Polycondensed Nitrogen Heterocycles. X (1a,b). 5,6,7,8-Tetrahydropyrrolo[1,2-*e*][1,5]benzodiazocin-7-ones. A New Ring System

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The synthesis of a new heterocyclic ring system is described. Condensation of 1,4-diketones **1a,b** with β-alanine gave the substituted propionic acids **2a,b** which upon reduction with palladium on charcoal afforded compounds **3a,b**. Title compounds **4a,b** were obtained by refluxing **3a,b** in toluene with *p*-toluenesulphonic acid as catalyst.

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In recent years, the central nervous system depressant, anticonvulsive, sleep prolonging and stimulant of the peripheral circulation activity of a number of 1,5-benzodiazocines have been the focus of a considerable amount of work (2-11).

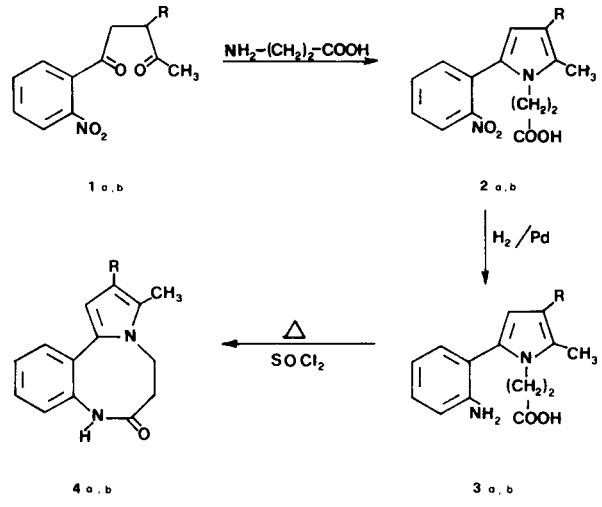
The biological effects of this class of compounds are similar to that of the well known 1,4-benzodiazepines which have found clinical applications, and this permits one to consider the close analogy between 1,5-benzodiazocines and 1,4-benzodiazepines.

The finding that annelated 1,4-benzodiazepines show more potent pharmacological profiles than the benzodiazepines from which they are derived (12), prompted us to consider as part of a continued program aimed at discovering poly-condensed nitrogen heterocycles with pharmaceutical properties (1), the synthesis of a novel class of annelated 1,5-benzodiazocines namely 5,6,7,8-tetrahydropyrrolo[1,2-*e*]1,5-benzodiazocin-7-one (**4a,b**).

These new structures would be expected to exhibit much of the CNS activity of the parent 1,5-benzodiazocines.

The approach to functionalized pyrrolobenzodiazocines is shown in scheme.

SCHEME



a R= $COOC_2H_5$; b R= $COCH_3$

Condensation of 1,4-diketones of type **1** (13-14) with β-alanine in refluxing acetic acid leads to the substituted propionic acids **2a,b**. Catalytic reduction with palladium on charcoal of **2a,b** afforded 2-methyl-3-*R*-5-(2-aminophenyl)pyrrol-1-yl-propionic acids **3a,b** in 85-88% yield. The ir spectra showed an NH_2 band at 3390-3280 cm^{-1} and a broad band (carboxylic OH) at 2650-2640 cm^{-1}. The nmr spectra exhibited one exchangeable singlet for two protons at δ 5.07 due to the NH_2 group, while the OH presence could be deduced by a decreased integral of the aromatic protons upon exchange with deuterium oxide.

Compounds **3a,b**, refluxed in toluene with traces of *p*-toluenesulphonic acid and azeotropic water removal or using thionyl chloride as the condensing agent, afforded an excellent yield of 5,6,7,8-tetrahydropyrrolo[1,2-*e*]-1,5-benzodiazocin-7-ones (**4a,b**).

The structures of compounds **4a,b** were supported by elemental analysis, exact mass measurements, ir and ^{1}H-nmr spectral data. The ir spectra showed an NH band at 3160-3180 cm^{-1} and two carbonyl stretching bands at 1700-1645 cm^{-1}. The nmr spectra, in addition to the signals due to the aromatic and substituent protons, exhibited two multiplets for two protons each, attributable to the CH_2-CH_2 at δ 2.83-2.85 and δ 4.06-4.13 and one singlet for one proton at δ 7.83-7.51 exchangeable with deuterium oxide due to the amide NH.

EXPERIMENTAL

All melting points were taken on a Buchi-Tottoli capillary melting point apparatus and are uncorrected; ir spectra were determined in Nujol mulls with a Perkin-Elmer 299 spectrophotometer; nmr spectra were obtained with a Varian FT 80 spectrometer (TMS as internal reference).

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Mass spectra were run on a JEOL JMS-01 SG-2 double focusing mass spectrometer operating with an electron beam energy of 75 eV and 10 kW accelerating voltage. Exact mass measurement were performed at 20,000 resolving power and were carried out to an accuracy of ± 10 ppm of theoretical values.

2-Methyl-3-*R*-5-(2-nitrophenyl)pyrrol-1-yl-propionic Acids (**2a,b**).

A mixture of **1a,b** (13-14) (10 mmoles) and β-alanine (10 mmoles) in acetic acid was refluxed for 3 hours. After cooling, the mixture was poured into crushed ice, alkalinized (sodium hydroxide 1*N*), and filtered. The clear alkaline solution was acidified with hydrochloric acid, 1*N* and extracted with ethyl ether. The organic layer was dried (sodium sulphate) and evaporated under reduced pressure. The residue which remained was purified.

Compound **2a**.

This compound was purified by chromatography on a dry column of silica gel (200 g) deactivated with water (15%) and eluted with ethyl acetate-light petroleum (bp 50-70°) (8:2). The collected fractions (15-30) (50 ml each) gave a red oil which was not susceptible to crystallization (yield 88%); ir: 2620 (broad OH), 1700 (CO), 1680 (CO) cm^{-1}; nmr (deuteriochloroform): 1.28 (3H, t, CH_2-C*H*$_3$, J = 7.2 Hz), 2.54 (2H, t, CH_2-CH_2, J = 4.7 Hz), 2.58 (3H, s, CH_3), 4.04 (2H, t, CH_2-CH_2, J = 4.7 Hz), 4.22 (2H, q, Ch_2-CH_3, J = 7.2 Hz), 6.43 (1H, s, CH), 7.40-7.90 (4H, m, C_6H_4), 9.17 (1H, s, exchangeable OH); ms: M$^+$ = 346.124; $C_{17}H_{18}N_2O_6$ required M = 346.116.

Compound **2b**.

This compound was recrystallized from benzene mp 94° (yield 85%). ir: 2700 (broad OH), 1720 (CO), 1600 (CO) cm^{-1}; nmr (deuteriochloroform): 2.35 (3H, s, CH_3), 2.55 (2H, t, CH_2), 2.62 (3H, s, CH_3), 4.06 (2H, t, CH_2), 6.39 (1H, s, CH), 7.20-8.05 (5H, m, C_6H_4 and exchangeable OH); ms: M$^+$ = 316.099; $C_{16}H_{16}N_2O_5$ required M = 316.106.

Anal. Calcd. for $C_{16}H_{16}N_2O_5$: C, 60.75; H, 5.10; N, 8.86. Found: C, 60.80; H, 5.13; N, 8.77.

2-Methyl-3-*R*-5-(2-aminophenyl)-pyrrol-1-yl-propionic Acids (**3a,b**).

Compounds **2a,b** were reduced on 10% palladium on charcoal in ethanol in a Parr apparatus at 50 psi for 8 hours at room temperature. The catalyst was filtered off and the solvent evaporated under reduced pressure. The obtained oils were purified.

Compound **3a**.

This compound was recrystallized from benzene mp 98° (yield 93%); ir: 3390 and 3300 (NH_2), 2640 (broad OH), 1710 (CO), 1690 (CO) cm^{-1}; nmr (deuteriochloroform): 1.34 (3H, t, CH_2-C*H*$_3$, J = 7.2 Hz), 2.51 (2H, t, CH_2-CH_2, J = 6.5 Hz), 2.60 (3H, s, CH_3), 4.05 (2H, t, CH_2-CH_2, J = 6.5 Hz), 4.28 (2H, q, C*H*$_2$-CH_3, J = 7.2 Hz), 5.07 (2H, s, exchangeable NH_2), 6.53 (1H, s, CH), 6.68-7.27 (5H, m, C_6H_4 and exchangeable OH); ms: M$^+$ = 316.153; $C_{17}H_{20}N_2O_4$ required M = 316.142.

Anal. Calcd. for $C_{17}H_{20}N_2O_4$: C, 64.54; H, 6.37; N, 8.86. Found: C, 64.43; H, 6.28; N, 8.92.

Compound **3b**.

This compound was purified by chromatography on a dry column of silica gel (200 g) deactivated with water (15%) and eluted with ethyl acetate. The collected fractions (25-42) (50 ml each) gave a residue which was recrystallized from ethanol, mp 175° (yield 70%); ir: 3350 and 3280 (NH_2), 2650 (broad OH), 1715 (CO), 1635 (CO) cm^{-1}; nmr (DMSO): 2.31 (3H, s, CH_3), 2.38 (2H, t, CH_2), 2.56 (3H, s, CH_3) 3.96 (2H, t, CH_2), 6.45 (1H, s, CH), 6.51-7.30 (7H, m, C_6H_4 and exchangeable OH and NH_2); ms: M$^+$ = 286.128; $C_{16}H_{18}N_2O_3$ required M = 286.132.

Anal. Calcd. for $C_{16}H_{18}N_2O_3$: C, 67.11; H, 6.34; N, 9.78. Found: C, 67.16; H, 6.54; N, 9.71.

2-*R*-3-methyl-5,6,7,8-tetrahydropyrrolo[1,2-*e*]1,5-benzodiazocin-7-ones (**4a,b**).

A.

A mixture of **3a,b** (10 mmoles) in toluene (100 ml) and thionyl chloride (10 mmoles) in toluene (30 ml) was refluxed for 8 hours. The solvent was then evaporated under reduced pressure and the residue was diluted with hydrochloric acid (1*N*) (100 ml) and extracted with chloroform (3 × 100 ml). The collected organic layers were dried (sodium sulphate) and evaporated under reduced pressure to give a solid residue which was recrystallized.

B.

A mixture of 10 mmoles of **3a,b** was refluxed for 10 hours in anhydrous toluene and traces of *p*-toluenesulphonic acid with azeotropic water removal (Markusson apparatus). After cooling in the case of **3a**, a precipitate was obtained which was collected, dried and recrystallized. In the case of **3b** the solvent was evaporated under reduced pressure, and the residue was diluted with hydrochloric acid (1*N*) and extracted with chloroform (3 × 100 ml). The collected organic layers were dried (sodium sulphate) and evaporated under reduced pressure to give a residue which was recrystallized.

Compound **4a**.

This compound was recrystallized from benzene (yield 75% (a), 85% (b)) mp 215°; ir: 3180 (NH), 1700 (CO), 1680 (CO) cm^{-1}; nmr (deuteriochloroform): 1.30 (3H, t, CH_2-C*H*$_3$), 2.58 (3H, s, CH_3), 2.83 (2H, m, CH_2), 4.06 (2H, m, CH_2), 4.24 (2H, q, C*H*$_2$-CH_3) 6.44 (1H, s, CH) 7.00-7.50 (4H, m, C_6H_4) 8.51 (1H, s, exchangeable NH); ms: M$^+$ = 298.121; $C_{17}H_{18}N_2O_3$ required 298.132.

Anal. Calcd. for $C_{17}H_{18}N_2O_3$: C, 68.44; H, 6.08; N, 9.39. Found: C, 68.51; H, 6.13; N, 9.33.

Compound **3b**.

This compound was recrystallized from ethanol (yield 30% (a), 50% (b)) mp 254°; ir: 3160 (NH), 1675 (CO), 1645 (CO) cm^{-1}; nmr (deuteriochloroform): 2.41 (3H, s, CH_3), 2.64 (3H, s, CH_3), 2.85 (2H, m, CH_2), 4.13 (2H, m, CH_2), 6.42 (1H, s, CH), 7.08-7.65 (4H, m, C_6H_4), 7.83 (1H, s, exchangeable NH); ms: M$^+$ = 268.133; $C_{16}H_{16}N_2O_2$ required M = 268.121.

Anal. Calcd. for $C_{16}H_{16}N_2O_2$: C, 71.62; H, 6.01; N, 10.44. Found: C, 71.51; H, 5.97; N, 10.53.

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