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Imidazolecarbohydrazides IV: Synthesis and Biological Evaluation

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Abstract □ A series of 1-methylimidazole-4,5-dicarboxylic acid hydrazides and a bicyclic compound imidazo[4,5-*d*]pyridazine were synthesized and their structures were elucidated. The compounds were subjected to a limited pharmacological evaluation (MAO inhibitory activity) and the results are reported.

Keyphrases □ 1-Methylimidazole-4,5-dicarboxylic acid hydrazides —synthesis, structure determination, screened for MAO inhibitory activity □ Imidazo[4,5-*d*]pyridazine—synthesis, structure determination, screened for MAO inhibitory activity □ Hydrazides, 1-methylimidazole-4,5-dicarboxylic acid—synthesis, structure determination, screened for MAO inhibitory activity □ MAO inhibitors, potential—synthesis and evaluation of 1-methylimidazole-4,5-dicarboxylic acid hydrazides and imidazo[4,5-*d*]pyridazine

The synthesis and certain biological properties of some imidazole-4(or 5)-mono- and 4,5-dicarboxylic acid esters, hydrazides, and hydrazones were reported previously (1, 2). The present paper reports the investigation of 1-methylimidazole-4,5-dicarboxylic acid derivatives and their bicyclic analogs.

The starting ester, dimethyl 1-methylimidazole-4,5-dicarboxylate (I), was synthesized by methods previously reported (1, 2). The reaction of I with hydrazine (II*a*) or methylhydrazine (II*b*), depending on the reaction conditions, gave the dihydrazide (III*a*) (1) or 1-methylimidazole-4,5-dicarboxylic acid bis(2-methylhydrazide) (III*b*), respectively, or their bicyclic analogs IV*a* (3) and 1,5-dimethyl-7-hydroxyimidazo[4,5-*d*]pyridazin-4-one (IV*b*), respectively. With phenylhydrazine (II*c*), only III*c* was obtained.

As depicted in Scheme I, some analogs of III were synthesized by sodium borohydride reduction of their respective hydrazones (4). In this study, the ethylidene derivative (VI) was found to be resistant to such reduction.

The reaction product of I and II*b* could possibly be IV*b*, IV*c*, or a mixture of the two. A relatively sharp melting point of the product, together with a single spot observed on a thin-layer chromatogram and the presence of only a single NMR peak for the CH_3 protons on the pyridazine, gave convincing evidence that the compound was not a mixture of the two isomers. The elucidation of the molecular structure of the compound was attempted by the following experimental procedure. Mixing stoichiometric quantities of an aqueous solution of silver nitrate and IV*a* gave a precipitate analogous to those reported (5) for purines on whose 6-position exists an OH or NH_2 with the 7 as pyridinic N, or on the 6-position a C=O with the 7 as pyrrolic NH. Separation of the precipitate by centrifugation, its dissolution in perchloric acid, and UV spectrophotometric analysis of both the dissolved precipitate and the supernate revealed a 1:1 silver–IV*a* chelate. Similar experiments on the bicyclic reaction product of I and II*b* did not produce any precipitate. Because the purine analog of IV*c* forms a water-insoluble silver chelate (5), the reaction product was assumed to be IV*b*.

The formation of IV*b* may possibly involve an intermediate half-ester half-hydrazide, 1-methylimidazole-4-carbomethoxy-5-(2-methylhydrazide), although it has not been isolated or identified. The phenyl analog of this compound, imidazole-4-carbomethoxy-5-(2-phenylhydrazide), however, has been shown (1) not to give an analogous bicyclic system. The possibility of III*b* being

Table I—1-Methylimidazole-4,5-dicarboxylic Acid Hydrazides or Acid Hydrazones and 1,5-Dimethyl-7-hydroxyimidazo[4,5-*d*]pyridazin-4-one

Compound	Crystallization Solvents	Yield, %	Melting Point	Analysis, % Calc.		Found
III*b*	Ethyl acetate–methanol	63	126–128°	C	42.48	42.09
				H	6.19	6.12
				N	37.17	37.42
III*c*	Ethanol	58	196–198°	C	61.70	61.33
				H	5.18	5.48
				N	23.99	24.27
IV*b*	Methanol–water	62	300°	C	46.66	46.42
				H	4.48	5.04
				N	31.10	30.79
V	Chloroform–methanol	77	226–228°	C	64.16	64.25
				H	4.85	5.07
				N	22.45	22.34
VI	Benzene–methanol	88	140–142°	C	47.99	48.13
				H	5.64	5.94
				N	33.58	33.48
VII	Benzene–methanol	85	227–229°	C	51.78	52.04
				H	6.52	6.63
				N	30.20	30.00
VIII	Ethyl acetate–methanol	75	86–88°	C	63.47	63.32
				H	5.86	5.41
				N	22.21	22.01
IX	Benzene–methanol	80	58–59°	C	51.07	50.91
				H	7.80	7.64
				N	29.80	29.40

the intermediate was excluded by recovering the compound intact after heating its butanolic solution for 24 hr.

EXPERIMENTAL[1]

1-Methylimidazole-4,5-dicarboxylic Acid Bis(2-methylhydrazide) (III*b*) and 1,5-Dimethyl-7-hydroxyimidazo[4,5-*d*]pyridazin-4-one (IV*b*)—To 2.0 g. (0.01 mole) of I was added 1.4 g. (0.03 mole) of methylhydrazine. The mixture was stirred at room temperature for 5 hr. The precipitated solid was washed with ether and then treated with a small amount of ethanol to give 1.5 g. (63%) of III*b*.

Heating of I and II*b* under reflux for 18 hr. gave 1.2 g. (62%) of IV*b*.

Compound III*c* was prepared under reaction conditions similar to those of IV*b*.

The preparation of the hydrazones and their respective hydrazides (Table I) are exemplified by the following methods described for V and VIII.

1-Methylimidazole-4,5-dicarboxylic Acid Bis(2-benzylidenehydrazide) (V) and 1-Methylimidazole-4,5-dicarboxylic Acid Bis(2-benzylhydrazide) (VIII)—Under nitrogen, a mixture of 1.9 g. (0.01 mole) of III*a* and 15 ml. of benzaldehyde was heated under reflux for 3 hr. The precipitated solid was washed with ether to give 2.9 g. (77%) of V.

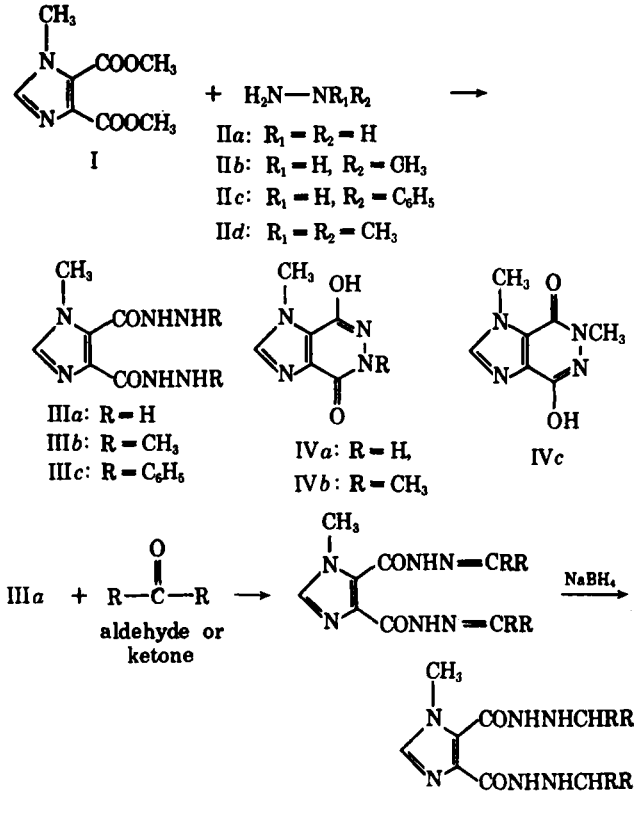
To a suspension of 1.85 g. (0.005 mole) of V in 50 ml. of water was added 0.8 g. (0.02 mole) of sodium borohydride. The mixture was heated under reflux on the steam bath for 1 hr. The solution was evaporated to 10 ml. and extracted twice with ether. The combined ether extracts was dried over sodium sulfate. After filtration, evaporation of solvent gave 1.4 g. (75%) of VIII.

Compound VI under such conditions could not be reduced.

DISCUSSION

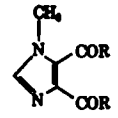
The compounds listed in Table II were evaluated for their MAO inhibitory activity by three methods which were described previously (1, 2). The results, listed in Table II, indicate that 1-methylimidazole-4,5-dicarbohydrazides possess about the same level of activity as their previously reported analogs. A similar level of activity was also detected for the bicyclic analog, IV*b*.

A broad biological evaluation of the compounds for such functions as cardiovascular effect and antitubercular activity may be justified by considering the therapeutic use of hydralazine and isoniazid. Compound IV*b* may be conceived of as an analog of purine, a system of interest in tumor research.

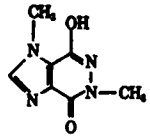


Scheme I

[1] Melting points were determined in open capillary tubes in a Thomas-Hoover melting-point apparatus and are not corrected. All evaporations were made *in vacuo* with rotatory evaporators. The IR spectra were determined (KBr) with a Beckman IR-8 instrument, and NMR spectra were determined with a Varian A-60 spectrophotometer at ambient temperature (tetramethylsilane as a reference and deuterated dimethyl sulfoxide as a solvent). Elemental analyses were done by Schwarzkopf Microanalytical Laboratory, Woodside, N. Y. Crystallization solvents, melting points, and elemental analysis (C, H, N) values are listed in Table I.



A



B

Table II—MAO Inhibitory Activity Evaluation of Hydrazides (Structures A and B)

Compound	R (Structure A)	Oral Dose, mmole/kg.	Activity Prior to Reserpine (2 mg./kg.)	Mean Ptotic Score	Body Temperature (± *SE*) after Reserpine (2 mg./kg.) 0 hr.	4 hr.	6 hr.	24 hr.	Hexobarbital-Induced Sleeping Time, min.[a]
Control[b]			Normal	3.75	35.8 ± 0.2°	29.9 ± 0.4°	26.3 ± 0.2°	26.6 ± 0.5°	8.3 ± 0.3
III*a*	$NHNH_2$	0.275	Increased	2.50	35.7 ± 0.3°	32.7 ± 0.3°	31.9 ± 0.4°	30.6 ± 0.5°	15.2 ± 0.2
III*b*	$NHNHCH_3$	0.275	Increased	2.90	36.1 ± 0.2°	31.5 ± 0.1°	31.0 ± 0.4°	33.6 ± 0.6°	12.7 ± 0.3
IV*b*	Structure B	0.275	Increased	2.66	35.9 ± 0.1°	32.2 ± 0.5°	30.9 ± 0.3°	28.9 ± 0.4°	13.4 ± 0.4
III*c*	$NHNHC_6H_5$	0.275	Increased	2.00	36.5 ± 0.3°	32.5 ± 0.2°	29.4 ± 0.5°	32.1 ± 0.3°	19.7 ± 0.1
V	$NHN{=}CHC_6H_5$	0.275	Increased	2.00	36.3 ± 0.3°	32.6 ± 0.4°	29.7 ± 0.6°	30.2 ± 0.5°	20.3 ± 0.3
VI	$NHN{=}CHCH_3$	0.275	Increased	2.50	35.7 ± 0.1°	32.6 ± 0.3°	31.6 ± 0.3°	32.7 ± 0.7°	14.9 ± 0.2
VII	$NHN{=}CHCH_3$	0.275	Increased	2.60	35.2 ± 0.4°	32.0 ± 0.5°	29.6 ± 0.5°	30.6 ± 0.3°	12.9 ± 0.1
VIII	$NHNHCH_2C_6H_5$	0.275	Increased	2.33	35.9 ± 0.1°	31.8 ± 0.3°	29.2 ± 0.6°	31.4 ± 0.5°	17.6 ± 0.3
IX	$NHNHCH(CH_3)_2$	0.275	Increased	1.83	35.6 ± 0.2°	32.6 ± 0.2°	30.8 ± 0.4°	32.4 ± 0.3°	22.0 ± 0.2
Isocarboxazid		0.1375	Increased	0.50	35.6 ± 0.5°	34.2 ± 0.1°	36.7 ± 0.4°	35.2 ± 0.4°	11.0 ± 0.1

[a] Hexobarbital was given intraperitoneally (5.5 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.

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Synthesis and Anticancer Activity of 5-(Propargyloxymethyl)-2-oxazolidinones

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Abstract □ To determine the feasibility of producing a tissue-specific anticancer agent, a series of 2-oxazolidinones bearing an alkynoxymethyl side chain in the 5-position was prepared. These compounds were submitted to the National Cancer Institute for testing against L-1210 and/or P-388 tumor test systems. None of the compounds showed significant anticancer activity. The synthetic procedures and NMR spectral properties of the title compounds are described.

Keyphrases □ 5-(Propargyloxymethyl)-2-oxazolidinones—synthesis, screened for anticancer activity □ 2-Oxazolidinones, 5-(propargyloxymethyl)—synthesis, screened for anticancer activity □ Anticancer agents, potential—synthesis and screening of 5-(propargyloxymethyl)-2-oxazolidinones

Interest in carbamates bearing an acetylenic function developed from an interest in tissue- or organ-specific anticancer agents, particularly those specific for the CNS. The investigation of the title compounds stems, in part, from the work of Dillard *et al.* (1) who first demonstrated the oncolytic action of propargyl carbamates against plasma cell tumor X-5563 and the atypical myelogenous leukemia C-1498. Among the structure–activity relationships they observed was the necessity of the ethynyl moiety for significant oncolytic