NEW CONDENSED TRIHETEROCYCLIC SYSTEMS ; PYRROLOTHIENOPYRIMIDINES

Yamien Effi, Michel Cugnon de Sevricourt, Sylvain Rault and Max Robba*

Laboratoire de Chimie thérapeutique,
U.E.R. des Sciences Pharmaceutiques, Université de Caen,
1, rue Vaubénard, 14000 Caen,
France

Abstract - Cyclisation of the azide derivative of the 1-(3-thienyl) pyrrolylcarboxylic acid resulted in the formation of 4,5-dihydropyrrolo[1,2-a]thieno[2,3-e]pyrimidin-4-one.

As part of our work on the study of tricyclic systems containing both thiophene and pyrrole rings, we have recently reported the synthesis of some pyrrolothienodiazepines-1,4 1) and pyrrolothienopyrazines 2). We wish to report herein the route for the synthesis of a new triheterocyclic compound namely 4,5-dihydropyrrolo[1,2-a]thieno[2,3-e]pyrimidin-4-one (V).

The starting material, methyl 3-(1-pyrrolyl)-2 thienylcarboxylate (Ia) 2) is available from 3-amino 2-thienylcarboxylate 3) using the method of Clauson-Kaas by reaction with 2,5-dimethoxytetrahydrofuran in hot acetic acid 4). Alkaline hydrolysis of the ester grouping affords the acid (Ib) which is decarboxylated at 180° in quinoline in presence of copper powder to give 1-(3-thienyl)pyrrole (Ic).

The more convenient route to access to the pyrimidine ring seemed to be the introduction of a nitro grouping in the pyrrole ring, but all attempts to nitrate the ester (Ia) or the 1-(3-thienyl)pyrrole (Ic) in numerous conditions gave in the best cases a mixture of 3 and 2-nitro compounds (IIa-b) and (IIc-d) respectively in very poor yields.

This unsuccessful reaction prompts us to cyclize the pyrimidine ring adjusting our method of synthesis of homologous pyrazines by cyclisation of the azide derivative of 1-(3-thienyl)-2 pyrrolycarboxylic acid (IVe) 2).

Contrary to the nitration, the Vilsmeier-Haack reaction affords in good yields a monosubstituted compound when it is carried out at 100° in dimethylformamide either starting with the ester (Ia), the acid (Ib) or the 1-(3-thienyl)pyrrole (Ic). ^{1}H nmr study of these substituted compounds shows that the formylation occurs in all cases at position 2 in the pyrrole ring and determines the structure of compounds (III) which is confirmed by unequivocal synthesis.

Thus alkaline hydrolysis of the ester aldehyde (IIIa) in sodium hydroxide solution gives the acid aldehyde (IIIb) which can be decarboxylated to furnish the aldehyde (IIIc).

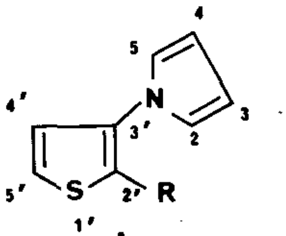
Table. M.p. and ^1H N.M.R. spectroscopic data of 1-(3-thienyl) pyrroles II, III, IV.

Compd.	M.p.	N.M.R. (DMSO_d_6 δ/p.p.m.)							
N°	(°C)	H2'	H4'	H5'	H2	H3	H4	H5	other protons
Ic	112° (ether)	7,38	7,36	7,55	7,05	6,13	6,13	7,05	
IIa	146°*		7,30	8,01		7,33	6,40	7,26	3,71 (CH3)
IIb	185°*		7,35	8,00	8,21		6,78	7,16	3,76 (CH3)
IIc	72°*	7,28	7,16	7,60		7,30	6,36	7,70	
IId	60°*	7,82	7,50	7,60	8,48		6,80	7,42	
IIIa	142° (acetone)		7,17	7,91		7,13	6,38	7,58	9,58 (CH),3,63 (CH3)
IIIb	240° (acetone)		7,11	7,83		7,10	6,33	7,26	9,40 (CH)
IIIc	$E_{0,5}$=150°	7,61	7,20	7,53		7,10	6,35	7,31	9,50 (CH)**
IVa E	94° (ether)	7,56	7,21	7,63		6,53	6,06	6,98	7,83 (CH),11,20 (OH)
IVa Z		7,56	7,21	7,63		7,21	6,06	6,98	7,21 (CH),10,80 (OH)
IVb	64° (ether)	7,73	7,45	7,73		7,10	6,35	7,45	
IVc	127° (ETOH/H_2O)	7,30	7,00	7,41		6,83	6,13	7,00	8,1-6,2 (NH2)
IVd	176° (ETOH)	7,50	7,06	7,48		6,90	6,20	7,10	3,8-3,0 (OH)

* Sublimation in vacuo ; ** JCHO/H5 = 0,6 Hz, JCHO/H4 = 0,3 Hz.

The corresponding acid (IVd) is then obtained by two ways ; either by direct oxidation of the aldehyde grouping using potassium permanganate in boiling acetone or better silver oxide in diluted sodium hydroxide solution ; either by hydrolysis of the nitrile (IVb) in alkaline medium.Condensation of hydroxylamine chloride with the aldehyde (IIIc) in presence of ammonium acetate gives the oxime (IVa) which is then deshydratated in boiling acetic anhydride to give the nitrile (IVb). The latter is then converted into the acid (IVd) directly in boiling concentrated sodium hydroxide solution or after isolation of the intermediate (IVc).

Treatment of the acid (IVd) with ethyl chloroformate and sodium azide in presence of triethylamine affords in the conditions described by Weinstock [6] the acid azide (IVe).Heating this latter either in the solid state or in boiling o-dichlorobenzene following the procedure described for the synthesis of homologous pyrrolothienopyrazines [2-5] gives the 4,5-dihydro pyrrolo [1,2-a] thieno [2,3-e] pyrimidin-4-one (V). The structure of compound (V) is supported by ir and nmr spectra ; mp 260° (sublimation in vacuo) ; ir spectrum (KBr)νC = 0 1650 cm^{-1}, nmr spectrum (DMSO)δppm 7.68 (1H,d,H1,J H1/H2 = 5.1 Hz); 8.12 (1H,d,H2, J H2/H1 = 5.1 Hz); 5.56 (1H,dd, H6, J H6/H7 = 3.6 Hz, J H6/H8 = 1.5 Hz) ; 6.33 (1H,dd, H7, J H7/H8 = 3.3 Hz); 7.31 (1H,dd,H8, J H8/H7 = 3.3 Hz, J H8/H6 = 1.5 Hz); 7.3 (1H,s,NH). Further reactions concerning theses compounds are in progress.

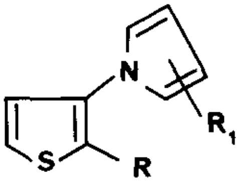


I

a, R = $COOCH_3$

b, R = COOH

c, R = H



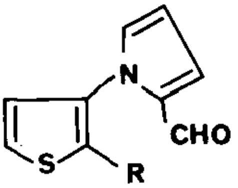
II

a, R = $COOCH_3$ R_1= 2-NO_2

b, R = $COOCH_3$ R_1= 3-NO_2

c, R = H R_1= 2-NO_2

d, R = H R_1= 3-NO_2

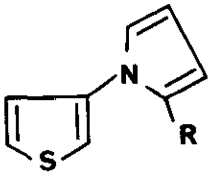


III

a, R = $COOCH_3$

b, R = COOH

c, R = H



IV

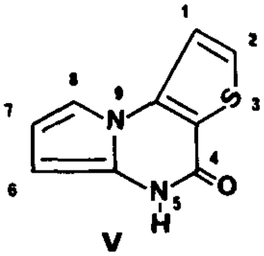
a, R = CHNOH (Z+ E)

b, R = CN

c, R = $CONH_2$

d, R = COOH

e, R = CON_3



V

REFERENCES AND A FOOTNOTE

All new compounds gave analytical results in agreement with the proposed structures.

1. S. Rault, M. Cugnon de Sevricourt and M. Robba, C.R. Acad. Sci. Paris, 1977, 284 (C), 533 ; idem, ibid., 1977, 285 (C), 381 ; idem, ibid., 1978, 287 (C), 117 ; S. Rault, M. Cugnon de Sevricourt, M. Robba and Nguyen-Huy Dung, Tetrahedron letters, 1979, 643 ; S. Rault, M. Cugnon de Sevricourt and M. Robba, Heterocycles, 1979, 12, 1009 ; Nguyen-Huy Dung, S. Rault and M. Robba, Acta Cryst., 1979, B 35, 1290.

2. S. Rault, M. Cugnon de Sevricourt and M. Robba, Heterocycles, 1980, 14, 651 ; idem, J.Heterocyclic Chem., 1981 (to be published).

3. H. Fiesselmann, German Patent, 1,055,007 (1957) ; 1,083,830 (1958) ; P.R. Huddleston and J.M. Barker, Synthetic communications, 1979, 9, 731.

4. N. Clauson-Kaas and Z. Tyle, Acta Chem. Scand., 1972, 6, 667.

5. M. Cugnon de Sevricourt, H. El Kashef, S. Rault and M. Robba, Synthesis, 1981, (to be published).

6. J. Weinstock, J. Org. Chem., 1961, 26, 3511.

Received, 11th April, 1981