Synthesis of CNS Potentially Active Bicyclic and Tricyclic Derivatives of Pyrazolo[1,5-*a*][1,3]diazepines

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Received July 12, 1989

Reaction of 5-ethylamino-3-phenylpyrazole with dicarboxylic acid anhydrides in tetrahydrofuran in the presence of 1,3-dicyclohexylcarbodiimide, afforded bicyclic and tricyclic derivatives of pyrazolo[1,5-*a*][1,3]-diazepines. The tricyclic derivatives constitute a new class of compounds. Characterisation of these products was effected with ir, pmr, and ^{13}C nmr spectral data.

J. Heterocyclic Chem., **27**, 695 (1990).

In recent years several papers have reported the remarkable activity in CNS of various pyrazolodiazepines and benzodiazepines condensed with heterocyclic systems. In particular, the interesting activity showed by pyrazolodiazepines has prompted further investigations into the synthesis of more selective and active derivatives of this system [1-2].

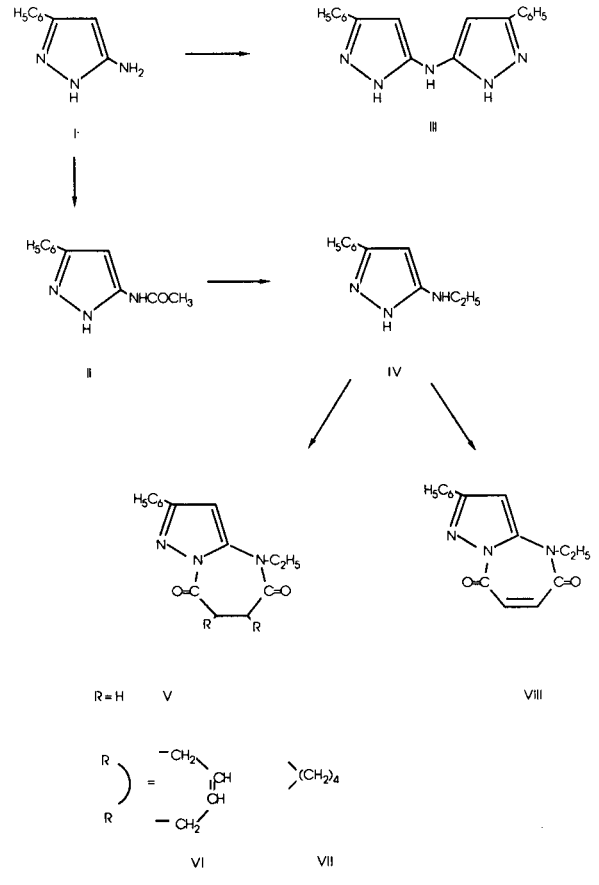
As part of a study aimed at the synthesis of heterocyclic systems condensed with a pyrazole ring, we thought it interesting to prepare some bicyclic pyrazolo[1,5-*a*][1,3]diazepines and some tricyclic pyrazolo[1,5-*a*][1,3]diazepines condensed with a saturated and unsaturated six membered ring. A special interest in these compounds arose from a survey of the literature, which revealed that pyrazolo[1,5-*a*][1,3]diazepines have thus far received little attention, the only reported synthesis being a ring expansion of a pyrazolo[1,5-*a*]pyrimidine [3-4]. Furthermore, pyrazolo-[1,5-*a*][1,3]diazepines condensed with a saturated and unsaturated six membered ring, constitute a new class of tricyclic compounds deserving of pharmacological investigation.

3-Phenyl-5-aminopyrazole **I** was chosen as the starting material for the synthesis of the above heterocyclic systems. This aminopyrazole had already been used by us for the synthesis of several pyrazolo[1,5-*a*]pyrimidine derivatives, which were found interesting as analgesic and anti-inflammatory drugs devoid of ulcerogenic properties [5-6]. The unusual mode of action of these substances, which renders them different from the majority of known NSAID's, may be explained by a possible interaction with the CNS. As matter of fact, several pyrazolo[1,5-*a*]pyrimidines are already known to be active on the CNS [7].

This paper is aimed therefore at evaluating what modifications to biological activity could be induced by enlargement of the pyrimidine ring to a seven-membered system.

The sequence of the synthetic steps is indicated in Scheme 1.

Scheme 1

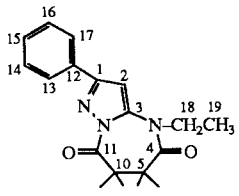


Acetylation of 3-phenyl-5-aminopyrazole **I** can be accomplished by reaction either with glacial acetic acid at reflux, or with acetic anhydride. The latter reaction gives an intermediate diacetylderivative, whose hydrolysis affords **II**. Although this second method is more wearisome, we followed it because refluxing **I** in glacial acetic acid yields notable amounts of a side-reaction product, to which, the structure of bis(3-phenylpyrazol-5-yl)amine **III** was attributed on the basis of elemental analysis, ir and ^1H nmr data.

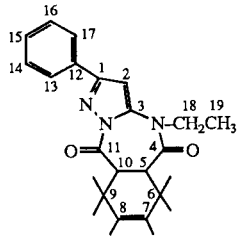
Other 5-aminopyrazoles are known to behave similarly

Table 1

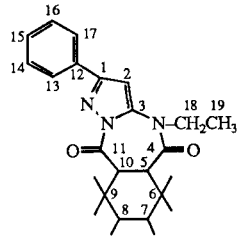
C-13 NMR Chemical Shifts



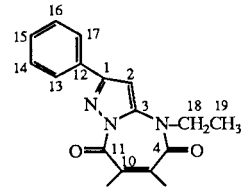
V



VI



VII



VIII

Compound No.	1	2	3	4	5	6	7	8	9	10
V	154.81	97.26	143.54	166.48	30.33					33.10
VI	154.95	97.05	143.02	168.88 [a]	37.78	26.57 [c]	123.78 [b]	125.99 [b]	25.57 [c]	44.81
VII	154.87	97.74	143.04	170.33 [a]	41.04	27.33 [b]	26.41 [b]	25.09 [b]	22.08 [b]	48.38
VIII	155.58	95.25	142.06	158.30 [a]	129.19					134.09

Compound No.	11	12	13	14	15	16	17	18	19
V	169.79	130.71	128.57	126.27	129.60	126.27	128.57	44.62	12.77
VI	169.92 [a]	130.77	128.47	126.12	129.42	126.12	128.47	44.98	12.82
VII	170.72 [a]	130.91	128.53	126.23	129.43	126.23	128.53	45.02	12.96
VIII	159.71 [a]		128.64	126.53	129.82	126.53	128.64	45.91	11.91

[a] [b] [c] Assignments may be reversed.

on treatment with glacial acetic acid at reflux [9].

Compound **II** was suspended in diethyl ether and reduced with lithium aluminum hydride to 5-ethylamino-3-phenylpyrazole **IV** [10], which was reacted with a series of dicarboxylic acid anhydrides, namely succinic, maleic, 4-cyclohexenedicarboxylic and cyclohexanedicarboxylic acid anhydrides. The reaction was carried out in tetrahydrofuran in the presence of 1,3-dicyclohexylcarbodiimide, according to a method employed in a peptide synthesis procedure [11]. The above condensation affords bicyclic and tricyclic derivatives of the pyrazolo[1,5-*a*][1,3]diazepine system, although in low yield. Alternative synthetic routes, such as isolation of reaction intermediates between **IV** and the above-mentioned carboxyanhydrides, which are then cyclized, proved unsuccessful, either because of the low reactivity of the reagents, or because of the formation of intractable tars.

Structure assignments to the products are based on spectral data, ir, ^{1}H- and ^{13}C-nmr (see Experimental). It is apparent that the amino group of **I** must be mono-blocked, since carboxyanhydrides are known to react smoothly with aminopyrazoles to yield imidopyrazoles [11].

Some compounds, were tested in preliminary experiments, to investigate their behavioural reactions according to Irwing technique, to be a useful indication of their systemic effects [12].

Compounds **V, VI, VII** were administered p.o. in a 1% carboxymethylcellulose suspension (0.1 ml/10 g) up to dose of 1 g/Kg to Swiss male rats weighing 20 ± 2 g. In Irwin's test none of the tested compounds showed any particular symptomatology.

EXPERIMENTAL

Melting points were determined with a Buchi 510 apparatus, and are uncorrected. The ir spectra were recorded on a Perkin-Elmer 681 spectrophotometer, in Nujol mulls. The ^{1}H-nmr spectra were measured with a Varian EM 60 spectrometer and chemical shifts are expressed in δ (ppm) downfield from TMS as an internal standard. Multiplicity is indicated by: s, singlet, d, doublet, t, triplet, m, multiplet, bs, broad singlet which exchanges with deuterium oxide. The ^{13}C-nmr spectra were run at 20 MHz on a Varian FT 80-A spectrometer. The temperature of measures was 38° and the concentration of samples was 10% (v/v) in DMSO-d_6. Chemical shifts are reported relative to TMS as internal standard. The purity of samples was determined by means of tlc., which was performed using Merk (Darmstadt) silica gel 60 F 254 plates. The mass spectra were obtained with a VG 70-70 EQ in-

strument (VG Analytical, Manchester, U.K.) in D.E.I. (Direct Eletro Impact) at M/ΔM = 1500 mass resolution (10% valley definition) and a run speed of 2 s per decade. The data were processed on a Digital PDP8/A computer system.

Bis(3-phenylpyrazol-5-yl)amine **III**.

A solution of 5 g of **I** in 10 ml of acetic acid was refluxed for 3 hours. The solution was diluted with 30 ml of water and the resulting precipitate was collected by filtration and recrystallized from 95% ethanol (yield 78%); colourless crystals, mp 276-277°; pmr (deuteriodimethyl sulfoxide): 8.10 (4 H, m, *ortho* H), 7.78 (3 H, b s, 3 NH, exchangeable), 7.50 (6 H, m, *meta*, *para* H), 6.90 (1 H, s, pyrazole H), 6.68 (1 H, s, pyrazole H) ppm; ms: m/z 286 (M + -NH) (base peak), 246.

Anal. Calcd. for $C_{18}H_{15}N_5$: C, 71.74; H, 5.02; N, 23.24. Found: C, 71.50; H, 5.00; N, 23.54.

5-Ethyl-3-phenylpyrazole **IV**.

To a suspension of 1.6 g (0.042 mole) of lithium aluminum hydride in 50 ml of dry ether, 5 g (0.020 mole) of **II** was added in small portions and stirred at room temperature for 1 hour. The mixture was gently refluxed for 4 hours, under cooling then some drops of water were carefully added. The mixture was washed with water and the ether layer was dried (sodium sulfate) and evaporated to give a colourless residue, which recrystallized from water, (yield 75%), mp 98-100°; pmr (deuteriochloroform): 7.50 (5 H, m, aromatic protons), 6.85 (2 H, b s, 2 NH, exchangeable), 5.85 (1 H, s, pyrazole H), 3.20 (2 H, q, CH_2), 1.20 (3 H, t, CH_3) ppm.

Anal. Calcd. for $C_{11}H_{13}N_3$: C, 70.56; H, 6.99; N, 22.44. Found: C, 70.68; H, 6.86; N, 22.56.

General Procedure for the Preparation of Bicyclic and Tricyclic Derivatives of Pyrazolo[1,5-*a*][1,3]diazepines **V**, **VI**, **VII**, **VIII**.

To a solution of equimolar amounts (0.010 mole) of **IV** and suitable anhydrides in 30 ml of dry tetrahydrofuran was added a solution of 1,3-dicyclohexylcarbodiimide (0.010 mole) in 10 ml of the same solvent. After the mixture had been stirred for 2 days at room temperature, a white precipitate was filtered and the tetrahydrofuran was evaporated under reduced pressure. The residue was taken up in isopropyl ether and collected by filtration. The crude products were further purified by recrystallization.

The ^{13}C-nmr chemical shifts of all compounds are reported in Table I and positional numbering of carbon atoms is arbitrary, as indicated in the structure diagrams.

4-Ethyl-5,6,7,8-tetrahydro-2-phenylpyrazolo[1,5-*a*][1,3]diazepin-5,8-dione **V**.

According to the general procedure, using succinic anhydride, white crystals were obtained from isopropyl ether-cyclohexane, (yield 6%), mp 153-155°; ir: cm^{-1} 1740, 1690, 1590, 1570, 1210, 770; pmr (deuteriochloroform): 7.90 (2 H, m, *ortho* H), 7.50 (3 H, m, *meta*, *para* H), 6.50 (1 H, s, pyrazole H), 4.00 (2 H, d, N-CH_2), 3.10 (4 H, m, CH_2 at 6- and 7-positions), 1.20 (3 H, t, CH_3) ppm.

Anal. Calcd. for $C_{15}H_{15}N_3O_2$: C, 66.90; H, 5.61; N, 15.60. Found: C, 66.75; H, 5.56; N, 15.75.

5,10-Dihydro-4-ethyl-2-phenylpyrazolo[1,5-*a*][1,3]-7-cyclohexendiazepin-5,10-dione **VI**.

According to the general procedure using 4-cyclohexendicarboxylic acid 1,2-anhydride; white crystals were obtained from isopropyl ether-cyclohexane (yield 30%), mp 185-187°; ir: cm^{-1} 1720, 1680, 1590, 1570, 1300, 760; pmr (deuteriochloroform): 7.90 (2 H, m, *ortho* H), 7.50 (3 H, m, *meta*, *para* H), 6.50 (1 H, s, pyrazole H), 5.98 (2 H, m, 2 CH), 2.60 (4 H, m, CH_2 at 6- and 9-positions), 1.29 (3 H, t, CH_3) ppm.

Anal. Calcd. for $C_{19}H_{19}N_3O_2$: C, 71.00; H, 5.95; N, 13.07. Found: C, 71.12; H, 6.00; N, 13.12.

5,10-Dihydro-4-ethyl-2-phenylpyrazolo[1,5-*a*][1,3]cyclohexandiazepin-5,10-dione **VII**.

According to the general procedure, using 1,2-cyclohexanedicarboxylic anhydride, white crystals were obtained from isopropyl ether-cyclohexane (yield 15%), mp 168-170°; ir: cm^{-1} 1720, 1680, 1590, 1570, 1520, 1350, 1220, 760; pmr (deuteriochloroform): 7.90 (2 H, m, *ortho* H), 7.45 (3 H, m, *meta*, *para* H), 6.45 (1 H, s, pyrazole H), 3.95 (2 H, m, N-CH_2), 3.20 (2 H, m, 2 CH), 1.80 (8 H, m, 4 CH_2 at 6-, 7-, 8-, and 9-positions), 1.30 (3 H, t, CH_3) ppm.

5,8-Dihydro-4-ethyl-2-phenylpyrazolo[1,5-*a*][1,3]diazepin-5,8-dione **VIII**.

As above general procedure, using maleic anhydride, yellow crystals were obtained from isopropyl ether-cyclhexane (yield 1%), mp, 160-164°; ir: cm^{-1} 1700, 1660, 1620, 1560, 1200, 760; pmr (deuteriochloroform): 7.90 (2 H, m, *ortho* H), 7.50 (3 H, m, *meta*, *para*H), 6.95 (2 H, s, $C_6H=C_7H$), 6.50 (1 H, s, pyrazole H), 4.20 (2 H, q, N-CH_2), 1.40 (3 H, t, CH_3) ppm.

Anal. Calcd. for $C_{15}H_{13}N_3O_2$: C, 67.40; H, 4.90; N, 15.72. Found: C, 67.32; H, 4.85; N, 15.80.

Acknowledgements.

The authors are grateful to Dr. P. Malmberg, Department of Pharmacology Aiazzi-Mancini University of Firenze for the pharmacological experiments. Mass spectral analyses were carried out at the "Mass Spectrometry Center", Faculty of Medicine, University of Firenze.

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