Imidazolecarbohydrazides. III. Chemistry and Biological Evaluation[1,2]

J. R. Nulu and Jay Nematollahi[3]

College of Pharmacy, University of Texas, Austin, Texas 78712

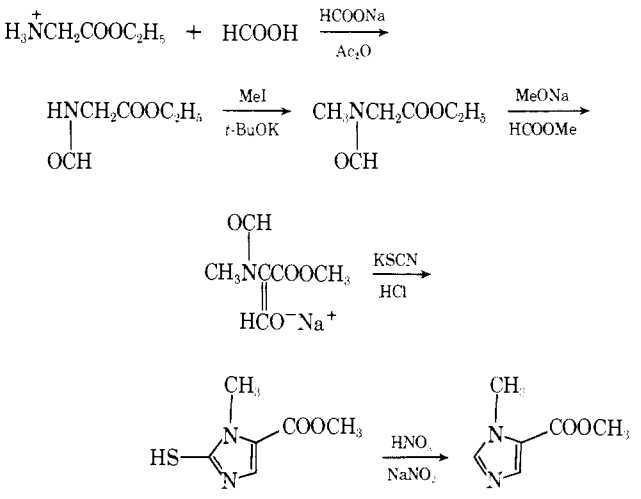
Received February 10, 1969

A series of imidazole-4-carbohydrazides and 1-methylimidazole-5-carbohydrazides was synthesized either by the hydrazinolysis of methyl imidazole-4(5)-carboxylates or reduction of appropriate hydrazones. The molecular structure of these compounds was proved by analysis and spectroscopy. The biological evaluation for their MAO inhibitory activity was performed as reported previously.[2] Under our experimental conditions, one of the compounds, imidazole-4-carboxylic acid 2-benzylhydrazide, manifested activity higher than isocarboxazid, which was employed as a control. The others in the series possessed activity about half of that of isocarboxazid. A feature which generally differentiated these compounds from the previously reported dicarbohydrazides was their potential to prolong, to a great extent, the sleeping time induced in mice by hexobarbital.

In our earlier papers,[2,4] we have reported the synthesis and biological evaluation of a series of imidazole-4,5-dicarbohydrazides. The structural elucidation of these and related molecules leading to an eventual establishment of a relationship between the stereochemistry of this series of compounds and their biological properties has necessitated further investigation along this line of research. This paper is the report of our investigation on the chemistry and biological properties of a series of imidazole-4-carbohydrazides and 1-methylimidazole-5-carbohydrazides.

Chemistry.—The starting compounds methyl imidazole-4-carboxylate (I) and methyl 1-methylimidazole-5-carboxylate (II) were synthesized by a method which involved the basic synthetic route reported by Jones.[5] In our hand the procedure, however, required a few necessary modifications. As shown in Scheme I,

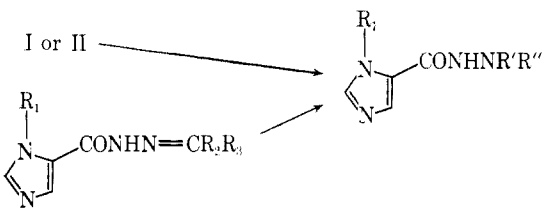
Scheme I



100% formic acid[6] was employed in the formylation, a step which had to precede alkylation. KO-*t*-Bu rather than NaOMe needed to be used as a base. Finally, the dissolution of enolate salt in H_2O had to be omitted. It is noteworthy that despite the use of glycine ethyl ester, the final product of this reaction is a Me ester. This transesterification occurs during the Claisen condensation step of methyl formate with N-formylglycine ethyl ester.

Recently a new method of synthesis of II has been reported,[7] which seems to be a simpler method than that shown in Scheme I.

The desired carbohydrazides were prepared by two major routes: (1) the hydrazinolysis of the esters I or II, and (2) the reduction of hydrazones which in turn had been prepared by treating imidazole-4- or 1-methylimidazole-5-carbohydrazide with a ketone or



an aldehyde. The molecular structure of the reaction products was elucidated by the elemental analysis, tlc, ir and nmr spectroscopy, and, less frequently, by synthesizing derivatives. The interaction of I or II with various hydrazines gave the following products: imidazole-4-carbohydrazide (III), imidazole-4-carboxylic acid 2-methylhydrazide (IV), 1-methylimidazole-5-carbohydrazide (V), and 1-methylimidazole-5-carboxylic acid 2-methylhydrazide (VI). The emergence of a single product rather than a mixture of two possible isomers, in the case of the ester-methylhydrazine interaction, was revealed by tlc (single spot) and nmr (single CH_3 peak). The position of the CH_3 group in the hydrazine moiety of IV and VI was assigned to N_2 by comparing their nmr spectra with the carboxamides, imidazole-4-carboxylic acid methylamide (VII) and 1-methylimidazole-5-carboxylic acid methylamide (VIII), which were prepared by treating the esters, separately, with methylamine. The position of the CH_3 peaks of IV and VI was identical, δ 2.53, and the position for the deshielded CH_3 peaks of amides VII and VIII were doublets at δ 2.83 and 2.79, respectively. The doublet arises as a result of a partial C=N characteristic which is due to the conjugation of the lone pair of electrons in N with C=O. This spectrometric structural proof was substantiated chemically by observing the unreactivity of the reaction products with

(1) This research was supported in part from the University of Texas Research Institute, Grant R-313.

(2) Previous paper of this series: J. Nematollahi and J. R. Nulu, *J. Med. Chem.*, **12**, 43 (1969).

(3) To whom inquiries should be directed.

(4) J. Nematollahi, W. Guess, and J. Actian, *J. Med. Chem.*, **9**, 660 (1966).

(5) R. G. Jones, *J. Am. Chem. Soc.*, **71**, 644 (1949).

(6) S. Winstein and R. Marshall, *ibid.*, **74**, 1120 (1952).

(7) P. K. Martin, H. R. Matthews, H. Rapoport, and G. Thyagarajan, *J. Org. Chem.*, **33**, 3758 (1968).

ketones and aldehydes, an indication of the absence of NH_2. As has been indicated,[4] the N–N bond cleavage of imidazolecarbohydrazides with Raney nickel for preparing amides for structural proof was not successful, apparently due to the complexation of imidazole with Ni.

The reaction of I with phenylhydrazine on a prolonged heating provided imidazole-4-carboxylic acid 2-phenylhydrazide (IX). Attempts to prepare the anilides of I or II for structural proof was unsuccessful. This refractoriness was ascribed to both the steric effect and the less basic nature of the N of aniline. However, since neither of the esters, I or II, reacted with cyclohexylamine, steric factors seemed to be dominant. The assignment of the position of Ph in IX was on the basis of its inertness toward ketones or aldehydes, similar to their Me analogs.

Phenylhydrazine did not react with II even when the reactants were placed in a sealed tube and heated at 120° for 60 hr. No change was observed by conducting the sealed-tube reaction under N_2, perhaps due to the steric effect of the Me group.

The hydrazides whose synthesis did not materialize, either due to the difficulty in acquiring certain substituted hydrazines or because of the lack of reactivity of certain hydrazines with esters I or II, were prepared *via* the reduction of their appropriate hydrazones. The catalytic hydrogenation of the hydrazones at a high temperature using PtO_2 was somewhat satisfactory with R_2 and R_3 as H or CH_3. With R_2 = Ph, this reduction, however, did not proceed. Attempted hydrogenations in the presence of Ru, Rh, or Pd on alumina or on charcoal were also unsuccessful. The reducing potential of various metal hydrides in a number of polar and nonpolar solvents was then explored. An aqueous solution of $NaBH_4$ was revealed to be the most valuable agent for converting carbohydrazones to their corresponding carbohydrazides. This method, whose mechanism, scope, and limitation has been reported,[8] possesses the virtue of being swift and simple, in addition to providing a high yield of the desired hydrazides.

The following hydrazones were prepared by treating III or V individually with acetone or benzaldehyde: imidazole-4-carboxylic acid 2-isopropylidenehydrazide (X), imidazole-4-carboxylic acid 2-benzylidenehydrazide (XI), 1-methylimidazole-5-carboxylic acid 2-isopropylidenehydrazide (XII), and 1-methylimidazole-5-carboxylic acid 2-benzylidenehydrazide (XIII).

The corresponding reduction products of these hydrazones are imidazole-4-carboxylic acid 2-isopropylhydrazide (XIV), imidazole-4-carboxylic acid 2-benzylhydrazide (XV), 1-methylimidazole-5-carboxylic acid 2-isopropylhydrazide (XVI), and 1-methylimidazole-5-carboxylic acid 2-benzylhydrazide (XVII). The molecular structure of these compounds was proven analogous to the previous compounds.

Experimental Section

Melting points were determined in open capillary tubes in a Thomas–Hoover melting point apparatus and those below 230° were corrected. All evaporations were made *in vacuo* from rotatory evaporators. Ir spectra were determined in KBr with a Beckman IR 8 instrument, and nmr spectra with a Varian A-60 spectrophotometer at ambient temperature (Me_4Si), DMSO-d_6 solvent. Elemental analyses were done by the Microanalytical Laboratory, Department of Chemistry, University of Texas at Austin, and in part by Schwarzkopf Microanalytical Laboratory, Woodside, N. Y.

Imidazole-4-carboxylic Acid Hydrazide (III).—To 1.2 g (0.01 mole) of I was added 2 g (0.06 mole) of dry $(NH_2)_2$. The solid, which was produced after 5 min of heating under reflux at 60°, was washed with Et_2O and crystallized from MeOH to give 1.1 g (91%) of III, mp 200–201° (lit.[9] mp 203–204°). This reaction proceeds equally well in *n*-BuOH.

Except for heating the reactants for 2 hr, IV was synthesized analogous to III; yield 64%, mp 220–221°. *Anal.* ($C_5H_8N_4O$) C, H, N: calcd, 39.98; found, 39.36. The completion of this reaction in the presence of *n*-BuOH required 6 hr of heating.

1-Methylimidazole-5-carboxylic Acid Hydrazide (V).—To 0.7 g (0.005 mole) of II was added 1.0 g (0.03 mole) of dry $(NH_2)_2$. The solid, which had been afforded after 15 min of heating under reflux at 70°, was washed with Et_2O–MeOH and crystallized from MeOH to give 0.6 g (85%) of V, mp 182–184° (lit.[9] mp 188–189°). The completion of this reaction in the presence of *n*-BuOH required 1 hr of heating.

Except for heating the reactants for 36 hr and using EtOAc–MeOH (90:10) as crystallizing solvent, VI was synthesized analogous to V; yield 53%, mp 135–136°. *Anal.* ($C_6H_{10}N_4O$) C, H, N.

Imidazole-4-carboxylic Acid 2-Phenylhydrazide (IX).—To 0.6 g (0.005 mole) of I was added 1 g (0.01 mole) of phenylhydrazine. The mixture was heated under reflux at 80° for 48 hr. A yellow solid which had been formed at this time was washed with Et_2O and crystallized from MeOH to give 0.65 g (65%) of IX, mp 226–228°. *Anal.* ($C_{10}H_{10}N_4O$) C, H, N. No product was formed if *n*-BuOH was used as a solvent.

Imidazole-4-carboxylic Acid 2-Isopropylidenehydrazide (X).—A suspension of 1.2 g (0.01 mole) of III in 50 ml of dry Me_2CO–MeOH (50:25) was heated under reflux for 20 min. The solution was evaporated. The residue was crystallized from EtOAc–MeOH to give 1.4 g (87%) of X, mp 228–230°. *Anal.* ($C_7H_{10}N_4O$) N; C: calcd, 50.59; found, 50.03; H: calcd, 6.07; found, 5.46.

Compound XII was prepared by an analogous method; yield 92%, mp 186–188°. *Anal.* ($C_8H_{12}N_4O$) C, H, N.

Imidazole-4-carboxylic Acid 2-Benzylidenehydrazide (XI).—To 1.8 g (0.015 mole) of III was added 8–10 ml of benzaldehyde (chlorine free). The mixture was heated under reflux at 50–60° for 45 min under dry N_2. The pale yellow solid, which had been separated, was washed with Et_2O and crystallized from 40% MeOH in H_2O to give 2.7 g (90%) of XI, mp 224–226°. *Anal.* ($C_{11}H_{10}N_4O$) C, H, N.

Compound XIII was synthesized by an analogous method; yield 84%, mp 176–178°. *Anal.* ($C_{12}H_{12}N_4O$) C, H, N.

Imidazole-4-carboxylic Acid 2-Isopropylhydrazide (XIV).—To a suspension of 0.8 g (0.005 mole) of X in 25 ml of H_2O was added 0.4 g (0.01 mole) of $NaBH_4$. The mixture was heated at 70° for 45 min. The solution was evaporated to about 8 ml wherein a white solid was precipitated. The solid was filtered and washed with a few milliliters of cold H_2O and then crystallized from 80% MeOH in H_2O to give 0.6 g (70%) of XIV, mp 159–161°. *Anal.* ($C_7H_{12}N_4O \cdot 0.25H_2O$) C, H, N: calcd, 32.44; found, 33.05.

Compound XV was prepared by an analogous method; yield 90%, mp 157–158°. *Anal.* ($C_{11}H_{12}N_4O$) C, H, N: calcd, 25.91; found, 25.40.

1-Methylimidazole-5-carboxylic Acid 2-Isopropylhydrazide (XVI).—To a suspension of 0.9 g (0.005 mole) of XII in 40 ml of H_2O was added 0.6 g (0.015 mole) of $NaBH_4$. The mixture was heated under reflux at 75° for about 30 min. After evaporating to about 15 ml, the solution was extracted with two 30-ml portions of Et_2O. The combined Et_2O extracts was dried (Na_2SO_4). Evaporation of the solvent gave a solid which was crystallized from PhH containing a few drops of MeOH to afford 0.8 g (86%) of XVI, mp 128–130°. *Anal.* ($C_8H_{14}N_4O$) C, H, N.

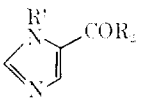
Compound XVII was synthesized by an analogous procedure. However, due to the hygroscopic nature of the base, its dihydrochloride salt was prepared by bubbling HCl into the solution of XVII in Et_2O; yield 70%, mp 193–195°. *Anal.* ($C_{12}H_{16}Cl_2N_4O \cdot 0.5H_2O$) C, H, N.

Pharmacology. MAO Inhibition.—The biological evaluation

(8) J. R. Nulu and J. Nematollahi, *Tetrahedron Lett.*, 1321 (1969).

(9) R. G. Jones and K. C. McLaughlin, *J. Am. Chem. Soc.*, **71**, 2444 (1949).

TABLE I



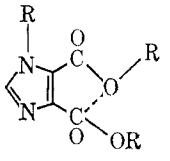
Compd	R_1	R_2	Oral dose, mmole/kg	Act. prior to reserpine (2 mg/kg)	Mean ptotic score	Hexobarb.-induced sleep time, min[a]	Effect of compd on reserpine-induced hypothermia, body temp, °C ± SE: 0 Hr after administrn	1 Hr after administrn	6 Hr after administrn	24 Hr after administrn
Control[b]				Normal	3.66	8.2 ± 0.4	36.2 ± 0.4	29.9 ± 0.5	29.2 ± 0.4	29.2 ± 1.1
III	H	$NHNH_2$	0.275	Increased	2.00	13.5 ± 1.6	35.9 ± 0.1	32.3 ± 0.7	30.9 ± 1.3	32.5 ± 0.7
IV	H	$NHNHCH_3$	0.275	Increased	1.16	14.6 ± 1.4	36.0 ± 0.1	34.8 ± 0.6	33.1 ± 0.8	34.1 ± 0.1
V	CH_3	$NHNH_2$	0.275	Increased	1.50	13.9 ± 1.4	36.6 ± 0.2	34.9 ± 0.1	32.0 ± 0.3	32.2 ± 0.8
VI	CH_3	$NHNHCH_3$	0.275	Increased	2.16	17.0 ± 1.8	36.3 ± 0.1	33.9 ± 0.5	32.9 ± 0.5	33.2 ± 0.9
IX	H	$NHNHC_6H_5$	0.275	Increased	2.33	22.3 ± 2.0	36.2 ± 0.2	33.2 ± 0.4	30.1 ± 1.2	31.9 ± 1.4
X	H	$NHN{=}C(CH_3)_2$	0.275	Increased	2.06	14.2 ± 1.0	36.3 ± 0.2	34.2 ± 0.2	32.3 ± 0.2	32.8 ± 0.6
XI	H	$NHN{=}CHC_6H_5$	0.275	Increased	1.83	16.3 ± 0.7	36.1 ± 0.1	33.3 ± 0.3	32.0 ± 0.6	33.2 ± 0.5
XII	CH_3	$NHN{=}C(CH_3)_2$	0.275	Increased	1.83	13.0 ± 1.0	36.0 ± 0.2	32.4 ± 0.4	31.5 ± 0.7	33.3 ± 0.4
XIII	CH_3	$NHN{=}CHC_6H_5$	0.275	Increased	2.00	12.1 ± 0.3	36.5 ± 0.1	32.3 ± 0.3	32.3 ± 0.7	32.5 ± 0.9
XIV	H	$NH{-}NHCH(CH_3)_2$	0.275	Increased	2.00	14.5 ± 0.7	36.0 ± 0.2	32.8 ± 0.8	33.4 ± 0.5	33.3 ± 0.1
XV	H	$NHNHCH_2C_6H_5$	0.138	Increased	0.16	54.2 ± 2.6	36.3 ± 0.1	35.8 ± 0.4	35.6 ± 0.4	36.2 ± 0.2
XVI	CH_3	$NHNHCH(CH_3)_2$	0.275	Increased	0.66	12.6 ± 0.7	36.7 ± 0.2	34.2 ± 0.3	33.0 ± 0.5	34.0 ± 0.2
XVII[c]	CH_3	$NHNHCH_2C_6H_5$	0.275	Increased	1.83	16.0 ± 2.5	36.1 ± 0.1	32.5 ± 0.3	31.0 ± 0.4	30.7 ± 0.6
Isocarboxazid			0.138	Increased	0.50	10.5 ± 0.5	35.8 ± 0.2	31.7 ± 0.7	34.2 ± 0.7	35.1 ± 0.2

[a] Hexobarbital was given intraperitoneally (55 mg/kg) 2 hr after intubation of the test compound. [b] Control implies reserpine in ptosis and hypothermia test, and hexobarbital in sleeping time prolongation test. [c] The base form rather than the HCl salt was administered.

of the compounds, listed in Table I, for MAO inhibitory activity was carried out as previously reported.[2] The tests consisted of the reversal of reserpine-induced ptosis and hypothermia and hexobarbital sleeping-time prolongation.

Results and Discussion

The result of the present and previous investigation[4] indicates that the reactivity of dimethyl imidazole-4,5-dicarboxylate and its 1-methyl derivative with hydrazine was greater than their monoester analogs I or II. This higher rate of reaction of diesters can be attributed to the existence of a quasi-bicyclic structure (XVIII), in which the elimination of OR group is facilitated.



XVIII

The variations among the C=O stretching in the ir spectra of the esters, however, was not substantial to render support for the presence or absence of XVIII.

As compared with I, the reactivity of II with hydrazines, due to steric and/or electronic influence of the CH_3 group, is retarded.

As illustrated in Table I, the MAO inhibitory activity of the imidazole monohydrazides is in general somewhat higher than their dihydrazide analogs.[2,4] Of particular interest is the significant activity manifested by XV (see Table I). This activity at the present can not be related to any particular moiety in the molecular structure of these imidazolecarbohydrazides. The absence of comparable activity in XVII, the ring-methyl-substituted analog of XV, is an indication of the necessity for further investigation in the series.

Acknowledgment.—The authors wish to thank Mr. Donald Haygood for his efficient assistance in this investigation.

Anthelmintic Quaternary Salts. IV. Aminopentadienylideneammonium Salts

D. L. GARMAISE, G. Y. PARIS, J. KOMLOSSY,

Abbott Laboratories Ltd., Montreal, Quebec, Canada

AND R. C. MCCRAE

Department of Parasitology, Abbott Laboratories, North Chicago, Illinois

Received March 17, 1969

The synthesis and anthelmintic activity of a group of aminopentadienylideneammonium salts is described. Compounds in which the N atoms were part of a pyrrolidine or piperidine ring were effective against common gastrointestinal nematodes of sheep and had prophylactic activity in protecting swine from infections of *Ascaris suum*.

Schiff bases of glutaconaldehyde have been widely used as chemical intermediates, particularly in the synthesis of azulenes, and have been the subject of extensive spectroscopic investigations. Their effects on biological systems do not appear to have been investigated previously, and it was considered of interest to prepare compounds of this class (Table I) for evaluation as anthelmintics because of their similarity to other cyanine dyes with known anthelmintic potency.

Chemistry.—The general method of preparation of