[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, ISRAEL INSTITUTE OF TECHNOLOGY]

Halogenation of Pyrogallol Trimethyl Ether and Similar Systems[1a]

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Received June 4, 1956

Halogenations of pyrogallol, its 1,3-dimethyl ether and its trimethyl ether with *t*-butyl hypochlorite, *N*-chlorosuccinimide, and *N*-bromosuccinimide are described.

In connection with a synthetic program involving compounds containing the 1,2,3-trimethoxyphenyl moiety, information was sought regarding the action of certain halogenating agents on this group. Although elementary halogens have been employed to effect chlorination and bromination of pyrogallol, the structure of certain compounds was not definitely established by the investigator involved (see below).[2,3] The action of *t*-butyl hypochlorite (TBH), *N*-chlorosuccinimide (NCS), and *N*-bromosuccinimide (NBS) on this substance, its 1,3-dimethyl ether, and its trimethyl ether was therefore studied.

Chlorination of pyrogallol trimethyl ether by means of one mole of TBH afforded the 4-chloro-derivative in 84% yield. The use of two and three moles of TBH gave the 4,6-derivative in 88% and 94% yield, respectively.

Chlorination by means of one mole of NCS, similarly gave the 4-chloro- compound. The use of 2 moles of NCS afforded a mixture of the 4-chloro- and 4,5,6-trichloro-derivatives while chlorination of 4-chloropyrogallol trimethyl ether with one mole of reagent or chlorination of pyrogallol trimethyl ether with three moles gave chiefly the 4,6-dichloro-compound.

NBS gave the corresponding bromo-derivatives. The halogenation results are summarized in Table I. It must be noted that only when a full molar excess of halogenating agent is used is a halogen atom sometimes introduced into the 5-position.

Halogenation of pyrogallol and its 1,3-dimethyl ether shows that the combined *o*,*p*-directing influence of the 1- and 3-hydroxyl groups in the first instance, and that of the 1- and 3-methoxyls in the latter, clearly outweighs the *p*-directing influence of the 2-hydroxyl group which is counteracted by the deactivating influence of the 1- and 3- substituents for substitution in the 5-position.

Peratoner[2] has not definitively formulated the structure of the dichloropyrogallol, m.p. 128°, which he obtained by the action of sulfuryl chloride on pyrogallol in ether solution. In the present work a dichloropyrogallol, m.p. 129°, was obtained by the action of NCS on pyrogallol. This was methylated by means of dimethyl sulfate in the presence of acetone-potassium carbonate. Nitration of the resulting substance yielded 4,6-dichloro-5-nitropyrogallol trimethyl ether, m.p. 103°. Peratoner's substance must therefore be formulated as 4,6-dichloropyrogallol.

Similarly, Perkin and Simonsen[3] obtained a dibromopyrogallol, m.p. 158°, whose structure has now been established as the 4,6- isomer since similar methylation and nitration of the NBS bromination product, m.p. 155°, gave 4,6-dibromo-5-nitropyrogallol trimethyl ether, m.p. 110–111°.

Kohn and Grün[4] described 4,5-dibromopyrogallol 1,3-dimethyl ether, m.p. 75–76° obtained in undisclosed yield. Methylation of this product followed by nitration gave a mononitro derivative, m.p. 84–86° which differed from the 4,6-dibromo-5-nitro- isomer. In our hands, NBS bromination yielded 4,6-dibromopyrogallol 1,3-dimethyl ether, m.p. 127–128°. Thus, it appears that the direct bromination of the 1,3 dimethyl ether with bromine, is the only known case in this series where the 5- position is substituted.

EXPERIMENTAL[5]

Halogenations with NBS. Pyrogallol trimethyl ether (0.05 mole) was brominated with the respective quantities of NBS, in boiling carbon tetrachloride (50 ml.). Pyrogallol dimethyl ether (0.02 mole) was similarly brominated in boiling carbon tetrachloride (25 ml.). Pyrogallol (0.08 mole) was similarly brominated in boiling ether (50 ml.). The succinimide and solvent were removed and the products either distilled or crystallized.

Halogenations with TBH. Pyrogallol trimethyl ether (0.02 mole) was chlorinated at room temperature with the respective quantities of TBH in carbon tetrachloride (10 ml.). The strongly exothermic reactions caused the solvent to boil and reflux was maintained for 30 min. The solvents were removed and the products distilled under reduced pressure.

Halogenations with NCS. Pyrogallol trimethyl ether (0.05 mole) was chlorinated with the respective quantities of NCS in boiling carbon tetrachloride (50 ml.) in the presence of a catalytic amount of dibenzoyl peroxide. Pyrogallol dimethyl ether (0.02 mole) was chlorinated in carbon tetrachloride at room temperature without added peroxide. The strongly

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[1] (a) Presented at XIXth meeting of the Israel Chemical Association, Rehovot, June, 1956. (b) This work forms part of Dvora Friedman's M.Sc. thesis, Israel Institute of Technology.

[2] Peratoner, *Gazz. chim. ital.*, **28**, 225 (1898).

[3] Perkin and Simonsen, *J. Chem. Soc.*, **87**, 863 (1905).

[4] Kohn and Grün *Monatshefte*, **46**, 75 (1925).

[5] Melting and boiling points are uncorrected.

TABLE I

HALOGENATION OF PYROGALLOL TRIMETHYL ETHER

Reagent	No. of Equiv.	Reac. time	Product	Yield	B.P. or M.P.	Proof of Structure	M.P.
NBS	1	3 hr.	4-Bromo-	70%	97° (0.5 mm.)	4-Bromo-5-nitro- 4-Bromo-5,6-dinitro-	85– 86[a] 134–135[b]
NBS	1 + 1	48	4,6-Dibromo-	72	90 (0.05 mm.)	4,6-Dibromo-5-nitro-	110–111[c]
NBS	2	6	4,6-Dibromo-	80	90 (0.05 mm.)	4,6-Dibromo-5-nitro-	110–111[c]
NBS	3	17	4,6-Dibromo- 4,5,6-Tribromo-	49 24	118 (0.4 mm.) 149 (0.4 mm.) 73–74	4,6-Dibromo-5-nitro- Admixture with authentic specimen[d]	110–111[c] 73– 74[a]
NCS	1	5	4-Chloro-	85	98 (0.6 mm.)	4-Chloro-5,6-dinitro-	116[e]
NCS	1 + 1	24	4,6-Dichloro-	73	80 (0.1 mm.)	4,6-Dichloro-5-nitro-	103[f]
NCS	2	7	4-Chloro- 4,5,6-Trichloro-	65 18	92 (0.5 mm.) 112 (0.5 mm.) 52–54	4-Chloro-5,6-dinitro- Admixture with authentic specimen	116[e] 53– 54[g]
NCS	3	20	4,6-Dichloro-	75	85 (0.2 mm.)	4,6-Dichloro-5-nitro-	103[f]
TBH	1	0.5	4-Chloro-	84	146 (22 mm.)	4-Chloro-5,6-dinitro-	116–117[e]
TBH	2	0.5	4,6-Dichloro-	88	80 (0.1 mm.)	4,6-Dichloro-5-nitro-	103[f]
TBH	3	0.5	4,6-Dichloro-	94	85 (0.2 mm.)	4,6-Dichloro-5-nitro-	103[f]

[a] Will, *Ber.*, **21**, 602 (1888), reports m.p. 92°. *Anal.* Calcd. for $C_9H_{10}NO_5Br$: C, 37.0; H, 3.4; N, 4.8; Br, 27.4 Found: C, 37.4; H, 3.3; N, 4.8; Br, 26.9. [b] Kohn and Grün, *Monatshefte*, **46**, 75 (1925) report m.p. 134–135°. [c] Kohn and Grün, ref. *b*, report m.p. 110°. [d] Prepared as described in ref. *a*. [e] Kohn and Gurewitch, *Monatshefte*, **49**, 173 (1928) report m.p. 116–118°. [f] Kohn and Gurewitch, ref. *e*, report m.p. 103–104°. [g] Prepared as described by Bartolotti, *Gazz. chim. ital.*, **27**, 290 (1897) with substitution of CCl_4 for AcOH. He reports m.p. 54°.

TABLE II

HALOGENATION OF PYROGALLOL AND ITS 1,3-DIMETHYL ETHER

Substance	Reagent	No. of Equiv.	Reac. time, Hr.	Product	Yield	B.P.	M.P.
Pyrogallol	NBS	1	2	4-Bromo-	37		119–120[a]
	NBS	2	3	4,6-Dibromo-	13		155[b]
	NBS	3	3	4,5,6-Tribromo-	5		168[c]
	NCS	1	3	4-Chloro-	52		144–145[d]
	NCS	2	4	4-Chloro-, 4,6-dichloro-	9 13		144–145[d] 129[e]
	NCS	3	20	4,6-Dichloro-, 4,5,6-trichloro-	13 22		129[e] 177[b]
Pyrogallol 1,3-dimethyl ether	NBS	1	4	4-Bromo-	55	88 (0.4 mm.)[f]	
	NBS	2	12	4,6-Dibromo-	50		127 128[g]
	NBS	3	12	4,5,6-Tribromo	40		134[h]
	NCS	1	0.25	4-Chloro-	71	87 (0.05 mm.)[i]	
	NCS	2	0.25	4,5,6-Trichloro-	48		119[j]
	NCS	3	0.25	4,5,6-Trichloro-	82		119[j]

[a] Einhorn and Cobliner, *Ber.*, **37**, 112 (1904) report m.p. 120°. [b] Perkin and Simonsen, *J. Chem. Soc.*, **87**, 863 (1905), report m.p. 158°. Methylation and nitration gave 4,6-dibromo-5-nitropyrogallol trimethyl ether, m.p. 110°. Kohn and Grün, ref. c, report m.p. 110°. [c] Kohn and Grün, *Monatshefte*, **46**, 75 (1925), report m.p. 168–170°. [d] Ginsburg, *J. Am. Chem. Soc.*, **73**, 2723 (1951), reports m.p. 144–145°. [e] Peratoner, *Gazz. chim. ital.*, **28**, 225 (1898), reports m.p. 128°. Methylation and nitration gave 4,6-dichloro-5-nitropyrogallol trimethyl ether, m.p. 103°. Kohn and Gurewitch, *Monatshefte*, **49**, 173 (1928), report m.p. 103–104°. [f] Methylation and nitration yielded 4-bromo-5,6-dinitropyrogallol trimethyl ether, m.p. 134–135°, Kohn and Grün, ref. *c*, report m.p. 134–135°. [g] *Anal.* Calcd. for $C_8H_8O_3Br_2$: C, 30.8; H, 2.5. Found: C, 30.7; H, 2.7. Kohn and Grün, ref. *c*, report 4,5-dibromo isomer, m.p. 75–76°. [h] Levine, *J. Am. Chem. Soc.*, **48**, 1608 (1926), reports m.p. 133.5°. [i] Bromination as described by Levine, *J. Am. Chem. Soc.*, **48**, 2719 (1926) gave 5,6-dibromo-4-chloropyrogallol-1,3-dimethyl ether, m.p. 124–125°. Levine reports m.p. 124–125°. [j] Levine, ref. *h* reports m.p. 121.5°.

exothermic reaction was complete within 15 min. Pyrogallol (0.12 mole) was chlorinated in boiling ether (50 ml.) in the presence of peroxide. The succinimide and solvent were removed and the products either distilled or crystallized.

In the case of pyrogallol halogenations, purification was aided through vacuum sublimation.

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