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Bromination of 3-(Trifluoromethyl)-phenol*

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Bromination of 3-(trifluoromethyl)-phenol in both carbon tetrachloride and bromine water has been investigated. Monobromination in carbon tetrachloride gave 2-bromo-5-(trifluoromethyl)-phenol and 4-bromo-3-(trifluoromethyl)-phenol. On attempted dibromination, 2-bromo-5-(trifluoromethyl)-phenol, 2,4-dibromo-5-(trifluoromethyl)-phenol, 2,6-dibromo-3-(trifluoromethyl)-phenol and 2,4,6-tribromo-3-(trifluoromethyl)-phenol were obtained. Bromination with bromine water yielded 2,4-dibromo-5-(trifluoromethyl)-phenol. Synthesis of 4-bromo-3-(trifluoromethyl)-phenol from 4-bromo-3-(trifluoromethyl)-aniline is also reported.

Discussion

A study has been made of the bromination of 3-(trifluoromethyl)-phenol, both in carbon tetrachloride and bromine water. Since 3-(trifluoromethyl)-phenol is relatively insoluble in water, only dilute solutions can be brominated in this manner. When appreciable quantities of products were desired, it was found most advantageous to brominate solutions of the phenol in carbon tetrachloride even though bromination occurred more slowly than in aqueous solutions. Bromination of 3-(trifluoromethyl)-phenol with bromine water has been mentioned by Jones[1] who reported that reaction proceeded slowly to give an oily product, the nature of which was not discussed.

The results obtained indicate that monobromination in carbon tetrachloride proceeds slowly, and that the slower rate of further bromination of monobrominated material approximates the rate of bromination of dibrominated material. Therefore, while it was possible to obtain high yields of monobromo phenols, attempted synthesis of the dibromo compounds always resulted in the formation of mixtures of mono-, di- and tribrominated products.

Reaction of one molecular equivalent of bromine with 3-(trifluoromethyl)-phenol gave an 85% yield of monobromophenols of which more than 95% was 2-bromo-5-(trifluoromethyl)-phenol, and less than 5% was 4-bromo-3-(trifluoromethyl)-phenol. In attempts to obtain dibromination, a mixture of 2-bromo-5-(trifluoromethyl)-phenol, 2,4-dibromo-5-(trifluoromethyl)-phenol, 2,6-dibromo-3-(trifluoromethyl)-phenol and 2,4,6-tribromo-3-(trifluoromethyl)-phenol was obtained.

The often assumed parallelism between the deactivating effect of nitro and trifluoromethyl groups on reactions of the benzene nucleus is not observed in bromination of the *m*-substituted phenol. Henley and Turner[2] have noted that monobromination of *m*-nitrophenol does not take place below 120° and that the principal product of the reaction is 4-bromo-3-nitrophenol. On attempted dibromination, only 4-bromo-3-nitrophenol and 2,4,6-tribromo-3-nitrophenol were obtained. Therefore, while the nitro group decidedly decreases the rate of bromination,[3] it does not direct the incoming substituent to the same positions as does the trifluoromethyl group.

The position at which substitution first occurs in the bromination of 3-(trifluoromethyl)-phenol is consistent with the widely accepted views of Ingold[4] concerning attack on the aromatic nucleus by halogen. Polarization of bromine by the solvent should lead to the molecule $(\delta+)\mathrm{Br}\text{—}\mathrm{Br}(\delta-)$. The electron depleted bromine atom would then be expected to attack preferentially the carbon atom of highest electron density. The positions ortho and para to the hydroxyl group of 3-(trifluoromethyl)-phenol do not have equal electron densities since the strong -I effect of the trifluoromethyl group tends to greatly decrease electron availability on the carbon atoms adjacent to it. Therefore, it would be expected that in 3-(trifluoromethyl)-phenol the 6-carbon would have the greatest electron density of the unsubstituted carbon atoms, and that a relatively positive bromine atom would attack this position. The qualitative observation that bromination of the fluorinated phenol proceeded more rapidly in water than in carbon tetrachloride is also in accord with Ingold's theories since a more polar solvent would be expected to increase polarization of the halogen molecule, thereby promoting the reaction rate.

Since bromination was inconvenient for the preparation of a sufficient quantity of 4-bromo-3-(trifluoromethyl)-phenol for characterization, a larger sample was prepared from 4-bromo-3-(trifluoromethyl)-aniline.[5] This amine was readily diazotized and the diazonium hydrogen sulfate was hydrolyzed to give 4-bromo-3-(trifluoromethyl)-phenol in 48% yield.

The structures of all compounds, with the exception of 2,6-dibromo-3-(trifluoromethyl)-phenol, were proved by hydrolysis of the trifluoromethyl group to a carboxyl group[6] and comparison of the products with known compounds. Since 2,4-dibromo-3-hydroxybenzoic acid is unknown, it was necessary to use other means for proof of structure of 2,6-dibromo-3-(trifluoromethyl)-phenol. Qualitative tests of this phenol with Gibb reagent[7] gave initial evidence for an unsubstituted para position. The phenol was then nitrated and the nitro compound hydrolyzed to the known 2,4-dibromo-3-hydroxy-6-nitrobenzoic acid.[8]

Experimental[9]

Monobromination.—A mixture of 80 g. (0.5 mole) of bromine in 100 ml. of carbon tetrachloride was added drop-

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[*] This paper contains material abstracted from the doctoral thesis of Edward Rapkin.

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(4) Ingold, *Chem. Revs.*, **15**, 271 (1934).

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(6) G. M. LeFave, *ibid.*, **71**, 4148 (1949).

(7) H. D. Gibb, *J. Biol. Chem.*, **72**, 649 (1927).

(8) T. A. Henry and T. M. Sharp, *J. Chem. Soc.*, **125**, 1049 (1924).

(9) Microanalyses by Dr. H. Galbraith.

wise to a stirred solution of 80 g. (0.5 mole) of 3-(trifluoromethyl)-phenol[10] in 100 ml. of refluxing carbon tetrachloride. The rate of addition was such that unreacted bromine did not accumulate in the reaction flask. After four hours, when all the bromine had reacted, the solvent was evaporated and the residue distilled at 10–12 mm. A light yellow oil (102 g.) boiling between 75–110° was obtained which represented an 85% yield of monobrominated phenols.

Separation of the mixture was accomplished by rectification at reduced pressure through a three-foot Todd column[11] with spiral wire packing. The colorless lower boiling fraction (b.p. 56–57.5° at 3.5–4 mm., m.p. 22–23°) comprising more than 95% of the mixture was 2-bromo-5-(trifluoromethyl)-phenol, n^{20}D 1.4958. The small quantity of higher-boiling light yellow liquid which solidified on standing was 4-bromo-3-(trifluoromethyl)-phenol (b.p. 61–63° at 3.5–4 mm.). Recrystallization of this low melting material from petroleum ether (30–60°) did not give a sharp melting point.

Anal. Calcd. for $C_7H_4BrF_3O$: C, 35.0; H, 1.67. Found: 2-bromo-5-(trifluoromethyl)-phenol, C, 35.0; H, 1.85; 4-bromo-3-(trifluoromethyl)-phenol, C, 34.8; H, 1.74.

The structures of these compounds were demonstrated by hydrolysis. Sulfuric acid hydrolysis of 2-bromo-5-(trifluoromethyl)-phenol readily gave a white solid which melted at 225–226°. This is in agreement with values reported by Beyer[12] and Buehler, *et al.*,[13] for the melting point of 4-bromo-3-hydroxybenzoic acid.

Hydrolysis of 4-bromo-3-(trifluoromethyl)-phenol was considerably more difficult than the above. A small sample of the hydrolysate decomposed between 179–183°. Beyer[12] has reported the decomposition temperature of 2-bromo-5-hydroxybenzoic acid as 185°.

Dibromination in Carbon Tetrachloride.—The procedure employed for dibromination of 40 g. (0.25 mole) of 3-(trifluoromethyl)-phenol with 80 g. (0.5 mole) of bromine was the same as that for monobromination. However, it was necessary to run the reaction for a five-day period in order to utilize all of the bromine. The crude oily product obtained after removal of the solvent weighed 75 g. Distillation of 60 g. of this mixture at 4 mm. gave 12 g. of monobromo-(trifluoromethyl)-phenol (b.p. 55–60°), 35 g. of oily yellow dibromo-(trifluoromethyl)-phenols (b.p. 96–99°), and 11 g. of dark fluid pot residue.

Rectification of the monobrominated material gave only 2-bromo-5-(trifluoromethyl)-phenol. The liquid dibromophenols were dissolved in petroleum ether (30–60°) and the solution was chilled. A solid precipitate was obtained which, after several recrystallizations, was white and melted at 73.5–74.5°. This solid was identified as 2,4-dibromo-5-(trifluoromethyl)-phenol by hydrolysis to a white material melting at 200–201°. This value is in good agreement with the melting point of 4,6-dibromo-3-hydroxybenzoic acid as reported by Robertson[14] and Lock and Hosaeus.[15]

Anal. Calcd. for $C_7H_3Br_2F_3O$: C, 26.3; H, 0.94. Found: C, 26.4; H, 0.97.

Evaporation of the mother liquors from the first crystallization of the dibrominated phenols gave several milliliters of an orange oil which subsequently could not be crystallized or purified by distillation. A 1-ml. portion of this oil was dissolved in 5 ml. of ice-cold fuming nitric acid and the mixture was permitted to stand for 15 minutes, then poured on ice, and the resulting yellow solid collected. Attempted purification by recrystallization from several solvents and solvent pairs gave only impure material. However, a small sample of this solid was hydrolyzed to give a material melting at 228–229°.

Since the oil before nitration gave a positive indophenol test, and both the initial nitration product and the hydrolysate gave colors characteristic of a *p*-nitrophenol in basic solution, it is believed that the oil consisted largely of 2,6-dibromo-3-(trifluoromethyl)-phenol. The melting point of 230° given by Henry and Sharp for 2,4-dibromo-3-hydroxy-6-nitrobenzoic acid tends to confirm this assumption. As a further check it was found, as expected, that of the other phenols, only 2-bromo-5-(trifluoromethyl)-phenol gave a positive indophenol test.

The dark pot residue from distillation of the original reaction mixture was dissolved in petroleum ether (90–100°) and decolorized with Norite. Vacuum evaporation of the solvent gave a light yellow oil which was then dissolved in pentane. By immersing the solution in a Dry Ice cooled bath solid 2,4,6-tribromo-3-(trifluoromethyl)-phenol was obtained. By repetition of this procedure it was possible to obtain a white solid melting at 43–44°.

Anal. Calcd. for $C_7H_2Br_3F_3O$: C, 21.1; H, 0.50. Found: C, 21.5; H, 0.54.

Hydrolysis of this solid gave a white material melting at 145–147°. This is in agreement with values reported by Robertson[14] and Leulier and Pinet[16] for the melting point of 3-hydroxy-2,4,6-tribromobenzoic acid.

Dibromination in Bromine Water.—A small quantity of 3-(trifluoromethyl)-phenol dissolved in water, was brominated according to the procedure of Shriner and Fuson.[17] Bromine decolorization was fairly rapid but ceased after addition of two molecular equivalents. The insoluble liquid product was collected, dissolved in ether, dried, and distilled. The only phenolic product identified was 2,4-dibromo-5-(trifluoromethyl)-phenol which was obtained in 70% yield.

4-Bromo-3-(trifluoromethyl)-phenol.—Dissolution of 10 g. (0.062 mole) of 4-bromo-3-(trifluoromethyl)-aniline in a heated mixture of 9.6 ml. of concentrated sulfuric acid and 43 ml. of water gave a clear solution from which the aniline hydrogen sulfate precipitated on cooling to 0°. An ice-cold solution of 2.95 g. (0.43 mole) of sodium nitrite in 20 ml. of water was added dropwise to the stirred suspension of amine salt. The rate of addition was adjusted to prevent the reaction temperature from rising above 2°. At the conclusion of nitrite addition, the resulting clear yellow solution was slowly added dropwise to a mixture of 20 ml. of concentrated sulfuric acid and 80 ml. of water through which steam was passed continuously. Hydrolysis and steam distillation of the resultant product were therefore concurrent. Steam distillation was continued until 1500 ml. of light yellow aqueous distillate was obtained.

The steam distillate was ether extracted and the extracts dried. After removal of the ether, the dark red residue was distilled at reduced pressure. 4-Bromo-3-(trifluoromethyl)-phenol (4.8 g., 48% yield) was obtained as a light yellow solid. This material was recrystallized from petroleum ether (30–60°) to give white crystals m.p. 44–46° (sealed tube). When exposed to the atmosphere for several minutes these crystals liquefied to give a colorless oil. By solution of the oil in petroleum ether and subsequent cooling, the original crystals could be recovered.

Anal. Calcd. for $C_7H_4BrF_3O$: C, 35.0; H, 1.67. Found: C, 34.75; H, 1.88.

Hydrolyses.—The hydrolytic procedure used to assign structures was essentially that of LeFave.[6] However, it was found that by use of nickel equipment silica contamination was eliminated and lighter colored products resulted.

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