Synthesis of 4,7-Dimethoxyindoles Bearing Substituents at the C-5 and C-6 Positions and Studies on their Demethylation Products

Giorgio Malesani, Fabio Galiano, Maria Grazia Ferlin and Sergio Masiero*

Institute of Pharmaceutical Chemistry of the University, Centro di Studio sulla Chimica del Farmaco e dei Prodotti Biologicamente Attivi del CNR, Via F. Marzolo, 5-35100, Padova, Italy

Received November 20, 1979

Syntheses of some 4,7-dimethoxyindoles bearing methyl, amino or acetamido groups at the C-5 and C-6 positions were investigated. The presence of these substituents made possible the isolation of the corresponding 4,7-dihydroxyindole derivatives obtained by long reflux with aluminium chloride in benzene solution.

J. Heterocyclic Chem., **17**, 563 (1980).

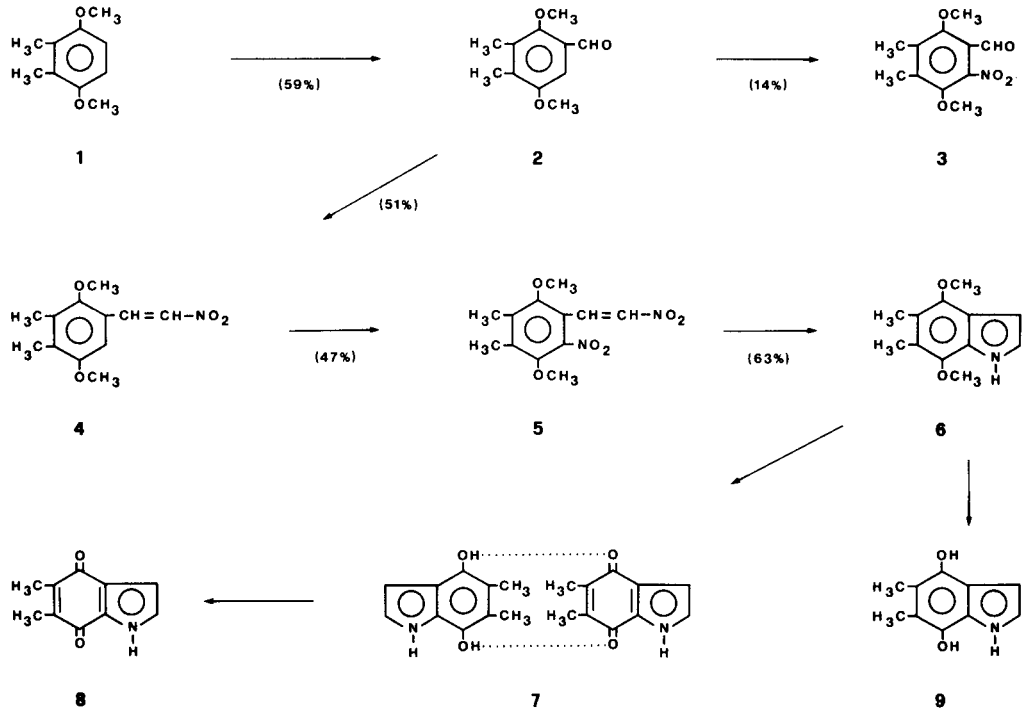
Introduction.

In the course of our studies on the synthesis and the demethylation of 4,7-dimethoxyindoles, we recently investigated the existence of an equilibrium between the 4,7-dihydroxy forms, obtained by dealkylation with anhydrous aluminium chloride in refluxing benzene (1), and the corresponding 4,7-dioxo-4,5,6,7-tetrahydro forms (2,3). We pointed out the role of the substituents on the C-2 or C-3 positions of the indole nucleus in the displacement of the phenol-keto equilibrium towards the 4,7-dihydroxy species, such as to permit their isolation and consequent easy oxidization to the corresponding indole-4,7-diones (2,4,5).

While the effect of alkyl groups on the fused pyrrole ring is irrelevant with regard to the stabilization of dihydroxy structures, the introduction of an electron-withdrawing group at the C-2 or C-3 positions leads to a partial or total isomerization to the dihydroxy species. A reasonable interpretation of this behaviour has been suggested in a previous paper (5). It assumes that a greater electron density is normally present at the C-5 and C-6 positions of the indole nucleus, with consequent migration into these positions of the hydrogen atoms from the hydroxyls found at the C-4 and C-7 positions, thus stabilizing the 4,7-dioxo-4,5,6,7-tetrahydro species. The presence of an electron-attracting group at the C-2 or C-3 positions reduces the partial negative charge at C-5 and C-6, therefore making the dihydroxy structures more stable.

Our interest in these indole derivatives is not only chemical but also becomes chemotherapeutic when con-

Scheme 1



0022-152X/80/030563-07$02.25

sidering the structural relationships with antibiotics of the mitomycin group (6,7) or with other simpler compounds synthesized and studied some years ago (8). It is common knowledge, in fact, that both the mitomycins and the simpler synthetic indole derivatives with antibacterial properties bear substituents at the C-5 and C-6 positions (6-8).

In this paper we describe the syntheses of some new 4,7-dimethoxyindoles having methyl, amino or acetamido groups at the C-5 or C-6 positions, and the study of their behaviour toward demethylation with a view to testing a possible microbiological activity of the corresponding dealkylated compounds.

Chemistry.

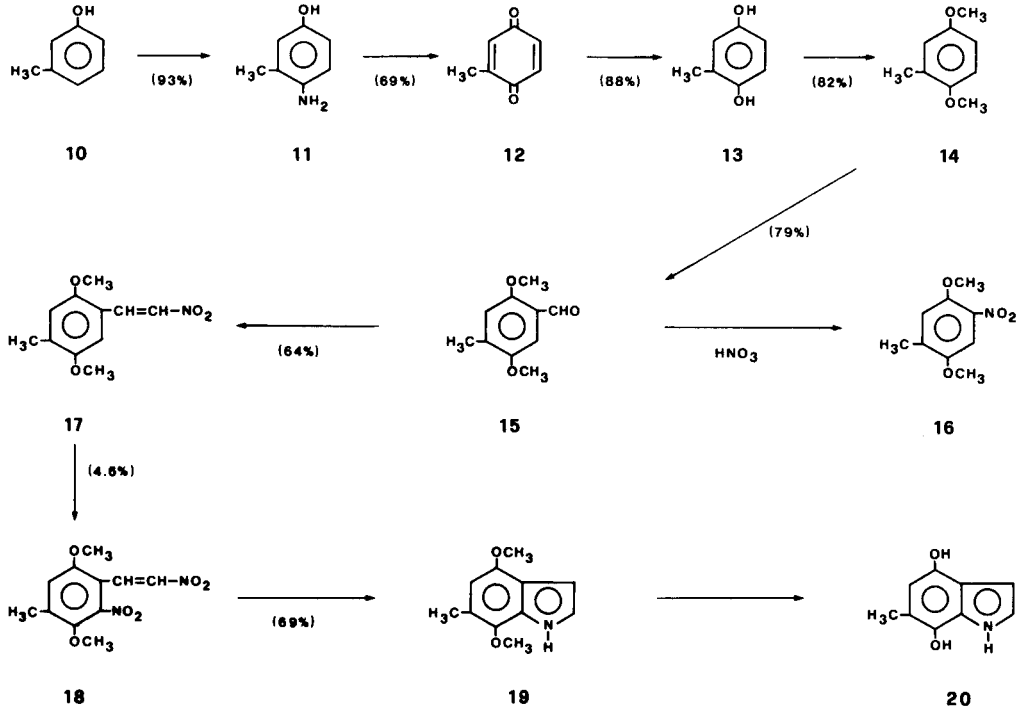
As presented in Scheme 1, in order to synthesize 4,7-dimethoxy-5,6-dimethylindole **6**, 2,5-dimethoxy-3,4-dimethylbenzaldehyde **2** was first prepared, following the procedure of Smith and Austin (9). The nitration of compound **2** under mild conditions, although carried out with particular care, always gave poor yields of 2,5-dimethoxy-3,4-dimethyl-6-nitrobenzaldehyde **3**. Therefore, it was preferred to transform **2** into the corresponding styryl derivative **4** (51% yield), which was easily nitrated in satisfactory yield (47%) to give 2,5-dimethoxy-3,4-dimethyl-6,β-dinitrostyrene (**5**). The reduction of this dinitrostyryl derivative accompanied by spontaneous cyclization afforded the expected 4,7-dimethoxy-5,6-dimethylindole (**6**) as a white crystalline product in 63% yield.

Demethylation of the indole derivative **6** by reflux in benzene solution with anhydrous aluminium chloride followed by extraction with ether and concentration on the rotary evaporation gave the quinhydrone **7**. After appropriate sublimation *in vacuo* **7** afforded 5,6-dimethylindole-4,7-dione (**8**). By performing dealkylation on **6** under the same conditions, but stirring the ethereal extract with an aqueous solution of sodium dithionite and evaporating it in a nitrogen stream it was possible to isolate 5,6-dimethyl-4,7-dihydroxyindole (**9**) in a stable crystalline state.

The reaction sequence employed for the synthesis of 6-methyl-4,7-dimethoxyindole (**19**) is summarized in Scheme 2. In order to obtain 2,5-dimethoxy-4-methylbenzaldehyde (**15**), a method similar to that described by Smith and Austin (9), and previously partly employed without definite experimental details by Sayigh, Ulrich and Green (10), was employed. This procedure, starting from *m*-cresol, furnished the expected benzaldehyde in a satisfactory total yield of 36.5% in five steps.

2,5-Dimethoxy-4-methylbenzaldehyde (**15**) on direct nitration under mild conditions underwent loss of the formyl group, yielding the dimethoxybenzene **16**. Condensation of nitromethane with the benzaldehyde **15** provided 2,5-dimethoxy-4-methyl-β-nitrostyrene (**17**) directly in 64% yield. The poor yield (4-5%) experienced in the nitration of **17** to give 2,5-dimethoxy-4-methyl-6,β-dinitrostyrene (**18**) was considered to be due to the poor initial reactivity of the starting material and to the instability of the pro-

Scheme 2



duct. Reductive cyclization of **18** furnished 6-methyl-4,7-dimethoxyindole (**19**) in good yield (69%) as a viscous, colourless oil, which sublimed easily *in vacuo*.

In this case also, demethylation carried out as previously indicated followed by stirring the ethereal extract with aqueous sodium dithionite, yielded 4,7-dihydroxy-6-methylindole (**20**) in a stable crystalline state.

The synthesis of 4,7-dimethoxy-5-aminoindole (**27**) was carried out according to the sequence of steps outlined in Scheme 3. In a manner similar to that already described, 2,5-dimethoxy-3-nitrobenzaldehyde (**21**) was initially condensed with nitromethane yielding the corresponding styryl derivative **22** (54%). The nitration of **22** with cold 65% nitric acid afforded a trinitrostyryl derivative in 51% yield. Reduction with iron powdered in an ethanol-acetic acid solution failed to provide the expected indole derivative, clearly showing that the previous nitration had furnished 2,5-dimethoxy-3,4-β-trinitrostyrene (**23**). Therefore, in order to prepare 4,7-dimethoxy-5-aminoindole, compound **21** was nitrated giving 2,5-dimethoxy-3,6-dinitrobenzaldehyde (**25**) in 62% yield. Base-catalyzed condensation with nitromethane gave 2,5-dimethoxy-3,6,β-trinitrostyrene (**26**) (43% yield). Upon treatment with reducing agents as mentioned above, **26** furnished the cyclized product, 4,7-dimethoxy-5-aminoindole (**27**) in 9% yield, the structure of which was confirmed by ir, nmr and elemental analysis.

Attempts to demethylate **27** with anhydrous aluminium chloride in refluxing benzene only led to decomposition. For this reason we transformed **27** into the corresponding acetamido derivative **28** (65% yield), which underwent a convenient demethylation to the stable 4,7-dihydroxy-5-acetamidoindole (**29**), when the ethereal extract of the reaction mixture was shaken in an aqueous reductive medium (sodium dithionite).

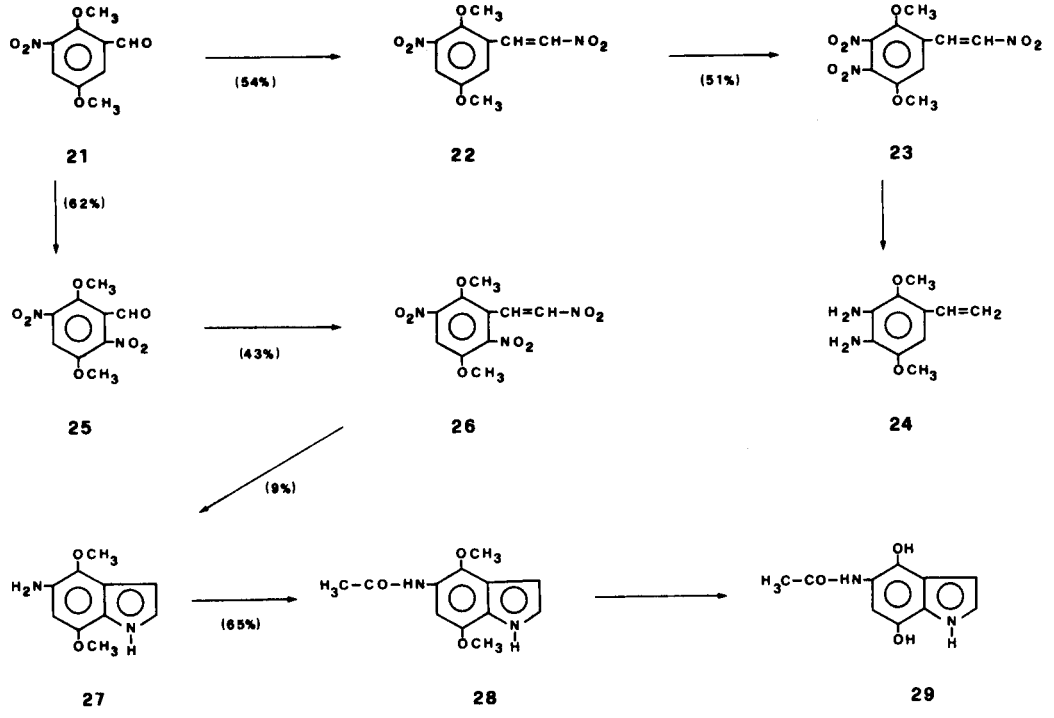
Results and Discussion.

In accordance with our expectations, the three 4,7-dimethoxyindole derivatives, now prepared by reduction of the 6,β-dinitrostyrenes, were demethylated by anhydrous aluminium chloride in refluxing benzene, yielding the corresponding stable 4,7-dihydroxy forms.

It is of interest to point out that the groups present at the C-5 or C-6 positions, although showing different electronic properties, confer remarkable stability on the dihydroxy forms, thus inhibiting a shift towards the dioxo species. Such behaviour may reasonably be due to the electron-donating effects of the substituents considered, that is, inductive for methyl groups and mesomeric for acetamido groups, with consequent dispersion of the partial negative charge from C-5 and C-6 of these 4,7-dihydroxyindoles.

We intend to test these newly prepared compounds for antimicrobial activity as soon as possible.

Scheme 3



EXPERIMENTAL

Melting points (uncorrected) were determined using a Büchi-Tottoli SPM-20 capillary melting point apparatus, which was heated at a rate of two degrees per minute. The samples were placed in the bath at 5° below the anticipated melting point. Infrared spectra were recorded with a Perkin-Elmer 457 spectrometer, calibrated with polystryene, as potassium bromide pressed discs or between sodium chloride plates. The absorptions are given in cm^{-1}. An Hitachi Perkin-Elmer R-24A or Bruker WP-60 spectrometer were used to record the ^1H-nmr spectra of all the compounds in deuterioacetone or deuteriodimethylsulfoxide using tetramethylsilane as an internal standard. In the case of multiplets, chemical shifts quoted were measured from the approximate center. Integrals correspond satisfactorily to the chemical formula. Elemental analyses were performed by the Microanalytical Laboratory of the Institute of Pharmaceutical Chemistry of the University of Padua. No attempt was made to optimize the yields of the reactions described. All evaporations were carried out *in vacuo* with a rotary evaporator.

3,6-Dimethoxy-1,2-dimethylbenzene (**1**), which was used as starting material for the synthesis of the compounds summarized in Scheme 1, was prepared by procedures quoted in the literature (9,11,12). The formylation of **1** (59% yield) was carried out according to the method described by Smith and Tess (11). *m*-Methylphenol **10**, the starting compound required for sequence outlined in Scheme 2, was purchased from Aldrich Chemical Co. 3-Nitro-2,5-dimethoxybenzaldehyde (**21**), which was used for the synthesis of the compounds outlined in Scheme 3, was prepared as described in our previous paper (14).

2,5-Dimethoxy-3,4-dimethyl-6-nitrobenzaldehyde (**3**).

Nitration was carried out with 65% nitric acid at 0° on slightly stirred aliquots of compound **2**. A reaction flask containing 1.4 g. of 2,5-dimethoxy-3,4-dimethylbenzaldehyde (m.p. 64°) was cooled in an ice water bath while 3 ml. of nitric acid added dropwise under stirring. Immediately following the addition, 15 g. of crushed ice was added to the resulting brown solution. After 15 minutes, the crude product was collected, thoroughly washed with water, dried and crystallized from toluene/petroleum ether to yield 0.26 g. of crude product, which was purified by sublimation at 2×10^{-2} torr (120°) giving yellow microcrystals (14% yield), m.p. 124°; ir (potassium bromide): 1692 (CHO), 1548 and 1367 (NO_2) cm^{-1}; nmr (deuterioacetone): δ 2.35 (6H, s, $2 \times CH_3$), 3.77-3.93 (6H, 2s, $2 \times OCH_3$), 10.19 (1H, s, CHO).

Anal. Calcd. for $C_{11}H_{13}NO_5$: C, 55.23; H, 5.48; N, 5.86. Found: C, 55.03; H, 5.55; N, 6.08.

2,5-Dimethoxy-3,4-dimethyl-β-nitrostyrene (**4**).

To a cooled mixture of 5.69 g. of 2,5-dimethoxy-3,4-dimethylbenzaldehyde **2** and 3.44 g. of nitromethane in 60 ml. of ethanol, a solution of 3.58 g. of potassium hydroxide in 6 ml. of water was added dropwise. The temperature was maintained at 4-5°. After standing for 48 hours at this same temperature, the yellow mixture was poured into 150 ml. of water, acidified with concentrated hydrochloric acid and then extracted with diethyl ether (3×300 ml.). The ethereal layer was washed first with a concentrated aqueous solution of sodium bisulfite and then with water. The solution was next dried over anhydrous sodium sulfate and evaporated under reduced pressure to give 7.99 g. of a needle-shaped residue, which was then dehydrated under reflux for 18 minutes with acetic anhydride (20 ml.) and fused sodium acetate (4 g.). After cooling, the mixture was diluted to 120 ml. with water and stirred to obtain a homogeneous suspension. The resulting precipitate was collected and washed several times with water. The crude product was crystallized from dioxane (12 ml.) giving woolly yellow crystals (3.5 g., 51% yield), m.p. 131°; ir (potassium bromide): 1622 (CH=CH), 1496, 1468 and 1324 (NO_2) cm^{-1}; nmr (deuteriodimethylsulfoxide): δ 2.12-2.16 (6H, 2s, $2 \times CH_3$), 3.64-3.80 (6H, 2s, $2 \times OCH_3$), 7.22 (1H, s, HC_6), 8.01-8.25 (2H, 2d, HC-β and HC-α).

Anal. Calcd. for $C_{12}H_{15}NO_4$: C, 60.75; H, 6.37; N, 5.90. Found: C, 60.89; H, 6.34; N, 5.79.

2,5-Dimethoxy-3,4-dimethyl-6,β-dinitrostyrene (**5**).

Nitration of small amounts of 2,5-dimethoxy-3,4-dimethyl-β-nitrostyrene **4** was performed with 65% nitric acid in an ice-water bath as mentioned above. Two nitrations, each beginning with 1.25 g. of starting material, produced a yellowish powder which was crystallized from ethanol, giving **5** as yellow-orange needles (1.4 g., 47% yield), m.p. 140°; ir (potassium bromide): 1631 (CH=CH), 1510, 1462, 1345, 1314 (NO_2) cm^{-1}; nmr (deuteriodimethylsulfoxide): δ 2.27 (6H, s, $2 \times CH_3$), 3.68-3.74 (6H, 2s, $2 \times OCH_3$), 7.81-7.55 (2H, 2d, HC-β and HC-α).

Anal. Calcd. for $C_{12}H_{14}N_2O_6$: C, 51.06; H, 5.00; N, 9.93. Found: C, 50.77; H, 5.09; N, 9.93.

4,7-dimethoxy-5,6-dimethylindole (**6**).

To a solution of 1.82 g. of 2,5-dimethoxy-3,4-dimethyl-6,β-dinitrostyrene **5** in 50 ml. of ethanol were added 8 g. of iron reduced powder and 40 ml. of glacial acetic acid. After refluxing for 30 minutes, the mixture was cooled and the iron filtered, being washed several times with boiling ethanol. The combined filtrates, diluted with 200 ml. of water and neutralized with sodium hydrogen carbonate, were then extracted with diethyl ether (3×600 ml.). The extracts were washed with water, dried over sodium sulfate and evaporated. The thick greenish residue (1.2 g.) was sublimed at 0.5×10^{-2} torr (115-120°) to give a colourless crystalline compound (0.83 g., 63% yield), m.p. 73-74°; ir (potassium bromide): 3393 (NH), 2982, 2922 and 2833 (CH_3, OCH_3) cm^{-1}; nmr (deuterioacetone): δ 2.17-2.21 (6H, 2s, $2 \times CH_3$), 3.73-3.82 (6H, 2s, $2 \times OCH_3$), 6.42-7.05 (2H, 2t, HC_3 and HC_2), 9.95 (NH, broad band).

Anal. Calcd. for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.82. Found: C, 70.40; H, 7.43; N, 6.68.

Demethylation of 4,7-Dimethoxy-5,6-dimethylindole.

Demethylation of compound **6** (0.6 g.) was carried out by refluxing for 6 hours in 50 ml. of dry benzene solution containing 6 g. of powdered anhydrous aluminium chloride. After cooling, the solid residue was broken up and treated with crushed ice. The mixture was extracted with ether (4×300 ml.) and the combined extracts were washed with water, dried over sodium sulfate and evaporated under reduced pressure to yield 0.59 g. of a crude residue.

a) Quinhydrone (**7**).

The violet residue was dissolved in 30 ml. of boiling ethyl acetate and the solution filtered, concentrated to *ca.* 10 ml. and, after the addition of 3 ml. of petroleum ether, left to crystallize at −10°, giving violet microcrystals which decomposed without melting above 350°. This product contains no methoxy groups. The analytical and spectral data support the structure of quinhydrone **7**; ir (potassium bromide): large absorption around 3300 (OH and NH) and typical peak at 1630 (C=O) cm^{-1}.

Anal. Calcd. for $C_{20}H_{20}N_2O_4$: C, 68.17; H, 5.72; N, 7.95. Found: C, 68.42; H, 5.65; N, 8.07.

b) 5,6-Dimethylindole-4,7-dione (**8**).

By evaporation to dryness of the ethyl acetate-petroleum ether solution, from which compound **7** was collected, a crude residue was obtained which by sublimation *in vacuo* (0.5×10^{-2} torr at 115-120°) yielded an orange crystalline product. This compound was purified by crystallization from toluene, orange-yellow needles, m.p. 213-214°; ir (potassium bromide): 3230 (NH sharp peak), 3108-3120 (CH_3), 1628-1655 (C=O) cm^{-1}; nmr (deuteriodimethylsulfoxide): δ 1.94 (6H, s, $2 \times CH_3$), 6.47 (1H, t, HC_3), 7.13 (1H, t, HC_2), 12.63 (1H, broad s, NH).

Anal. Calcd. for $C_{10}H_9NO_2$: C, 68.56; H, 5.18; N, 8.00. Found: C, 68.61; H, 5.09; N, 8.10.

4,7-Dihydroxy-5,6-dimethylindole (**9**).

In order to obtain the title dihydroxy compound, the experimental procedure used was similar to that now described for the preparation of **8**, except that after demethylation of 4,7-dimethoxy-5,6-dimethylindole (0.6 g.) by means of refluxing with aluminium chloride in benzene solution, the ethereal extract was shaken with an aqueous solution of sodium

hydrosulfite. The yellow extract was then distilled of under a vigorous nitrogen stream. The crude residue was dissolved in 20 ml. of boiling acetone. The brown-yellow solution was filtered and concentrated to *ca.* 6 ml. and 2 ml. of petroleum ether was added. After refrigeration at −10°, a brown crystalline compound was collected, m.p. 163-164° dec. The analysis for OCH_3 showed that this product was totally demethylated; ir (potassium bromide): broad adsorption from 3450 and 3090 (OH and NH) cm^{-1}; nmr (deuteriodimethylsulfoxide): δ 1.97, 1.99, 2.09 [6H, 3s (one coupled), 2 × CH_3], 6.55 (1H, t, HC_3), 7.16 (1H, t, HC_2), 7.32-7.45 (2H, 2 × OH), 12.56 (1H, broad s, NH).

Anal. Calcd. for $C_{10}H_{11}NO_2$: C, 67.78; H, 6.26; N, 7.91. Found: C, 67.66; H, 6.10; N, 7.65.

3-Methyl-4-aminophenol (**11**).

This compound was prepared from 3-methylphenol by a procedure similar to that described by Smith and Austin for obtaining *o*-xyloquinone (9). Sulfanilic acid (101 g.) was diazotized with 40.7 g. of sodium nitrite in the presence of 31 g. of sodium carbonate by means of acidification with a solution of 36% hydrochloric acid (122 ml.) in 350 ml. of water. The cold mixture of the diazo salt was slowly stirred into the cooled phenol solution. The mixture was allowed to stand overnight, then cooled to 5° and stirred with 195 g. of sodium hydrosulfite added in one portion. The cooling bath was removed and the mixture was stirred for 5 hours. The aminophenol was filtered by suction, washed with cold water and dried giving 52.5 g. of hazel powder (93% yield), m.p 173°. One analytical sample was sublimed *in vacuo* (10^{-2} torr at 135°). The white sublimate melted at 181°; ir (potassium bromide): 3390, 3283, 1345, 1288, 1222 (NH and OH) cm^{-1}; nmr (deuteriodimethylsulfoxide): δ 1.99 (3H, s, CH_3), 5.04 (3H, broad band, NH_2 and OH), 6.38 (3H, s, aromatic protons).

Anal. Calcd. for C_7H_9NO: C, 68.27; H, 7.37; N, 11.37. Found: C, 68.48; H, 7.48; N, 11.28.

Toluquinone (**12**).

This compound was prepared by the oxidative method of Arnold and Zaugg (12). Methylaminophenol (45 g.) were dissolved by warming in 1300 ml. of water containing 70 ml. of concentrated sulfuric acid. The resulting deep red solution of the amine salt was oxidized by the dropwise addition of it to a suspension of 346 g. of manganese dioxide in 1300 ml. of water containing 40 ml. of concentrated sulfuric acid, with continuous removal of the product by steam distillation. The distillate was cooled and the crude quinone in the distillate was removed. The filtrate was extracted with ether until colorless, the solvent was evaporated and the crystalline residue was added to the previous compound giving 30.6 g. of a yellow crystalline product of 68.5% yield, m.p. 68°; nmr (deuterioacetone): δ 2.02 (3H, d, CH_3), 6.44 (1H, m, HC_5), 6.75 (2H, s, HC_2 and HC_6).

Anal. Calcd. for $C_7H_6O_2$: C, 68.84; H, 4.95. Found: C, 68.69; H, 5.27.

2-Methylhydroquinone (**13**).

The title compound was obtained in 88% yield when an ethereal solution of the toluquinone (24 g. in 800 ml.) was shaken at room temperature with an excess of aqueous sodium hydrosulfite (180 g. in 800 ml. of water) until the yellow color disappeared (*ca.* 4 hours). The ethereal layer was separated, the aqueous phase was then extracted with ether and the extracts were combined and dried over sodium sulfate. Removal of the solvent yielded 21.5 g. (88%) of a white crystalline product, m.p. 126°; ir (potassium bromide): 3298 (broad band), 1382 and 1198 (OH) cm^{-1}; nmr (deuterioacetone): δ 2.15 (3H, s, CH_3), 6.52 (1H, s, HC_5), 6.57 (2H, s, HC_2 and HC_6), 7.39 (2H, s, OH).

Anal. Calcd. for $C_7H_8O_2$: C, 67.73; H, 6.50. Found: C, 67.65; H, 6.74.

2-Methylhydroquinone Dimethyl Ether (**14**).

2-Methylhydroquinone (84.9 g.) was dissolved in 900 ml. of methanol and a methanolic solution of potassium hydroxide (900 g. in 1800 ml.) was added with shaking as rapidly as possible. The mixture was heated at 65° and vigorously stirred while 900 ml. of dimethyl sulfate was added dropwise. After 8 hours of reflux, the reaction mixture was steam-distilled and the distillate was extracted with ether. After drying over sodium sulfate, the solvents were removed giving 89.6 g. (82% yield) of a pale yellow fluid. One analytical sample was purified by distillation at 20-22°/76 mm; ir (sodium chloride plates): 2987, 2936, 2833 (OCH_3, CH_3) cm^{-1}; nmr (deuterioacetone): δ 2.16 (3H, s, CH_3), 3.65-3.70 (6H, 2s, 2 × OCH_3), 6.68 (3H, s, aromatic protons).

Anal. Calcd. for $C_9H_{12}O_2$: C, 71.02; H, 7.95. Found: C, 70.71; H, 7.90.

2,5-Dimethoxy-4-methylbenzaldehyde (**15**).

Dimethyl ether **14** was formylated according to the procedure previously developed (11). Compound **14** (45 g.) was dissolved in dry tetrachloroethane (450 ml.). Oven dried zinc cyanide (80 g.) was added and the mixture stirred vigorously at room temperature while a continuous stream of dry hydrogen chloride was introduced. After 1 hour, the brown mixture was thoroughly cooled at 0° and 72 g. of anhydrous aluminium chloride was added. Hydrogen chloride was passed into the mixture for an additional 2 hours, maintaining the temperature at 65-70°. Additional dry zinc cyanide (40 g.) was then added, while continuing introduction of the dry gas for an additional 2 hours. Further zinc cyanide (40 g.) was added again and introduction of the gas was continued for an additional 4 hours. Sulfuric acid (550 ml., 2.5 *N*) was added slowly to the cooled mixture, which was then allowed to stand overnight at room temperature. The mixture was slowly heated to the boiling point and then steam distilled. The organic solvent came over first and was collected separately; this was followed by the whitish title aldehyde (42.1 g., 79% yield), which was crystallized from ethanol giving a crystalline white product, m.p. 85°; ir (potassium bromide): 3005, 2932, 2858, 2828 (OCH_3 and CH_3), 1655 (CHO) cm^{-1}; nmr (deuterioacetone): δ 2.22 (3H, s, CH_3), 3.78-3.85 (6H, 2s, 2 × OCH_3), 6.94-7.11 (2H, 2s, HC_3 and HC_6), 10.26 (1H, s, CHO).

Anal. Calcd. for $C_{10}H_{12}O_3$: C, 66.65; H, 6.71. Found: C, 66.54; H, 6.71.

The *p*-nitrophenylhydrazone crystallized from acetic acid and had m.p. 256-257°.

Anal. Calcd. for $C_{16}H_{17}N_3O_4$: C, 60.94; H, 5.43; N, 13.33. Found: C, 60.56; H, 5.46; N, 13.20.

2,5-Dimethoxy-4-methylnitrobenzene (**16**) (13).

The aldehyde **15** (0.65 g.) was pulverized and mixed with 2 g. of crushed ice in an ice bath, while 4 ml. of cooled 65% nitric acid was added dropwise with stirring. After about 40 minutes of stirring at 0°, the yellow compound was filtered by suction and washed with cold water. The crude product was crystallized from 75% ethanol giving fine yellow needles, m.p. 118-119°; ir (potassium bromide): 2918-2840 (OCH_3, CH_3), 1511, 1342, 1330 (NO_2) cm^{-1}; nmr (deuterioacetone): δ 2.25 (3H, s, CH_3), 3.85-3.89 (6H, 2s, 2 × OCH_3), 7.13-7.35 (2H, 2s, aromatic protons).

Anal. Calcd. for $C_9H_{11}NO_4$: C, 54.82; H, 5.62; N, 7.10. Found: C, 54.62; H, 5.79; N, 7.08.

2,5-Dimethoxy-4-methyl-β-nitrostyrene (**17**).

2,5-Dimethoxy-4-methylbenzaldehyde **15** (5.49 g.) was dissolved by heating in 60 ml. of ethanol. To the cold solution, while vigorously stirring in an ice bath, 3.43 g. of nitromethane diluted with 60 ml. of ethanol was added slowly. An aqueous cold solution of potassium hydroxide (3.55 g. in 6 ml. of water) was introduced dropwise and the mixture was then allowed to stand at 5° for 2 days. The suspension was then diluted with 200 ml. of ice water and acidified with concentrated hydrochloric acid. The mixture was extracted with ether (3 × 500 ml.). The combined extracts were washed first with a saturated aqueous solution of sodium bisulfite, then with water, and dried over sodium sulfate. Removal of the ether left 8.4 g. of a crude solid residue, which was dealcoholized by refluxing with 20 ml. of acetic anhydride and 4 g. of fused sodium acetate. After 20 minutes, the mixture was cooled, diluted with 100 ml. of ice water and stirred vigorously. The crude material which separated was collected and crystallized from 12 ml. of dioxane, yielding a yellow compound which was recrystallized from ethanol (35 ml.). Light yellow needles (4.34 g., 63.8 % yield) were isolated, m.p. 126°; ir (potassium bromide): 1612 (CH=CH), 1490-1352 (NO_2) cm^{-1}; nmr (deuterioacetone): δ 2.25 (3H, s, CH_3), 3.84-3.93 (6H, 2s 2 × OCH_3), 6.98-7.24 (2H, 2s, HC_3

and HC_6), 7.89-8.20 (2H, 2d, HC-β and HC-α).

Anal. Calcd. for $C_{11}H_{13}NO_4$: C, 59.18; H, 5.87; N, 6.28. Found: C, 59.25; H, 5.81; N, 6.42.

2,5-Dimethoxy-4-methyl-6,β-dinitrostyrene (**18**).

Nitration was performed with 65% nitric acid in an ice water bath on small amounts of 2,5-dimethoxy-4-methyl-β-nitrostyrene **17**. The yields were always very poor (4-5%), even when using precautionary measures in order to optimize conversion to the dinitrostyryl derivative.

Into a flask containing 1.5 g. of carefully powdered **17**, immersed in ice, cooled 65% nitric acid (6 ml.) was added with mixing. After 25 minutes of mild stirring, during which time the starting material at first melted and then changed into a solid yellowish mass, the reaction product was filtered and dried by suction. Crystallization from ethanol yielded a crude substance, m.p. 162°. One analytical sample was prepared by sublimation at 0.5×10^{-2} torr (150°) and recrystallization from ethanol giving a yellow crystalline product, m.p. 167-168°; ir (potassium bromide): 1629 (CH=CH), 1530, 1509, 1344, 1310 (NO_2) cm^{-1}; nmr (deuteriodimethylsulfoxide): δ 2.41 (3H, s, CH_3), 3.75-3.99 (6H, 2s, 2 × OCH_3), 7.36 (1H, s, HC_3), 7.47-8.02 (2H, 2d, HC-β and HC-α).

Anal. Calcd. for $C_{11}H_{12}N_2O_6$: C, 49.25; H, 4.51; N, 10.45. Found: C, 49.33; H, 4.67; N, 10.23.

4,7-Dimethoxy-6-methylindole (**19**).

The above dinitrostyrene **18** was converted into indole **19** in 69% yield by the method previously described for the reduction of the corresponding dimethyl compound **5**. The crude product was purified by sublimation *in vacuo* (0.8×10^{-2} torr at 65-70°), giving a colourless fluid, which did not undergo any modification on standing at room temperature; ir (sodium chloride plates): 3408 (NH), 2992, 2933 and 2840 (CH_3, OCH_3) cm^{-1}; nmr (deuterioacetone): δ 2.33 (3H, s, CH_3), 3.78-3.85 (6H, 2s, 2 × OCH_3), 6.29 (1H, s, HC_5), 6.49-7.12 (2H, 2t, HC_3 and HC_2), 10.10 (1H, broad band, NH).

Anal. Calcd. for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85; N, 7.33. Found: C, 69.19; H, 7.17; N, 7.35.

4,7-Dihydroxy-6-methylindole (**20**).

Demethylation of compound **19** (0.6 g.) was carried out by refluxing it for 6 hours in 40 ml. of benzene solution with the addition of 6 g. of powdered anhydrous aluminium chloride. After cooling, the solid residue was shattered and treated with ice-cold water. After extraction with ether (3 × 300 ml.), the combined extracts were washed first with an aqueous solution of sodium hydrosulfite and then with water, dried over sodium sulfate and evaporated to dryness in a nitrogen stream. Crystallization from toluene-petroleum ether produced the title compound **20** in a brown crystalline state, m.p. 158-159° dec; nmr (deuteriodimethylsulfoxide): δ 2.03-2.29 [3H, 2s (one coupled), CH_3], 7.16 (1H, s, HC_5), 7.21-7.32 (2H, 2t, HC_3 and HC_2), 11.93 (1H, broad s, NH).

Anal. Calcd. for $C_9H_9NO_2$: C, 66.24; H, 5.56; N, 8.58. Found: C, 66.54; H, 5.38; N, 8.40.

2,5-Dimethoxy-3,β-dinitrostyrene (**22**).

To a solution of 3.43 g. of 2,5-dimethoxy-3-nitrobenzaldehyde **21** in 80 ml. of ethanol and 2.07 g. of nitromethane, cold aqueous potassium hydroxide (2.16 g. in 4 ml. of water) was added in small portions in an ice bath. The solution was allowed to stand at 5° for 38 hours. Afterwards, 300 ml. of ice water were added to the resulting orange mixture and the solution was acidified to *p*H 1 with 36% hydrochloric acid. The aqueous layer was extracted into ether (3 × 600 ml.). The organic phase was washed with a concentrated aqueous solution of sodium bisulfite and then with water, dried (anhydrous sodium sulfate) and evaporated *in vacuo* to yield a solid residue which was dehydrated by refluxing for 15 minutes with 12 ml. of acetic anhydride and 2.4 g. of fused sodium acetate. Dilution with 60 ml. of water and stirring yielded a crude residue which was crystallized from dioxane (10 ml.) giving 2.2 g. (54% yield). After recrystallization from toluene the product had m.p. 164°; ir (potassium bromide): 1632 (CH=CH), 1528, 1478, 1426 and 1350 (NO_2) cm^{-1}; nmr (deuteriodimethylsulfoxide): δ 3.85 (6H, s, 2 × OCH_3), 7.63-7.78 (2H, 2d, HC_3 and HC_2), 8.00-8.36 (2H, 2d, HC-β and HC-α).

Anal. Calcd. for $C_{10}H_{10}N_2O_6$: C, 47.25; H, 3.97; N, 11.02. Found: C, 47.36; H, 3.93; N, 10.82.

2,5-Dimethoxy-3,4-β-trinitrostyrene (**23**).

2,5-Dimethoxy-3-β-dinitrostyrene **22** was nitrated with 99% cold nitric acid. Concentrated nitric acid (8 ml.) was added dropwise under stirring to 2.6 g. of **22** in a flask immersed in an ice bath. After 20 minutes at 0°, 15 g. of crushed ice was added and the resulting mixture stored at room temperature until the ice melted. The crude product was collected, washed with water and crystallized from ethanol (70 ml.). Recrystallization of the resulting solid (1.9 g.) from 30 ml. of absolute ethanol gave 1.6 g. (51% yield) of yellow needles, m.p. 153-154°; ir (potassium bromide): 1610 (CH=CH), 1538, 1490 and 1348 (NO_2) cm^{-1}; nmr (deuteriodimethylsulfoxide): δ 3.89-4.03 (6H, 2s, 2 × OCH_3), 7.97-8.46 (2H, 2d, HC-β and HC-α), 8.12 (1H, s, HC_6).

Anal. Calcd. for $C_{10}H_9N_3O_8$: C, 40.14; H, 3.03; N, 14.05. Found: C, 40.04; H, 3.01; N, 14.21.

Reduction of 2,5-Dimethoxy-3,4-β-trinitrostyrene.

Powdered iron (7.5 g.), was added to a mixture of **23** (1 g.) in 30 ml. of ethanol and 30 ml. of acetic acid and refluxed for 40 minutes. After suction filtration, water was added to the solution, which was next neutralized with sodium bicarbonate and extracted with ether. The extract was washed with water, dried over sodium sulfate and evaporated. The yellow-brown crude residue (0.63 g.) was sublimed *in vacuo* (120° at 0.5 × 10^{-2} torr). The sublimate, crystallized from benzene, yielded 2,5-dimethoxy-3,4-diaminostyrene **24** by addition of 50% of petroleum ether, m.p. 152-153°.

Anal. Calcd. for $C_{10}H_{14}N_2O_2$: C, 61.83; H, 7.27; N, 14.42. Found: C, 61.62; H, 7.10; N, 14.10.

2,5-Dimethoxy-3,6-dinitrobenzaldehyde (**25**).

Nitration of compound **21** with 99% nitric acid was performed as described in our previous paper (14). 2,5-Dimethoxy-3,6-dinitrobenzaldehyde **25** was a yellow solid and had m.p. 133°; ir (potassium bromide): 2958, 2903 (OCH_3), 1684 (CHO), 1529, 1345 (NO_2) cm^{-1}; nmr (deuterioacetone): δ 4.05-4.10 (6H, 2s, 2 × OCH_3), 8.11 (1H, s, HC_4), 10.24 (1H, s, CHO).

2,5-Dimethoxy-3,6-β-trinitrostyrene (**26**).

The procedure described above for the preparation of **22** was followed in an almost identical manner except for the purification method. The mixture of 7.6 g. of 2,5-dimethoxy-3,6-dinitrobenzaldehyde **25** in 180 ml. of ethanol, 4.8 g. of nitromethane and 4.7 g. of potassium hydroxide in 9 ml. of water was stored at 0° for 28 hours before being acidified with ice cold concentrated hydrochloric acid. Isolation with diethyl ether in the usual manner gave 7.9 g. of a gum, which was heated at reflux for 15 minutes with 30 ml. of acetic anhydride and 6 g. of fused sodium acetate. After the work-up, the mixture was hydrolyzed by stirring with 100 ml. of water at room temperature. After standing overnight at −15°, the aqueous phase was decanted and the residual gum was subjected to vacuum distillation (10^{-2} torr at 130°) to yield 3.8 g. (43%) of the title compound, from which no solid could be obtained when attempts were made to crystallize it from a variety of solvents. One analytical sample was prepared by resublimation giving a resinous light yellow oil; ir (sodium chloride plates): 1643-1612 (CH=CH), 1530, 1478, 1419 and 1350 (NO_2) cm^{-1}; nmr (deuterioacetone): δ 3.95-4.08 (6H, 2s, 2 × OCH_3), 7.80 (2H, s, HC-β and HC_4), 7.96 (1H, s, HC-α).

Anal. Calcd. for $C_{10}H_9N_3O_8$: C, 40.14; H, 3.03; N, 14.05. Found: C, 40.48; H, 2.85; N, 13.88.

5-Amino-4,7-dimethoxyindole (**27**).

Reduction of a solution of **26** (1.98 g.) in a mixture of 55 ml. of ethanol and 55 ml. of acetic acid with 15 g. of iron powder under reflux for 45 minutes, following the preceding procedure of ethereal extraction (3 × 700 ml.) after suitable *p*H adjustment with aqueous sodium bicarbonate, gave 0.94 g. of a sticky brown residue. This residue was fractionally

sublimated *in vacuo* (0.2×10^{-1} torr) first at 80-90°, in order to separate the secondary whitish product and then at 130-140°. On standing at room temperature the yellow oil, thickened into a dense mass, which quickly browned when exposed to air; ir (sodium chloride plates): 3398-3336 (NH_2; NH), 2936, 2834 (OCH_3), 1590 (NH) cm^{-1}; nmr (deuterioacetone): δ 3.79 (8H, 2 × OCH_3 and NH_2), 6.21 (1H, s, HC_6), 6.33-7.06 (2H, HC_3 and HC_2), 10.08 (1H, NH, s broad band); (deuteriodimethylsulfoxide): δ 3.71 (3H, s, OCH_3), 3.78 (5H, s, OCH_3 and NH_2), 6.16 (1H, s, HC_6), 6.22-7.01 (2H, 2t, HC_3 and HC_2).

Anal. Calcd. for $C_{10}H_{12}N_2O_2$: C, 62.48; H, 6.29; N, 14.58. Found: C, 62.12; H, 6.36; N, 14.50.

5-Acetamido-4,7-dimethoxyindole (**28**).

Acetic anhydride (7 ml.) was added to a solution of crude **27** (0.53 g.) in 50 ml. of dry benzene and 7 ml. of pyridine. The mixture was refluxed for 6 hours. Ice and water were then added, the solvents were removed by evaporation and the residue (0.72 g.) was distilled *in vacuo* (0.5×10^{-2} torr at 100-105°) yielding 0.42 g. of an oil (65.5%) which soon thickened into a dense mass. This compound showed facile hygroscopicity; ir (sodium chloride plates): 3318 (NH), 1684-1658 (NH-CO), 1240 (C-O) cm^{-1}; nmr (deuteriodimethylsulfoxide): δ 2.09 (3H, s, CH_3), 3.86 (6H, s, 2 × OCH_3), 6.49 (1H, t, HC_3), 7.07 (1H, s, HC_6), 7.22 (1H, t, HC_2), 9.11 (1H, broad s, NHCO), 11.22 (1H, broad s, NH).

Anal. Calcd. for $C_{12}H_{14}N_2O_3$: C, 61.52; H, 6.02; N, 11.96. Found: C, 61.36; H, 6.06; N, 12.09.

5-Acetamido-4,7-dihydroxyindole (**29**).

Demethylation of compound **28** (0.34 g.) was carried out by heating in 30 ml. of benzene solution containing 3 g. of powdered anhydrous aluminium chloride for 6 hours over a water bath in a flask equipped with a reflux condenser protected with a calcium chloride drying tube. After cooling, the solid mass was broken up and treated with 40 ml. of ice-cold water. The organic layer was then separated and the aqueous layer extracted with diethyl ether. The combined extracts were washed at first with a concentrated solution of sodium dithionite, then with water, dried over sodium sulfate and evaporated to dryness in a nitrogen stream. The crude residue (0.25 g.) was dissolved in 40 ml. of boiling ethyl acetate, the solution filtered and concentrated to *ca.* 3-4 ml. in a rotary evaporator. After cooling at −10°, a yellow-brown crystalline product was collected by suction, m.p. >300°. This compound contains no methoxy groups; nmr (deuteriodimethylsulfoxide): δ 2.08-2.21 (3H, 2s, CH_3), 6.59 (1H, t, HC_3), 7.19 (1H, t, HC_2), 7.28 (2H, HC_5 and OH), 9.59 (1H, broad s, NHCO), 9.98 (1H, broad s, NH).

Anal. Calcd. for $C_{10}H_{10}N_2O_3$: C, 58.25; H, 4.89; N, 13.58. Found: C, 58.28; H, 4.88; N, 13.62.

REFERENCES AND NOTES

(1) In the course of demethylation trials of 4,7-dimethoxyindoles with the usual halo acids, black polymeric compounds were isolated, the structures of which have been recently reported; G. Malesani, F. Galiano, A. Pietrogrande and G. Rodighiero, *Tetrahedron*, **34**, 2355 (1978).

(2) G. Malesani, U. Quintily and G. Chiarelotto, *Z. Naturforsch.*, **34b**, 333 (1979).

(3) G. Malesani, G. Rigatti and G. Rodighiero, *Tetrahedron Letters*, **48**, 4173 (1969).

(4) G. Malesani, G. Chiarelotto, F. Marcolin and G. Rodighiero, *Farmaco, Ed. Sci.*, **25**, 972 (1970).

(5) G. Malesani and G. Chiarelotto, *Gazz. Chim. Ital.*, **105**, 293 (1975).

(6) J. S. Webb, D. B. Cosulich, J. H. Mowat, J. B. Patrick, R. W. Broschard, W. E. Meyer, R. P. Williams, C. F. Wolf, W. Fulmor, C. Pidacks and J. E. Lancaster, *J. Am. Chem. Soc.*, **84**, 3185 (1962); *Idem., ibid.*, **84**, 3187 (1962); *Idem., ibid.*, **84**, 3188 (1962).

(7) J. B. Patrick, R. P. Williams, W. E. Meyer, W. Fulmor, D. B. Cosulich, R. W. Broschard and J. S. Webb, *ibid.*, **86**, 1889 (1964).

(8) M. J. Weiss, G. S. Redin, G. R. Allen, A. C. Dornbush, H. L. Lindsay, J. F. Poletto, W. A. Remers, R. H. Roth and A. E. Sloboda, *J. Med. Chem.*, **11**, 742 (1968), and references cited therein.

(9) L. J. Smith and F. L. Austin, *J. Am. Chem. Soc.*, **64**, 528 (1942).

(10) A. A. R. Sayigh, H. Ulrich and M. Green, *J. Chem. Soc.*, 3482 (1964).

(11) L. J. Smith and R. W. Tess, *J. Am. Chem. Soc.*, **66**, 1523 (1944).

(12) R. T. Arnold and H. E. Zaugg, *ibid.*, **63**, 1317 (1941).

(13) Attempts at nitrating **15** (2,5-dimethoxy-4-methylbenzaldehyde) under still milder conditions, *i.e.*, with shorter reaction times or more dilute cold nitric acid, were unsuccessful. No reactions occurred and the starting material was recovered unchanged.

(14) G. Malesani, F. Marcolin, G. Rodighiero and P. Benetti, *Eur. J. Med. Chem.-Chim. Ther.*, **5**, 255 (1970).