

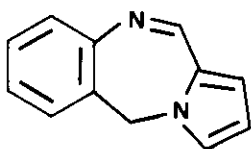
HETEROCYCLIC SYSTEMS. V. SYNTHESIS OF 1H,4H,6H-PYRAZOLO[3,4-e]PYRROLO-[2,1-c][1,4]OXAZEPINE DERIVATIVES

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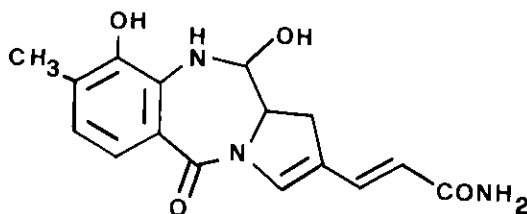
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Abstract - The synthesis of derivatives of a new tricyclic heteroaromatic ring, 1H,4H,6H-pyrazolo[3,4-e]pyrrolo[2,1-c][1,4]oxazepine, is described. Formylation of 4-ethoxycarbonyl-1-phenyl-5-(1-pyrrolyl)pyrazole, prepared from 5-amino-4-ethoxycarbonyl-1-phenylpyrazole by Clauson-Kaas method, afforded 4-ethoxycarbonyl-5-(2-formyl-1-pyrrolyl)-1-phenylpyrazole, which was then reduced to 4-hydroxymethyl-5-(2-hydroxymethyl-1-pyrrolyl)-1-phenylpyrazole. Treatment of the diol with phosphorus pentoxide led to 1-phenyl-1H,4H,6H-pyrazolo[3,4-e]pyrrolo[2,1-c][1,4]oxazepine. 4-Methyl and 4-phenyl derivatives of the latter compound were also prepared.

During past researches on potential antitumor tricyclic compounds containing a bridge-head nitrogen atom we reported the synthesis of various novel rings having structural affinities with 5H-pyrrolo[2,1-c][1,4]benzodiazepine (1), the parent nucleus of anthramycin (2) and other pyrrolobenzodiazepine antitumor antibiotics^{1,2}.



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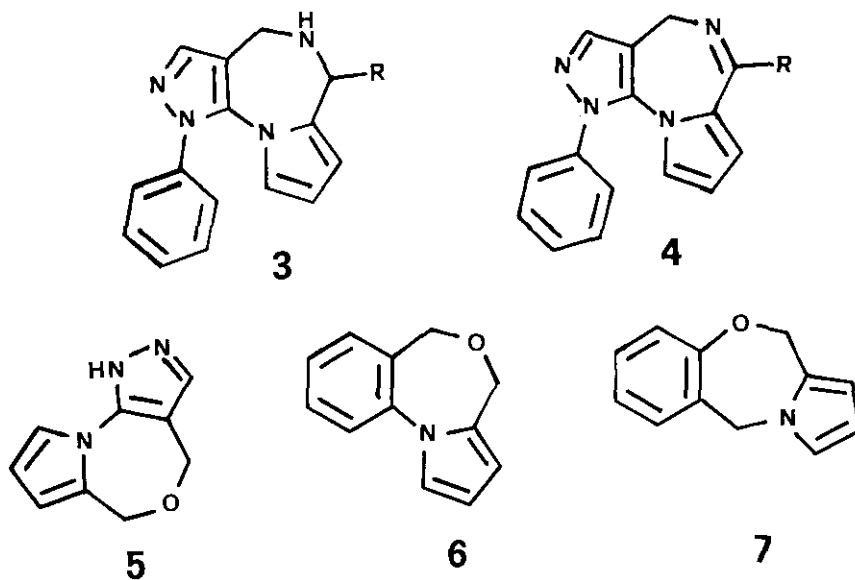


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Some compounds we synthesized have been used by other authors as starting material for the preparation of new CNS pharmacologically active agents³. Then our pursuing in these studies originates from the constatation that tricyclic systems with a bridge-head nitrogen atom have been intensively explored in the last years because of their both interesting antitumor and anxiolytic activities displayed in the biological and pharmacological tests.

Recently we were interested in diazepines annelated with two heterocyclic rings, namely pyrazole and pyrrole. As an approach to this project we synthesized derivatives of 1H,4H-pyrazolo[4,3-f]pyrrolo[1,2-a][1,4]diazepine (3) and (4) by intramolecular cyclization involving Mannich or Bischler-Napieralski reaction⁴.

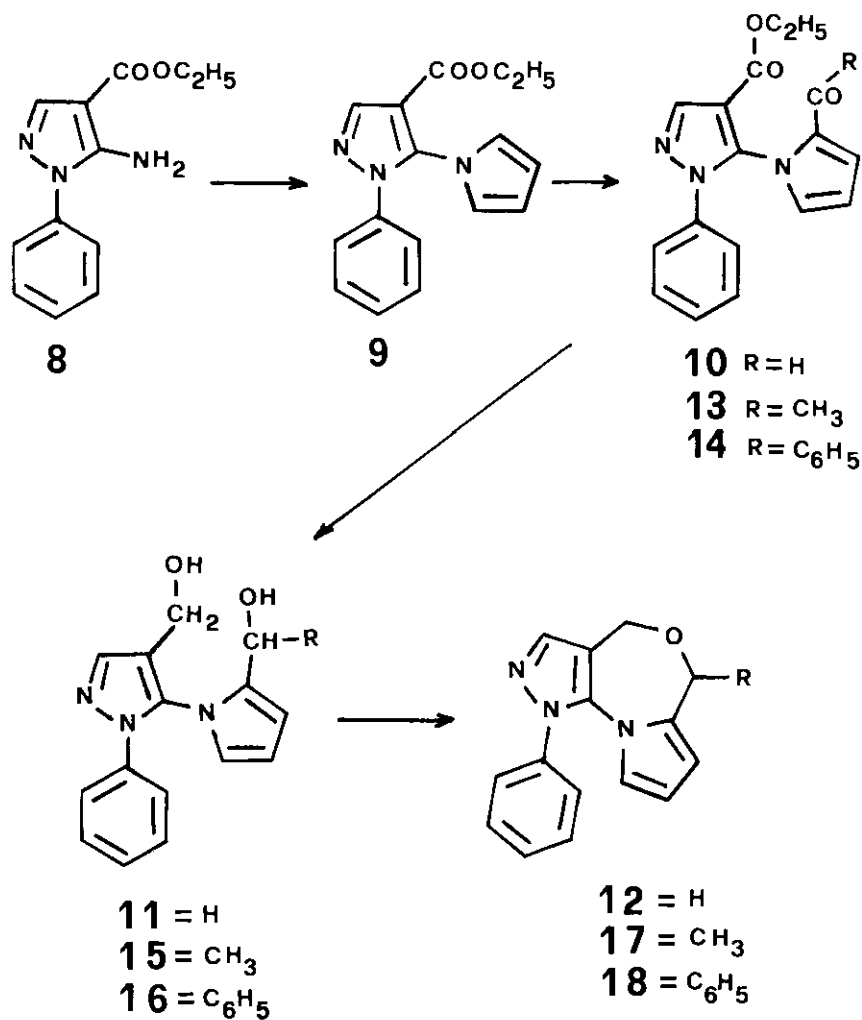
Following our research we describe now the synthesis of some derivatives of 1H,4H,6H-pyrazolo[3,4-e]pyrrolo[2,1-c][1,4]oxazepine (5), a novel tricyclic ring with four heteroatoms. Despite fairly intensive researches in the field of oxazine synthesis no example of this system has been reported in the literature up to day; only the similarly structured pyrrolobenzoxazepines (6) and (7) received recently some attention⁵⁻⁷.



For the synthesis of the title compounds we started from the known 5-amino-4-ethoxycarbonyl-1-phenylpyrazole (8)⁸, which was transformed by Clauson-Kaas method⁹ into the key derivative 4-ethoxycarbonyl-1-phenyl-5-(1-pyrrolyl)pyrazole (9). Vilsmeier-Haack formylation of (9) with N,N-dimethylformamide-POCl₃ complex afforded 4-ethoxycarbonyl-5-(2-formyl-1-pyrrolyl)-1-phenylpyrazole (10), which was then re-

duced by the action of lithium aluminum hydride to 4-hydroxymethyl-5-(2-hydroxymethyl-1-pyrryl)-1-phenylpyrazole (11). Dehydration of the diol (11) by ebullition with phosphorus pentoxide in anhydrous benzene led to tricyclic 1-phenyl-1H,4H,6H-pyrazolo[3,4-e]pyrrolo[2,1-c][1,4]oxazepine (12).

Derivatives of (12) bearing a methyl or a phenyl group at 4 position were synthesized by a similar route involving the Friedel-Crafts reaction as initial step. Treatment of (9) with acetyl chloride or benzoyl chloride afforded (13) and (14) respectively. Lithium aluminum hydride reduction of these ketoesters gave the corresponding diols (15) and (16), which were then cyclized intramolecularly to the



required tricyclic pyrazolopyrrolooxazepines (17) and (18) by the action of phosphorus pentoxide as above reported for compound (12).

NMR spectra of compounds (12), (17) and (18) were in agreement with the tricyclic expected structure.

EXPERIMENTAL

All melting points were taken on a Fisher-Johns apparatus and are uncorrected. Infrared spectra (nujol mulls) were run on a Perkin-Elmer model 297 spectrophotometer. Nuclear magnetic resonance spectra (TMS as internal standard) were recorded on a Varian EM-390 instrument. The mass spectra were recorded on a Hewlett-Packard 5908-A mass spectrometer with an electron beam energy of 70 eV. Merck according to Brockmann alumina, silica gel 60 and florisil were used for chromatographic purifications. Elemental analyses were performed by A. Pietrogrande, Padova, Italy.

4-Ethoxycarbonyl-1-phenyl-5-(1-pyrryl)pyrazole (9): A mixture of 5-amino-4-ethoxycarbonyl-1-phenylpyrazole (8) (9 g, 0.039 mole), 2,5-dimethoxytetrahydrofuran (5.1 g, 0.039 mole) and 70 ml of glacial acetic acid was heated at 120-130°C for 30 min while stirring. After evaporation of the solvent under reduced pressure the residue was treated with crushed ice (200 g), then solid sodium hydrogen carbonate was added in small portions until neutralization was complete. The mixture was extracted with ethyl acetate, the combined extracts were dried on anhydrous sodium sulphate and then evaporated *in vacuo* to give a solid residue, which was chromatographed on a florisil column (benzene as eluent). The collected eluates were evaporated to give 9.5 g (87%) of (9), mp 112-113°C (from ethanol); IR: 1720 cm^{-1} (CO ester); $\text{C}_{16}\text{H}_{15}\text{N}_3\text{O}_2$ calc. C 68.31, H 5.38, N 14.94, found C 68.42, H 5.27, N 14.85.

4-Ethoxycarbonyl-5-(2-formyl-1-pyrryl)-1-phenylpyrazole (10): Phosphorus oxychloride (1.53 g, 0.01 mole) was dropped into N,N-dimethylformamide (0.73 g, 0.01 mole) cooled in an ice-bath while stirring. Then a solution of 4-ethoxycarbonyl-1-phenyl-5-(1-pyrryl)pyrazole (9) (1.4 g, 0.005 mole) in 7.5 ml of N,N-dimethylformamide was gradually added during 30 min. The mixture was stirred for 2.5 h at 110-120°C, then poured into crushed ice (150 g) and made alkaline by

adding conc. ammonium hydroxide. The precipitate which formed was chromatographed on silica gel eluting with a cyclohexane-benzene 1:10 mixture first, then with benzene. Evaporation of benzene eluates gave (10) (1.5 g; 97%), mp 73-74°C (from ethanol); IR: 1720 cm^{-1} (CO ester) and 1680 cm^{-1} (CHO); $\text{C}_{17}\text{H}_{15}\text{N}_3\text{O}_3$ calc. C 66.01, H 4.89, N 13.59, found C 66.27, H 4.79, N 13.47.

5-(2-Acetyl-1-pyrryl)-4-ethoxycarbonyl-1-phenylpyrazole (13): A mixture of acetyl chloride (1.96 g, 0.025 mole) and aluminum trichloride (3.3 g, 0.025 mole) in 15 ml of 1,2-dichloroethane was dropped into a solution of 4-ethoxycarbonyl-1-phenyl-5-(1-pyrryl)pyrazole (9) (7.03 g, 0.025 mole) in 50 ml of the same solvent while stirring. When adding stopped the mixture was stirred 15 min more, then heated at reflux for 20 min. After cooling the mixture was treated with crushed ice (150 g), conc. hydrochloric acid (2 ml) and 1,2-dichloroethane (100 ml). The organic layer was separated, dried on anhydrous sodium sulphate and evaporated under reduced pressure. The solid residue was recrystallized from ethanol to give 4.7 g (58%) of (13), mp 103-105°C; IR: 1710 cm^{-1} (CO ester) and 1660 cm^{-1} (COCH_3); $^1\text{H-NMR}$ (CDCl_3): δ 1.15 (t, 3H, CH_3CH_2), 2.22 (s, 3H, COCH_3), 4.18 (q, 2H, CH_3CH_2), 6.40 (m, 1H, pyrrole α -H), 7.00 (m, 2H, pyrrole β -H), 7.14-7.42 (superimposed multiplets, 5H, benzene protons) and 8.20 ppm (s, 1H, pyrazole proton); $\text{C}_{18}\text{H}_{17}\text{N}_3\text{O}_3$ calc. C 66.86, H 5.30, N 13.00, found C 66.97, H 5.23, N 12.89.

5-(2-Benzoyl-1-pyrryl)-4-ethoxycarbonyl-1-phenylpyrazole (14): Prepared in 55% yield as reported for (13) by heating at 90°C for 12 h. After purification by passing through an alumina column (cyclohexane-benzene 1:10 first, then benzene as eluent) (14) had mp 123-124°C (from ethanol); IR: 1720 cm^{-1} (CO ester) and 1640 cm^{-1} (COC_6H_5); $^1\text{H-NMR}$ (CDCl_3): δ 1.20 (t, 3H, CH_3CH_2), 4.20 (q, 2H, CH_3CH_2), 6.45 (m, 1H, pyrrole C_5 -H), 6.82 (m, 1H, pyrrole C_4 -H), 7.10 (m, 1H, pyrrole C_3 -H), 7.20-7.70 (m, 10H, protons of benzene rings) and 8.24 ppm (s, 1H, pyrazole proton); $\text{C}_{23}\text{H}_{19}\text{N}_3\text{O}_3$ calc. C 71.67, H 4.97, N 10.90, found C 71.53, H 4.86, N 11.19.

4-Hydroxymethyl-5-(2-hydroxymethyl-1-pyrryl)-1-phenylpyrazole (11): A solution of (10) (0.6 g, 0.002 mole) in anhydrous THF (20 ml) was dropped into a well stirred suspension of lithium aluminum hydride (0.6 g) in the same solvent (50 ml). The mixture was stirred for 2 h at room temperature, then poured onto crushed ice (100 g) and the inorganic precipitate was filtered by suction. The

solution was concentrated in vacuo to a small volume and the oil which separated was extracted with ethyl acetate. The extracts were collected, washed with water and dried on anhydrous sodium sulphate. Removal of solvent gave a solid which was recrystallized from benzene to yield 0.25 g (67%) of (11), mp 126-128°C; IR: 3350 cm^{-1} (OH); $\text{C}_{15}\text{H}_{15}\text{N}_3\text{O}_2$ calc. C 66.70, H 5.61, N 15.61, found C 66.79, H 5.56, N 15.75.

4-Hydroxymethyl-5-[2-(1-hydroxyethyl)-1-pyrrolyl]-1-phenylpyrazole (15): Prepared in 59% yield by lithium aluminum hydride reduction of (13) as described for (11), mp 117-118°C (from benzene); IR: 3250 cm^{-1} (OH); $\text{C}_{16}\text{H}_{17}\text{N}_3\text{O}_2$ calc. C 67.82, H 6.05, N 14.83, found C 67.76, H 6.11, N 14.85.

4-Hydroxymethyl-5-[2-(α -hydroxybenzyl)-1-pyrrolyl]-1-phenylpyrazole (16): Prepared in 82% yield from (14) as described for derivatives (11) and (15), mp 201-203°C (from ethanol); IR: 3250 cm^{-1} (OH); $\text{C}_{21}\text{H}_{17}\text{N}_3\text{O}_2$ calc. C 73.02, H 5.55, N 12.17, found C 73.21, H 5.50, N 12.11.

1-Phenyl-1H,4H,6H-pyrazolo[3,4-e]pyrrolo[2,1-c][1,4]oxazepine (12): A solution of (11) (2.0 g, 7.4 mmol) in dry benzene (50 ml) was added to a well stirred suspension of phosphorus pentoxide (2.0 g) in the same solvent (200 ml). The mixture was refluxed for 2 h, then cooled to room temperature and the supernatant solution kept on a separatory funnel. The benzene solution was washed with 5% aqueous sodium hydrogen carbonate, then dried on anhydrous sodium sulphate and evaporated to give a solid residue which was recrystallized from diethyl ether. (12) weighed 1.1 g (59%) and had mp 97-98°C; $^1\text{H-NMR}$ (CDCl_3): δ 4.62 and 4.72 (2s, 4H, CH_2 groups), 6.10 (m, 1H, pyrrole α -proton), 6.20-6.30 (2m, 2H, pyrrole β -protons), 7.48 (s, 5H, benzene protons) and 7.58 ppm (s, 1H, pyrazole proton); $\text{C}_{15}\text{H}_{13}\text{N}_3\text{O}$ calc. C 71.59, H 5.21, N 16.72, found C 71.49, H 5.30, N 16.99.

4-Methyl-1-phenyl-1H,4H,6H-pyrazolo[3,4-e]pyrrolo[2,1-c][1,4]oxazepine (17): Prepared in 78% yield as above reported for (12) starting from (15). After chromatographic purification on alumina column eluting with benzene (17) was recrystallized from diethyl ether, mp 89-91°C; $^1\text{H-NMR}$ (CDCl_3): δ 1.62 (d, 3H, CH_3), 4.70 (superimposed multiplets, 3H, CH_2 and CH of oxazepine nucleus), 6.10 (m, 1H, pyrrole α -proton), 6.22-6.35 (2m, 2H, pyrrole β -protons), 7.47 (s, 5H, benzene pro-

tons) and 7.60 ppm (s, 1H, pyrazole proton); $C_{16}H_{15}N_3O$ calc. C 72.43, H 5.70, N 15.84, found C 72.59, H 5.57, N 15.69.

1,4-Diphenyl-1H,4H,6H-pyrazolo[3,4-e]pyrrolo[2,1-c][1,4]oxazepine (18): Prepared in 76% yield from (16) by the procedure described for derivative (12), mp 142-143°C (from diethyl ether); 1H -NMR ($CDCl_3$): δ 4.90 (s, 2H, CH_2), 5.78 (superimposed multiplets, 2H, CH oxazepine and pyrrole α -proton), 6.03 and 6.38 (2m, 2H, pyrrole β -protons), 7.42 (m, 10H, benzene protons) and 7.62 ppm (s, 1H, pyrazole proton); $C_{21}H_{17}N_3O$ calc. C 77.04, H 5.23, N 12.84, found C 77.21, H 5.19, N 12.76.

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