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Syntheses of two Analogues of 2-(2-Phenylphenoxy)-ethyldiethylamine (Dacorene)

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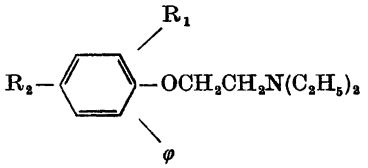
2-(2-Methyl-6-phenylphenoxy)ethyldiethylamine (*2*) and 2-(2,4-dimethyl-6-phenylphenoxy)-ethyldiethylamine (*3*) have been prepared and examined for their effect on the heart. In contrast to 2-(2-phenylphenoxy)-ethyldiethylamine (*1*, Dacorene) they had little or no effect. In connection with this work, some divergences in the literature, concerning some of the intermediates, have been explained.

2-(2-Phenylphenoxy)-ethyldiethylamine (*1*, F1262, Dacorene) was prepared by Strickler[1] and was found, by him and co-workers[2,3] to exert a pronounced antifibrillatory effect. However, pharmacologially active aromatic substances may be strongly activated or de-activated by introduction of *ortho*-substituents, as was found in studies on β-diethylamino-2,6-dimethylacetanilide (Xylocaine ®) and related substances. The present paper reports the syntheses of two derivatives of Dacorene, 2-(2-methyl-6-phenylphenoxy)-ethyldiethylamine (*2*) and 2-(2,4-dimethyl-6-phenylphenoxy)-ethyldiethylamine (*3*). Pharmacological tests on these substances showed that they exert only a small, if any, effect on the heart compared with Dacorene.



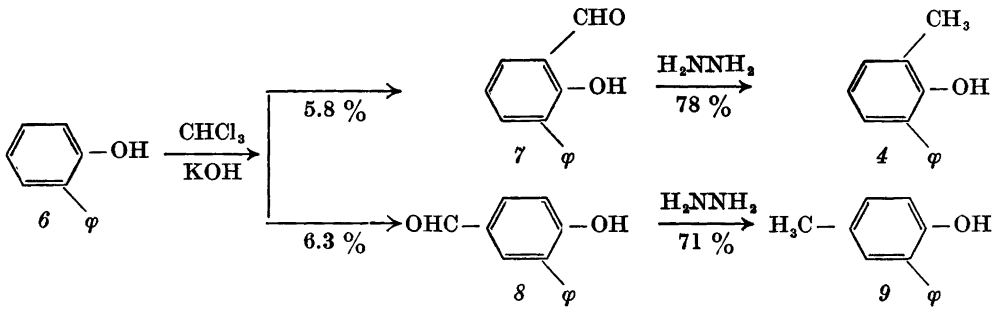
1. $R_1=R_2=H$
2. $R_1=CH_3$, $R_2=H$
3. $R_1=R_2=CH_3$

These substances were prepared by reaction of 2-methyl-6-phenylphenol (*4*) and 2,4-dimethyl-6-phenylphenol (*5*) with 2-(chloroethyl)-diethylamine.

2-Methyl-6-phenylphenol (*4*) was prepared by two methods. The first (Chart 1) started from *o*-hydroxybiphenyl (*6*), which was converted by a

* Deceased.

Chart 1.

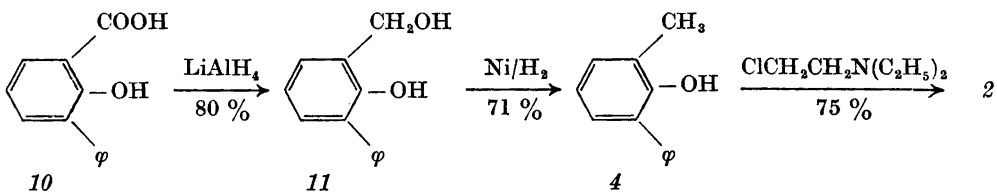


Reimer-Tiemann reaction into a mixture of the *ortho*- (*7*) and the *para*- (*8*) formyl derivatives, which were separated by distillation. The derivative with a high melting point was characterized as the *para*-derivative (*8*) by reducing it to the previously known 4-methyl-2-phenylphenol (*9*) (see below). The compound with a low melting point was obtained as an addition complex with *o*-hydroxybiphenyl, m.p. 76°, which could be separated into its components by chromatography or by precipitation of the *o*-hydroxyaldehyde (7) as the Cu(II) complex. The pure aldehyde (*7*) melted at 46—47°, and when mixed with *o*-hydroxybiphenyl and recrystallized from ethanol, the above addition complex was re-formed. The aldehyde was further characterized by oxidation to 3-phenylsalicylic acid (*10*). It was finally reduced to 4.

Slotta and Nold [5] report another synthesis of 3-phenylsalicylaldehyde (*7*), m.p. 69—70°, also starting from *o*-hydroxybiphenyl. It seems obvius that they did not isolate the pure substance, but the addition complex mentioned above. Mukai,[6] who prepared the substance by a different method, reports m.p. 45.5—46° for the pure substance and m.p. 103° for its anilide, in good agreement with the values found by us.

2-Methyl-6-phenylphenol (*4*) was obtained in a better yield by another method (Chart 2). Following the general directions given by Cameron *et al.*[7] 3-phenylsalicylic acid (*10*) [6] was prepared by a Kolbe-Schmitt reaction from *o*-hydroxybiphenyl (*6*), and was reduced with lithium aluminium hydride to the benzylalcohol (*11*) and further to 4 by catalytical hydrogenation, using Raney-nickel in strongly alkaline solution.

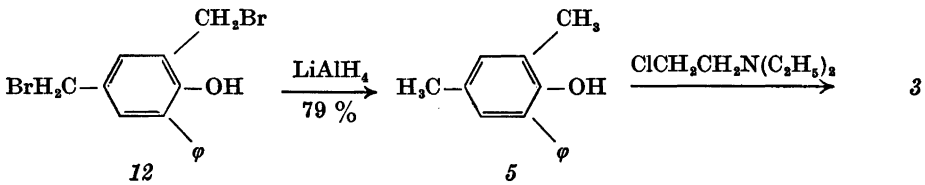
Chart 2.



Colbert and Lacy [8] have reported the syntheses of 2- and 4-methyl-6-phenylphenol by reaction between phenyldiazonium chloride and *o*- and *p*-cresol, respectively, in strongly acidic solution. They characterized their products as the crystalline benzenesulphonates. The reported melting points of these derivatives do not, however, agree with those of the same derivatives prepared by us. In the light of the present work, and the fact that our value for the melting point of 4-methyl-6-phenylphenol (*9*) is in good agreement with published values,[9,10] the results of Colbert and Lacy [8] seem to be questionable. It is possible that the melting points given for their benzenesulphonates have been confused.

2,4-Dimethyl-6-phenylphenol (*5*) was prepared from 2,4-di(bromomethyl)-6-phenylphenol (*12*) [11] by reduction with lithium aluminium hydride (Chart 3).

Chart 3.



12 *5*

EXPERIMENTAL

Melting points are corrected, boiling points uncorrected.

2-Formyl-6-phenyl- and *4-formyl-2-phenylphenol* (*7 and 8*). To a solution of *o*-hydroxybiphenyl (*6*) (350 g) in ethanol (900 ml) was added a solution of potassium hydroxide (600 g) in water (1200 ml). The mixture was heated to 77°, and chloroform (390 g) was added under stirring at such a rate that gentle reflux was maintained without external heating. After 90 min, when the reaction had ceased, the mixture was refluxed for a further 2 h. The organic solvents were removed by steam distillation and the residue acidified with concentrated hydrochloric acid. The dark brown oil which separated was dissolved in ether, dried over sodium sulphate and the ether distilled off. The residue was distilled at 83—156°/0.2 mm to give a yellow oil which crystallized. This was fractionated at 0.2 mm, using a 30 cm Vigreux-column. The first fraction (122 g), b.p. 87—89°/0.2 mm, consisted of *6*. The second fraction (57 g), b.p. 90—130°/0.2 mm was a mixture of *6* and *7*. The third fraction (30 g), b.p. 154—156°/0.2 mm consisted of *8*.

On crystallization from ethanol, the second fraction yielded the addition complex between *6* and *7* (48 g), m.p. 76°. After further recrystallization, the m.p. decreased to 69—70°. The product (48 g) was dissolved in hot ethanol (150 ml) and poured, under stirring, into a solution of cupric acetate (50 g) in water (400 ml), kept at 50°. The brown precipitate was collected after 12 h and washed with ethanol. It was then covered with ether and decomposed by addition of 18 % sulphuric acid. The aqueous phase was extracted with ether, the combined ether phases were dried over sodium sulphate, filtered through a short column of aluminium oxide and concentrated. The residue solified and was crystallized from 70 % ethanol to give light yellow prisms (24 g), m.p. 45—46°. (Found: C 78.5; H 5.15. Calc. for $C_{13}H_{10}O_2$: C 78.8; H 5.08).

By chromatography on dimethylsulphoxide impregnated paper,[12] using ether as irrigant, the complex was separated into two components, having the same R_F-values and colour reactions as *6* and *7*. 2,6-Dibromoquinone-chlorimide and *p*-phenylenediamine were used as spraying reagents.

A portion of *7* was oxidised in a melt of sodium hydroxide-potassium hydroxide, 1:1, at 207° for 20 min, to give 3-phenylsalicylic acid (*10*), m.p. 184—185°, undepressed

on admixture with an authentic sample. Another portion was converted to the aniline derivative,[7] m.p. 103°.

The third fraction obtained on distillation of the Reimer-Tiemann reaction product, on recrystallization from toluene, yielded pure *8* (26 g) as white needles, m.p. 111–113°. (Found: C 78.6; H 5.00. $C_{13}H_{10}O_2$ requires: C 78.8; H 5.09). A portion of this product was converted to 4-methyl-2-phenylphenol (*9*) by reduction with hydrazine, as described below for the *o*-isomer. The product was crystallized from light petroleum to give white needles, m.p. 67–68°. *9* was further characterized as the 3,5-dinitrobenzoate,[10] m.p. 115–116°, and the benzenesulphonate, m.p. 50–51° (from isopropanol). Colbert and Lacy [8] report a melting point of 80–81° for this substance.

2-Hydroxy-3-phenylbenzylalcohol (*11*). To a stirred solution of 3-phenylsalicylic acid (*10*) (32 g) in dry ether (400 ml), kept under an atmosphere of argon, was added a solution of lithium aluminium hydride (13.7 g) in ether (400 ml). When, after 45 min, the spontaneous reaction had ceased, the mixture was refluxed for 30 min, cooled to 0° and water (50 ml) was added. After further cooling to −10°, 10 % sulphuric acid (250 ml) was added, the ether phase separated and the aqueous phase extracted with ether (2 × 100 ml). The combined ether solutions were dried over sodium sulphate and concentrated. The residue crystallized and was recrystallized from benzene (25 ml). The mother liquors were worked up and the total yield of 11, as colourless prisms, m.p. 96–98°, was 23 g. (Found: C 78.0; H 6.03. $C_{13}H_{12}O_2$ requires: C 78.0; H 6.04).

2-Methyl-6-phenylphenol (*14*). *A*. A solution of *7* (35 g), 85 % hydrazine hydrate (17.9 g) and potassium hydroxide (23.8 g) in diethyleneglycol (180 ml) was refluxed at 115° for one hour and then distilled until the temperature of the reaction mixture reached 195°. The mixture was then refluxed for 4 h, cooled, and water (150 ml) was added. The mixture was acidified with concentrated hydrochloric acid and extracted with ether. The ether solution was dried over sodium sulphate, concentrated, and the residue distilled at 0.2 mm, using a 15 cm vacuum-jacketed column, to give 4 as a colourless oil (25 g), b.p. 83–84°, n_D^{25} 1.6039. (Found: C 84.3; H 6.31. Calc. for $C_{13}H_{12}O$: C 84.7; H 6.57).

B. A suspension of Raney-nickel in ethanol (0.8 g) was added to a solution of *11* (2.0 g) in 19 % sodium hydroxide (10 ml). After shaking for 4 h under an atmosphere of hydrogen at room temperature and atmospheric pressure, when the theoretical amount of hydrogen had been consumed, the mixture was neutralized with 10 % sulphuric acid and extracted with ether. The ether solution was dried over sodium sulphate, concentrated and distilled, to give pure *4*, b.p. 83–85°/0.2 mm, n_D^{25} 1.6033.

The benzenesulphonate of *4*, from either preparation, melted at 80–81° (crystallized from ethanol). Colbert and Lacy [8] report 37–38°.

2,4-Dimethyl-6-phenylphenol (*5*). A mixture of lithium hydride (4.4 g) and lithium aluminium hydride (3.4 g) in tetrahydrofuran (125 ml) was stirred and refluxed under an atmosphere of argon. 2,4-Di-(bromomethyl)-6-phenylphenol (*12*) in tetrahydrofuran (120 ml) was added at such a rate that gentle reflux was maintained. The mixture was then refluxed for a further 3 h, cooled to 15°, and a mixture of tetrahydrofuran-water, 3:2 (60 ml) was added, followed by water (60 ml). Finally the product was poured into a mixture of ice (200 g), water (200 ml), and concentrated sulphuric acid (40 ml). The separation of the phases was slow, requiring about 12 h. The aqueous phase was extracted with ether, the combined organic phases were dried over sodium sulphate and concentrated. The residue was distilled to give *5* as an oil (22 g), b.p. 97°/0.15 mm, n_D^{25} 1.9555, which did not crystallize. (Found: C 84.5; H 7.06 $C_{14}H_{14}O$ requires: C 84.8; H 7.17).

2-(2-Phenylphenoxy)-ethyldiethylamine (*2*). A solution of *4* (7.0 g) in toluene (20 ml) was added, under an atmosphere of argon, to a stirred suspension of sodium hydride (2.0 g of a 48 % oil suspension) in toluene (40 ml). The residue was refluxed for 30 min and then a solution of 2-(chloroethyl)-diethylamine (from 9.0 g of the corresponding hydrochloride) in toluene was added and the mixture refluxed for 7 h. It was then cooled to room temperature, water was added to dissolve the sodium hydroxide and the solution was washed with 10 % potassium hydroxide, dried over sodium sulphate and concentrated. The residue was distilled and *2* was obtained as a colourless oil, (8.4 g), b.p. 138°/0.4 mm, n_D^{25} 1.5462. (Found: Equiv. wt. 283.4. $C_{19}H_{25}NO$ requires: 283.0).

The hydrochloride of *2* was prepared and crystallized from isopropylether-isopropanol, to give fine needles, m.p. 121–123°. (Found: Cl 11.2. $C_{19}H_{26}ClNO$ requires: Cl 11.1).

2-(2,4-Dimethyl-6-phenylphenoxy)-ethyldiethylamine (*3*) was prepared as described above for *2*, starting from *5* (10.0 g). *3* was obtained as a colourless oil (11.9 g), b.p. 135—138°/0.2 mm, n_D^{25} 1.5440. (Found: Equiv. wt. 297.4. $C_{20}H_{27}NO$ requires: 297.0).

The hydrochloride was prepared and crystallized from acetone to give long needles, m.p. 133—135°. (Found: Cl 10.6. $C_{20}H_{28}ClNO$ requires Cl 10.6)

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