Acylation and alkylation of 1,3-dimethoxybenzene in polyphosphoric acid

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Products of the reaction of 3-halo- and 3-ethoxypropionic acids with 1,3-dimethoxybenzene (**4**) in polyphosphoric acid have been shown to be 2′,4′-dimethoxy-3-(2,4-dimethoxyphenyl)-propiophenone (**6**) and 1,5-bis[3-(2,4-dimethoxyphenyl)-3-keto-propyl]-2,4-dimethoxybenzene (**15**) and these have been prepared by unambiguous syntheses. 2′,4′-Dimethoxy-3-ethoxypropiophenone (**3***a*) and 2′,3,4′-trimethoxypropiophenone (**3***d*) have been synthesized by the reaction of 3-chloro-2′,4′-dimethoxypropiophenone (**3***c*) with ethanol and methanol respectively.

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Friedel–Crafts acylation of aromatic compounds with bifunctional reagents (1) like halo- or alkoxypropionic acids in polyphosphoric acid (PPA) is rather difficult (2). Musgrave and coworkers (3) have reported unsuccessful attempts at acylations of 3,4-dimethoxyphenyl-, as well as 3,5-dimethoxyphenylacetic esters with substituted octanoic acids (**1***a*,*b*,*c*). One example wherein acylation employing 3-chloropropionic acid in PPA is successful, is that of Davis and Watkins (4) who have prepared the 3-chloropropionyl ketone **2***a* by the reaction of 3-chloropropionic acid with the ester **2***b*.

In connection with a synthetic project on hand, we needed 2′,4′-dimethoxy-3-ethoxypropiophenone (**3***a*) as a starting material. We thought of preparing compound **3***a* by acylation of 1,3-dimethoxybenzene (**4**) with 3-ethoxypropionic acid using PPA. First, PPA was chosen as the reagent as, unlike aluminium chloride, it is known to effect Friedel–Crafts acylations without causing aryl–alkyl ether cleavage (2, 5–8). We also anticipated that at lower reaction temperatures, the alkyl–alkyl ether linkage will remain unaffected.

Adopting Dev's general procedure (8) for PPA acylations with minor modifications, we treated 1,3-dimethoxybenzene with 3-ethoxypropionic acid in the presence of PPA at 40° for about 3–5 min.[1] The neutral product of the reaction was chromatographed on alumina to give two[2] ketonic substances, designated **A** and **B**, in 1:4 ratio. The occurrence of the M^+ peak at *m/e* 330 in the mass spectrum[3] of ketone **A** substantiated the molecular formula $C_{19}H_{22}O_5$. This ketone showed λ_{max} at 226, 269, and 300 mμ (ε 22 000, 14 500, and 8600) indicating the presence of a 2,4-dimethoxybenzoyl chromophore (10) in the molecule. The presence of a benzoyl group was indicated by peaks at 1661 (C=O of conjugated carbonyl), 1605, and 1575 cm^{-1} (aromatic C=C) in the infrared (i.r.) spectrum. Further, it gave the following signals in the nuclear magnetic resonance (n.m.r.) spectrum: 3.10 (m, 8 H), 3.81 (s, 6 H, two aromatic methoxyls), 3.87 (s, 6 H, two aromatic methoxyls), 6.33–6.70 (m, 4 H), 7.09 (d, 1 H, J = 9.5 Hz), and 7.83 δ (d, 1 H, J = 9.5 Hz).

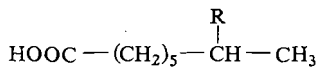
Sodium borohydride reduction of ketone **A** gave a carbonyl-free hydroxylic substance, while its hydrogenolysis with diborane (11) gave the desoxo compound **5***a*. On the basis of the above data, ketone **A** was assigned the structure, 2′,4′-dimethoxy-3-(2,4-dimethoxyphenyl)-propiophenone (**6**). The mass spectral fragments *m/e* 165 (strong, **7**), 151 (strong, **8**), and 138 (weak, **9**) further substantiated this structure, which was proved by its unambiguous synthesis (*vide infra*).

Ketone **B**, which had an M^+ peak at *m/e* 522 in its mass spectrum showed λ_{max} at 227, 268, and 304 mμ (ε 40 800, 27 600, and 17 900), characteristic of a 2,4-dimethoxybenzoyl chromophore (10). The presence of carbonyl group and aromatic ring was indicated by peaks at 1661 (C=O of conjugated carbonyl), 1605, and 1575 cm^{-1} (aromatic C=C) in the i.r. spectrum. The

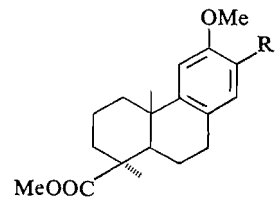
[1]In acylations employing PPA, reaction temperature and time are found to be critical factors (9).

[2]Thin-layer chromatography showed the presence of small amounts of other substances, which are under investigation.

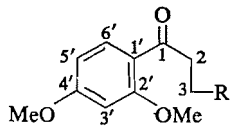
[3]We are thankful to Dr. J. S. Shannon, Division of Entomology, C.S.I.R.O., Chatswood, New South Wales, Australia, for his help in obtaining the mass spectra reported herein and their interpretation.



1 *a*, R = OAc
b, R = OMe
c, R = Br



2 *a*, R = $COCH_2CH_2Cl$
b, R = H



3 *a*, R = OEt
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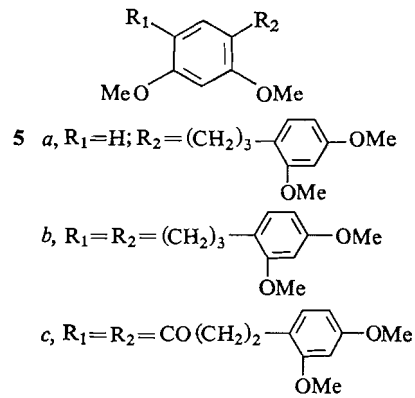
c, R = Cl
d, R = OMe



5 *a*, R_1 = H; R_2 = $(CH_2)_3$
b, $R_1 = R_2 = (CH_2)_3$
c, $R_1 = R_2 = CO(CH_2)_2$
d, R_1 = H; $R_2 = CH_2CH_2COOH$
e, R_1 = H; $R_2 = CH_2CH_2COOMe$
f, $R_1 = R_2 = CH_2CH_2COOH$

complex n.m.r. spectrum showed peaks at 2.75–3.37 (m, 8 H), 3.81, 3.83, and 3.85 (18 H, probably six aromatic methoxyls), 6.37–6.60 (m, 5 H), 6.93 (s, 1 H), and 7.83 δ (d, 2 H, J = 9.5 Hz). Sodium borohydride reduction of ketone **B** gave a carbonyl-free hydroxylic substance, while diborane reduction gave a carbonyl-free desoxo compound **5***b*, indicating its benzylic nature.

The molecular weight as well as the presence of the fragments *m/e* 357 (weak, **10**), 343 (strong, **11**), 177 (weak, **12**), 165 (strong, **7**), and 151 (weak, **13**) in its mass spectrum led us to consider structures **14** or **15** for this ketone. The mass spectrum clearly ruled out the third alternative structure **5***c*, as it is not possible to derive the ion at *m/e* 343 from it. Further, structure **5***c* could be precluded on mechanistic grounds also (12).

In order to differentiate between structures **14** and **15**, these compounds were prepared by unambiguous methods as follows:

[1] **4** + **5***d* → **6** + **14**

[2] **4** + **5***f* → **15**

Preparation of the acid **5***d* has already been reported (13, 14). However, we tried alternative methods for preparing this acid. For example, treatment of 7-methoxydihydrocoumarin, obtained by high pressure hydrogenation (15) of 7-methoxycoumarin over Raney nickel catalyst, with cold alkali, followed by methylation with dimethyl sulfate in the presence of potassium carbonate in refluxing acetone, and saponification gave the acid **5***d* in good yields. The best and easiest method for the preparation of **5***d* was by the addition of methyl acrylate to 1,3-dimethoxybenzene in pyrophosphoric acid,[4] followed by saponification.

Reaction of the acid **5***d* with a fourfold excess of 1,3-dimethoxybenzene in PPA gave in good yield, according to eq. [1], the monoketone **6** and the unsymmetrical diketone **14** in 2:1 ratio. Compound **6** was identical with the aforementioned ketone **A**. The n.m.r. spectrum of the unsymmetrical diketone **14** was significantly

[4]Cf. Gardner *et al.* (16).

different from that of ketone **B** in the aromatic region (see Experimental).

Acylation of 1,3-dimethoxybenzene with the diacid **5***f* (16) in PPA according to eq. [2] led to the exclusive formation of the symmetrical diketone **15**, which was identical with the previously mentioned ketone **B**.

Having failed to obtain the required propiophenone **3***a* by the reaction of 1,3-dimethoxybenzene with 3-ethoxypropionic acid, we carried out the acylation of 1,3-dimethoxybenzene with 3-bromopropionic acid in PPA with a view to getting the bromoketone **3***b* which could easily be converted to the ethoxyketone **3***a* by known procedures. Chromatography of the neutral product from this reaction gave only the aforementioned ketones **6** and **15** in 3:1 ratio.

Acylation of 1,3-dimethoxybenzene with either 3-ethoxypropionyl chloride (cf. ref. 17) in the presence of aluminium chloride (7, 18) in carbon disulfide medium or with 3-chloropropionic acid in PPA, resulted only in the formation of the ketones **6** and **15**.

In the present work, the formation of monoketone **6** can be visualized by initial acylation (7) of 1,3-dimethoxybenzene with one molecule of 3-halo- or alkoxy-propionic acid, and subsequent electrophilic attack on a second molecule of the highly reactive aromatic ether **4** (7). The alkylation reaction might proceed by either of the following mechanisms:

(*a*) Elimination of 3-halo or alkoxy group to give the corresponding α,β-unsaturated carbonyl derivative followed by alkylation (7), or

(*b*) Formation of the intermediate complexes such as **16**, or **17** (1, 19, 20), which *in situ* might attack the aromatic ether **4**.

In order to get a clear picture of this mechanism, we carried out the reaction of the chloroketone **3***c* (*vide infra*) with 1,3-dimethoxybenzene in PPA. Thin-layer chromatography (t.l.c.) of the neutral product showed the presence of the starting chloroketone[5] as well as ketones **6** and **15**. In the light of this result and that of Davis and Watkins (4), mechanism (*a*) could be ruled out.

Since acylation of 1,3-dimethoxybenzene as the first step might result in the exclusive formation of the intermediate complex **16** or **17**, there is no possibility for the formation of the unsymmetrical ketone **14** in these reactions by further acylation of the monoketone **6**. However, the symmetrical ketone **15** may be formed by further alkylation of the ketone **6** or by simultaneous dialkylation of 1,3-dimethoxybenzene by the intermediate complex **16** or **17**. This is evident from the aforementioned alkylation reaction of 1,3-dimethoxybenzene with the chloroketone **3***c*. This is further substantiated by the reaction of either of the alkoxy ketones **3***a* or **3***d*[6] with 1,3-dimethoxybenzene in PPA, when the same ketones **6** and **15** were formed.

Finally, the required ethoxypropiophenone **3***a* was prepared by acylation of 1,3-dimethoxybenzene with 3-chloropropionyl chloride in the presence of aluminium chloride in carbon disulfide medium (cf. ref. 18), followed by heating the resulting chloroketone **3***c* with either ethanolic potassium hydroxide (17, 21) or sodium iodide in ethanol (17). Similarly, the corresponding methoxypropiophenone **3***d* was also synthesized. The structures of ketones **3***a* and **3***d* were confirmed by their ultraviolet (u.v.), i.r., and n.m.r. spectra.

Experimental

Melting points (hot stage) and boiling points reported herein are uncorrected. Ultraviolet (ethanol solution) and infrared (i.r.) spectra were recorded on a Beckmann DU and a Perkin–Elmer model 137B Infracord spectrophotometers respectively. Nuclear magnetic resonance spectra were taken in $CDCl_3$ or CCl_4 solution on a Varian A-60 spectrometer using tetramethylsilane as internal standard. All organic extracts were dried over anhydrous sodium sulfate. Neutral alumina and silica gel were used for column chromatography and thin-layer chromatography (t.l.c.) respectively. Light petrol refers to fraction boiling 45–65°. Microanalyses were carried out by Messrs. B. R. Seetharamia and H. S. Thyagarajan of this department.

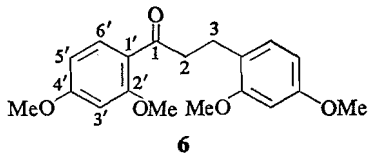
Reaction of 1,3-Dimethoxybenzene

(a) With 3-Ethoxypropionic Acid

A mixture of 1,3-dimethoxybenzene (6.9 g, 0.05 mole) and 3-ethoxypropionic acid (5.9 g, 0.05 mole) was added in one lot to PPA (phosphorus pentoxide (35 g) and *ortho*-phosphoric acid (15 ml)) at 40° and stirred vigorously for 3–5 min. The pale-red viscous reaction mixture was decomposed with ice-cold water and the resulting oily organic material was extracted with benzene. The benzene extract was washed successively with water, saturated aqueous sodium bicarbonate, and water. The solvent was distilled off and the residue (8 g) was chromatographed. The benzene – light petrol fraction (1 g) gave, on crystallization from ethanol, ketone **6**, m.p. 88–89°.

[5]However, the chloroketone could not be isolated after chromatography over neutral alumina, as it probably underwent decomposition.

[6]These experiments were suggested by one of the referees.



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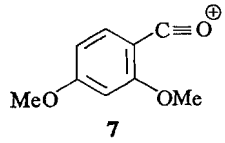

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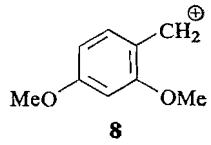

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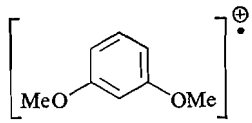

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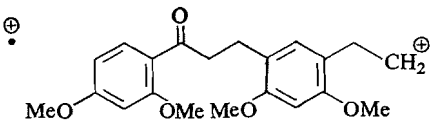

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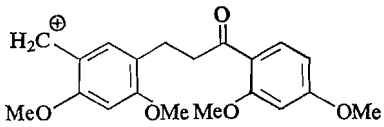

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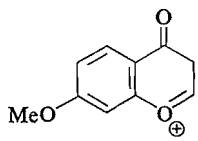

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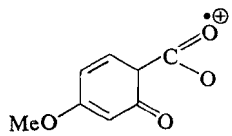

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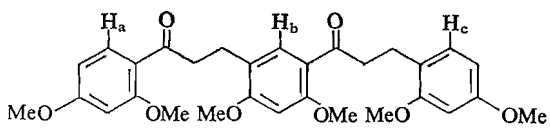

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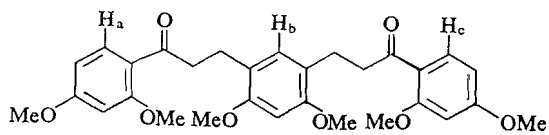

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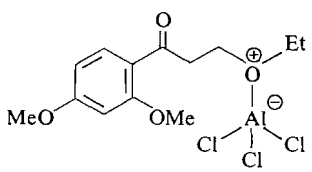

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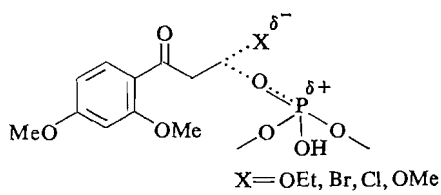

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Anal. Calcd. for $C_{19}H_{22}O_5$: C, 69.07; H, 6.71. Found: C, 68.73; H, 6.52.

The 2,4-dinitrophenylhydrazone was recrystallized from ethanol, m.p. 121–123°.

Anal. Calcd. for $C_{25}H_{26}N_4O_8$: N, 10.97. Found: N, 11.16.

The fraction (4.2 g) eluted with benzene–ether was crystallized from ethanol to afford 1,5-bis[3-(2,4-dimethoxyphenyl)-3-ketopropyl]-2,4-dimethoxybenzene (**15**), m.p. 125–127°.

Anal. Calcd. for $C_{30}H_{34}O_8$: C, 68.95; H, 6.56. Found: C, 69.08; H, 6.6.

The bis-2,4-dinitrophenylhydrazone was recrystallized from ethyl acetate, m.p. 200–202°.

Anal. Calcd. for $C_{42}H_{42}N_8O_{14}$: N, 12.7. Found: N, 13.01.

(b) With 3-Bromopropionic Acid

A mixture of 1,3-dimethoxybenzene (3.5 g, 0.025 mole) and 3-bromopropionic acid (3.9 g, 0.025 mole) was poured in one lot into PPA (phosphorus pentoxide (16.25 g) and *ortho*-phosphoric acid (9.8 ml)) kept at 0°. The mixture was stirred vigorously and the temperature gradually raised to 20° during 15 min. Stirring was continued for a further 30 min at 40° during which time evolution of hydrogen bromide was observed. The reaction mixture was worked up as before to yield an oily residue (4.5 g) which, on chromatography, gave two fractions; the benzene fraction (2.9 g), on crystallization from ethanol, afforded ketone **6**, m.p. 88–89°, while recrystallization of the ether fraction (0.9 g) from ethanol furnished diketone **15**, m.p. 125–127°.

(c) With 3-Ethoxypropionyl Chloride

Powdered aluminium chloride (16 g) was added during 1 h to a stirred mixture of 1,3-dimethoxybenzene (16 g) and 3-ethoxypropionyl chloride (15 g) in carbon disulfide (32 ml) at 0°. The mixture was stirred at room temperature and let stand overnight. The supernatant liquid was decanted and the dark-red complex decomposed with crushed ice. The organic material was extracted with ether; the extract was washed successively with water, 5% aqueous sodium hydroxide, and water. The residue (20 g), obtained after evaporation of the solvent, was chromatographed; the light petrol – benzene fraction (2 g), on crystallization from ethanol, gave ketone **6**, m.p. 88–89°; the benzene–ether fraction (14 g), on crystallization from ethanol, yielded diketone **15**, m.p. 125–127°.

(d) With 3-Chloropropionic Acid

A mixture of 1,3-dimethoxybenzene (3.45 g) and 3-chloropropionic acid (2.71 g) was added in one lot to PPA (phosphorus pentoxide (17.5 g) and *ortho*-phosphoric acid (7.5 ml)) at 35° and stirred for 30 min. After work-up, the residue (4 g), on chromatography followed by crystallization from ethanol, gave ketone **6** (1.5 g), m.p. 88–89°, and diketone **15** (0.5 g), m.p. 125–127°.

(e) With 3-Chloro-2',4'-dimethoxypropiophenone (3c)

The chloroketone **3***c* (5.7 g, 0.025 mole) was added in one lot to a mixture of 1,3-dimethoxybenzene (3.45 g, 0.025 mole) and PPA (phosphorus pentoxide (17.5 g) and *ortho*-phosphoric acid (7.5 ml)) at 45° and stirred vigorously for 30 min. After work-up, the residue was chromatographed to give two fractions; the benzene fraction (3.8 g), on crystallization from ethanol, afforded ketone **6**, m.p. 88–89°, and the chloroform fraction (2 g) yielded diketone **15**, m.p. 125–127°.

(f) With 2',3,4'-Trimethoxypropiophenone (3d)

The methoxypropiophenone **3***d* (1.12 g) was added to a mixture of 1,3-dimethoxybenzene (0.69 g) and PPA (phosphorus pentoxide (3.5 g) and *ortho*-phosphoric acid (1.5 ml)) at 45° and stirred vigorously for 10 min. After work-up, the residue was chromatographed into two fractions; crystallization from ethanol gave monoketone **6** (0.4 g), m.p. 88–89°, and the diketone **15** (0.2 g), m.p. 125–127°.

(g) With 2',4'-Dimethoxy-3-ethoxypropiophenone (3a)

The ethoxypropiophenone **3***a* (0.6 g) was added to a mixture of 1,3-dimethoxybenzene (0.35 g) and PPA (phosphorus pentoxide (1.75 g) and *ortho*-phosphoric acid (0.75 ml)) at 45° and stirred vigorously for 10 min. After work-up, the residue was chromatographed to give two fractions; the benzene fraction (0.22 g), on crystallization from ethanol, afforded ketone **6**, m.p. 88–89°, and the chloroform fraction (0.15 g) yielded diketone **15**, m.p. 125–127°.

*Hydrogenolyses of Ketones **6** and **15** with Diborane*

(*i*) A solution of borontrifluoride–etherate (5 ml) and diglyme (13 ml) was added to ketone **6** (0.30 g) and sodium borohydride (0.95 g). After 3 h at room temperature, the reaction mixture was heated at 40–50° for 2 h, and cooled. Methanol was added to destroy the excess of diborane, the mixture diluted with ice-cold water, and extracted with benzene. The extract was washed with water. Removal of benzene followed by purification gave 2',4'-dimethoxy-3-(2,4-dimethoxyphenyl)propylbenzene (**5***a*) as an oil (0.29 g), b.p. 120°/1–2 mm (bath temperature); ν_{max} (neat): 1613 and 1587 cm^{-1}; λ_{max}: 226 and 279 mμ (ε 17 250 and 6300).

Anal. Calcd. for $C_{19}H_{24}O_4$: C, 72.15; H, 7.59. Found: C, 72.28; H, 7.18.

(*ii*) Similarly, hydrogenolysis of diketone **15** afforded 1,5-bis[3-(2,4-dimethoxyphenyl)propyl]-2,4-dimethoxybenzene (**5***b*) as an oil, b.p. 175–180°/1–2 mm (bath temperature); ν_{max} (neat): 1613 and 1587 cm^{-1}; λ_{max}: 227 and 280 mμ (ε 30 000 and 11 500).

Anal. Calcd. for $C_{30}H_{38}O_6$: C, 72.85; H, 7.74. Found: C, 72.81; H, 7.71.

7-Methoxydihydrocoumarin and its Conversion into 2,4-Dimethoxyphenylpropionic Acid (5d)

A solution of 7-methoxycoumarin (22) (10 g) in ethanol (80 ml) was hydrogenated over Raney nickel catalyst (3 g) at 90–100° at 200 atm of hydrogen for 45 min. After cooling the solution, the catalyst was filtered off, and the ethanol evaporated. The residue (10.5 g) yielded, on distillation, 7-methoxydihydrocoumarin (13) as an oil, b.p. 158–160°/0.5–1 mm; ν_{max} ($CHCl_3$): 1770, 1631, and 1590 cm^{-1}. Treatment of 7-methoxydihydrocoumarin with 5% aqueous sodium hydroxide followed by acidification afforded 2-hydroxy-4-methoxyphenylpropionic acid, m.p. 138–139°; (lit. (13), m.p. 138–139.5°).

A solution of 2-hydroxy-4-methoxyphenylpropionic acid (0.10 g) and dimethyl sulfate (0.1 ml) in acetone (10 ml) was refluxed in the presence of anhydrous potassium carbonate (0.30 g) for 20 h. The mixture was cooled, filtered, and the solvent removed *in vacuo* in the cold. The residue was treated with water, extracted with ether, and the solvent distilled off. A benzene solution of the residue was filtered through alumina (3 g) and distilled to give **5***e* (0.10 g), b.p. 135–140°/1–2 mm (bath temperature); (lit. (14), b.p. 160°/10 mm); $n_D^{25.7}$ 1.5170; ν_{max} (neat): 1757, 1610, and 1585 cm^{-1}.

Anal. Calcd. for $C_{12}H_{16}O_4$: C, 64.27; H, 7.19. Found: C, 64.32; H, 7.04.

Saponification (16) of the ester **5***e* gave the acid **5***d*, m.p. 103–104°; (lit. (13, 14), m.p. 102.5–103.5°).

Methyl 2,4-Dimethoxyphenylpropionate (5e)

Methyl acrylate (18.8 g) was added during 20 min to a

stirred mixture of pyrophosphoric acid (150 g) and 1,3-dimethoxybenzene (90 g), maintained at 65°. Stirring was continued for an additional 30 min. The reaction mixture was poured onto crushed ice and water (400 ml), and let stand for a while. The resulting oily product was extracted with ether, and the extract washed successively with water, saturated aqueous sodium bicarbonate, and water. Removal of ether and distillation of the residue yielded the ester **5***e* (30 g), b.p. 154–155°/1–2 mm.

*2′,4′-Dimethoxy-3-(2,4-dimethoxyphenyl)-propiophenone (**6**) and 2,4-Dimethoxy-1-[1-keto-3-(2,4-dimethoxyphenyl)-propyl]-5-[3-keto-3-(2,4-dimethoxyphenyl)-propyl]-benzene (**14**)*

A mixture of 1,3-dimethoxybenzene (13.80 g) and the acid **5***d* (5.25 g) was poured in one lot into PPA (phosphorus pentoxide (35 g) and *ortho*-phosphoric acid (15 ml)) maintained at 50–53° and stirred vigorously for 15 min. The residue was chromatographed; the benzene fraction (5 g), on crystallization from ethanol, afforded ketone **6**, m.p. 88–89°; crystallization of the benzene–chloroform fraction (2.5 g) from ethanol furnished the diketone **14**, m.p. 143–144°; λ_{max}: 227, 267, and 304 mμ (ε 39 100, 26 000, and 16 800); ν_{max} (Nujol): 1661, 1597, and 1575 cm^{-1}; n.m.r.: 2.71–3.41 (m, 8 H), 3.80, 3.89 (s, 18 H, six aromatic methoxyls), 6.41–6.59 (m, 5 H, aromatic protons), 7.08 (d, 1 H, J = 9.5 Hz, proton H_c), 7.67 (s, 1 H, proton H_b), and 7.81 δ (d, 1 H, J = 9.5 Hz, proton H_a).

Anal. Calcd. for $C_{30}H_{34}O_8$: C, 68.95; H, 6.56. Found: C, 69.29; H, 6.97.

The bis-2,4-dinitrophenylhydrazone was recrystallized from ethyl acetate, m.p. 209–210°.

Anal. Calcd. for $C_{42}H_{42}N_8O_{14}$: N, 12.7. Found: N, 12.6.

*1,5-bis[3-Keto-3-(2,4-dimethoxyphenyl)-propyl]-2,4-dimethoxybenzene (**15**)*

A mixture of the diacid **5***f* (4.2 g) and 1,3-dimethoxybenzene (15 g) was added in one lot into PPA (phosphorus pentoxide (35 g) and *ortho*-phosphoric acid (15 ml)) kept at 50–52° and stirred vigorously for 10 min. The dark-red reaction mixture after work-up gave a viscous oil (8 g) which, on trituration with light petrol followed by recrystallization from ethanol, afforded diketone **15**, m.p. 126–128°.

*3-Chloro-2′,4′-dimethoxypropiophenone (**3c**)*

A solution of 1,3-dimethoxybenzene (7.2 g) in carbon disulfide (10 ml) was added during 30 min to a stirred mixture of 3-chloropropionyl chloride (5.9 g) and powdered aluminium chloride (6.9 g) in carbon disulfide (10 ml) at 0–5°. Stirring was continued at room temperature for further 8 h and the reaction mixture was allowed to stand overnight. After work-up, a crystalline solid (10.5 g) was obtained, which, on recrystallization from methanol, yielded white needles of chloroketone **3***c* (8 g), m.p. 101–102°; ν_{max} (Nujol): 1658, 1603, and 1572 cm^{-1}; λ_{max}: 229, 268, and 305 mμ (ε 13 400, 12 100, and 8 500).

Anal. Calcd. for $C_{11}H_{13}ClO_3$: C, 57.77; H, 5.69. Found: C, 57.32; H, 5.30.

*2′,4′-Dimethoxy-3-ethoxypropiophenone (**3a**)*

(*i*) A solution of the chloroketone **3***c* (1 g) in ethanolic potassium hydroxide (2 g in 60 ml) was stirred at room temperature for 5 min followed by heating on a steam bath for 5 min. The reaction mixture, after cooling, was neutralized with 4 *N* acetic acid, ethanol was removed *in vacuo* in the cold, and the residual oil was extracted with benzene. The extract was washed successively with water, saturated aqueous sodium bicarbonate, and water. Removal of benzene gave a crystalline solid (1 g) which, on recrystallization from light petrol, afforded white plates of ketone **3***a*, m.p. 42–43°; ν_{max} (Nujol): 1658, 1605, and 1572 cm^{-1}; λ_{max}: 228, 267, and 302 mμ (ε 14 000, 12 400, and 8 150); n.m.r.: 1.12 (t, 3 H), 2.87–3.70 (m, 6 H), 3.78 (s, 3 H), 3.85 (s, 3 H), 6.31–6.50 (m, 2 H), and 7.60 δ (d, J = 9.5 Hz, 1 H).

Anal. Calcd. for $C_{13}H_{18}O_4$: C, 65.53; H, 7.61. Found: C, 65.38; H, 7.58.

(*ii*) A mixture of the chloroketone **3***c* (1.5 g) and anhydrous sodium iodide (10 g) in dry ethanol (50 ml) was refluxed on a steam bath for 36 h. About half of the solvent was removed *in vacuo*, and ether (200 ml) was added to the mixture. The ether solution was washed with 5% aqueous sodium thiosulfate and water. Ether was distilled off and the residue (1.5 g) crystallized from light petrol to give ketone **3***a* (1.2 g), m.p. 42–43°.

*2′,3,4′-Trimethoxypropiophenone (**3d**)*

A solution of the chloroketone **3***c* (1 g) in methanolic potassium hydroxide (2 g in 60 ml) was stirred for 5 min at room temperature followed by heating on a steam bath for 5 min. The cooled reaction mixture was neutralized with 4 *N* acetic acid. Methanol was removed *in vacuo* in the cold, and the crystalline residue was filtered off, washed with water, and dried. Recrystallization from light petrol yielded white needles of the ketone **3***d* (0.8 g), m.p. 56–57°; ν_{max} (Nujol): 1658, 1605, and 1572 cm^{-1}; λ_{max}: 228, 267, and 303 mμ (ε 14 000, 12 400, and 8 200); n.m.r.: 2.84–3.70 (m, 4 H), 3.21 (s, 3 H), 3.73 (s, 3 H), 3.81 (s, 3 H), 6.17–6.42 (m, 2 H), and 7.51 δ (d, J = 9.5 Hz, 1 H).

Anal. Calcd. for $C_{12}H_{16}O_4$: C, 64.27; H, 7.19. Found: C, 64.18; H, 7.04.

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