Experimental

Dimethyl 5-Cyano-3,4-pyrazoledicarboxylate (II).—Dimethyl acetylenedicarboxylate (40 g., 0.282 mole) was added to a solution of diazoacetonitrile[4] (approximately 20–25 g., 0.3–0.37 mole) in 3.5 l. of ether and the mixture allowed to stand overnight. Evaporation of the solvent left a crystalline residue which was pressed dry on a porous clay plate (45 g., 76.3%). In several runs the yield varied slightly (72–90%) because of the somewhat erratic results in the preparation of the diazoacetonitrile solution. Diazoacetonitrile was always allowed to react in dry ethereal solution because it was inconvenient to isolate large quantities of the rather explosive compound. Recrystallization from an ether–petroleum ether mixture yielded white crystals, m.p. 102–103.5°.

Anal. Calcd. for $C_8H_7N_3O_4$: C, 45.94; H, 3.38; N, 20.09. Found: C, 45.87; H, 3.30; N, 20.34.

Ammonium Salt of 3,4-Dicarbamoyl-5-cyanopyrazole (III).—A mixture of dimethyl 5-cyanopyrazole-3,4-dicarboxylate (2 g., 0.096 mole) and concentrated aqueous ammonia was heated in a sealed tube in a steam bath for 2 hr. The light yellow mass (1.3 g., 70%) which precipitated on cooling was filtered and recrystallized from hot water, m.p. 275–280° (dec. with gas evolution).

Anal. Calcd. for $C_6H_8N_6O_2$: N, 42.84. Found: N, 43.02.

The same compound was obtained after having allowed the diester to stand with aqueous ammonia for 4 days.

3,4,5-Tricyanopyrazole (I).—The ammonium salt of 3,4-dicarbamoyl-5-cyanopyrazole (5 g., 0.026 mole) was suspended in 25 ml. of phosphorus oxychloride and the mixture refluxed for 1 hr. Then it was decomposed with ice not allowing the temperature to rise above 10–15° and extracted with ether in a Soxhlet apparatus for 0.5 hr. Evaporation of the ether gave a crude product (3.14 g., 86%), m.p. 170–183°. Recrystallization from water (charcoal) yielded white needles, m.p. 193–194°. The compound is very soluble in hot water, but only slightly in cold water.

Anal. Calcd. for C_6HN_5: C, 51.53; H, 0.71; N, 48.92. Found: C, 51.50; H, 0.85; N, 48.43.

The infrared spectrum exhibited characteristic absorptions at 3.10 μ, 4.42 μ, 6.42 μ, 6.80 μ, 7.78 μ, 8.68 μ, 9.74 μ, 13.22 μ.

The silver salt of I was prepared by adding an equimolar amount of silver nitrate solution to an aqueous solution of tricyanopyrazole which had been previously neutralized with sodium bicarbonate.

Anal. Calcd. for C_6N_5Ag: Ag, 42.1. Found: Ag, 42.8.

N-Methyl-3,4,5-tricyanopyrazole (VI).—An ethereal solution of diazomethane was added to a solution of tricyanopyrazole (0.7 g., 0.0045 mole) in ether (20 ml.) until the yellow color persisted. There was a crystalline precipitate. Evaporation of the solvent and recrystallization of the crystalline residue (0.7 g., 91%) from ethanol furnished colorless crystals, m.p. 102–103°.

Anal. Calcd. for $C_7H_3N_5$: C, 53.51; H, 1.93; N, 44.58. Found: C, 53.70; H, 1.62; N, 44.07. The infrared spectrum did not exhibit any NH absorption.

Dicyanoacetylene was prepared by dehydration of dicarbamoylacetylene with phosphorus pentoxide[5] in 25–35% yield.

Ethyl 3,4-Dicyano-5-pyrazolecarboxylate (IV).—A solution of dicyanoacetylene (8 g., 0.105 mole) in 35 ml. of ether was added dropwise to a solution of ethyl diazoacetate (11.5 g., 0.1 mole) in 50 ml. of ether over a period of 10 min. The reaction flask was surrounded by an ice bath. After the addition had been completed, the mixture was kept at 0° for 2 hr. and then allowed to stand at room temperature overnight. Evaporation of the ether left an oil which crystallized after having been allowed to stand for 1 day. The crystalline mass was freed of oil by pressing it on a clay plate. The light yellow crystals (8.14 g., 40%) were recrystallized from water and gave colorless needles, m.p. 101°.

Anal. Calcd. for $C_6H_6N_4O_2 \cdot H_2O$: C, 46.14; H, 3.87; N, 26.91. Found: C, 45.86; H, 4.28; N, 26.76.

If the crystals were kept in a desiccator they liquified. Exposure to air, however, or recrystallization from water again gave the original compound.

The infrared spectrum exhibited characteristic bands at 2.89 μ, 4.52 μ, 5.82 μ.

The compound was soluble in benzene, ether, alcohol, and acetonitrile.

3,4-Dicyano-5-carbamoylpyrazole (V).—Ethyl 3,4-dicyano-5-pyrazolecarboxylate (2.2 g., 0.0107 mole) was dissolved in a mixture of 10 ml. of concentrated aqueous ammonia and 1 ml. of methanol and allowed to stand for 12 hr. Evaporation of the mixture to dryness gave a solid residue (1.67 g., 96%) which was dissolved in hot ethanol and reprecipitated with ether. The compound became yellow at 200° but did not melt.

Anal. Calcd. for $C_6H_3N_5O$: N, 43.47. Found: N, 43.58. The infrared spectrum exhibited characteristic bands at 2.96 μ, 3.22 μ, 4.55 μ, 6.05 μ.

Tricyanopyrazole.—3,4-Dicyano-5-carbamoylpyrazole (1 g., 0.0062 mole) was suspended in 8 ml. of phosphorus oxychloride and the mixture refluxed for 15 min. Then it was decomposed with ice and extracted with ether in a Soxhlet apparatus. Evaporation of the solvent gave tricyanopyrazole (0.73 g., 83%), m.p. 193° (from water).

Mixed melting point with the sample obtained earlier was 193°. The infrared spectra of both samples were identical.

Acknowledgment.—The author wishes to thank Dr. G. R. Coraor for many helpful suggestions.

(4) M. T. S. Dewar and R. Pettit, *J. Chem. Soc.*, 2026 (1956).

(5) A. T. Blomquist and E. C. Winslow, *J. Org. Chem.*, **10**, 149 (1945).

The Chemistry of Neuraminic Acids. I. The Ehrlich Reaction[1]

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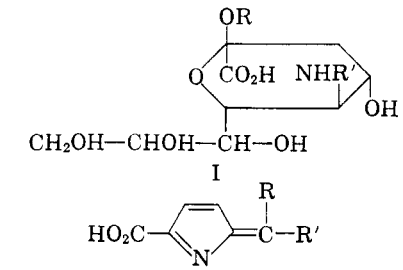
Received April 9, 1962

In the process of studying the chemistry of neuraminic acid (I, R = R′ = H), it was necessary to reinvestigate the Ehrlich reaction between I (R = R′ = H) and *p*-dimethylaminobenzaldehyde (PDAB). Previously, I (R′ = H, R = Ac) has been demonstrated to undergo degradation in acid or base leading to pyrrole-2-carboxylic acid, which upon reacting with PDAB produces the violet color usually associated with the Ehrlich reaction.[2] The present note reports the formation of III from the reaction between pyrrole-2-carboxylic acid and *p*-dimethylaminobenzaldehyde and evidence for the proposed structure. The reaction between pyrrole-2-carboxylic acid (2 moles) and PDAB (1 mole) in ethanolic perchloric acid

(1) These studies were supported by funds from the National Heart Institute, Public Health Service (H-2942).

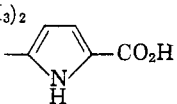
(2) A. Gottschalk, "The Chemistry and Biology of Sialic Acids and Related Substances," Cambridge University Press, Cambridge, England, 1960.

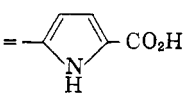
(10%) gave in reasonable yield 5,5′-dicarboxy-*ms*-(*p*-dimethylaminophenyl)dipyrrylmethene-(2,-2′) (III). When the molar ratios are 1:1, II can be isolated which is readily converted into III when resubjected to the Ehrlich reaction with 1 mole of pyrrole-2-carboxylic acid. The strong absorption of III in methanolic 0.1 *M* perchloric acid: λ_{max} 242, ϵ 13,000; 350, ϵ 41,000; 540 mμ, ϵ 72,000 requires conjugation of both pyrrole rings with the formyl group of *p* dimethylaminobenzaldehyde. That the condensation is with the formyl group of PDAB is demonstrated by the degradation of III with 48% hydrobromic acid leading to 5,5′-dicarboxydipyrrylmethene-(2,2′) (IV). Independent synthesis of IV was accomplished under the conditions of the general dipyrrylmethene synthesis[3] from pyrrole-2-carboxylic acid and formaldehyde; indistinguishable (ultraviolet and n.m.r. spectra) from the degradation product, IV.



I

II. R = H, R′ = *p*-$C_6H_4N(CH_3)_2$

III. R = *p*-$C_6H_4N(CH_3)_2$, R′ = 

IV. R = H, R′ = 

The n.m.r. spectrum of IV (at 60 Mc. in dimethyl sulfoxide) contains one broad peak at τ −1.75 (pyrrolic NH proton). The protons, adjacent to carboxyls, at C-4 and C-4′ show the expected resonance τ 3.16 as in pyrrole-2-carboxylic acid, and the protons at C-3 and C-3′ are doublets at τ 3.75 which in base change to singlets. The 2,2′-linkages in III and IV are demonstrated by the isolation of pyrrole-2,5-dicarboxylic acid from the alkaline–peroxide oxidation of IV.

The product isolated from the Ehrlich reaction between N-acetylneuraminic acid (I, R = H, R′ = Ac) and *p*-dimethylaminobenzaldehyde was identical to III.

(3) A. H. Corwin and K. J. Brunings, *J. Am. Chem. Soc.*, **64**, 2106 (1942).

(4) Analyses by Alfred Bernhardt, Max Planck Institut, Microanalytisches Laboratorium, Mulheim (Rühr), Germany. Melting points are uncorrected. Ultraviolet absorption spectra were obtained on the Baird Associates double beam spectrophotometer.

Experimental[4]

5,5′-Dicarboxy-*ms*-(*p*-dimethylaminophenyl)dipyrrylmethene-(2,2′) Perchlorate (III).—Pyrrole-2-carboxylic acid (500 mg., 4.5 mmoles) was dissolved in a minimum amount of 95% ethanol and added to a solution of 680 mg. (4.5 mmoles) of *p*-dimethylaminobenzaldehyde and 0.4 ml. of perchloric acid in 20 ml. of 95% ethanol. The reaction mixture was allowed to stand at room temperature for 1 hr., evaporated *in vacuo* to one-third volume and stored at 0° for several days. Deep red needles of **5-carboxypyrryl-2-*p*-dimethylaminophenylmethene perchlorate (II)** separated which recrystallized from chloroform–ethanol, m.p. 247–250° dec., 600 mg. (38%).

Anal. Calcd. for $C_{14}H_{15}N_2O_2ClO_4$: C, 49.06; H, 4.41; N, 8.17. Found: C, 49.14; H, 4.59; N, 7.92.

Treatment of II with an equivalent amount of pyrrole-2-carboxylic acid in 20 ml. of ethanol and 0.10 ml. of perchloric acid afforded **5,5′-dicarboxy-*ms*-(*p*-dimethylaminophenyl)dipyrrylmethene-(2,2′) perchlorate (III)**, m.p. 204–205°, violet needles (recrystallized from 95% ethanol), 254 mg. (33%).

Anal. Calcd. for $C_{19}H_{18}N_3O_4ClO_4$: C, 50.51; H, 4.02; N, 9.30. Found: C, 50.62; H, 4.09; N, 9.12.

5,5′-Dicarboxydipyrrylmethene-(2,2′) Hydrobromide (IV).—Heating III (200 mg., 0.44 mmole) in 50 ml. of 95% ethanol containing 2 ml. of 48% hydrobromic acid for 2 hr. at 80° afforded upon cooling and concentrating *in vacuo* to one-half volume, **5,5′-dicarboxydipyrrylmethene-(2,2′) hydrobromide**, m.p. with dec. > 320°, recrystallized from ethanol as deep red microcrystals, 50 mg. (27%).

Anal. Calcd. for $C_{11}H_9N_2O_4Br$: C, 32.13; H, 2.21; N, 30.66. Found: C, 32.10; H, 2.32; N, 30.52.

Synthesis of IV.—An independent synthesis of IV (42%) was accomplished under the conditions of the general dipyrrylmethene synthesis[3] using pyrrole-2-carboxylic acid and formaldehyde. Comparison (ultraviolet and n.m.r. spectra) of the synthetic IV with the sample isolated from III proved identical.

Oxidation of IV.—To a solution of 313 mg. (0.76 mmole) of IV in 1.1 ml. of 1 *N* sodium hydroxide, 1.43 g. (1.3 mmoles) of 3% hydrogen peroxide was added in one portion. A change from deep orange to yellow was accompanied by an exothermic reaction. Upon cooling to room temperature and neutralizing with 1 *N* hydrochloric acid (Congo red paper) a yellow solid separated which was collected and recrystallized from 95% ethanol as colorless microcrystals of pyrrole-2,5-dicarboxylic acid,[5] m.p. 260–262°, 34 mg. (29%).

Anal. Calcd. for $C_6H_5NO_4$: C, 46.46; H, 3.25; N, 9.03. Found: C, 46.23; H, 3.31; N, 8.93.

Ehrlich Reaction between N-Acetylneuraminic Acid (I, R = H, R′ = Ac) and *p*-Dimethylaminobenzaldehyde.—N-Acetylneuraminic acid (15 mg., 0.058 mmole) and *p*-dimethylaminobenzeldehyde (5 mg., 0.034 mmole) in 50 ml. of ethanol were treated with 0.1 ml. of perchloric acid in 5 ml. of ethanol. The mixture was warmed on a steam bath for 10 min., cooled to room temperature and evaporated *in vacuo* to a volume of 10 ml. Cooling at 0° for 2 days afforded 7 mg. (54%) of III, m.p. and mixture m.p. 204–205°.

Acknowledgment.—The authors wish to express their sincere thanks to Dr. G. S. Berenson for encouragement and discussion and to Dr. A. F. Fishkin for generous samples of N-acetylneuraminic acid.

(5) G. Ciamician and P. Silber, *Ber.*, **20**, 2529 (1887).