Heterocyclic Systems. VIII. Synthesis of 1*H*,4*H*-Pyrazolo[4,3-*f*]pyrrolo[1,2-*a*]azepine Derivatives

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The synthesis of the unknown title compounds is described. The preparation involves intramolecular acylation of 3-[1-phenyl-5-(1-pyrryl)pyrazol-4-yl]propanoic acid **9** to the tricyclic ketone **10**, which was then transformed into 1*H*,4*H*-pyrazolo[4,3-*f*]pyrrolo[1,2-*a*]azepine **12** and its dihydro derivative **13** by reductive procedures.

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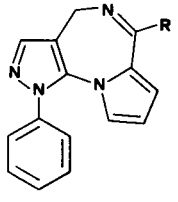
During our searches on nitrogen heterocyclic systems we were interested in new tricyclic compounds bearing both pyrazolo and pyrrolo moieties.

Previously we have described the synthesis of 1*H*,4*H*-pyrazolo[4,3-*f*]pyrrolo[1,2-*a*][1,4]diazepine **1** and 1*H*,4*H*,6*H*-pyrazolo[3,4-*e*]pyrrolo[2,1-*c*][1,4]oxazepine **2** derivatives showing structural affinities with CNS and antitumor agents [1,2].

Now we wish to report herein the synthesis of 1-phenyl-1*H*,4*H*-pyrazolo[4,3-*f*]pyrrolo[1,2-*a*]azepine **3**, a novel tricyclic ring which represents an isosteric system of the above cited compounds **1** and **2**. Our interest in this heterocyclic substance is also due to its analogy with another tricyclic system, namely 1-phenyl-1*H*-pyrazolo[3,4-*e*]indolizine **4**, recently described by us [3] in connection with our studies on potential antitumor agents.



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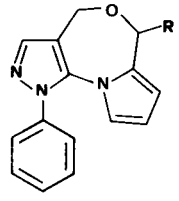

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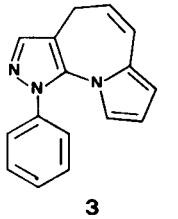

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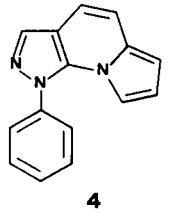

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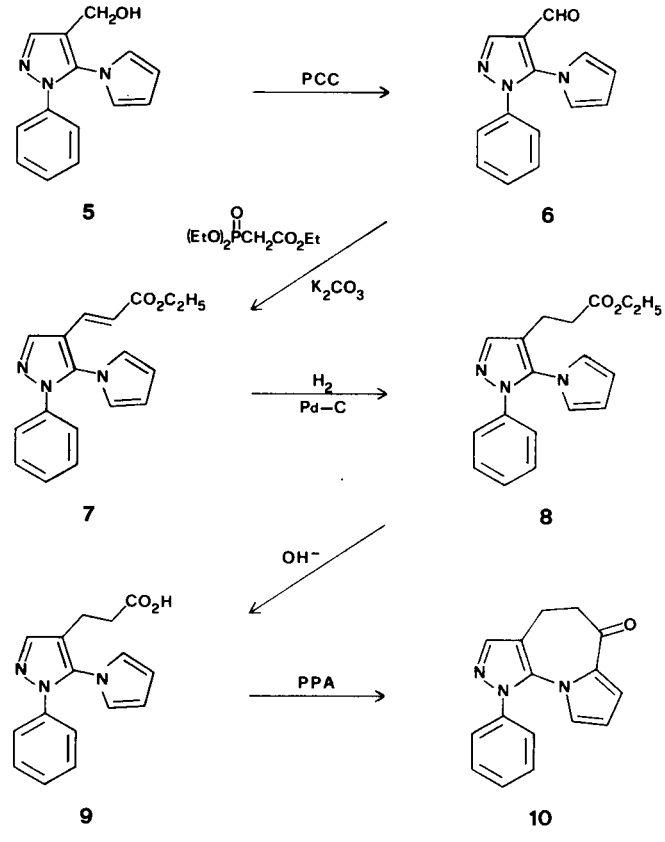
For the synthesis of the title compounds we started from 4-hydroxymethyl-1-phenyl-5-(1-pyrryl)pyrazole **5** (Scheme 1), readily obtained as previously reported [3].

Scheme 1

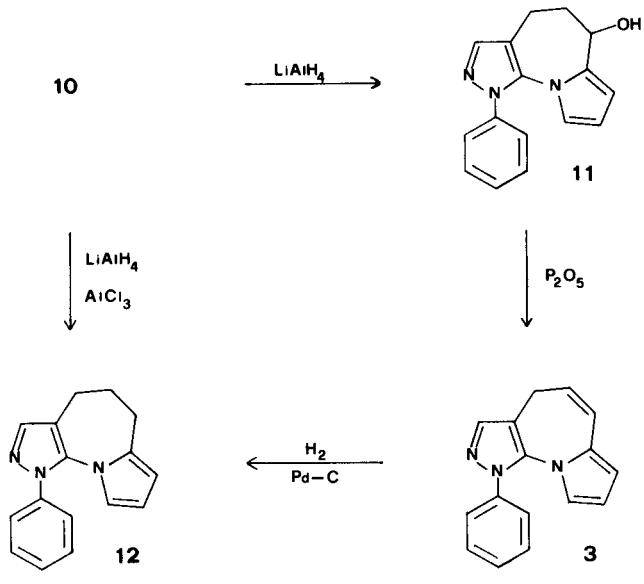


Oxidation of **5** with pyridinium chlorochromate (PCC) afforded the corresponding aldehyde **6**, which was subjected to a Wittig-Horner condensation with triethyl phosphonoacetate under solid-liquid transfer conditions, following the procedure described by Moulongui *et al.* [4]. This reaction exhibited a high degree of stereoselectivity as only the *trans*-3-[1-phenyl-5-(1-pyrryl)pyrazol-4-yl]propenoic acid ethyl ester **7** was obtained (86% yield). Catalytic hydrogenation of **7** provided in 97% yield the saturated ester **8**, which was in turn hydrolyzed quantitatively

in alkaline medium to the corresponding acid **9**. The tricyclic ketone **10** was obtained in 92% yield by intramolecular acylation of **9** in the presence of polyphosphoric acid (PPA).

The conversion of 5,6-dihydro-6-oxo-1-phenyl-1*H*,4*H*-pyrazolo[4,3-*f*]pyrrolo[1,2-*a*]azepine **10** into deoxygenated derivatives is depicted in Scheme 2.

Scheme 2



Lithium aluminum hydride reduction of **10** furnished the alcohol **11**, which was dehydrated to 1*H*,4*H*-pyrazolo-[4,3-*f*]pyrrolo[1,2-*a*]azepine **3** by the action of phosphorus pentoxide in boiling benzene. Subsequent hydrogenation of **3** gave the tricyclic compound **12**, which was also directly obtained in good yield from the ketone **10**, by lithium aluminum hydride/aluminum chloride reduction.

EXPERIMENTAL

Melting points were determined on an Electrothermal IA-6304 apparatus and are uncorrected. Infrared spectra (Nujol mulls) were run on a Perkin-Elmer 297 spectrophotometer. The pmr spectra were recorded in deuteriochloroform (TMS as the internal standard) on a Varian EM-390 spectrometer. Merck alumina and silica gel (70-230 mesh ASTM) were used for chromatographic purifications. Microanalyses were performed by A. Pietrogrande, Padova, Italy.

4-Formyl-1-phenyl-5-(1-pyrryl)pyrazole (**6**).

To a well-stirred suspension of powdered pyridinium chlorochromate (7.5 g, 0.035 mole) in dry dichloromethane (50 ml), a solution of the alcohol **5** (5.5 g, 0.023 mole) in the same solvent (15 ml) was added. The mixture was stirred at room temperature for 1.5 hours. Then diethyl ether (50 ml) was added and the supernatant liquid was decanted. The solid residue in the flask was triturated with diethyl ether (3 × 10 ml) and finally discarded. The combined organic solution was filtered through a short column of magnesium trisilicate hydrate (50 g). The filtrate was evaporated under reduced pressure to give a solid residue, which was purified by chromatography on a silica gel column. Elution with benzene:chloroform (1:1) afforded 5.3 g (97%) of pure aldehyde **6**, mp 83-84° (from cyclohexane); ir: ν CHO 1680 cm^{-1}; pmr: δ 6.37 (m, 2H, pyrrole β-protons), 6.77 (m, 2H, pyrrole α-protons), 7.1-7.5 (m, 5H, phenyl), 8.23 (s, 1H, pyrazole proton), 9.82 ppm (s, 1H, CHO).

Anal. Calcd. for $C_{14}H_{11}N_3O$: C, 70.87; H, 4.67; N, 17.71. Found: C, 70.67; H, 4.55; N, 17.65.

Ethyl *trans*-3-[1-Phenyl-5-(1-pyrryl)pyrazol-4-yl]propenoate (**7**).

To a mixture of triethyl phosphonoacetate (17.3 g, 0.077 mole) and anhydrous potassium carbonate (26.1 g, 0.189 mole) a solution of aldehyde **6** (14.9 g, 0.063 mole) in absolute ethanol (140 ml) was added in one portion. The mixture was warmed at 70° for 2 hours while stirring. After cooling it was diluted with water (400 ml) and extracted with diethyl ether (3 × 150 ml). The ether layer was washed with brine (3 × 100 ml), dried over anhydrous sodium sulfate and evaporated to give 16.6 g (86%) of pure ester **7**, mp 117-118° after recrystallization from benzene:petroleum ether; ir: ν $COOC_2H_5$ 1710 cm^{-1}; pmr: δ 1.25 (t, 3H, $COOCH_2CH_3$), 4.22 (q, 2H, $COOCH_2CH_3$), 6.16 (d, J = 16.5 Hz, 1H, olefinic H-2), 6.35 (m, 2H, pyrrole β-protons), 6.67 (m, 2H, pyrrole α-protons), 7.05-7.40 (m, 5H, phenyl), 7.43 (d, J = 16.5 Hz, 1H, olefinic H-3), 8.05 ppm (s, 1H, pyrazole proton).

Anal. Calcd. for $C_{18}H_{17}N_3O_2$: C, 70.34; H, 5.58; N, 13.67. Found: C, 70.40; H, 5.52; N, 13.50.

Ethyl 3-[1-Phenyl-5-(1-pyrryl)pyrazol-4-yl]propanoate (**8**).

A solution of ester **7** (9.2 g, 0.03 mole) in ethyl acetate (150 ml) was hydrogenated in a Parr apparatus for 6 hours at 45° and at the initial pressure of 50 psi in the presence of 10% palladium on charcoal (400 mg). After removal of the catalyst by filtration, the solution was evaporated under reduced pressure to give 9.0 g (97%) of **8** as an analytically pure oil which crystallized on standing, mp 36-39°; ir: ν $COOC_2H_5$ 1780 cm^{-1}; pmr: δ 1.22 (t, 3H, $COOCH_2CH_3$), 2.62 (m, 4H, aliphatic chain), 4.13 (q, 2H, $COOCH_2CH_3$), 6.33 (m, 2H, pyrrole β-protons), 6.66 (m, 2H, pyrrole α-protons), 7.05-7.45 (m, 5H, phenyl), 7.66 ppm (s 1H, pyrazole proton).

Anal. Calcd. for $C_{18}H_{19}N_3O_2$: C, 69.88; H, 6.19; N, 13.58. Found: C, 69.77; H, 6.20; N, 13.41.

3-[1-Phenyl-5-(1-pyrryl)pyrazol-4-yl]propanoic Acid (**9**).

A mixture of ester **8** (4.0 g, 0.013 mole), 95% ethanol (6.5 ml) and 10% aqueous potassium hydroxide (22 ml, 0.039 mole) was refluxed for 75 minutes. The cooled solution was acidified by adding concentrated hydrochloric acid and the precipitate which formed was taken up into chloroform (2 × 30 ml). The combined extract was washed with water and dried over anhydrous sodium sulfate. Removal of the solvent afforded 3.6 g (98%) of pure 3-[1-phenyl-5-(1-pyrryl)pyrazol-4-yl]propanoic acid **9**, mp 101-103° (from benzene:cyclohexane); ir: ν COOH 1725 cm^{-1}; pmr: δ 2.60 (m, 4H, aliphatic chain), 6.30 (m, 2H, pyrrole β-protons), 6.63 (m, 2H, pyrrole α-protons), 7.0-7.4 (m, 5H, phenyl), 7.70 (s, 1H, pyrazole proton), 8.0 ppm (br s, 1H, COOH).

Anal. Calcd. for $C_{16}H_{15}N_3O_2$: C, 68.31; H, 5.38; N, 14.94. Found: C, 68.20; H, 5.35; N, 14.83.

5,6-Dihydro-6-oxo-1-phenyl-1*H*,4*H*-pyrazolo[4,3-*f*]pyrrolo[1,2-*a*]azepine (**10**).

Finely powdered acid **9** (7.0 g, 0.025 mole) was added in small portions to polyphosphoric acid (70 g) pre-heated at 90°. After stirring at the same temperature for 1 hour, the mixture was diluted with water (1000 ml) and vigorously stirred for 30 minutes, then ethyl acetate (200 ml) was added. The organic layer was separated, washed with 5% sodium bicarbonate solution, then brine and finally dried over anhydrous sodium sulfate. Evaporation of the solvent under reduced pressure gave a solid residue which was chromatographed on an alumina column eluting with chloroform. Removal of the solvent from the first eluates provided 6.05 g (92%) of pure tricyclic ketone **10** as a white solid, mp 146-149° after recrystallization from ethanol; ir: ν C=O 1630 cm^{-1}; pmr: δ 2.86 (m, 4H, methylene groups), 6.18 (m, 1H, H-8), 6.50 (m, 1H, H-9), 7.2-7.5 (m, 6H, H-7 and phenyl), 7.63 ppm (s, 1H, pyrazole proton).

Anal. Calcd. for $C_{16}H_{13}N_3O$: C, 72.98; H, 4.98; N, 15.96. Found: C, 72.76; H, 5.00; N, 15.89.

5,6-Dihydro-6-hydroxy-1-phenyl-1*H*,4*H*-pyrazolo[4,3-*f*]pyrrolo[1,2-*a*]-azepine (**11**).

To a stirred suspension of lithium aluminum hydride (0.144 g, 3.8 mmoles) in anhydrous tetrahydrofuran (10 ml) a solution of the ketone **10** (1.0 g, 3.8 mmoles) in the same solvent (30 ml) was added dropwise. After stirring for 3 hours at 60° the mixture was cooled (0-5°) and water was carefully added. The precipitate which formed was filtered off and the solution was concentrated to a small volume. Ethyl acetate and water were added and the organic layer was separated and dried (sodium sulfate). The oily residue obtained by removing the solvent *in vacuo* was purified by column chromatography on alumina. Elution first with dichloromethane, then with dichloromethane:ethyl acetate (1:1) afforded 800 mg (79%) of alcohol **11**, mp 93-96° (from toluene:ligroin); ir: ν OH 3300 cm^{-1}; pmr: δ 1.96-2.76 (m, 4H, methylene groups), 2.85 (br s, 1H, OH), 4.93 (m, 1H, H-6), 6.03 (m, 1H, H-8), 6.24 (m, 2H, H-7,9), 7.37 (m, 5H, phenyl), 7.50 ppm (s, 1H, pyrazole proton).

Anal. Calcd. for $C_{16}H_{15}N_3O$: C, 72.43; H, 5.70; N, 15.84. Found: C, 72.29; H, 5.71; N, 15.77.

1-Phenyl-1*H*,4*H*-pyrazolo[4,3-*f*]pyrrolo[1,2-*a*]azepine (**3**).

Phosphorus pentoxide (8.6 g, 0.06 mole) was added in one portion to a solution of hydroxy derivative **11** (4.0 g, 0.015 mole) in dry benzene (50 ml) and the mixture was refluxed for 2.5 hours. After cooling the supernatant liquid was decanted and the gummy residue in the flask was washed with benzene (2 × 10 ml). The cloudy solution was filtered, washed with 5% sodium bicarbonate solution, then with water and finally dried (sodium sulfate). Evaporation of the solvent gave pure 1-phenyl-1*H*,4*H*-pyrazolo[4,3-*f*]pyrrolo[1,2-*a*]azepine **3** (2.0 g, 54%), which was recrystallized from 2-propanol, mp 120-122°; pmr: δ 3.20 (d, $J_{4,5}$ = 5.3 Hz, 2H, H-4), 5.9 (dt, $J_{4,5}$ = 5.3 Hz and $J_{5,6}$ = 14.3 Hz, 1H, H-5), 6.1 (m, 1H, H-8), 6.25 (m, 2H, H-7,9), 6.50 (d, $J_{5,6}$ = 14.3 Hz, 1H, H-6), 7.1-7.4 (m, 5H, phenyl), 7.50 ppm (s, 1H, pyrazole proton).

Anal. Calcd. for $C_{16}H_{13}N_3$: C, 77.71; H, 5.30; N, 16.99. Found: C, 77.80; H, 5.26; N, 16.94.

5,6-Dihydro-1-phenyl-1*H*,4*H*-pyrazolo[4,3-*f*]pyrrolo[1,2-*a*]azepine (**12**) I.

A solution of 1-phenyl-1*H*,4*H*-pyrazolo[4,3-*f*]pyrrolo[1,2-*a*]azepine **12** (990 mg, 4.0 mmoles) in ethyl acetate (50 ml) was hydrogenated in a Parr apparatus at 40° and at the initial pressure of 50 psi in the presence of 10% palladium on charcoal (100 mg). The catalyst was filtered off and the clear solution was evaporated to an oily residue. Column chromatography on alumina (chloroform as eluent) afforded 700 mg (70%) of pure **12**, mp 89-91° after recrystallization from petroluem ether; pmr: δ 2.05 (m, 2H, H-5), 2.5-2.9 (m, 4H, H-4,6), 6.05 (m, 2H, H-7,8), 6.25 (m, 1H, H-9), 7.4 (m, 5H, phenyl), 7.57 ppm (s, 1H, pyrazole proton).

Anal. Calcd. for $C_{16}H_{15}N_3$: C, 77.08; H, 6.06; N, 16.86. Found: C, 77.15; H, 6.00; N, 16.85.

II.

A solution of aluminum chloride (840 mg, 6.3 mmoles) in anhydrous diethyl ether (8 ml) was rapidly added to a suspension of lithium aluminum hydride (240 mg, 6.3 mmoles) in the same solvent (8 ml). After stirring at room temperature for 10 minutes, a solution of ketone **10** (1.32 g, 5 mmoles) and aluminum chloride (670 mg, 5 mmoles) in anhydrous diethyl ether (40 ml) and anhydrous tetrahydrofuran (30 ml) was dropped into the above mixture. The resulting suspension was stirred at room temperature for 45 minutes, then carefully diluted with water (10 ml) and 6*N* sulfuric acid (10 ml). The organic layer was separated, washed with brine (3 × 100 ml) and dried over anhydrous sodium sulfate. Removal of the solvent furnished an oily residue which was chromatographed on alumina eluting with chloroform to give 1.1 g (88%) of pure 5,6-dihydro-1-phenyl-1*H*,4*H*-pyrazolo[4,3-*f*]pyrrolo[1,2-*a*]azepine **12**.

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