THE CONDENSATION OF PHENOLIC ALDEHYDES AND THEIR ETHERS WITH METHYL ETHYL KETONE.

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Harries and Müller(1) showed that, in the presence of an alkali, methyl ethyl ketone condenses with benzaldehyde to form the α-benzylidene derivative, $C_6H_5CH:CHCOC_2H_5$, and, in the presence of hydrochloric acid, to form the γ-benzylidene derivative, $C_6H_5CH:C(CH_3)COCH_3$. Ichikawa(2) reported that methyl ethyl ketone condenses with vanillin in the presence of an alkali, to yield 3-methoxy-4-hydroxystyryl ethyl ketone, $C_6H_3(OH)(OCH_3)CH:CHCOC_2H_5$, and, in the presence of hydrochloric acid, to give rise to the

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(1) *Ber.*, 35 (1902), 966.

(2) *Sci. Rep. Tohoku. Imp. Univ.*, 14 (1925), 127.

bimolecular compound, $C_6H_3(OH)(OCH_3)CH:CHCOC(CH_3):CHC_6H_3(OH)(OCH_3)$. Claisen and Claperède⁽¹⁾ found that, in the presence of hydrochloric acid, benzaldehyde condenses with acetone to form dibenzylidene acetone, $C_6H_5CH:CHCOCH:CHC_6H_5$, and Nomura and Hotta⁽²⁾ observed that divanillylidene acetone, $C_6H_3(OH)(OCH_3)CH:CHCOCH:CHC_6H_3(OH)(OCH_3)$, was formed by the condensation of vanillin with acetone in the presence of concentrated hydrochloric acid.

From these results, it appears that acetone condenses with benzaldehyde or with vanillin in the presence of hydrochloric acid, to form a bimolecular compound, arising from the condensation of two molecules of aldehyde and one of acetone, whilst, in the presence of hydrochloric acid, methyl ethyl ketone gives different condensation products, according as benzaldehyde or vanillin is condensed with it. Therefore, it seemed interesting to study the condensation of various phenolic aldehydes and their ethers with methyl ethyl ketone,—alkali, consentrated hydrochloric acid, or dry gaseous hydrogen chloride being used as the condensing agents.

The author condensed methyl ethyl ketone with protocatechualdehyde, veratraldehyde, piperonal, p-hydroxybenzaldehyde, anisaldehyde, m-hydroxybenzaldehyde, or with m-methoxybenzaldehyde under various conditions. The condensation may be represented by one of the following three cases:—

$$RCHO + CH_3COC_2H_5 \longrightarrow RCH:CHCOC_2H_5. \qquad (A.)$$

$$RCHO + CH_3COC_2H_5 \longrightarrow RCH:C(CH_3)COCH_3. \qquad (B.)$$

$$2RCHO + CH_3COC_2H_5 \longrightarrow RCH:CHCOC(CH_3):CHR. \qquad (C.)$$

The constitution of the products (A) and (B) was determined by analysis, and by the formation of oxime and dibromide, and they were differentiated from each other by using sodium hypochlorite, when substance (B) yielded chloroform and an acid with one fewer carbon atom than the original ketone, as shown in the following scheme:—

$$RCH:C(CH_3)COCH_3 + 3NaClO = RCH:C(CH_3)COONa + CHCl_3 + 2NaOH.$$

The compounds which were expected to be, on analysis, of the type (C) had no definite melting point and it was difficult to convert them into crystalline derivatives.

When protocatechualdehyde or veratraldehyde was condensed with methyl ethyl ketone in equi-molecular quantity in the presence of hydrochloric acid, a bimolecular compound of type (C) was obtained. In the case of p-hydroxybenzaldehyde or anisaldehyde, the condensation product, in the presence of hydrochloric acid, was a unimolecular compound when each molecule of aldehyde and ketone was used, and this was the case even when

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(1) *Ber.*, **14** (1881), 350.

(2) *Sci. Rep. Tohoku Imp. Univ.*, **14** (1925), 123.

half the quantity of the latter was used, i.e. a condition which is in favour of bimolecular formation of the compound. It thus follows that the formation of a bimolecular compound is not the effect of the hydroxyl or methoxyl group in para-position to the aldehyde group. On the contrary, it is the effect of the hydroxyl or methoxyl group in meta-position to the aldehyde group. In the support of this view, the substance of type (C) was the sole product of the condensation of methyl ethyl ketone with m-hydroxybenzaldehyde and its ether, in the presence of hydrochloric acid, even when each molecule of aldehyde and ketone, favourable to the formation of a unimolecular compound, was used.

In the presence of dilute alkali, the condensation products of methyl ethyl ketone with various aldehydes were found to be unimolecular compounds.

Experimental.

α-Methyl-3:4:3′:4′-tetramethoxydistyryl Ketone, $(CH_3O)_2C_6H_3CH:C(CH_3)COCH:CHC_6H_3(OCH_3)_2$. A mixture of veratraldehyde (3 gr.), methyl ethyl ketone (1.5 gr.) and concentrated hydrochloric acid (d=1.19; 6 c.c.) was allowed to stand for 6 days, and the black, violet product was ground in dilute alkali, collected, washed with water and dried. It was dissolved in benzene, boiled with the addition of animal charcoal, and after being filtered, precipitated with petroleum ether. On repeating this process, a dark, yellow, amorphous powder was obtained (Found: C=71.77; H=6.31. $C_{22}H_{24}O_5$ requires C=71.70; H=6.57%).

When half the above quantity of the ketone was used, the result was the same.

α-Methyl-3:4:3′:4′-tetrahydroxydistyryl Ketone, $(OH)_2C_6H_3CH:C(CH_3)COCH:CHC_6H_3(OH)_2$. To an ice-cooled mixture of protocatechualdehyde (2 gr.; 1 mol.) and methyl ethyl ketone (1 gr.; 1 mol.), concentrated hydrochloric acid (d=1.19; 5 c.c.) was added. After standing for 6 days, the black mass was ground, collected and washed with water. It was dissolved in glacial acetic acid and precipitated with water. On repeating this operation, it separated as a black, violet powder, which, after being dried at 90–100° under reduced pressure, was analysed (Found: C=69.14; H=5.13. $C_{18}H_{16}O_5$ requires C=69.20; H=5.16%). On heating, this substance carbonises without melting.

The same result was obtained by using ½ mol. of the ketone and 1 mol. of the aldehyde.

The Methyl Ether, $(CH_3O)_2C_6H_3CH:C(CH_3)COCH:CHC_6H_3(OCH_3)_2$. α-Methyl-3:4:3′:4′-tetrahydroxydistyryl ketone was methylated with methyl sulphate and alkali. After being purified by dissolving it in benzene and precipitating it with petroleum ether, a brown, amorphous substance was obtained (Found : C=71.44 ; H=6.28. $C_{22}H_{24}O_5$ requires C=71.70 ; C=6.57%).

α-Methyl-p-methoxystyryl Methyl Ketone, $(CH_3O)C_6H_4CH:C(CH_3)COCH_3$. A mixture of anisaldehyde (27 gr.) and methyl ethyl ketone (15 gr.) was cooled in ice-water, saturated with dry hydrogen chloride, and allowed to stand overnight. The dark, green product was made alkaline and extracted with ether, washed with water and dried. After the removal of the ether, the residual oil was fractionated under a reduced pressure of 12 mm., when a faint, yellow oil (26 gr.) boiling at 278–281° passed over, which, on cooling, solidified to yellow crystals. These were recrystallised from a mixture of ether and petroleum ether with the addition of animal charcoal, when they separated in colourless crystals, m.p. 27.5–28° (Found : C=75.62 ; H=7.26. $C_{12}H_{14}O_2$ requires C=75.76 ; H=7.42%).

When concentrated hydrochloric acid was used instead of dry hydrogen chloride, the result was almost the same, but the yield was poor. When the quantity of the aldehyde was doubled in the above case, nothing definite could be isolated.

The Oxime, $(CH_3O)C_6H_4CH:C(CH_3)C(:NOH)CH_3$. A solution of the ketone (2 gr.), hydroxylamine hydrochloride (0.8 gr.) and sodium acetate (1.6 gr.) in dilute alcohol was boiled for $1\frac{1}{2}$ hours under a reflux condenser. On recrystallising the crude product from alcohol, colourless needles, m.p. 126,5–128°, were obtained (Found : N=6.88. $C_{12}H_{15}O_2N$ requires N=6.83%).

The Dibromide, $(CH_3O)C_6H_4CHBrC(CH_3)BrCOCH_3$. To a chloroform solution of the ketone, a solution of bromine in the same solvent was added drop by drop, and allowed to stand for 10 minutes. The chloroform was removed under diminished pressure without the application of heat, and the residue was recrystallised from a mixture of ether and petroleum ether, when it separated in colourless crystals, m.p. 70.5–71°, which decomposed gradually (Found : Br=45.57. $C_{12}H_{14}O_2Br_2$ requires Br=45.67%).

Action of Sodium Hypochlorite. To a freshly prepared solution of sodium hypochlorite from bleaching powder and sodium carbonate, the ketone was added and warmed until the evolution of chloroform had ceased. The solution was acidified with dilute sulphuric acid and the precipitate was recrystallised from dilute alcohol, from which it separated in colourless crystals, m.p. 154.5–155° (Found : C=68.73 ; H=6.37. $C_{11}H_{12}O_3$ requires C=68.71 ; H=6.30%).

Perkin(1) gave 154° as its melting point.

p-Methoxystyryl Ethyl Ketone, $(CH_3O)C_6H_4CH:CHCOC_2H_5$. To a mixture of 50 c.c. of water and 20 gr. of a 10% solution of sodium hydroxide, 2

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(1) *J. Chem. Soc.*, 31 (1877), 411.

gr. of anisaldehyde and 1.1 gr. of methyl ethyl ketone were added. After shaking the whole for 2 days, the yellow crystals which separated were collected, washed with water and dried. Colourless scales, m.p. 58.5–59°, were obtained after recrystallisation from a mixture of ether and petroleum ether (Found: C = 75.87; H = 7.48. $C_{12}H_{14}O_2$ requires C = 75.76; H = 7.42%).

Ryan and Cahill⁽¹⁾ gave 53° as its melting point.

The Oxime, $(CH_3O)C_6H_4CH{:}CHC({:}NOH)C_2H_5$. This was prepared in the same way as *α*-methyl-p-methoxystyryl methyl ketoxime. It crystallised in colourless needles, m.p. 138–139°, from alcohol (Found: N = 7.00. $C_{12}H_{15}O_2N$ requires N = 6.83%).

The Dibromide, $(CH_3O)C_6H_4CHBrCHBrCOC_2H_5$. This compound was also synthesised in the same manner as its isomer. It is colourless crystals which decompose at 87.5° (Found: Br = 45.58. $C_{12}H_{14}O_2Br_2$ requires Br = 45.67%).

Ryan and Cahill described 85° as its melting point.

α-Methyl-p-hydroxystyryl Methyl Ketone, $(OH)C_6H_4CH{:}C(CH_3)COCH_3$. A well-cooled mixture of p-hydroxybenzaldehyde (5 gr.) and methyl ethyl ketone (3 gr.) was saturated with dry hydrogen chloride, when a green mass was obtained. After standing overnight, it was dissolved in dilute alkali solution, filtered, and acidified with dilute hydrochloric acid. The grey crystals which were deposited were collected and recrystallised from dilute alcohol with the addition of animal charcoal, when they separated in yellow crystals, m.p. 108.5–109.5° (Found: C = 74.96; H = 6.87. $C_{11}H_{12}O_2$ requires C = 74.79; H = 7.17%).

The condensation product was the same as that described above, when the condensation was effected with concentrated hydrochloric acid or when half the quantity of the ketone was used.

The Oxime, $(OH)C_6H_4CH{:}C(CH_3)C({:}NOH)CH_3$. This was prerared in the same manner as *α*-methyl-p-methoxystyryl methyl ketoxime. The oxime was colourless and melted at 147–148° (Found: N = 7.39. $C_{11}H_{13}O_2N$ requires N = 7.33%).

The Benzoyl Derivative, $(C_6H_6COO)C_6H_4CH{:}C(CH_3)COCH_3$. *α*-Methyl-p-hydroxystyryl methyl ketone was benzoylated by Schotten-Baumann's method and the raw product was recrystallised from dilute alcohol, from which it separated in colourless crystals, m.p. 124–125° (Found: C = 77.26; H = 6.02. $C_{18}H_{16}O_3$ requires C = 77.11; H = 5.76%).

The Methyl Ether, $(CH_3O)C_6H_4CH{:}C(CH_3)COCH_3$. *α*-Methyl-p-hydroxystyryl methyl ketone was methylated with methyl iodide and alcoholic potash and the crude product was recrystallised from a mixture of ether and

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(1) *J. Chem. Soc.*, 128 (1925), 1, 558.

petroleum ether, when it crystallised in colourless crystals, m.p. 27.5–28.5°. The melting point was not changed by admixture with α-methyl-p-methoxystyryl methyl ketone obtained by the condensation of anisaldehyde with methyl ethyl ketone.

α-Methyl-m : m′-dimethoxydistyryl Ketone, $(CH_3O)\,C_6H_4CH : C\,(CH_3)COCH:CHC_6H_4(OCH_3)$. An ice-cooled mixture of m-hydroxybenzaldehyde (1 gr.; 1 mol.) and methyl ethyl ketone (0.55 gr.; 1 mol.) was saturated with dry hydrogen chloride when a deep, scarlet, viscid oil was obtained. After being allowed to remain overnight, it was extracted with ether, washed with water and dried. The ether was removed and the residue was dissolved in benzene and precipitated with petroleum ether. On repeating this operation, a small quantity of yellow, amorphous substance was obtained, which, after being dried at 80–90° under reduced pressure, was analysed (Found: C=77.78 ; H=6.98. $C_{20}H_{20}O_3$ requires C=77.88 ; H=6.54%).

The same substance was obtained by condensing 1 mol. of the aldehyde with ½ mol. of the ketone.

α-Methyl-m : m′-dihydroxydistyryl Ketone, $(OH)C_6H_4CH:C(CH_3)COCH:CHC_6H_4(OH)$. To a mixture of m-hydroxybenzaldehyde (2 gr.) and methyl ethyl ketone (1.2 gr.), cooled in ice-water, 5 c.c. of concentrated hydrochloric acid (d=1.19) was added and left for 6 days. The dark, brown mass thus obtained was treated similarly as in the case of the condensation product of protocatechualdehyde with methyl ethyl ketone, when a brick-red powder was obtained which was analysed after being dried at 80–90° for an hour under reduced pressure (Found: C=77.25 ; H=5.86. $C_{18}H_{16}O_3$ requires C=77.11 ; H=5.76%).

The product was the same on condensing half the quantity of the ketone with the aldehyde.

The Methyl Ether, $(CH_3O)C_6H_4CH:C(CH_3)COCH:CHC_6H_4(OCH_3)$. This substance was prepared by shaking the ketone with methyl sulphate and alkali, and purified by precipitating it from the benzene solution with petroleum ether as described in the case of α-methyl-3:4:3′:4′-tetramethoxydistyryl ketone, when it separated as a dark, yellow powder, which was analysed after being dried at 90-100° under reduced pressure (Found: C=78.16 ; H=6.25. $C_{20}H_{20}O_3$ requires C=77.88 ; H=6.54%).

3:4-Methylendioxystyryl Ethyl Ketone, $CH_2O_2C_6H_3CH:CHCOC_2H_5$. To a mixture of 100 c.c. of water and 20 c.c. of a 10% sodium hydroxide solution, 5 gr. of piperonal and 2.5 gr. of methyl ethyl ketone were added and allowed to stand for 2 days, when yellow crystals were separated. On recrystallising from dilute alcohol, they separated in yellow crystals, m.p. 101.5–102° (Found: C=70.73 ; H=5.99. $C_{12}H_{12}O_3$ requires C=70.55 ; H=5.93%).

Ryan and Cahill gave 101–102° as its melting point.

The Oxime, $CH_2O_2C_6H_3CH{:}CHC({:}NOH)C_2H_5$. This was prepared by the same method as in the synthesis of p-methoxystyryl ethyl ketoxime. The crude product was recrystallised from alcohol in faint, yellow crystals, m.p. 173° (decomp.) (Found : N = 6.50 ; $C_{12}H_{13}O_3N$ requires N = 6.39%).

The Dibromide, $CH_2O_2C_6H_3CHBrCHBrCOC_2H_5$. This was synthesised by the same method as in the case of p-methoxystyryl ethyl ketone dibromide. It crystallised in colourless crystals, m.p. 93.5–94°, from a mixture of ether and petroleum ether (Found : Br = 43.94. $C_{12}H_{12}O_3Br_2$ requires Br = 43.92%).

In conclusion, the author wishes to express his hearty thanks to Professor Hiroshi Nomura under whose guidance this investigation was carried out.

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