[CONTRIBUTION FROM THE PURDUE RESEARCH FOUNDATION AND THE DEPARTMENT OF CHEMISTRY, PURDUE UNIVERSITY]

DERIVATIVES OF THE PYRIDOQUINOLINES[1]

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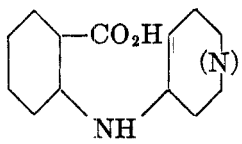
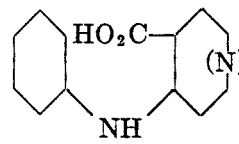
As part of the antimalarial program pursued in this laboratory it was decided to attempt the preparation of compounds like Atabrine (quinacrine) but with one of the benzene rings replaced by a pyridine ring. There is good evidence that an electron withdrawing group in the 2-position of the Atabrine nucleus can replace the usual 3-chloro group without marked diminution in activity. Thus, the 2-nitro and the pyrido(3,2-a) derivatives of 7-methoxy-9-substituted-amino-acridines are reported active (1, 2).

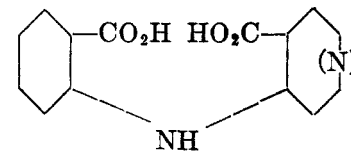
A reasonable approach to pyridoquinolines would appear to be *via* ring closure reactions on acids of the following types.



Ia



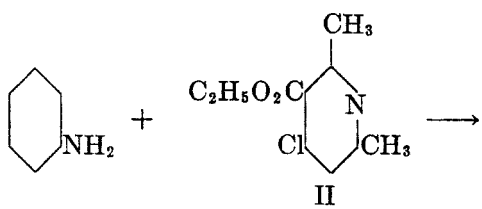
Ib



Ic

The resulting pyridoquinolones (using H_2SO_4) or chloropyridoquinolines (using $POCl_3$) could then be converted into the desired amino derivatives by processes which are well known in the acridine series. Actually it was found that acids of type Ia will decarboxylate before they will dehydrate to pyridoquinolones, acids of type Ib will undergo ring closure only under certain unfavorable circumstances, and acids of type Ic (only one of which was tested) give no detectable amounts of pyridoquinolones when heated in the form of their calcium salt to 400°. These observations correspond for the most part with previously reported results. Kermack (3) and Petrow (4) were unable to cyclize various N-pyridyl-anthranilic acids (type Ia) and N-anthranylpyridines (type Ib).

Our approach to pyrido(4.3-b)quinolones is illustrated below.



II

[1] From the Ph.D. thesis of R. S. Barker, Purdue University, June 1948. Read before the Organic Division at the St. Louis meeting of the American Chemical Society, September 1948.

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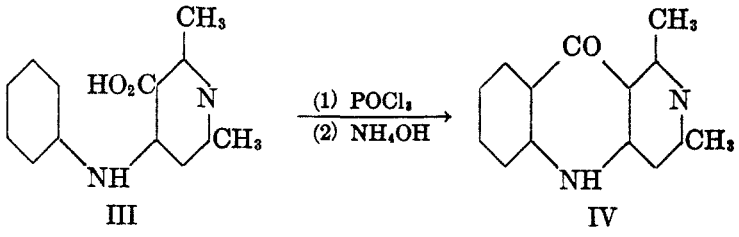
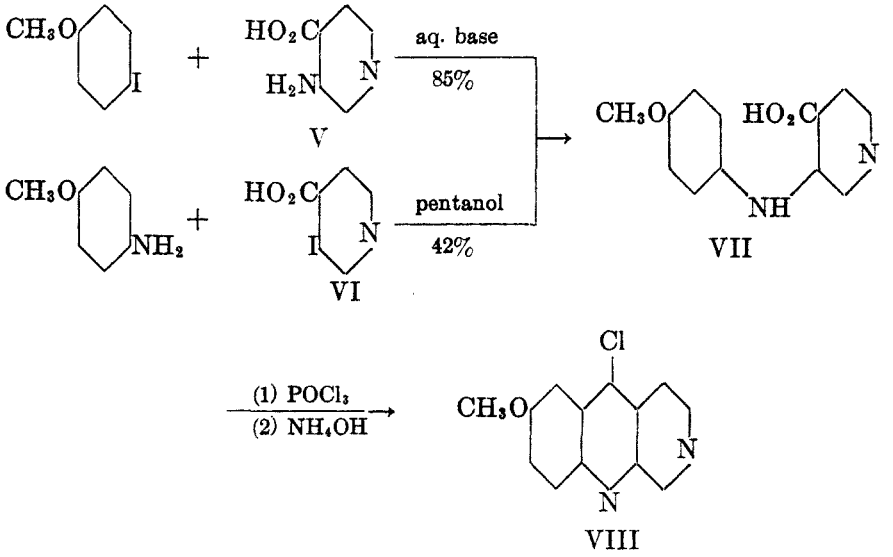


III IV

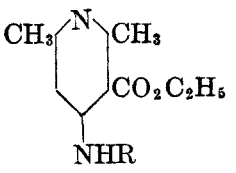
The reactions proceeded in excellent yields, but all attempts to convert IV to a 9-chloropyridoquinoline with $POCl_3$, PCl_5, etc. were unsuccessful. Furthermore, if the methyl substituents of II were eliminated, not even a pyridoquinolone could be obtained. Ring closure is apparently dependent on the presence of activating groups such as methyl. Attempts to prepare 9-aminopyridoquinolines directly, by heating IV with urea, ammonium formate, or 3-diethylaminopropylamine, were completely unsuccessful. Also treatment of IV with P_2S_5 did not yield the 9-thiol (5).

The pyrido(3.4-b)quinolones were approached as shown in formulas V–VIII

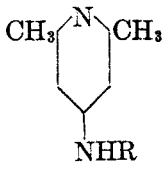


Treatment of VII with $POCl_3$ did not give the desired pyridoquinolone or the chloropyridoquinoline (VIII).

Synthesis of intermediates. Ethyl 4-chloro-2,6-dimethylnicotinate (II) was prepared from ethyl 3-aminocrotonate through treatment with $POCl_3$, in twice the yields obtained previously (6), by reaction at 100° in the absence of solvents. Its condensation with amines (aniline, *p*-anisidine, 2-naphthylamine, 6-methoxy-8-aminoquinoline, and 4-diethylamino-1-methylbutylamine) gave not only products like III but also the corresponding ester IX and the decarboxylated pyridine X. Appreciable amounts of X were also isolated when III was treated with $POCl_3$.

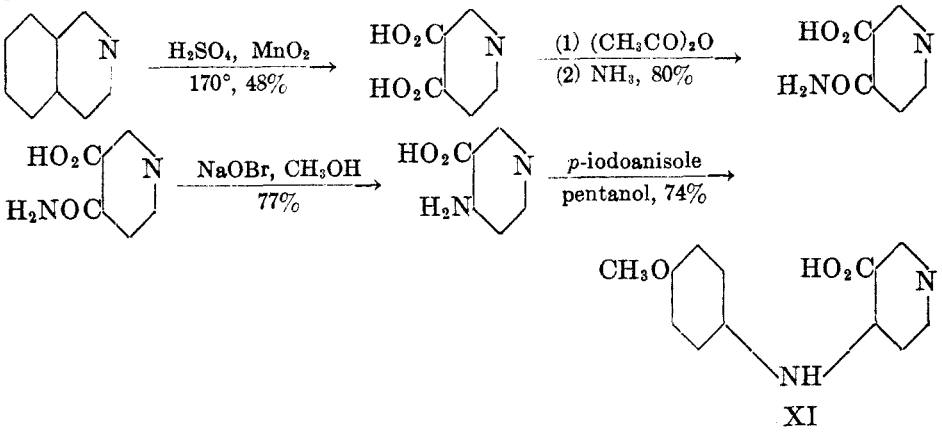


IX



X

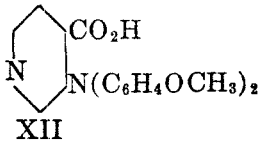
The preparation of unmethylated III was laborious. Isoquinoline was sulfonated and then oxidized by MnO_2 to cinchomeronic acid. This was converted to 4-aminonicotinic acid by improved procedures and then condensed with *p*-iodoanisole to give XI.



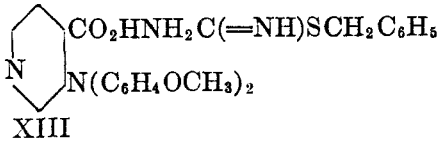
XI

Numerous attempts to convert XI to the desired chloropyridoquinoline or even to the pyridoquinolone were unsuccessful. Products of unknown structure and tars were obtained.

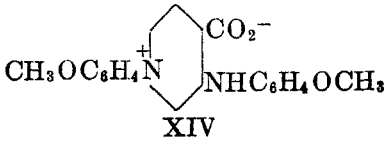
3-Aminoisonicotinic acid (V) was prepared from cinchomeronimide *via* the Hofmann degradation with hypobromite. Its condensation with *p*-iodoanisole gave VII under the indicated conditions, but in refluxing hexanol an entirely different product (XII) was obtained. Condensation of *p*-anisidine with 3-iodoisonicotinic acid (VI), obtained by the diazotization of V, also gave VII.



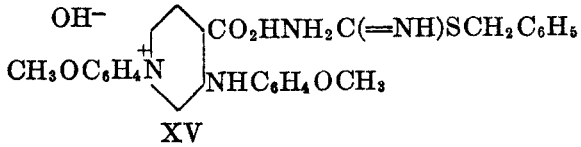
XII



XIII



XIV



XV

An analysis of the S-benzylthiouronium salt (XIII) helped in determining the structure of XII. The percentages of carbon, hydrogen, and sulfur showed that XIII and hence XII had been formed, rather than XV and hence XIV.

Pharmacological testing. The hydrochlorides of IV were found inactive against *Streptococcus hemolyticus*, influenza virus, tetanus, rabic virus, and trypanosomes. The hydrochloride of IX, when R was 6-methoxy-8-aminoquinolinyl, showed no activity as a germicide or bacteriostatic agent. It was slightly active as an amebicide. The hydrochlorides of X, when R was the 4-diethylamino-1-methylbutylamine side chain, and of IV and IX showed no antimalarial activity.

Acknowledgment. The authors wish to express their appreciation to Eli Lilly and Company for financial support in the form of a fellowship and for pharmacological testing.

EXPERIMENTAL

Ethyl 4-chloro-2,6-dimethylnicotinate (II). *cf.* (6). Ethyl 3-aminocrotonate (6, 7), 785 g., was slowly added to stirred phosphorus oxychloride, 1890 g., at 100°. The mixture was stirred until the evolution of hydrogen chloride became negligible, the excess phosphorus oxychloride was removed under a vacuum and the mixture was carefully poured into 6 kg. of cracked ice. After neutralization with alkali below 25°, the product was extracted with benzene, dried with sodium carbonate, treated with Norit, filtered, and distilled to yield 393 g. (70%) of product, b.p. 97–105° (2 mm.), n_D^{27} 1.5032.

4-Substituted-2,6-dimethylnicotinic acids (III). These were all prepared essentially in the same way. *p*-Anisidine, 12 g., and ethyl 4-chloro-2,6-dimethylnicotinate, 10 g., were cautiously warmed to 150° and the reaction allowed to proceed spontaneously. The temperature rose to 205°, where it was held for 4 minutes. The cooled gummy residue was dissolved in a mixture of benzene and dilute alkali, the aqueous phase treated with Norit, filtered and neutralized with dilute hydrochloric acid. When crystallized from 50% methanol or 5% acetic acid, 4-(*p*-methoxyphenylamino)-2,6-dimethylnicotinic acid, 7.2 g., m.p. 271–272°, was obtained.

Anal. Calc'd for $C_{15}H_{16}N_2O_2$: N, 10.28. Found: N, 10.08, 10.20.

The benzene layer was extracted with water, dried and distilled. The residue was crystallized from isopropyl ether to yield a small amount of ethyl 4-(*p*-methoxyphenylamino)-2,6-dimethylnicotinate (IX), m.p. 92–93°. This compound was also prepared by heating equal quantities of the chloro ester and *p*-anisidine on a steam-bath for several hours. The residue was made alkaline, extracted with a large quantity of ether, dried, and the ether was distilled. The residue was crystallized from isopropyl ether a number of times.

Anal. Calc'd for $C_{17}H_{20}N_2O_3$: N, 9.34. Found: N, 9.35, 9.49.

The 4-phenylamino analog of III was crystallized from cold water, m.p. 244–245° (6); the hydrochloride from chloroform-ether, m.p. 167–168°.

The 4-(2′-naphthylamino) analog of III was crystallized from aqueous ethanol, m.p. 262–263°.

Anal. Calc'd for $C_{18}H_{16}N_2O_2$: N, 9.59. Found: N, 9.65, 9.57.

Pyrido(4.3-b)quinolones (IV). These were all prepared in the same manner. 4-(*p*-Methoxyphenylamino)-2,6-dimethylnicotinic acid, 22.5 g., was gently refluxed 3–4 hours with phosphorus oxychloride, 100 g. About one-third of the solvent was removed under vacuum and the residual mixture was poured on ice. The black solution was neutralized with aqueous potassium carbonate, the precipitate washed with ether and crystallized from ethanol to yield yellow crystals of 1,3-dimethyl-8-methoxypyrido(4.3-b)quinolone, m.p. 298–299°. The hydrochloride, 14.7 g. (69.9%), from ethanol, melted at 319–320° (d.) (copper block, 60 seconds).

Anal. Calc'd for $C_{15}H_{14}N_2O_2(HCl)$: N, 9.64; Cl, 12.22.
Found: N, 9.73, 9.66; Cl, 12.22, 12.09.

The alkaline carbonate filtrate from the initial reaction was extracted with ether and all the ether washings were combined and dried with sodium hydroxide, filtered, and saturated with hydrogen chloride, to yield the hydrochloride of 4-(*p*-methoxyphenylamino)-2,6-dimethylpyridine (X), m.p. 229–230°, (from ethanol-ether).

Anal. Calc'd for $C_{14}H_{16}N_2O(HCl)$: N, 10.59. Found: N, 10.42, 10.48.

A similar reaction with 4-phenylamino-2,6-dimethylnicotinic acid yielded 1,3-dimethylpyrido(4.3-b)quinolone, m.p. 319–320° (d.), (from ethanol); hydrochloride (from ethanol), 376–378° (d.).

Anal. Calc'd for $C_{14}H_{12}N_2O(HCl)$: N, 10.72; Cl, 13.59.
Found: N, 10.62, 10.70; Cl, 13.59, 13.52.

4-(2′-Naphthylamino)-2,6-dimethylnicotinic acid yielded pale-yellow 1,3-dimethylpyrido(4.3-b)benzo(f)quinolone, m.p. 280–282° (d.), (from pyridine or acetic acid).

Anal. Calc'd for $C_{18}H_{14}N_2O$: N, 10.21. Found: N, 10.00, 9.92.

Ethyl 2,6-dimethyl-4-(6′-methoxy-8′-quinolinylamino)nicotinate. Ethyl 4-chloro-2,6-dimethylnicotinate, 48 g., was added to butanol (300 ml.) containing 10 g. of hydrogen chloride, and 45 g. of 8-amino-6-methoxyquinoline. After refluxing for twenty-four hours the butanol was removed under vacuum, the residue taken up in water and neutralized with alkali. The precipitate was washed with a small amount of ether and crystallized from di-*n*-butyl ether (Norit) to yield 41 g. (42.5%) of product, m.p. 149–150°. The hydrochloride (from butanol-ether, or 2-propanol) melted at 247–248°. The original ether washings were shaken with Norit and powdered sodium hydroxide, filtered, and cooled overnight to yield 7.5 g. (7.9%) more product.

Anal. Calc'd for $C_{20}H_{21}N_3O_3(HCl)$: N, 10.83. Found: N, 10.76, 10.81.

2,6-Dimethyl-4-(5′-diethylamino-2′-pentylamino)pyridine. Ethyl 4-chloro-2,6-dimethylnicotinate, 30 g., 4-diethylamino-1-methylbutylamine, 35 g., sodium iodide, 0.2 g., and copper powder, 0.1 g., were held at 205° for three hours. The reaction mixture was cooled and shaken with a mixture of ether and 5 *N* sodium hydroxide. The ether layer was dried over potassium hydroxide and distilled to yield 19 g. of the 4-substituted pyridine, b.p. 163–165° (2 mm.). On redistillation the product boiled at 130–135° (0.5–1 mm.). The chloroplatinate derivative, red buttons from 50% ethanol, melted at 229–230°.

Anal. Calc'd for $C_{16}H_{29}N_3$: C, 72.90; H, 11.12; N, 15.98.
Found: C, 72.77, 72.70; H, 10.95, 11.02; N, 16.04, 16.15.

Cinchomeronic acid. The procedure is essentially that of van de Kamp and Sletzinger (8), for the preparation of quinolinic acid from quinoline. The product, however, was isolated in a different manner. The amber-colored solution obtained from the oxidation of sulfonated isoquinoline, instead of being treated with a cupric salt, was neutralized with sodium carbonate to *p*H 1 and the precipitated cinchomeronic acid filtered off after fifteen hours. The yields were 48–55%.

4-Cinchomeronic acid amide (9). Cinchomeronic anhydride (10) (prepared by refluxing 100 g. of the acid with 400 g. of acetic anhydride for 30 minutes, filtering, and removing the acetic acid and anhydride under vacuum, then distilling the product under vacuum) was taken up in 2 l. of benzene and 35 g. of dry ammonia bubbled into the refluxing and stirred solution. The mixture was cooled, hot water added and the aqueous phase was removed and saturated with sulfur dioxide at 25° to precipitate the acid amide. The filtrate yielded more product (total 65 g. or 80%) on standing overnight in an ice-box. The product was crystallized from water, washed with acetone and dried, m.p. 170–171°.

4-Aminonicotinic acid (9). Thirty-six grams of 4-cinchomeronic acid amide was dissolved with vigorous stirring and cooling in 325 ml. of 7% sodium methoxide in methanol. The solution was chilled to 0°, 32 g. of bromine slowly added, stirred for one hour at 0°, then refluxed for 20 minutes. The milky mixture was distilled under vacuum to remove the methanol, the residue was dissolved in hot water containing 40 g. of sodium hydroxide and the mixture was refluxed for several hours. It was concentrated to about 250 ml., 50 ml. of

5 *N* hydrochloric acid was added and the *p*H adjusted to 5–6 with acetic acid. The crystalline product which precipitated, 21.5 g. (77.5%), was crystallized from hot water (Norit), m.p. 338–341°.

Cinchomeronimide (11). Cinchomeronic anhydride, from 250 g. of the acid, was stirred with 240 g. of acetamide at 100° for 60 hours, the mixture cooled and triturated with cold water, then filtered. Upon crystallization from acetic acid, 189 g. (91%) of the imide, m.p. 226–227° [reported 229–230° (11)], was obtained.

3-Aminoisonicotinic acid (V). This compound was prepared according to the method of Gabriel and Coleman (12) from cinchomeronimide by the Hofmann hypobromite reaction. The product melted at 319–320° (reported 307–310°) after a number of crystallizations from hot water.

4-(p-Methoxyphenylamino)nicotinic acid (XI). A mixture of 29 g. of 4-aminonicotinic acid, 55 g. of *p*-iodoanisole, 30 g. of potassium carbonate, 125 ml. of *n*-pentanol, and 0.2 g. of a copper-copper oxide mixture (1:1) was refluxed (nitrogen atmosphere and stirring) for seventy-two hours, cooled, diluted with ether, and filtered. The precipitate was dissolved in hot dilute alkali, treated with Norit, then fractionally precipitated by the addition of small amounts of dilute hydrochloric acid. The solid precipitate, 38 g. (74%) was crystallized from hot water to yield white needles, m.p. 290–291°. It was easily soluble in methanol, less soluble in ethanol and difficultly soluble in propanol. It was soluble to the extent of 0.3–0.4% in hot water and was practically insoluble in cold water.

Anal. Calc'd for $C_{13}H_{12}N_2O_3$: C, 63.93; H, 4.95; N, 11.47.
Found: C, 63.52, 63.63; H, 5.18, 5.14; N, 11.40, 11.49.

An S-benzylthiouronium salt was prepared according to the method of Donleavy (13). No reproducibly sharp melting point could be obtained. The range was 160–175°, depending on the amount of sample and the rapidity of heating.

Anal. Calc'd for $C_{21}H_{22}N_4O_3S$: C, 61.46; H, 5.40; S, 7.82.
Found: C, 61.55, 61.51; H, 5.40, 5.45; S, 8.04, 7.92.

3-(N,N-Di-p-methoxyphenylamino)isonicotinic acid (XII). A mixture of 38.5 g. of 3-aminoisonicotinic acid, 68 g. of *p*-iodoanisole, 200 ml. of hexanol, 48 g. of potassium carbonate, and 0.5 g. of a copper-copper oxide (1:1) mixture was refluxed for seventy-two hours (nitrogen atmosphere and stirring), then steam distilled. The residue was dissolved in alkali, treated with Norit, filtered, and the mixture adjusted to exactly 0.1 *N* with hydrochloric acid. The red mixture was heated to 95° (more hydrochloric acid being added to adjust the *p*H) and allowed to cool. The orange product which separated was filtered off and crystallized from ethanol, m.p. 239–240°. The aqueous mother liquors on neutralization with alkali precipitated the starting amino acid. The orange product (XII) was red in acid solutions up to *p*H 4, going slowly to yellow at *p*H 7, and becoming practically colorless at higher *p*H's. It was insoluble in 0.1 *N* acids but soluble in stronger acids.

Anal. Calc'd for $C_{20}H_{18}N_2O_4$: C, 68.56; H, 5.14; N, 7.99.
Found: C, 68.37, 68.43; H, 4.98, 5.08; N, 7.98, 8.05.

An S-benzylthiouronium derivative was prepared according to the method of Donleavy (13). It did not have a satisfactory melting point.

Anal. Calc'd for $C_{28}H_{28}N_4O_4S$: C, 65.10; H, 5.46; S, 6.20.
Found: C, 64.82, 64.95; H, 5.44, 5.43; S, 6.26, 6.40.

3-Iodoisonicotinic acid (VI). 3-Aminoisonicotinic acid, 13 g., in water, 200 ml., and concentrated sulfuric acid, 25 g., were diazotized at 0° with potassium nitrite, 8.6 g., in water, 50 ml. After the solution showed no reaction to starch iodide paper (urea was sometimes added if too much nitrite was present) it was poured into 100 ml. of water containing 20 g. of sodium iodide, allowed to stand overnight and then held at 50–60° until the evolution of nitrogen had ceased. (In those reactions where no nitrogen was evolved during the first few minutes of heating, the heating step was omitted.) The mixture was finally chilled, and the black precipitate crystallized from acetic acid to yield 18 g. (76%) of yellowish 3-iodoisonicotinic acid, m.p. 240–241°. The aqueous filtrate was saturated with sulfur dioxide and allowed to remain overnight at 0° to recover further amounts of product. All of the

product was dissolved in a minimal amount of hot pyridine, about 125 ml. of ethanol added, the solution treated with Norit, cooled, and saturated with sulfur dioxide at about 15°. A small amount of the precipitated product was crystallized from ethanol (Norit) to yield white granular crystals, m.p. 244–244.5°.

Anal. Calc'd for $C_6H_4INO_2$: C, 28.93; H, 1.61.
Found: C, 29.07, 29.13; H, 1.83, 1.88.

3-(p-Methoxyphenylamino)isonicotinic acid (VII). Method A. 3-Iodoisonicotinic acid, 2.5 g., *p*-anisidine, 3.0 g., potassium carbonate, 2.8 g., pentanol, 7 ml., and copper-copper oxide, 0.1 g., were refluxed (nitrogen atmosphere and stirring) for ten hours. The black mixture was steam distilled, treated with Norit, and the product fractionally precipitated with 5 *N* hydrochloric acid. The desired golden-yellow product precipitated first, 1.0 g. (42%) m.p. 310–312° (d.) (from pyridine-water or acetic acid). The product was titrated at 70° (phenolphthalein) with hydrochloric acid: neutral equivalent 241 (theory, 244).

Method B. 3-Aminoisonicotinic acid, 14 g., *p*-iodoanisole, 24 g., potassium carbonate, 28 g., Aerosol O.T., 1 g., copper-copper oxide, 0.5 g., propanol, 10 ml., and water, 100 ml., were refluxed for seventy hours, the reaction mixture was steam distilled, and the aqueous residue was treated as described in Method A. Nineteen grams (82%) of product was obtained.

Anal. Calc'd for $C_{13}H_{12}N_2O_3$: C, 63.93; H, 4.95; N, 11.46.
Found: C, 63.89, 63.83; H, 4.92, 4.98; N, 11.43, 11.50.

3-(Phenylamino)isonicotinic acid. Fourteen grams of 3-aminoisonicotinic acid and 22 g. of iodobenzene were treated as in Method B (above) to obtain a 60% yield of yellow crystals, m.p. 305–306° (d.).

Anal. Calc'd for $C_{12}H_{12}N_2O_2$: N, 12.98. Found: N, 12.79, 13.06, 12.73.

3-(2'-Carboxy-4'-methoxyphenylamino)isonicotinic acid (Ic). 3-Iodoisonicotinic acid, 12.5 g., 5-methoxyanthranilic acid, 10.2 g., copper-copper oxide, 0.1 g., potassium carbonate, 28 g., and water, 100 ml., were treated as in Method B (reflux for 10 hours). The product was crystallized from pyridine-water or acetic acid to yield 12.3 g. (85%) of yellow crystals, m.p. 317–319° (d.).

Anal. Calc'd for $C_{14}H_{12}N_2O_5$: N, 9.41. Found: N, 9.46, 9.46.

The calcium salt of Ic (4 g.) was mixed with fine sand and held at 400° for 30 minutes under 2 mm. pressure. No pyridoquinolone sublimed. The residue was extracted with hot ethanol and the ethanol evaporated. No residue was obtained. (The desired product should be soluble in alcohol by analogy with IV).

10-Amino-x-chloro-6-methoxypyrido(4.3-b)quinoline (VIII). 3-(*p*-Methoxyphenylamino) isonicotinic acid, 2.4 g., and phosphorus oxychloride, 50 g., were refluxed for two hours, the red solution partially distilled under vacuum and then poured into a mixture of ice, chloroform, and dilute ammonia. The organic constituents were extracted with chloroform, stirred with potassium carbonate on a cold water-bath, and then allowed to dry overnight with fresh carbonate. The red chloroform solution (smelling of ammonia) was chromatographed through a mixture of Hyflo and alumina. Only a brownish-orange diffuse band was noted. After several fractional crystallizations from the chloroform solution (Norit) a yellow crystalline material, m.p. 261–262° (d.) was obtained.

Anal. Calc'd for $C_{13}H_{10}ClN_3O$: Cl, 13.68; N, 16.19.
Found: Cl, 13.75, 13.61; N, 16.36, 16.25.

The position occupied by the chlorine atom was not determined, although it was assumed to be in the benzene ring. The chlorine was not present as a hydrochloride since it was not removed by warm 2 *N* sodium hydroxide.

SUMMARY

Several pyrido(4.3-b)quinolones and 4-substituted-amino-2,6-dimethylnicotinic acids have been prepared and tested pharmacologically.

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