215. *Some Derivatives of Catechol and Pyrogallol. Part I.*

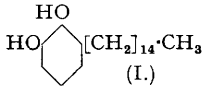
By Robert D. Haworth and David Woodcock.

In view of the vesicancy attributed to catechol derivatives occurring in natural lacquers, a number of 3- and 4-acyl- and -alkyl-catechols containing from C_4 to C_{18} side chains have been synthesised. A similar range of 4-acyl- and -alkyl-pyrogallols have been prepared.

None of the compounds exhibit marked vesicancy.

Certain species of the *Rhus*, *Melanhorrhœa*, and *Semecarpus* families are the common sources of lacquers. Contact with these plants produces a typical dermatitis, and some fatal cases of poisoning have been reported. The chemistry of the lacquers has been investigated by several workers, and in particular by Majima (*Ber.*, **1907**, **40**, 4392; **1909**, **42**, 1419, 3664; **1912**, **45**, 2727; **1913**, **46**, 4080, 4089; **1915**, **48**, 1593, 1597, 1603, 1606; **1920**, **53**, 1907; **1922**, **55**, 172, 191) who claimed that the skin irritant properties resided in an oily fraction which was purified by distillation in a high vacuum. The active principles, which vary in constitution with the origin of the lacquer, are catechol derivatives with lengthy and unsaturated side chains, but it is probable that the purified distillates contain a number of closely related compounds differing in the degree of unsaturation of the side chain.

Urushiol, which occurs in Chinese and Japanese lacquers (*Rhus vernicefera*), in Indian marking nut (*Semecarpus anacardium*) (Pillay and Siddiqui, *J. Ind. Chem. Soc.*, **1931**, **8**, 517), and in the leaves and branches of poison ivy (*Rhus toxicodendron*) (Hill, Mattacocci, and Graham, *J. Amer. Chem. Soc.*, **1934**, **56**, 2736) is probably a mixture of (I), (II), and (III) and possibly more highly unsaturated compounds of the same carbon skeleton.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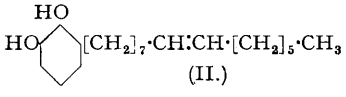
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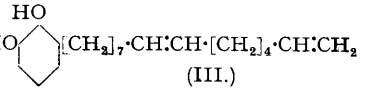
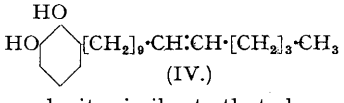

(III.)

As the composition of the oil approximates to (III) the latter is usually referred to as urushiol and (I) and (II) are regarded as tetra- and dihydro-urushiol respectively. These conclusions are supported by oxidation and bromination experiments, by the observation that catalytic reduction of crude urushiol gives high yields of the crystalline tetrahydro-derivative (I), and by the synthesis of the dimethyl ether of (I).

Recently Backer and Haack (*Rec. Trav. chim.*, 1938, **57**, 225) have isolated a crystalline substance named renghol from renghos fruit (*Semecarpus heterophylla*). Structure (IV), isomeric with dihydrourushiol (II), has been established by ozonisation and by an additional synthesis of the dimethyl ether of dihydrorenghol.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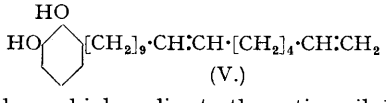
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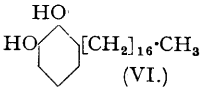
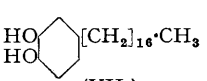

(VI.)

A complexity similar to that observed with urushiol applies to the active oil, laccol, which has been isolated from Indochinese lac from Tonkin (*Rhus succedanea*), Formosa lac (*Semecarpus vernicifera*), Tsuti-urushi lac (*Rhus ambigua* or *orientalis*) and from the fruit of *Gluta Renghos* (Bertrand, Backer, and Haack, *Bull. Soc. chim.*, 1939, **6**, 1690). The experiments of Majima suggest that laccol is composed of (V) together with di- and tetra-hydro-derivatives, and reduction of crude laccol gives high yields of tetrahydrolaccol (VI) which has been synthesised. More recently Brooks (*Actualités Scientifiques et Industrielles*, 1934, No. 94; *Bull. Soc. chim.*, 1933, **53**, 432) has described laccol as a crystalline solid, m. p. 23°.

The irritant properties of Burmese lac (*Melanorrhœa usitata*) according to Majima are due to an oil, thitsiol, containing a mixture of closely related 4-alkylated catechol derivatives differing in degree of unsaturation of the side chain, but the inferior yields of tetrahydrothitsiol obtained by catalytic reduction indicate that the oil is also contaminated with much neutral and possibly unrelated material. The structure (VII) for tetrahydrothitsiol has been confirmed synthetically, but the position of the double bonds in the natural product has not been established.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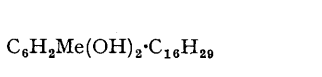
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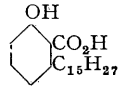
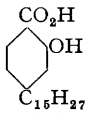
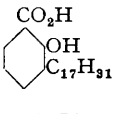

(IX.)

The Indochinese lac from Cambodia, unlike that from Tonkin, is derived from *Melanorrhœa laccifera* Bertrand and Brooks (*Compt. rend.*, **1933**, **197**, 661) isolated the active principle, moreakol, as a solid, m. p. 28°

containing two double bonds, which is isomeric with thitsiol and laccol and which probably contains a nuclear substituted methyl group as in (VIII). The orientation of the nucleus, apart from the catechol grouping, and the position of the ethylenic linkages in the side chains have not been determined.

Two naturally occurring salicylic acid derivatives are known to have skin irritant action. Anacardic acid, obtained from the husk of *Anacardium occidentale* and *A. orientale* and from the shell of the cashew nut have been investigated by Smit (*Proc. K. Akad. Wetensch. Amsterdam*, 1931, **34**, 165), Pillay (*J. Ind. Chem. Soc.*, 1935, **12**, 226, 231), and Gokhale, Patel, and Shah (*Current Science*, 1940, **9**, 362). It probably has


(X.)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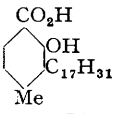
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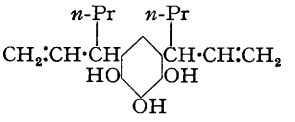
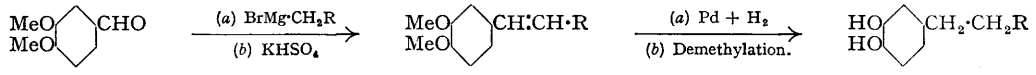

(XIII.)

structure (IX) or (X), containing two ethylenic linkages at unknown positions in the side chain. Pelandjauic acid, obtained from the wood of *Pentaspadon motleyi* Hook, and investigated by van Rombergh and van Veen (*Proc. K. Akad. Wetensch. Amsterdam*, 1929, 1204; 1930, 589, 690) is regarded as a mixture of (XI) and (XII), but neither the orientation of the substituents nor the positions of the two ethylenic linkages in the side chain has been established.

The irritant properties of a few synthetic phenols have been reported; Kawai (*Sci. Papers Inst. Phys. Chem. Res. Tokyo*, 1927, **6**, 53) states that 3-geranylcatechol, an oil obtained by the action of heat on *O*-geranylcatechol, produces strong itching which lasts for several weeks, and Hurd and Parrish (*J. Amer. Chem. Soc.*, 1935, **57**, 1731) mention the activity of a number of substances such as dihexenylpyrogallol (XIII).

Several 4-acylcatechols have been prepared by Miller, Hartung, Rock, and Crossley (*J. Amer. Chem. Soc.*, 1938, **60**, 7) and Majima (*Ber.*, 1915, **48**, 1599) by condensing catechol with aliphatic acids in the presence of zinc chloride (Nencki reaction), and the Fries reaction has been employed by Rosenmund and Lohfert (*Ber.*, 1928, **61**, 2605) for other compounds of the series. Some alkylpyrogallols have been prepared by the Nencki reaction by Hart and Woodruff (*J. Amer. Chem. Soc.*, 1936, **58**, 1957). In our hands the Nencki reaction was in general more convenient and gave high yields in the pyrogallol series. Clemmensen reduction of the ketones gave 4-alkyl-catechols and -pyrogallols in satisfactory yields, but in order to obtain good analytical results it is advisable to distil the products in a high vacuum before crystallisation in order to remove traces of inorganic impurities.

Owing to the inaccessibility of some of the higher aliphatic acids, particularly those containing an odd number of carbon atoms, the conversion of veratraldehyde into dimethoxyphenyl-olefins and -paraffins, which yield alkylcatechols on demethylation, has been developed along the following lines:—



The reactions proceeded smoothly as far as the demethylation stage where it became necessary to determine optimum conditions for each; hydriodic and hydrobromic acids were used under the three conditions described in the Experimental section. It was necessary to free all the products by distillation in a high vacuum from small amounts of catechol and high boiling by-products of the reaction. Using *o*-veratraldehyde instead of veratraldehyde, Backer and Haack (*loc. cit.*) employed these reactions for the synthesis of tetrahydrolaccol dimethyl ether, and we have explored the reactions widely in the synthesis of 3-alkylcatechol derivatives.

The vesicant properties of the alkyl phenols together with a few acyl derivatives were tested by Dr. K. Harrison by applying a 2 mm. diameter drop of 10 per cent. w/w solution in benzene, alcohol, or chloroform to the skin of the upper arm of two men, the spread of the drop being controlled to cover a circular area of 1·5 mm. diameter. None of the compounds produced vesication, but several caused erythema and the symbols E— and E in Table III indicate slight reddening and reddening respectively; the subscript numerals are the number of days which elapse before erythema is apparent. The following are the main points emerging from the investigation:

(1) Catechols are more irritant than the corresponding pyrogallol derivatives.

(2) In the 4-alkylcatechol series the members from butyl to octyl have approximately the same activity which decreases with increasing length of the side chain.

(3) In the 3-alkylcatechol series optimum activity is found in the 3-heptyl derivative, but there is no pronounced difference in the activity of 3- and 4-alkylcatechols.

(4) Acyl-catechols and -pyrogallols are completely inactive.

(5) The slight activity of 4-amylresorcinol suggests that the irritant properties are not limited to the catechol series.

Specimens of 4-butyl- and 4-heptyl-catechol were oxidised in ethereal solution with silver oxide according to the method of Willstätter *et al.* (*Ber.*, 1904, **37**, 4744; 1908, **41**, 2580; 1911, **44**, 2172). The corresponding *o*-quinones were obtained as red oils which could not be purified, but in contrast to the parent catechol derivatives they were entirely lacking in skin irritant properties.

Experimental.

I. *Nencki Reaction.*—Two methods were used. (*a*) The phenol (1 mol.), aliphatic acid (2·1 mols.), and anhydrous zinc chloride (1 mol.) were heated at 135—140° for 2 hours. The mixture was cooled and treated with dilute hydrochloric acid, and the product taken up in ether. The extract was washed three times with water in order to remove most of the unreacted phenol, and the residue from the dried ethereal solution was distilled at 0·5 mm. Unchanged acid was recovered, and after distillation the 4-acylphenol was crystallised.

(*b*) Equal weights of the phenol, aliphatic acid, and anhydrous zinc chloride were heated at 135—140° for 2 hours. The mixture was cooled and treated with dilute hydrochloric acid; if solid, the product was collected and washed well with water to remove unchanged phenol; if liquid, the lower aqueous layer was separated and the upper layer washed several times with water. The residue was taken up in ether, dried, the solvent removed, and the residue treated with light petroleum (b. p. 40—60°) which removed unreacted acid. The residue was then distilled at 0·5 mm.

This method (*b*) was introduced for the more complex acylphenols, and increased yields of these were obtained. It is probable that the yields of lower members could be increased by the use of (*b*) but this point has not been tested in many cases.

II. *Fries Reaction.*—Two methods were used. (*a*) The catechol diester (1 mol., prepared by heating catechol with 2 mols. of acid chloride until evolution of hydrogen chloride ceased), catechol (1 mol.), and aluminium chloride (2 mols.) in nitrobenzene (20 mols.) were heated at 80—100° for 2 hours. The product was cooled and decomposed with dilute hydrochloric acid, and the nitrobenzene removed in steam; the product, isolated with ether, was purified by distillation at 0·5 mm.

(*b*) The phenol (1 mol.) and aluminium chloride (1·5 mols.) were stirred in carbon disulphide (20 parts) during the gradual addition of acid chloride (1 mol.). After warming at 40—50° the solvent was removed and the residue heated at 150° for 4 hours. Dilute hydrochloric acid was added and the product, isolated with ether, was purified as in II (*a*). The properties of the new acylphenols are included in Table I together with those showing marked m. p. discrepancies from those reported in the literature.

Table I.

Acylphenol.	M. p. *ex* benzene.	Method of prep.	Yield (%).	Found (%). C.	Found (%). H.	Formula.	Required or calc. (%). C.	Required or calc. (%). H.
4-Heptanoylcatechol	93—94° Lit (i) gives 79°.	II*b*	50	70·1	8·2	$C_{13}H_{18}O_3$	70·3	8·1
4-*Nonanoylcatechol*	92—93	II*a*	40	72·3	9·1	$C_{15}H_{22}O_3$	72·0	8·8
4-*Undecanoylcatechol*	105	I*b*	15	73·7	9·7	$C_{17}H_{26}O_3$	73·4	9·3
4-*Dodecanoylcatechol*	97—98	I*b*	20	73·7	10·0	$C_{18}H_{28}O_3$	74·0	9·6
4-*Tetradecanoylcatechol*	98—99	I*b*	20	74·6	10·1	$C_{20}H_{32}O_3$	75·0	10·0
4-*Hexadecanoylcatechol*	99—100	I*b*	10	75·7	10·4	$C_{22}H_{36}O_3$	75·8	10·3
4-Octadecanoylcatechol	100—101 Lit (ii) gives 70°.	I*b*	10	76·2	10·7	$C_{24}H_{40}O_3$	76·6	10·6
4-Butyroylpyrogallol	90—91 Lit (iii) gives 101°.	I*a*	60	61·0	6·2	$C_{10}H_{12}O_4$	61·2	6·1
4-Hexanoylpyrogallol	72—74 Lit (iii) gives 86°.	I*a*	50	64·1	7·3	$C_{12}H_{16}O_4$	64·3	7·1
4-*Octanoylpyrogallol*	73—74	I*a*	40	66·5	8·2	$C_{14}H_{20}O_4$	66·7	8·0
4-*Undecanoylpyrogallol*	76—77	I*a*	35	68·7	8·9	$C_{17}H_{26}O_4$	69·4	8·8
4-*Dodecanoylpyrogallol*	76—77	I*a*	30	70·2	9·3	$C_{18}H_{28}O_4$	70·1	9·1
4-*Tetradecanoylpyrogallol*	82—84	I*a*	25	70·8	9·9	$C_{20}H_{32}O_4$	71·4	9·5
4-*Hexadecanoylpyrogallol*	89—90	I*a*	30	72·2	10·0	$C_{22}H_{36}O_4$	72·5	9·9
4-*Octadecanoylpyrogallol*	91—93	I*a*	25	72·9	10·2	$C_{24}H_{40}O_4$	73·5	10·2

Lit (i) Miller, Hartung, Rock, and Crossley (*loc. cit.*).
,, (ii) Rosenmund and Lohfert (*loc. cit.*).
,, (iii) Hart and Woodruff (*loc. cit.*).

III. *Clemmensen Reduction.*—The acylphenol (1 part), amalgamated zinc (5 parts), and concentrated hydrochloric acid (5 parts) were refluxed for 24 hours. The product was extracted with ether, washed with sodium bicarbonate solution, dried, and distilled at 0·5 mm. Yields varied from 50 to 65%.

IV. *Demethylation Process.*—(*a*) *Preparation of dimethoxyphenylolefins.* The Grignard reagent, prepared from magnesium (1 mol.) and the appropriate alkyl bromide or iodide (1 mol.) in ether (10 parts), was gradually added with stirring to an ice-cold solution of veratraldehyde or *o*-veratraldehyde (6 g.) in ether. The suspension was refluxed for 2 hours and decomposed with 2N-sulphuric acid, and the ether layer was washed with sodium hydrogen sulphite solution, dried, and the solvent removed. The residual oil was heated for ½ hour with potassium hydrogen sulphate (0·7 g.) at 180°, taken up in ether, washed with dilute sodium hydroxide, the ether removed, and the product distilled at 0·5 mm.

The b. ps. gradually increase from 85°/0·5 mm. for 2 : 3-dimethoxyphenyl-Δ^1-butene to 190°/0·5 mm. for the corresponding Δ^1-pentadecene. Table II includes only the olefins and alkylveratroles which have been obtained crystalline.

Table II.

Dimethoxyphenylolefin or alkylveratrole.	M. p. *ex* alcohol.	Method of prep.	Yield (%).	Found (%). C.	Found (%). H.	Formula.	Required or calc. (%). C.	Required or calc. (%). H.
3 : 4-*Dimethoxyphenyl*-Δ^1-*heptadecene*	40—41°	IV*a*	60	80·3	11·4	$C_{25}H_{42}O$	80·2	11·2
3 : 4-Dimethoxyphenylheptadecane (tetrahydrothitsiol dimethyl ether)	53—54	IV*b*	100	79·7	11·5	$C_{25}H_{44}O_2$	79·8	11·7
2 : 3-*Dimethoxyphenyl*-Δ^1-*pentadecene*	52	IV*a*	35	79·6	11·2	$C_{23}H_{38}O_2$	79·8	11·0
2 : 3-*Dimethoxyphenylpentadecane*	34—36	IV*b*	100	79·1	11·6	$C_{23}H_{40}O_2$	79·3	11·5

(*b*) *Catalytic reduction.* The dimethoxyphenylolefin (5 g.) in alcohol (10 c.c.) was shaken with 10% palladium–carbon (0·5 g.) in hydrogen until gas absorption ceased (4—12 hours depending on the activity of the catalyst). After filtration from the catalyst, the solvent was removed and the residue distilled at 0·5 mm.

(*c*) *Demethylation.* (i) The reduction product (5 g.) was heated in a sealed tube at 180° with hydrobromic acid (15 c.c.; *d* 1·72) and a trace of red phosphorus for 4 hours. After dilution with water the product was isolated with ether, washed with sodium bicarbonate solution, dried, and the solvent removed; the residue was fractionated at 0·5 mm. The first drops of distillate frequently contained catechol, and a high-boiling fraction was always obtained, but this has not been examined. The alkylcatechol was obtained from the intermediate fraction.

(ii) The methyl ether (5 g.) was refluxed with hydrobromic acid (40 c.c.; *d* 1·5) and glacial acetic acid (40 c.c.) for 5—6 hours. The mixture was diluted with water, and the product, isolated with ether, was washed with water and sodium bicarbonate solution, and distilled as described in (i).

TABLE III.

Alkylphenol.	M. p.	Solvent.	Method of prep.	Found (%). C.	H.	Required or calc. (%). Formula.	C.	H.	Vesicancy tests.	
4-Butylcatechol	39—41° Lit (i) gives b. p. only.	Ligroin	III	72·1	8·7	$C_{10}H_{14}O_2$	72·3	8·4	E_1	E_1
4-Amylcatechol	57—59 Lit (i) gives b. p. only.	Ligroin	III or IV*c*	73·2	9·0	$C_{11}H_{16}O_2$	73·3	9·0	E_1	E
4-Hexylcatechol	Oil b. p. 145—150°/ 0·5 mm. Lit (i) gives 164°/ 5 mm.	—	III	74·1	9·3	$C_{12}H_{18}O_2$	74·2	9·3	E_1	E_1
4-Heptylcatechol	65—67 Lit (i) gives 40°.	Ligroin	III	75·0	9·7	$C_{13}H_{20}O_2$	75·0	9·6	E_1	E_1
4-Octylcatechol	57—58 Lit (i) gives 40°.	Ligroin	III	75·7	10·0	$C_{14}H_{22}O_2$	75·6	10·0	E_1	E_1
4-*Nonylcatechol*	68	Ligroin	III	75·9	10·2	$C_{15}H_{24}O_2$	76·3	10·2	E_1–	E_1–
4-*Undecylcatechol*	81—82	Ligroin	III	76·9	10·7	$C_{17}H_{28}O_2$	77·3	10·6	E_4	E_4–
4-*Dodecylcatechol*	75—76	Ligroin	III	78·0	10·5	$C_{18}H_{30}O_2$	77·7	10·8	E_1	E_4–
4-*Tetradecylcatechol*	65—67	Ligroin	III	78·1	10·9	$C_{20}H_{34}O_2$	78·4	11·1	E_4	E_4
4-*Hexadecylcatechol*	75—76	Ligroin	III	78·7	11·4	$C_{22}H_{38}O_2$	79·0	11·4	nil	nil
4-Heptadecylcatechol (tetrahydrothitsiol)	93—95 Lit (iv) gives 95°.	Acetic acid	IV*c*	79·1	11·6	$C_{23}H_{40}O_2$	79·3	11·5	E_1–	nil
4-*Octadecylcatechol*	78—79	Ligroin	III	79·3	11·6	$C_{24}H_{42}O_2$	79·5	11·6	nil	nil
3-*Butylcatechol*	33—36	Ligroin	IV*c* (i)	72·2	8·5	$C_{10}H_{14}O_2$	72·3	8·4	E_1	E_1–
3-*Amylcatechol*	34—35	Ligroin	IV*c* (ii)	73·1	9·1	$C_{11}H_{16}O_2$	73·3	9·0	nil	nil
3-*Hexylcatechol*	30—31	Ligroin	IV*c* (ii)	74·2	9·2	$C_{12}H_{18}O_2$	74·2	9·3	E_1	E_1–
3-*Heptylcatechol*	Solid at 5°	—	IV*c* (ii)	75·0	9·6	$C_{13}H_{20}O_2$	75·0	9·6	E_1	E_4
3-*Octylcatechol*	Oil b. p. 135—140°/ 0·4 mm.	—	IV*c* (ii)	75·5	9·9	$C_{14}H_{22}O_2$	75·6	10·0	E_1–	E_1–
3-Pentadecylcatechol (tetrahydrourushiol)	57—59 Lit (iv) gives 59°.	Ligroin	IV*c* (iii)	78·6	11·4	$C_{21}H_{36}O_2$	78·7	11·2	E_1	E_1–
3-Heptadecylcatechol (tetrahydrolaccol)	59 Lit (iv) gives 63°.	Ligroin	From laccol.	79·0	11·5	$C_{23}H_{40}O_2$	79·3	11·5	E_4	nil
4-Butylpyrogallol	82—83 Lit (iii) gives 88°.	Benzene	III	65·8	7·9	$C_{10}H_{14}O_3$	65·9	7·7	nil	nil
4-Hexylpyrogallol	98—99 Lit (iii) gives 104°.	Benzene	III	68·3	8·7	$C_{12}H_{18}O_3$	68·6	8·6	E_4	nil
4-Heptylpyrogallol	109—111 Lit (iii) gives 116°.	Benzene	III	69·5	9·1	$C_{13}H_{20}O_3$	69·6	8·9	E_1–	E_1
4-*Octylpyrogallol*	106—107	Benzene	III	70·6	9·5	$C_{14}H_{22}O_3$	70·6	9·2	E_1	E_1–
4-*Nonylpyrogallol*	109—110	Benzene	III	71·3	9·5	$C_{15}H_{24}O_3$	71·4	9·5	E_4	nil
4-*Undecylpyrogallol*	110—111	Benzene	III	73·0	10·3	$C_{17}H_{28}O_3$	72·8	10·0	E_1–	E_1–
4-*Dodecylpyrogallol*	109—110	Benzene	III	73·2	10·3	$C_{18}H_{30}O_3$	73·5	10·2	nil	nil
4-*Tetradecylpyrogallol* ...	112—113	Benzene	III	74·3	10·4	$C_{20}H_{34}O_3$	74·5	10·6	nil	nil
4-*Hexadecylpyrogallol* ...	116	Benzene	III	75·2	10·8	$C_{22}H_{38}O_3$	75·4	10·9	nil	nil
4-*Octadecylpyrogallol*	114—115	Benzene	III	75·9	10·9	$C_{24}H_{42}O_3$	76·2	11·1	nil	nil
4-Amylresorcinol	71—72 Lit (i) gives 71°.	Ligroin	III	73·0	9·0	$C_{11}H_{16}O_2$	73·3	8·9	E_1–	nil

Lit (i), (ii), and (iii)—as for Table I. Lit (iv), Majima (*loc. cit.*).

(iii) The ether (5 g.) was refluxed with hydriodic acid (25 c.c.; *d* 1·88) and a trace of red phosphorus for 5 hours. Water was added and the product, isolated with ether, was purified as described in (i) and (ii). The most suitable method gave yields of about 60%. Table III includes the properties of the alkylphenols.

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