Some 2-Hydroxyethyl and Nitrogen Mustard Derivatives of *p*-Aminoarylarylacetonitriles

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The reactions of six *p*-aminoarylarylacetonitriles with ethylene oxide are described. These reactions are apparently influenced by steric hindrance and the relative basicities of the amines. The conversion of the bis-(2-hydroxyethyl) derivatives of the *p*-aminoarylarylacetonitriles to the bis-(2-chloroethyl) derivatives is likewise described, along with subsequent hydrolysis of the nitrile groups to both amide and acid groups. Attempts to obtain bis-(2-chloroethyl) derivatives of compounds containing methoxy substituents were unsuccessful.

THE *p*-aminoarylarylacetonitriles employed in this investigation have been described previously (*1*). Their 2-hydroxyethyl derivatives were obtained through treatment with ethylene oxide following procedures similar to those of other workers (*2*). The bis-(2-hydroxyethyl) derivatives were in turn converted to the bis-(2-chloroethyl) compounds using phosphorus oxychloride according to the method described by Wain *et al.* (*3*). Hydrolysis of these nitrogen mustard derivatives using concentrated sulfuric acid at room temperature for about 4 hours, followed by pouring into ice and water, produced the corresponding amides. Hydrolysis of the nitrogen mustard derivatives using 50% sulfuric acid at 110° to 115° C. for about 3 hours, produced the corresponding acids. The transformations of this investigation can be pictured by the following reaction scheme.

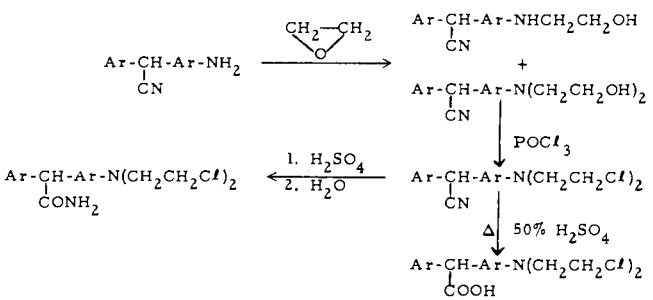

Table I lists the compounds which were isolated and identified. Identification was based chiefly on elemental analysis, infrared spectra, and similarity in the reactions involved to known transformations.

Table I. 2-Hydroxyethyl and Nitrogen Mustard Derivatives of *p*-Aminophenylphenylacetonitriles

Compound	M.P., ° C.[a]	Yield, %	Recrystallization Solvent	Analysis, %[b]
4-*N*-(2′-Hydroxyethyl)amino-3-methylphenylphenylacetonitrile	84–86	87	Benzene	C, 76.66; H, 6.81; N, 10.52 C, 76.67; H, 6.57; N, 10.35
4-*N*-(2′-Hydroxyethyl)amino-3-methoxyphenylphenylacetonitrile[c]	60–62	11	Benzene–pet. ether[d]	C, 72.32; H, 6.43; N, 9.24 C, 72.61; H, 6.48; N, 9.24
4-*N*,*N*-Bis-(2′-hydroxyethyl)aminophenylphenylacetonitrile	89–90	82	Benzene	C, 72.94; H, 6.80; N, 9.46 C, 72.80; H, 7.06; N, 9.40
4-*N*,*N*-Bis-(2′-hydroxyethyl)aminophenyl-4-chlorophenylacetonitrile	82–83	85	Benzene–pet. ether[d]	C, 65.35; H, 5.97 C, 65.59; H, 5.94
4-*N*,*N*-Bis-(2′hydroxyethyl)aminophenyl-4-methoxyphenylacetonitrile	87	71	Benzene	C, 69.91; H, 6.79 C, 69.99; H, 6.83
4-*N*,*N*-Bis-(2′ hydroxyethyl)amino-3-methylphenylphenylacetonitrile	...[e]	80		
4-*N*,*N*-Bis-(2′-chloroethyl)aminophenylphenylacetonitrile	97	81	Methanol	C, 64.87; H, 5.44; Cl, 21.28 C, 64.73; H, 5.49; Cl, 21.38
4-*N*,*N*-Bis-(2′-chloroethyl)aminophenyl-4-chlorophenylacetonitrile	...[e]	92		
4-*N*,*N*-Bis-(2′-chloroethyl)amino-3-methylphenylphenylacetonitrile	...[e]	91		
4-*N*,*N*-Bis-(2′-chloroethyl)aminophenylphenylacetamide	165	87	Benzene	C, 61.54; H, 5.74; N, 7.97 C, 61.51; H, 5.75; N, 7.75
4-*N*,*N*-Bis-(2′-chloroethyl)aminophenyl-4-chlorophenylacetamide	123–124	74	Ethanol	C, 56.04; H, 4.97; Cl, 27.58 C, 56.19; H, 4.96; Cl, 27.85
4-*N*,*N*-Bis-(2′-chloroethyl)amino-3-methylphenylphenylacetamide	116–117	66	Benzene–pet. ether[d]	C, 62.47; H, 6.07; N, 7.66 C, 62.86; H, 6.37; N, 7.70
4-*N*,*N*-Bis-(2′-chloroethyl)aminophenylphenylacetic acid	115	90	Benzene–pet. ether[d]	C, 61.37; H, 5.43 C, 61.30; H, 5.46
4-*N*,*N*-Bis-(2′-chloroethyl)aminophenyl-4-chlorophenylacetic acid	83–85	53	Benzene	C, 55.90; H, 4.69 C, 56.25; H, 4.90
4-*N*,*N*-Bis-(2′-chloroethyl)amino-3-methylphenylphenylacetic acid	92	34	Benzene–pet. ether[d]	C, 62.30; H, 5.78 C, 61.98; H, 5.91

[a] All melting points uncorrected. [b] Analyses by Midwest Microlab, Inc., Indianapolis, Ind. First series calculated, second found. [c] Isolated using column chromatography. [d] Petroleum ether, b.p. 60–71° C. [e] Isolated as an oil. In calculating yields for subsequent reactions, oil assumed to be pure.

The reaction of ethylene oxide with *p*-aminoarylarylacetonitriles apparently is susceptible to steric hindrance from groups substituted ortho to the amino group. After the usual reaction time, 24 hours, the mono-2-hydroxyethyl derivatives for the compounds containing the methyl group and the methoxy group ortho to the amine function were isolated, while the compounds without a substituent ortho to the amino group produced the bis-(2-hydroxyethyl) derivatives in good yield. After an 8-day reaction time using a large excess of ethylene oxide, the bis-(2-hydroxyethyl) derivative of 4-amino-3-methylphenylphenylacetonitrile was obtained as an oil. Subsequent reactions showed the oil to be authentic. Prolonged reaction time in the presence of ethylene oxide failed to hydroxyethylate 4-amino-3-chlorophenylphenylacetonitrile; the starting material was recovered unchanged. Both steric hindrance and the weaker basicity of the amine may be responsible for this failure to react.

A number of attempts to isolate and identify nitrogen mustard derivatives of 4-aminophenyl-4-methoxyphenylacetonitrile and 4-amino-3-methoxyphenylphenylacetonitrile were unsuccessful.

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Trifluoroacylation

Synthesis of ω-Trifluororesacetophenone and ω-Trifluorophloroacetophenone

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The aluminum chloride–catalyzed reaction of trifluoroacetic anhydride with resorcinol and with phloroglucinol afforded ω-trifluororesacetophenone and ω-trifluorophloroacetophenone, respectively.

SINCE large quantities of ω-trifluororesacetophenone (I) were needed, possible methods of synthesis were explored. The reported Hoesch reaction of resorcinol with relatively expensive trifluoromethyl cyanide involves several steps (*6*). Furthermore, Whalley (*6*) has reported that trifluoromethyl cyanide fails to react with orcinol, pyrogallol, and phloroglucinol. Accordingly, a more convenient synthesis for ω-trifluororesacetophenone was undertaken. The acylation of aromatics with trifluoroacetic anhydride has been cited by Parish and Stock (*3*) and by Tedder (*5*). In the present investigation, relatively inexpensive, commercially available trifluoroacetic anhydride was caused to react with resorcinol in 1,2-dichloroethane in the presence of aluminum chloride to afford compound I in 68 to 73% yields.

To establish the generality of this reaction, it was extended to phloroglucinol. Under similar experimental conditions, aluminum chloride catalyzed the trifluoroacylation of phloroglucinol with trifluroacetic anhydride in 1,2-dichloroethane to give ω-trifluorophloroacetophenone (II, α,α,α-trifluoro-2,4,6-trihydroxyacetophenone) in 40% yield. Infrared and nuclear magnetic resonance data are reasonable for the proposed structure. Further evidence for the structure of compound II is the formation of phloroglucinol on heating with alkali (*2*).

EXPERIMENTAL

Melting points were taken with a Thomas Hoover capillary melting point apparatus and are corrected. The infrared spectra were taken with a Perkin-Elmer Model 21 spectrophotometer. Proton magnetic resonance spectra were taken with a Varian model A-60 instrument. Values are reported in τ units using tetramethylsilane as internal reference. Fluorine magnetic resonance spectra were taken with a Varian model V-4300-2 40 mc. per sec. spectrometer. Values are reported in θ^* ($CFCl_3$ reference). Analyses were performed by the Microanalytical Section of these laboratories.

Materials. Resorcinol (Mallinckrodt) was dried at room temperature in a vacuum desiccator at 0.5 to 1 mm. of Hg for several days before use. Phloroglucinol (Eastman white label) was dried in an oven at 100° C. and stored in a Drierite-containing desiccator. 1,2-Dichloroethane was distilled from phosphoric anhydride at atmospheric pressure, b.p. 82–83° C. Aluminum chloride (anhydrous) (Matheson, Coleman, and Bell) was used from a freshly opened bottle. Trifluoroacetic anhydride was distilled from phosphoric anhydride at atmospheric pressure, b.p. 40–42° C. It was prepared in this study by dehydration of trifluoroacetic acid (3M Company) with phosphoric anhydride. Trifluoroacetic anhydride is available commercially (Matheson, Coleman, and Bell).

Apparatus. A three-necked, round-bottomed flask of suitable size was equipped with a high-torque mechanical stirrer, pressure-equalizing addition funnel, and a water-cooled condenser topped with a dry ice–acetone condenser (to condense volatile trifluoroacetic anhydride). To the top condenser was attached a calcium chloride drying tube followed by a hydrogen chloride gas trap (*1*). To ensure dryness, the apparatus was purged with dry nitrogen for 1 to 2 hours and discontinued before a reaction was conducted.

ω-Trifluororesacetophenone (I). To effect a maximum solubility of resorcinol in 1,2-dichloroethane at ice bath tem-