AN IMPROVED SYNTHESIS OF 2-METHYL-4-(2'-CARBOXYETHYL)PYRROLE. POTENTIAL INHIBITORS OF PORPHOBILINOGEN DEAMINASE

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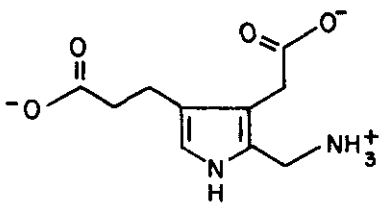
Abstract - Improved syntheses of 2-methyl-4-(2'-carboxyethyl)pyrrole (10) (49% overall yield) and of several O- and S-containing β-(5-ring heterocyclic)-substituted propionic acids are described. Some of these compounds have been found to be inhibitors of porphobilinogen deaminase.

In connection with a study of porphobilinogen (PBG) deaminase, an enzyme of the heme biosynthetic pathway, we sought to examine the potential of simple heterocyclic carboxylic acid derivatives to act as inhibitors of the enzyme. PBG deaminase catalyzes the head-to-tail tetramerization of PBG (1) to form the tetrapyrrylmethane or bilane (2).



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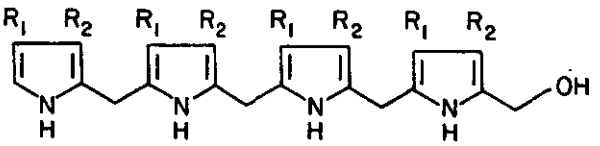

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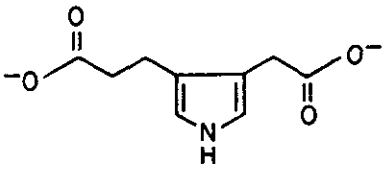
$R_1 = -CH_2CH_2COO^-$

$R_2 = -CH_2COO^-$

Bogorad[3] has reported that opsopyrroledicarboxylic acid (3) is a competitive inhibitor of the enzyme, but that PBG lactam (4) is without effect. Carpenter and Scott[4] have found that both (3) and iso-PBG (5) are competitive inhibitors with K_i values of 0.28 mM and 0.51 mM, respectively. Davies and Neuberger[5] observed that lactam (4) and N-acetyl PBG (6) had no effect on the enzyme. In addition, the monopyrroles (3), (5), (7), (8), and (9), have been found by Frydman and Frydman[6] and by Frydman and Feinstein[7] to inhibit rather than act as substrates for the enzyme. 5-Carboxyporphobilinogen had no effect on enzyme activity nor did esters of any

of the monopyrroles tested. Frydman and Frydman[6] concluded that the minimum structural requirements for substrate specificity and hence also for inhibition of PBG incorporation into product are: one free α-position and one propionic acid side chain on the pyrrole ring. No pyrrole possessing only these minimum requirements has been tested as a potential inhibitor, however.



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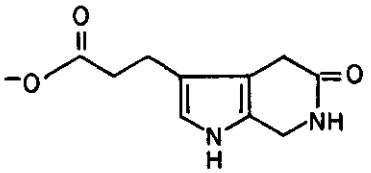

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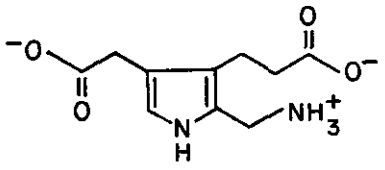

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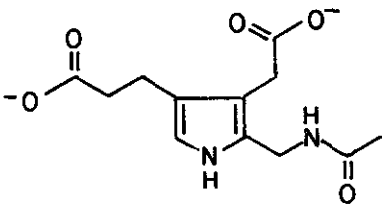

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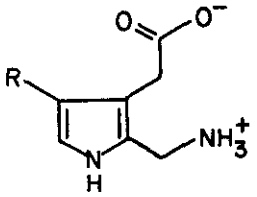
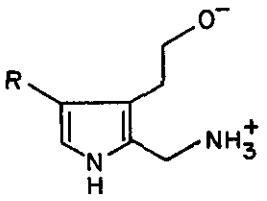
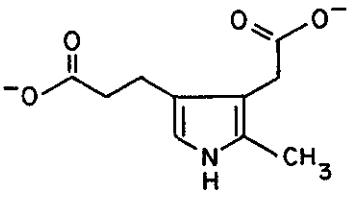


7 (a) R_1 = H
(b) R_1 = $-CH_2-COO^-$



8 (a) R = $-CH_3$
(b) R = $-C_2H_5$



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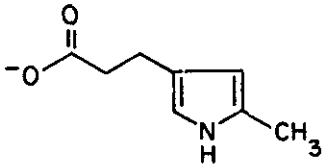
The PBG analog 2-methyl-4-(2'-carboxyethyl)pyrrole (10) was selected to test the accuracy of the above minimum structural requirement. In this compound, chosen for the simplicity of its



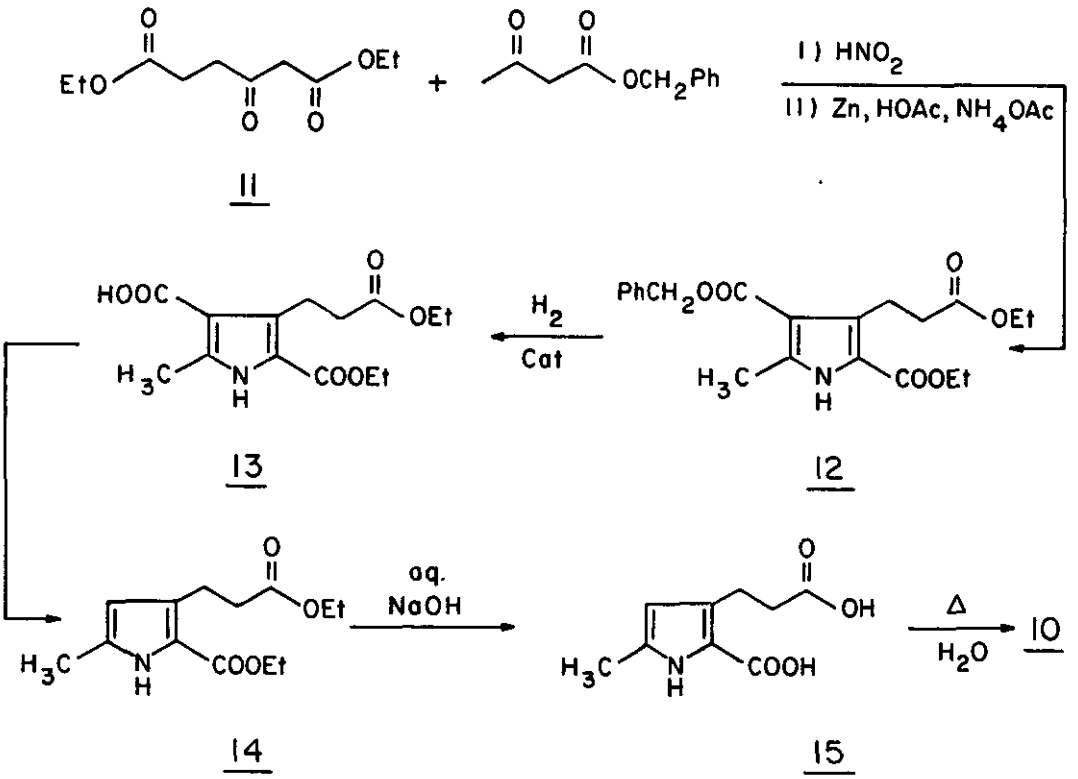
10

preparation, a methyl group takes the place of the α-aminomethyl group of PBG (as in 9). Compound 10 may thus serve as an inhibitor of PBG deaminase but it cannot be deaminated, hence formation of a bilane is precluded.

In addition, we sought to probe the possible role played by the heterocyclic ring itself during the initial substrate-enzyme interaction in order to gain some insight into limiting steric factors and the number of substrate binding sites involved. Two specific questions asked were: (a) is the size of the ring crucial, and (b) does the NH moiety of the pyrrole ring participate in binding substrate to active site. To answer these questions, several simple heterocyclic systems were synthesized and tested as potential inhibitors of PBG deaminase. Each met the minimum structural conditions outlined above.

SYNTHESES

Compound 10 had been previously prepared by MacDonald and coworkers[8,9] in five steps from diethyl β-ketoadipate 11 with an overall yield of 17%. Their synthesis is outlined in Scheme I. Our own synthesis, which is patterned after Scheme I, incorporates a number of modifications and improvements that are reported here.



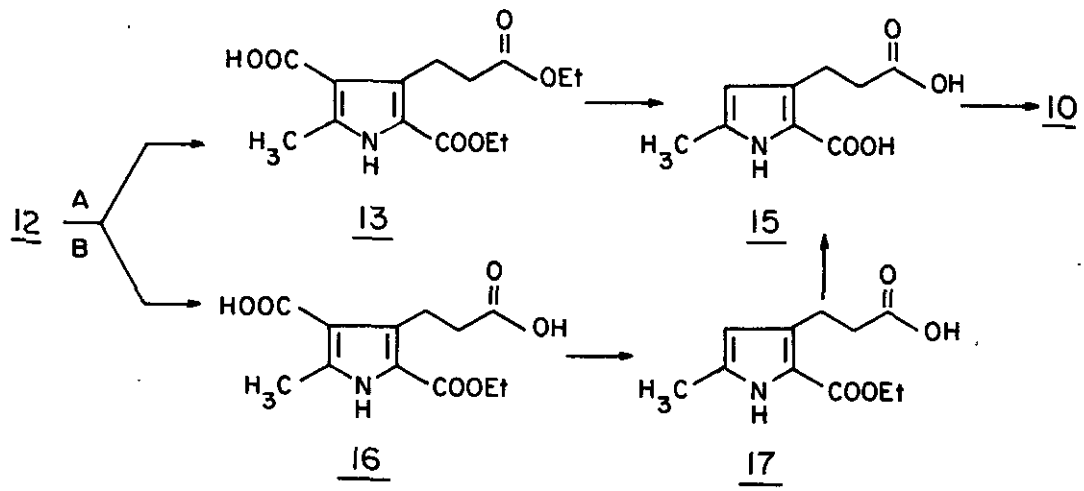
Scheme I

β-Ketoester 11 has been most recently prepared by acylation of ethyl tert-butyl malonate.[10,11] We have found that 11 may be more easily prepared by acylation of Meldrum's acid with β-ethoxycarbonylpropionyl chloride.[12] The acyl derivative of Meldrum's acid need not be isolated.[13]

Knorr condensation of 11 and benzyl acetoacetate led to pyrrole 12. Application of the combined saponification-decarboxylation sealed tube procedure described by MacDonald and MacDonald[14] led directly to 10 in low yield. However, the cumbersome and erratic nature of this procedure led us to abandon it in favor of stepwise degradation which gave consistently reproducible results.

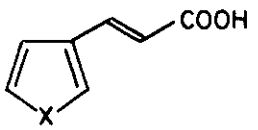
Catalytic debenzylation of 12, earlier effected at high temperature and pressure in the presence of Raney nickel,[9] was carried out at low pressure and room temperature in the presence of palladium.[15] This procedure led to an easily separated mixture of 13 and 16 (Scheme II).[16] Application of the cupric acetate/quinoline decarboxylation procedure[11,17] was superior to the earlier applied thermal degradations.[9,18] Decarboxylation of 13 followed by saponification of the resultant diester 14 without isolation resulted in diacid 15. Similar decarboxylation of 16 led to 17 which was hydrolyzed to 15.

The earlier assignment of the carboxyalkyl and of the carbethoxy group positions to the structures of compounds 16 and 17 was based on the fact that pyrrole α-carboxyl groups are known to decarboxylate with ease[8,9] and would be expected not to survive the β-COOH decarboxylation step. We present spectroscopic data which confirm these assignments. Diacid 15 could be decarboxylated to 10 upon melting or preferably, on heating in boiling water. In our hands, acid 10 was obtained with an overall yield of 49% (Scheme II, path B).



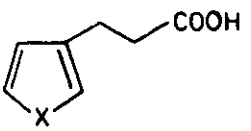
Scheme II

Compounds 18a and b; and 19a and b were prepared by modification of known reactions. Condensation of 3-furan- and 3-thiophenecarboxaldehydes with malonic acid led to 18a and 19a. Catalytic hydrogenation of 18a and reduction of 18b with sodium-lead alloy converted the substituted acrylic acids to the corresponding substituted propionic acids 19a, and 19b, respectively.



18

(a) X = O
(b) X = S



19

(a) X = O
(b) X = S

INHIBITION STUDIES

Table I summarizes the effects of various carboxylic acids on the activity of PBG deaminase at a concentration of 40-56 mM (1000 x K_M for PBG). The five-membered ring heterocyclic carboxylic acids appeared to be somewhat more effective inhibitors than either cyclopentanecarboxylic acid or the six-membered ring carboxylic acids. Compounds 18a, 19a and 19b are weak non-competitive inhibitors of deaminase with K_i values ranging from 63-170 mM.

While the minimum structural requirements for inhibition of PBG as suggested by Frydman and Frydman[6] do seem to be met by compound 10, it proved to be a comparatively weak competitive inhibitor of the enzyme (K_i 60 mM). However, it is a good oxygen scavenger and the enzyme assay had to be revised because it prevented total oxidation of uroporphyrinogen to uroporphyrin. The properties of 10 as an anti-oxidant are being investigated further.

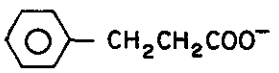
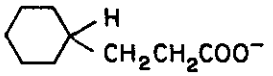
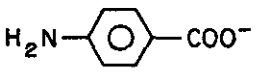
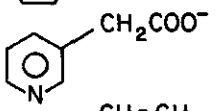
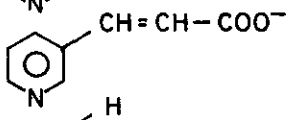
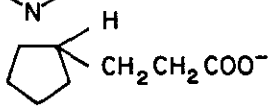
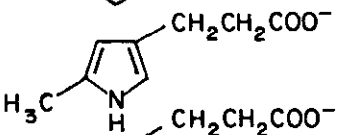
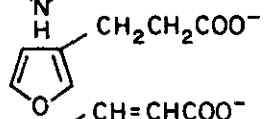
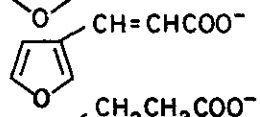
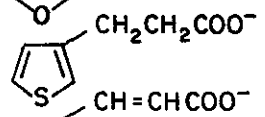
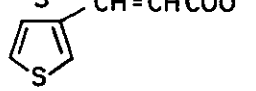
EXPERIMENTAL SECTION

Melting points were determined in a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 247 grating spectrophotometer. ^{1}H NMR spectra were determined on Varian EM360A (60 MHz) and JEOL MH-100 (100 MHz) spectrometers. Chemical shifts are reported in parts per million downfield from internal standard $(CH_3)_4Si$. ^{13}C NMR spectra were recorded broad-band decoupled on a Bruker WM 500 spectrometer operating at 125.76 MHz. Mass spectra (70 eV) were obtained with a Varian MAT CH-5 instrument with sample introduction via the direct inlet system.

Diethyl β-ketoadipate (11). Meldrum's acid (2,2-dimethyl-1,2-dioxane-4,6-dione)[19] (50 g, 0.35 mol) was stirred with 150 mL of dichloromethane and 56 g of pyridine until the solid dissolved. A solution of β-ethoxycarbonylpropionyl chloride[20] (62 g, 0.38 mol) in 60 mL dichloroethane was added dropwise to the stirred solution of Meldrum's acid at 0-3°C under

Table I

Effect of Carboxylic Acids on the Activity of PBG Deaminase[a]

Compound		Concentration[b] (mM)	Activity Remaining[c] (%)
		40	94
		40	53[d]
		40	93
		40	55
		40	94
		40	84
	10	56[e]	43
	19a	50	58
	18a	50	56
	19b	50	77
	18b	50	(100)

(a) Measured as uroporphyrin. All inhibitors were preincubated with the enzyme for 30 min prior to addition of PBG. (b) Inhibitor concentrations are 1000 x Michaelis Constant for PBG, K_M = 50μM. (c) [PBG] = 164μM. (d) Detergent effect. (e) [PBG] = 69μM.

nitrogen over a period of 1 h and stirred additionally 1 h. The reaction mixture was washed with HCl (1:1), with water, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was stirred and refluxed with absolute ethanol (150 mL) for 1 h. Following evaporation of the solvent, ether was added (150 mL), the ether solution washed with water (3x) and dried. The ether was removed by rotary evaporation and the residue distilled to give 38 g (51%) of liquid:

bp 106-108°C (0.4 mm) [lit.[10,11] 109-111°C (0.35 mm)].

Debenzylation of ethyl 2-ethoxycarbonyl-4-benzyloxycarboxy-5-methylpyrrole-3-propionate (12). Compound 12 [8.0 g, 0.021 mol, mp 142-143°C,[21] prepared according to ref. 9 (mp 142-143°C)] was dissolved in 300 ml of 95% ethanol. Triethylamine (10 drops), and palladium (10% on carbon, 0.4 g) were added and the mixture hydrogenated at 2 atmospheres in a Parr apparatus for 5 h. The crude product from three identical hydrogenations was combined, concentrated in vacuo, dissolved in aqueous NaOH (4.5 g in 350 mL H_2O) and filtered to remove the catalyst. Introduction of gaseous CO_2 led to a precipitate which was collected and the filtrate was reserved. The solid was washed with water and dried under vacuum. The product, 13, 5.84 g (32%) was recrystallized first from ethanol then from acetone, mp 226-227°C (dec) [lit.[9] 230°C (dec)].

The filtrate above was treated with acetic acid leading to compound 16, 8.95 g (54%), recrystallized three times from 95% ethanol, mp 257-257.5°C (dec) [lit.[9] 253°C (dec)].[16]

Compound 13: IR (KBr) 1730, 1670, 1655 cm^{-1} (three C=O); ^1H NMR ($CDCl_3$, 60 MHz) δ 11.8 (br s, 1 H, COOH), 4.19 (m, 4 H, CH_2O), 2.5, 3.3 (both m, 4 H, CH_2CH_2), 2.46 (s, 3 H, 5-CH_3), 1.25 (q, 6 H, CH_3, CH_3).

Compound 16: IR (KBr) 1700, 1670, 1655 cm^{-1} (three C=O); ^1H NMR ($CDCl_3$, 60 MHz) δ 11.85 (br s, 1 H, COOH), 11.7 (br s, 1 H, COOH), 4.27 (q, 2 H, CH_2O), 2.5, 3.3 (both m, 4 H, CH_2CH_2), 2.44 (s, 3 H, 5-CH_3), 1.31 (t, 3 H, CH_3).

2-Ethoxycarbonyl-5-methylpyrrole-3-propionic acid (17). Diacid 16 (0.60 g, 0.0022 mol) was dissolved in 3 mL quinoline, 10 mg cupric acetate was added and the mixture stirred and heated (190-210°C) under nitrogen for 3 h. Ether (50 mL) was added to the cooled reaction mixture, and the latter was treated with 2 N HCl until strongly acidic. The ether layer was separated, combined with the ether extract of the water layer, washed with brine and dried (Na_2SO_4). Concentration of the ether solution led to 0.48 g (96%) of 17, mp 140°. Purification was effected by chromatography (silica gel, ethyl acetate) and recrystallization from methylene chloride, mp 153-154°C [Lit.[9] 153°C]: IR (KBr) 1715 (C=O), 1620 cm^{-1} (C=O); ^1H NMR ($CDCl_3$, 100 MHz) δ 9.12 (br s, 1 H, COOH), 5.80 (s, 1 H, pyrrole β-H), 4.25 (q, 2 H, CH_2O), 3.03 (t, 2 H, CH_2), 2.60 (t, 2 H, CH_2), 2.22 (s, 3 H, 5-CH_3), 1.39 (t, 3 H, CH_3); MS, m/e 225 (M^+), 180 (M^+-COOH), 179 (M-C_2H_5OH), 178 (M^+-H , C_2H_5OH), 166 (M^+-CH_2COOH).

2-Carboxy-5-methylpyrrole-3-propionic acid (15). (a) From 13: Compound 13 (3.0 g, 0.010 mol) was decarboxylated in quinoline-$Cu(OAc)_2$ as above. The crude low-melting solid product (14, 2.2 g) was dissolved in 12 mL 95% ethanol, aqueous NaOH (8% w/v, 16 mL) added, and the resulting solution stirred and heated to reflux for 1 h. Most of the solvent was removed in a rotary evaporator, the residue dissolved in 12 mL water and extracted with 30 mL ether. The remaining aqueous solution was cooled to 0°C and acidified by introduction of SO_2 gas. The

precipitate (15) was filtered and dried in vacuo: 1.7 g (86%). Recrystallization of crude 15 (1.5 g) from ether afforded 0.95 g product, mp 132-133°C (dec) [lit.[8] 132°C (dec)]: IR (KBr) 1715 (C=O), 1640 cm^{-1} (C=O); ^{13}C NMR (D_2O-CD_3COCD_3), δ 176.4 (COOH), 163.5 (α-COOH), 134.3 (C-5 [$\underline{C}$-CH_3]), 132.9 (C-3), 117.2 (C-2), 110.1 (C-4), 35.1 (CH_2), 22.7 (CH_2), 12.4 (CH_3).[22]

(b) From 17: Compound 17 (2.0 g, 0.0089 mol) was dissolved in 10 mL 95% ethanol. Aqueous NaOH (8% w/v, 12 mL) was added and the solution stirred and refluxed 1 h. The reaction mixture was reduced to a small volume in vacuo, dissolved in 10 mL H_2O, extracted with ether, the water layer cooled to 0°C, acidified with SO_2 gas, and the precipitated solid filtered and dried (vacuum overnight, R.T.): 1.74g 15 (98%) purified as described above.

2-Methyl-4-(2'-carboxyethyl)pyrrole (10). Diacid 15 (0.42 g, 0.0021 mol) was decarboxylated in water (0.75 ml; 100°C). When gas evolution ceased, the reaction mixture was rapidly chilled and the solid collected: 0.28 g (85%), mp 75-77°C (lit.[8] mp 79-81°C) after drying in vacuo at room temperature. Purification was effected by dissolution in ether; pentane was added, the resulting oil was removed and the ether-pentane solution concentrated in vacuo at room temperature to yield light pink crystals, mp 77-78°C: IR (KBr) 1685 cm^{-1} (C=O); ^1H NMR ($CDCl_3$, 60 MHz), δ 7.7, 7.27 (v br, s, 2 H, NH/COOH), 6.46 (br s, 1 H, α-H), 5.90 (br s, 1 H, β-H), 2.72 (m, 4 H, CH_2CH_2), 2.24 (s, 3 H, CH_3); MS, m/e 153 (M^+), 108 (M^+-COOH), 94 (M^+-CH_2COOH).

Acid 10 is a relatively unstable substance (freezer storage protected from light). It appears preferable to store the stabler precursor 15 and to generate 10 as required. The decarboxylation may be monitored by ^{13}C NMR spectroscopy which differentiates the two carboxyl carbons: ^{13}C NMR (H_2O-CD_3COCD_3) of 10: δ 174.4 (COOH), 127.8 (C-2 [C-CH_3]), 114.0 (C-5), 106.7 (C-3), 36.2 (CH_2), 23.4 (CH_2), 12.9 (CH_3) [C-4 below noise level][22].

Diacid 15 could be decarboxylated in 0.075 M TRIS Buffer, pH 8.2, by heating in a boiling water bath for five minutes. The course of the reaction could be followed by TLC (Brinkman Polygram "Sil G", no gypsum) using ethyl acetate as developing solvent, R_F (15) = 0.60, R_F (10) = 0.74. The chromatogram was developed with Ehrlich spray [2% w/v p-dimethylaminobenzaldehyde (DMAB) in 5 N HCl]. Compound 15 gave a pink-purple color and 10 a purple color. On Whatman #3 paper, using butanol-acetic acid-water (63:11:26) mobile phase, 1 had an R_F = 0.54, 10 and 15 both had R_F = 1.00 with 1 giving a blue-purple color with Ehrlich spray. With the quantitative Ehrlich reagent of Mauzerall and Granick[23] the λ_{max} of 10 is 545 nm (ϵ_M = 5.94 x 10^4). Compound 10 was easily air-oxidized or oxidized by I_2. A colored material with a maximum at 467 nm and shoulder near 500 nm was formed. This reaction interfered with porphyrin determinations in enzymatic studies of PBG deaminase and is being studied further. Uroporphyrin and uroporphyrinogen could be separated from 10 and oxidized material by paper chromatography

and eluted with 2% H_2SO_4 in methanol. On Whatman #3 paper (2,6-lutidine-water (5:3.5 v/v) as developing solvent with beakers of conc. NH_3, 2,6-lutidine and water in the tank), uroporphyrin, visualized under UV light, has R_F = 0, and 10, visualized with Ehrlich reagent, has R_F = 0.55 (minor components appeared as pink and blue spots with R_F = 0.25 and 0.14, respectively).

3-(3-Furanyl)acrylic acid 18a. This compound was prepared by condensation of 3-furancarboxaldehyde[24] and malonic acid (86%), mp 153-153.5°C after recrystallization from 30% aq. EtOH (lit. 152.5-154°C).[26,27]

3-(3-Furanyl)propionic acid 19a. Compound 18a, dissolved in 15% aq. KOH, was hydrogenated at 65 psi over 5% Pd on $SrCO_3$ according to the procedure of Rallings and Smith.[28a,b] Following acidification of the filtered reaction mixture, acid 19a was isolated, recrystallized from hexanes (-78°C), mp 64-65°C. Anal. Calcd. for $C_7H_8O_3$: C, 60.00; H, 5.75. Found: C, 60.10; H, 5.91. ^1H NMR ($CDCl_3$): δ 10.5 (br s, 1 H, COOH), 7.4 (d, 2 H, 4,5-ArH), 6.4 (s, 1 H, 2-ArH), 2.7 (m, 4 H, CH_2CH_2).

3-(3-Thienyl)acrylic acid 18b. This acid was prepared from 3-thiophenecarboxaldehyde by the procedure of Kingsbury and Max,[29] mp 151-152°C (lit. 153-153.5°C).[30]

3-(3-Thienyl)propionic acid 19b. Acid 18b was reduced with commercial lead-sodium alloy according to the procedure of Tabei et al.[31] The crude acid was extracted with pentane and recrystallized from hexanes (-78°C), mp 58-60°C (lit. 62-62.5°C).[32]

Enzyme Assay Procedure Stock solutions of inhibitors (200 mM) were prepared in 0.01 M phosphate buffer or 0.075 M TRIS buffer, pH 8.2. Wheat germ PBG deaminase, prepared according to Bogorad[33] or purified further on Affi-gel 501,[34] 100 μl, was preincubated with inhibitor to give the desired concentration for 0.5 h at 37°C. For kinetic studies there was no pre-incubation. PBG (164 μM, 25 μl) was added and enough buffer to give a total of 175 μl and the mixtures incubated at 37°C for 1 hr. Then 0.5 ml of 0.01% I_2 in 0.5 N HCl was added and after 10 min, 0.5 ml of 0.5 N HCl was added. The activity was measured as O.D. at 405 nm, the λ_{max} for uroporphyrin I in 0.5 N HCl. When 10 was studied, uroporphyrin was separated from inhibitor by paper chromatography as described above.

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