methyl *t*-butyl ketone. These results can best be explained by use of the six-membered ring transitory state proposed as a common basis for the "abnormal reactions" of the Grignard reagent with carbonyl compounds.[3]

STANFORD, CALIFORNIA RECEIVED APRIL 24, 1950

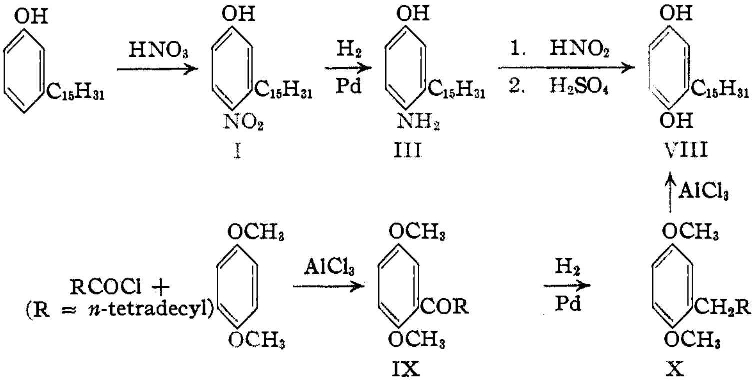
[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, COLUMBIA UNIVERSITY]

Cashew Nut Shell Liquid. VIII. A Proof of Structure of the Mono-nitro and Mono-amino Derivatives of 3-Pentadecylphenol (Hydrocardanol)[1]

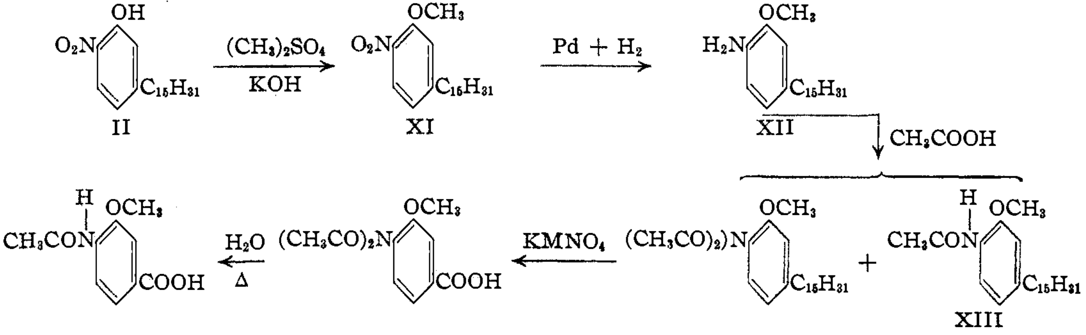
BY DAVID WASSERMAN[2] AND CHARLES R. DAWSON

During the past few years an increasing amount of work on cashew nut shell liquid and the products derived from it has appeared in the literature.[3,4,5,6,7] The main product of the decarboxylation and vacuum distillation of cashew nut shell liquid is a 3-alkenylphenol (cardanol) which upon catalytic hydrogenation and vacuum fractionation yields 3-pentadecylphenol (hydrocardanol). This unique alkyl phenol is produced commercially in a high state of purity.[8]

A: Proof of structure of 4-nitro-3-pentadecylphenol.



B: Proof of structure of 6-nitro-3-pentadecylphenol.



The 4-amino-3-pentadecylphenol is particularly well suited for use as a gasoline gum inhibitor because of its insolubility in aqueous alkali, its solubility in gasoline, and its strong anti-oxidant activity. This amine and its isomer, 6-amino-3-pentadecylphenol, were first obtained from 3-pentadecylphenol by direct nitration, separation of the isomeric nitro compounds, and then catalytic reduction. The structures of the two isomeric amines (and the corresponding nitro compounds) were established by the synthetic procedures indicated below. An alternative method of synthesizing 4-amino-3-pentadecylphenol, which involved the coupling of sodium 3-pentadecylphenolate with diazotized aniline or sulfanilic acid and subsequent reduction of the azo compound with sodium hydrosulfite, resulted in a pure compound, uncontaminated by the 6-amino isomer, in excellent yields.

The 4 position of the nitro group in the higher melting mononitro isomer (I) of 3-pentadecylphenol was established by converting it into 2-pentadecylhydroquinone (VIII) and comparing this product by mixed melting point with that obtained by the unequivocal route of synthesis outlined in Chart IA.

The reactions outlined in Chart IB were used to establish the 6 position of the nitro group in the lower melting mono-nitro isomer (II) by converting it into 3-methoxy-4-acetaminobenzoic acid.

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[1] For the seventh article in this series, see Izzo and Dawson, *J. Org. Chem.*, **15**, 707 (1950).

[2] Chemical Products Division, Irvington Varnish and Insulator Co., Irvington, N. J.

[3] Wasserman and Dawson, THIS JOURNAL, **70**, 3675 (1949).

[4] Sletzinger and Dawson, *ibid.*, **68**, 345 (1946).

[5] Wasserman and Dawson, *Ind. Eng. Chem.*, **37**, 396 (1945).

[6] Backer and Haack, *Rec. Trav. Chem.*, **60**, 661 (1941).

[7] Harvey and Caplan, *Ind. Eng. Chem.*, **32**, 1306 (1940).

[8] Produced by the Chemical Products Division of the Irvington Varnish and Insulator Co., Irvington, N. J.

Experimental

All melting points were taken with a Bureau of Standards Thermometer and are corrected.

Nitration of 3-Pentadecylphenol.—To 20 g. of 3-pentadecylphenol dissolved in 75 cc. of chloroform in a 250-ml. beaker was added 1.2 equivalents (5.3 g.) of 90% nitric acid (d. 1.52) dropwise with stirring and cooling with an ice-bath. The temperature was maintained at 5–10° during the ten minutes of addition of acid, and the stirring was continued for twenty minutes at 10°. The reaction mixture was poured into water, solvent removed *in vacuo*, and the residue solidified on cooling by the addition of ice. After filtration and drying, the 23 g. of red-orange solid melted at 43–53°.

4-Nitro-3-pentadecylphenol (I).—The crude solid of mixed mononitro isomers of 3-pentadecylphenol was dissolved in 150 ml. of petroleum ether and cooled overnight. About 8 g. of light tan powder separated. The filtrate was saved for the isolation of the 6-nitro isomer. During four recrystallizations of the powder from a mixture of two parts of Skelly solvent B,[9] and one part of Skelly solvent D,[9] the melting point rose from 60–66° to 71.5–72°; yellow plates.

Anal. Calcd. for $C_{21}H_{35}O_3N$: N, 4.01. Found: N, 4.23.

6-Nitro-3-pentadecylphenol (II).—The 6-nitro isomer was obtained in the form of a dark brown oil from the filtrate mentioned above by vacuum removal of the solvent. The oil was taken up in 95% ethanol, treated with carbon and filtered. Upon cooling slowly, 5.5 g. of a solid melting at 38–41° was obtained. Three recrystallizations from ethanol yielded light yellow needles melting at 43–44°.

Anal. Calcd. for $C_{21}H_{35}O_3N$: C, 72.16; H, 10.10; N, 4.01. Found: C, 72.41; H, 10.11; N, 3.90.

4-Amino-3-pentadecylphenol (III).—A 30-g. sample of pure I in 150 ml. of 95% ethyl alcohol was reduced for several hours under two atmospheres of hydrogen in the presence of 3 g. of palladium on carbon catalyst. The theoretical amount of hydrogen was absorbed. After filtering off the catalyst, the alcohol was evaporated, and the brown solid residue was recrystallized twice from Skelly solvent D, and once from ethyl acetate to yield 21 g. (77%) of white needles with a faint pink tinge, melting at 105.5–106.5°. Pure white crystals for analysis were obtained by a molecular distillation at 0.4 mm. (Wood's metal-bath at 160–175°). Analyses for carbon and hydrogen were run on a sample which was stored in an evacuated sealed test-tube.

Anal. Calcd. for $C_{21}H_{37}ON$: C, 78.94; H, 11.67. Found: C, 79.04; H, 11.42.

6-Amino-3-pentadecylphenol (IV).—A 2-g. sample of pure II in 100 ml. of ethyl acetate was reduced for several hours at atmospheric pressure of hydrogen in the presence of 0.5 g. of Raney nickel catalyst. The theoretical amount of hydrogen was absorbed. After filtering off the catalyst, the ethyl acetate solution was condensed *in vacuo* under nitrogen to one-third its volume and cooled. White crystals were obtained which on another recrystallization from ethyl acetate yielded white needles faintly tinged with pink melting at 133–134°. Pure white needles were obtained by sublimation at 0.4 mm. (Wood's metal-bath at 165–170°). The crystals were sealed under vacuum and analyzed.

Anal. Calcd. for $C_{21}H_{37}ON$: C, 78.94; H, 11.67. Found: C, 79.20; H, 11.72.

4-Amino-3-pentadecylphenol Hydrochloride (V).—The hydrochloride was prepared by adding concd. hydrochloric acid to an ethanol solution of III. The resulting tan precipitate was dried and then recrystallized three times from an ethyl acetate–ethanol mixture (2.5:1) to yield long white needles with a faint blue tinge; dec. 135°.

Anal. Calcd. for $C_{21}H_{38}ONCl$: C, 70.84; H, 10.68. Found: C, 70.67; H, 10.85.

6-Amino-3-pentadecylphenol Hydrochloride (VI).—A sample of IV was treated as described above for V; tan needles, dec. 135°.

Anal. Calcd. for $C_{21}H_{38}ONCl$: C, 70.84; H, 10.68. Found: C, 70.86; H, 10.66.

4-Nitro-3-pentadecylanisole (VII).—The methyl ether of 15 g. of the 4-nitro isomer was prepared in the usual way using sodium hydroxide and dimethyl sulfate. After hydrolyzing the excess dimethyl sulfate, the system was diluted with hot alcohol, inorganic salts were separated, and the filtrate was concentrated. Upon standing at 0°, 15.4 g. (98%) of a white solid melting at 48–49° separated. Two recrystallizations from acetone yielded an analytical sample melting at 49–50°.

Anal. Calcd. for $C_{22}H_{37}O_3N$: C, 72.68; H, 10.26. Found: C, 72.51; H, 9.96.

4-Amino-3-pentadecylphenol (III): Sulfanilic Acid Method.—A solution of 75 g. (0.25 mole) of 3-pentadecylphenol dissolved in 39 g. (0.687 mole) of potassium hydroxide in 500 ml. of 95% ethanol was placed in a three-liter three-neck flask and cooled to 0–5°. To this was slowly added the diazonium salt from 52.5 g. of sulfanilic acid dihydrate suspended in cold ethanol.

The resulting red dye solution was stirred two hours and then reduced by adding, in a continuous stream, a saturated solution containing 114 g. of technical sodium hydrosulfite in water at 45–75°. The reduction required about fifteen minutes. A solution of 40 g. of acetic acid in 300 ml. of water was added at reflux temperature, and the flask was cooled to 0°. A quantitative yield of the aminophenol (80 g.) was filtered off and vacuum dried, m. p. 95–97°. After one recrystallization from Skelly solvent D, the melting point was 104–106° (75–85% yield). A mixed melting point with a known sample of 4-amino-3-pentadecylphenol resulted in no depression of the melting point.

2-Pentadecylhydroquinone (VIII): Derived from the Nitrophenol (I) (a) Diazotization with Sodium Nitrite.—A 1.1-g. sample of the aminophenol (III) was dissolved in 10 ml. of pyridine and added slowly at 0° to a solution containing 0.6 g. of sodium nitrite, 7.0 ml. of water and 15 ml. of sulfuric acid. After the last addition of the pyridine solution, 0.5 g. of urea was added to remove the excess nitrous acid. The foamy yellow emulsion was added to a boiling solution of 10 ml. of sulfuric acid and 7.5 ml. of water (boiling temperature 150°) to decompose the diazonium compounds. A rapid evolution of nitrogen occurred and a tarry residue was deposited on cooling. The tarry material was extracted with ether, the ether layer dried with anhydrous magnesium sulfate and the ether evaporated. The residue upon sublimation at 170° and 1 mm. pressure yielded 0.4 g. of colorless solid melting at 86–92°. After three recrystallizations from Skelly solvent D, and two more from chloroform, white needles of 2-pentadecylhydroquinone were obtained which melted at 105.5–106°.

Anal. Calcd. for $C_{21}H_{36}O_2$: C, 78.69; H, 11.32. Found: C, 78.83; H, 11.38.

The product gave a positive Tollens test, turned brown on addition of ferric chloride and did not form a hydrochloride, thereby differentiating it from the starting material. Nitrogen tests by the Dumas method (CuO oxidation) were negative. A mixed melting point with a sample of the pure starting material (4-amino-3-pentadecylphenol, m. p. 105.5–106.5°) melted at 98–100°.

(b) Diazotization with Amyl Nitrite.—A 5-g. sample of III was dissolved in 200 ml. of ether (U. S. P.) and saturated with dry hydrogen chloride gas with vigorous stirring to yield a finely divided suspension of the hydrochloride salt. The suspension was cooled to 0–5°, 2.5 g. of amyl nitrite was added, and the mixture was stirred for two hours at 0–5°. The insoluble diazonium salt was filtered, dried, and immediately suspended in a cold solution (0°) of 30 g. of water and 54 g. of concd. sulfuric

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[9] Hydrocarbon solvents supplied by the Skelly Oil Co., Solvent B b. p. 40–60°, Solvent D, b. p. 90–110°.

acid. This solution was then poured into a boiling solution of 60 g. of water and 108 g. of concd. sulfuric acid with stirring. After the frothing had subsided, the mixture was cooled by the addition of ice and the residual red oil was extracted with ether. The ether extract was washed with water, dried with anhydrous magnesium sulfate, filtered, ether evaporated, and the residue molecularly distilled at 0.5 mm. (Wood's metal-bath at 170–190°). The white solid so obtained melted at 91–97° and weighed 1.9 g., representing a yield (38%) of 2-pentadecylhydroquinone comparable to that obtained by method (a) but of somewhat better quality.

2-Pentadecylhydroquinone (VIII). Synthetic: (a) **Pentadecanoyl Chloride.**—A 121-g. sample of pentadecanoic acid[10] (0.5 mole) in 200 ml. of carbon tetrachloride was added to 70 g. (0.59 mole) of $SOCl_2$ and slowly brought to reflux on the steam-bath. After refluxing for one-half hour the solvent and excess $SOCl_2$ were removed and the acid chloride was distilled at 183–185° at 11 mm. (Wood's metal-bath at 185°); yield was 120 g. (92%).

(b) **2-Pentadecanoylhydroquinone Dimethyl Ether (IX).**—To 52.8 g. (0.383 mole) of hydroquinone dimethyl ether (Eastman Kodak Co.) in 200 ml. of tetrachloroethane was slowly added 51.2 g. of aluminum chloride and 100 g. (0.383 mole) of pentadecanoyl chloride with stirring at 0°. The mixture was stirred for three hours and then allowed to stand at 4° for seventy-two hours. The deep red solution was poured onto 200 g. of ice, 20 ml. of concd. hydrochloric acid added, and the solvent was removed by steam distillation. The ketone was extracted with ether, washed with 10% sodium hydroxide in 50% methanol, and then with 50% methanol. After drying with anhydrous magnesium sulfate, the ether was removed and the residual oil distilled at 0.5 mm. A yield of 126.8 g. (90.5%) of 2-pentadecanoylhydroquinone dimethyl ether boiling at 205–207° (Wood's metal-bath at 234–245°) and melting at 36–38° was obtained. A small sample was recrystallized twice from methanol and yielded white plates melting at 37.5–38.5°.

Anal. Calcd. for $C_{23}H_{38}O_3$: C, 76.19; H, 11.10. Found: C, 76.04; H, 11.09.

(c) **2-Pentadecylhydroquinone Dimethyl Ether (X).**—Catalytic hydrogenation proved to be better than the Clemmensen method for reducing the above ketone. To 30.9 g. of IX dissolved in 150 ml. of glacial acetic acid was added 3 g. of 5% palladium on carbon catalyst. Under a pressure of three atmospheres the theoretical amount of hydrogen was absorbed in three hours at 65°. After filtering off the catalyst, the acetic acid was removed *in vacuo* and the residue was recrystallized from ethanol to yield 25.7 g. (86.5%) of long white needles melting at 44–45°.

Anal. Calcd. for $C_{23}H_{40}O_2$: C, 79.30; H, 11.60. Found: C, 79.42; H, 12.02.

(d) **2-Pentadecylhydroquinone (VIII).**—A 5-g. sample of the dimethyl ether X was refluxed for twelve hours with 5 g. of aluminum chloride in 50 cc. of pure dry benzene. The reaction mixture was cooled, and poured into 75 cc. of cold 50% methanol containing 5 cc. of concd. hydrochloric acid. The benzene layer was separated, washed with 50% methanol, dried over anhydrous $MgSO_4$, and evaporated. The residue was molecularly distilled, and recrystallized three times from Skelly solvent D. The yield (white needles) was 2.9 g. (62%) of 2-pentadecylhydroquinone (m. p. 105.5–106°).

Anal. Calcd. for $C_{21}H_{36}O_2$: C, 78.69; H, 11.32. Found: C, 78.60; H, 11.16.

The melting points of mixtures containing varying proportions of the above hydroquinone and the hydroquinone derived from hydrocardanol *via* the nitro and amino derivatives (I and III) showed no depression.

6-Nitro-3-pentadecylanisole (XI).—The dry potassium salt of the 6-nitrophenol II was formed by dissolving 24.3 g. of the phenol in the minimum amount of dioxane, and adding a solution of 3.8 g. of potassium hydroxide dissolved in 20 ml. of absolute methanol. The orange-red precipitate which formed on cooling the mixture was filtered and dried (21.6 g.). To the dry salt was added 75 ml. of dry xylene, and 10 g. of freshly distilled dimethyl sulfate. The mixture was slowly brought to reflux temperature and heated for one-half hour to complete the reaction. The excess dimethyl sulfate was destroyed in the usual manner. After pouring the reaction mixture into water, the upper layer was separated and washed with dilute acid and then with water. The xylene and water were removed *in vacuo* and the residue was recrystallized from methanol to yield 17.4 g. (89%) of white needles melting at 38–39°. An analytical sample (m. p. 39–40°) was obtained by recrystallization from ethanol and molecular distillation at 0.5 mm. (Wood's metal-bath at 140–165°).

Anal. Calcd. for $C_{22}H_{37}O_3N$: C, 72.68; H, 10.26. Found: C, 72.32; H, 10.32.

6-Amino-3-pentadecylanisole (XII).—A 11.0-g. sample of XI was dissolved in 100 ml. of ethyl acetate and catalytically reduced under 30 lb. pressure of hydrogen using 1.0 g. of 5% palladium on carbon as the catalyst. After removal of the catalyst and solvent, the residue was recrystallized from ethanol in about 95% yield (m. p. 67–67.5°). An analytical sample was obtained by molecular distillation at 0.5 mm. (Wood's metal-bath at 160°).

Anal. Calcd. for $C_{22}H_{39}ON$: C, 79.20; H, 11.81. Found: C, 79.14; H, 11.86.

The sulfate salt of the above amine was prepared by dissolving it in dioxane and adding an equivalent amount of dilute sulfuric acid. Upon dilution with water the crystalline salt precipitated. It was soluble in hot polar solvents but insoluble in Skelly B and D. Attempts at diazotization and subsequent decomposition in boiling 50% copper sulfate or 50% sulfuric acid to yield a 6-hydroxy-3-pentadecylanisole were unsuccessful.

6-Acetamino-3-pentadecylanisole (XIII).—A 3-g. sample of XII was acetylated by slowly distilling the acetic acid and water from a solution of the compound in glacial acetic acid over a period of four hours. The residue was cooled, poured into cold water, filtered, dried, and molecularly distilled at 0.5 mm. (Wood's metal-bath at 160°) to yield 3.2 g. (90%) of colorless solid melting at 90–93°. An analytical sample melting at 93–94° was obtained by two recrystallizations from Skelly solvent D and a molecular distillation.

Anal. Calcd. for $C_{24}H_{41}O_2N$: C, 76.75; H, 11.00. Found: C, 76.71; H, 10.99.

3-Methoxy-4-acetaminobenzoic Acid.—A solution of 24 g. of potassium permanganate and 18 g. of magnesium sulfate in 500 ml. of water was used to oxidize 5 g. of XIII (partially purified m. p. 90–93°) by refluxing for 24 hours. All the permanganate was converted to manganese dioxide. The manganese dioxide was filtered off while hot, and washed with hot water twice. The combined filtrates were condensed by vacuum distillation and acidified with dilute hydrochloric acid. The very small amount of crystalline material which precipitated was dried and sublimed at 0.5 mm. (Wood's metal-bath at 150–170°). The resulting 10 mg. of pink solid (m. p. 182–184°) analyzed correctly in nitrogen for a methoxydiacetaminobenzoic acid, and presumably was derived from small amounts of 6-diacetamino-3-pentadecylanisole present as an impurity in the starting material XIII.

Anal. Calcd. for $C_{12}H_{13}O_5N$: N, 5.57. Found: N, 5.68.

Hydrolysis of a 5-mg. sample of the methoxydiacetaminobenzoic acid to the corresponding monoacetamino compound was accomplished by refluxing with 10 ml. of water for 30 minutes. The material which separated on cooling melted at 201–204° and was crystallized from dilute hydrochloric acid following treatment with decolorizing carbon (Darco) to yield short white needles of melting point 205–207°, whose melting point when mixed with varying proportions of an authentic sample of 3-methoxy-4-acetaminobenzoic acid[11] was not depressed.

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[10] Ruhoff, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 292.

[11] Simonsen and Rau, *J. Chem. Soc.*, 111, 238 (1917).

The authentic sample of 3-methoxy-4-acetaminobenzoic acid was obtained from the corresponding nitro methoxy acid prepared from *m*-cresol by nitration, methylation and oxidation.

Acknowledgment.—The authors are indebted to the Irvington Varnish and Insulator Company of Irvington, New Jersey, for a grant which made this investigation possible, and for the supply of 3-pentadecylphenol (Hydrocardanol). The authors also wish to thank Miss Lois May and Miss Lathrop Baker who carried out the microanalyses reported in this communication.

Summary

1. The two mono-nitro derivatives resulting from the direct nitration of 3-pentadecylphenol (Hydrocardanol) have been separated and their structures established as 4-nitro-3-pentadecylphenol and 6-nitro-3-pentadecylphenol, respectively.

2. The corresponding mono-amino derivatives have been prepared by catalytic reduction for investigation of their properties as oil soluble antioxidants and gasoline gum inhibitors. The 4-amino-3-pentadecylphenol has also been prepared by an independent method.

3. The structures of these nitro and amino derivatives of 3-pentadecylphenol have been established by synthetic and degradative methods involving a number of structurally related compounds.

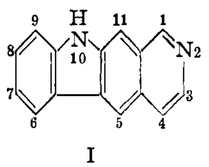
NEW YORK, N. Y. RECEIVED FEBRUARY 15, 1950

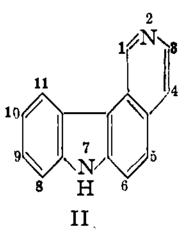
[CONTRIBUTION FROM THE RESEARCH LABORATORY, DOMINION RUBBER CO. LTD., GUELPH, ONTARIO]

Synthesis of Some Pyridocarbazoles

BY RICHARD H. F. MANSKE AND MARSHALL KULKA

The fusion of the isoquinoline ring to the 2,3-position of indole or the fusion of the pyridine ring to carbazole may result in six isomeric pyridocarbazoles, namely, 10H-pyrido[3,4-b]- (I), 7H-pyrido[4,3-c]- (II), 11H-pyrido[4,3-a]- (III), 11H-pyrido[3,4-a]- (IV), 6H-pyrido[4,3-b]- (V) and 7H-pyrido[3,4-c]- (VI) carbazoles. Three of these pyridocarbazoles, III, IV and I or II have recently been synthesized by the ring closure of the hydrazones of cyclohexanone and 5-, 8- and 7-hydrazinoisoquinolines, respectively.[1] Since the ring closure of the hydrazone of cyclohexanone and 7-hydrazinoisoquinoline can theoretically take place in two directions, the resulting single pyridocarbazole had to be assigned the structure I or II. The purpose of the present investigation was to synthesize the remaining three pyridocarbazoles, V, VI and I or II and to attempt to distinguish between I and II.


I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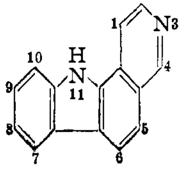
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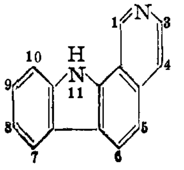
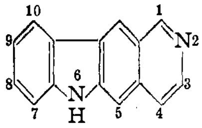

IV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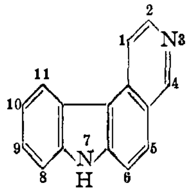
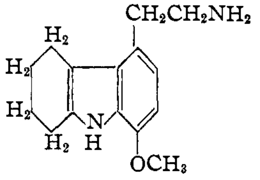
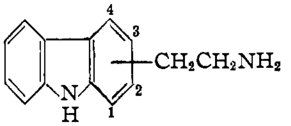

VI


VII


VIII (substituent in 4-position)
IX (substituent in 3-position)
X (substituent in 2-position)

6-Aminoisoquinoline, which was prepared from 6-hydroxyisoquinoline[2] by the Bucherer reaction, was to serve as the starting material for the synthesis of V or VI. However, an attempt to convert 6-aminoisoquinoline to 6-hydrazinoisoquinoline was not successful. Apparently the hydrazine is too unstable to withstand isolation in the pure state. A second attempt to prepare VI succeeded only in part. When 1-methoxy-4-β-aminoethyl-5,6,7,8-tetrahydrocarbazole (VII)[3] was treated with ethyl formate and the resulting N-formyl derivative cyclized by heating with phosphorus oxychloride in benzene, the product was 6-methoxy-8,9,10,11-tetrahydro-7H-pyrido-[3,4-c]carbazole. However, attempted dehydrogenation of this by heating with platinum catalyst at 300° in an atmosphere of nitrogen resulted only in resinification and heating at 200°

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(1) Manske and Kulka, *Can. J. Research*, 27B, 291 (1949).

(2) Robinson, THIS JOURNAL, 69, 1940, 1945 (1947).

(3) Manske and Kulka, *Can. J. Research*, 28B, 443 (1950).