[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY]

Steroidal Hormone Analogs. X. 6-(1,2,3,4-Tetrahydro-2-naphthyl)-2(1*H*)-pyridones[1]

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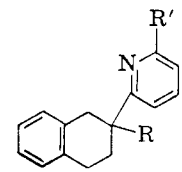
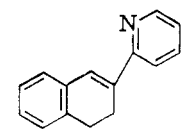
The reaction of 6-methoxy-2-tetralone with 6-ethoxy-2-pyridyllithium gave the alcohol III which was converted to a mixture of vinylpyridines. Hydrogenation of this mixture afforded 6-ethoxy-2-(6-methoxy-1,2,3,4-tetrahydro-2-naphthyl)-pyridine (VI). Hydrolysis of VI gave 6-(6-hydroxy-1,2,3,4-tetrahydro-2-naphthyl)-2(1*H*)-pyridone (VII) which on methylation yielded 2-(6-methoxy-1,2,3,4-tetrahydro-2-naphthyl)-6-methoxypyridine (IX), 6-(6-methoxy-1,2,3,4-tetrahydro-2-naphthyl)-2(1*H*)-pyridone (VIII), and 6-(6-methoxy-1,2,3,4-tetrahydro-2-naphthyl)-1-methyl-2(1*H*)-pyridone (Xa). Hydrolysis of the latter compound gave 6-(6-hydroxy-1,2,3,4-tetrahydro-2-naphthyl)-1-methyl-2(1*H*)-pyridone (Xb).

In an earlier report[3] from these laboratories we described some nitrogen-containing tricyclic analogs of 18-nor-D-homoestrone and 18-nor-D-homoestradiol having anti-inflammatory activity. This pharmacological finding prompted us to prepare some related tricyclic analogs having a pyridone ring D. The preparation of these 6-substituted 2-(1*H*)-pyridones is the subject of this paper.

The reaction of 2-pyridyllithium with 2-tetralone afforded 2 - (2 - hydroxy - 1,2,3,4 - tetrahydro - 2-naphthyl)pyridine (Ia).[4] This carbinol could also be prepared by refluxing a mixture of 2-picolinic acid and 2-tetralone in *p*-cymene (Hammick reaction)[5]; however, this method gave poor yields. Treatment of 2-(2-hydroxy-1,2,3,4-tetrahydro-2-naphthyl)pyridine (Ia) with thionyl chloride followed by treatment of the product with methanolic potassium hydroxide[6] gave an excellent yield of 2 - (3,4 - dihydro - 2 - naphthyl)pyridine (II).[7] The structure of II is based on its ultraviolet spectrum which exhibits an absorption band at 320 mμ, characteristic of the fully conjugated system. The lack of any other absorption band between 241 and 320 mμ indicates the absence of any appreciable amount of the isomeric 2-(1,4-dihydro-2-naphthyl)pyridine.[8] The selective hydrogenation of II using palladium-on-charcoal proceeded smoothly and gave 2-(1,2,3,4-tetrahydro-2-naphthyl)pyridine (Ib).



Ia. R = OH, R' = H
b. R = R' = H
c. R = OH, R' = OC_2H_5



II

The desired 6-substituted 2-pyridones were prepared using 2-bromo-6-ethyoxypyridine[9] in a reaction sequence similar to that described above for the preparation of Ib. Metallation of 2-bromo-6-ethoxypyridine with *n*-butyllithium followed by the addition of 2-tetralone or 6-methoxy-2-tetralone to the organometallic reagent gave the corresponding ethoxypyridyl carbinols, Ic and III, respectively. Dehydration of 6-ethoxy-2-(2-hydroxy-6-methoxy - 1,2,3,4 - tetrahydro - 2-naphthyl)pyridine

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(3) N. A. Nelson, R. S. P. Hsi, J. M. Schuck, and L. D. Kahn, *J. Am. Chem. Soc.*, 82, 2573 (1960).

(4) Pyridine *N*-oxides have been observed to rearrange under the influence of phosphorus oxychloride to 2-chloropyridines [see, for example, (a) E. Ochiai and M. Ikehara, *Pharm. Bull. Japan*, 2, 72 (1954) and (b) M. Ikehara, *Pharm. Bull. Japan*, 2, 111 (1954)]. This fact, combined with the knowledge of the dehydrating power of this reagent led us to investigate the action of phosphorus oxychloride on the oxide of Ia in the hope of obtaining a 2-chloro-6-dihydronaphthylpyridine, which on hydrolysis would give the corresponding 2-pyridone. We therefore converted the substituted pyridine Ia to 2-(2-hydroxy-1,2,3,4-tetrahydro-2-naphthyl)pyridine *N*-oxide and treated the oxide with phosphorus oxychloride. A mixture of products was formed from which 2-(2-naphthyl)pyridine was the only product isolated.

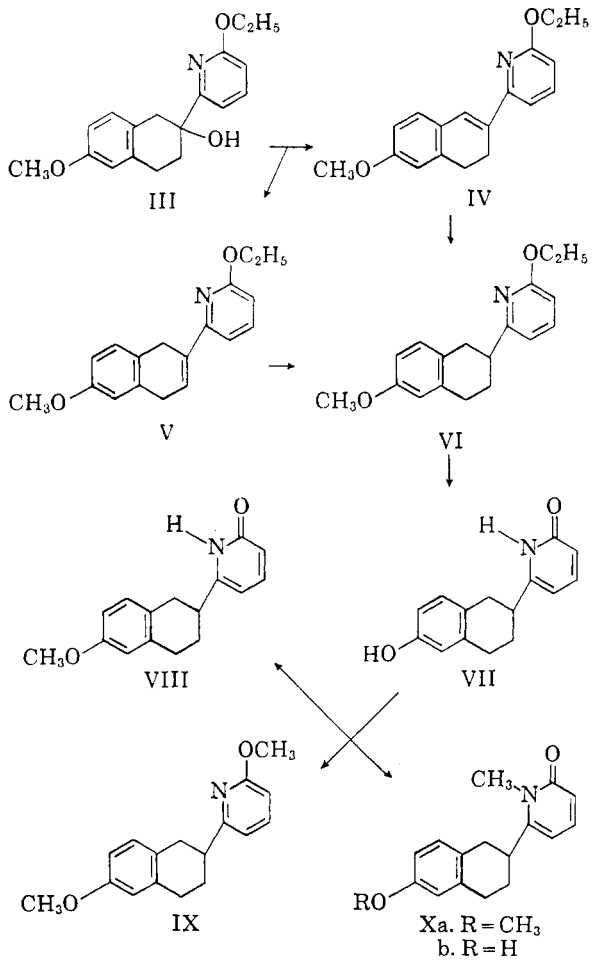
(5) H. Rapoport and E. J. Volcheck, Jr., *J. Am. Chem. Soc.*, 78, 2451 (1956), and references contained therein.

(6) H. A. Iddles, E. H. Lang, and D. C. Gregg, *J. Am. Chem. Soc.*, 59, 1945 (1937).

(7) W. E. Doering and R. A. N. Weil [*J. Am. Chem. Soc.*, 69, 2461 (1947)] have reported that 2- and 4-vinylpyridines undergo Michael-type additions with various nucleophilic reagents. From the reaction of 2-vinylpyridine with sodiomalonic ester, followed by hydrolysis, decarboxylation, and hydrogenation of the intermediate, these workers obtained α-norlupinone. As a matter of interest, we investigated the possibility of converting 2-(3,4-dihydro-2-naphthyl)pyridine (II) to an azachrysene using the same sequence of reactions. However, attempted Michael additions of malonic ester to II under a wide variety of experimental conditions gave only recovered II. Similar results were obtained in the reaction of II with the Reformatsky reagent derived from ethyl bromoacetate and in attempted Michael additions to the methiodide of II.

(8) The ultraviolet spectrum of this isomer should exhibit absorption bands between about 250–300 mμ characteristic of the isolated chromophores.

(9) H. J. den Hertog and J. P. Wibaut, *Rec. trav. chim.*, 55, 122 (1936).



(III), using the thionyl chloride–methanolic potassium hydroxide procedure described above, gave a mixture of 2-(3,4-dihydro-6-methoxy-2-naphthyl)-6-ethoxypyridine (IV) and 2-(1,4-dihydro-6-methoxy-2-naphthyl)-6-ethoxypyridine (V) in a ratio of about 3.5 to 1, respectively. The structural assignment of the isomers IV and V is based on their ultraviolet spectra, the fully conjugated isomer IV showing more intense absorption and with its maximum at a longer wave length. An alternative structure for one of the isomers which should be considered is 2-(1,2-dihydro-6-methoxy-2-naphthyl)-6-ethoxypyridine. This substance could arise easily through a base-catalyzed migration of the olefinic double bond of V from the Δ^2-position of the dihydronaphthylene group to the alternative conjugated Δ^3- position. This alternative structure can be ruled out on the basis that it contains two isolated chromophores, neither of which would be expected to absorb strongly above 280 mμ. Both of the isomers exhibited an intense absorption band at longer wave lengths.

The hydrogenation of 2-(3,4-dihydro-6-methoxy-2-naphthyl)-6-ethoxypyridine (IV) or 2-(1,4-dihydro - 6 - methoxy - 2 - naphthyl) - 6 - ethoxypyridine (V) using 10% palladium-on-carbon catalyst gave 6-ethoxy-2-(6-methoxy-1,2,3,4-tetrahydro-2-naphthyl)pyridine (VI) isolated as the perchlorate derivative. The conversion of 6-ethoxy-2-(2-hydroxy-6-methoxy-1,2,3,4-tetrahydro-2-naphthyl)pyridine (III) to 6-ethoxy-2-(6-methoxy - 1,2,3,4 - tetrahydro - 2 - naphthyl)pyridine (VI) was accomplished in 87–90% yields when the intermediates IV and V were not isolated. Treatment of VI with either refluxing 48% hydrobromic acid or refluxing 6*N* hydrochloric acid resulted in cleavage of both ether functions and gave 6-(6-hydroxy - 1,2,3,4 - tetrahydro - 2 - naphthyl)-2(1*H*)-pyridone (VII) in excellent yields.

Methylation of the sodium salt of the pyridone VII with methyl sulfate under relatively mild conditions afforded 64% of 6-(6-methoxy-1,2,3,4-tetrahydro - 2 - naphthyl) - 2(1*H*) - pyridone (VIII), illustrating the difference in reactivity between the phenolic and pyridone portions of this substance. Under more vigorous conditions, the methylation of VII gave a mixture of products which was easily separated by chromatography on alumina giving 29% of 2-(6-methoxy-1,2,3,4-tetrahydro - 2 - naphthyl) - 6 - methoxypyridine (IX), isolated as its perchlorate derivative, 48% of 6 - (6 - methoxy - 1,2,3,4 - tetrahydro - 2-naphthyl) - 1 - methyl - 2(1*H*) - pyridone (Xa), and 19% of 6 - (6 - methoxy - 1,2,3,4 - tetrahydro-2 - naphthyl) - 2(1*H*) - pyridone (VIII). Finally, treatment of the pyridone Xa with refluxing 48% hydrobromic acid gave an excellent yield of 6-(6 - hydroxy - 1,2,3,4 - tetrahydro - 2 - naphthyl)-1-methyl-2(1*H*)-pyridone (Xb).

Physiological testing. Several of the compounds prepared were evaluated in the Cancer Chemotherapy National Service Center bioassay program. In the androgenic and myogenic assay (seminal vesicle, levator ani, and ventral prostate weight gain) the *N*-oxide of Ia, the perchlorate of III and compounds VII and Xb showed no appreciable activity (less than 5%). The *N*-oxide of Ia and compounds VII, VIII, Xa, and Xb showed less than 5% uterotropic activity at a total dose of 1.6 μg., however, compounds VII and Xb did cause an increase in the weight of the uterus at a 10 μg. total dose which was approximately equivalent to 0.32 μg. of estrone standard. At higher dose levels, the phenolic pyridone VII showed up to 29% estrogen inhibition, however, the dose-response was not linear. When compared to cortisol in the thymolytic and anti-inflammatory assay, the *N*-oxide of Ia and compound VII showed no appreciable activity (less than 5%).

EXPERIMENTAL[10]

2-(2-Hydroxy-1,2,3,4-tetrahydro-2-naphthyl)pyridine (Ia). A solution of 63.2 g. of 2-bromopyridine in 100 ml. of anhydrous ether was added over a 15-min. period to a cold (−18°) solution of *n*-butyllithium (prepared from 54.9 g. of *n*-butyl bromide and 6.9 g. of lithium wire) in 350 ml. of ether, and the red solution was stirred under a nitrogen atmosphere for 20 min.[11] To the cold solution of 2-pyridyl-

lithium was added over a 30-min. period 61.4 g. of 2-tetralone[12] in 100 ml. of ether. The mixture was stirred at −18° for 30 min., and the temperature was then allowed to rise to 0° when the mixture was hydrolyzed with an ice-cold saturated solution of ammonium chloride. The ether layer was extracted with 10% hydrochloric acid, and the acidic extract was made alkaline with 20% sodium hydroxide solution. The product was extracted with ether and distilled *in vacuo* giving 29.7 g. of an oil, b.p. 153–156° (0.69 mm.) which on crystallization from ether–ligroin gave 25.5 g. of 2-(2-hydroxy-1,2,3,4-tetrahydro-2-naphthyl)pyridine, m.p. 78–79°. The analytical sample of Ia, prepared using the Hammick reaction,[5] had m.p. 79°, λ_{max} 261 mμ (4370) with inflections at 225 (3925), 267 (3340), and 272 mμ (1535).

Anal. Calcd. for $C_{15}H_{15}NO$: C, 79.97; H, 6.71. Found: C, 79.79; H, 6.88.

2-(2-Hydroxy-1,2,3,4-tetrahydro-2-naphthyl)pyridine picrate was prepared in the usual manner and crystallized from ethanol, m.p. 141–141.6°. Rapid cooling of the ethanolic solution afforded a second crystalline modification, m.p. 153.5–154.5° (mixed m.p. with the above sample, 153.5–154.5°).

Anal. Calcd. for $C_{21}H_{18}N_4O_8$: C, 55.51; H, 3.99. Found: C, 55.50; H, 4.10.

2-(3,4-Dihydro-2-naphthyl)pyridine (II). Thionyl chloride (59.5 g.) was added slowly with stirring and ice-cooling to 30 g. of 2-(2-hydroxy-1,2,3,4-tetrahydro-2-naphthyl)pyridine, and the resulting mixture was then refluxed for 1 hr. Saturated methanolic potassium hydroxide (250 ml.) was added cautiously over a period of 2 hr., and the resulting solution was refluxed for 1 hr. The mixture was cooled, diluted with 400 ml. of 10% sodium hydroxide solution, and extracted with ether. The dried ether extract was distilled *in vacuo* to give 25.4 g. of a pale yellow oil, b.p. 145–148° (0.45 mm.) n_D^{25} 1.6635. The analytical sample of II had b.p. 118–120° (0.17 mm.) n_D^{23} 1.6660, λ_{max} 228 (10,550), 235 (12,520), 241 (11,680), and 320 mμ (14,380). The possibility that this sample contains a small amount of the less conjugated isomer, 2-(1,4-dihydro-2-naphthyl)pyridine, cannot be excluded.

Anal. Calcd. for $C_{15}H_{13}N$: C, 86.92; H, 6.32. Found: C, 87.28; H, 6.60.

2-(3,4-Dihydro-2-naphthyl)pyridine picrate was recrystallized from alcohol and had m.p. 161–161.5°.

Anal. Calcd. for $C_{21}H_{16}N_4O_7$: C, 57.80: H, 3.70. Found: C, 57.89; H, 3.75.

2-(3,4-Dihydro-2-naphthyl)pyridine methiodide was prepared in the usual way in 94% yield, m.p. 164.5–167.5°. The analytical sample was recrystallized from ethanol–ether and had m.p. 169–169.5°, λ_{max} 217 (32,900), 263 (9040), and 337 mμ (5480).

Anal. Calcd. for $C_{16}H_{16}IN$: C, 55.03; H, 4.62. Found: C, 55.01; H, 4.69.

2-(2-Hydroxy-1,2,3,4-tetrahydro-2-naphthyl)pyridine N-oxide. To 22.5 g. of 2-(2-hydroxy-1,2,3,4-tetrahydro-2-naphthyl)pyridine in 100 ml. of glacial acetic acid was added 10.0 ml. of 30% hydrogen peroxide, and the resulting solution was heated on a steam bath for 2 hr. The residue obtained by removing the acetic acid *in vacuo* was dissolved in chloroform and the chloroform solution was washed with sodium bicarbonate solution, dried, and concentrated. The residue was crystallized from acetone–ligroin to give 16.9 g. (70%) of platelets, m.p. 115–116.5°. Three recrystallizations of this material from ethanol–water gave white needles of the hemihydrate of 2-(2-hydroxy-1,2,3,4-tetrahydro-2-naphthyl)pyridine *N*-oxide, m.p. 72.5–73°.

Anal. Calcd. for $C_{15}H_{15}NO_2 \cdot 1/2\ H_2O$: C, 71.98; H, 6.44; N, 5.60. Found: C, 72.30; H, 6.87; N, 5.58.

When the hemihydrate was dried *in vacuo* at 70°, the anhydrous form of 2-(2-hydroxy-1,2,3,4-tetrahydro-2-naphthyl)pyridine *N*-oxide was obtained, m.p. 119.5–120.5° $\gamma_{max}^{CCl_4}$ 3250 (m, OH), λ_{max} 216 (29,000), and 266 mμ (10,600).

Anal. Calcd. for $C_{15}H_{15}NO_2$: C, 74.66; H, 6.27; N, 5.81. Found: C, 74.55; H, 6.57; N, 5.75.

2-(2-Naphthyl)pyridine. Treatment of 2-(2-hydroxy-1,2,3,-4-tetrahydro-2-naphthyl)pyridine *N*-oxide with phosphorus oxychloride under the conditions described by Ikehara[4b] gave a yellow oil which was converted to *2-(2-naphthyl)-pyridine picrate*, m.p. 175–175.5° dec.

Anal. Calcd. for $C_{21}H_{14}N_4O_7$: C, 58.07; H, 3.25; N, 12.90. Found: C, 57.74; H, 3.08; N, 12.89.

Regeneration of the free base from the picrate gave a white solid, m.p. 71–72°, which on recrystallization from ether–ligroin afforded an analytical sample of 2-(2-naphthyl)-pyridine, m.p. 78–78.5°, λ_{max} 211 (30,700), 247 (42,200), 268 (15,500), 277 (13,350), and 292 mμ (15,200). The infrared spectrum of the crude product (yellow oil above) and the analytical sample showed a number of differences indicating that the former was a mixture.

Anal. Calcd. for $C_{15}H_{11}N$: C, 87.77; H, 5.40. Found: C, 87.52; H, 5.30.

2-(1,2,3,4-Tetrahydro-2-naphthyl)pyridine (Ib). One gram of freshly distilled 2-(3,4-dihydro-2-naphthyl)pyridine in 25 ml. of ethanol was hydrogenated at atmospheric pressure and room temperature using a 10% palladium-on-charcoal catalyst. The hydrogen uptake (1 mol. equiv.) ceased after 2 hr. at which time the catalyst was separated, and the product was converted to the picrate; yield 1.9 g. (88%), m.p. 135–136°. The analytical sample of *2-(1,2,3,4-tetrahydro-2-naphthyl)pyridine picrate* was crystallized from absolute ethanol, m.p. 137–138°.

Anal. Calcd. for $C_{21}H_{18}N_4O_7$: C, 57.53; H, 4.14; N, 12.78. Found: C, 57.32; H, 4.17; N, 12.77.

The free base was regenerated from the picrate in the usual manner to give an analytical sample of 2-(1,2,3,4-tetrahydro-2-naphthyl)pyridine, b.p. 115–120° (0.1 mm.), λ_{max} 255 (5820), 261.5 (5580), 268 (4460), and 295 mμ (920) with an inflection at 272.5 mμ (2230).

Anal. Calcd. for $C_{15}H_{15}N$: C, 86.08; H, 7.23; N, 6.69. Found: C, 86.05; H, 7.46; N, 6.58.

6-Ethoxy-2-(2-hydroxy-1,2,3,4-tetrahydro-2-naphthyl)-pyridine (Ic). Using the procedure for the preparation of Ia above, 20.2 g. of 2-bromo-6-ethoxypyridine[9] (containing about 10% of 2,6-diethoxypyridine)[13] in 100 ml. of ether was allowed to react with *n*-butyllithium (prepared from 20.6 g. of *n*-butyl bromide and 3.5 g. of lithium at −18°), and the resulting 6-ethoxy-2-pyridyllithium was treated with 21.9 g. of 2-tetralone in 100 ml. of ether. Work-up of the reaction mixture gave a residue which was distilled *in vacuo* to give 2.2 g. of material, b.p. 27° (1 mm.), and 6.6 g. (24%) of material, b.p. 155–160° (0.1 mm.), in addition to a center cut which was not investigated. Gas chromatography[10] of the low-boiling fraction indicated that it was 97% pure. The major component of the low-boiling fraction

(10) Melting points and boiling points are uncorrected. The infrared spectra were determined with a Baird (Model B) spectrophotometer fitted with a sodium chloride prism. Ultraviolet spectra were determined in 95% ethanol with a Cary recording spectrophotometer (Model 11 MS); molecular extinction coefficients are given. The microanalyses were performed by Dr. S. M. Nagy and his associates. Gas chromatographic analyses were obtained using a 6 mm. × 215 cm. column at 200° packed with approximately 20% Dow-Corning No. 550 silicone oil suspended on 50–80-mesh firebrick support. Helium at 10–15 p.s.i. was used as the carrier gas, and thermistors were employed for the detection of the sample peaks. Percentage compositions reported refer only to the relative areas observed for the different components.

(11) H. Gilman and S. M. Spatz, *J. Org. Chem.*, 16, 1485 (1951).

(12) A. J. Birch, *J. Chem. Soc.*, 430 (1944).

(13) This impurity was isolated by gas chromatography[10] and had m.p. 21.5° (reported[9] for 2,6-diethoxypyridine, m.p. 21.5°).

was isolated and converted to its picrate, m.p. 131–132° (lit.[14] m.p. 131–133° for the picrate of 2-ethoxypyridine).

6-Ethoxy-2-(2-hydroxy-1,2,3,4-tetrahydro-2-naphthyl)pyridine perchlorate was prepared in the usual manner from the higher boiling fraction and was recrystallized from absolute ethanol, m.p. 164–165°, λ_{max} 214 (16,950) and 273.5 mμ (7400).

Anal. Calcd. for $C_{17}H_{20}ClNO_6$: C, 55.21; H, 5.45; N, 3.79. Found: C, 55.27; H, 5.46; N, 3.72.

6-Ethoxy-2-(2-hydroxy-1,2,3,4-tetrahydro-2-naphthyl)-pyridine was regenerated from the perchlorate in the usual way and had b.p. 157° (0.12 mm.), λ_{max} 212 (17,600) and 273.5 mμ (7600) with inflections at 216 (17,200) and 270 mμ (6650).

Anal. Calcd. for $C_{17}H_{19}NO_2$: C, 75.81; H, 7.11; N, 5.20. Found: C, 75.50; H, 7.09; N, 5.22.

6-Ethoxy-2-(2-hydroxy-6-methoxy-1,2,3,4-tetrahydro-2-naphthyl)pyridine (III). Using the procedure for the preparation of Ia above, 11.0 g. of 90% 2-bromo-6-ethoxypyridine (containing about 10% of 2,6-diethoxypyridine)[13] in 35 ml. of anhydrous ether was allowed to react with *n*-butyllithium (prepared from 8.9 g. of *n*-butyl bromide and 1.04 g. of lithium), and the resulting 6-ethoxy-2-pyridyllithium was treated with 8.8 g. of 6-methoxy-2-tetralone[3] in 35 ml. of ether. Work-up of the reaction mixture gave material which was concentrated *in vacuo* to remove 2,6-diethoxypyridine and other low-boiling impurities, and the residue from the distillation was converted to its perchlorate derivative to give 7.1 g. (35%) of material, m.p. 168–169° dec. The analytical sample of *6-ethoxy-2-(2-hydroxy-6-methoxy-1,2,3,4-tetrahydro-2-naphthyl)pyridine perchlorate* was recrystallized from ethanol, m.p. 169–170° dec., λ_{max} 218 (12,250) and 277 mμ (7150).

Anal. Calcd. for $C_{18}H_{22}ClNO_7$: C, 54.04; H, 5.55; N, 3.50. Found: C, 54.04; H, 5.61; N, 3.58.

6-Ethoxy-2-(2-hydroxy-6-methoxy-1,2,3,4-tetrahydro-2-naphthyl)pyridine was regenerated from the perchlorate in the usual way to give a solid, m.p. 82–83°. The analytical sample was crystallized from ligroin, m.p. 89–90.5°, λ_{max} 218 (15,600) and 276 mμ (8480).

Anal. Calcd. for $C_{18}H_{21}NO_3$: C, 72.21; H, 7.07; N, 4.68. Found: C, 72.10; H, 7.09; N, 4.88.

Dehydration of 6-ethoxy-2-(2-hydroxy-6-methoxy-1,2,3,4-tetrahydro-2-naphthyl)pyridine (III). A solution of 4.0 g. of III and 15 ml. of thionyl chloride was heated rapidly to reflux and then stirred for 30 min. while it returned to room temperature. The mixture was cooled and rendered strongly alkaline by the cautious addition of methanolic potassium hydroxide. The solution was heated to reflux and stirred for 60 min. while it returned to room temperature. The mixture was diluted with ether and washed with water. The organic layer was dried and concentrated *in vacuo* to give 3.55 g. (94%) of a pale yellow oil. This oil was fractionally crystallized from ligroin to give 0.60 g. of material with m.p. 98–101° and 2.11 g. of material with m.p. 75–76.5°. Several recrystallizations of the high-melting isomer gave an analytical sample of *2-(1,4-dihydro-6-methoxy-2-naphthyl)-6-ethoxypyridine* (V), m.p. 105–106°, λ_{max} 240 (12,700), 291 (12,200), and 296 mμ (12,300) with inflections at 220 (16,000) and 325 mμ (3400).

Anal. Calcd. for $C_{18}H_{19}NO_2$: C, 76.84; H, 6.81; N, 4.98. Found: C, 76.90; H, 6.90; N, 5.26.

The lower melting isomer was recrystallized from ligroin to give an analytical sample of 2-(3,4-dihydro-6-methoxy-2-naphthyl)-6-ethoxypyridine (IV), m.p. 78.5° λ_{max} 240 (13,100) and 339 mμ (27,300).

Anal. Calcd. for $C_{18}H_{19}NO_2$: C, 76.84; H, 6.81; N, 4.98. Found: C, 76.93; H, 6.81; N, 5.14.

6-Ethoxy-2-(6-methoxy-1,2,3,4-tetrahydro-2-naphthyl)-pyridine (VI). A solution of 500 mg. of 2-(1,4-dihydro-6-methoxy-2-naphthyl)-6-ethoxypyridine (V) in 30 ml. of absolute ethanol was hydrogenated at atmospheric pressure and room temperature in the presence of 100 mg. of 10% palladium-on-charcoal. When the hydrogen uptake (106% of 1 mol. equiv.) ceased, the catalyst was separated and the solvent was removed *in vacuo* to give 480 mg. of an oil. This oil was converted to 6-ethoxy-2-(6-methoxy-1,2,3,4-tetrahydro-2-naphthyl)pyridine perchlorate which was crystallized from ethanol–ether, m.p. 162–162.5°, λ_{max} 218 (16,100) and 277 mμ (9060).

Anal. Calcd. for $C_{18}H_{22}ClNO_6$: C, 56.33; H, 5.78; N, 3.65. Found: C, 56.48; H, 5.86; N, 3.61.

The free base was regenerated from the perchlorate in the usual manner to give an analytical sample of 6-ethoxy-2-(6-methoxy-1,2,3,4-tetrahydro-2-naphthyl)pyridine, b.p. 160° (0.55 mm.), λ_{max} 217 (19,300), 277.5 (8970), and 317 mμ (452).

Anal. Calcd. for $C_{18}H_{21}NO_2$: C, 76.29; H, 7.47; N, 4.94. Found: C, 76.44; H, 7.68; N, 4.80.

Similarly, 500 mg. of 2-(3,4-dihydro-6-methoxy-2-naphthyl)-6-ethoxypyridine (IV) was hydrogenated as described above (uptake of hydrogen, 98% of 1 mol. equiv.) to give 500 mg. of an oil which was converted to its perchlorate derivative, m.p. 161.5–162.5°. A mixed melting point of this material with 6-ethoxy-2-(6-methoxy-1,2,3,4-tetrahydro-2-naphthyl)pyridine perchlorate described above showed no depression.

In subsequent work the mixture of the two isomers IV and V was hydrogenated directly to give 6-ethoxy-2-(6-methoxy-1,2,3,4-tetrahydro-2-naphthyl)pyridine in 87–90% yields from the starting alcohol III.

6-(6-Hydroxy-1,2,3,4-tetrahydro-2-naphthyl)-2-(1H)-pyridone (VII). A 5.45-g. sample of 6-ethoxy-2-(6-methoxy-1,2,3,4-tetrahydro-2-naphthyl)pyridine (VI) was refluxed with 125 ml. of 48% hydrobromic acid for 48 hr. The mixture was diluted with water, cooled, and the precipitated hydrobromide was collected on a filter. The precipitate was stirred with warm concd. ammonium hydroxide, and the resulting solid was collected on a filter and washed with water and acetone to give 4.35 g. (94%) of a greyish white powder, m.p. 298–299° dec. Recrystallization of this material from glacial acetic acid gave an analytical sample of VII, m.p. 300° dec., λ_{max} 224 (15,050) and 307 mμ (8870) with inflections at 294 (8000) and 344 mμ (2080).

Anal. Calcd. for $C_{15}H_{15}NO_2$: C, 74.66; H, 6.27; N, 5.81. Found: C, 74.50; H, 6.22; N, 5.91.

Methylation of 6-(6-hydroxy-1,2,3,4-tetrahydro-2-naphthyl)-2(1H)-pyridone (VII). A 1.1-g. sample of VII was dissolved in a solution of sodium ethoxide (prepared from 2.0 g. of sodium and 50 ml. of absolute ethanol), and the solution was refluxed for 6 hr. The solution was cooled in an ice bath while 15.2 g. of dimethyl sulfate was added over a period of 15 min., and the mixture was then refluxed for 36 hr. Dilute ammonium hydroxide was added to the cooled reaction mixture to decompose excess dimethyl sulfate, and the mixture was then concentrated *in vacuo*. The residue was dissolved in chloroform and the resulting solution was dried and concentrated *in vacuo*. The oily residue was chromatographed on Alcoa alumina (Brockmann activity III). Elution with hexane gave 350 mg. (29%) of 2-(6-methoxy-1,2,3,4 - tetrahydro - 2 - naphthyl) - 6 - methoxypyridine (IX) which was converted to its perchlorate and crystallized from ethanol, yield 410 mg., m.p. 167–168.5°. The analytical sample of *2-(6-methoxy-1,2,3,4-tetrahydro-2-naphthyl)-6-methoxypyridine perchlorate* was recrystallized from ethanol, m.p. 168.5–169.5°, λ_{max} 217 (17,300) and 276 mμ (9120).

Anal. Calcd. for $C_{17}H_{20}ClNO_6$: C, 55.21; H, 5.45. Found: C, 55.53; H, 5.46.

Further elution of the column with benzene gave 590 mg. (48%) of 6-(6-methoxy-1,2,3,4-tetrahydro-2-naphthyl)-1-methyl-2(1*H*)-pyridone (Xa) which was recrystallized from

(14) G. T. Newbold and F. S. Spring, *J. Chem. Soc.*, 1864 (1948).

benzene–ligroin, m.p. 144.5–145.5°, λ_{max} 229.5 (12,000), 289.5 (7120), and 310 mμ (9100).

Anal. Calcd. for $C_{17}H_{19}NO_2$: C, 75.81; H, 7.11; N, 5.20. Found: C, 75.64; H, 7.05; N, 5.22.

Further elution of the column with methanol gave 220 mg. (19%) of 6-(6-methoxy-1,2,3,4-tetrahydro-2-naphthyl)-2-(1*H*)-pyridone (VIII) which was recrystallized from 95% ethanol, m.p. 239–239.5°, λ_{max} 227 (13,820), 289 (8275), 306 (9350), and 361 mμ (605).

Anal. Calcd. for $C_{16}H_{17}NO_2$: C, 75.27; H, 6.71; N, 5.49. Found: C, 75.43; H, 6.70; N, 5.50.

The infrared spectra of the three methylation products are fully consistent with the structural assignments.

In a different methylation experiment a solution prepared from 500 mg. of 6-(6-hydroxy-1,2,3,4-tetrahydro-2-naphthyl)-2(1*H*)-pyridone, 75 mg. of sodium hydride, and 25 ml. of methanol was cooled and treated with 5 ml. of dimethyl sulfate, and the resulting mixture was refluxed for 2 hr. Work-up of the reaction mixture gave, on evaporation of the chloroform, 330 mg. (64%) of 6-(6-methoxy-1,2,3,4-tetrahydro-2-naphthyl)-2(1*H*)-pyridone (VIII), m.p. 236.5–238°.

6-(6-Hydroxy-1,2,3,4-tetrahydro-2-naphthyl)-1-methyl-2-(1H)-pyridone (Xb). A solution of 900 mg. of 6-(6-methoxy-1,2,3,4 - tetrahydro - 2 - naphthyl) - 1 - methyl - 2(1*H*)-pyridone (Xa) and 15 ml. of 48% hydrobromic acid was refluxed for 3 hr., cooled, and filtered to give 1.08 g. of the crude pyridone hydrobromide, m.p. 232–235° dec. The hydrobromide was stirred with warm concd. ammonium hydroxide, and the resulting solid was collected on a filter to give 716 mg. of product, m.p. 251–253°. The analytical sample of Xb crystallized from aqueous acetic acid in white platelets, m.p. 254°, λ_{max} 225 (10,800), 230 (10,750), and 310 mμ (9230) with an inflection at 294 mμ (7650). The infrared spectrum is consistent with the structural assignment.

Anal. Calcd. for $C_{16}H_{17}NO_2$: C, 75.27; H, 6.71. Found: C, 74.79; H, 6.72.

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[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT, UNIVERSITY OF CALIFORNIA, DAVIS]

Amines Derived from Dihalopropenes. II. Synthesis of (±)- and (−)-1-(2-Methylene-1-aziridinyl)-3-buten-2-ol[1]

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Treatment of *N*-(2-bromoallyl)-2-hydroxy-3-butenylamine (IV) with sodium amide in liquid ammonia has been found to yield 1-(2-methylene-1-aziridinyl)-3-buten-2-ol (III) together with a small amount of 1-(2-propynylamino)-3-buten-2-ol (V). (±)-IV was prepared from 2-bromoallylamine and butadiene monoxide, and (−)-IV was prepared from 2,3-dibromopropene and (−)-1-amino-3-buten-2-ol. The relationship of III to Tetramin (I), the broad spectrum antineoplastic agent, is discussed.

The finding that Tetramin[2a] (I) has a broad spectrum of antineoplastic activity[2b] is striking in that the vast majority of "alkylating agents" that have shown promise as antineoplastic agents are capable of functioning as dialkylating agents,[3] whereas the components of I appear to be capable of acting only as a monoalkylating agent. Thus, the action of Tetramin in rapidly multiplying cells may be quite different from that of dialkylating agents, or one of the components of I may be converted in these cells to another compound which can function in a manner similar to that of a dialkylating agent. It is noteworthy that biological oxidation of the hydroxyl group of Ia would yield the amino ketone (II). II can function as a dialkylating agent because of the possibility of Michael-type addition to the α,β-unsaturated ketone part of the molecule as well as through a nucleophilic displacement reaction at one of the ring carbons.[4]

It has been found that the DPN (diphosphopyridine nucleotide) concentration in various animal tumors is depressed by the addition of I, and the reduction in DPN concentration parallels the curative action of I.[5] It is interesting to speculate that I is oxidized by DPN, and the oxidation product—*i.e.*, II—reacts with the reduced DPN in such a manner that reoxidation of the reduced

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(2)(a) Although Tetramin, the product from the reaction of aziridine and butadiene monoxide, was assigned the 1-(1-aziridinyl)-3-buten-2-ol (Ia) structure,[3] Tetramin is a two to one mixture of Ia and 2-(1-aziridinyl)-3-buten-1-ol (XIIe, R_1R_2 = —CH_2CH_2—). The isomers have been separated and characterized by NMR spectroscopy. (Private communication from E. M. Chamberlin.)

(2)(b) See *Cancer Chemotherapy Reports*, issued by the Cancer Chemotherapy National Service Center, National Institutes of Health, Bethesda 14, Md., August 1959, p. 52, for a summary of the clinical data on Tetramin, compiled by F. R. White.

(3) D. A. Karnofsky, *Ann. N. Y. Acad. Sci.*, **68**, 1261 (1958).

(4) E. J. Reist, I. G. Junga, and B. R. Baker, *J. Org. Chem.*, **25**, 1674 (1960), have pointed out that the relatively selective antineoplastic activity and lesser toxicity of Tetramin (I), as compared with analogs of the components of I which contain hydroxyl groups that are less readily oxidized, might be due to oxidation of I in normal cells to a relatively nontoxic substance (presumably II). The antineoplastic activity and toxicity of II are of obvious interest.

(5) H. Holzer and H. Kröger, *Klin. Wochschr.*, **36**, 677 (1958); H. Kröger, B. Ulrich, and H. Holzer, *Arzneimittel-Forsch.*, **9**, 598 (1959).