# Heterocyclic System. XI. Synthesis of 1*H*,4*H*-Pyrazolo[4,3-*b*]pyrrolizine and 2*H*,4*H*-Pyrazolo[4,3-*b*]pyrrolizine Derivatives



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Cyclization of pyrrolidinocarboxamide derivatives of 1-phenyl-5-(1*H*-pyrrol-1-yl)-1*H*-pyrazole-4-carboxylic acid and 2-phenyl-3-(1*H*-pyrrol-1-yl)-1*H*-pyrazole-4-carboxylic acid afforded imminium salts which were transformed into the corresponding ketones. Further reduction of the latter compounds furnished the title derivatives.

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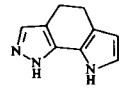
In previous works we reported the synthesis of new nitrogen heterocyclic compounds incorporating both pyrrolo and pyrazolo moieties [1-3]. When suitably substituted, these structures allow different derivatives connected to biologically and pharmacologically interesting compounds to be obtained.

Recently we have realized the synthesis of some derivatives of 1(2),8-dihydropyrrolo[3,2-*g*]indazole (**1**) [4] and 1*H*-pyrazole[3,4-*e*]indolizine (**2**), two tricyclic nitrogen systems closely related to the pyrroloindole subunits of the antitumoral antibiotic CC-1065. A biological study on some derivatives of **2** has been also performed to test their potential antitumor activity [5].



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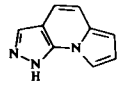

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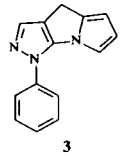

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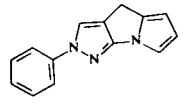

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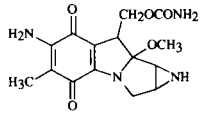

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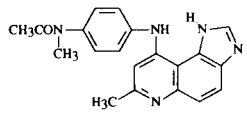

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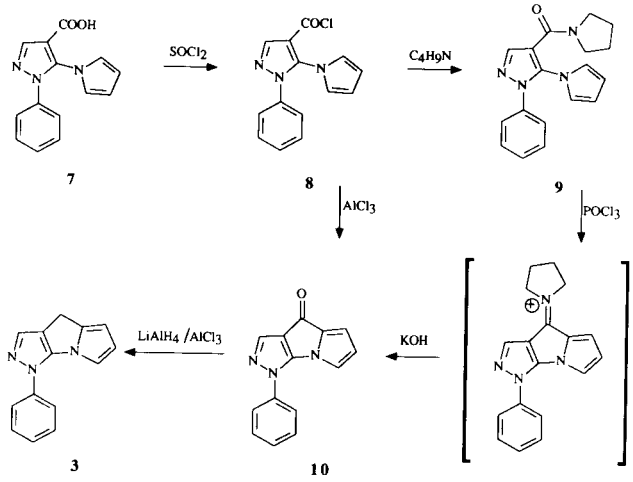
Getting along with our research we have been now interested in the synthesis of derivatives of two new isomeric tricyclic systems, 1-phenyl-1*H*,4*H*-pyrazolo[4,3-*b*]-pyrrolizine (**3**) and the 2-phenyl-2*H*,4*H*-pyrazolo[4,3-*b*]-pyrrolizine (**4**), closely tied up to the previous ones.

These structures are the first examples reported in literature of tricyclic 5,5,5 systems having a pyrrolizine moiety fused with a pyrazole ring.

The presence of the pyrrolizine system makes pyrazolo-[4,3-*b*]pyrrolizine derivatives interesting as potential anticancer agents. In fact, several natural substances belonging to the pyrrolizine class [6] as well as other related polycyclic compounds of pharmaceutical value, *e.g.* Mitomycin C **5** and Acodazole **6**, were found to display useful anticancer activities.

The synthesis of **3** was accomplished starting from 1-phenyl-5-(1*H*-pyrrol-1-yl)-1*H*-pyrazole-4-carboxylic acid (**7**) [7], which was transformed into the corresponding acyl chloride **8** with thionyl chloride. Treatment of **8** with pyrrolidine gave the amide **9**. Bischler-Napieralski cyclization of **9** in boiling phosphoryl chloride produced an iminium salt, which was hydrolyzed to the ketone **10** by the action of the aqueous sodium hydroxide, according mostly to the procedure of Rault [8]. Higher yield of compound **10** was obtained, by Friedel-Crafts cyclization of the crude acyl chloride **8**. Reduction of **10** with lithium aluminum hydride in the presence of aluminum trichloride afforded the required 1-phenyl-1*H*,4*H*-pyrazolo[4,3-*b*]pyrrolizine (**3**) (Scheme 1).

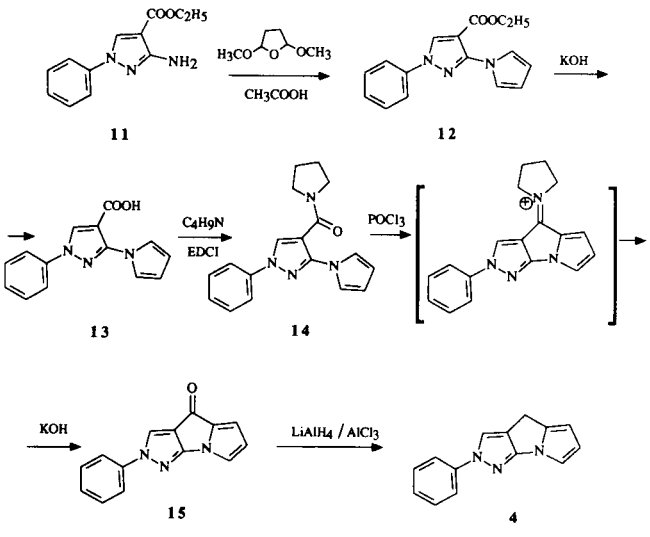
Scheme 1



The tricyclic compound **4** was obtained by a similar synthetic pathway. Reaction of 3-amino-1-phenyl-1*H*-pyrazole-4-carboxylic acid ethyl ester (**11**) [9] with 2,5-dimethoxytetrahydrofuran in glacial acetic acid according to the Clauson-Kaas method [10] gave 1-phenyl-3-(1*H*-pyrrol-1-yl)-1*H*-pyrazole-4-carboxylic acid ethyl ester (**12**). This compound was subjected to alkaline hydrolysis to afford the acid **13**, which was then transformed into the pyrrolidinocarboxamide **14** by reaction with pyrrolidine and *N*-(dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride (EDCI). Cyclization of the amide **14** with phosphoryl chloride afforded the tricyclic ketone **15**. This cyclization procedure proved to be highly valuable in this case, because the instability of the acyl chloride of **13** did not allow to employ Friedel-Crafts intramolecular cyclization as an alternative route to **15**.

By reducing the ketone **15** with a large excess of lithium aluminum hydride and aluminum trichloride the tricyclic compound 2-phenyl-2*H*,4*H*-pyrazole[4,3-*b*]indolizine (**4**) was obtained (Scheme 2).

Scheme 2




## EXPERIMENTAL

Melting points (Buchi 530 melting point apparatus) are uncorrected. The ir spectra (nujol mulls) were recorded on a Perkin-Elmer 297 instrument. The pmr spectra were recorded on a Varian EM-390 spectrometer, with TMS as internal standard. Microanalyses were performed by A. Pietrogrande, University of Padova, Italy.

1-Phenyl-5-(1*H*-pyrrol-1-yl)-1*H*-pyrazole-4-carbonyl Chloride (**8**).

A stirred suspension of **7** (1.26 g, 0.005 mole), *N*,*N*-dimethylformamide (two drops) and thionyl chloride (3.9 ml) in anhydrous benzene (25 ml) was refluxed for 1 hour. After cooling the mixture was evaporated *in vacuo*. The crude residue was used in the next step without further purification.

1-Phenyl-5-(1*H*-pyrrol-1-yl)-1*H*-pyrazole-4-carboxylic Acid Pyrrolidinamide (**9**).

A solution of the crude acyl chloride **8** (1.35 g, 0.005 mole) in anhydrous benzene (20 ml) was slowly added to a solution of pyrrolidine (1.0 ml, 0.012 mole) in anhydrous benzene (50 ml). The mixture was stirred for 2 hours at room temperature, then was diluted with ethyl acetate (20 ml) and extracted with 10% hydrochloric acid solution (1 x 50 ml), 10% sodium carbonate solution (1 x 50 ml) and brine (2 x 50 ml). The organic layer was dried (sodium sulfate) and evaporated to afford 1.5 g (100%) of **9**, mp 148-149° (from ethanol); ir: $\nu$ CO amide 1630 $cm^{-1}$; pmr (deuteriochloroform): $\delta$ 1.80 (m, 4H, pyrrolidine $\beta$-protons), 3.03 and 3.53 (2 m, 2H, pyrrolidine $\alpha$-protons), 6.27 (m, 2H, pyrrole $\beta$-protons), 6.73 (m, 2H, pyrrole $\alpha$-protons), 7.07-7.47 (m, 5H, phenyl), 7.97 ppm (s, 1H, pyrazole proton).

*Anal.* Calcd. for $C_{18}H_{18}N_4O$: C, 70.56; H, 5.92; N, 18.29. Found: C, 70.25; H, 5.98; N, 18.11.

4-Oxo-1-phenyl-1*H*,4*H*-pyrazolo[4,3-*b*]pyrrolizine (**10**).

Method A.

A stirred solution of **9** (1.84 g, 0.006 mole) in phosphorus oxychloride (25 ml) was refluxed for 3 days. After cooling the mixture was diluted with water (200 ml), made basic with 50% potassium hydroxide solution and extracted with ether (3 x 100 ml). The organic layer was washed with brine (3 x 100 ml), dried (sodium sulfate) and evaporated to give **10** as a brown solid, which crystallized from benzene:ligroin (1:1) (0.79 g, 56%), mp 138-139°; ir: $\nu$ CO 1680 $cm^{-1}$; pmr (deuteriochloroform): $\delta$ 6.08 (m, 1H, H-6), 6.60 (m, 1H, H-5), 6.83 (m, 1H, H-7), 7.40-7.73 ppm (m, 6H, phenyl and pyrazole protons).

*Anal.* Calcd. for $C_{14}H_9N_3O$: C, 71.48; H, 3.86; N, 17.86. Found: C, 71.45; H, 3.78; N, 17.79.

Method B.

A solution of the crude residue **8** (1.35 g, 0.005 mole) in 1,2-dichloroethane (20 ml) was carefully added to a suspension of aluminum trichloride (4.0 g, 0.03 mole) in 1,2-dichloroethane (15 ml). The mixture was stirred for 30 minutes at room temperature and then was heated at reflux for 1 hour. After cooling the reaction mixture was quenched with ice and 12 *N* hydrochloric acid (10 ml) was added. After stirring for 20 minutes the organic layer was separated and the aqueous phase was extracted with chloroform (3 x 50 ml). The organic extracts were collected, washed with brine (3 x 100 ml), dried (sodium sulfate) and evaporated *in vacuo*. The residue was purified by column chromatography (silica gel/chloroform) to afford 0.9 g (77%) of pure **10**.

1-Phenyl-1*H*,4*H*-pyrazolo[4,3-*b*]pyrrolizine (**3**).

To a stirred suspension of lithium aluminum hydride (0.24 g, 0.006 mole) and aluminum trichloride (0.83 g, 0.006 mole) in anhydrous tetrahydrofuran (20 ml), a solution of **10** (1.2 g, 0.005 mole) and aluminum trichloride (0.67 g, 0.005 mole) in anhydrous tetrahydrofuran (50 ml) was added. The resulting suspension was stirred at room temperature for 45 minutes, then 2*N* hydrochloric acid was added dropwise until *p*H 4-5 and the mixture was concentrated *in vacuo*, diluted with water (100 ml) and extracted with ether (3 x 50 ml). The organic layer was washed with brine (3 x 50 ml), dried (sodium sulfate) and evaporated to yield a solid residue which was purified by chromatography on a silica gel column. Elution with chloroform:benzene (1:1) afforded 1.51 g (73%) of pure **3**, mp 136-137° (from ligroin); pmr (deuteriochloroform): $\delta$ 3.62 (s, 2H, $CH_2$), 6.06-6.33 (m, 2H, pyr-

role β-protons), 6.90 (m, 1H, pyrrole α-proton), 7.33-7.83 ppm (m, 6H, phenyl and pyrazole proton).

*Anal.* Calcd. for $C_{14}H_{11}N_3$: C, 75.99; H, 5.01; N, 18.99. Found: C, 76.05; H, 5.04; N, 18.87.

3-Amino-1-phenyl-1*H*-pyrazole-4-carboxylic Acid Ethyl Ester (**11**).

A solution of benzaldehyde phenylhydrazone (19.6 g, 0.10 mole) and ethyl ethoxymethylenecyanoacetate (19.6 g, 0.12 mole) in xylene (80 ml) was refluxed for 3 days. After cooling the precipitate was filtered, washed with ether (3 x 20 ml), dissolved in ethanol (60 ml) containing conc. hydrochloric acid (10 ml) and refluxed for 15 minutes. The mixture was evaporated *in vacuo*, diluted with 10% potassium hydroxide solution (200 ml) and extracted with chloroform (3 x 100 ml). The organic layer was washed with brine (3 x 100 ml), dried (sodium sulfate) and evaporated to afford an oily residue, which was purified by passing it through a silica gel column. Elution with chloroform gave 15.02 g (65%) of pure **11**, mp 98-100°, lit [9].

1-Phenyl-3-(1*H*-pyrrol-1-yl)-1*H*-pyrazole-4-carboxylic Acid Ethyl Ester (**12**).

A solution of **11** (11.55 g, 0.05 mole) and 2,5-dimethoxytetrahydrofuran (9.7 ml, 0.075 mole) in glacial acetic acid (200 ml) was heated at reflux for 30 minutes, then the reaction mixture was cooled and evaporated *in vacuo*. The residue was purified by column chromatography (silica gel-chloroform). Compound **12** was obtained as a white solid (8.6 g, 61%), mp 92-94° from cyclohexane; ir: ν $COOC_2H_5$ 1710 $cm^{-1}$; pmr (deuteriochloroform): δ 1.33 (t, 3H, $CH_3$), 4.33 (q, 2H, $CH_2$), 6.37 (m, 2H, pyrrole β-protons), 7.30-7.90 (m, 7H, phenyl and pyrrole α-protons), 8.50 ppm (s, 1H, pyrazole proton).

*Anal.* Calcd. for $C_{16}H_{15}N_3O_2$: C, 68.31; H, 5.37; N, 14.94. Found: C, 68.23; H, 5.33; N, 15.05.

1-Phenyl-3-(1*H*-pyrrol-1-yl)-1*H*-pyrazole-4-carboxylic Acid (**13**).

A stirred solution of **12** (14.05 g, 0.05 mole) in ethanol (50 ml) was refluxed with 10% potassium hydroxide solution (90 ml) for 75 minutes. The reaction mixture was cooled, diluted with water (300 ml), acidified with 2 *N* hydrochloric acid solution and extracted with ether (3 x 100 ml). The organic layer was dried over anhydrous sodium sulfate and evaporated *in vacuo* to leave 12.27 g (97%) of **13** as a white solid, mp 187-188° from benzene; ir: ν COOH 1680 $cm^{-1}$; pmr (DMSO-$d_6$): δ 6.30 (m, 2H, pyrrole β-protons), 7.40-8.00 (m, 7H, phenyl and pyrrole α-protons), 9.17 ppm (s, 1H, pyrazole proton).

*Anal.* Calcd. for $C_{14}H_{11}N_3O_2$: C, 66.40; H, 4.38; N, 16.59. Found: C, 66.37; H, 4.58; N, 16.47.

1-Phenyl-3-(1*H*-pyrrol-1-yl)-1*H*-pyrazole-4-carboxylic Acid Pyrrolidinamide (**14**).

To a solution of **13** (1.3 g, 0.005 mole) in dichloromethane (50 ml) *N*-(dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride (1.15 g, 0.006 mole), pyrrolidine (0.43 g, 0.006 mole) and triethylamine (1.2 g, 0.012 mole) were added. The mixture was stirred for 20 hours at room temperature, then water (100 ml) was added. The organic layer was separated, washed with 2*N* hydrochloric acid (1 x 50 ml), 5% sodium carbonate solution (1 x 50 ml) and brine (2 x 50 ml), then dried (sodium sulfate) and evaporated *in vacuo* to leave 1.38 g (90%) of **14** as a white solid, mp 113-115° from cyclohexane; ir: ν 1600 $cm^{-1}$; pmr (deuteriochloroform): δ 1.80 (m, 4H, pyrrolidine β-protons), 2.98 (m, 2H, pyrrolidine α-protons), 3.62 (m, 2H, pyrrolidine α-protons), 6.33 (m, 2H, pyrrole β-protons), 7.25 (m, 2H, pyrrole α-protons), 7.30-7.85 (m, 5H, phenyl), 8.20 ppm (s, 1H, pyrazole proton).

*Anal.* Calcd. for $C_{18}H_{18}N_4O$: C, 70.56; H, 5.92; N, 18.25. Found: C, 70.84; H, 6.03; N, 18.06.

4-Oxo-2-phenyl-2*H*,4*H*-pyrazolo[4,3-*b*]pyrrolizine (**15**).

A stirred solution of **14** (1.5 g, 0.005 mole) in phosphorus oxychloride (20 ml) was refluxed for 3 days. After cooling the mixture was diluted with water (200 ml), made basic with 50% potassium hydroxide solution and extracted with ether (3 x 100 ml). The organic layer, washed with brine (3 x 100 ml), was dried (sodium sulfate) and evaporated to give **15** as a yellow solid, which was crystallized from benzene (0.41 g, 35%), mp 168-169°; ir: ν CO 1650 $cm^{-1}$; pmr (deuteriochloroform): δ 6.30 (m, 1H, H-6 proton), 6.73 (m, 1H, H-5 proton), 7.13 (m, 1H, H-7 proton), 7.27-7.80 (m, 5H, phenyl), 8.03 ppm (s, 1H, pyrazole proton).

*Anal.* Calcd. for $C_{14}H_9N_3O$: C, 71.48; H, 3.86; N, 17.86. Found: C, 71.53; H, 3.81; N, 17.74.

2-Phenyl-2*H*,4*H*-pyrazolo[4,3,-*b*]pyrrolizine (**4**).

To a stirred suspension of lithium aluminum hydride (0.95 g, 0.025 mole) and aluminum chloride (3.33 g, 0.025 mole) in anhydrous tetrahydrofuran (100 ml), a solution of **15** (1.2 g, 0.005 mole) and aluminum chloride (1.33 g, 0.010 mole) in the same solvent (50 ml) was added. The resulting suspension was stirred at room temperature for 90 minutes, then 2*N* hydrochloric acid solution was added dropwise until *p*H 4-5. The mixture was concentrated *in vacuo*, diluted with water (100 ml) and extracted with ether (3 x 50 ml). The organic layer was washed with brine (3 x 50 ml), dried (sodium sulfate) and evaporated to yield a solid residue, which was purified by chromatography on a silica gel column. Elution with chloroform:*n*-hexane (1:1) afforded 0.78 g (71%) of pure **4**, mp 125-126° (from *n*-hexane); pmr (deuteriochloroform): δ 3.73 (s, 2H, $CH_2$), 6.12 (m, 1H, pyrrole β-proton), 6.37 (m, 1H, pyrrole β-proton), 7.17-7.73 ppm (m, 7H, pyrrole α-, phenyl and pyrazole protons).

*Anal.* Calcd. for $C_{14}H_{11}N_3$: C, 75.99; H, 5.01; N, 18.99. Found: C, 75.92; H, 4.99; N, 19.12.

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