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SYNTHESIS OF 4,6-(AND 5,7-)DIMETHOXY-3,3-DIMETHYL-1-INDANONES

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Abstract—Grignard reaction of ethyl 3-(3,5-dimethoxyphenyl)-propionate (**4**) followed by cyclodehydration of the carbinol (**5**) with conc H_2SO_4 gave 4,6-dimethoxy-3,3-dimethylindane (**6**). Oxidation of the indane (**6**) with CrO_3-pyridine complex in methylene chloride gave 4,6-dimethoxy-3,3-dimethylindan-1-one (**1**) in high yield. Conjugate addition of methyl magnesium iodide to methyl α-cyano-β-methyl-3,5-dimethoxycinnamate (**11**), prepared from 3,5-dimethoxyacetophenone (**10**) by Knoevenagel condensation, resulted in methyl 2-cyano-3-(3,5-dimethoxyphenyl)-3,3-dimethylpropionate (**12**). Refluxing the ester (**12**) with aq DMSO containing sodium chloride gave the corresponding nitrile (**15**) which underwent Höesch reaction to yield 5,7-dimethoxy-3,3-dimethylindan-1-one (**2**).

In connection with the studies on modified steroids, the key intermediates 4,6-dimethoxy-3,3-dimethylindan-1-one (**1**) and 5,7-dimethoxy-3,3-dimethylindan-1-one (**2**) have been synthesised for the first time.

Some syntheses of dimethoxyindanones involve cyclisation of the corresponding acid under Friedel-Crafts conditions and other methods involve photooxidation[2] of the corresponding indane and thermolysis of suitably substituted diazoketones.[3]

Initially, Friedel-Crafts cyclisation of 3-(2,4-dimethoxyphenyl)-isovaleric acid was attempted for the synthesis of indanone (**1**), but without success.[4] Alternatively, the synthesis of this indanone was achieved by oxidation of the corresponding indane (**6**), prepared as indicated in Chart 1. Catalytic reduction of ethyl *trans* 3,5-dimethoxycinnamate[5] (**3**) in presence of 10% Pd-C yielded the dihydroester (**4**). Grignard reaction of the ester (**4**) with methyl magnesium iodide gave 4-(3,5-dimethoxyphenyl)-2-methyl-2-butanol (**5**) in quantitative yield. The carbinol (**5**) was treated with conc H_2SO_4 at 0° to give a single product (VPC), identified as 4,6-dimethoxy-3,3-dimethylindane (**6**).

Oxidation of indane to indan-1-one has been achieved by ceric ammonium nitrate[6] and by photoirradiation.[2] Further, DDQ in methanol is known to oxidise tetralin to tetralone.[7] The oxidation of the indane (**6**) to the corresponding indanone (**1**) could not however be achieved using the above conditions. Chromium trioxide-pyridine complex[8] in pyridine or methylene chloride is an effective reagent for allylic oxidation[9] under non-acidic conditions. As indanones are known to be sensitive to acidic reagents, we presumed that the oxidation of indane (**6**) to indanone (**1**) might be favoured with this reagent. Stirring the indane (**6**) with freshly prepared chromium trioxide-pyridine complex in

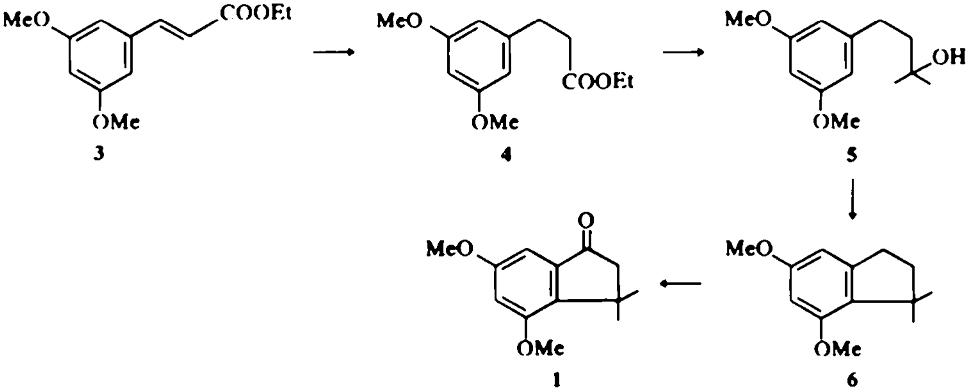

CHART 1.

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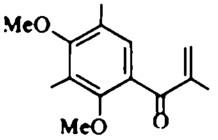
methylene chloride for about 15 h gave, after purification, the starting indane (**6**, 40%) and the required indanone (**1**, 48%) which showed absorption at 1700 (conjugated C=O), 1385 and 1372 cm^{-1} (*gem* dimethyl doublet) in the IR spectrum. The NMR spectrum which showed peaks at 1·45 (s, 6H, *gem* dimethyl), 2·55 (s, 2H, CH_2), 3·8 (s, 3H, $-OCH_3$), 3·85 (s, $-OCH_3$), 6·65 (d, J = 1·5 Hz, 1H, ar–H) and 6·75 δ (d, J = 1·5 Hz, 1H, ar–H) confirmed its structure.

Synthesis of the indanone (**8**) has been reported[10] by Friedel-Crafts type cyclisation of the corresponding α,β-unsaturated ketone (**7**) using conc H_2SO_4. A similar reaction with 2′,4′-dimethoxy-2-dehydroisovalerophenone[11] (**9**), however, resulted in the exclusive formation of 2,4-dimethoxyacetophenone by a retro-aldol reaction. Synthesis of the required indanone (**2**) was achieved by a scheme represented in Chart 2 starting from 2,5-dimethoxyacetophenone[12] (**10**) prepared by an alternate method. Reaction of 3,5-dimethoxybenzoyl chloride,[13] with magnesium salt of diethyl malonate in a mixture of alcohol-ether followed by hydrolysis and decarboxylation of the resulting diester, gave the ketone (**10**) in good yield. Knoevenagel condensation of the ketone (**10**) with methyl cyanoacetate,[14] gave the corresponding unsaturated cyano ester (**11**). The presence of *cis*- and *trans*- isomers in the product was quite evident from its NMR spectrum (Experimental).

Conjugate 1,4-addition of methyl magnesium iodide to the cyanoester (**11**) occurred in fairly good yield in the absence of copper chloride catalyst in accordance with the observation of Sukh Dev and Pandey.[15] Esterification of the cyano ester (**12**) with methanol saturated with hydrogen chloride gas followed by saponification and decarboxylation[15] did not yield the expected acid (**13**) in good yield. Further, Höesch reaction of the cyano ester (**12**) gave a mixture of the β-ketoester (**14**) and the indanone (**2**) in very low yield. The low yield of the products in this reaction may well be attributed to the presence of an electron-withdrawing group in the α-position to the nitrile group.[16] The β-ketoester (**14**) on boiling with water for longer time, gave the indanone (**2**) which showed peaks at 1695 (conjugated C=O), 1379 and 1362 cm^{-1} (*gem* dimethyl doublet) in the IR spectrum. The NMR spectrum of this compound (**2**), which differed from that of indanone (**1**) significantly in the aromatic region, showed signals at 1·36 (s, 6H, *gem* dimethyl), 2·51 (s, 2H, CH_2), 3·89 (s, 6H, 2–OCH_3), 6·29 (d, J = 1·5 Hz, 1H, ar-H) and 6·47 δ (d, J = 1·5 Hz, 1H, ar-H).

Hydrolysis and decarboxylation of the cyano ester (**12**) was achieved by refluxing it with DMSO-water mixture containing NaCl, to yield the nitrile (**15**) in about 65% yield. Höesch reaction of the nitrile (**15**) under the usual conditions gave in good yield the indanone (**2**), which was separated from the starting material (**15**) by column chromatography.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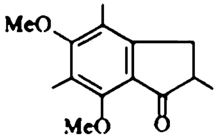
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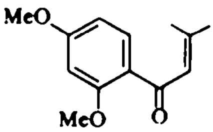
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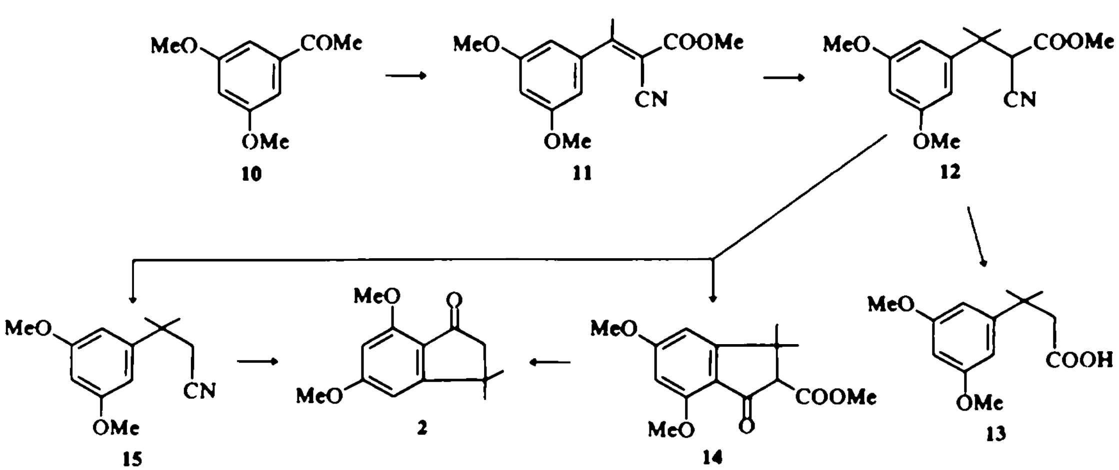

CHART 2.

EXPERIMENTAL

M.ps (hot stage) and b.ps are uncorrected. UV (EtOH soln) and IR spectra were recorded on a Unicam SP700 and a Perkin-Elmer model 700 Infracord spectrophotometers respectively. NMR spectra were taken in $CDCl_3$ or CCl_4 soln either on Varian A 60 or HA 100 D spectrometers using TMS as internal standard and all chemical shifts are reported in δ values. Mass spectra were taken on AEI-MS 702 spectrometer with a built-in direct inlet system. All organic extracts were dried over Na_2SO_4. Light petrol refers to fraction boiling between 45–65°.

Ethyl 3-(3,5-dimethoxyphenyl)-propionate 4. A mixture of *trans*-3 (7·8 g) and Pd-C (10%, 1·1 g) in EtOH (50 ml) was stirred in an atmosphere of H_2 till H_2 uptake ceased (7 h). The catalyst was filtered off, washed with EtOH and the solvent removed. Purification of the residue by distillation gave 4 (7·6 g), b.p. 125–130°/3 mm; IR (neat): ν_{max} 1735 cm^{-1} (COOEt); NMR (CCl_4): 1·2 (t, J = 6 Hz, 3H, $-CH_2-C\underline{H}_3$), 2·3–3·0 (m, 4H, benzylic and ketomethylenes), 3·7 (s, 6H, $-OCH_3$), 3·9–4·3 (q, J = 6 Hz, 2H, $-CH_2-CH_3$) and 6·1–6·3 (m, 3H, ar-H). (Found: C, 65·15; H, 7·75. $C_{13}H_{18}O_4$ requires: C, 65·54; H, 7·56%).

4-(3,5-Dimethoxyphenyl)-2-methyl-2-butanol (5). To a cooled (0°) soln of MeMgI in dry ether (60 ml), prepared from MeI (18 ml) and Mg (3·3 g), was added a soln of 4 (7·5 g) in ether (50 ml) over a period of 0·5 h. The mixture was stirred at 0° for 1 h and left overnight at room temp. The mixture was refluxed for 2 h, cooled (0°) and decomposed with satd. NH_4Cl aq. The ether layer was separated and the aqueous layer extracted well with ether. The combined ether extract was washed with water and dried. Solvent removal gave 5 (7·3 g) which was sufficiently pure for the next reaction: IR (Neat): ν_{max} 3440 cm^{-1} (OH); NMR (CCl_4): 1·4 (s, 6H, $>C(CH_3)_2$), 1·6 (b.s., 1H, O–H), 3·8 (s, 6H, $2-OCH_3$) and 6·3–6·6 (m, 3H, ar-H).

4,6-Dimethoxy-3,3-dimethylindane (6). Conc H_2SO_4 (25 ml) was added during 0·5 h to 5 (0°; 7·3 g) with efficient stirring. The mixture, after stirring for one more h at the same temp, was poured on to ice and extracted with ether. The ether extract was washed with $NaHCO_3$ aq, water and dried. The material, obtained after removal of solvent, was distilled to give 6 (5·1 g), b.p. 102–105°/2·5 mm; NMR (CCl_4): 1·27 (s, 6H, $>C(CH_3)_2$); 1·8 (t, J = 8 Hz, 2H, $Ar-CH_2-C\underline{H}_2-$), 2·77 (t, J = 8 Hz, 2H, benzylic CH_2), 3·7 (s, 3H, $-OCH_3$), 3·75 (s, 3H, $-OCH_3$), 6·1 (d, J = 1·5 Hz, 1H, ar-H) and 6·15 (d, J = 1·5 Hz, 1H, ar-H) (Found: C, 76·64; H, 8·94. $C_{13}H_{18}O_2$ requires: C, 76·42; H, 8·82%).

4,6-Dimethoxy-3,3-dimethylindan-1-one (1). To a mixture of pyridine (4 ml) and CH_2Cl_2 (25 ml), CrO_3 (1·75 g) was added during 5 min, keeping the temp between 20–22°. The mixture was stirred for 15 more min. A soln of 6 (0·6 g) in CH_2Cl_2 (2 ml) was added in one lot to the above complex and the mixture stirred at room temp for 15 h. The solid was filtered off and washed with ether. The combined CH_2Cl_2-ether filtrate was washed successively with 5% NaOH aq, HCl (5%), $NaHCO_3$ (satd soln) and dried. The material, obtained after removal of solvent, was chromatographed over neutral alumina (15 g). Elution with light petrol gave 6 (0·25 g). Further elution with light petrol-benzene (1:1) gave the 1 (0·39 g), m.p. 105° (hexane–benzene); UV: λ_{max} 219 nm (ε 28610) and 268 nm (7330); M.S.: (*m/e*) 220 (M^+), 205 (M-15), 192 (M-28), 189 (M-31), 177 (M-43), 162 (M-58) and 151 (M-69) (Found: C, 70·91; H, 7·29. $C_{13}H_{16}O_3$ requires: C, 70·82; H, 7·29%).

3,5-Dimethoxyacetophenone (10). To a vigorously stirred soln of MgOEt, prepared from Mg (6 g) and abs EtOH (8 ml) containing CCl_4 (2·5 ml), was added dropwise during 20 min a soln of diethyl malonate (33 ml) in a mixture of abs EtOH (20 ml) and dry ether (17·5 ml) such that the vigorous reaction was maintained. The mixture was refluxed for 3 h and cooled to room temp. A soln of 3,5-dimethoxybenzoyl chloride[14] (34 g) in dry ether (30 ml) was added gradually during 25 min and the mixture refluxed for 1·5 h. The cooled mixture, after decomposition with dil H_2SO_4, was extracted with ether. The combined ether extract was washed with water and dried. The crude diester (~ 48 g), obtained after removal of solvent was hydrolysed and decarboxylated by refluxing (20 h) with a mixture of AcOH (60 ml), conc H_2SO_4 (8 ml) and water (40 ml) to yield, after the usual work up, 10 (17·3 g), b.p. 135–140°/7 mm (lit.[15] b.p. 143–146°/8–9 mm); IR (neat): ν_{max} 1685 cm^{-1}; NMR (CCl_4): 2·5 (s, 3H, $-CH_3$), 3·79 (s, 6H, $2-OCH_3$), 6·5–6·6 (m, 1H, ar-H) and 6·85–6·95 (m, 2H, ar-H); M.S.: (*m/e*) 180 (M^+), 165 (M-15), 137 (M-43), 122 (M-58), 107 (M-73) and 43 ($COCH_3$).

Methyl α-cyano-β-methyl-3,5-dimethoxycinnamate (11). A mixture of benzyl amine (1·07 g), AcOH (5 ml), benzene (100 ml), methyl cyanoacetate (10 g) and 3,5-dimethoxyacetophenone (17 g) was refluxed for 12 h using a Dean-Stork apparatus. The cooled benzene soln was washed repeatedly with brine and dried to give, after purification, 11 (17 g), b.p. 193–195°/5 mm; IR (neat): ν_{max} 2245, 1735, 1590 and 1500 cm^{-1}; NMR (CCl_4): 2·49, 2·62 (s, 3H, $-CH_3$), 3·6–3·85 (m, 9H, $3-OCH_3$), and 6·25–6·48 (m, 3H, ar-H) (Found: C, 64·4; H, 5·75; N, 5·81. $C_{14}H_{15}NO_4$ requires: C, 64·37; H, 5·75; N, 5·36%).

Methyl 2-cyano-3-(3,5-dimethoxyphenyl)-3,3-dimethylpropionate (12). A soln of 11 (17 g) in dry ether (125 ml) was added during 0·5 h to a vigorously stirred soln of MeMgI prepared from Mg (3·7 g) and MeI (20 ml) in dry ether (125 ml). The mixture was stirred at room temp for 3 h followed by refluxing for 2 h. The cooled mixture was decomposed with dil HCl and thoroughly extracted with ether. The combined ether extract was washed and dried to give, after purification, a product in which the major amount was 12 (14 g) accompanied by small amounts of starting material, b.p. 196–198°/4 mm. An analytical sample was prepared by repeated fractional distillation; IR (neat): ν_{max} 2240, 1690, 1580, 1380, and 1360 cm^{-1}; NMR (CCl_4); 1·53 (s, 6H, $>C(CH_3)_2$), 3·82 (s, 9H, $3-OCH_3$), 3·61 (s, 1H, $-\overset{|}{\underset{|}{C}}-H$) and 6·25–6·59 (m, 3H, ar-H); M.S.: (*m/e*) 277 (M^+) (Found: C, 64·98; H, 6·82. $C_{15}H_{19}NO_4$ requires: C, 64·98; H, 6·86%).

3-(3,5-Dimethoxyphenyl)-3,3-dimethylpropionitrile (15). A soln of 12 (2·4 g) in water (0·4 ml) and DMSO (8 ml) containing NaCl (0·25 g) was refluxed (5 h) till the evolution of CO_2 ceased. Water (~ 150 ml) was added to the cooled mixture and extracted thoroughly with ether. The ether extract was washed with satd $NaHCO_3$ aq, brine and dried to give, after purification (short path distillation), 15 (1·2 g), b.p. 160°/4 mm (bath temp); IR (neat): ν_{max} 2200, 1590, 1380, and 1360 cm^{-1}; NMR (CCl_4): 1·44 (s, 6H, $>C(CH_3)_2$), 2·48 (s, 2H, $-CH_2-$), 3·74 (s, 6H, $2-OCH_3$), 6·39 (d, 1H, ar-H), 6·47 (d, 1H, ar-H) and 6·8 (m, 1H, ar-H) (Found: C, 71·27; H, 7·76; N, 6·02. $C_{13}H_{17}NO_2$ requires: C, 71·24; H, 7·76; N, 6·39%).

5,7 *Dimethoxy-3,3-dimethylindan-1-one* (2)

(a) *By Höesch reaction of the nitrile* (15). Dry HCl gas was bubbled into a soln (0°) of 15 (1 g) in dry ether (10 ml) containing freshly fused $ZnCl_2$ (1 g) for 5 h and left at 0° for 2 days. The ether layer was decanted from the gummy material and the latter was washed with dry ether and benzene. Water (100 ml) was added to this gummy material and refluxed for 2 h. The cooled mixture was extracted with ether, washed with satd $NaHCO_3$ aq and dried. Residue obtained after removal of ether was chromatographed over silica gel (25 g). Elution with light petrol–benzene (1:1) and benzene gave 15. Further elution with benzene–chloroform (3:1) gave 2 (0·65 g) as a solid. This was crystallized from benzene, m.p. 95·5°; UV: λ_{max} 230 nm (ϵ 13,950), 274 nm (13,420) and 301 nm (sh, 5640); IR (neat): ν_{max} 1695, 1362, and 1379 cm^{-1}; M.S: (*m/e*) 220 (M^+) (Found: C, 70·84; H, 7·3. $C_{13}H_{16}O_3$ requires C, 70·91; H, 7·27%).

(b) *By Höesch reaction of the nitrile* (12). This reaction was carried out, as described above, using 12 (0·8 g), freshly fused $ZnCl_2$ (1 g) and dry ether (10 ml). The usual work up gave a mixture of products, which was separated by preparative TLC (silica gel), to yield 12 (0·2 g), the required 2 (0·02 g) and 14 (0·02 g); IR (neat): ν_{max} 3350–3400 (w), 1730 and 1690 cm^{-1}; NMR (CCl_4): 1·4 (s, 6H, $>C(CH_3)_2$), 3·78 (s, 3H, $-CO_2CH_3$); 3·84 (s, 3H, $-OCH_3$), 3·95 (s, 3H, $-OCH_3$), 6·28 (d, J = 1·5 Hz, 1H, ar-H) and 6·46 (d, J = 1·5 Hz, 1H, ar-H).

The ester 14 on boiling with water for a longer period gave 2.

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