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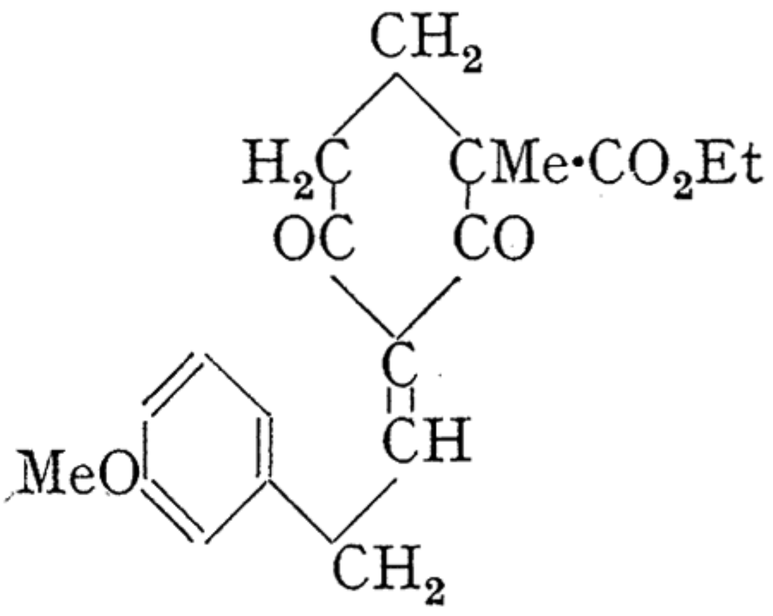
379. *Experiments on the Synthesis of Substances related to the Sterols. Part XXV.*

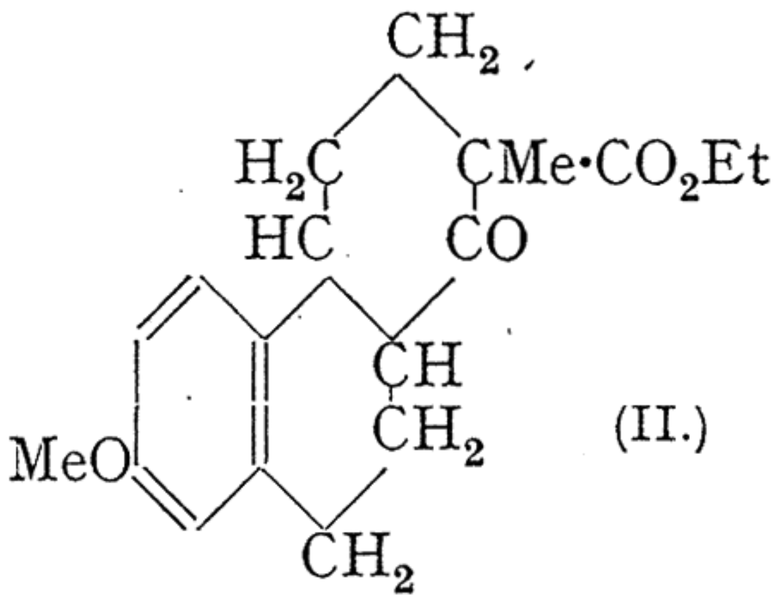
By K. H. Lin and Robert Robinson.

1-*Carbethoxy*-1-*methyl*cyclo*hexane*-2 : 4-*dione* and m-*methoxyphenylacetaldehyde* have been synthesised with the idea that the condensation of these two compounds might yield the substance (I), from which the ester (II) described in Part IX (Robinson and Walker, J., 1936, 752) or a naphthalenoid analogue might be obtainable.

(I.)



(II.)



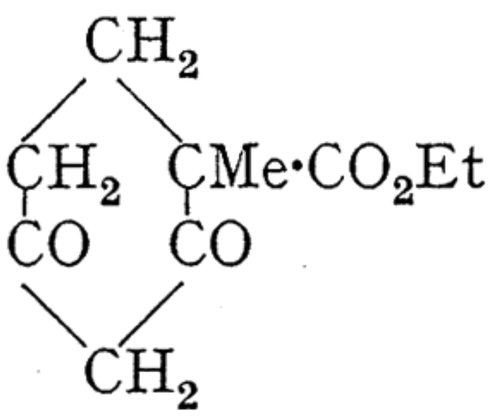
Model experiments on the condensation of phenylacetaldehyde and dimethyldihydroresorcinol showed, however, that the aldehyde condenses with two molecules of the ketone under a wide variety of conditions.

Condensation of methyl β-chloroethyl ketone with ethyl sodiomethylmalonate afforded *ethyl methyl*-β-*acetylethylmalonate*, $CH_3{\cdot}CO{\cdot}CH_2{\cdot}CH_2{\cdot}CMe(CO_2Et)_2$ (III), and this was smoothly converted by sodium ethoxide into 1-*carbethoxy*-1-*methyl*cyclo*hexan*-2 : 4-*dione* (IV). m-*Methoxyphenylacetaldehyde* proved very difficult to prepare; it could not be obtained from *m*-methoxycinnamic acid or *m*-methoxyphenylglycidic acid by any of the processes applicable in the case of phenylacetaldehyde. It was eventually obtained by an adaptation of Stephen's method of reduction of nitriles (J., 1925, **127**, 1874), although even in this case special precautions in the hydrolysis of the aldimine stannichloride were found to be essential. The condensation of *m*-methoxyphenylacetaldehyde with (IV) was attempted, but no ketonic compound was isolated from the product.

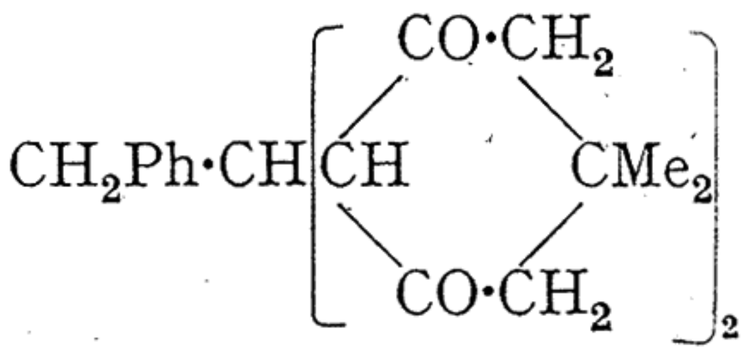
As a simple case we examined the condensation of piperonylacetaldehyde with dimethyldihydroresorcinol (dimedone) and obtained a ketone, characterised as a *dinitrophenyl*-

hydrazone. It appeared that the dimedone suffered loss of an *iso*propylidene residue and a provisional interpretation is offered in the experimental section.

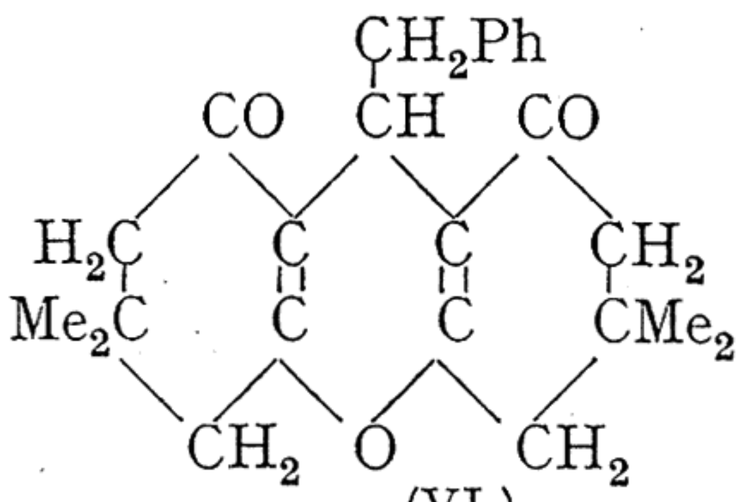
Furthermore, the condensation of phenylacetaldehyde with dimedone was exhaustively studied, a variety of catalysts and conditions being used, and it invariably gave the 1 : 2 product (V). This was dehydrated to (VI) under the influence of either acetic anhydride or phosphoric oxide.



(IV.)

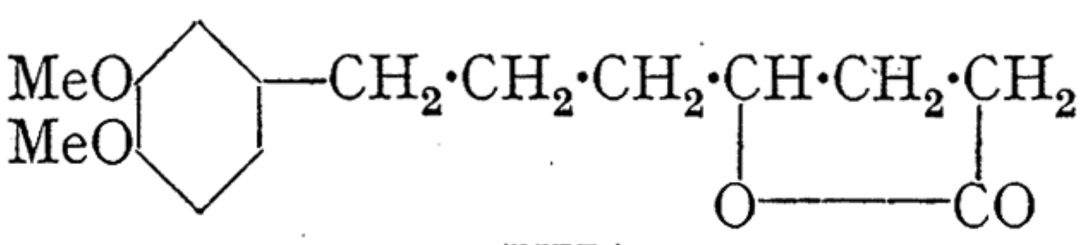


(V.)

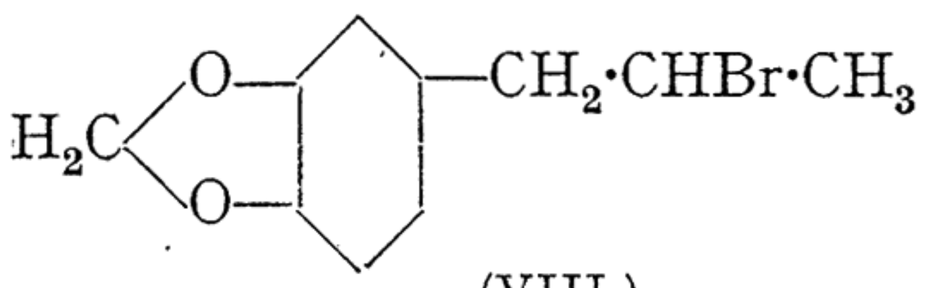


(VI.)

In continuation of an investigation adumbrated in Part XVI (Lin, Resuggan, Robinson, and Walker, J., 1937, 68), the *lactone* of 4-*hydroxy*-7-3′ : 4′-*dimethoxyphenylheptoic acid* (VII) has been synthesised by methods similar to those previously used for the *m*-methoxy-analogue. It would have facilitated work along these lines if the direction of addition of hydrogen bromide to safrole (or eugenol methyl ether) could have been reversed by the peroxide effect (Kharasch). In the case of eugenol methyl ether some demethylation occurred (under the conditions recorded on p. 2008 it was considerable) and therefore safrole was used in most of the experiments. The product of the reaction was β-bromodihydrosafrole (VIII) under all the conditions tried. Kharasch and Potts (*J. Org. Chem.*, 1937, **2**, 195) have, however, shown that allylbenzene is susceptible to the peroxide effect and hence it must be concluded that the methylenedioxy-group exerts a powerful antioxidant action (cf. Smith, *Chem. and Ind.*, 1938, **57**, 461).



(VII.)



(VIII.)

The work on the substance (VII) was initiated in the hope that γ-bromopropylveratrole might become readily accessible and, pending the solution of the problem of reversing the direction of addition of hydrogen bromide to eugenol methyl ether and safrole, there is no advantage to be gained in pursuing the investigation.

Experimental.

Ethyl Methyl-β-*acetylethylmalonate* (III).—Methyl β-chloroethyl ketone (Blaise and Maire, *Bull. Soc. chim.*, 1908, **3**, 268) (7·2 g.) was added to ethyl sodiomethylmalonate (from 13 g. of ethyl methylmalonate and 1·56 g. of powdered sodium) under dry ether (150 c.c.) and the mixture was refluxed for 1·5 hours and kept for 12 hours. The *product* was worked up in the usual manner and obtained as a colourless oil, b. p. 114—116°/0·4 mm. (Found: C, 58·8; H, 8·3. $C_{12}H_{20}O_5$ requires C, 59·0; H, 8·2%).

1-*Carbethoxy*-1-*methyl*cyclo*hexane*-2 : 4-*dione* (IV).—A mixture of ethyl methyl-β-acetylethylmalonate (11 g.), sodium ethoxide (4·6 g.), and dry alcohol (80 c.c.) was refluxed for 1 hour. The yellow precipitate was collected and dissolved in water (80 c.c.), dilute sulphuric acid (45 c.c.) added gradually with stirring, the mixture extracted with ether, and the solvent evaporated; the residue crystallised after 2 weeks. The solid was washed with dry ether–light petroleum (b. p. 40—60°) (1 : 1) and dried in a vacuum. The colourless crystals had m. p. 81·5—82·5° (Found: C, 60·4; H, 7·2. $C_{10}H_{14}O_4$ requires C, 60·6; H, 7·1%) (yield, 36·4%). A reddish-brown colouration was developed with alcoholic ferric chloride.

m-*Methoxyphenylacetaldehyde*.—*m*-Methoxyphenylacetonitrile (10 g.) was added to a solution of anhydrous stannous chloride (19·3 g.) in dry ether (100 c.c.) saturated with hydrogen chloride at 0° and a slow stream of the gas was passed for 12 hours. The yellow, crystalline aldimine stannichloride was collected, washed with ether, and decomposed, in the presence of

a Sörensen neutral phosphate buffer solution, by the addition of sodium hydroxide solution whenever necessary to preserve neutrality. The product was taken up in ether, the solvent removed, and the residual oil suspended in the phosphate buffer and distilled in steam. The *aldehyde* was isolated from the distillate by means of ether and distilled as an almost colourless oil, b. p. 117—119°/13 mm. (Found: C, 71·5; H, 6·8. $C_9H_{10}O_2$ requires C, 72·0; H, 6·7%).

The *semicarbazone* crystallised from aqueous alcohol in colourless prismatic needles, m. p. 130—131° (Found: C, 58·2; H, 6·3; N, 20·3. $C_{10}H_{13}O_2N_3$ requires C, 58·0; H, 6·3; N, 20·3%).

ββ-*Bis*-(1′ : 3′-*diketo*-5′ : 5′-*dimethyl*-2′-cyclo*hexyl*)*ethylbenzene* (V).—Phenylacetaldehyde (2·32 c.c.) and then piperidine (8 drops) were added to a suspension of dimedone (5·6 g.) in alcohol (15 c.c.). The mixture was shaken, kept for 15 minutes, and then refluxed for ½ hour. The precipitate crystallised from alcohol in white prisms (6·5 g.), m. p. 164—165° (Found: C, 75·4; H, 7·9. $C_{22}H_{30}O_4$ requires C, 75·4; H, 7·8%). The ferric reaction in alcoholic solution was a dark-red coloration. Despite the repetition of the condensation under a large variety of conditions the required ethylidene derivative was not obtained.

9-*Benzyl*-3 : 3 : 6 : 6-*tetramethyloctahydroxanthen*-1 : 8-*dione* (VI).—This substance was prepared by an application of the method of Vorländer and Strauss (*Annalen*, 1899, **309**, 259) for the preparation of the corresponding phenyltetramethyloctahydroxanthendione. A mixture of bis(diketodimethyl*cyclo*hexyl)ethylbenzene (2 g.) and acetic anhydride (8 c.c.) was refluxed for 3 hours and then added to water. The solid which gradually formed was dissolved in ether, and the solution washed with aqueous sodium carbonate and then with water, dried, and evaporated. The residue crystallised from light petroleum (b. p. 40—60°) and then from light petroleum–ethyl acetate (1 : 1) in colourless needles, m. p. 125—126° (Found: C, 79·0; H, 8·2. $C_{24}H_{28}O_3$ requires C, 79·1; H, 7·7%). The same *substance* was obtained when the bis-(diketodimethyl*cyclo*hexyl)ethylbenzene was treated with phosphoric oxide in boiling benzene solution. The product in this case crystallised from ethyl acetate in colourless needles, m. p. 125—126°, alone or mixed with the specimen obtained as above (Found: C, 79·4; H, 7·7%). The substance gives no ferric reaction in alcoholic solution.

2 : 4-*Dinitrophenylhydrazone of* 6 : 7-*Methylenedioxy*-2-*acetyl*-1-*methylnaphthalene*.—A specimen of piperonylacetaldehyde prepared by the method of Erdtman and Robinson (J., 1933, 1530) had polymerised to a hard glass, but it was resolved into the unimolecular form on distillation under diminished pressure. A mixture of the aldehyde (5·9 g.) and dimethyldihydroresorcinol (5 g.) was heated at 160—165° for 4 hours; steam was allowed to escape at intervals. On cooling, the orange-yellow, viscous syrup set to a hard resin, which could be readily powdered and evidently could not contain as much as 3 g. of unchanged aldehyde. The product was dissolved in hot acetic acid (40 c.c.) and, after cooling, sulphuric acid (10 c.c.) was added; the mixture was then heated on the steam-bath for a few seconds and allowed to cool. Water and ether were added, and the ethereal solution was washed with water, aqueous sodium carbonate and sodium hydroxide solution, dried with sodium sulphate, and evaporated. The residue was dissolved in alcohol (50 c.c.) and acetic acid (5 c.c.) and, after the addition of Girard's reagent-P (5 g.), the solution was refluxed for 15 minutes. Aqueous sodium acetate and ether were added to the cooled solution and after separation the aqueous layer was extracted with fresh ether and again separated. This aqueous solution clouded quickly and an oil was deposited, so, in spite of the addition of sodium acetate, it appeared that hydrolysis of the hydrazone was rapid and loss of the desired product by passage into the ethereal layers must have occurred at this stage. The hydrolysis was hastened by the addition of hydrochloric acid and the ketone was isolated by means of ether as an oil that showed a tendency to crystallise; it was at once treated with Brady's reagent diluted with an equal volume of alcohol. The red, amorphous precipitate obtained dissolved in ethyl acetate, but at once separated in a crystalline form. It was recrystallised from ethyl acetate, forming minute, diamond-shaped, glistening plates, m. p. 299—300° with vigorous decomp. and slight previous decomp. (Found: C, 58·5; H, 4·4; N, 13·9. $C_{20}H_{16}O_6N_4$ requires C, 58·8; H, 3·9; N, 13·7%).

The composition of the ketone corresponding to this formula for the *dinitrophenylhydrazone* is $C_{14}H_{12}O_3$ and, if this is correct, it appears that a molecule of acetone has been eliminated from the dimethyldihydroresorcinol at some stage. The possible intermediate is acetylacetone and the formulation tentatively suggested at the head of the section is that anticipated from the cyclisation of a condensation product of piperonylacetaldehyde and acetylacetone.

4-*Keto*-7-3′ : 4′-*dimethoxyphenylheptoic Acid*.—A mixture of γ-3 : 4-dimethoxyphenylbutyric acid (Haworth and Mavin, J., 1932, 1486) (33 g.), thionyl chloride (32 c.c.), and chloroform (150 c.c.) was refluxed for 1 hour. Chloroform and thionyl chloride were removed below 40°

under diminished pressure, benzene added to the residue, and the distillation resumed; this process was repeated. The dark red residue was kept over solid potassium hydroxide in a vacuum for some hours (yield, 41 g.).

The procedure adopted for the synthesis of the keto-acid was similar to that used for 4-keto-7-*m*-methoxyphenylheptoic acid (Part XVI, J., 1937, 69). γ-3 : 4-Dimethoxyphenylbutyryl chloride (from 66 g. of the acid) was condensed with ethyl sodioacetylsuccinate (from 100 g. of ester and 8 g. of sodium) in ethereal solution, and the isolated product was dissolved in alcohol (250 c.c.) and shaken for 22 hours with aqueous potassium hydroxide (3000 c.c. of 4·5%). The mixture of crude acids (68 g.) separated after acidification was esterified with diazomethane (from 110 g. of nitrosomethylurea). On distillation methyl dimethoxyphenylbutyrate and methyl 4-keto-7-3′ : 4′-dimethoxyphenylheptoate (21 g.), b. p. 195—198°/0·3 mm., were obtained. The keto-ester was hydrolysed by means of aqueous methanolic potassium hydroxide, and the *keto-acid* purified by the process described in Part XVI; it crystallised from benzene–light petroleum (b. p. 40—60°) (1 : 1) in colourless needles, m. p. 69—70° (Found: C, 64·2; H, 7·1. $C_{15}H_{20}O_5$ requires C, 64·3; H, 7·1%). The *semicarbazone* crystallised from aqueous alcohol (50%) in colourless prisms, m. p. 158—159° (Found: C, 57·0; H, 6·7; N, 12·3. $C_{16}H_{23}O_5N_3$ requires C, 57·0; H, 6·8; N, 12·5%).

Lactone of 4-Hydroxy-7-3′ : 4′-dimethoxyphenylheptoic Acid (VII).—This was prepared exactly as described in Part XVI (*loc. cit.*) for the *m*-methoxyphenyl analogue; the viscous colourless oil had b. p. 203—208°/0·22 mm. (Found: C, 68·0; H, 7·4. $C_{15}H_{20}O_4$ requires C, 68·2; H, 7·5%). This *lactone* was condensed with β-carbomethoxypropionyl chloride in the presence of aluminium chloride; the reaction appeared to proceed normally, but the product could not be induced to crystallise.

Action of Hydrogen Bromide on Eugenol Methyl Ether in the Presence of Perbenzoic Acid.—Air and hydrogen bromide were passed during 5 hours into a solution of eugenol methyl ether (59 g.) in dry benzene (600 c.c.) along with perbenzoic acid (10 c.c. of 0·3N solution in benzene). At intervals of 2 days further quantities (5 c.c., making 25 c.c. in all) of the perbenzoic acid solution were added. After 8 days the product was isolated (86·5 g.) and fractionated: 156°/10 mm. (5·5 g.), largely eugenol methyl ether; 158—164°/9 mm. (65·3 g.), a nearly colourless, heavy oil; 167—177°/9 mm. (2 g.), reddish and very viscous. The main fraction was redistilled, b. p. 161—163°/10 mm. (43·1 g.) (b. p. 160—163°/10 mm. on redistillation) (Found: C, 49·6; H, 5·3; Br, 32·3. $C_{10}H_{13}O_2Br$ requires C, 49·0; H, 5·3; Br, 32·7%). The substance is therefore a *hydroxymethoxybromopropylbenzene*. It was probably contaminated with a little of the dihydroxy-derivative, because the ferric reaction in alcoholic solution was a deep green coloration.

Addition of Hydrogen Bromide to Safrole.—Only one of the many experiments made is here described. A mixture of freshly distilled safrole (8·1 g.), a solution of perbenzoic acid in benzene (2 c.c. of 0·3N), and benzene (100 c.c.) was saturated with hydrogen bromide (2 hours). On each of the next 7 days perbenzoic acid solution (1 c.c.) was added, and the mixture shaken and kept for 17 days. The mixture was then washed with water, dilute aqueous sodium carbonate, and again water and the benzene layer was separated, dried, and distilled. The fraction (6·5 g.), b. p. 145·5—153°/9·5 mm., was a colourless, mobile liquid and was identified as the known safrole hydrobromide; Robinson and Zaki (J., 1927, 2489) give b. p. 160°/16 mm.

The addition of hydrogen bromide to safrole was also carried out (*a*) in the presence of α-heptenylheptaldehyde, and (*b*) in the presence of anhydrous ferric chloride. The same β-bromodihydrosafrole was obtained in both cases. The product was identical with the hydrobromide made under ordinary conditions and it did not react with potassium phthalimide, which is an indication of *sec.*-bromide structure.