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Ca^{++}-MODULATORS. UNUSUAL HIGHLY STEREOSPECIFIC HANTZSCH-LIKE CYCLIZATION: FIRST AUTHENTICATED EXAMPLE OF 2-CHLOROMETHYLENE-1,2,3,4-TETRAHYDROPYRIDINE

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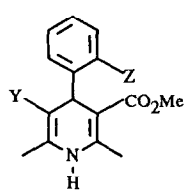
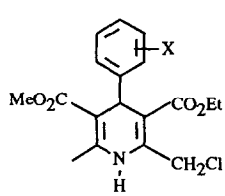
Summary: Hantzsch cyclization of ethyl 4-chloro-2-benzylidene-acetoacetates **5** with methyl 3-aminocrotonate **6** leads to 2-chloromethylene-1,2,3,4-tetrahydropyridine-3,5-dicarboxylic esters **7**. X-ray structure analysis and ^{1}H-NMR of **7a** established the configuration at C_3-C_4 as trans, *with both the two bulky substituents in the axial position*, while the exocyclic double bond is present only in the Z configuration.

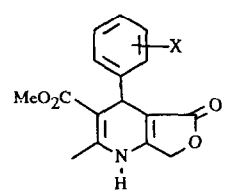
The Hantzsch pyridine synthesis[1] has been well known since last century and widely applied for 1,4-dihydropyridine preparation[2]. 1,4-Dihydropyridines (DHPs) such as Nifedipine **1** and Bay K-8644 **2** are well recognized modulators of calcium ions fluxes across cellular membranes regulating in an opposite way the contractility of smooth muscle[3]. Great efforts have been undertaken to understand the molecular basis of action of these substances and to improve their pharmacological profile[4]; novel and attractive research tools might be offered by DHPs substituted at the methyl groups, which have been scarcely investigated up to now[4a].



1: Y = CO_2Me, Z = NO_2
2: Y=NO_2, Z = CF_3



3 a,b



4 a,b

a: X = 3-NO_2 ; b: X = 2,3-di-Cl

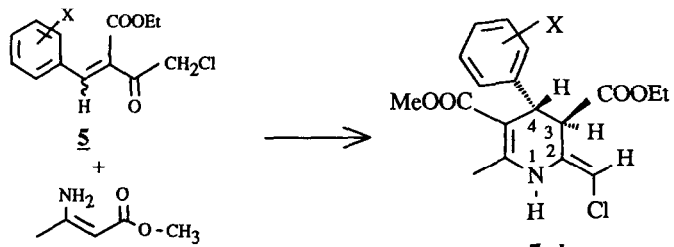
In this perspective, time consuming synthesis of the necessary γ-substituted-β-ketoesters and repetitive Hantzsch cyclizations could be avoided if 2-chloromethyl-1,4-dihydropyridine such as **3a,b** were easily available as key synthetic intermediates.

In a classical three component cyclization (γ-chloro-β-ketoester, benzaldehyde and

3-aminocrotonate; EtOH, reflux, 18-24 hrs) the high reactivity of the allylic chlorine of **3a,b** seems to preclude the recovery of the desired compound, and the bicyclic lactones 1,4,5,7-tetrahydrofuro-[3,4-b]-pyridines[5] **4a,b** are the only reaction products. Only moderate yields of **3** (38-69%) arise from the Čupka and Svetlík alternative procedure[6].

As we observed that Knoevenagel condensation of γ-chloro-β-ketoesters with benzaldehydes leads to (E,Z)-4-chloro-2-benzylidene-acetoacetates **5** in high yields (80-90%)[7], the unwanted lactonization process must occur during Michael addition of 3-aminocrotonate **6** to **5** and/or during the following dihydropyridine ring closure. On the basis of this experimental finding, the two component Michael reaction of **5** with **6** in EtOH at reflux temperature for 10-20 minutes was found to give rise to a complex mixture of "polar adducts" (TLC monitoring) whose treatment with 5-10% mol. equiv. of gaseous HCl affords **3a,b** (85-90% yield) free from any bicyclic by-products **4a,b**, after spontaneous cooling to room temperature.

Unexpectedly when the reaction mixture was cooled to room temperature ***before*** acid treatment a different substance, **7**, whose structure has been later defined as 2-chloromethylene-1,2,3,4-tetrahydropyridine, crystallized (e.g. **7a** m.p. 125-127°C, yields: 55-70%; **7b** m.p. 102-105°C, y: 45-60%). **7** is quite stable in pyridine or methanol solutions, while it isomerizes quickly to **3** in chloroform (5', r.t.), or in warm acidic ethanol.



The structure of **7** was elucidated both by chemical and spectroscopic methods. Oxidation (DDQ-pyridine, r.t.) of both **3** and **7** leads to the same pyridine derivative. Acidification (CF_3CO_2D) of a methanol-d_4 solution of **7a** leads to the incorporation of one deuterium in the chloromethyl group of **3a** [^{1}H-NMR($CDCl_3$): **7a** C**H**DCl δ 4.7 ppm, bs; **3a** CH_2Cl δ_A 4.83, δ_B 4.97, J_{AB} 12.8 Hz].

The UV-spectrum (MeOH, c $5x10^{-5}$M) of **7** differs greatly from that of **3**, showing only one maximum at 305 nm (**7a** λ 304 nm, ε 23000; **7b** λ 305 nm, ε 23700) while 1,4-dihydropyridines possess two maxima[8] (e.g. **3a** λ_1 240 nm, ε 23500; λ_2 350 nm, ε 6000).

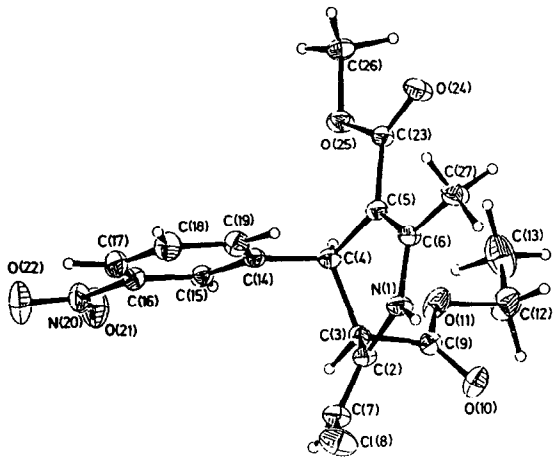
The ^{1}H-NMR spectrum (200 MHz, Py-d_5) of **7a** shows a sharp singlet at δ 5.60 for C=C**H**Cl and two doublets for H_3 and H_4 respectively at δ 3.87 and δ 5.21 with J 1.8 Hz, thus suggesting, according to the Karplus equation, that the dihedral angle between H_3 and H_4 must be close to 65°or 115°.

The ^{13}C-NMR spectrum (20.15 MHz, Py-d_5) of **7a** confirms the presence of two sp_3-methine groups [δ 41.5 and δ 49.5 for C_3 and C_4] and one sp_2-methine group [δ 98.3 (C=C**H**Cl)].

The single crystal X-ray diffraction analysis (Fig.1)[9] indicates that **7a** is a single diastereoisomer

wherein the relative configuration at C_3 and C_4 of the tetrahydropyridine ring is trans (Θ=69.5°) and the configuration of the exocyclic double bond is Z, the C-Cl and N-H bonds being parallel to one another.

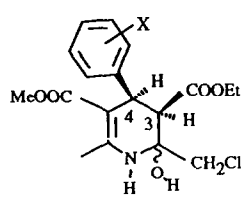
Figure 1: ORTEP of **7a**



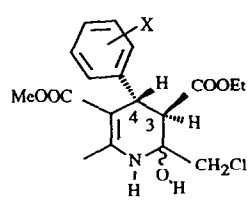
It is worth to underline that compound **7** contains the quite unusual and reactive isolated moiety NH-C=CHCl[10] whose structural features (bond lengths and angles) have not been, until now, deeply studied.

The elucidation of the structure of **7** may offer a new insight into the mechanism of Hantzsch cyclization suggesting that a quick Michael addition of methyl 3-aminocrotonate **6** to Z- and E- benzylidene **5**, leading to "polar adducts" intermediates 2-hydroxy-1,2,3,4-tetrahydropyridines[11] **8-cis** and **8-trans**, is followed by the rate limiting dehydration process to endo- or exo-cyclic double bond.

Moreover only a regio- and stereoselective dehydration process on intermediates **8** may explain the formation of the single geometrical isomer **7a**, possessing a Z-exocyclic double bond, with C-Cl and N-H bonds mutually parallel, through stereoselective abstraction of only one proton of CH_2Cl group. Further, the trans stereochemistry of the pseudo axial substituents at C_3 and C_4 (Figure 1) strongly indicates that the formation of intermediate **8-cis**, at least in the described reaction conditions, is unlikely or forbidden.



8-cis



8-trans

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7. Experimental conditions: equimolar amounts of X-substituted-benzaldehyde and ethyl 4-chloro-acetoacetate were refluxed in benzene (2-4 hrs) in presence of 10% mol. equiv. piperidine acetate, with azeotropic removal of water.

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9. Single crystals of 7a suitable for X-ray diffraction study were grown from a saturated MeOH solution containing 2% triethylamine.
Crystal data of 7a: $C_{18}H_{19}ClN_2O_6$ M_r= 394.81. Cell parameters were obtained by fitting 25 reflections in the range $16<\theta<25°$: a=15.343(2), b=14.974(2), c=8.505(1)Å, β=104.11(1)°, V=1895.0(4)Å^3, monoclinic $P2_1/c$ Z=4, D_x=1.384 gcm^{-3}, μ=2.3 cm^{-1}, F(000)=824, room temperature. 4338 unique reflections were collected up to θ=27.5° on a Nonius CAD4 diffractometer with graphite monochromated MoKα radiation λ=0.71069Å. Three standard reflections do not show any decay; corrections for Lorentz and polarization effects were applied. 2893 data with $I > \sigma(I)$ were as being considered observed and used in structure analysis. Selected bond distances in Å: (numeration according to ORTEP-Fig.1) N(1)-C(2) 1.392(3), N(1)-C(6) 1.372(3), C(2)-C(3) 1.497(3), C(2)-C(7) 1.319(3), C(3)-C(4) 1.544(3), C(4)-C(5) 1.514(3), C(5)-C(6) 1.363(3).

10. a) Some examples of this structure may be found in natural products, see for example indole alkaloid chartellamide A and B [U.Anthoni, K.Bock, L.Chevolot, C.Larsen, P.H.Nielsen and C.Christophersen, J. Org. Chem., 52, 5638, (1987)]. b) Duhamel and coworkes studied the preparation and metal exchange reaction of simple β-halogeno enamines [see for ex.: L.Duhamel and J.M.Poirer, J. Am. Chem. Soc., 99, 8356, (1977); L.Duhamel and J.M.Poirer, J. Org. Chem., 44, 3585, (1979); see also: D.Scholz and H.G.Viehe, Chimia, 29, 512, (1975)].

11. Baxter and coworkers described diethyl 2-hydroxy-2-trifluoromethyl-4-(substituted-phenyl)-6-methyl-1,2,3,4-tetrahydropyridine-3,5-dicarboxylic acid. Dehydration to 1,4-dihydropyridine is obtained by means of trifluoroacetic anhydride. A.J.G.Baxter, J.Dixon, K.J.Gould, T.McInally and A.C.Tinker, Eur.Pat. Appl. 125803 ; Chem. Abstr. 102, 203874, (1985).

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