Multiplication of (13) by M giving the right-hand side of (14) retains only one parameter B for comparing various substances in the form of P. Although B is a proportionality constant, it possesses the dimensions of energy and not of volume. The term B can be expected to be constitutive since it depends upon the atomic and molecular configurations.

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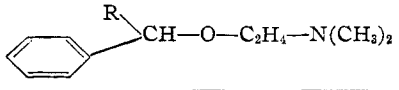
Basically Substituted Pyrimidine and Imidazoline Derivatives as Histamine Antagonists

BY CHARLES H. TILFORD, M. G. VAN CAMPEN, JR., AND ROBERT S. SHELTON

A recent report[1] from this Laboratory showed the effectiveness of 2-[α-(2-dimethylaminoethoxy)-α-methylbenzyl]-pyridine (I) as an antihistaminic agent. The dimethylaminoethyl ethers of α-phenyl-4-methyl-6-methoxy-2-pyrimidinemethanol and α-phenyl-2-imidazolinemethanol have now been prepared and when tested *in vitro* were about 0.0025 as active as I.



R	Free base B. p. °C.	Mm.	Yield, %	Hydrochloride Formula	M. p., °C. (cor.)	% Halogen[a] (ionizable) Calcd.	Obs.	Activity,[b] γ/ml.
4-Methyl-6-methoxy-2-pyrimidyl	135–140	0.2	30	$C_{17}H_{23}O_2N_3 \cdot HCl$	149–151	10.49	10.40	20
				$C_{17}H_{23}O_2N_3 \cdot 2HCl$	176–178	18.95	18.90	20
2-Imidazolinyl	155–160	0.08	63	$C_{14}H_{21}ON_3 \cdot 2HCl$	246–247	22.14	22.0	20

[a] Determined by titration with silver nitrate using dichlorofluorescein indicator. [b] Minimal concentration of test compound necessary to antagonize 0.1 γ/ml. of histamine diphosphate on isolated guinea pig intestine.

Experimental

α-Phenyl-4-methyl-6-methoxy-2-pyrimidinemethanol.—To a stirred solution of 50 g. (0.23 mole) of α-phenyl-4-methyl-6-hydroxy-2-pyrimidinemethanol[2] in 300 ml. of 4% sodium hydroxide was added 34 g. (0.28 mole) of dimethyl sulfate over a period of thirty minutes at 50–60°. The reaction mixture was then stirred and heated on the steam-bath at 90–95° for two hours, made alkaline with 60 ml. of 10% sodium hydroxide, and extracted with 250 ml. of toluene. From the aqueous layer, 15 g. of unchanged starting pyrimidinemethanol was obtained by acidifying with glacial acetic acid and collecting the precipitate at the filter. The toluene extract was treated with a slight excess of alcoholic hydrochloric acid, cooled to −20°, and filtered. The yield of crude product melting at 153–156° (dec.) was 27 g. (63% based on unrecovered original pyrimidinemethanol). A sample was recrystallized from a butanone–ethanol mixture to give white crystals melting at 172–175° (dec.).

Anal. Calcd. for $C_{13}H_{14}O_2N_2 \cdot HCl$: Cl, 13.3. Found: Cl, 13.3.

α-Phenyl-2-imidazolinemethanol.—The procedure of Brockmuhl and Knoll[3] was followed using 71 g. (0.33 mole) of ethyl mandelimidate hydrochloride[4] and 20 g. (0.33 mole) of anhydrous ethylenediamine. The yield of crude base melting at 182–186° was 51 g. (88%). A sample was recrystallized from a butanone–ethanol mixture giving white crystals melting at 184–186°. The white crystalline hydrochloride was prepared and melted at 224–226°.

Anal. Calcd. for $C_{10}H_{12}ON_2 \cdot HCl$: Cl, 16.68. Found: Cl, 16.60

Aminoethers.—The general method of preparation is given in reference 1.

DEPARTMENT OF ORGANIC CHEMISTRY
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(1) Tilford, Shelton and Van Campen, THIS JOURNAL, **70**, 4001 (1948).

(2) Pinner, *Ber.*, **23**, 2948 (1890).

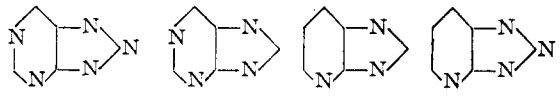
(3) Brockmuhl and Knoll, U. S. 1,999,989 (1931).

(4) Mackenzie, *J. Chem. Soc.*, **113**, 2 (1918).

Triazolo and Imidiazopyridines

BY J. R. VAUGHAN, JR., J. KRAPCHO[1] AND J. P. ENGLISH

The preparation and antibacterial properties of 1-ν-triazolo[d]pyrimidines (I) substituted analogously to the naturally-occurring purines (II) have been reported.[2] Since the *in vivo* activities of those compounds were not very striking, attention was turned to two other nuclei, both isoelectronic with the purine nucleus as is 1-ν-triazolo[d]-pyrimidine. This involved substituting a pyridine ring for the pyrimidine ring of the purines and the triazolo[d]pyrimidines, giving imidazo[b]pyridines (III) and pyrido[2,3-d]ν-triazoles (IV), respectively.



I II III IV

None of the compounds prepared (see Table I) showed antibacterial activity against strains of *Mycobacterium*, *Erssipelothrix*, pneumococcus streptococcus and *Pasteurela multocida*.[3]

The common starting material for these compounds is 2,3-diaminopyridine or some substituent thereof. The use of 5-chloro-2,3-diaminopyridine was much more satisfactory for a number of reasons. The development of an improved procedure for the preparation of 2-amino-5-chloro-

(1) Present address: Chemistry Department, University of Michigan, Ann Arbor, Michigan.

(2) Roblin, Lampen, English, Cole and Vaughan, THIS JOURNAL, **67**, 290 (1945).

(3) Tested under the direction of Dr. Harold J. White of these laboratories.

TABLE I

IMIDAZO[b]PYRIDINES

Substituents	M. p., °C.[g]	Molecular formula	Analyses, %[h] Calcd. C	H	N	Cl	Found C	H	N	Cl
6-Chloro-	237–238	$C_6H_4ClN_3$	46.9	2.6	27.4	23.1	46.8	2.8	27.1	23.2
2-Hydroxy-6-chloro-	338–340	$C_6H_4ClN_3O$	42.5	2.4	24.8	..	42.6	2.6	24.7	..
2-Thio-6-chloro-[a]	352–354	$C_6H_4ClN_3S$	38.8	2.2	..	..	39.0	2.4	..	..
None[b,f]	144–145	$C_6H_5N_3$	60.5	4.2	35.3	..	59.8	4.3	35.2	..
None[c]	214–215	$C_6H_5N_3 \cdot HCl$	..	...	..	22.8	..	...	..	22.7
2-Hydroxy-[b]	238–239	$C_6H_5N_3O$	53.3	3.7	31.1	..	52.8	3.8	31.0	..
5-Formylamino-	256–258	$C_7H_6N_4O$	51.9	3.7	34.6	..	51.9	4.1	35.0	..
5-Amino-[d]	290–292	$C_6H_6N_4 \cdot 2HCl$	34.8	3.9	27.1	..	34.9	3.9	26.8	..
N-Oxide[e]	235–237 (dec.)	$C_6H_5N_3O \cdot HCl$	42.0	3.5	..	..	41.7	3.7	..	..
		Pyrido[2,3-d]ν-triazoles								
6-Chloro-	166–167	$C_5H_3ClN_4$	38.9	2.0	36.3	..	38.7	2.0	36.6	..
None[e]	206–207	$C_5H_4N_4$	..	...	46.7	..	..	...	46.8	..
4,5,6,7-Tetrahydro-	164–165	$C_5H_8N_4$	48.4	6.5	45.1	..	48.5	6.7	45.5	..

[a] Calculated: S, 17.3. Found: S, 17.1. [b] A satisfactory analysis for carbon was not obtained. [c] Monohydrochloride. [d] Dihydrochloride. [e] The recorded melting point is 195° (ref. 9). [f] Since completion of this work this compound has been reported as its picrate, m. p. 190–193° (ref. 6). [g] All melting points are corrected. [h] The analyses were carried out in these laboratories under the direction of Dr. J. A. Kuck. The values reported represent the average of two values not differing by more than 0.3.

pyridine[4] made this readily available and the nitration of this material gave a single product in contrast to the results obtained in the nitration of 2-aminopyridine. It was also found that the diamine resulting from the hydrosulfite reduction was much more stable when the chlorine atom was present. The halogen atom was easily removed in the finished products by catalytic hydrogenation.

The 5-chloro-2,3-diaminopyridine reacted with anhydrous formic acid, phosgene and thiophosgene to give compounds of the imidazo[b]pyridine series; with nitrous acid a pyrido[2,3-d]ν-triazole resulted. The dehalogenation of the latter compound had interesting facets. When either platinum or palladium was used the reduction led to the tetrahydropyridotriazole. When a mixture of the two catalysts was used, however, in the presence of a trace of sodium hydroxide only dehalogenation took place.

2,3,6-Triaminopyridine[5] was prepared in good yield by the catalytic reduction of 2,6-diamino-3-phenylazopyridine and with formic acid gave 5-formylaminoimidazo[b]pyridine. The latter was deacylated to the 5-amino compound with hydrochloric acid. The 7-aminoisomer of this material, which is an analog of the purine adenine, has been reported recently by Kögl.[6] Attempts to convert 5-aminoimidazo[b]pyridine into the N-oxide preliminary to chlorination in the 4-position of the pyridine ring were unsuccessful, although, in the case of the unsubstituted compound, the N-oxide was readily obtained.

(4) English, Clark, Clapp, Seeger and Ebel, THIS JOURNAL, **68**, 453 (1946).

(5) Chichibabin and Hoffmann, *Compt. rend.*, **205**, 153 (1937); Engelmann, U. S. Patent 2,136,044 (1938).

(6) Kögl, Van Der Want and Salemink, *Rec. trav. chim.*, **67**, 29 (1948).

Experimental

2-Amino-3-nitro-5-chloropyridine.—The procedure of Chichibabin and Egorov[7] was modified to give the desired product directly and to eliminate the isolation of the intermediate 2-nitramino-5-chloropyridine and the dangerous and sometimes explosive rearrangement of this material.

A 257-g. sample of 2-amino-5-chloropyridine[4] was dissolved in one liter of concentrated sulfuric acid and the solution heated to 55°. Concentrated nitric acid (129 cc., 1.0 equivalent) was then added dropwise with stirring (caution!) at such a rate that the temperature of the reaction mixture remained at 55°. The addition required four hours after which the mixture was allowed to stir one hour longer at the same temperature, then poured over 4–6 kg. of ice and partially neutralized with 1.5 kg. of 40% sodium hydroxide to precipitate the product as a yellow powder. More water was added to make 12 l. of solution, and the insoluble product removed and washed by resuspension in 2 l. of water; dried at 60°; yield, 227 g. (65.5%), m. p. 190–193°. The material may be purified in 86% yield by dissolving in hot glacial acetic acid and reprecipitating by addition of water; m. p. 195–196°. This is not necessary, however, for the subsequent reduction of the compound.

2,3-Diamino-5-chloropyridine.—A 64-g. sample of crude 2-amino-3-nitro-5-chloropyridine was dissolved in 640 cc. of boiling water and 220 g. of powdered sodium hydrosulfite added over a period of five minutes. Boiling was continued for five to ten minutes. The reaction mixture was then cooled and dilute sodium hydroxide added until no more product was precipitated. This was removed, redissolved in 300 cc. of cold water by the addition of hydrochloric acid, treated with Darco[8] and filtered. On addition of ammonium hydroxide to this filtrate, the product separated as a light yellow solid. This was removed and purified by recrystallization from water (Darco) in the presence of a very small amount of sodium hydrosulfite. The product separated on cooling as colorless, crystalline needles; yield, 17.7 g. (33.5%), m. p. 174–176°. The reported melting point is 164.5–165°.[9]

Anal. Calcd. for $C_5H_6ClN_3$: C, 41.8; H, 4.2. Found: C, 42.0; H, 4.3.

(7) Chichibabin and Egorov, *J. Russ. Phys.-Chem. Soc.*, **66**, 683 (1928); *C. A.*, **23**, 2182 (1929).

(8) The terms "Darco" and "Norit" refer to commercial grades of decolorizing carbon.

(9) Chichibabin and Kirsanow, *Ber.*, **60**, 775 (1927).

The material may also be prepared, but in lower yield (20-30%), by the hydrogenation of 2-amino-3-nitro-5-chloropyridine in alcohol at 5° using a platinum-on-charcoal catalyst.

6-Chloroimidazo[b]pyridine.—Five grams of 2,3-diamino-5-chloropyridine was dissolved in 25 cc. of 98-100% formic acid and the solution evaporated to dryness to yield a light tan, crystalline residue. This was recrystallized twice from water (Norit)[8] to yield 4.50 g. (84%) of product as colorless, crystalline needles.

6-Chloropyrido[2,3-d]-ν-triazole.—Five grams of 2,3-diamino-5-chloropyridine was dissolved with warming in 150 cc. of water containing 5 cc. of concentrated sulfuric acid and the solution cooled to less than 10°. A second solution containing 2.5 g. of sodium nitrite in 10 cc. of cold water was then added with shaking. A yellow color developed immediately and the product separated rapidly as light yellow, crystalline needles. These were recrystallized from water (Norit) to yield 4.1 g. (76%) of material as colorless crystalline blades.

2-Hydroxy-6-chloroimidazo[b]pyridine.—A slow stream of phosgene was passed into a solution of 5.0 g. of 2,3-diamino-5-chloropyridine in 1:1 hydrochloric acid at ice-bath temperature for two hours to precipitate a crystalline phosgene adduct of the desired product. This was removed and decomposed by washing with water. The resulting granular product was recrystallized from 125 cc. of glacial acetic acid as colorless needles; yield, 2.73 g. (46%). An additional 1.0 g. (17%) of material was obtained by basifying the original acid filtrate and recrystallizing the resulting precipitate as above.

2-Thio-6-chloroimidazo[b]pyridine.—A mixture of 3.0 g. of 2,3-diamino-5-chloropyridine and 5 cc. of thiophosgene in 60 cc. of 1:1 hydrochloric acid was allowed to stand at room temperature for twenty-four hours. The crystalline precipitate which separated was washed with alcohol and dried. A satisfactory solvent for recrystallization was not found, but the material was purified in low yield by dissolving it in dilute ammonium hydroxide containing a trace of sodium hydrosulfite, treating the solution several times with Darco and reprecipitating the product with acetic acid; yield, 0.2 g. (5%).

Imidazo[b]pyridine.—A 3.3-g. sample of 6-chloroimidazo[b]pyridine and 3.5 g. of palladium hydroxide (5%) on calcium carbonate were placed in 75 cc. of water and shaken under 50 lb./sq. in. of hydrogen pressure at room temperature for seven hours. After removing the catalyst, the solution was concentrated to dryness and the residue sublimed under vacuum (2 mm.) at a bath temperature of 210° to yield 0.75 g. (29%) of product as colorless needles. The product was converted to its monohydrochloride by dissolving it in acetic acid, treating the solution with hydrochloric acid and precipitating with ethyl acetate. The salt separated slowly as colorless, crystalline blades.

2-Hydroxyimidazo[b]pyridine.—A mixture of 2.2 g. of 2-hydroxy-6-chloroimidazo[b]pyridine and 6.5 g. of palladium hydroxide (5%) on calcium carbonate in 100 cc. of alcohol was shaken under hydrogen pressure as in the previous example for eighteen hours. Removal of the catalyst and concentration of the alcohol solution gave a white solid. This was recrystallized twice from water to yield 1.0 g. (57%) of product as colorless needles.

Pyrido[2,3-d]ν-triazole.—A 2.0-g. sample of 6-chloropyrido[2,3-d]ν-triazole was added to 1.0 g. of platinum (10%) on charcoal and 1.0 g. of palladium (10%) on charcoal in 200 cc. of 1% sodium hydroxide solution and shaken for one hour at room temperature under 50 lb./sq. in. of hydrogen pressure. The theoretical hydrogen absorption was observed. The catalyst was removed and the filtrate neutralized with hydrochloric acid, treated with Darco and concentrated to 25 cc. On addition of a slight excess of hydrochloric acid and cooling the solution, the product crystallized as colorless needles. These were recrystallized from water; yield, 1.2 g. (76%).

Tetrahydropyrido[2,3-d]ν-triazole.—A mixture of 1.0 g. of 6-chloropyrido[2,3-d]ν-triazole and 3.0 g. of palladium hydroxide (5%) in 50 cc. of water was heated to 80° and then shaken under hydrogen pressure as in the previous examples. The theoretical hydrogen absorption was obtained in one hour. The catalyst was removed and the filtrate concentrated to 10 cc. On cooling, 0.55 g. (68%) of product separated as colorless needles.

2,3,6-Triaminopyridine Dihydrochloride.—A 12.5-g. sample of 2,6-diamino-3-phenylazopyridine hydrochloride[10] was placed in 100 cc. of water with 25 cc. of concentrated hydrochloric acid and 5 g. of platinum (10%) on charcoal and shaken under 50 lb./sq. in. of hydrogen pressure at room temperature for fifteen to twenty minutes to complete the reduction. The catalyst was removed and saved since it lost none of its activity. The filtrate was concentrated to 50 cc. and cooled to crystallize the product as stout needles; yield, 6.9 g. (70%). Recrystallization of these from constant-boiling hydrochloric acid (20.2%) gave 5.6 g. of pure material as colorless needles which decomposed indefinitely above 200°. The recorded melting point for this compound is 230°.[11]

Anal. Calcd. for $C_5H_8N_4 \cdot 2HCl$: C, 30.5; H, 5.1. Found: C, 30.5; H, 5.3.

5-Formylaminoimidazo[b]pyridine.—A mixture of 5.0 g. of 2,3,6-triaminopyridine dihydrochloride and 3.5 g. (2 equivalents) of sodium formate in 50 cc. of 98-100% formic acid was heated under reflux for one and one-half hours and then concentrated to dryness. The residue was washed well with cold water and crystallized from 50 cc. of glacial acetic acid (Darco) to yield 1.6 g. (39%) of product as colorless crystals.

5-Aminoimidazo[b]pyridine Dihydrochloride.—A 0.3-g. sample of 5-formylaminoimidazo[b]pyridine was placed in 3 cc. of concentrated hydrochloric acid and heated on a steam-bath for fifteen minutes. The clear solution was treated with Darco, filtered and diluted with two volumes of alcohol. On cooling, colorless crystalline needles separated; yield, 0.1 g. (26%). The product was recrystallized from a mixture of alcohol and concentrated hydrochloric acid.

Imidazo[b]pyridine-N-oxide Hydrochloride.—A solution of 5.0 g. of imidazo[b]pyridine in 100 cc. of dioxane was cooled to 15° and added slowly with stirring to a solution of 11.7 g. (1.5 equivalents) of monoperphthalic acid[12] in 90 cc. of ether. The mixture was maintained at 15° in a water-bath. An oil separated rapidly and slowly crystallized over a two-hour period; yield, 8.8 g. (70%). A 5.0-g. sample of this colorless solid, which is an equimolecular complex of imidazo[b]pyridine-N-oxide and phthalic acid,[13] was placed in 15 cc. of 10% hydrochloric acid and warmed gently for ten to fifteen minutes. On cooling the resulting solution, phthalic acid crystallized out in 75% yield (2.1 g.). The filtrate was concentrated to dryness and the residue purified by dissolving it in 100 cc. of alcohol and decolorizing with Darco. On addition of 200 cc. of acetone to the hot filtrate and cooling, the product separated slowly as crystalline blades; yield, 1.6 g. (56%), m. p. 225-230° (dec.). Concentration of the filtrate gave an additional 1.1 g. (37%) of material melting between 190-200° (dec.). The product was purified by two additional crystallizations from alcohol-acetone.

(10) Chichibabin, *et al.*, *J. Russ. Phys.-Chem. Soc.*, **50**, 522 (1920); *C. A.*, **18**, 1496 (1924); THIS JOURNAL, **56**, 1711 (1934).

(11) Chichibabin and Hoffman, *Compt. rend.*, **205**, 153 (1937).

(12) "Organic Syntheses," **20**, 70 (1940).

(13) Bachman and Cooper, *J. Org. Chem.*, **9**, 307 (1944); Bobrański, Kochańska and Kowalewska, *Ber.*, **71**, 2385 (1938).

CHEMOTHERAPY DIVISION
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Azeotrope in Cyclohexene-1,4-Dioxane System

BY ALBERT T. WATSON AND LOUIS J. BIRCHER

In the course of a systematic study of the deviations of binary liquid systems containing cyclo-