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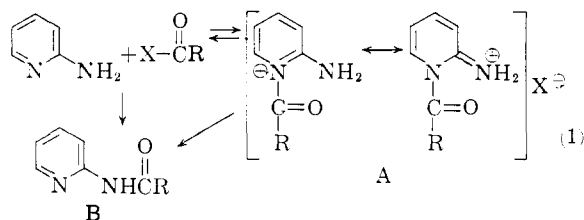
Aminopyridines. I.  $\beta$ -Hydroxyalkylaminopyridines via Glycolamidopyridines<sup>1</sup>

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The condensation of aminopyridines with substituted glycolic acids provided a convenient route to a series of substituted glycolamidopyridines. Lithium aluminum hydride reduction of these gave the corresponding  $\beta$ -hydroxyalkylaminopyridines. Exceptionally, 2-aminopyridine reacted with benzoic acid to give only 2-diphenylmethylaminopyridine, although it is significant that the desired 2-benzilamidopyridine could be obtained by reaction with methyl benzoate under similar conditions. 2-Amino-3-picoline reacted with mandelic acid to yield a cyclized product, presumably an imidazopyridinone. A number of the aminopyridine derivatives displayed analgesic activity. Many of the compounds also have interneuronal blocking properties.

The literature presents several demonstrations that 2-aminopyridines are alkylated predominantly at the ring nitrogen except when the steric requirements of the alkyl halide are great enough to direct reaction to the exocyclic nitrogen.<sup>2</sup> On the other hand, acylation normally occurs at the exocyclic nitrogen.<sup>3</sup> It would appear that the alkylation reactions are subject to rate control and the acylations to equilibrium control, an interpretation in accord with the presumed relative instability of a 1-acyl derivative. On this basis acylation could be roughly formulated as in (1).



The postulated conversion A  $\rightarrow$  B could proceed intra- and/or inter-molecularly.

Interest in the preparation of aminopyridine derivatives substituted on the amino nitrogen, then, prompted this study of the acylation of aminopyridines with substituted glycolic acids. The resulting amides (see Table I) were smoothly reduced with lithium aluminum hydride to provide good yields of the  $\beta$ -hydroxyalkylaminopyridine derivatives described in Table II. A number of the derivatives listed in Tables I and II have been found to have promising analgesic activity.<sup>4</sup> It is particularly intriguing that in quite a few of the compounds analgesic activity is accompanied by marked interneuronal blocking action.<sup>4</sup>

For the most part, the glycolamidopyridines were prepared by refluxing equimolar quantities of the glycolic acid and the aminopyridine in xylene with

continuous separation of the water produced. Yields were generally in the range 50-60%. Heating the reactants without solvent at oil-bath temperatures of 180-200° afforded much lower yields associated with considerable decomposition. The bright yellow-orange color of the reaction solutions and the frequently bright yellow color of the crude products suggests that the remaining material contained 1-substituted product(s) formed either by cyclization of the glycolamidopyridine or by initial reaction at the ring nitrogen. On the basis of their physical properties and chemical behavior<sup>5</sup> as well as the evidence in the literature,<sup>3</sup> there can be no question that the isolated products are amides involving the amino nitrogen, as formulated in Table I.

Methyl or halogen substituents on the 4-, 5- or 6-position of the 2-aminopyridine nucleus had no appreciable effect on the course of reaction. When, however, a 3-substituted derivative, 3-methyl-2-aminopyridine, was treated with *dl*-mandelic acid under the usual conditions, no mandelamide product was isolated but only a yellow, crystalline substance, the empirical formula of which showed that cyclization had occurred. The ultraviolet spectrum<sup>5</sup> of the product clearly indicated the involvement of the ring nitrogen in the reaction and thus ruled out a cyclization of an intermediate acylaminopyridine at the 3-methyl group, either to an azaindole (by a Madelung process) or to a tetrahydro-azaquinoline. Since it has recently been shown<sup>6</sup> that 3-methyl-2-aminopyridine adds to ethyl acrylate exclusively at the ring rather than the amino nitrogen, it appears likely that the same, presumably steric, effect of the 3-substituent prevailed here. On this basis initial reaction must have been at the ring nitrogen and might have involved either acylation<sup>7</sup> or alkylation. The ultimate product is therefore presumed to be an imidazopyridinone, either XX or XXa.

Although no evidence which would permit a definite assignment of structure has as yet been obtained, our admittedly intuitive preference is for XX on the ground that under the reaction conditions initial alkylation of the ring nitrogen seems less likely than acylation.

In contrast to the 2-aminopyridines, 4-aminopyridine yielded only starting material when reacted

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

(2) E.g., A. E. Chichibabin, R. A. Kononova and A. Kononova, *Ber.*, **54**, 814 (1921); T. M. Sharp, *J. Chem. Soc.*, 1855 (1939); I. A. Kaye, I. C. Kogan and C. L. Parris, *THIS JOURNAL*, **74**, 403 (1952); Ya. L. Gol'dfarb and Ya. L. Danyushevskii, *Doklady Akad. Nauk S.S.S.R.*, **87**, 223 (1952); *C.A.*, **48**, 679<sup>e</sup> (1954).

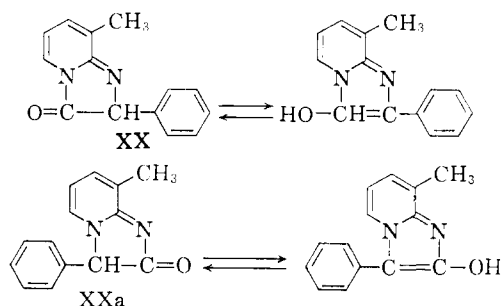
(3) A. E. Chichibabin and I. G. Bylinken, *Ber.*, **55**, 998 (1922); A. E. Chichibabin, *ibid.*, **57**, 2092 (1924); E. H. Huntress and H. C. Walter, *J. Org. Chem.*, **13**, 735 (1948).

(4) T. B. O'Dell, L. R. Wilson, M. D. Napoli, H. D. White and J. H. Mirsky, *J. Pharmacol. Exptl. Therap.*, in press; one of the compounds, 2-( $\beta$ -hydroxyphenethylamino)pyridine (X), is currently undergoing extensive clinical trials as a combined analgesic and muscle relaxant.

(5) See also A. P. Gray, D. E. Heitmeier and E. E. Spinner, *THIS JOURNAL*, **81**, 4351 (1959).

(6) G. R. Lappin, *J. Org. Chem.*, **23**, 1358 (1958).

(7) To our knowledge acylation of the ring nitrogen has only been demonstrated in those cases in which a cyclized, completely conjugated structure is ultimately produced; e.g., G. R. Lappin, *THIS JOURNAL*, **70**, 3348 (1948); R. Adams and I. J. Pachter, *ibid.*, **74**, 5491 (1952).



with mandelic acid either in boiling xylene or without solvent. Since amide formation is surely a process in which the neutral aminopyridine effects cleavage of the acyl-oxygen bond of the neutral acid (or of the lactide<sup>8</sup>), explanation would seem to lie in the much greater basicity of 4-aminopyridine as compared with the 2-derivative.<sup>9</sup> Presumably, the 4-aminopyridinium mandelate salt is stabilized sufficiently to preclude, for practical purposes, lactide and/or amide formation. In order to prepare the desired derivative, reaction with *dl*-O-acetylmandelyle chloride was resorted to. This yielded a crude product, presumably 4-(O-acetylmandelamido)-pyridine, which could not be purified and was reduced directly with lithium aluminum hydride to provide 4-( $\beta$ -hydroxyphenethylamino)-pyridine (XI).

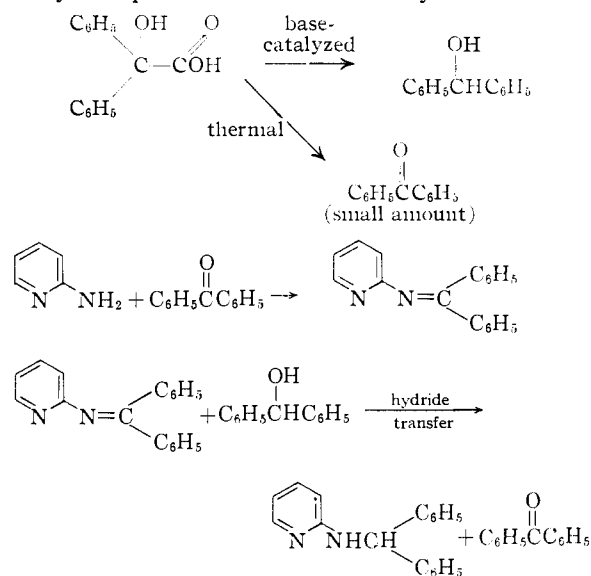
The monosubstituted glycolic acids (lactic, mandelic, hexahydromandelic) formed amides with 2-aminopyridine with about equal facility. The disubstituted glycolic acid, benzilic acid, on the other hand, reacted differently. In boiling xylene benzilic acid and 2-aminopyridine interacted to afford a poor yield of a product which was not the benzilamide derivative. Surprisingly, a much better yield (60%) of the same material was obtained when the reaction was carried out at 185° in the absence of solvent. Analysis, the melting points of the base and the hydrochloride salt, and the melting points of mixtures with authentic material revealed the product to be 2-diphenylmethylaminopyridine. The over-all reaction, therefore, involved elimination of the elements of water and carbon dioxide.

In attempting to plot the course of this reaction, it is significant to note that 2-benzilamidopyridine (IX) was successfully prepared by treating 2-aminopyridine with the methyl ester of benzilic acid in boiling xylene containing a catalytic amount of metallic sodium. (Use of the ester in place of the acid, in those cases in which a direct comparison was made, appeared—as was expected—to give slightly better yields of amides and less in the way of decomposition products. In general, the advantages did not seem great enough to justify introducing the extra step of preparing the ester.) The difference in behavior of benzilic acid and its methyl ester rules out the rather remote possibility that loss of CO<sub>2</sub> might have taken place subsequent to amide formation and indicates that the benzilic acid lost the elements of carbon dioxide either prior to or simultaneously with reaction. The literature states

(8) K. Stutz, *Ber.*, **44**, 3485 (1911).

(9) A. Albert, R. Goldacre and J. Phillips, *J. Chem. Soc.*, 2240 (1948), report for 2-aminopyridine, *pKa* 6.86; for 4-aminopyridine, *pKa* 9.17.

that thermal decomposition of benzilic acid gives the products to be expected of an  $\alpha$ -hydroxy carboxylic acid, *i.e.*, benzophenone, carbon monoxide, possibly diphenyl ketene and diphenylacetic acid.<sup>10</sup> On the other hand, typical base-catalyzed decarboxylation does take place, when the barium salt of benzilic acid is distilled with soda lime, to give benzhydrol and carbon dioxide.<sup>11</sup> In this connection note might be taken of the recent report<sup>12</sup> that heating  $\alpha$ -methylphenethylamine with benzilic acid, under essentially the same conditions used here, afforded the corresponding imine of benzophenone, a result difficult to reconcile with the present findings. Inspection of the data reported by the other workers,<sup>12</sup> however, reveals that their product was incompletely characterized and may possibly have been the diphenylmethylamine derivative. Certainly their analytical results accord at least as well with the amine as with the imine structure. Suggestive also is the fact that the compound was obtained in better yield from benzilic acid (34%) than from benzophenone (17%). On the basis of the information at hand, the present reaction may tentatively be represented in a skeletal way as



Of course in the absence of further evidence nothing can be said concerning the details of the reaction or, alternatively, as to whether some kind of concerted process, in which decarboxylation and alkylation are interrelated, might be involved. In any case it would appear that with the monosubstituted glycolic acids amide formation proceeds more rapidly than the analogous side reactions.

The properties of many of these compounds are further discussed in the following paper.<sup>5</sup>

### Experimental<sup>13</sup>

**Intermediates.**—O-Acetylmandelyle chloride,<sup>14</sup> b.p. 120° (7 mm.), hexahydromandelic acid,<sup>15</sup> m.p. 132–134°, and

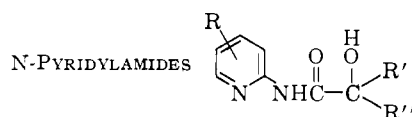
(10) H. Staudinger, *Ber.*, **44**, 543 (1911); A. Lachman, *This Journal*, **44**, 335 (1922).

(11) A. Jena, *Ann.*, **155**, 77 (1870).

(12) S. I. Shapiro, I. M. Rose and L. Freedman, *This Journal*, **80**, 6065 (1958).

(13) 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.

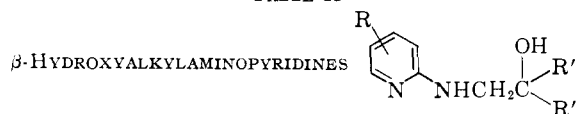
TABLE I



	R	R'	R''	Salt	M.p., °C. <sup>c</sup>	Formula	Carbon, %		Hydrogen, %		Chlorine, % <sup>a</sup>	
							Calcd.	Found	Calcd.	Found	Calcd.	Found
I	H	Phenyl	H	..	119.5-121	C <sub>13</sub> H <sub>12</sub> N <sub>2</sub> O <sub>2</sub>					6.14 <sup>b</sup>	6.05 <sup>b</sup>
				HCl	182-184	C <sub>13</sub> H <sub>13</sub> ClN <sub>2</sub> O <sub>2</sub>	58.98	59.23	4.95	4.90	13.40	13.14
II	4-Methyl	Phenyl	H	..	143-146	C <sub>14</sub> H <sub>14</sub> N <sub>2</sub> O <sub>2</sub>					5.78 <sup>b</sup>	5.72 <sup>b</sup>
				HCl	188-189	C <sub>14</sub> H <sub>15</sub> ClN <sub>2</sub> O <sub>2</sub>	60.34	60.56	5.42	5.68	12.74	12.66
III	4,6-Di-methyl	Phenyl	H	..	167-169	C <sub>15</sub> H <sub>16</sub> N <sub>2</sub> O <sub>2</sub>					5.46 <sup>b</sup>	5.40 <sup>b</sup>
				HCl	195-196	C <sub>15</sub> H <sub>17</sub> ClN <sub>2</sub> O <sub>2</sub>	61.54	61.82	5.85	5.84	12.11	11.86
IV	5-Methyl	Phenyl	H	..	141-142	C <sub>14</sub> H <sub>14</sub> N <sub>2</sub> O <sub>2</sub>					5.78 <sup>b</sup>	5.62 <sup>b</sup>
				HCl	203	C <sub>14</sub> H <sub>15</sub> ClN <sub>2</sub> O <sub>2</sub>	60.34	60.57	5.42	5.32	12.74	12.15
V	5-Chloro	Phenyl	H	..	146-148	C <sub>13</sub> H <sub>11</sub> ClN <sub>2</sub> O <sub>2</sub>					5.33 <sup>b</sup>	4.98 <sup>b</sup>
				HCl	169	C <sub>13</sub> H <sub>12</sub> Cl <sub>2</sub> N <sub>2</sub> O <sub>2</sub>	52.20	52.07	4.04	4.14	11.85	11.81
VI	5-Bromo	Phenyl	H	..	155-156	C <sub>13</sub> H <sub>11</sub> BrN <sub>2</sub> O <sub>2</sub>					4.56 <sup>b</sup>	4.36 <sup>b</sup>
				HCl	175	C <sub>13</sub> H <sub>12</sub> BrClN <sub>2</sub> O <sub>2</sub>	45.43	45.79	3.52	3.43	10.32	9.94
VII	H	Methyl	H	..	126-128	C <sub>8</sub> H <sub>11</sub> ClN <sub>2</sub> O <sub>2</sub>	47.40	47.28	5.47	5.36	17.50	17.35
VIII	H	Cyclo-hexyl	H	..	118-120	C <sub>13</sub> H <sub>18</sub> N <sub>2</sub> O <sub>2</sub>					5.98 <sup>b</sup>	6.06 <sup>b</sup>
IX	H	Phenyl	Phenyl	..	215-216	C <sub>19</sub> H <sub>16</sub> N <sub>2</sub> O <sub>2</sub>					4.60 <sup>b</sup>	4.31 <sup>b</sup>
				HCl	205	C <sub>19</sub> H <sub>17</sub> ClN <sub>2</sub> O <sub>2</sub>	66.96	67.41	5.03	5.09	10.40	10.35

<sup>a</sup> Potentiometric determination of ionic chlorine. <sup>b</sup> Basic nitrogen, by acetous perchloric titration. <sup>c</sup> The salts melt with decomposition. <sup>d</sup> B.p. 140-143° (1 mm.).

TABLE II



	R	R'	R''	Salt	M.p., °C. <sup>c</sup>	Formula	Carbon, %		Hydrogen, %		Halogen, % <sup>a</sup>	
							Calcd.	Found	Calcd.	Found	Calcd.	Found
X	H	Phenyl	H	..	83-85	C <sub>13</sub> H <sub>14</sub> N <sub>2</sub> O					6.54 <sup>b</sup>	6.44 <sup>b</sup>
				HCl	140-142	C <sub>13</sub> H <sub>15</sub> ClN <sub>2</sub> O	62.27	62.54	6.03	6.17	14.14	13.92
				CH <sub>3</sub> I	164-166	C <sub>14</sub> H <sub>17</sub> IN <sub>2</sub> O	47.21	47.54	4.81	5.20	35.64	35.24
XI	H <sup>d</sup>	Phenyl	H	..	132-133	C <sub>13</sub> H <sub>15</sub> ClN <sub>2</sub> O	62.27	61.83	6.03	5.99	14.14	14.07
XII	4-Methyl	Phenyl	H	..	90-91	C <sub>14</sub> H <sub>16</sub> N <sub>2</sub> O					6.13 <sup>b</sup>	6.01 <sup>b</sup>
				HCl	135-136.5	C <sub>14</sub> H <sub>17</sub> ClN <sub>2</sub> O	63.53	63.65	6.47	6.58	13.40	13.19
XIII	4,6-Di-methyl	Phenyl	H	..	77-78	C <sub>15</sub> H <sub>18</sub> N <sub>2</sub> O					5.77 <sup>b</sup>	5.65 <sup>b</sup>
				HCl	131-133	C <sub>15</sub> H <sub>19</sub> ClN <sub>2</sub> O	64.64	64.67	6.87	6.82	12.72	12.56
XIV	5-Methyl	Phenyl	H	..	97-99	C <sub>14</sub> H <sub>16</sub> N <sub>2</sub> O					6.13 <sup>b</sup>	5.92 <sup>b</sup>
				HCl	115-117	C <sub>14</sub> H <sub>17</sub> ClN <sub>2</sub> O	63.53	63.03	6.47	6.17	13.40	13.43
XV	5-Chloro	Phenyl	H	..	102-103	C <sub>13</sub> H <sub>13</sub> ClN <sub>2</sub> O					5.63 <sup>b</sup>	5.43 <sup>b</sup>
				HCl	177-178	C <sub>13</sub> H <sub>14</sub> Cl <sub>2</sub> N <sub>2</sub> O	54.76	55.01	4.95	5.16	12.43	12.38
XVI	5-Bromo	Phenyl	H	..	110-111	C <sub>13</sub> H <sub>13</sub> BrN <sub>2</sub> O					4.78 <sup>b</sup>	4.81 <sup>b</sup>
				HCl	185-187	C <sub>13</sub> H <sub>14</sub> BrClN <sub>2</sub> O	47.36	47.83	4.28	4.40	10.75	10.70
XVII	H	Methyl	H	..	164-165	C <sub>8</sub> H <sub>13</sub> ClN <sub>2</sub> O	50.93	50.22	6.94	6.93	18.79	18.84
XVIII	H	Cyclo-hexyl	H	..	86-88	C <sub>13</sub> H <sub>20</sub> N <sub>2</sub> O					6.36 <sup>b</sup>	6.28 <sup>b</sup>
				HCl	141-143	C <sub>13</sub> H <sub>21</sub> ClN <sub>2</sub> O	60.80	60.76	8.24	8.21	13.81	13.72
XIX	H	Phenyl	Phenyl	..	167-169	C <sub>19</sub> H <sub>15</sub> N <sub>2</sub> O					4.82 <sup>b</sup>	4.74 <sup>b</sup>
				HCl	200-202	C <sub>19</sub> H <sub>16</sub> ClN <sub>2</sub> O	69.81	69.72	5.86	5.98	10.85	10.73

<sup>a</sup> Potentiometric determination of ionic halogen. <sup>b</sup> Basic nitrogen, by acetous perchloric titration. <sup>c</sup> The salts melt with decomposition. <sup>d</sup> 4-Aminopyridine derivative. <sup>e</sup> Light yellow oil.

methyl benzilate,<sup>16</sup> m.p. 69-71°, were prepared by the usual procedures. Bromination of 2-aminopyridine<sup>17</sup> provided 5-bromo-2-aminopyridine, m.p. 136-138°, together with

3,5-dibromo-2-aminopyridine, m.p. 103-105°. The other aminopyridines used were obtained from the Reilly Tar and Chemical Co.

**Preparation of Amides by Reaction with  $\alpha$ -Hydroxy Acids.** **2-Mandelamidopyridine (I).**—An example will illustrate the method used for the preparation of most of the compounds described in Table I. In a flask fitted with a moisture trap were placed 18.8 g. (0.2 mole) of 2-aminopyridine, 30.4 g. (0.2 mole) of *dl*-mandelic acid and 120 ml. of xylene. The mixture was heated under reflux in an oil-bath (bath temperature 165-170°) for 20 hours during which time 3.2 ml. (90%) of water was collected. On cooling the

(14) F. K. Thayer, "Organic Syntheses," Coll. Vol. 1, second edition, John Wiley and Sons, Inc., New York, N. Y., 1947, p. 12.

(15) F. F. Blicke and W. K. Johnson, *J. Am. Pharm. Assoc., Sci. Ed.*, **45**, 437 (1956).

(16) S. F. Acree, *Ber.*, **37**, 2764 (1904).

(17) A. E. Chichibabin and V. S. Tyazhlova, *J. Russ. Phys.-Chem. Soc.*, **50**, 483 (1920); *C. A.*, **18**, 1495 (1924); H. L. Bradlow and C. A. VanderWerf, *J. Org. Chem.*, **16**, 81 (1951).

resultant orange solution, a thick oil precipitated and partially crystallized. Dilution of the mixture with benzene afforded 23.2 g. of bright yellow crystals, m.p. 117–119°. This material was recrystallized from aqueous ethanol to give 20.0 g. of long, flat, almost colorless needles, m.p. 119.5–121°. The original benzene-xylene mother liquor was extracted with dilute acid, the acid solution was made alkaline and extracted with ether. Drying and removal of the ether left an oil which crystallized on standing. Recrystallization from aqueous ethanol afforded an additional 6.2 g. of product, m.p. 118–121°. The total yield of I was 26.2 g. (57%).

**2-Mandelamidopyridine hydrochloride**, recrystallized from methanol-ether, showed m.p. 182–184° dec.

**Reaction of 2-Aminopyridine with Benzilic Acid. 2-Diphenylmethylaminopyridine.**—When this reaction was run in xylene at reflux for 40 hours as described for the mandelic acid derivative, 75% of the calculated amount of water was collected but the only isolable product was a basic substance, m.p. 101–102°, obtained in 20% yield. Without solvent the same product was obtained in much better yield. A mixture of 15.0 g. (0.16 mole) of 2-aminopyridine and 36.5 g. (0.16 mole) of benzilic acid was heated in an oil-bath at 185° for 3 hours. The reaction mixture was diluted with benzene, washed with 10% sodium carbonate and then with water. Drying of the benzene layer and evaporation left a solid which was crystallized from isopropyl alcohol to give 29.0 g. (60% yield) of white crystalline material, m.p. 100–101°. A mixture of this and authentic 2-diphenylmethylaminopyridine (m.p. 101–102°), prepared as described by Kaye, *et al.*,<sup>2</sup> melted at 101–102°.

*Anal.* Calcd. for C<sub>18</sub>H<sub>16</sub>N<sub>2</sub>: N (basic), 5.38. Found: N, 5.21.

The hydrochloride salt melted at 197–198° after recrystallization from ethanol-ether. The melting point of a mixture with authentic 2-diphenylmethylaminopyridine hydrochloride (lit.<sup>18</sup> m.p. 192–193°) was not depressed.

*Anal.* Calcd. for C<sub>18</sub>H<sub>17</sub>ClN<sub>2</sub>: C, 72.85; H, 5.77; Cl, 11.94. Found: C, 72.65; H, 5.62; Cl (ionic), 12.03.

**Reaction of 2-Aminopyridine with Methyl Benzilate. 2-Benzilamidopyridine (IX).**—To a solution of 15.0 g. (0.16 mole) of 2-aminopyridine and 39.0 g. (0.16 mole) of methyl benzilate in 100 ml. of dry xylene was added 0.5 g. of metallic sodium. The reaction mixture was heated under reflux in an oil-bath (bath temperature 180–185°) for 40 hours. The cooled solution, diluted with benzene, afforded a solid precipitate which was recrystallized from isopropyl alcohol to yield 15.8 g. (32%) of IX, colorless needles, m.p. 215–216°.

**IX hydrochloride**, recrystallized from ethanol, showed m.p. 205° dec.

**Reaction of 4-Aminopyridine with *dl*-O-Acetylmandelyl Chloride.**—A mixture of 25.0 g. (0.12 mole) of *dl*-O-acetylmandelyl chloride, 11.1 g. (0.12 mole) of 4-aminopyridine and 25 g. (0.23 mole) of anhydrous sodium carbonate in 100 ml. of benzene was heated under reflux, with occasional swirling, for 7 hours on the steam-bath. The cooled reaction mixture was washed with water, dried and concentrated *in vacuo* to give 17.0 g. of crude 4-(O-acetylmandelamido)-pyridine as a light yellow oil which solidified to a glass on cooling. This material could not be crystallized and was used in the reduction step without further purification.

**Reaction of 3-Methyl-2-aminopyridine with Mandelic Acid. *x*-Phenyl-8-methylimidazo[1,2-*a*]pyridin-*y*(*xH*)-one (XX or XXa).**—A mixture of 35.0 g. (0.33 mole) of 3-methyl-2-aminopyridine, 52 g. (0.34 mole) of mandelic acid and 150 ml. of xylene was placed in a flask fitted with a moisture trap and heated at reflux for 20 hours. The re-

sultant solution afforded a precipitate of gummy solid on cooling. A chloroform solution of this was washed with 10% sodium carbonate and then with water. Drying and removal of the chloroform left an oily solid residue that was crystallized and recrystallized from methanol to provide 9.0 g.<sup>19</sup> of yellow needles, m.p. 247–249°.

*Anal.* Calcd. for C<sub>14</sub>H<sub>12</sub>N<sub>2</sub>O: C, 75.00; H, 5.39; N (basic), 6.23. Found: C, 74.76; H, 5.33; N (basic), 6.04.

The hydrochloride salt formed colorless crystals, m.p. 224–226° dec.

*Anal.* Calcd. for C<sub>14</sub>H<sub>13</sub>ClN<sub>2</sub>O: C, 64.50; H, 5.02; Cl, 13.60. Found: C, 64.17; H, 5.18; Cl (ionic), 13.50.

**The Lithium Aluminum Hydride Reduction of the Amidopyridines.**—The amidopyridines listed in Table II were all prepared by this method which is illustrated by the following examples.

**A. 2-( $\beta$ -Hydroxyphenethylamino)-pyridine (X).**—To a slurry of 35.0 g. (0.92 mole) of lithium aluminum hydride in 1400 ml. of dry ethylene glycol dimethyl ether was added, in small portions with stirring, 140 g. (0.61 mole) of I. After the addition was complete, the reaction mixture was stirred for 5 hours at room temperature. Ethyl acetate was added to decompose the excess reagent. The ice-cold reaction mixture was cautiously treated with water, acidified with dilute hydrochloric acid, and concentrated *in vacuo* to a small volume in order to remove the glycol ether. An aqueous solution of 100 g. of tartaric acid was added to the residual liquor, which was then made strongly alkaline and extracted with ether. Drying and removal of the ether and crystallization of the oil residue from benzene-Skellysolve B followed by recrystallization from aqueous methanol afforded 106 g. (81%) of X as colorless crystals, m.p. 83–85°.

The hydrochloride salt of X formed colorless, hygroscopic crystals from ethanol-ether, m.p. 140–142° with gas evolution.

The methiodide of X, prepared in ethanol and recrystallized from ethanol-methanol, melted at 164–166°.

**B. 2-( $\beta$ -Hydroxyphenethylamino)-4-picoline (XII).**—To a slurry of 5.0 g. (0.13 mole) of lithium aluminum hydride in 300 ml. of dry ether was added, dropwise with stirring, a solution of 20.0 g. (0.08 mole) of II in 250 ml. of dry, purified tetrahydrofuran. The reaction mixture was stirred and heated under reflux for 7 hours on a steam-bath. The ice-cold reaction mixture was treated with ethyl acetate, water and then acidified with 10% hydrochloric acid. Tartaric acid (40 g.) was added to the separated acid layer which was then made strongly alkaline. Extraction with ether, drying and evaporation of the ether layer left an oil which was crystallized from isopropyl alcohol. Recrystallization provided 15.5 g. (85%) of XII, m.p. 90–91°.

The hydrochloride salt of XII, crystallized from ethanol-ether, formed colorless needles, m.p. 135–136.5° dec.

**C. 4-( $\beta$ -Hydroxyphenethylamino)-pyridine (XI).**—Essentially as described for XII, 15.0 g. (0.05 mole) of crude 4-(O-acetylmandelamido)-pyridine was treated with 5.0 g. (0.13 mole) of lithium aluminum hydride to yield 10.0 g. of XI as a pale yellow oil which resisted crystallization.

The hydrochloride salt of XI, recrystallized from ethanol-ether, showed m.p. 132–133° dec.

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(18) L. A. R. Hall and J. H. Burckhalter, *THIS JOURNAL*, **73**, 473 (1951).

(19) Since about half the product was inadvertently lost during the work-up, the actual yield was appreciably better than that indicated.