62. *A New Route to Iminazoles : Synthesis of 2-ω-Aminoalkyl Derivatives of 4-Methyliminazole.*

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A new synthesis of the iminazole heterocyclic system by condensation of iminoethers with α-aminocarbonyl compounds is described.* 2-ω-Aminoalkyl derivatives of 4-methyliminazole have been prepared from ω-acylamidoalkylcarboxylic iminoethers and aminoacetone followed by deacylation of the 4-methyl-2-ω-aminoalkyliminazoles thus produced.

These analogues of histamine were prepared for examination for vaso-dilating and broncho-constricting activity.

DIFFICULTIES associated with the preparation of histamine—4-(2-aminoethyl)iminazole—led to a search for more accessible analogues which might possess similar pharmacological properties. 1-(2-Aminoethyl)iminazole has been prepared by Lur'e, Kuleshova, and Kochetov (*J. Gen. Chem. Russia*, 1939, **9**, 1933), but since this is an *N*-substituted iminazole it is not a true analogue of histamine. Accordingly methods were devised for the synthesis of the unknown 2-(2-amino-ethyl)iminazole and its homologues ; availability of intermediates limited the work in the first instance to the preparation of the corresponding derivatives of 4-methyliminazole.
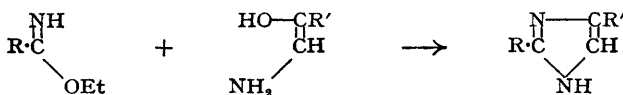
Attention was first directed to the classical method of forming the iminazole system by condensation of amidines with α-halogeno-carbonyl compounds (Kunckell, *Ber.*, 1901, **34**, 637) but, under all the varied reaction conditions employed, benzamidoacetamidine and chloro-acetone failed to give the desired iminazole. Similarly interaction of benzamidoacetamidine with αβ-dibromoethylene in presence of an acid acceptor did not yield the iminazole ; contrast the condensation of amidines and trimethylene dibromide with production of dihydropyrimidines (Pinner, *Ber.*, 1893, **26**, 2122, 2124).

The synthesis of the pyrimidine nucleus by condensation of (aminomethylene)malononitrile and ethyl (aminomethylene)cyanoacetate with (i) thioamides (Wuest and Hoffer, U.S.P. 2,271,503 ; Kenner, Lythgoe, Todd, and Topham, *J.*, 1943, 388 ; B.P. 546,624) and with (ii) iminoethers
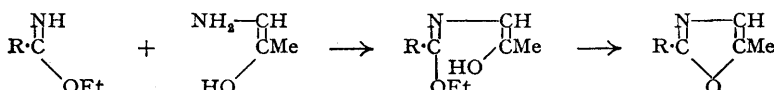
* The new synthesis of iminazoles was developed in 1946 and forms the subject matter of B.P. 27,427/46 (filed September 12th, 1946).

(B.P. 486,414; Hromatka, D.R.-P. 667,990) and also the synthesis of iminazolines by condensation of iminoethers with ethylene diamine (B.P. 529,055; F.P. 671,362; Klaver and Urech, *Helv. Chim. Acta*, 1944, **27**, 1762) suggested two new possible routes to the iminazole system by substitution of an α-aminocarbonyl for the α-aminomethylene compound. It was found that, while the aminoacetone failed to react in the designed manner with benzamidothioacetamide, it condensed satisfactorily with benzamidoacetiminoethyl ether under carefully controlled conditions to yield *4-methyl-2-benzamidomethyliminazole*. Similarly, aminoacetone and β-benzamidopropioniminoethyl ether yielded *4-methyl-2-(2-benzamidoethyl)iminazole*.

It would appear that the synthetic route

$$\underset{\substack{\diagdown \\ \text{OEt}}}{\overset{\substack{\text{NH} \\ \|}}{\text{R·C}}} \quad + \quad \underset{\substack{\diagup \\ \text{NH}_2}}{\overset{\substack{\text{HO--CR'} \\ | \\ \text{CH}}}{}} \quad \longrightarrow \quad \underset{\substack{\diagdown \quad \diagup \\ \text{NH}}}{\overset{\substack{\text{N---CR'} \\ \| \quad | \\ \text{R·C} \quad \text{CH}}}{}}$$

is novel and of general applicability for the preparation of 2-substituted iminazoles; the requisite iminoethers R·C(:NH)·OEt are readily accessible from the cyanides RCN and various α-aminocarbonyl compounds, including aminoacetaldehyde, are available in the form of their salts. Condensation of α-aminocarbonyl compounds and iminoethers takes place only between the free bases and it is necessary to employ anhydrous conditions to restrict formation of amide from the iminoether. In the two cases investigated the yields of the desired iminazoles were of the order of 40%, and it is probable that the factors which reduce yield are (i) interaction of the iminoether with the solvent (alcohol) to form ortho-ester, (ii) self-condensation of the aminoacetone base to give 2 : 5-dimethyl-1 : 4-dihydropyrazine, and (iii) condensation of the aminoacetone with the iminoether by elimination of ammonia and production of the *N*-acetonyliminoether (reverse condensation) which by loss of alcohol can cyclise to the 2-substituted oxazole (cf. Cornforth, *J.*, 1947, 96).

$$\underset{\substack{\diagdown \\ \text{OEt}}}{\overset{\substack{\text{NH} \\ \|}}{\text{R·C}}} \quad + \quad \underset{\substack{\diagup \\ \text{HO}}}{\overset{\substack{\text{NH}_2\text{--CH} \\ | \\ \text{CMe}}}{}} \quad \longrightarrow \quad \underset{\substack{\diagdown \quad \diagup \\ \text{HO} \quad \text{OEt}}}{\overset{\substack{\text{N----CH} \\ \| \quad | \\ \text{R·C} \quad \text{CMe}}}{}} \quad \longrightarrow \quad \underset{\substack{\diagdown \quad \diagup \\ \text{O}}}{\overset{\substack{\text{N----CH} \\ \| \quad | \\ \text{R·C} \quad \text{CMe}}}{}}$$

In order to limit formation of dihydropyrazine it was found expedient to mix the stable aminoacetone hydrochloride (1 mol.) with the iminoether base (1 mol.) and release the base of the former by the portionwise addition of alcoholic sodium ethoxide (1 mol.). Even at temperatures well below 0°, however, considerable quantities of ammonia were developed signifying progress of the " reverse " condensation.

Isolation of the 4-methyl-2-benzamidoalkyliminazoles from the reaction mixture was facilitated by their solubility in cold dilute mineral acid and their insolubility in cold acetone. Hydrolysis was effected by boiling 5N-hydrochloric acid to give *4-methyl-2-aminomethyliminazole* and *4-methyl-2-(2-aminoethyl)iminazole* which were isolated in the form of their *dihydrochlorides*. In both cases the free base was a viscid oil which resisted distillation and analysis owing to hygroscopicity and affinity for atmospheric carbon dioxide. By condensation of the free bases with 5 : 8-dichloro-3-methoxyacridine in the presence of phenol they were converted respectively into (8-*chloro-3-methoxy-5-acridylamino*)-(4-*methyl-2-iminazolyl)methane* and 1-(8-*chloro-3-methoxy-5-acridylamino*)-2-(4-*methyl-2-iminazolyl)ethane* which are both well-defined crystalline compounds suitable for analysis. Attention is drawn to the utility of 5 : 8-dichloro-3-methoxyacridine as a reagent for identifying primary amines since the formation of the derivative is facile, the weight is increased, and the products are usually well defined with reasonably high melting points containing both halogen and nitrogen. The iminazole nucleus appears not to condense with the reagent under the conditions selected.

The physiological properties of these new analogues of histamine will be reported elsewhere.

EXPERIMENTAL.

4-Methyl-2-benzamidomethyliminazole.—Benzamidoacetiminoethyl ether hydrochloride (Goldberg and Kelly, *J.*, 1947, 1374; 128 g.; 0·5 mol.) was added portionwise during 10 minutes to a stirred solution of sodium (0·65 mol.; 15·2 g.) in anhydrous alcohol (400 c.c.) at —5°. After a further 15 minutes a solution of aminoacetone hydrochloride (0·5 mol.; 54 g.) in anhydrous alcohol (200 c.c.) was added dropwise during ½ hour, the mixture stirred at —5° for a further 1 hour and then allowed to stand at room temperature for 24 hours. The mixture was again cooled to —5° and a solution of sodium (7·7 g.; 0·35 mol.) in anhydrous alcohol (150 c.c.) added with stirring during 1 hour. After keeping at room temperature for 3 days the insoluble material was removed and the filtrate evaporated to dryness at reduced pressure. The gummy residue was dissolved in boiling acetone (100 c.c.), the solution filtered (charcoal) and allowed

to stand on ice, 4-*methyl-2-benzamidomethyliminazole* separating as a microcrystalline powder; this was collected, triturated with cold acetone (60 c.c.), drained, and dried at low temperature (yield, 32·5 g.; m. p. 184—186°). The acetone mother-liquors and washings were evaporated to dryness at reduced pressure, the residual gum dissolved in cold 2N-hydrochloric acid (120 c.c.) and the solution kept on ice for several hours. The crystalline precipitate (A) was removed and the filtrate basified with saturated aqueous sodium carbonate. The oil which separated crystallised on keeping for 48 hours in the ice chest; this, on recrystallisation from boiling acetone (50 c.c.), gave a further amount (13 g.) of 4-methyl-2-benzamidomethyliminazole, m. p. 184—186° (total yield, 45·5 g.; 42%). For analysis a sample was recrystallised from acetone and obtained in colourless prisms, m. p. 185—186° (Found : C, 66·8; H, 6·1; N, 19·8. $C_{12}H_{13}ON_3$ requires C, 67·0; H, 6·0; N, 19·5%).

The *by-product* which separated from the cold HCl solution (A) crystallised from acetic acid in colourless plates (6·5 g.), m. p. 238—240°, which were insoluble in cold dilute mineral acid and in alkali (Found : N, 12·9. $C_{12}H_{12}O_2N_2$ requires N, 13·0%). This was not further investigated.

4-*Methyl-2-aminomethyliminazole.*—The foregoing benzamido-compound (32·5 g.) was refluxed with 5N-hydrochloric acid (320 c.c.) for 4 hours, the solution chilled, the precipitate of benzoic acid removed, and the filtrate evaporated to dryness at 50° at reduced pressure. The residue was dissolved in the minimum amount of boiling water (15 c.c.), alcoholic hydrogen chloride (4% w/w; 200 c.c.) added, and the solution stood in the ice-chest; 4-*methyl-2-aminomethyliminazole dihydrochloride* (21 g.; 75%) slowly separated in large colourless prisms, m. p. 248—250° (Found : C, 31·9; H, 5·6; N, 24·0; Cl, 38·2. $C_5H_9N_3,2HCl$ requires C, 32·6; H, 6·0; N, 22·8; Cl, 38·6%).

The foregoing dihydrochloride (15·3 g.) was refluxed with a solution of sodium (3·5 g.) in anhydrous methyl alcohol (60 c.c.) for 15 minutes. After sodium chloride and solvent had been removed 4-methyl-2-aminomethyliminazole was obtained in theoretical yield as a gum. On attempted distillation the bulk decomposed; on mixing an alcoholic solution of the small distillate with a slight excess of alcoholic hydrogen chloride, the dihydrochloride separated in colourless prisms, m. p. 246° alone and in admixture with the sample described below.

A mixture of 2-aminomethyl-4-methyliminazole dihydrochloride (0·94 g.) was refluxed with a solution of sodium (0·23 g.) in anhydrous alcohol (20 c.c.) for 5 minutes, the sodium chloride removed, and a hot solution of *p*-nitrobenzoic acid (3·0 g.) in alcohol (30 c.c.) added; on cooling, 4-*methyl-2-aminomethyl-iminazole di-p-nitrobenzoate* (2·2 g.) separated. For analysis it was recrystallised twice from alcohol and obtained in slender needles, m. p. 190—192°, with sintering at 186° (Found : C, 51·0; H, 4·2; N, 16·0. $C_5H_9N_3,2C_7H_5O_4N$ requires C, 51·2; H, 4·3; N, 15·7%).

(8-*Chloro-3-methoxy-5-acridylamino*)-(4-*methyl-2-iminazolyl*)*methane.*—A solution of 5 : 8-dichloro-3-methoxyacridine (7·5 g.) in phenol (50 g.) was heated to 115° for 15 minutes and then a solution of 4-methyl-2-aminomethyliminazole (4·3 g.) in phenol (30 c.c.) added with shaking. The solution was heated to 115° (internal) for 6 hours, cooled, and poured into an excess of anhydrous ether. After standing overnight the yellow precipitate (11 g.) was collected, dried over sulphuric acid, and then shaken with an excess of cold 2·5N-sodium hydroxide and glass beads for 2 hours. The free base (9·0 g.) was collected, washed well with cold water until free from alkali, and crystallised twice from dilute alcohol. The *derivative* separated in small yellow tablets, m. p. 150—154° (Found : N, 15·7; Cl, 10·0. $C_{19}H_{17}ON_4Cl$ requires N, 15·9; Cl, 10·1%).

4-*Methyl-2-*(2-*benzamidoethyl*)*iminazole.*—Crude β-benzamidopropioniminoethyl ether hydrochloride (Goldberg and Kelly, *loc. cit.*), from β-benzamidopropionitrile (20 g.), was suspended in benzene (60 c.c.), and this suspension added rapidly to a stirred solution of sodium (3·6 g.) in anhydrous alcohol (80 c.c.) at −5°. After a further 10 minutes a solution of aminoacetone hydrochloride (10·8 g.) in anhydrous ethyl alcohol (150 c.c.) was added dropwise during a period of 1½ hours with rapid stirring at −5°. The mixture was left for 24 hours on ice, cooled again to −5°, and a solution of sodium (1·0 g.) in anhydrous alcohol (30 c.c.) added with stirring; the suspension was then kept on ice for 48 hours and finally for a further 24 hours at room temperature. The precipitate of sodium chloride was removed, the filtrate distilled to dryness at reduced pressure at 30° and the residue dissolved in 2N-hydrochloric acid (50 c.c.). After being kept in the ice-chest overnight the small precipitate was removed and the filtrate basified with concentrated aqueous sodium carbonate; the oil which precipitated crystallised on being kept at 0°. This was separated and redissolved in 2N-hydrochloric acid, the solution filtered, and the base reprecipitated with sodium carbonate solution. The solid thus obtained was ground with hot acetone (150 c.c.), the mixture kept on ice for 12 hours, and the undissolved microcrystalline 4-*methyl-2-*(2-*benzamidoethyl*)*iminazole* (7·2 g.; m. p. 204—206°) drained and dried at low temperature. A sample crystallised from a large volume of boiling acetone in small colourless needles, m. p. 206—208° (Found : C, 68·2; H, 6·5; N, 18·4. $C_{13}H_{15}ON_3$ requires C, 68·1; H, 6·5; N, 18·3%).

4-*Methyl-2-*(2-*aminoethyl*)*iminazole.*—The foregoing benzamido-compound (5 g.) was refluxed with 5N-hydrochloric acid (50 c.c.) for 4 hours. After being chilled, the benzoic acid (2·1 g.) was removed and the filtrate evaporated almost to dryness at reduced pressure. The residue was dissolved in the minimum amount of hot water (3 c.c.), alcoholic hydrogen chloride (2% w/w; 60 c.c.) added, and the solution chilled; 4-*methyl-2-*(2-*aminoethyl*)*iminazole dihydrochloride* (3·7 g.) separated in colourless plates, m. p. 260—262°. A sample for analysis crystallised from the same solvent in colourless plates, m. p. 262—264°, with sintering at 258° (Found : N, 22·2; Cl, 35·3. $C_6H_{11}N_3,2HCl$ requires N, 21·2; Cl, 35·8%).

The dihydrochloride (1·0 g.) was added to a solution of sodium (0·23 g.) in alcohol (25 c.c.). The precipitate of sodium chloride was removed and the filtrate mixed with a hot solution of *p*-nitrobenzoic acid (2·7 g.) in alcohol (25 c.c.) and refrigerated for 24 hours, 4-*methyl-2-*(2-*aminoethyl*)*iminazole di-p-nitrobenzoate* separating in large pale yellow transparent prisms, m. p. 164—166°. A sample recrystallised several times from alcohol had m. p. 180—182° (Found : C, 52·5; H, 4·5; N, 15·1. $C_6H_{11}N_3,2C_7H_5O_4N$ requires C, 52·3; H, 4·6; N, 15·3%).

1-(8-*Chloro-3-methoxy-5-acridylamino*)-2-(4-*methyl-2-iminazolyl*)*ethane.*—A solution of 5 : 8-dichloro-3-methoxyacridine (8·0 g.) and 4-methyl-2-(2-aminoethyl)iminazole (4·5 g.; isolated from the dihydrochloride in the manner described for the lower homologue) in phenol (80 g.) was heated at 112—115° (internal temp.) for 6 hours and then poured into excess of anhydrous ether. After standing overnight

the precipitate was collected, converted into the base by grinding with cold 2·5N-sodium hydroxide, and the *base* (9·0 g.) collected, washed free from alkali, and recrystallised three times from dilute pyridine. The product separated in yellow microcrystalline aggregates, m. p. 106—112° decomp. (Found in material dried over phosphoric oxide at 20°/1 mm. for 30 days : N, 15·2; Cl, 9·6. $C_{20}H_{19}ON_4Cl$ requires N, 15·3; Cl, 9·7%).

Phthalimidoacetone.—The method described by Fourneau ("Organic Medicaments and their Preparation", trans. Silvester, 1925, p. 210) for the preparation of chloroacetone gave poor yields owing to the use of insufficient water and calcium carbonate. The following modification of the procedure gave consistent yields of 60—65% of redistilled monochloroacetone. Marble chips the size of grains of maize (500 g.; 5 mols.) were covered with industrial grade acetone (580 g.; 733 c.c.; 10 mols.) and the mixture heated to the boiling point. External heating was discontinued and a current of dry chlorine passed in through a sintered-glass gas distributor at a rate of 1·25—1·30 g. of chlorine per minute for 9½ hours during which time water (240 c.c.; 13·3 mols.) was added dropwise at a uniform rate. The reaction started rapidly and the heat generated was sufficient to maintain the reaction temperature at *ca.* 60° throughout. At the end of this period the marble had completely disappeared and the weight of the mixture had increased by 630 g., *i.e.* 86% of the theoretical. The mixture was cooled, water (200 c.c.) *immediately* added in order to prevent crystallisation of calcium chloride dihydrate, and the lower aqueous layer removed. The chloroacetone layer was washed with water (200 c.c.), dried overnight over calcium chloride, then for a further 3 hours over fresh calcium chloride, and distilled through an 8 in. Vigreux column. This gave the following fractions : (*a*) 185 g., b. p. 114°/745 mm.; (*b*) 525 g., b. p. 114—117°/745 mm., together with 30 g. of residue. Fraction (*a*) was redistilled to yield : (*aa*) 99 g., b. p. 114°/745 mm., and (*ab*) 77 g., b. p. 114—117°/745 mm., together with 6 g. of residue. Fractions (*b*) and (*ab*) were combined and refractionated to yield 564 g. of pure chloroacetone as a colourless oil, b. p. 116—118°/745 mm., after rejection of a head fraction of 15 g., b. p. 116°/745 mm. The uniformly high yields of phthalimidoacetone from this material indicate its purity.

Chloroacetone (92·5 g.), potassium phthalimide (150 g.), and xylene (160 c.c.) were heated at 125—130° (bath temp.) for 1½—2 hours. The xylene was removed by steam-distillation, the residual solid drained and dissolved in boiling alcohol (400 c.c.), and the small amount of inorganic material removed and washed into the filtrate with boiling alcohol (50 c.c.). The filtate was brought to the b. p., boiling water (360 c.c.) added, and the filtered (charcoal) solution allowed to cool. Phthalimidoacetone (138 g.) separated in flat pale yellow prisms, m. p. 118—120°.

Aminoacetone Hydrochloride (cf. Gabriel, *Ber.*, 1893, **26**, 2197; 1902, **35**, 3807).—Crude phthalimidoacetone (203 g.) was refluxed with 7N-hydrochloric acid (1250 c.c.) for 2 hours (oil-bath). The mixture was allowed to cool in order that phthalic acid could crystallise and then reheated to the reflux temperature for a further 2 hours. (If the solution was not cooled after the initial heating it was invariably found that the phthalic acid crystallised at the b. p. with considerable violence.) The mixture was cooled, the phthalic acid (180 g.) removed, and the filtrate evaporated to complete dryness at reduced pressure at 40—50°. The residue was heated with alcohol (200 c.c.) and 3N-alcoholic hydrogen chloride (20 c.c.) and the insoluble ammonium chloride rapidly filtered off and washed with boiling alcohol (50 c.c.) into the filtrate which was then evaporated again to complete dryness at reduced pressure at 50°. This treatment was repeated, the filtrate concentrated to small volume (*ca.* 90 c.c.), and the solution chilled. Addition of anhydrous ether (120 c.c.) with shaking effected rapid crystallisation of the aminoacetone hydrochloride which was immediately filtered off, washed with anhydrous ether, and dried in a vacuum over sulphuric acid (yield, 74 g. of nearly white needles, m. p. 80°).

Benzamidoacetone.—A solution of the foregoing amine hydrochloride (44 g.) in water (100 c.c.) was added dropwise during ¾ hour to a rapidly stirred mixture of sodium carbonate (44 g.), water (200 c.c.), and benzoyl chloride (60 c.c.) at 5—10°; during this period a solution of sodium carbonate (44 g.) in water (100 c.c.) was simultaneously added at such a speed that the pH of the mixture was maintained between 8·0 and 10·0. After the addition of a further amount of benzoyl chloride (6 c.c.) the mixture was stirred at room temperature for 4 hours and chilled, the solid collected, drained on porous pot, and extracted with boiling benzene (2 × 200 c.c.). Benzene was distilled from the filtrate until the solution had a volume of *ca.* 150 c.c., the latter cooled, diluted with ligroin (100 c.c.; b. p. 60—80°) and chilled. The benzamidoacetone rapidly separated as a mass of crystals which were collected and dissolved in benzene (225 c.c.) and the filtered solution chilled and diluted with ligroin (150 c.c.; b. p. 60—80°); the solution was seeded, diluted with a further amount of ligroin (50 c.c.), and allowed to stand overnight. The compound (36 g.) separated in glistening nacreous flakes, m. p. 84° (Found : N, 8·1. Calc. for $C_{10}H_{11}O_2N$: N, 7·9%). It is slightly soluble in water; at 30° the saturated aqueous solution contains *ca.* 7 g. of benzamidoacetone per litre; when this solution is stirred and saturated with sodium chloride the compound separates in nacreous flakes (4·8 g.).

The 2 : 4-*dinitrophenylhydrazone* separated from a mixture of aqueous alcohol, pyridine, and dioxan in small orange prisms, m. p. 218—220° (Found : N, 19·4. $C_{16}H_{15}O_5N_5$ requires N, 19·6%). It is soluble in pyridine but almost insoluble in alcohol.

The *thiosemicarbazone* separated from dilute alcohol in glittering colourless plates, m. p. 220—222° (Found : N, 22·4; S, 12·7. $C_{11}H_{14}ON_4S$ requires N, 22·4; S, 12·8%).

The *oxime* crystallised from boiling water in glittering colourless leaves, m. p. 132—134° (Found : N, 14·8. $C_{10}H_{12}O_2N_2$ requires N, 14·6%).

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