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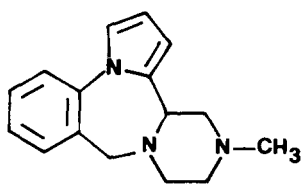
SYNTHESIS OF A NEW TETRACYCLIC SYSTEM RELATED TO APTAZAPINE (CGS 7525A) BY ONE-POT DOUBLE ANNELATION

Silvio Massa* and Antonello Mai
Dipartimento di Studi Farmaceutici, Università "La Sapienza",
P.le Aldo Moro, 5- 00185 Roma (Italy).

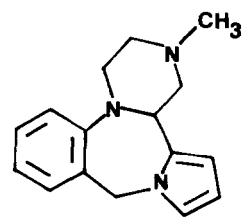
Federico Corelli*
Dipartimento Farmaco Chimico Tecnologico,
via Banchi di Sotto, 55- 53100 Siena (Italy).

Abstract : Tandem annelation of the acetal **5** in acidic medium gave the intermediate tetracyclic amide **4**, which was in turn reduced to 3b,4,6,7-tetrahydro-5-methyl-5H,9H-pyrazino-[2,1-c]pyrrolo[1,2-a][1,4]benzodiazepine**1**.

Development of novel antidepressant agents with a lower incidence of extrapyramidal and cardiovascular effects is a matter of lively current interest in medicinal chemistry[1]. Following our searches on new heterocyclic systems having a fused pyrrole moiety as potential CNS agents[2], we became interested in synthesizing new condensed heterocycles, which may show such an intriguing pharmacological profile. This paper describes the synthesis of 3b,4,6,7-tetrahydro-5-methyl--5H,9H-pyrazino[2,1-c]pyrrolo[1,2-a][1,4]benzodiazepine**1**, which represents a new tetracyclic ring system closely related to the isomeric compound aptazapine (CGS 7525A) **2** , a "non-classic" antidepressant drug that is currently under clinical trials in the United States[3].

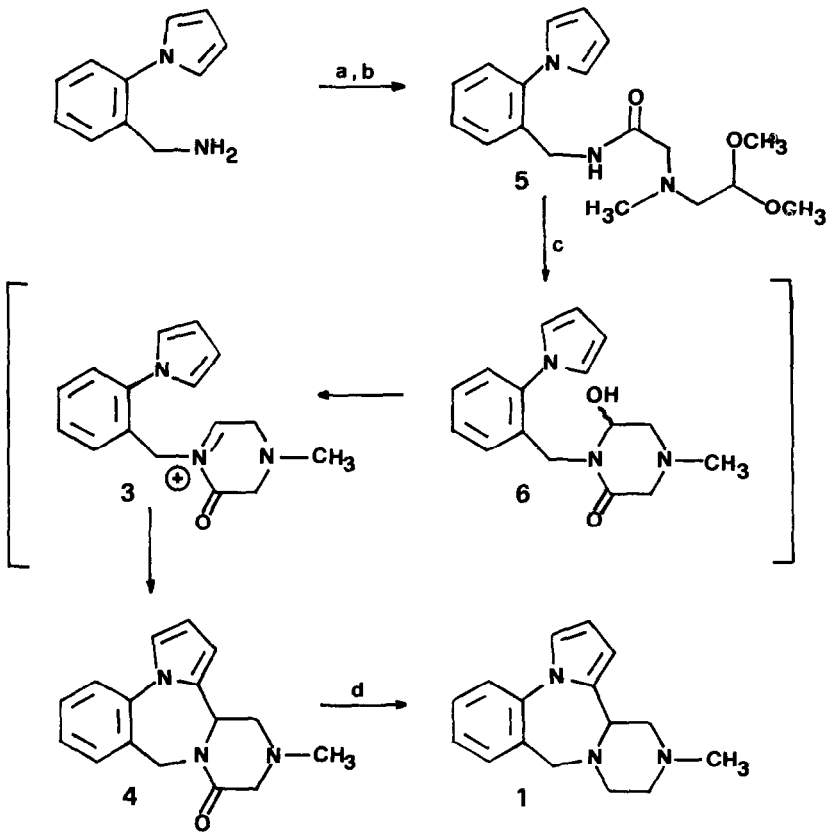


1



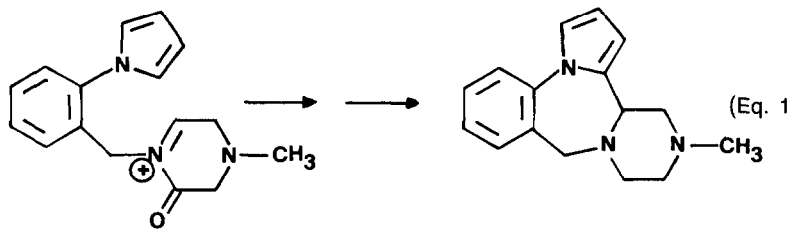
2

Scheme



Reagents: a) $ClCH_2COCl$, NEt_3, THF, 0°; b) $CH_3NHCH_2CH(OCH_3)_2$, K_2CO_3, DMF, 70°; c) 37% HCl, THF, R.T. to reflux ; d) LAH, H_2SO_4, THF, 0°.

A wide variety of heterocyclic systems has been prepared by π-cyclization of several kinds of N-acyliminium ions[4]. Such a procedure presents the distinctive advantage to offer a quite direct access to even complex polycyclic compounds. Consequently, π-cyclization of the suitable N-acyliminium ion **3** seemed to us an attractive route to our target compound **1** (Eq. 1).



3 **1** (Eq. 1)

In particular we wish to report on the one-pot, acid catalyzed preparation of the tetracyclic derivative **4** starting from the amidoacetal **5** (Scheme), by an experimentally simple, high yielding process involving sequentially: i) hydrolysis of **5** to the intermediate hydroxyamide **6**; ii) dehydration of **6** to give the N-acyliminium ion **3**; iii) π-cyclization to **4**. This sequence, therefore, allows the direct transformation of the open-chain compound **5** into the tetracyclic derivative **4** by a tandem annelation procedure.

The required acetal **5**[5] was obtained in two steps from the known 1-(2-aminomethylphenyl)-1H-pyrrole[6] by treatment with chloroacetyl chloride, followed by reaction with methylaminoacetaldehyde dimethyl acetal (64% overall yield)[7]. Subsequent cyclization to the tetracyclic compound **4**[8] was readily performed by stirring **5** in THF with 37% HCl (2N real acid concentration) (80% yield). Final reduction of **4** with lithium aluminum hydride/sulfuric acid (2:1) afforded in 89% yield the desired 3b,4,6,7-tetrahydro-5-methyl-5H,9H-pyrazino[2,1-c]pyrrolo[1,2-a][1,4]benzodiazepine **1**[9].

Pharmacological properties of the tetracyclic compounds here described are under current investigation and will be reported elsewhere.

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5) Oil. PMR (90 MHz), $CDCl_3$, ∂: 2.30 (s, 3H), 2.53 (d, J=6 Hz, 2H), 3.07 (s, 2H), 3.22 (s, 6H), 4.28-4.47 (m, 2H+1H), 6.32 (m, 2H), 6.82 (m, 2H), 7.27-7.73 (m, 4H+NH).

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7) All yields refer to isolated and purified materials.

8) M.p.152-4°. PMR (90 MHz), $CDCl_3$, ∂: 2.37 (s, 3H), 2.73-3.62(m, 4H), 3.70 (d, J=15 Hz, 1H), 4.50 (dd, J=11 and 4.5 Hz, 1H), 5.53 (d, J=15 Hz, 1H), 6.23-6.43 (m, 2H), 7.07 (m, 1H), 7.37-7.60 (m, 4H).

9) Oil. PMR (90 MHz), $CDCl_3$, ∂: 2.25 (s, 3H), 2.37-2.83 (m, 6H), 3.12 (m, 1H), 3.40 (d, J= 15 Hz, 1H), 3.70 (d, J=15 Hz, 1H), 6.20 (m, 2H), 6.90 (m, 1H), 7.12-7.47 (m, 4H).

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