109. 4-(4′-*Aminobenzenesulphonamido*)*resorcinol* 3-*Benzoate and Some Related Compounds.*

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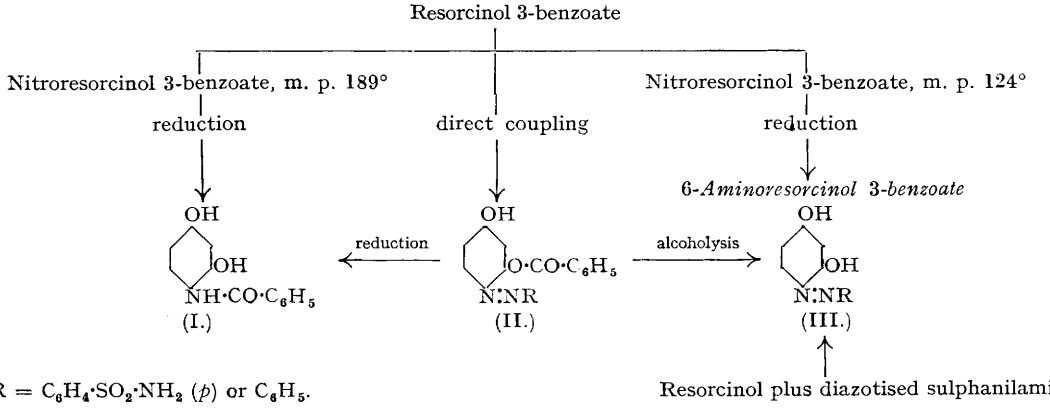
A number of arylsulphonamido- and acylamido-resorcinols, including 4-sulphanilamidoresorcinols, have been prepared for examination as antibacterial agents. 4-(4′-*Sulphonamidobenzeneazo*)*resorcinol* has been characterised and differed from that obtained by Magidson and Rubtsov (*J. Gen. Chem. U.S.S.R.*, 1940, **10**, 756). Molecular rearrangements occurred on the reduction of 4-nitro-, and 4-azo-substituted, resorcinol 3-benzoate to give 2′ : 4′-*dihydroxybenzanilide*. The orientation of 4- and 6-nitroresorcinol 3-benzoates has been confirmed.

The use of 4-*n*-hexylresorcinol as an antibacterial agent prompted the preparation of 4-(4′-*aminobenzenesulphonamido*)*resorcinol* and 4-(4′-*sulphonamidobenzeneazo*)*resorcinol* in order to determine whether the activity of both nuclei would be retained in the compounds.

Nitration of resorcinol 3-benzoate gave two mononitro-derivatives, m. p. 189° and 124°, the orientation of which has been established. The former isomer on reduction with sodium hydrosulphite gave, by intramolecular rearrangement, 2′ : 4′-*dihydroxybenzanilide* (I), which was identified by methylation to the known 2′ : 4′-dimethoxybenzanilide, whereas the lower-melting isomer gave the corresponding aminoresorcinol 3-benzoate. Similar migrations of a benzoyl radical from a phenolic hydroxyl to an amino-group in the *o*-position are known (cf. Raiford and Huey, *J. Org. Chem.*, 1941, **6**, 858; Raiford and Shelton, *ibid.*, 1939, **4**, 207), but have not been encountered where *m*- and *p*-substituents are concerned. Hence the higher-melting compound must be 4-nitroresorcinol 3-benzoate and the lower, 6-nitroresorcinol 3-benzoate. Accordingly the required derivatives of 4-aminoresorcinol were prepared by condensation of 6-*aminoresorcinol* 3-*benzoate* with the appropriate acid chloride in the usual way, followed by acid or alkaline hydrolysis.



Resorcinol 3-benzoate was coupled with diazotised sulphanilamide, yielding 4-(4′-*sulphonamidobenzeneazo*)-*resorcinol* 3-*benzoate* (II), which gave 4-(4′-sulphonamidobenzeneazo)resorcinol (III) on debenzoylation. This product, the dihydroxy-analogue of prontosil rubrum, had previously been described by Magidson and Rubtsov (*loc. cit.*) as melting above 300° and showing little solubility in organic solvents : that obtained in this research melted at 207° (decomp.) and was readily soluble in alcohol, acetone and acetic acid. Furthermore, 4-(4′-sulphonamidobenzeneazo)resorcinol 3-benzoate (II), from which the material melting at 207° was obtained by debenzoylation, gave 2′ : 4′-dihydroxybenzanilide (I) on reduction with sodium hydrosulphite : this result can be explained by the intramolecular rearrangement of the intermediate, 4-aminoresorcinol 3-benzoate. As

4-*benzeneazoresorcinol* 3-*benzoate* (II) gave the known 4-benzeneazoresorcinol (III) on alcoholysis, there is no reason to suspect any abnormality during the debenzoylation of 4-(4′-sulphonamidobenzeneazo)resorcinol 3-benzoate. There can be little doubt, therefore, that the substance melting at 207° is in fact 4-(4′-sulphonamidobenzeneazo)resorcinol. An attempt to resolve this anomaly was made by repeating the preparation of the Russian workers by direct coupling of diazotised sulphanilamide with resorcinol: the product, obtained in 72% yield, melted at 207° and gave no depression of melting point when mixed with our material. A repetition of this preparation using a large excess of alkali during the coupling gave a mixture of mono- and bisazo-derivatives and on separation the 4 : 6-*bis*-(4′-*sulphonamidobenzeneazo*)*resorcinol* melted above 300° and was almost insoluble in organic solvents. It cannot be assumed that the compound obtained by the Russian workers was this bisazo-derivative, as their analytical figures agreed with those of the monoazo-compound.

6-(4′-*Acetamidobenzenesulphonamido*)*resorcinol* 3-*benzoate* and 6-*nicotinamidoresorcinol* 3-*benzoate* were obtained by treatment of 6-aminoresorcinol 3-benzoate with the appropriate acid chloride. The former was converted into 4-(4′-aminobenzenesulphonamido)resorcinol by acid hydrolysis and the latter into 4-*nicotinamidoresorcinol* by treatment with aqueous potash.

Experimental.

4-*Nitroresorcinol* 3-*Benzoate and* 6-*Nitroresorcinol* 3-*Benzoate.*—Resorcinol (44 g.) was dissolved in a solution of hydrated sodium carbonate (88 g.) in water (1300 ml.) containing sodium hydrosulphite (5 g.), benzoyl chloride (56 g.) added dropwise with efficient stirring during 5—6 hours, and stirring continued for a further 2 hours. The crude resorcinol 3-benzoate (57 g.) which separated was washed free from alkali, dried, and twice triturated with benzene to remove resorcinol dibenzoate. The purified material (53 g.), m. p. 132—133°, required no further purification.

The nitration of resorcinol 3-benzoate was effected in acetic acid (Kauffmann and Kugel, *Ber.*, 1911, **44**, 754), giving 39% of 4-nitroresorcinol 3-benzoate, m. p. 189°, and 44% of 6-nitroresorcinol 3-benzoate, m. p. 124°. The orientation of these substances suggested by Kauffmann and Kugel was not accepted in Beilstein's " Handbuch " (**9**, 132, 1st. supl. 72) but has been confirmed by reduction (*vide infra*).

4-*Benzeneazoresorcinol* 3-*Benzoate.*—Aniline (23·5 g.), dissolved in 5N-hydrochloric acid (200 ml.), was diazotised at 0—5° with sodium nitrite (19 g.) in water (70 ml.). After removal of excess of nitrous acid with urea the solution was neutralised with sodium bicarbonate and added to a cooled solution of resorcinol monobenzoate (51 g.) in alcohol (1000 ml.), and the mixture saturated with sodium acetate and kept for 12 hours. On large dilution a brown precipitate (m. p. 168—170°) appeared, which was purified by solution in benzene containing a little acetone, filtering and precipitating by addition of light petroleum (b. p. 60—80°). Repetition of the purification process gave fine yellow needles, m. p. 192°. Yield, 60% (Found: C, 71·7; H, 4·6; N, 8·9. $C_{19}H_{14}O_3N_2$ requires C, 71·7; H, 4·45; N, 8·8%).

Debenzoylation was effected by leaving overnight a mixture of 3·18 g. in alcohol (60 ml.) and aqueous potassium hydroxide (34 ml. of 5%). The bulky yellow precipitate was collected, washed, dried, and recrystallised from alcohol. It occurred in red needles, m. p. 169—170°, and gave no depression on admixture with 4-benzeneazoresorcinol prepared by direct coupling of diazotised aniline and resorcinol (Vorochtov and Borkov, *J. Gen. Chem. U.S.S.R.*, 1932, **2**, 421).

4-(4′-*Sulphonamidobenzeneazo*)*resorcinol* 3-*Benzoate.*—In a similar manner *p*-aminobenzenesulphonamide (5·2 g.) was diazotised and coupled with resorcinol 3-benzoate (6·4 g.): the solution obtained was poured into excess of dilute hydrochloric acid, and the precipitate collected, washed, and dried. Purification was effected by charcoal in alcohol–benzene solution, followed by evaporation to low bulk and precipitation with light petroleum. Repetition of the purification gave a bright yellow, microcrystalline powder, m. p. 199—200°; yield 58% (Found: C, 57·0; H, 4·1; N, 10·4. $C_{19}H_{15}O_5N_3S$ requires C, 57·4; H, 4·1; N, 10·4%).

4-(4′-*Sulphonamidobenzeneazo*)*resorcinol.*—(*a*) 4-(4′-Sulphonamidobenzeneazo)resorcinol 3-benzoate (0·9 g.), dissolved in alcohol (18 ml.), was treated with potassium hydroxide solution and left at room temperature for 12 hours. The flocculent yellowish-brown precipitate obtained on pouring into excess of dilute hydrochloric acid was contaminated with ethyl benzoate. Repeated crystallisation from hot acetone gave small, bright red prisms, m. p. 207° (Found: C, 49·3; H, 4·1; N, 14·3. $C_{12}H_{11}O_4N_3S$ requires C, 49·1; H, 3·8; N, 14·3%).

(*b*) Diazotised *p*-aminobenzenesulphonamide was coupled with resorcinol in alkaline solution, the conditions of Magidson and Rubtsov (*loc. cit.*) being strictly followed. The product was completely soluble in alcohol and in acetone and gave no depression in m. p. when mixed with the substance produced as in (*a*). Repetition of the experiment in presence of a large excess of sodium hydroxide gave a product, m. p. about 300°, sparingly soluble in alcohol. This was purified by precipitation from pyridine solution by the addition of alcohol [Found: N, 17·9. 4 : 6-*Bis*-(4′-*sulphonamidobenzeneazo*)*resorcinol*, $C_{18}H_{16}O_6N_6S_2$, requires N, 17·6%].

2′ : 4′-*Dihydroxybenzanilide.*—(*a*) 4-Benzeneazoresorcinol 3-benzoate (12 g.) in 50% alcohol (500 ml.) was reduced by the gradual addition of sodium hydrosulphite whilst heating on a water-bath. On pouring into sodium chloride solution (1200 ml. of 20%) a white crystalline precipitate appeared, which was collected after 1 hour, washed, and dried. Recrystallisation from benzene gave fine needles, m. p. 193·5°; yield 87% (Found: C, 67·6; H, 5·1; N, 6·05. $C_{13}H_{11}O_3N$ requires C, 68·1; H, 4·85; N, 6·1%). The material gave no colour with ferric chloride and showed no tendency to oxidation when dissolved in sodium hydroxide solution. It was insoluble in dilute and concentrated hydrochloric acid and failed to react with a solution of *p*-dimethylaminobenzaldehyde in acid solution. The migration of a benzoyl radical from the phenolic hydroxyl to an amino-group in the *o*-position was suspected and this was proved by methylation of the compound with methyl sulphate in alkaline solution, a substance, m. p. 173·5°, being isolated. 2′ : 4′-Dimethoxybenzanilide, m. p. 173°, had previously been prepared by Bechhold (*Ber.*, 1889, **22**, 2377) by the action of benzoyl chloride on 4-aminoresorcinol dimethyl ether.

(*b*) The reduction of 4-(4′-sulphonamidobenzeneazo)resorcinol 3-benzoate with sodium hydrosulphite as in (*a*) gave needles (yield 93%), m. p. 193·5°, not depressed by 2′ : 4′-*dihydroxybenzanilide* obtained as above. The formation of 2′ : 4′-dihydroxybenzanilide in this reaction indicated that the azo- and the benzoyloxy-group were ortho to one another in the starting material and this confirms the orientation of 4-(4′-sulphonamidobenzeneazo)resorcinol 3-benzoate and its product of hydrolysis, 4-(4′-sulphonamidobenzeneazo)resorcinol.

(*c*) Reduction of 4-nitroresorcinol 3-benzoate in a similar manner again gave 2′ : 4′-dihydroxybenzanilide in fine needles, m. p. 193·5°; yield 20%. The nitro-group must therefore be ortho to the benzoate and the result confirms the orientation of 4-nitroresorcinol 3-benzoate.

6-*Aminoresorcinol* 3-*Benzoate.*—6-Nitroresorcinol 3-benzoate (22·7 g.), suspended in 50% alcohol (300 ml.), was reduced by the gradual addition of sodium hydrosulphite. The flocculent precipitate which appeared when the hot solution was poured into sodium chloride solution (1500 ml. of 20%) was collected and recrystallised from alcohol in presence of a trace of sodium hydrosulphite. The pure substance consisted of shining platelets, m. p. 177—178° (with

previous darkening) and was readily soluble in alcohol and acetone but sparingly soluble in benzene. Yield 58%. It was soluble in dilute acid and gave a diazo-coupling reaction. As migrations of groups similar to those noted above have not been encountered in derivatives of *m*- or *p*-aminophenols, and considering the directive influence of the hydroxyl group, the formation of the corresponding amine is in accord with the orientation of 6-nitroresorcinol 3-benzoate (Found: C, 68·1; H, 4·7; N, 5·9. $C_{13}H_{11}O_3N$ requires C, 68·1; H, 4·85; N, 6·1%).

6-(4′-*Acetamidobenzenesulphonamido*)*resorcinol* 3-*Benzoate*.—4-Acetamidobenzenesulphonyl chloride (17·5 g.) in solution in dry acetone (125 ml.) was added to a solution of 6-aminoresorcinol 3-benzoate (17·4 g.) and pyridine (17 ml.) in acetone (125 ml.). After 15 minutes' refluxing, the solution was acidified with acetic acid (25 ml.) and carefully diluted with water (350 ml.); after several hours a crystalline precipitate appeared. Recrystallisation from alcohol or 50% acetic acid gave microscopic prisms, m. p. 206—207°. Yield 88%. The compound was soluble in acetone and alcohol, sparingly soluble in benzene, insoluble in dilute hydrochloric acid, and failed to diazotise (Found: C, 59·2; H, 4·3. $C_{21}H_{18}O_6N_2S$ requires C, 59·3; H, 4·25%).

4-(4′-*Aminobenzenesulphonamido*)*resorcinol*.—The preceding compound (1·2 g.) was hydrolysed by refluxing for 2½ hours in alcohol (16 ml.) containing dilute hydrochloric acid (16 ml. of 20%). The solution obtained on pouring into hydrochloric acid (100 ml. of 5%) was washed with ether to remove esters, neutralised with sodium bicarbonate, saturated with sodium chloride, and completely extracted with ether. Crystallisation from dilute alcohol gave needles, m. p. 176°. Yield, 32%. The substance was soluble in dilute acid, alcohol and acetone, but was only sparingly soluble in benzene. It gave a positive diazo-reaction (Found: C, 51·7; H, 4·7; N, 9·7. $C_{12}H_{12}O_4N_2S$ requires C, 51·4; H, 4·3; N, 10·0%).

6-*Nicotinamidoresorcinol* 3-*Benzoate*.—Nicotinyl chloride hydrochloride (8·9 g.), prepared according to Späth and Spitzer (*Ber.*, 1926, **59**, 1479, 1482), was added to a solution of 6-aminoresorcinol 3-benzoate (10·5 g.) and pyridine (22 ml.) in dry acetone (50 ml.). After refluxing for 15 minutes, the solution was cooled, acidified with acetic acid (25 ml.), and diluted with water until precipitation commenced. After standing in the cold a fine crystalline precipitate (14·2 g.) appeared, which on recrystallisation from acetic acid or from alcohol melted at 212°. Yield 80%. The product was insoluble in benzene, sparingly soluble in alcohol and acetic acid and rather more so in acetone. It was freely soluble in dilute alkali, giving a yellow coloration (Found: C, 67·9; H, 4·5; N, 8·4. $C_{19}H_{14}O_4N_2$ requires C, 68·2; H, 4·2; N, 8·3%).

4-*Nicotinamidoresorcinol*.—Aqueous potassium hydroxide solution (17 ml. of 6%) was added to finely powdered 6-nicotinylamidoresorcinol 3-benzoate (2 g.) suspended in alcohol (33 ml.), and the mixture shaken until a clear solution was formed. After 12 hours the dark olive-green solution was poured into dilute hydrochloric acid (200 ml. of 2%), and the solution neutralised with sodium bicarbonate and extracted with ether after saturation with sodium chloride. The ethereal solution was washed with water and with brine, and the solvent removed. The residue (0·77 g.), m. p. 240—243°, was recrystallised from acetone, yielding needles, m. p. 243° (with previous charring). Yield 56% (Found: C, 62·6; H, 4·5; N, 12·2. $C_{12}H_{10}O_3N_2$ requires C, 62·6; H, 4·35; N, 12·2%).

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