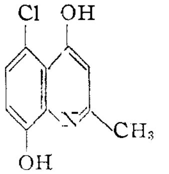
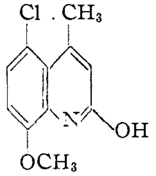
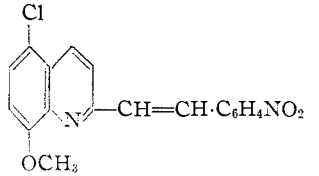
in the normal way to give the corresponding 2-nitrostyryl-5-chloro-8-methoxyquinolines (III)



I



II



III

Experimental

(In collaboration with S. Bursteinas)

Ethyl β-(2-Hydroxy-5-chloroanilino)-crotonate.—A mixture of 10 g. of 4-chloro-2-aminophenol[5] and 9 g. of ethyl acetoacetate was heated at 80° for four hours. Traces of iodine were found to catalyze the reaction. The solid product was filtered, washed with methanol and recrystallized from the same solvent. It formed slightly yellowish needles, m. p. 133–134; yield, 35%.

Anal. Calcd. for $C_{12}H_{14}O_3NCl$: N, 5.5. Found: N, 5.8.

4,8-Dihydroxy-5-chloroquinaldine (I).[6]—The preceding ester was heated in paraffin oil at 200° for fifteen minutes and the solid reaction product filtered, washed with ether and recrystallized from nitrobenzene, giving brownish crystals of m. p. 235° (dec.); yield, 40%.

Anal. Calcd. for $C_{10}H_8O_2NCl$: N, 6.7. Found: N, 6.8.

2-Methoxy-5-chloroacetoacetanilide.—A mixture of 3 g. of 4-chloro-2-aminoanisole and 10 g. of ethyl acetoacetate was heated at 160° for fifteen minutes. The excess of the ester was removed *in vacuo* and the residue triturated with, and then recrystallized from, ethyl alcohol, giving shiny platelets of m. p. 92°. Their alcoholic solution gave a dark violet color reaction with ferric chloride.

Anal. Calcd. for $C_{11}H_{12}O_3NCl$: N, 5.8. Found: N, 5.6.

2-Hydroxy-4-methyl-5-chloro-8-methoxyquinoline (II).—A mixture of 1 g. of the preceding substance and 1 cc. of concentrated sulfuric acid was heated for thirty minutes at 80° and for further fifteen minutes at 100°. Addition of ice water precipitated the desired substance (0.6 g.), which was recrystallized from alcohol, giving brown crystals, m. p. 213°.

Anal. Calcd. for $C_{11}H_{10}O_2NCl$: N, 6.3 Found: N, 6.1.

8-Hydroxy-5-chloroquinoline.[7]—A mixture of 17.3 g. of 2-amino-4-chlorophenol, 14.7 g. of arsenic oxide, 28.4 g. of glycerol and 41.4 g. of concentrated sulfuric acid was heated for six hours at 150–160° (oil-bath temperature). The reaction mixture was poured into ice-water, filtered and made alkaline with sodium carbonate solution. The quinoline derivative so obtained was recrystallized from ethyl alcohol and had m. p. 130°; yield, 35%.

8-Methoxy-5-chloroquinoline.—The reaction of 20 g. of 2-amino-4-chloroanisole, 17.7 g. of arsenic oxide, 36.4 g. of glycerol and 50.4 g. of concentrated sulfuric acid gave the desired product in 40% yield. It was purified by distillation (b. p. 210–215° (20 mm.)) and subsequent recrystallization from 50% alcohol; m. p. 54°.

Anal. Calcd. for $C_{10}H_8ONCl$: C, 62.2; H, 4.2. Found: C, 62.3; H, 4.25.

8-Hydroxy-5-chloroquinaldine.—The mixture of 10 g. of 2-amino-4-chlorophenol, 9 cc. of paraldehyde and 25 cc. of concentrated hydrochloric acid was heated at 100° for two hours and subsequently at 120° for four hours. After addition of 70 cc. of water, the solution was filtered and made alkaline. The product was distilled and then recrystallized from methyl alcohol, giving white needles, m. p. 68°; yield, 30%.

Anal. Calcd. for $C_{10}H_8ONCl$: N, 7.3. Found: N, 7.3.

8-Methoxy-5-chloroquinaldine.—The crude product obtained in the same way from 10 g. of 2-amino-4-chloroanisole, 8.4 cc. of paraldehyde and 20 cc. of concentrated hydrochloric acid was boiled for fifteen minutes with 5 cc. of acetic anhydride; the solution was diluted with water, neutralized and the solid collected and first distilled *in vacuo* (b. p. 140° (25 mm.)) and finally recrystallized from light-petroleum; m. p. 93°; yield, 53%.

Anal. Calcd. for $C_{11}H_{10}ONCl$: N, 6.8. Found: N, 7.1.

Picrate, yellow crystals from toluene, m. p. 228°. **Methoiodide**, yellow needles from methanol, m. p. 222°.

Anal. Calcd. for $C_{12}H_{13}ONClI$: I, 36.4. Found: I, 36.2.

2-(*p*-Nitrostyryl)-8-methoxy-5-chloroquinoline (III).—The mixture of 1 g. of the preceding substance, 0.75 g. of 4-nitrobenzaldehyde and 2 g. of acetic anhydride was boiled for five hours. Upon cooling, the condensation product separated spontaneously. It was recrystallized from glacial acetic acid and had m. p. 164–165°; yield, 90%.

Anal. Calcd. for $C_{18}H_{13}O_3N_2Cl$: N, 8.2. Found: N, 8.5.

2-(*o*-Nitrostyryl)-8-methoxy-5-chloroquinoline, obtained analogously in 80% yield, had m. p. 163°, after recrystallization from alcohol or glacial acetic acid.

Anal. Calcd. for $C_{18}H_{13}O_3N_2Cl$: N, 8.2. Found: N, 8.2.

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[5] Fierz-David, "Farbenchemie," 4th edition, 1938, p. 66.

[6] This substance might be of interest in connection with xanthurenic acid, which is a dihydroxy-quinolinecarboxylic acid; Musajo, *Gazz. chim. ital.*, **67**, 165 (1937); Musajo and Minchilli, *ibid.*, **70**, 301 (1940).

[7] "Beilstein," Vol. 21, p. 95.

A Tetraethylbiphenyl from the Ethylation of Ethylbenzene

By J. V. Karabinos and J. F. R. Kuck, Jr.[1]

The action of aluminum chloride on benzene at room temperature has been reported[2] to give a variety of products, including biphenyl. However the isolation and identification of alkylbiphenyls from the Friedel–Crafts reaction has not been thoroughly investigated.

During the synthesis of a ten-gallon quantity of *s*-triethylbenzene[3,4] by the ethylation of ethylben-

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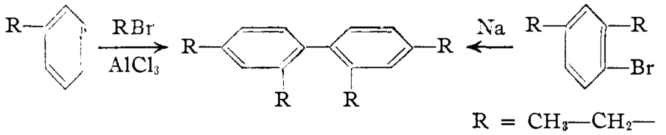
[1] Present address: Department of Chemistry, University of Virginia, Charlottesville, Virginia.

[2] E. Wertyporoch and H. Sagel, *Ber.*, **66**, 1306 (1933).

[3] L. C. Gibbons, *et al.*, This Journal, **68**, 1130 (1946).

[4] The biphenyl was isolated as a by-product from the synthesis of *s*-triethylbenzene during the program on the "Synthesis and Purification of Aromatic Hydrocarbons" at the NACA Cleveland Laboratory and the identification was carried out at the University of San Francisco.

zene with ethyl bromide and aluminum chloride,[5] we had occasion to investigate the residue from the triethylbenzene preparation. There was isolated a small amount of a crystalline, high melting solid. Ultraviolet absorption spectra indicated a biphenyl derivative and this was substantiated by the analytical data which indicated a tetraethylbiphenyl. Assuming that the tetraethylbiphenyl is symmetrical (indicated by the high m. p.) we would have six possible isomers none of which were known. We then synthesized 2,2′,4,4′-tetraethylbiphenyl by the action of sodium on 1,3-diethyl-4-bromobenzene[6] and obtained a compound identical with that isolated from the Friedel–Crafts reaction. The reactions are summarized as



Experimental

Isolation of 2,2′,4,4′-Tetraethylbiphenyl from the Friedel–Crafts Reaction.[4]—A glass-lined 25-gallon reactor equipped with a stirrer, a tank for the addition of ethyl bromide and a trap to absorb the hydrogen bromide was used. Ethylbenzene (21.2 kg., 200 moles) was placed in the reactor along with 53.4 kg. of aluminum chloride and cold water was circulated through the jacket. Ethyl bromide (a total of 43.6 kg., 400 moles) was added over a period of eight hours, the temperature maintained below 20°. After standing overnight at room temperature the complex was hydrolyzed by passing it into a 50-gallon reactor filled with cracked ice. The hydrocarbon layer was then separated, washed with aqueous sodium bicarbonate and dried by passing it through a column of anhydrous alumina. The material was distilled on a 100-theoretical plate column and the physical constants were recorded.[3] Approximately 2 gallons of residue was obtained from the distillation column and this was further concentrated to a volume of one liter. The residue was diluted with an equal volume of absolute ethanol and on cooling a crystalline product was deposited. After collection by filtration and recrystallization from a benzene–ethanol mixture, 10.5 g. of material, m. p.[7] 291–293°. The melting point was unchanged on recrystallization from benzene.

Anal. Calcd. for $C_{20}H_{26}$: C, 90.16; H, 9.84; mol. wt., 266.4. Found: C, 90.34; H, 9.88; mol. wt. (Rast), 267, 251.

Examination of the absorption spectrum of the compound (*E vs.* wave length in mμ) showed a maximum at 255 mμ and a minimum at 235 mμ.

Fittig Synthesis of 2,2′,4,4′-tetraethylbiphenyl.—To 5 g. of 1,3-diethyl-4-bromobenzene[6] (n^{20}D, 1.540) in 25 ml. of dry ether was added 3 g. of thinly sliced sodium metal and the mixture allowed to stand several days at room temperature. After centrifugation the solution was concentrated *in vacuo* to a viscous oil which gave a crystalline product (2.2 g., 61%) after standing in ethanol. The crystals were then recrystallized from a benzene–ethanol mixture and fine needles obtained, m. p. 288–290°. Further recrystallization raised the m. p. to 290–291°. A mixed m. p. with the tetraethylbiphenyl isolated from the Friedel–Crafts reaction gave no depression. The crystalline form of both products appeared identical. The ultraviolet absorption curves of both products were also identical.

The biphenyl was also synthesized in low yield by refluxing 1,3-diethyl-4-bromobenzene with precipitated copper.

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(5) J. F. Norris and D. R. Rubinstein, This Journal, **61**, 1163 (1939), alkylated benzene with three moles of ethyl bromide and aluminum chloride at low temperatures.

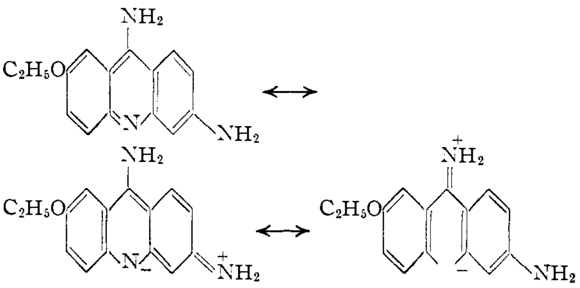
(6) J. E. Copenhaver and E. E. Reid, This Journal, **49**, 3157 (1927).

(7) All melting points were taken on a modified Berl-Kullmann block as described by F. W. Bergstrom, *Ind. Eng. Chem., Anal. Ed.*, **9**, 340 (1937), and are uncorrected.

Quaternary 3-Ethoxy-7,9-diaminoacridinium Salts

By A. Weizmann

In the course of experiments on the technical synthesis of Rivanol (3-ethoxy-7,9-diaminoacridinium lactate) an attempt was made to improve the chemotherapeutic index of the drug by converting it into quaternary ammonium salts. The contribution of resonance forms such as those shown in the formulas to the actual state of the Rivanol molecule may well be a factor determining the activity of the drug,[1,2] and it was thought that a charged molecule would be still more easily absorbed by the cell protein of the pathogenic bacteria than the zwitter-ionic forms depicted in the formulas.[3] Indeed the quaternary salts Proflavine and Trypaflavine have been found more effective against staphylococci than Rivanol.[4,5]



The experiments have confirmed these expectations. The methiodide, the methochloride and the methosulfate of the Rivanol base have practically the same toxicity and bacteriostatic power as Rivanol, but they have considerably greater bactericidal activity. All three salts are effective against *Staphylococcus aureus* at concentrations as low as 1:10,000, whereas Rivanol is bactericidal only in solutions stronger than 1:5,000. The methosulfate is the most active of the three salts, being still effective at a concentration of 1:50,000. Similar results were obtained with *Bacterium coli.*[6]

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(1) Sharp, Sutherland and Wilson, *J. Chem. Soc.*, 344 (1943).

(2) Albert and Goldacre, *ibid.*, 454 (1943); Albert and Ritchie, *ibid.*, 458 (1943).

(3) See Bradbury and Jordan, *Biochem. J.*, **36**, 287 (1942).

(4) Browning, Cohen and Gulbranson, *J. Path. Bact.*, **27**, 212 (1924); **31**, 134 (1928).

(5) Morgenroth and Wreschner, *Deut. med. Wochschr.*, **49**, 745 (1923).

(6) Dr. E. Hellinger of the Sieff Institute kindly carried out these tests.