Acta Crystallographica Section E
Structure Reports Online
ISSN 1600-5368

2-Hydroxybenzoic acid salt of physostigmine

Judith L. Flippen-Anderson,[a]* Jeffrey R Deschamps,[a] Arnold Brossi[b] and Nigel H. Greig[c]

[a]Laboratory for the Structure of Matter, Code 6030, Naval Research Laboratory, Washington, DC 20375, USA, [b]School of Pharmacy, University of North Carolina at Chapel Hill, Chapel Hill, NC 27599-7361, USA, and [c]Drug Design and Development Section, Laboratory of Neurosciences, Gerontology Research Center (4E02), National Institute on Aging, National Institutes of Health, 5600 Nathan Shock Drive, Baltimore, MD 21224-6825, USA

Correspondence e-mail: flippen@nrl.navy.mil

Key indicators

Single-crystal X-ray study
T = 293 K
Mean σ(C–C) = 0.004 Å
R factor = 0.045
wR factor = 0.124
Data-to-parameter ratio = 7.6

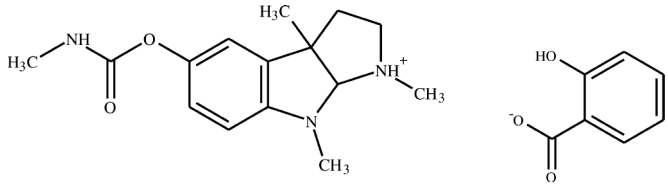
For details of how these key indicators were automatically derived from the article, see http://journals.iucr.org/e.

Received 27 June 2002
Accepted 9 July 2002
Online 19 July 2002

Physostigmine, $C_{15}H_{22}N_3O_2$, is the major alkaloid found in the seeds of Calabar beans. It was the first anticholinesterase used in the treatment of Alzheimer's disease and is still used in the treatment of glaucoma. The structure of its 2-hydroxybenzoate salt, *viz*. 5-carbamoyloxy-1,2,3,3a,8,8a-hexahydro-1,3a,8-trimethylpyrrolo[2,3-*b*]indol-1-ium benzoate, $C_{15}H_{22}N_3O_2^+\cdot C_7H_5O_3^-$, is reported.

Comment

Anticholinesterases represent the current drugs of choice in the treatment of Alzheimer's disease, with four thus far approved by the US Government Food and Drug Administration and some half dozen in current clinical development. Considerable background for the development of these agents as well as for our understanding of the fundamental physiology and biochemistry of the cholinergic system has come from the use of the alkaloid physostigmine as a pharmacological tool. In this regard, physostigmine was the first active agent to be isolated as a natural product and used in medicine.



(I)

Physostigmine, also called eserine, the major alkaloid of the seeds of the West African vine *Physyostigma venosum* (Calabar beans), was isolated in 1864 (Jobst & Hesse, 1864). It was used by Laqueur as early as 1877 as a therapeutic in the treatment of glaucoma, one of its few remaining clinical uses. This was some half a century prior to the discovery of acetylcholine as a neurotransmitter in 1914, and physostigmine's structural elucidation in 1923 (Polonovski, 1925; Stedman & Barger, 1925; Holmstedt, 1972). The agent is the methylcarbamate ester of (3a*S*-*cis*)-hexahydro-1,3a,8-trimethyl-pyrrolo[2,3-*b*]indol-5-ol, as confirmed by its total synthesis and analysis (Julian & Pikl, 1935; Brossi, 1985). It potently inhibits acetylcholinesterase (EC 3.1.1.7) and butyrylcholinesterase (EC 3.1.1.8) that terminate the action of acetylcholine at cholinergic synapses. Physostigmine thereby increases brain levels of acetylcholine in a temporal and spatial manner associated with cholinergic stimulation (Greig *et al.*, 1995).

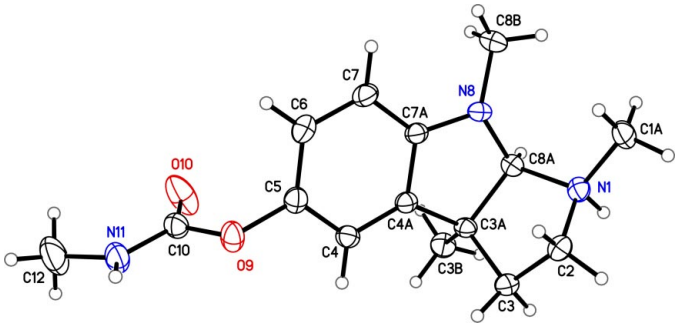


Figure 1
View of the title physostigmine cation, shown with 20% probability ellipsoids.

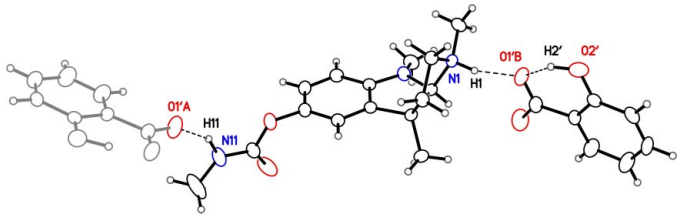


Figure 2
The asymmetric unit and the hydrogen bonding between the hydroxybenzoic acid and physostigmine ions. The hydroxybenzoic acid shown in gray is a symmetry mate of the molecule in the asymmetric unit.

The cholinergic forebrain deficit found early in the Alzheimer brain (Whitehouse *et al.*, 1982), together with the critical role of cholinergic function in memory and learning (Drachman & Leavitt, 1974), spurred the use of physostigmine as the first anticholinesterase in the treatment of Alzheimer's disease (Davis & Mohs, 1979; Thal & Fuld, 1983). However, its short duration of action (approximately 90 min), low bioavailability (2%) and narrow therapeutic window limited its clinical potential (Greig *et al.*, 1995) and initiated the development of analogs with a greater selectivity between acetyl- and butyrylcholinesterase, a longer action and a preferential distribution to the brain (Greig *et al.*, 1995, 2000; Brossi *et al.*, 1996; Yu *et al.*, 1999, 2001). The structure of the free base of physostigmine has been reported (Pauling & Petcher, 1973) and it compares well with our determination. There is a *cis* junction between the five-membered rings. The central five-membered ring is planar (±0.02 Å) and the other has an envelope conformation, with O2 the out-of-plane atom (0.62 Å). The angle between the two five-membered rings is 61 (1)°.

Experimental

The title compound was synthesized and crystals grown at NIH by Brossi and colleagues.

Crystal data

$C_{15}H_{22}N_3O_2^+\cdot C_7H_5O_3^-$
M_r = 413.47
Orthorhombic, $P2_12_12_1$
a = 9.970 (3) Å
b = 10.945 (3) Å
c = 19.874 (3) Å
V = 2168.8 (9) Å^3
Z = 4
D_x = 1.266 Mg m^{-3}
Cu $K\alpha$ radiation
Cell parameters from 25 reflections
θ = 20.8–38.3°
μ = 0.74 mm^{-1}
T = 293 (2) K
Prism, colorless
0.40 × 0.25 × 0.20 mm

Data collection

Bruker $P4$ diffractometer
$\theta/2\theta$ scans
Absorption correction: none
2333 measured reflections
2131 independent reflections
2094 reflections with $I > 2\sigma(I)$
R_{int} = 0.044
θ_{max} = 57.6°
$h = -10 \rightarrow 4$
$k = 0 \rightarrow 11$
$l = 0 \rightarrow 21$
3 standard reflections
every 97 reflections
intensity decay: none

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.045
$wR(F^2)$ = 0.124
S = 0.80
2131 reflections
282 parameters
H atoms refined by a mixture of constrained and independent refinement
$w = 1/[\sigma^2(F_o^2) + (0.1362P)^2 + 0.3533P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = 0.026
$\Delta\rho_{max}$ = 0.16 e Å^{-3}
$\Delta\rho_{min}$ = −0.14 e Å^{-3}
Absolute structure: Flack (1983), 417 Friedel pairs
Flack parameter = −1.0 (3)

Table 1
Hydrogen-bonding geometry (Å, °).

D—H···A	D—H	H···A	D···A	D—H···A
N1—H1···O1′B	0.92 (3)	1.76 (3)	2.664 (3)	165 (3)
O2′—H2′···O1′B	1.03 (5)	1.54 (5)	2.509 (4)	154 (4)
N11—H11···O1′A^i	0.82 (5)	2.13 (5)	2.860 (4)	149 (4)

Symmetry code: (i) $\frac{1}{2}+x, \frac{1}{2}-y, -z$.

Data collection: *XTAPE* (Nicolet, 1983); cell refinement: *XTAPE*; data reduction: *XDISK* (Nicolet, 1983); program(s) used to solve structure: *SHELXTL* (Bruker, 2001); program(s) used to refine structure: *SHELXTL*; molecular graphics: *SHELXTL*; software used to prepare material for publication: *SHELXTL*.

The NRL authors acknowledge financial support from the Office of Naval Research, Mechanics Division and the National Institute on Drug Abuse.

References

Brossi, A. (1985). *J. Nat. Prod.* **48**, 878–883.
Brossi, A., Pei, X.-F. & Greig, N. H. (1996). *Aust. J. Chem.* **49**, 171–190.
Bruker (2001). *SHELXTL*. Bruker AXS Inc., Madison, Wisconsin, USA.
Davis, K. L. & Mohs, R. C. (1979). *New Engl. J. Med.* **301**, 946–956.
Drachman, D. A. & Leavitt, J. (1974). *J. Arch.* Neurol. **30**, 113–121.
Flack, H. D. (1983). *Acta Cryst.* A**39**, 876–881.
Greig, N. H., DeMicheli, E., Utsuki, T., Holloway, H. W., Yu, Q. S., Perry, T. A., Brossi, A., Deutsch, J., Ingram, D. K, Lahiri, D. K. & Soncrant, T. T. (2000). *Acta Neurol. Scand.* **102**, 74–84.
Greig, N. H., Pei, X. F., Soncrant, T. T., Ingram, D. K. & Brossi, A. (1995). *Med. Res. Rev.* **15**, 3–31.
Holmstedt, B. (1972). *The Ordeal Bean of Old Calabar: The Pageants of Physostigmine Vanosum in Medicine*, edited by T. Swain. Cambridge, MA: Harvard University Press (USA publishers).
Jobst, J. & Hesse, O. (1864). *Ann. Chemie Pharm.* **129**, 115.
Julian, P. L. & Pikl, J. J. (1935). *J. Am. Chem. Soc.* **57**, 755.
Nicolet (1983). *XTAPE* and *XDISK* for DOS. Nicolet Analytical X-ray Instruments, Madison, Wisconsin, USA.
Pauling, P. & Petcher, T. J. (1973). *J. Chem. Soc. Perkin Trans.* 2, pp. pp. 1342–1345.
Polonovski, M. (1925). *Bull. Soc. Chim. Fr.* p. 744.
Stedman, E. & Barger, G. (1925). *J. Chem. Soc.* **127**, 247.

Thal, J. & Fuld, P. A. (1983). *New Engl. J. Med.* **308**, 708–718.
Yu, Q. S., Holloway, H. W., Flippen-Anderson, J. L., Hoffman, B., Brossi, A. & Greig, N. H. (2001). *J. Med. Chem.* **44**, 4062–4071.
Yu, Q. S., Holloway, H. W., Utsuki, T., Brossi, A. & Greig, N. H. (1999). *J. Med. Chem.* **42**, 1855–1861.
Whitehouse, D., Price, D. L. & Struble, R. (1982). *Science*, **215**, 1237–1239.