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.

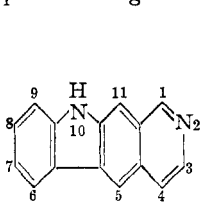
NEW YORK, N. Y. RECEIVED FEBRUARY 15, 1950

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

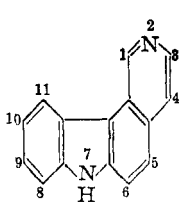
Synthesis of Some Pyridocarbazoles

BY RICHARD H. F. MANSKE AND MARSHALL KULKA

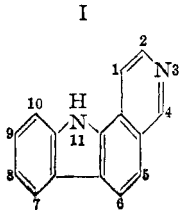
The fusion of the isoquinoline ring to the 2,3-position of indole or the fusion of the pyridine ring to carbazole may result in six isomeric pyridocarbazoles, namely, 10H-pyrido[3,4-b]- (I), 7H-pyrido[4,3-c]- (II), 11H-pyrido[4,3-a]- (III), 11H-pyrido[3,4-a]- (IV), 6H-pyrido[4,3-b]- (V) and 7H-pyrido[3,4-c]- (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.



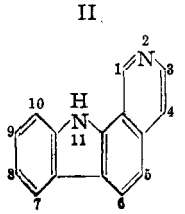
I



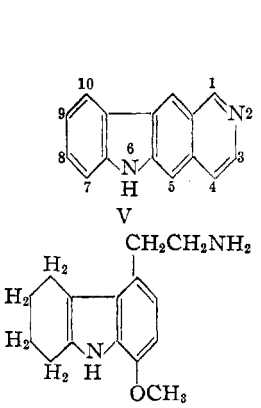
II



III



IV



V 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°

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

(2) Robinson, THIS JOURNAL, **68**, 1940, 1945 (1947).

(3) Manske and Kulka, *Can. J. Research*, **28B**, 448 (1950).

with platinum catalyst yielded only unchanged material. The yield of 6-methoxy-8,9,10,11-tetrahydro-7H-pyrido[3,4-c]carbazole was extremely low but this was not surprising in view of the fact that the N-formyl-3-β-aminoethyl-5,6,7,8-tetrahydrocarbazole could not be cyclized successfully.[4]

VI was finally synthesized by cyclizing the N-formyl derivative of 4-β-aminoethylcarbazole (VIII).[3] The remaining pyridocarbazoles I or II and V were similarly synthesized from 3-β-aminoethyl- (IX)[3] and from 2-β-aminoethylcarbazole (X),[3] respectively. Although the cyclization of N-formylarylethylamines generally yields 3,4-dihydroisoquinolines, the N-formylcarbazolylethylamines in most cases gave the fully aromatic isoquinoline derivatives (pyridocarbazoles) possibly mixed with small amounts of the dihydropyridocarbazoles. It is quite likely that the dehydrogenation of the dihydropyridocarbazoles took place during the purification which in all cases consisted of sublimation at low pressure and high temperature (230°).

It is to be noted that the N-formyl derivatives of IX and X can each theoretically ring close in two directions to form linear and angular structures. However, only one compound formed in each case. That N-formyl-2-β-aminoethylcarbazole (N-formyl-X) ring closed in the direction to form the linear pyridocarbazole V was proven by comparison with the angular isomer IV which was synthesized unambiguously from 8-hydrazinoisoquinoline.[1] The cyclization of N-formyl-3-β-aminoethylcarbazole (N-formyl-IX) yielded a pyridocarbazole I or II which was different from that I or II prepared from 7-hydrazinoisoquinoline.[1] However, both of these synthetic methods are ambiguous and therefore I and II are not distinguishable. At present the linear structure I is tentatively assigned to the higher melting compound obtained from 3-β-aminoethylcarbazole (IX) and the angular structure II to the lower melting one prepared from 7-hydrazinoisoquinoline[1] on the basis that higher melting isomers of this type are usually linear.[5] Furthermore the reactive position of 7-substituted isoquinolines[6,7] is the 8- and not the 6-position. Therefore it is reasonable to expect the hydrazone of 7-hydrazinoisoquinoline to ring close to the 8-position and therefore give the angular pyridocarbazole (II).

When in dilute solution the pyridocarbazoles exhibit a fluorescence varying from strong purple (I) to very little fluorescence (VI). Though the inorganic salts of the pyridocarbazoles are fairly soluble in water, those of the 7,8,9,10-tetrahydro derivatives of III and IV are extremely insoluble. The solubility of the nitrate of 7,8,9,10-tetrahydro-11H-pyrido[4,3-a]carbazole in water at 25° is less than one gram per liter.

(4) Manske and Kulka, *Can. J. Research*, **25B**, 376 (1947).
(5) Mosettig and Robinson, THIS JOURNAL, **57**, 902 (1935).
(6) Manske and Kulka, *Can. J. Research*, **27B**, 161 (1949).
(7) Woodward and Doering, THIS JOURNAL, **67**, 860 (1945).

Experimental

6-Aminoisoquinoline.—Into a suspension of 6-hydroxyisoquinoline[2] (1.0 g.) and water (15 cc.), sulfur dioxide was passed until 1 g. was absorbed. Then concentrated ammonium hydroxide (20 cc.) was added and the reaction mixture heated in a sealed tube at 150° for fifteen hours. The cooled reaction mixture was filtered, the precipitate washed with dilute sodium hydroxide, with water and dried. The yield of white solid was 0.85 g. or 85%, m. p. 217–218°; crystallized from benzene, white needles, m. p. 217–218°. *Anal.* Calcd. for $C_9H_8N_2$: C, 74.99, H, 5.56; N, 19.44. Found: C, 74.80, 75.09; H, 5.62, 5.37; N, 19.30.

N-Formyl-4-β-aminoethylcarbazole.—4-β-Aminoethylcarbazole (VIII)[3] (1.0 g.) and dry ethyl formate (3 cc.) were heated in a sealed tube at 120° for seven hours. The precipitated formyl derivative was filtered from the cooled reaction mixture and washed with a little ethyl formate and dried, m. p. 149–150°, crystallized from ethyl formate, white needles, m. p. 150–151°, yield, 0.90 g. or 85%. *Anal.* Calcd. for $C_{15}H_{14}N_2O$: C, 75.63; H, 5.88; N, 11.76. Found: C, 75.79, 75.51; H, 5.69, 5.86; N, 11.80.

N-Formyl-1-methoxy-5,6,7,8-tetrahydro-4-β-aminoethylcarbazole.—This was prepared from 1-methoxy-5,6,7,8-tetrahydro-4-β-aminoethylcarbazole (VII)[3] as above, crystallized from ethyl formate containing a little methanol, m. p. 152–153°. *Anal.* Calcd. for $C_{16}H_{20}O_2N_2$: C, 70.58; H, 7.35; N, 10.29. Found: C, 70.28, 70.45; H, 7.07, 7.24; N, 10.28.

N-Formyl-3-β-aminoethylcarbazole.—This was prepared from 3-β-aminocarbazole (IX)[3] as above, crystallized from ethyl formate, m. p. 142–143°. *Anal.* Calcd. for $C_{15}H_{14}N_2O$: C, 75.63; H, 5.88; N, 11.76. Found: C, 75.86; H, 5.20; N, 11.67.

N-Formyl-2-β-aminoethylcarbazole.—This was prepared from 2-β-aminoethylcarbazole (X)[3] as above, crystallized from benzene, m. p. 188–189°, fine white needles. *Anal.* Calcd. for $C_{15}H_{14}N_2O$: C, 75.63; H, 5.88; N, 11.77. Found: C, 75.55, 75.39; H, 6.04, 6.03; N, 11.70.

7H-Pyrido[3,4-c]carbazole (VI).—To a hot solution of N-formyl-4-β-aminoethylcarbazole[3] (N-formyl-VIII) (0.75 g.) in dry benzene (200 cc.) and ethyl formate (3 cc.) was added phosphorus oxychloride (3 cc.) and the reaction mixture heated under reflux for one-half hour. Then the benzene was distilled off under reduced pressure as rapidly as possible and the residue extracted with a boiling solution of water (200 cc.) and concentrated hydrochloric acid (20 cc.). The extract was filtered and the filtrate basified with sodium hydroxide. The white precipitate was extracted with ether, the ether extract washed with water and the solvent removed. The residue was sublimed at 230° (0.5 mm.). The sublimate could be purified by repeated crystallization but it was found that a purer product was obtained by dehydrogenation first. The sublimate was mixed with Adams platinum catalyst (0.1 g.), then heated at 200° for two hours in an atmosphere of nitrogen and then resublimed. The sublimate on crystallization from acetone gave light-yellow needles, m. p. 245–246°, yield 0.25 g. or 30%. *Anal.* Calcd. for $C_{15}H_{10}N_2$: C, 82.56; H, 4.59; N, 12.83. Found: C, 82.29, 82.67; H, 5.01, 4.72; N, 12.77.

6-Methoxy-8,9,10,11-tetrahydro-7H-pyrido[3,4-c]carbazole.—This was prepared from N-formyl-1-methoxy-5,6,7,8-tetrahydro-4-β-aminoethylcarbazole (N-formyl-VII) in the same manner as was VI above, white prisms from acetone, m. p. 225–226°, yield 5%. *Anal.* Calcd. for $C_{16}H_{18}ON_2$: C, 75.59; H, 7.09; N, 11.03. Found: C, 76.19; H, 6.34; N, 11.00. This compound suffered little change when heated with Adams platinum catalyst at 200° for two hours in an atmosphere of nitrogen but complete resinification occurred when the temperature was raised to 300°.

6H-Pyrido[4,3-b]carbazole (V).—This was prepared from N-formyl-2-β-aminoethylcarbazole (N-formyl-X) in

the same manner as was VI above, light-yellow prisms from methanol, m. p. 283–284°, yield 55%. *Anal.* Calcd. for $C_{15}H_{10}N_2$: C, 82.56; H, 4.59; N, 12.83. Found: C, 82.21, 82.14; H, 5.98, 5.89; N, 12.57. In this case the ring closure yielded pure (V) directly so that no dehydrogenation was necessary. The isomeric 11H-pyrido[3,4-a]carbazole (IV)[1] melts at 280–282° but when it was mixed with (V) there was a thirty-degree depression of melting point.

10H-Pyrido[3,4-b]carbazole (I).—This was prepared from N-formyl-3-β-aminoethylcarbazole (N-formyl-IX) in the same manner as was VI above, light-yellow needles from methanol or acetone, m. p. 270–271°, yield 12%. *Anal.* Calcd. for $C_{15}H_{10}N_2$: C, 82.56; H, 4.59; N, 12.83. Found: C, 83.00, 82.92; H, 4.50, 4.49; N, 12.57. The pyridocarbazole (II)[1] obtained from 7-hydrazinoisoquinoline melts at 249–250°.

Summary

Three new pyridocarbazoles, namely, 6H-pyrido(4,3-b)-, 10H-pyrido(3,4-b)- and 7H-pyrido[3,4,-c]carbazole have been synthesized by the ring closure of the N-formyl derivatives of 2-, 3- and 4-β-aminoethylcarbazole, respectively.

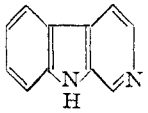
ONTARIO, CANADA RECEIVED APRIL 15, 1950

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, THE FLORIDA STATE UNIVERSITY]

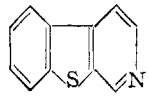
Sulfur Analogs of β-Carbolines

BY WERNER HERZ

The presence of the β-carboline nucleus in a number of alkaloids, particularly those of *Peganum harmala* and yohimbé bark, has led to the development of several methods for the synthesis of β-carbolines.[1] The isosteric relationship between –NH– and sulfur groups demonstrated, for example, in the amino acid series[2] suggested the application of these methods to the synthesis of compounds of possible physiological interest in which the indole moiety of β-carboline (I) is replaced by a thianaphthene nucleus (II).



I



II

In this communication the preparation of two such compounds, 1-methyl- (III) and 1-phenylthianaphtheno(2,3-*C*)-pyridine (IV) is reported. III is the sulfur analog of the alkaloid harman and suitable variation of the starting materials might be expected to yield analogs of other indole alkaloids.

The accompanying diagram illustrates the method of synthesis which represents an adaptation of the scheme employed by Späth and Lederer[3] in the synthesis of harman and harmaline. Lithium aluminum hydride reduction[4] of 3-cyanomethylthianaphthene[5] gave β-3-thianaphthylethylamine in 30–35% yield. The acetyl (V) and benzoyl (VI) derivatives of this base were cyclized smoothly *via* the Bischler–Napieralski reaction,[6] using the method recommended by Whaley and Hartung.[7] The resulting 1-substituted 3,4-dihydrothianaphtheno-(2,3-*C*)-pyridines were converted to the desired aromatic compounds by dehydrogenation with palladium black.[3]

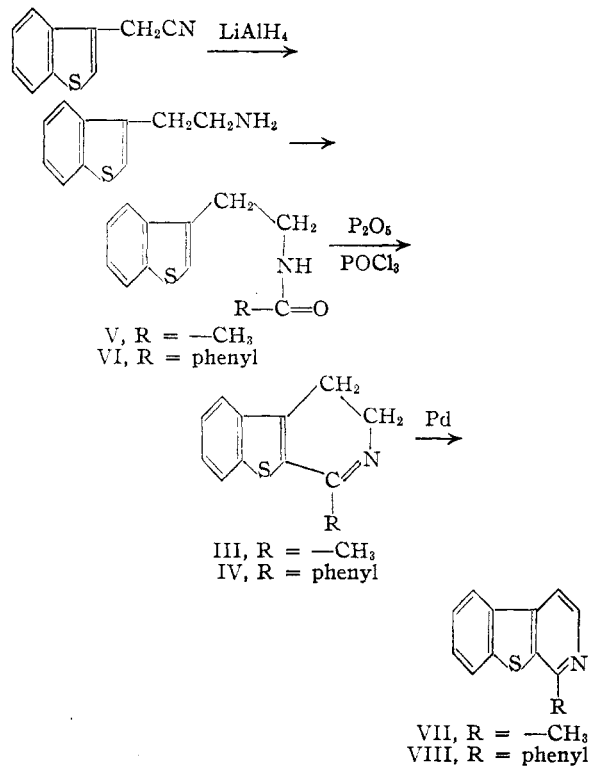


Fig. 1.

For comparison with reported spectra of β-carbolines[8] the ultraviolet absorption curves of compounds III, IV, VII and VIII are reproduced in Figs. 2 and 3. As expected, the increase in conjugation brought about by dehydrogenation results in displacement of the curves toward

(1) Henry, "The Plant Alkaloids," J. A. Churchill Ltd., London, 4th edition, 1949, p. 485, *et seq.*

(2) Herz, Dittmer and Cristol, THIS JOURNAL, **70**, 504 (1948).

(3) Späth and Lederer, *Ber.*, **63**, 120 (1930).

(4) Nystrom and Brown, THIS JOURNAL, **70**, 3738 (1948).

(5) Avakian, Moss and Martin, *ibid.*, **70**, 3075 (1948); Blicke and Sheets, *ibid.*, **70**, 3768 (1948).

(6) Bischler and Napieralski, *Ber.*, **26**, 1903 (1893).

(7) Whaley and Hartung, *J. Org. Chem.*, **14**, 650 (1949).

(8) Kharasch, Stanger, Bloodgood and Legault, *Science*, **83**, 36 (1936); Pruckner and Witkop, *Ann.*, **554**, 127 (1944); Raymond-Hamet, *Compt. rend.*, **221**, 387 (1945).