naphthoic Acid Lactone (XI).—In the same manner as used for the synthesis of I there was obtained from 1.2 g of phenylpropiolic acid and the preceding trideuteriocinnamyl alcohol 1.6 g of brown oil, presumed to be *trans*-α,α,β-**trideuteriocinnamyl phenylpropiolate**: $\nu_{max}^{CHCl_3}$ at 2210, 1710, and 965 cm^{-1}. Cyclization of 1.5 g of this ester gave 0.6 g (30%) of product, mp 190–192°, obtained as needles (mp 193–194°) on recrystallization from methanol: ν_{max} at 1750 cm^{-1}.

Anal. Calcd for $C_{18}H_{11}D_3O_2$: D, 21.43 atom % excess. Found: D, 20.60 atom % excess.

Nmr Spectra—All nmr spectra were determined by means of a Varian Associates A-60 instrument by use of tetramethylsilane as an internal standard and (unless otherwise specified) deuteriochloroform as solvent. Lactone II showed a spectrum which consisted of a complex of peaks for nine aromatic protons in the region δ = 6.7–7.6 ppm and a series of at least 18 lines (for a total of five aliphatic protons) in the region 2.4–4.9 ppm. The latter absorption lines occurred at 164, 174, 180 (most intense), 187, 189, 195, 201, 203, 210, 216, 218, 225, 232, 240, 249, 273, 282, and 290 cps, of which the trios in the regions 230–250 and 270–290 appeared as two pseudotriplets. The dideuteriolactone X showed a spectrum which was virtually superimposable on that of II except that both pseudotriplets (corresponding to protons on the CCH_2O grouping) were missing. The trideuteriolactone XI showed the same aromatic multiplet plus a broad band for two protons (benzylic type) at δ = 2.93 ppm. Through the courtesy of Varian Associates the spectra of these three compounds were also run on an HA-100 instrument. Computer analysis of the two sets of spectra gave nearly consistent values for the parameters of chemical shifts (ν in cycles per second) and coupling constants (J in cycles per second). Parameters for the A-60 spectrum of II are as follows (*cf.* formula II): ν_a = 281.2 ± 0.1, ν_b = 240.0 + 0.1, ν_c = 203.8 ± 0.2, ν_d = 170.8 ± 0.2, ν_e = 180.4 ± 0.4; J_{ab} = −8.7 ± 0.2, J_{ac} = 8.9 ± 0.3, J_{bc} = 8.9 ± 0.2, J_{cd} = 17.2 ± 0.3, J_{ce} = 5.7 ± 0.4, and J_{de} = −15.2 ± 0.2 cps. The variations in the values given are probable errors and the root-mean-square error of all values is 0.42 cps.[16]

Some 4-Aryl-4,5,6,7-tetrahydroimidazo[4,5-*c*]pyridines Derived from Histamine

FRED B. STOCKER,[1] MICHAEL W. FORDICE, JERRY K. LARSON, AND JOSEPH H. THORSTENSON

Macalester College, Saint Paul, Minnesota 55101

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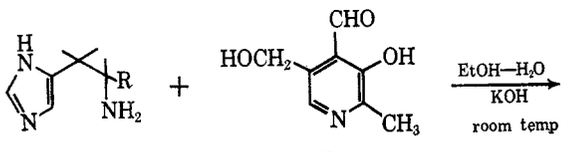
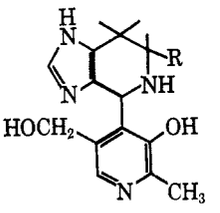
A number of 4-aryl-4,5,6,7-tetrahydroimidazo[4,5-*c*]pyridines (VI) and their isomeric Schiff bases (VII) have been prepared from histamine and aromatic aldehydes. The scope of the cyclization reaction was investigated and the structure for VI was firmly established by means of nmr analysis.

In 1948 Folkers and co-workers reported the preparation of 4-aryl-4,5,6,7-tetrahydroimidazo[4,5-*c*]pyridines (III) from both histidine (Ib)[2] and histamine (Ia)[3] by treatment with pyridoxal (vitamin B_6, II) in alkaline solution. The desired products were the corresponding Schiff bases (IV). Indeed, in the absence of alkali, histamine condenses with pyridoxal in alcoholic solution to yield IVa, a bright yellow compound which readily absorbs a molar equivalent of hydrogen. In contrast to their isomeric Schiff bases, compounds IIIa and IIIb are colorless and resistant to hydrogenation. These facts, plus structures previously formulated for spinaceamine (Va)[4] and spinacine (Vb)[5] which were prepared by the acid-catalyzed Pictet–Spengler[6] reaction, caused Folkers to postulate the 4,5,6,7-tetrahydroimidazo[4,5-*c*]pyridine ring system for compounds IIIa and IIIb.

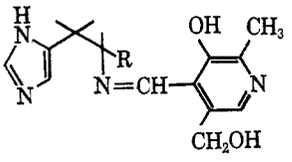


Ia, R = H
b, R = COOH

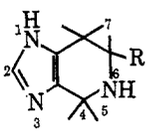
II



IIIa, R = H
b, R = COOH

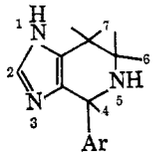


IVa, R = H
b, R = COOH



Va, R = H
b, R = COOH

We embarked on this research with the intention of finding evidence that would unequivocally establish the structure of these new ring-closure products. Furthermore, because of histamine's remarkable physiological acitivity and also because products of carbonyl compounds and β-arylethylamines (*e.g.*, tetrahydroharman, narcotine, laudanosine, hydrastine, etc.) are generally pharmacologically important, we wanted to

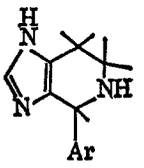


VI

(1) To whom inquiries should be addressed.
(2) D. Heyl, S. A. Harris, and K. Folkers, *J. Am. Chem. Soc.*, **70**, 3429 (1948).
(3) D. Heyl, E. Luz, S. A. Harris, and K. Folkers, *ibid.*, **70**, 3669 (1948).
(4) S. Frankel and K. Zeimer, *Biochem. Z.*, **110**, 234 (1920).
(5) J. Welisch, *ibid.*, **49**, 173 (1913).
(6) W. M. Whaley and T. R. Govindachari, *Org. Reactions*, **6**, 151 (1951).

TABLE I

4-ARYL-4,5,6,7-TETRAHYDROIMIDAZO[4,5-c]PYRIDINES



VI

Ar	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N	Yield, %	Mp, °C	λ_{max}^{EtOH}, mμ (log ε)
Phenyl	$C_{12}H_{13}N_3$	72.34	6.58	21.09	72.59	6.31	21.03	93	196.5–198	*a*
4-Methoxyphenyl	$C_{13}H_{15}N_3O$	68.10	6.59	18.33	68.23	6.67	18.16	91	195–198	225 (4.22)
4-Chlorophenyl	$C_{12}H_{12}ClN_3$	61.67	5.18	17.98	61.82	5.33	17.92	86	178–179	217 (4.24)
3-Nitrophenyl	$C_{12}H_{12}N_4O_2$	59.01	4.95	22.94	58.95	4.93	22.98	65	181–183	215 (4.06)
3,4-Methylenedioxyphenyl	$C_{13}H_{13}N_3O_2$	63.92	5.78	17.20	63.96	5.42	16.95	78	184–186	*a*
										286 (3.18)
4-Methylphenyl	$C_{13}H_{15}N_3$	73.21	7.09	19.70	73.17	6.94	19.53	90	178–180	216 (4.27)
3-Fluorophenyl	$C_{12}H_{12}FN_3$	66.35	5.57	19.34	66.58	5.13	19.45	68	221–223	*a*
4-Pyridyl	$C_{11}H_{12}N_4$	65.98	6.04	27.98	65.70	6.19	28.12	52	194–196	*a*
4-Fluorophenyl	$C_{12}H_{12}FN_3$	66.35	5.57	19.34	66.41	5.39	19.26	87	197–200	*a*
3-Bromophenyl	$C_{12}H_{12}BrN_3$	51.82	4.35	15.11	51.53	4.62	15.29	84	203–205	*a*
3-Methoxyphenyl	$C_{13}H_{15}N_3O$	68.10	6.59	18.34	67.95	6.52	18.34	88	158–160	*a*
4-Bromophenyl	$C_{12}H_{12}BrN_3$	51.82	4.35	15.11	51.76	4.42	14.91	85	175–178	218 (4.22)
2-Chlorophenyl	$C_{12}H_{12}ClN_3$	61.67	5.18	17.98	61.38	5.17	17.72	64	204–205	*a*
b	$C_{18}H_{20}N_6$	67.48	6.29	26.23	67.28	6.21	26.16	58	250–255 dec	*a*

[a] Rising end absorption. [b] Ring-closure product of histamine and terephthaldehyde; 4,4′-p-phenylenebis-4,5,6,7-tetrahydroimidazo-[4,5-c]pyridine.

prepare a series of ring-closure products of histamine with aromatic aldehydes (VI, Folkers' structure) to be examined for their pharmacological properties.

We have prepared a series of such compounds (Table I)[6a] using a procedure similar to that of Folkers, and consistent with his findings these compounds resist hydrogenation and are generally colorless.

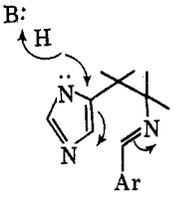
We have developed a method whereby we can easily prepare the Schiff bases VII (Table II), without solvent, by simply mixing the aromatic aldehyde and histamine at room temperature. These compounds are generally colored and will absorb a molar equivalent of hydrogen in the presence of Adams catalyst.

Although van der Merwe[7] claimed the preparation of both the anisaldehyde and piperonal Schiff bases of histamine, his reported melting points (186 and 180°, respectively) are far above the melting points we have found for these compounds. In fact, they approximate the melting points for the isomeric ring-closure products. We repeated his procedure, which is a direct thermal process without solvent, and we were able to establish that van der Merwe's products are identical with the histamine–aldehyde ring-closure products prepared in alcoholic KOH. In the Experimental Section we report the synthesis of several other ring-closure products prepared without the use of either solvent or alkaline catalyst, and we also report an example of a ring-closure process that takes place in an organic solvent in the absence of alkali.

Aliphatic aldehydes and ketones and alkyl aryl ketones fail to undergo the ring-closure reaction with histamine *via* the alkaline solvent process, presumably because of competitive aldol reactions. Attempts, using acid conditions, to condense either acetaldehyde or pyruvic acid with histidine as reported by Welisch[5] were also unsuccessful.

We have attempted acid-catalyzed cyclizations such as the Pictet–Spengler reaction of histamine with various aromatic aldehydes[8] and the Bischler–Napieralski reaction of N^{α}-benzoylhistamine[9] without success. The failure of these reactions can be attributed to the presence, in acid media, of the imidazolium ion which is resistant to electrophilic attack.

The role of the alkaline catalyst in the cyclization of histamine Schiff bases apparently is to facilitate the loss of the imino proton, thereby increasing the nucleophilicity at the 4(5)-position.



The intramolecular nature of this mechanism apparently is crucial to its success. Attempts at analogous intermolecular reactions, such as that of imidazole with the Schiff base of *p*-chlorobenzaldehyde and α-phenylethylamine in alkaline solution, have failed.[10]

In approaching the problem of determining the structure of the ring-closure products we felt compelled to consider, along with Folkers' proposed structure, the isomeric 5-aryl-5,6,7,8-tetrahydroimidazo[1,5-c]py-

(6a) NOTE ADDED IN PROOF.—*Chem. Abstr.*, **64**, 9710*a* (1966), reveals an article by T. Vitali, F. Mossini, and G. Bertaccini, *Farmaco* (Pavia), *Ed. Sci.*, **20**, 634 (1965), wherein the authors report the synthesis from histamine of the following 4-aryl-4,5,6,7-tetrahydroimidazo[4,5-c]pyridines reported in Table I: Ar = phenyl, 2-chlorophenyl, 4-chlorophenyl, 4-methylphenyl, 3-nitrophenyl, 3-methoxyphenyl, 4-methoxyphenyl, and 3,4-methylenedioxyphenyl.

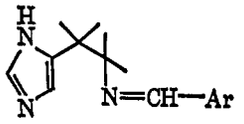
(7) P. van der Merwe, *Z. Physiol. Chem.*, **177**, 301 (1928).

(8) We are grateful to Mr. David Egberg for performing these experiments.

(9) We are indebted to Miss Patricia Canton for these experiments. The catalysts used were $POCl_3$, P_2O_5, and polyphosphoric acid.

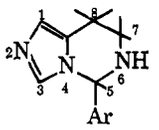
(10) We are grateful to Miss Kathleen Kutzke for performing these experiments.

TABLE II
HISTAMINE SCHIFF BASES



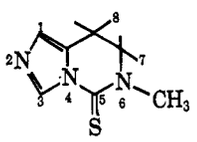
VII

Ar	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N	Mp, °C	Infrared C=N stretch, cm^{-1}	λ_{max}^{EtOH}, mμ (log ε)
4-Methoxyphenyl	$C_{13}H_{15}N_3O$	68.10	6.59	18.33	67.91	6.77	18.59	113–114	1642	268 (4.22) 213 sh (4.26)
4-Chlorophenyl	$C_{12}H_{12}ClN_3$	61.67	5.18	17.98	61.84	5.32	18.14	128–129	1637	253 (4.28)
3-Nitrophenyl	$C_{12}H_{12}N_4O_2$	59.01	4.95	22.94	58.94	5.06	23.10	122–124	1640	234 (4.39)
3,4-Methylenedioxyphenyl	$C_{13}H_{13}N_3O_2$	63.92	5.78	17.20	63.74	5.63	17.08	104.5–106.5	1640	307 (3.97) 267 (4.02) 223 (4.25)
4-Methylphenyl	$C_{13}H_{15}N_3$	73.21	7.09	19.70	72.93	6.88	19.52	114–115	1642	254 (4.12)
2-Chlorophenyl	$C_{12}H_{12}ClN_3$	61.67	5.18	17.98	61.98	5.22	17.76	160–162	1630	247 (4.13)
4-Hydroxyphenyl	$C_{12}H_{13}N_3O$	66.96	6.09	19.52	67.07	6.15	19.34	163–164	1640	271 (4.29) 214 (4.34)
4-Nitrophenyl	$C_{12}H_{12}N_4O_2$	59.01	4.95	22.94	59.13	5.11	22.88	142–154	1640	281 (4.18)
2,4-Dichlorophenyl	$C_{12}H_{11}Cl_2N_3$	53.75	4.13	15.67	53.48	4.31	15.45	93–94	1639	254 (4.18)
4-Acetamidophenyl	$C_{14}H_{16}N_4O$	65.60	6.29	21.86	65.90	6.26	21.89	173–173.5	1638	295 (4.25) 280 (4.37) 246 (3.62)
4-Bromophenyl	$C_{12}H_{12}BrN_3$	51.82	4.35	15.11	51.75	4.26	14.95	125–127	1645	257 (4.02)
4-Dimethylaminophenyl	$C_{14}H_{18}N_4$	69.39	7.49	23.12	69.17	7.60	22.84	150–151	1634	327 (4.34)



VIII

rimidine ring system (VIII)[11] which would result if the histamine Schiff bases cyclized to the 1-position of the imidazole ring. The chemistry of the imino group is consistent with such a structure. Fortunately, several articles in the recent literature contain nmr data for these ring systems. Vitali and Bertaccini[12] reported proton shift values for several 4,5,6,7-tetrahydroimidazo[4,5-*c*]pyridines in both acidic (D_2O–HCl) and basic (D_2O–NaOD) solutions. The following δ values[13] for spinacine (Vb) are representative: 2-proton, 9.07 (acid), 7.76 (base); 4-proton, 4.74 (acid), 3.87 (base); 6-proton, 4.84 (acid), 3.50 (base); 7-protons, 3.57 (acid), 2.81 (base). For purposes of reference they also determined chemical shift data for the 4(5)-proton of histamine and related compounds. The δ values are, for histamine, 7.67 (acid), for N^{α},N^{α}-dimethylhistamine, 7.70 (acid), 7.18 (base), and for histidine, 7.70 (acid), 7.16 (base). The fact that the resonances in acidic media are at lower field is attributable to the deshielding effects of the protonated N atoms and, as would be expected, these effects are more pronounced for the imidazole 2-proton ($\Delta\delta \sim 1.2$) than for the imidazole 4(5)-proton ($\Delta\delta \sim 0.5$). Also reported for spinacine[14] are proton shift data determined in trifluoroacetic acid. The δ values[15] in this solvent are 2-proton, 8.81; 4-proton, 4.95; 6-proton, 4.95; and 7-protons, 3.75. An nmr analysis reported by Mechoulain, *et al.*,[16] of the alkaloid zapotidine (IX) provided data for the tetrahydroimidazo[1,5-*c*]pyrimidine ring system. The δ values are 1-proton, 6.81; 3-proton, 8.42; 7-protons, 3.67 (triplet); and 8-protons, 3.05 (triplet). The rather low-field resonance of the 3-proton is due to the deshielding effect of the thione group.



IX

For comparison purposes we determined the nmr spectra of some of our histamine Schiff bases. Representative of these is the spectrum of *p*-chlorobenzylidenehistamine in deuteriochloroform which shows peaks (δ values) at 8.14 (singlet, one proton), 7.67–7.25 (multiplet, four protons), 7.19 (singlet, one proton), 6.82 (singlet, one proton), 3.87 (triplet, two protons), and 2.98 (triplet, two protons) which correspond, respectively, to the anil proton, the four phenyl protons, the imidazole 2-proton, the imidazole 4(5)-proton, the two protons α to the side-chain N atom, and the two protons β to the side-chain N atom. The imino proton and the phenyl ring protons tended to show resonances

(11) Compounds containing this ring system were first synthesized by K. Schlögl and H. Woidich, *Monatsh. Chem.*, **87**, 679 (1956).

(12) T. Vitali and G. Bertaccini, *Gazz. Chim. Ital.*, **94**, 296 (1964).

(13) The original shift values, which were recorded at 54.4 Mc and reported in cycles per second relative to the methyl singlet of *t*-butyl alcohol, have been converted to parts per million and adjusted to become comparable with TMS by adding 1.23 ppm, the shift of methyl group of *t*-butyl alcohol downfield from DSS (sodium 2,2-dimethyl-2-silapentane-5-sulfonate) in deuterium oxide solution.

(14) D. Ackermann and G. Hoppe-Seyler, *Z. Physiol. Chem.*, **336**, 283 (1964).

(15) Determined on a Varian A-60 spectrometer using tetramethylsilane as an internal reference.

(16) R. Mechoulain, F. Sondheimer, A. Melera, and F. A. Kincl, *J. Am. Chem. Soc.*, **83**, 2022 (1961).

in the region of the imidazole 2-proton, thus complicating the interpretation of the spectra.

Spectra of the ring-closure products determined in neutral organic solvents such as $CDCl_3$ or CD_3SOCD_3 had similar interferences in the 7–8-ppm region. The variable N-proton resonances presented the greatest problem. By recrystallizing the ring-closure product of *p*-tolualdehyde and histamine from D_2O a sample essentially free of N protons was afforded which gave an improved nmr spectrum (in $CDCl_3$) exhibiting the following peaks (δ values): 7.05 (singlet), 4.85 (singlet), 3.02 (distorted triplet), 2.58 (distorted triplet), and 2.27 (singlet) with respective areas 5:1:2:2:3. In accord with structure VI, the peak at δ 7.05 corresponds to the four phenyl ring protons included with the imidazole 2-proton, the δ 4.85 peak represents the 4-proton, the two 6-protons at δ 3.02 are coupled with the two 7-protons at δ 2.58 displayed as triplets in the A_2X_2 pattern, and the δ 2.27 peak is attributable to the three methyl protons. It is noteworthy that the spectrum of this deuterated sample exhibited two fewer protons, as determined by the integral lines, than the nondeuterated compound.

Probably even more persuasive evidence for structure VI is found in the trifluoroacetic acid nmr spectrum of the *p*-tolualdehyde–histamine ring-closure product. This spectrum (δ values) shows a one-proton singlet at 8.72, a four-proton singlet at 7.27, a one-proton singlet at 6.03, and a pair of broad two-proton peaks centered at 3.94 and 3.45. In the light of comparative data reported above it is clear that the δ 8.72 peak is due to the 2-proton, the δ 7.27 peak represents the four phenyl ring protons, the δ 6.03 peak is due to the 4-proton, and the δ 3.94 and 3.45 peaks are due to the 6- and 7-protons. None of the nmr spectra recorded for these ring-closure products exhibited resonances that could be attributed to an imidazole ring 4(5)-proton. This body of spectral evidence thus confirms the structure proposed by Folkers.

Experimental Section[17]

General Procedure for Preparation of 4-Aryl-4,5,6,7-tetrahydroimidazo[4,5-c]pyridines (VI). Method A.—Histamine dihydrochloride (0.01 mole) was added to 0.03 mole of KOH dissolved in 10 ml of water. A solution of aromatic aldehyde (0.01 mole) dissolved in 25 ml of ethanol was added followed by 125 ml of water. (The volume of water added must be sufficient to dissolve precipitated inorganic salts but not enough to force the aldehyde from solution.) The solution was heated on the steam bath in an open flask to allow slow evaporation of the solvent. As the volume decreased crystals began to appear. At this point the solution was allowed to cool to room temperature to facilitate crystallization of the product. (When electron-releasing substituents are present on the phenyl ring of the aromatic aldehyde, reaction rates are slow and unreacted aldehyde may oil out during the evaporation process. Addition of more ethanol followed by further heating will allow the process to continue to incipient crystallization.) Because the crude product separates out by crystallization, it is often of relatively high purity. Usually one additional crystallization from hot water will provide a sample suitable for analysis.

Method B. Van der Merwe's Procedure.[7]—(Our experience with this procedure is limited to four aromatic aldehydes: anisaldehyde, benzaldehyde, *p*-fluorobenzaldehyde, and *p*-chlorobenzaldehyde.)

Carefully weighed molar equivalents of histamine (free base) and aromatic aldehyde were combined and placed on the steam bath. The resulting viscous oil was stirred to guarantee homogeneity and heating was continued until the oil solidified. With reactive aldehydes such as *p*-fluorobenzaldehyde, solidification will occur in about 45 min, whereas with anisaldehyde more than 5 hr was required. Yields by this procedure are essentially quantitative. Van der Merwe's procedure calls for recrystallization from alcohol–ether but water will work equally well.

Method C. Preparation of 4-Phenyl-4,5,6,7-tetrahydroimidazo[4,5-c]pyridine in Boiling Benzene–Ethanol Solution.—Histamine (free base, 0.02 mole) and benzaldehyde (0.02 mole) were dissolved together in 20 ml of ethanol. To this solution was added 180 ml of benzene. The solution was boiled for 2 hr, charcoal was added, and after 5 min of additional boiling the solution was filtered. On cooling, the filtrate deposited approximately a 25% yield of 4-phenyl-4,5,6,7-tetrahydroimidazo[4,5-c]pyridine in the form of white microcrystals, mp 196–198°.

General Procedure for Preparation of Histamine Schiff Bases (VII).—Precisely weighed equimolar quantities of histamine free base and aldehyde were mixed to homogeneity. In most cases a mildly exothermic reaction ensued which resulted in a sudden solidification of the viscous, oily mixture to give essentially a quantitative yield of Schiff base. In those few cases when solidification does not quickly occur a brief period on the steam bath may be used to complete the reaction. Prolonged heating must be avoided at this point and during the recrystallization process owing to the possibility of cyclization. Recrystallization was from benzene.

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(17) Melting points were taken on a Kofler micro hot stage and are corrected. Microanalyses were by Galbraith Laboratories, Inc., Knoxville, Tenn. Infrared spectra were determined on a Beckman Model IR-5A spectrophotometer and ultraviolet spectra were recorded on a Beckman DK-2A spectrophotometer with ethanol used as the solvent. The nmr spectra were determined on a Varian A-60 spectrometer using tetramethylsilane as an internal reference.