Anal. Calcd. for $C_{18}H_{22}O_4S_2$: C, 58.99: H, 6.05; S, 17.49. Found: C, 59.19; H, 5.94; S, 17.40.

3,5-Dimethyl-4-methoxybenzenesulfonyl Chloride.—Chlorosulfonic acid (50 g., 28 ml.) was added dropwise to an ice-cold solution of 2,6-dimethylanisole (10 g.) in 50 ml. of chloroform. The temperature was kept below 8° during the addition and considerable evolution of hydrogen chloride was observed as the mixture turned dark brown. After the addition of the chlorosulfonic acid was completed, the mixture was allowed to warm to room temperature and then stirred for 30 min. The contents of the flask were poured onto 250 g. of crushed ice and 100 ml. of chloroform was added. The organic layer was separated, washed with cold water, and dried over calcium sulfate. The removal of the solvent under reduced pressure yielded a light brown oil (15.29 g.) which later crystallized, m.p. 40–45°. Recrystallizations from petroleum ether (b.p. 60–90°) gave 3,5-dimethyl-4-methoxybenzenesulfonyl chloride as a white crystalline solid melting at 44–46°.

From the above benzenesulfonyl chloride and concentrated ammonium hydroxide solution, 3,5-dimethyl-4-methoxybenzenesulfonamide, m.p. 131–132°, was prepared.

Anal. Calcd. for $C_9H_{13}NO_3S$: C, 50.21; H, 6.08; N, 6.51. Found: C, 50.37; H, 5.95; N, 6.41.

In contrast to the above results, Baliah and Uma[12] have reported that 3,5-dimethyl-4-methoxybenzenesulfonyl chloride is a yellow oil and the sulfonamide derived from it melts at 108–110°.

3,5-Dimethyl-4-methoxybenzenesulfinic Acid.—A mixture of 3,5-dimethyl-4-methoxybenzenesulfonyl chloride (2.35 g.), sodium bisulfite (2.08 g.), and sodium hydroxide (0.04 g.) was gently heated in 100 ml. of water for 4 hr. In order to keep the mixture alkaline, 50% sodium hydroxide was added periodically. During the heating period, the sulfonyl chloride gradually dissolved until finally a clear solution was obtained. The solution was cooled to 0° and carefully was acidified with dilute sulfuric acid while keeping the mixture cold in an ice bath. A copious quantity of white solid precipitated during the acidification. The solid was separated and dried under vacuum yielding 1.68 g. of product melting at 83–90°. This solid was unstable and decomposed upon standing at room temperature. The product was used immediately after isolation for the next step. An analytical sample, m.p. 86–89°, was obtained by dissolving the product in cold diethyl ether and then concentrating the solution under vacuum until a white solid separated.

Anal. Calcd. for $C_9H_{12}O_3S$: C, 53.98; H, 6.04. Found: C, 54.2; H, 6.18.

Disproportionation of 3,5-Dimethyl-4-methoxybenzenesulfinic Acid.—A solution of freshly prepared 3,5-dimethyl-4-methoxybenzenesulfinic acid (1.0 g.) in 80 ml. of cyclohexane was refluxed for 1 hr. The white solid gradually dissolved during the heating period and a brown oil separated. The supernatant clear solution was decanted, and the brown oil was extracted twice with 15-ml. portions of hot cyclohexane. The cyclohexane solutions were combined and concentrated to yield a white solid (0.55 g.) melting at 121–124°. A mixture melting point with the dimethyl ether prepared from I showed no depression and the infrared spectra of the samples were identical.

Bis(3,5-dimethyl-4-hydroxyphenyl) Sulfoxide.—Anhydrous aluminum chloride (4.45 g.) was added to a well-stirred, ice-cold solution of 2,6-dimethylphenol (6.1 g.) dissolved in 50 ml. of carbon tetrachloride. Thionyl chloride (2.4 ml.) was added then to the above cold solution over a period of 5 min. The reaction mixture was stirred at room temperature for 2 hr. and was decomposed by pouring onto 100 g. of crushed ice containing 5 ml. of concentrated hydrochloric acid. The solid which precipitated was separated and washed with water. The crude product (7.21 g.) melted at 184–198° dec. Recrystallizations from either acetonitrile or ethyl acetate yielded a white product (5.39 g.) with a lower melting point of 167–167.5° dec.

Anal. Calcd. for $C_{16}H_{18}O_3S$: C, 66.17; H, 6.25; S, 11.04. Found: C, 66.14; H, 6.42; S, 11.06.

Bis(3,5-dimethyl-4-hydroxyphenyl) Sulfide.—A procedure similar to that described by Oae and Zalut[3] was used.

Thionyl chloride (12 ml., 17.5 g.) was added to a cold solution of 2,6-dimethylphenol (52.0 g.) dissolved in 50 ml. of chloroform. The yellow solution was allowed to stand at room temperature for 2 days. During this time a white crystalline solid precipitated from the reaction mixture. The solid was separated and recrystallized from cyclohexane to yield white needles (31.69 g.) melting at 121–122°, lit.[13] m.p. 121.5–122°.

Anal. Calcd. for $C_{16}H_{18}O_2S$: C, 70.03; H, 6.61; S, 11.68. Found: C, 69.79; H, 6.58; S, 11.51.

From the chloroform filtrate, 2,6-dimethyl-4-chlorophenol, m.p. 80–81°, was obtained.

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(12) V. Baliah and M. Uma, *J. Indian Chem. Soc.*, **40**, 381 (1963).

(13) J. L. Binder, J. C. Ambelang, and F. J. Webb, *J. Am. Chem. Soc.*, **81**, 3608 (1959).

Ring Cleavage of 2,3-Dihydro-2-imino-4*H*-1,3-benzothiazin-4-one[1]

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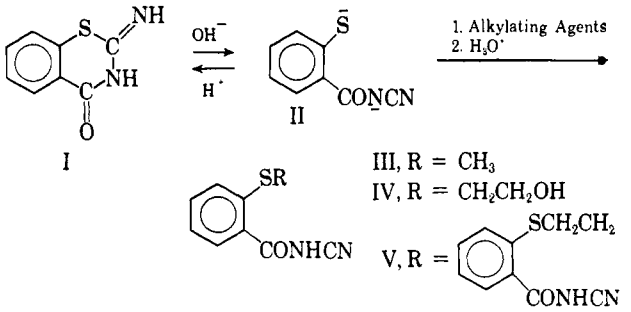
In connection with another problem we observed that the title compound (I) was insoluble in concentrated ammonia at 50°, but dissolved in excess warm 10% sodium hydroxide and evolved hydrogen immediately in the cold with sodium hydride. Neutralization of the basic solutions regenerated I. As at least two equivalents of base were required to effect complete solution, it appeared reasonable that a ring cleavage of I to the disodium salt of *o*-mercaptobenzoyl cyanamide (II) was occurring. This was shown to be so by the reaction of these solutions with methyl iodide. A good yield of *o*-(methylthio)benzoyl cyanamide (III) was obtained, identical with III prepared from *o*-(methylthio)benzoyl chloride and sodium cyanamide. The reaction of I with ethylene oxide and ethylene bromide gave, respectively, *o*-(2-hydroxyethylthio)benzoyl cyanamide (IV) and the 1,2-bis substituted ethane V.



The acidity of acylcyanamides (or N-cyanoacetamides) has inspired little interest since the dissociation constants were determined conductimetrically by Bader[2] nearly 75 years ago. He discovered that the acetyl, butyryl, and benzoyl cyanamides gave pK_a's of 3.82, 3.95, and 2.7, respectively. We found III to have a pK_a of 2.81

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(2) R. Bader, *Z. phys. Chem.*, **6**, 304 (1890).

± 0.06. From the standpoint of medicinal chemistry, the acylcyanamide group would seem to be of particular interest. Its substitution for the carboxyl function in amino acids and peptides would introduce a group capable of undergoing nucleophilic addition reactions while still retaining the inner salt structure of the natural substance.

Experimental[3]

o-(**Methylthio**)**benzoyl Cyanamide** (**III**). **Method A. From I.**—To 1.8 g. (0.01 mole) of I[4] was added 10 ml. (0.025 mole) of 10% sodium hydroxide, and the mixture was heated on the steam bath for several minutes to effect complete solution. It was then cooled to room temperature and 2 ml. (0.04 mole) of methyl iodide in 7 ml. of dimethylformamide was added. After 15 min. the solution was added dropwise to excess dilute hydrochloric acid. The precipitate was collected, washed with water, and dried under vacuum at room temperature. The yield was 1.5 g. (78%), m.p. 117–118°. Recrystallization from chloroform raised the melting point to 118.5–119°; $\lambda_{max\ (\mu)}^{CHCl_3}$ 4.35 (s), 5.80 (s), 6.25 (m).

Anal. Calcd. for $C_{10}H_{10}N_2O_2S$: C, 56.23; H, 4.19; N, 14.57; S, 16.68. Found: C, 56.53; H, 3.95; N, 14.18; S, 16.87.

Determination of pK_a.[5]—To 25 ml. of 95% ethanol was added 0.1925 g. (1.00 mmole) of III and 70 ml. of carbon dioxide-free distilled water. The titration was carried out under nitrogen with carbon dioxide-free 0.100 *N* potassium hydroxide, and the pH was measured at every 0.1 equivalent by a Radiometer PHM4C pH meter equipped with a type GK 2021-C combined electrode. The pK_a calculated at 0.1 to 0.9 equivalents was 2.81 ± 0.06.

Method B. From *o*-(**Methylthio**)**benzoyl Chloride.**—To 8 ml. of 10% sodium hydroxide (0.02 mole) and 1.0 g. (0.02 mole) of cyanamide in an ice bath was added 1.96 g. (0.01 mole) of the acid chloride.[6] After stirring overnight the pH was 5. The mixture was made alkaline with 4 ml. of 10% sodium hydroxide, filtered, and the filtrate was acidified with dilute hydrochloric acid. The precipitate was collected, stirred into 25 ml. of 5% sodium bicarbonate, filtered, and the filtrate dripped into dilute ice-cold hydrochloric acid. The precipitate was collected, washed with water, and dried under vacuum at room temperature. The yield was 0.9 g. (47%), m.p. 119–120°. The infrared spectra in chloroform were identical for III prepared by both methods.

o-(**2-Hydroxyethylthio**)**benzoyl Cyanamide** (**IV**).—This was prepared by the addition of ethylene oxide to a solution of I in sodium hydroxide prepared as in method A and cooled to 0°. Work-up of the product was the same as for III. The crude yield was 2.0 g. (90%), m.p. 89–90°. Recrystallization from chloroform raised the melting point to 94–95°; $\lambda_{max\ (\mu)}^{CHCl_3}$ 4.35 (m), 5.80 (s), 6.25 (m). A mineral oil mull showed hydroxyl stretching at 2.75 μ.

Anal. Calcd. for $C_{10}H_{10}N_2O_2S$: C, 54.03; H, 4.53; S, 14.43. Found: C, 53.85; H, 4.62; S, 14.32.

1,2-Bis[*o*-(**N-cyanocarboxamido**)**phenylthio**]**ethane** (**V**).—To a 500-ml; three-neck flask equipped with sealed stirrer, condenser, addition funnel, and gas inlet tube was placed 18 g. (0.10 mole) of I and 150 ml. of dry dimethylformamide. To the stirred mixture at 19° under dry nitrogen was added 10 g. of a 55% sodium hydride–mineral oil dispersion (0.23 mole). After about 15 min. the temperature began to rise and gas evolution occurred. The temperature rose to 35° despite the surrounding ice bath. After 35 min. from the start of the reaction 9 ml. (0.1 mole) of ethylene bromide was added slowly through the funnel. The temperature was kept at 30–40° over the 5-min. addition period. After the temperature had dropped to 20°, the reaction mixture was poured into 500 ml. of ice–water and extracted with two 200-ml. of ether and 100 ml. of petroleum ether. The aqueous phase was acidified with 50 ml. of concentrated hydrochloric acid, and the colorless precipitate was collected and dried at room temperature. The yield of crude product, m.p. 155–160°, was 15.4 g. (80%). Recrystallization from acetone–petroleum ether gave pale yellow crystals which changed to an amorphous orange mass at 184–185°.

Anal. Calcd. for $C_{18}H_{14}N_4O_2S_2$: C, 56.53; H, 3.69; N, 14.65; S, 16.77. Found: C, 56.67; H, 3.79; N, 14.20; S, 16.62.

(3) Melting points are uncorrected and were obtained on a Mel-Temp block; analyses were by the Clark Microanalytical Laboratory, Urbana, Ill.; and spectra were recorded on a Perkin-Elmer Model 137-B infrared spectrophotometer.

(4) K. Hasspacher, U. S. Patent 2,978,448 (April 4, 1961); *Chem. Abstr.*, **55**, 19,965 (1961).

(5) A. Albert and E. P. Serjeant, "Ionization Constants of Acids and Bases," John Wiley and Sons, Inc., New York, N. Y., 1962, p. 28.

(6) E. W. McClelland and L. A. Warren, *J. Chem. Soc.*, 2625 (1929).

Orientation in Some Friedel–Crafts Acylations of 2,2′-Dimethoxybiphenyl, and the Cyclization of the Reaction Products

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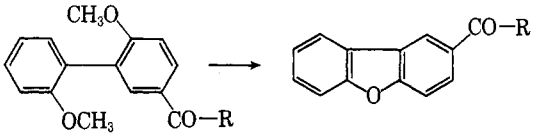
In continuation of our research on orientation in Friedel–Crafts acylations of variously substituted biphenyls,[1] we have investigated the reactivity of 2,2′-dimethoxybiphenyl, a compound obtainable in 88% yield from commercial 2,2′-dihydroxybiphenyl with dimethyl sulfate and aqueous sodium hydroxide, an easy preparation that is in sharp contrast to the difficulties encountered in the dimethylation of 1,8-dihydroxynaphthalene.[2] Further, derivatives of 2,2′-dimethoxybiphenyl would supply a convenient route to dibenzofuran compounds, provided that a satisfactory cyclization method could be evolved.

It was found that 2,2′-dimethoxybiphenyl underwent monoacetylation under standard conditions for Friedel–Crafts reactions, to give good yield of a ketone, which was 5-acetyl-2,2′-dimethoxybiphenyl (I), as it



I, R = CH_3
II, R = C_2H_5

III, R = CH_3
IV, R = C_2H_5

could be readily converted by prolonged heating with anhydrous pyridine hydrochloride into 2-acetyldibenzofuran (III). Propionylation gave 5-propionyl-2,2′-dimethoxybiphenyl (II), which was likewise converted to 2-propionyldibenzofuran (IV), with excellent yields; these two acyldibenzofurans previously had been prepared directly from dibenzofuran.[3] The cyclization of 2,2′-dihydroxybiphenyl and its derivatives had generally been accomplished by more drastic procedures such as using zinc chloride,[4] or hydriodic acid,[5] or at high temperatures,[6] although in one exceptional case it had occurred during a very mild reaction, when 2,3-

(1) N. P. Buu-Hoï and M. Sy, *J. Org. Chem.*, **21**, 136 (1956); N. P. Buu-Hoï, M. Sy, and J. Riché, *ibid.*, **22**, 668 (1957); N. P. Buu-Hoï, L. Petit, and D. C. Thang, *Bull. soc. chim. France*, 335 (1960).

(2) H. Gilman, J. Swiss, and L. C. Cheney, *J. Am. Chem. Soc.*, **62**, 1963 (1940); N. P. Buu-Hoï and D. Lavit, *J. Chem. Soc.*, 2412 (1956).

(3) W. Borsche and W. Bothe, *Ber.*, **41**, 1943 (1908); E. Mosettig and R. A. Robinson, *J. Am. Chem. Soc.*, **57**, 2186 (1935); N. P. Buu-Hoï and R. Royer, *Rec. trav. chim.*, **67**, 175 (1948).

(4) G. Kraemer and R. Weissgerber, *Ber.*, **34**, 1662 (1901).

(5) J. Schüler, *Arch. Pharm.*, **245**, 275 (1907).

(6) E. Bamberger and J. Brun, *Ber.*, **40**, 1952 (1907).