# Preparation of Mononitrophloroglucinol Methyl Ethers and Benzenesulphonates

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Mononitration of phloroglucinol dibenzenesulphonate gave 2-nitro-1,3- and -3,5-dibenzenesulphonate, from which mononitrophloroglucinol and its possible mono-, di-, and tri-methyl ethers and benzenesulphonates can be prepared. Similar nitration of phloroglucinol monobenzenesulphonate monomethyl ether gave three mononitro-compounds which were separated and characterised as the possible monoester monoethers of mononitrophloroglucinol.

In a general study of nitro-compounds of polyhydric phenols, the 1,3-diesters and diethers of 2-nitrophloroglucinol were useful in the synthesis of 1,2,3,5-tetrahydroxybenzene derivatives. Previous attempts to prepare these compounds from mononitrophloroglucinol were unsuccessful, and complete *O*-substitution followed by partial hydrolysis gave us only *o*-nitrophenols, probably because the relative power is $o > p$ for the influence of a nitro-group on the ease of hydrolysis of methoxybenzenes by acids [1] and of benzenesulphonates by alkalis.[2] Therefore, nitration of phloroglucinol diesters and diethers is the only method for the preparation of these *p*-nitrophenols. 2-Nitrophloroglucinol 1,3-dimethyl ether can be most easily prepared from the diester by replacement of the benzenesulphonyl by methyl groups, as the nitration of the diester can be more easily controlled to proceed without giving more heavily nitrated products and resins which it is difficult to remove. This paper describes a method for the preparation of all the possible methyl ethers and benzenesulphonates of mononitrophloroglucinol.

Nitration of phloroglucinol dibenzenesulphonate,[3] gave a mixture of two mononitro-compounds, A and B,

[1] R. Robinson and J. C. Smith, *J. Chem. Soc.*, 1926, 393.
[2] E. Kampouris, *J. Chem. Soc.* (*C*), 1967, 1235.
[3] E. Kampouris, *J. Chem. Soc.*, 1965, 2651.

which were separated. Compound A, the less soluble in benzene, can be reduced by sodium dithionite to an amine which, when examined by the spot test method,[4] gave the characteristic blue spot of reactive *p*-aminophenols. It was 2-nitrophloroglucinol 1,3-dibenzenesulphonate, and compound B was the only possible 2-nitrophloroglucinol 3,5-dibenzenesulphonate. Partial hydrolysis released only *o*-hydroxy-groups, and the two possible monoesters, 2-nitrophloroglucinol 1- and 5-benzenesulphonate, respectively, were obtained. Complete hydrolysis gave mononitrophloroglucinol from both compounds. Methylation of B followed by partial hydrolysis yielded the 5-benzenesulphonate 1-methyl ether, while the methyl ether of A gave a mixture of the unchanged diester and the completely hydrolysed diol. This was because the diester is less soluble than the monoester in the reaction medium, and because of like reactivity of the two ester groups, which are both *ortho* to the nitro-group Complete hydrolysis of the methyl ether diesters gave the 5- and the 3-methyl ether of 2-nitrophloroglucinol, respectively Methylation of the products of the partial hydrolysis of nitro-compound A and B yielded the dimethyl ether monesters, which can be hydrolysed to give 2-nitrophloroglucinol 3,5- and 1,3-dimethyl ether

Nitration of phloroglucinol monomethyl ether monobenzenesulphonate [3] gave a mixture of three mononitrocompounds, C, D, and E which can be separated. Compound C, the least soluble in xylene, gave on hydrolysis 2-nitrophloroglucinol 3-methyl ether, while on reduction only this one of the three yielded an amine showing the blue spot of the reactive *p*-aminophenols and thus characterised as the 2-nitrophloroglucinol 1-benzenesulphonate 3-methyl ether. Compound D, the least soluble in acetic acid and methanol, gave on hydrolysis 2-nitrophloroglucinol 5-methylether, while methylation yielded 2-nitrophloroglucinol 1-benzenesulphonate 3,5-dimethyl ether, confirming that the nitro-group is *ortho* to the ester and *para* to the ether group; thus, D was identified as the 2-nitrophloroglucinol 3-benzenesulphonate 5-methyl ether. Compound E, isolated with difficulty from the mother-liquors, was identified as the only possible 2-nitrophloroglucinol 5-benzenesulphonate 3-methyl ether, obtained also by partial hydrolysis of the methyl ether of nitro-compound B.

## EXPERIMENTAL

*Nitration of Phloroglucinol Dibenzenesulphonate.*[3]—Nitric acid (*d* 1·4; 10 ml.) was added dropwise, at 40° with shaking, to a dispersion of pulverised phloroglucinol dibenzenesulphonate (40·6 g.) in benzene (150 ml.). Shaking was continued at this temperature for 10 min. after the diester had disappeared, and yellow needles precipitated. The mixture was cooled to room temperature, kept for 1 hr. with periodical shaking, and the precipitate was filtered off, washed with benzene and with water, and dried, to give 2-*nitrophloroglucinol* 1,3-*dibenzenesulphonate* (11·5 g., 25%). It formed needles, m. p. 179° (from xylene) (Found: S, 14·0; N, 2·9. $C_{18}H_{13}NO_9S_2$ requires S, 14·2; N, 3·1%). Acetylation yielded the acetate, prisms, m. p. 141° (from xylene), while benzenesulphonylation in pyridine gave 2-*nitrophloroglucinol tribenzenesulphonate*, m. p. 140° (from acetic acid) (Found: N, 2·3; S, 16·5. $C_{24}H_{17}NO_{11}S_3$ requires N, 2·4; S, 16·3%). Methylation with dimethyl sulphate yielded 2-*nitrophloroglucinol* 1,3-*dibenzenesulphonate* 5-*methyl ether*, prisms, m. p. 152—153° (from benzene) (Found: N, 2·9; S, 13·6. $C_{19}H_{15}NO_9S_2$ requires N, 3·0; S, 13·8%).

The benzene mother-liquors from the nitration were washed with water and evaporated, and the residue was treated with cold xylene (2 × 10 ml.), and the undissolved part was collected and dried, to give 2-*nitrophloroglucinol* 3,5-*dibenzenesulphonate* (27 g., 60%). It formed yellow prisms, m. p. 108—109° [from acetic acid (3 g. in 10 ml.)] (Found: N, 3·0; S, 14·4%). Acetylation gave the acetate, m. p. 138° (from xylene); benzenesulphonylation yielded the nitrophloroglucinol tribenzenesulphonate, m. p. 140°; methylation produced 2-*nitrophloroglucinol* 3,5-*dibenzenesulphonate* 1-*methyl ether*, m. p. 107—108° (from methanol) (Found: N, 2·8; S, 14·0%).

*Partial Hydrolysis of* 2-*Nitrophloroglucinol* 1,3-*Dibenzenesulphonate.*—Potassium hydroxide solution (20%; 17 ml.) was added, at 30°, to a stirred solution of 2-nitrophloroglucinol 1,3-dibenzenesulphonate (9 g.) in methanol (100 ml.). The mixture was kept for 10 min. at 30°, diluted with water to 1 l., acidified with hydrochloric acid, cooled for complete deposition, and the precipitate was filtered off, washed with water, and dried, to give 2-*nitrophloroglucinol* 1-*benzenesulphonate* (5·3 g., 85%), m. p. 170° (from benzene) (Found: N, 4·3; S, 10·4. $C_{12}H_9NO_7S$ requires N, 4·5; S, 10·3%). Methylation with dimethyl sulphate gave 2-*nitrophloroglucinol* 1-*benzenesulphonate* 3,5-*dimethyl ether*, m. p. 131—132° (from benzene) (Found: N, 4·0; S, 9·4. $C_{14}H_{13}NO_7S$ requires N, 4·1; S, 9·5%).

2-*Nitrophloroglucinol* 5-*Benzenesulphonate.*—The monoester was obtained (90%) by partial hydrolysis of 2-nitrophloroglucinol 3,5-dibenzenesulphonate, m. p. 131° (from benzene) (Found: N, 4·4; S, 10·5%). Acetylation gave the diacetate, m. p. 115—116° (from methanol), while methylation yielded 2-*nitrophloroglucinol* 5-*benzenesulphonate* 1,3-*dimethyl ether*, m. p. 161°, prisms (from benzene) (Found: N, 4·1; S, 9·7%).

2-*Nitrophloroglucinol* 5-*Benzenesulphonate* 1-*Methyl Ether.*—The monoester monoether prepared by partial hydrolysis of pulverised 3,5-diester 1-ether, was obtained as the hydrate, m. p. 55—57° (from benzene–light petroleum, 1 : 2). Acetylation gave 2-*nitrophloroglucinol* 3-*acetate* 5-*benzenesulphonate* 1-*methyl ether*, m. p. 94—95° (from methanol) (Found: C, 49·1; H, 3·6; N, 3·6; S, 8·6. $C_{15}H_{13}NO_8S$ requires C, 49·0; H, 3·6; N, 3·8; S, 8·7%). Methylation yielded 2-nitrophloroglucinol 5-benzenesulphonate 1,3-dimethyl ether, m. p. 161°.

2-*Nitrophloroglucinol* 3,5-*Dimethyl Ether.*—The diether prepared by hydrolysis of pulverised 1-ester 3,5-dimethyl ether, formed yellow plates, m. p. 131° (from benzene) (Found: C, 48·1; H, 4·4; N, 6·9. $C_8H_9NO_5$ requires C, 48·2; H, 4·6; N, 7·0%). Acetylation gave the acetate m. p. 120—121°, plates (from methanol), while methylation yielded mononitrophloroglucinol trimethyl ether, m. p. 151—152° (from methanol) (lit., 151—152°; [5] 152° [6])

[4] F. Feigl, ' Spot Tests in Organic Analysis,' Elsevier, London, 1960, p. 413.

[5] H. Leuchs, *Annalen*, 1928, **460**, 17.

[6] S. Stanley and S. Zuffanti, *J. Org. Chem.*, 1954, **19**, 1359.

(Found: C, 50·5; H, 5·1; N, 6·0. Calc. for $C_9H_{11}NO_5$: C, 50·7; H, 5·2; N, 6·1%).

*2-Nitrophloroglucinol 1,3-Dimethyl Ether.*—The diether, prepared by hydrolysis of pulverised 5-ester 1,3-diether at 55—60°, forms yellow needles, m. p. 165—166° (from benzene) (Found: C, 48·3; H, 4·5; N, 6·8. $C_8H_9NO_5$ requires C, 48·2; H, 4·6; N, 7·0%). Acetylation gave the acetate, m. p. 100°, prisms (from methanol), while methylation yielded the trimethyl ether, m. p. 151—152°.

*Mononitrophloroglucinol.*—Potassium hydroxide solution (20%, 22·5 ml.) was added, at 60°, to a stirred solution of 2-nitrophloroglucinol 1,3- or 3,5-dibenzenesulphonate (4·5 g.). The mixture was kept at 60° for 15 min., diluted with water to 300 ml., acidified with hydrochloric acid, and cooled for complete deposition. The separated needles were filtered off, washed with cool water, and dried ($CaCl_2$), to give 2-nitrophloroglucinol monohydrate (1·5 g., 80%). Anhydrous red needles crystallised from benzene, m. p. 187—189° (lit., 183—185°;[6] 186—187°;[7] 205°[8]) (Found C, 42·0; H, 2·7; N, 8·0. Calc. for $C_6H_5NO_5$: C, 42·1; H, 2·9; N, 8·2%). Acetylation gave *mononitrophloroglucinol triacetate*, m. p. 107, prisms (from methanol) (Found: C, 48·3; H, 3·5; N, 4·6. $C_{12}H_{11}NO_8$ requires C, 48·5; H, 3·7; N, 4·7%). Methylation yielded the trimethyl ether, m. p. 151—152°.

*2-Nitrophloroglucinol 5-Methyl Ether.*—The monoether was obtained (85%) by complete hydrolysis of the 1,3-diester 5-methyl ether, m. p. 153—154°, orange needles (from benzene) (Found: C, 45·5; H, 3·6; N, 7·5. $C_7H_7NO_5$ requires C, 45·4; H, 3·8; N, 7·6%). Acetylation gave the diacetate, m. p. 119°, needles (from benzene), while methylation yielded the trimethyl ether.

*2-Nitrophloroglucinol 3-Methyl Ether.*—The product prepared by complete hydrolysis of 3,5-dibenzenesulphonate 1-methyl ether was obtained as the monohydrate, yellow needles which easily decomposed in air. Anhydrous yellow-orange needles were obtained from benzene–methanol (3 : 1), m. p. 187° (Found: C, 45·3; H, 3·7; N, 7·6. $C_7H_7NO_5$ requires C, 45·4; H, 3·8; N, 7·6%). Acetylation gave the diacetate, m. p. 77°, needles (from methanol), while methylation yielded the trimethyl ether.

[7] H. Leuchs and A. Geserick, *Ber.*, 1908, **41**, 4182.
[8] A. Rüdiger, *Arch. Pharm.*, 1914, **252**, 180.

*Nitration of Phloroglucinol Monomethyl Ether Monobenzenesulphonate.*[3]—Nitric acid (*d* 1·4, 1 ml.) was added to a solution of phloroglucinol monobenzenesulphonate monomethyl ether (5·6 g.) in acetic acid (25 ml.), and the mixture was kept at 10° for 5 hr., with periodical shaking. The precipitated product was filtered off, washed with a little cool acetic acid and with water, and dried, to give *2-nitrophloroglucinol 3-benzenesulphonate 5-methyl ether* (1 g., 15%), yellow crystals (from xylene), m. p. 118—119° (Found: C, 47·8; H, 3·3; N, 4·1; S, 10·0. $C_{13}H_{11}NO_7S$ requires C, 47·9; H, 3·4; N, 4·3; S, 9·9%). Acetylation gave the acetate, m. p. 83°, prisms (from methanol); methylation yielded the 1-ester, 3,5-dimethyl ether, m. p. 131—132°; and hydrolysis produced the 5-methyl ether, m. p. 131°. Benzenesulphonylation in pyridine gave the 1,3-ester 5-methyl ether, m. p. 152—153°.

The acetic acid mother-liquors were diluted with water to 300 ml., the separated reddish resinous mass was collected, dried in a flash evaporator with acetone, and treated with xylene (10 ml.), the solid product was filtered off, washed with cold xylene (2 × 5 ml.), and crystallised from xylene, to give 3-ester 5-methyl ether (0·3 g., total 20%) and *2-nitrophloroglucinol 1-benzenesulphonate 3-methyl ether* (first precipitated; 2 g., 30%), m. p. 161—162°, prisms (from xylene) (Found: C, 48·0; H, 3·2; N, 4·3; S, 9·8. $C_{13}H_{11}NO_7S$ requires C, 47·9; H, 3·4; N, 4·3; S, 9·9%). Acetylation gave the acetate, m. p. 94—95° (hydrate), 114—115° (anhydrous; from methanol). Methylation yielded the 1-ester 3,5-dimethyl ether, m. p. 131—132°; benzenesulphonylation gave the 3,5-diester 1-ether, m. p. 107—108°; hydrolysis produced 2-nitrophloroglucinol 3-methyl ether, m. p. 187°.

The xylene mother-liquors were warmed with activated alumina (1 g.) and filtered, the filtrates were evaporated, the residue was treated with trichloroethylene (10 ml.), the undissolved residue was filtered off, and the filtrates were evaporated, to leave a yellow oil consisting of impure 2-nitrophloroglucinol 5-benzenesulphonate 1-methyl ether. Acetylation gave an impure acetate which on fractional crystallisation from methanol gave 2-nitrophloroglucinol 3-acetate 5-benzenesulphonate 1-methyl ether (0·5 g., 7%), m. p. 94—95°.

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