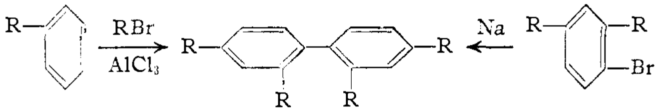
zene with ethyl bromide and aluminum chloride,[5] we had occasion to investigate the residue from the triethylbenzene preparation. There was isolated a small amount of a crystalline, high melting solid. Ultraviolet absorption spectra indicated a biphenyl derivative and this was substantiated by the analytical 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



R = CH_3—CH_2—

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.

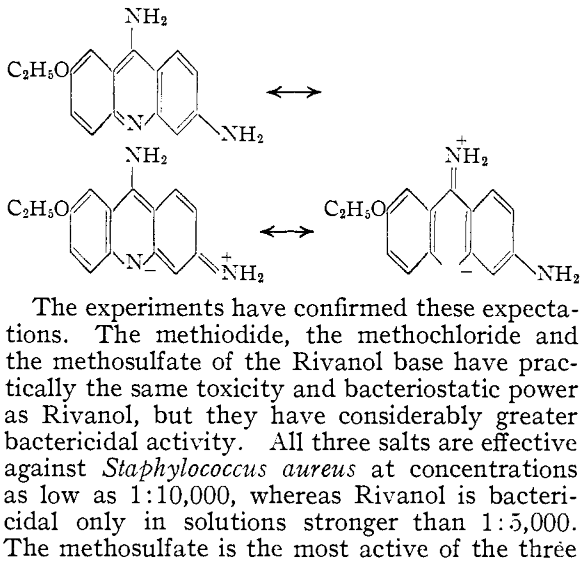
[6] J. E. Copenhaver and E. E. Reid, THIS JOURNAL, **49**, 3157 (1927).

[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.

Experimental

3-Ethoxy-7,9-diaminoacridinium Methiodide.—To a solution of 5.5 g. of the diaminoacridine base (m. p. 124°) in 50 cc. of methanol 5 g. of methyl iodide was added at room temperature. After standing for twelve hours the salt separated as a yellow powder; yield 50%. The substance was soluble in water or methyl alcohol and insoluble in acetone. After repeated crystallization from water–acetone (1:5) it melted at 332–334°, dec. The solubility in water at 35–38° was 1:2,000.

Anal. Calcd. for $C_{16}H_{18}O_2N_3I$: N, 10.6. Found: N, 11.1.

Methochloride.—A filtered solution of 2 g. of the diaminoacridine base in 100 cc. of methanol was saturated with gaseous methyl chloride in an autoclave and the autoclave then heated slowly to 95–100° in the course of two hours; the pressure rose to 8–10 atmosphere. Upon standing, a greenish-yellow powder precipitated and this when crystallized from a mixture of glacial acetic acid and ethyl acetate melted at 357–358°. Solubility in water at 25° was 1:1,000.

Anal. Calcd. for $C_{26}H_{18}ON_3Cl$: N, 13.8. Found: N, 13.5.

Methosulfate.—To a filtered solution of 2.5 g. of the diaminoacridine in a 1:4 mixture of methanol and acetone a solution of 3 g. of dimethyl sulfate in 3 cc. of acetone was added. In the course of two days at room temperature 1.2 g. of bright yellow salt precipitated. After crystallization from methanol–acetone it melted at 235°. Solubility in water at 35–38° was 1:1,000.

Anal. Calcd. for $C_{17}H_{21}O_5N_3S$: N, 11.5. Found: N, 11.0.

TABLE I

BIOLOGICAL TESTS

Bacteriostatic (A) and bactericidal (B) activity (duplicate series) against *Staphylococcus aureus:* 0 = no growth, + = turbid, showing growth·

Substance	Dilution in tryptic broth	A Bacterial growth after 24 hr. at 37°		B Viable bacteria counts[a]	
		Series I	Series II	Series I	Series II
Methiodide	5,000	0	0	0	0
	10,000	0	0	0	0
	50,000	+	+		
Methochloride	5,000	0	0	0	0
	10,000	0	0	0	0
	50,000	+	+		
Methosulfate	5,000	0	0	0	0
	10,000	0	0	0	0
	50,000	+	0	Many	Many
Rivanol	5,000	0	0	Many	0
	10,000	0	0	Many	Many
	50,000	+	+		

[a] In 1/1000 cc. of test dilutions showing inhibition (bacteriostasis) after twenty-four hours at 37° as recorded under a.

Slightly different results were obtained with *Bacterium coli*. All substances tested were bacteriostatic at a dilution of 1:50,000, but only the methochloride was bactericidal at a dilution of 1:10,000.

Toxicity determinations kindly carried out by Professor S. Adler of the Hebrew University, Jerusalem, showed that the quaternary salts have the same order of toxicity as Rivanol:

Under the skin of mice:

Maximum tolerated dose = 0.095 g./kg.
Maximum lethal dose = 0.1 g./kg.

In the abdominal cavity of mice:

Maximum tolerated dose = 0.065 g./kg.
Maximum lethal dose = 0.07 g./kg.

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REHOVOTH, PALESTINE
RECEIVED OCTOBER 1, 1945

Molecular Complexes with 2,4,7-Trinitrofluorenone. II[1]

BY MILTON ORCHIN,[2] LESLIE REGGEL[2] AND E. OSCAR WOOLFOLK[2]

In a previous communication[3] it was shown that 2,4,7-trinitrofluorenone (T.N.F.) formed molecular complexes with a variety of polynuclear hydrocarbons. All of these complexes were composed of one mole of the hydrocarbon and one mole of T.N.F. We have now found that T.N.F., in common with picric acid and *s*-trinitrobenzene, forms complexes with some hydrocarbons in other than 1:1 molar proportions. The behavior of 1,4-diphenylbutadiene is of particular interest. As can be seen from Fig. 1, this hydrocarbon forms two compounds with T.N.F., one corresponding to a molar ratio of 1:2 and the other to 3:1 of the hydrocarbon to T.N.F. The 1:2 compound is quite stable and is easily obtained pure from solution; the 3:1 compound cannot be obtained pure, since recrystallization leads to the isolation of the more stable, more insoluble 1:2 compound.

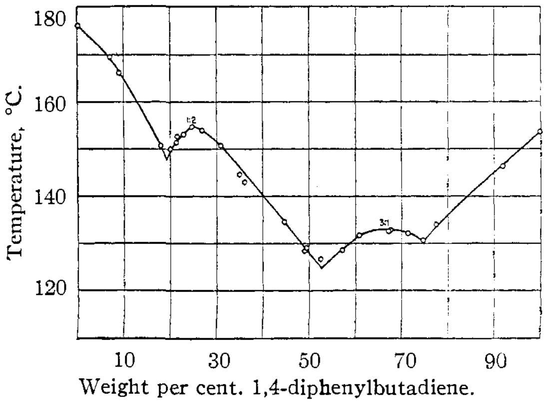

Fig. 1.—Melting point–composition curve: 2,4,7-trinitrofluorenone–1,4-diphenylbutadiene.

In an extension of the use of T.N.F. to some simple low-molecular weight derivatives of naphthalene, it has been found that, in several instances, extensive dissociation of the complex takes place when alcohol or benzene is used as a solvent for the complex. However, if acetic acid is used in these cases, it is frequently possible to isolate a complex. It appears that, in general, *s*-trinitrobenzene or picric acid is to be preferred to T.N.F. for the characterization of very soluble,

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[2] Organic Chemist, Central Experiment Station, U. S. Bureau of Mines, Pittsburgh, Pa.

[3] Orchin and Woolfolk, THIS JOURNAL, 68, 1727 (1946).