lower melting point than the unsymmetrical isomer, a reversal of the relationship for analogous aliphatic esters.

The aromatic β-monoglyceride was less soluble and had a higher m. p. than the α-isomer, in contrast to the reverse relationship for α- and β-monopalmitins.

PITTSBURGH, PENNA. RECEIVED SEPTEMBER 26, 1938

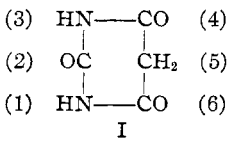
[CONTRIBUTION NO. 142 FROM THE DEPARTMENT OF CHEMISTRY AND CHEMICAL ENGINEERING, THE UNIVERSITY OF TEXAS]

The Synthesis of Colored Derivatives of Nirvanol

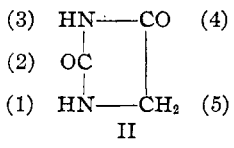
BY JAMES J. SPURLOCK[1] WITH HENRY R. HENZE

Reports are to be found in the literature of attempts to synthesize colored compounds of pronounced physiological activity. Rising[2] and collaborators have extended this type of investigation to the field of barbituric acid derivatives and have produced, from phenobarbital, mono- and dis-azo dyes in which the chromophoric grouping is attached to a phenyl radical linked to the 5-carbon atom of the barbituric acid nucleus. Buck[3] has attacked the same problem from a different angle by producing azo dyes in which the chromophore is attached to a phenyl grouping which replaces hydrogen linked to a nitrogen atom in the 1-position of the nucleus.

The definite structural similarity of barbituric acid (I) and hydantoin (II) is well known, as is

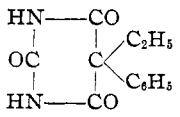


I

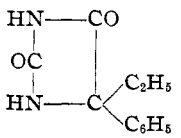


II

also the close analogy in the existence of compounds derived from substitution of identical groupings for the hydrogen atoms in the 1-, 3- and 5,5-positions of both heterocycles. Likewise, in at least one instance, substitution of ethyl and phenyl for the hydrogens attached at the 5,5-positions in both nuclei has produced useful sedatives, namely, phenobarbital (III) and nirvanol (IV), respectively. It seemed of interest, therefore, to attempt to convert nirvanol into azo dyes whose pharmacological properties might be studied subsequently.



III



IV

Nirvanol was nitrated and yielded a material whose behavior during recrystallization indicated it to be a mixture, and a pure mononitro derivative was not obtained even after ten recrystallizations. Although this mixture could be reduced catalytically, fractional crystallization proved to be unsatisfactory as a means of separating the isomeric amines formed.

Since the structure of these products, obtained from nirvanol by nitration and subsequent reduction, was uncertain, it appeared best to approach this problem from simpler compounds of established structure. Following the nitration of propiophenone, the meta derivative[4] was separated readily from its alkali-insoluble isomers and converted into 5-*m*-nitrophenyl-5-ethylhydantoin by means of the procedure of Bucherer.[5] In turn, the nitrated hydantoin was reduced in the presence of the Adams catalyst, the anticipated *m*-amine crystallizing from water as a monohydrate.

The 5-*m*-aminophenyl-5-ethylhydantoin has been diazotized and coupled with β-naphthol, β-naphthylamine, dimethylaniline and G Salt, respectively, to form azo compounds. The dyes derived from β-naphthylamine and from dimethylaniline dye wool and silk from either acid or alkaline solution; that derived from 2-naphthol-6,8-disulfonic acid dyes only from acid solution. The azo derivative of β-naphthol possesses no dyeing properties from either alkaline solution or glacial acetic acid solution.

Experimental

Nitration of Phenylethylhydantoin.—Phenylethylhydantoin was prepared according to the method of Bucherer[5]

(1) Presented before the Division of Medicinal Chemistry at the 95th meeting of the American Chemical Society, April 18 to 21, 1938, at Dallas, Texas.

(2) (a) Rising, Shroyer and Stieglitz, THIS JOURNAL, **55**, 2818 (1933); (b) Pierce and Rising, *ibid.*, **58**, 1361 (1936).

(3) Buck, *ibid.*, **59**, 1249 (1937).

(4) Comanducci and Pescitelli, *Gazz. chim. ital.*, **36**, II, 787 (1906).

(5) Bucherer and Lieb, *J. prakt. Chem.*, [2] **141**, 5 (1934).

and was dissolved in concd. sulfuric acid, cooled to −10° and nitrated with fuming nitric acid. After pouring into water, separating and drying the solid was twice recrystallized from alcohol; the yield represented 84% of the theoretical. After ten additional recrystallizations, the product, still not homogeneous, was reduced catalytically and yielded a mixture which could be fractionated by tedious recrystallization. The amines could be diazotized and coupled with β-naphthol forming a mass of deep red-colored crystals; analysis of the latter indicated that the hydantoin nucleus is stable toward diazotization and coupling.

Preparation of *m*-Nitrophenyl Ethyl Ketone.—One hundred twenty cc. of concd. sulfuric acid was placed in a 500-cc. three-necked flask fitted with a mechanical stirrer, dropping funnel and thermometer so placed that the bulb was immersed in the liquid in the flask. The acid was cooled to −5° and 26.8 g. (0.20 mole) of phenyl ethyl ketone was added during a period of ten minutes. There was then added, during a period of six minutes, a cooled mixture of 15 cc. of concd. sulfuric acid and 19.65 g. (0.22 mole) of 70% nitric acid. The temperature was at no time allowed to rise above 4°, and during most of the time it remained below 0°. The mixture was stirred for five minutes and poured over about 400 g. of cracked ice in a beaker. The oily mixture was allowed to come to room temperature and was then extracted three times with ether and the extracts washed with a 5% aqueous solution of sodium bicarbonate until the aqueous layer was no longer colored. This treatment removed the alkali-soluble isomers. The ether layer was washed with water, dried and the ether removed by evaporation on a steam cone. The resulting oil was dissolved in hot benzene, and petroleum ether then added until the solution began to cloud. Six and seven-tenths grams of light yellow crystals, m. p. 97–100°, was obtained, and, in addition, 7 g. of unreacted ketone was recovered. Based on the quantity of ketone which reacted, the yield of *m*-nitrophenyl ethyl ketone was 25%. Further recrystallization gave a product melting at 99–100° (corr.) as compared with 98° reported by Comanducci and Pescitelli,[4] and 100° recorded by Barry.[6]

Preparation of 5-*m*-Nitrophenyl-5-ethylhydantoin.—This compound was prepared by the method of Bucherer,[5] *i. e.*, by the interaction of ammonium carbonate, alkali cyanide and ketone. Two grams (0.011 mole) of *m*-nitrophenyl ethyl ketone (m. p. 99–100°), 1.0 g. (0.015 mole) of potassium cyanide and 4.0 g. (0.035 mole) of ammonium carbonate were placed in a 125-cc. flask together with 20 cc. of 95% ethyl alcohol and 10 cc. of water. The flask was fitted with an air condenser and the mixture heated at a temperature of 58–60° for a period of ten hours. The flask was shaken at intervals in order to facilitate solution and reaction of the ketone. At the end of this time the condenser was removed and the temperature raised to 85° in order to decompose the excess of ammonium carbonate and to evaporate much of the alcohol. After half an hour, 15 cc. of water was added, the solution cooled, acidified with dilute hydrochloric acid and filtered. After washing with water and drying, 2.7 g. of material, melting at 210–213°, was obtained. Recrystallization from dilute alcohol yielded 2.2 g. of white crystals melting at 219–220° (corr.); this amount represents a yield of 80% of the theoretical.

(6) Barry, *Ber.*, **6**, 1007 (1873).

Anal. Calcd. for $C_{11}H_{11}N_3O_4$: C, 53.01; H, 4.45; N, 16.86. Found: C, 53.10; H, 4.36; N, 16.94.

Preparation of 5-*m*-Aminophenyl-5-ethylhydantoin.—Four grams (0.016 mole) of 5-*m*-nitrophenyl-5-ethylhydantoin was suspended in 200 cc. of acetone and reduced catalytically in the presence of the Adams catalyst at room temperature and about one atmosphere pressure, the reduction being complete in two hours. The acetone was removed on a steam cone and the resulting residue crystallized from water, yielding 2.7 g. of light yellow crystals melting at 82–83° (corr.); on further heating the fused mass lost water at about 120°, solidified, and remelted at 165–166° (corr.).

Anal. Calcd. for $C_{11}H_{13}N_3O_3.H_2O$: C, 55.68; H, 6.37; N, 17.71. Found: C, 55.62; H, 6.54; N, 17.59.

Since the results of analysis of this compound indicate a monohydrate, the yield based on the amount of monohydrate theoretically obtainable is 71%. The hydrate was found to be somewhat unstable at room temperature and was dried *in vacuo* at 100° under 3 mm. pressure to obtain the anhydrous form; m. p. 165–166° (corr.).

Anal. Calcd. for $C_{11}H_{13}N_3O_3$: C, 60.26; H, 5.98; N, 19.17. Found: C, 60.51; H, 5.98; N, 19.13.

Preparation of 5-β-Naphthol-*m*-azophenyl-5-ethylhydantoin.—One gram (0.004 mole) of 5-*m*-aminophenyl-5-ethylhydantoin was dissolved in a mixture of 5 cc. of concd. hydrochloric acid and 50 cc. of water and cooled to −5°. Thirty-five hundredths gram (0.005 mole) of sodium nitrite was dissolved in 15 cc. of water, the solution cooled and added to that of the amine. The resulting solution of the diazonium salt was then added to 0.70 g. (0.005 mole) of β-naphthol dissolved in 100 cc. of ethyl alcohol. The mixture became light orange in color and on the addition of 10 g. of hydrated sodium acetate, dissolved in 25 cc. of water, a bulky orange-red precipitate formed. The product was allowed to stand for six hours before being filtered and recrystallized from acetic acid. The compound crystallized in bright red needles melting at 276–277° (corr.) with slight decomposition. A yield of 1.05 g., representing 67% of the theoretical, was obtained. The azo compound is very easily soluble in dilute alkali with the formation of a deep red color, is slightly soluble in glacial acetic acid, very slightly soluble in ethanol and insoluble in water.

Anal. Calcd. for $C_{21}H_{18}N_4O_3$: C, 67.37; H, 4.85; N, 14.96. Found: C, 67.31; H, 4.66; N, 15.00.

Preparation of 5-β-Naphthylamine-*m*-azophenyl-5-ethylhydantoin.—One gram (0.004 mole) of 5-*m*-amino phenyl-5-ethylhydantoin was dissolved, as before, in a solution of 5 cc. of concd. hydrochloric acid and 50 cc. of water, and cooled to −5°. There was then added the cooled solution of 0.35 g. of sodium nitrite in 20 cc. of water. After five minutes 0.3 g. of urea was added to the solution of the diazonium salt and the mixture allowed to stand for fifteen minutes, during this time some gas formation was noted. The solution was then added to one of 0.76 g. (0.005 mole) of β-naphthylamine in 100 cc. of ethyl alcohol. The solution became yellow in color, and upon the addition of 10 g. of crystalline sodium acetate, as before, an orange precipitate formed. The reaction mixture was allowed to warm slowly to room temperature and

was heated finally at 55° for five hours, cooled and filtered. Recrystallization from ethanol and ethyl acetate resulted in 1.21 g. of orange needles, a yield of 77%. On slow heating these needles sinter at 220°, then show no further change until they melt at 247–248° (corr.). When the crystals are placed in a bath at a temperature slightly below 220°, they melt at 220–221° (corr.), resolidify and melt again at 247–248° (corr.). The azo compound is soluble in concd. hydrochloric acid to form a deep red solution and in alkali to yield a bright orange solution. Also, it is slightly soluble in ethanol and in ethyl acetate, but insoluble in water.

Anal. Calcd. for $C_{21}H_{19}N_5O_2$: C, 67.55; H, 5.13; N, 18.76. Found: C, 67.48; H, 5.33; N, 18.80.

Preparation of 5-Dimethylaniline-*m*-azophenyl-5-ethylhydantoin.—One gram (0.004 mole) of 5-*m*-aminophenyl-5-ethylhydantoin was diazotized as before, with addition to the solution of diazonium salt derived from 0.56 g. (0.46 mole) of dimethylaniline dissolved in 1 cc. of concd. hydrochloric acid and 20 cc. of water. An orange precipitate formed on the addition of 10 g. of hydrated sodium acetate. The mixture was allowed to warm to room temperature, was filtered and the solid crystallized from ethanol and then from ethyl acetate. One and eleven-hundredths grams of light orange needles melting at 233–235° was obtained, or 75% of the theoretical yield. The azo dye is soluble in dilute hydrochloric acid, somewhat less soluble in dilute alkali, slightly soluble in ethanol and ethyl acetate and insoluble in water.

Anal. Calcd. for $C_{19}H_{21}N_5O_2$: C, 64.93; H, 6.02; N, 19.93. Found: C, 64.94; H, 5.92; N, 19.89.

Preparation of 5-[2-Naphthol-6,8-disulfonic acid-*m*-azophenyl]-5-ethylhydantoin.—Three grams (0.013 mole) of 5-*m*-aminophenyl-5-ethylhydantoin was diazotized using 1 g. of sodium nitrite and to the solution was added 7 g. of G Salt dissolved in 50 cc. of water. No appreciable color change was noted until the solution was made alkaline with sodium hydroxide, after which it gradually became deep red in color. The reaction mixture was allowed to stand for twenty-four hours at 0°, when an unsuccessful attempt was made to salt-out the sodium salt through addition of sodium chloride. Six grams of barium chloride dissolved in 20 cc. of water was added and the solution allowed to stand for twenty-four hours, during which time orange material separated from solution. The solid was filtered and recrystallized from water, 4.15 g. of product being obtained. Analysis of this material, dried at room temperature, indicated it to be the octahydrated barium salt; on this basis the yield represented 40% of the theoretical.

Anal. Calcd. for $C_{21}H_{16}N_4O_9S_2Ba.8H_2O$: Ba, 16.88; S, 7.88; N, 6.89. Found: Ba, 16.91; S, 8.13; N, 7.76.

The free sulfonic acid, obtained by decomposing the barium salt with the calculated amount of sulfuric acid, is very soluble in water; the aqueous solution is colored deep red by alkali and orange by acid. Because of its extremely hygroscopic nature it was not possible to prepare the disulfonic acid in a state of analytical purity.

Summary

Colored meta-azo derivatives of nirvanol have been synthesized.

AUSTIN, TEXAS RECEIVED AUGUST 5, 1938

[CONTRIBUTION FROM THE AVERY LABORATORY OF CHEMISTRY OF THE UNIVERSITY OF NEBRASKA]

The Mutarotation of *d*-Galactose[1]

BY B. CLIFFORD HENDRICKS AND ROBERT E. RUNDLE

The mutarotation of *d*-galactose has received more attention than other sugars in recent years[2–6] due to its reaction being other than the traditional first order type.

Two groups[4,6] of investigators have developed independently what might be termed a three-sugar postulate. In the language of one group[7] "our method of analysis enables us to calculate: (1) the proportions of these sugars in the final equilibrium mixture; (2) the velocity coefficients of the four unimolecular actions by which they are converted into one another; and (3) the approximate rotatory power of the unknown intermediate sugar." The constants thus deduced by these two groups, however, do not agree. Riiber and co-workers made their deductions from dilatometer studies of *d*-galactose mutarotations while Lowry and his assistants derived theirs from polarimetric data.

One of the authors[8] has shown that the constants reported by Lowry can be used to compute the rotations of "thermal-mutarotations" and of predetermined proportions of α-*d*-galactose and β-*d*-galactose mixtures. The computed data are shown to agree with the observed values made by Isbell and Pigman[9] in a very satisfactory way while calculations made for the same conditions

(1) Presented at the Joint Program of the Division of Organic Chemistry and the Division of Sugar Chemistry and Technology at the ninety-sixth meeting of The American Chemical Society, Milwaukee, Wisconsin, September 8, 1938.

(2) Lowry, *J. Chem. Soc.*, **85**, 1570 (1904).

(3) Hudson and Yanovsky, THIS JOURNAL, **39**, 1013 (1917).

(4) Riiber and Minsaas, *Ber.*, **59**, 2266 (1926).

(5) Worley and Andrews, *J. Phys. Chem.*, **32**, 307 (1928).

(6) Smith and Lowry, *J. Chem. Soc.*, 666 (1928).

(7) Lowry and Smith, *J. Phys. Chem.*, **33**, 7–21 (1929).

(8) Rundle, Thesis, University of Nebraska, 1938.

(9) Isbell and Pigman, *Bur. Standards J. Research*, **18**, 141 (1937).