Fourth International Electronic Conference on Synthetic Organic Chemistry (ECSOC-4), www.mdpi.org/ecsoc-4.htm, September 1-30, 2000

[A0047]

Bicyclic Organophosphorus Fluoridates as Inhibitors of Acetylcholinesterase

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Received: 29 July 2000 / Uploaded: 31 July 2000

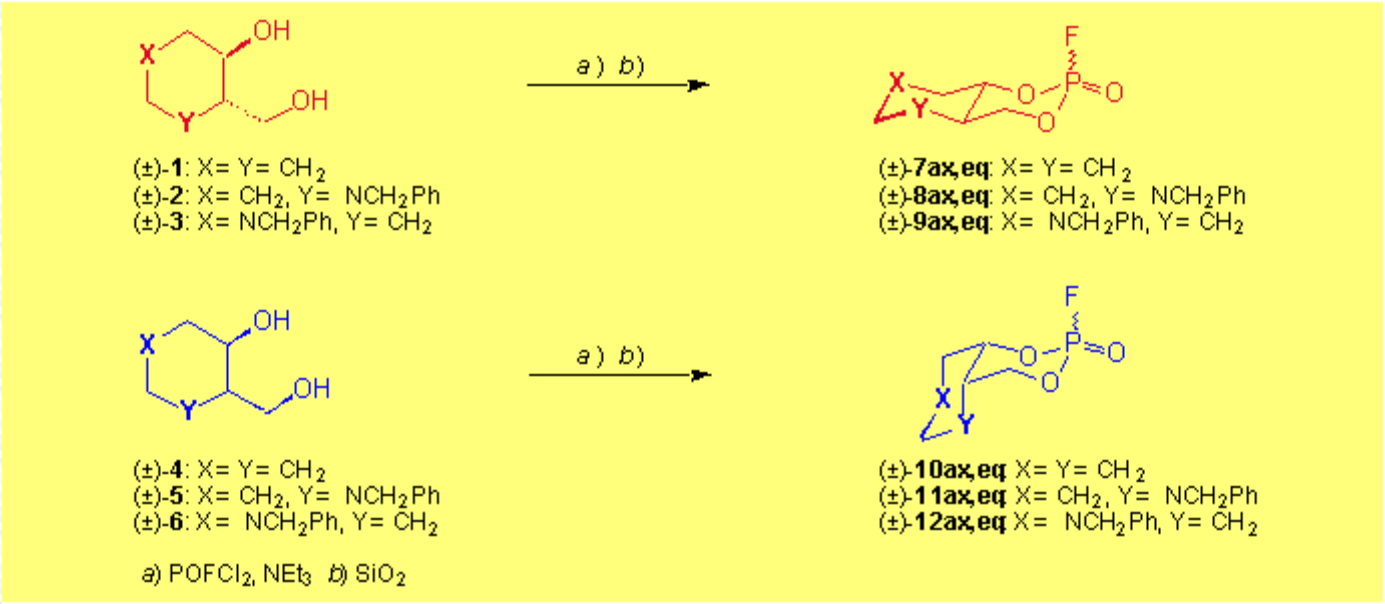
Introduction

Continuing our investigations (poster1, 2) concerning the irreversible inhibition of serine-hydrolases (acetylcholinesterase, chymotrypsin) by organophosphates [1][2] we have prepared the racemic 3-fluoro-2,4-dioxa-3l^5-phosphabicyclo[4.4.0]decan-3-ones (±)-**7**-(±)-**12**. Being conformationally restricted, these *cis*- and *trans*-decaline-type congeners with the F-substituent in the *axial* and *equatorial* position fit differently into the active site of acetylcholinesterase (AChE) as represented by their k_{ass}-values.

Synthesis

The bicyclic organophosphates were synthesized from the corresponding diols ((±)-**1**-(±)-**6**) with $POFCl_2$ in the presence of triethylamine. Chromatographic separation yielded the *axially* and *equatorially* F-substituted epimers. The starting diols have been prepared by reduction of the corresponding oxo-esters: (±)-**1**/(±)-**4** from ethyl 2-oxocyclohexanecarboxylate [2], (±)-**3**/(±)-**6** from ethyl (1-benzyl-3-oxopiperidin-4-yl)carboxylate [3] and chromatographic separation of the *cis*- and *trans*-isomers. The piperidine diols (±)-**2**/(±)-**5** were obtained from 3-hydroxy-2-(hydroxymethyl)pyridine after several reaction steps [4].

The X-ray structures of (±)-**8ax**,**eq**/(±)-**11ax**,**eq** (see the separate Poster A0048) show the influence of the anomeric effect on the *equatorially* substituted congeners, where the F-substituent adopts a pseudo-axial position.



Inhibitory activity

Irreversible organophosphorous inhibitors form a covalent bond between the activated Ser^{200} of AChE and the P-atom, F being the leaving group [5]. The resulting tetrahedral phosphate is regarded as a stable transition state analogue of AChE and its natural substrate acetylcholine (ACh) [6].

The k_{ass}-values of the irreversible inhibitors were measured according to the method of Baici [7] in the presence of substrate. Some of the compounds seem not to bind covalently to AChE but they interact weekly in a reversible manner. The corresponding K_I-values were determined by Lineweaver-Burk plots [8].

As the organophosphates represent *N*-benzylated, uncharged ACh-mimetics we tentatively conclude that the strongest irreversible inhibitor (±)-**8ax** is closest to the conformation of ACh during the inhibition.

k_{ass} [$M^{-1}min^{-1}$] K_I [mM]	axial	equatorial		axial	equatorial
(±)-**7**	k_{ass} = 1100	k_{ass} = 350	(±)-**10**	K_I = 225	k_{ass} = 490
(±)-**8**	k_{ass} = 2100	k_{ass} = 360	(±)-**11**	k_{ass} = 325	K_I = 1000
(±)-**9**	k_{ass} = 570	k_{ass} = 1200	(±)-**12**	k_{ass} = 470	K_I= 500

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