ylenedioxyisoquinoline (32).—To a suspension of 3,4-dihydro-1-[*p*-(isopropylsulfonyl)phenyl]-6,7-(methylenedioxy)isoquinoline (70.8 g) in EtOH (500 ml) was added at room temperature with stirring $NaBH_4$ (23 g) in portions and the mixture was heated on a water bath (90°) for 5 hr. The solvent was then removed and the residue was treated with dilute HCl (3.5 l., 0.5 *N*) and filtered. The filtrate was made alkaline with 28% NH_4OH and extracted (CH_2Cl_2), and the latter was washed (H_2O), dried (Na_2SO_4), and removed to give a viscous oil. The **hydrochloride** was prepared in EtOH: mp 267–269°.

1,2,3,4-Tetrahydro-1-[*p*-(isopropylsulfonyl)phenyl]-2-methyl-6,7-(methylenedioxy)isoquinoline Hydrochloride (33).—1,2,3,4-Tetrahydro-1-[*p*-(isopropylsulfonyl)phenyl]-6,7-(methylenedioxy)isoquinoline (10 g), formic acid (10 ml, 99%), and formaldehyde (15 ml, 40%) were allowed to react and the reaction product was isolated exactly in the same way as for **27**.

The Synthesis and Pharmacology of 2-(2-Aminoethyl)imidazole (2-Isohistamine)[1]

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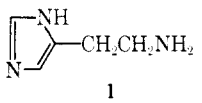
The compound prepared by Jones, which was assigned the structure 2-(2-aminoethyl)imidazole (**3**), is actually 5-aminomethyl-2-methylimidazole (**14**). Authentic **3** has been synthesized from 1-benzyl-2-chloromethylimidazole (**7**) by cyanide displacement in DMSO to yield nitrile **10**, followed by reduction to the amine **12** and debenzylation. Reaction of 1-benzyl-2-lithioimidazole (**15**) with N-(2-bromoethyl)phthalimide (**16**) gave 2-(2-aziridinocarbonylbenzoyl)-1-benzylimidazole (**19**) rather than the expected alkylation product **17**. Compound **3** has weak histamine-like activity on smooth muscle and on blood pressure but none on gastric secretion.

Extensive investigations on the chemistry and pharmacology of heterocyclic analogs of histamine (**1**) have been in progress in these laboratories for more



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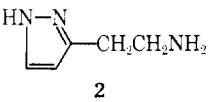
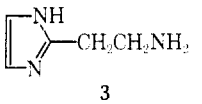


2

than two decades.[2] As a result of these studies 3-(2-aminoethyl)pyrazole (**2**)[3] has been introduced into clinical medicine. This drug, which is an effective stimulant of gastric secretion, is used in place of histamine in tests of gastric function. Because of its minimal side effects it is more convenient to use than is histamine itself.

Recently Jones[4] has reviewed the structure–activity relationships of some 210 derivatives and analogs of histamine and has concluded that "compounds possessing appreciable histamine-like activity consist of small nitrogen heterocyclic rings to which are attached 2-aminoethyl side chains." Among the very few exceptions to this simple generalization, one has appeared especially anomalous. It would be anticipated *a priori* that one of the most interesting analogs of histamine would be the isomer, 2-isohistamine (**3**), with the



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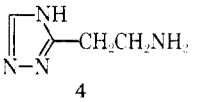

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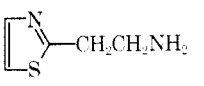
side chain in the 2 rather than in the 4 position. This compound was reported from these laboratories in 1949,[2a] but unexpectedly it was found[2i] to be devoid of histamine activity. In contrast to this observation, heterocyclic ethylamines containing the 3-(1,2,4-triazolyl) (**4**),[2j] 2-thiazolyl (**5**), and 4-pyrazolyl (**6**) moie-



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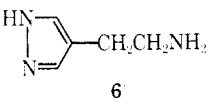

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ties showed very significant activity.[4] This inconsistency was without an explanation until recently Gutsche and Voges[5] provided evidence that the structure assigned to analog **3** was incorrect.

The method devised originally by Jones[2a] for the synthesis of **3** involved reaction of 1-benzyl-2-chloromethylimidazole (**7**) with cyanide to yield 1-benzyl-2-cyanomethylimidazole (**10**). The nitrile **10** was then to be reduced to the β-aminoethyl derivative **12**, which on debenzylation would afford "2-isohistamine" (**3**). Gutsche showed by nmr analysis that the nitrile isolated in the procedure of Jones was in fact not **10** but rather the isomer **11** (see Chart I). This meant that subsequent reduction gave **13**, not **12**, and debenzylation led to 5-aminomethyl-2-methylimidazole (**14**) rather than to 2-isohistamine (**3**). Since **14** is a benzylamine and not an aminoethyl derivative, it is not surprising that it showed no histamine-like activity.

Although the rearrangement that occurred in the cyanide reaction with the chloride **7** to yield **11** was unexpected, it is not without explanation or precedent. Ionization of **7** would give the resonance hybrid [**8a** ↔ **8b**], which with cyanide ion could react at either the "normal" benzylic position or at the 5 position to give the nitrile **10** or its isomer **11**, respectively. Analogy for this dichotomy is found in the similar behavior of furfuryl chloride, which with cyanide gives either 2-cyano-

(1) After this manuscript was completed an independent synthesis of 2-isohistamine was reported in a preliminary communication by G. J. Durant, M. E. Foottit, C. R. Ganellin, J. M. Loynes, E. S. Pepper, and A. M. Roe, *Chem. Commun.*, 108 (1968).

(2) (a) R. G. Jones, *J. Amer. Chem. Soc.*, **71**, 383 (1949); (b) *ibid.*, **71**, 3994 (1949); (c) *ibid.*, **74**, 4207 (1952); (d) R. G. Jones, E. C. Kornfeld, and K. C. McLaughlin, *ibid.*, **72**, 3539 (1950); (e) *ibid.*, **72**, 4526 (1950); (f) R. G. Jones and M. J. Mann, *ibid.*, **75**, 4048 (1953); (g) R. G. Jones and K. C. McLaughlin, *ibid.*, **71**, 2444 (1949); (h) R. G. Jones and K. C. McLaughlin, *J. Org. Chem.*, **19**, 1428 (1954); (i) H. M. Lee and R. G. Jones, *J. Pharmacol. Exp. Ther.*, **95**, 71 (1949); (j) T. M. Lin, R. S. Alphin, F. G. Henderson, and K. K. Chen, *ibid.*, **134**, 88 (1961); (k) T. M. Lin, R. S. Alphin, F. G. Henderson, D. N. Benslay, and K. K. Chen, *Ann. N. Y. Acad. Sci.*, **99**, 30 (1962); (l) T. M. Lin, F. G. Henderson, K. K. Chen, and D. N. Benslay, *Proc. Intern. Pharmacol. Meeting, 1st, Stockholm, 1961*, **7**, 351 (1962); (m) C. Ainsworth, *J. Amer. Chem. Soc.*, **75**, 5728 (1953); (n) *ibid.*, **79**, 5242 (1957); (o) C. Ainsworth and R. G. Jones, *ibid.*, **75**, 4915 (1953); (p) *ibid.*, **76**, 3172 (1954); (q) *ibid.*, **76**, 5651 (1954); (r) *ibid.*, **77**, 621 (1955).

(3) Histalog®, betazole hydrochloride, Lilly. C. B. Clayman, J. B. Kirsner, and H. Ford, *J. Amer. Med. Ass.*, **175**, 908 (1961).

(4) R. G. Jones in "Handbook of Experimental Pharmacology," Vol. XVIII/1, Springer-Verlag, Berlin, 1966, Chapter I.

(5) C. D. Gutsche and H. Voges, *J. Org. Chem.*, **32**, 2685 (1967).

CHART I

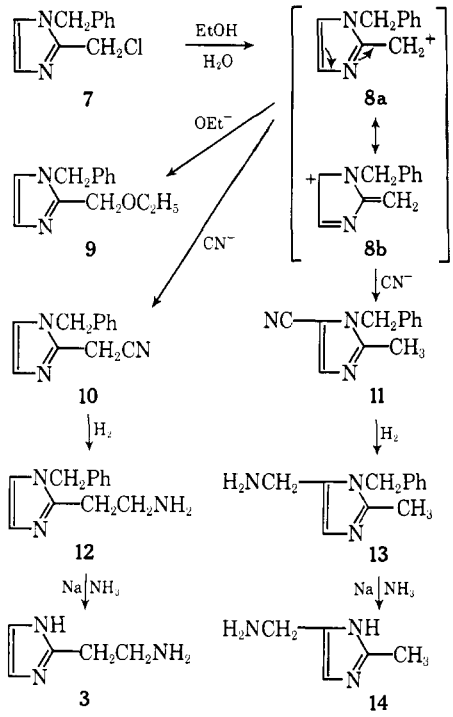
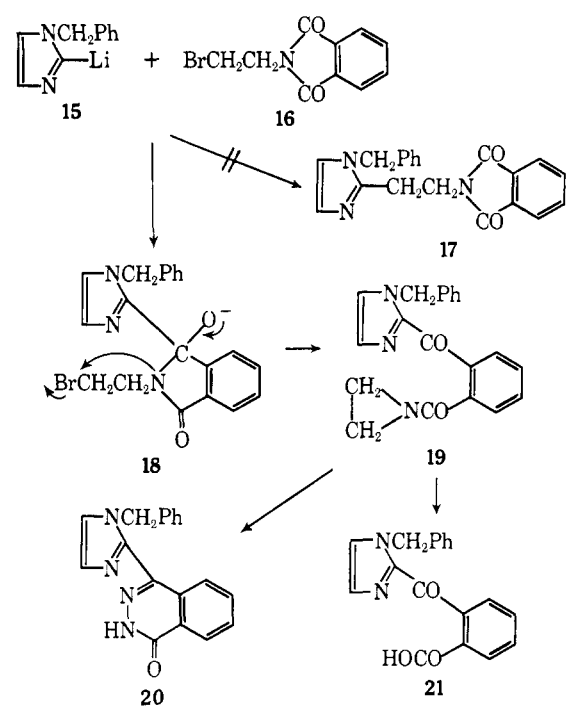


CHART II



methylfuran or 2-cyano-5-methylfuran depending upon conditions.[6]

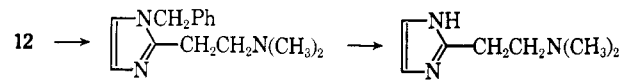
Since authentic 2-isohistamine (**3**) was, therefore, unknown, it became the objective of the present work to synthesize this compound and to examine its pharmacology.

Initial attempts in this direction were made using the 2-lithio derivative of 1-benzylimidazole (**15**).[7] This intermediate on reaction with N-(2-bromoethyl)phthalimide (**16**) gave a product of the expected composition (Chart II). However, the physical and chemical properties of the compound indicated that it was not the normal alkylation product **17**. Its structure was rather that of the aziridine amide **19**. Reaction of the lithium derivative **15** had taken place initially at the carbonyl group of the phthalimide **16** rather than at the bromine. The intermediate thus formed (**18**) lost bromide ion (arrows) to yield the amide **19**.[8] Hydrazinolysis of the amide **19** afforded the phthalazinone **20**, while acid hydrolysis cleaved the amide to the benzoic acid derivative **21**.

Since this approach was abortive, we reexamined the original cyanide reaction on 1-benzyl-2-chloromethylimidazole (**7**) (Chart I). When this reaction was carried out according to the procedure of Jones[2a] (KCN in aqueous–ethanol), nmr analysis indicated that the mixture contained *three* products. *Both* of the isomeric nitriles **10** and **11** were present in about equal quantity, and about 5% of the ethyl ether **9** was also produced. Fractionation of the picrate salts afforded only the rearranged or "abnormal" nitrile **11** (22%). Thus, although the Jones procedure gave significant yields of the desired nitrile **10**, only the "abnormal" product **11** was originally isolated. Of even greater interest was the subsequent observation that reaction of the chloride **7** with sodium cyanide in dimethyl sulfoxide gave *only* the "normal" nitrile **10** in 86% yield. This key intermediate thus became readily available for further transformations.

Debenzylation of **10** gave 2-cyanomethylimidazole, while hydrogenation, catalyzed by Raney nickel, led to the amine (**12**) (Chart I). The latter compound on debenzylation then gave the long-sought 2-isohistamine (**3**).

With our primary objective thus in hand, we used standard procedures to convert **12** also to the dimethyl derivatives **22** and **23**.



Finally, it seemed pertinent to restudy the synthesis of 2-(2-aminoethyl)-1-methylimidazole (**26**) as reported by Jocelyn.[9] In this case a similar rearrangement was possible. When 2-chloromethyl-1-methylimidazole (**24**) was caused to react with cyanide in aqueous–ethanol, the product was a mixture of nitriles **25** and **27** in a ratio of about 2:1 (Chart III). Picrate salt fractionation in this instance gave only the "normal" isomer **25**; therefore, Jocelyn's structure for **26** seems secure. When dimethyl sulfoxide was employed in the cyanide reaction, only **25** (and no **27**) was produced.

Pharmacology.—The results of tests using standard assay procedures suggest that 2-isohistamine resembles histamine in its pharmacological properties. The addition of isohistamine to a bath containing a strip of guinea pig ileum caused a contraction of the muscle. The time course of this response was very similar to

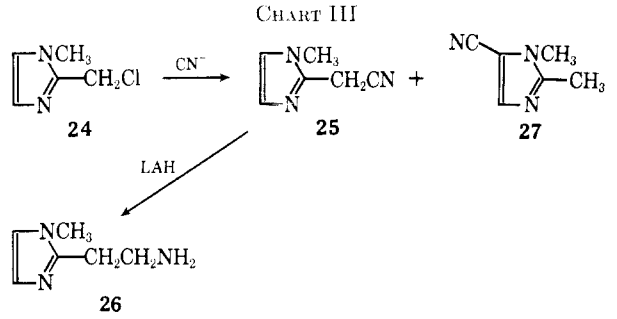
(6) K. Y. Novitskii, K. Gresl, and Y. K. Yurev, *Khim. Geterotsikl. Soedin., Akad. Nauk Latv. SSR*, 829 (1966).

(7) (a) A. M. Roe, *J. Chem. Soc.*, 2195 (1966); (b) P. E. Iversen and H. Lund, *Acta Chem. Scand.*, **20**, 2649 (1966).

(8) The nmr spectrum of **19** at 100 Hz in $CDCl_3$ shows nonequivalence of the benzyl methylene hydrogens (δ_A 5.04 and δ_B 4.95 ppm, J_{AB} = 15.5) as well as of all four protons of the aziridine ring (δ_C 4.36, δ_D 4.36, δ_E 4.07, and δ_F 3.15 ppm; J_{EF} = 10.5; E and F are each coupled by about 6 and 7 cps to both C and D). This observation requires hindered rotation about the amide bond and at least one other exocyclic bond.

(9) (a) P. C. Jocelyn, *J. Chem. Soc.*, 3305 (1957); (b) P. C. Jocelyn, *Arch. Int. Pharmacodyn. Ther.*, **113**, 251 (1958).

CHART III



that encountered when the same muscle was treated with histamine. Rough quantitation of the data suggests that it takes about 1000 times as much isohistamine to achieve this response. The maximal response of the muscle to histamine or isohistamine was, however, of the same magnitude. The depressor response in cats anesthetized with chloralose to the intravenous injection of either isohistamine or histamine were similar. A dose of 300 μg/kg of isohistamine was roughly equivalent to 0.3 μg/kg of histamine. In both these preparations, mixtures of histamine and isohistamine were additive in activity. Pretreatment with diphenhydramine, a classical antihistaminic agent, markedly reduced the response to both histamine and isohistamine.

Isohistamine was given to dogs with a Heidenhain vagally denervated pouch under basal conditions at doses of 1, 2, 5, and 10 mg/kg iv. In no instance was isohistamine alone able to stimulate HCl secretion. Histamine in doses of 2 μg/kg iv consistently caused an increase in volume and acidity of gastric secretion.

In one Heidenhain dog and two dogs with a Heidenhain pouch and an innervated stomach fistula, isohistamine was given after a steady-state HCl secretion, induced by histamine, was established for at least three successive 15-min control periods. The HCl output in the three periods following injection of isohistamine was compared with that prior to administration of isohistamine, and the results indicate that at all the dose levels described, there was no clear trend of an effect of the molecule on the acid-producing machinery. From these 20 observations we are led to believe that isohistamine does not have the structural requirements necessary for the triggering of HCl production by the parietal cells.[2k]

Thus, it would appear that isohistamine, like the thiazole analog of histamine (**5**),[2k] can effect an increase in smooth muscle tone while being relatively inactive as a secretory agent. Therefore, *two* nitrogen atoms, one α and one β to the side-chain position, appear necessary for gastric secretory activity.

Experimental Section[10]

2-(2-Aziridinocarbonylbenzoyl)-2-benzylimidazole (19).—To a stirred solution of 90 g of 15% butyllithium–hexane in 200 ml of dry Et_2O, under N_2, was added gradually a solution of 26.4 g of 1-benzylimidazole[7] in 500 ml of Et_2O. The resulting mixture was stirred at room temperature for 2 hr. A solution of 42.5 g of N-β-bromoethylphthalimide (**16**) in 1 l. of C_6H_6 was then added dropwise with continued stirring. Stirring was maintained for 2 hr, after which the reaction mixture was allowed to stand overnight. Excess dilute HCl was then added with stirring, and the aqueous layer was separated and made basic with NaOH solution. The product was extracted with C_6H_6, and the extracts were dried ($MgSO_4$). The solvent was distilled *in vacuo*, leaving a dark oil from which the product crystallized slowly: yield 5.4 g, mp 142–144°, ir 5.83 μ (CO). A sample was recrystallized from C_6H_6–Et_2O. *Anal.* ($C_{20}H_{17}N_3O_2$) C, H, N.

The hydrochloride salt was obtained from EtOH–Et_2O; mp 200–203°. *Anal.* ($C_{20}H_{17}N_3O_2 \cdot HCl$) C, H, N.

4-(1-Benzyl-2-imidazolyl)-1(2H)-phthalazinone (20).—A mixture of 1.0 g of the amide **19** and 5.0 ml of hydrazine hydrate was heated on the steam bath for 16 hr. Excess hydrazine was evaporated *in vacuo*, and the residual product was taken up in H_2O, filtered, and washed with H_2O; yield 0.78 g; mp 183–185°; ir, 3.97 (NH), 6.00 μ (CO).

A sample was recrystallized from DMF–MeOH–H_2O. *Anal.* ($C_{18}H_{14}N_4O$) C, H, N.

2-(1-Benzyl-2-imidazolylcarbonyl)benzoic Acid (21).—A mixture of 1.0 g of the amide and 40 ml of concentrated HCl was heated under reflux for 24 hr. The solution was concentrated to dryness *in vacuo*, and the residue was taken up in H_2O. The product was filtered and washed with H_2O; yield 0.66 g, mp 161–163°. A sample was recrystallized from EtOH. *Anal.* ($C_{18}H_{14}N_2O_3$) C, H, N, O.

Reaction of 1-Benzyl-2-chloromethylimidazole Hydrochloride with Cyanide in Aqueous Ethanol.[2a]—To a solution of 9 g of KCN in 10 ml of H_2O, cooled in an ice bath, was added dropwise (10 min) with stirring a mixture of 3.7 g of 1-benzyl-2-chloromethylimidazole hydrochloride in 25 ml of EtOH. Stirring was continued at 0° for 0.5 hr and then at 25° for 2 hr. The mixture was concentrated to dryness *in vacuo*, and the residue was taken up in CH_2Cl_2. The resulting mixture was washed several times with H_2O and dried ($MgSO_4$, Al_2O_3), and the solvent was evaporated. The crude product (2.77 g) was shown by nmr assay to be a mixture of the isomeric nitriles **10** and **11** in about equal proportion together with about 5% of the ether **9**. Picrate fractionation of the mixture by the method of Jones[2a] gave pure 1-benzyl-5-cyano-2-methylimidazole (**33**), mp 119–120°. *Anal.* ($C_{12}H_{11}N_3$) C, H, N.

1-Benzyl-2-cyanomethylimidazole (10).—Dry, powdered NaCN (40 g) was added to 320 ml of dry DMSO with stirring. 1-Benzyl-2-chloromethylimidazole hydrochloride[2a] (40 g) was then added in portions with stirring during about 5 min. The temperature was kept below 45° by brief cooling, and then it was maintained at 40° for 1 hr. The reaction mixture was diluted with 1 l. of CH_2Cl_2, and the resulting solution was washed four times with 800-ml portions of H_2O and dried ($MgSO_4$, Al_2O_3), and most of the solvent was distilled *in vacuo*. A few volumes of petroleum ether (bp 60–70°) were added to the residue, and the product was filtered and washed with petroleum ether; yield 28 g (86%), mp 101–103°. A sample was recrystallized either from MeOH–Et_2O or from C_6H_6–petroleum ether; mp 102.5–103.5°. *Anal.* ($C_{12}H_{11}N_3$) C, H, N. A mixture melting point with the isomeric nitrile **11**[2a] was 83–90°. The hydrochloride salt recrystallized from EtOH had mp 196–202°. *Anal.* ($C_{12}H_{11}N_3 \cdot HCl$) C, H, Cl, N.

1-Benzylimidazole-2-acetamide.—Crude 1-benzyl-2-cyanomethylimidazole was dissolved in EtOH and excess dry HCl was added. The solution was evaporated to dryness, and the residue was made alkaline with aqueous NaOH. The product was extracted with CH_2Cl_2, the extract was dried ($MgSO_4$), solvent was distilled, and the product was crystallized from EtOH; mp 123–126°, ir 5.96 μ (CO). *Anal.* ($C_{12}H_{13}N_3O$) C, H, N.

1-Benzyl-2-ethoxymethylimidazole (9).—To a solution of 1.12 g of sodium in 65 ml of absolute EtOH, cooled in ice, was added slowly with stirring 2.43 g of 1-benzyl-2-chloromethylimidazole hydrochloride. The ice bath was removed, and stirring was continued for 2.5 hr. The reaction mixture was evaporated to dryness *in vacuo*, and the residue was taken up in CH_2Cl_2. The solution was washed three times with H_2O. The washed mixture was dried ($MgSO_4$, Al_2O_3), and the solvent was distilled. The crude product was an oil, 1.9 g (88%). It was converted to the picrate in EtOH. The salt was recrystallized from EtOH–Et_2O, mp 109.5–111°. *Anal.* ($C_{19}H_{19}N_5O_8$) C, H, N.

2-(2-Aminoethyl)-1-benzylimidazole (12) Dihydrochloride.—1-Benzyl-2-cyanomethylimidazole (**10**), 20 g, was reduced at 36 atm of hydrogen pressure at 80° during 4 hr in a mixture of 225 ml of EtOH and 100 ml of liquid NH_3. Raney nickel (4 g) was used as catalyst. The catalyst was filtered, and the solvents were

(10) Melting points are corrected and were determined on a Mel-Temp apparatus. Infrared and nmr spectra were recorded for all compounds. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values.

distilled. The crude product was dissolved in 500 ml of 1:1 C_6H_6–Et_2O, and excess dry HCl was used to prepare the dihydrochloride salt, which was crystallized from 75 ml of EtOH; yield 22 g (79%), mp 158–160°. The pK_a in 66% DMF was 4.5 and 9.1. *Anal.* ($C_{12}H_{15}N_3 \cdot 2HCl$) C, H, N.

2-(2-Aminoethyl)imidazole (3) Dihydrochloride.—2-β-Aminoethyl-1-benzylimidazole dihydrochloride, 5.48 g, was dissolved in 100 ml of liquid NH_3, and to the solution were added with stirring small pieces of sodium until a blue color persisted (1.6–1.9 g). The mixture was stirred for 10 min, after which 2 g of NH_4Cl was added, and the NH_3 was allowed to evaporate completely. The residue was extracted with 50 ml of hot EtOH. Sodium chloride was filtered, and excess dry HCl was passed into the EtOH extract. The product was filtered and washed with EtOH and Et_2O; yield 2.82 g (76%). It was recrystallized from 50 ml of 1:4 H_2O–EtOH; mp 265–266°; pK_a in 66% DMF was 5.4 and 9.3. *Anal.* ($C_5H_9N_3 \cdot 2HCl$) C, H, Cl, N.

2-Cyanomethylimidazole.—To a solution of 8.85 g of 1-benzyl-2-cyanomethylimidazole (**10**) in 100 ml of liquid NH_3 were added sodium pieces with stirring until a blue color persisted (2.6 g). The mixture was stirred for 10 min, after which 6.05 g of NH_4Cl was added, and the NH_3 was evaporated completely. The residue was extracted with hot EtOH, and the crude product (4 g) was obtained by concentrating the extract. The product was recrystallized from H_2O; mp 166.5–167.5°; pK_a in 66% DMF was 4.05 and 13.8. *Anal.* ($C_5H_5N_3$) C, H.

1-Benzyl-2-(2-dimethylaminoethyl)imidazole (22).—2-(2-Aminoethyl)-1-benzylimidazole dihydrochloride (5.0 g) was converted to the free base using 50% NaOH. The amine was extracted with C_6H_6–Et_2O, and the solution was dried over KOH. Removal of the solvents left 3.7 g of amorphous base that was then dissolved in 150 ml of EtOH and 50 ml of 37% formaldehyde. The solution was hydrogenated for 20 hr at 3–4 atm hydrogen pressure using 1.5 g of 5% Pd–C. The catalyst was filtered, and the solvents were distilled *in vacuo*. The crude product was dissolved in CH_2Cl_2, and the solution was extracted with aqueous HCl. The extract was made basic (NaOH), and the product was reextracted into CH_2Cl_2. Concentration left 1.9 g of product as an oil. A dipicrate salt was prepared and recrystallized from Me_2CO, mp 180–185°. *Anal.* ($C_{14}H_{19}N_3 \cdot 2C_6H_3N_3O_7$) C, H, N. The same dimethyl derivative (**22**) was also prepared by methylation of the primary amine (**12**) with formaldehyde–formic acid.

2-(2-Dimethylaminoethyl)imidazole (23) Dihydrochloride.—The benzyl derivative above (**22**), 1.6 g, was dissolved in 50 ml of liquid NH_3, and sodium pieces were added with stirring until a blue color persisted. After 15 min 0.37 g of NH_4Cl was added, and the NH_3 was evaporated completely. The residue was extracted with hot EtOH, excess dry HCl was added, and the solvent was distilled. The crude product was recrystallized from EtOH–Me_2CO; yield 0.6 g, mp 213–216°. *Anal.* ($C_7H_{13}N_3 \cdot 2HCl$) C, H, N.

Acknowledgment.—We wish to thank Dr. W. W. Hargrove and associates for the microanalyses and physical measurements and Mr. E. Lavagnino and associates and Mrs. Barbara Spry for preparing some of the intermediates. We are indebted to Dr. R. G. Jones for stimulating our interest in this problem.

Metabolism of Brompheniramine

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A. H. Robins Company, Inc., Research Laboratories, Richmond, Virginia

Received March 28, 1968

The metabolism of brompheniramine-^{14}C has been investigated in the dog and the human. Six metabolites have been identified and quantitated in dog urine and five of these have also been found in human urine. These account for approximately 50% of the dose in each species. Nine brompheniramine-related compounds have been synthesized as possible metabolites. The following were found to be present in the urine after an oral dose: unchanged brompheniramine, the mono- and didemethylated derivatives, 2-{*p*-bromo-α-[2-(dimethylamino)-ethyl]benzyl}pyridine N′-oxide (not found in the human), β-(*p*-bromophenyl)-2-pyridinepropionic acid, and its glycine conjugate.

Brompheniramine maleate is an antihistamine used extensively for the prevention and control of allergic reactions. Chemically it is 2-{*p*-bromo-α-[2-(amino)-ethyl]benzyl}pyridine maleate.

The metabolism of this drug has not been presented previously and it is the purpose of this report to submit the findings from a study of its metabolism in dogs and humans. Chlorpheniramine, the chloro derivative of pheniramine, is metabolized to the mono- and didemethylated derivatives.[1] Corresponding metabolites have been found to occur from brompheniramine administration and, in addition, other metabolites have been identified and quantitated.

Experimental Section

The experimental part of this study involved two phases: synthesis of metabolites and identification of these metabolites in the urine of dogs and humans given oral doses of brompheniramine maleate.

Preliminary investigation by tlc of the base extractables of urine, from dogs that had received brompheniramine, indicated that unchanged drug and at least two additional related compounds were present. Brompheniramine-^{14}C was then synthesized so that further investigation of these and other metabolites could be carried out. A number of related compounds were also synthesized as possible metabolites.

Metabolism Studies.—Oral doses of 7.5 mg/kg of brompheniramine-^{14}C were administered to mongrel dogs weighing 8.5–10 kg. Urine and feces were collected for 96 hr and stored in the freezer until analyzed.

Normal, male, human subjects were given four oral doses of brompheniramine-^{14}C of 8.0 mg each over a period of 12 hr. Following the first dose and continuing for 48 hr after the final dose, each urine void was collected in separate containers. After that time, pooled 24-hr specimens were collected for 5 days. Feces were collected for 3 days.

Analytical Methods. Isotopes.—Radioactivity in liquid samples was measured using a Packard liquid scintillation spectrometer, Series 314E. The aqueous phosphor consisted of toluene–dioxane–EtOH (4:4:2.4) containing 80 g of naphthalene and 5 g of PPO/l.

Feces were counted after oxidation to CO_2. They were dried in a vacuum oven at 55° and ground in a blender. The dried, ground samples were combusted in a combustion furnace by a modification of the method described by Peets, *et al.*[2] The liberated CO_2 was counted in a phosphor consisting of 4 g of PPO/l. of toluene.

Chemical Analysis.—The chemical method of analysis involved the oxidation of brompheniramine to *p*-bromophenyl 2-pyridyl ketone and its subsequent determination by glpc, using chlor-

(1) E. Peeto, R. Weinstein, and S. Symchlwicy, *Pharmacologist*, **9**, 216 (1967).

(2) E. A. Peets, J. R. Florini, and D. A. Buyske, *Anal. Chem.*, **32**, 1465 (1960).