Experimental

Infrared spectra were obtained on a Perkin-Elmer Model 21 Spectrophotometer, using a sodium chloride prism. The samples were examined as potassium bromide discs.

The hydroxyquinone oxime III was prepared as described by Kozlov and Vorozhtzov,[2] any excess of nitrous acid being destroyed by urea before boiling. As to the decomp. point, the higher value favored by Bryson[5] seems to describe better the behavior of the compound on heating. The Russian workers gave adequate analytical values for III and also its lead salt. In the present work, the molecular weight was obtained by the Osmometer method to be sure the substance was not dimeric.

Mol. wt. Calcd. for $C_{10}H_7NO_3$: 189. Found: 190.

Hydrolysis of III.—A mixture of 150 mg. (0.79 mmole) of the juglone 4-oxime and 200 ml. of 2.5 *N* sulfuric acid was steam distilled for 6 hr. The yellow distillate was extracted twice with ether and the extracts dried and evaporated. A residue of 112 mg. of crystalline material was left. Yield: 81.1%. The spectrum of this product was identical to that of authentic juglone. It also formed the characteristic violet solutions in alkalies. Juglone for comparison was obtained by the method of Fieser and Dunn,[14] from 1,5-dihydroxynaphthalene.

Nitration of III.—A suspension of 0.25 g. (1.32 mmoles) of the hydroxy quinone oxime in 15 ml. of acetic acid was heated to boiling and cooled to 40–50°. A good part of the material crystallized at this temperature, and 5 ml. of 70% nitric acid was added slowly with stirring. The temperature was kept below 50°. After 15 min. at 40–50°, the mixture was cooled, diluted with 6 volumes of water, and left 1 hr. The tetranitro compound was filtered, washed with water, and dried. Yield 285 mg. or 63%. This product becomes red with alkali without solution as described by Thomson *et al.*[9] Comparison of infrared spectra with the authentic product showed identity.

To prepare a comparison sample of the tetranitro compound V, Thomson's work was repeated.[9] A poor yield of yellow-orange crystalline powder was produced which decomp. above 250°.

Authentic 2,4,8-trinitro-1-naphthol was prepared by the procedure of Graebe and Oeser.[8]

Preparation of VI.—This was carried out substantially as for III,[2] except that 40% sulfuric acid was used for the diazotization because of the weaker basicity and more sparing solubility of 3,8-dinitro-1-naphthylamine. Urea was added before boiling. The product was obtained as a yellowish crystalline powder in about 37% yield. The mixture of 3,5- and 3,8-dinitro-1-naphthylamines was prepared from 3-nitro-1-naphthylamine as described by Ward and coworkers,[12] and separated as they direct.[15]

The nitroquinone oxime VI was purified by recrystallization from aqueous methanol. On heating, it darkens above 180°, with softening at 225°, and forms a black smear above 250°.

Anal. Calcd. for $C_{10}H_6N_2O_5$: N, 11.966. Found: N, 11.99.

Acknowledgment.—The authors express thanks to Mrs. Dobbie Roisen for infrared spectra, and to W. M. Padgett II and Dr. J. Hyman for suggestions during the work.

(14) L. F. Fieser and J. T. Dunn, *J. Am. Chem. Soc.*, **59**, 1018 (1937).

(15) The diazo decomposition reaction on 3,5-dinitro-1-naphthylamine provides a compound which is probably authentic 3,5-dinitro-1-naphthol.

The Mannich Condensation of 3-Amino-1,2-propanediol with 2,2-Dinitropropanol and the Nitration of the Product

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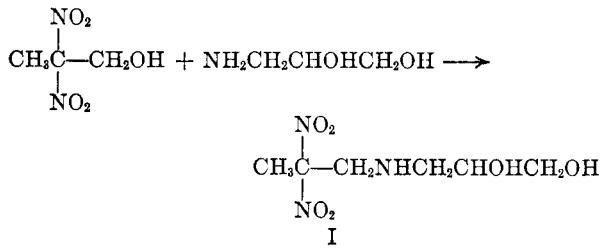
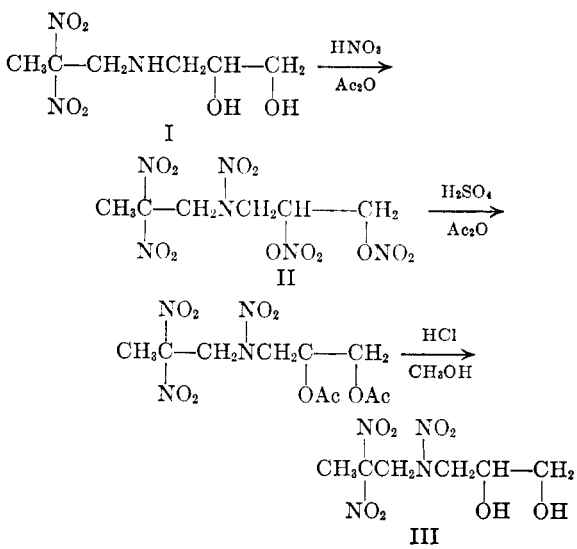
The Mannich condensation of 2,2-dinitro-1-alkanols and some reactions of the products have been reported.[1-4] In the present work, the nitration of the condensate of 3-amino-1,2-propanediol and 2,2-dinitropropanol has yielded a novel product.

Heating an aqueous suspension of 2,2-dinitropropanol with a solution of 3-amino-1,2-propanediol to 50° gave a dark water-insoluble oil, presumably 6,6-dinitro-4-aza-1,2-heptanediol (I). However, since this material could not be purified without decomposition, the crude product was used directly in the subsequent reactions.



I

The nitration of I, which was expected to yield 1,2-dinitroxy-4,6,6-trinitro-4-azaheptane (II), was carried out at 0° in acetic anhydride. An oil was isolated which was sensitive to impact. This oil



III

(1) H. Feuer, G. B. Bachman, and W. May, *J. Am. Chem. Soc.*, **76**, 5124 (1954).

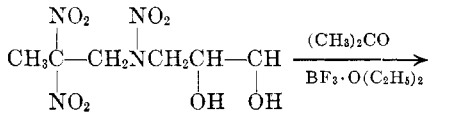
(2) K. Klager, *J. Org. Chem.*, **23**, 1519 (1958).

(3) M. B. Frankel and K. Klager, *J. Am. Chem. Soc.*, **79**, 2953 (1957).

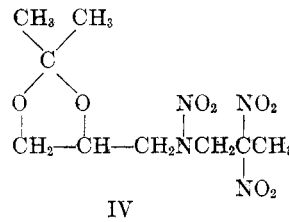
(4) H. Feuer and W. A. Swarts, U. S. 2,981,750 (April 25, 1961).

was acetylated with a 10:1 mixture of acetic anhydride and sulfuric acid in order to prepare 1,2-diacetoxy-4,6,6-trinitro-4-azaheptane, which it was hoped would be a solid derivative. The product, however, was again an oil which could not be crystallized. The acetylated material was then transesterified in refluxing methanolic hydrochloric acid to give 4,6,6-trinitro-4-aza-1,2-heptanediol (III), m.p. 60°.

The reaction of III with acetone in the presence of boron trifluoride etherate gave the cyclic ketal, 2,2 - dimethyl- 4 - (2,4,4 - trinitro - 2 - azapentyl)-dioxalene (IV).

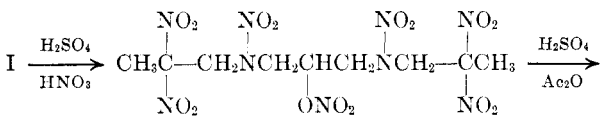


III

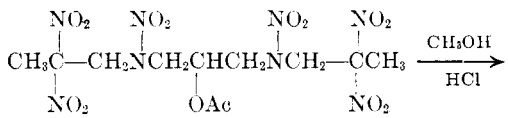


IV

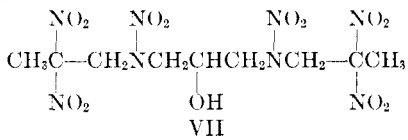
The nitration of I took a different course when a mixture of nitric and sulfuric acids was used as the nitrating agent. This reaction at 50° yielded 6 - nitroxy - 2,2,4,8,10,10 - hexanitro - 4,8 - diaza-undecane (V), m.p. 158–159°. This compound was acetylated at 0° using acetic anhydride and sulfuric acid to prepare 6-acetoxy-2,2,4,8,10,10-hexanitro-4,8-diazaundecane (VI), m.p. 145°. The acetate was then transesterified with refluxing methanolic hydrochloric acid to yield 6-hydroxy-2,2,4,8,10,10 - hexanitro - 4,8 - diazaundecane (VII), m.p. 168.5–169°.



V

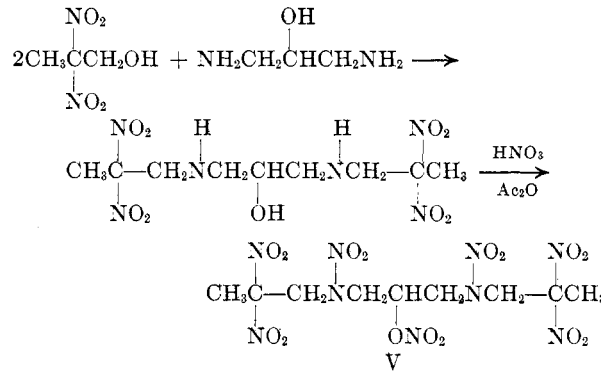


VI



VII

As a final structure proof of V, an independent synthesis was carried out by condensing 1,3-diamino-2-propanol with 2,2-dinitropropanol. The product, an oil, was nitrated under mild conditions, using nitric acid in acetic anhydride at 0 to 5°, to give V. This material was identical to that



V

prepared in the nitration of I with sulfuric acid and nitric acid.

The formation of compound V in the nitration of the condensation product of 3-amino-1,2-propanediol might take place by the alkylation of the amino group of I by a reactive derivative (sulfate or nitrate) of the terminal hydroxyl of a second molecule of I. Nitrolysis of the dihydroxypropyl group of the resulting tertiary amine would lead to compound V.

Experimental[5]

3-Amino-1,2-propanediol.—3-Amino-1,2-propanediol was prepared in 68% yield by the reaction of excess aqueous ammonia with glycidol, as reported by Knorr.[6] Similar yields were obtained by the reaction of ammonia with glycerol α-monochlorohydrin followed by the neutralization of the resulting hydrochloride. This method is preferred because of the commercial availability of the starting material.

Glycerol-α-monochlorohydrin (800 g., 7.23 moles) was added with stirring to 16 l. of 28% ammonia. After 24 hr., the solution was concentrated under vacuum to 5 l., and 478 g. (7.23 moles) of 85% potassium hydroxide pellets in 2 l. of methanol was added. The water and methanol were removed under vacuum, and 2 l. of methanol was added. The potassium chloride precipitate was removed by filtration, and was washed with 1 l. of methanol. The combined filtrate and washings were stripped under aspirator vacuum; the residue was distilled to yield 437 g. (4.80 moles, 66.4% yield) of 3-amino-1,2-propanediol, b.p. 80–106° at 0.1 to 0.15 mm.

Condensation of 3-Amino-1,2-propanediol and 2,2-Dinitropropanol (I).—A solution of 30 g. (0.33 mole) of 3-amino-1,2-propanediol in 30 ml. of water was added slowly to a stirred suspension of 52.4 g. (0.33 mole, 96% assay) of 2,2-dinitropropanol, and this mixture was heated to 50° for 15 min. A dark red oil separated. This oil was then dried under vacuum, and the product (27.05 g., 36.8% yield as 6,6-dinitro-4-aza-1,2-heptanediol) was used in subsequent reactions without further purification.

4,6,6-Trinitro-4-aza-1,2-heptanediol (III).—The crude condensation product of 3-amino-1,2-propanediol and 2,2-dinitropropanol (27.05 g.) was dissolved in 270 ml. of acetic anhydride, and 150 ml. of 100% nitric acid was added dropwise with stirring. The temperature of the solution was maintained at −20 to −25° during the addition, and then at 0° for an additional 3.5 hr. The solution was poured over 2 l. of crushed ice and the ice was allowed to melt. The water was decanted, and the residue was dissolved in 1.5 l. of methylene chloride and dried over sodium

(5) Elemental analysis by Dr. Adalbert Elek, Los Angeles, Calif.
(6) L. Knorr, *Ber.*, **32**, 752 (1899).

sulfate. The solvent was removed leaving 26.4 g. of an oil, impact sensitivity 6 cm. using a 2-kg. weight.[7]

This oil was dissolved in 360 ml. of acetic anhydride and 30 ml. of concd. sulfuric acid was added dropwise with stirring. The temperature was kept at −10 to −20° during the addition, and then at 0° for 2 hr. The reaction mixture was poured into 1.5 l. of ice water, and the gummy residue which separated was filtered off, dissolved in methylene chloride, dried with sodium sulfate, and the solvent was removed.

The residue (10.2 g.) was heated at reflux for 2 hr. in a mixture of 370 ml. of methanol and 17 ml. of concd. hydrochloric acid. The product was stripped under vacuum and recrystallized twice from methylene chloride to yield 3.55 g. of 4,6,6-trinitro-4-aza-1,2-heptanediol (11% over-all yield if it is assumed that the condensation product consisted entirely of 6,6-dinitro-4-aza-1,2-heptanediol), m.p. 60°, with a crystalline phase change at 50°.

Anal. Calcd. for $C_6H_{12}N_4O_8$: C, 26.87; H, 4.48; N, 20.89. Found: C, 26.81; H, 4.79; N, 20.79.

2,2-Dimethyl-4-(2,4,4-trinitro-2-azapentyl)dioxalane (IV).—To a solution of 3.00 g. (0.0112 mole) of 4,6,6-trinitro-4-aza-1,2-heptanediol in 200 ml. of dry acetone was added slowly, with stirring, 1.67 g. (0.0177 mole) of boron trifluoride etherate. The temperature of the solution was kept below 20° by means of an ice bath. After 5 min. the solution was poured into 100 ml. of ice water and a solid crystallized. This solid was filtered, dried, and recrystallized from isopropyl ether to give 2.55 g. (74% yield) of 2,2-dimethyl-4-(2,4,4-trinitro-2-azapentyl)dioxalane, m.p. 84.5–86°.

Anal. Calcd. for $C_9H_{16}N_4O_8$: C, 35.07; H, 520; N, 18.39. Found: C, 34.93; H, 5.00; N, 18.21.

6-Nitroxy-2,2,4,8,10,10-hexanitro-4,8-diazaundecane (V) by Nitration of I.—The condensation product of 3-amino-1,2-propanediol and 2,2-dinitropropanol (25 g., 0.11 mole as 6,6-dinitro-4-aza-1,2-pentanediol) was added dropwise to a mixture of 125 ml. of 100% nitric acid and 115 ml. of concd. sulfuric acid at 55°, and the mixture was heated at this temperature for an additional 3 hr. The reaction mixture was then added to 2 l. of ice and water. The product was filtered and slurried with 1.5 l. of boiling ethylene dichloride. A small amount of insoluble residue was filtered from the hot solution, and the filtrate was concentrated and cooled. The product which crystallized was filtered and washed with a small amount of ether to yield 7.6 g. (28% yield assuming this condensation product was pure 6,6-dinitro-4-aza-1,2-heptanediol) of 6-nitroxy-2,2,4,8,10,10-hexanitro-4,8-diazaundecane, m.p. 158–159°. An analytical sample was recrystallized from ethylene dichloride.

Anal. Calcd. for $C_9H_{15}N_9O_{15}$: C, 22.08; H, 3.07; N, 25.77. Found: C, 22.42; H, 3.03; N, 25.29.

6-Nitroxy-2,2,4,8,10,10-hexanitro-4,8-diazaundecane (V) from 1,3-Diamino-1-propanol.—1,3-Diamino-2-propanol (7 g., 0.0556 mole) was added slowly to a swirled suspension of 17.3 g. (0.112 mole) of 2,2-dinitropropanol (96% assay) in 20 ml. of water. An oil formed, which was separated from the aqueous layer and dried under vacuum. The residue weighed 10.9 g. (55.4% yield). This oil was dissolved in 10 ml. of acetic anhydride and 105 ml. of 100% nitric acid was added dropwise, with stirring, while the temperature was kept at 0–5°. The solution was stirred at 0° for an additional 2 hr. and then was poured over 2 l. of crushed ice. The ice was allowed to melt, and the water was decanted from a gum-like residue. This residue was recrystallized from ethylene chloride, to yield 6.1 g. of V, (40.5% yield assuming the condensation product was pure 6-hydroxy-2,2,10,10-tetranitroundecane), m.p. 158–159°. A mixed melting point with the above product gave no depression.

6-Acetoxy-2,2,4,8,10,10-hexanitro-4,8-diazaundecane (VI).—6-Nitroxy-2,2,4,8,10,10-hexanitro-4,8-diazaundecane (7.6 g., 0.0155 mole) was dissolved in 80 ml. of acetic anhydride and 8 ml. of concd. sulfuric acid was added dropwise while the temperature of the solution was kept at −10 to −20°. The solution was stored at 0° for 24 hr. and then was poured in to 2l. of ice water. The gum-like precipitate was recrystallized from methylene chloride to yield 6.5 g. (0.0134 mole, 86% yield) of 6-acetoxy-2,2,4,8,10,10-hexanitro-4,8-diazaundecane, m.p. 145°.

Anal. Calcd. for $C_{11}H_{18}N_8O_{14}$: C, 27.16; H, 3.71; N, 23.05. Found: C, 26.92; H, 3.31; N, 23.41.

6-Hydroxy-2,2,4,8,10,10-hexanitro-4,8-diazaundecane (VII).—6-Acetoxy - 2,2,4,8,10,10 - hexanitro - 4,8 - diazaundecane (6.5 g., 0.0134 mole) was heated under reflux for 4 hr. in a mixture of 390 ml. of methanol and 40 ml. of concd. hydrochloric acid. The volatile materials were removed under vacuum and the residue was recrystallized from methylene chloride to yield 2.7 g. (0.0061 mole, 45.4% conversion, 61% yield) of 6-hydroxy-2,2,4,8,10,10-hexanitro-4,8-diazaundecane, m.p. 168.5–169°. Some starting material, 6-acetoxy-2,2,10,10-tetranitro - 4,8 - dinitrazeundecane (1.6 g., 0.0033 mole) was recovered upon concentration of the filtrate.

Anal. Calcd. for $C_9H_{16}N_8O_{13}$: C, 24.32; H, 3.60; N, 25.22. Found: C, 24.51; H, 3.43; N, 25.37.

Acknowledgment.—We are indebted to the Office of Naval Research for the financial support of this work.

(7) Bureau of Mines Bulletin No. 346.

Variations of Alkyl Groups in 4-(4-Dialkylaminostyryl)quinolines[1,2]

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Although slight modifications in the structure of aminostyrylquinolines sometimes destroy their antitumor effects, the replacement of the dimethylamino group in 4-(4-dimethylaminostyryl)quinoline by an $—NH_2$, and $—N(C_2H_5)CH_2C_6H_5$ or an $—N{=}CH—C_6H_4—N(CH_3)_2$, produced compounds with good antitumor activity.[3–6] A series of dialkylaminostyryl compounds, listed in Table I, has been prepared in order to determine the optimum chain length. In the course of these preparations, three monoalkylamino compounds were obtained as by-products and others were then sought.

A number of Schiff bases were prepared by treating 4-(4-aminostyryl)quinoline with a variety

(1) This research was aided by grants from the American Cancer Society and the National Institute of Health.

(2) Presented in part at the Southeastern Region Meeting of the American Chemical Society in Birmingham, Ala., November, 1960.

(3) C. T. Bahner, Lydia Moore Rives, Emma Brown Senter, Dorothy Bettis Bales, Fred Hannan, and Bobby Pettyjohn, *J. Org. Chem.*, **23**, 1060 (1958).

(4) Margaret Reed Lewis, Boland Hughes, Aubrey L. Bates, and Carl Tabb Bahner, *Cancer Res*, **20**, 691 (1960).

(5) A. Haddow, private communication.

(6) K. Sugiura, private communication.