Potential Histidine Decarboxylase Inhibitors. II. 3-(4-Imidazolyl)-2-pyridine and Piperidinecarboxylates

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The synthesis of methyl 3-(4-imidazolyl)-2-pyridine (**12**) and piperidinecarboxylates (**13**) is described. Hydrolysates of these esters were found to be devoid of inhibitory activity against histidine decarboxylase. 3-Bromoacetyl-2-picoline (**2**) could be converted to 3-(4-imidazolyl)-2-picoline (**6**) by two different routes. Treatment of **6** with peroxide and acetic anhydride, followed by transesterification yielded the 2-hydroxymethyl pyridine (**9**). Oxidation of **9** followed by esterification gave the imidazole pyridine acid ester (**12**) which after hydrogenation afforded the imidazolylpiperidine ester (**13**).

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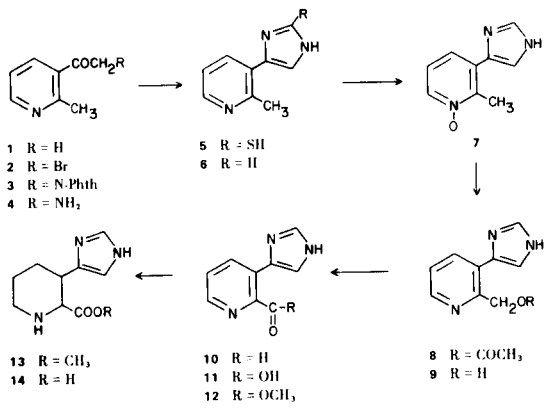
In the first paper (1) of this series, we reported the synthesis and enzyme inhibitory properties of some α- and β-alkyl substituted histidine analogs. As an extension of this work and that reported by Pages and Burger (2), we wished to assess the effect of linking the β-carbon and amino nitrogen of histidine *via* a pyridine or piperidine ring as in the imidazolyl pyridine or piperidine carboxylic acids (**11** and **14**). The synthesis of the respective esters (**12** and **13**) and measurement of the inhibitory effect of their hydrolysates on mammalian histidine decarboxylase is the subject of this communication.

3-Acetyl-2-picoline (**1**), the starting material for the synthesis (Scheme 1), was obtained *via* the condensation of propargaldehyde and 4-amino-3-buten-2-one (3). Bromination of **1** in a 48% hydrobromic-acetic acid mixture afforded the bromomethyl ketone (**2**) as the hydrobromide salt. Displacement of the bromide with potassium phthalimide in dimethyl formamide yielded the phthalimido ketone (**3**) which after acid hydrolysis gave the amino ketone (**4**) as the hydrochloride salt. Condensation of crude **4** with aqueous potassium thiocyanate gave the mercaptoimidazole (**5**) in a 10% yield from **3**.

Initial attempts to obtain the key intermediate pyridine acid (**11**) entailed direct oxidation of **5** with alkaline potassium permanganate. It was expected that the thiol would be oxidized to the sulfonate ion providing stabilization of the imidazole ring while further oxidative attack could take place on the pyridyl methyl group. Treatment of **5** with permanganate solution rapidly consumed the required amount for thiol oxidation, however, the more vigorous conditions required for further reaction caused oxidation of the imidazole ring to afford 2-methylnicotinic acid as the only isolable product.

Scheme I



Compound **5** was readily desulfurized by treatment with nickel in 2-methoxyethanol at 100° to yield the imidazole (**6**). A more convenient process for the preparation of **6** consisted of heating a formamide solution of the bromoketone (**2**) at 100° by the general procedure of Ressner *et al.* (4). The imidazole picoline (**6**) was then oxidized with hydrogen peroxide in acetic acid and the intermediate *N*-oxide (**7**) directly rearranged to the 2-pyridylacetate (**8**) by reaction with acetic anhydride at 100°. The ester moiety was removed by transesterification (sodium methoxide) in methanol to yield the crystalline hydroxymethyl compound (**9**).

The alcohol (**9**) was not affected by hot 6*N* nitric acid, however, 3 equivalents of potassium permanganate were tapidly taken up at room temperature, with subsequent persistence of the reagent color. Workup of the reaction followed by treatment with methanolic hydrogen chloride gave only a 2% yield of the imidazolyl picolinic ester (**12**) after purification by preparative thin layer chromatography. A more acceptable method for oxidation of **9** was the treatment with manganese dioxide in acetone. The intermediate aldehyde (**10**) was not observed and the oxidation proceeded directly to the acid (**11**), isolated and characterized as the methyl ester (**12**). Acid hydrosis of **12** regenerated the acid (**11**).

The ester (**12**) was hydrogenated in 0.1*N* hydrochloric acid over platinum oxide to give the piperidine ester (**13**). The ester (**13**) was saponified in dilute alkali and the liberated carboxylate (**14**) along with **11** was examined for inhibitory action (1) on mammalian histidine decarboxylase. Both **11** and **14** were completely inactive at a level of 10^{-4}*M*.

EXPERIMENTAL

3-Bromoacetyl-2-picoline Hydrobromide (**2**).

3-Acetyl-2-picoline (**1**) was prepared in 64% yield by the procedure of Pasedach and Seefelder (3). A solution of 26.6 g. (0.197 mole) of **1** in a medium containing 40 ml. of 48% hydrobromic acid and 40 ml. of acetic acid was treated over 30 minutes with 50 ml. (0.20 mole) of 4*M* bromine in acetic acid. After 15 hours, the white crystalline precipitate was collected by filtration and dried to afford 53.8 g. (92%) of **2** as the hydrobromide salt, m.p. 193° dec.

Anal. Calcd. for $C_8H_8BrNO \cdot HBr$: C, 32.6; H, 3.08; N, 4.75; Br, 54.2. Found: C, 32.7; H, 3.35; N, 4.69; Br, 53.9.

3-Phthalimidoacetyl-2-picoline (**3**).

To a stirred suspension of 1.48 g. (5.0 mmoles) of the hydrobromide salt of **2** in 50 ml. of dimethyl formamide was added 345 mg. (2.5 mmoles) of ground potassium carbonate to give a colorless solution. Potassium phthalimide (925 mg., 5.0 mmoles) was added and the mixture was heated 1 hour on the steam bath and partitioned between 50 ml. of water and 50 ml. of chloroform. The aqurous solution was extracted with another four 15-ml. portions of chloroform, and the combined organics were washed with 50 ml. of 10% sodium carbonate and four 50-ml. portions of water. The extract was dried over magnesium sulfate and evaporated to leave 1.2 g. of brown solid. The material was twice recrystallized from 60% ethanol to give 0.57 g. (40%) of tan crystals, m.p. 150-154°.

Anal. Calcd. for $C_{16}H_{12}N_2O_3$: C, 68.6; H, 4.32; N, 10.0. Found: C, 68.3; H, 4.62; N, 10.0.

3-(2-Mercapto-4-imidazolyl)-2-picoline (**5**).

A mixture of 12.0 g. of the phthalimidomethyl ketone (**3**) and 150 ml. of 3*N* hydrochloric acid was refluxed for 3 hours. After chilling for 5 hours, the mixture was filtered and the filtrate twice extracted with 250-ml. portions of ether. The dark aqueous solution was evaporated *in vacuo* and the residue triturated with 50 ml. of hot ethanol to afford 5.0 g. of the amino ketone (**4**) as the hydrochloride salt; nmr (deuterium oxide): 8.90 (2H, m, C-4, 6H's), 8.10 (1H, m, C-5H), 4.75 (2H, s, CH_2), 2.94 (3H, s, CH_3).

A mixture of 3.70 g. (16.6 mmoles) of **4**, 1.80 g. (19 mmoles) of potassium thiocyanate and 40 ml. of water was heated at 100° for 20 hours. The dark brown solution was made strongly acid with conc. hydrochloric acid and heated for 10 minutes. The solution was cooled, alkalized to *p*H 10-11 with 10% sodium hydroxide and washed with three 100-ml. portions of dichloromethane. The aqueous portion was adjusted to *p*H 7-8 and continusously extracted with ethyl acetate for 24 hours. Evaporation of the solvent gave 0.70 g. of yellow crystals, which after trituration with ethyl acetate yielded 0.60 g. (19%). An analytical sample, m.p. 251-252°, was obtained from acetone; uv λ (ethanol): 263 nm; nmr (perdeuteriomethanol): 8.56 (1H, m, pyr-6H), 8.00 (1H, m, pyr-4H), 7.48 (1Y, m, pyr-5H), 7.20 (1H, s, Im-5H), 2.75 (3H, s, CH_3).

Anal. Calcd. for $C_9H_9N_3S$: C, 56.5; H, 4.75; S, 16.7. Found: C, 56.3; H, 4.77; S, 16.7.

3-(4-Imidazolyl)-2-picoline (**6**). Method A.

A mixture of 0.90 g. of the thiol (**5**), 1/2 teaspoon of Raney nickel (Grace No. 28) and 50 ml. of 2-methoxyethanol was stirred at 100° for 6 hours. After filtration, the solvent was evaporated *in vacuo* to leave 0.50 g. of an amber gum which slowly solidified; tlc (silica gel, chloroform-methanol, 5:1) R_f 0.50, single uv spot (**5** ran as single spot, R_f 0.70); nmr (deuteriochloroform-perdeuteriomethanol): 7.2-8.5 (5H, m, Ar-H), 2.86 (3H, s, CH_3).

Method B.

A solution of 5.0 g. of the bromoketone hydrobromide (**2**) in 55 ml. of formamide was heated at 100° for 24 hours. Evaporation of the solvent was followed by a partition of the residue between 50 ml. of saturated sodium bicarbonate and 200 ml. of ether. The aqueous phase was extracted with another two 200-ml. portions of ether and the extracts dried and evaporated to leave a dark residue. Extraction of the residue with 100 ml. of hot benzene followed by evaporation of the solvent afforded 1.1 g. (41%) of yellow gum, identical with material prepared by Method A by tlc and nmr.

2-Hydroxymethyl-3-(4-imidazolyl)pyridine (**9**).

A mixture of 1.90 g. of **6**, 3.0 ml. of 30% hydrogen peroxide and 15 ml. of acetic acid was stirred at 70-80° for 15 hours (5). The solvent was evaporated and the residue partitioned between 20 ml. of saturated sodium bicarbonate and 50 ml. of dichloromethane. The aqueous solution was saturated with salt and extracted with two 50-ml. portions of 1-butanol. The butanol solution was dried and evaporated to leave 1.2 g. of the crude *N*-oxide (**7**) as a yellow foam; tlc (chloroform-methanol, 5:1) showed a single spot R_f 0.2, free of **6**. The material was dissolved in 30 ml. of acetic anhydride and heated for 1.5 hours on the steam bath. The solvent was removed *in vacuo* and the residue partitioned between 24 ml. of saturated sodium bicarbonate and 50 ml. of chloroform-2-propanol (4:1). Evaporation of the organic extract yielded 1.1 g. of **8** as a dark syrup; ir: 5.75 μ (C=O), 8.0 (acetate C-O).

The crude ester was dissolved in 30 ml. of methanol containing a catalytic amount of sodium methoxide. The solution was refluxed for 30 minutes and evaporated to dryness. The residue was taken up in 10 ml. of water and the dark solution extracted twice with 20-ml. portions of chloroform-2-propanol, 4:1. The extract was washed with 5 ml. of water, dried over magnesium sulfate and evaporated to leave 300 mg. of pale yellow gum. Crystallization from 20 ml. of dichloromethane gave 175 mg. of white crystals, m.p. 153-155°; nmr (acetone-d_6-deuterium oxide) 8.64 (1H, m, pyr-6H), 8.49 (1H, m, pyr-4H), 8.10 (1H, s, Im-2H), 7.80 (1H, s, Im-5H), 7.56 (1H, m, pyr-5H), 4.73 (2H, s, CH_2).

Anal. Calcd. for $C_9H_9N_3O \cdot 1/4H_2O$: C, 60.2; H, 5.32; N, 23.4. Found: C, 60.6; H, 5.07; N, 23.6.

Methyl 3-(4-Imidazolyl)-2-pyridinecarboxylate (**12**).

To a solution of 180 mg. of the alcohol (**9**) in 20 ml. of acetone was added 3.0 g. of activated manganese dioxide (Beacon) and the mixture stirred at ambient temperature for 40 hours. The reagent was removed by filtration and further extracted in a Sohxlett apparatus with methanol for 2 hours. The acetone and methanol extracts were combined and evaporated to leave 120 mg. of a clear gum, whose infrared spectrum showed strong carbonyl absorption. The residue was refluxed with 5 ml. of methanolic hydrogen chloride for 6 hours, followed by evaporation and partition between 5 ml. of saturated sodium bicarbonate and 5 ml. of chloroform. The aqueous portion was again extracted with 5 ml. of chloroform and the chloroform solution dried and evaporated to leave 60 mg. of clear gum. The material was further purified by preparative thin layer chromatography on silica gel (chloroform-methanol, 5:1) to afford 30 mg; tlc single spot R_f 0.50 (alcohol **9** ran at R_f 0.40); nmr (deuteriochloroform): 9.44 (1H, NH), 8.77 (1H, m, pyr-6H), 8.33 (1H, m, pyr-4H), 7.94 (1H, s, Im-2H), 7.64 (2H, m, Im-5H, pyr-5H), 3.90 (3H, s, CH_3).

The picrate had m.p. 195-200° dec.

Anal. Calcd. for $C_{16}H_{12}N_6O_9 \cdot 1/2H_2O$: C, 43.5; H, 2.94; N, 19.0. Found: C, 43.9; H, 2.90; N, 18.7.

A solution of 30 mg. of the ester in 2 ml. of 3*N* hydrochloric acid was refluxed for 3 hours. After evaporation, the residue was

stirred with 5 ml. of acetone and collected to afford 30 mg. of the acid (**11**) as the hydrochloride salt; m/e 189 (amino acid).

Methyl 3-(4-Imidazolyl)piperidine-2-carboxylate Hydrochloride (**13**).

A mixture of ~20 mg. of the pyridine ester (**12**), 20 mg. of platunim oxide and 5 ml. of 0.1*N* hydrochloric acid was stirred under one atmosphere of hydrogen for 3.5 hours. The catalyst was removed by centrifugation and the solvent evaporated *in vacuo* to leave the hydrochloride salt of **13** as a gum; tlc chloroform-methanol, 5:1 with 1% triethylamine) single spot R_f 0.25 (**12** ran at R_f 0.50 in this system): nmr (deuterium oxide exchanged) 8.92 (1H, s, Im-2H), 7.66 (1H, s, Im-5H), 3.50 (3H, s, CH_3), 3.20 (3H, m, CH_2N, ImCH), 1.80 (4H, m, CH_2). The nmr of the free base (deuteriochloroform) showed the piperidine 2-H as a multiplet at 3.20 and the 3-H as a multiplet at 2.78 ppm.

The ester **13** was hydrolyzed with 1*N* sodium hydroxide by warming at 80-90° for 1 hour; tlc showed none of the ester remaining. The *p*H was adjusted to **7** with acetic acid and the hydrolysate was assayed for histidine decarboxylase inhibition (1).

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