Heterocyclic Systems. VII [1]. Synthesis of 1*H*-Pyrazolo[3,4-*e*]indolizine Derivatives

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Suitable 1-phenyl-5-(1-pyrryl)pyrazole intermediates underwent Knoevenagel or Wittig intramolecular olefination to give derivatives of 1*H*-pyrazolo[3,4-*e*]indolizine, a hitertho unknown tricyclic heteroaromatic system.

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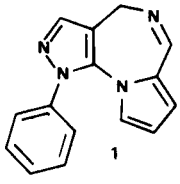
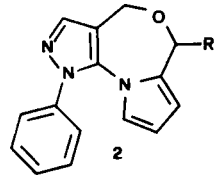
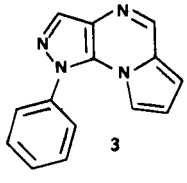
Tricyclic systems with a bridge-head nitrogen atom have been extensively studied over last years owing to their interesting activities displayed in biological and pharmacological tests.

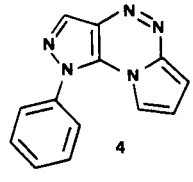
Recently, we have reported on the synthesis of 1*H*,4*H*-pyrazolo[4,3-*f*]pyrrolo[1,2-*a*][1,4]diazepine **1** and 1*H*,4*H*,6*H*-pyrazolo[3,4-*e*]pyrrolo[2,1-*c*][1,4]oxazepine **2** derivatives as potential antianxiety and antitumor agents [2,1].

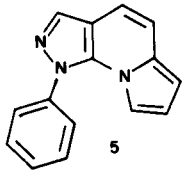
The finding of antiviral and antineoplastic properties of 1-phenylpyrazolo[3,4-*b*]pyrazine, recently claimed in the patent literature [3], has elicited an interest in the preparation of related compounds for biological evaluation as well as in the synthesis of new condensed heterocycles containing the pyrazolo[3,4-*b*]pyrazine moiety. In 1985 Světlik described 1-phenyl derivatives of pyrazolo[4,3-*e*]pyrrolo-[1,2-*a*]pyrazine **3** and of pyrazolo[3,4-*e*]pyrrolo[2,1-*c*]-[1,2,4]-triazine **4**, new tricyclic ring systems annellating a pyrrole nucleus on the pyrazolo[3,4-*b*]pyrazine or the pyrazolo[3,4-*e*]-*as*-triazine units [4].

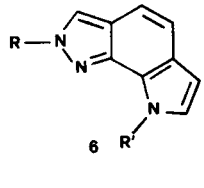


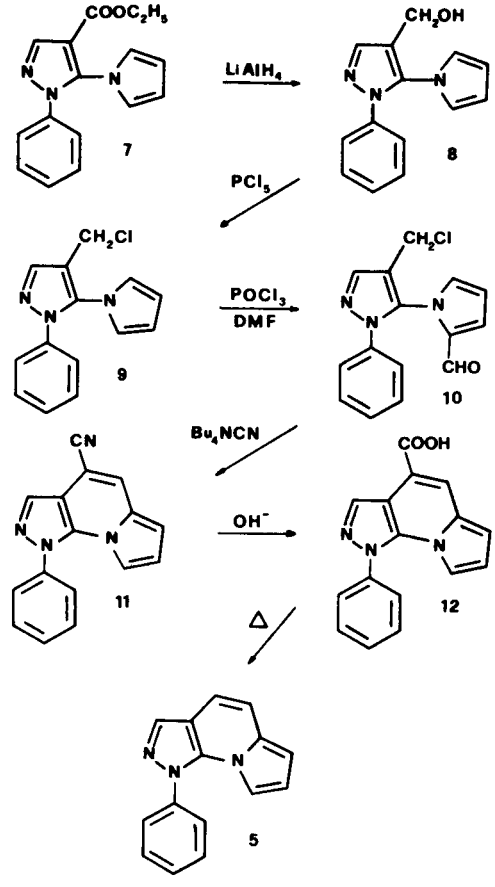












Scheme I

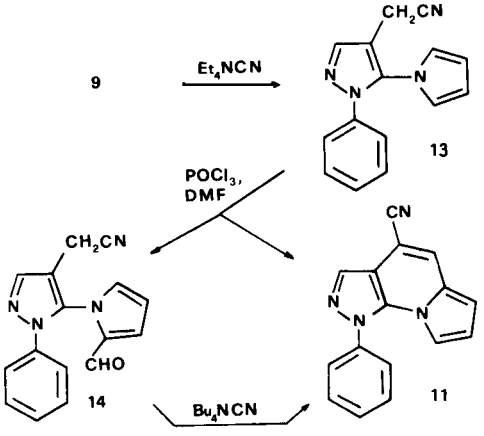
Pursuing our searches on new nitrogen heterocyclic compounds incorporating both pyrrolo and pyrazolo moieties, we decided to investigate synthetic routes to 1-phenyl-1*H*-pyrazolo[3,4-*e*]indolizine **5**, which has not previously been reported in the literature. This heteroaromatic nucleus is also closely related to the isomeric 2,8-dihydropyrrolo[3,2-*g*]indazole system **6**, that we have studied recently [5] as a pyrazolo analog of PDE I and PDE II benzodipyrrole skeleton [6].

The strategy we devised for the synthesis of 1-phenyl-1*H*-pyrazolo[3,4-*e*]indolizine **5** involved as a final step the construction of the central pyridine ring by a Knoevenagel or Wittig intramolecular condensation starting from suitable 1-phenyl-5-(1-pyrryl)pyrazole intermediates.

4-Chloromethyl-1-phenyl-5-(1-pyrryl)pyrazole **9** [7] seemed to be an attractive synthon for the preparation of the title compounds. Such a chloro derivative **9** was obtained from 4-ethoxycarbonyl-1-phenyl-5-(1-pyrryl)pyrazole **7** [3] by reduction with lithium aluminum hydride and subsequent treatment of the alcohol **8** with phosphorus pentachloride.

A first approach to 1-phenyl-1*H*-pyrazolo[3,4-*e*]indolizine **5** involved Vilsmeier-Haack formylation of **9** to the chloroaldehyde **10**. Treatment of **10** with tetraalkylammonium cyanide in organic solvents afforded directly the tricyclic cyano derivative **11** with the intermediacy of 4-cyanomethyl-5-(2-formyl-1-pyrryl)-1-phenylpyrazole which was not isolated under the reaction conditions. Alkaline hydrolysis of **11** and subsequent decarboxylation of the acid **12** led to the tricyclic compound **5**, albeit in a moderate yield (Scheme I).

Additionally, the tricyclic nitrile **11** was prepared as illustrated in Scheme II.

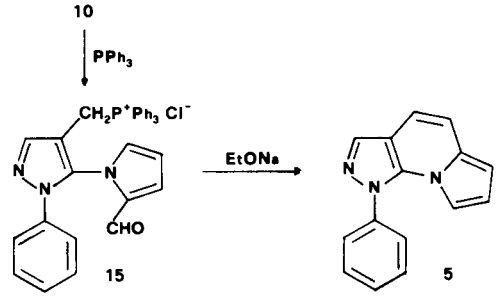


Scheme II

Various reaction conditions were attempted to synthesize 4-cyanomethyl-1-phenyl-5-(1-pyrryl)pyrazole **13** starting from the chloro derivative **9**. The use of sodium or potassium cyanide in different water/organic solvent systems suffered from the fact that a low yield of the desired nitrile was obtained along with substantial amounts of hydroxy derivative **8** and other by-products deriving probably from hydrolysis of the nitrile itself. However, 4-cyanomethyl-1-phenyl-5-(1-pyrryl)pyrazole **13** was achieved in 89% yield by reacting **9** with tetraethylammonium cyanide in acetonitrile.

Vilsmeier-Haack formylation of **13**, followed by usual alkaline work-up, gave a mixture of **11** and 4-cyanomethyl-5-(2-formyl-1-pyrryl)-1-phenylpyrazole **14** in the molar ratio 2:3. Column chromatography on alumina allowed this mixture to be separated and **14** could be readily transformed into **11** by treatment with a catalytic amount of tetraalkylammonium cyanide as a base.

Finally, a more convenient access to 1-phenyl-1*H*-pyrazolo[3,4-*e*]indolizine **5** is reported in Scheme III.



Scheme III

The phosphonium salt **15**, obtained by heating equimolar quantities of **10** and triphenylphosphine, was converted by sodium ethoxide into the corresponding ylide which directly afforded the Wittig condensation product **5**.

All tricyclic compounds described herein will be biologically tested for their potential antitumor activities.

EXPERIMENTAL

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

4-Hydroxymethyl-1-phenyl-5-(1-pyrryl)pyrazole (**8**).

To a stirred and cooled (0-5°) suspension of lithium aluminum hydride (4.86 g, 0.128 mole) in anhydrous tetrahydrofuran (200 ml) a solution of 4-ethoxycarbonyl-1-phenyl-5-(1-pyrryl)pyrazole **7** [3] (21.3 g, 0.075 mole) in the same solvent (200 ml) was added dropwise. After stirring for 2 hours at room temperature water was carefully added and the precipitate which formed was filtered off. The solution was concentrated under reduced pressure and diluted with chloroform (200 ml). The solution was dried (sodium sulfate), and evaporated to give in quantitative yield **8** as an analytically pure oil which crystallized on standing, mp 69-70°; ir: ν OH 3350 cm^{-1}; pmr (deuteriochloroform): δ 3.1 (br s, 1H, OH), 4.42 (s, 2H, CH_2), 6.28 (m, 2H, pyrrole β-protons), 6.68 (m, 2H, pyrrole α-protons), 7.1-7.4 (m, 5H, phenyl), 7.73 ppm (s, 1H, pyrazole proton).

Anal. Calcd. for $C_{14}H_{13}N_3O$: C, 70.27; H, 5.48; N, 17.56. Found: C, 69.95; H, 5.30; N, 17.40.

4-Chloromethyl-1-phenyl-5-(1-pyrryl)pyrazole (**9**).

Phosphorus pentachloride (25.3 g, 0.121 mole) was added in small portions to a cooled (0-5°) solution of **8** (29.0 g, 0.121 mole) in dry chloroform (350 ml). The mixture was magnetically stirred for 1.5 hours at room temperature, then poured into crushed ice. The organic layer was separated, washed with 5% sodium carbonate solution, then with brine and dried (sodium sulfate). Removal of the solvent afforded an oily residue which was purified by column chromatography (silica gel-

benzene) to give 27.5 g (88%) of 4-chloromethyl-1-phenyl-5-(1-pyrryl)pyrazole **9** as white needles (petroleum ether), mp 66-67°; pmr (deuteriochloroform): δ 4.42 (s, 2H, CH_2), 6.33 (m, 2H, pyrrole β-protons), 6.68 (m, 2H, pyrrole α-protons), 7.0-7.4 (m, 5H, phenyl), 7.82 ppm (s, 1H, pyrazole proton).

Anal. Calcd. for $C_{14}H_{12}ClN_3$: C, 65.24; H, 4.70; Cl, 13.76; N, 16.30. Found: C, 65.43; H, 4.68; Cl, 13.94; N, 16.42.

4-Chloromethyl-5-(2-formyl-1-pyrryl)-1-phenylpyrazole (**10**).

A solution of 4-chloromethyl-1-phenyl-5-(1-pyrryl)pyrazole **9** (2.48 g, 0.01 mole) in *N,N'*-dimethylformamide (5 ml) was added dropwise to the complex obtained from *N,N'*-dimethylformamide (1.55 ml, 0.02 mole) and phosphoryl chloride (1.83 ml, 0.02 mole) at 0-5°. The reaction mixture was stirred at room temperature for 18 hours, then warmed at 60° for 3 hours. After cooling the mixture was diluted with 1,2-dichloroethane (50 ml) and 10% sodium carbonate solution (200 ml), then stirred for 30 minutes at room temperature. The organic layer was separated, washed with water (2 x 100 ml), dried over sodium sulfate and evaporated to give a brownish oil. Purification by column chromatography on silica gel-benzene afforded 2.2 g (77%) of **10**, mp 81-82° after recrystallization from ligroin; ir: ν CHO 1660 cm^{-1}; pmr (deuteriochloroform): δ 4.34 (dd, J = 19.5 Hz, 2H, CH_2), 6.48 (m, 1H, H-4), 7.05-7.45 (m, 7H, H-3,5 and phenyl), 7.85 (s, 1H, pyrazole proton), 9.37 ppm (s, 1H, CHO).

Anal. Calcd. for $C_{15}H_{12}ClN_3O$: C, 63.05; H, 4.23; Cl, 12.41; N, 14.71. Found: C, 63.39; H, 4.30; Cl, 12.36; N, 14.86.

4-Cyano-1-phenyl-1*H*-pyrazolo[3,4-*e*]indolizine (**11**). I.

Tetrabutylammonium cyanide (0.84 g, 0.0031 mole) was added to a solution of the chloroaldehyde **10** (0.685 g, 0.0024 mole) in tetrahydrofuran (10 ml). After stirring at room temperature for 6 hours, the brown solution was treated with 5% aqueous sodium bicarbonate (20 ml) and concentrated under reduced pressure. The organic product was isolated by extraction with diethyl ether. The ether layer was washed with brine, dried (sodium sulfate) and evaporated to yield 0.6 g of a crude oil which was purified by passing it through an alumina column. Elution with benzene gave 0.50 g (81%) of the tricyclic nitrile **11** which was recrystallized from ligroin-benzene (2:1), mp 147-149°; ir: ν CN 2250 cm^{-1}; pmr (deuteriochloroform): δ 6.7-6.9 (m, 2H, H-6,7), 6.9-7.0 (m, 1H, H-8), 7.5-7.7 (m, 6H, H-5 and phenyl), 8.10 ppm (s, 1H, H-3).

Anal. Calcd. for $C_{16}H_{10}N_4$: C, 74.40; H, 3.90; N, 21.70. Found: C, 74.43; H, 3.80; N, 21.62.

II.

Phosphoryl chloride (1.83 ml, 0.02 mole) was dropped into *N,N'*-dimethylformamide (1.55 ml, 0.02 mole) cooled in an ice-bath. To this complex a solution of the nitrile **13** (2.48 g, 0.01 mole) in *N,N'*-dimethylformamide (10 ml) was added slowly. The mixture was stirred overnight at 50-60°, then cooled at room temperature, poured onto crushed ice (50 g) and finally basified with 2*N* sodium hydroxide solution. The oil which formed was extracted with methylene chloride. The organic extracts were combined, washed several times with water and dried over anhydrous sodium sulfate. Removal of the solvent afforded an oily residue which was separated by column chromatography (alumina-benzene) to give 1.0 g (39%) of 4-cyano-1-phenyl-1*H*-pyrazolo[3,4-*e*]indolizine **11**. Further elution of the above column with methylene chloride provided 1.5 g (54%) of 4-cyanomethyl-5-(2-formyl-1-pyrryl)-1-phenylpyrazole **14**, mp 126-127° from ligroin-benzene (1:1); ir: ν CN 2250, ν CHO 1680 cm^{-1}; pmr (deuteriochloroform): δ 3.33 (dd, J = 21 Hz, 2H, CH_2), 6.9-7.4 (m, 7H, H-3,5 and phenyl), 7.85 (s, 1H, pyrazole proton), 9.50 ppm (s, 1H, CHO).

Anal. Calcd. for $C_{16}H_{12}N_4O$: C, 69.55; H, 4.38; N, 20.28. Found: C, 69.62; H, 4.27; N, 20.19.

Treatment of **14** with tetrabutylammonium cyanide (0.3 molar equivalent) in tetrahydrofuran, as described for **10**, afforded the tricyclic nitrile **11** in 83% yield.

1-Phenyl-1*H*-pyrazolo[3,4-*e*]indolizin-4-carboxylic Acid (**12**).

A mixture of 3.4 g (0.013 mole) of 4-cyano-1-phenyl-1*H*-pyrazolo[3,4-*e*]-indolizine **11**, 4 g (0.071 mole) of potassium hydroxide pellets and 25 ml of ethylene glycol was heated at 140° overnight. After cooling the solution was poured onto crushed ice and acidified with 6*N* hydrochloric acid. The precipitate was filtered, washed with water and air-dried to give, after crystallization from toluene, 1.6 g (44%) of 1-phenyl-1*H*-pyrazolo[3,4-*e*]indolizin-4-carboxylic acid **12**, mp 238-240°; ir: ν COOH 1710 cm^{-1}; pmr (deuteriochloroform): δ 6.73 (m, 1H, H-7), 6.93 (m, 2H, H-6,8), 7.70 (s, 5H, phenyl), 8.10 (s, 1H, H-5), 8.53 ppm (s, 1H, H-3).

Anal. Calcd. for $C_{16}H_{11}N_3O_2$: C, 63.30; H, 4.00; N, 15.16. Found: C, 69.11; H, 3.97; N, 14.98.

1-Phenyl-1*H*-pyrazolo[3,4-*e*]indolizine (**5**). I.

A mixture of 700 mg (0.0025 mole) of acid **12**, 150 mg of copper powder and 20 ml of quinoline was refluxed for 2 hours under an atmosphere of nitrogen. After cooling the mixture was diluted with chloroform (70 ml) and washed with 5% hydrochloric acid, then with 5% sodium carbonate solution, finally with water to neutrality. After drying over anhydrous sodium sulfate the solvent was removed under reduced pressure to yield an oil which was filtered through a short column of silica gel eluting with chloroform. Recrystallization from ligroin afforded 210 mg (36%) of pure **5**, mp 94-95°; pmr (deuteriochloroform): δ 6.55 (m, 2H, H-6,7), 6.75 (m, 1H, H-8), 7.0 (dd, 2H, H-4,5), 7.5 (m, 5H, phenyl), 7.90 ppm (s, 1H, H-3).

Anal. Calcd. for $C_{15}H_{11}N_3$: C, 77.23; H, 4.75; N, 18.02. Found: C, 77.10; H, 4.61; N, 18.11.

II.

A mixture of 2.9 g (0.01 mole) of 4-chloromethyl-5-(2-formyl-1-pyrryl)-1-phenylpyrazole **10** and 2.6 g (0.01 mole) of triphenylphosphine was heated at 140° for 30 minutes. After cooling the solid which formed was triturated with benzene, filtered and air-dried to give 4.5 g (82%) of the phosphonium salt **15** which, without further purification, was dissolved in 100 ml of absolute ethanol. The latter solution was added dropwise to a solution of sodium ethoxide prepared by dissolving 0.01 g-atom of sodium in 20 ml of absolute ethanol. After stirring at room temperature for 2 hours the solution was diluted with 120 ml of water and extracted with diethyl ether. The ether layer was washed with water, dried (sodium sulfate) and evaporated to give a yellow oil which was chromatographed on a silica gel column. Elution with chloroform afforded 1.2 g (63%) of 1-phenyl-1*H*-pyrazolo[3,4-*e*]indolizine **5**.

4-Cyanomethyl-1-phenyl-5-(1-pyrryl)pyrazole (**13**).

A solution of 4-chloromethyl-1-phenyl-5-(1-pyrryl)pyrazole **9** (27.5 g, 0.107 mole) and tetraethylammonium cyanide (21.6 g, 0.138 mole) in acetonitrile (550 ml) was stirred at room temperature for 3 hours. After addition of 5% sodium bicarbonate solution (750 ml) the mixture was extracted with diethyl ether (3 x 150 ml). The combined organic layers were washed with brine and dried over anhydrous sodium sulfate. Removal of the solvent furnished an oily residue which was purified by column chromatography (alumina-benzene) to give 23.6 g (89%) of **13**, mp 66° (from ligroin-diethyl ether); ir: ν CN 2250 cm^{-1}; pmr (deuteriochloroform): δ 3.43 (s, 2H, CH_2), 6.35 (m, 2H, pyrrole β-protons), 6.65 (m, 2H, pyrrole α-protons), 7.1-7.4 (m, 5H, phenyl), 7.78 ppm (s, 1H, pyrazole proton).

Anal. Calcd. for $C_{15}H_{12}N_4$: C, 72.56; H, 4.89; N, 22.57. Found: C, 72.44; H, 4.80; N, 22.44.

Acknowledgement.

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[6] V. L. Reynolds, J. P. McGovren, and L. H. Hurley, *J. Antibiotics*, **39**, 319 (1986) and references cited therein.

[7] We previously obtained this compound as the main detectable product (33% yield) in an attempt to cyclize 4-acetamidomethyl-1-phenyl-5-(1-pyrryl)pyrazole with phosphoryl chloride in chloroform solution; *cf.* reference [2].