

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

Jean-Pierre MAFFRAND^{**}, Fernand ELOYDépartement Recherche et Développement, Parcor, 195, route d'Espagne
31024 Toulouse Cédex, France

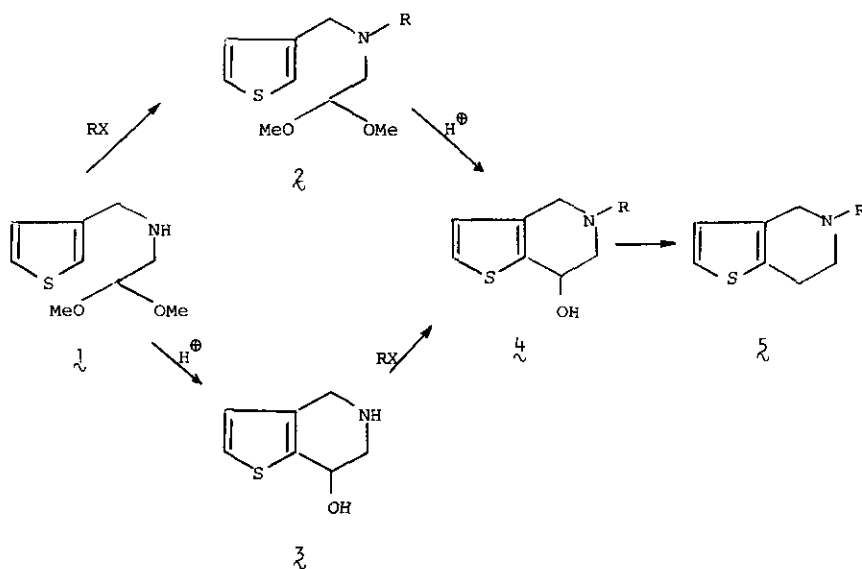
Marc LUCAS

Laboratoire de Chimie Organique des Hormones, Collège de France,
11, place Marcellin Berthelot, 75231 Paris Cédex 05, France

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 communication¹ we showed that Ticlopidine² ($\tilde{2}$, R = 2-Cl-C₆H₅-CH₂), a new inhibitor of platelets aggregation and antithrombotic agent^{3,4}, could be synthesised according to the following reaction sequence :

Scheme I



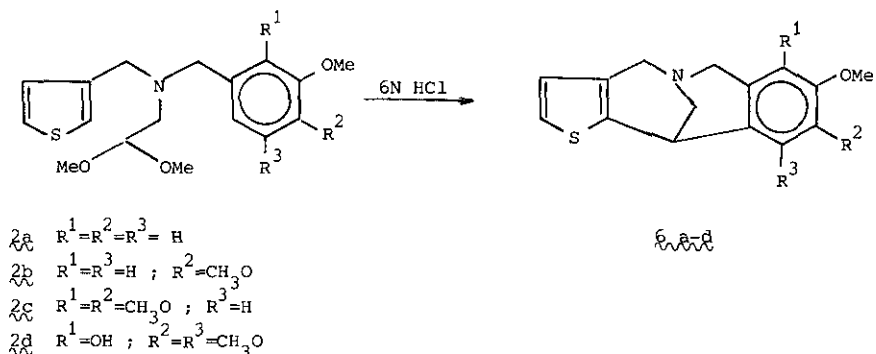
This cyclisation process derived from Bobbitt's synthesis of isoquinolines⁵.

N-Alkylation of (1) or (3) with various alkyl halides RX (K₂CO₃ 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.

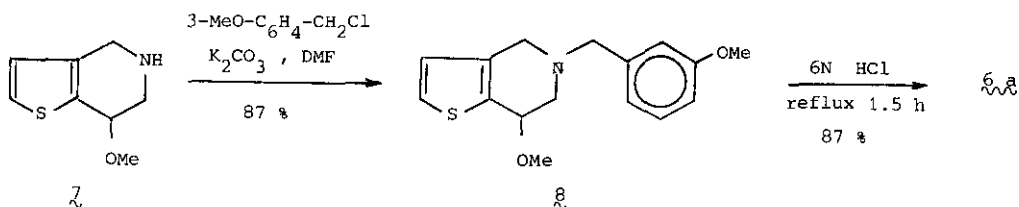
Scheme II



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

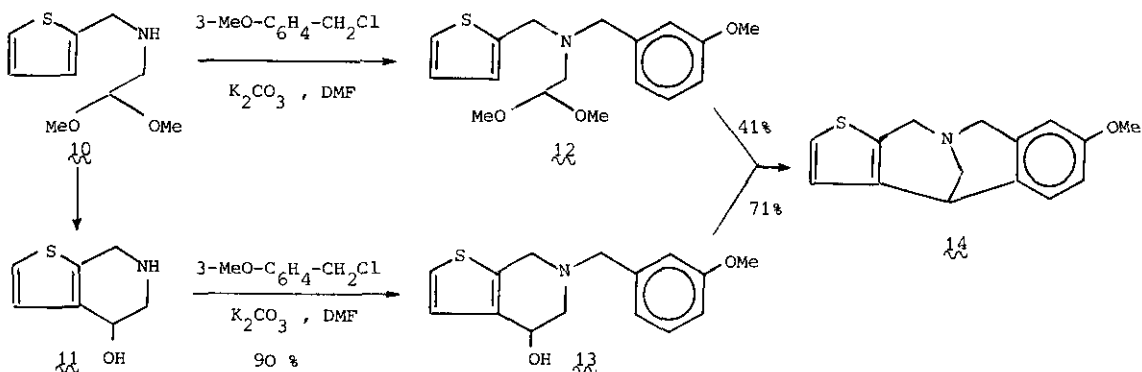
The same new tetracyclic compounds were also prepared from the methoxytetrahydrothienopyridine (7)⁷ as illustrated in the following reaction. (Scheme III).

Scheme III



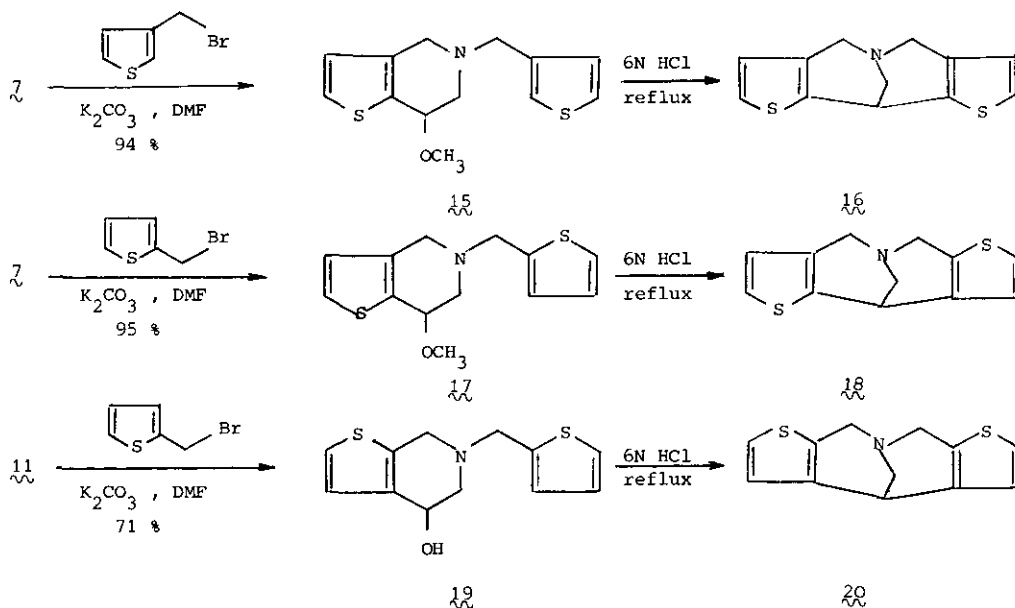
When the intermediates¹ (10) or (11) were used as exemplified in scheme IV, the isomeric benzo(c)thieno[3,2-f] 1-azabicyclo[3.3.1] nonane (14) was formed.

Scheme IV



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

Scheme V

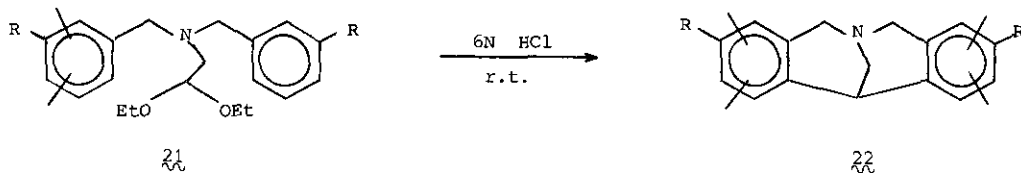


TABLE

Tetracyclic Compounds	Yield %	mp °C (Solvent)	1H - NMR δ ($CDCl_3$)
15a	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)
15b	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)
15c	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)
15d	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 work⁸ 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



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 acid¹⁰, we were able to prepare cyclic analogs of (5a-d) or (14) which did not contain a methoxy or hydroxy groups in the right position.

ACKNOWLEDGEMENTS. Alain Andrieu and Alain Badorc rendered skilful technical assistance.

REFERENCES.

1. J.P. MAFFRAND and F. ELOY, J.Heterocyclic Chem., 1976, 13, 1347.
2. J.P. MAFFRAND and F. ELOY, Eur.J.Med.Chem., 1974, 9, 483.
3. M. PODESTA, D.AUBERT and J.C. FERRAND, ibid., 1974, 9, 487.
4. J.J. THEBAULT, C.E. BLATRIX, J.F. BLANCHARD and E.A. PANAK, Clin.Pharmacol.Ther., 1975, 18, 485.
5. J.M. BOBBITT, Adv.Heterocyclic Chem., 1973, 15, 99.
6. J.P. MAFFRAND, Brevet Français n° 75 17 007.
7. A. HEYMES and J.P. MAFFRAND, Brevet Français n° 75 16 635.
8. J.M. BOBBITT and S. SHIBUYA, J.Org.Chem., 1970, 35(4), 1181.
9. H. TAKAYAMA, M. TAKAMOTO and T. OKAMOTO, Tetrahedron Lett., 1978, (15), 1307.
10. H. TAKAYAMA, T. SUZUKI, M. TAKAMOTO and T. OKAMOTO, Heterocycles., 1978, 9(10), 1429.

Received, 12th December, 1980