± 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°; $\lambda_{\max (\mu)}^{\mathrm{CHCl_3}}$ 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°; $\lambda_{\max (\mu)}^{\mathrm{CHCl_3}}$ 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

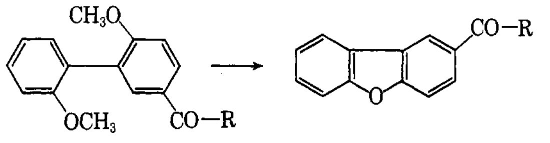
N. P. BUU-HOÏ, L. PETIT, AND D. C. THANG

Institut de Chimie des Substances Naturelles du Centre National de la Recherche Scientifique, Gif-sur-Yvette (S.-et-O.), France

Received July 10, 1963

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 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-



I, R = CH_3 III, R = CH_3
II, R = C_2H_5 IV, R = C_2H_5

---

[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).

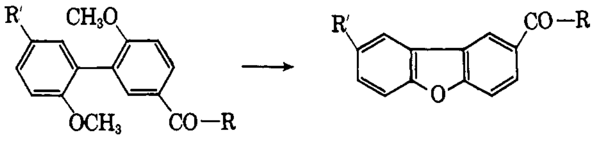
[4] G. Kraemer and R. Weissgerber, *Ber.*, **34**, 1662 (1901).

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

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

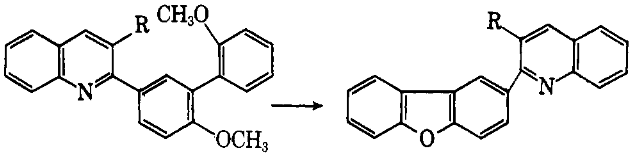
dimethoxydibenzofuran was obtained by heating the diazo derivative of 2′,4,5-trimethoxy-2-nitrobiphenyl.[7]

5-Alkyl-2,2′-dimethoxybiphenyls (prepared by Wolff-Kishner reduction of 5-acyl-2,2′-dimethoxybiphenyls, using the Huang-Minlon technique[8]) likewise readily underwent Friedel-Crafts acylations, to give 5′-acyl-5-alkyl-2,2′-dimethoxybiphenyls (V), which also could be cyclized to 2-acyl-7-alkyldibenzofurans (VI). This route might be useful for the preparation of unsymmetrical 2,7-disubstituted dibenzofurans.



V VI

The present dibenzofuran ring closure could be extended to more complex derivatives of 2,2′-dimethoxybiphenyl. Thus, 2-(2,2′-dimethoxy-5-biphenylyl)quinoline (VII) and its homolog (VIII), prepared by thermal decarboxylation of the appropriate cinchoninic acids (which were obtained from ketones I and II by Pfitzinger reactions), were converted to the corresponding 2-(2-dibenzofuryl)quinolines (IX and X).



VII, R=H
VIII, R=CH_3

IX, R=H
X, R=CH_3

Experimental[9]

5-Acetyl-2,2′-dimethoxybiphenyl (I).—To an ice-cooled solution of 21.4 g. of 2,2′-dimethoxybiphenyl, m.p. 154–155°, in 250 ml. of anhydrous carbon disulfide, 30.7 g. of finely powdered aluminum chloride was added in small portions, and this well-stirred mixture was treated dropwise with 8 g. of acetyl chloride, left at room temperature for 12 hr., and the reaction then terminated by a brief refluxing on the water bath. After decomposition with ice and dilute hydrochloric acid, the reaction product was taken up in chloroform; the chloroform solution was washed several times with 5% aqueous sodium hydroxide, then with water, and dried over calcium chloride. The residue from evaporation of the solvent yielded, on recrystallization from methanol, 18 g. of colorless prisms, m.p. 161°.

Anal. Calcd. for $C_{16}H_{16}O_3$: C, 75.0; H, 6.3. Found: C, 74.9; H, 6.4.

5-Propionyl-2,2′-dimethoxybiphenyl (II).—Prepared from 21.4 g. of 2,2′-dimethoxybiphenyl, 9.2 g. of propionyl chloride, and 30.7 g. of aluminum chloride, this **ketone** (19 g.) crystallized from methanol as shiny colorless prisms, m.p. 168°.

Anal. Calcd. for $C_{17}H_{18}O_3$: C, 75.5; H, 6.7. Found: C, 75.4; H, 6.7.

2-Acetyldibenzofuran (III).—A mixture of 25 g. of ketone I and 130 g. of redistilled pyridine hydrochloride was refluxed for 48 hr., and, after cooling, the mixture was treated with dilute hydrochloric acid; the product was taken up in benzene, the benzene solution dried over calcium chloride, the solvent removed, and the residue vacuum fractionated. The portion, b.p. 210–212° (15 mm.), crystallized from methanol as colorless prisms (13 g.), m.p. 81°, lit.[3] m.p. 81°.

2-Propionyldibenzofuran (IV), prepared similarly from ketone II, crystallized from ethanol as silky colorless needles, m.p. 100–101° (lit.[3] m.p. 101.5–102.5°), yield 45%.

5-Ethyl-2,2′-dimethoxybiphenyl.—A solution of 25.6 g. of ketone I and 9.7 g. of 98% hydrazine hydrate in 150 ml. of diethylene glycol was treated at 100° with 22.4 g. of potassium hydroxide in small portions, and the mixture refluxed for 5 hr.; after cooling and dilution with water, the precipitate formed was collected, washed with water, dried, and recrystallized from cyclohexane, giving shiny colorless needles, m.p. 104°, yield 19.4 g.

Anal. Calcd. for $C_{16}H_{18}O_2$: C, 79.3; H, 7.5. Found: C, 79.3; H, 7.5.

Treatment of 2.4 g. of this compound with 12 g. of pyridine hydrochloride, as above, afforded 1.5 g. of **2-ethyldibenzofuran**, b.p. 168–170° (14 mm.), lit.[3] b.p. 168–174° (14 mm.). The same reaction, performed with the crude Wolff-Kishner reduction product of ketone II, afforded **2-propyldibenzofuran** as a pale yellow oil, b.p. 176–178° (14 mm.), yield 65%.

Anal. Calcd for $C_{15}H_{14}O$: C, 85.7; H, 6.7. Found: C, 85.7; H, 6.7.

5′-Propionyl-5-ethyl-2,2′-dimethoxybiphenyl (V, **R** = **R′** = C_2H_5).—Prepared from 24.4 g. of 5-ethyl-2,2′-dimethoxybiphenyl, 9.2 g. of propionyl chloride, and 30 g. of aluminum chloride in methylene chloride, this **ketone** (13 g.) crystallized from cyclohexane as colorless prisms, m.p. 82°.

Anal. Calcd. for $C_{19}H_{22}O_3$: C, 76.5; H, 7.4. Found: C, 76.4; H, 7.3.

5′-Acetyl-5-propyl-2,2′-dimethoxybiphenyl (V, **R** = CH_3, **R′** = C_3H_7) crystallized from cyclohexane as colorless prisms, m.p. 68°, yield 70%.

Anal. Calcd. for $C_{19}H_{22}O_3$: C, 76.5; H, 7.4. Found: C, 76.5; H, 7.3.

This last ketone, cyclized by heating for 12 hr. with pyridine chloride, furnished **2-acetyl-7-propyldibenzofuran** in 40% yield, as a pale yellow viscous oil, b.p. 237–239° (12 mm.), $n^{25}D$ 1.6224.

Anal. Calcd. for $C_{17}H_{16}O_2$: C, 80.9; H, 6.4. Found: C, 81.0; H, 6.1.

2-(2,2′-Dimethoxy-5-biphenylyl)cinchoninic Acid.—A solution of 25.6 g. of ketone I and 22 g. of isatin in 120 ml. of ethanol was refluxed for 12 hr. with 16.8 g. of potassium hydroxide (dissolved in a minimum of water), and the ethanol then distilled on a water bath; the residue was dissolved in water, and the aqueous solution washed with ether and acidified with acetic acid. The precipitate (24 g.) was recrystallized from acetic acid, giving yellowish needles, m.p. 200°.

Anal. Calcd. for $C_{24}H_{19}NO_4$: C, 74.8; H, 5.0; N, 3.6. Found: C, 74.6; H, 4.8; N, 3.5.

Heating this compound above its melting point and vacuum distillation of the residue gave **2-(2,2′-dimethoxy-5-biphenylyl)-quinoline** (VII) in 90% yield, crystallizing from benzene as shiny colorless prisms, m.p. 112°.

Anal. Calcd. for $C_{23}H_{19}NO_2$: C, 80.9; H, 5.6; N, 4.1. Found: C, 81.0; H, 5.5; N, 4.0.

Cyclization of this compound with pyridine hydrochloride furnished 2-(2-dibenzofuryl)quinoline (IX) as yellowish prisms from ethanol, m.p. 139° (lit.[3] m.p. 139°), yield 45%.

2-(2,2′-Dimethoxy-5-biphenylyl)-3-methylcinchoninic Acid.—Prepared from 22 g. of isatin, 27 g. of ketone II, and 16.8 g. of potassium hydroxide, this acid (24 g.) crystallized from acetic acid as yellowish needles, m.p. 241°.

Anal. Calcd. for $C_{25}H_{21}NO_4$: C, 75.2; H, 5.3; N, 3.5. Found: C, 75.0; H, 5.5; N, 3.5.

Thermal decarboxylation gave **2-(2,2′-dimethoxy-5-biphenylyl)-3-methylquinoline** (VIII), crystallizing from benzene as colorless needles, m.p. 136°, yield 80%.

Anal. Calcd. for $C_{24}H_{21}NO_2$: C, 81.1; H, 6.0. Found: C, 81.0; H, 6.3.

Cyclization with pyridine hydrochloride gave **2-(2-dibenzofuryl)-3-methylquinoline** (**X**), crystallizing from ethanol as shiny colorless needles, m.p. 110° (lit.[3] m.p. 110°), yield 45%.

---

(7) J. F. W. McOmie and S. D. Thatte, *J. Chem. Soc.*, 5298 (1962).

(8) Huang-Minlon, *J. Am. Chem. Soc.*, **68**, 2487 (1946).

(9) With Miss J. Gouot.