Synthesis of Pyrazole Analogues of Isoaptazepine

Silvio Massa, Marino Artico*, Antonello Mai and Antonella Mancuso

Dipartimento di Studi Farmaceutici, Università di Roma "La Sapienza", p.le A. Moro 5, 00185 Roma, Italy

Federico Corelli

Dipartimento Farmaco-Chimico-Biologico, Università di Siena, Banchi di Sotto 55, 53100 Siena, Italy

Received July 2, 1992

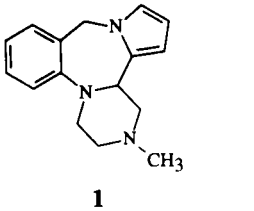
The synthesis of the novel tetracyclic rings **5** and **6** is described starting from 4-cyano-1-methyl-5-(1*H*-pyrrol-1-yl)-1*H*-pyrazole and its 3-(1*H*-pyrrol-1-yl)- isomer, respectively. The pathway employed is based on a one-pot double annelation reaction involving the transformation of **13** into the required tetracyclic derivative **16**. Lithium aluminum hydride/sulfuric acid reduction of the last compound furnished **5**. A similar way was used for the synthesis of **6** by cyclization of **20**.

J. Heterocyclic Chem., **29**, 1851 (1992).

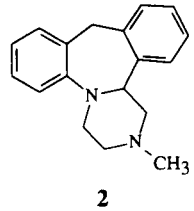
Tetracyclic benzodiazepines with a piperazine moiety have been widely explored after the discovery of aptazepine **1**, an excellent antidepressant agent related to mianserin **2** [1]. Two novel analogues of aptazepine, respectively isoaptazepine **3** and 10-methyl-10-azaaptazepine **4** have been synthesized by our team in recent years [2-4].

As a further development of our search on aptazepine-related tetracyclic systems we reported now the synthesis of derivatives **5** and **6**, two pyrazole analogues of isoaptazepine **3**.

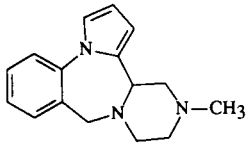
Recently, various pyrazole compounds have been developed as atypical antipsychotic agents. These include derivatives **7**, **8** and **9**, the last one being closely related to clozapine and flumazepine [5-7]. On the basis of good pharmacological profile exhibited by such derivatives, we can argue that substitution of benzene in compound **3** with pyrazole ring to acquire **5** and **6** would provide novel lead systems, useful for planning potential psychotropic agents.



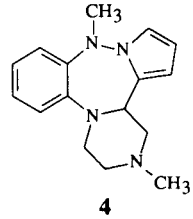
1



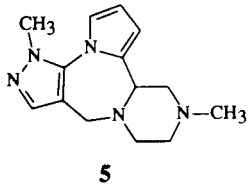
2



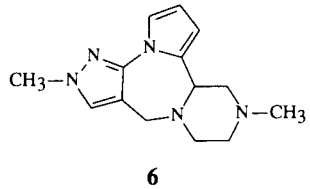
3



4

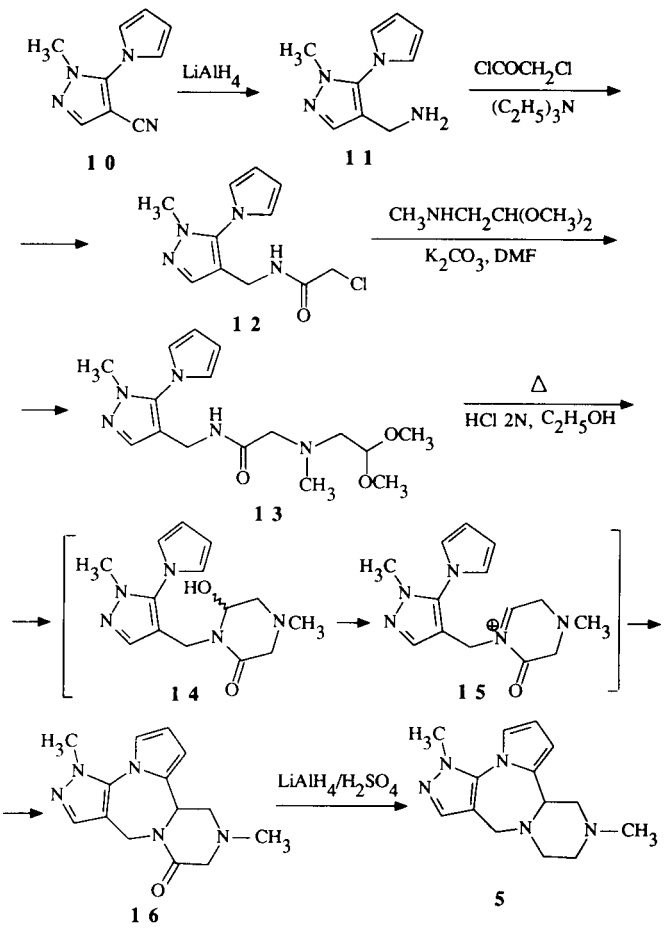


5



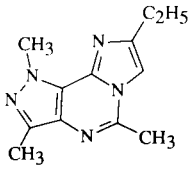
6

Scheme 1

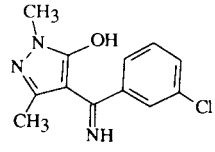


To synthesize **5** we used the one-pot double annelation procedure previously reported for the preparation of **3** [2,3]. Starting from 5-amino-4-cyano-1-methyl-1*H*-pyrazole,

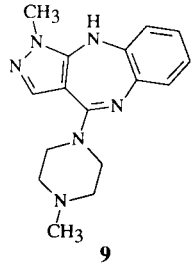
we prepared by the Clauson-Kaas method [8] 4-cyano-1-methyl-5-(1*H*-pyrrol-1-yl)-1*H*-pyrazole (**10**), which was then reduced by lithium aluminum hydride to the corresponding amino derivative **11**. Acylation of this compound with chloroacetyl chloride gave **12**, which was reacted with methylaminoacetaldehyde dimethylacetal in the presence of potassium carbonate to afford the amidoacetal **13**.



7



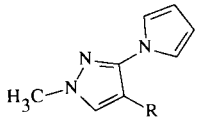
8



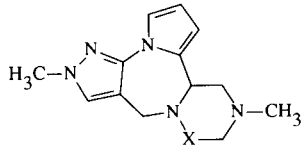
9

Treatment with concentrated hydrochloric acid in boiling ethanol directly transformed **13** into the tetracyclic derivative **16**. This reaction involved π-cyclization of the intermediate *N*-acyliminium ion **15** generated from the hydroxylactam **14** as established elsewhere [9-11]. Subsequent reduction of **16** with lithium aluminum hydride/sulfuric acid (2:1) [11] afforded the required product **5** (Scheme 1).

Starting from **17** we prepared compound **6**, *via* the intermediates **18-21**, by the same procedure adopted for the synthesis of **5**.



17 R = CN
18 R = CH_2NH_2
19 R = $CH_2NHCOCH_2Cl$
20 R = $CH_2NHCOCH_2N(CH_3)CH_2CH(OCH_3)_2$



21 X = CO
6 X = CH_2

EXPERIMENTAL

Melting points were determined on an Electrothermal IA6304 apparatus and are uncorrected. Infrared spectra were run on a Perkin-Elmer 1310 spectrophotometer in nujol mulls. The ^1H nmr spectra were recorded on a Varian EM-390 (90 MHz) spectrometer using tetramethylsilane as internal standard. Column chromatography purifications were performed on silica gel Merck (70-230 mesh) and alumina Merck (70-230 mesh). Stratocrom SIF Carlo Erba (silica gel precoated plates with fluorescent indicator) and Stratocrom ALF Carlo Erba (aluminum oxide precoated plates with fluorescent indicator) were used for thin layer chromatography. Developed plates were visualized by uv light. Organic solutions were dried over anhydrous sodium sulfate. Concentration of solutions after reactions and extractions involved the use of a rotary evaporator (Büchi) operating at reduced pressure (approximately 20 bar). Elemental analyses were performed in the laboratories of Professor A. Pietrogrande, University of Padova, Italy.

4-Cyano-1-methyl-5-(1*H*-pyrrol-1-yl)-1*H*-pyrazole (**10**).

To a well-stirred hot solution of 5-amino-4-cyano-1-methyl-1*H*-pyrazole (20 mmoles, 2.4 g) in glacial acetic acid (100 ml) 2,5-dimethoxytetrahydrofuran (25 mmoles, 3.2 ml) was added and the mixture was heated at reflux for 30 minutes. After cooling, the solvent was removed under reduced pressure, the residue was dissolved in water and the solution made basic with sodium carbonate. Extraction with chloroform (3 x 50 ml) gave a solution, which was washed with brine (2 x 100 ml), dried and evaporated. The residue was chromatographed on a silica gel column (chloroform as eluent) to afford **10** as a colorless oil, yield 100%; ir: 2220 cm^{-1}; ^1H nmr (carbon tetrachloride): δ 3.83 (s, 3H, CH_3), 6.45 (m, 2H, pyrrole β-protons), 6.87 (m, 2H, pyrrole α-protons), 7.73 (s, 1H, pyrazole proton).

Anal. Calcd. for $C_9H_8N_4$: C, 62.77; H, 4.68; N, 32.55. Found: C, 62.90; H, 4.70; N, 32.40.

4-Cyano-1-methyl-3-(1*H*-pyrrol-1-yl)-1*H*-pyrazole (**17**).

This compound has been prepared as reported for derivative **10**. Removal of the solvent from the combined extracts gave a crude residue which was recrystallized (*n*-hexane) to give pure **17** (88%), mp 75-76°; ir: 2225 cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.87 (s, 3H, CH_3), 6.42 (m, 2H, pyrrole β-protons), 7.47 (m, 2H, pyrrole α-protons), 7.80 (s, 1H, pyrazole proton).

Anal. Calcd. for $C_9H_8N_4$: C, 62.77; H, 4.68; N, 32.55. Found: C, 62.68; H, 4.60; N, 32.60.

4-Aminomethyl-1-methyl-5-(1*H*-pyrrol-1-yl)-1*H*-pyrazole (**11**).

A solution of **10** (17 mmoles, 3.0 g) in dry tetrahydrofuran (100 ml) was gradually added to an ice-cooled suspension of lithium aluminum hydride (35 mmoles, 1.3 g) in the same solvent (100 ml). The mixture was stirred at room temperature for 6 hours, then quenced carefully with water and filtered. The solution was evaporated and the residue was extracted with chloroform (3 x 50 ml). The organic phase was washed with brine (2 x 100 ml), dried and evaporated. The oily residue was chromatographed on alumina column (ethyl acetate as eluent) to give **11** (71%); ir: 3300, 3360 cm^{-1}; ^1H nmr (carbon tetrachloride): δ 1.33 (s broad, 2H, NH_2), 3.50 (s, 2H, CH_2), 3.60 (s, 3H, CH_3), 6.33 (m, 2H, pyrrole β-protons), 6.80 (m, 2H, pyrrole α-protons), 7.40 (s, 1H, pyrazole proton). Compound **11** was analyzed as hydrochloride, mp 209-211°.

Anal. Calcd. for $C_9H_{13}ClN_4$: C, 50.82; H, 6.16; Cl, 16.67; N, 26.35. Found: C, 51.09; H, 6.36; Cl, 16.47; N, 26.32.

4-Aminomethyl-1-methyl-3-(1*H*-pyrrol-1-yl)-1*H*-pyrazole (**18**).

This derivative was prepared as reported above for derivative **11**, yield 94%; ir: 3300, 3340 cm^{-1}; ^1H nmr (carbon tetrachloride): δ 1.42 (s broad, 2H, NH_2), 3.62 (s, 2H, CH_2), 3.65 (s, 3H, CH_3), 6.35 (m, 2H, pyrrole β-protons), 7.40 (m, 2H, pyrrole α-protons), 7.63 (s, 1H, pyrazole proton). Compound **18** was analyzed as hydrochloride, mp 212-215°.

Anal. Calcd. for $C_9H_{13}ClN_4$: C, 50.82; H, 6.16; Cl, 16.67; N, 26.35. Found: C, 50.64; H, 6.25; Cl, 16.79; N, 26.32.

4-Chloroacetamidomethyl-1-methyl-5-(1*H*-pyrrol-1-yl)-1*H*-pyrazole (**12**).

A solution of 2-chloroacetyl chloride (16 mmoles, 1.3 ml) in dichloromethane (100 ml) was gradually added to an ice-cooled

solution of **11** (16 mmoles, 2.9 g) and triethylamine (33 mmoles, 4.6 ml) in the same solvent (50 ml). After stirring at room temperature for 1 hour, the mixture was washed once with water (100 ml), saturated solution of sodium carbonate (100 ml) and brine (100 ml) and then dried and evaporated. The residue was purified by passing through a silica gel column eluting with ethyl acetate. The eluates were collected and evaporated to afford **12** (72%). An analytical sample was recrystallized from carbon tetrachloride, mp 65-67°; ir: 1640, 3270 cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.67 (s, 3H, CH_3), 4.00 (s, 2H, CH_2CO), 4.25 (d, 2H, CH_2NH), 6.50 (m, 2H, pyrrole β-protons), 6.87 (m, 2H, pyrrole α-protons), 7.63 (s, 1H, pyrazole proton).

Anal. Calcd. for $C_{11}H_{13}ClN_4O$: C, 52.28; H, 5.19; Cl, 14.03; N, 22.17. Found: C, 52.50; H, 5.25; Cl, 13.89; N, 22.09.

4-Chloroacetamidomethyl-1-methyl-3-(1*H*-pyrrol-1-yl)-1*H*-pyrazole (**19**).

Starting from **18** this compound has been prepared as reported for **12**, yield 61%; ir: 1655, 3290 cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.85 (s, 3H, CH_3), 4.02 (s, 2H, CH_2CO), 4.39 (d, 2H, CH_2NH), 6.33 (m, 2H, pyrrole β-protons), 7.05 (m, 2H, pyrrole α-protons), 7.48 (s, 1H, pyrazole proton).

Anal. Calcd. for $C_{11}H_{13}ClN_4O$: C, 52.28; H, 5.19; Cl, 14.03; N, 22.17. Found: C, 52.17; H, 5.20; Cl, 14.10; N, 22.27.

1-Methyl-4-(*N*-methyl-*N*-2,2-dimethoxyethyl)aminoacetamidomethyl-5-(1*H*-pyrrol-1-yl)-1*H*-pyrazole (**13**).

A solution of **12** (20 mmoles, 5.0 g) in freshly distilled *N,N*-dimethylformamide (10 ml) was added dropwise into a mixture of methylaminoacetaldehyde dimethylacetal (24 mmoles, 3.1 ml), anhydrous potassium carbonate (40 mmoles, 5.5 g) and freshly distilled *N,N*-dimethylformamide (10 ml). The mixture was heated at 90° for 1 hour, then cooled, diluted with water (200 ml) and extracted with ethyl acetate (3 x 100 ml). The organic extracts were washed with brine (3 x 100 ml), dried and evaporated to afford a residue, which was chromatographed on silica gel eluting with ethyl acetate. The collected eluates were evaporated to give **13** (87%) as an oil; ir: 1655, 3320 cm^{-1}; ^1H nmr (carbon tetrachloride): δ 2.33 (s, 3H, $CH_2N(CH_3)CH_2$), 2.49 (d, 2H, NCH_2CH), 2.93 (s, 2H, $COCH_2N$), 3.27 (s, 6H, OCH_3), 3.60 (s, 3H, pyrazole N-CH_3), 4.11 (d, 2H, CH_2NHCO), 4.37 (t, 1H, $CH(OCH_3)_2$), 6.33 (m, 2H, pyrrole β-protons); 6.83 (m, 2H, pyrrole α-protons), 7.47 (s, 1H, pyrazole proton).

Anal. Calcd. for $C_{16}H_{25}N_5O_3$: C, 57.29; H, 7.51; N, 20.88. Found: C, 57.08; H, 7.50; N, 21.01.

1-Methyl-4-(*N*-methyl-*N*-2,2-dimethoxyethyl)aminoacetamidomethyl-3-(1*H*-pyrrol-1-yl)-1*H*-pyrazole (**20**).

Starting from **19** this compound has been prepared as reported for **13**, yield 75%; ir: 1660, 3330 cm^{-1}; ^1H nmr (carbon tetrachloride): δ 2.27 (s, 3H, $CH_2N(CH_3)CH_2$), 2.46 (d, 2H, NCH_2CH), 2.95 (s, 2H, $COCH_2N$), 3.20 (s, 6H, OCH_3), 3.83 (s, 3H, pyrazole-N-CH_3), 4.25-4.45 (m, 3H, CH_2NHCO and $CH(OCH_3)_2$), 6.22 (m, 2H, pyrrole β-protons), 7.03 (m, 2H, pyrrole α-protons), 7.45 (s, 1H, pyrazole proton).

Anal. Calcd. for $C_{16}H_{25}N_5O_3$: C, 57.29; H, 7.51; N, 20.88. Found: C, 57.40; H, 7.72; N, 20.70.

5,12-Dimethyl-10-oxo-10,11,13,13a-tetrahydro-5*H*,8*H*,12*H*-pyrazino[2,1-*c*]pyrazolo[4,3-*f*]pyrrolo[1,2-*a*][1,4]diazepine (**16**).

A solution of **13** (10 mmoles, 3.3 g) in ethanol 95° (120 ml) containing 12*N* hydrochloric acid (24 ml) was heated at reflux for 12 hours. After cooling, the solution was concentrated, made basic with 2*N* sodium hydroxide and extracted with chloroform (3 x 50 ml). The combined extracts were washed with brine (2 x 100 ml), dried and evaporated. The residue was chromatographed on silica gel column (1:1 ethyl acetate/ethanol as eluent) to give **16** (67%). An analytical sample was recrystallized from acetone, mp 139-141°; ir: 1620 cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.40 (s, 3H, piperazine N-CH_3), 3.03-3.30 (m, 4H, piperazine CH_2), 3.85 (d, 1H, half of AB quartet, J = 15 Hz, diazepine CH_2), 4.03 (s, 3H, pyrazole N-CH_3), 4.52 (t, 1H, CH), 5.17 (d, 1H, half of AB quartet, J = 15 Hz, diazepine CH_2), 6.47 (m, 2H, pyrrole β-protons), 7.10 (m, 2H, pyrrole α-protons), 7.53 (s, 1H, pyrazole proton).

Anal. Calcd. for $C_{14}H_{17}N_5O$: C, 61.97; H, 6.32; N, 25.81. Found: C, 62.18; H, 6.17; N, 25.67.

6,12-Dimethyl-10-oxo-10,11,13,13a-tetrahydro-6*H*,8*H*,12*H*-pyrazino[2,1-*c*]pyrazolo[4,3-*f*]pyrrolo[1,2-*a*][1,4]diazepine (**21**).

Compound **21** was prepared as reported for compound **16**, yield 76%, mp 132-135°; ir: 1635 cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.42 (s, 3H, piperazine N-CH_3), 3.03-3.27 (m, 4H, piperazine CH_2), 3.93 (s, 3H, pyrazole N-CH_3), 4.20 (d, 1H, half of AB quartet, J = 15 Hz, diazepine CH_2), 4.63 (t, 1H, CH), 5.03 (d, 1H, half of AB quartet, J = 15 Hz, diazepine CH_2), 6.38 (m, 2H, pyrrole β-protons), 7.28 (m, 2H, pyrrole α-protons), 7.42 (s, 1H, pyrazole proton).

Anal. Calcd. for $C_{14}H_{17}N_5O$: C, 61.97; H, 6.32; N, 25.81. Found: C, 62.09; H, 6.40; N, 25.70.

5,12-Dimethyl-10,11,13,13a-tetrahydro-5*H*,8*H*,12*H*-pyrazino-[2,1-*c*]pyrazolo[4,3-*f*]pyrrolo[1,2-*a*][1,4]diazepine (**5**).

Concentrated sulfuric acid (7.5 mmoles, 0.74 g) was carefully added to an ice-cooled suspension of lithium aluminum hydride (15 mmoles, 0.56 g) in anhydrous tetrahydrofuran (50 ml). The mixture was stirred for 30 minutes, then a solution of **16** (1.1 mmoles, 0.3 g) in anhydrous tetrahydrofuran was gradually added and stirring was continued for 1 hour at 0-5°. The mixture was then cooled at −15°, quenched carefully with 2*N* sodium hydroxide and extracted with chloroform (3 x 50 ml). The combined extracts were washed once with brine (100 ml), dried and evaporated. The oily residue was purified by passing through an alumina column (ethyl acetate as eluent) to give **15**, yield 98%; ^1H nmr (deuteriochloroform): δ 2.33 (s, 3H, piperazine N-CH_3), 2.58-2.80 (m, 6H, piperazine CH_2 protons), 3.25-3.37 (m, 1H, CH), 3.52 (s, 2H, diazepine CH_2), 4.00 (s, 3H, pyrazole N-CH_3), 6.43 (m, 2H, pyrrole β-protons), 6.79 (m, 2H, pyrrole α-protons), 7.47 (s, 1H, pyrazole proton).

Anal. Calcd. for $C_{14}H_{19}N_5$: C, 65.34; H, 7.44; N, 27.22. Found: C, 65.17; H, 7.40; N, 27.24.

6,12-Dimethyl-10,11,13,13a-tetrahydro-6*H*,8*H*,12*H*-pyrazino-[2,1-*c*]pyrazolo[4,3-*f*]pyrrolo[1,2-*a*][1,4]diazepine (**6**).

Compound **6** was prepared as reported for compound **15**, yield 98%; ^1H nmr (deuteriochloroform): δ 2.33 (s, 3H, $CH_2N(CH_3)CH_2$), 2.62-2.85 (m, 6H, piperazine CH_2 protons), 3.30-3.42 (m, 1H, CH), 3.58 (s, 2H, diazepine CH_2), 4.00 (s, 3H, pyrazole N-CH_3), 6.36 (m, 2H, pyrrole β-protons), 7.25 (m, 2H, pyrrole α-protons), 7.45 (s, 1H, pyrazole protons).

Anal. Calcd. for $C_{14}H_{19}N_5$: C, 65.34; H, 7.44; N, 27.22. Found: C, 65.45; H, 7.45; N, 27.10.

Acknowledgments.

The authors are indebted to the Italian MURST (60% fund) for financial support.

REFERENCES AND NOTES

[1] S. Ankier, Progress in Medicinal Chemistry, Vol **23**, G. P. Ellis and G. B. West, eds, Elsevier, 1986, pp 121-185.

[2] S. Massa, A. Mai and F. Corelli, *Tetrahedron Letters*, **29**, 6471 (1988).

[3] S. Massa, A. Mai, M. Artico, F. Corelli and M. Botta, *Tetrahedron*, **45**, 2763 (1989).

[4] G. Stefancich and R. Silvestri, *J. Heterocyclic Chem.*, **26**, 745 (1989).

[5] *Annu. Rep. Med. Chem.*, **24**, 7 (1989).

[6] *Annu. Rep. Med. Chem.*, **23**, 6 (1988).

[7] J. K. Chakrabarti, T. M. Hotten, I. A. Pullar and N. C. Tye, *J. Med. Chem.*, **32**, 2573 (1989).

[8] N. Clauson-Kaas and Z. Tyle, *Acta Chem. Scand.*, **6**, 667 (1952).

[9] J. Klaver, H. Hiemstra and W. N. Speckamp, *Tetrahedron*, **44**, 6729 (1988).

[10] S. Kano, Y. Yuasa and S. Shibuya, *Synthesis*, 1071 (1984).

[11] C. Thebtaranonth and Y. Thebtaranonth, *Tetrahedron*, **46**, 1385 (1990).