NEW HETEROCYCLIC SYSTEMS : THIOPHEN CONDENSED 1-AZA BICYCLO[3.3.1]NONANES

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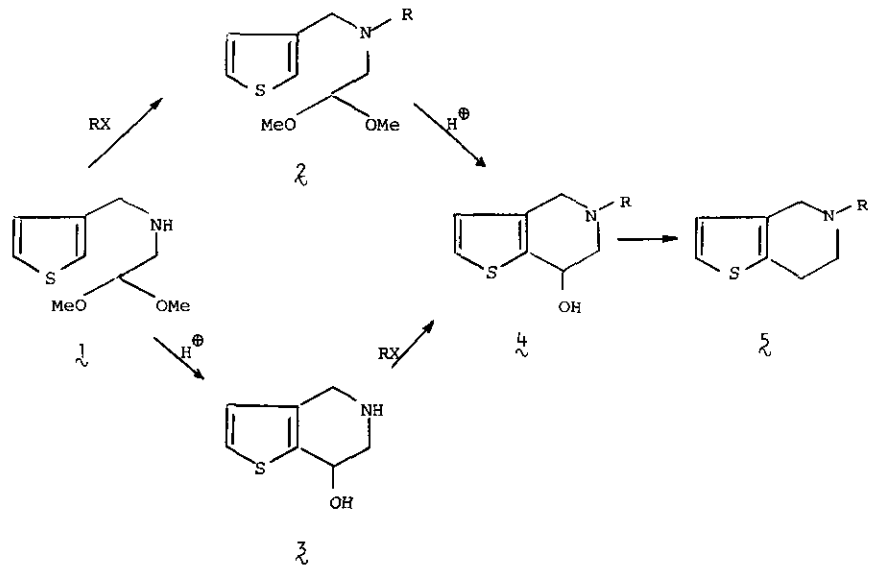
Abstract - *We described the synthesis of new heterocyclic systems by acidic treatment of N-benzyl, N-thenyl or N,N-dithenyl aminoacetaldehyde dimethylacetals.*

In a previous communication[1] we showed that Ticlopidine[2] (5, R= 2-Cl-C_6H_5-CH_2), a new inhibitor of platelets agregation and antithrombotic agent[3,4], could be synthetised according to the following reaction sequence :

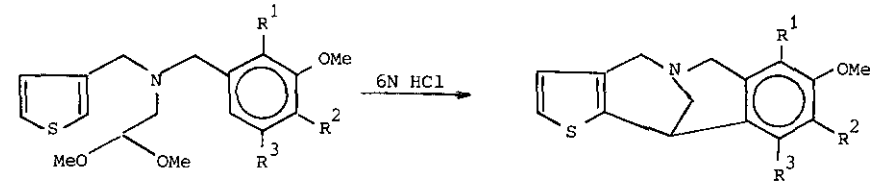
Scheme I



This cyclisation process derived from Bobbitt's synthesis of isoquinolines[5].
N-Alkylation of (1) or (3) with various alkyl halides RX (K_2CO_3 2eq, KI cat., DMF, 90°) gave the expected tertiary amines (2) or (4)[6].
But amines (2 a-c) (Scheme II), obtained by alkylation of (1) with the corresponding meta-methoxy substituted benzyl halides, cyclized to benzo(c)thieno[2,3-f] 1-azabicyclo[3.3.1]nonanes (6 a-c)

by treatment in 6N hydrochloric acid at room temperature or, more rapidly, at reflux.

Scheme II



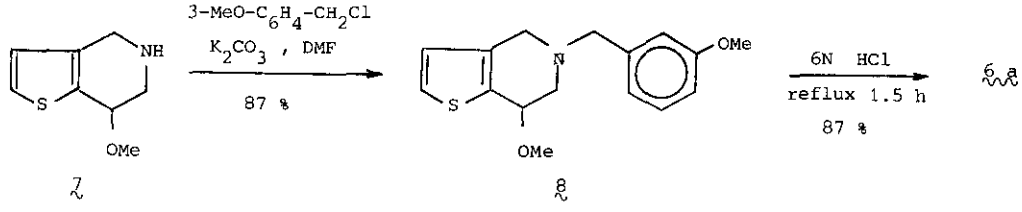
2a $R^1=R^2=R^3=H$
2b $R^1=R^3=H$; $R^2=CH_3O$
2c $R^1=R^2=CH_3O$; $R^3=H$
2d $R^1=OH$; $R^2=R^3=CH_3O$

6a-d

On the same conditions, (2d) obtained by Mannich condensation of guaicol and (1) with formaldehyde (40 % aqueous solution, ethanol, r.t., 69 % yield) cyclized into (6d).

The same new tetracyclic compounds were also prepared from the methoxytetrahydrothienopyridine (7)[7] as illustrated in the following reaction . (Scheme III).

Scheme III



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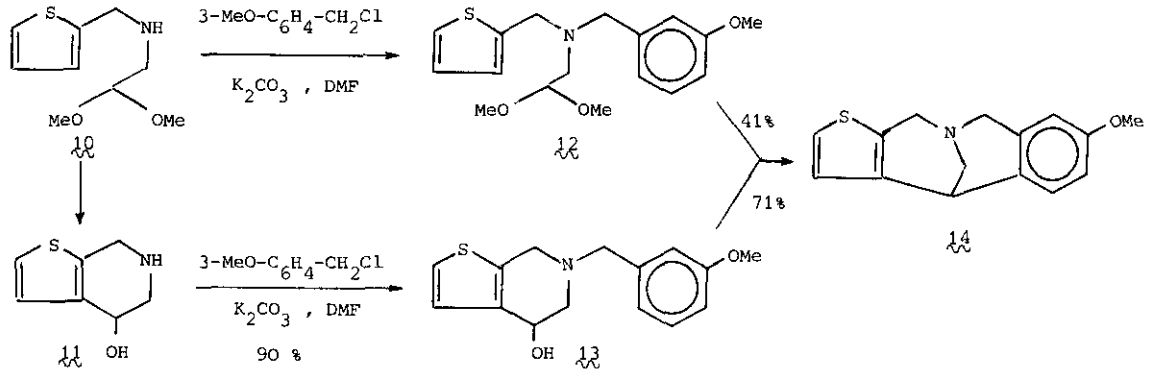
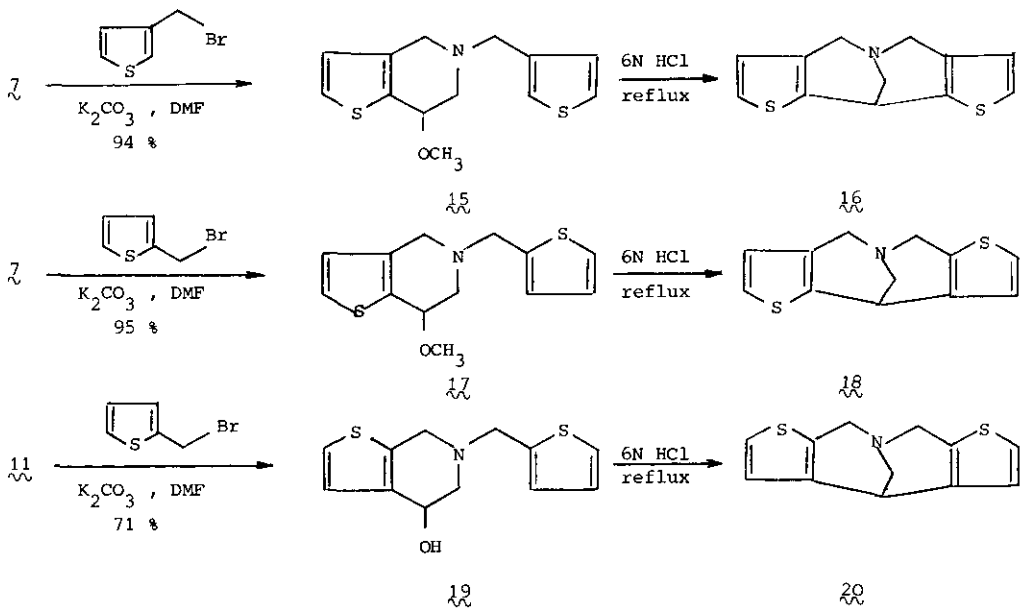
When the intermediates[1] (10) or (11) were used as exemplified in scheme IV, the isomeric benzo(c) thieno[3,2-f] 1-azabicyclo[3.3.1] nonane (14) was formed.

Scheme IV



Such a double cyclisation also occured when the methoxyphenyl ring was replaced by the thiophene nucleus as illustrated in scheme V.

Scheme V

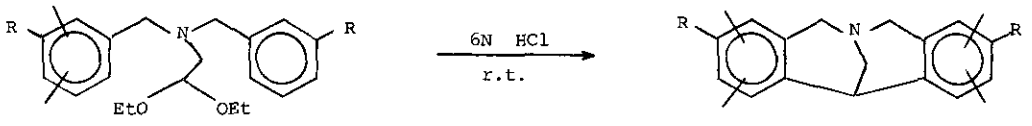


TABLE

Tetracyclic Compounds	Yield %	mp°C (Solvent)	^{1}H - NMR δ ($CDCl_3$)
6a	69	104-106 (iPr_2O)	6,91(d,1H,J=8Hz);6,70(d,1H,J=5Hz);3,50(s,3H); 3,19(m,2H)
6b	39	hydrochloride > 260	6,78(d,1H,J=5Hz); 6,53(d,1H,J=5Hz); 6,57(s,1H); 6,37(s,1H); 3,77(s,3H); 3,64(s,3H); 3,26(s,2H)
6c	67	hydrochloride 245-255	6,87(d,1H,J=5Hz); 6,62(d,1H,J=5Hz);6,26(s,1H); 4,02(s,3H); 3,76(s,3H); 3,69(s,3H)
6d	50	hydrochloride > 260	6,98(d,1H,J=5Hz); 6,67(d,1H,J=5Hz); 6,63(s,2H); 3,70(s,3H); 3,17(m,2H)
14	71	74-76 (iPr_2O)	4,40(d,1H,J=17Hz); 3,65(d,1H,J=17Hz);3,40(s,3H); 4,30(d,1H,J=17Hz); 3,60(d,1H,J=17Hz); 3,05(m,2H)
16	66	83-85 (iPr_2O)	6,75(d,1H,J=5Hz); 6,45(d,1H,J=5Hz); 4,40(d,2H,J=17Hz); 3,65(d,2H,J=17Hz)
18	59	107-109 (iPr_2O)	4,45(d,1H,J=17Hz); 3,75(d,1H,J=17Hz);4,55(d,1H,J=17Hz); 3,85(d,1H,J=17Hz); 3,30(m,2H)
20	61	145-147 (iPr_2O)	6,95(d,1H,J=5Hz); 6,70(d,1H,J=5Hz); 4,55(d,2H(J=17Hz); 3,80(d,2H,J=17Hz); 3,15(m,2H)

All these cyclisations were also expected since Bobbitt's work[8] on the formation of dibenzo[c,f]-1-azabicyclo[3.3.1]nonanes (22) from the dibenzylamines (21) in which R was a hydroxy or methoxy substituant (scheme VI).

Scheme VI



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Recently, Takayama and coll.[9] showed that the cyclisation of (21) analogs could be carried out even in the absence of electron-donating group if the reaction was performed in 70 % perchloric acid. Nevertheless, neither with this reagent nor with trifluoromethanesulfonic acid[10], we were able to prepare cyclic analogs of (6 a-d) or (14) which did not contain a methoxy or hydroxy groups in the right position.

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