[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF PENNSYLVANIA]

Metabolite Analogs. VIII. Syntheses of Some Imidazopyridines and Pyridotriazoles

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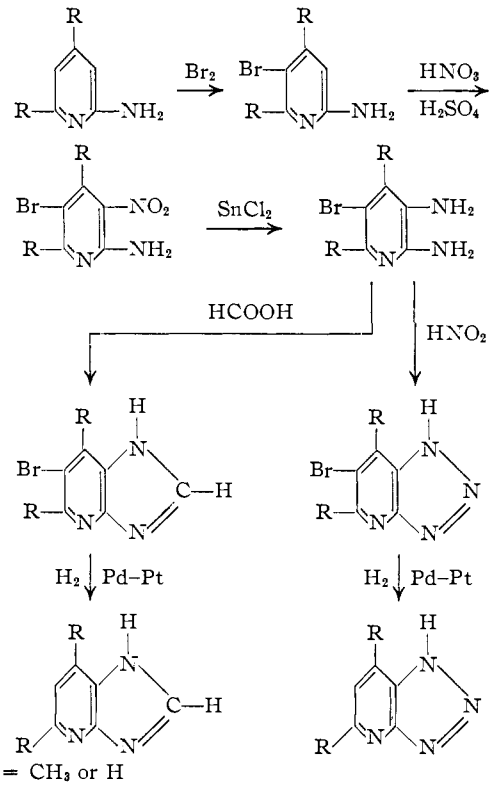
A number of substituted imidazo[b]pyridines, imidazo[c]pyridines, pyrido[2,3-d]-v-triazoles and pyrido[3,4-d]-v-triazoles have been synthesized. These compounds are being screened for antimetabolite activity.

The syntheses described in this paper were undertaken to prepare some new imidazopyridines and pyridotriazoles which might be useful as antimetabolites. The intermediates necessary for these syntheses were substituted 2,3-diaminopyridines and substituted 3,4-diaminopyridines. The work may be divided conveniently into four main parts: (1) syntheses of 6-bromoimidazo[b]pyridine, 6-bromopyrido[2,3-d]-v-triazole and methyl substituted imidazo[b]pyridines and pyrido[2,3-d]-v-triazoles; (2) syntheses of imidazo[b]pyridine-6-sulfonic acid, pyrido[2,3-d]-v-triazole-6-sulfonic acid and derivatives thereof; (3) syntheses of 5-hydroxyimidazo[b]pyridine and 5-hydroxypyrido[2,3-d]-v-triazole; and (4) syntheses of 7-aminoimidazo[c]pyridine and 7-aminopyrido[3,4-d]-v-triazole.

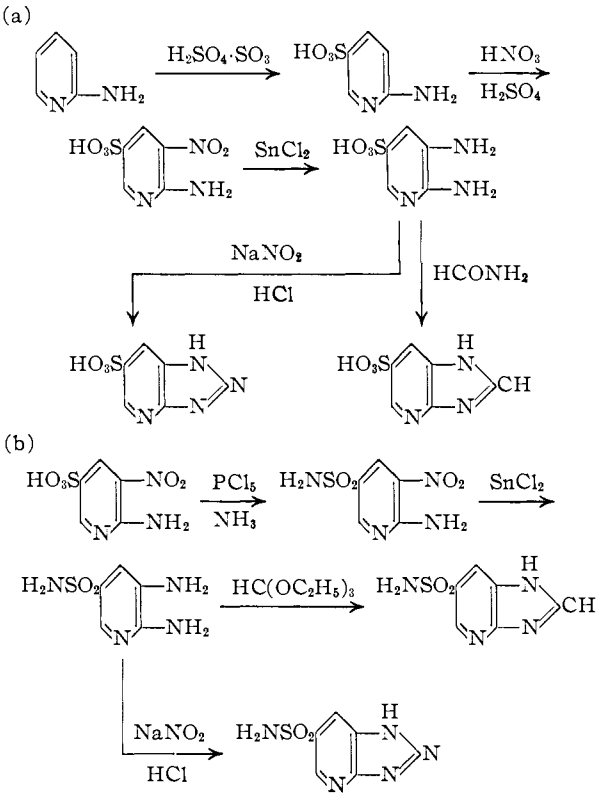
Part 1. The compounds in part 1 were prepared by the general scheme



2-Aminopyridine, 2-amino-4-methylpyridine, 2-amino-6-methylpyridine and 2-amino-4,6-dimethylpyridine were used as starting compounds in this series. The brominations were carried out in anhydrous ethanol,[2] except in the case of 2-amino-4,6-dimethylpyridine. The latter was converted to its acetyl derivative and then brominated in acetic acid solution. The nitrations were carried out by a previously described method.[3]

The nitro compounds were reduced to the corresponding diamines with stannous chloride in concentrated hydrochloric acid.[4] Finally the diamines were converted to the corresponding imidazoles by heating with formic acid and to the corresponding triazoles by treating with sodium nitrite in dilute hydrochloric acid.

Part 2. The following scheme illustrates the preparation of the compounds in this series.



Sulfonation of 2-aminopyridine was accomplished by the method of Chichibabin and Vialatout.[5] 2-Amino-5-pyridinesulfonic acid was more difficult to nitrate. Best results were obtained with concentrated sulfuric acid and fuming nitric acid at 50–55°.

(1) Smith, Kline and French Fellow, 1955–1956; Minneapolis Honeywell Regulator Co. Fellow, 1956–1957.

(2) F. Case, THIS JOURNAL, **68**, 2576 (1946).

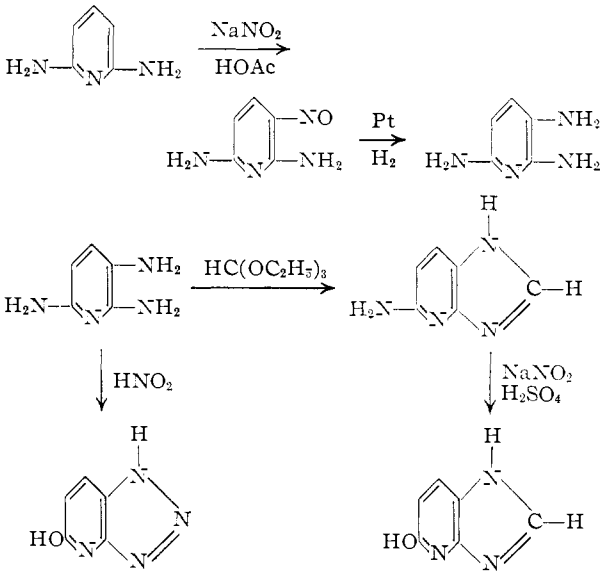
(3) J. R. Vaughan, Jr., J. Krapcho and J. P. English, *ibid.*, **71**, 1885 (1949).

(4) This method gave better results than the use of sodium dithionate (see ref. 3) or catalytic hydrogenation over platinum.

(5) A. E. Chichibabin and M. Vialatout, *Bull. soc. chim.*, **6**, 736 (1939).

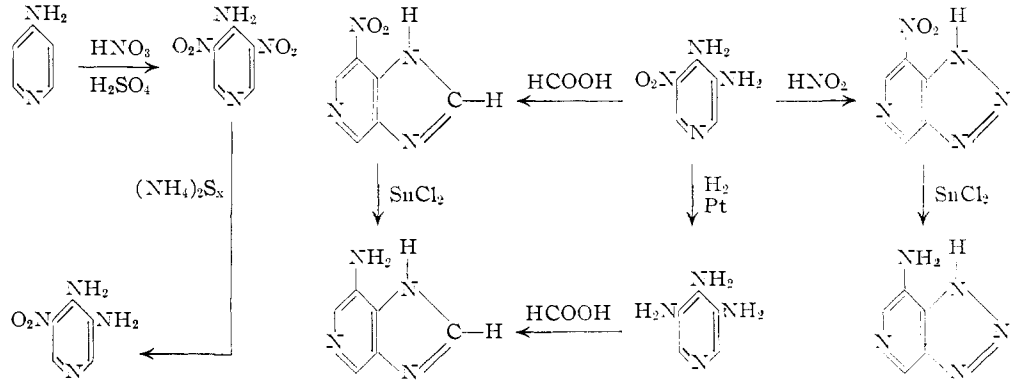
The reduction of the nitro compounds in this series was most effectively accomplished with stannous chloride in concentrated hydrochloric acid. 2,3-Diamino-5-pyridinesulfonic acid could not be converted to the corresponding imidazole by refluxing with formic acid. The conversion readily was effected, however, by heating with formamide at 150°. 2-Amino-3-nitro-5-pyridinesulfonyl chloride was isolated only as a brown oil. Since it could not be purified, it was used in this form for the next step.

Part 3. The following outline illustrates the preparation of 5-hydroxyimidazo[b]pyridine and the corresponding triazole.



During the course of preliminary work it was found that nitration of 2,6-diacetamidopyridine as reported by Chichibabin and Seide[6] could not be reproduced. Consequently nitrosation was carried out instead. The method of Titov[7] gave excellent results. He recommended the use of acetic acid in place of hydrochloric acid which was used by previous workers. The triamine was isolated as its hydrochloride or sulfate. The free base is very unstable in air.

Part 4. The compounds prepared in this section were obtained from 4-aminopyridine.



Koenigs was the first to nitrate 4-aminopyridine.[8] He isolated the intermediate nitramino compound before treating it with a second molecule of nitric acid. In the present work, the reaction was carried out as a continuous process without isolating any intermediates. It is important to note that 4-amino-3-nitropyridine is relatively inert to further nitration. Thus if any of the intermediate nitramino compound rearranges before the second mole of nitric acid is added, the reaction may stop at that point. The reductions of 7-nitroimidazo[c]pyridine and 7-nitropyrido[3,4-d]-v-triazole with stannous chloride and concentrated hydrochloric acid appeared to proceed very well but because of the difficulties encountered in removing tin from the final product the yields were relatively low. Other reduction methods proved even less satisfactory.

All of the imidazoles and triazoles prepared in this investigation were high melting compounds. All were colorless except the nitro derivatives which were pale yellow. Most of the compounds could be recrystallized from water, the imidazoles being more soluble than the triazoles. The imidazoles were more basic than the triazoles, forming hydrochlorides readily. The triazoles did not form hydrochlorides. The imidazoles usually were soluble in dilute acids and the triazoles insoluble. Both types were soluble in dilute alkalies. The fused ring systems were very resistant to reduction. Nitro groups can be reduced and halogens replaced with hydrogen without reduction of either ring.

Experimental

All melting points were taken in an apparatus similar to that described by Wagner and Meyer.[9] The rate of heating was approximately one degree per minute within 10–15° of the melting point. All values are uncorrected.

Preparations. I, II. 2-Amino-5-bromopyridine.—The method was essentially that of Case.[2] The crude product was washed with ligroin (65–110°) and recrystallized from water or benzene. The yield of pure product was 46%, m.p. 136–137°.

III. 2,3-Diamino-5-bromopyridine.—To a mixture of 76 g. (0.4 mole) of anhydrous stannous chloride in 200 ml. of concentrated hydrochloric acid was gradually added 22.8 g. (0.1 mole) of 2-amino-3-nitro-5-bromopyridine (II).[3] Cooling was required to keep the solution from boiling. The solution finally was heated on a steam-bath for 30 minutes, cooled and made strongly alkaline with 40% sodium hydroxide solution. The remaining white solid was removed, washed with water and dried. The crude product was re-

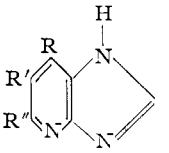
(6) A. E. Chichibabin and O. A. Seide, *J. Russ. Phys. Chem. Soc.*, **50**, 522 (1920).

(7) A. I. Titov, *J. Gen. Chem. U.S.S.R.*, **8**, 1483 (1938).

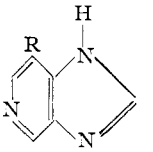
(8) E. Koenigs, G. Kinne and W. Weisse, *Ber.*, **57**, 1172 (1924).

(9) E. C. Wagner and J. F. Meyer, *Ind. Eng. Chem., Anal. Ed.*, **10**, 584 (1939).

TABLE I

IMIDAZO[b]PYRIDINES 

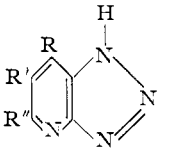
Compound	Substituents R	R′	R″	Yield, %	M.p., °C.	Formula	Analyses, % Calcd. C	H	N	S	Found C	H	N	S
IV	H	Br	H	57	227–228	$C_6H_4N_3Br$	36.39	2.04	21.20	...	36.58	2.22	21.02	...
IX[a]	H	Br	CH_3	100	204–205	$C_7H_6N_3Br$	39.63	2.85	19.82	...	39.73	3.00	19.79	...
X	H	H	CH_3	36	218–219	$C_7H_7N_3$	63.14	5.30	31.56	...	63.16	5.22	31.55	...
XVI[a,b]	CH_3	Br	H	100	262–263	$C_7H_6N_3Br$	39.63	2.85	19.82	...	39.47	2.88	19.59	...
XVII	CH_3	H	H	100	146–147	$C_7H_7N_3$	63.14	5.30	31.56	...	63.19	5.40	31.68	...
XXV[a,c]	CH_3	Br	CH_3	100	279–280 d.	$C_8H_8N_3Br$	42.50	3.57	18.59	...	42.43	3.55	18.53	...
XXVI hydrochloride of XXV				75	308–309 d.	$C_8H_9N_3BrCl$	36.59	3.46	16.01	...	36.68	3.52	15.73	...
XXVII[d]	CH_3	H	CH_3	43	217–218	$C_8H_9N_3$	65.28	6.16	28.55	...	65.38	6.11	28.47	...
XXXIII	H	SO_2OH	H	62	>360	$C_6H_5N_3SO_3$	36.17	2.53	21.10	16.10	35.99	2.67	21.24	16.27
XXXVII	H	SO_2NH_2	H	83	289–290	$C_6H_6N_4SO_2$	36.36	3.05	28.27	16.18	36.23	3.21	28.49	16.31
XLI	H	H	NH_2	72	259–260 d.	$(C_6H_6N_4)_2H_2SO_4$	39.33	3.85	30.59	8.77	39.42	4.02	30.39	8.56
XLII	H	H	OH	37	311–313 d.	$C_6H_5N_3O$	53.33	3.73	31.10	...	53.30	3.54	31.02	...

IMIDAZO[c]PYRIDINES 

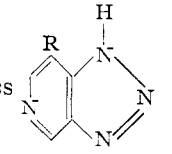
XLVI[a,c]	NO_2		100	275–276	$C_6H_4N_4O_2$	43.91	2.46	34.15	...	44.07	2.46	34.15	...
XLIX	NH_2		97	240–241 d.	$C_6H_6N_4H_2SO_4$	31.03	3.47	24.13	13.81	31.16	3.28	24.22	13.96

[a] Prepared by method A from the corresponding diamine. [b] Recrystallized from xylene. [c] Recrystallized from nitrobenzene. [d] Prepared from XXV by method used for X.

TABLE II

PYRIDO[2,3-d]-v-TRIAZOLES 

Compounds	Substituents R	R′	R″	Yield, %	M.p., °C.	Formula	Analyses, % Calcd. C	H	N	S	Found C	H	N	S
V	H	Br	H	83	208–209	$C_5H_3N_4Br$	30.17	1.52	28.15	...	30.21	1.62	27.92	...
XI	H	Br	CH_3	71	201.5–202 d.	$C_6H_5N_4Br$	33.81	2.37	26.30	...	33.98	2.55	26.43	...
XII[e]	H	H	CH_3	71	249–251 d.	$C_6H_6N_4$	53.72	4.51	41.77	...	53.65	4.38	41.57	...
XVIII[c]	H	Br	CH_3	74	229–230 d.	$C_6H_5N_4Br$	33.81	2.37	26.30	...	33.67	2.40	26.35	...
XIX[d]	H	H	CH_3	100	219–220	$C_6H_6N_4$	53.72	4.51	41.77	...	53.79	4.42	41.96	...
XXVIII[c]	CH_3	Br	CH_3	71	190–191	$C_7H_7N_4Br$	37.02	3.11	24.67	...	37.23	3.09	24.89	...
XXIX	CH_3	H	CH_3	33	213–214	$C_7H_6N_4$	56.77	5.45	37.77	...	56.65	5.63	37.85	...
XXXIV	H	SO_2OH	H	67	[a]	$C_6H_5N_4O_3SNa$	25.00	2.10	23.34	...	25.00	2.31	23.49	...
XXXVIII[c]	H	SO_2NH_2	H	85	249 d.	$C_6H_5N_5SO_2$	30.14	2.53	35.16	16.10	30.00	2.61	35.06	16.31
XLIII	H	H	OH	16	280–282 d.	$C_6H_4N_4O$	44.12	2.96	41.17	...	44.07	3.12	41.34	...
LI	H	SH	H	81	234–235 d.	$C_5H_4N_4S$	39.46	2.65	36.83	21.07	39.64	2.46	36.67	21.27

PYRIDO[3,4-d]-v-TRIAZOLES 

XLVII	NO_2		100	266–268 d.	$C_5H_3N_5O_2$	36.37	1.83	42.42	...	36.32	1.70	42.65	...
L	NH_2		38	[b]	$C_5H_5N_5$	44.44	3.73	51.83	...	44.25	3.83	51.80	...

[a] Decomposes indefinitely >200°. [b] Decomposes indefinitely >300°. [c] Prepared from corresponding diamine by method B. [d] Prepared from XVIII by method used for XI. [e] Prepared from XI by method used for X.

crystallized from water, yield 68%, m.p. 163–164° (lit. value 165–166°). Reduction of 2-amino-3-nitro-5-bromopyridine with sodium hydrosulfite[3] gave only a 34% yield, m.p. 163–164°.

Method A for Imidazo[b]pyridines. IV. 6-Bromoimidazo[b]pyridine.—2,3-Diamino-5-bromopyridine (5 g., 0.026 mole) was dissolved in 25 ml. of 98–100% formic acid, and the resulting solution was refluxed for 1 hr. and then evaporated to dryness on a steam-bath. The residue was recrystallized from water.

V. 6-Bromopyrido[2,3-d]-v-triazole.—2,3-Diamino-5-bromopyridine (5.64 g., 0.03 mole) was dissolved in 150 ml. of warm water containing 5 ml. of concentrated sulfuric acid. The resulting solution was cooled below 10° and a solution of 2.3 g. (0.033 mole) of sodium nitrite in 25 ml. of water was added dropwise with stirring. After 1 hr. of additional stirring, the brown solid was removed, washed with water and dried. It was recrystallized from a large excess of 2 *N* hydrochloric acid.

VII. 2-Amino-3-nitro-5-bromo-6-methylpyridine.—2-Amino-5-bromo-6-methylpyridine (VI)[10] (93.5 g., 0.5 mole)

(10) R. Adams and A. W. Schrecker, THIS JOURNAL, **71**, 1186 (1949).

was added with stirring to 400 ml. of cold concentrated sulfuric acid. The resulting solution was warmed to 55° and 32 ml. (0.5 mole) of concentrated nitric acid added dropwise at such a rate that the temperature remained at 55–60°. This required 3 hr. The solution was stirred for one more hour, poured over a kg. of cracked ice and treated with 40% sodium hydroxide solution to precipitate the product. The latter was removed, washed with water and dried. It was recrystallized from butanol-1 and obtained as yellow needles, yield 82%, m.p. 210–211°.

Anal. Calcd. for $C_6H_6N_3O_2Br$: C, 31.05; H, 2.62; N, 18.11. Found: C, 31.32; H, 2.72; N, 18.12.

VIII. 2,3-Diamino-5-bromo-6-methylpyridine was prepared from 2-amino-3-nitro-5-bromo-6-methylpyridine by the method used for making compound III. The product was purified by recrystallization from water, yield 88%, m.p. 136–137°.

Anal. Calcd. for $C_6H_8N_3Br$: C, 35.66; H, 3.99; N, 20.80. Found: C, 35.47; H, 3.80; N, 20.99.

X. 5-Methylimidazo[b]pyridine.—5-Methyl-6-bromoimidazo[b]pyridine (3.8 g., 0.018 mole) was added to a suspension of 2 g. of 5% palladium-on-carbon and 0.2 g. of platinum oxide in 150 ml. of 1% sodium hydroxide solution which had been activated previously in a Parr hydrogenation apparatus. The reduction was then carried out at 50 p.s.i. for 30 minutes. The catalyst was removed and the filtrate was neutralized with hydrochloric acid. The solution was evaporated *in vacuo* and the residue extracted with boiling toluene. On cooling the product crystallized. Salemink and Van Der Want previously had reported the isolation of the picrate of this compound, but they did not prepare the free base.[11]

Method B for Pyrido[2,3-d]-v triazoles. XI. 5-Methyl-6-bromopyrido[2,3-d]-v-triazole.—2,3-Diamino-5-bromo-6-methylpyridine (4.04 g., 0.02 mole) was dissolved in 100 ml. of 5% hydrochloric acid and the solution cooled to 5–10°. A solution of 1.73 g. (0.025 mole) of sodium nitrite in 25 ml. of water was added dropwise with stirring. The mixture was stirred for another hour. The solid was removed, washed with a little water and recrystallized from water.

XIII. 2-Amino-4-methyl-5-bromopyridine.—2-Amino-4-methylpyridine was brominated by the method of Case.[2] The crude product was washed with ligroin (65–110°) and then recrystallized from cyclohexane, yield 69%, m.p. 147–147.5°.

Anal. Calcd. for $C_6H_7N_2Br$: C, 38.51; H, 3.77; N, 14.98. Found: C, 38.45; H, 3.95; N, 15.14.

XIV. 2-Amino-3-nitro-4-methyl-5-bromopyridine.—2-Amino-4-methyl-5-bromopyridine was nitrated by the same procedure used for making compound VII. The solution obtained by pouring the nitrating mixture over cracked ice was adjusted to a *p*H of 5 with ammonium hydroxide to precipitate the product. The latter was removed, washed with water and recrystallized from aqueous alcohol, yield 75%, m.p. 168–169°.

Anal. Calcd. for $C_6H_6N_3O_2Br$: C, 31.05; H, 2.82; N, 18.11. Found: C, 30.91; H, 2.73; N, 18.23.

XV. 2,3-Diamino-4-methyl-5-bromopyridine.—2-Amino-3-nitro-4-methyl-5-bromopyridine (23.2 g., 0.1 mole) was added gradually to a solution of 76 g. (0.4 mole) of anhydrous stannous chloride in 200 ml. of concentrated hydrochloric acid. The rest of the procedure was the same as that used for compound III except that the product was recrystallized from toluene, yield 73%, m.p. 161–162°. The use of sodium hydrosulfite to reduce the nitro compound gave a lower yield, 42%.

Anal. Calcd. for $C_6H_8N_3Br$: C, 35.66; H, 3.99; N, 20.80. Found: C, 35.62; H, 4.01; N, 20.79.

XVII. 7-Methylimidazo[b]pyridine.—Compound XVI was debrominated by the method described for compound X. The hydrogenation was much slower in this case, requiring 7 hr. The filtrate from the catalyst was partly evaporated *in vacuo* to precipitate the product. The latter may be purified by recrystallization from water or toluene.

(11) C. A. Salemink and G. M. Van Der Want, *Rec. trav. chim.*, **68**, 1013 (1949).

XXI. 2-Acetamido-4,6-dimethyl-5-bromopyridine was prepared by the method of Mariella and Belcher[12] from 2-acetamido-4,6-dimethylpyridine and then hydrolyzed to 2-amino-4,6-dimethyl-5-bromopyridine (XXII).

XXIII. 2-Amino-3-nitro-4,6-dimethyl-5-bromopyridine.—2-Amino-4,6-dimethyl-5-bromopyridine was nitrated by the procedure described for compound VII. After pouring the reaction mixture over 1 kg. of cracked ice a liter of water was added, the product removed and washed with water. It was recrystallized from 95% alcohol, yield 72%, m.p. 169–170°.

Anal. Calcd. for $C_7H_8N_3O_2Br$: C, 34.16; H, 3.28; N, 17.07. Found: C, 33.96; H, 3.14; N, 17.19.

XXIV. 2,3-Diamino-4,6-dimethyl-5-bromopyridine.—Compound XXIII was reduced by the stannous chloride method used for the preparation of compound III. The product was recrystallized from water or toluene, yield 92%, m.p. 183–184°.

Anal. Calcd. for $C_7H_{10}N_3Br$: C, 38.91; H, 4.67; N, 19.45. Found: C, 38.80; H, 4.74; N, 19.21.

XXIX. 5,7-Dimethylpyrido[2,3-d]-v-triazole.—The bromine atom of compound XXVIII was replaced with hydrogen by the method used for preparing compound X.

XXXI. 2-Amino-3-nitro-5-pyridinesulfonic Acid.—The preparation of this compound has been reported by Räth,[13] but the compound which was obtained in the present study was not the compound described by Räth. 2-Amino-5-pyridinesulfonic acid (XXX)[5] (54.2 g., 0.3 mole) was dissolved in 200 ml. of concentrated sulfuric acid. The solution was warmed to 50° and 16.4 ml. (0.3 mole) of fuming nitric acid was added dropwise at such a rate that the temperature remained at 50–55°. The solution was stirred at this temperature for an additional hour and stirring was continued until room temperature was reached. The reaction mixture was poured over 600 g. of crushed ice. The resulting precipitate was removed and washed with ethanol and ether. It was recrystallized from water, yields 27–32%, m.p. decomposes above 300°.

Anal. Calcd. for $C_5H_5N_3SO_5$: C, 27.40; H, 2.30; N, 19.17; S, 14.62. Found: C, 27.28; H, 2.35; N, 19.21; S, 14.43.

XXXII. 2,3-Diamino-5-pyridinesulfonic Acid.—2-Amino-3-nitro-5-pyridinesulfonic acid (21.9 g., 0.1 mole) was added in small portions to a solution of 76 g. (0.4 mole) of anhydrous stannous chloride in 200 ml. of concentrated hydrochloric acid. After heating the mixture on a steam-bath for 30 minutes, it was cooled and the complex tin chloride salt of XXXII removed by filtration. The salt was suspended in 150 ml. of 0.3 *N* hydrochloric acid. The hot suspension was treated with hydrogen sulfide to precipitate the tin. The filtrate from the stannic sulfide was then cooled to precipitate the product. It was recrystallized from water, yield 70%, m.p. 308–309° dec.

Anal. Calcd. for $C_5H_7N_3SO_3$: C, 31.74; H, 3.72; N, 22.21; S, 16.95. Found: C, 31.91; H, 3.68; N, 22.07; S, 17.12.

XXXIII. Imidazo[b]pyridine-6-sulfonic Acid.—2,3-Diamino-5-pyridinesulfonic acid (3.78 g., 0.02 mole) was suspended in 25 ml. of formamide and heated for 2 hr. with stirring. After cooling, 50 ml. of dry ethanol and excess dry ether were added to precipitate the ammonium salt of the product. The latter was converted to the free acid by dissolving in 50 ml. of 2 *N* hydrochloric acid, refluxing for 30 minutes and cooling. The product so obtained was recrystallized from water.

XXXIV. Pyrido[2,3-d]-v-triazole-6-sulfonic Acid.—A suspension of 2,3-diamino-5-pyridinesulfonic acid (4.04 g., 0.02 mole) in 100 ml. of 5% hydrochloric acid was cooled to 5–10°, and a solution of 1.73 g. (0.025 mole) of sodium nitrite in 25 ml. of water was added dropwise. The diamine slowly dissolved. Stirring was continued for 2 hr. and the solution evaporated *in vacuo*. The residue was extracted with ethanol and the product precipitated from this extract with dry ether.

XXV. 2-Amino-3-nitropyridine-5-sulfonamide.—2-Amino-3-nitropyridine-5-sulfonic acid (21.9 g., 0.1 mole) and 41.9 g. (0.2 mole) of phosphorus pentachloride were

(12) R. P. Mariella and E. P. Belcher, THIS JOURNAL, **74**, 1916 (1952).

(13) C. Räth, *Ann.*, **487**, 105 (1931).

heated at 170–180° for 3 hr. After cooling, 150 ml. of dry benzene was added and the mixture was filtered. The filtrate was distilled *in vacuo* to remove benzene and phosphorus oxychloride. The residual brown oil was dissolved in 100 ml. of dioxane and 100 ml. of water added. The solution was cooled and 150 ml. of concentrated ammonium hydroxide was added dropwise with stirring. After stirring for 2 hr., 200 ml. of water was added and the solution then acidified with concentrated hydrochloric acid to complete the precipitation of the product. The product was removed and washed with dioxane. It was purified by dissolving in dilute sodium hydroxide and reprecipitating with concentrated hydrochloric acid. The yield was 51% (yellow platelets), m.p. 287–289° dec.

Anal. Calcd. for $C_5H_6N_4SO_4$: C, 27.52; H, 2.77; N, 25.68; S, 14.70. Found: C, 27.70; H, 2.89; N, 25.41; S, 14.53.

XXXVI. 2,3-Diaminopyridine-5-sulfonamide Hydrochloride.—The nitro compound XXXV was reduced by the procedure used for making compound XXXII. The product was recrystallized from methanol, yield 61%, m.p. 231–232° dec.

Anal. Calcd. for $C_5H_8N_4SO_2 \cdot HCl$: C, 26.74; H, 4.04; N, 24.94. Found: C, 26.70; H, 4.10; N, 24.97.

XXXVII. Imidazo[b]pyridine-6-sulfonamide.—2,3-Diaminopyridine-5-sulfonamide hydrochloride (2.5 g., 0.011 mole) was added to 50 ml. of ethyl orthoformate and the solution refluxed for 2 hr. The product separated on cooling the solution. The crude product was recrystallized from water.

XL. 2,3,6-Triaminopyridine Dihydrochloride.—2,6-Diamino-3-nitrosopyridine (XXXIX) was hydrogenated in water solution using platinum as the catalyst. The reaction mixture was filtered and the filtrate collected in concentrated hydrochloric acid. The dihydrochloride was obtained by concentrating this solution under reduced pressure. The crude product was recrystallized from water. The yield was 84%, m.p. 270–271°. A much lower melting point is reported in the literature.[7] When the filtrate from the hydrogenation mixture was collected in sulfuric acid, the sulfate of XL separated. After washing with water and drying it melted at 242–243° dec. The sulfate is very insoluble.

XLI. Bis-5-aminoimidazo[b]pyridine Sulfate.—2,3,6-Triaminopyridine dihydrochloride (9.85 g., 0.05 mole) was added to 75 ml. of 98–100% formic acid, and the solution was refluxed for 8 hr. The formic acid was removed *in vacuo*, and the oily residue was dissolved in 50 ml. of 2 *N* sulfuric acid. The solution was refluxed for 30 minutes. Addition of 50 ml. of methanol and excess ether precipitated the product. It was recrystallized from ethanol–water. The dihydrochloride of 5-aminoimidazo[b]pyridine was prepared by Vaughan, Krapcho and English.[3] The preparation of the picrate was reported by Salemink and Van Der Want.[11]

XLII. 5-Hydroxyimidazo[b]pyridine.—Compound XLI (7.32 g., 0.02 mole) was dissolved in 150 ml. of water containing 5 ml. of concentrated sulfuric acid. After cooling to 5–10°, a solution of 2.76 g. (0.04 mole) of sodium nitrite in 25 ml. of water was added dropwise with stirring. After stirring for two more hours, the solution was neutralized with 2 *N* sodium hydroxide to precipitate the product. The latter was recrystallized from water.

XLIII. 5-Hydroxypyrido[2,3-d]-v-triazole.—2,3,6-Triaminopyridine sulfate (11.1 g., 0.1 mole) was suspended in 100 ml. of water, and 50 ml. of concentrated hydrochloric acid was added. After cooling to 5–10°, a solution of 13.8 g. (0.02 mole) of sodium nitrite in 75 ml. of water was added dropwise with stirring. After stirring for an additional hour, the solution was almost neutralized by the addition of aqueous ammonia and the dark solid removed by filtration. It was recrystallized from water.

XLIV. 4-Amino-3,5-dinitropyridine.—The method of Koenigs, Kinne and Weise[8] was modified considerably for this preparation. 4-Aminopyridine (47 g., 0.5 mole) was added gradually to 200 ml. of well cooled, concentrated sulfuric acid. Keeping the temperature below 10°, 27 ml. (0.5 mole) of fuming nitric acid was added dropwise over a period of 30 minutes. The solution was allowed to warm to room temperature (about 1 hr.) and then was heated to 85°, at which point a spontaneous rise in temperature was noted and some cooling was necessary. When this reaction was over, 27 ml. (0.5 mole) of fuming nitric acid was added dropwise with stirring and the temperature was held at 85–90°. This required about 30 minutes. Stirring was continued until the solution reached room temperature. The red solution was then poured over 1 kg. of cracked ice and the resulting solution partially neutralized with 40% sodium hydroxide solution to precipitate the product as a brown powder. It was removed and washed with water. More product was obtained by making the filtrate strongly basic with concentrated aqueous ammonia. The crude yields were 60–65%. The product can be recrystallized from water, with great difficulty, to give bright yellow plates, m.p. 168–169°.

XLV. 3,4-Diamino-5-nitropyridine.—4-Amino-3,5-dinitropyridine (36.8 g., 0.2 mole) was added gradually with stirring to 200 ml. of 2 *N* ammonium hydroxide which had been saturated previously with hydrogen sulfide at 0–5°. The temperature was kept below 10° during the addition and stirring was continued for an additional hour. The crude product was removed and recrystallized from water. It was obtained as ruby-red needles, yield 47%, m.p. 239°.

Anal. Calcd. for $C_5H_6N_4O_2$: C, 38.97; H, 3.92; N, 36.36. Found: C, 39.15; H, 3.82; N, 36.52.

XLVII. 7-Nitropyrido[3,4-d]-v-triazole was prepared from 3,4-diamino-5-nitropyridine by the procedure used for making compound XI except that 2 *N* hydrochloric acid was used in place of 5 *N*. Recrystallization was accomplished from large volumes of water. Both XLVI and XLVII appeared as yellow granules.

XLVIII. 3,4,5-Triaminopyridine Trihydrochloride.—The 3,4-diamino-5-nitropyridine was hydrogenated in 95% ethanol using platinum as the catalyst. After removing the catalyst, concentrated hydrochloric acid was added to the filtrate to precipitate the trihydrochloride, m.p. 275–278° dec.[14] When concentrated sulfuric acid was added to an aqueous solution of the trihydrochloride, a quantitative yield of the disulfate was obtained. It was purified by dissolving in warm water and reprecipitating with concentrated sulfuric acid, m.p. 252–253° dec.

Anal. Calcd. for $C_5H_8N_4 \cdot (H_2SO_4)_2$: C, 18.75; H, 3.78; N, 17.49; S, 20.02. Found: C, 18.72; H, 3.88; N, 17.59; S, 20.07.

XLIX. 7-Aminoimidazo[c]pyridine Sulfate.—3,4,5-Triaminopyridine disulfate (6.4 g., 0.02 mole) was suspended in 50 ml. of 98–100% formic acid and refluxed for 4 hr. After removing the formic acid under reduced pressure, the residual brown oil was dissolved in 50 ml. of 2 *N* sulfuric acid and refluxed for 30 minutes. The solution was concentrated to half its volume and the product precipitated by adding 100 ml. of methanol and excess ether. The product was recrystallized from methanol–2 *N* sulfuric acid.

Compound XLIX also was obtained from 7-nitroimidazo[c]pyridine by reduction with stannous chloride in concentrated hydrochloric acid. Attempts were made to isolate the product as its hydrochloride. The analytical data were close for a dihydrochloride, but a pure sample could not be obtained. The hydrochloride was converted to the sulfate by recrystalllization from methanol–2 *N* sulfuric acid.

L. 7-Aminopyrido[3,4-d]-v-triazole.—7-Nitropyrido[3,4-d]-v-triazole (6.25 g., 0.038 mole) was added gradually to 30 g. (0.16 mole) of anhydrous stannous chloride in 100 ml. of concentrated hydrochloric acid. The mixture was then heated on a steam-bath for 30 minutes. After cooling, the tin double salt was removed by filtration and decomposed in 0.3 *N* hydrochloric acid with hydrogen sulfide. The filtrate from the stannic sulfide was evaporated to dryness. The residue was dissolved in 50 ml. of 2 *N* sodium hydroxide solution and refluxed for 30 minutes. Partial neutralization of the solution with hydrochloric acid precipitated the product. It was recrystallized from water.

LI. 6-Mercaptopyrido[2,3-d]-v-triazole.—2-Amino-3-nitropyridine-5-sulfonic acid (21.9 g., 0.1 mole) and 41.9 g. (0.2 mole) of phosphorus pentachloride were intimately mixed and heated at 178–180° until solution occurred. Heating was continued for two more hours. After cooling, the mixture was mixed thoroughly with 150 ml. of benzene and filtered. The filtrate was heated *in vacuo* to remove benzene and phosphorus oxychloride. The residual brown oil was added gradually, with stirring, to 152 g. (0.8 mole) of anhydrous stannous chloride in 300 ml. of concentrated

(14) J. B. Ziegler, THIS JOURNAL, **71**, 1186 (1949).

hydrochloric acid. Cooling was necessary to keep the solution from refluxing. The mixture was then heated on the steam-bath for 1 hr. After cooling, the tin double salt was removed and air-dried. The yield was 34 g., 71%.

Five grams of the double salt (0.0106 mole) was dissolved in 50 ml. of 2 *N* hydrochloric acid and cooled to 5–10°. A solution of 1.38 g. (0.02 mole) of sodium nitrite in 25 ml. of water was added dropwise with stirring. Stirring was continued for two more hours. The red precipitate was removed, washed with water and then recrystallized from dimethylformamide–water. The crystals were pale red in color.

PHILADELPHIA, PENNA.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

Stereochemistry of Corynantheine, Dihydrocorynantheine and Corynantheidine[1]

BY EUGENE E. VAN TAMELEN, PAUL E. ALDRICH AND THOMAS J. KATZ

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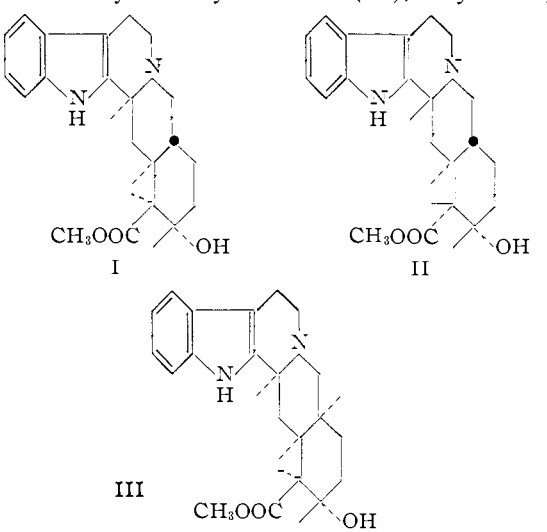
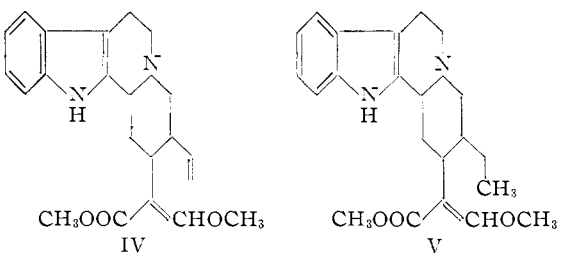
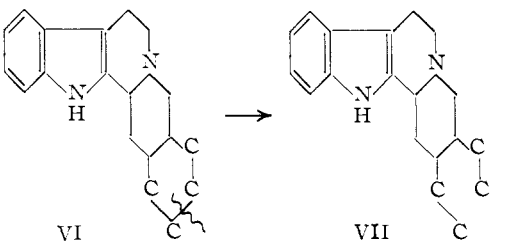
On the basis of a stereospecific synthesis of *dl*-corynantheane, as well as interpretations of previously recorded data, the stereoformulas of corynantheine, dihydrocorynantheine and corynantheidine (excluding C-3) are derived. The nature of the isomerism between the corynantheic acids is established and the stereoselectivity of decarboxylation displayed by these acids is discussed.

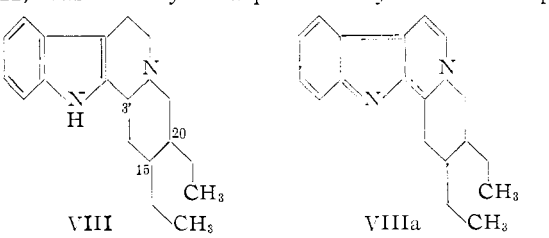
Yohimbe alkaloids which have been isolated from *Pseudocinchona Africana* A. Chev. include the well-known pentacyclic isomers corynanthine (I), pseudoyohimbine (II) and α-yohimbine (rauwolscine, corynanthidine) (III), along with the novel tetracyclic corynantheine (IV), dihydrocorynantheine and corynantheidine (V).[2] The concurrence of the two groups is of particular importance, in that it lends further support to the hypothesis of ring-E cleavage[3] of the pentacyclic indole type (VI), which is considered to generate the embryonic skeleta (VII) of several important alkaloid classes, for example, the ajmaline, strychnine, heteroring-E and curare groups. Consequently, illumination of the genealogies and branches in this family becomes of interest; and with the gross structures of many members now established, there remains the matter of clarifying the stereochemical relationships involved. Although the nature of all the asymmetric centers in the yohimbine class has been carefully determined,[4] stereochemical structures of the tetracyclic group (IV and V) have not been derived. In this contribution, we describe results which permit assignment of stereochemistry to the corynantheine system.







In assessing the various means by which information about the stereochemistry of these *seco*-alkaloids might be gained, it became clear that a pair of transformation products, dihydrocorynantheane and corynantheidane, both represented by formula VIII, was the key to a particularly attractive approach. These diastereoisomers were first prepared several years ago by Janot and Goutarel,[5] who con-



(1) Preliminary communication: *Chemistry & Industry*, 793 (1956).

(2) R. H. F. Manske and H. L. Holmes, "The Alkaloids," Vol. II, Academic Press, Inc., New York, N. Y., 1952, p. 420.

(3) R. B. Woodward, *Nature*, **162**, 155 (1948).

(4) For a review, see J. E. Saxton, *Quart. Revs.*, **10**, 108 (1956). For results requiring the revised stereoformula III for α-yohimbine, see (a) C. Huebner and E. Wenkert, THIS JOURNAL, **77**, 4180 (1955); (b) P. A. Diassi, F. L. Weisenborn, C. M. Dylion and O. Wintersteiner, *ibid.*, **77**, 4687 (1955); (c) E. E. van Tamelen and P. Hance, *ibid.*, **77**, 4692 (1955).

(5) M.-M. Janot and R. Goutarel, *Compt. rend.*, **231**, 152 (1950); *Bull. soc. chim. France*, 588 (1951).