Synthesis of 2,3-Dihydro-3-hydroxy-2-(pyrrol-1-ylmethyl)-1*H*-isoindol-1-one. An Intermediate for the Synthesis of Tetracyclic Systems

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N-Chloromethylphthalimide **1** and the potassium salt of pyrrole gave *N*-(pyrrol-1-ylmethyl)phthalimide **2**. Reduction of **2** led to the hydroxyisoindolone **3**. This hydroxylactam cyclized under acidic conditions to lead to a pyrroloimidazoloisoindolone **4** *via* an acyliminium ion. Transformation of **3** with acetic acid derivatives provided **5**, **7** and **9** which gave by intramolecular cyclization, tetracyclic compounds **6**, **10** and **11**.

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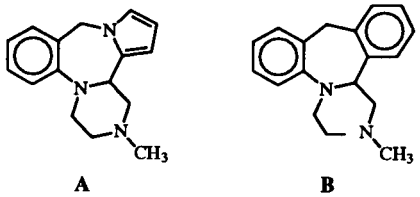
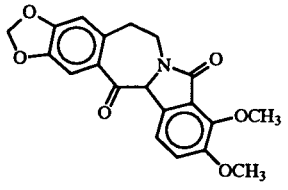
Tricyclic and tetracyclic benzodiazepines with an imidazole, triazole or pyrrole moiety have received great attention in the last year. The importance of the pyrrole ring in tetracyclic structures is documented by aptazepine **A**, an antidepressant agent related to mianserin **B** [1].

Scheme 1



A **B**

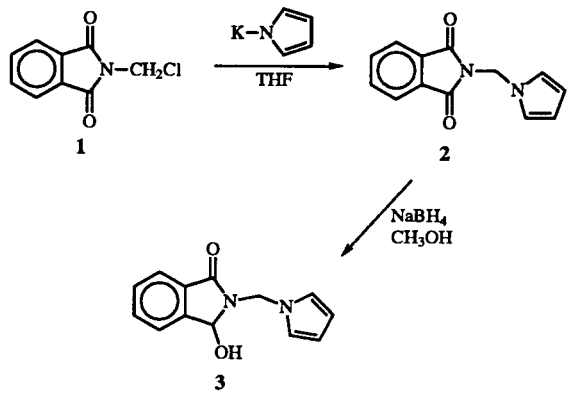


C

As a development of our investigations on the synthesis of tetracyclic diazepines fused to an isoindole and a pyrrole ring [2] we wish to report the synthesis of a pyrrolo[1,3]diazepinone containing the isoindole moiety, which is analogous to the alkaloid chilenine **C** [3], *via* an hydroxy(pyrrol-1-ylmethyl)isoindolone **3**. This key intermediate was also used to obtain azocino and imidazolo tetracyclic systems.

As indicated in Scheme 2, *N*-chloromethylphthalimide **1** treated with the potassium salt of pyrrole in tetrahydrofuran gave the expected 2-(pyrrol-1-ylmethyl)phthalimide **2** in 78% yield, which was reduced by sodium borohydride to the hydroxyisoindole **3** in 82% yield. Treatment

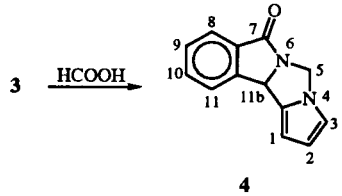
Scheme 2



1 **2** **3**

of **3** with formic acid at room temperature during 3 days led to the pyrroloimidazoloisoindolone **4** (27% yield). The structure of this compound was supported by spectroscopic data and microanalysis. The ^{1}H nmr spectrum shows the signals of a monosubstituted pyrrole ring protons which appear as a doublet of doublets with coupling constants of 1.7, 2.4 and 3.3 Hz. The H_5 protons are non-equivalent and exhibit a large difference of 1.4 ppm in chemical shift (J = 14.5 Hz) which is due to the influence of the lone pair of the nitrogen atom on one of the two protons as previously noted in indolizine [4] or thiazine [5] systems. Finally, the signal of the H_{11b} proton appears as a singlet (δ = 5.44 ppm).

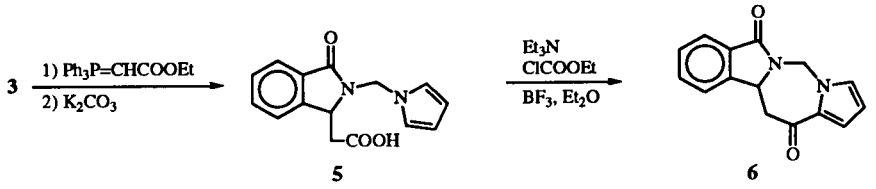
Scheme 3



4

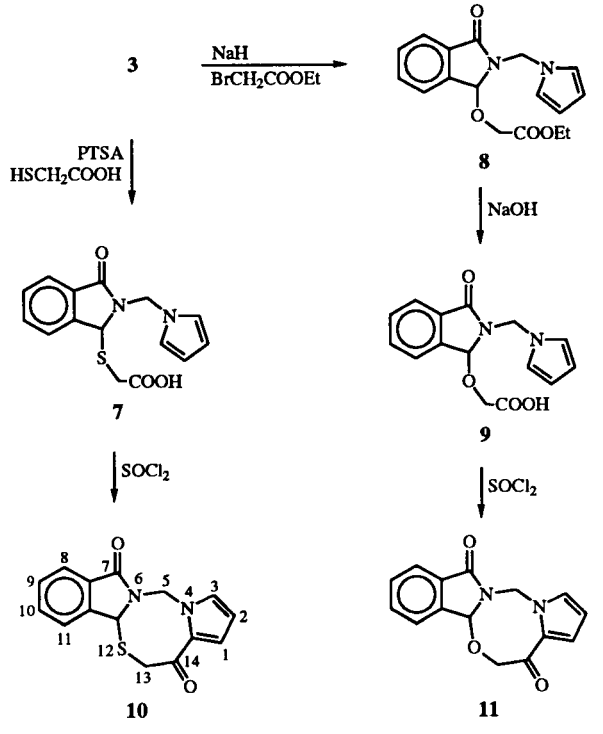
The Wittig reaction on **3**, using ethoxycarbonylmethylidenetriphenylphosphorane followed by basic hydrolysis of the nonisolated ester derivative gave the isoindolone acetic acid **5** in good yield (75%). The acid **5** was cyclized by successive treatment with triethylamine, ethyl chloroformate and boron trifluoride etherate to give ketone **6** (52% yield). As reported elsewhere [6], this method gave the best results since polyphosphoric acid and Friedel and Crafts conditions led to poor yields associated with extensive resinification.

Scheme 4



The fact that hydroxylactams easily gave nucleophilic substitution products *via* an acyliminium ion [7] led us to consider the synthesis of glycolic and thioglycolic derivatives from **3**. The isoindolone thioglycolic acid **7** was obtained directly by the action of thioglycolic acid in the presence of *para*-toluenesulfonic acid on the hydroxylactam **3** (62% yield). On the other hand, glycolic acid failed to react as in thienylmethyl *N*-substituted hydroxylactams [8]. Therefore, the carboxyethyloxyester derivative **8** was obtained by an *O*-alkylation of **3** using sodium hydride in tetrahydrofuran and ethyl bromoacetate. Saponification of the ethyl ester group gave the expected acid **9** (58% yield from **3**). Intramolecular cyclization of **7** and **9** using thionyl chloride in dichloromethane led to the cyclic ketones **10** and **11**, only in a low yield (14 and 15% respectively). Under these conditions, we did not observe the formation of the acid chloride derivative as reported in the synthesis of pyrrolopyridazinoisoindolones [6]. Other reagents (Lewis acids, polyphosphoric acid) only led to degradation or polymerization products.

Scheme 5



The ^{1}H nmr spectra of ketones **10** and **11** are very similar and exhibit two AB systems (H_5 and H_{13}) and the signals of the three protons of the monosubstituted pyrrole ring. For example, in the thiadiazocine **10** spectrum, the H_{13} protons appear as two well resolved doublets (δ = 2.30 and 2.85 ppm, J = 15.1 Hz) as well as the H_5 protons (δ = 5.40 and 6.05 ppm, J = 14.1 Hz). In addition, the signal of the H_{11b} proton appears as a singlet with a chemical shift of 5.30 ppm and the protons of the monosubstituted pyrrole exhibit three doublet of doublet with characteristic coupling constants (J = 1.8, 2.5 and 3.4 Hz).

In conclusion, the synthesis of pyrrolylmethyl *N*-substituted hydroxylactam is a convenient route to various tetracyclic systems containing a pyrrole and an isoindole moiety. Further investigations are in progress to extend the scope of these synthetic routes.

EXPERIMENTAL

All melting points were determined on a Leitz hot plate apparatus and are uncorrected. Infrared spectra were recorded on a Philips analytical PU 9800 FT-IR spectrometer (potassium bromide). The ^{1}H nmr spectra were recorded on a Bruker AC-200 instrument in deuteriochloroform solution and chemical shift (δ) are expressed in ppm relative to internal tetramethylsilane. Progress of the reactions was monitored by tlc on precoated plates of silicagel 60F 254 (Merck) and the spots were visualized using an uv lamp. Merck silicagel 60F (70-300 mesh) was used for column chromatography. The elemental analyses were carried out by the Department of Analytical Chemistry of Slovak Technical University, Bratislava, Slovakia.

2-(Pyrrol-1-ylmethyl)isoindole-1,3-dione (**2**).

To a well stirred suspension of the potassium salt [prepared from pyrrole (3.35 g, 0.05 mole) and potassium (1.9 g, 0.049 mole)] in anhydrous tetrahydrofuran (150 ml) under nitrogen

was added dropwise a solution of *N*-chloromethylphthalimide (9.78 g, 0.05 mole) dissolved in the same solvent (150 ml) at room temperature. The mixture was heated under reflux for 2 hours and then, stirred 20 hours at room temperature. The solvent was evaporated and the residue was treated with water and filtered to give the crude compound **1** which was recrystallized from ethanol (8.67 g, 78%), mp 162-164°; ir: 1701 (C=O) cm^{-1}; ^1H nmr: δ 5.70 (s, 2H, $-CH_2-N$), 6.14 (t, 2H, $H_{3'}$ and $H_{5'}$, J = 2.7 Hz), 6.94 (t, 2H, $H_{2'}$ and $H_{5'}$, J = 2.7 Hz), 7.66-7.94 (m, 4H, H arom).

Anal. Calcd. for $C_{13}H_{10}N_2O_2$: C, 69.02; H, 4.46; N, 12.38. Found: C, 68.62; H, 4.55; N, 12.31.

2,3-Dihydro-3-hydroxy-2-(pyrrol-1-ylmethyl)-1*H*-isoindol-1-one (**3**).

To a well stirred suspension of **2** (2.26 g, 0.01 mole) in dry methanol (100 ml) at 0° was added sodium borohydride (1.12 g, 0.03 mole) in a period of 45 minutes. The mixture was stirred at 0° for 2 hours. After removal of the solvent, the residue was acidified with 10% hydrochloric acid to *p*H = 5. The resulting precipitate was collected by filtration and washed with water. Recrystallization from ethanol gave 1.88 g (82%) of hydroxylactam **3**, mp 164-165°; ir: 3474 (OH), 1728 (C=O) cm^{-1}; ^1H nmr: δ 3.49 (d, 1 H, OH, J = 11.6 Hz), 5.14 (d, 1H, CH_2-N, J = 14 Hz), 5.56 (d, 1H, CH_2-N, J = 14 Hz), 5.63 (d, 1H, H_3, J = 11.6 Hz), 6.10 (t, 2H, $H_{3'}$ and $H_{4'}$, J = 2.8 Hz), 6.80 (t, 2H, $H_{2'}$ and $H_{5'}$, J = 2.8 Hz), 7.44-7.71 (m, 4H, H arom).

Anal. Calcd. for $C_{13}H_{12}N_2O_2$: C, 68.41; H, 5.30; N, 12.27. Found: C, 68.67; H, 5.17; N, 12.02.

5,11b-Dihydropyrrolo[1',2':3,4]imidazolo[5,1-*a*]isoindol-7-one (**4**).

A solution of **3** (0.46 g, 2 mmoles) in formic acid (10 ml) was stirred for 3 days at room temperature. After removal of formic acid *in vacuo*, the residue was taken up in dichloromethane, washed with brine, dried and evaporated. An analytical sample was obtained by recrystallization from ethanol (115 mg, 27%), mp 258-263°; ir: 1703 (C=O) cm^{-1}; ^1H nmr: δ 4.91 (d, 1H, H_5, J = 14.5 Hz), 5.44 (s, 1H, H_{11b}), 5.70 (dd, 1H, H_2, J = 2.4, 3.3 Hz), 6.20 (dd, 1H, H_1, J = 1.7, 3.3 Hz), 6.31 (d, 1H, H_5, J = 14.5 Hz), 6.92 (dd,1H, H_3, J = 1.7, 2.4 Hz), 7.31-7.92 (m, 4H, H arom).

Anal. Calcd. for $C_{13}H_{10}N_2O$: C, 74.27; H, 4.79; N, 13.32. Found: C, 74.29; H, 4.51; N, 13.14.

2,3-Dihydro-1-oxo-2-(pyrrol-1-ylmethyl)-1*H*-isoindol-3-acetic Acid (**5**).

A mixture of hydroxylactam **3** (2.28 g, 0.01 mole) and carbethoxycarbonyltriphenylphosphorane (4.1 g, 0.012 mole) in toluene (50 ml) was refluxed with stirring for 10 hours. The solvent was evaporated under reduced pressure and potassium carbonate (2.4 g), methanol (24 ml) and water (6 ml) were added. The mixture was refluxed for 8 hours, then concentrated under reduced pressure. Water and dichloromethane were added and the organic layer was discarded. The aqueous layer was washed with dichloromethane and acidified with hydrochloric acid (10%) to *p*H = 2. The residue was extracted with dichloromethane. After removal of the solvent, the desired acetic acid **5** was recrystallized from acetone (2 g, 76%), mp 149-152°; ir: 3379 (OH), 1724 (COOH), 1674 (C=O) cm^{-1}; ^1H nmr (DMSO-d_6): δ 2.76 (dd, 1H, CH_2-CO, J = 7.1, 14.6 Hz), 3.09 (dd, 1H, CH_2-CO, J = 4.8, 14.6 Hz), 4.70 (dd, 1H, H_3, J = 4.8, 7.1 Hz), 5.38 (d, 1H, CH_2-N, J = 15.1 Hz), 5.89 (d, 1H, CH_2-N, J = 15.1 Hz), 6.00 (t, 2H, $H_{3'}$ and $H_{4'}$, J = 2.9 Hz), 6.90 (t, 2H, $H_{2'}$ and $H_{5'}$, J = 2.9 Hz), 7.50-7.75 (m, 4H, H arom).

Anal. Calcd. for $C_{15}H_{14}N_2O_3$: C, 66.66; H, 5.22; N, 10.36. Found: C, 66.74; H, 5.08; N, 10.49.

5,11b-Dihydro-12*H*-pyrrolo[1',2';3,4]diazepino[7,1-*a*]isoindole-7,13-dione (**6**).

To a stirred solution of the acid **5** (2.7 g, 0.01 mole) and triethylamine (1.11 g, 0.011 mole) was added dropwise ethyl chloroformate (1.2 g, 0.011 mole) at 0°. The reaction mixture was stirred at the same temperature for 2 hours. Then, boron trifluoride etherate (48%, 5.6 ml, 0.021 mole) was added dropwise at 0° and the reaction mixture was stirred at room temperature for 5 hours. The mixture was poured into ice-water and extracted with dichloromethane. The organic layer was washed with 10% aqueous solution of sodium hydroxide and then with water, dried and concentrated *in vacuo*. The residue was purified by chromatography on a silica gel column eluting with dichloromethane (1.2 g, 48%), mp 167-170°; ir: 1728 and 1649 (C=O) cm^{-1}; ^1H nmr: 3.10 (dd, 1H, H_{12}, J = 5.9, 15 Hz), 3.55 (dd, 1H, H_{12}, J = 5.1, 15 Hz), 5.02 (dd, 1H, H_{11b}, J = 5.1, 5.9 Hz), 5.53 (d, 1H, H_5, J = 13.7 Hz), 6.12 (d, 1H, H_5, J = 13.7 Hz), 6.15 (dd, 1H, H_2, J = 2.5, 3.3 Hz), 6.97 (dd, 1H, H_1, J = 1.8, 3.3 Hz), 7.05 (dd, 1H, H_3, J = 1.8, 2.5 Hz), 7.45-7.80 (m, 4H, H arom).

Anal. Calcd. for $C_{15}H_{12}N_2O_2$: C, 71.42; H, 4.79; N, 11.10. Found: C, 70.99; H, 4.88; N, 11.38.

2,3-Dihydro-2-(pyrrol-1-ylmethyl)-1*H*-isoindol-3-thioglycolic Acid (**7**).

To a mixture of hydroxylactam **3** (2.28 g, 0.01 mole) and mercaptoacetic acid (1.4 g, 0.015 mole) in dichloromethane was added a catalytic amount of *p*-toluenesulfonic acid. The reaction mixture was stirred for one week at room temperature. After removal of the solvent, the residue was diluted with a saturated solution of potassium carbonate and washed with dichloromethane. The aqueous layer was acidified with 10% aqueous hydrochloric acid, the precipitate was collected, washed with water and with ether. Recrystallization from acetone afforded 1.88 g (62%) of the acid **7**, mp 180-183°; ir: 3405 (OH), 1738 (COOH), 1672 (C=O) cm^{-1}; ^1H nmr: δ 2.30 (d, 1 H, CH_2-S, J = 15.9 Hz), 2.79 (d, 1H, $N-CH_2$, J = 14 Hz), 6.12 (t, 2H, $H_{3'}$ and $H_{4'}$, J = 2.7 Hz), 6.82 (t, 2H, $H_{2'}$ and $H_{5'}$, J = 2.7 Hz), 7.46-7.86 (m, 4H, H arom).

Anal. Calcd. for $C_{15}H_{14}N_2O_3S$: C, 59.59; H, 4.67; N, 9.27. Found: C, 59.27; H, 4.39; N, 9.02.

Ethyl 2,3-Dihydro-2-(pyrrol-1-ylmethyl)-1*H*-isoindol-1-one-3-glycolate (**8**).

Sodium hydride (0.332 g, 0.0138 mole) was added to a solution of hydroxylactam **3** (2.8 g, 0.0123 mole) in anhydrous tetrahydrofuran (60 ml) at room temperature. The reaction mixture was stirred for 2 hours at room temperature under nitrogen, and then a solution of ethyl bromoacetate (2.05 g, 0.0123 mole) in anhydrous tetrahydrofuran (20 ml) was added. The reaction mixture was refluxed for 10 hours and after cooling the solvent was removed *in vacuo*. The residue was dissolved in dichloromethane, and the organic layers were washed with brine, dried and evaporated. The residue was recrystallized from ethanol to give 2.7 g of the ester **8** (70%), mp 129-131°; ir: 1753 and 1671 (C=O) cm^{-1}; ^1H nmr: δ 1.12 (t, 3H, CH_3), 4.10 (q, 2H,

O-CH_2CH_3), 4.51 (d, 1H, O-CH_2, J = 9.1 Hz), 4.67 (d, 1H, O-CH_2, J = 9.1 Hz), 5.53 (s, 1H, H_3), 5.58 (d, 1H, CH_2-N, J = 14.1 Hz), 6.12 (d, 1H, CH_2-N, J = 14.1 Hz), 6.09 (t, 2H, $H_{3'}$ and $H_{4'}$, J = 2.8 Hz), 6.85 (t, 2H, $H_{2'}$ and $H_{5'}$, J = 2.8 Hz), 7.45-7.87 (m, 4H, H arom).

Anal. Calcd. for $C_{17}H_{18}N_2O_4$: C, 64.96; H, 5.77; N, 8.91. Found: C, 65.31; H, 5.52; N, 8.64.

2,3-Dihydro-2-(pyrrol-1-ylmethyl)-1*H*-isoindol-1-one-3-glycolic Acid (**9**).

The ester **8** (2.64 g, 8.4 mmoles) was dissolved in 26 ml of ethanol/tetrahydrofuran mixture (1:1), and 5% aqueous sodium hydroxide (22.4 ml) was slowly added. The reaction mixture was stirred at room temperature for 4 hours, concentrated and acidified with 10% aqueous hydrochloric acid until *p*H 3-4. The suspension was extracted with dichloromethane, and the organic phase was washed with brine, dried and concentrated. The residue was crystallized from ethanol to give 1.98 g (82%) of the acid **9**, mp 148-151°; ir: 3410 (OH), 1734 and 1665 (C=O) cm^{-1}; ^1H nmr: δ 4.52 (d, 1H, O-CH_2, J = 9 Hz), 4.64 (d, 1H, O-CH_2, J = 9 Hz), 5.56 (s, 1H, H_3), 5.6 (d, 1H, CH_2-N, J = 14.1 Hz), 6.09 (d, 1H, CH_2-N, J = 14.1 Hz), 6.13 (t, 2H, $H_{3'}$ and $H_{4'}$, J = 2.8 Hz), 6.83 (t, 2H, $H_{2'}$ and $H_{5'}$, J = 2.8 Hz), 7.46-7.85 (m, 4H, H arom).

Anal. Calcd. for $C_{15}H_{14}N_2O_4$: C, 62.93; H, 4.93; N, 9.79. Found: C, 63.10; H, 4.79; N, 9.51.

5,11b-Dihydro-13*H*-pyrrolo[1',2':5,6][1,3,5]thiadiazocino-[2,3-*a*]isoindole-7,14-dione (**10**).

Thionyl chloride (0.26 g, 2.2 mmoles) was added to a solution of acid **7** (0.57 g, 2 mmoles) in dry dichloromethane. The reaction mixture was stirred at room temperature for 10 hours, and then was poured onto crushed ice, basified with 10% aqueous sodium hydroxide and extracted with dichloromethane. The organic layers were washed with brine, dried and evaporated. The residue was chromatographed on silica gel eluting with dichloromethane to give 80 mg of **10** (14%), mp 174-176°; ir: 1730 and 1686 (C=O) cm^{-1}; ^1H nmr: δ 2.30 (d, 1H, H_{13}, J = 15.1 Hz), 2.85 (d, 1H, H_{13}, J = 15.1 Hz), 5.30 (s, 1H, H_{11b}), 5.40 (d, 1H, H_5, J = 14.1 Hz), 6.05 (d, 1H, H_5, J = 14.1 Hz), 6.13 (dd, 1H, H_2, J = 1.8, 3.4 Hz), 6.84 (dd, 1H, H_1, J = 2.5, 3.4 Hz), 7.08 (dd, 1H, H_3, J = 1.8, 2.5 Hz), 7.45-7.84 (m, 4H, H arom).

Anal. Calcd. for $C_{15}H_{12}N_2O_2S$: C, 63.36; H, 4.25; N, 9.85. Found: C, 63.53; H, 4.36; N, 9.48.

5,11b-Dihydro-13*H*-pyrrolo[1',2':5,6][1,3,5]oxadiazocino-[2,3-*a*]isoindole-7,14-dione (**11**).

This compound was obtained in a yield of 15%, starting from **9**, under the same conditions as for compound **10**, mp 164-167°; ir: 1727 and 1675 (C=O) cm^{-1}; ^1H nmr: δ 4.52 (d, 1H, H_{13}, J = 9.1 Hz), 4.65 (d, 1H, H_{13}, J = 9.1 Hz), 5.56 (s, 1H, H_{11b}), 5.58 (d, 1H, H_5, J = 13.9 Hz), 6.03 (d, 1H, H_5, J = 1.8, 3.3 Hz), 6.17 (dd, 1H, H_2, J = 2.4, 3.3 Hz), 6.99 (dd, 1H, H_1, J = 1.8, 3.3 Hz), 7.10 (dd, 1H, H_3, J = 1.8, 2.4 Hz), 7.45-7.88 (m, 4H, H arom).

Anal. Calcd. for $C_{15}H_{12}N_2O_3$: C, 67.16; H, 4.51; N, 10.44. Found: C, 67.48; H, 4.34; N, 10.26.

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