A Short Synthesis of Praziquantel

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The synthesis of praziquantel (**1**), a potent anthelmintic agent, is reported. The synthesis requires five steps and proceeds in 16% yield.

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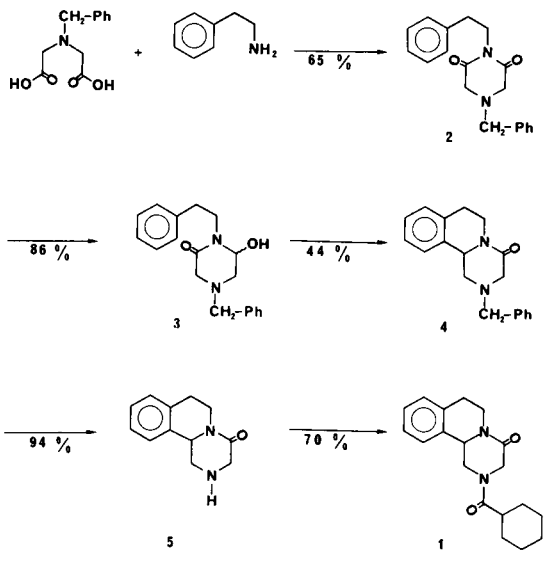
Praziquantel (**1**), a drug jointly developed by E. Merck and Bayer A. G. [1], has emerged as an exciting anthelmintic agent for mass therapy of schistosomiasis and cestodiasis in veterinary and human medicine [2]. The promising pharmacological profile and high effectiveness of **1** made it a worthwhile target for synthesis.

While the original multistep synthesis of **1** [1,3] using isoquinoline as the starting material has been described only in patents, a more direct route was desired for production on an industrial scale. Two other different approaches have also recently been described in the literature [4,5].

We now wish to report a related synthesis in which the basic strategy for the construction of the tricyclic framework, the selective reduction of the imide function in a piperazine-2,6-dione followed by cyclization in acidic medium, is the same as reported [4]. However, the preparation of the suitably protected 1-phenethyl-2,6-piperazinedione was carried out by a more direct route in which the commercially available *N*-benzyliminodiacetic acid was the starting material. Moreover, this approach (Scheme I) allows to prepare a variety of 2-acyl-1,2,3,6,7,11b-hexahydro-4*H*-pyrazino[2,1-*a*]isoquinolin-4-ones which also displays anthelmintic activity [3].

SCHEME I



The 4-benzyl-1-phenethyl-2,6-piperazinedione (**2**) was prepared in 65% yield by heating at 200° *N*-benzyliminodiacetic acid with phenethylamine for 1 hour. The partial reduction of the imide group of **2** was carried out using the metal catalyzed reduction procedure [6]. Thus, when **2** was treated with sodium borohydride (5 molar equivalents) and cupric chloride dihydrate (1.1 molar equivalents) in ethanol at 0° for 45 minutes, a 86% yield of the α-hydroxylactam **3** was obtained. Ring closure of the compound **3** was effected by heating it for 5 hours with 37% hydrochloric acid to produce **4** in 44% yield. Hydrogenolysis of **4** in methanol-2*N* aqueous hydrochloric acid (6:1), over 5% palladium on carbon under 4.5 atmospheres at 60° gave 94% of amine **5**. Acylation of **5** with cyclohexanecarboxylic acid chloride in dry dimethoxyethane containing 1 molar equivalent of anhydrous triethylamine at room temperature afforded **1** in 70% yield.

EXPERIMENTAL

Melting points were taken on a Culatti capillary melting point apparatus and are corrected. Column chromatography was carried out by using Merck Silica gel 60 (0.063-0.2 mm). The preparative tlc plates were of Merck (Silica gel 60 F-254, 20 × 20 × 0.2 cm). In order to follow the progress of the reaction or the purity of the compounds, we used Merck-F254 thin layer plates (250 μm) cut into small slides (5 × 2.5 cm). The products were visualized by uv absorption or iodine vapor. Infrared spectra were taken on a Perkin-Elmer 283b instrument. The ^1H and ^{13}C nmr spectra were obtained with a Varian FT-80A spectrometer with tetramethylsilane as an internal standard, and are expressed as δ values. Mass spectra were recorded on a Hewlett-Packard 5985-B spectrometer at 70 eV.

4-Benzyl-1-phenethyl-2,6-piperazinedione (**2**).

A mixture of 1.116 g (5 mmoles) of *N*-benzyliminodiacetic acid and 0.606 g (5 mmoles) of phenethylamine freshly distilled was heated in an oil bath at 200° for 1 hour. After cooling at room temperature, the mixture was dissolved in 15 ml of methanol and cooled at 0° to assist crystallization. The crystalline solid was filtered, washed with cold methanol and air dried to give 1.0 g (65%) of **2**, mp 76-78°; ir (chloroform): 1685 cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.85 (m, 2H, $ArCH_2$), 3.55 (s, 4H, C-3 and C-5 protons), 3.75 (s, 2H, $ArCH_2N$), 3.95 (m, 2H, CH_2NCO), 7.25 (s, 5H, aromatic protons), 7.35 (s, 5H, aromatic protons); ms: m/e 308 (M^+, 62), 217 (18), 120 (43), 91 (100), 42 (47).

Anal. Calcd. for $C_{19}H_{20}N_2O_2$: C, 74.0; H, 6.5; N, 9.1. Found: C, 74.1; H, 6.5; N, 9.2.

4-Benzyl-6-hydroxy-1-phenethylpiperazin-2-one (**3**).

To a mixture of 2.0 g (6.5 mmoles) of **2** and 1.21 g (7.1 mmoles, 1.1 molar equivalents) of copper(II) chloride dihydrate in 150 ml of ethanol cooled at 0°, 1.23 g (32.5 mmoles, 5 molar equivalents) of sodium borohydride were added. The reaction mixture was stirred at 0° for 45 minutes, poured in 800 ml of water and extracted with chloroform (5 × 130 ml). The organic phase was washed with water, dried and concentrated *in vacuo*. The crystalline residue was recrystallized from ethyl acetate-hexane to give 1.73 g (86%) of **3** as white crystals, mp 114-116°; ir (chloroform): 3530, 1655 cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.35 (dd, J = 12, 2 Hz, 1H, H-5), 2.65-3.05 (m, 3H, Ar-CH_2 and H-5'), 3.20-4.05 (m, 5H, CH_2-NCO, C-3 protons and OH), 3.55 (s, 2H, $ArCH_2N$), 4.15-4.45 (br, 1H; t, J = 2 Hz after deuterium oxide addition, H-6), 7.22 (s, 5H, aromatic protons), 7.28 (s, 5H, aromatic protons); ^{13}C nmr (deuteriochloroform): δ 167.23 (s, C-2 carbonyl), 139.22 (s), 136.28 (s), 129.05 (d), 128.92 (d), 128.56 (d), 128.48 (d), 127.76 (d), 126.38 (d), 78.91 (d, C-6), 61.39 (t, C-3), 57.63 (t, C-5), 56.29 (t, $ArCH_2N$), 46.45 (t, CH_2NCO), 34.29 (t, $ArCH_2$); ms: m/e 310 (M^+, 5), 292 (10), 219 (7), 120 (34), 91 (100), 65 (18), 42 (21).

Anal. Calcd. for $C_{19}H_{22}N_2O_2$: C, 73.5; H, 7.1; N, 9.0. Found: C, 73.4; H, 7.1; N, 9.1.

2-Benzyl-1,2,3,6,7,11b-hexahydro-4*H*-pyrazino[2,1-*a*]isoquinolin-4-one (**4**).

To 2.51 g (8.1 mmoles) of the alcohol **3** was added 16.7 ml of 37% hydrochloric acid and the resulting solution was heated at 60° for 5 hours. After cooling, the reaction mixture was neutralized with solid sodium bicarbonate and extracted with chloroform (5 × 30 ml). The extracts were washed with water, dried and concentrated. The residue (2.84 g) was chromatographed on 85 g of silica gel with hexane-ethyl acetate (20:80) as the eluent. The eluates were concentrated (1.60 g) and rechromatographed on ten preparative chromatoplates by using hexane-ethyl acetate (10:90) as the developing solvent. Elution with acetone gave 1.03 g (44%) of **4** as an inestable reddish oil; ir (film): 1653 cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.37 (dd, J = 12, 10 Hz, 1H, H-1), 2.60-3.15 (m, 4H, C-7 protons, H-6 and H-3), 3.35-3.75 (m, 2H, H-1' and H-3'), 3.63 (s, 2H, $ArCH_2N$), 4.55-5.00 (m, 2H, H-6' and H-11b), 6.90-7.50 (m, 9H, aromatic protons); ms: m/e 292 (M^+, 30), 173 (59), 145 (100), 131 (50), 91 (54).

Anal. Calcd. for $C_{19}H_{20}N_2O$: C, 78.0; H, 6.9; N, 9.6. Found: C, 78.3; H, 6.8; N, 9.5.

1,2,3,6,7,11b-Hexahydro-4*H*-pyrazino[2,1-*a*]isoquinolin-4-one (**5**).

A solution of 0.144 g (0.49 mmole) of **4** in 3 ml of methanol and 0.5 ml of 2*N* aqueous hydrochloric acid was stirred with 0.048 g of 5% Pd/C under 4.5 atmospheres of hydrogen at 60°. After 4 hours the reaction mixture was filtered through Celite. The filtrates were neutralized with 2% aqueous sodium hydroxide and concentrated *in vacuo*. The residue was purified by preparative chromatography in one chromatography plate with methanol-ethyl acetate (60:40) as the developing solvent. The acetone eluates gave 0.093 g (94%) of **5** as pale yellow oil; ir (chloroform): 3345, 1639 cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.08 (S, 1H, interchangeable with deuterium oxide, NH), 2.55-3.20 (m, 4H, C-7 protons, H-6 and H-1), 3.30-3.60 (m, 2H, C-3 protons), 3.75 (dd, J = 10, 4 Hz, 1H, partially overlapped with the preceding signal, H-1'), 4.55-5.0 (m, 2H, H-6' and H-11b), 7.18 (s, 4H, aromatic protons); ms: m/e 202 (M^+, 59), 173 (66), 145 (100), 131 (85), 130 (72).

Anal. Calcd. for $C_{12}H_{14}N_2O$: C, 71.3; H, 7.0; N, 13.8. Found: C, 71.0; H, 7.1; N, 13.9.

2-(Cyclohexylcarbonyl)-1,2,3,6,7,11b-hexahydro-4*H*-pyrazino[2,1-*a*]isoquinolin-4-one (**1**).

A solution of 0.093 g (0.46 mmole) of **5**, 0.067 g (0.46 mmole) of cyclohexanecarboxylic acid chloride and 0.046 g (0.46 mmole) of anhydrous triethylamine in 4 ml of dry 1,2-dimethoxyethane was stirred at room temperature for 20 hours. The solution was evaporated to dryness and the residue dissolved in 30 ml of chloroform. The organic phase was washed with 10 ml of 5% aqueous sodium bicarbonate and with 10 ml of water. After being dried and concentrated *in vacuo* a white solid was obtained. Recrystallization from ethyl acetate-hexane gave 0.100 g (70%) of **1**, mp 129-131°, mp 134-137° (mixed); **1** was identical with an authentic sample (mp 135-136°) as judged by chromatographic and spectral comparisons; ir (chloroform): 1645 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.0-2.05 (m, 10H, cyclohexyl protons), 2.20-3.15 (m, 5H, CHCON, H-6, H-1 and C-7 protons), 4.0 (d, J = 18 Hz, 1H, H-3), 4.45 (d, J = 18 Hz, 1H, H-3'), 4.50-4.95 (m, 2H, H-1' and H-11b), 5.10 (br d, J = 15 Hz, 1H, H-6'), 7.22 (s, 4H, aromatic protons); ^{13}C nmr (deuteriochloroform): δ 174.56 (s, C-4 carbonyl), 164.53 (s, cyclohexyl carbonyl), 135.01 (s, C-7a), 132.84 (s, C-11a), 129.35 (d, C-8), 127.50 (d, C-11), 126.96 (d, C-9), 125.39 (d, C-10), 55.19 (d, C-11b), 48.94 (t, C-3), 45.40 (t, C-1), 40.80 (d), 39.04 (t, C-6), 29.29 (t), 28.81 (t, C-7), 25.76 (t); ms: m/e 312 (M^+, 53), 201 (83), 132 (94), 83 (58), 55 (100).

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