Selective Adrenal Cortical and Gonadal Inhibitors

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The synthesis of 3-pyridyl-substituted tetralones is presented. The alterations in the corticoid hormonal pattern caused by inhibitors of the 11β- and 17α-hydroxylase enzyme systems and the gonadal inhibition by 17α-hydroxylase inhibitors are discussed. The biological activity of compounds VII and IX is being further investigated.

Although the chemistry of pinacolone type compounds has been the subject of intensive research for many years, it has not been until the past decade that such ketones have been evaluated pharmacologically. In this connection the following two isomeric pairs of pinacolones, all of which possess unusual biological activity, have been studied in our laboratories.[1,2]

$RCOC(CH_3)_2R$	$CH_3COC(CH_3)R_2$
I, R = *p*-$C_6H_4NH_2$	II, R = *p*-$C_6H_4NH_2$, (amphenone)
III, R = 3-Pyridyl, (mepyrapone[3])	IV, R = 3-Pyridyl

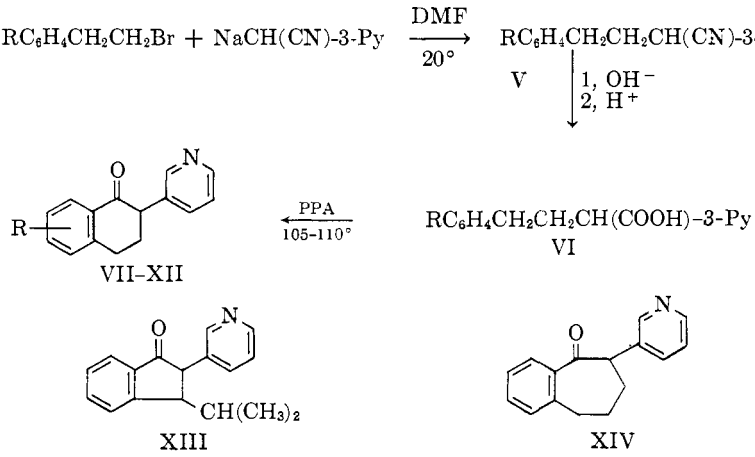
In the course of our continued search for adrenal cortical inhibitors, a number of compounds were found which altered the hormonal pattern in the adrenal effluent of the dog in a fashion different from the established changes in the hormonal output as evoked by mepyrapone. These substances are classified as inhibitors of the 17α-hydroxylase system[4] and their chemistry and biological activity serve as the subject matter of this report.

Chemistry.—Our most potent 17α-hydroxylase inhibitors were found in a series of pyridyl-substituted tetralones, the synthesis of which is outlined in Scheme 1.

In cyclization of the *meta*-substituted acid (VI, R = *m*-Cl) ring closure occurred in the *ortho* and *para* positions relative to the chlorine atom. The lower melting form constituted the major fraction and was assigned structure VIII. A strong band at 863 cm.$^{-1}$ in the infrared absorption spectrum, indicative of 1,2,4-aromatic substitution, served to confirm this assignment. The structure of the higher melt-

(1) W. L. Bencze and M. J. Allen, *J. Med. Pharm. Chem.*, **1**, 395 (1958).
(2) J. J. Chart and H. Sheppard, *ibid.*, **1**, 407 (1958).
(3) Metopirone®; previous designation, Su-4885.
(4) J. J. Chart, H. Sheppard, R. Mowles, and N. Howie, *Endocrinology*, **71**, 479 (1962).

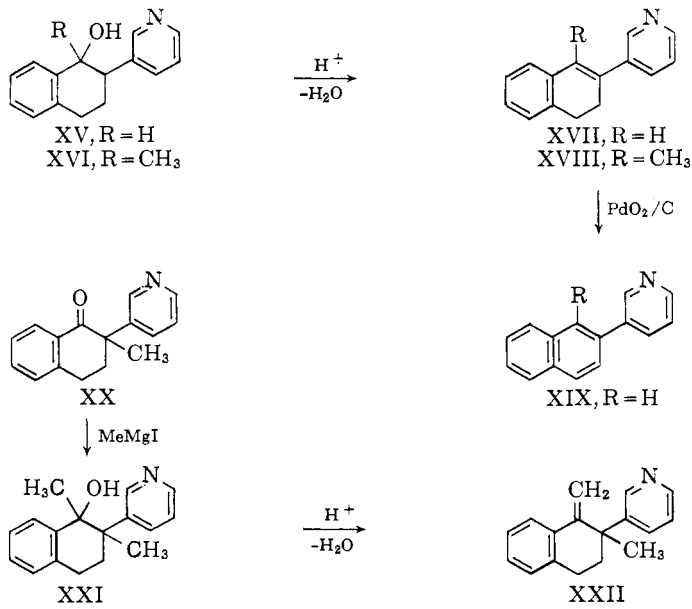
SCHEME 1

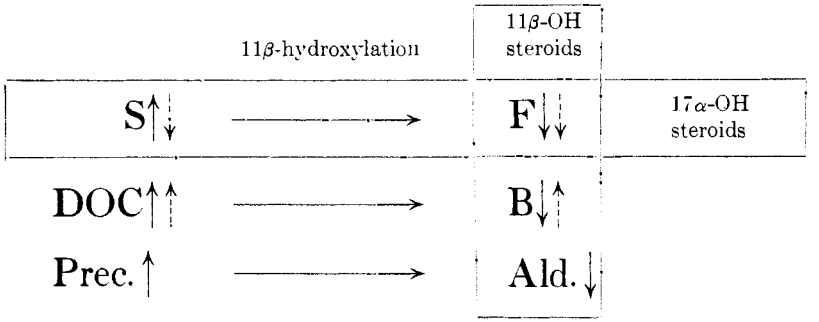


ing form (X) was supported by the strong absorption band at 786 cm.$^{-1}$ for 1,2,3-aromatic substitution.

Compound (VII) was subjected to reactions which afforded 3,4-dihydro-1,2,3,4-tetrahydronaphthalene and naphthalene derivatives as illustrated in Scheme 2.

SCHEME 2





Legends:

11β-Hydroxylase inhibitors cause
↓ a decrease in the plasma levels of F, B. Ald. and
↑ an increase in the plasma levels of S, DOC, Prec.
17α-Hydroxylase inhibitors cause
⇣ a decreased plasma concentration of S, F and
⇡ an increased plasma concentration of DOC, B.

Designations, trivial names, structural names:

S (Reichstein's compound S), 11-deoxycortisol, 17α,21-dihydroxy-4-pregnene-3,20-dione.
F cortisol, 11β,17α,21-trihydroxy-4-pregnene-3,20-dione.
DOC deoxycorticosterone, 21-hydroxy-4-pregnene-3,20-dione.
B corticosterone, 11β,21-dihydroxy-4-pregnene-3,20-dione.
Prec. designates several precursors of aldosterone, since oxidation at C-18 may occur prior and subsequent to 11β- and 21-hydroxylation.
Ald. aldosterone, 11β,21-dihydroxy-3,20-dioxo-4-pregnen-18-al.

Fig. 1.—Action of selective hydroxylase inhibitors on the biosynthesis of hormones in the adrenal cortex.

Biological Activity.—The effect on the main adrenal cortical hormones of the 11β- and 17α-hydroxylase inhibitors is outlined in Fig. 1.

Structure and Activity.—Since our last review[1] a great number of compounds containing the 3-pyridyl residue were prepared and screened as adrenal inhibitors. Simple pyridine compounds, such as 3-pyridyl methyl ketone and 3-pyridylacetonitrile, were also found to be active as 11β-hydroxylase inhibitors, although their effect was weak. As a general rule, it was found that the 3-pyridyl moiety is to be preferred over the 4-pyridyl group, while 2-pyridyl substituted compounds were substantially less active. Inhibition of the 11β-hydroxylase system is a property of numerous pyridine compounds, whereas the inhibitory activity of 17α-hydroxylase is more structure specific. The procedure of pharmacologic screening and evaluation of

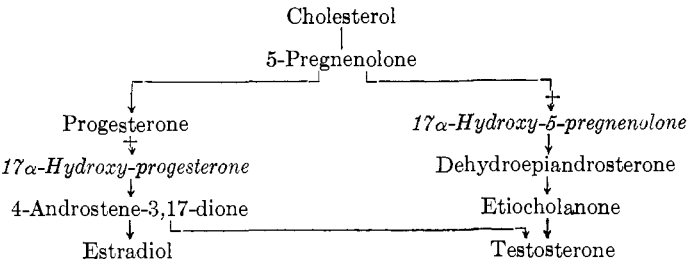


Fig. 2.—Inhibition of the biosynthesis of testosterone and estradiol by 17α-hydroxylase inhibitors.

several new compounds capable of blocking the 17α-hydroxylase system has been described recently by Chart, *et al.*[4]

Among the compounds reported herein the tetralones (VII–XII) possessed the highest inhibitory activity, and all of them blocked the 17α-hydroxylase system. The indanone (XIII) and benzosuberone (XIV) were less potent, while the intermediate nitriles (V) and acids (VI) were only weakly active. Substitution in the benzenoid part of tetralone (VII) did not improve the activity with the exception of tetralone (IX) which appears to be our most potent 17α-hydroxylase inhibitor.

The study of structure-activity relationships became more intriguing with the observation that 17α-hydroxylase inhibition of tetralone (VII) was changed to 11β-hydroxylase inhibition upon conversion of the carbonyl group to a secondary or tertiary hydroxyl group (XV, XXI).

The latter compounds then could be reconverted to 17α-hydroxylase inhibitors by means of dehydration (XVII, XVIII) and aromatization (XIX).

The cyclized pinacolone (XX) and the unsaturated substance (XXII) derived from (XX) possess a new type of inhibitory activity.[5]

Discussion.—The new 17α-hydroxylase inhibitors may be regarded as adrenal cortical and gonadal inhibitors, because they block the two known routes in the biosynthesis of testosterone and estradiol, respectively, as illustrated in Fig. 2.

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(5) Both substances (XX and XXII) caused a decrease in the plasma concentration of compounds F, B, and S and an increase in that of DOC (see Fig. 1). This finding suggests that these compounds are able to block both the 11β- and the 17α-hydroxylase systems. However, at low doses (1 and 5 mg./kg. intravenously in the dog) substance XXII exhibited a different activity; it caused inhibition of the biosynthesis of compound F concomitant with the accumulation of compounds B, S and DOC.

Dr. G. deStevens for his helpful comments. Their thanks also are due to Mr. L. Dorfman and his staff for the analytical and spectral data.

Experimental

Melting and boiling points are uncorrected.

General Procedure: Synthesis of Compounds Listed in Table I. A. Substituted 3-Pyridylacetonitriles (V).—A solution of the monosodium salt of 3-pyridylacetonitrile was prepared by addition of sodium hydride (53% mineral oil suspension, 4.65 g., 0.1 mole) to a cooled and stirred mixture (ice bath) of 3-pyridylacetonitrile (11.8 g., 0.1 mole) and dimethylformamide (70 ml.). After cessation of hydrogen evolution the correspondingly substituted (2-bromoethyl)-benzene (0.1 mole) in toluene (50 ml.) was added dropwise to the organic salt with stirring. The clear yellow solution was allowed to stand at room temperature for 15–20 hr. The precipitated sodium bromide was filtered off and the clear filtrate concentrated under reduced pressure to approximately 30–50 ml. Water was added to the oily residue and the product taken up in ether. The ethereal solution was extracted 3 times with 2 *N* hydrochloric acid. The acidic extracts were neutralized and the liberated base was extracted 3 times with ether. The combined extracts were washed with a saturated solution of sodium chloride, dried over anhydrous sodium sulfate and evaporated to dryness. The residual oily product was fractionated in high vacuum.

The following two nitriles were similarly prepared from 3-pyridylacetonitrile, and 1-chloro-2-methylphenylpropane and 1-chloro-3-phenylpropane, respectively:

4-Methyl-3-phenyl-2-(3-pyridyl)valeronitrile, m.p. 96–97°, yield 36%.

Anal. Calcd. for $C_{17}H_{18}N_2$: C, 81.56; H, 7.25. Found: C, 81.34; H, 7.33.

5-Phenyl-2-(3-pyridyl)valeronitrile, b.p. 145–152° (0.04 mm.), yield 46%.

Anal Calcd. for $C_{16}H_{16}N_2$: C, 81.32; H, 6.83. Found: C, 81.56; H, 6.97.

B. Substituted 3-Pyridylacetic Acids (VI).—A mixture of nitrile (V, 0.05–0.08 mole), ethanol (60 ml.) and sodium hydroxide (30 g.) in water (30 ml.) was heated under reflux for 60 hr. The ethanol was exchanged for water and the desired acid was liberated with excess acetic acid. The free acid was extracted 3–6 times with ethyl acetate. The combined extracts were treated as in step A. The crude acids were recrystallized from benzene and hexane or ethanol and water. The following two acids were prepared similarly:

4-Methyl-3-phenyl-2-(3-pyridyl)valeric acid, m.p. 197–198°, yield 83%.

Anal. Calcd. for $C_{17}H_{19}NO_2$: C, 75.81; H, 7.11; N, 5.20. Found: C, 75.92; H, 7.16; H, 5.33.

5-Phenyl-2-(3-pyridyl)valeric acid, m.p. 114–116°, yield 42%.

Anal. Calcd. for $C_{16}H_{17}NO_2$: C, 75.27; H, 6.71; N, 5.49. Found: C, 75.69; H, 6.86; N, 5.52.

C. Substituted 3-(1,2,3,4-Tetrahydro-1-oxo-2-naphthyl)pyridines (VII–XII).—Polyphosphoric acid (Victor Chem. Co., 5 times the weight of the acid to be cyclized) was preheated to 90–95°. The crystalline acid was added in one portion and stirred into the polyphosphoric acid with a thermometer. The inside temperature of the reaction mixture was raised to 105–110° (in the case of acid VI (R = *p*-Cl) to 150–155°) and maintained in this range for 0.5 hr. The hot reaction mixture was poured into ice water and the pH was adjusted to about 8 with aqueous sodium hydroxide and sodium carbonate solutions. The tetralones

TABLE I

2-(3-PYRIDYL)-1-TETRALONES AND INTERMEDIATES

No.	R	Yield, %	M.p., or b.p. °C. (mm.)	Empirical formula	Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
)	H	60	147–150 (0.01)	$C_{15}H_{14}N_2$	81.05	6.35	12.60	81.00	6.46	12.48
V	*m*-Cl	61	160–162 (0.05)	$C_{15}H_{13}ClN_2$	70.17	5.10	10.91	69.84	5.23	11.10
)	*p*-Cl	58	168–175 (0.05)	$C_{15}H_{13}ClN_2$	70.17	5.10	10.91	70.17	5.36	10.73
)	*m*-OCH_3	60	160–163 (0.04)	$C_{16}H_{16}N_2O$	76.16	6.39	11.10	76.32	6.51	11.13
)	H	86	110–112	$C_{15}H_{15}NO_2$	74.66	6.27	5.81	74.40	6.17	6.03
VI	*m*-Cl	55	147–148	$C_{15}H_{14}ClNO_2$	65.34	5.12	5.08	65.39	4.99	5.06
)	*p*-Cl	75	149–140	$C_{15}H_{14}ClNO_2$	65.34	5.12	5.08	65.27	5.30	4.99
)	*m*-OCH_3	64	93–94	$C_{76}H_{17}NO_3$	70.83	6.32	5.16	70.81	6.41	5.13
VII[a]	H	87	79–80	$C_{15}H_{13}NO$	80.69	5.87	6.27	80.44	5.81	5.45
VIII	6-Cl	51	99–100	$C_{15}H_{12}ClNO$	70.08	4.70	5.44	70.11	4.74	5.27
IX[b]	7-Cl	86	95–96	$C_{15}H_{12}ClNO$	70.08	4.70	5.44	69.88	4.65	5.41
X	8-Cl	6.5	142–144	$C_{15}H_{12}ClNO$	70.08	4.70	5.44	69.99	4.84	5.74
XI	6-OCH_3	55	117–118	$C_{16}H_{15}NO_2$	75.87	5.97	5.53	75.58	6.12	5.72
XII[c]	6-OH	62	212–222	$C_{15}H_{13}NO_2$	75.30	5.48	5.85	75.15	5.64	6.08

[a] Su-9055. [b] Su-10603. [c] Prepared by heating XI in 48% HBr for 5 hr.

were extracted 3 times with ethyl acetate. The combined extracts were treated as under A. The products were distilled in high vacuum and crystallized from benzene and pentane.

The hydrochloride salt of VII melted at 226–228°.

Anal. Calcd. for $C_{15}H_{14}ClNO$: C, 69.36; H, 5.43. Found: C, 69.20; H, 5.4.

The oxime of tetralone VII melted at 180–182° (from ethanol and water).

Anal. Calcd. for $C_{15}H_{14}N_2O$: C, 75.60; H, 5.92; N, 11.76. Found: C, 75.86; H, 5.94; N, 11.84.

3-(3-Methyl-1-oxo-2-indanyl)pyridine (XIII), b.p. 125–130° (0.1 mm.), yield 73%.

Anal. Calcd. for $C_{17}H_{17}NO$: C, 81.24; H, 6.82; N, 5.57. Found: C, 80.97; H, 6.80; N, 5.72.

3-(6,7,8,9-Tetrahydro-5-oxo-6-benzocycloheptyl)pyridine (XIV), b.p. 138–140° (0.04 mm.), yield 59%.

Anal. Calcd. for $C_{16}H_{15}NO$: C, 80.98; H, 6.37. Found: C, 80.87; H, 6.42.

Oxime of compound XIV, m.p. 172–174°.

Anal. Calcd. for $C_{16}H_{16}N_2O$: C, 76.16; H, 6.39; N, 11.10. Found: C, 75.89; H, 6.47; N, 10.89.

Separation of Tetralones VIII and X.—Cyclization of acid VI (*m*-Cl, 8.7 g.) in polyphosphoric acid (43.5 g.) as described in procedure C afforded 7.2 g. of crude product. Upon crystallization from ethanol and water 2.0 g. of colorless crystals (VIII) was obtained, m.p. 99–100°. The filtrate was evaporated to dryness and the residue (5.2 g.) was chromatographed on aluminum oxide (Woelm, neutral, activity grade 3, 160 g.). Mixtures of benzene and hexane 1:1, 6:4 and 7:3 eluted 2.2 g. more of compound VIII, m.p. 99–100°. Further elution of the aluminum oxide column with mixtures of benzene and hexane 8:2, 9:1 and benzene alone afforded fractions which melted at 88–140°. They were combined, recrystallized from benzene and pentane, distilled at 190–198° (0.08 mm.) and finally recrystallized from ethanol to give X, m.p. 142–144°.

3-(1,2,3,4-Tetrahydro-1-hydroxy-2-naphthyl)pyridine (XV).—A solution of VII (10.0 g.) in 50 ml. of methanol was stirred and cooled in an ice bath while sodium borohydride (3.0 g.) was added in portions. After completion of the addition of the reducing agent (15 min.) water was added. The colorless crystalline precipitate was collected, washed twice with water and dried (9.6 g.). Recrystallization from ethanol and water yielded 9.2 g. of product, m.p. 135–145°. On repeated recrystallizations from ethanol and water a higher melting form (a) m.p. 153–155°, and a smaller amount of a lower melting form (b) m.p. 130–132° were isolated.

Anal. Calcd. for $C_{15}H_{15}NO$: C, 79.97; H, 6.71; N, 6.22. Found: (a) C, 79.76; H, 6.74; N, 6.13; (b) C, 80.14; H, 6.73; N, 6.08.

3-(3,4-Dihydro-2-naphthyl)pyridine (XVII).—The secondary alcohol XV (9.2 g.) was heated under reflux in concd. hydrochloric acid for 1 hr. The free base appeared as an oil after neutralization with aqueous sodium hydroxide and was extracted 3 times with ether. The ethereal extracts yielded the product which was distilled at 125–130° (0.1 mm.). The colorless distillate (8.0 g.) crystallized on standing. After recrystallization from hexane and pentane the melting point was 33–34°.

Anal. Calcd. for $C_{15}H_{13}N$: C, 86.92; H, 6.32; N, 6.76. Found: C, 86.63; H, 6.33; N, 6.88; λ_{max} 306–312 mμ, ϵ = 8,110 (ethanol).

3-(2-Naphthyl)pyridine (XIX).—The unsaturated compound XVII (1.6 g.) was mixed with 20% palladium charcoal catalyst (0.5 g.) and the mixture was heated in a test tube to 180–225° (bath temperature) for 20 min. The product was taken up in chloroform, the catalyst filtered off and the filtrate evaporated to dryness. The solid residue triturated with a mixture of ether and pentane (1:10) to yield 1.28 g. of the product, m.p. 99–101°. A small amount of the product was recrystallized for analysis from hexane and pentane, m.p. 102–103°.

Anal. Calcd. for $C_{15}H_{11}N$: C, 87.77; H, 5.40; N, 6.82. Found: C, 87.67; H, 5.50; N, 6.77.

3-(1,2,3,4-Tetrahydro-1-hydroxy-1-methyl-2-naphthyl)pyridine (XVI).—To a Grignard reagent prepared from methyl iodide (4.3 g.) and magnesium (0.75 g.) in 50 ml. of ether a solution of tetralone VII (2.0 g.) in 50 ml. of benzene was added dropwise with stirring. The reaction mixture was heated under reflux for 5 hr. and allowed to stand at room temperature for 15 hr. The Grignard complex was hydrolyzed with aqueous ammonium chloride solution and the product was extracted with ethyl acetate. Repeated crystallizations of the crude product from ethanol and water afforded a higher and a lower melting fraction, m.p. 182–191° (1.57 g.) and m.p. 145–155°, respectively. The pure forms melted at 196–198° and 167–169°. An admixture of the two forms melted at 167–169°.

Anal. Calcd. for $C_{16}H_{17}NO$: C, 80.30; H, 7.16; N, 5.85. Found: high melting form C, 80.31; H, 7.16; N, 5.90; low melting form C, 79.98; H, 7.44; N, 5.98.

3-(1-Methyl-3,4-dihydro-2-naphthyl)pyridine (XVIII).—The tertiary alcohol XVI (300 mg.) was heated under reflux in 5 ml. of concd. hydrochloric acid for 1 hr. The dehydrated product was isolated in the same fashion as XVII, b.p. 120–125° (0.07 mm.), yield, 260 mg., λ_{max} 218–224 mμ, ε 7,890.

Anal. Calcd. for $C_{16}H_{15}N$: C, 86.84; H, 6.83; N, 6.33. Found: C, 86.77; H, 6.75; N, 6.24.

Attempts to obtain XVIII in a crystalline form failed. Therefore, the above product (200 mg.) was converted to its picrate in ethanol. The crude salt (340 mg.) melted at 180.5–182°. After recrystallization from ethanol, m.p. 182–183°; yield 300 mg.

Anal. Calcd. for $C_{22}H_{18}N_4O_7$: C, 58.66; H, 4.03. Found: C, 58.36; H, 4.02.

The picrate was suspended in 20 ml. of 1 *N* aqueous sodium carbonate solution and the liberated base was extracted 3 times with ether. The combined extracts were washed with small volumes of saturated aqueous sodium bicarbonate solutions until the yellow color of the organic layer faded. Evaporation of the dried ethereal extract afforded the parent base which was distilled at 120–125° (0.08 mm.). The distillate proved to be analytically pure base (XVIII). The infrared and ultraviolet spectra of this specimen and those of the base before the conversion to the picrate were superimposable.

3-(1,2,3,4-Tetrahydro-2-methyl-1-oxo-2-naphthyl)pyridine (XX).—Tetralone VII (11.2 g.) was dissolved in dimethylformamide, and sodium hydride (53% mineral oil suspension, 2.4 g.) was added in portions with stirring. After hydrogen evolution ceased (20 min.) methyl iodide (7.1 g.) in benzene (50 ml.) was added dropwise to the stirred amber solution of the organic salt. The reaction mixture was allowed to stand at room temperature for 15 hr. Addition of ether to the reaction mixture caused the precipitation of the addition compound of sodium iodide and dimethylformamide. The precipitate was filtered off and the filtrate concentrated to approximately 30 ml. The residual oil was taken up in 2 *N*

hydrochloric acid (100 ml.), and the resultant acidic solution was extracted twice with pentane. These extracts were rejected. The clear aqueous layer was made basic and extracted 5 times with ether. The combined extracts were dried over anhydrous sodium sulfate, filtered and evaporated to dryness. The oily residue was distilled, b.p. 135–140° (0.01 mm.); yield, 10.9 g.

Anal. Calcd. for $C_{16}H_{15}NO$: C, 80.98; H, 6.36; N, 5.90. Found: C, 80.73; H, 6.52; N, 5.92.

3-(1,2,3,4-Tetrahydro-1,2-dimethyl-1-hydroxy-2-naphthyl)pyridine (XXI).— To a Grignard reagent prepared from methyl iodide (12.4 g.) and magnesium (2.43 g.) in 50 ml. of ether, a solution of tetralone XX (6.0 g.) in 25 ml. of benzene was added dropwise. The reaction mixture was stirred and heated under reflux for 4 hr., and allowed to stand at room temperature for 15 hr. The Grignard complex was decomposed with aqueous ammonium chloride solution. The product was extracted 5 times with ethyl acetate. The combined, dried extracts yielded 5.2 g. of the crude product. Three subsequent crystallizations from ethanol and water afforded the pure high melting form, m.p. 190.5–192°. The low melting form was not isolated.

Anal. Calcd. for $C_{17}H_{19}NO$; C, 80.57; H, 7.56; N, 5.53. Found: C, 80.64; H, 7.54; N, 5.52.

The bulk of the product (3.9 g.) melted at 135–148° and was used as such for the subsequent dehydration.

3-(1,2,3,4-Tetrahydro-1-methylene-2-methyl-2-naphthyl)pyridine (XXII).— Crude tertiary carbinol (XXI) (1.0 g.) was heated under reflux in 15 ml. of concd. hydrochloric acid for 1 hr. The product was isolated in a fashion similar to XVII and XVIII, b.p. 115–120° (0.02 mm.). Upon storage at room temperature the compound crystallized, m.p. 52–53° (from pentane), λ_{max} 247–248 mμ, ε 12,700 (ethanol).

Anal. Calcd. for $C_{17}H_{17}N$: C, 86.77; H, 7.28; N, 5.95. Found: C, 86.47; H, 7.16; N, 6.08.