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Absolute configuration of (−)-4-(3,4-dichlorophenyl)-4-(2-pyridyl)butanoic acid: essential information to determine crucial steric features of arpromidine-type histamine H_2 receptor agonists

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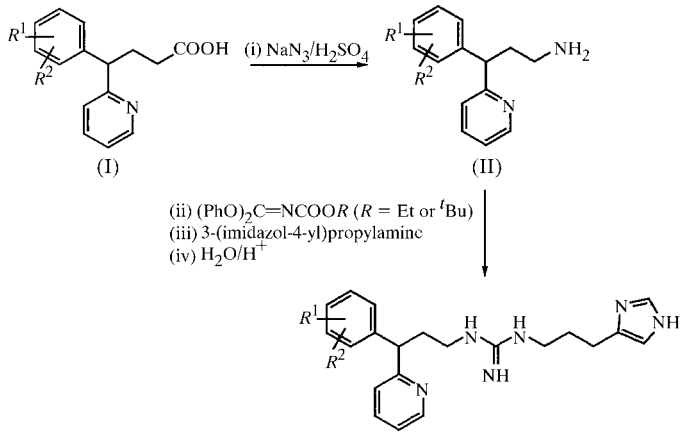
The structural information gained from the study of the chiral building block (*R*)-(−)-4-(3,4-dichlorophenyl)-4-(2-pyridyl)-butanoic acid–L-(−)-ephedrine [methyl(1-hydroxy-1-phenylprop-2-yl)ammonium 4-(3,4-dichlorophenyl)-4-(2-pyridyl)-butanoate], $C_{10}H_{16}NO^+\cdot C_{15}H_{12}Cl_2NO_2^-$, can be used to deduce the absolute configuration of highly potent arpromidine-type histamine H_2 receptor agonists, as the chiral butanoic acid can be converted to (*R*)-(−)-3-(3,4-dichlorophenyl)-3-(2-pyridyl)propylamine and to the corresponding *R*-configured arpromidine analogue.

Comment

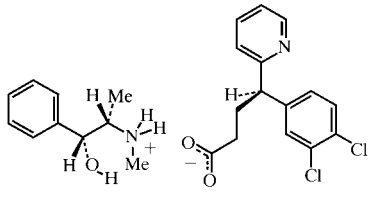
Arpromidine, *N*-[3-(4-fluorophenyl)-3-(2-pyridyl)propyl]-*N*′-[3-(1*H*-imidazol-4-yl)propyl]guanidine, and related guanidines, (III), are the most potent histamine H_2 receptor agonists described in the literature (Buschauer, 1989*a*). Moreover, these chiral compounds are very promising new cardiovascular agents which may be useful for the treatment of severe congestive heart failure (Felix *et al.*, 1995). A small number of optical antipodes could be synthesized from enantiomeric phenyl(pyridyl)propylamines prepared *via* diastereomeric salts or from enantiomers of alkyl guanidine-*N*-carboxylic acid esters which were separated by means of high-pressure liquid chromatography (Schuster, Bernhardt *et al.*, 1998). The pharmacological investigation for histamine H_2 agonism in the isolated guinea pig right atrium revealed an eudismic (Lehmann *et al.*, 1976) ratio in the range of 5–10 (to be published elsewhere), but the absolute configurations of the eutomers (Lehmann *et al.*, 1976) were unknown.

Information on the stereochemical features is necessary with respect to the potential therapeutic use as well as for theoretical considerations, *e.g.* for molecular modelling and for the development of a three-dimensional model for the interaction with the histamine H_2 receptor. In the case of the phenyl(pyridyl)alkyl guanidines, owing to poor crystal quality X-ray analyses of the optical antipodes could not yet be performed. Therefore, our pronounced interest was focused on the synthesis and elucidation of the absolute configuration of key chiral building blocks such as halogen-substituted 4-phenyl-4-(2-pyridyl)butanoic acids, (I), or 3-phenyl-3-(2-pyridyl)propylamines, (II), which can be converted to the corresponding H_2 agonists, (III), according to the scheme below.



R^1 and R^2: H, *meta*- or *para*-F, Cl, 3,4-F_2, 3-5-F_2, 3,4-Cl_2, ...

The crystal structure of (−)-4-(3,4-dichlorophenyl)-4-(2-pyridyl)butanoic acid–L-(−)-ephedrine, (IV), gives proof of the *R*-configuration of the (−)-enantiomer. A view of the molecule (IV) is given in Fig. 1. Consequently, (−)-3-(3,4-dichlorophenyl)-3-(2-pyridyl)propylamine prepared from the (*R*)-(−)-butanoic acid by the Schmidt reaction and the corresponding guanidine are also *R*-configured. This



(IV)

allows us to deduce the absolute configuration of close structural analogues in these series of compounds by interpretation of CD (circular dichroism) correlation spectra (Schuster, Bollwein *et al.*, 1998). According to such investigations the eutomers of the pharmacologically tested arpromidine-type histamine H_2 receptor agonists are *S*-configured. Additionally, the structural information gained from this study turned out to be useful for the determination of the absolute configuration of several neuropeptide Y Y_1 receptor antagonists (Schuster, Bollwein *et al.*, 1998), which were prepared from the title compound or from chemically derived phenyl(pyridyl)alkylamines (Aiglstorfer *et al.*, 1998; Uffrecht, 1996).

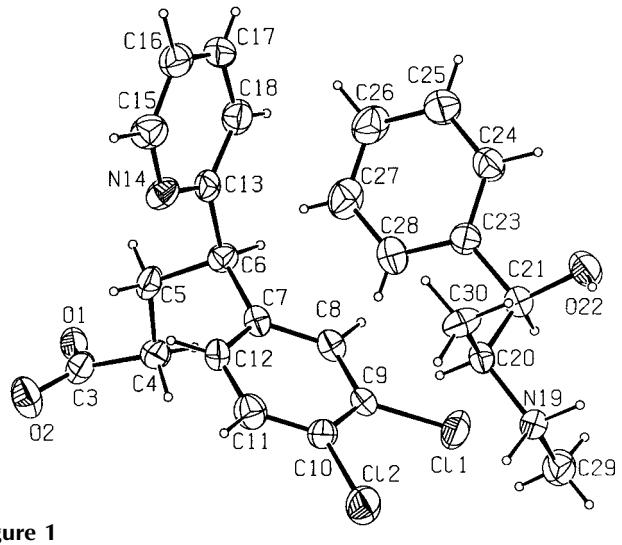


Figure 1
A view of (IV) with the atom-numbering scheme. Displacement ellipsoids for non-H atoms are drawn at the 50% probability level.

Experimental

Preparation of (*R*)-(−)-4-(3,4-dichlorophenyl)-4-(2-pyridyl)butanoic acid–L-(−)-ephedrine, (IV): (±)-4-(3,4-dichlorophenyl)-4-(2-pyridyl)butanoic acid was prepared from (3,4-dichlorophenyl)(2-pyridyl)acetonitrile by analogy with the method described for the synthesis of (±)-4-(4-fluorophenyl)-4-(4-pyridyl)butanoic acid (Buschauer, 1989*b*). Yield 65%, colourless crystals, m.p. 393 K (ether); ^{1}H NMR [Bruker WM-250 (250 MHz), d_6-DMSO; TMS as internal standard]: δ (p.p.m.) = 12.08 (*br s*, 1H, COOH), 8.53 (*ddd*, ^3J = 4.8, ^4J = 1.9, ^5J = 0.9 Hz, 1H, py-6H), 7.69 (*ddd*, $^3J_{(py\text{-}4H,\ py\text{-}3H)}$ = $^3J_{(py\text{-}4H,\ py\text{-}5H)}$ = 7.7, ^4J = 1.9 Hz, 1H, py-4H), 7.60 (*m*, 1H, Cl_2Ph-2H), 7.51 (*m*, ^3J = 8.3 Hz, 1H, Cl_2Ph-5H), 7.37–7.29 (*m*, 2H, py-H and Cl_2Ph-6-H), 7.24–7.16 (*m*, 1H, py-H), 4.13 (*t*, ^3J = 7.7 Hz, 1H, CH), 2.53–2.29 (*m*, 1H, CH-C*H*H-CH_2), 2.29–2.14 (*m*, 1H, CH-CH*H*-CH_2), 2.14–2.00 (*m*, 2H, CH_2-COOH); $C_{15}H_{13}Cl_2NO_2$ (M_r = 310.2), analysis calculated C 58.09, H 4.22, N 4.52%; found C 58.12, H 4.26, N 4.66%.

From a concentrated ethanolic solution of equimolar amounts of (±)-4-(3,4-dichlorophenyl)-4-(2-pyridyl)butanoic acid and L-(−)-ephedrine, a mixture of the diastereomeric salts precipitated after adding ten times the volume of diethyl ether. Pure (IV) was obtained after fivefold recrystallization from mixtures of ether and ethanol [starting with ether/ethanol 7:1 (*v*/*v*), then 5:1 (*v*/*v*), and three times 3.5:1 (*v*/*v*)]. Ether was always added after dissolving the salt in ethanol at 303–313 K. The solution was stored at room temperature to allow very slow crystallization of colourless needles suitable for the single-crystal X-ray experiment (m.p. 399 K; $C_{10}H_{16}NO\cdot C_{15}H_{12}Cl_2NO_2$ (M_r = 475.4), analysis calculated C 63.16, H 5.94, N 5.89, Cl 14.91%; found C 63.19, H 5.96, N 5.92, Cl 14.87%; $[\alpha]_D^{20}$ = −37° (*c* = 1, methanol); %ee = 95.8 [ee refers to the *R*-configured butanoic acid and was determined by capillary zone electrophoresis (Schuster, Bollwein *et al.*, 1998)].

Crystal data

$C_{10}H_{16}NO^+\cdot C_{15}H_{12}Cl_2NO_2^-$	D_x = 1.328 Mg m^{-3}
M_r = 475.39	Mo $K\alpha$ radiation
Monoclinic, $P2_1$	Cell parameters from 4193 reflections
a = 13.2380 (11) Å	θ = 2.59–25.61°
b = 5.9089 (4) Å	μ = 0.302 mm^{-1}
c = 16.3148 (15) Å	T = 150 (2) K
β = 111.335 (9)°	Needle, translucent colourless
V = 1188.72 (17) Å^3	0.44 × 0.08 × 0.04 mm
Z = 2	

Data collection

Stoe IPDS diffractometer	R_{int} = 0.047
Rotation scans	θ_{max} = 25.61°
6243 measured reflections	$h = -16 \rightarrow 16$
2475 independent reflections (plus 1758 Friedel-related reflections)	$k = -7 \rightarrow 6$
	$l = -19 \rightarrow 19$
2388 reflections with $I > 2\sigma(I)$	Intensity decay: none

Refinement

Refinement on F^2	$w = 1/[\sigma^2(F_o^2) + (0.0193P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
$R(F)$ = 0.040	$(\Delta/\sigma)_{max}$ = 0.001
$wR(F^2)$ = 0.072	$\Delta\rho_{max}$ = 0.19 e Å^{-3}
S = 0.721	$\Delta\rho_{min}$ = −0.20 e Å^{-3}
4233 reflections	Absolute structure: Flack (1983)
309 parameters	Flack parameter = −0.04 (7)
H-atom parameters constrained	

Table 1
Selected bond lengths (Å).

Cl1—C9	1.729 (4)	N14—C15	1.325 (5)
Cl2—C10	1.749 (5)	N14—C13	1.335 (5)
O1—C3	1.286 (5)	N19—C29	1.473 (4)
O2—C3	1.244 (5)	N19—C20	1.513 (5)
O22—C21	1.421 (5)		

Table 2
Hydrogen-bonding geometry (Å, °).

D—H···A	D—H	H···A	D···A	D—H···A
N19—H19A···O2^{i}	1.004 (17)	1.750 (17)	2.724 (4)	162.5 (10)
N19—H19B···O1^{ii}	1.01 (2)	1.75 (2)	2.737 (4)	166.6 (11)
O22—H22···N19	0.84	2.62	2.947 (4)	104
C24—H24···O22	0.95 (3)	2.34 (2)	2.708 (5)	102.9 (15)

Symmetry codes: (i) $x-1, y-1, z$; (ii) $x-1, y, z$.

H atoms were generated and refined isotropically except for the hydroxy-H atom which was fixed (O—H = 0.84 Å).

Data collection: *IPDS Software* (Stoe, 1997); cell refinement: *IPDS Software*; data reduction: *IPDS Software*; program(s) used to solve structure: *SIR*97 (Altomare *et al.*, 1993); program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997); molecular graphics: *PLATON* (Spek, 1990); software used to prepare material for publication: *PLATON*.

Supplementary data for this paper are available from the IUCr electronic archives (Reference: KA1342). Services for accessing these data are described at the back of the journal.

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