

Synthesis and Reactions of *N*-(*p*-Carbethoxy)phenyl-4-piperidone (1)

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Studies on the inhibition of thymidylate synthetase by analogs of *N*<sub>5</sub>,*N*<sub>10</sub>-methylene tetrahydrofolic acid (2) led to the attempted synthesis of some decahydropyridine-[3,4-*b*]pyrazines and octahydropyridino[2,3-*b*]quinoxaline derivatives. One approach to the synthesis of these compounds is through condensation of ethylenediamine or *o*-phenylenediamine with the appropriate 3,4-diketopiperidine.

The most general method used for the synthesis of *N*-substituted 4-piperidones is through the Dieckmann cyclization of *N*-substituted diethyl  $\beta,\beta'$ -dipropionate which is obtained by Michael addition of a primary amine to ethyl acrylate. Although ethyl acrylate is reported to react with aniline under the catalysis of cuprous chloride to give ethyl phenylamino- $\beta,\beta'$ -dipropionate (3) it gave only ethyl (*p*-carbethoxy)phenylamino- $\beta$ -propionate when treated with *p*-aminobenzoate under the same conditions. The difference in reactivity between aniline and ethyl *p*-aminobenzoate in this case is probably due to a difference in nucleophilicity.

The reports (4) that chelidonic acid 1 reacts with various primary amines to give the corresponding chelidamic

acid led to the condensation of 1 with ethyl *p*-aminobenzoate to give *N*-(*p*-carbethoxy)phenyl chelidamic acid 2 (Scheme 1). Decarboxylation by dry distillation gave a poor yield of *N*-(*p*-carbethoxy)phenyl-4-pyridone (3). Improved yields of (3) were obtained when decarboxylation was carried out in diglyme at 160°.

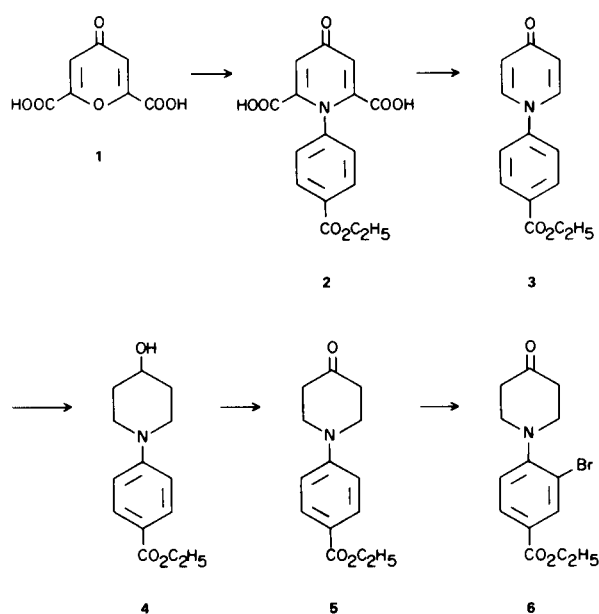
No reaction occurred when the pyridine (3) was subjected to catalytic reduction with 10% Pd/C in various solvents such as acetic acid, ethanol, and ethyl acetate. When platinum oxide/ethanol was used as the catalyst, the hydrogen uptake was slow at room temperature and atmospheric pressure; The products isolated were *N*-(*p*-carbethoxy)phenyl-4-piperidol (4), the starting material, and a small amount of *N*-(*p*-carbethoxy)phenyl-4-piperidone (5) detected by tlc when the reduction was stopped at two mole equivalents of hydrogen uptake. Since it was not practical to reduce compound 3 selectively to 5, compound 3 was therefore overreduced to the alcohol 4 by using platinum oxide/ethanol at 40 lbs/in pressure. Compound 4 was then oxidized to the ketone by DMSO, DCC, and pyridinium trifluoroacetate (5). Jones reagent (6) and Sarett reagent (7) were also used for the oxidation of alcohol 4, but proved unsuccessful.

Bromination of 5 with bromine in glacial acetic acid (8) gave a gum which showed a very weak signal in its nmr spectrum in the aromatic region suggesting ring bromination was predominant. Similar results were observed when the hydrobromic acid salt of 5, instead of the free base, was used as the starting material for bromination. When 1 mole equivalent of *N*-bromosuccinimide was used (9) it gave instead of the desired compound, a ring brominated product 6, which was identified by its nmr spectra. Ring bromination also was observed when pyridinium hydrobromide perbromide (10) or pyridinium perbromide (11) were used as the brominating agents.

Attempts to synthesize *N*-(*p*-carbethoxyphenyl)-3,4-piperidinedione by selenium dioxide oxidation of 5 in either ethanol, dioxane or acetic anhydride failed. Nitrosation of 5 with sodium nitrite and acetic acid also failed to give the  $\alpha$ -nitrosation product.

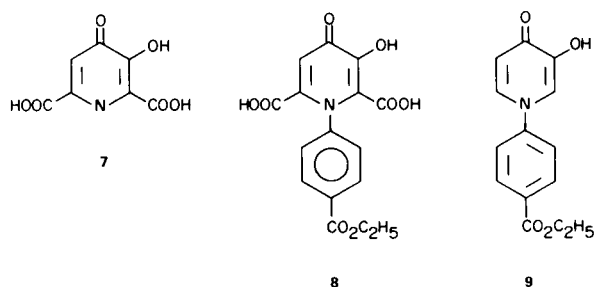
Another possible approach for the synthesis of the diketone was *via* the use of meconic acid (7), instead of chelidonic acid (1) as the starting material (Scheme 2). Compound 7 was synthesized according to the reported procedure (12). Treatment of meconic acid (7) with ethyl

SCHEME 1



*p*-aminobenzoate gave **8** in 20% yield. This was decarboxylated in refluxing diglyme to give *N*-(*p*-carboxy)phenyl-3-hydroxy-4-pyridone (**9**). Condensation of **9** with *o*-phenylenediamine in dimethylformamide, benzene, or dioxane failed to give the desired pyridino[3,4-*b*]quinoxaline. No reaction occurred when **9** was subjected to catalytic hydrogenation in glacial acetic acid, ethanol, or methanol, using platinum oxide or Pd/C as the catalyst at room temperature and atmospheric pressure.

SCHEME 2



## EXPERIMENTAL (13)

*N*-(*p*-Carboxyphenyl)chelidamic Acid (**2**).

Chelidonic acid monohydrate (**1**, 10 g., 0.054 mole) and ethyl *p*-aminobenzoate (10 g., 0.06 mole) were refluxed in 500 ml. of water for 6-8 hours. The solution was filtered while hot and the filtrate was evaporated to about 100 ml. under reduced pressure. After cooling in an ice bath, the yellow precipitate was collected and suspended in 200 ml. of water. Sodium bicarbonate powder was added in small portions to dissolve the acid. The solution was filtered and the filtrate was acidified with concentrated hydrochloric acid. The precipitates were collected and washed with water and then acetone until the washing solution was clear. The fine yellow crystals of **2** weighed 8 g. (44%), m.p. 180° dec. The crude product obtained was subjected to decarboxylation without further purification.

*N*-(*p*-Carboxyphenyl)-4-pyridone (**3**).

Compound **2** (6 g., 0.016 mole) was suspended in 50 ml. of diglyme. The suspension was heated under a condenser with stirring. The decarboxylation took place when the temperature reached the boiling point of the solvent and was completed within 15-20 minutes. The solution was filtered while hot, 3-4 volumes of water added, and the solution was stored at 5° overnight. The long yellow needles (3.5 g., 80%) were collected and washed with water. Recrystallization from *p*-dioxane and water mixed solvent gave **3** as pale yellow needles, m.p. 178-179°; ir (Nujol) 1720 (ester C=O), and 1640 cm<sup>-1</sup> (C=O); nmr (deuteriochloroform)  $\delta$  1.40 (t, 3,  $J = 7.5$  Hz, -O-CH<sub>2</sub>-CH<sub>3</sub>), 4.42 (q, 2,  $J = 7.5$  Hz, -O-CH<sub>2</sub>), 6.46 (d, 2,  $J = 7.5$  Hz, phenyl-3,5-H), 7.43 (d, 2,  $J = 8$  Hz, pyridone-3,5-H), 7.65 (d, 2,  $J = 7.5$  Hz, phenyl-2,6-H), 8.20 (d, 2,  $J = 8$  Hz, pyridone-2,6-H).

*Anal.* Calcd. for C<sub>14</sub>H<sub>13</sub>NO<sub>3</sub>: C, 69.13; H, 5.35; N, 5.76. Found: C, 69.14; H, 5.54; N, 5.81.

*N*-(*p*-Carboxyphenyl)-4-piperidinol (**4**).

Compound **3** (2.3 g., 0.0095 mole) was dissolved in 50 ml. of 95% ethanol. Platinum oxide (0.5 g.) was added and the mixture was hydrogenated under 40 lbs/in<sup>2</sup> pressure for 6 hours. The catalyst was removed by filtration and the solvent evaporated to dryness under reduced pressure. The residue was recrystallized from benzene and Skelly B mixed solvent to give 1.6 g. of **4** as fine white crystals. More crystals (0.4 g.) were obtained from the filtrate to give a 90% total yield, m.p. 109-110°; ir (chloroform) 3620 and 3450 (-OH), and 1700 cm<sup>-1</sup> (ester C=O); nmr (deuteriochloroform)  $\delta$  1.35 (t, 3,  $J = 7$  Hz, -O-CH<sub>2</sub>-CH<sub>3</sub>), 1.80 (m, 5, piperidine-3,5-H and O-H), 3.05 and 3.70 (m, 5, -N-C-H and O-C-H), 4.32 (q, 2,  $J = 7$  Hz, -O-CH<sub>2</sub>-), 6.83 (d, 2,  $J = 9$  Hz, phenyl-3,5-H), and 7.91 (d, 2,  $J = 9$  Hz, phenyl-2,6-H).

*Anal.* Calcd. for C<sub>14</sub>H<sub>19</sub>NO<sub>3</sub>: C, 67.47; H, 7.63; N, 5.66. Found: C, 67.62; H, 7.73; N, 5.63.

*N*-(*p*-Carboxyphenyl)-4-piperidone (**5**).

Compound **4** (3 g., 0.012 mole) was dissolved in DMSO (15 ml.) and benzene (30 ml.) containing DCC (7.5 g., 0.036 mole) and pyridine (0.96 ml., 12 mmoles). Trifluoroacetic acid (0.58 ml., 6 mmoles) was added with cooling and the mixture was stored at room temperature overnight. Ethyl acetate (100 ml.) was added and the precipitated urea was removed by filtration. The filtrate was washed with water (150 ml.) four times, dried (sodium sulfate) evaporated to dryness under reduced pressure. The oily residue solidified after standing and was recrystallized from benzene and Skelly B (b.p. 60-70°) mixed solvent to give 2 g. (70%) of **5** as white leaflets, m.p. 63-64.5°; ir (Nujol) 1715 (C=O) and 1700 cm<sup>-1</sup> (ester C=O); nmr (deuteriochloroform)  $\delta$  1.38 (t, 3,  $J = 7$  Hz, -O-CH<sub>2</sub>-CH<sub>3</sub>), 2.58 (t, 4,  $J = 6$  Hz, piperidone-3,5-H), 3.80 (t, 4,  $J = 6$  Hz, piperidone-2,6-H), 4.39 (q, 2,  $J = 7$  Hz, -O-CH<sub>2</sub>-), 6.95 (d, 2,  $J = 9$  Hz, phenyl-3,5-H), 8.20 (d, 2,  $J = 9$  Hz, phenyl-2,6-H).

*Anal.* Calcd. for C<sub>14</sub>H<sub>17</sub>NO<sub>3</sub>: C, 68.02; H, 6.88; N, 5.67. Found: C, 68.19; H, 6.91; N, 5.67.

*N*-(2-Bromo-4-carboxyphenyl)-4-piperidone (**6**).

Compound **5** (0.5 g., 2 mmoles) and NBS (0.35 g., 2 mmoles) were suspended in 35 ml. of carbon tetrachloride. The suspension was refluxed with IR lamp illumination for 5 minutes. After cooling, the succinimide was removed by filtration and the solvent was evaporated to dryness. The residue was recrystallized from carbon tetrachloride and Skelly B (b.p. 60-70°) mixed solvent to give **6** as light yellow crystals, m.p. 108-110°; ir (Nujol) 1710 cm<sup>-1</sup> (ester and keto C=O); nmr (deuteriochloroform)  $\delta$  1.42 (t, 3,  $J = 7.0$  Hz, -O-CH<sub>2</sub>-CH<sub>3</sub>-), 2.68 (t, 4,  $J = 6.0$  Hz, -CO-CH<sub>2</sub>-), 3.46 (t, 3,  $J = 7.0$  Hz, -N-CH<sub>2</sub>-), 4.40 (q, 2,  $J = 7.0$  Hz, -O-CH<sub>2</sub>-), 7.12 (d, 1,  $J = 9.0$  Hz, phenyl-6'-H), 8.00 (m, 1,  $J = 9.0$  and 2.5 Hz, phenyl-5'-H), 8.30 (d, 1,  $J = 2.5$  Hz, phenyl-3'-H).

*Anal.* Calcd. for C<sub>14</sub>H<sub>16</sub>BrNO<sub>3</sub>: C, 51.53; H, 4.91; N, 4.29. Found: C, 51.64; H, 4.75; N, 4.46.

*N*-(*p*-Carboxyphenyl)-3-hydroxy-4-pyridone-2,3-dicarboxylic Acid (**8**).

Meconic acid (**9**) (**7**) (2 g., 0.01 mole) and ethyl *p*-aminobenzoate (2 g., 0.012 mole) were refluxed in water (50 ml.) for 6-8 hours. Charcoal (0.1 g.) was added and the solution was boiled for 2 minutes. The solution was filtered; the filtrate was evaporated to 10 ml. under reduced pressure. The precipitate was collected, washed with water and ethanol to give 0.7 g. (20%) of **8** as a yellow powder, m.p. 197-198° dec. It gave a red color with ferric chloride test solution. The compound was used for decarboxy-

lation without further purification.

*N*-(*p*-Carbomethoxyphenyl)-3-hydroxy-4-pyridone (**9**).

The acid **8** (1.2 g.) was suspended in 20 ml. of diglyme (Practical grade). The suspension was refluxed for 20 minutes. Decarboxylation took place rapidly and gave a clear brown solution. The solution was filtered while hot; an equal amount of water was added and chilled. The yellow crystals of **9** (0.5 g., 55%) were collected and recrystallized from ethyl acetate, m.p. 207-209° dec.; ir (Nujol) 1705 (ester C=O), and 1640  $\text{cm}^{-1}$  (conj. C=O).

*Anal.* Calcd. for  $\text{C}_{14}\text{H}_{14}\text{NO}_4$ : C, 64.86; H, 5.02; N, 5.40. Found: C, 64.96; H, 5.27; N, 5.14.

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