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1*H*-Imidazo[1,2-*a*]imidazoles†

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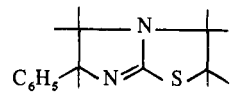
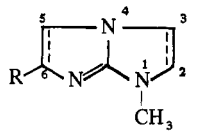
Tetramisole (6-phenyl-2,3,5,6-tetrahydroimidazo[2,1-*b*]-thiazole) has been found to be a potent broad spectrum anthelminthic agent, effective for the treatment of helminthiases in domestic animals.[1] A logical extension of this development was the replacement of the thiazole S of tetramisole with a substituted N to give an aza analog which might be expected to demonstrate similar activity. Accordingly, the



tetramisole

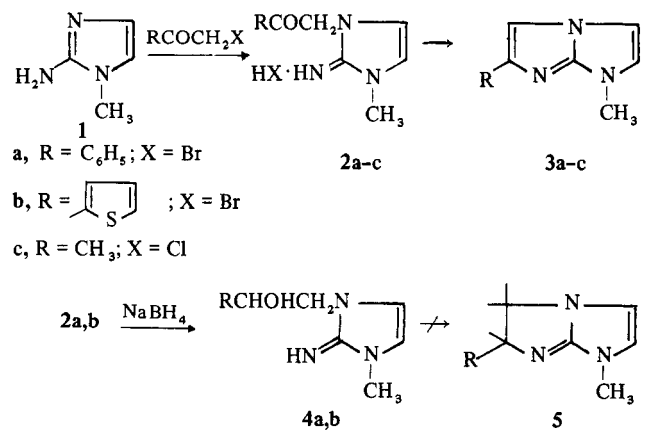


1-methyl-1*H*-imidazo[1,2-*a*]imidazole

synthesis of a series of 6-substituted 1-methyl-1*H*-imidazo-[1,2-*a*]imidazoles was undertaken, wherein the ring system was unsaturated, dihydrogenated, and tetrahydrogenated. The 6 position substituents chosen were methyl (unsaturated system only), Ph, and thienyl.

Chemistry. The imidazo[1,2-*a*]imidazole moiety was first reported by Pierron[2] in 1919, however, the vast majority of work in this area has been done by McKay and coworkers who prepared a series of 1-substituted 2,3,5,6-tetrahydro-1*H*-imidazo[1,2-*a*]imidazoles. McKay's method of synthesis[3] involved the reaction of 1-(2-hydroxyethyl)imidazolidin-2-thione with a primary amine, giving an amino-substituted 2-aminoimidazoline which was then treated with $SOCl_2$ and base to yield a bicyclic product. This method was not particularly applicable to our needs. We felt that we could more easily prepare the target compounds by alkylation of 2-amino-1-methylimidazole (**1**) or 2-amino-1-methylimidazoline (**6**) with an α-halo ketone. Thus, reaction of **1** (Scheme I) with 2-bromoacetophenone yielded 2-imino-3-methyl-1-phenacyl-4-imidazoline hydrobromide (**2a**). Similarly, reaction of **1** with 2-(bromoacetyl)thiophene[4] and chloro-2-propanone gave **2b** and **2c**, respectively. **2a** and **2c** were readily cyclized to the 6-substituted 1-methyl-1*H*-imidazo-[1,2-*a*]imidazoles (**3a,c**) by refluxing in dil acid. **2b** was more resistant to cyclization, requiring polyphosphoric acid.

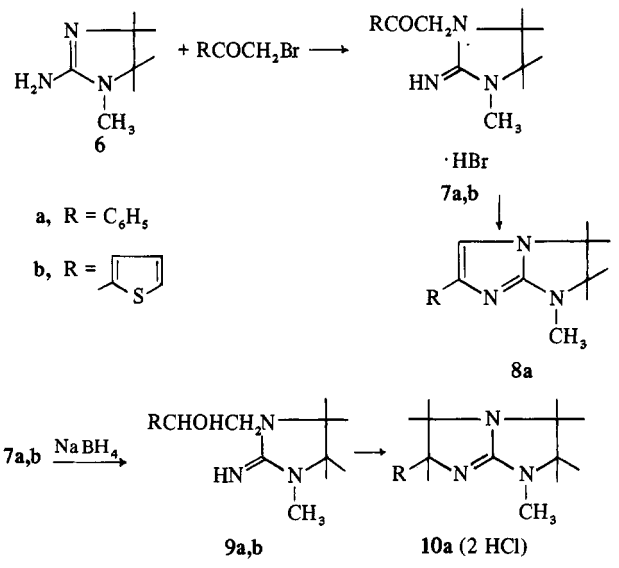
Scheme I



Attempts were made to prepare 6-substituted 5,6-dihydro-1*H*-imidazo[1,2-*a*]imidazoles (**5**). Reduction of **2a** and **b** with $NaBH_4$ gave the expected β-substituted hydroxyethyl derivatives (**4a, b**), however, in our hands these could not be converted to the bicyclic products.

Alkylations of **6** (Scheme II) were accomplished by methods similar to those described for **1**, giving **7a** and **b**. **7a** was readily converted to **8a** in concd acid, however, the thiophene derivative (**7b**) resisted cyclization. Reduction of **7a** and **b** with $NaBH_4$ gave **9a** and **b**, respectively. Treatment of **9a** with $SOCl_2$ gave the tetramisole analog, 1-methyl-6-phenyl-2,3,5,6-tetrahydro-1*H*-imidazo[1,2-*a*]imidazole (**10a**), however, **9b** could not be cyclized. **10a**, which was isolated as its dihydrochloride salt, showed a double melting point and investigation of this phenomenon under controlled conditions revealed that thermolysis caused ring opening with the loss of HCl. The product was shown by spectral and analytical data to be 2-imino-3-methyl-1-(*trans*-styryl)-imidazolidine hydrochloride (**11**).

Scheme II



Structure Proof. One problem associated with the synthetic procedure was the possibility of obtaining isomeric products from the alkylations of **1** and **6**. Two sites were available for alkylation—on the endocyclic N or on the exocyclic N. Acylations of these compounds are known to occur on the exocyclic N,[5] however, no information has appeared on their alkylation. By analogy to the 2-aminothiazolines[1] alkylation would be expected to occur on the ring, and while the nmr spectra of our compounds suggested that this was the case, the evidence was not conclusive. The structural relationships were further clouded by the fact that **1** was considerably less basic than **6**, and it was conceivable that these 2 compounds could be alkylated in different positions. We therefore wished to devise a structure proof which would unequivocally identify the site of alkylation.

During an investigation of nitroguanidine derivatives, Amos[6] and coworkers found that 1,3-dibenzyl-2-nitroimino-

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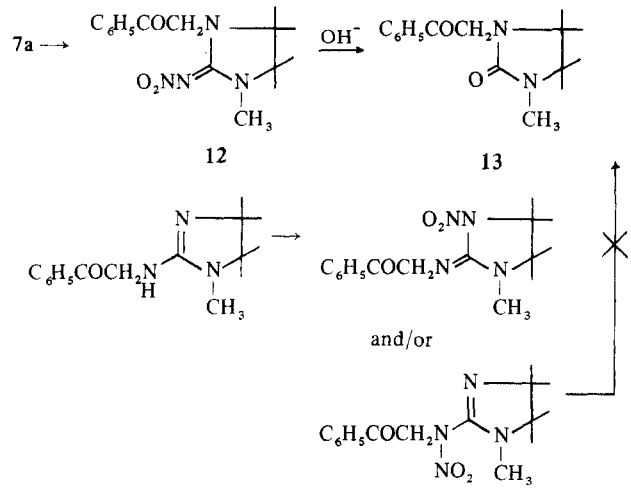
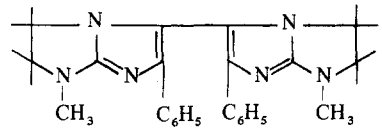
imidazolidine could be hydrolyzed with base to give 1,3-dibenzyl-2-imidazolidinone. Accordingly, **7a** was nitrated

Scheme III



with acetyl nitrate (Scheme III) to give **12**. Hydrolysis of **12** with base gave a good yield of the imidazolidone, **13**, which was readily characterized by its elemental analysis and spectral properties. As indicated by Scheme III, only a ring-alkylated imidazoline would be expected to give **13**. There remained the question of whether the alkylations of **1** and **6** had occurred at the same site. One way of solving this problem was by converting one of the compounds from the imidazoline series (**7–10**) to the corresponding imidazole (**2–5**) or *vice versa*. Martin[7] and coworkers have reported the oxidation of 4- or 5-substituted imidazolines to imidazoles using MnO_2. Unfortunately, treatment of **8a** under these conditions failed to yield the desired product, **3a**. Instead, **8a** dimerized to give 5,5′-bis(2,3-dihydro-1-methyl-6-phenyl-1*H*-imidazo[1,2-*a*]imidazole) (**14**), a fluorescent compound whose structure was confirmed by spectral data.



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Other unsuccessful attempts at dehydrogenation were made by treating **7a** with DDQ, chloranil, and Se. However, catalytic reduction of **4a** gave a compound which was shown by its ir spectrum and by mmp determination to be identical with **9a**, thus establishing that **1** and **6** had alkylated at the same site.

Biological Screening. Anthelmintic screening of the above compounds (excluding **12** and **13**) was carried out in mice against *Nematospiroides dubious* and *Ascaris lumbricoides* using tetramisole as a standard, however, no activity was found. Routine screening for antibacterial, antiprotozoal, CNS, and cardiovascular activity also proved negative.

Experimental Section

Melting points were taken in open capillary tubes with a calibrated thermometer using a Thomas-Hoover melting point apparatus. Elemental analyses were performed by Spang Microanalytical Laboratory, Ann Arbor, Mich. Compounds were analyzed for C, H, and N, and where applicable, Br, Cl, and S. All values were within ±0.4% of theoretical. The ir and nmr spectra of each compound were consistent with the assigned structure. Mass spectra were measured by Morgan-Schaffer Corp., Quebec, Canada, using a Hitachi-Perkin-Elmer RMU-6D mass spectrometer. The standard drying agent for drying organic solvents was anhyd $MgSO_4$. Solvents were removed under vacuum on a rotary evaporator.

2-Imino-3-methyl-1-phenacyl-4-imidazoline Hydrobromide (2a). A quantity of 2-amino-1-methylimidazole hydrochloride[8] was treated with excess 50% NaOH. The aq phase was extd with $CHCl_3$, which was dried and evapd. The free base (**1**) (5.6 g; 0.058 mole) and 2-bromoacetophenone (11.2 g; 0.056 mole) in abs EtOH (150 ml) were refluxed until the pH had dropped to 6 (*ca.* 10 min) and then chilled. The product was filtered off, washed with cold EtOH, and dried, giving crude **2a** (15 g). Recrystn from abs EtOH gave pure **2a**, mp 248–249° dec (lit.[9] 234–236° dec).

2-Imino-3-methyl-1-(2-thenoylmethyl)-4-imidazoline Hydrobromide (2b). To a soln of **1** (19.4 g; 0.2 mole) in acetone (500 ml) was added 60% 2-(bromoacetyl) thiophene[4] (62 g; *ca.* 0.19 mole). The soln was refluxed for 15 min during which time the product crystd. The solid was filtered off giving crude **2b** (48.8 g). Recrystn from CH_3NO_2 gave pure **2b**, mp 242–244° dec.

1-Acetonyl-2-imino-3-methyl-4-imidazoline Hydrochloride (2c). A soln of **1** (5.2 g; 0.054 mole) was refluxed in acetone (150 ml) as chloro-2-propanone (5 g; 0.054 mole) in acetone (30 ml) was added. The pH of the refluxing soln was monitored and after 30 min had dropped to 5, indicating completion of the reaction. The soln was cooled, yielding an oily layer which soon crystd. The solid was filtered off and dried to give **2c** (7.2 g). Recrystn from *i*-PrOH gave pure **2c**, mp 188–190°.

1-Methyl-6-phenyl-1*H*-imidazo[1,2-*a*]imidazole (3a). A soln of **2a** (36 g; 0.12 mole) in 5% HCl (300 ml) was refluxed for 5 min, cooled, and basified to pH 10 with 10% NaOH. The aq phase was extd with $CHCl_3$, which was dried and evapd. The residue was crystd twice from C_6H_6–cyclohexane to yield pure **3a** (21.5 g), mp 122–124°.

1-Methyl-6-thienyl-1*H*-imidazo[1,2-*a*]imidazole (3b). A quantity of **2b** (30 g; 0.066 mole) was added to polyphosphoric acid (250 g) to give a paste which was stirred until evolution of HBr ceased. The paste was dild with cold H_2O and basified with NH_4OH. The aq phase was extd with $CHCl_3$, which was dried and evapd. Crystn from petr ether (bp 90–100°) gave pure **3b** (7.5 g), mp 126.5–128.5°.

1,6-Dimethyl-1*H*-imidazo[1,2-*a*]imidazole Hydrochloride (3c). A soln of **2c** (33 g; 0.185 mole) in 5% HCl (250 ml) was refluxed for 10 min and evapd. The residue was taken up in abs EtOH (200 ml) and the vol reduced to 60–70 ml on a hot plate. After refrigeration, the solid product (30.2 g) was recrystd from abs EtOH to give pure **3c**, mp 218–221°.

1-(2-Hydroxyphenethyl)-2-imino-3-methyl-4-imidazoline (4a). A slurry of **2a** (25 g; 0.084 mole) in H_2O (150 ml) was maintained at 5° as $NaBH_4$ (3.2 g; 0.085 mole) was added portionwise. The soln was allowed to warm to 25°, stirred for 0.5 hr, and excess borohydride was destroyed with concd HCl. The acid soln was heated to boiling, cooled, and basified to pH 11 with 10% NaOH. The aq phase was extd with $CHCl_3$, which was dried and evapd, giving a crude solid. Recrystn from C_6H_6 gave pure **4a** (12.9 g), mp 158–160°.

1-(2-Hydroxy-2-thienylethyl)-2-imino-3-methyl-4-imidazoline (4b). A slurry of **2b** (2 g; 0.007 mole) in H_2O (25 ml) was maintained at 5° as $NaBH_4$ (0.25 g; 0.007 mole) was added. The mixt was stirred cold for 30 min and excess borohydride was destroyed with concd HCl. The soln was heated to boiling, cooled, and basified to pH 11 with 10% NaOH. The aq phase was extd with $CHCl_3$, which was dried and evapd. The solid obtained (1.2 g) was recrystd from C_6H_6 to give pure **4a**, mp 136–138°.

2-Imino-3-methyl-1-phenacylimidazolidine Hydrobromide (7a). To 500 ml of abs EtOH was added Na (9.6 g; 0.417 g-atom), and the mixt was stirred until soln was complete. The solvent was evapd and NaOEt dissolved in DMF (100 ml). The soln was warmed to 50° and 2-amino-1-methylimidazoline hydrobromide[2] (75 g; 0.417 mole) was added and stirred for 5 min. The free base (**6**) and 2-bromoacetophenone (83 g; 0.417 mole) were stirred until the pH had dropped to 7 (*ca.* 30 min). The NaBr was filtered off and the filtrate refrigerated. Filtration of the solid gave crude **7a** (108 g). Recrystn from CH_3CN gave pure **7a**, mp 214.5–215.5°.

2-Imino-3-methyl-1-(2-thenoylmethyl)imidazolidine Hydrobromide (7b). To a soln of **6** (21 g; 0.21 mole) in acetone (200 ml) was slowly added 70% 2-(bromoacetyl)thiophene[4] (60.1 g; *ca.* 0.21 mole), causing the acetone to boil. The pH of the soln rapidly dropped to 5 and the product crystd. Filtration of the solid gave pure **7b**, mp 223° dec.

2,3-Dihydro-1-methyl-6-phenyl-1*H*-imidazo[1,2-*a*]imidazole Hydrobromide (8a). A soln of **7a** (5 g; 0.017 mole) in concd HBr

(50 ml) was refluxed for 4 hr and evapd. Crystn from CH_3CN gave pure **8a** (3.5 g), mp 233–233.5°. A methiodide salt was prepared, mp 163–164°.

1-(2-Hydroxyphenethyl)-2-imino-3-methylimidazolidine (9a). A slurry of **7a** (30 g; 0.1 mole) in H_2O (250 ml) was maintained at 5° as $NaBH_4$ (4.2 g; 0.11 mole) was added portionwise. The mixt was stirred cold for 0.5 hr and the excess borohydride was destroyed with concd HCl. The soln was heated to boiling, cooled, basified to pH 11 with 10% NaOH and extd with $CHCl_3$. The organic phase was dried and evapd to give crude **9a** (18 g). Recrystn from cyclohexane gave pure **9a**, mp 88–90°.

1-(2-Hydroxy-2-thienylethyl)-2-imino-3-methylimidazolidine Hydrochloride (9b). A slurry of **7a** (20 g; 0.066 mole) in H_2O (125 ml) was maintained at 5° as $NaBH_4$ (2.5 g; 0.066 mole) was added portionwise. The mixt was stirred cold for 15 min and excess borohydride was destroyed with concd HCl. The soln was heated to boiling, cooled, basified to pH 11 with 10% NaOH, and evapd. The residue was treated with Me_2CO–Et_2O (1:1) and filtered to remove inorganic material. The filtrate was treated with ethereal HCl to ppt **9b** (9.6 g). Recrystn from abs EtOH gave pure **9b**, mp 203–206°.

1-Methyl-6-phenyl-2,3,5,6-tetrahydro-1*H*-imidazo[1,2-*a*]imidazole Dihydrochloride (10a). A soln of **9a** (7 g; 0.032 mole) in $SOCl_2$ (100 ml) was refluxed for 1.5 hr and evapd. Residual $SOCl_2$ was destroyed with H_2O (25 ml) and the aq phase was extd with $CHCl_3$. The organic phase was dried and evapd to give an oil which was dissolved in hot $MeNO_2$ and chilled. Filtration of the solid gave **10a** (3.4 g), first mp 176–178° with resolidification at 178°, second mp 300°.

2-Imino-3-methyl-1-(*trans*-styryl)imidazolidine Hydrochloride (11). Method A. A sample of **10a** (3.4 g; 0.012 mole) in a flask under N_2 was carefully melted over a flame so as to avoid charring. The gummy residue (2.8 g) was crystd from DMF to give pure **11** (0.6 g), mp 300° dec. The nmr spectrum [(DMSO-d_6)–δ 3.05 (3 H, singlet, CH_3N), 3.80 (4 H, singlet, imidazolidine ring protons), 5.98 (1 H, doublet, J = 14 cps, vinyl proton α to phenyl ring), 7.33 (5 H, multiplet, Ph ring protons), 8.03 (1 H, doublet, J = 14 cps, vinyl proton β to Ph ring), 9.13 (2 H broad singlet, exchangeable with D_2O, NH)] revealed the configuration.

Method B. A quantity of **10a** (7.1 g; 0.025 mole) was heated under vacuum (80 mm) at 100° for 65 hr to give a virtually quant yield (6.1 g) of **11**, mp 300° dec.

3-Methyl-2-nitroimino-1-phenacylimidazolidine (12). To a soln of Na (0.39 g; 0.017 g-atom) in abs EtOH (50 ml) was added **7a** (5 g; 0.017 mole), the mixt was heated to reflux and evapd. The residue was triturated with C_6H_6 (50 ml) which was filtered to remove NaBr and evapd. The oily free base (3 g) was taken up in Ac_2O (5 ml), chilled to 5°, and stirred as acetyl nitrate[10] (13.5 g) was slowly added. The soln was stirred at 25° for 1 hr, poured into cold Et_2O (200 ml), and refrigerated. The gummy ppt (3.3 g) was chromatographed on silica gel‡ (200 g) using CH_3CN as eluant. The initially eluted material (1.6 g) was recrystd from *i*-PrOH to give pure **12**, mp 150–153°.

3-Methyl-1-phenacyl-2-imidazolidinone (13). A soln of **12** (2.6 g; 0.01 mole) in 20% NaOH (50 ml) was refluxed for 10 min, cooled, and extd with $CHCl_3$. The $CHCl_3$ was dried and evapd to give a crude oil (1.9 g) which was shown by tlc (silica gel, CH_3CN) to be primarily one compd. Crystn from heptane gave pure **13**, mp 113–116°.

5,5'-Bis(2,3-dihydro-1-methyl-6-phenyl-1*H*-imidazo[1,2-*a*]imidazole) (14). A soln of **8a** (14.5 g; 0.073 mole) as the free base in $CHCl_3$ (350 ml) was stirred at 25° for 4.5 hr with excess active MnO_2[7] (42 g). The MnO_2 was filtered off and the filtrate evapd to give **14** (7.7 g). Recrystn from acetone gave pure **14**, mp 217–220°, mass spectrum, M^+ = 396.

Reduction of 4a. A soln of **4a** (1 g; 4.6 mmoles) in abs EtOH (30 ml) was reduced under atm pressure with prereduced PtO_2 (0.1 g) for 19 days. Uptake of H_2 was measured as 120 ml; theoretical uptake for 1 equiv of H_2, *ca.* 115 ml. The catalyst was filtered off and the solvent evapd. Recrystn from cyclohexane gave white needles, mp 92–94°, whose ir spectrum was identical with that of **9a**. Mmp with **9a** showed no depression.

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‡Silica gel was purchased from Gebr. Hermann, D5000 Köln Ehrenfeld, West Germany, under the name kieselgel.

Synthesis and Central Nervous System Activity of New Piperazine Derivatives. 4

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Earlier, we reported the synthesis and CNS depressant activity of compounds incorporating the 3,4,5-trimethoxyphenyl and piperazine groupings linked by various connecting bridges.[1] The most active compounds obtained were Mannich bases having $COCH_2CH_2$ linkage. The presence of the 3,4,5-trimethoxycinnamoyl group in rescinnamine (another important therapeutically active alkaloid of *Rauwolfia*) and the interesting physiological properties exhibited by vinylogs[2] of various drugs suggested the extension of the work. The present note describes the synthesis and study of Mannich bases and related compounds having the general formula I (see Table I).

Chemistry. The title compounds were prepared by Mannich reaction of 3,4,5-trimethoxy- or unsubstituted benzalacetone and various N-monosubstituted piperazines. However, when the Mannich reaction with *N*-(α,α,α-trifluoro-*m*-tolylpiperazine hydrochloride was carried out under the same conditions, α,α-bis-N^4-(α,α,α-trifluoro-*m*-tolyl) piperazinyl-N^1-methyl 3,4,5-trimethoxystyrylmethyl ketone resulted instead of the desired product.

Some Mannich bases were reduced to the corresponding alcohols with $NaBH_4$ in order to see the effect on the activity.

The structures of compounds described are assigned on the basis of known synthetic route, elemental analyses, and spectral measurements. The ir and uv spectra of the compounds are in accordance with these assignments.

Pharmacology. The CNS activity of the compounds was studied in mice by methods described earlier.[1] The gross observation of intact mice, spontaneous motor activity, and potentiation of barbital hypnosis revealed that few of the compounds (**5**, **7**, **8**, **11**) possessed good CNS depressant activity. Compounds having aryl substitution in the N^4 position of the piperazine displayed better activity than the rest. Further, the compounds having F in the ortho or para position of the N^4 Ph ring exhibited significant CNS depressant activity.

The cardiovascular effect of most of these compounds were studied in normotensive dogs under pentobarbital