Synthesis of 7,7-Diaryl-4,5,6,7-tetrahydroimidazo-[4,5-*c*]pyridines

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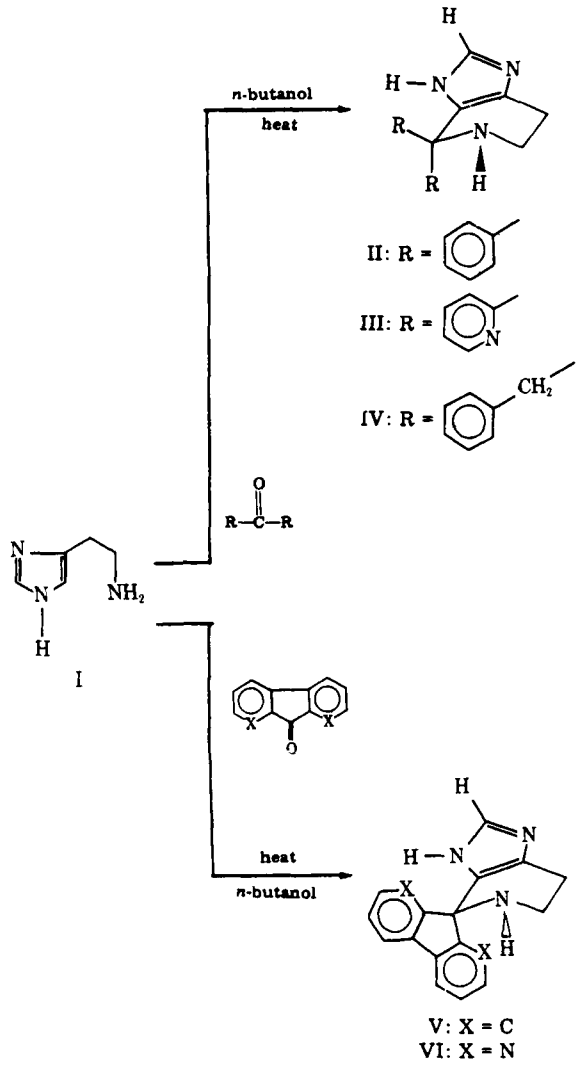
Abstract □ The synthesis and characterization of various 7,7-diaryl-4,5,6,7-tetrahydroimidazo-[4,5-*c*]pyridines are reported. Convulsant activity was observed with a dipyridyl compound.

Keyphrases □ Histamine—condensation reactions to form 7,7-diaryl-4,5,6,7-tetrahydroimidazo-[4,5-*c*]pyridines □ Spirocyclic-4,5,6,7-tetrahydroimidazo-[4,5-*c*]pyridines—synthesis and characterization □ Convulsants—activity in rats, synthesized dipyridyl compound

As part of a continuing research program in the condensation reactions of histamine (I) with various carbonyl compounds, the synthesis of several novel diaryl-4,5,6,7-tetrahydroimidazo-[4,5-*c*]pyridines will be described. While a variety of condensation products were previously described (1–3), an examination of this Pictet-Spengler type reaction of histamine with diaryl ketones has not been reported.

In general, previously reported methods for the condensation of histamine with aldehydes involved the reaction of histamine dihydrochloride in a basic media with the appropriate aldehyde. Good yields of the aldehyde and ketone condensation products can also be realized by refluxing histamine free base with the desired carbonyl compounds in *n*-butanol. Under these conditions, the Schiff-base intermediates undergo ring closure at the C-5 position of the imidazole ring and the products can then be isolated by removal of the reaction solvent.

This rather simple synthesis has been successfully adapted to include examples of both acyclic and, more recently, cyclic ketones such as 9-fluorenone and 1,8-diazafluorene (Scheme I). The resulting 7-spirocyclic-4,5,6,7-tetrahydroimidazo-[4,5-*c*]pyridines (V and VI) as well as the acyclic ketone analogs (II–IV) have all been characterized by NMR, IR, and elemental analysis (Tables I and II).



Scheme I

Table I—Physical Data for Diaryl-4,5,6,7-tetrahydroimidazo-[4,5-*c*]pyridines

Compound	Melting Point Free Base	Yield, %	Formula	Analysis, % Calc.	Found
II	100–105°	50	$C_{18}H_{17}N_3$	C 78.54	78.34
				H 6.14	6.36
				15.27	15.36
III	220–222°	66	$C_{16}H_{15}N_5$	C 69.31	69.19
				H 5.41	5.38
				N 25.27	25.65
IV	218–219°	60	$C_{20}H_{21}N_3$	C 79.48	79.46
				H 6.94	6.95
				N 13.89	13.97
V	258°	69	$C_{18}H_{15}N_3$	C 79.41	79.35
				H 5.15	5.51
				N 15.44	15.41
VI	250° (dec.)	41	$C_{16}H_{15}N_5Cl_2$ (dihydrochloride)	C 55.36	54.95
				H 4.08	4.34
				N 20.17	20.01

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Table II—Spectral Data for Diaryl-4,5,6,7-tetrahydroimidazo-[4,5-c]pyridines

Compound	IR Spectrum (KBr): ν_{max}, cm^{-1}	^{1}H-NMR Spectrum (deuterodimethylsulfoxide), ppm
II	3100–2800 (bd), 1610, 750, and 695	2.5 (t, 2H, C-4, CH_2), 2.7 (t, 2H, C-5, CH_2), and 7.16–7.4 (m, 11H, Ar, C-2)
III	3250–2850 (bd), 1610, 775, and 745	2,6 (t, 2H, C-4, CH_2), 2.9 (t, 2H, C-5, CH_2), 7.2 (m, 2H, Ar), 7.6 (5H, Ar, C-2), and 8.3 (2H, Ar)
IV	3100–2600 (bd), 1610, 750, and 695	2.16 (t, 2H, C-4, CH_2), 2.7 (t, 2H, C-5, CH_2), 2.9 (d, 2H, CH_2), 3.4 (d, 2H, CH_2), 7.2 (m, 10H, Ar), and 7.6 (S, 1H, C-2)
V	3200–2850 (bd), 1620 and 745	3.3 (t, 2H, C-4, CH_2), 3.75 (t, 2H, C-5, CH_2), 8.06 (S, 1H, C-2), and 7.6 (m, 8H, Ar)
VI	3200–2800 (bd), 1620, 1580, 790, and 755	2.6 (t, 2H, C-4, CH_2), 3.1 (t, 2H, C-5, CH_2), 6.8 (m, 2H, Ar), 7.8 (m, 3H, Ar, C-2), and 8.3 (m, 2H, Ar)

RESULTS AND DISCUSSIONS

The condensation of histamine free base (I) and a variety of aromatic and heteromatic ketones has given rise to a series of novel 4,5,6,7-tetrahydroimidazo-[4,5-c]pyridines. The proposed structures are supported by pertinent spectral data and are consistent with ring closure at C-5 of the imidazole ring with concomitant loss of the characteristic aromatic proton at 6.9 ppm.

A preliminary gross behavioral evaluation of each of these compounds in mice at three different dose levels (33, 54, and 66 mg/kg) has shown that the dipyridyl compound (III) exhibits a marked degree of convulsant activity. None of the other compounds were found to produce convulsions at the same dose levels. Research is currently in progress to establish the possible mode of action of this novel heterocyclic system.

EXPERIMENTAL[1]

All syntheses were carried out by dissolving the appropriate ketone in *n*-butanol and treating the stirred solution with one equivalent of histamine-free base in *n*-butanol. The solutions were refluxed and monitored using TLC (cellulose; *n*-butanol–acetic acid–water, 4:1:1) until no further ketone could be detected. Removal of the solvent under reduced pressure followed by repeated dilutions with methanol and then with acetone caused the precipitation of the crude free bases of the condensation products. The resulting free bases were converted to their corresponding hydrochlorides which could be recrystallized from ethanol–acetone.

REFERENCES

(1) D. Heyl, E. Luz, S. Harris, and K. Folkess, *J. Am. Chem. Soc.*, **70**, 3669 (1943).

(2) F. Stocker, M. Fordice, J. Larson, and T. H. Thorestenson, *J. Org. Chem.*, **31**, 2380 (1966).

(3) G. Habermehl and W. Ecsy, *Heterocycles*, **5**, 127 (1976).

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[1] Melting points for all compounds are uncorrected and were determined on a Thomas-Hoover melting point apparatus. IR spectra were recorded on a Perkin-Elmer 137 spectrometer. NMR spectra were recorded on a Varian T-60 spectrometer in deuterodimethylsulfoxide using tetramethylsilane as the internal standard. All C, H, and N analyses were performed by the M-H-W Laboratories, Phoenix, Ariz.

Quality Control of Phenylbutazone II: Analysis of Phenylbutazone and Its Decomposition Products in Drugs by High-Pressure Liquid Chromatography

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Received June 2, 1980, from the *Laboratoire de Chimie Analytique, Faculté de Pharmacie, 34060 Montpellier Cedex, France.* Accepted for publication June 17, 1981.

Abstract □ A rapid, sensitive, accurate, and reproducible procedure for the simultaneous separation and determination of phenylbutazone and three major degradation products is proposed using reversed-phase high-pressure liquid chromatography and UV detection. The method is ~20 times more sensitive than TLC and allows an accurate determination of degradation products without decomposition during the analysis.

Keyphrases □ Phenylbutazone—analysis by high-pressure liquid chromatography, decomposition products □ High-pressure liquid chromatography—analysis of phenylbutazone and its decomposition products □ Degradation—phenylbutazone, analysis by high-pressure liquid chromatography

An earlier report (1) outlined the difficulties relative to the establishment of an analytical procedure to detect the intermediate products of oxidation and hydrolysis of phenylbutazone (I). These products are 4-hydroxyphenylbutazone (II), *N*-(2-carboxycaproyl)hydrazobenzene (III), and *N*-(2-carboxy-2-hydroxycaproyl)hydrazobenzene (IV). GLC and TLC are not reliable procedures to monitor the stability of I, because artifacts are formed. TLC can only be used with special precautions as a qualitative and quantitative test to determine I–IV (1).

Reversed-phase high-pressure liquid chromatography (HPLC) is often used in stability studies because it is selective and rapid, and it is particularly recommended when the compound is easily oxidized and when extraction procedures may be degradative. No sample preparation is required for aqueous solutions and reversed-phase HPLC is especially attractive for injections of I because I undergoes decomposition in aqueous medium. Re-

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