Synthesis and Preliminary *in vitro* Metabolic Studies on *N,N*-Dimethyl-*N'*-2-imidazolyl-*N'*-benzyl-1,2-ethanediamine, an Analog of the Carcinogenic Antihistamine Methapyrilene

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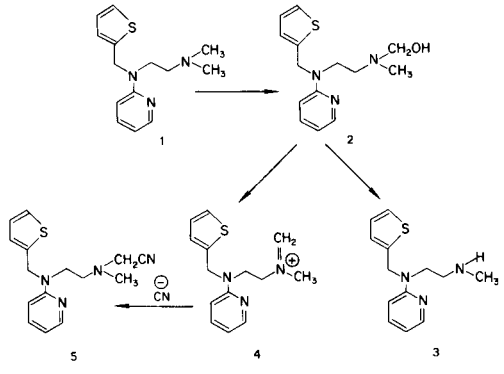
Recieved February 1, 1982

This paper describes the synthesis and preliminary metabolic studies on *N,N*-dimethyl-*N'*-2-imidazolyl-*N'*-benzyl-1,2-ethanediamine (compound **12**), an imidazole analog of the carcinogenic antihistamine methapyrilene. The 2-aminoimidazole starting material is carried through a five-step reaction sequence which involves introduction of the benzyl and dimethylaminoethyl side chains *via* sequential acylation of the 2-amino group and reduction of each intermediate amide. Metabolic studies on compound **12** and a d_2-analog were performed with rabbit liver microsomes. Chemical ionization mass spectral analysis indicates the presence of metabolites formed by *N*-demethylation and imidazole *C*-oxidation. In addition, a seven membered ring metabolite has been identified which apparently is formed by intramolecular cyclization of an intermediate methylene iminium ion.

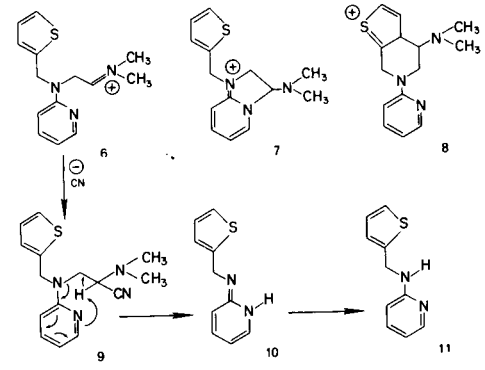
J. Heterocyclic Chem., **19**, 1403 (1982).

Introduction.

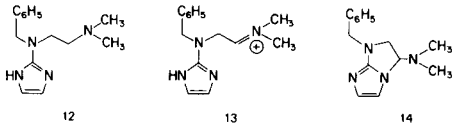
Methapyrilene (**1**), a histamine H_1-receptor antagonist commonly used in the past to relieve symptoms of the common cold, has been shown to be a hepatocarcinogen in rats (1). We have examined the liver microsomal metabolism of this drug in an attempt to characterize biotransformation pathways that might lead to the formation of chemically reactive metabolites with genotoxic potential (2). In view of earlier results on the metabolism of the tertiary amines, nicotine (3) and 1-benzylpyrrolidine (4), our studies on methapyrilene have focused on the possible metabolic formation of electrophilic iminium ions. Iminium ions may form by ionization of the corresponding intermediate alpha-carbinolamines. For example, in the case of methapyrilene, a liver microsomal, NADPH dependent oxidation of **1** leads to the intermediate carbinolamine **2** which then may undergo cleavage to normethapyrilene (**3**) and formaldehyde or ionization to iminium ion **4**. When microsomal incubations of methapyrilene also contain sodium cyanide, the stable *N*-cyanomethylnormethapyrilene (**5**) is formed. The possibility that nucleophilic functionalities on biomacromolecules also may form covalent bonds with iminium ions such as **4** has led us to propose that this metabolic pathway may be associated with some of the toxic properties of tertiary amines such as the carcinogenicity of methapyrilene.



In this connection we also have sought evidence for the formation of the iminium ion **6** since delocalization of the positive charge (structures **7** and **8**) might stabilize this electrophilic species and facilitate its transport across the nuclear membrane where it may interact with DNA. Attempts to trap **6** as its alpha-cyano derivative **9** however were frustrated by the ease with which compound **9** undergoes a reverse Michael reaction to yield the secondary amine **11** *via* intermediate **10**.



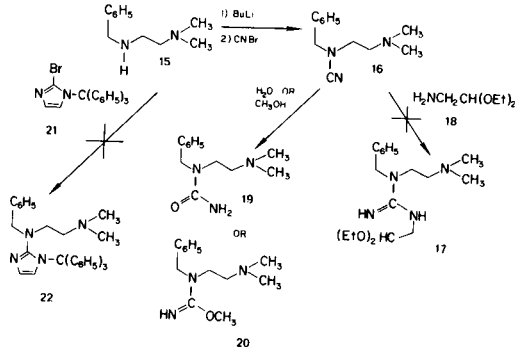
In order to explore further the possible conversion of tertiary amines to electrophilic iminium ion metabolites, we have elected to examine the liver microsomal metabolism of the methapyrilene analog **12**. Interest in compound **12** is based in part on the possible formation of iminium ion **13**. If formed, **13** might undergo intramolecular reaction to yield the cyclic species **14** which, unlike **9**, might survive the conditions of the incubation. The present paper describes the synthesis of compound **12** and preliminary results on its *in vitro* metabolic fate.



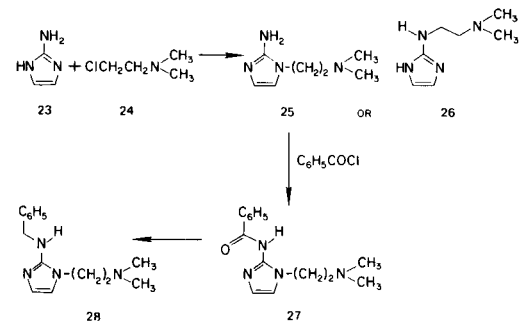
12 13 14

Chemistry.

Several synthetic approaches to imidazole **12** were examined. Treatment of the lithio salt of the benzylamine derivative **15** with cyanogen bromide provided the corresponding cyanamide **16**. Attempts to convert **16** to the guanidino intermediate **17** with aminoacetaldehyde diethyl acetal (**18**) in preparation for cyclization to **12** however failed. Under a variety of conditions only the hydrolysis and methanolysis products **19** and **20**, respectively, could be detected in these reaction mixtures. Similarly all attempts to displace the bromo group of the imidazole derivative **21** with amine **15** to give **22** were unsuccessful. Only starting imidazole could be recovered even when the sodium salt of **15** was employed. This behavior of imidazole **21** contrasts with that of 2-bromothiazole which is reported to react smoothly with amine **15** (5).



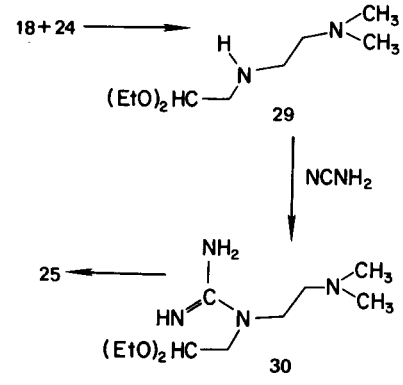
In yet another approach, 2-aminoimidazole (**23**) was treated with dimethylaminoethyl chloride (**24**) in an attempt to alkylate the side chain amino functionality. A reasonable yield of a mono-alkylated product was obtained. Since compound **23** is a potential ambident nucleophile, however, alkylation may take place either on the ring nitrogen atom to produce **25** or on the amino group to produce the desired symmetrical product **26**. The nmr spectrum of the isolated product in deuterium oxide displayed a single low field resonance for the imidazole protons H-4 and H-5 as a broad singlet at δ 6.70. In deuteriochloroform however, the signals for H-4 and H-5 appeared as two doublets centered at δ 6.45 and 6.58. Although these spectra were consistent with the asymmetric product **25**, the corresponding benzamide **27** displayed the imidazole ring protons as a sharp singlet at δ 6.66. Following reduction to the amine **28**, these signals again appeared as two doublets at δ 6.43 and 6.64.



23 24 25 OR 26

28 27

In order to establish unequivocally the structure of this alkylation product, an independent synthesis of compound **25** was undertaken. Treatment of dimethylaminoethyl chloride (**24**) with aminoacetaldehyde diethyl acetal (**18**) followed by reaction of the resulting condensation product **29** with cyanamide provided the guanidino derivative **30**. Cyclization was effected by heating **30** in aqueous acid. The resulting ring alkylated imidazole **25** proved to be identical to the alkylation product obtained with 2-aminoimidazole thus ruling out direct alkylation of **23** as a route to **12**.

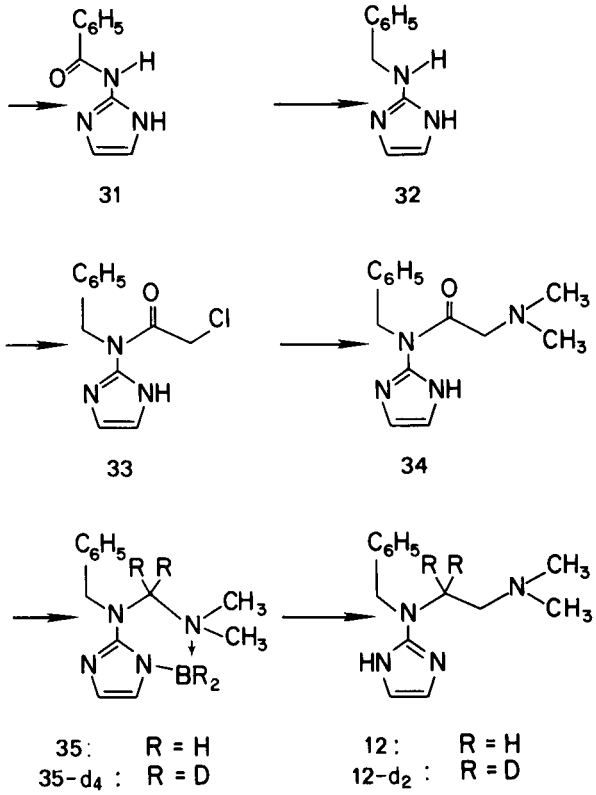


29 30

In an attempt to avoid ring substitution, 2-aminoimidazole was converted first to the known 2-benzoylaminoimidazole (**31**) (6) which underwent reduction with aluminum hydride somewhat sluggishly to yield 2-benzylaminoimidazole (**32**). Treatment of amine **32** with chloracetyl chloride gave crude **33** which was converted to the corresponding aminoacetyl derivative **34** without further purification. Consistent with amino acylation (as opposed to ring nitrogen acylation), the signals for the imidazole H-4 and H-5 protons in all of these products appeared as sharp singlets. Unexpectedly the signals for the protons of the two methylene groups present in compound **34** (and **33**) appeared in deuteriochloroform solution as two singlets for each group of methylene protons. In perdeuterated dimethylsulfoxide, these signals collapsed to singlets although in the case of the benzyl protons the signal was broad. A possible explanation to account for these nmr characteristics would be to assume that these compounds

in deuteriochloroform exist as two slowly interconverting conformers.

Reduction of the aminoacetyl intermediate **34** with boron hydride in tetrahydrofuran provided a product which displayed the imidazole ring protons H-4 and H-5 as two coupled doublets (J = 2.2 Hz) which clearly was not consistent with the desired structure, compound **12**. The chemical ionization mass spectrum of this material showed two pseudomolecular ions (MH^+) at masses 257 and 258 in the ratio of 3:1. These characteristics are those expected for the borane intermediate **35**. Compound **35** proved to be extremely resistent to acid hydrolysis, probably because of the coordination of the boron atom with the dimethylamino functionality to form a seven membered ring structure as indicated in **35**. Optimal conditions for hydrolysis proved to be 24-30 hours at reflux in 2*N* hydrochloric acid. The use of more concentrated acid led to significant cleavage of the benzyl group. Purificiation of the resulting crude *bis*-hydrochloride of **12** could be achieved by column chromatography on silica which provided pure **12** as its mono-hydrochloride salt. The product was further characterized as its *bis*-picrate. A deuterium labeled analog (**12**-d_2) required for metabolic studies also was prepared by reduction of compound **34** with boron deuteride in tetrahydrofuran. The isotopic composition of the final product was established by chemical ionization mass spectrometry to be 84%-d_2, 15%-d_1, and 1%-d_0.



Metabolic Studies.

We have carried out preliminary studies on the *in vitro* metabolic fate of this imidazole analogue of methapyrilene. Six month old male Dutch rabbits were used as a source of 100,000 × g liver microsomal preparations. Incubations were carried out both in the presence and in the absence of the reduced form of the mixed function oxidase cofactor nicotinamide adenine dinucleotide (NADPH) in order to assess the enzymatic nature of metabolite formation. All metabolite analyses were performed by chemical ionization ms on crude postincubate *p*H 10 chloroform extracts. Since chemical ionization ms yields primarily pseudo-molecular ions (MH^+) with little fragmentation, these mass spectral data can be particularly useful in making tentative structure assignments. Chemical ionization ms analysis of metabolite mixtures has been utilized in the past with considerable success (7).

In the present study, we have examined the metabolism of **12** and its deuterium labeled analog **12**-d_2. Except for pathways involving loss of the label, metabolites derived from **12**-d_2 will display MH^+ values 2 atomic mass units higher than the corresponding metabolite derived from unlabeled **12**. An additional characterization of metabolites was achieved by substituting deuterium oxide for isobutane as the chemical ionization ms reagent gas. Analysis of the resulting spectra provided information on the number of exchangeable protons pesent in the metabolite. Finally, a limited effort to characterize metabolites through the aid of gas chromatography-electron ionization mass spectrometry (gc-ei ms) has been pursued.

The results of the chemical ionization ms study are summarized in Table I which lists the various ions in order of decreasing abundance. The most abundant ion present in the mass specrum of the crude extracts appears at mass 245 and corresponds to the MH^+ ion of the parent compound **12**. As required, this ion shifts to mass 247 with **12**-d_2 as substrate. When deuterium oxide is used as the reagent gas, the ion at mass 245 is replaced by an ion cluster at masses 247, 248 and 249; the ion at mass 247 is replaced by an analogous cluster at masses 249, 250 and 251. These data are consistent with the complete exchange of the imidazole NH proton and the partial exchange of two additional protons in the molecule, presumably those located at C-4 and C-5 of the imidazole ring (protons H-4 and H-5, respectively).

The second most abundant ion present in the mass spectrum appears at mass 231 (233 with **12**-d_2). When run in the presence of deuterium oxide the parent ion gives rise to an ion cluster involving the exchange of 2 to 4 protons. Based on these data it is possible to assign the structure of this metabolite as the *N*-desmethyl compound **36**.

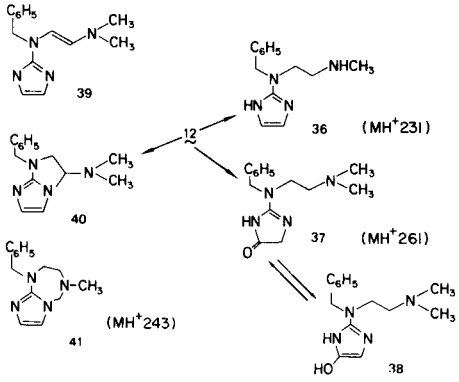
The next most abundant species appears at mass 261 (263 with **12**-d_2) which is consistent with a mono-oxygenat-

Table I

Chemical Ionization Mass Spectral Analysis of Metabolites from **12** and **12**-d_2

Compound **12**		Compound **12**-d_2				
MH^+ (isobutane)	MD^+ (deuterium oxide)	MH^+ (isobutane)	MD^+ (deuterium oxide)	Present in control?	Abundance	Possible Structure
245	247, 248, 249	247	249, 250, 251	Yes	Major	**12**
231	234, 235, 236	233	236, 237, 238	No	Intermittant	**36**
261	265	263	267	Yes	Intermittant	**37/38**
243	244	245	246	No	Intermittant	**41**
190	192	192	194	No	Weak	?
200	201, 202, 203	202	203, 204, 205	Yes	Weak	?
221	225	223	227	No	Weak	?

Metabolic Scheme



ed product. Possible oxidation products could be formed *via* epoxidation of the phenyl or imidazole ring and *N*-oxidation of one of the nitrogen atoms. Three protons of this metabolite exchange readily and completely with deuterium oxide to form a pseudomolecular ion (MD^+) at mass 265. Since only partial exchange of the imidazole ring protons is observed for compound **12**, it seems reasonable to assume that modification of the 2-aminoimidazole moiety has occurred. *N*-Oxidation products of this moiety should result in a less basic imidazole ring and a decreased rate of ring protonation. Therefore, one would expect the exchange of ring protons with deuterium oxide reagent gas plasma to be retarded. On the other hand, complete exchange of three protons is readily accomodated by the amide structure **37** which should exist in tautomeric equilibrium with the enol **38**.

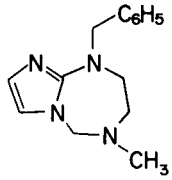
The ion appearing at mass 243 can be accomodated by three possible structures, the enamine **39**, the five membered ring product **40**, and the seven membered ring product **41**. The corresponding metabolite derived from substrate **12**-d_2 displayed a pseudomolecular ion at mass 245. Since both deuterium atoms are retained in this product, the enamine structure **39** can be eliminated. Consistent with this conclusion, the chemical ionization ms obtained with deuterium oxide as reagent gas indicated that this metabolite does not have any exchangeable protons.

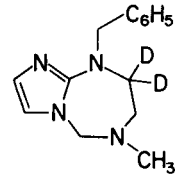
Table II

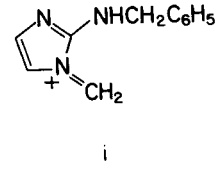
Fragment Ions (relative %) Present in the EI Spectra of **41** and its d_2-Analog

d9		d10	
242 M^+	(16)	244 M^+	(33)
199 ($-CH_2$=N-Me)	(2)	201	(4)
198 ($-CH_2$NH-Me)	(4)	200, 199	(5,4)
186 (-Me-N-CH=CH_2)	(8)	186 (-Me-N-CH=CD_2)	(15)

d11			
172 ($-CH_2$-NMe-CH=CH_2)	(10)	172 ($-CH_2$-NMe-CH=CD_2)	(16)
151 ($-PhCH_2$)	(8)	153	(8)
108 ($-PhCH_2$, -MeN=CH_2)	(30)	110	(34)
91 ($PhCH_2^+$)	(42)	91	(45)
70 (CH_2=CH-N^+(Me)=CH_2)	(100)	72 (CD_2=CH-N^+(Me)=CH_2)	(100)


41


41 – d_2


i

We were able to obtain a gc-ei mass spectrum of this compound and of the corresponding metabolite obtained with **12**-d_2. A summary of the fragmentation patterns is given in Table II. Although assignments of the structures for the various ions must be considered tentative, it seems reasonable to speculate that the key ion at m/z 186 may be assigned to species **i** which is formed by loss of the methylvinylamine radical from the parent ion. The metabolite derived from substrate **12**-d_2 displayed this fragment ion at the same mass. Therefore it is likely that the structure of this metabolite is that of the seven membered ring compound **41**. Fragmentation of the five membered ring compounds **40** and **40**-d_2 is not expected to yield a common ion

of mass 186 since this would require rearrangement of an *N*-methyl group prior to the fragmentation which leads to **i**. A more definitive interpretation of these results, including the possible presence of a mixture of isomeric species, must await additional work.

A number of additional ions present in the chemical ionization ms of the postincubate extracts could be due to metabolically derived products. These include ions at masses 190, 200 and 221. All of these ions show the required shifts with substrate **12**-d_2 and are present only in those extracts of incubation mixtures which contained NADPH. Efforts presently underway should provide more definitive structural information on the metabolites of this methapyrilene analog.

EXPERIMENTAL

All reactions were carried out under a nitrogen atmosphere. Solvents for reactions were dried and distilled prior to use. Proton nmr spectra were recorded in deuteriochloroform (tetramethylsilane reference), perdeuterated dimethylsulfoxide (tetramethylsilane reference), or deuterium oxide (dimethylsilylpentane sulfonate reference) on a Varian FT-80 MHz instrument. Chemical shifts are reported in parts per million (ppm) relative to tetramethylsilane or dimethylsilylpentane sulfonate as an internal standard; s = singlet, d = doublet, t = triplet, m = multiplet, br = broad. Melting points were determined on a Thomas Hoover melting point apparatus and are uncorrected. Chemical ionization mass spectra (cims) were obtained on an AEI MS-902 instrument modified for chemical ionization. Gas chromatography-electron ionization mass spectra (gc-eims) were obtained on a 2 m × 2 mm id glass column packed with 3% OV-25 coupled either to an AEI MS-12 mass spectrometer *via* a Watson-Biemann separator or to an AEI MS-902S instrument *via* a glass jet separator. Elemental analyses were performed by the Microanalytical Laboratory, University of California, Berkeley.

N,N-Dimethyl-*N'*-benzyl-1,2-ethanediamine (**15**).

A mixture of 14.4 g of dimethylaminoethyl chloride hydrogen chloride (0.1 mole) and 32.2 g of benzylamine (0.3 mole) was stirred with initial cooling (water bath, 22°). Then the temperatue (oil bath) was slowly increased to 135° and kept at 135-140° for 2.5 hours. After cooling, dichloromethane (100 ml) and an excess of cold 20% potassium hydroxide were added. The dried (magnesium sulfate) dichloromethane layer was concentrated and the residue subjected to fractional distillation to yield unreacted benzylamine (bp 35-40°/0.1 mm) and pure **15** (6.55 g, 0.037 mole, 37%), bp 61-62°/0.1 mm [lit (8) bp 82-83°/0.3 mm]; cims 179 (MH^+).

N,N-Dimethyl-*N'*-benzyl-*N'*-cyano-1,2-ethanediamine (**16**).

To an ice cold solution of compound **15** (0.89 g, 5 mmoles) in dry ether (20 ml) was added 1.6 *M* butyllithium in hexane (3.1 ml, 5 mmoles) followed by cyanogen bromide (0.53 g, 5 mmoles) in 20 ml of anhydrous ether. After 90 minutes at 0°, water (50 ml) was added, the ether layer was separated and the aqueous phase was further extracted with dichloromethane. The glc analyses (3% OV-25, 150°, 6°/0.1 mm) showed the presence of starting amine **15** and cyanamide **16** which eluted at 110° and 135°, respectively. Distillation yielded **15** (bp 60-80°/0.1 mm), an intermediate fraction (bp 80-110°) and **16** (0.40 g, 2 mmoles, 40%), bp 110-115°/0.1 mm; cims 204 (MH^+).

Anal. Calcd. for $C_{12}H_{17}N_3$: C, 70.90; H, 8.43; N, 20.67. Found: C, 71.14; H, 8.45; N, 20.30.

1-(2-Dimethylaminoethyl)-2-aminoimidazole (**25**).

(A) Alkylation of 2-Aminoimidazole (**23**).

A mixture of 2-aminoimidazole sulfate (1.32 g, 5 mmoles, 10 meq. 2-aminoimidazole), 2-dimethylaminoethyl chloride hydrogen chloride (**24**, 1.44 g, 10 mmoles) and sodium amide (1.2 g, 30 mmoles) was stirred at room temperature in anhydrous dimethylformamide (20 ml) for 16 hours. A cold solution of 2*N* potassium carbonate (100 ml) was added and the aqueous solution was extracted with butanol (3 × 50 ml). The butanol phase was washed with water (2 × 10 ml) and evaporated *in vacuo*. The residue was freed from potassium carbonate by dissolution in methanol, filtration and evaporation. Analysis by tlc [chloroform:methanol (3:2)] showed the presence of **23** and **25** (R_f-values 0.1 and 0.3, respectively). Preparative tlc yielded 0.5 g (3.2 mmoles, 32%) of **25**, which was eluted from the silica gel with methanol; nmr (deuteriochloroform): δ 2.27 (s, 6H, CH_3), 2.58 (t, J = 5 Hz, 2H, CH_2NMe_2), 3.78 (t, J = 5 Hz, 2H, CH_2-CH_2NMe_2), and 6.45 and 6.58 (J = 1.5 Hz, 2H, H-4 and H-5); nmr (deuterium oxide): δ 2.40 (s, 6H, CH_3), 2.92 (t, J = 6.6 Hz, 2H, CH_2NMe_2), 4.01 (t, J = 6.6 Hz, 2H, $CH_2CH_2NMe_2$) and 6.73 (bd, 2H, H-4 and H-5); cims 155 (MH^+). A *bis*-picrate of **25** was prepared by partial evaporation of a methanol-dichloromethane solution of **25** containing an excess of picric acid, mp 219-220°.

Anal. Calcd. for $C_{19}H_{20}N_{10}O_{14}$: C, 37.26; H, 3.29; N, 22.64. Found: C, 37.40; H, 3.19; N, 22.64.

(B) Ring Synthesis.

A mixture of 2-dimethylaminoethyl chloride hydrogen chloride (2.88 g, 20 mmoles) and aminoacetaldehyde diethylacetal (5.8 g, 44 mmoles) was heated on a steam bath for 10 minutes following which dichloromethane (20 ml) and saturated aqueous potassium carbonate (5 ml) were added. The organic layer was washed with water, dried over magnesium sulfate, and evaporated to dryness to yield a residue which upon distillation provided 0.93 g (4.6 mmoles, 23%) of *N*-(dimethylaminoethyl)aminoacetaldehyde diethyl acetal (**29**), bp 117-122°/16 mm; cims 205 (MH^+).

Anal. Calcd. for $C_{10}H_{24}N_2O_2$: C, 58.79; H, 11.84; N, 13.71. Found: C, 58.80; H, 11.94; N, 13.79.

A mixture of **29** (0.24 g, 1.2 mmoles), cyanamide (0.6 g, 14.3 mmoles), acetic acid (0.3 g, 5.0 mmoles) and water (1 ml) was heated on a steam bath for 80 minutes. The reaction mixture was cooled and after the addition of cold 2*N* potassium carbonate (20 ml) was extracted with chloroform (3 × 10 ml). Evaporation of the dried (magnesium sulfate) chloroform layer yielded 0.26 g of the guanine derivative **30**, cims 247 (MH^+). Crude **30** in 1*N* hydrochloric acid (10 ml) was heated on a steam bath for 1 hour. The solvent was removed *in vacuo* and the residue in 2 ml of saturated aqueous potassium carbonate was extracted exhaustively with chloroform. Removal of the dried (magnesium sulfate) solvent provided crude **25** which was characterized by nmr and cims. The *bis*-picrate obtained from this product and that described above had the same mp and mmp.

1-(2-Dimethylaminoethyl)-2-benzoylaminoimidazole (**27**).

Compound **25** (0.35 g, 2.3 mmoles) in pyridine (2 ml) and dichloromethane (10 ml) was treated with benzoyl chloride (1.0 g, 7.1 mmoles). After stirring for 2 hours at room temperature, the reaction mixture was added to concentrated hydrochloric acid-ice (10 ml). This mixture was washed with dichloromethane, made basic with solid potassium carbonate, and the product extracted with dichloromethane. Preparative tlc [chloroform:methanol (3:2), R_f = 0.35, elution with methanol] yielded 0.2 g (0.8 mmole, 35%) of **27**; nmr (deuteriochloroform): δ 2.28 (s, 6H, CH_3), 2.66 (t, J = 6.4 Hz, 2H, CH_2NMe_2), 4.09 (t, J = 6.4 Hz, 2H, CH_2-CH_2NMe_2), 6.66 (s, 2H, H-4 and H-5), 7.40 (m, 3H, Ph*H*), and 8.23 (m, 2H, Ph*H*); cims 259 (MH^+). A *bis*-picrate of **27** was prepared in ethanol and crystallized from acetone-water and recrystallized from acetone-ethanol, mp 214-216°.

Anal. Calcd. for $C_{26}H_{24}N_{10}O_{15}$: C, 43.58; H, 3.38; N, 19.55. Found: C, 43.79; H, 3.61; N, 19.04.

1-(2-Dimethylaminoethyl)-2-benzylaminoimidazole (**28**).

To a solution of aluminum hydride [prepared by careful addition of aluminium chloride (1.33 g, 10 mmoles) to lithium aluminum hydride (0.38 g, 10 mmoles) in tetrahydrofuran (30 ml)] was added a solution of

compound **27** (0.1 g, 0.4 mmole) in tetrahydrofuran (5 ml). Progress of the reaction was followed by cims (disappearance of MH^+ 259 and appearance of MH^+ 245). After 10 days at room temperature, excess reagent was decomposed with ice and the basified (potassium carbonate) mixture extracted with dichloromethane to provide crude **28**; nmr (deuteriochloroform): δ 2.10 (s, 6H, CH_3), 2.60 (t, J = 4.7 Hz, 2H, CH_2NMe_2), 3.79 (t, J = 4.7 Hz, 2H, $CH_2CH_2NMe_2$), 4.62 (s, 2H, $PhCH_2$). Since this ring alkylated product was of no value for our metabolic work, further purification was not pursued.

2-Benzylaminoimidazole Hydrogen Chloride (**32** Hydrogen Chloride).

A solution of 2-benzoylaminoimidazole (7) (**31**, 2.5 g, 13 mmoles) in 200 ml of dry tetrahydrofuran was treated carefully with 1.0 g of lithium aluminium hydride (26 mmoles) and 3.4 g of aluminium chloride (26 mmoles). The reaction was followed by tlc (chloroform:methanol (9:1), R_f of **31** = 0.8; R_f of **32** = 0.2). After 2 days additional reagents [lithium aluminium hydride (0.6 g) and aluminium chloride (1.5 g)] were added and the reaction was allowed to proceed with occasional stirring at room temperature for 8 more days. The reaction mixture then was poured onto excess 2*N* hydrochloric acid-ice and extracted with dichloromethane. The organic layer was discarded and the aqueous phase was basified with a large excess of cold 2*N* potassium carbonate and extracted thoroughly with chloroform. The combined chloroform extracts were dried (magnesium sulfate), filtered, treated with an excess of 2*N* hydrochloric acid in methanol, and evaporated to dryness. The residue was crystallized from methanol-ether to yield 2.1 g (10 mmoles, 77%) of the hydrochloride salt of **32**, mp 156-157°.

Anal. Calcd. for $C_{10}H_{12}ClN_3$: C, 57.28; H, 5.78; N, 20.04; Cl, 16.91. Found: C, 57.39; H, 5.79; N, 19.90; Cl, 16.90.

The free base [cims 174 (MH^+)] in deuteriochloroform displayed the following nmr signals: δ 4.36 (s, 2H, $PhCH_2$), 6.55 (s, 2H, H-4 and H-5), and 7.27 (s, 5H, Ph*H*).

2-(*N*-Chloroacetyl-*N*-benzyl)aminoimidazole (**33**).

2-Benzylaminoimidazole hydrogen chloride (2.0 g, 9.5 mmoles) was heated with 5 ml of chloroacetyl chloride at 80° for 16 hours. Excess reagent was evaporated *in vacuo* and the residue dissolved in dichloromethane (50 ml). The dichloromethane solution was washed with cold 1*N* potassium carbonate, dried (magnesium sulfate) filtered, and evaporated to dryness to yield crude **33**; nmr (deuteriochloroform): δ 4.16 (s, 2H, CH_2Cl), 5.22 (s, 2H, $PhCH_2$), 6.90 (s, 2H, H-4 and H-5), 7.25 (s, 5H, Ph*H*); cims 250 and 252 (MH^+, 3 to 1 ratio). Because of its instability, further purification of **33** was not attempted.

2-(*N*-Dimethylaminoacetyl-*N*-benzyl)aminoimidazole (**34**).

The above crude **33** in dry dichloromethane (100 ml) containing molecular sieves (10 g) was treated with dimethylamine hydrogen chloride (5.0 g) and triethylamine (8 ml). The reaction mixture was kept at room temperature for 1 day and then washed with 2*N* potassium carbonate, and water, dried (magnesium sulfate) and evaporated to dryness to give a residue which was chromatographed on silica with chloroform-methanol (first 19:1 then 93:7) to yield crystalline **34** (1.18 g, 4.5 mmoles, 47% calculated on **32**). The analytical sample was recrystallized from acetone-hexane: mp 170°; nmr (deuteriochloroform): δ 2.31 (s, 6H, CH_3), 3.11 and 3.19 (2s, 2H, $COCH_2$), 5.20 and 4.47 (2s, 2H, $PhCH_2$), 6.86 (s, 2H, H-4 and H-5), and 7.24 (s, 5H, Ph*H*); nmr (perdeuterated dimethylsulfoxide): δ 2.17 (s, 6H, CH_3), 3.06 (s, 2H, $COCH_2$), 4.87 (br s, 2H, $PhCH_2$), 6.89 (s, 2H, H-4 and H-5), and 7.24 (s, 5H, Ph*H*); cims 259 (MH^+).

Anal. Calcd. for $C_{14}H_{18}N_4O$: C, 65.14; H, 7.02; N, 21.69. Found: C, 64.80; H, 6.98; N, 21.41.

2-(*N*-2-Dimethylaminoethyl-*N*-benzyl)aminoimidazole (**12**).

Amide **34** (1.0 g, 3.9 mmoles) was allowed to react with boron hydride in tetrahydrofuran (20 ml of a 0.98 *M* solution, 20 mmoles) for 16 hours at room temperature. Ice and 2*N* hydrochloric acid were added and the resulting solution evaporated to dryness *in vacuo*. This residue was dissolved in methanol (20 ml) and then the methanol was removed *in vacuo*. This treatment was repeated two additional times to yield the crude borane **35** as its hydrochloride salt; nmr (deuterium oxide): δ 2.64 (s, 6H, CH_3), 3.15 and 3.60 (2m, 4H, CH_2CH_2), 5.48 (s, 2H, $PhCH_2$), 6.78 and 6.85 (2d, J = 2.2 Hz, 2H, H-4 and H-5), and 7.44 (s, 5H, Ph*H*); cims: (free base) 257 and 256 (MH^+, ratio of 3 to 1). This salt was heated under reflux in 2*N* hydrochloric acid for 24-30 hours. The residue obtained after removing the volatile components *in vacuo* was treated repeatedly by the addition and evaporation of methanol to remove the boric acid. The residue was subjected to column chromatography on silica. Elution with chloroform:methanol (3:1) gave 0.35 g (1.4 mmoles, 37%) of **12** hydrogen chloride slightly contaminated with **35** hydrogen chloride followed by 0.5 g (2.0 mmoles, 52%) of chromatographically pure **12** hydrogen chloride; nmr (deuterium oxide): δ 2.74 (s, 6H, CH_3), 3.18 (t, J = 6 HZ, 2H, Me_2NCH_2), 3.67 (t, J = 6 Hz, 2H, $Me_2NCH_2CH_2$), 6.76 (s, 2H, H-4 and H-5), and 7.36 (m, 5H, Ph*H*); cims: (free base) 245 (MH^+). The *bis*-picrate was prepared by adding ethanolic picric acid to a solution of **12** (free base) in dichloromethane. Partial removal of the solvent followed by long standing in the refrigerator gave a crystalline, analytically pure sample, mp 210°.

Anal. Calcd. for $C_{26}H_{26}N_{10}O_{19}$: C, 44.45; H, 3.75; N, 19.94. Found: C, 44.26; H, 3.66; N, 19.45.

The corresponding d_2 product (**12**-d_2) was prepared in an analogous fashion from amide **34** and boron deuteride in tetrahydrofuran. The isotopic composition was shown by cims to be 84% d_2, 15% d_1 and 1% d_0.

Acknowledgements.

The authors wish to thank the Katholieke Universiteit Leuven for providing support for the sabbatical leave of Dr. F. Compernolle who also was a recipient of a NATO research grant. This research was supported by Center Grant GM 26691-03.

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