bromine, the actual ratio of reactivities becomes 3.11. If comparison is made directly through the slopes of the aforementioned plots—which represent bromination by free bromine—the ratio of rate constants becomes similarly 3.16. This is the factor by which the rate is reduced in the less polar solvent. Subject to the uncertainty in ΔH and ΔS for K,[7] this slowdown in rate is caused entirely by a lowering of the activation entropy, because in 50% acetic acid at the same concentrations of sodium bromide and sodium perchlorate the activation energy is 16.8 kcal. and $\Delta S^{\ddagger}$ is -12.1 e.u. That the activation entropy should be responsible for lowering the rate on going from a more to a less aqueous solvent is not unreasonable for a reaction in which ions are formed from neutral molecules.[8]

EXPERIMENTAL

All inorganic materials and the glacial acetic acid were as described before.[4] The naphthalene (Baker Analyzed Reagent) melted at 80.4–80.7°, after three crystallizations from ethanol. The 60% (by volume) aqueous acetic acid was prepared by mixing three volumes of glacial acetic acid with two volumes of distilled water, both of which had been thermostatted at 25.0°. The kinetic data were not affected when different batches of solvent mixture were used. Stock solutions of reagents were prepared at temperatures at which kinetic runs were carried out. The procedures for the kinetic runs and the determination of rate constants have been described.[4] Because runs were relatively fast, blanks due to volatility of bromine were small and within the experimental errors and were discarded. The rate constants recorded in the Table (except for those under A) are average values of at least duplicate runs, which usually agreed to within better than 2%. Data for one kinetic run follow.

A KINETIC RUN IN THE BROMINATION OF NAPHTHALENE IN 60% AQUEOUS ACETIC ACID

Naphthalene 0.01222 M, Br_2 0.003215 M, NaBr 0.20 M, $NaClO_4$ 0.30 M, T 25.0°

Time, Min.	0.01969N Thiosulfate, Ml.	$k_{obs} \times 10^3$, l. mole^{-1} sec.$^{-1}$
0	3.266	—
10	3.094	7.45
25	2.848	7.59
40	2.620	7.71
60	2.360	7.67
85	2.084	7.61
110	1.850	7.52
140	1.606	7.49

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(7) It is assumed that these values are not very different in 50% and 60% aqueous acetic acid.

(8) A. A. Frost and R. G. Pearson, *Kinetics and Mechanism*, second ed., John Wiley and Sons, Inc., New York, N. Y., 1961, p. 137 *ff*.

The Synthesis of 1-(β-1-Naphthylethyl)-2(1*H*)-pyridones

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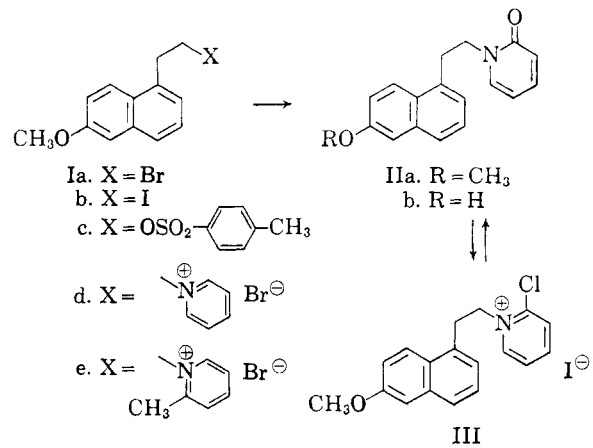
In connection with studies on the anti-inflammatory activity of nitrogen-containing steroid analogs, it became of interest to undertake the synthesis of 1-(β-1-naphthylethyl)-2(1*H*)-pyridones. The preparation of related 6-(1,2,3,4-tetrahydro-2-naphthyl)-2(1*H*)-pyridones has already been reported.[2]



III

Our initial approaches to the system IIa were uniformly unsuccessful; included were attempts to alkylate β-(6-methoxy-1-naphthyl)ethyl bromide (Ia),[3] iodide (Ib),[4] and tosylate (Ic) with 2-pyridone salts,[5] to oxidize the pyridinium bromide (Id) with alkaline potassium ferricyanide,[6] to condense Id with 2-pyridone salts,[7] and to submit the picolinium salt (Ie) to the conditions of the King reaction.[8–10]

A successful synthesis of IIa was achieved when the bromide Ia was treated with 2-ethoxypyridine at 110–130° for twenty four hours in the absence of solvent. The reaction of 2-ethoxypyridine with

(1) Department of Chemistry, The Upjohn Company, Kalamazoo, Mich.

(2) N. A. Nelson and L. A. Paquette, *J. Org. Chem.*, **27**, 964 (1962).

(3) W. E. Bachmann, W. Cole, and A. L. Wilds, *J. Am. Chem. Soc.*, **62**, 824 (1940).

(4) W. E. Bachmann and R. E. Holmen, *J. Am. Chem. Soc.*, **73**, 3660 (1951).

(5) *Cf. inter alia*, M. Barash and J. M. Osbond, *Chem. & Ind.*, 490 (1958).

(6) *Cf. inter alia*, E. E. van Tamelen and J. S. Baran, *J. Am. Chem. Soc.*, **80**, 4659 (1958), and references cited therein.

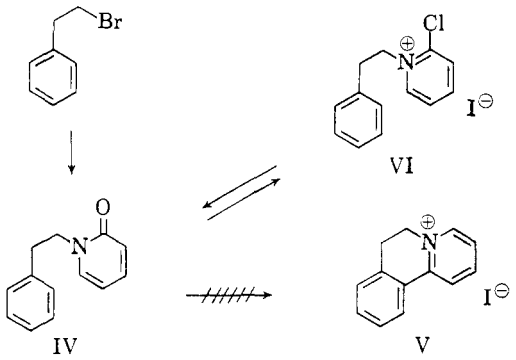
(7) These conditions would be analogous to those developed for the Kröhnke reaction, *cf.* F. Kröhnke, *Ber.*, **71**, 2583 (1938).

(8) J. A. Berson and T. Cohen, *J. Am. Chem. Soc.*, **78**, 416 (1956).

(9) F. Kröhnke and K. F. Gross, *Ber.*, **92**, 22 (1959).

(10) J. A. Berson and J. S. Walia, *J. Org. Chem.*, **24**, 756 (1959).

β-arylethyl bromides appears to be of general applicability, for phenethyl bromide gave the corresponding pyridone (IV) in good yield. Previously, only methyl iodide had been used to convert 2-alkoxypyridines to *N*-substituted 2-pyridones.[11-14]



The action of 48% hydrobromic acid in an inert atmosphere on IIa gave an almost quantitative yield of the corresponding phenolic pyridone IIb.

Previously, several workers[15-17] had reported the facile conversion of 1-β-arylethyl-2-pyridones to benzoquinolizinium iodides (*cf.*, IV to V). During the course of this work a correction of the erroneous description of these compounds was published by Sugasawa, Akaboshi, and Ban[18] in which the correct formulation of these substances as 2-chloropyridinium iodides (*cf.*, VI) was made. We have substantiated that the chloropyridinium iodide VI results when IV is heated with phosphorus oxychloride and then treated with potassium iodide. The action of warm aqueous sodium hydroxide on VI readily afforded IV.

Likewise, submission of IIa to the action of phosphorus oxychloride followed by potassium iodide yielded the chloropyridinium iodide III, which readily reverted to IIa in good yield when treated with base.

In further attempts to effect ring closure of IIa to a tetracyclic system, the substance was treated with anhydrous hydrogen bromide in refluxing acetic acid. A good yield of the phenolic pyridone IIb as its hemihydrobromide was obtained. The action of anhydrous hydrogen chloride in refluxing diphenyl ether, 70% sulfuric acid, or polyphosphoric acid on IIa gave uncharacterizable materials, while anhydrous hydrogen fluoride gave a white solid which, on treatment with ammonium hydroxide, regenerated the starting material.

(11) L. Knorr and P. Rabe, *Ber.*, **30**, 927 (1892).
(12) E. Späth and G. Koller, *Ber.*, **56**, 2454 (1923).
(13) E. C. Taylor, Jr., A. J. Crovetti, and H. M. Loux, *J. Am. Chem. Soc.*, **77**, 5445 (1955).
(14) E. C. Taylor, Jr., and A. J. Crovetti, *J. Am. Chem. Soc.*, **78**, 214 (1956).
(15) T. R. Govindachari and B. S. Thyagarajan, *Proc. Ind. Acad. Sci.*, **39A**, 232 (1954).
(16) S. Sugasawa, S. Akaboshi, and M. Suzuki, *Yakugaku Zasshi*, **72**, 1273 (1952); *Ber.*, **72**, 979 (1939).
(17) S. Akaboshi, *Yakugaku Zasshi*, **72**, 1277 (1952).
(18) S. Sugasawa, S. Akaboshi, and Y. Ban, *Chem. Pharm. Bull. (Tokyo)*, **7**, 263 (1959); *cf.* also Y. Ban, *Chem. Pharm. Bull. (Tokyo)*, **7**, 609 (1959).

EXPERIMENTAL[19]

β-(6-Methoxy-1-naphthyl)ethyl tosylate (Ic). β-(6-Methoxy-1-naphthyl)ethyl alcohol[20] was converted in 75% yield to its tosylate in the usual manner. Pure Ic was obtained as white prisms from ether, m.p. 59–60°.

Anal. Calcd. for $C_{20}H_{20}O_4S$: C, 67.40; H, 5.66. Found: C, 67.18; H, 5.81.

β-(6-Methoxy-1-naphthyl)ethyl pyridinium bromide (Id). A solution of 9.0 g. (0.034 mole) of the bromide Ia and 5.5 g. (0.078 mole) of anhydrous purified pyridine in 100 ml. of anhydrous toluene was refluxed for 10 hr. After cooling the reaction mixture, the precipitated quaternary salt was filtered, washed with ether, and dried to give 11.7 g. (100%) of white crystals, m.p. 184–184.5°. Three recrystallizations of the crude product from ethanol-ether gave the pure pyridinium bromide, m.p. 184.5–185°. λ_{max} 229 (50,800), 259 (8,030), 266 (7,350), 277 (5,350), 288 (4,675), 317 (2,340), and 331 mμ (2,680).

Anal. Calcd. for $C_{18}H_{18}BrNO$: C, 62.80; H, 5.27; N, 4.07. Found: C, 63.10; H, 5.23; N, 3.88.

β-(6-Methoxy-1-naphthyl)ethyl 2-picolinium bromide (Ie). A solution of 1.0 g. (3.77 mmoles) of the bromide Ia in 5 to 6 ml. of dry, purified 2-picoline was allowed to stand at room temperature for 1 month. At the end of this time, the mixture was heated on the steam bath for 8 hr. to complete the reaction. The precipitated quaternary salt was filtered, washed with ether, and dried to give 1.0 g. (74%) of pale yellow solid, m.p. 202–205°. Three recrystallizations of this solid from ethanol-ether gave the pure quaternary salt as colorless crystals, m.p. 209–210°. λ_{max} 230 (55,700), 267 (9,530), 274 (8,650), 287 (4,420), 318 (1,910) and 321.5 mμ (2,195).

Anal. Calcd. for $C_{19}H_{20}BrNO$: C, 63.69; H, 5.63; N, 3.91. Found: C, 63.70; H, 5.73; N, 3.85.

1-(β-6-Methoxy-1-naphthylethyl)-2(1H)-pyridone (IIa). A mixture of 22.0 g. (0.083 mole) of the bromide Ia and 10.0 g. (0.083 mole) of 2-ethoxypyridine was heated at 110–130° for 24 hr. with stirring. The cooled reaction mixture was chromatographed directly on 350 g. of deactivated Merck basic alumina (Brockmann activity III). Elution of the column with petroleum ether removed the unchanged bromide and 2-ethoxypyridine; elution with ether gave 11.5 g. (49.6%) of a colorless oil which slowly crystallized, m.p. 102.5–104°. Three recrystallizations of the crude product from benzene-ligroin gave the pure pyridone, m.p. 104–105.5°. λ_{max} 229 (62,100), 268 (5,540), 278 (7,300), 289 (8,020), and 330 mμ (4,040).

Anal. Calcd. for $C_{18}H_{17}NO_2$: C, 77.39; H, 6.13; N, 5.01. Found: C, 77.61; H, 6.34; N, 5.03.

1-(β-6-Hydroxy-1-naphthylethyl)-2(1H)-pyridone (IIb). A mixture of 558 mg. (2.0 mmoles) of 1-(β-6-methoxy-1-naphthylethyl)-2(1*H*)-pyridone (IIa) and 10 ml. of 48% hydrobromic acid was refluxed under nitrogen for 4 hr. After cooling the reaction mixture, the pale violet solid was filtered. This solid was slurried with warm concentrated ammonium hydroxide and filtered. After recrystallization of this material from 95% ethanol there was obtained 490 mg. (94.3%) of a pale yellow-green solid, m.p. 201–202°. If this reaction was not performed in an inert atmosphere, the resulting phenolic pyridone was rapidly air-oxidized to

(19) Melting points are uncorrected. Ultraviolet spectra were determined in 95% ethanol with a Cary recording spectrophotometer (Model 11MS); molecular extinction coefficients are given. The microanalyses were performed by Dr. S. M. Nagy and his associates.
(20) E. Buchta, M. Klish, S. Maier, and H. Bayer, *Ann.*, **576**, 7 (1952).

give dark, polymeric tars and only an 18.4% yield of IIb was obtained. Three additional recrystallizations of the above crude solid from 95% ethanol gave pure product as a greyish-white solid, m.p. 202–202.5°. λ_{max} 229 (60,500), 270 (5,380), 281 (7,570), 292.5 (8,560), and 309 mμ (6,700).

Anal. Calcd. for $C_{17}H_{15}NO_2$: C, 76.96; H, 5.71; N, 5.28. Found: C, 76.72; H, 5.66; N, 5.33.

1-β-Phenethyl-2(1H)-pyridone (IV). A mixture of 1.5 g. (0.81 mmole) of phenethyl bromide and 2.0 g. (1.62 mmoles) of 2-ethoxypyridine was heated at 128–130° with stirring for 48 hr. At the end of this time, 50 ml. of water was added and the mixture was steam distilled. To the cooled residue was added saturated sodium hydroxide solution until a strongly basic solution was obtained. This solution was extracted with three 100-ml. portions of chloroform; the combined chloroform layers were dried over magnesium sulfate and filtered. After removal of the solvent, the residual brownish oil was crystallized from benzene-ligroin to give 1.23 g. (76.5%) of white platelets, m.p. 100–102°. Two further recrystallizations of this solid from benzene-ligroin gave the pure pyridone, m.p. 104.5–105°.[15] λ_{max} 299 (5,675) and 305 mμ (4,460).

1-(β-6-Methoxy-1-naphthylethyl)-2-chloropyridinium iodide (III). A solution of 350 mg. (1.25 mmoles) of IIa in 5 ml of anhydrous benzene was refluxed with 2 ml. of phosphorus oxychloride for 3 hr. The reaction mixture was cooled and treated with a large excess of petroleum ether. After 1 hr. in the refrigerator, the solvent was decanted from the pale yellow oil which had settled to the bottom. The oil was dissolved in 7 ml. of 0.2*N* hydrochloric acid and the resulting clear solution was warmed and treated with excess of a saturated aqueous potassium iodide solution. The precipitate was filtered, washed well with cold water, dried, and recrystallized from ethanol to give 363 mg. (68.2%) of fine yellow needles, m.p. 195–197° (dec.). When the reaction was performed in xylene according to the directions of Wiley, Smith, and Knabeschuh,[21] a 59.5% yield of III was obtained, m.p. 195–197° (dec.). Three additional recrystallizations of the above material from ethanol gave pure quaternary iodide, m.p. 200–201° (dec.). λ_{max} 228 (60,700), 268 (7,700), 275 (8.820), 317 (2,100), and 331.5 mμ (2,230).

Reaction of III *with aqueous sodium hydroxide.* To a mixture of 147 mg. (0.346 mmole) of III in 10 ml. of water was added a solution of 250 mg. (6.25 mmoles) of sodium hydroxide in 3 ml. of water. The solution was heated on the steam bath for 2 hr. After cooling the mixture, it was extracted with three 10-ml. portions of chloroform. The organic layers were combined, washed with water, and dried over magnesium sulfate; filtration and evaporation of this solution yielded a dark brown oil which was crystallized from ligroin-benzene (decolorized with Norit) to give 85 mg. (88.5%) of a white solid, m.p. 100–102°. Three additional recrystallizations of this material from benzene-ligroin gave white crystals, m.p. 104–105.5°. A mixed melting point determination of this material with a sample of the pure pyridone IIa showed no depression; the elemental analysis was also in agreement with this structure.

Reaction of 1-(β-6-methoxy-1-naphthylethyl)-2(1H)-pyridone (IIa) *with anhydrous hydrogen bromide.* Into a solution of 558 mg. (2.0 mmoles) of IIa in 5 ml. of glacial acetic acid was passed a steady stream of anhydrous hydrogen bromide. The solution was slowly heated to reflux and was refluxed for 0.5 hr. The acetic acid was removed under reduced pressure and the residual brown oil was crystallized from ethanol-ether to give 475 mg. (77.7%) of white crystals, m.p. 185–187° (gas evolution). Three further recrystallizations of this solid from ethanol-ether gave an analytical sample of the hemihydrobromide of IIb, m.p. 187–187.5° (gas evolution).

Anal. Calcd. for $C_{17}H_{15}NO_2 \cdot 1/2$ HBr: C, 66.77; H, 5.11; N, 4.58. Found: C, 66.69; H, 5.31; N, 4.63.

(21) R. H. Wiley, N. R. Smith, and L. H. Knabeschuh, *J. Am. Chem. Soc.*, **75**, 4482 (1953).

A small sample of the above material was warmed on the steam bath for 15 min. with concentrated ammonium hydroxide. After extracting the reaction mixture with chloroform, the combined organic layers were dried over magnesium sulfate, filtered, and evaporated to yield a residue which was crystallized from ethanol to give pale yellow crystals, m.p. 197–199°. This material, on admixture with an authentic sample of IIb, m.p. 202°, gave a melting point of 197–199°; the infrared spectra of the two samples were identical.

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Structures Related to Morphine. XXI.[1] An Alternative Synthesis of Diastereoisomeric 2′-Hydroxy-2,5,9-trimethyl-6,7-benzomorphans

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Cyclization of 2-(*p*-methoxybenzyl)-1,3,4-trimethyl-1,2,5,6-tetrahydropyridine with 48% hydrobromic acid leads to a mixture of diastereoisomeric benzomorphans IV and VI in a ratio of about 12:1, respectively.[3] The analgesic activity (in mice) of the lesser isomer (VI) was seven times that of IV and five times that of morphine.[3] Furthermore, VI had little if any abstinence-suppressing capacity in the monkey in an established morphine addiction.[4] Consequently, a more extensive study of this compound and relatives seemed warranted, and a more satisfactory method of preparation was therefore sought.

Efforts to increase the yield of VI in the above-mentioned ring closure have, to date, been unsuccessful. Thus we centered our attention on the 9-methylcarbinol (I),[5] the demethoxy relative of which had previously been converted (in low yield) to 2,5,9-trimethyl-6,7-benzomorphan[6] by catalytic hydrogenation of the corresponding 9-methylene derivative. By a similar sequence of reactions we can now obtain either IV or VI[3] depending upon the medium used in the hydrogenation of the 9-methylene compound (II).

(1) Paper XX, S. Saito and E. L. May, *J. Org. Chem.*, **27**, 948 (1962).

(2) Visiting scientist from Osaka, Japan.

(3) E. L. May and J. H. Ager, *J. Org. Chem.*, **24**, 1432 (1959). For convenience compounds III and IV (methyl oriented away from nitrogen) will be designated α and V, and VI designated β. NMR and methiodide-rate-formation studies (to be published) confirm our original, tentative configurational assignments.

(4) Personal communication from Dr. G. Deneau, Department of Pharmacology, University of Michigan.

(5) E. L. May and H. Kugita, *J. Org. Chem.*, **26**, 188 (1961).

(6) E. L. May and E. M. Fry, *J. Org. Chem.*, **22**, 1366 (1957).