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E. I. duPont de Nemours & Company

Jackson Laboratory

May 26, 1942

Preparation of Intermediates for Azo Research

JLR-30-155, No. 64 Serial Number 18034

E. I. duPont de Nemours & Company

Jackson Laboratory

New Products Division

G. E. Holbrook

Progress Report

May 26, 1942

Preparation of Intermediates for Azo Research

Group Leader - C. W. Croco

Work Done By - J. R. Schaffer Work Started - 10-8-40

Reported By - J. R. Schaffer Completed - 2-12-41

J. M. TINKER W. S. CALCOTT

ASSISTANT DIRECTOR DIRECTOR

Preparation of Intermediates for Azo Research (Project No. 599)

J. R. Schaffer

JLR-30-155, No. 64 Serial Number 18034

Object of the Investigation:

To prepare intermediates for Azo Colors research.

Period Covered by the Report:

October 8, 1940 to February 12, 1941.

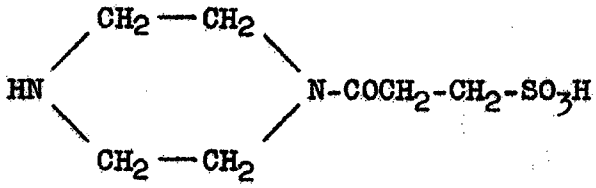
Historical Background:

These intermediates were requested by the Azo Division for their research work.

Summary and Conclusions:

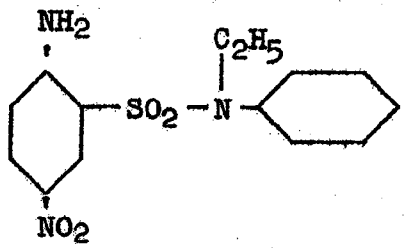
The following compounds have been prepared by the methods outlined:

(1) Mono-N-beta-Sulfo-Propionyl-Piperazine: (308/3460)



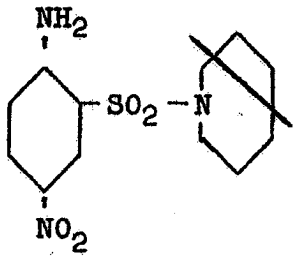
Piperazine hexahydrate + sulfo propionic anhydride → product. The yield was 80% based on either starting material.

(2) 4-Nitro-Aniline-2-Ethyl Phenyl Sulfonamide: (208.6/1923)



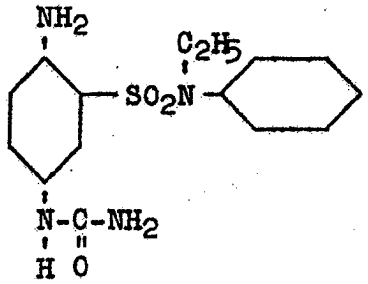
4-Nitro-chlorbenzene-2-potassium sulfonate + phosphorus pentachloride → 4-nitro-chlorobenzene-2-sulfonchloride + ethyl aniline → 4-nitro-chlorobenzene-2-ethyl phenyl sulfonamide + ammonia → product. The yield was 74%.

(3) 4-Nitro-Aniline-2-Sulfon-Hexamethylene Imide: (307/3040)



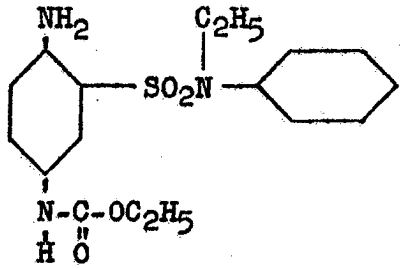
4-Nitro-chlorobenzene sulfonchloride + hexamethylene imine → 4-nitro-chlorobenzene sulfon hexamethylene imide + ammonia → product. The yield was 16%.

(4) 4-Ureido Aniline-2-Ethyl-Phenyl Sulfonamide: (208.6/1923)



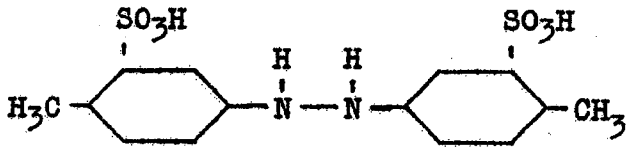
4-Nitro-aniline-2-ethyl phenyl sulfonamide $\xrightarrow{\text{reduce}}$ 4-phenylene diamine-2-ethyl phenyl sulfonamide + potassium cyanate → product. The yield was 70%.

(5) 4-Carbethoxy Amino Aniline-2-Ethyl Phenyl Sulfonamide: (208.6/1923)



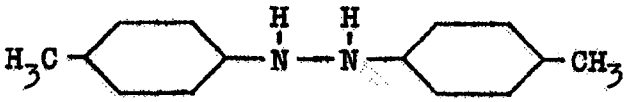
4-Phenylene diamine-2-ethyl phenyl sulfonamide + ethyl chloroformate → product. The yield was 74%.

(6) 4,4'-Hydrazo-Toluene-3,3'-Disulfonic Acid: (210/2082)



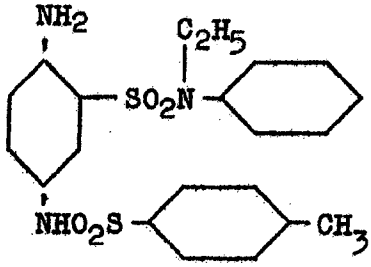
4-Nitrotoluene-2-sodium sulfonate + reduce $\xrightarrow[Ba(OH)_2]{Zn}$ product. The product could not be freed from diazotizable amine.

(7) para,para'-Hydrazo-Toluene: (210/1950)



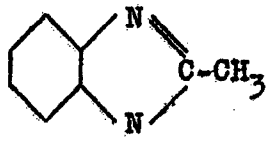
4-Nitrotoluene + reduce $\xrightarrow[NaOH]{Zn}$ product. The yield was 40%.

(8) 4-(Toluene Sulfonamino) Aniline-2-Ethyl Phenyl Sulfonamide: (208.6/1923)



4-Phenylene diamine-2-ethyl phenyl sulfonamide + 4-toluene sulfonchloride → product. The yield was 75%.

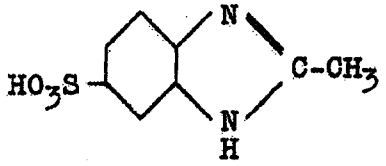
(9) 2-Methyl Benzimidazole: (308/3474)



ortho-Nitro-aniline + acetic anhydride → ortho-nitro-acetyl-aniline reduce→ ortho-amino-acetyl aniline ring close→ product. The yield was 50.8%.

The preparation of the following compounds was attempted by the methods of synthesis indicated. The products were tested without identification. No data was obtained for the calculation of yields on these products.

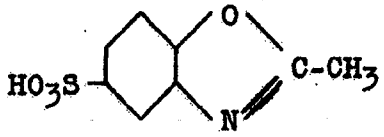
(10) 2-Methyl Benzimidazol-4-Sulfonic Acid: (308/3707)



(1) 2-Nitro-aniline-4-sulfonic acid $\xrightarrow{\text{reduce}}$ ortho-phenylene diamine para-sulfonic acid + acetic anhydride $\xrightarrow{\text{ring close}}$ product.

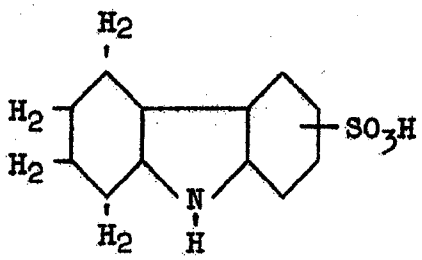
(2) 2-Methyl benzimidazol + oleum → product.

(11) 2-Methyl Benzoxazol-4-Sulfonic Acid: (312/4333)



2-Aminophenol-4-sulfonic acid + acetic anhydride $\xrightarrow{\text{ring close}}$ product.

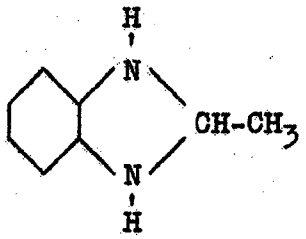
(12) Sulfonated Tetra Hydrocarbazole: (307/3378)



Carbazole $\xrightarrow[\text{Na + isopropyl alcohol}]{\text{Reduce}}$ tetrahydro-carbazole $\xrightarrow{\text{sulfonate}}$ product.

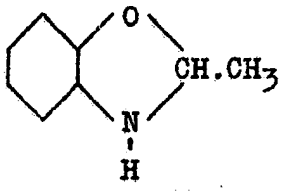
The following compounds were not obtained by the methods outlined:

(13) Hydrogenated 2-Methyl Benzimidazole: (308/3474)



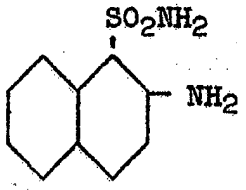
2-Methyl-benzimidazole $\xrightarrow{\text{hydrogenate}}$ no reaction. Hydrogenation did not take place under the conditions used.

(14) Hydrogenated 2-Methyl Benzoxazol: (312/4194)



2-Methyl benzoxazol $\xrightarrow{\text{hydrogenate}}$ No Reaction. Hydrogenation did not take place under the conditions used.

(15) 2-Amino-Naphthalene-1-Sulfonamide: (208.6/1923)



2-Acetylamino naphthalene-1-sulfonic acid + PCl_5 → 2-acetyl amino-naphthalene-1-sulfonchloride + NH_4OH → 2-acetylamino-naphthalene-1-sulfonamide $\xrightarrow{\text{hydrolyze}}$ product.

Attempts to hydrolyze the acetyl derivative resulted in hydrolysis of both the acetyl and amide group.

Patent Situation:

The following compounds are believed to be new:

(1) Mono-N-beta-sulfopropionyl-piperazine.
(2) 4-Nitroaniline-2-ethyl phenyl sulfonamide.
(3) 4-Nitroaniline-2-sulfon-hexamethylene imide.
(4) 4-Ureido-aniline-2-ethyl phenyl sulfonamide.
(5) 4-Carbethoxy amino-aniline-2-ethyl phenyl sulfonamide.
(6) 4,4'-Hydrazo toluene,3,3'-disulfonic acid.

(8) 4-Toluene sulfon-amino aniline-2-ethyl phenyl sulfonamide.
(10) 2-Methyl benzimidazol-4-sulfonic acid.
(11) 2-Methyl benzoxazol-4-sulfonic acid.
(12) Sulfonated tetrahydro carbazole.
(13) Hydrogenated 2-methyl benzimidazol.
(14) Hydrogenated 2-methyl benzoxazol.
(15) 2-Amino-naphthalene-1-sulfonamide.

EXPERIMENTAL PART

(1) Mono-N-Beta-Sulfoprioionyl-Piperazine: (JLNB 3392-93)

A solution of 34 g. of sulfopropionic anhydride in 150 cc. of dioxane was added over 45 minutes with rapid stirring at 30-35°C. to a solution of 48.5 g. of piperazine hexahydrate in 150 cc. of dioxane. The mixture was stirred for 2 hours and filtered and washed product with 100 cc. of dioxane. The product was placed in 150 °C. oven for 20 hours in order to complete the reaction. Yield: 80% based on either starting material. Analysis: N = 11.94%; S = 12.87%. Calculated for $C_7H_{14}O_4N_2S$: N = 12.6%; S = 14.4%.

(2) 4-Nitro-Aniline-2-Ethyl Phenyl Sulfonamide: (JLNB 3392-97, 101)

About 4 lbs. of para-nitrochlorobenzene-ortho-magnesium sulfonate was dissolved in about 10 qts. of boiling water and added potassium chloride until the hot solution yielded no more precipitate. The product was filtered and dried at 50°C. The yield was about 4 lbs. of the potassium salt of para-nitrochlorobenzene-ortho-sulfonic acid.

A mixture of 827 g. of this material, 624 g. of phosphorus penta-chloride and 175 cc. of phosphorus oxychloride was heated in a 5 liter flask fitted with a thermometer, reflux and agitator to 100°C. When the mixture had become sufficiently liquid, it was stirred for 1.5 hours at 100°C., cooled to 25-30°C. and added slowly to an ice-water mixture at 0-15°C. The mixture was filtered and the cake washed with 2 liters of ice water, and sucked dry as possible. A mixture of about 85% of this wet material was refluxed for 5 hours with agitation in 1500 cc. of toluene, 363 g. of ethyl aniline and 375 g. of sodium acetate. The mixture was cooled and filtered.

The toluene was distilled from filtrate with steam and the residue added to filter cake. The combined mass was slurried in water and made alkaline to Brilliant Yellow by adding 30% sodium hydroxide. The crude product was filtered and washed with 1 liter of 3% hydrochloric acid. The yield of crude product was approximately 800 g. or 87% based on para-nitro-chlorobenzene-ortho-potassium sulfonate.

300 Grams of this crude material and 80 g. of ammonia dissolved in 1200 cc. of 2B alcohol was heated in a 2 liter autoclave for 6 hours at 135-140°C. The mixture was filtered and the alcohol

distilled from the filtrate under reduced pressure. The residue was combined with filter cake. Another amination run was made using 450 g. of crude material by the same procedure as described above. Yield: 650 g. or 74% based on 4-nitro-chlorobenzene-2-potassium sulfonate. Analysis: S = 8.97%; N = 14.01%; NO_2 = 13.27%. Calculated for $C_{14}H_{15}O_4N_3S$: S = 9.97%; N = 13.09%; NO_2 = 14.34%.

(3) 4-Nitroaniline-2-Sulfon-Hexamethylene Imide: (JLNB 3392-115)

276 Grams of 4-nitrochlorobenzene-2-potassium sulfonate was treated with 208 g. of phosphorus pentachloride by the procedure described in Exp. 2, page 6. One-half of the wet 4-nitrochlorobenzene-2-sulfon chloride and 130 g. of sodium acetate in 300 cc. of benzene was stirred in a 3 liter flask and 100 g. of 50% hexamethylene imine added over 30 minutes at 20-40°C. The mixture was stirred for 45 minutes at 20-30°C. and 500 cc. of water added. The mixture was stirred for 30 minutes and filtered. The filter cake was crystallized from alcohol. Yield: 26 g. of product melting at 126°C. 17 Grams addition product melting at 120°C. was obtained from the benzene layer of the filtrate by evaporating the benzene to low volume under reduced pressure.

The combined yield of product was aminated with 50 g. of ammonia in 750 cc. of 2B alcohol by heating the mixture for 6 hrs. at 135-140°C. in a 1 liter autoclave. The buff colored product was filtered from alcohol. The product melted at 118-120°C. Yield: 25 g. or 16% based on 4-nitrochlorobenzene-2-potassium sulfonate. Analysis: NO_2 = 14.79%; S = 10.22%; N = 10.81%. Calculated for $C_{12}H_{17}O_4N_3S$: NO_2 = 15.38%; S = 10.70%; N = 14.05%.

(4) 4-Ureido-Aniline-2-Ethyl Phenyl Sulfonamide: (JLNB 3392-108)

14 Grams of potassium cyanate was added to a solution of 50 g. of para-phenylene diamine-2-ethyl phenyl sulfonamide in dilute hydrochloric acid solution at 30°C. with rapid agitation. The product separated out as oil. The water solution was decanted off and the product slurried in dilute hydrochloric acid solution. The product was dried on steam bath. Yield: 45 g. or 70% based on para-phenylene diamine-2-ethyl phenyl sulfonamide. Analysis: N = 14.82%; S = 9.34%. Calc'd. for $C_{15}H_{18}N_4SO_3$: N = 16.76%; S = 9.59%

(5) 4-Carbethoxy-Amino-Aniline-2-Ethyl Phenyl Sulfonamide: (JLNB 3392-110)

550 Grams of 4-nitro-aniline-2-ethyl phenyl sulfonamide was hydrogenated in an autoclave at 100°C. and 500 lbs./sq.in. hydrogen

pressure. The mixture was nucharred, filtered, and methanol distilled from the filtrate under reduced pressure. The residue was dissolved in dilute hydrochloric acid solution, nucharred, and the brownish-gray product precipitated with ammonia. Yield: 343 g. or approximately 66% based on 4-nitro-aniline-2-ethyl phenyl sulfonamide. Analysis: N = 14.04%; S = 10.77%; NO_2 = 0.10%, Nitrite Value = 51.4%. Calculated for $C_{14}H_{17}O_2N_3S$: N = 14.43%; S = 10.99%.

50 Grams of this product was dissolved in 300 cc. of toluene and 20.6 g. of ethyl chloroformate was added dropwise at 20-30°C. The product was precipitated from the solution. The filter cake was filtered and slurried in cold dilute hydrochloric acid solution. Additional product was obtained by distilling off the toluene from the filtrate under reduced pressure. Yield: 42 g. or 74% based on 4-phenylene diamine-2-ethyl phenyl sulfonamide. Analysis: N = 11.59%; S = 8.73%. Calculated for $C_{17}H_{21}O_4N_3S$: N = 11.3%; S = 8.81%.

(6) 4,4'-Hydrazo-Toluene-3,3'-Disulfonic Acid: (JLNB 3392-12)

A mixture of 2 mols. of para-nitrotoluene-2-sulfonic acid, 2 moles of barium hydroxide, and 2 liters of water in a 5-liter, 4-neck flask was heated with stirring to 90°C. A total of 300 g. of zinc dust in 3 g. portions was added over 2.5 hours. The heat of reaction held the temperature at 90 ± 5°C. When all of the zinc had been added, the reaction mixture turned from a dark red to a yellow color. Carbon dioxide was passed into the mixture until it was only slightly alkaline to Brilliant Yellow. The mixture was filtered through a covered Büchner through which was passed a stream of CO_2. On standing overnight in a stoppered flask, crystals of the barium salt of the sulfonic acid settled out. This product gave a positive test for diazotizable amine. The product was recrystallized from water but an amino-free product was not obtained.

Since the Azo Division desired a product free of diazotizable amine, it was decided to attempt the preparation of 4,4'-hydrazotoluene which might be obtained free of amine and which would be satisfactory to the Azo Division. See Exp. 7, pages 8 and 9.

(7) 4,4'-Hydrazo-Toluene: (JLNB 3392-14)

A solution of 274 g. of 4-nitrotoluene was heated in 700 cc. of solvent naphtha in a 3-liter, 4-neck flask equipped with agitation, thermometer and a reflux condenser on a water bath to 80°C. 100 cc. of 30% sodium hydroxide was added in 3-5 cc. portions and 350 grams of zinc dust in 3-5 gram portions

was added over 2.5 hours at 80-90°C. At the end of the zinc and caustic additions, the solvent naphtha layer turned from a red to a greenish yellow color. The hot solvent naphtha layer was filtered immediately on a funnel through which was passed a stream of carbon dioxide. The crystalline product which separated out of the cooled solvent naphtha filtrate was filtered off and the product crystallized three times from alcohol. The white product melted at 128-132°C. (Lit. M.P. for 4,4'-hydrazo-toluene is 134°C.) The product showed a negative test for free amino compound. Yield: 40% based on 4-nitrotoluene. Analysis: Purity - 80.2% (Product was sent for analysis without drying.)

The product was tested immediately on isolation by the Azo Division. On standing for two weeks, the product turned bright yellow in color, while the melting point of the material rose to 140°C.

(8) 4-Toluene Sulfonamino-Aniline-2-Ethyl Phenyl Sulfonamide: (JLNB 3392-124)

A mixture of 29 g. of para-phenylene diamine-2-ethyl phenyl sulfonamide, 10 g. of para-toluene sulfonchloride and 13 g. of sodium acetate was stirred in 300 cc. of water for 1 hour at 25-30°C. The temperature was raised to 50°C. and stirred for 15 minutes. The water was decanted off and the residue dissolved in 3% sodium hydroxide solution. The product was precipitated by making the solution slightly acid to Congo Red with hydrochloric acid. The light brown product was filtered off and dried in air at room temperature. Yield: 35 g. or 75% based on para-phenylene diamine-2-ethyl phenyl sulfonamide. Analysis: N = 9.23%; S = 13.65%. Calculated for $C_{21}H_{22}O_4N_3S_2$: N = 9.41%; S = 14.35%.

(9) 2-Methyl Benzimidazol: (JLNB 3392-75)

A mixture of 276 g. of 2-nitroaniline, 214 g. of acetic anhydride, and 250 cc. of acetic acid was heated in a 3-liter flask with stirring for 18 hours at 90-100°C. The mixture was drowned in 3 liters of ice water, and the light yellow product filtered off. This product gave a negative test for diazotizable amine. The 2-nitro-acetyl aniline was reduced in a hydrogenation autoclave in methanol solution at 100°C. and 500 lbs./sq. in. hydrogen pressure. The nickel catalyst was filtered off and the methanol distilled off under reduced pressure. This material was heated with 450 cc. of glacial acetic acid on steam bath for 12 hours. The solution was neutralized with ammonium hydroxide and the buff colored product filtered off on crystallization from water; the M.R. was 166-170°C. A portion of this material was

crystallized three times from alcohol. The M.R. was 174-176°C. Literature M.P. of 2-methyl benzimidazol is 175°C. Yield: 133 g. or 50.8% based on 2-nitroaniline.

(10) 2-Methyl-Benzimidazol-4-Sulfonic Acid: (JLNB 3392-64, 76)

(1) 327 Grams of 2-nitroaniline-4-sulfonic acid was reduced with iron and acetic acid in 800 cc. of water. The mixture was made alkaline to Brilliant Yellow with soda ash, filtered hot and the filtrate cooled to 20°C. 153 g. of acetic anhydride was added to the filtrate at 23 to 35°C. with stirring and the mixture heated to 80°C. over 1 hour. This mixture was evaporated to dryness on the steam bath. An alkaline solution of this material was tested by the Azo Division for use as a Diagen stabilizer.

(2) 15 Grams of 2-methyl-benzimidazol was added to 100 cc. of 22% oleum at 10-25°C. over 1 hour in a 500 cc. flask equipped with agitation and cooled in an ice bath. The mixture was drowned in an ice-water mixture with stirring, and the gray colored precipitate filtered off. This material was readily soluble in soda ash solution. When tested by the Azo Division it was found not to take up diazo, indicating that sulfonation had taken place on the $\rangle$N-H of the heterocyclic ring.

(11) 2-Methyl-Benzoxazol-4-Sulfonic Acid: (JLNB 3392-68)

A mixture of 1 mol of 2-aminophenol-4-sulfonic acid, 1.5 mols of acetic anhydride, and 200 cc. of acetic acid was stirred in a 2 liter flask at reflux for 6 hours. Two mols of sodium acetate was added and the mixture stirred for 20 hours. The reaction mixture was evaporated to dryness on the steam bath. An alkaline solution of this residue was sent to the Azo Division for testing as a Diagen stabilizer.

(12) Sulfonated Tetra-Hydrocarbazole: (JLNB 3392-60)

245 Grams of sodium was added as rapidly as possible at reflux to a mixture of 140 g. of carbazole and 3500 g. of iso-amyl alcohol in a 5-liter flask equipped with agitation. The mixture was stirred for 1 hour after all of the sodium was added, and then 1.5 liters of iso-amyl alcohol was distilled from the mixture. The solution remaining in the flask was drowned with more iso-amyl alcohol. The alcohol layer was separated and the alcohol distilled off under reduced pressure. The crude hydrogenated carbazole crystallized on cooling from the residue. The crude product was treated with Nuchar and Norite A in hot alcohol and crystallized four times from alcohol. 32 Grams of white product was obtained,

M.P. 110-114°C. Literature M.P. for tetra-hydrocarbazole is 114°C. The alcohol filtrates were diluted with water, filtered and the filter cake crystallized twice from 75% 2B alcohol. 34 g. additional product which had a M.R. of 106-110°C. was obtained.

15 Grams of the product melting at 110-114°C. was added with stirring to 100 cc. of monohydrate at 20-35°C. and the mixture warmed to 150°C. over 2 hours. The mixture was cooled and drowned in about 250 g. of ice with stirring. The precipitated material was filtered off and a portion dissolved in soda ash solution. This alkaline solution was tested by the Azo Division as a Diagen stabilizer. Further work on this preparation was abandoned on the advice of the Azo Division.

(13) Hydrogenated 2-Methyl-Benzimidazol: (JLNB 3392-77, 119)

The hydrogenation of 25 g. of 2-methyl-benzimidazol was attempted in an autoclave at 200°C. and 1000 lbs. per square inch of hydrogen pressure in the presence of nickel catalyst and using cyclohexane as the solvent. The 2-methyl-benzimidazol was recovered unchanged.

Other attempts to hydrogenate this compound in which palladium catalyst and methyl alcohol were used at 100°C. and 500 lbs. per sq. in. hydrogen pressure also produced no change in the material. It is suggested that other catalysts or higher temperatures and pressures be tried.

(14) Hydrogenated 2-Methyl-Benzoxazole: (JLNB 3392-122)

The hydrogenation of 25 g. of 2-methyl-benzoxazole was attempted in an autoclave at 200°C. and 500 lbs. per sq. in. hydrogen pressure using cyclohexane as the solvent. The nickel catalyst was filtered off and the cyclohexane distilled off under reduced pressure. The product was tested by the Azo Division for use as a Diagen stabilizer.

(15) 2-Amino-Naphthalene-1-Sulfonamide: (JLNB 3392-70)

265 Grams of acetyl Tobias Acid was added to a mixture of 218 g. of phosphorus pentachloride and 150 cc. of phosphorus oxychloride at 30-37°C. with stirring in a 3-liter, 4-neck flask. The mixture was stirred at 65-70°C. for 1 hour, cooled, and drowned in ice-water mixture at 0-5°C. with stirring. The water was decanted off and the semi-solid 2-acetyl-amino-naphthalene-1-sulfonchloride was washed with ice water. The sulfonchloride was added with rapid stirring to 300 cc. of 28% ammonium hydroxide at

20-30°C. and stirred at 20-30°C. for 18 hours. The buff colored sulfonamide was isolated by acidifying the mixture with hydrochloric acid. Analysis: N = 7.63%; S = 10.34%. Calculated for $C_{10}H_{12}O_3N_2S$: N = 11.3%; S = 12.9%.

The hydrolysis of 0.11 mol of this product was attempted by heating in 263 g. of dilute hydrochloric acid solution containing 0.13 mol of hydrogen chloride at reflux for 12 hours. The mixture was filtered and the filtrate made alkaline to Brilliant Yellow with ammonium hydroxide. The product was filtered off and dried at 50°C. Analysis: N = 10.35%; S = 0.04%. Calculated for $C_{10}H_{10}O_2N_2S$: N = 12.6%; S = 14.42%.

The analysis indicates that the sulfonamide group was hydrolyzed along with the acetyl group.

Another hydrolysis was attempted using the same materials and conditions as above except that 50% alcohol was used instead of water as the solvent. Analysis: N = 11.43%; S = 7.53%; Nitrite Value = 55.3%.

This analysis indicates a partial hydrolysis of both the acetyl and the sulfonamide groups.

The hydrolysis of 25 g. of the 2-acetyl-amino-naphthalene-1-sulfonamide in 5% sodium hydroxide solution by refluxing for 18 hours was tried. Some beta-naphthylamine was isolated along with some tar and unhydrolyzed material from the reaction mixture.

Further work on this preparation was stopped on the advice of Dr. C. W. Croco.

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