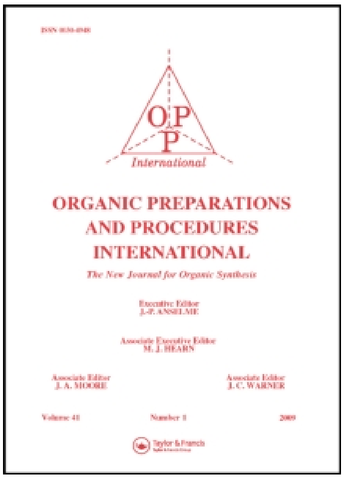

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THE SYNTHESIS OF SUBSTITUTED PHENYLENE DIISOCYANATES

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THE SYNTHESIS OF SUBSTITUTED PHENYLENE DIISOCYANATES

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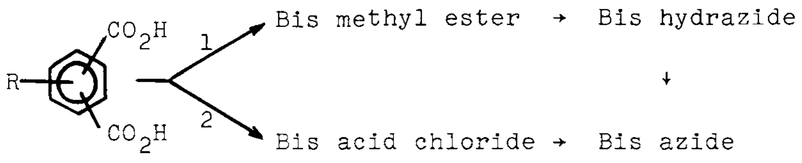
Although the Curtius reaction[3] has been known for many years in the synthesis of isocyanates and amines from carboxylic acids, very little work has been done using dicarboxylic acids. Yoneno, Abe and Namba[4] recently reported the synthesis of 5-nitro-m-phenylene diisocyanate from 5-nitro isophthalic acid through the acid chloride and Curtius and Davidis[5] had earlier reported the conversion of isophthalic and terephthalic acids to the corresponding hydrazides, azides and urethanes.

In the present investigation, we have synthesized a series of 5-substituted m-phenylene diisocyanates, where the substituents are bromo, chloro, methyl, methoxy, nitro and cyano. We have also prepared 2-chloro-p-phenylene diisocyanate.



Bis azide → Bis isocyanate → Bis urethane

1. R = 5-Cl, 5-Br, 5-CN-m-phenylene
2. R = 5-Cl, 5-CH_3, 5-CH_3O, 5-NO_2-m-phenylene, 2-Cl-p-phenylene

Because of the reactivity of the diisocyanates, there was no attempt to determine their properties other than their I.R. absorption bands. All diisocyanates were converted to their n-butyl or isopropyl diurethanes.

The starting point for each of the synthetic pathways depended on the substiuent group desired. In the syntheses several unreported esters, acid chlorides and azides were prepared. 5-Bromo-m-phenylene diisocyanate was prepared by brominating isophthalic acid using the method of Derbyshire and Waters[6] followed by conversion to the azide and then to the diisocyanate.

5-Chloro-m-phenylene diisocyanate was prepared from 5-aminoisophthalic acid via a Sandmeyer reaction to give 5-chloroisophthalic acid which was converted to the diisocyanate by both the ester-hydrazide-azide pathway and the acid chloride-azide pathway.

The nitric acid oxidation of mesitylene gave 5-methylisophthalic acid which was converted to the diisocyanate via the ester-hydrazide pathway. 5-Methoxyphenylene diisocyanate was prepared from 5-hydroxyisophthalic acid by methylation with dimethylsulfate to give dimethyl-5-methoxyisophthalate followed by conversion to the diisocyanate by way of the hydrazide-azide pathway. 5-Nitrophenylene diisocyanate was prepared from 5-nitroisophthalic acid by the ester-hydrazide pathway and 5-cyanophenylene diisocyanate was obtained from 5-aminoisophthalic acid by means of the Sandmeyer reaction using cuprous cyanide and sodium cyanide followed by conversion to the diisocyanate through the ester-hydrazide route. 2-Chloro-p-phenylene diisocyanate had as its starting compound the corresponding xylene, which on oxidation gave the desired 2-chloroterephthalic acid. 2-Chloro-p-phenylene diisocyanate was obtained via the ester-hydrazide route.

SYNTHESIS OF SUBSTITUTED PHENYLENE DIISOCYANATES

Experimental

Sodium azide, thionyl chloride, and xylenes were reagent grade and used as received. The dicarboxylic acids were reagent grade, but were recrystallized before use. Hydrazine hydrate (95+%) was supplied by Eastman; the alcohols used for preparing derivatives were spectroquality. Butanol-1 was fractionated on a spinning band column and stored over magnesium.

Toluene and chlorobenzene used for the rearrangement of the azides were dried by distillation from sodium and were subsequently stored over sodium. The acetone was dried over calcium sulfate.

The melting points were taken on a Fisher-Johns melting point apparatus.

The infrared spectra were obtained on a Perkin-Elmer Model 337 spectrophotometer using potassium bromide plates. The solvents used are listed for each compound.

The analysis of compounds for carbon, hydrogen and nitrogen were performed by Galbraith Laboratories.

5-Bromoisophthalic Acid (I). —The title compound was prepared from 36.5 g (0.22 mole) of isophthalic acid, 15 ml of bromine, 40 g of silver sulfate, and 500 ml of concentrated sulfuric acid by heating at 100-110° for 32 hours.[6] Excess bromine was removed by distillation and the solution poured into 1.5 ℓ of water. The solution was cooled, filtered and the solid dissolved in sodium bicarbonate solution, and filtered into 6 N sulfuric acid. The white solid was collected and recrystallized from acetone-water mixture giving 50.6 g (95%) of white needles. The product melted at 282-3° with rapid heating and sublimed at 247° on slow heating; ir (KBr), 5.82 μ (C=O); 19.4 μ (C-Br).

Anal. Calcd for $C_8H_5O_4Br$: C, 39.21; H, 2.06. Found: C, 39.32; H, 2.26.

5-Bromoisophthaloyl Diazide (II). —Product II was prepared by refluxing 5 g (0.02 mole) of I with 2 ml of thionyl chloride for 2 hours. Excess thionyl chloride was removed by distillation and dry nitrogen flow, leaving a white solid which melted at 188-189^o. Only enough sample was removed for a melting point determination and the remainder of the 5-Bromoisophthoyl dichloride was dissolved in 50 ml of dry acetone and cooled to 0-5^o in an ice-salt bath. Sodium azide (3.3 g, 0.05 mole) dissolved in 10 ml of water was added slowly while the temperature was kept below 5^o. After having been stirred for 15 min, the solution was poured into 500 ml of ice water and the white crystals which precipitated were filtered with suction, washed with water, and dried under vacuum to give a white solid mp 112-113^o which flashed in an open flame and exploded at its mp when heated rapidly; ir (Nujol), 4.63 μ, 4.54 μ, 7.70 μ (N_3); 5.89 μ (C=O); 17.68 μ (C-Br).

5-Bromo-m-Phenylene Diisocyanate (III). —Compound II was refluxed with 75 ml of dry toluene for one hour, cooled, and filtered. The toluene was removed with heating and dry nitrogen flow and a white solid remained. mp 37-38^o, ir (CCl_4), 4.41 μ (NCO).

5-Bromo-m-Phenylene Dibutyl Urethane (IV). —Product III was mixed with 10 ml of dry butanol-1 and the mixture heated for 15 min. Removal of the excess butanol gave 2.8 g (36%) of a yellow solid which was recrystallized from hexane to give 2 g (25%) of white needles. mp 84-85^o; ir (Nujol), 3.00 μ (N-H); 5.90 μ (C=O); 19.6 μ (C-Br).

Anal. Calcd for $C_{16}H_{23}BrN_2O_4$: C, 49.62; H, 5.99; N, 7.23. Found: C, 49.41; H, 5.95; N, 7.00.

Dimethyl-5-Methoxyisophthalate (V). —5-Hydroxyisophthalic acid (3.6 g, 0.02 mole) recrystallized from hot water, was refluxed with 246 ml of dry acetone ($CaSO_4$), 56.7 ml (0.6 mole) dimethyl sulfate, and 82.9 g (0.6 mole) anhydrous potassium carbonate for 14 hours. The reaction was carried out in a hood. A drying tube was used to prevent water from entering the system through the condenser. After having been cooled, the solution was filtered into a sidearm flask. The potassium carbonate was washed with a few ml of acetone and the wash was combined with the filtrate. The solution was concentrated by removing the acetone at the water aspirator vacuum in a hot water bath.

The dark syrup was taken up in hot water-methanol and cooled. White platelets precipitated and were collected and dissolved in ether. The ethereal solution was extracted with two portions of both sodium hydroxide and water to remove starting material. The ether was then removed and the solid recrystallized from methanol-water yielding 3.5 g (78%) white platelets, mp 111-111.5°; ir (Nujol), 5.72 μ(C=O); 7.99 μ (C-O, ether).

Anal. Calcd for $C_{11}H_{12}O_5$: C, 58.92; H, 5.40. Found: C, 59.07; H, 5.52.

5-Methoxyisophthalic Acid Dihydrazide (VI). —Hydrazine (10 ml), ethanol (30 ml), and 3.2 g of ester V were refluxed for 2.5 hours. After cooling, a solid separated and was removed by filtration and washed with ethanol and ether. After drying, the white crystals weighed 2.9 g (91%), mp 247-8°; ir (Nujol), 2.99 μ (NH); 6.03 μ (C=O); 7.57 μ (C-O).

5-Methoxyisophthaloyl Diazide (VII). —The diazide was prepared from 2.9 g (0.013 mole) of VI, 55 ml of 1.2M hydrochloric acid and 2.6 g (0.038 mole) of sodium nitrite in 10 ml of water. The solution was stirred for 5 min and the white solid was extracted with ether. After drying the ethereal extract over $CaCl_2$, the latter was decanted and a small sample evaporated, mp 101°; ir (ether evaporated), 4.65μ and 7.58μ (N_3); 5.89μ (C=O); 7.59μ (C-O).

5-Methoxy-m-Phenylene Diisocyanate (VIII). —The dry ethereal extract of VII was added to 100 ml of toluene. After removing the ether, the azide was rearranged by refluxing the toluene solution for 2 hours. A small sample was removed and the toluene evaporated, leaving a white solid which was recrystallized from hexane. mp 52-3°; ir (CCl_4), 4.40μ (NCO); 7.90μ (C-O).

5-Methoxy-m-Phenylene Dibutyl Urethane (IX). —The toluene solution containing VIII was filtered into a flask containing dry butanol-1. After warming for 15 min, the solution was cooled overnight. The toluene and butanol were removed by distillation leaving a yellow oil which was recrystallized from hexane to give 1.9 g (59%) white needles. mp 81.5-82.0°; ir (Nujol), 2.94μ and 3.00μ (NH); 5.86μ (C=O); 7.79μ (C-O).

Anal. Calcd for $C_{17}H_{26}N_2O_5$: C, 60.33; H, 7.76; N, 8.28. Found: C, 60.14; H, 7.61; N, 8.27.

5-Chloro-m-Phenylene Dibutyl Urethane (X). —5-Chloro-m-phenylene diisocyanate was prepared in a manner similar to the preparation of 5-bromo-m-phenylene diisocyanate. 5-Chloroisophthalic acid was prepared in 46% yield from 5-aminoisophthalic acid via the Sandmeyer process as described for p-chlorotoluene by Vogel[8], mp 289-290°; lit. mp 278°.[7] 5-Chloroisophthalic acid (11.5 g, 0.056 mole) was converted to the acid chloride and to the diazide by means of sodium azide as described in II. Rearrangement of the azide in toluene by refluxing for 2 hours gave a white solid, mp 28.5-29.0° which was not further isolated.

The toluene solution of the diisocyanate was filtered into a flask containing 10 ml of dry butanol-1. After setting for one hour at room temperature the solvents were removed by distillation leaving a viscous liquid. Recrystallization from hexane gave white needles (8 g, 35%). mp 77-78°; ir (Nujol), 2.99 μ (N-H); 5.88 μ (C=O); 19.6 μ (C-Cl).

Anal. Calcd for $C_{16}H_{23}N_2O_4Cl$: C, 56.06; H, 6.76; N, 8.17. Found: C, 55.79; H, 6.50; N, 8.30.

5-Methyl-m-Phenylene Dibutyl Urethane (XI). —5-Methyl-m-phenylene diisocyanate was prepared from 5-methylisophthalic acid by the same general method as given for VIII. 5-Methylisophthalic acid was prepared in 53% yield by the oxidation of mesitylene with 45% nitric acid. mp 298°; lit. mp 298°.[7] 5-Methylisophthalic acid was converted to the methyl ester in 89% yield, mp 95-96°; lit. mp 98°.[7] Conversion of the ester to the diazide was carried out as described for VII. Refluxing the diazide in toluene for 2 hours gave a product which was not isolated except to determine the bp and ir. bp 133.5°-134.5°/17mm. ir (Toluene) 4.40 μ (NCO). The toluene solution of the diisocyanate was filtered into 10 ml of dry butanol-1. After warming for 30 min, the solvents were removed, leaving a dark viscous oil which was recrystallized from hexane. The oil crystallized after setting two weeks to form white crystals (2.9 g, 39%). mp 56-57°; ir (Nujol), 2.99 μ (N-H); 5.88 μ (C=O).

Anal. Calcd for $C_{17}H_{26}N_2O_4$: C, 63.33; H, 8.13; N, 8.69. Found: C, 63.12; H, 8.23; N, 8.59.

5-Nitro-m-Phenylene Diisopropyl Urethane (XII). —5-Nitro-m-phenylene diisocyanate was prepared from 5-nitroisophthalic acid via the ester-hydrazide pathway as described for VIII. The treatment of dimethyl-5-nitrophthalate (12 g, 0.05 mole) with ethanol (30 ml) and hydrazine (50 ml) gave 9.6 g (80%) of 5-nitro-m-phenylene dihydrazide, mp 280°; ir (Nujol), 2.97 μ (N-H); 6.02 μ (C=O); 6.52 μ and 7.51 μ (NO_2). Treatment of the hydrazide as described for VII gave the diazide, mp 110°, ir (Nujol), 4.65 μ and 7.68 μ (N_3). The ether solution of the diazide was added to toluene and rearranged to give the diisocyanate. mp 65-67°; ir (KBr), 4.41 μ (NCO); 6.51 μ and 7.40 μ (NO_2).

The toluene solution of the diisocyanate was filtered into 10 ml of cold propanol-2. The solution was left overnight at room temperature. Removal of the solvent by distillation gave a viscous liquid. Crystallization from ethanol-water solution (80%) gave light yellow needles (5.4 g, 83%) of the diisopropyl urethane, mp 147.5-148°; ir (Nujol); 3.00 μ (N-H); 5.82 μ (C=O); 6.47 μ and 7.44 μ (NO_2).

Anal. Calcd for $C_{14}H_{19}N_3O_6$: C, 51.68; H, 5.90; N, 12.92. Found: C, 51.52; H, 6.05; N, 12.79.

5-Cyanoisophthalic Acid (XIII).—Cuprous cyanide (15.4 g, 0.09 mole) and sodium cyanide (16 g, 0.33 mole) were dissolved in 40 ml of water and heated in a water bath (in hood) to 60-70°. The diazonium salt was prepared from 24.4 g (0.13 mole) of 5-aminoisophthalic acid (recrystallized for methanol-water), 68 ml of 6N hydrochloric acid, and 4.8 g of sodium nitrite in 20 ml of water.

The cold diazonium salt was added slowly (10 min) with vigorous stirring to the warm cyanide solution. The solution was then heated to boiling for 40 min. After cooling, the mixture was filtered and the filtrate extracted with ether. The ether was evaporated and the residual solid combined with the filter cake. The combined solids were dissolved in sodium bicarbonate solution, filtered, and the filtrate acidified with dilute sulfuric acid. Then the solid which precipitated was separated by filtration. The filtrate was extracted with ether as above and all the solid again combined. The solid weighed 15.8 g (61.5%) and was obtained as pure, light yellow needles by dissolving in 5 ml of methanol and precipitating with 100 ml of water, mp 251-251.5°; ir (Nujol), 4.43 μ (C≡N), 5.83 μ (C=O).

Anal. Calcd for $C_9H_5NO_4$: C, 56.55; H, 2.64; N, 7.33. Found: C, 56.30; H, 2.65; N, 7.42.

Dimethyl-5-Cyanoisophthalate (XIV). —XIII (8.2 g, 0.04 mole) was refluxed with methanol (40 ml) and concentrated hydrochloric acid (2.5 g) as described previously to give 5.9 g (63%) of large yellow needles of dimethyl-5-cyanoisophthalate, mp 174.5-175°; ir (Nujol), 4.41 μ (C≡N); 5.72 μ (C=O).

Anal. Calcd for $C_{11}H_9NO_4$: C, 60.27; H, 4.15; N, 6.39. Found: C, 60.48; H, 4.15; N, 6.42.

5-Cyano-m-Phenylene Diisopropyl Urethane (XV). —XIV was converted to the hydrazide in 98% yield as described previously to give a yellow solid, mp 300-301°. The dihydrazide was converted to the diazide, mp 128°, which on rearrangement in toluene gave the diisocyanate, mp 92-94° (from hexane); ir (Toluene), 4.38 μ (NCO).

The toluene solution of the diisocyanate was added to 10 ml of propanol-2, warmed and the solvent removed by distillation to give a yellow solid. Recrystallization from ligroine (bp 90-120°) gave 4.5 g (59%) of white needles, mp 164-165°; ir (Nujol), 3.04 μ (NH); 4.46 μ (C≡N); 5.85 μ (C=O).

Anal. Calcd for $C_{15}H_{19}N_3O_4$: C, 59.00; H, 6.28; N, 13.76. Found: C, 59.12; H, 6.32; N, 13.67.

2-Chloro-p-Phenylene Diisopropyl Urethane (XVI). —XVI was prepared from 2-chloroterephthalic acid (7.4 g, 0.037 mole) through the ester-hydrazide-azide pathway. The dihydrazide was obtained as a white solid (5 g, 75%), mp 229°. Conversion to the diazide gave a product of mp 72-73°. The diazide was rearranged as described previously except for the use of chlorobenzene as the rearranging media. The diisocyanate melted at 30-35° (from hexane). Addition of the chlorobenzene solution of the diisocyanate to 10 ml of propanol-2 yielded XVI which on recrystallization from hexane gave 3.3 g (51%) of white needles, mp 137-138°; ir (Nujol), 3.02 μ (NH); 5.88 μ (C=O); 20.1 μ (C-Cl).

Anal. Calcd for $C_{14}H_{19}ClN_2O_4$: C, 53.41; H, 6.10; N, 8.90. Found: C, 53.22; H, 6.04; N, 9.11.

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(1) From the M.S. Thesis of Lawrence Harris.

(2) The work of L. Harris was supported by the W. S. Dickey Clay Company, Pittsburg, Kansas.

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