THIENOPYRROLIZINES : NEW CONDENSED TRIHETEROCYCLIC SYSTEMS

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Abstract - Cyclisation of amide derivatives of 2-(3)-(1-pyrrolyl)-3 (2)-thienylcarboxylic acids resulted in the formation of thieno-[2,3 (3,2)-b] pyrrolizin-4-ones whose reduction gave the corresponding 4H pyrrolizines.

In view of *antitumor activity of mitomycin* 1 [1] and related compounds, considerable interest has been recently directed to the synthesis of pyrroloindoles 2 [2]. As part of our project for the synthesis of new heterocyclic systems containing both thiophene and pyrrole rings we have recently reported the synthesis of pyrrolothienodiazepines,[3] -pyrazines [4] or pyrimidines [5]. We wish to report herein a facile route for the synthesis of new triheterocyclic systems namely thieno [2,3-b] pyrrolizine 3 and thieno [3,2-b] pyrrolizine 4. However it must be pointed out that Reinhoudt [6] has described some tetrahydrothieno [3,2-b] pyrrolizines obtained as by-products of the cycloaddition of 3-pyrrolidinothiophenes with dimethyl acetylenedicarboxylate.

Numerous syntheses of pyrroloindoles were described but the more common routes, particularly cyclisation of 2-(1-pyrrolyl)benzoic acids could not be applied in thiophenic series starting from 2 (3)-(1-pyrrolyl-3-(2)-thenoic acid 5a-6a. Thus these failures prompted us to study a novel method of cyclisation starting with amide derivatives of these acids following the procedure described below.

The esterification of the thenoic acid 5a with diazomethane in ether gave the methyl carboxylate 5b which could be condensed with boiling pyrrolidine to afford the pyrrolidinocarboxamide 5e. In a similar manner condensation of methyl carboxylate 6b [5] gave the isomer 6e. Then cyclisation of these pyrrolidinocarboxamides in boiling phosphoryl chloride yielded thienopyrrolizinones 7 and 8.

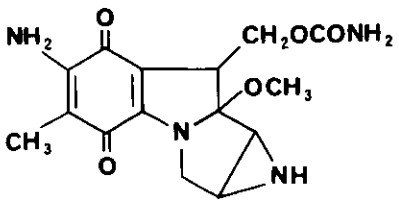
Table 1 : M.p. or b.p., IR ^{1}H NMR spectroscopic data of thienylpyrroles

Compd. N°	b.p. or m.p. (°C)	IR (KBr) (νC=O, cm^{-1})	H NMR (DMSOd$_6$/δppm)				
			H4	H5	H2'-5'	H3'-4'	OTHERS
5b	70	1710	7,38	7,48	7,08	6,28	CH_3 : 3,73
5c	200/1mm	1800	7,35	7,46	7,03	6,23	CH_2 : 4,23 ; CH_3 : 1,23
5d	130/1mm	1625	7,00	7,32	6,86	6,20	CH_3 : 2,85, 2,55
5e	180/1mm	1610	7,03	7,31	6,90	6,20	CH_2 : 3,30, 2,80, 1,66
6c	48	1800	7,20	7,86	7,06	6,13	CH_2 : 4,16 ; CH_3 : 1,03
6d	180/1mm	1620	7,20	7,70	6,86	6,16	CH_3 : 2,80, 2,60
6e	110°	1600	7,20	7,70	6,93	6,20	CH_2 : 3,33, 2,66, 1,63

Table 2 : M.p. or b.p., IR ^{1}H NMR spectroscopic data of thienylpyrrolizines

Compd. N°	b.p. or m.p. (°C)	IR(KBr) (νC=O or C=C and OH cm^{-1})	H NMR (DMSOd$_6$/δppm)						
			H1	H2	H3	H5	H6	H7	OTHERS
7	123	1675 (CO)	-	7,05	6,90	6,63	6,10	7,36	-
8	112	1670 (CO)	7,16	8,03	-	6,60	6,06	7,23	-
9	145	3330 (OH)	-	6,95	6,95	6,20	6,20	7,00	CH : 5,42 OH : 3,40
10	82	3350 (OH)	7,10	7,50	-	6,10	6,10	7,00	CH : 5,40 OH : 5,70
3	200/1mm	1545 (C=C)	-	7,06	6,96	6,06	6,20	7,10	CH_2: 3,70
4	74	1550 (C=C)	7,16	7,43	-	6,00	6,13	7,06	CH_2: 3,83

Therefore better results were obtained starting with dimethyl thenamides 5d-6d. The latter could be achieved via the intermediate of the mixed anhydrides 5c-6c obtained by the reaction of ethyl chloroformate with the acids 5a-6a in the presence of triethylamine. This reaction was quantitative when it was carried out using benzene solution of dimethylamine. Then in similar conditions, the above cyclisation occurred in good yields. A typical experiment is as follows : 15g of amide 5d or 6d in 80 ml of phosphoryl chloride are refluxed for 1.5 h, then excess of phosphoryl chloride is distilled in vacuo. The dark brown residue is dissolved in cold water (200 ml), and the solution is made alkaline by addition of 6N sodium hydroxide solution (200 ml). The solid which precipitates out is filtered, thoroughly washed with water and dried. Crystallisation from ether gives 7 (red crystals, 8.5g, 72%) or 8 (yellow crystals, 9.3g, 78%).



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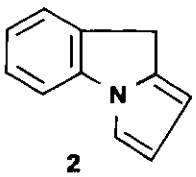

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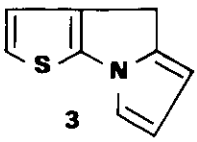

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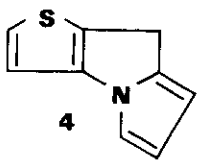

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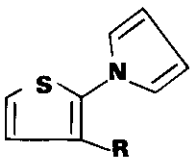

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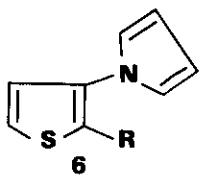
a R = COOH
b R = $COOCH_3$
c R = $COOCO_2C_2H_5$
d R = $CON(CH_3)_2$
e R = 



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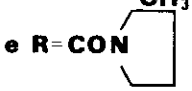
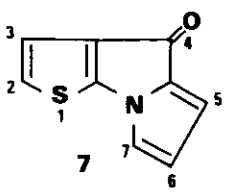
a R = COOH
b R = $COOCH_3$
c R = $COOCO_2C_2H_5$
d R = $CON(CH_3)_2$
e R = 



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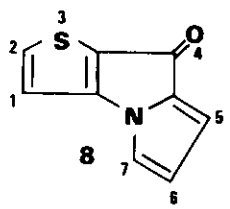

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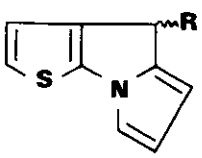
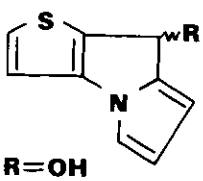


9 R = OH



10 R = OH

Further, hydrogenation of thienopyrrolizinones 7 and 8 with 2 equivalents of lithium aluminium hydride in boiling ether gave selectively the alcohols 9 and 10 respectively. However when this reaction was carried out with 1.75 equivalent of lithium aluminium hydride and in presence of 3.5 equivalents of aluminium chloride, the reduction was complete and furnished the 4H-thienopyrrolizines 3 and 4 quantitatively.

Further studies concerning these compounds and biological investigation are in progress.

REFERENCES AND FOOTNOTE

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

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