

216. Some Derivatives of Catechol and Pyrogallol. Part II.

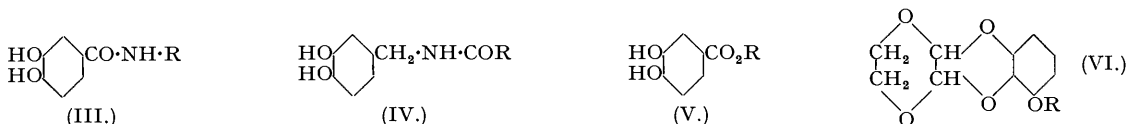
By ROBERT D. HAWORTH and ALEX. H. LAMBERTON.

A miscellaneous selection of 4-substituted catechol derivatives containing saturated or unsaturated side chains have been prepared, and a new method has been employed for the preparation of 3-alkoxycatechols, based upon the alkylation and subsequent hydrolysis of 2 : 3-(3'-hydroxy-*o*-phenylene)dioxydioxan (VI; R = H). The compounds lack marked vesicant properties.

In order to examine the influence of two catechol groupings on vesicancy 1 : 5-di-(3' : 4'-dihydroxyphenyl)pentane (I) and 1 : 3-di-(3' : 4'-dihydroxyphenyl)cyclohexane (II) have been prepared from di-(3' : 4'-dimethoxybenzylidene)acetone and 2 : 6-di-(3' : 4'-dimethoxybenzylidene)cyclohexanone respectively by two stage reduction and subsequent demethylation. Both substances were non-irritant to the skin.



Numerous unsuccessful attempts have been made to prepare catechol derivatives with ethylenic side chains, but amides of types (III) and (IV) have been prepared in which R represents an unsaturated radical.



3 : 4-Carbonyldioxybenzoyl chloride (Barger, *J.*, 1908, 567) reacts with allylamine and undec-10-enylamine (Krafft and Tritschler, *Ber.*, 1900, **33**, 3583) to yield *N*-allyl- (III; R = CH₂:CH:CH₂) and *N*-undec-10-enyl- (III; R = [CH₂]₉:CH:CH₂) *protocatechuic amides* respectively.

N-(3 : 4-Dihydroxybenzyl)sorbic amide (IV; R = CH:CH:CH:CH₃) and *N*-(3 : 4-dihydroxybenzyl)-undec-10-enoic amide (IV; R = [CH₂]₈:CH:CH₂) have been prepared by Einhorn's method (*Annalen*, 1905, **343**, 207) from catechol and *N*-methylsorbic amide or *N*-methylundec-10-enoic amide (Jones and Pyman, *J.*, 1925, 2588) respectively. These four unsaturated amides were non-irritant; *allyl protocatechuate* (V; R = CH₂:CH:CH₂) and *undec-10-enyl protocatechuate* (V; R = [CH₂]₉:CH:CH₂), prepared from 3 : 4-carbonyldioxybenzoyl chloride and allyl or undec-10-enyl alcohol (Grun and Wirth, *Ber.*, 1922, **55**, 2208) respectively, were also inactive.

Attempts to prepare 3-alkoxycatechols by the direct alkylation of pyrogallol led to a mixture of mono-, di-, and tri-alkyl derivatives, but pyrogallol carbonate has been converted into 3-methoxycatechol by the action of diazomethane and subsequent hydrolysis (Hillemann, *Ber.*, 1938, **71**, 41).

As considerable hydrolysis of the carbonate group occurred when the methylation was effected with methyl iodide and potassium carbonate in acetone solution, this method of protection was abandoned. We have found that 2 : 3-dichlorodioxan reacts with pyrogallol in warm benzene solution to give 2 : 3-(3'-hydroxy-*o*-phenylene)dioxydioxan (VI; R = H) in 33% yield. No difficulty was experienced in alkylation of the phenolic group, and *ethyl*, *propyl*, *butyl*, *amyl*, *hexyl*, *heptyl*, *octyl*, *hexadecyl*, and *allyl* derivatives have been prepared. Hydrolysis of the dioxan group presented difficulties; the compounds were stable towards alkalis, and brown amorphous products were obtained by boiling with mineral acids. The formation of these undesirable products is probably due to the action of the liberated glyoxal on the catechol derivative and they could be avoided to a large extent by hydrolysis with hydrochloric acid in the presence of urea. In this way 3-ethoxy- and 3-propoxy-catechol were prepared, but higher members were very resistant to hydrolysis and poor yields were obtained. The physiological tests show that some of these substances produce erythema, and maximum activity is observed with 3-propoxy- and 3-butoxy-derivatives.

EXPERIMENTAL.

Di-(3' : 4'-dimethoxybenzylidene)acetone.—Veratraldehyde (20 g.), acetone (4 c.c.), and 8% sodium hydroxide (12 c.c.) were kept at 15° for 20 hours. The solid (16 g.), m. p. 118—120°, was collected, washed with alcohol, and crystallised from alcohol; light yellow plates, m. p. 122—123° (Found : C, 71.3; H, 6.3. Calc. for C₂₁H₂₂O₅ : C, 71.2; H, 6.2%). Stobbe and Haertel (*Annalen*, 1909, **370**, 104), Dickenson, Heilbron, and Irvine (*J.*, 1927, 192), and Sugawara and Yoshikawa

(*J.*, 1933, 1584) give m. p. 84°. In some experiments we obtained the low-melting form and the discrepancy is possibly due to dimorphism.

Reduction of Di-(3' : 4'-dimethoxybenzylidene)acetone.—The unsaturated ketone (10 g.) in ethyl acetate (100 c.c.) was reduced in the presence of a 10% palladium-carbon catalyst during two hours. The mixture was filtered and evaporated, and the product taken up in ether (35 c.c.). The 1 : 5-di-(3' : 4'-dimethoxyphenyl)pentan-3-one which gradually separated (4.2 g.) crystallised from alcohol in needles, m. p. 85° (Found : C, 70.2; H, 7.5. Calc. for $C_{21}H_{26}O_5$: C, 70.4; H, 7.3%). Sugasawa and Yoshkawa (*loc. cit.*) give m. p. 85°. The oxime melted at 138° as stated by Sugasawa and Yoshkawa. The ethereal mother liquor was evaporated and the residue crystallised from aqueous alcohol; needles (3.5 g.), m. p. 83–85°, were obtained. These were 1 : 5-di-(3' : 4'-dimethoxyphenyl)pentan-3-ol (Found : C, 69.6; H, 7.8. $C_{21}H_{28}O_5$ requires C, 70.0; H, 7.8%).

1 : 5-Di-(3' : 4'-dimethoxyphenyl)pentane, obtained in 50% yield by Clemmensen reduction of the above ketone, crystallised from aqueous alcohol in needles, m. p. 56–57° (Found : C, 73.2; H, 8.5. $C_{21}H_{28}O_4$ requires C, 73.1; H, 8.1%).

1 : 5-Di-(3' : 4'-dihydroxyphenyl)pentane.—1 : 5-Di-(3' : 4'-dimethoxyphenyl)pentane (1.7 g.) was refluxed with hydriodic acid (20 c.c.) and phenol (7 g.) for 70 minutes in a stream of carbon dioxide. After removal of the phenol in steam an ethereal extract was washed with water and aqueous sodium thiosulphate, and evaporated to dryness. The residual compound crystallised from water (charcoal) in needles (0.58 g.), m. p. 129–130° (Found : C, 70.8; H, 7.1. $C_{17}H_{20}O_4$ requires C, 70.8; H, 7.0%).

Reduction of 2 : 6-Di-(3' : 4'-dimethoxybenzylidene)cyclohexanone.—The unsaturated ketone (Samdahl, *Centr.*, 1928, I, 2256) (5 g.) was reduced in acetic acid suspension as described above. The solvent was removed under reduced pressure and the residue crystallised from methyl alcohol. The first crop (2.7 g.), m. p. 93–95°, yielded 2 : 6-di-(3' : 4'-dimethoxybenzyl)cyclohexanone in felted needles, m. p. 112° (Found : C, 71.9; H, 7.2. $C_{24}H_{30}O_5$ requires C, 72.3; H, 7.5%), after a further crystallisation from methyl alcohol. The alcohol liquors were evaporated and the residue crystallised three times from benzene-ligroin; 2 : 6-di-(3' : 4'-dimethoxybenzyl)cyclohexanol was obtained in needles, m. p. 110–111° (Found : C, 71.7; H, 8.0. $C_{24}H_{32}O_5$ requires C, 72.0; H, 8.0%).

2 : 6-Di-(3' : 4'-dimethoxybenzyl)-1-methylcyclohexanol, prepared by the action of methylmagnesium iodide on an ether-benzene solution of 2 : 6-di-(3' : 4'-dimethoxybenzyl)cyclohexanone, separated from benzene-ligroin in needles, m. p. 168–172° (Found : C, 72.7; H, 8.2. $C_{15}H_{24}O_5$ requires C, 72.4; H, 8.2%).

1 : 3-Di-(3' : 4'-dimethoxybenzyl)cyclohexane, obtained in 50% yield by Clemmensen reduction of 2 : 6-di-(3' : 4'-dimethoxybenzyl)cyclohexanone, crystallised from alcohol-ligroin in needles, m. p. 75–77° (Found : C, 74.8; H, 8.7. $C_{22}H_{28}O_4$ requires C, 74.9; H, 8.3%). All attempts to demethylate it yielded oils which could not be purified, and were non-irritant.

N-Allylprotocatechuic Amide (III; R = $CH_2 \cdot CH \cdot CH_2$).—3 : 4-Carbonyldioxybenzoyl chloride (Barger, *loc. cit.*) (2 g.) in ether (20 c.c.) was gradually added with cooling and shaking to allylamine (1.5 g.) in ether (15 c.c.). After $\frac{1}{2}$ hour *N*/3-hydrochloric acid (30 c.c.) was added; after shaking, the product was collected and refluxed with *N*-ammonia (20 c.c.) for 15 minutes. The solution was cooled, filtered, and acidified with concentrated hydrochloric acid (4 c.c.); the *amide* (III; R = $CH_2 \cdot CH \cdot CH_2$) separated in needles (0.3 g.), m. p. 198–199°, which gave an intense green ferric test (Found : C, 62.5; H, 5.9. $C_{10}H_{11}O_3N$ requires C, 62.2; H, 5.7%).

N-Undec-10-enylprotocatechuic Amide (III; R = $[CH_2]_9 \cdot CH \cdot CH_2$).—3 : 4-Carbonyldioxybenzoyl chloride (1 g.) in ether (10 c.c.) was added to an ice-cold solution of undec-10-enylamine (Krafft and Tritschler, *Ber.*, 1900, **33**, 3583) in ether (7 c.c.). The ethereal suspension was washed with dilute hydrochloric acid, and the collected product warmed with sodium hydroxide solution (12 c.c. of *N*/3) for 15 minutes on the water-bath. The cooled solution was made strongly alkaline with *N*-sodium hydroxide (6 c.c.), washed with ether, acidified, and the free *phenol* extracted with ether and crystallised from ether-ligroin; needles (0.4 g.), m. p. 110–111° (Found : C, 70.8; H, 9.2. $C_{18}H_{27}O_3N$ requires C, 70.8; H, 8.9%), giving an intense green ferric test, were obtained.

N-Methylsorbic Amide.—Sorbic amide (2 g.), 40% formaldehyde (1.4 c.c.), potassium carbonate (0.1 g.), and water (10 c.c.) were heated on the water-bath for 2 hours. Next day the *product* was collected, washed with water, dried, and crystallised from acetone; slender needles (2 g.), m. p. 137° (Found : C, 59.6; H, 8.0. $C_7H_{11}O_2N$ requires C, 59.5; H, 7.8%), were obtained.

N-(3 : 4-Dihydroxybenzyl)sorbic Amide (IV; R = $CH \cdot CH \cdot CH \cdot CH \cdot CH_2$).—A solution of *N*-methylsorbic amide (1.8 g.), catechol (1.4 g.), concentrated hydrochloric acid (5 c.c.), and alcohol (5 c.c.) was kept for 48 hours. The product, isolated with ether, was taken up in *N*-sodium hydroxide, recovered by acidification, and extracted with ether. After removal of the solvent the residue was triturated with water and the solid (1.7 g.) collected and dried in a vacuum. Crystallisation from acetone-benzene gave the *amide* as a microcrystalline powder, m. p. 134–136° (Found : C, 67.8; H, 6.5. $C_{13}H_{15}O_3N$ requires C, 67.0; H, 6.5%).

N-(3 : 4-Dihydroxybenzyl)undec-10-enoic Amide (IV; R = $[CH_2]_9 \cdot CH \cdot CH_2$).—*N*-Methylundec-10-enoic amide, m. p. 77–78° (Jones and Pyman, *loc. cit.*) (3.8 g.), catechol (1.7 g.), and concentrated hydrochloric acid (2 c.c.) were kept for 48 hours in cold alcoholic solution (30 c.c.). After dilution with water the *product* was taken up in ether, washed with water, and extracted with dilute sodium hydroxide solution. The alkaline liquors were acidified, extracted with ether, and evaporated, and the residue was freed from catechol by trituration with water. The residual brown oil was taken up in ether and dried, and light petroleum (b. p. 40–60°) added until crystallisation commenced. The *amide* separated in small needles (0.1 g.), m. p. 85–86° (Found : C, 71.0; H, 9.1. Calc. for $C_{18}H_{27}O_3N$: C, 70.8; H, 8.9%) (Jones and Pyman, *loc. cit.*, give m. p. 70–74°), which are soluble in cold dilute sodium hydroxide solution, contain nitrogen, and give a deep green ferric test.

Allyl Protocatechuate (V; R = $CH_2 \cdot CH \cdot CH_2$).—3 : 4-Carbonyldioxybenzoyl chloride (2 g.) and allyl alcohol (3 c.c.) were heated on the water-bath until hydrogen chloride evolution ceased (6 hours). Distillation yielded the crude ester carbonate as an oil (2.2 g.), b. p. 160–180°/1.2 mm., which partially solidified on cooling. The product was boiled with water (24 c.c.), and 2*N*-ammonia (28 c.c.) was added during 5 minutes. After boiling for 20 minutes the mixture was cooled, made alkaline with excess of ammonia, filtered, and treated suitably with ether, acid, and sodium bicarbonate to isolate the phenolic *ester* from neutral and acidic materials. The product crystallised from hot water (carbon) in prisms (0.5 g.), m. p. 108–110° (Found : C, 61.7; H, 5.4. $C_{10}H_{10}O_4$ requires C, 61.9; H, 5.2%), which gave a bright green ferric test.

Undec-10-enyl Protocatechuate (V; R = $[CH_2]_9 \cdot CH \cdot CH_2$).—Undec-10-enyl alcohol (1.05 g.) (Grun and Wirth, *Ber.*, 1922, **55**, 2208) and 3 : 4-carbonyldioxybenzoyl chloride (1 g.) were heated at 100° for 3 hours. The mixture, which partially solidified on cooling, was heated for 15 minutes at 100° with *N*-ammonia (16 c.c.), cooled, and shaken with ether (20 c.c.) and 2*N*-sodium hydroxide (20 c.c.). The alkaline layer was acidified, extracted thrice with ether, the ethereal extract washed with aqueous sodium bicarbonate, dried, and the solvent removed. The residual *ester* crystallised from ligroin in prisms (1 g.), m. p. 83–85° with previous sintering at 75° (Found : C, 69.8; H, 8.3. $C_{18}H_{26}O_4$ requires C, 70.5; H, 8.6%), which gave a green ferric test.

2 : 3-(3'-Hydroxy-o-phenylene)dioxydioxan (VI; R = H).—2 : 3-Dichlorodioxan (20 c.c.; prepared by the method of

Kucera and Carpenter, *J. Amer. Chem. Soc.*, 1935, **57**, 2346), pyrogallol (12 g.), pyridine (28 c.c.), and benzene (60 c.c.) were heated on the water-bath for 16 hours. The mixture, which separated into two layers, was shaken with excess of sodium bicarbonate solution and twice extracted with benzene. The extract was dried, the solvent removed, and the dark residue distilled. The fraction of b. p. 150—170°/0.5 mm. was shaken with a mixture of water and ether; the ethereal layer was dried (Na₂SO₄), concentrated slightly, and ligroin added. On standing, the substance (VI; R = H) separated (6.9 g., m. p. 95—100°). Crystallisation from benzene-ligroin gave cubical crystals, m. p. 105—106° (Found: C, 57.1; H, 5.1. C₁₀H₁₀O₅ requires C, 57.1; H, 4.8%).

Preparation of Ethers (VI; R = alkyl).—The phenol (VI; R = H) (2 g.), the alkyl bromide or iodide (4—5 c.c.), and powdered anhydrous potassium carbonate (2 g.) were refluxed in acetone (5 c.c.) for 20—48 hours. After addition of water, the ether (VI; R = alkyl) was isolated with ether, washed with dilute sodium hydroxide solution, and crystallised from ether-ligroin. With some of the higher ethers a distillation was advisable before crystallisation. The properties of the ethers are included in Table I; they gave a negative ferric test and in general were obtained in 80% yields.

TABLE I.

Substance.	M. p.	Solvent.	Found (%)		Formula.	Required (%)	
			C.	H.		C.	H.
2 : 3-(3'-Ethoxy-o-phenylene)dioxydioxan	87°	Ether	60.1	6.1	C ₁₂ H ₁₄ O ₅	60.5	5.9
2 : 3-(3'-n-Propoxy-o-phenylene)dioxydioxan ...	72	Benzene-ligroin	62.0	6.7	C ₁₃ H ₁₆ O ₅	61.9	6.4
2 : 3-(3'-n-Butoxy-o-phenylene)dioxydioxan ...	74	Ether-ligroin	63.7	7.1	C ₁₄ H ₁₈ O ₅	63.2	6.8
2 : 3-(3'-n-Amyloxy-o-phenylene)dioxydioxan	40	Ether-ligroin	64.5	7.3	C ₁₅ H ₂₀ O ₅	64.3	7.1
2 : 3-(3'-n-Hexyloxy-o-phenylene)dioxydioxan	76	Ether-ligroin	64.5	7.6	C ₁₆ H ₂₂ O ₅	65.3	7.5
2 : 3-(3'-n-Heptyloxy-o-phenylene)dioxydioxan	54	Ether-ligroin	66.3	8.1	C ₁₇ H ₂₄ O ₅	66.2	7.9
2 : 3-(3'-n-Octyloxy-o-phenylene)dioxydioxan ...	75	Ether-ligroin	67.5	8.3	C ₁₈ H ₂₆ O ₅	67.1	8.1
2 : 3-(3'-n-Hexadecyloxy-o-phenylene)dioxydioxan	87	Ether-ligroin	71.6	10.0	C ₂₆ H ₄₂ O ₅	71.9	9.8
2 : 3-(3'-Allyloxy-o-phenylene)dioxydioxan ...	92	Ether-ligroin	63.0	6.0	C ₁₃ H ₁₄ O ₅	62.4	5.6

TABLE II.

Substance.	M. p. ex ligroin.	Found (%)		Formula.	Required (%)		Vesicancy tests.
		C.	H.		C.	H.	
3-Ethoxycatechol	91—93°	62.2	6.5	C ₉ H ₁₀ O ₃	62.3	6.5	E ₁ -; nil.
3-n-Propoxycatechol	90—91	64.5	7.3	C ₉ H ₁₂ O ₃	64.3	7.2	E ₁ -; E ₁ -; E ₄ .
3-n-Butoxycatechol	50—51	66.1	7.9	C ₁₀ H ₁₄ O ₃	65.9	7.8	E ₁ -; E ₁ -; E ₄ .
3-n-Amyloxycatechol	59—60	67.3	8.4	C ₁₁ H ₁₆ O ₃	67.4	8.2	E ₁ -; nil.

Preparation of 3-Alkoxycatechols.—The ether (VI; R = alkyl) (1 g.), urea (1 g.), acetic acid (5 c.c.), concentrated hydrochloric acid (8 c.c.), and water (2 c.c.) were refluxed for 6 hours. After dilution with water, the product was extracted with ether and the extract washed with sodium bicarbonate solution. The phenol was removed in 2% sodium hydroxide solution and recovered by acidification and ether extraction. The residue from the dried extract was purified either by distillation at 0.5 mm. or by crystallisation from ligroin. Yields of 30—35% were obtained with the 3-amlyoxy- and lower ethers. The hydrolysis of the higher ethers was extremely slow; yields were very small and the products were oils, which were devoid of vesicant properties. The properties of the solid 3-alkoxycatechols are given in table II: the oily higher members, like the crystalline lower members, were soluble in sodium hydroxide and with ferric chloride gave greenish-blue colorations which gradually became brown.

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THE UNIVERSITY, SHEFFIELD.

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