PYRROLOTHIENOPYRIMIDINES II.[1] SYNTHESIS OF 4-AMINOPYRROLO[1,2-a]THIENO[3,2-e] (AND[2,3-e]) PYRIMIDINES

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Abstract —— Cyclization of the appropriate cyanothienylpyrrolylcarboxylic acid azides in boiling ortho-dichlorobenzene conducted to the corresponding aminopyrrolothienopyrimidines.

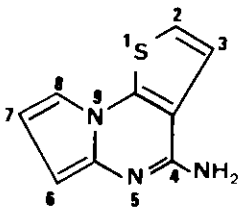
In continuation of our work on the synthesis of fused triheterocyclic systems containing both thiophene and pyrrole rings, we have recently published the synthesis of some pyrrolothienopyrazines,[2] - pyrimidines,[1] - diazepines,[3] and thienopyrrolizines,[4]. We wish to describe heres a convenient route to the new 4-aminopyrrolo[1,2-a]thieno [3,2-e] (and[2,3-e]) pyrimidines 1 and 2.

The aminopyrimidine 1 was obtained in four steps starting from 2-(1-pyrrolyl)-3 thiophenecarbonitrile 3. First Vilsmeier-Haack reaction gave the monoaldehyde 4 [5] which was then oxidized by potassium permanganate in acetone to give the cyano acid 5. Reaction of this acid with éthyl chloroformate followed by sodium azide in the presence of triethylamine in ice cold acetone gave the azidocarbonyl compound 6. Heating of this azide in boiling o.dichlorobenzene in the presence of small amounts of water leaded to Curtius rearangement with subsequent cyclization to give the aminopyrimidine 1 in good yield. The structure of compound 1 is supported by ir, nmr and mass spectra, and by comparison with those of the isomer 5-aminopyrrolo[1,2-a]thieno[3,2-e]pyrazine[6]. Further, study of the nmr spectrum of 1 shows two superimposed spectra due to a slow exchange between the two tautomeric forms : aminopyrimidine 1 and dihydroiminopyrimidine 1a. mp 260°C (sublimation in vacuo) ; ir spectrum (KBr) ν max NH : 3470, 3305 and 3090 cm^{-1} ; nmr spectrum (DMSO) δ ppm 7.46 (1H, d, H3), 7.01 (1H, dd, H8), 6.51 (1H, dd, H7), 5.78 (1H, dd, H6), 6.60 (2H broad, NH_2).

Following the same procedure, the aminopyrimidine 2 was obtained in eight steps starting from methyl 3-(1-pyrrolyl)-2-thènoate 7 [5].

Reduction with lithium aluminium hydride in tetrahydrofuran gave the alcohol 8 which was then oxidized with manganese dioxide in boiling chloroform to give the aldehyde 9. Condensation of this aldehyde with hydroxylamine hydrochloride in boiling pyridine conducted to the oxime 10 as a mixture of an equivalent amount of E and Z forms. Dehydratation of the oxime 10 in boiling acetic anhydride furnished the cyano compound 11. On the other hand the cyanoazidocarbonyl compound 14 was obtained by the intermediate of formyl 12 and acid 13. Cyclization of 14 was conducted in a similar manner as for 6 and the structure of 2 was confirmed by ir, nmr and mass spectra and by comparison with isomeric 5-amino pyrrolo[1,2-a]thieno[3,2-e]pyrazine [6]. The aminopyrimidine 2 exhibits a tautomeric equilibrium with the dihydro iminopyrimidine 2a.

TABLE I



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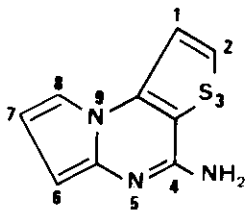

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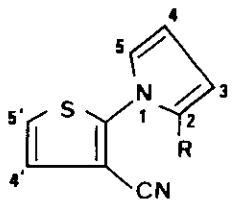
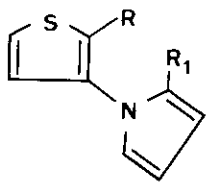


3 R = H
4 R = CHO
5 R = COOH
6 R = CON_3



7	R = $COOCH_3$	R_1 = H
8	R = CH_2OH	R_1 = H
9	R = CHO	R_1 = H
10	R = CHNOH	R_1 = H
11	R = CN	R_1 = H
12	R = CN	R_1 = CHO
13	R = CN	R_1 = COOH
14	R = CN	R_1 = CON_3

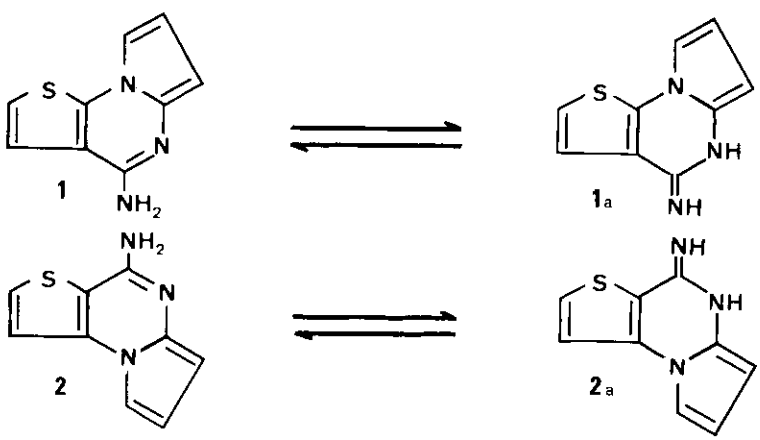


Table II. mp or bp, ir and ^{1}HNMR spectral data of compounds 5 ⟶ 14

Compound	mp°C (solvant for recristallisation) or bp°C	IR (KBr) max (cm^{-1})	^{1}HNMR (DMSO) δ ppm						
			H4'	H5'	H2	H3	H4	H5	Other signals
5	222°C (EtOH)	2220 (C≡N) 1690 (C=O)	7.45	7.78	-	7.11	6.45	7.38	OH=4.00
6	90°C (Et_2O)	2220 (C≡N) 2160 (N_3) 1680 (C=O)	7.10	7.43	-	7.23	6.13	6.86	-
8	100/5mm	3350 5OH)	7.03	7.41	6.96	6.15	6.15	6.96	OH=5.10 CH_2=4.55
9	100/5mm	1650 (C=O)	7.34	8.10	7.28	6.25	6.25	7.28	CH=9.80
10 (Z)	85°C	3200 (OH)	7.06	7.71	6.93	6.16	6.16	6.93	CH=7.36 OH=12.05
(E)			7.06	7.50	6.93	6.16	6.16	6.93	CH=7.95 OH=11.28
11	58°C (Et_2O)	2225 (C≡N)	7.46	8.03	7.31	6.16	6.16	7.31	
12	104°C (Et_2O)	2230 (C≡N) 1665 (C=O)	7.10	7.33	-	7.28	6.50	7.50	CHO=9.55
13	220°C (EtOH)	3200 2240 (C≡N)	7.30	7.83	-	7.08	6.31	7.31	OH=8.60
14	150°C (Et_2O)	2240 (C≡N) 2160 (N_3) 1670 (C=O)	7.20	7.50	-	7.25	6.15	6.93	-

δmp 240°C (EtOH) ; ir spectrum (KBr) max NH 3440 and 3300 cm^{-1} ; nmr spectrum (DMSO) ppm 7.99 (1H, d, H2), 7.72 (1H, d, H1), 7.38 (1H, dd, H8), 6.47 (3H, broad H7, NH_2), 5.78 (1H, dd, H6).

Further studies concerning these series are in progress.

REFERENCES

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

1. Y. Effi, M. Cugnon de Sevricourt, S. Rault and M. Robba, Heterocycles, 1981, 16, 1519.
2. S. Rault, M. Cugnon de Sevricourt and M. Robba, Heterocycles, 1980, 14, 651. S. Rault, M. Cugnon de Sevricourt, Nguyen Huy Dung and M. Robba, J. Heterocyclic Chem., 1981, 18, 739 ; Y. Effi, J.C. Lancelot, S. Rault and M. Robba, ibid, 1983, 20, 913 ; J.P. Rioult, M. Cugnon de Sevricourt, S. Rault and M. Robba, ibid., 1984, 21, 1449.
3. S. Rault, M. Cugnon de Sevricourt and M. Robba, Heterocycles, 1979, 12, 1009 ; S. Rault, M. Cugnon de Sevricourt, Nguyen Huy Dung and M. Robba, Tetrahedron Letters, 1979, 643 ; Nguyen Huy Dung, S. Rault and M. Robba, Acta Cryst., 1979, B35, 1290.
4. S. Rault, J.C. Lancelot, Y. Effi and M. Robba, Heterocycles, 1983, 20, 447 ; C. Laporte-Wojcik, A.M. Godard, S. Rault and M. Robba, ibid, 1985, 23, 1471.
5. S. Rault, M. Cugnon de Sevricourt, Y. Effi, J.C. Lancelot and M. Robba, J. Heterocyclic Chem., 1983, 20, 17.
6. S. Rault, Y. Effi, J.C. Lancelot and M. Robba (to be published).

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