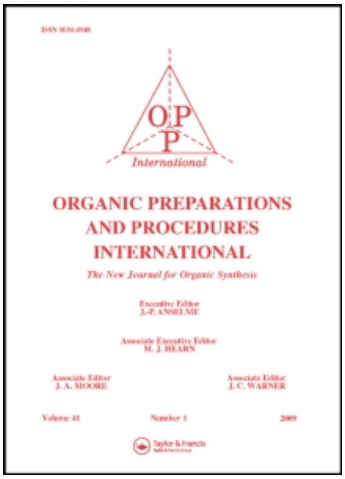

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CONDENSATION OF FORMALDEHYDE WITH PHLOROGLUCINOL AND ITS MONOMETHYL ETHER

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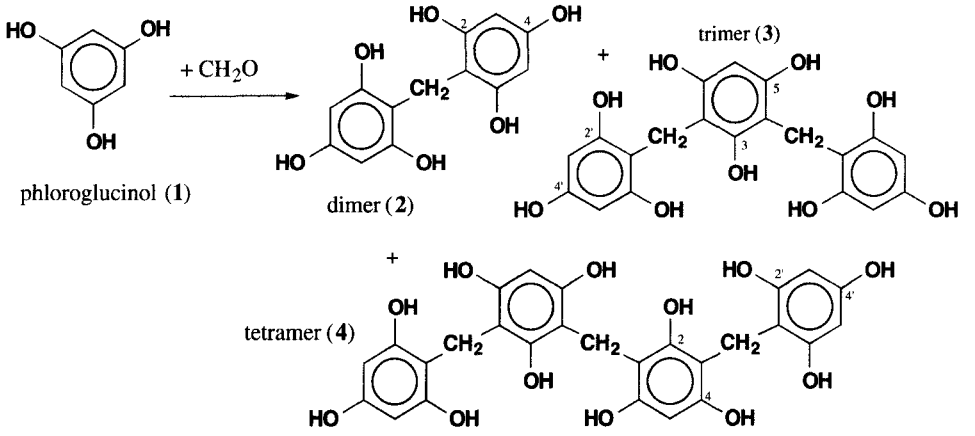
Our interest in the development of efficient procedures for cleaving the interflavanoid bonds of condensed tannins has prompted us to investigate the synthesis of phloroglucinol-aldehyde condensation products as convenient tannin model compounds. The reaction of phenol with formaldehyde in alkaline medium, first reported in 1872 by von Baeyer,[1] is well known and gives thermosetting resins of considerable industrial importance.[2] Under carefully controlled experimental conditions, cyclic condensation products (so-called "calixarenes") are formed in high yields with para-substituted phenols.[3] The acid-catalyzed reaction of resorcinol with aldehydes other than formaldehyde and subsequent derivatization produces tetrameric "cavitands" with interesting host-guest complexation properties.[4]

The condensation reactions of aldehydes with phloroglucinol (1,3,5-benzenetriol, **1**), the most nucleophilic polyhydric phenol, have been studied less extensively. The formation of *bis*(2,4,6-trihydroxyphenyl)methane ("dimer", **2**) from **1** and formaldehyde was first described by Councler[5] and Boehm[6]. Boehm proved its structure by reductive degradation which afforded phloroglucinol and 2-methylphloroglucinol as main products as well as small amounts of di- and trimethylphloroglucinol (from higher oligomers). More recently, Hemingway[7] and Foo[8,9] have shown that, in the presence of acid, aldehydes react rapidly and reversibly with **1** in aqueous methanol or ethanol to form initially soluble dimers and ultimately insoluble polymers; however, they did not elucidate the product structures.

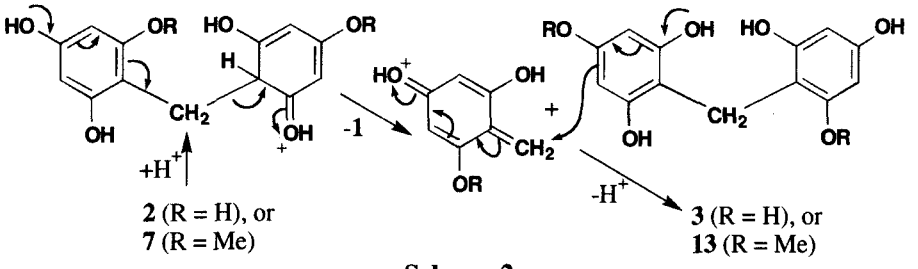
The high nucleophilicity of the unsubstituted ring carbons of phloroglucinol leads to rapid polycondensation in alkaline solution. This is also observed in strongly acidic media (conc. H_3PO_4, conc. HCl) because of the reversible nature of the electrophilic aromatic substitution: competing electrophilic attack by the protonated aldehyde (condensation, Scheme 1) and by protons (protolytic cleavage) give ultimately the product of lowest solubility in the chosen solvent, *i.e.*, the polymer (molar ratio **1**/CH_2O = 1:1 if linear, 2:3 if cross-linked), even if **1** and aldehyde are used in the molar ratio of 2:1 required for dimer formation.

By generating formaldehyde (0.5 mole per mole of phloroglucinol) slowly by sulfuric acid-catalyzed hydrolysis of trioxane in EtOAc solution, we obtained 9% dimer (**2**) and 2% 2,4-*bis*(2',4',6'-trihydroxybenzyl)phloroglucinol ("trimer", **3**) from anhydrous phloroglucinol after 18 hrs



Scheme 1

reflux, vs. 16% **2**, 13% **3** and some polymer (red precipitate) after 74 hrs reflux. The trimer was the main product (32% yield, based on CH_2O, vs. 8% **2**) of the acetic acid-catalyzed reaction of formalin with **1** in 10% aqueous ethanol (18 hrs/25°) and the exclusive product isolated (in 36% yield) when the condensation was carried out in dilute aqueous HCl as described by Boehm,[6] while mainly *bis*(2,4,6-trihydroxy-3-(2',4',6'-trihydroxybenzyl)phenyl)methane ("tetramer", **4**) precipitated after 18 hrs from an acidified solution of the aldehyde and **1** in 50% aqueous methanol. Unreacted phloroglucinol was detected by TLC in all cases. Using formalin or methylal as source of formaldehyde, water as solvent and dilute HCl as catalyst afforded the highest yields (78-88%) of di- and trimer, with **3** predominating after 4-5 days at 25° (**2/3** molar ratio ~ 1:4) and **2** predominating (**2/3**~7:1) after 12 hrs at 4°. The observed reversal of the dimer/trimer ratio on extending the reaction time and raising the temperature, when virtually all of the available aldehyde has already reacted, indicates slow cleavage of the sp^2-sp^3 bond of **2** and re-condensation of the transient quinone methide fragment with a second dimer molecule (Scheme 2), which gradually shifts the equilibrium toward the less soluble trimer (and



Scheme 2

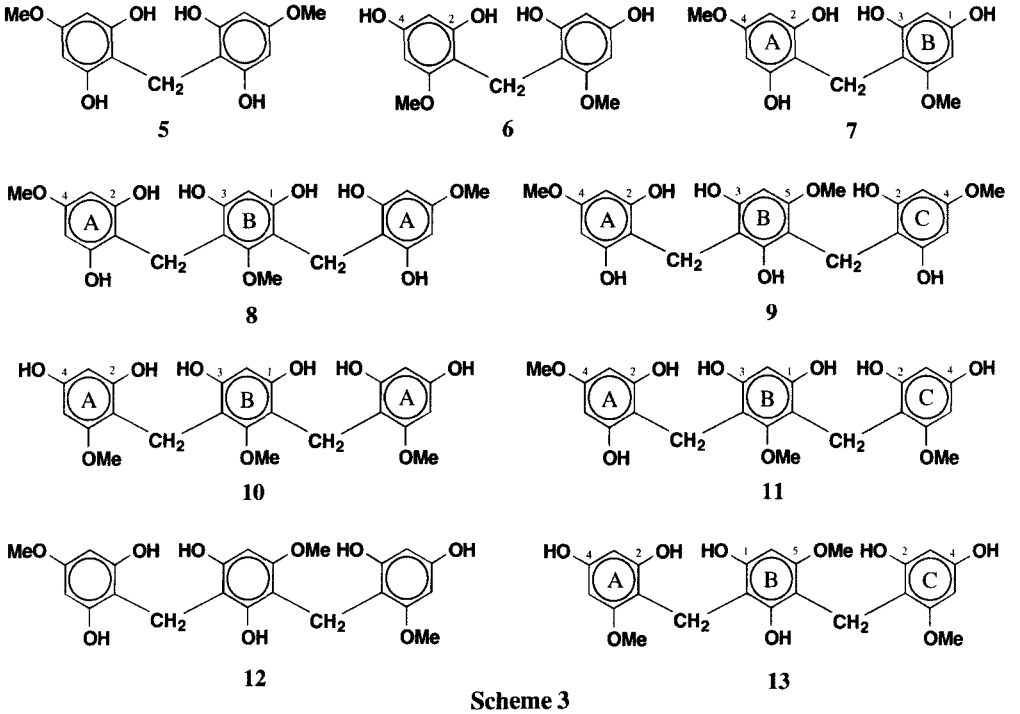
some tetramer). The formation of **1** and **3** on treatment of **2** with dilute aqueous HCl for several days at 25° and the isolation of **4** as main product when 50% aqueous methanol is used as solvent confirm this interpretation.

Phloroglucinol (**1**) and its condensates **2, 3** and **4** are readily separated by TLC on cellulose or by GPC on Sephadex LH20 (see Experimental Section), and characterized by their distinctly different NMR spectra. The absorption signals of the aromatic (δ 5.99-6.11) and methylene protons (δ 3.68-3.72) shift slightly downfield with increasing molecular weight; the substantial downfield shift of the OH proton signals of **3** (from δ 8.09 to 9.75) as one proceeds from the periphery toward the center of the molecule is believed to reflect increasing degrees of intramolecular hydrogen bonding. The carbon chemical shifts (δ 17.0-18.1 for $>CH_2$, δ 96.5-97.6 for ArH, δ 106.4-108.0 for $ArCH_2$-, and δ 156.5-158.0 for ArOH), on the other hand, do not change significantly with increasing degree of condensation; however, the presence of the next higher homologue is revealed by the appearance of an additional set of signals for the new monomeric unit. None of the NMR spectra showed signals characteristic of benzhydrols, which is in accord with the high reactivity of these intermediates.[10]

5-Methoxyresorcinol offers two nucleophilic sites for electrophilic attack by formaldehyde: *ortho* or *para* to the methoxy group; the former is sterically less accessible but statistically favored by a factor of two. The structures of the three possible dimeric isomers and the six possible trimeric isomers are shown in Scheme 3: *bis*(2,6-dihydroxy-4-methoxyphenyl)methane (**5**), *bis*(2,4-dihydroxy-6-methoxyphenyl)methane (**6**), 4-(2,6-dihydroxy-4-methoxybenzyl)-5-methoxyresorcinol (**7**), 4,6-*bis*(2,6-dihydroxy-4-methoxybenzyl)-5-methoxyresorcinol (**8**), 2,4-*bis*(2,6-dihydroxy-4-methoxybenzyl)-5-methoxyresorcinol (**9**), 4,6-*bis*(2,4-dihydroxy-6-methoxybenzyl)-5-methoxyresorcinol (**10**), 4-(2,6-dihydroxy-4-methoxybenzyl)-6-(2,4-dihydroxy-6-methoxybenzyl)-5-methoxyresorcinol (**11**), 2-(2,6-dihydroxy-4-methoxybenzyl)-4-(2,4-dihydroxy-6-methoxybenzyl)-5-methoxyresorcinol (**12**) and 2,4-*bis*(2,4-dihydroxy-6-methoxybenzyl)-5-methoxyresorcinol (**13**).

We detected all but one (**12**) of these compounds in the mixture of products formed from 5-methoxyresorcinol and formalin in dilute aqueous acid. Among the dimers the unsymmetrical structure **7** was found to be the major isomer (molar ratio **7/6/5** = 6.7:2.7:1), while **13** and **11** prevailed among the trimers. The trimers **13, 11** and **10** are derived from the major dimers **7** and **6** by electrophilic attack of a 2-methoxy-4,6-dihydroxybenzyl cation *ortho* to a methoxy group (Scheme 2: R = Me). The formation of **5, 8, 9** (minor) and **12** (not detected), on the other hand, requires attack by the less favorable 4-methoxy-2,6-dihydroxybenzyl cation. Thus, the condensation is not regiospecific but substitution at the aromatic carbons *ortho* to MeO is preferred, *i.e.*, two *ortho*-hydroxy groups destabilize the intermediate benzylic cation. This result agrees with the reported[6] isolation of 4-methyl-5-methoxyresorcinol as product of reductive dimer cleavage, though Boehm failed to detect trimeric condensates and their cleavage to 2,4-dimethyl-5-methoxyresorcinol and C-methylated dimers. As observed with phloroglucinol, the trimers predominated at room temperature (trimer/dimer ratio ~ 1.1 after 18 hrs) and in the second crops (trimer/dimer ratio>10) obtained when the acidic aqueous filtrates of the initially formed precipitates were allowed to stand at 25° for an additional day. Dimers

prevailed over trimers (dimer/trimer ratio ~ 4/3), as estimated by integration of the ArH (5.9-6.3), MeO and CH_2 regions (δ 3.6-4.0) of their ^1H NMR spectra, when the temperature was lowered to 4° and the reaction time shortened to 12 hrs.



Scheme 3

In summary, the acid-catalyzed reaction of 5-methoxyresorcinol with formaldehyde proceeds in high yield (77% based on CH_2O) and gives mainly trimeric (39%) and dimeric (16%) condensation products in aqueous solution (18 hrs at 25°). With phloroglucinol as nucleophile, low-molecular weight condensation products can be isolated only by choosing weakly acidic reaction conditions, low temperature, low aldehyde concentrations, short reaction times and solvents in which the oligomeric products are insoluble. Even then, to stop the reaction at the dimer stage is difficult.

EXPERIMENTAL SECTION

Melting points (uncorrected) were recorded on a Fisher-Johns melting point apparatus, NMR spectra on a Bruker spectrometer (400 MHz). Chemical shifts are reported relative to the acetone-d_6 peaks centered at δ 2.04 (^1H NMR) and 29.80 ppm (^{13}C NMR). Analytical thin layer chromatography (TLC) was performed on Merck Cellulose F (0.1 mm) DC-Plastikfolien (eluant: 6% aq. HOAc), gel permeation chromatography (GPC) on Sephadex LH20 (eluant: 95% EtOH). Elemental analyses were determined on a Carlo Erba Elemental Analyzer model 1106. Formalin (Formaldehyde Solution, 40% USP), phloroglucinol (dihydrate) and methylal were purchased from Fisher Scientific, 5-methoxyresorcinol (98%) and trioxane (99%) from Aldrich Chemical Company.

***bis*(2,4,6-Trihydroxyphenyl)methane (dimer, 2).**- To a stirred solution of 1.62 g (10.0 mmoles) phloroglucinol dihydrate in 200 mL water were added 5 mL conc. HCl and 0.375 mL formalin (equiv. to 5.0 mmoles CH_2O) at 4°. The flocculent white precipitate which started to form after 20 min. was collected after 16 hrs of refrigeration, washed with ice-cold water and dried *in vacuo* (P_2O_5) to give a beige solid (1.18g) consisting of **2** (64% yield) and **3** in the molar ratio 7:1 (by ^1H NMR). The dimer (TLC: R_f 0.35) was separated from the trimer (R_f 0.19) by GPC (37x3.8 cm column, flow rate 5 mL/min, 10 mL/test tube) of 200 mg crude product; it eluted in fractions 39-51 (trimer: fractions 65-88).

Anal. Calcd. for $C_{13}H_{12}O_6 \cdot 2H_2O$: C, 55.32; H, 5.00. Found: C, 55.90; H, 4.94

^1H NMR (Me_2CO-d_6): δ (ppm) 3.68 (2H, s, CH_2), 5.99 (4H, s, H-3/5), 8.09 (2H, s, OH-4) and 9.05 (4H, s, OH-2/6). ^{13}C NMR (Me_2CO-d_6): δ (ppm) 17.0 (CH_2), 96.5 (C-3/5), 106.7 (C-1), 156.5 (C-2,6) and 158.0 (C-4), in close agreement with the chemical shifts in Me_2CO-d_6/D_2O reported by G. W. McGraw *et al.*[11] (assignments for C-4 and C-2/6 reversed). The peracetate[11] was obtained by acetylation with Ac_2O/pyridine: ^1H NMR (Me_2CO-d_6): δ (ppm) 2.20 (12H, AcO-2/6), 2.23 (6H, AcO-4), 3.65 (2H, CH_2) and 6.87 (4H, H-3/5).

2,4-*bis*(2',4',6'-Trihydroxybenzyl)phloroglucinol (trimer, 3).- a) Boehm's procedure.[6] Formalin (231 µL, 3.08 mmoles CH_2O) was added to a stirred solution of 1.00 g (6.17 mmoles) phloroglucinol dihydrate in 90 mL 4.0 M aq. HCl. The initially formed white precipitate turned orange within 5 min. It was filtered, washed (5x50 mL water), resuspended in water and extracted with ether (3x150 mL), leaving the main (polymeric) portion undissolved in the aqueous layer. The clear ether layer was dried ($MgSO_4$) and filtered, the solvent evaporated, and the yellow, oily residue dissolved in 15 mL EtOAc. On addition of benzene (200 mL), filtration and drying *in vacuo* (P_2O_5) nearly pure **3** (35% yield) was obtained as amorphous tan powder.

^1H NMR (Me_2CO-d_6): δ (ppm) 3.70 (4H, s, CH_2), 6.00 (4H, s, H-3'/5'), 6.10 (1H, s, H-5), 8.13 (2H, s, H-4'), 9.07 (2H, s, OH-4/6), 9.23 (4H, s, OH-2'/6') and 9.75 (1H, s, OH-2). ^{13}C NMR (Me_2CO-d_6): δ (ppm) 17.6 (CH_2), 96.6 (C-3'/5'), 97.5 (C-5), 106.4 (C-1'), 107.8 (C-1/3), 153.0 (C-2), 154.6 (C-4/6), 156.3 (C-2'/6') and 158.0 (C-4').

b) To a stirred solution of 325 mg (2.00 mmoles) phloroglucinol dihydrate in 35 mL water were added 75 µL formalin (equiv. to 1.0 mmole CH_2O) and 1.0 mL conc. HCl at 25°. A flocculent white precipitate started to form after 20 min. The reaction mixture was allowed to stand 16 hrs at 25°. Filtration, washing (water) and drying *in vacuo* (P_2O_5) afforded a beige solid (197 mg) consisting of **3** (77% yield) and **2** in the molar ratio 4:1 (by ^1H NMR). The trimer **3** (TLC: R_f 0.14) was purified by GPC (see dimer above).[12]

Anal. Calcd. for $C_{20}H_{18}O_9 \cdot 2H_2O$: C, 54.80; H, 5.06. Found: C, 53.40; H, 4.81

***bis*(2,4,6-Trihydroxy-3-(2',4',6'-trihydroxybenzyl)phenyl)methane (tetramer, 4).**- When a solution of 6.49 g (40.0 mmoles) phloroglucinol dihydrate and 1.77 mL formaldehyde (20.0 mmoles) in 720 mL 0.33 M aq. HCl was allowed to stand 4 days at 25°, a beige solid (3.60 g, 80% yield) precipitated slowly which, after filtration, washing and drying (see above), was found to contain dimer **2**, trimer **3** and tetramer **4** in the approximate molar ratio 1:5:0.4. A second crop (136 mg) obtained from

the acidic filtrate after another 5 days at 25° contained a higher proportion of tetramer (TLC: R_f 0.06) as well as small amounts of higher oligomers. A sample of tetramer was purified by GPC (see dimer: fractions 94-136). ^{1}H NMR (Me_2CO-d_6): δ (ppm) 3.69 (4H, s, periph. CH_2), 3.72 (2H, s, central CH_2), 6.01 (4H, s, H-3'/5'), 6.11 (2H, s, H-5), 8.20, 9.11 and 9.6 (br s) (ArOH). ^{13}C NMR (Me_2CO-d_6): d (ppm) 17.5 (periph. CH_2), 18.1 (central CH_2), 96.5 (C-3'/5'), 97.6 (C-5), 106.3 (C-1'), 107.6 (C-3), 108.0 (C-1), 153.0 (C-2), 154.4 (C-4), 154.6 (C-6), 156.3 (C-2'/6') and 158.0 (C-4'). NMR signals characteristic of the branched isomer (tris(2',4',6'-trihydroxybenzyl)-phloroglucinol) were conspicuously absent. The tetramer **4** was also the main component (17% yield) of the precipitate formed from **1** and CH_2O (molar ratio 3:1) in 2.4 M HCl in 50% aq. MeOH (18 hrs/25°).[12]

Conversion of Dimer 2 to Trimer 3.- a) A mixture of **2** and **3** (31 mg, molar ratio 7:1, free of phloroglucinol **1**) was suspended in 3.5 mL 0.33 M aq. HCl, stirred 72 hrs at 25° and extracted with EtOAc (3x2 mL). The cream-colored solid (22 mg) left after extraction with EtOAc (3x2 mL), washing (4x2 mL water), drying ($MgSO_4$) of the organic layer and solvent evaporation was found (by ^{1}H NMR) to contain **2, 3** and **1** in the molar ratio 4.3:1:0.3, corresponding to the conversion of approx. 12 mole-% **2** to 6% **3** and 6% **1**.

b) The solution of a mixture of **2** and **3** (31mg, molar ratio 7:1, free of **1**) in 1.5 mL MeOH and 1.5 mL 0.8 M aq. HCl was stirred 24 hrs at 25°. Solvent evaporation gave a reddish-brown solid residue (30 mg) containing **2, 3** and **1** (molar ratio 1.5:1:3.0) as well as higher oligomers, i.e., most of the dimer had been converted to condensation products of higher molecular weight.

Condensation of Formaldehyde with 5-Methoxyresorcinol.- a) Formalin (75 µL, 1.00 mmole CH_2O) and 1.0 mL conc. HCl were added to a solution of 5-methoxyresorcinol (285 mg, 2.00 mmoles) in 35 mL water. The white precipitate which started to form after 10 min was filtered after 18 hrs at 25°, washed acid-free and dried *in vacuo* (217 mg). It was estimated (from the peak areas of the CH_2 and MeO protons in the ^{1}H NMR spectrum) to contain trimeric (**8 - 13**) and dimeric (**5 -7**) condensation products in the approximate molar ratio 1.1:1. GPC (column: 30x2.0 cm, flow rate 1.6 mL/min, 8 mL/test tube) permitted a rough separation of the mixture into 5-methoxyresorcinol (fractions 7-14, 52mg), dimers (fr.15-18, 16% yield), trimers (fr.19-24, 39%) and oligomers (fr. 25-34). In the dimer fractions, the components **5, 6** and **7** were readily identified and quantitated (molar ratio 1:2.7:6.7) by NMR spectroscopy. ^{1}H NMR (Me_2CO-d_6) of **5**: δ (ppm) 3.65 (6H, s, OMe), 3.70 (2H, s, CH_2), 6.05 (4H, s, ArH) and 9.13 (4H, s, OH); **6**: δ (ppm) 3.69 (2H, s, CH_2), 3.88 (6H, s, OMe), 6.00 (2H, d, J 2.3 Hz, H-3), 6.08 (2H, d, J 2.3 Hz, H-5, 8% enhanced by saturation at δ 3.88), 8.19 (2H, s, OH-4) and 8.30 (2H, s, OH-2); **7**: δ (ppm) 3.65 (3H, s, MeO-4), 3.69 (2H, s, CH_2), 3.93 (3H, s, MeO-5), 6.00 (2H, s, H-3/5), 6.09 (1H, d, J 2.3 Hz, H-2), 6.14 (1H, d, J 2.3 Hz, H-6, 8% enhanced by satn. at δ 3.93), 8.01 (1H, s, OH-1), 8.52 (2H, s, OH-2/6) and 8.99 (1H, s, OH-3). The isomeric trimers were partially separated by flash chromatography on silica gel 60 (40-63 µm, Merck #9385), using EtOAc/hexanes (2:3) as eluant. Compound **13** was the major component of all collected fractions, comprising an estimated 70% of the entire trimer mixture, followed by **11** (~20%), small amounts of **9** and **10**, and a trace of **8**. ^{1}H NMR (Me_2CO-d_6): see table; NOE of **13**: H-5 (ring A) doublet at δ 6.07

enhanced 9% by saturation of MeO at δ 3.89, H-6 (ring B) singlet at δ 6.13 enhanced 14% by saturation of MeO at δ 3.83, H-5 (ring C) doublet at δ 6.10 enhanced 7% by saturation of MeO at δ 3.91.

b) To a stirred, ice-cooled solution of 5-methoxyresorcinol (283 mg, 2.00 mmoles) in 35 mL water were added 0.30 mL conc. HCl and 75.0 μL formalin (1.00 mmole CH_2O). The light brown precipitate (132 mg) formed after 24 hrs refrigeration was filtered, washed acid-free and dried *in vacuo* (P_2O_5); it was found by integration of the ^1H NMR spectrum to consist of dimers and trimers in the approximate molar ratio 4:3. A second crop of condensation products (91 mg), isolated from the acidic aqueous filtrate after another 14 hrs refrigeration, contained >90% trimers as well as dimers and traces of higher oligomers.

TABLE. ^1H NMR Chemical Shifts of Trimeric Condensation Products of 5-Methoxyresorcinol[a]

Compound		**8**	**9**	**10**	**11**	**13**
Ring A	MeO	3.64	3.64	3.91	3.64	3.89
	H-3	6.05	6.01	6.02d	5.98	5.99d
	H-5	-	-	6.09d	-	6.07d
	CH_2(AB)	3.73	3.76	3.71	3.73	3.75
Ring B	MeO	3.95	3.85	3.95	3.95	3.83
	ArH	6.26	6.19	6.22	6.21	6.13
	CH_2(BC)	-	3.73	-	3.71	3.71
Ring C	MeO	-	3.65	-	3.91	3.91
	H-3	-	5.98	-	6.09d	6.04d
	H-5	-	-	-	6.14d	6.10d

a) Solvent: acetone-d_6; d = doublet (J 2.2 Hz), all other signals are singlets.

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12. The water of hydration tenaciously held by the hydrophilic condensation products is not removed by vacuum drying at 25° and prolonged heating leads to the gradual interconversion of oligomers and change of composition. Thus, the C/H percentages vary with the drying conditions which are difficult to reproduce [and misled early investigators (ref 5 and 6) to incorrect conclusions about the degree of condensation]. Tetramer **4** (monohydrate: 4.80%H, 57.14%C calcd) isolated in only small amounts by GPC, was always found (by NMR) to be contaminated with some pentamer (dihydrate: 4.90%H, 57.14%C calcd) of virtually indistinguishable elemental composition. It was, therefore, not submitted for elemental analysis.

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