# 2-(4-Imidazolyl)cyclopropylamine[1a]

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The synthesis of 2-(4-imidazolyl)cyclopropylamine from a branched ester of N-triphenylmethylurocanic acid was performed, using dimethylsulfoxonium methylide as a source of carbene, and degrading $CO_2H$ to $NH_2$. The amine was a potent MAO inhibitor *in vitro* but had only low activity in tests relating to the biosynthesis or actions of histamine.

In the wake of the discovery of the potent monoamine oxidase inhibitory and antidepressant activity[2] of 2-phenylcyclopropylamine,[3,4] a number of heterocyclically substituted 2-cyclopropylamines were tested,[5] but none with a heteroring system that also occurs in a natural biogenic amine. Yet the qualitative and quantitative pharmacologic changes brought about by branching of the ethylamine chain, *e.g.*, in α-alkylhistamine,[6] α-alkyltryptamine,[7] or α-alkylserotonin derivatives,[7,8] invites comparison with cyclopropylamine analogs in these very ring systems. We are reporting a synthesis and pharmacological study of 2-(4-imidazolyl)cyclopropylamine (**1**), a cyclopropylog of histamine.

We had used diazomethane as a one-carbon source in constructing the cyclopropane ring of a cyclopropylog of histidine,[9] but N-acetylurocanate esters did not react with diazomethane, nor did they furnish intelligible products with dimethylsulfoxonium methylide. This situation was changed, however, when the imidazole NH was blocked by the bulky triphenylmethyl group;[10] the ylide now added as expected to branched-alkyl N-triphenylmethylurocanate esters (see the 2-butyl ester **2**), yielding two reaction products, **3** and **6** (Scheme I). One of them, 2-butyl 2-(1-triphenylmethyl-4-imidazolyl) cyclopropanecarboxylate (**3**) was saponified to 2-(1-triphenylmethyl-4-imidazolyl) cyclopropanecarboxylic acid (**4**)[11] and this was degraded to 2-(1-triphenylmethyl-4-imidazolyl)-1-carbethoxyaminocyclopropane (**5**). Alkaline hydrolysis of this carbamate followed by deblocking with dilute acid led to **1**.

The other product from the ylide interaction with the acrylate ester **2** was obtained when the reaction mixture was poured into $H_2O$ instead of dilute HCl. This compound appeared to be 5-(1-triphenylmethyl-4-imidazolyl)-1,3-dioxo-1-methyl-2,3,5,6-tetrahydrothiazinonium 2-ylide (**6**) on the basis of analytical and spectral evidence (see Experimental Section). Similar ylides were described by Corey and Chaykovsky, as products of the reactions of dimethylsulfoxonium methylide with ethyl cinnamate[12] and ethyl cyclohexenecarboxylate.[13] When **6** is dissolved in 0.05 *M* HCl and the solution is neutralized after some time, a second product (**7**), $C_{26}H_{22}N_2O_2$, is formed. Compound **7** is also obtained when the ylide reaction mixture of **2** is poured into dilute HCl, and the solution is neutralized after extraction of **3**. The structure of **7** was not investigated further.

2-(4-Imidazolyl)cyclopropylamine (!) dihydrochloride was a potent inhibitor of rat brain MAO *in vitro*.[14] Its concentration required to inhibit the enzyme by 50% ($I_{50}$) was $7.5 \times 10^{-6} M$, which was 77% the potency of tranylcypromine sulfate, and 111 times that of iproniazide under the same conditions. In tests for inhibitory activity on specific histidine decarboxylase[15] which depends on the release of $^{14}CO_2$ from histidine-$^{14}CO_2H$, **1**·2HCl at $10^{-2} M$ did not inhibit significantly an enzyme preparation from rat gastric mucosa.

Tests were also carried out[16] for histaminic activity on the isolated guinea pig ileum, and on gastric secretion using the anesthetized-rat perfused stomach preparation which is very suitable for assaying agonist activity for histamine analogs. The method is described in the Experimental Section. As can be seen from Table I, **1** produced histamine-like responses; while very much weaker than histamine, it had about five times the activity of α-methylhistamine on gastric secretion.

Using a technique described by Shimizu, *et al.*,[17] **1** did stimulate cyclic AMP—$^{14}C$ in guinea pig cerebral cortex slices but its activity was only about 10% that of histamine in this test.

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(11) The configuration of **4** could not be determined with certainty by nmr spectroscopy. In other cases, the reaction of dimethylsulfoxonium methylide with *t*-butyl or 2-pentyl arylacrylates furnishes over 90% of the *trans*-cyclopropanecarboxylate esters [C. Kaiser, B. M. Trost, J. Benson, and J. Weinstock, *J. Org. Chem.*, **30**, 3972 (1965)].

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(14) Tests were performed by Dr. Robert Pendleton, Smith Kline and French Laboratories, Philadelphia, Pa. We are grateful to Dr. Pendleton for permission to quote his observations.

(15) Tests were performed by Dr. A. M. Roe of Smith Kline and French Research Institute, Welwyn Garden City, England. We are obliged to Dr. Roe for permission to publish these results.

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SCHEME I

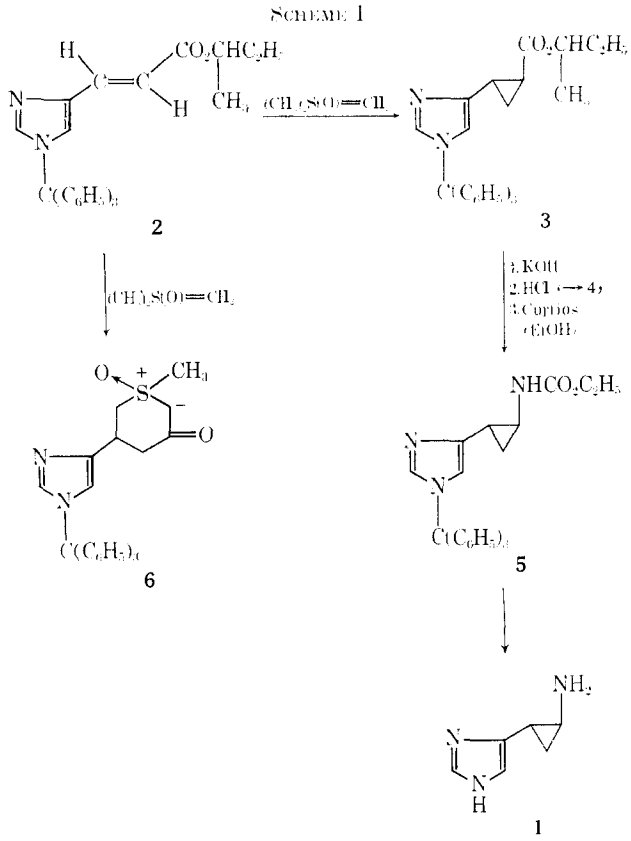


TABLE I
HISTAMINIC POTENCY

| Compd | Molar ratio: Guinea pig ileum | Molar ratio: Rat gastric secretion |
|---|---|---|
| Histamine·2HCl | 100 | 100 |
| **1**·2HCl | 0.78 (0.74–0.82) | 1.6 |
| α-Methylhistamine·2HCl | 0.38 (0.35–0.41) | 0.3 |

## Experimental Section

Melting points were determined in a Thomas–Hoover melting point apparatus and are corrected. Ir and nmr spectra were measured on a Perkin-Elmer spectrophotometer Model 337 (KBr), and on a Varian Model A-60 (TMS, in $CDCl_3$, unless otherwise stated), respectively. Chemical shifts are reported as ppm ($\delta$). Ir and nmr spectra were taken for all compounds but have not been recorded in this paper if they were only confirmatory and as expected. Analyses indicated only by symbols of the elements were within the ±0.4% limit and were performed by Galbraith Laboratories, Knoxville, Tenn. Petroleum ether used had bp 30–60°.

**Pharmacology.**[15] *In Vivo* **Tests.**—For tests for histaminic activity, rats were anesthetized with urethan, and their stomachs were denervated vagally at the diaphragm levels. By means of cannulas inserted through the antrum, esophagus, and fundus, the acid-secreting mucosa of the main portion of the stomach was perfused continually with 5% glucose solution at 37°. The perfusate passed over a glass electrode system in a flow cell, and the output from the pH meter, after passing through a suitable anti-log function generator, was recorded on a flat bed recorder as a linear function of $H^+$ activity. The drugs were given intravenously, and the rats' body temperature was kept at 37°.

**Chemistry. 2-Butyl *trans*-3-(4-Imidazolyl)acrylate.**—A mixture of 21 g (0.15 mole) of *trans*-urocanic acid,[18] 700 ml of 2-BuOH, 300 ml of $C_6H_6$, and 10 ml of concentrated $H_2SO_4$ was refluxed under a Dean–Stark water trap for 24 hr. The cooled solution was poured into $Et_2O$ (1 l.). The $Et_2O$ layer was washed (10% NaOH, $H_2O$), dried ($MgSO_4$), and evaporated *in vacuo*, and the residue distilled to give 27.5 g (95%) of a viscous yellow liquid, bp 158–160° (0.2 mm) (nmr).

**2-Butyl *trans*-3-(1-Triphenylmethyl-4-imidazolyl)acrylate (2).** To a solution of 2-butyl *trans*-3-(4-imidazolyl)acrylate (25.2 g, 0.13 mole) and $Et_3N$ (13.2 g, 0.13 mole) in $CHCl_3$ (300 ml) was added 38 g (0.135 mole) of $Ph_3CCl$. The solution was stirred magnetically in a stoppered flask at *ca.* 28° for 12 hr, washed ($H_2O$), dried ($MgSO_4$), and evaporated to dryness *in vacuo*. Two recrystallizations of the residue from absolute EtOH gave a colorless solid (47 g, 84%), mp 144–146°, ir spectra as expected. *Anal.* ($C_{35}H_{32}N_2O_2$) C, H, N.

**2-Butyl 2-(1-Triphenylmethyl-4-imidazolyl)cyclopropanecarboxylate (3).** To 9.7 g (44 mmoles) of $Me_3SO^+I^-$[19] and 1.8 g (44 mmoles) of NaH (50.6% in mineral oil) under $N_2$ was added dropwise with stirring DMSO (150 ml, distilled from $CaH_2$). After all the DMSO had been added, the mixture was stirred for 30 min, and then a solution of 17.5 g (40 mmoles) of **2** in 200 ml of 1:1 THF–DMSO was added dropwise. The solution was stirred at *ca.* 28° for 1 hr, at 55–60° for 45 min, cooled, and poured into cold 2.5 *M* HCl (400 ml), and the mixture was extracted ($Et_2O$). The extract was dried ($MgSO_4$) and evaporated (vacuum), and the colorless crystalline residue (10 g, 55%) was recrystallized from petroleum ether: mp 125–127°; ir (cm$^{-1}$) 1720 (C=O), no peak at 1635 (C=C); nmr ($CCl_4$), low-intensity multiplets at $\delta$ 1.5–3.0 (cyclopropane *H*), partially overlapping with 2-Bu *H*. *Anal.* ($C_{36}H_{38}N_2O_2$) C, H, N.

**2-(4-Imidazolyl)cyclopropanecarboxylic Acid.**—A solution of **3** (0.5 g) in 5% HCl (10 ml) was refluxed for 6 hr and filtered from precipitated $Ph_3COH$, and the filtrate was evaporated to dryness in a rotating vacuum evaporator. The residue was dissolved in absolute EtOH, and the solution was filtered and diluted with absolute $Et_2O$. The precipitated solid, after recrystallization from absolute EtOH–$Et_2O$, had mp 169–170° dec; nmr ($D_2O$), $\delta$ 1.68 (2 H, multiplet, geminal cyclopropane *H*), 2.10 and 2.66 (1 H, multiplet, cyclopropane *H*), 7.40 and 8.76 (1 H, singlet, imidazole *H*'s). *Anal.* ($C_7H_8ClN_2O_2$) C, H, N.

**2-(1-Triphenylmethyl-4-imidazolyl)cyclopropanecarboxylic Acid (4).** A solution of **3** (14 g, 30 mmoles) in EtOH (150 ml) was stirred at 40–50° while 150 ml of 12% aqueous KOH was added in portions. After being stirred at 50–60° for 12 hr, the solution was cooled, diluted ($H_2O$, 300 ml), extracted ($Et_2O$), and then acidified to pH 6 with 0.5 *M* HCl. The precipitate obtained was filtered off and air-dried (10.7 g, 90% yield). The colorless solid was recrystallized from THF–petroleum ether (1:1), mp 234° dec. *Anal.* ($C_{26}H_{22}N_2O_2$) C, H, N.

**2-(1-Triphenylmethyl-4-imidazolyl)-1-carbethoxyaminocyclopropane (5).**—A solution of **4** (5.9 g, 15 mmoles) was treated with 15 mmoles of $Et_3N$, $ClCO_2Et$, and $NaN_3$ by the standard procedure.[20a] The dried ether solution of the carboxazide was treated with EtOH (50 ml), heated gently to remove $Et_2O$, and then refluxed for 6 hr. Solvent was removed *in vacuo* and the semisolid residue recrystallized twice (EtOH) to give 3.9 g of pure carbamate: mp 174–176°; ir spectrum as expected; nmr, $\delta$ 1.15 (3 H, $CH_3$ triplet, $J$ = 7 cps, overlapped with 2 H, multiplet, geminal cyclopropane *H*), 2.0 and 2.82 (1 H, multiplet, cyclopropane *H*), 4.10 (2 H, multiplet, $CH_2$), 5.75 (1 H, broadened NH), 6.65 (1 H, imidazole *H*), 7.28 (16 H, multiplet, aromatic *H* overlapping with imidazole *H*). *Anal.* ($C_{29}H_{27}N_3O_2$) C, H, N.

**2-(4-Imidazolyl)cyclopropylamine (1).**—A solution of **5** (3 g, 6.9 mmoles) and KOH (1 g) in absolute EtOH (60 ml) was refluxed under $N_2$ for 3 hr. Most of the solvent was removed under vacuum, cold $H_2O$ (200 ml) was added, and the mixture was extracted ($Et_2O$). The $Et_2O$ solution was washed ($H_2O$) and extracted twice with cold 0.5 *M* HCl (35 + 15 ml). The aqueous phase was heated on a steam bath for 15 min, cooled, and filtered to remove $Ph_3COH$. A hot solution of 4 g of picric acid in 100 ml of $H_2O$ was added and the solid yellow dipicrate recrystallized ($H_2O$), mp 189–191° dec. *Anal.* ($C_{15}H_{15}N_9O_{14}$) C, H, N. This salt was mixed with $H_2O$ (20 ml) and concentrated HCl (5 ml), warmed at 80°, and extracted ($C_6H_6$) to remove the picric acid. The aqueous layer was treated with charcoal and filtered, and the solvent was removed under vacuum. The viscous residue was triturated with a few drops of EtOH and cooled. Tan needles

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of dihydrochloride (0.8 g, 60%) were recrystallized from absolute EtOH; mp 192–193°; nmr (DDS as standard in $D_2O$), $\delta$ 1.57 (2 H, multiplet, geminal cyclopropane *H*), 2.6 and 3.08 (1 H, multiplet, cyclopropane *H*), 7.34 and 8.63 (1 H, singlet, imidazole *H*). *Anal.* ($C_6H_{11}Cl_2N_3$) C, H, N.

**5-(1-Triphenylmethyl-4-imidazolyl)-1,3-dioxo-1-methyl-2,3,-5,6-tetrahydrothiazinonium 2-Ylide (6).**—When the mixture from the reaction of **2** with $Me_2S(O)(=CH_2)$ was poured into cold $H_2O$, instead of 25 m*M* HCl (*vide supra*), a colorless solid precipitated. Any cyclopropane compound (**3**) was extracted from the solid with several portions of $Et_2O$, and the remaining solid was filtered off and recrystallized (absolute EtOH), sintering at 134–138°, mp 234–235° dec. The sintering appeared to be due to crystallization with 1 mole of EtOH that was lost at 140–144° as shown in the nmr spectrum. The product was soluble in dilute acids. *Anal.* ($C_{28}H_{26}N_2SO_2 \cdot C_2H_5OH$) C, H, N. Spectra were recorded for the dried (EtOH-free) material: nmr $\delta$ 2.55 (2 H, doublet, $J$ = 6.5 cps, $CH_2CO$), 3.33 (3 H, singlet, $CH_3$), 3.5–4.28 (3 H, multiplet, $CH_2S$ superimposed on C*H*), 4.47 (1 H, singlet C*H*), 6.70 (1 H, singlet, imidazole *H*), 7.3 (16 H, multiplet, aromatic *H*, superimposed on imidazole *H*); mass spectrum, the product decomposed thermally, giving $M^+$ 390, probably losing $CH_3SOH$; fragmentation pattern as expected.

When **6** was dissolved in 0.05 *M* HCl and the solution was neutralized (NaOH) after 30 min, a colorless solid (**7**) precipitated out. Filtration and repeated recrystallization from MeOH gave a sample of mp 176–178°; $M^+$ 394; ir ($cm^{-1}$) 1775 (C=O), 1168 (C–O), and typical peaks for $C(C_6H_5)_3$; nmr, $\delta$ 2.75 (2 H, doublet, $J$ = 7 cps), 3.7 (1 H, multiplet), 4.42 (2 H, multiplet), 6.7 (1 H, singlet, imidazole *H*), 7.28 (16 H, multiplet, aromatic *H* superimposed on imidazole *H*). *Anal.* Calcd for $C_{28}H_{22}N_2O_2$: C, 79.2; H, 5.58; N, 7.10. Found: C, 79.34; H, 5.58; N, 7.11.

# A Novel Type of Substituted Piperazine with High Antiserotonin Potency[1]

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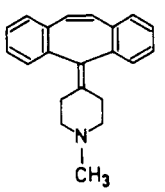
Speculation as to the structural relationship between phenbenzamine and cyproheptadine led to the synthesis of a series of tetracyclic compounds containing as a characteristic moiety a condensed piperazine ring resulting from the fixation of the ethylenediamine chain of phenbenzamine, whereas the two benzene nuclei of the latter are linked by a bond or a bridge of one or two carbon atoms. The piperazine ring system was formed by condensation of the respective diamines with diethyl oxalate (Riebsomer reaction), followed by reduction with diborane or $LiAlH_4$. These compounds (**4–7**) as well as the diphenylpiperazine (**3**) were tested pharmacologically and one of them, 2-methyl-1,2,3,4,10,14b-hexahydro-2H-pyrazino[1,2-*f*]morphanthridine (**5**), mianserin, proved to have an antiserotonin potency of the same order as cyproheptadine (**1**). In animals **5** was found to have a less pronounced CNS depressant effect and lower acute toxicity than **1**.

It is a common view that a pharmacological requirement of an antiallergic compound should be a high antihistamine activity. On the other hand it is believed that histamine is responsible for only some manifestations of anaphylactic reactions.[3] Indeed, during hypersensitivity reactions along with histamine other substances are released, serotonin being one of them.[4] In man, however, the role of serotonin as an allergic mediator is not likely,[5] although antiserotonin compounds proved to have clinically useful effects in disorders including vascular headaches and dumping syndrome.[6]

The object of the present work was to develop a compound with high antiserotonin potency. Of the many drugs capable of antagonizing one or more of the effects of serotonin, cyproheptadine (**1**) is of particular interest because its antagonism toward both histamine and serotonin is of a high order. The so called antihistaminics, as, for example, phenbenzamine (**2**), are much less potent, and in particular their antiserotonin activity is of a low order. Comparison of the structure of

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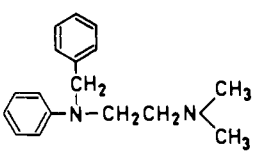


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these two compounds led to the question whether a structural modification of the phenbenzamine molecule might enhance its antiserotonin activity.

The most characteristic feature of the cyproheptadine molecule is the rigidity of its tricyclic ring system, which is connected with the N-containing fourth ring by a double bond, which again does not allow a free rotation. In the phenbenzamine molecule rotation of all groups is possible. Some structural similarities are, however, also present. Two benzene nuclei and one aliphatic tertiary N are present in both compounds. The second N of phenbenzamine is absent in cyproheptadine, but the double bond with its high electron density might play a comparable role with respect to its pharmacological activity. These considerations led to the idea of modifying the phenbenzamine molecule in a way that would result in similar structural rigidity. This may be done by attaching the ethylenediamine chain to the benzyl $CH_2$ and by connecting the benzene nuclei or introducing a bridge of one or two carbon atoms between them (compounds **4–7**).

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(2) Author to whom inquiries should be addressed.

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