

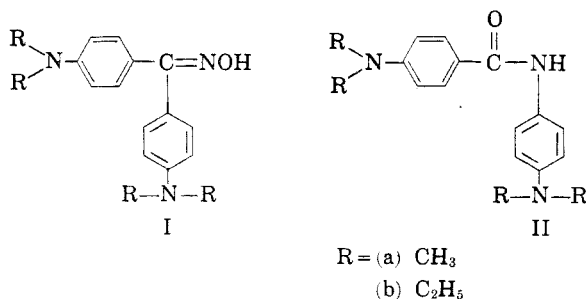
Preparation and Characterization of 4,4'-Bis(dimethylamino)- and 4,4'-Bis(diethylamino)-benzophenone Oxime

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The oximes of Michler's ketone and its ethyl analog were prepared and characterized. The products previously cited in the literature to be the oximes of these ketones were identified as anilides arising from a Beckmann rearrangement of the oximes.

Reaction of 4,4'-bis(dimethylamino)benzophenone (Michler's ketone) with hydroxylamine hydrochloride in ethyl alcohol was reported by Munchmeyer to yield the oxime derivative (Ia) with a melting point of 233°. Under similar reaction conditions, 4,4'-bis(diethylamino)benzophenone gave a product melting at 135° which was similarly reported as being the oxime (Ib) of the ketone.² It has now been established that neither of these products are oximes; instead, they have been characterized as anilides (II) resulting from the Beckmann rearrangement of the oximes sought.



Treatment of Michler's ketone with hydroxylamine hydrochloride in pyridine yielded principally a product that melted at 216–217° shown subsequently to be the true oxime; and a small amount of a product that melted at 232–233° which was identified as the anilide IIa. However, by conducting the oximation in an excess of alcoholic potassium hydroxide solution, only the product melting at 216–217° was formed. Mixture melting points showed that the product melting at 232° was identical with the anilide prepared from *p*-dimethylaminobenzoic acid and *N,N*-dimethyl-*p*-phenylenediamine.

Identification of the product melting at 216–217° as the oxime of Michler's ketone (Ia) was based on the observation that it formed a dark green complex with ferric chloride, and that it readily liberated the original ketone when refluxed in dilute hy-

drochloric acid. Excess alcoholic hydrogen chloride did not affect Ia, but upon refluxing in alcohol containing pyridine hydrochloride, Ia was transformed into a product identical to IIa. Finally, the benzoate ester of Ia was prepared.

Identity of the substance melting at 232–233° with the substituted benzanilide (IIa) was shown on the basis that it did not give the ferric chloride test, was unaffected by dilute hydrochloric acid, and was hydrolyzed by aqueous sodium hydroxide to *p*-dimethylaminobenzoic acid and *N,N*-dimethyl-*p*-phenylenediamine. Identification of IIa was completed by synthesis from the acid chloride of *p*-dimethylaminobenzoic acid and *N,N*-dimethyl-*p*-phenylenediamine.

By a similar sequence of reactions, the product previously reported as the oxime of 4,4'-bis(diethylamino)benzophenone² was identified as the anilide that would be expected from the Beckmann rearrangement of the oxime.

DISCUSSION

Baither³ had previously reported obtaining the oxime Ia by treatment of thio Michler's ketone with hydroxylamine hydrochloride and an amount of potassium hydroxide slightly less than that required to neutralize the hydroxylamine salt. However, he also reported that numerous recrystallizations from ethanol were required before a substance with a sharp melting point was finally isolated. Apparently, the reaction system used by Baither was not sufficiently alkaline to prevent rearrangement of the oxime to the anilide. The initial product isolated by Baither presumably contained some of the oxime; however, because the oxime is more soluble in ethanol than the anilide, the repeated recrystallizations eventually afforded the anilide instead of the oxime. Baither further indicated that his product was readily hydrolyzed to Michler's ketone by refluxing in dilute hydrochloric acid, but he neglected to specify what specimen he used for this experiment. Since it is the anilide and not the oxime that he obtained in pure form, it must be con-

(1) Munchmeyer, *Ber.*, **19**, 1852 (1886); **20**, 228 (1887).(2) Lynch and Reid, *J. Am. Chem. Soc.*, **55**, 2518 (1933).(3) Baither, *Ber.*, **20**, 1735 (1887).

cluded that the hydrolysis was made on one of the impure products that still contained appreciable quantities of the oxime.

The effect of dialkylamino substituents on the rate of rearrangement of the migrating phenyl ring in the Beckmann rearrangement does not appear to have been studied. However, Pearson⁴ recently confirmed earlier observations by Chapman⁵ and Higman⁶ that the rate of rearrangement depends partly on the relative tendency of the migrating group to donate a pair of electrons to the oximino nitrogen atom. For example, the rate of rearrangement of a series of para-substituted acetophenone oximes was found to be in the order: MeO >> Me = *tert*-Bu > H > Cl >> NO₂.⁷ The strong electrophilic influence of dialkylamino groups presumably explains the ease of rearrangement of oximes Ia and Ib in relatively weakly acidic systems, such as alcoholic solutions of hydroxylamine hydrochloride or pyridine hydrochloride. No rearrangement takes place in alcoholic hydrogen chloride solutions, because, in the absence of a strong proton acceptor, the dialkylamino substituents become positively charged dialkylammonium substituents that normally exhibit nucleophilic properties like those of the nitro group.

EXPERIMENTAL

4,4'-Bis(dimethylamino)benzophenone oxime. (a). *Potassium hydroxide method*. A mixture of 26.8 g. (0.10 mole) of Michler's ketone, 27.8 g. (0.40 mole) of hydroxylamine hydrochloride, 60 g. of potassium hydroxide, 600 ml. of alcohol, and 50 ml. of water was refluxed for 2 hours. After standing overnight at room temperature, the reaction mixture was concentrated to a thick suspension and poured into 1500 ml. of ice-water. The crude product obtained weighed 28.0 g. (99%), m.p. 213–216°. Recrystallization from a mixture of ethanol and benzene yielded colorless needles, m.p. 216–217°.

Anal. Calc'd for C₁₇H₂₁N₃O: C, 72.2; H, 7.5; N, 14.9. Found: C, 72.0; H, 7.3; N, 14.2.

(b). *Pyridine method*. A mixture of 93.8 g. (0.35 mole) of Michler's ketone, 97.3 g. (1.4 mole) of hydroxylamine hydrochloride, 250 ml. of pyridine, and 250 ml. of ethanol was refluxed for 3 hours. After evaporation to half the initial volume under reduced pressure on a steam bath, the resulting slurry was poured into 2 liters of ice-water. The light-brown, crude product was recrystallized twice from a mixture of ethanol and benzene to yield 23.6 g. (24%) of colorless needles, m.p. 215–216°. The melting point was not depressed when mixed with the oxime prepared by the potassium hydroxide method.

The mother liquors from the above recrystallizations were evaporated to dryness, and the residue was boiled with 500 ml. of benzene. The undissolved material was collected and recrystallized twice from benzene to yield 4.0 g. (4%) of colorless needles, m.p. 231–232°. The melting point was not depressed when mixed with a sample of *4,4'*-bis(dimethyl-

amino)benzanilide synthesized from the corresponding acid and amine.

4,4'-Bis(dimethylamino)benzanilide. A mixture of 3.3 g. (0.02 mole) of *p*-dimethylaminobenzoic acid⁸ and 4.8 g. (0.04 mole) of thionyl chloride in 20 ml. of carbon tetrachloride was refluxed for 4 hours while being protected from moisture by a calcium chloride tube. The carbon tetrachloride and excess thionyl chloride were removed under reduced pressure at 50°. The resulting acid chloride was dissolved in 40 ml. of benzene and added with stirring to 5.5 g. (0.04 mole) of *N,N*-dimethyl-*p*-phenylenediamine dissolved in 100 ml. of ether. An immediate reaction occurred, and a precipitate formed. After standing for 30 minutes, the reaction mixture was shaken with 200 ml. of ice-water and filtered with suction. Recrystallization of the crude solid from ethanol yielded 4.8 g. (85%) of colorless needles, m.p. 230–231°. A second recrystallization from ethanol raised the melting point to 232–233°.

Anal. Calc'd for C₁₇H₂₁N₃O: C, 72.2; H, 7.5; N, 14.9. Found: C, 72.1; H, 7.2; N, 14.5.

4,4'-Bis(dimethylamino)benzophenone oxime benzoate. To a mixture of 2.8 g. (0.01 mole) of Michler's ketone oxime and 10 ml. of *N* sodium hydroxide in 50 ml. of acetone cooled to 10° was added dropwise with stirring, 1.4 g. (0.01 mole) of benzoyl chloride. After 10 minutes, 150 ml. of ice-water was added, and the resulting precipitate was collected and dried in a vacuum desiccator. Recrystallization by the addition of pentane to a benzene solution of the crude product yielded 2.7 g. (69%) of nearly colorless needles. The material exhibited double melting points of 127° and 170°. Exposure to light caused the material to change gradually from buff to bright yellow.

Anal. Calc'd for C₂₄H₂₅N₃O₂: C, 74.4; H, 6.5; N, 10.8. Found: C, 74.5; H, 6.6; N, 10.3.

Hydrolysis of 4,4'-bis(dimethylamino)benzophenone oxime. A mixture of 1.4 g. (0.005 mole) of Michler's ketone oxime and 15 ml. of *N* HCl was refluxed for 2 hours. The clear solution was cooled and neutralized with dilute, aqueous NaOH. The solid which precipitated was collected, washed with water, and air-dried to give 1.2 g. of a white powder melting at 170–173°. After recrystallization from alcohol, the product melted at 173–175° and did not depress the melting point of an authentic specimen of Michler's ketone.

Hydrolysis of 4,4'-bis(dimethylamino)benzanilide. A 2.83-g. (0.01 mole) sample of the rearranged Michler's ketone oxime melting at 231–232° was hydrolyzed by refluxing with 15 ml. of 2 *N* alcoholic KOH for 4 hours. The alcohol was partially evaporated and the residue was diluted with water and extracted with ether. The ether extract was evaporated and the residue was treated with 5 ml. of acetic anhydride and warmed for 5 minutes. Treatment with water and dilute NaOH caused the solid acetyl derivative of *N,N*-dimethyl-*p*-phenylenediamine to separate; its m.p. of 134–135° after recrystallization from alcohol-water was identical with the m.p. of an authentic specimen obtained from *N,N*-dimethyl-*p*-phenylenediamine.

The alkaline solution from the hydrolysis was neutralized to pH 6 with dilute HCl and the solid which separated was recovered by filtration. After recrystallization from alcohol it melted at 240–241° and was found to be identical with a known specimen of *p*-dimethylaminobenzoic acid.

Rearrangement of 4,4'-bis(dimethylamino)benzophenone oxime by pyridine hydrochloride. A solution of 2.8 g. (0.01 mole) of Michler's ketone oxime, 10 ml. of pyridine, and 10 ml. of ethanol was treated with a stream of dry hydrogen chloride for 10 minutes. After refluxing for 18 hours, the mixture was treated with 10 ml. of pyridine and 400 ml. of ice-water. The resulting solid, after recrystallization from ethanol, yielded 1.7 g. (61%) of colorless needles, m.p. 229–231°. A second recrystallization raised the melting point to

(4) Pearson and Ball, *J. Org. Chem.*, **14**, 118, (1949).

(5) Chapman, *J. Chem. Soc.*, 1550 (1934); 448 (1936).

(6) Higman, *Nature*, **156**, 242 (1945).

(7) Pearson, Baxter, and Martin, *J. Org. Chem.*, **17**, 1511 (1952).

(8) Breslow, *J. Am. Chem. Soc.*, **72**, 4244 (1950).

232–233°, which was not depressed when mixed with an authentic sample of 4,4'-bis(dimethylamino)benzanilide.

4,4'-Bis(diethylamino)benzophenone oxime. (a) *Potassium hydroxide method.* This method gave a 67% yield of the oxime Ib, nearly colorless crystals from ethanol-benzene, m.p. 200–201°.

Anal. Calc'd for $C_{21}H_{29}N_3O$: C, 74.4; H, 8.56; N, 12.4. Found: C, 74.5; H, 8.46; N, 12.4.

(b) *Pyridine method.* This method gave only a 50% yield of the desired oxime.

(c) *Base-free method.* Following the procedure of Lynch and Reid,² a mixture of 7.5 g. (0.023 mole) of 4,4'-bis(diethylamino)benzophenone, 2.5 g. (0.036 mole) of hydroxylamine hydrochloride, and 30 ml. of alcohol was refluxed for 4 hours. The alcohol was evaporated in a stream of air, and the thick residual oil was dissolved in dilute hydrochloric acid. Treatment with ammonium hydroxide deposited a

sticky gum from which the aqueous mother liquor was decanted. The gum was dissolved in hot benzene, and on cooling crystals were deposited; yield, 2.7 g., m.p. 134–135°. After recrystallization from ethanol, this product melted at 140–141° and was identical with synthesized 4,4'-bis(diethylamino)benzanilide.

4,4'-Bis(diethylamino)benzanilide. This compound was prepared from the acid chloride obtained from 3.8 g. (0.02 mole) of *p*-diethylaminobenzoic acid (m.p. 190–191°) and 6.6 g. (0.02 mole) of *N,N*-diethyl-*p*-phenylenediamine; yield, 5.7 g. (84%) of buff-colored needles, m.p. 125–127°. Treatment with charcoal and recrystallization from aqueous ethanol gave colorless needles, m.p. 140–141°.

Anal. Calc'd for $C_{21}H_{29}N_3O$: C, 74.4; H, 8.6; N, 12.4. Found: C, 73.9; H, 8.3; N, 12.2.

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