aminopyridine was isolated as the hydrochloride and crystallized from ethanol. It slowly decomposed above 200°.

Anal. Calcd. for $C_5H_2ON_2 \cdot HCl$: C, 40.97; H, 4.81; N, 19.11; Found: C, 41.26; H, 4.43; N, 19.05.

Conversion to the base gave 2-hydroxylaminopyridine which melted at 83–84°. It gave a positive Tollens test and with ferric chloride a blue color which became green, then yellow with additional reagent. This color test is given by 2-hydroxylaminopyridine according to Newbold and Spring[2] who observed a m.p. of 83–85°.

NEWARK, N. J.

(2) G. T. Newbold and F. S. Spring, *J. Chem. Soc.*, S 133 (1949).

[CONTRIBUTION FROM THE UNIVERSITY OF NEW MEXICO, LABORATORY OF PHARMACEUTICAL CHEMISTRY]

Pyridylimidazolidines and Pyridyloxazolidines

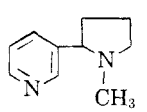
RAYMOND N. CASTLE

Received July 10, 1957

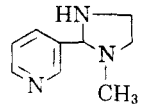
Nine pyridylimidazolidines and three pyridyloxazolidines have been prepared as structural and position analogs of nicotine. These compounds were screened for pharmacological activity and found inactive. The ultraviolet absorption spectra of some of these compounds have been determined. The ultraviolet absorption spectrum of 3-methyl-2-(2-pyridyl)oxazolidine indicates that this compound is unstable in aqueous solution, regenerating the original aldehyde and aminoalcohol.

This work continues a search for analogs of physiologically active compounds which retain the desirable physiological properties of the parent compound but have lesser undesirable activities and toxicity.

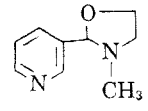
The recent availability of pyridine aldehydes, especially pyridine-3-aldehyde, prompted the synthesis of structural and position analogs of nicotine. The pyrrolidine ring of nicotine has been replaced by imidazolidine and oxazolidine rings, respectively, and the position of attachment of the five-membered rings to the pyridine rings has been 2-, 3-, and 4-, respectively. Structures I, II, and III show nicotine, 1-methyl-2-(3-pyridyl)imidazolidine, and 3-methyl-2-(3-pyridyl)oxazolidine, respectively. Compounds II and III were designed as complete structural analogs of nicotine. Besides II, eight other pyridylimidazolidines have been prepared, as shown in Table I.



I



II



III

TABLE I

PYRIDYLIMIDAZOLIDINES

Compound	B.P., °C	Yield, %	Refractive Index	Formula	Analyses Calcd. C	Calcd. H	Calcd. N	Found, % C	Found, % H	Found, % N
1-Methyl-2-(2-pyridyl)-imidazolidine	97°–0.1 mm.	56	n_D^{26} 1.5410	$C_9H_{13}N_3$	66.23	8.03		65.95	7.85	
1-Methyl-2-(3-pyridyl)-imidazolidine	97°–0.1 mm.	62	n_D^{25} 1.5450	$C_9H_{13}N_3$	66.23	8.03		66.50	8.07	
1-Methyl-2-(4-pyridyl)-imidazolidine	100°–0.05 mm.	55	$n_D^{25.5}$ 1.5440	$C_9H_{13}N_3$	66.23	8.03	25.75	65.83	8.07	26.00
1-Methyl-2(6-methyl-2-pyridyl)imidazolidine	94°–0.05 mm.	53	n_D^{23} 1.5390	$C_{10}H_{15}N_3$	67.76	8.53	23.71	67.56	8.33	23.90
4,4-Dimethyl-1-isopropyl-2-(2-pyridyl)imidazolidine	101°–0.08 mm.	77	n_D^{20} 1.5121	$C_{13}H_{21}N_3$	71.19	9.65		71.55	9.93	
4,4-Dimethyl-1-isopropyl-2-(3-pyridyl)imidazolidine	106°–0.07 mm.	85	n_D^{20} 1.5180	$C_{13}H_{21}N_3$	71.19	9.65		70.52	9.24	
4,4-Dimethyl-1-isopropyl-2-(4-pyridyl)imidazolidine	105.5°–0.1 mm.	82	n_D^{20} 1.5131	$C_{13}H_{21}N_3$	71.19	9.65		70.60	9.60	
4,4-Dimethyl-1-isopropyl-2-(6-methyl-2-pyridyl)-imidazolidine	114°–0.1 mm.	78	n_D^{20} 1.5104	$C_{14}H_{23}N_3$	72.06	9.93		71.49	9.98	
2,6-Bis(4,4-dimethyl-1-isopropyl-2-imidazolidinyl)-pyridine	168°–0.1 mm. M.p. 52–53°	68		$C_{21}H_{37}N_5$	70.14	10.37		69.40	10.13	

The imidazolidines were synthesized by reaction of a pyridine aldehyde with the appropriate primary-secondary diamine. Water was removed, during the reflux period, by azeotropic distillation with benzene.

Two other oxazolidines, besides III, were prepared by condensing the appropriate pyridine aldehyde with methylaminoethanol. The structure of the oxazolidines has been assured simply by choosing a β-aminoalcohol in which one of the hydrogen atoms attached to the nitrogen atom is replaced by a methyl group, which prevents isomerization of the oxazolidine to the open chain Schiff base.[1] The same reasoning was applied to the structure of the imidazolidines, since only primary-secondary diamines were used in their preparation. The structures of similar imidazolidines have been confirmed by Riebsomer and associates,[2,3] by chemical and ultraviolet spectral evidence. The ultraviolet absorption spectra in Table II show that these compounds have the cyclic structure.

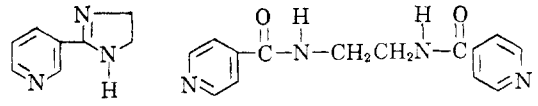
TABLE II

ULTRAVIOLET ABSORPTION SPECTRA

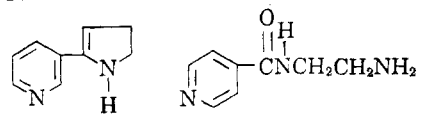
Compound	Maxima λ, mμ	Maxima ε × 10⁻³	Minima λ, mμ	Minima ε × 10⁻³
4,4-Dimethyl-1-isopropyl-2-(2-pyridyl)imidazolidine	236	2.56	224	1.92
	260	3.06	246	2.42
4,4-Dimethyl-1-isopropyl-2-(3-pyridyl)imidazolidine	235	2.14	224	1.98
	260	2.38	248	1.90
4,4-Dimethyl-1-isopropyl-2-(4-pyridyl)imidazolidine	258	1.84	241	1.46
4,4-Dimethyl-1-isopropyl-2-(6-methyl-2-pyridyl)imidazolidine)	235	3.05	222	2.22
	265	3.86	250	2.76
2,6-Bis(4,4-dimethyl-1-isopropyl-2-imidazolidinyl)-pyridine	236	4.02	226	3.28
	242	4.02	240	3.95
	254	4.72	246	3.97
	262	4.90	257	4.68
3-Methyl-2-(2-pyridyl)-oxazolidine	260	3.13	228	1.04
3-Methyl-2-(3-pyridyl)-oxazolidine	261	2.56	(225-234)	1.00
3-Methyl-2-(4-pyridyl)-oxazolidine	253	2.60	228	1.10
Pyridine-2-aldehyde	233	3.46	249	2.36
	260	2.95		
Pyridine-2-aldehyde[a]	236	5.01	253	2.79
	266	3.58		
3-Methyl-2-(2-pyridyl)-oxazolidine[a]	236	5.25	254	2.93
	266	3.48		
Pyridine-4-aldehyde	258	2.25	238	1.08
Pyridine-3-aldehyde	231	5.39	251	2.52
	260	2.96	263	2.78
	265	2.84		

[a] These spectra were determined in distilled water. All others were determined in absolute ethanol.

Attempts to synthesize the imidazoline analog, IV, of nordihydronicotyrine, V, by condensing ethylenediamine with ethyl nicotinate were not successful. However, when methyl isonicotinate and ethylenediamine were condensed, a mixture of *N*, *N'*-bis(isonicotinoyl)ethylenediamine, VI, and N-β-aminoethylisonicotinamide, VII, resulted. None of the expected 2-(4-pyridyl)imidazoline was found.



IV VI



V VII

The oxazolidines, compound II, and the two isonicotinamides were screened for pharmacological activity,[4] but were all essentially inactive. In fact, compound III and the corresponding 2-(4-pyridyl)-oxazolidine produced no symptoms or side effects in doses as high as 2000 mg./kg. in mice. These compounds produced no significant effects when administered intravenously. To explain this rather surprising lack of activity, the ultraviolet absorption spectra of the original aldehydes were determined (Table II). The spectra of pyridine-2-aldehyde was also determined in distilled water and compared with the spectrum of 3-methyl-2-(2-pyridyl)oxazolidine in water. It can be seen in Table II that the spectra of these compounds in water are identical, indicating that the oxazolidine is completely decomposed into the original aldehyde and aminoalcohol in less than one hour after solution in distilled water. The spectrum of 3-methyl-2-(2-pyridyl)oxazolidine in absolute alcohol is much different than the spectrum of this compound in water. This implies that the oxazolidine is stable in absolute ethanol solution. It is suggested that this cleavage in aqueous solution is responsible for the lack of activity or toxicity in this series of oxazolidines.

Some of the highly substituted imidazolidines were examined for pharmacological activity in our laboratories.[5] These compounds were also found to be largely inactive, causing only a mild blood pressure increase.

EXPERIMENTAL

Some of the carbon and hydrogen analyses and all of the nitrogen analyses were carried out by Dr. G. Weiler and Dr. F. B. Strauss, Oxford.

Starting material. The pyridine aldehydes were obtained from the Aldrich Chemical Co., from Dr. F. Raschig, Lud-

(1) E. D. Bergmann, *Chem. Revs.*, **53**, 309 (1953).
(2) J. L. Riebsomer, *J. Org. Chem.*, **15**, 237 (1950).
(3) R. J. Ferm, J. L. Riebsomer, E. L. Martin, and G. H. Daub, *J. Org. Chem.*, **18**, 643 (1953).

(4) The author is indebted to Dr. Glenn E. Ullyot of the Smith, Kline and French Laboratories for arranging for the pharmacological screening.

(5) The author is indebted to Dr. H. C. Ferguson of the University of New Mexico Laboratory of Pharmacology for examining some of the compounds for blood pressure effects in rats.

wigschafen, and from Organic Research Chemicals, Ltd. Pyridine-2-aldehyde, pyridine-3-aldehyde, pyridine-4-aldehyde, and 6-methylpyridine-2-aldehyde were distilled in vacuum before use and were protected from oxidation by a nitrogen atmosphere. Extra care was taken with the aldehyde specimens subjected to spectral studies to insure freedom from oxidation. Pyridine-2,6-dialdehyde was used without purification.

Methylaminoethylamine was prepared by the method of O'Gee and Woodburn[6] and at a later stage obtained from the Sapon Laboratories. The 2-amino-1-isopropylamino-2-methylpropane was obtained from the Commercial Solvents Corp. These diamines were distilled before use as was the Eastman Kodak ethylenediamine. The methyl isonicotinate was obtained from the Reilly Tar and Chemical Corp. and fractionated before use. The Eastman Kodak methylaminoethanol was also fractionated before use.

Pyridylimidazolidines. The preparation of these compounds is illustrated by the following procedure. Pyridine-3-aldehyde, 10.7 g. (0.1 mole), and methylaminoethylamine, 7.4 g. (0.1 mole), were mixed and the mixture swept with dry nitrogen. Dry benzene was added in sufficient quantity to azeotrope off the water, formed as a result of the cyclization. The mixture was refluxed one hour at pot temperatures up to 132°, during which time the theoretical quantity of water was collected in a Dean-Stark tube situated at the top of a twenty four-inch glass helix-packed column. The benzene was removed under reduced pressure and the imidazolidine purified by repeated vacuum distillation.

3-Methyl-2-(2-pyridyl)oxazolidine. Pyridine-2-aldehyde, 16.1 g. (0.15 mole), and methylaminoethanol, 11.3 g. (0.15 mole), were mixed and heat was immediately evolved. Dry nitrogen was bubbled through the mixture and dry benzene was added. The mixture was refluxed at pot temperatures up to 185° for two hours, during which time the theoretical amount of water was collected in the apparatus described above. The benzene was removed in vacuum and the residue distilled, giving 69% of a colorless oil boiling at 127–129°, at 13 mm. The analytical specimen, obtained by redistillation, boiled at 129°, at 13 mm., n_D^{25} 1.5210.

Anal. Calcd. for $C_9H_{12}N_2O$: C, 65.82; H, 7.37. Found: C, 65.45; H, 7.34.

3-Methyl-2-(3-pyridyl)oxazolidine. Pyridine-3-aldehyde, 16.1 g. (0.15 mole), and methylaminoethanol, 11.3 g. (0.15 mole), were treated as above. After four distillations under reduced pressure, an analytical specimen was obtained which boiled at 136°, at 13 mm., n_D^{20} 1.5253. The yield of the product was 72%.

Anal. Calcd. for $C_9H_{12}N_2O$: C, 65.82; H, 7.37. Found: C, 65.28; H, 7.38.

3-Methyl-2-(4-pyridyl)oxazolidine. Pyridine-4-aldehyde, 13.7 g. (0.128 mole), and methylaminoethanol, 9.6 g. (0.128 mole), were treated as above. After distillation there was obtained a yield of 81% of an oil boiling at 137°, at 14 mm., $n_D^{20} = 1.5254$.

Anal. Calcd. for $C_9H_{12}N_2O$: C, 65.82; H, 7.37. Found: C, 65.33; H, 7.47.

The attempted synthesis of 2-(4-pyridyl)imidazoline. Methyl isonicotinate, 27.4 g. (0.2 mole), and ethylenediamine, 18.9 g. (0.3 mole), were mixed. After standing at room temperature a short time, an exothermic reaction set in and a white crystalline mass separated. The evolution of heat was sufficient to boil the liberated methanol. After standing for 45 min., during which time the temperature rose to 85°, the solid mass was heated for 30 min., until most of the methanol distilled through an 18-inch Vigreaux column. When the pot temperature reached 193°, the ethylenediamine began to distill. At this time the reaction pot was changed to the glass helix-packed column with the Dean-Stark water separator and benzene was added. The mixture was refluxed for 2.5 hr. at 220–245°. Upon cooling to 150°, the mass began to solidify. The crude yellow residue after removal of the benzene weighed 28 g. and melted from 120–200°. Recrystallization of a small portion of the solid from ethanol gave white needles, m.p. 271–280°. After recrystallization from hot water, there were obtained white needles, m.p. 281–282°, whose analysis indicated that this fraction was *N,N'*-bisisonicotinoylethylenediamine.

Anal. Calcd. for $C_{14}H_{14}N_4O_2$: C, 62.21; H, 5.22; N, 20.73. Found: C, 62.19; H, 5.18; N, 20.60.

N,N'-Bisisonicotinoylethylenediamine was also prepared by heating 27.4 g. (0.2 mole) of methyl isonicotinate with 6.0 g. (0.1 mole) of ethylenediamine on a steam bath for 1 hr. There was no spontaneous evolution of heat on mixing the components in the above proportions. On cooling the mixture, a white solid separated. It was then collected and washed twice with benzene and allowed to dry in air. The yield of white needles was 15.1 g. which melted at 281–282°, after crystallization from hot water.

From the attempted synthesis of 2-(4-pyridyl)imidazoline, a water soluble component was isolated by extracting the original yellow solid with cold water. Upon evaporation of the aqueous extract and crystallization of the residue from ethyl acetate, large plates and prisms were obtained melting at 108.5–109°. These upon analysis were shown to be N-β-aminoethylisonicotinamide.

Anal. Calcd. for $C_8H_{11}N_3O$: C, 58.16; H, 6.71; N, 25.44. Found: C, 58.23; H, 6.70; N, 24.80.

Ultraviolet absorption spectra. The data in Table II were determined with the Beckman DU quartz spectrophotometer.

Acknowledgment. The author is indebted to the Smith, Kline and French Laboratories, Philadelphia, for generous financial assistance in connection with this work and to Dr. Glenn E. Ullyot for his encouragement and advice.

ALBUQUERQUE, N. M.

(6) R. C. O'Gee and H. M. Woodburn, *J. Am. Chem. Soc.*, **73**, 1370 (1951).