

NEW CONDENSED TRIHETEROCYCLIC SYSTEMS; PYRROLOTHIENOPYRAZINES

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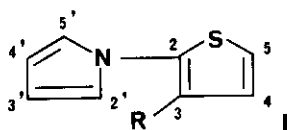
Abstract - Cyclization of the azide derivatives of 2 (3)-(1-pyrrolyl)-3-(2)-thienylcarboxylic acids resulted in the formation of the 4,5-dihydropyrrolo[1,2-a]thieno[3,2-e]pyrazin-5-one and the 4,5-dihydropyrrolo[1,2-a]thieno[2,3-e]pyrazin-5-one.

As part of our project for the synthesis and evaluation of the biological properties of tricyclic compounds containing both thiophene and pyrrole rings ¹⁻⁴⁾ we wish to report herein a convenient synthesis of hitherto unknown compounds namely 4,5-dihydropyrrolo[1,2-a]thieno[3,2-e]pyrazin-5-one and 4,5-dihydropyrrolo[1,2-a]thieno[2,3-e]pyrazin-5-one.

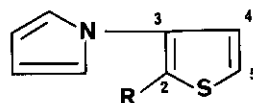
Starting with 2-amino-3-cyanothiophene ⁵⁾, the 2-(1-pyrrolyl)-3-thienylcarboxylic acid (Ib)^x; mp 178° (ethanol); nmr spectrum (DMSO) δ ppm 7.41(1H,d,H5, J H5/H4 = 5.80 Hz); 7.30(1H,d,H4); 7.05(2H,m,H2',H5'); 6.23(2H,m,H3',H4'); ir spectrum (KBr) ν C=O:1680 cm⁻¹; could be obtained in two steps, first by condensation with 2,5-dimethoxytetrahydrofuran in hot acetic acid ⁶⁾ to give (Ia), followed by hydrolysis of the cyano group in alkaline medium. The latter acid (Ib) could be converted to the corresponding acid azide (Ic); ir spectrum (KBr) ν N₃:2160 cm⁻¹; using the method of Weinstock ⁷⁾. Heating the azide (Ic) whether in the solid state or in high boiling solvent affected the ring closure giving the 4,5-dihydropyrrolo[1,2-a]thieno[3,2-e]pyrazin-5-one (II).

A typical experiment is as follows : 2 g of (Ic) in 50 ml of o-dichlorobenzene are refluxed for 15 min. After cooling to room temperature a white crystalline product separated out, this was filtered, washed with ether and dried (1.6g; 92%). The structure of compound (II) was supported by ir and nmr spectra; mp 272° (sublimation in vacuo); nmr spectrum (DMSO) δ ppm 7.42 (1H,dd,H8, J H8/H7 = 2.4 Hz, J H8/H6 = 1.3 Hz); 7.30(1H,d,H2, J H2/H3 = 5.7 Hz); 6.98(1H,dd,H6, J H6/H7 = 4.2 Hz); 6.92(1H,d,H3); 6.58(1H,dd,H7); 11.2(1H,s,NH); ir spectrum (KBr) ν C=O:1650 cm⁻¹.

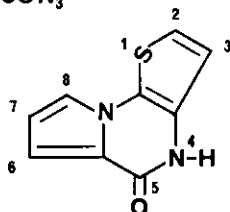
On the other hand, gentle heating of the azide (Ic) in dichloromethane afforded a mixture of the starting material and the isocyanate intermediate; ir spectrum ν N=C=O:2260 cm⁻¹. Trials to isolate this latter intermediate were unsuccessful due to the reactivity of the pyrrole ring which favours the closure.



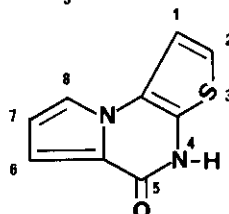
a; R = CN
b; R = COOH
c; R = CON₃



III
a; R = COOCH₃
b; R = COOH
c; R = CON₃



II



IV

In a similar manner, the reaction of methyl 3-amino-2-thienylcarboxylate⁸⁾ with 2,5-dimethoxytetrahydrofuran gave the methyl 3-(1-pyrrolyl)-2-thienylcarboxylate (IIIa); bp_{4mm}: 130°; nmr spectrum (DMSO) δ ppm 7.83 (1H, d, H5, J H5/H4 = 5.45 Hz); 7.17 (1H, d, H4); 7.08 (2H, m, H2', H5'); 6.17 (2H, m, H3', H4'); 3.74 (3H, s, CH₃); ir spectrum (KBr) ν C=O: 1700 cm⁻¹; which was converted to the corresponding acid (IIIb) by alkaline hydrolysis of the ester grouping; mp 185° (ethanol); nmr spectrum (DMSO) δ ppm 7.80 (1H, d, H5, J H5/H4 = 5.40 Hz); 7.17 (1H, d, H4); 7.08 (2H, m, H2', H5'); 6.15 (2H, m, H3', H4'); ir spectrum (KBr) ν C=O: 1675 cm⁻¹. Under the same conditions described above the azide (IIIc) ir spectrum (KBr) ν N₃: 2150 cm⁻¹, derivative of the acid (IIIb) afforded the other isomer 4,5-dihydropyrrolo[1,2-a]thieno[2,3-e]pyrazin-5-one (1.4 g 81%); mp 276° (sublimation in vacuo); nmr spectrum δ ppm 7.83 (1H, dd, H8, J H8/H7 = 2.6 Hz, J H8/H6 = 1.3 Hz); 7.55 (1H, d, H2, J H2/H1 = 5.7 Hz); 7.18 (1H, d, H1); 6.97 (1H, dd, H6, J H6/H7 = 4.2 Hz); 6.55 (1H, dd, H7); 11.5 (1H, s, NH); ir spectrum (KBr) ν C=O: 1635 cm⁻¹. Further studies concerning these compounds and biological screening are under investigations.

REFERENCES AND A FOOTNOTE

^x all new compounds gave analytical results in agreement with the proposed structures.

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