polypeptides can be interpreted in terms of the constituent amino acid residues. The spectra of the complexes indicate that more than one group on the protein is perturbed by the combined dodecyl sulfate.

In the case of serum albumin, tests indicate that the protein is not denatured during the process of taking a spectrum. The presence of absorption characteristic of the amide linkage, therefore, offers conclusive evidence of the presence of such a structure in a native globular protein.

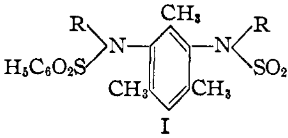
EVANSTON, ILLINOIS RECEIVED NOVEMBER 22, 1948

[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

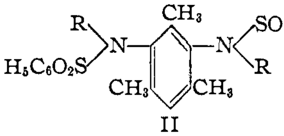
Restricted Rotation in Substituted Aromatic Amines. VII. Stereoisomers of N,N'-Dimethyl-N,N'-diarylsulfonyldiaminomesitylenes

BY ROGER ADAMS AND MORTON ROTHSTEIN

In the preceding paper,[1] pairs of isomers of various N,N'-dialkyl-N,N'-dibenzenesulfonyldiaminomesitylenes (I and II), in which R was ethyl, *n*-butyl, *n*-dodecyl, benzyl, carbethoxymethyl and carboxymethyl, were described. The isomerism was explained on the basis of two points of restricted rotation in the molecules.



I

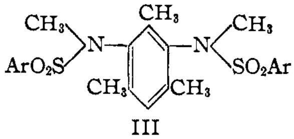


II

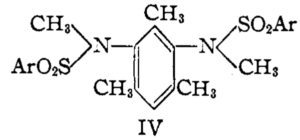
The method of preparation of these compounds consisted of alkylation in alkaline medium of N,N' - dibenzenesulfonyldiaminomesitylene. An alternative and unsatisfactory procedure, the benzenesulfonation of the N,N'-dialkyldiaminomesitylenes, was investigated in the case of the N,N'-diethyl derivative. The expected product was not obtained, but instead an ethyl group was eliminated and N-ethyl-N,N'-dibenzenesulfonyldiaminomesitylene was formed.

The present communication describes the results of a study of the synthesis of N,N'-dimethyl-N,N'-dibenzenesulfonyldiaminomesitylene by the two methods previously explored for the synthesis of the corresponding diethyl derivative. Replacement of benzenesulfonyl groups by substituted benzenesulfonyl groups has also been investigated.

Methylation of N,N'-dibenzenesulfonyldiaminomesitylene with methyl iodide proceeded smoothly to the N,N'-dimethyl-N,N'-dibenzenesulfonyldiaminomesitylene, and the *cis*- and *trans*-forms (III and IV) were readily isolated. Benzenesulfonation of N,N'-dimethyldiaminomesitylene resulted in the same two isomers. No methyl group was lost as was observed when the diethyl derivative was subjected to the same reaction. However, unidentified oily by-products accompanied the desired products and hindered the isolation of the latter in a pure state. The method was therefore not as satisfactory as the synthesis by methylation of dibenzenesulfonyldiaminomesitylene.



III



IV

Ar = phenyl, *p*-tolyl, *p*-bromophenyl or *p*-nitrophenyl

The N,N'-di-*p*-toluenesulfonyl, *p*-bromobenzenesulfonyl and *p*-nitrobenzenesulfonyl derivatives of diaminomesitylene were synthesized. These were in turn methylated and in all instances pairs of isomers (III and IV) were isolated. The reaction of *p*-toluenesulfonyl chloride and diaminomesitylene differed from that of the benzene or *p*-bromobenzenesulfonyl chlorides. A substantial quantity of the mono-*p*-toluenesulfonyldiaminomesitylene was found in the reaction product even though a large excess of reagent was used; this compound could be converted to the disubstituted derivative by further treatment. The preparation of the N,N'-di-*p*-nitrobenzenesulfonyldiaminomesitylene was not entirely satisfactory. An oily by-product contaminated the product and no method for its removal was found. However, methylation of the crude material gave two dimethylated isomers which appeared to be pure.

When diaminomesitylene was methylated with methyl iodide in aqueous or methanolic solution, the reaction proceeded stepwise. With one mole equivalent of methyl iodide the product was N-methyldiaminomesitylene contaminated with only minimum quantities of unmethylated or dimethylated homologs. With two mole equivalents or excess over that quantity, the N,N'-dimethyldiaminomesitylene was formed exclusively. Under the mild conditions used, the introduction of additional methyl groups is apparently inhibited by the crowded condition of the atoms in the molecule. This dimethyl derivative is identical with that described previously,[2] formed from the action

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[1] Adams and Tjepkema, THIS JOURNAL, **70**, 4204 (1948).

[2] Adams and Chase, *ibid.*, **70**, 4202 (1948).

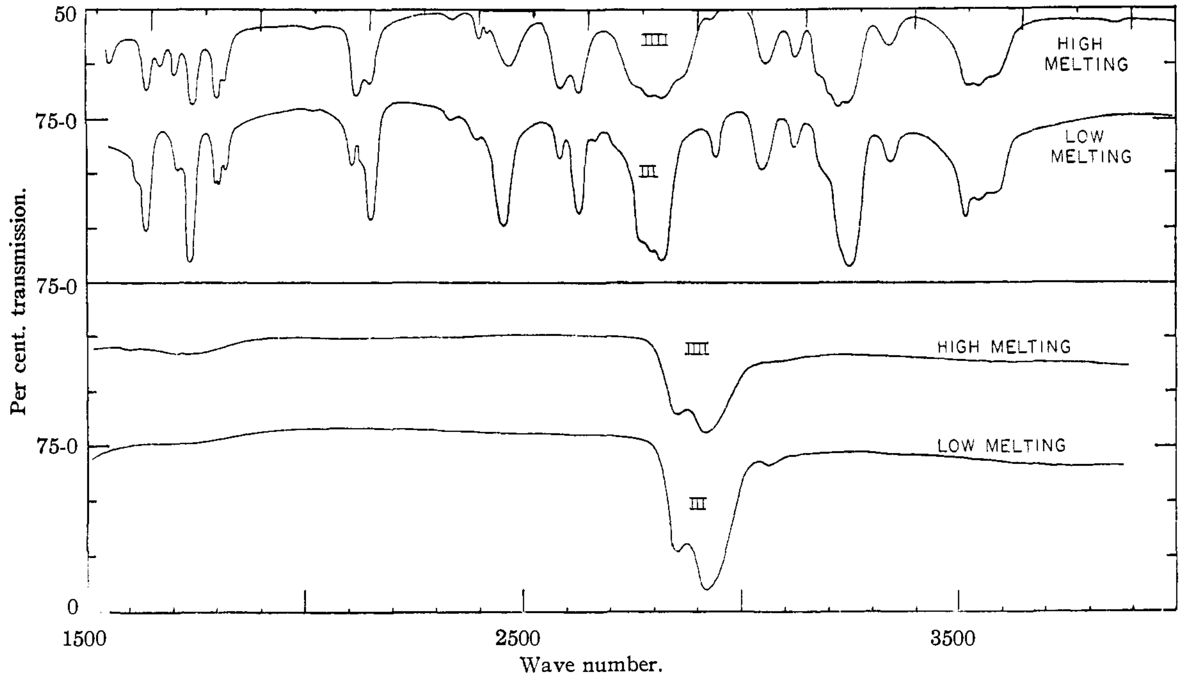

Chart I.—Infrared absorption spectra of: III, low-melting N,N′-dimethyl-N,N′-dibenzenesulfonyldiaminomesitylene; IV, high-melting N,N′-dimethyl-N,N′-dibenzenesulfonyldiaminomesitylene. Both spectra were run in Nujol which shows C–H bonds at 2920 and 2850 cm.$^{-1}$, and at 1460 and 1375 cm.$^{-1}$.

of dimethyl sulfate on diaminomesitylene and purification through the dinitroso compound. This new procedure is much to be preferred to the older one.

N-Methyl-N,N′-dibenzenesulfonyldiaminomesitylene was obtained both by limited methylation of N,N′-dibenzenesulfonyldiaminomesitylene and by benzenesulfonation of N-methyldiaminomesitylene. Neither method was entirely satisfactory. By methylation of this mono methyl derivative, the *cis*- and *trans*-N,N′-dimethyl-N,N′-dibenzenesulfonyldiaminomesitylenes resulted. This procedure represents a third route to this same pair of isomers.

It is obvious that *cis*- and *trans*-forms, represented by formulas I and II or III and IV and due to two points of restricted rotation in the molecule, may usually be expected regardless of the character of the arylsulfonyl or the alkyl group.

The infrared spectra of the two N,N′-dimethyl-N,N′-dibenzenesulfonyldiaminomesitylenes show the characteristic differences described for the previously prepared pairs of similar character (Chart I). The purity of the individual isomers was established by infrared analyses.

The authors are indebted to Mrs. Agatha R. Johnson for determination and interpretation of the infrared spectra.

Experimental

N-Methyldiaminomesitylene.—A mixture of 15 g. of diaminomesitylene and 150 ml. of water was shaken for fifteen hours with 14.2 g. of methyl iodide in a tightly stoppered flask. The reaction mixture was then made strongly alkaline with sodium hydroxide and extracted three times with ether. The ether solution was filtered and dried over potassium hydroxide. After filtration, the ether was evaporated and 11.5 g. (70%) of dark liquid remained. Upon distillation, a colorless liquid resulted, which darkened on standing; b. p. 123–124° (3 mm.), d^{20}_4 1.013, n^{20}_D 1.5705.

Anal. Calcd. for $C_{10}H_{16}N_2$: C, 73.17; H, 9.76. Found: C, 73.58; H, 10.15.

The slightly high carbon and hydrogen analyses may be accounted for by the presence of small amounts of N,N′-dimethyldiaminomesitylene.

N,N′-Dimethyldiaminomesitylene.—A solution of 30 g. of diaminomesitylene in 100 ml. of methanol was refluxed for twelve hours with 85.2 g. of methyl iodide. The methanol was then evaporated and the residue dissolved in water. The solution was made strongly alkaline with potassium hydroxide and extracted with three portions of ether. After the ether extracts were dried over potassium hydroxide and filtered, the solvent was evaporated and the dark liquid residue distilled. The product was a faintly yellow oil; b. p. 106–110° (2 mm.). The yield was 22 g. (62%). Adams and Chase[2] reported b. p. 114–116° (3 mm.). The picrates were also shown to be identical.

***cis*- and *trans*-N,N′-Dimethyl-N,N′-dibenzenesulfonyldiaminomesitylene by Methylation of N,N′-Dibenzenesulfonyldiaminomesitylene.**—To a mixture of a solution of 1.12 g. of potassium hydroxide in 40 ml. of methanol and 4.3 g. of N,N′-dibenzenesulfonyldiaminomesitylene in 50 ml. of acetone was added 4.26 g. of methyl iodide. After heating under reflux for one hour, 1 ml. more of methyl iodide was added, and the heating continued for two hours. Upon cooling, a white solid separated and was filtered. After washing with warm water, the product was recrystallized from methyl ethyl ketone; colorless crystals, m. p. 229–229.5° (cor.).

Anal. Calcd. for $C_{23}H_{26}O_4N_2S_2$: C, 60.26; H, 5.68. Found: C, 60.44; H, 5.80.

The filtrate was evaporated to dryness, and the residue washed thoroughly with warm water. It was then extracted several times with hot ethanol. The extracts, on cooling, yielded a white crystalline material, which, after five recrystallizations from ethanol and water, melted at 201.5–202° (cor.).

Anal. Calcd. for $C_{23}H_{26}O_4N_2S_2$: C, 60.26; H, 5.68. Found: C, 60.30; H, 5.66.

***cis*- and *trans*-N,N′-Dimethyl-N,N′-dibenzenesulfonyldiaminomesitylene by Benzenesulfonylation of N,N′-Dimethyldiaminomesitylene.**—A solution of 7.74 g. of benzenesulfonyl chloride in 15 ml. of pyridine was added slowly, with stirring, to a solution of 5 g. of N,N′-dimethyldiaminomesitylene in 15 ml. of pyridine. Heat was evolved. The mixture was allowed to stand overnight, and was then poured with stirring into cold water. The rubbery yellow precipitate which formed was filtered and allowed to dry at room temperature. The yield was 5.2 g. (44%).

The crude material was extracted first with 20 ml. of cold ethanol to remove a contaminating yellow oil, and then with 100 ml. of hot ethanol in three portions. The residue, remaining undissolved, was recrystallized from acetone and water to yield a powdery white solid, which was then washed with hot ethanol. Subsequent crystallization from methyl ethyl ketone gave white crystals, m. p. 229–229.5° (cor.). A melting point of this compound mixed with the higher-melting product obtained in the preceding experiment showed no depression.

The combined hot ethanol extracts were evaporated to about 25 ml. on a steam cone, and allowed to cool. The small yellow needles, thus obtained, were recrystallized from ethanol and water to give colorless crystals, m. p. 201.5–203° (cor.). A melting point of this compound mixed with the lower-melting product obtained in the preceding experiment showed no depression.

N-Methyl-N,N′-dibenzenesulfonyldiaminomesitylene from N,N′-Dibenzenesulfonyldiaminomesitylene.—To a solution of 4.3 g. of N,N′-dibenzenesulfonyldiaminomesitylene in 50 ml. of acetone was added a solution of 0.561 g. of potassium hydroxide in 25 ml. of methanol. After heating to reflux, a solution of 1.42 g. of methyl iodide in 20 ml. of methanol was added dropwise with mechanical stirring. After the addition was complete, refluxing and stirring were continued for thirty minutes. The mixture was allowed to cool, filtered, the solvent evaporated, and the residue washed with warm water. It was then extracted with 75 ml. of hot ethanol. A second extract with 50 ml. of hot ethanol and subsequent washings with cold ethanol were kept separate. The residue consisted of 0.3 g. of white powder. Two recrystallizations from methyl ethyl ketone gave white crystals, m. p. 225–226°. A melting point of this product mixed with the higher-melting N,N′-dimethyl-N,N′-dibenzenesulfonyldiaminomesitylene showed no depression.

Upon cooling the first hot ethanol extract, a white crystalline material (A) separated. Recrystallization from ethanol gave a product which proved to be the lower-melting N,N′-dimethyl-N,N′-dibenzenesulfonyldiaminomesitylene.

The mother liquor of (A) was added to the second hot ethanol extract and the cold ethanol washings. On standing overnight, a white solid (B) precipitated, m. p. 160–170°. A second crop was obtained by evaporating the mother liquor of (B) to one-third of its volume. This second crop was combined with (B), and the mixture extracted three times with 20-ml. portions of warm ethanol. The residue melted at 236–242°; after recrystallization it was shown to be starting material, N,N′-dibenzenesulfonyldiaminomesitylene.

The warm ethanol extracts yielded crystals which, after six recrystallizations from ethanol, melted at 183–184° (cor.). The analyses indicated the product to be N-methyl-N,N′-dibenzenesulfonyldiaminomesitylene.

Anal. Calcd. for $C_{22}H_{24}O_4N_2S_2$: C, 59.46; H, 5.40. Found: C, 59.47; H, 5.11.

N-Methyl-N,N′-dibenzenesulfonyldiaminomesitylene from N-Methyldiaminomesitylene.—To a solution of 4.19 g. of N-methyldiaminomesitylene in 15 ml. of pyridine, placed in an ice-bath, 9 g. of benzenesulfonyl chloride in 25 ml. of pyridine was added slowly, with stirring. The mixture was warmed on a steam-bath for ten minutes and allowed to stand for thirty minutes. It was then poured slowly, with stirring, into 400 ml. of water and 100 g. of ice. A dark oily mass separated. After standing for five hours without solidifying, 50 ml. of concentrated hydrochloric acid was added with vigorous stirring. Within ten minutes, the oil had become a yellow solid. This was filtered off and washed thoroughly with dilute hydrochloric acid, and then with water. Attempted recrystallization from an ethanol–water mixture gave a yellow powdery solid with a semi-colloidal supernatant liquid. Decantation of this liquid, followed by recrystallization of the solid from an ethanol–water mixture, yielded a small amount of yellow crystalline material, m. p. 173–176°. Two subsequent crystallizations gave a faintly buff material, m. p. 176–178°. A melting point of a sample with N-methyl-N,N′-dibenzenesulfonyldiaminomesitylene from the preceding experiment showed no depression.

N,N′-Dimethyl-N,N′-dibenzenesulfonyldiaminomesitylene from N-Methyl-N,N′-dibenzenesulfonyldiaminomesitylene.—To a mixture of a solution of 0.165 g. of N-methyl-N,N′-dibenzenesulfonyldiaminomesitylene and a solution of 0.025 g. of potassium hydroxide in 3 ml. of methanol, 0.071 g. of methyl iodide in 2 ml. of methanol was added. After heating under reflux for ten minutes, an additional 0.071 g. of methyl iodide was introduced, and refluxing continued for another ten minutes. On cooling, a white solid (A) separated. On recrystallization from methyl ethyl ketone it had a m. p. of 225.5–227°.

The filtrate from the crystals was evaporated to dryness and the residue washed thoroughly with warm water. The residue was extracted with hot ethanol, leaving undissolved a product, m. p. 225.5–227°, which was combined with (A). It proved to be the higher-melting N,N′-dimethyl-N,N′-dibenzenesulfonyldiaminomesitylene.

On cooling the hot ethanol extract, a white crystalline material separated. Two recrystallizations from ethanol yielded a product which melted the same as the lower-melting N,N′-dimethyl derivative. A melting point of this mixed with the lower-melting N,N′-dimethyl-N,N′-dibenzenesulfonyldiaminomesitylene showed no depression.

N,N′-Di-*p*-bromobenzenesulfonyldiaminomesitylene.—A solution of 17.4 g. of *p*-bromobenzenesulfonyl chloride in 25 ml. of pyridine was added slowly, with stirring, to a solution of 5 g. of diaminomesitylene in 15 ml. of pyridine. The mixture was allowed to stand overnight, and then poured with stirring into a beaker containing 300 ml. of water, 50 ml. of concentrated hydrochloric acid, and 100 g. of ice. After filtering the resulting yellow precipitate, a sticky residue adhering to the beaker remained, which became solid upon treatment with dilute hydrochloric acid. This solid was added to the filtered precipitate, which was then washed thoroughly with dilute hydrochloric acid and with water. Recrystallization from a mixture of methyl ethyl ketone and dilute ethanol gave 9.8 g. (50%) of pure product, which began to darken at 273° and melts at 276–278° (cor.) with decomposition.

Anal. Calcd. for $C_{21}H_{20}O_4N_2Br_2S_2$: C, 42.86; H, 3.40. Found: C, 42.98; H, 3.63.

N,N′-Dimethyl-N,N′-di-*p*-bromobenzenesulfonyldiaminomesitylene.—A solution of 1.07 g. of potassium hydroxide in 25 ml. of methanol was added to 5 g. of N,N′-di-*p*-bromobenzenesulfonyldiaminomesitylene (m. p. 270–273°) in 40 ml. of acetone, and the mixture refluxed until solution was complete. To this was added 2.84 g. of methyl iodide, and refluxing was continued for one hour. An additional 1 ml. of methyl iodide was introduced and refluxing continued for thirty minutes. The solvent was evaporated and the residue washed thoroughly with warm water. The residue was a faintly yellow solid weighing 4.8 g. (91%). This was extracted with a hot mixture of 16 ml. of acetone and 4 ml. of ethanol, followed by extraction with 10 ml. of cold acetone. The residual solid was then recrystallized five times from acetone and water; fine colorless needles, m. p. 223–224° (cor.).

Anal. Calcd. for $C_{23}H_{24}O_4N_2Br_2S_2$: C, 44.81; H, 3.90. Found: C, 44.74; H, 4.05.

The acetone–ethanol and acetone extracts were combined and water was added to precipitate all of the solute, which was filtered and extracted with cold acetone. The product obtained by evaporation of the acetone extract was recrystallized four times from dioxane and water; small white platelets, m. p. 216–217° (cor.). A melting point of a mixture of this with the higher-melting isomer showed a depression of 7°.

Anal. Calcd. for $C_{23}H_{24}O_4N_2Br_2S_2$: C, 44.81; H, 3.90. Found: C, 44.63; H, 3.99.

N,N'-Di-*p*-toluenesulfonyldiaminomesitylene.—A solution of 10.4 g. of *p*-toluenesulfonyl chloride dissolved in 15 ml. of pyridine, was added dropwise over a period of three hours into a mechanically stirred solution of 3 g. of diaminomesitylene in 10 ml. of pyridine. The mixture was allowed to stand overnight at room temperature, and was then poured with stirring into a mixture of 300 ml. of water, 50 ml. of concentrated hydrochloric acid and 100 g. of ice. The brownish precipitate which formed was filtered and washed with dilute hydrochloric acid and finally with water. It was recrystallized from ethanol forming fine light yellow needles (A). The yield was 3.3 g.

Upon neutralizing the hydrochloric acid filtrate with 10% aqueous sodium hydroxide, 3.7 g. of yellow solid (B) separated. Since this product was soluble in both acid and basic media, it was assumed to be mono *p*-toluenesulfonyldiaminomesitylene. It was therefore dissolved in 15 ml. of pyridine and 7.6 g. of *p*-toluenesulfonyl chloride was added with stirring. After the addition was completed, the mixture was allowed to stand overnight. It was then poured slowly with stirring into a mixture of ice, water and hydrochloric acid. The yield was 4.5 g. of material identical with (A).

The total yield of N,N'-di-*p*-toluenesulfonyldiaminomesitylene was 8.2 g. (85.5%). It was recrystallized from dioxane and water, m. p. 234–235° (cor.).

Anal. Calcd. for $C_{23}H_{26}O_4N_2S_2$: C, 60.26; H, 5.94. Found: C, 60.14; H, 5.92.

N,N'-Dimethyl-N,N'-di-*p*-toluenesulfonyldiaminomesitylene.—From 1.68 g. of potassium hydroxide in 30 ml. of ethanol, 6 g. of di-*p*-toluenesulfonyldiaminomesitylene in 150 ml. of acetone, 4.26 g. and 4 g. of methyl iodide, following the procedure used for the corresponding *p*-bromobenzenesulfonyl derivative, 5 g. (78%) of product resulted.

This material was extracted with two 100-ml. portions of cold ethanol and then recrystallized several times from dioxane and water; white plates, m. p. 195.5–196.5° (cor.).

Anal. Calcd. for $C_{25}H_{30}O_4N_2S_2$: C, 61.73; H, 6.17. Found: C, 61.46; H, 6.27.

From the combined ethanol extracts after standing overnight, tiny needles (A), m. p. 177–180°, deposited. These were filtered and the mother liquor evaporated to one-half volume. Upon cooling, more crystals separated. These were crystallized once from methanol, and then extracted with two 50-ml. portions of cold ethanol. The extracts were combined and evaporated to one-quarter volume. Fine needles deposited upon cooling, which after recrystallization from ethanol were combined with (A). Five crystallizations from ethanol and water gave fine colorless needles, m. p. 181.5–182° (cor.).

Anal. Calcd. for $C_{25}H_{30}O_4N_2S_2$: C, 61.73; H, 6.17. Found: C, 61.92; H, 6.34.

N,N'-Di-*p*-nitrobenzenesulfonyldiaminomesitylene.—A solution of 16.6 g. of *p*-nitrobenzenesulfonyl chloride in 45 ml. of pyridine was added slowly with stirring to 5 g. of diaminomesitylene in 15 ml. of pyridine. The mixture was allowed to stand for two hours at room temperature, and was then poured into a mixture of 300 ml. of water, 50 ml. of concentrated hydrochloric acid and 100 g. of ice. The brown precipitate which formed was filtered and washed with dilute hydrochloric acid and water. The resulting sticky material was crystallized from ethanol, and 3.6 g. of a yellow powder resulted. The mother liquor was evaporated to one-half volume and allowed to cool. The yellow solid which separated was covered by a layer of sticky brown oil. The solvent was decanted and the residue boiled with 3 ml. of a 10% sodium hydroxide solution in 25 ml. of ethanol. On acidification, a yellow solid was obtained, apparently oil-free. The decanted mother liquor yielded a further 1.4 g. of yellow powder after precipitation with water, and treatment of the precipitate with an ethanolic sodium hydroxide solution. Thus the total yield of apparently oil-free material was 8 g. (46%). However, subsequent recrystallization from ethanol, methanol or acetone failed to yield a solid not contaminated with some oil. The highest melting point observed was 239–241.5°, after repeated treatment with an acetone–water mixture, decantation of warm solvent from the oil which separated first, and cooling. The analyses of the product did not agree closely with those expected.

N,N'-Dimethyl-N,N'-di-*p*-nitrobenzenesulfonyldiaminomesitylene.—A solution of 1.23 g. of potassium hydroxide in 30 ml. of ethanol, was added to a solution of 5 g. of crude N,N'-di-*p*-nitrobenzenesulfonyldiaminomesitylene in 60 ml. of acetone. To this was added 3.55 g. of methyl iodide and the mixture refluxed for one hour. An additional 2 g. of methyl iodide was introduced, and refluxing continued for one hour. On cooling, fine yellow needles separated. These were filtered and washed with methanol (A). The compound was crystallized from dioxane and water, but apparently decomposed slightly in this solvent since it turned deep yellow and melted lower than the crude material. Subsequent recrystallization was effected from acetone; tiny buff-colored needles, m. p. 234–235.5° (cor.).

Anal. Calcd. for $C_{23}H_{26}O_8N_4S_2$: C, 50.36; H, 4.38. Found: C, 50.31; H, 4.43.

Water was added to the filtrate of (A). The red-brown oil-covered solid was washed with water and treated with 50 ml. of boiling ethanol to remove the oil. It was then extracted with cold acetone and the acetone solution treated with water to effect precipitation of the product. After five crystallizations from acetone and water, faintly brownish crystals resulted, m. p. 202–204° (cor.), with slight decomposition.

Anal. Calcd. for $C_{23}H_{26}O_8N_4S_2$: C, 50.36; H, 4.38. Found: C, 50.56; H, 4.49.

Summary

1. By methylation of N,N'-dibenzenesulfonyldiaminomesitylene, by methylation of N-methyl-N,N'-dibenzenesulfonyldiaminomesitylene, or by benzenesulfonation of N,N'-dimethyldiaminomesitylene, the *cis*- and *trans*-forms of N,N'-dimethyl-N,N'-dibenzenesulfonyldiaminomesitylene were obtained. The isomers result from two points of restricted rotation in the molecules.

2. From diaminomesitylene and *p*-toluenesulfonyl, *p*-bromobenzenesulfonyl or *p*-nitrobenzenesulfonyl chlorides, the N,N'-diarylsulfonyldiaminomesitylenes resulted. Upon methylation, pairs of isomers of the N,N'-dimethyl derivatives were formed in each case.

3. Diaminomesitylene reacts stepwise with methyl iodide to form first N-methyldiaminomesitylene, then N,N'-dimethyldiaminomesitylene. Even with excess of reagent, under the conditions used, no trimethyl or tetramethyl derivative was produced.

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