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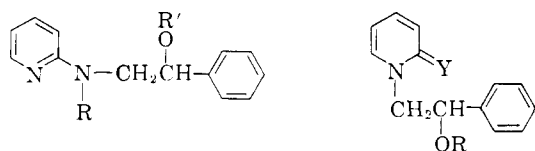
Aminopyridines. II. The Preparation and Properties of 2-(Hydroxyalkylamino)-pyridines¹

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Other approaches to substituted 2-(hydroxyalkylamino)-pyridines have been explored. Reaction of the sodium salt of 2-aminopyridine with styrene oxide has provided a useful route to 2-(β -hydroxyphenethylamino)-pyridine. With 2-aminopyridine itself, the 1-substituted derivative is formed. The reaction of a 2-halopyridine with a phenylalkanamine, although of more limited value, has also afforded desired aminopyridine derivatives. The chemical behavior, ultraviolet absorption spectra and basicities of these compounds have been studied.

The interesting analgesic and interneuronal blocking properties of many of the glycolamidopyridines and hydroxyalkylaminopyridines described in the preceding paper² stimulated further work in this area. The present report is concerned with other synthetic approaches to hydroxy substituted phenylalkylaminopyridine derivatives. Chemical behavior, ultraviolet absorption characteristics and apparent dissociation constants are also considered. For convenience in this discussion the Roman numeral identification of structures is sequential with that in Part I.²



X, R = R' = H

XXI, R = H, R' = $-\text{C}(=\text{O})\text{CH}_3$ XXII, R = H, R' = $-\text{C}(=\text{O})\text{NHCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$ XXIII, R = CH₃, R' = H

XXIV, Y = NH, R = H

XXV, Y = $\text{N}(\text{C}(\text{O})\text{CH}_3)$, R = $-\text{C}(=\text{O})\text{CH}_3$

XXVI, Y = O, R = H

Of immediate concern was the designing of a synthesis more adaptable to the preparation of larger quantities of 2-(β -hydroxyphenethylamino)-pyridine (X). The reaction of the sodium salt of 2-aminopyridine with styrene oxide, based on the experience with alkyl halides,³ seemed likely to provide a useful approach to the amino nitrogen substituted compound. Without added basic reagent ethylene oxide has been shown to react at the ring nitrogen⁴; however, in the presence of sodamide and liquid ammonia, ethylene oxides substitute at the α -carbon of the formally analogous 2- or 4-alkylpyridines.⁵

In the presence of one equivalent of sodamide, 2-aminopyridine was indeed found to react with

(1) Presented in part before the Division of Medicinal Chemistry at the 135th Meeting of the American Chemical Society, Boston, Mass., April, 1959.

(2) A. P. Gray and D. E. Heitmeier, *THIS JOURNAL*, **81**, 4347 (1959).

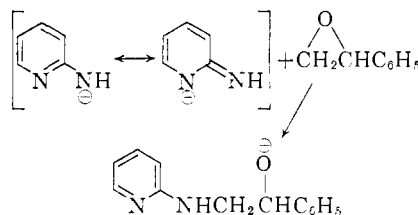
(3) A. E. Chichibabin, R. A. Kononova and A. A. Kononova, *Ber.*, **54**, 814 (1921); T. M. Sharp, *J. Chem. Soc.*, 1855 (1939).

(4) Ya. L. Gol'dfarb and M. A. Pryanishnikova, *Zhur. Obshchei Khim.*, **25**, 1003 (1955); *C. A.*, **50**, 3433f (1956).

(5) F. E. Cislak, U. S. patent 2,750,392 (1956); F. E. Cislak and C. K. McGill, U. S. Patent 2,759,946 (1956).

styrene oxide to produce X, identical with the product obtained in two steps from mandelic acid.² The formation of the same product in both processes confirms the direction of cleavage of the oxide ring, expected on the presumption of a base-catalyzed bimolecular displacement.⁶ When the sodamide was omitted or, in fact, when a catalytic amount (5 mole per cent.) of sodium ethoxide in ethanol was used, the 1-substituted isomer XXIV was the only basic product isolated. The action of acetic anhydride smoothly converted this to the di-acetylated derivative XXV. Saponification of XXIV afforded the known pyridone XXVI.

The rate-determining step in the styrene oxide process for the preparation of X must involve a reaction of the aminopyridine anion and may likely be formulated



The reaction was found not to proceed in the cold in liquid ammonia, but took place with considerable vigor and evolution of heat after most of the ammonia had evaporated, to give poor yields of product, and presumably, polymers. Much better results were realized when the reaction was carried out with sodamide in an inert solvent, optimally when the reactants were first contacted with sodamide in liquid ammonia and the ammonia was gradually replaced with the inert solvent as it evaporated. Apparently this provided a convenient means of moderating the reaction, which went most smoothly at temperatures of 30–40°. In this way yields of up to 70% but usually between 40 and 50% obtained. As to the "inert" solvent, benzene, toluene and ether proved inferior to the dimethyl ether of ethylene glycol which was found to be particularly effective. The efficacy of the diether no doubt reflects its ability to solubilize the sodium salt of the aminopyridine, and, perhaps, a more direct effect of its polarity. It might be mentioned that no products resulting from the reaction of two moles of styrene oxide were encountered.

The action of acetic anhydride on X is worth noting. Under mild conditions, excess acetic anhy-

(6) Cf. C. L. Browne and R. E. Lutz, *J. Org. Chem.*, **17**, 1187 (1952).

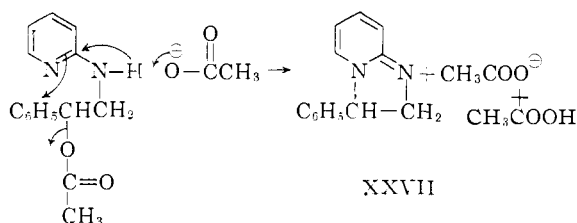
TABLE I
 PHYSICAL PROPERTIES OF AMINOPYRIDINE DERIVATIVES

Compound		Ultraviolet ^a λ_{\max} , m μ (log ϵ)	pK_a^b
I	2-Mandelamidopyridine	237 (4.10), 276 (3.89)	2.94
II	2-Mandelamido-4-picoline	239 (4.17), 274 (3.90)	3.25
VII	2-Lactamidopyridine ^c	235 (4.18), 275 (3.92)	
X	2-(β -Hydroxyphenethylamino)-pyridine	243 (4.24), 303 (3.63)	5.85
XI	4-(β -Hydroxyphenethylamino)-pyridine		8.49
XII	2-(β -Hydroxyphenethylamino)-4-picoline		6.50
XIV	6-(β -Hydroxyphenethylamino)-3-picoline		6.30
XV	2-(β -Hydroxyphenethylamino)-5-chloropyridine		3.70
NVII	2 (2-Hydroxypropylamino)-pyridine		6.10
NIX	2-(β -Hydroxy- β,β -diphenylethylamino)-pyridine		5.50 ^d
XX	<i>x</i> -Phenyl-8-methylimidazo[1,2-a]pyridin- <i>y</i> (xH)-one	259 (4.07), 363 (3.86)	
XXI	2-(β -Acetoxyphenethylamino)-pyridine		5.85 ^d
XXIV	1-(β -Hydroxyphenethyl)-2-imino-1,2-dihydropyridine	233 (3.98), 307 (3.81) 311 (3.74) ^e	11.0 ^d
XXV	1-(β -Acetoxyphenethyl)-2-acetylimino-1,2-dihydropyridine	273 (3.94), 338 (4.04)	5.83
XXIX	2-(γ -Hydroxy- γ -phenylpropylamino)-pyridine		6.15
XXX	2-Phenethylaminopyridine	243 (4.18), 305 (3.61)	6.10

^a The ultraviolet absorption spectra listed are, unless noted otherwise, of the free bases dissolved in 95% ethanol. A Beckman DU spectrophotometer was used. ^b Apparent pK_a 's were measured by titration of *ca.* 0.01 *M* solutions of the hydrochloride salts in 60:40 dimethylformamide-carbon dioxide-free water with 0.1 *N* NaOH at 25°. A Beckman model G pH meter was used. The listed values are averages of at least two determinations. ^c Ultraviolet spectrum of the hydrochloride salt in 95% ethanol. ^d Approximate value. ^e Ultraviolet spectrum of an ethylene glycol dimethyl ether solution of the free base. This solvent absorbed too strongly below 250 m μ to allow measurement of the position of the short wave length peak.

drine in glacial acetic acid containing a little hydrogen chloride, a monoacetyl derivative was formed. Assignment of the O-acetyl structure XXI rather than the N-acetyl structure to this rests mainly on the apparent dissociation constant of the hydrochloride salt (Table I), which is about the same as that found for the starting alcohol, X hydrochloride, and much higher than the values for the amidopyridines. The formulation as XXI fits with its preparation under acidic conditions and is in accord with the difficulties encountered here in attempts to acylate the nitrogen of 2-(monosubstituted amino)-pyridines.⁷

In an attempt to force diacetylation, in order to obtain the structural isomer of XXV, X was subjected to boiling acetic anhydride. These conditions, however, afforded none of the desired diacetyl derivative but only a poor yield of a product resulting from cyclization, presumably the dihydroimidazopyridine XXVII. It seems likely that XXVII arose as a result of the action of acetate ion on the intermediate monoacetyl derivative, *viz.*

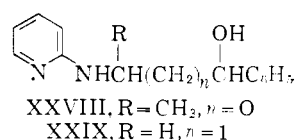


Reaction of X with *n*-butyl isocyanate yielded a product, considered by analogy to be the carbamate

(7) Unpublished data gathered in these laboratories. Our experience indicates that although 2-aminopyridine is readily acylated, attachment of a single alkyl substituent to the amino nitrogen renders the derivative difficult to acylate even under forcing conditions. Of course, the difficulties are not insurmountable; *cf.* L. Toldy and M. Kraut, *Magyar Kim. Folyóirat*, **63**, 23 (1957); *C. A.*, **52**, 18402i (1958).

derivative XXII. The N-methyl derivative XXIII was obtained in two steps by first treating X with formaldehyde and then reducing the crude oxazolidine product with lithium aluminum hydride.

Another route to X analogs involved the reaction of a 2-halopyridine with a phenylalkanolamine. Although substitution could conceivably take place at either the nitrogen or the oxygen of the alkanolamine, in accord with the literature,⁸ only N-substituted derivatives were isolated. The structural designation follows from the fact that the products were monoacidic bases. Compounds XXVIII and XXIX were obtained in poor yield by reaction with *dl*-norephedrine and with 3-amino-1-phenyl-1-propanol, respectively.



Physical Properties.—The ultraviolet absorption maxima and apparent dissociation constants, recorded in Table I, have some interesting implications. Unexceptionally, the 2-amidopyridines (I, II) are much weaker bases ($\Delta pK_a \sim 3$) than the corresponding 2-aminopyridine derivatives (X, XII). The basicities of the 2-amido- and amino-pyridine derivatives are affected in the same way by the attachment of substituents to the pyridine nucleus as is the base strength of the parent pyridine.⁹ Thus, a 4-methyl group increases basicity by 0.3–0.6 of a pK unit (I *vs.* II, X *vs.* XII). The fact that a 5-methyl derivative XIV is less basic by about 0.2 pK unit than the 4-methyl isomer XII, in close agreement with the ΔpK_a of 0.3 found by Brown and Mihm⁹ for

(8) N. Weiner and I. A. Kaye, *J. Org. Chem.*, **14**, 868 (1949).

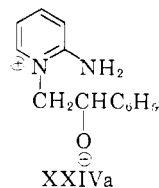
(9) H. C. Brown and X. R. Mihm, *THIS JOURNAL*, **77**, 1723 (1955); I. C. Brown and D. H. McDaniel, *ibid.*, **77**, 3752 (1955).

the corresponding pyridines, accords with protonation of the ring nitrogen in forming the 2-aminopyridine cation. A 5-chloro substituent (XV) has the expected, large base-weakening effect.

The changes in basicity produced by alterations in the structure of the group attached to the exocyclic nitrogen of the 2-aminopyridine nucleus are of significance. Attachment of a hydroxyl group at the β -position to give X lowers the basicity of 2-phenethylaminopyridine (XXX) 0.25 of a pK unit. Comparison of the pK'_a values of XVII and X, and of X and XIX, indicates that each introduction of β -phenyl into a 2-(β -hydroxyalkylamino)-pyridine weakens base strength by 0.25–0.35 pK unit. In contrast, a β -phenyl substituent lowers the pK_a of ethylamine by 0.8, a β -hydroxyl by 0.9–1.1 units.¹⁰ That hydrogen bonding with the β -hydroxyl has a negligible effect on the basicity of the aminopyridine derivatives is tenuously suggested by the fact that O-acetylation does not alter base strength (XXI *vs.* X).¹¹ Thus, it appears that the influence of the hydroxyl as well as of the phenyl group can be primarily attributed to inductive effects. The apparent dampening of these effects in the aminopyridine derivatives is entirely in accord with the presumption that the positive charge in the salts is distributed toward the ring rather than the amino nitrogen. In agreement with this is the fact that the 4-isomer (XI) of β -hydroxyphenethylaminopyridine is 2.6 pK units more basic than the 2-isomer X as compared with a ΔpK_a of 2.3 for the corresponding parent aminopyridines,¹² *i.e.*, the influence of the hydroxyl and phenyl groups is of less significance when further removed from the ring nitrogen. Shifting the phenyl and hydroxyl groups from the β - to the γ -position of the 2-alkylaminopyridine, of course, also reduces base-weakening effects (XXIX *vs.* X). The markedly increased basicity of the 1-substituted aminopyridine (XXIV) is unexceptional¹³ as is the sharp reduction in base strength brought about by acetylating the imino nitrogen (XXV).

Examination of the ultraviolet absorption data indicates that the weak absorption of the β -phenyl group does not mask the absorption of the aminopyridine system (VII *vs.* I). A 4-methyl group also has little apparent effect on the spectrum (I *vs.* II). In ether or dioxane solution 1-methyl-2-pyridonimine has been shown¹⁴ to have an absorption peak at about 350 $m\mu$, a peak which undergoes a marked hypsochromic shift to that of the parent aminopyridine ($\lambda_{max} \sim 300 m\mu$) on the addition of water. This was demonstrably the result of an equilibrium between the strongly basic pyridonimine and the hydroxylic solvent to give the aminopyridinium ion.¹⁴ A comparison of the corresponding absorption maximum of X (303 $m\mu$) with that of

XXIV in ethanol (307 $m\mu$) and in ethylene glycol dimethyl ether (311 $m\mu$) indicates that XXIV is predominantly in the aminopyridinium form even in the absence of a proton-donating solvent. Thus it would appear that the compound exists largely as the zwitterion XXIVa. In line with this it can be seen that there is a definite hypsochromic shift



in going from 2-substituted aminopyridine (X) to amidopyridine (I), whereas, in complete contrast, acetylation of the exocyclic nitrogen of a pyridonimine produces an extremely marked bathochromic shift (XXIV *vs.* XXV). This, taken with the relatively weak basicity of XXV, indicates that there is essentially no protolytic equilibrium between XXV and the alcohol solvent, and that the compound is almost exclusively in the free pyridonimine form.¹⁵

The spectrum of XX firmly supports assignment of an imidazopyridinone structure, involving substitution on the ring nitrogen. However, there are definite differences in the spectra of XX and XXV. Since XX could exist in an enol form,² which would account for the spectral differences, the absorption data do not permit a choice as to the nitrogen to which the carbonyl group is attached.

Pharmacological Properties.¹⁶—As has been briefly mentioned,² many of the compounds discussed in this and the preceding paper have promising analgesic activity. Evaluated in mice, the potencies of a number of the compounds compared favorably with that of codeine. It is particularly intriguing that quite a few of the same compounds also displayed interneuronal blocking properties of the order of mephenesin. Unfortunately, it is difficult to relate activity to structure. First, the biological measurements are not quantitatively precise. Second, almost nothing is known at the molecular level concerning the way in which relief from pain is produced in an organism, so that a correlation would have to be empirical rather than rational. No generally satisfying correlation has therefore been evolved. It might be mentioned that the active compounds include both amido- and aminopyridine derivatives. Significance may or may not attach to the fact that optimum analgesic and interneuronal blocking activity is associated with compounds containing a phenethanolamine moiety, a structural unit which has been implicated in the analgesic properties of some groups of medicinal agents.¹⁷

(15) This conclusion is in agreement with a recent spectral study; *cf.* Yu. N. Sheinker, *Doklady Akad. Nauk S.S.S.R.*, **113**, 1080 (1957); *C. A.*, **51**, 14718d (1957).

(16) These are reported in detail by T. B. O'Dell, L. R. Wilson, M. D. Napoli, H. D. White and J. H. Mirsky, *J. Pharmacol. Exptl. Therap.*, in press.

(17) A. Burger, "Medicinal Chemistry," Interscience Publishers, Inc., New York, N. Y., 1951, Chapter XI.

(10) See H. K. Hall, Jr., *THIS JOURNAL*, **79**, 5441 (1957), and references cited therein; M. M. Tuckerman, J. R. Mayer and F. C. Nachod, *ibid.*, **81**, 92 (1959).

(11) It is recognized that the influence of hydrogen bonding would not be readily predictable in these cases; *cf.* V. Prelog and O. Häfner, *Helv. Chim. Acta*, **33**, 2021 (1950); T. A. Geissman, B. D. Wilson and R. B. Medy, *THIS JOURNAL*, **76**, 4182 (1954).

(12) A. Albert, R. Goldacre and J. Phillips, *J. Chem. Soc.*, 2240 (1948).

(13) See S. J. Angyal and C. I. Angyal, *ibid.*, 1461 (1952).

(14) L. C. Anderson and N. V. Seeger, *THIS JOURNAL*, **71**, 340 (1949).

Experimental¹⁸

Reaction of 2-Aminopyridine with Sodamide and Styrene Oxide. 2-(β -Hydroxyphenethylamino)-pyridine (X).—This reaction was thoroughly studied. The following example illustrates preferred conditions. To a slurry of 225 g. (5.7 moles) of commercial sodamide in 4 liters of liquid ammonia was added, in small portions with stirring, 470 g. (5 moles) of 2-aminopyridine. After half an hour 540 g. (4.5 moles) of styrene oxide was introduced, dropwise. Stirring was continued for a period of 3.5 hours during which the evaporating ammonia was gradually replaced by 2 liters of ethylene glycol dimethyl ether. The solution was stirred for an additional 1.5 hours and allowed to stand at room temperature overnight. A little isopropyl alcohol was added to decompose any excess sodamide, the solution was diluted with an equal volume of water and extracted with ether. The organic layer was concentrated *in vacuo* and the residue was dissolved in dilute hydrochloric acid, the acid solution was washed with ether, made alkaline and extracted with ether. Drying and removal of the ether left an oil which was crystallized from aqueous methanol to yield 687 g. (70%) of X, m.p. 82–85°, undepressed on admixture with the product obtained by lithium aluminum hydride reduction of I.²

Anal. Calcd. for C₁₃H₁₄N₂O: N (basic), 6.54. Found: N, 6.36.

The hydrochloride salt showed m.p. 138–140° dec.

Anal. Calcd. for C₁₃H₁₆ClN₂O: Cl, 14.14. Found: Cl (ionic), 14.21.

1-(β -Hydroxyphenethyl)-2-imino-1,2-dihydropyridine (XXIV).—A solution of 18.8 g. (0.2 mole) of 2-aminopyridine and 24.0 g. (0.2 mole) of styrene oxide in 20 ml. of ethanol was heated at reflux on a steam-bath for three hours and allowed to stand at room temperature overnight. The yellow crystalline precipitate which had formed was recrystallized from ethanol to give 10.4 g. (24%) of XXIV as bright yellow cubes, m.p. 170–172°.

Anal. Calcd. for C₁₃H₁₄N₂O: N (basic), 6.54. Found: N, 6.40.

The hydrochloride salt of XXIV, recrystallized from ethanol-ether, formed colorless needles, m.p. 200–202° dec.

Anal. Calcd. for C₁₃H₁₆ClN₂O: C, 62.27; H, 6.03; Cl, 14.14. Found: C, 62.44; H, 6.05; Cl (ionic), 13.95.

2-Phenethylaminopyridine (XXX).—The reaction of excess 2-aminopyridine with sodamide and phenethyl bromide in toluene on a steam-bath afforded a 33% yield of XXX as a straw-yellow oil, b.p. 128–130° (0.9 mm.).¹⁹

The hydrochloride salt of XXX, recrystallized from isopropyl alcohol-ether, showed m.p. 92–95°.

Anal. Calcd. for C₁₃H₁₆ClN₂: C, 66.51; H, 6.45; Cl, 15.11. Found: C, 66.23; H, 6.47; Cl (ionic), 15.20.

Reaction of a 2-Halopyridine with Phenylalkanolamines. **A.** 2-(β -Hydroxy- α -methylphenethylamino)-pyridine (XXVIII).—A mixture of 20.0 g. (0.13 mole) of *dl*-nor-ephedrine,²⁰ 21.5 g. (0.13 mole) of 2-bromopyridine, 20 g. (0.15 mole) of potassium carbonate and 1.0 g. of copper powder was heated, with stirring, in an oil-bath at 160° for 8 hours. The cooled reaction mixture was taken up in benzene, the inorganic salts were filtered off and the green benzene solution was extracted with 5% hydrochloric acid. The separated acid solution was charcoaled, made alkaline with 20% sodium hydroxide and extracted with ether. Drying and removal of the ether left an oil. This was dissolved in anhydrous ether and treated with ethereal hydrogen chloride. The precipitate, twice recrystallized from isopropyl alcohol-ether, yielded 9.2 g. (26%) of XXVIII hydrochloride, m.p. 161–162° dec.

Anal. Calcd. for C₁₄H₁₇ClN₂O: C, 63.53; H, 6.47; Cl, 13.39. Found: C, 63.54; H, 6.33; Cl (ionic), 13.27.

B. 2-(γ -Hydroxy- γ -phenylpropylamino)-pyridine (XXIX).—An intimate mixture of 25.0 g. (0.17 mole) of 3-amino-1-

phenyl-1-propanol [b.p. 126–130° (1.5 mm.), m.p. 60–61°],²¹ 18.8 g. (0.17 mole) of 2-chloropyridine and 29 g. of powdered sodium carbonate was heated for 9 hours in an oil-bath (bath temperature 190°). The cooled reaction mixture was extracted with warm benzene and the benzene extract concentrated to give a light yellow oil residue. This was dissolved in ether, the ether solution was extracted with dilute hydrochloric acid, the acid extract was made alkaline and extracted with ether. Drying and removal of the ether left an oil which partially solidified. Crystallization from isopropyl alcohol afforded 8.6 g. (22%) of XXIX, m.p. 123–124°.

Anal. Calcd. for C₁₄H₁₆N₂O: N (basic), 6.13. Found: N, 6.07.

The hydrochloride salt of XXIX, recrystallized from ethanol-ether, showed m.p. 138–140° dec.

Anal. Calcd. for C₁₄H₁₇ClN₂O: C, 63.53; H, 6.47; Cl, 13.39. Found: C, 62.96; H, 6.55; Cl (ionic), 13.35.

2-(β -Acetoxypheethylamino)-pyridine (XXI).—To a solution of 10.7 g. (0.05 mole) of X in 50 ml. of glacial acetic acid was added *ca.* 15 ml. of ethereal hydrogen chloride and 11.5 ml. (12.5 g., 0.12 mole) of acetic anhydride. The solution was warmed gently on the steam-bath for one hour and allowed to stand for two days at room temperature. After concentrating the solution *in vacuo* the oil residue was dissolved in isopropyl alcohol and precipitated with ether to give an oil which was vacuum dried and reprecipitated several times from isopropyl alcohol-ether. Drying over phosphorus pentoxide *in vacuo* yielded 10.5 g. (72%) of XXI as extremely hygroscopic, pale yellow crystals, shrinking and softening at about 55° and flowing at about 80°.

Anal. Calcd. for C₁₅H₁₇ClN₂O₂: C, 61.54; H, 5.85; Cl, 12.11; O-acetyl, 14.7. Found: C, 61.40; H, 6.07; Cl (ionic), 11.51; O-acetyl 13.2.

3-Phenyl-2,3-dihydroimidazo[1,2-a]pyridine (XXVII).—A mixture of 24.0 g. (0.11 mole) of X and 40 g. (0.39 mole) of acetic anhydride was boiled for 3 hours and allowed to stand overnight at room temperature. The reaction mixture was then poured into water, made alkaline with solid potassium carbonate and extracted with ether. Drying and removal of the ether afforded 19 g. of dark oil residue. This was twice distilled to give a fraction of 9.0 g., b.p. 135–138° (0.2 mm.), which was dissolved in ether and put through an acid-base extraction to yield, after recrystallization from benzene-Skellysolve B, 4.3 g. (20%) of XXVII as yellow needles, m.p. 84–86°.

Anal. Calcd. for C₁₃H₁₂N₂: N (basic), 7.14. Found: N, 6.97.

The hydrochloride salt of XXVII, recrystallized from isopropyl alcohol-ether, showed m.p. 105–107°.

Anal. Calcd. for C₁₃H₁₃ClN₂: C, 67.10; H, 5.63; Cl, 15.24. Found: C, 66.41; H, 5.52; Cl (ionic), 15.58.

2-[β -(*N*-*n*-Butylcarbamyloxy)-phenethylamino]-pyridine (XXII).—To a solution of 11.3 g. (0.053 mole) of X in 50 ml. of benzene was added 5.2 g. (0.052 mole) of *n*-butyl isocyanate. After standing for 20 hours at room temperature the solution was diluted with Skellysolve B to the point of cloudiness and refrigerated to yield a crystalline precipitate, 7.4 g. (45%) of XXII, m.p. 95–98°.

Anal. Calcd. for C₁₅H₂₃N₃O₂: C, 69.01; H, 7.40; N (basic), 4.47. Found: C, 68.66; H, 7.44; N, 4.46.

2-(*N*-Methyl- β -hydroxyphenethylamino)-pyridine (XXIII).—A solution of 30.0 g. (0.14 mole) of X and 18 g. of 37% aqueous formaldehyde solution (0.22 mole) in 100 ml. of isopropyl alcohol was heated on a steam-bath for 2 hours. Concentration under reduced pressure gave a residue of 33 g. of thick oil which resisted crystallization but which was presumed to be crude 3-(2-pyridyl)-5-phenyl-oxazolidine.

To a slurry of 6.5 g. (0.17 mole) of lithium aluminum hydride in 250 ml. of dry ether was added, dropwise with stirring, an ether solution of 27.0 g. (0.12 mole) of the crude oxazolidine. Stirring was continued and the reaction mixture was heated at reflux for 3 hours on a steam-bath. Ethyl acetate was added to decompose the excess reagent and then water was cautiously introduced. The reaction mixture was acidified with 10% hydrochloric acid, the separated acid layer was treated with 40 g. of tartaric acid,

(21) Prepared as described by S. L. Meisel, J. J. Deckert, Jr., and H. I. Hartough, *THIS JOURNAL*, **78**, 4782 (1956).

(18) Microanalyses were performed by the Clark Microanalytical Laboratories, Urbana, Ill., and by the Micro-Tech Laboratories, Skokie, Ill. Melting points are corrected for stem exposure.

(19) F. F. Blicke and M. U. Tsao, *THIS JOURNAL*, **68**, 905 (1946), report b.p. 145–148° (2 mm.). British Patent 606,181 (1948), *C. A.*, **43**, 3471h (1949), gives b.p. 175° (4 mm.), m.p. 51°.

(20) Obtained through the courtesy of J. H. De Lamar & Son, Inc., Chicago, Ill.

