NEW CONDENSED TRIHETEROCYCLIC SYSTEMS; PYRROLOTHIENOPYRAZINES

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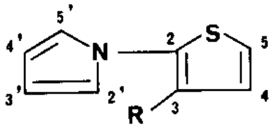
Abstract - Cyclization of the azide derivatives of 2 (3)-(1-pyrrolyl)-3-(2)-thienylcarboxylic acids resulted in the formation of the 4,5-dihydropyrrolo[1,2-a]thieno[3,2-e]pyrazin-5-one and the 4,5-dihydropyrrolo[1,2-a]thieno[2,3-e]pyrazin-5-one.

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) νN$_3$: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).

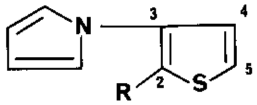
A typical experiment is as follows : 2 g of (Ic) in 50 ml of o-dichlorobenzene are refluxed for 15 min. After cooling to room temperature a white crystalline product separated out, this was filtered, washed with ether and dried (1.6g; 92%). The structure of compound (II) was supported by ir and nmr spectra; 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) νC=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 νN=C=O:2260 cm^{-1}. Trials to isolate this latter intermediate were unsuccessfull due to the reactivity of the pyrrole ring which favours the closure.



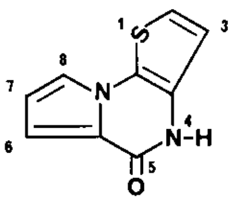
I

a; R = CN
b; R = COOH
c; R = CON$_3$

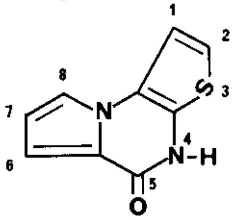


III

a; R = COOCH$_3$
b; R = COOH
c; R = CON$_3$



II



IV

In a similar manner, the reaction of methyl 3-amino-2-thienylcarboxylate $^{8)}$ with 2,5-dimethoxytetrahydrofuran gave the methyl 3-(1-pyrrolyl)-2-thienylcarboxylate (IIIa); bp$_{4mm}$: 130º; 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,CH$_3$); 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 185º (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 N$_3$: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 276º (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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