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The structures of some coloured compounds from dihydric phenols and alkylamines[†]

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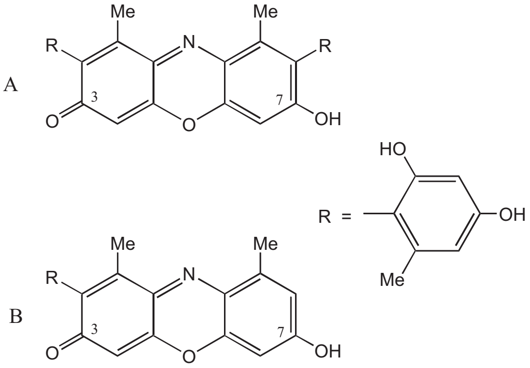
The coloured products from the reaction of resorcinols with methylamine, dimethylamine and other alkylamines have been studied. Phenoxazinones, xantheines and other nitrogenous compounds are formed.

Keywords: orcinol, resorcinol, alkylamines, phenoxazinones, xantheines

In an investigation of the Mannich reaction of a variety of phenols, the formation of coloured by-products was observed and was traced to the reaction of certain 1,3-dihydric phenols with organic bases.[1] Coloured compounds were found to result from the reaction of 1,3-dihydroxybenzenes (resorcinols) having alkyl and alkenyl substituents, notably cardanol,[2] with primary, secondary, primary/secondary (diethylenetriamine) and even tertiary amines. The reaction of ammonia with resorcinols, giving orceine and litmus compounds, has been studied in great detail.[3-5] These investigations were concerned with the chemistry of litmus, and led to the formulation of synthetic products as primarily tautomeric phenoxazin-3-ones and –7-ones: type A, with two orcinyl groups (R), which were considered to possess hindered rotation, and thus could exist as *cis* (meso) or *trans* (racemic) forms, and type B, which contain one orcinyl group.



To our knowledge, investigation of the reaction of organic bases with resorcinols is novel. The formation and structures of materials from resorcinol and orcinol is the subject of the present communication, about which a preliminary account has appeared.[6] The present work in the main describes the reactions of orcinol with methylamine and of resorcinol with dimethylamine. Support for our structural findings was found from the known ammonia/orcinol reaction[3] which in our work was used as a reference system, with the novel use of trimethylsilylation and analysis by mass spectroscopy.

The described reaction of hydroxy-β-orcinol with n-hexylamine[7] has also been reexamined, from which we believe that it follows a different course from that proposed.

Generally, complex reactions occur between dihydric phenols and amines, leading to *N*-alkylphenoxazinones, xanthenes, and other unidentified structures.

From our preliminary qualitative experiments, the colourations of a variety of phenols with diethylenetriamine were examined, and are reported in Table 1. The colourations of resorcinol and of orcinol with different classes of amine were studied, and are given in Table 2, and those of resorcinol and methylresorcinols with ammonia and methylamines are shown in Table 3.

Table 1 Colouration of phenols and resorcinols with DETA upon heating

Phenol	Observation
Unsubst. phenol	Clear colourless soln at ambient temp but yellow with heat
Cardanol[a]	Colourless, then yellow
Cardol[a]	Red solution
2-Methylcardol	Red solution
Resorcinol	Deep red
5-methylresorcinol	Deeper red colour
4-methylresorcinol	Deep red colour
2-methylresorcinol	Orange solution, deepening to deep red on heating

[a]See ref. 2.

The reaction of resorcinol and of orcinol with methylamine, and separation of the resulting mixtures by preparative TLC, led to the need to use the reaction of orcinol with ammonia as a reference system, and the aid of mass spectrometry of the separated trimethylsilylated components, leading to their characterisation as phenoxazinones. The reaction of resorcinol with dimethylamine and with diethylamine followed a different reaction course, with the formation of xantheines. The reaction of the hydroquinone 2,5-dimethyl-1,2,4-trihydroxybenzene with n-hexylamine, led, we believe, to a quinhydrone, a result at variance with previous work.[7]

Results and discussion

The Mannich reaction of the mixed primary/secondary amine diethylenetriamine (DETA) with monohydric and dihydric phenols[1] was the origin of the present study, made in order to identify the causes of coloured products which were observed. As shown in Table 1, the colour formation is primarily a property of the various 1,3-dihydric phenols.

However, from further experiments it became clear that all the amine classes investigated afforded coloured products with resorcinol, as seen in Table 2.

Although classical studies[3-5] have concentrated on the colourations formed by ammonia with orcinol, it is apparent that methylamine and dimethylamine also yield a variety of

Table 2 Colouration of resorcinol with different classes of amines

Amine	Observation
$(H_2NCH_2CH_2)_2NH$ (DETA)	Orange-red
$(HOCH_2CH_2)_2NH$	Pink colour (lighter than resorcinol/DETA)
$H_2N(CH_2)_6NH_2$	Orange-red (similar to resorcinol/DETA)
$H_2N(CH_2)_2NH(CH_2)_2OH$	Deep red (darker than resorcinol/DETA)
$H_2NCH_2CH_2NH_2$	Deep red
$(CH_3CH_2)_3N$	Colouration produced (perhaps due to impurities)

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Table 3 The colours formed in reaction of resorcinols with excess of base in aqueous solution at ambient temperature

Phenol	Time (days)	NH_3	$MeNH_2$	Me_2NH
Resorcinol	14	Dark blue[a]	Dark red	Blue-black
Orcinol	21	Dark blue-black[a]	Dark blue-black	Red
Hydroxy-β-orcinol	2	Dark blue	Dark blue-black[b]	Dark blue-black

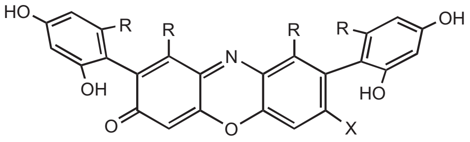
[a] Resorcinol and orcinol with ammonia described[4,5], but with no MS data.
[b] Red with H^+, blue with OH^-.

coloured products with resorcinol, orcinol, and hydroxy-β-orcinol, as listed in Table 3. It is, most probably, a general property of alkylamines.

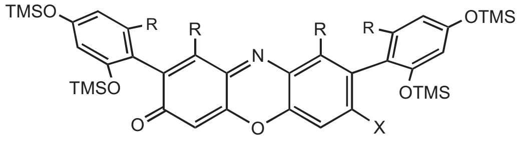
Phenoxazinones. A great range of products generally was found from the reaction of dihydric phenols with primary and with secondary amines, and TLC purification was required to separate the components. Microanalytical data were frequently not satisfactory on separated fractions but trimethylsilyl derivatives afforded derivatives suitable for mass spectroscopy and characterisation.

The phenoxazinone from orcinol and methylamine is considered to have the zwitterionic structure **4**, R = Me, and its TMS derivative **5**, R = Me, in which the counter-ion is believed to be an acetamide anion. Structure **4** is analogous to compounds from orcinol and ammonia.[3] It seems probable that **4**, R = Me, exists as a tautomeric mixture of phenoxazinones of type **A**, but type **B** was not found. Restricted rotation of the 3- and 6-orcinyl groups, to give *cis* and *trans* (racemic) forms appear to be feasible for **4**, as with the products from ammonia[3], although in our work these compounds have not been isolated. Structure **4** is believed to result from the biphenylpentaol **1**, formed by autoxidation of orcinol, followed by methylamination at the site of the reactive OH group to give **2**. Reaction then with **1** leads to the diphenylamine **3** which is oxidised to the indophenol and cyclised with dehydration to the phenoxazinone **4**. Trimethylsilylation gives the pentakistrimethylsiloxy compound **5** which can also exist as *cis* (meso) and *trans* (racemic) forms as depicted in Scheme 1.

TMS derivatives have not previously been employed in this series of compounds and we examined this strategy first with the known phenoxazinone **6**, R = Me, X = OH, obtained from orcinol and ammonia[3,5], along with the simultaneously formed amino analogue **6**, R = Me; X = NH_2. Both were readily silylated to afford **7**, R = Me; X = OTMS and $N(TMS)_2$, having possible *cis* and *trans* forms due to restricted rotation, although these were not isolated. Structures **6** and **7** possessed major MS peaks having the expected masses, and thus proved useful reference trimethylsilyl compounds.



6 (X = OH, NH_2)



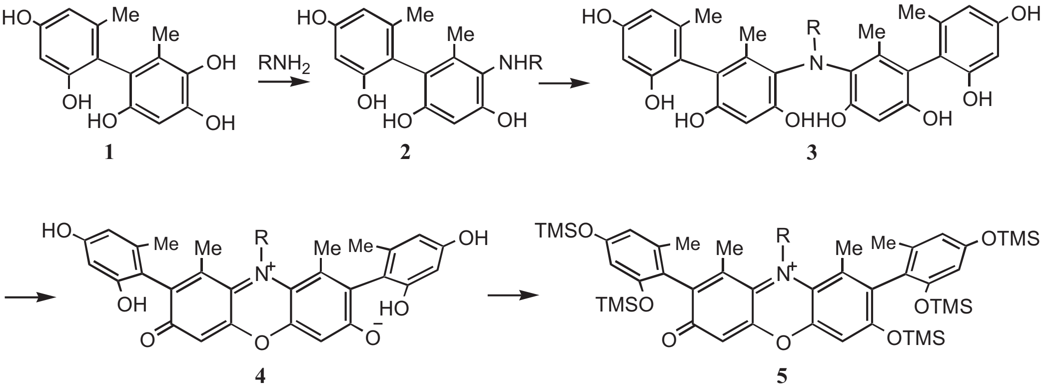
7 (X = OTMS, $N(TMS)_2$)

From the reactions of resorcinol, orcinol and 2-methylresorcinol, structures related to **2**, R = $(CH_2)_2NH(CH_2)_2NH_2$, and a phenoxazinone, a bis-**4**, in which both NH_2 groups of DETA have reacted, appear possible.

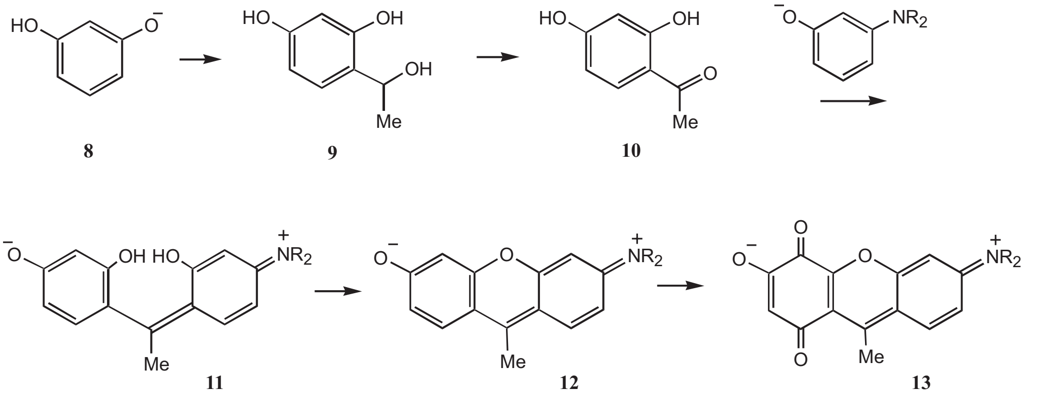
In the case of the red materials from the reaction of pentadecenylresorcinol (cardol)[2] (containing mono, di and trienyl constituents) with DETA, which was the objective of the original study,[1] the product from TLC is a very complex mixture. The formation of phenoxazinones related to **4** with $ArC_{15}H_{31\text{-}n}$ in place of ArMe and R = Me, from cardol and methylamine, and **4** with $ArC_{15}H_{31\text{-}n}$ in place of ArMe and R = $CH_2CH_2NHCH_2CH_2NH_2$, from cardol and DETA, would be expected.

Xantheines. In the reaction of resorcinol with dimethylamine and with diethylamine a range of coloured products was isolated. From resorcinol and dimethylamine, a xantheine resulted which we believe to have structure **13**, R = Me, while diethylamine most probably affords a diethyl analogue.

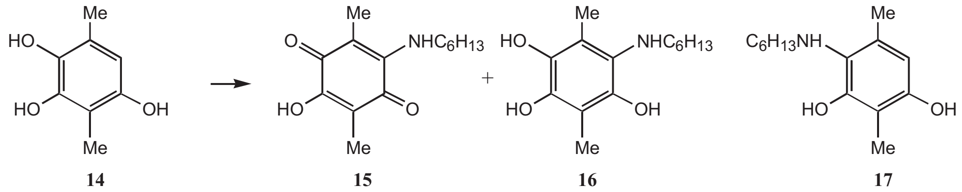
We speculate that the pathway to the xantheine starts from the anion (**8**) of resorcinol, unlike the phenoxazinone compounds described which follow an autoxidative sequence. Nucleophilic addition to acetaldehyde, formed along with some acetic acid, by decarboxylative degradation through a reverse aldol reaction of the diketo tautomer of resorcinol, could yield **9** and thence, oxidatively, **10**. Alkylation with 3-dimethylaminophenol[6] (formed from the monoanion of resorcinol and dimethylamine) would give **11** and thence **12** by dehydration in the azeotropic recovery process with etherification. Oxidation would furnish



Scheme 1



Scheme 2



Scheme 3

a 1,4-quinonoid structure (**13**, R = Me), although a satisfactory mechanism for the formation of this final quinone of Scheme 2 has not been formulated.

The structures of the dark blue and purple components isolated have not been established. The MS of TMS derivatives indicates they are polyhydroxy compounds.

While several alternative quinonoid structures can be proposed, based on calculated ^{1}H NMR data,[8] the observed spectra favour the representation **13**, R = Me. Related xantheine structures have been described.[9,10] The blue and purple compounds simultaneously formed and separated by TLC may be isomeric imino keto materials, $C_{14}H_{11}NO_6$, mol. wt. 289, although structures have not been established.

In the reaction of resorcinol with DETA a xantheine such as **13**, R = $CH_2CH_2NH_2$, could be formed from reaction of the NH group of DETA.

*Hydroxy-*β*-orcinol:* The results from the reaction of hydroxy-β-orcinol (**14**) and *n*-hexylamine were partially confirmed (Scheme 3). However, it is thought that the product conforms, from its spectral and elemental analytical data and deep colour, to the structure of a quinhydrone, composed of **15** and **16**, rather than a salt (from **17**) as suggested.[7] Although its formulation as a phenoxazinone is attractive, the spectral data do not support this. The abstracts[7] of the original publication are obscure and appear to be uninformative.

Experimental

Chromatography: TLC was effected on microscope slides self-coated with Merck Kiesegel G type 60 (analytical plates, 0.25 mm and 20 × 20 cm preparative plates, 1.00 mm) and visualised by spraying with 0.1% ethanolic rhodamine 6G, viewing under UV light. GLC was carried out with a Pye Unicam Gas Chromatograph (GCD) equipped with FID and an Infotronics GRS 201 programmed integrator. Column chromatography was carried out on Kieselgel G type 60 (mesh 70-230) in glass columns equipped with a zero porosity disc and monitored by TLC.

^{1}H NMR spectra were recorded on a Varian T60 (60 MHz) and on a Varian FT-80A by Varian Associates (Beaconsfield, Bucks) of samples with TMS as internal standard; ^{13}C spectra were measured on a Varian CFT-20. Infrared spectra were recorded on a Perkin-Elmer 700 with a SP2000 instrument and UV spectra were obtained on a Pye-Unicam SP800. Mass spectrometry was carried out on an AEI modified MS902; accurate mass measurements were provided by the PCMU, Harwell.

Microanalyses were carried out at the School of Pharmacy, University of London.

Materials: phenols and amines were obtained from Aldrich Chemical Co. and diethylenetriamine (DETA) from Kodak Ltd.
Qualitative reaction of phenols with diethylenetriamine (Table1)
Mixtures of DETA (0.011 g, 1 mmol) and ethanolic solutions of phenol (0.10 g), resorcinol (0.12 g), 5-methylresorcinol (0.12 g), 4-methylresorcinol (0.13 g), 2-methylresorcinol (0.13 g), 3-pentadecylphenol (saturated cardanol) (0.30 g), 2-methyl-5-pentadecylbenzene-1,3-diol (2-methylcardol) (0.30 g) and of 5-pentadecylbenzene-1,3-diol (cardol) were heated under reflux for 1 h. on a steam-bath.

Qualitative reactions of resorcinols with primary and secondary amines (Table 2)
Diethanolamine (0.087 g), diethylenetriamine (DETA) (0.096 g), hexamethylenediamine (0.11 g), and *N*-(2-aminoethyl)ethanolamine (0.096 g) were added separately to methanolic solutions of resorcinol (0.10 g) and left for 15 days.

Qualitative comparison of coloured products with ammonia, methylamine and dimethylamine (Table 3)
Aqueous solutions of resorcinol, orcinol and hydroxy-β-orcinol each with ammonia, methylamine and dimethylamine, respectively were reacted at ambient temperature for various time periods.

Reactions of resorcinol and orcinol with bases
Resorcinol and methylamine: initially, resorcinol and excess of 25% aqueous methylamine reacted upon heating to give a dark red product which was shown by TLC to contain no major product but a very complex mixture which proved too intractable to separate by preparative TLC.

Orcinol and methylamine: the reaction of orcinol (0.71 g) with methylamine (0.62 g) over 7 days gave a simpler mixture, and upon dilution with water and filtration, followed by drying, a blue-black solid (0.120 g) was isolated. By prep. TLC on silica gel with acetone–benzene (3: 1), a red-purple solid was separated (**4**, R = Me), mol.wt. 499, R_f 0.25; UV (MeOH): λ_{max} 534, 510, 277, 245, 226, 206 nm. NMR: δ_H (CD_3OD), 1.30 (s, Me), 1.92 (d, MeAr), 2.27 (d, MeAr, NMe), 6.35 (m, HAr), 6.55 (m, HAr). MS: *m/z*, pentakistrimethylsilyl deriv. (**5**, R = Me), 860, 771 (–$OSiMe_3$), and double charged peaks, 429, 430; $C_{44}H_{65}O_7NSi_5^+$ requires 860.

Resorcinol and orcinol with ammonia: for comparison and reference purposes, resorcinol and orcinol were reacted with ammonia and the trimethylsilyl derivatives (prepared from bis-trimethylsilylacetamide in pyridine) were examined.

Resorcinol (5.05 g) and excess of aqueous ammonia were left for 14 days and a dark blue precipitate (0.370 g) was then collected. Two components, a blue material (10 mg), R_f 0.47, λ_{max} (MeOH) 612, 292, 258, 206 nm, and a red-purple material (20 mg), R_f 0.15, λ_{max} (MeOH) 546, 291, 271, 207 nm, were isolated, but not silylated.

Orcinol (3.72 g) and excess of ammonia solution were left for 21 days and a blue black precipitate was then collected (0.50 g) which by TLC contained at least 14 components. Two red components, (1, R_f 0.59 and 2, R_f 0.28) were isolated by prep TLC. *Red component 1* (**6**, R = Me, X = OH), mol wt. 485; UV: λ_{max} (MeOH) 564, 532, 242, 206 nm. MS: *m/z* of pentakistrimethylsilyl deriv. (**7**, R = Me, X = OTMS) 845.372 ($C_{43}H_{63}NO_4Si_5$ requires 845.345), 830, 757 (-OSiMe$_3$). *Red component 2* (**6**, R = Me; X = NH$_2$), mol.wt. 484. UV: λ_{max} (MeOH) 585, 572, 538, 488, 285, 225, 207 nm; hexakistrimethylsilyl deriv. (**7**, R = Me; X = N(SiMe$_3$)$_2$), MS: *m/z* 830.3215, 919, 847 (TMS impurity of HO analogue), 830, 758 (–OSiMe$_3$).

Reaction of resorcinol with dimethylamine

Resorcinol (5.05 g, 0.05 mol) and 25% aqueous dimethylamine (9.0 g, 0.05 mol) were heated under reflux on a steam-bath for 5 h. The mixture was evaporated *in vacuo* and the residue (6.60 g) column-separated (silica gel G, 70–230 mesh) with the successive solvents chloroform-diethyl ether (40: 60), ethyl acetate, acetone-methanol (80: 20) and finally methanol. A series of blue, green, grey and yellow fluorescent fractions and red, dark blue and light blue non-fluorescent bands resulted. Repetition of the reaction with resorcinol (100 g) and 25% aqueous dimethylamine (163.6 g), followed by removal of unreacted resorcinol (90 g) by extraction with benzene and evaporation of the aqueous portion *in vacuo* gave a residue which was column-separated, as before. The fractions obtained were prep. TLC separated to give the dark blue material (7.7 mg), yellow fluorescent material (43.2 mg) and a purple fraction (5.2 mg) with R_f similar to that of the dark blue fraction.

Yellow fluorescent fraction (**14,** R = Me): No m.p. up to 300°C. R_f 0.2 (acetone-methanol, 9: 1). IR (KBr): ν_{max} 3440, 2930, 1631, 1580, 1515, 1470, 1397, 1290, 1210, 1170, 1120, 921 and 850 cm^{-1}. UV (MeOH): λ_{max} 512, 482, 324, 285, 243 nm. The fluorescence was lost on acidification, reduction with sodium borohydride, and silylation. NMR (D$_2$O): δ_H 0.62 (m), 1.75 (m), 1.91 (s, =C-Me), 2.90 (m), 3.30 (d, = N$^+$Me$_2$), 4.66 (m), 6.60–6.85 (m, HAr), 7.40 (d, *J* = 9 Hz, HAr), 8.50 (s, HAr). MS: *m/z* 283.0837 (100), 184.0525 (76.5), 137.1332 (2.55), 137.0015 (3.29). Reqd. for $C_{16}H_{13}NO_4$, 283.0844; trimethylsilyl derivative, 355.1245, 283, 256, 147. Reqd. for $C_{19}H_{21}NO_4Si$, 355.1239.

Dark blue fraction: No m.p. up to 300°C. Found: C, 50.89; H, 4.47; N, 2.9%; ν_{max} (KBr), 3450, 1600, 1512, 1385, 1320, 1194, 1117, 985, 860 cm^{-1}. UV (MeOH): λ_{max} 608, 286, 211 nm. MS: *m/z*, 288.1556 (5.6), 287.1534 (24),161.0594 (47), 138.0919 (100), 137.0840 (13.7); trimethylsilyl deriv., 863.3342, 775, 429, 400, 341, 147.

Purple fraction: No clear m.p. UV: λ_{max} (nm, MeOH), 550, 297, 291, 210; *m/z* 288.1543 (1.5), 287.1521 (4), 147.0438 (1.3), 138.0911 (11.2), 137.0835 (81),136.0760 (100); trimethylsilyl deriv. *m/z* 585, 576, 533.2013, 503, 488.2465, 279, 234, 147. The structures of these dark blue and purple materials remain to be found.

Reaction of resorcinol with diethylamine; formation of **14**, R = Et

Resorcinol (33 g, 0.3 mol) and diethylamine (21.9 g, 0.3 mol) were dissolved in water (1 l) and heated on a steam-bath for 24 h. The mixture was then evaporated to dryness and residual resorcinol was extracted with benzene. The residue, which was similar in TLC pattern to the product from dimethylamine, was column chromatographed to yield a yellow fluorescent fraction, which was purified by prep. TLC to give a yellow material (11 mg) with no clear m.p. UV (MeOH): λ_{max} 512, 477, 325, 283, 243, 207 nm.

Reaction of (a) resorcinol, (b) orcinol and (c) 2-methylresorcinol with diethylenenetriamine (DETA)

(a) Resorcinol (5.50 g, 0.05 mol) and DETA (5.15 g, 0.05 mol) were refluxed in ethanol for 2.5 h. The solvent was then evaporated and water (20 cm^3) added, after which the stoppered mixture was left for one month, then filtered and dried to yield a dark red product (4.2 g), m.p. >300°C. IR (KBr): ν_{max} 3230, 1600, 1450, 1399, 1220, 1170, 1000, 980, 815 cm^{-1}. UV (1M HCl): 462, 258-280 nm. NMR: δ_H (DMSO), 2.45 (m, DMSO), 2.8–3.1 [m, (CH$_2$)], 5.20 (m, NH, NH$_2$, OH, exch.), 6,23 (m, HAr), 5,80 (m, HAr); δ_C (D$_2$O), 136.8, 134.7, 133.7, 132.5, 132.0, 67.3, 54.2, 52.7, 52.35, 52.1, 45.5. Found: N, 11.65. $C_{16}H_{21}O_4N_3.2H_2O$ requires N, 11.79%.

(b) Orcinol (1.24 g, 0.01 mol) and DETA (1.03 g, 0.01 mol) similarly afforded a dark red product (1.13 g) with no well-defined m.p. IR (KBr): ν_{max} 2800 (br) cm^{-1}. NMR (DMSO): δ_H 3.53, [m, (CH$_2$)$_n$], 6.20 (m, HAr), no exch. peaks. Found: N, 12.00. $C_{18}H_{25}N_3O_4$ requires 12.17%.

(c) In a similar way, 2-methylresorcinol (1.24 g, 0.01 mol) and DETA (1.03 g, 0.01 mol) gave a red product (0.89 g) with similar spectroscopic properties to the resorcinol and orcinol products. Satisfactory C/H/N analyses could not be obtained for these products.

Reaction of hydroxy-β-orcinol with n-hexylamine; formation of **15**

Hydroxy-β-orcinol (2,5-dimethyl-1,3,4-trihydroxybenzene) was prepared by the Thiele reaction from 2,5-dimethyl-1,4-benzoquinone, *via* 2,5-dimethyl-1,3,4-triacetoxybenzene (98% yield), m.p. 106–108°C (lit.[5] 108°C); hydrolysis of the triacetate in hot hydrochloric acid gave the product (65%yield), m.p. 156–158°C *ex* benzene (lit.[7] 158°C). NMR (acetone-*d*$_6$): δ_H 2.11 (6H, s, 2Me), 6.23 (1H,s, HAr), 7.00–7.33 (3H, bs, ArOH, exch.).

Hydroxy-β-orcinol (0.50 g) and n-hexylamine (0.33 g) in methanol were reacted at ambient temperature for 3 days. The violet precipitate (0.078 g) which formed was found to be relatively pure (TLC), m.p. 132–138°C (lit.[7] 135-143°C). NMR (CDCl$_3$): δ_H 0.93 (3H, t, Me), 1.33 [10H, m, (CH$_2$)$_5$], 2.25 (6H, s, 2MeAr), 6.50 (2H, s, HOAr, exch.), 6.87, 1H, 1H,s, NH exch.); δ_C 181.6, 147.6, 100.7, 78.6, 75.4, 44.9, 40.65, 31.4, 30.8, 26.4, 22.5, 13.9, 9.9, 8.05. Found: C, 66.81; H, 8.78; N, 4.07. Calcd. for a phenoxazinone $C_{22}H_{28}NO_5$, C, 68.37; H, 7.25; N, 3.62%, calcd. for a salt of the quinone (**15**) and (**17**), C, 71.48; H, 8.94; N, 5.95. Calcd.for a quinhydrone, (**15** + **16**), C, 66.93; H, 8.36; N, 5.57% (a small amount of n-hexylamine may be present as a salt).

Hydroxy-β-orcinol with dimethylamine formed, after two days, a dark solid which became red-blue on basification and yellow on acidification, indicating a range of components, as with resorcinol.

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