acetone.
Monobromodicarbethoxycurcumin tetrabromide,	$\text{CHBr}(\text{CO}\cdot\text{CHBr}\cdot\text{CHBr}\cdot\text{C}_6\text{H}_3[\text{OMe}]\cdot\text{O}\cdot\text{CO}_2\text{Et})_2$					Chloroform.
Dibromodicarbethoxycurcumin tetrabromide,	$\text{CBr}_2(\text{CO}\cdot\text{CHBr}\cdot\text{CHBr}\cdot\text{C}_6\text{H}_3[\text{OMe}]\cdot\text{O}\cdot\text{CO}_2\text{Et})_2$					Chloroform.

From these observations, it may be inferred that (1) auxochromic groups, (2) the labile hydrogen atoms, (3) the double bonds, and (4) the symmetry of the molecule increase fluorescence, but are not the invariable factors of fluorescence.

EXPERIMENTAL.

Benzylidenecurcumin, $\text{C}_6\text{H}_5\cdot\text{CH}:\text{C}_{21}\text{H}_{18}\text{O}_6$.—A current of dry hydrogen chloride was passed through a mixture of benzaldehyde (0.5 gram), curcumin (1.8 gram), and alcohol (40 c.c.) cooled with ice. The colour became dark violet, probably owing to the formation of curcumin hydrochloride, and in about a day the whole of the curcumin dissolved and the colour changed to orange-red. After forty-eight hours, the mixture was poured into ice-cold water, when a greenish-yellow precipitate was obtained which could not be crystallised. It was purified by solution in acetic acid and fractional precipitation by sodium acetate (sample I), and subsequently in the same way by precipitation from an alcoholic solution by water (sample II). It is soluble in alcohol, acetic acid, acetone, or chloroform, shrinks slightly at 170° , and melts at 200° :

I. 0.1000 gave 0.2695 CO_2 and 0.0486 H_2O . $\text{C}=73.5$; $\text{H}=5.4$.

II. 0.1104 „ 0.2965 CO_2 „ 0.0527 H_2O . $\text{C}=73.25$; $\text{H}=5.3$.

$\text{C}_{28}\text{H}_{24}\text{O}_6$ requires $\text{C}=73.68$; $\text{H}=5.26$ per cent.

Condensation Product of Curcumin and Nitrosodimethylaniline, $\text{N}(\text{CH}_3)_2\cdot\text{C}_6\text{H}_4\cdot\text{N}:\text{C}_{21}\text{H}_{18}\text{O}_6$.—One part of curcumin and one part of nitrosodimethylaniline were dissolved in alcohol, two parts of zinc

chloride were added, and the mixture was warmed for a few minutes on the water-bath. When the colour became brown, the product was precipitated by water. A good deal of tarry matter was dissolved by treatment with 30 per cent. acetic acid. The residue could not be crystallised, but was purified by fractional precipitation from acetic acid solution by water. The substance obtained in this way is fairly readily soluble in alcohol, acetic acid, or acetone, shrinks at 98° , and melts and decomposes at $144\text{--}145^{\circ}$. Two fractions obtained by precipitation with water from acetic acid solution had the same melting point, and gave the following results on analysis:

I. 0.1502 gave 7.6 c.c. N_2 at 30° and 760 mm. $N=5.7$.

II. 0.1430 ,, 7.1 c.c. N_2 ,, 29° ,, 758 mm. $N=5.61$.

$C_{29}H_{28}O_6N_2$ requires $N=5.8$ per cent.

Monobromocurcumin, $C_{21}H_{19}O_6Br$.—Half a gram of curcumin was dissolved in 35 c.c. of warm chloroform, the solution cooled until curcumin began to separate, and 4.5 c.c. of a 5 per cent. solution of bromine in chloroform were then gradually added, avoiding rise of temperature. The solution became quite clear on the first addition of the bromine solution (1 c.c.), and hydrogen bromide was evolved. After ten minutes, air was blown through the mixture to drive off the chloroform, and the residual emulsion was rubbed with a little alcohol. Needle-shaped crystals of monobromocurcumin separated, which were soluble in alcohol, chloroform, acetic acid, acetone, or toluene, shrank at 131° , and melted at 136° :

0.1187 gave 0.0510 AgBr. $Br=18.2$.

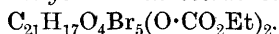
$C_{21}H_{19}O_6Br$ requires $Br=17.9$ per cent.

Monobromodicarbethoxycurcumin, $C_{21}H_{17}O_4Br(O\cdot CO_2Et)_2$, prepared in a similar way from dicarbethoxycurcumin, crystallises from much alcohol in needles melting at $165\text{--}170^{\circ}$:

0.1172 gave 0.0382 AgBr. $Br=13.87$.

$C_{27}H_{27}O_{10}Br$ requires $Br=13.47$ per cent.

Monobromodicarbethoxycurcumin tetrabromide,



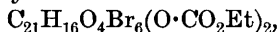
—Dicarbethoxycurcumin (1 gram) was dissolved in the minimum quantity of cold chloroform and treated with 40 c.c. of a 2.5 per cent. solution of bromine in the same solvent. After remaining at the ordinary temperature for one and a-half hours, the chloroform was driven off by a current of air. The product was extracted successively with boiling ethyl and methyl alcohols, leaving a residue which could not be crystallised, but was purified by dissolving in chloroform and fractionally precipitating with alcohol. It is

sparingly soluble in alcohol or light petroleum, and melts and decomposes at 209—210°. Different fractions gave the same analytical results:

0.1397 gave 0.1438 AgBr. Br=43.8.

$C_{27}H_{27}O_{10}Br_5$ requires Br=43.9 per cent.

Dibromodicarbethoxycurcumin tetrabromide,



was obtained by brominating dicarbethoxycurcumin in cold chloroform solution with excess of bromine. It separated from alcohol in colourless crystals, softening at 148° and melting at 152°. It remains unchanged on boiling with water:

0.1278 gave 0.1460 AgBr. Br=48.61.

$C_{27}H_{26}O_{10}Br_6$ requires Br=48.48 per cent.

Monobromodiacetylcurcumin, $C_{21}H_{17}O_4Br(OAc)_2$.—Ciamician and Silber's diacetylcurcumin was brominated in cold chloroform solution with a little more than the theoretical quantity of a chloroform solution of bromine (as in the preparation of monobromodicarbethoxycurcumin). It crystallises from alcohol in needles melting at 173—174°, and is brighter in colour than diacetylcurcumin itself:

0.1162 gave 0.042 AgBr. Br=15.38.

$C_{25}H_{23}O_8Br$ requires Br=15.03 per cent.

Dibromodiacetylcurcumin tetrabromide, $C_{21}H_{16}O_4Br_6(OAc)_2$, was obtained by brominating diacetylcurcumin in cold chloroform solution with excess of bromine, and was crystallised from alcohol. It melts and decomposes at 80—83°:

0.1477 gave 0.1785 AgBr. Br=51.43.

$C_{25}H_{22}O_8Br_6$ requires Br=51.45 per cent.

Monobromodimethylcurcumin, $C_{21}H_{17}O_4Br(OMe)_2$, was obtained by treating dimethylcurcumin in cold chloroform solution with a little more than the theoretical quantity of bromine. It crystallises from alcohol in needles melting at 140—141°:

0.1200 gave 0.0468 AgBr. Br=16.6.

$C_{23}H_{23}O_6Br$ requires Br=16.49 per cent.

Dibromodimethylcurcumin tetrabromide, $C_{21}H_{16}O_4Br_6(OMe)_2$.—Dimethylcurcumin dissolved in chloroform was treated with excess of bromine, when hydrogen bromide was evolved, and, after half an hour, the chloroform was evaporated. This substance could not be crystallised, but was purified by precipitation from its hot alcoholic solution with water. Distinct fractions possessed the same melting point (softens at 96°, melts at 102—104°) and gave

identical analytical results. It is soluble in chloroform or acetic acid:

0.1120 gave 0.1437 AgBr. Br=54.6.

$C_{23}H_{22}O_6Br_6$ requires Br=54.87 per cent.

Conversion of Dicarbethoxycurcumin into Heller's Dicarbethoxyisocurcumin.

A mixture of 1 gram of dicarbethoxycurcumin, 10 c.c. of acetic anhydride, and 1 c.c. of pyridine was digested at the boiling point for forty-five minutes. Alcohol (6 c.c.) and a little water were added to the cooled mixture, and the supernatant liquid was decanted from the viscous mass which thus separated. From the latter, by stirring with 2 c.c. of glacial acetic acid, a solid product was obtained, and this when crystallised from alcohol melted at 142° , which is identical with the melting point given by Heller for dicarbethoxyisocurcumin.

Found: C=63.0; H=5.5

$C_{27}H_{28}O_{10}$ requires C=63.28; H=5.46 per cent.

Acetylation of Curcumin with Acetic Anhydride and Pyridine.

Curcumin was digested with acetic anhydride and pyridine under the same conditions as described in the last paragraph, and a solid product isolated. The yellow solid obtained in this way was fractionally crystallised from acetic acid. The first fraction (which was only a minor portion) melted at $169-170^\circ$, and was found to be identical with Ciamician and Silber's diacetylcurcumin (mixed melting point). The second fraction (major portion) melted at 154° , and this, it is interesting to note, is identical with that given by Jackson for his diacetyl compound obtained by means of acetic anhydride and sodium acetate.

Found: C=66.4; H=5.23.

$C_{25}H_{24}O_8$ requires C=66.37; H=5.3 per cent.

Deacetylation of Diacetylcurcumin (m. p. 154°) and Isolation of Heller's isoCurcumin.

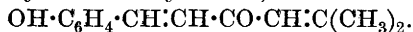
One gram of this diacetyl compound was dissolved in 15 c.c. of acetic acid, 1 c.c. of sulphuric acid (D 1.84) added, the mixture warmed for a minute, cooled, and poured into water. The yellow precipitate was dried on porous porcelain and extracted with hot benzene. The benzene solution, on cooling, deposited the substance as a yellow, amorphous powder, soluble in cold alcohol, acetic acid, acetone, ethyl acetate, or chloroform, sintering at 140° and melting

about 280°. There could be little doubt that this compound was identical with Heller's *isocurcumin*:

0.1130 gave 0.2822 CO₂ and 0.0571 H₂O. C=68.1; H=5.6.

C₂₁H₂₀O₆ requires C=68.4; H=5.43 per cent.

p-Hydroxybenzylidenemesityl oxide,



—To an alcoholic solution of 2.4 grams of *p*-hydroxybenzaldehyde and 1 gram of mesityl oxide, 1.5 grams of zinc chloride were added, and the liquid was boiled for two hours. The solution, after concentration, was poured into water, causing the deposition of oily drops, which became crystalline on agitation. On recrystallisation from alcohol, yellow crystals were obtained, which melted at 120° and dyed yellow shades on chrome-mordanted wool:

0.1210 gave 0.3590 CO₂ and 0.0784 H₂O. C=80.91; H=7.2.

C₁₃H₁₄O₂ requires C=81.25; H=7.36 per cent.

o-Hydroxybenzylidenemesityl oxide was prepared in a similar way to the corresponding *p*-hydroxy-compound. The crude product separated as an oil, which was obtained crystalline by dissolving in aqueous potassium hydroxide, allowing to remain for a few days, and precipitating with hydrochloric acid. The substance dissolves with a very beautiful orange-red colour in potassium hydroxide solution:

0.1000 gave 0.2970 CO₂ and 0.0667 H₂O. C=81.0; H=7.42.

C₁₃H₁₄O₂ requires C=81.25; H=7.36 per cent.

Piperonylidenemesityl oxide,



—Piperonal (2.6 grams) and mesityl oxide (2 grams) were dissolved in alcohol, and alcoholic potassium hydroxide was added to render the solution fairly alkaline. The mixture was boiled for a few minutes, when an orange-coloured substance began to separate. On cooling, this solid was collected, dissolved in acetic acid, and reprecipitated with water, when it melted at 130—135° (*A*). This proved to be a mixture of two substances melting at 148—153° and 175—178° respectively, which can be separated either by fractional precipitation by alcohol from acetic acid or by extraction with alcohol, in which the substance of higher melting point is scarcely soluble. The hot alcoholic extract, on cooling, deposits the substance, which melts at 148—153° (*B*). The insoluble residue, dissolved in chloroform and fractionally precipitated by alcohol (the first fraction being rejected), melted at 175—178° (*C*):

(*A*) 0.1000 gave 0.2662 CO₂ and 0.0558 H₂O. C=72.6; H=6.2.

(*B*) 0.1150 „ 0.3040 CO₂ „ 0.0580 H₂O. C=72.1; H=5.6.

(*C*) 0.1021 „ 0.2710 CO₂ „ 0.0533 H₂O. C=72.4; H=5.8.

C₁₄H₁₄O₃ requires C=73.0; H=6.08 per cent.

Cinnamylidenemesityl oxide,

was prepared in the same way as the above piperonylidene compound. On cooling the reaction mixture, some viscous substance was deposited, from which the supernatant liquid was decanted and poured into water. The semi-solid mass was dissolved in acetic acid and precipitated with alcohol. It melts and decomposes at $180\text{--}182^\circ$ (α). Addition of water to the filtrate caused the separation of a second substance, which melted and decomposed at 88° (β). Both the α - and β -compounds were soluble in alcohol, chloroform, acetone, or toluene, but could not be crystallised from any of these solvents. Experiment showed that these compounds were interconvertible; the former (α) on boiling with acetic acid for two to three minutes and adding water to the solution gave the β -compound melting at 88° , whereas the latter on boiling with alcohol for about five minutes gave, on cooling the solution thus obtained, a deposit of the α -compound melting at $180\text{--}182^\circ$.

The α -compound is less readily soluble in alcohol than the β :

(α) 0.1082 gave 0.3365 CO_2 and 0.0670 H_2O . $\text{C}=84.4$; $\text{H}=6.8$.

(β) 0.1494 „ 0.4610 CO_2 „ 0.0808 H_2O . $\text{C}=84.1$; $\text{H}=6.0$.

$\text{C}_{14}\text{H}_{15}\text{O}$ requires $\text{C}=84.4$; $\text{H}=6.4$ per cent.

Divanillylidenemesityl oxide (II, p. 293).—A current of dry hydrogen chloride was passed into an ice-cooled alcoholic solution of 2.6 grams of vanillin and 1 gram of mesityl oxide, when the liquid became deep blue. After two days, the solution was poured into cold water, the precipitate collected and triturated with sodium acetate solution. The brown, amorphous powder obtained in this way could not be crystallised, and was purified by fractional precipitation from acetic acid with water solution. It is soluble in alcohol, chloroform, or acetone, softens at 165° , and melts at 178° . Distinct fractions obtained by the above described method gave identical analytical results:

I. 0.1200 gave 0.316 CO_2 and 0.067 H_2O . $\text{C}=71.8$; $\text{H}=6.2$.

II. 0.1065 „ 0.282 CO_2 „ 0.059 H_2O . $\text{C}=72.21$; $\text{H}=6.1$.

$\text{C}_{22}\text{H}_{22}\text{O}_5$ requires $\text{C}=72.1$; $\text{H}=6$ per cent.

I take this opportunity of thanking Prof. B. N. Das for his kind help and encouragement during the progress of the work.

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