740. 1-*Aminoimidazoles and Derivatives. Part I. The Synthesis of* 1-*Amino-derivatives of* 5-*Amino-*2-*methylimidazole-*4-*carboxamide.*

By C. L. Leese and G. M. Timmis.

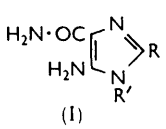
The products obtained by reaction between ethyl *N*-(carbamoylcyanomethyl)acetimidate and hydrazines are shown to be 1-amino-derivatives of 5-amino-2-methylimidazole-4-carboxamide and not derivatives of 1,2-dihydro-1,2,4-triazine which could have arisen by an alternative mode of ring closure.

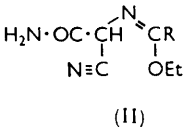
Several new 1-alkylimidazoles and αω-di-imidazolylalkanes are also described.

Several examples of interference with *de novo* purine biosynthesis by the intervention of co-factor antagonists and with transamination in the formation of purine nucleotides [1] from ribose 5-phosphate and glycine are known. Thus the glutamine antagonists *O*-diazoacetyl-L-serine (Azaserine) and 6-diazo-5-oxo-L-norleucine (D.O.N.) prevent the conversion of formylglycine amide " ribotide " into formylglycine amidine " ribotide." [1,2] Sulphonamides [3] and folic acid antagonists,[4] by virtue of their interference with the formation of folic acid and its reduction to the folinic acid co-factors, respectively, prevent the incorporation of single carbon units in the biosynthesis of inosinic acid.

In contrast, antagonism to the various substances which form stages in the *de novo* biosynthetic pathway of purine nucleotides is much less well established. Analogues of the intermediary compounds in this sequence are therefore of considerable interest.

The present paper describes the synthesis of a number of analogues related to 5-amino-1-β-D-ribofuranosylimidazole-4-carboxamide (I; R′ = β-D-ribofuranosyl, R = H), the 5′-phosphate of which is one stage in the biosynthesis of the purine nucleotide. These compounds were prepared by the method of Shaw, Warrener, Butler, and Ralph [5]


(I)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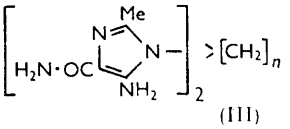
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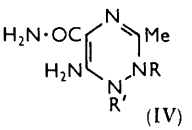
(IV)

in which the 1-substituent is introduced by reaction of a primary amine with an ethyl *N*-(carbamoylcyanomethyl)imidate (II). Several compounds (I) [R = Me, R′ = CH_2·CH_2OH, CH_2·CH_2·CH_2·OH, furfuryl, and CH_2·$CH(OEt)_2$] were thus obtained and, in addition, three αω-(5-amino-4-carbamoyl-2-methylimidazol-1-ylalkanes (III; $n = 2$, 6, and 10).

Reaction between ethyl *N*-(carbamoylcyanomethyl)acetimidate and various hydrazines gave highly crystalline products which were first considered to be 1,2-dihydro-1,2,4-triazines (IV), which would be themselves potential intermediates to 7-azapteridines. However, the formation of a similar product from 1,1-dimethylhydrazine suggested that they were 1-amino-derivatives of imidazoles (I). They had ultraviolet absorption spectra very similar to that [6] of 5-amino-4-carbamoyl-1-ribosylimidazole in ethanol at pH 7 (Table 1).

[1] Buchanan, Flaks, Hartman, Levenberg, Lukens, and Warren, " Chemistry and Biology of Purines," Ciba Foundation Symposium, J. & A. Churchill, London, 1957, p. 233.
[2] Hartman, Levenberg, and Buchanan, *J. Amer. Chem. Soc.*, 1955, **77**, 501; Levenberg and Buchanan, *ibid.*, 1956, **78**, 504.
[3] Nimmo-Smith, Lascelles, and Woods, *Brit. J. Exp. Path.*, 1948, **29**, 264.
[4] Nichol and Welch, *Proc. Soc. Exp. Biol.* N.Y., 1950, **74**, 403.
[5] Shaw, Warrener, Butler, and Ralph, *J.*, 1959, 1648.
[6] Greenberg and Spilman, *J. Biol. chem.*, 1956, **219**, 411.

TABLE 1. *Ultraviolet absorption bands of compounds* (I; R = Me).

Subst., R′	NH_2	NHMe	NMe_2	Ribosyl
$\lambda_{max.}$ (mμ)	270	270	270	268
ε	11,940	10,620	14,160	12,800

No product could be obtained by condensation of the imidate (II) with 1,2-dimethylhydrazine which, whilst capable of yielding a 1,2,4-triazine (IV) would not form a 1-aminoimidazole. 1,5-Diamino-2-methylimidazole-4-carboxamide yielded the 1-benzylideneamino-derivative (I; R = Me; R′ = N:CHPh) whose structure was proved by preparation of the compound from benzylidenehydrazine and ethyl *N*-(carbamoylcyanomethyl)-acetimidate (II).

EXPERIMENTAL

Analyses are by Mr. P. R. W. Baker, Beckenham.

1-*Alkyl-5-amino-2-methylimidazole-4-carboxamides.*—These compounds were prepared by the general method of Shaw *et al.*[5] in which ethyl *N*-(carbamoylcyanomethyl)acetimidate (1 equiv.) and an amine (1·5 equiv.) were heated on a steam bath for 5—10 min. The mixture was then cooled in ice and the solid *product* isolated (see Table 2).

TABLE 2. *Products* (I; R = Me).

		Yield	Found (%)				Required (%)		
R′	M. p.	(%)	C	H	N	Formula	C	H	N
$CH_2{\cdot}CH_2{\cdot}OH$	239—240°	67	45·5	6·6	30·7	$C_7H_{12}N_4O_2$	45·6	6·6	30·4
$CH_2{\cdot}CH_2{\cdot}CH_2{\cdot}OH$	240—241	75	48·6	6·9	28·4	$C_8H_{14}N_4O_2$	48·5	7·1	28·3
Furfuryl	234—235	64	54·7	5·7	25·4	$C_{10}H_{12}N_4O_2$	54·5	5·5	25·4
$CH_2{\cdot}CH(OEt)_2$ ...	173—174	65	51·7	7·6	22·0	$C_{11}H_{20}N_4O_3$	51·6	7·9	21·9

αω-*Di-*(5-*amino*-4-*carbamoyl*-2-*methylimidazol*-1-*yl*)*alkanes.*—Ethyl *N*-(carbamoylcyanomethyl)acetimidate (2 equiv.) and an αω-diaminoalkane (1 equiv.) were dissolved in a small quantity of methanol and left overnight. The *products* (see Table 3) were removed by filtration and purified by precipitation from hot dilute acetic acid by ammonia.

TABLE 3. *Products* (III).

		Yield	Found (%)				Required (%)		
n	M. p.	(%)	C	H	N	Formula	C	H	N
2	dec. >320°	73	45·4	6·1	35·3	$C_{12}H_{18}N_8O_2,\frac{1}{2}H_2O$	45·7	6·1	35·5
6	267—268	54	52·2	7·1	30·5	$C_{16}H_{26}N_8O_2,\frac{1}{2}H_2O$	51·8	7·3	30·2
10	243—244	71	55·1	7·9	25·7	$C_{20}H_{34}N_8O_2,H_2O$	55·0	8·3	25·7

1,5-*Diamino*-2-*methylimidazole*-4-*carboxamide.*—Ethyl *N*-(carbamoylcyanomethyl)acetimidate (9 g.) and hydrazine hydrate (3 g.) in methanol (50 ml.) were heated on a steam-bath for 10 min., yielding white crystals which were collected and washed with ether. Recrystallisation from water gave 1,5-*diamino*-2-*methylimidazole*-4-*carboxamide* (6 g.), m. p. 272—273° (Found: C, 38·5; H, 5·9; N, 45·0. $C_5H_9N_5O$ requires C, 38·7; H, 5·85; N, 45·1%).

5-*Amino*-1-*benzylideneamino*-2-*methylimidazole*-4-*carboxamide.*—(*a*) 1,5-Diamino-2-methylimidazole-4-carboxamide (0·5 g.), benzaldehyde (0·4 g.), and acetic acid (2 ml.) were heated for 10 min. on a steam-bath, diluted with ethanol (5 ml.), and cooled. The *product* (0·5 g.), m. p. 269—270°, was obtained as yellow needles from methanol (Found: C, 59·4; H, 5·7; N, 28·4. $C_{12}H_{13}N_5O$ requires C, 59·3; H, 5·4; N, 28·8%).

(*b*) Ethyl *N*-(carbamoylcyanomethyl)acetimidate (1·7 g.) and benzylidenehydrazine (1·2 g.) in methnol (10 ml.) were heated under reflux for 30 min. Ice-cooling afforded a product (1·2 g.), m. p. 269—270°, identical with that prepared by method (*a*).

5-*Amino*-1-*anilino*-2-*methylimidazole*-4-*carboxamide.*—Ethyl *N*-(carbamoylcyanomethyl)-acetimidate (11 g.) and phenylhydrazine (7·1 g.) in methanol (60 ml.), when heated for 5 min. on a steam-bath, gave white crystals. A hot solution of the product in dimethylformamide, when treated with water, yielded 5-*amino*-1-*anilino*-2-*methylimidazole*-4-*carboxamide* (9·0 g.), m. p. 303—304° as prisms (Found: C, 57·2; H, 5·5; N, 30·2. $C_{11}H_{13}N_5O$ requires C, 57·1; H, 5·7; N, 30·3%).

5-*Amino*-1-*methylamino*-2-*methylimidazole*-4-*carboxamide*.—Ethyl *N*-(carbamoylcyanomethyl)acetimidate (14 g.) was added to a solution of methylhydrazine [prepared by treating methylhydrazine sulphate (13 g.) in methanol (70 ml.) with an equivalent of sodium methoxide and removing the precipitated sodium sulphate], and the mixture was heated for 30 min. on a steam-bath. Cooling and collection of the product, followed by recrystallisation from water, yielded the 1-*methylaminoimidazole* (5·1 g.), m. p. 261—262° (Found: C, 42·3; H, 6·35; N, 41·3. $C_6H_{11}N_5O$ requires C, 42·6; H, 6·55; N, 41·4%).

5-*Amino*-1-*dimethylamino*-2-*methylimidazole*-4-*carboxamide*.—Ethyl N-(Carbamoylcyanomethyl)acetimidate (6 g.) and 1,1-dimethylhydrazine (3·2 ml.) in methanol (15 ml.) similarly gave the 1-*dimethylamino-compound* (3·5 g.) as white prisms, m. p. 211—212° (Found: C, 46·0; H, 7·3; N, 38·4. $C_7H_{13}N_5O$ requires C, 45·9; H, 7·15; N, 38·2%).

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