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HOW TO OBTAIN TWO OPTICAL ANTIPODES OF AN OCTAHYDRO-2H-PYRIDO [1,2-a] PYRAZINE STARTING FROM A SINGLE CHIRAL SYNTHON.

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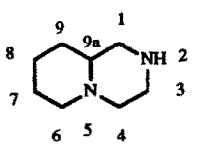
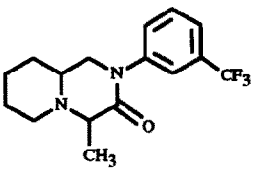
Abstract: The synthesis of a (+)-(R,S)-2-aryl-4-methyl-3-oxo, octahydro-2H-pyrido [1,2-a]pyrazine and of its optical antipode (-)-(S,R)-2-aryl-4-methyl-3-oxo, octahydro-2H-pyrido[1,2-a]pyrazine, with a single synthetic sequence, and by making use of the natural ethyl lactate methansulfonate as the only chiral synthon, is described.

Octahydro-2H-pyrido[1,2-a]pyrazine (I) derivatives are not extensively described in literature [1]; nevertheless, as shown in a recent Italian patent [2], certain 2-aryl-4-methyl-3-oxo derivatives shown a remarkable interest as psychotrope drugs. In this patent special attention has been turned to two compounds (compound C, pharmacologically active and its isomer, compound D), both corresponding to the structure of 2-(3-trifluoromethylphenyl)-4-methyl-3-oxo, octahydro-2H-pyrido[1,2-a]pyrazine (2).



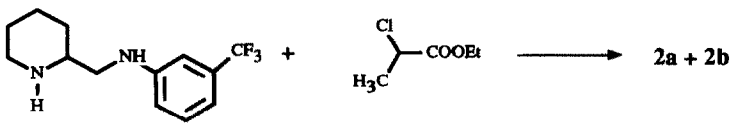
1



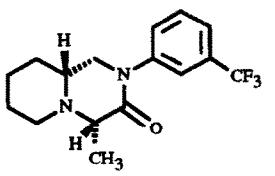
2

According to the above-mentioned patent, a mixture of these two substances is obtained by simple heating of ethyl 2-chloropropionate (3) with 2-(3-trifluoromethylphenyl) aminomethyl-piperidine (4) without solvents and catalysts and separated through chromatography on a silica-gel column.

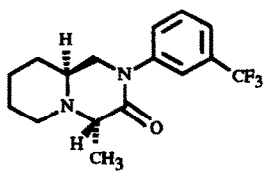
Even if the same patent provides the description of certain chemico-physical characteristics pertaining to the two compounds, no conclusions are drawn on their stereospecificity. Nevertheless, the phenomenon recently observed, according to which compound C is obtained from D in a basic environment through short heating in an inert solvent, makes observers attribute structures **2a** and **2b** to the two compounds respectively.



4 3



2a (C)

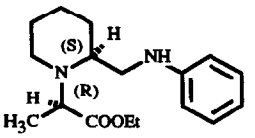


2b (D)

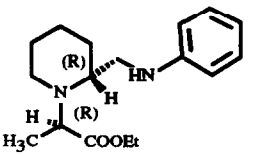
In fact, it is easy to verify, by means of molecular models, that in a 4 substituted octahydro-pyrido[1,2-a]pyrazine , the most stable isomer is the one in which the two hydrogen atoms at 4 and 9a are cis (equatorial methyl in the trans-fused form)[3]. The NMR spectra [4] confirm the above. In fact, in compound **2a** the proton in position 4 (axial) appears as a quartet centred at 2.81, whereas in compound **2b** such a proton (equatorial) appears at lower fields [5].

Actually, a pair of optical antipodes corresponds to structure **2a** (which is the one of interest to us). From the molecular models it is clear that if for an optical antipode the absolute configuration of the carbon atom in position 4 is R, the absolute configuration of the carbon atom in position 9a must be S and vice versa for the other antipode.

At present, in order to verify the influence of optical isomerism on the biological behaviour of **2a**, we are facing the problem of obtaining the two optical antipodes in pure form. After some unsuccessful attempts of separation through salts with optically active acids, we have taken up the asymmetric synthesis by using chiral derivatives of propionic acid carrying a suitable leaving group in position 2. In particular, a mixture of 103.2 g (0.4 Mol.) of 4 and 39.3 g (0.2 Mol.) of lactic acid ethyl ester methansulfonate (configuration S,$[\alpha]_D$ -52.0 c 1, $CHCl_3$) was heated for 16 hours at 90°C under a nitrogen atmosphere. The GC - MS analysis of the residue obtained after normal work up (72 g) showed that its main components were comparable quantities of two isomers; on the basis of mass spectra as well as of mechanistic considerations (Walden inversion), we attributed to the two isomers the structures of the two diastereoisomers **5a** and **5b**, in which the carbon atom linked to the carbethoxy group has, in both cases, configuration R, whereas the carbon atom in position 2 of the piperidine ring has configuration S in one case (**5a**) and configuration R in the other (**5b**). An unexpected good result was obtained when we tried to separate a small part of the mixture on a preparative silica column.



5a



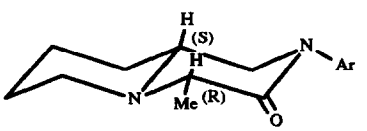
5b

In fact, it was clear that one of the two products loses alcohol during the chromatographic process in order to give the 2a (2a(+)) dextrorotatory isomer. Since the conditions in which the cyclization occurs are extremely mild, we should not assume that inversions have occurred. It was then easy for us, from the molecular models, to attribute to the cyclized compound also the absolute configuration as the R,S one.

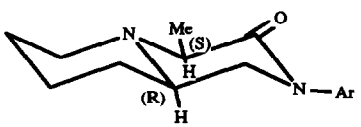
The residue of the raw mixture was chromatographed on a preparative column, after pretreatment in methanolic solution with 10 weights of SiO_2 at 70°C for 12 hours in order to induce cyclization, thus obtaining 14 g of 2a as an oil, $[\alpha]_D$ +33.0 (c 4.5, EtOH), hydrochloride m.p. 168-70°, and 17 g of 5b. The ^{1}H-NMR spectrum of 2a(+) in CCl_4 after addition of 0.7 equivalents of the chiral shift reagent tris-3-(heptafluorpropyl-hydroxymethylen)-d-camphorato europium(III), Eu(hfc)$_3$, did not detected the enantiomer[6].

We obtained an even better result when we observed that, with 0.5 Mol. of sodium hydride in refluxing toluene, 5b was converted within two hours, into a compound to which the structure to be attributed is not the 2b, but the one belonging to the laevorotatory optical antipode of 2a, $[\alpha]_D$ -31.5 (c 4.0, EtOH), hydrochloride m.p. 170-72° having S,R absolute configuration.

This phenomenon finds its explanation in what has been said above, that is, compounds 2b turn into compounds 2a through heating in a basic environment, clearly by inversion of configuration at C4. In practice, a series of extremely simple operations have made it possible not only to obtain the two desired optical antipodes of the octahydro-pyrido[1,2-a]pyrazine being studied and know their absolute configuration, but also to obtain this result by using a single asymmetric synthon.



2a (+)



2a (-)

In order to confirm the above, we repeated the process by using the ethyl 2-bromopropionate having configuration R, instead of the ethyl lactate methansulfonate having conformation S.

Under similar conditions, we have obtained laevorotatory **2a(-)**, through cyclization with silica, and dextrorotatory **2a(+)**, through subsequent thermal cyclization of the second isomer.

The optical purity of the compound obtained through the second synthesis is lower than the purity obtained through the first synthesis ($[\alpha]_D$ -16.0 (c 2.8, EtOH); this is due to the fact, well known in literature, that the ethyl 2-bromopropionate is obtained with a rather low optical purity [7]. However, it should be noted that it will not be difficult to obtain samples of **2a** isomers having a satisfactory degree of optical purity; in fact, such isomers lead to a racemate (m.p. 74-6°) which can be separated quite easily from partially active mixtures through simple fractional crystallization from hexane thus improving the optical purity of the residue.

References and notes

1 - A certain number of octahydro-2H-pyrido[1,2-a] pyrazines with hypotensive properties was studied by R.Day and others in the 1960s (*J. Org. Chem.* **1960**, *25*, 2108; *J. Het. Chem.* **1969**, 301; *J. Med. Chem.* **1966**, *9*, 311), whereas a few years later R. Cahill and T.A. Crabb (*J. Chem. Soc. Perkin II* **1972**, 1374) studied their conformational aspects.

2 - L. Baiocchi and B. Silvestrini, *Italian Patent* 1204803 (1989)

3 - According to R. Cahill and T. A. Crabb (*J. Chem. Soc. Perkin II* **1972**, 1374), the favourite conformation of the octahydro-pyrido[1,2-a]pyrazines is the trans-fused conformation in which a substituent in 4 is in equatorial position when the hydrogens in 4 and 9a are in cis position.

4 - ^{1}H-NMR Spectra (60MHz) in CCl_4

Compound C 1.35 (d, J = 6 cps), 3H; 1.60 (m), 6H; 2.40 (m),2H; 2.81 (q, J = 6 cps), 1H; 3.00-3.80 (m), 3H; 7.47 (s),3H; 7.61 (m, 1H)

Compound D 1.25 (d, J = 6 cps), 3H; 1.50 (m), 6H; 2.55 (m), 2H; 2.70-3.75 (ms), 4H; 7.47 (s), 3H; 7.61 (m, 1H)

5 - Robert M. Silverstein, G. Clayton Bassler and Terence C. Morril *Spectrometric Identification of Organic Compounds*. Wiley Edition 4th (1981) Pg. 190.

6 - The racemate ^{1}H-NMR of **2a** in presence of $Eu(hfc)_3$ shows two singlets at 10.04 and 9.89 δ ($\Delta\delta$0.15) an two doublets centered at 10.63 and 10.30 δ ($\Delta\delta$ 0.33). In the spectrum of **2a(+)** isomer only the singlet and the doublet at higher field are present.

7 - The product was prepared according to J. W. Walker, *J. Chem. Soc.* **1895**, *67*, 914.