Troponoid. V.[1] Crystallographic studies on AY-27110 — a dopamine agonist of the troponylpiperazine series[2]

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The crystal structure and absolute configuration of a *p*-bromobenzoyl derivative, **2**, of the (−)2-[4-[2-hydroxy-2-(3′,4′-dimethylphenyl)ethyl]-1-piperazinyl]-2,4,6-cycloheptatrien-1-one, **3***a* (AY-27110), which is a dopamine agonist, have been determined by an X-ray analysis. Crystals of $C_{28}H_{29}BrN_2O_5$, fw = 553.47, are monoclinic $P2_1$, a = 12.553(2), b = 6.359(1), c = 17.575(3) Å, β = 108.32(1)°, V = 1331.81 Å^3, Z = 2, ρ_c = 1.380, ρ_o = 1.384 g cm^{-3}. For 2155 observed reflexions, the final R is 0.036 and $R(w)$ is 0.039. The chirality of this enantiomer is shown to be $S(-)$, based on 18 reflexions with significant differences in the intensities of the corresponding Friedel pairs. The piperazine ring has a distorted chair form that is flattened at the N atom nearest the cycloheptatriene ring as for the psychoactive agents loxapine and amoxapine.

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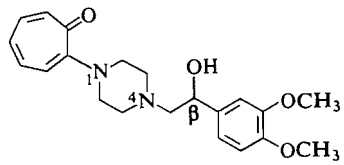
On a déterminé par analyse aux rayons X la structure cristalline et la configuration absolue d'un dérivé *p*-bromobenzoyle (**2**) de la (−)[(hydroxy-2(diméthyl-3′,4′ phényl)-2 éthyl)-4 pipérazinyl-1]-2 cycloheptatriène-2,4,6 one-1 (**3***a*) (AY-27110) qui est un antagoniste de la dopamine. Les cristaux de $C_{28}H_{29}BrN_2O_5$, pm = 553,47, sont monocliniques et appartiennent au groupe d'espace $P2_1$ avec a = 12,553(2), b = 6,359(1), c = 17,575(3) Å, β = 108,32(1)°, V = 1331,81 Å^3, Z = 2, ρ_c = 1,380, ρ_o = 1,384 g cm^{-3}. On a résolu la structure et on l'a ajusté jusqu'à des valeurs conventionnelles de R = 0,036 et de $R(w)$ = 0,039 pour 2155 réflexions observées. On montre que la chiralité de cet énantiomère est $S(-)$ à partir 18 réflexions avec des différences d'intensité significatives des paires de Friedel correspondantes. Le cycle pipérazine a une forme chaise déformée qui est applatie au niveau de l'atome de N le plus près du cycloheptatriène comme dans le cas de la loxapine et l'amoxapine; des agents psychoactifs.

[Traduit par le journal]

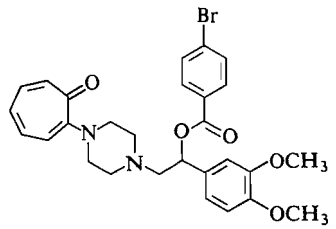
Introduction

Central dopaminergic mechanisms are known to be impaired in Parkinson's disease (2). Bromocriptine (CB-154), a dopamine agonist, has recently been reported to alleviate these symptoms (3). However, bromocriptine, an ergot derivative, affects not only the dopaminergic system but also other neuronal systems; its effect therefore is not specific. One of the objectives of our synthesis program was to discover a non-ergot dopamine agonist which is more specific than bromocriptine.

We have recently synthesized a series of troponylpiperazine derivatives (4), some of which demonstrated dopamine agonist activity (5). Compound **1** (2-[4-[2-hydroxy-2-(3′,4′-dimethoxyphenyl)ethyl]-1-piperazinyl]-2,4,6-cycloheptatrien-1-one) emerged as the compound of choice for further biological investigation. It was resolved into its optical enantiomers **3***a* (AY-27,110) and **3***b* using ditoluyl tartaric acids. It was found that the biological activity (5) was associated with the (−) enantiomer **3***a*. It was therefore of interest to establish the absolute configuration of the carbon atom β to the N-4 of the piperazine ring (see formula **1**). For this purpose compound **3***a* was converted to its *p*-



1



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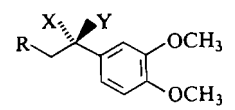

R = troponylpiperazine

3*a*, $S(-)$, X = H, Y = OH

3*b*, $R(+)$, X = OH, Y = H

[1]For parts I–IV, see ref. 1.

[2]NRCC No. 20519.

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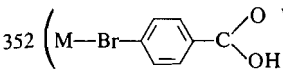
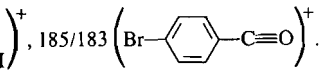
bromobenzoyl derivative **2** and subjected to X-ray studies.

Experimental

Preparation of 4-bromobenzoic acid, 1-(3,4-dimethoxyphenyl)-2-[4-(7-oxo-1,3,5-cycloheptatrien-1-yl)-1-piperazinyl]ethyl ester (2)

Triethylamine (0.218 g, or 0.3 mL, 1.8 equiv.) was added to a solution of alcohol **3***a* (0.444 g, 1 equiv.) in methylene chloride (4 mL); then 4-bromobenzoyl chloride (0.473 g, 1.8 equiv.) was added. The mixture was stirred for 3.5 h at room temperature, diluted with chloroform, washed with water, dried, and the solvent was removed. The residue was filtered through silica gel (50 g) and the product eluted with ethyl acetate. The product thus obtained was recrystallized twice from chloroform–ether to yield pure product (0.33 g, 69.8%) mp 129–133°C. *Anal.* calcd. for $C_{28}H_{29}BrN_2O_5$ (553.47): C 60.76, H 5.28, N 5.06; found: C 60.46, H 5.23, N 5.10. Infrared ($CHCl_3$) 1715, 1560 cm^{-1}, nmr ($CDCl_3$), δ7.55–7.9 (4H, m, arom.), 6.8 (8H, m, arom.), 6.1 (1H, m, C*H*—O), 3.85–3.8 (6H, 2 × s, C*H*$_3$—O), 3.2 (4H, m, C*H*$_2$—N), 2.75 (6H, m, C*H*$_2$—N), ms: *m/e* 554/552 $(M)^+$,

352  , 185/183  .

X-ray crystallographic analyses

(−) 4-Bromobenzoic acid, 1-(3,4-dimethoxyphenyl)-2-[4-(7-oxo-1,3,5-cycloheptatrien-1-yl)-1-piperazinyl]ethyl ester

$C_{28}H_{29}BrN_2O_5$ fw = 553.47

Monoclinic, $P2_1$, a = 12.553(2), b = 6.359(1), c = 17.575(3) Å, β = 108.32(1)°, V = 1331.81 Å^3, Z = 2, ρ_c = 1.380, ρ_o = 1.384 g cm^{-3}, $F(000)$ = 572, μ(Cu) = 24.25 cm^{-1}.

Measurements were carried out on an Enraf-Nonius CAD-4F diffractometer with Ni-filtered Cu radiation ($\lambda(K\alpha_1)$ = 1.54056, $\lambda(K\alpha_2)$ = 1.54439 Å) on a prismatic crystal, 0.09 × 0.11 × 0.40 mm, mounted with its length along the φ axis. The cell parameters were based on 15 well-centered reflexions, θ = 30–40°, and the indexing was for a right-handed set of unit-cell axes. The intensity data were measured by ω–2θ scans for ω ranges of (0.8 + 0.14 tan θ), extended by 25% at each end for the backgrounds, at scan speeds of 0.64 to 2.51° min^{-1} in ω. A total of 2991 reflexions in the hkl and $\bar{h}kl$ octants with θ = 0–75° were measured, and of these 2153 were considered observed at the 2σ(I) level. Three standard reflexions, scanned after every hour of exposure time, showed small random variations within ±1.5% of their mean values. The net intensities were corrected for Lorentz and polarization effects, and for absorption by the Gaussian integration method (6) assuming a 4 × 4 × 6 point grid. The range of the absorption corrections to the intensities was 1.20–1.51. Similarly, the Friedel pairs of hkl and $\bar{h}kl$ with θ = 0–20° were scanned and treated in the same way. The discrepancy index for the structure amplitudes of the 50$h0l$ and $\bar{h}0\bar{l}$ Friedel pairs which have no imaginary components was only 0.014.

Structure determination was by the heavy-atom method. After refinement of the non-hydrogen atomic parameters to R = 0.064 for the observed reflexions, the H atoms were located from a difference map and included in the refinement with isotropic B values. When R was reduced to 0.046, the effect of the anomalous dispersion of Br was tried for the two possible enantiomorphs. The corresponding R indexes, after one cycle of refinement for each, were 0.0434 and 0.0422, indicating a correct determination of the absolute configuration at the 0.5% level (the Hamilton ratio $\mathcal{R}_{1,1726,0.005}$ = 1.0024 while the experimental R ratio = 1.028 and R_w ratio = 1.030). Also, all the 18 Friedel pairs listed in Table 1 which showed the most significant anomalous dispersion effect consistently favoured one enantiomorph. Further refinement of the parameters for the correct enantiomorph produced the values listed in Tables 2 and 3,[3] for which R = 0.036 and $R(w)$ = 0.039.[3] The refinement was by block-diagonal least-squares on $\Sigma w(F_o - F_c)^2$ with $w^{-1} = 1 + [(|F_o| - p_2)/p_1]^2$, $p_1 = 30$ and $p_2 = 15$ in the last three cycles (to make $\Sigma w(F_o - F_c)^2$ independent of $|F_o|$). The unobserved reflexions were excluded, as were ($\bar{2}04$) and ($\bar{2}67$) which showed relatively high discrepancies. The scattering factor curves were from ref. 7 and the computer programs were those of ref. 8. In the final cycle, the mean parameter shift was 0.2σ (maximum = 1.2σ) and $[\Sigma w(\Delta F)^2/(m - n)]^{1/2}$ = 0.6. The final difference map contained random electron densities between −0.25 and 0.19 e Å^{-3}.

TABLE 1. Friedel pairs (θ = 0–20°) with the most significant anomalous dispersion effect

hkl	$I(hkl)$	$I(\bar{h}\bar{k}\bar{l})$	$\frac{I(hkl)}{I(\bar{h}\bar{k}\bar{l})}$	$\left[\frac{F_c(hkl)}{F_c(\bar{h}\bar{k}\bar{l})}\right]^2$
111	32025	29213	1.10	1.05
−111	442	779	0.57	0.68
112	11070	10254	1.08	1.04
−122	966	1040	0.93	0.92
−113	11258	9938	1.13	1.11
−123	1618	1430	1.13	1.09
211	15810	14998	1.05	1.04
−213	8434	7668	1.10	1.06
−215	2140	2684	0.80	0.89
311	808	674	1.20	1.15
−311	8371	7563	1.11	1.06
−312	4043	4417	0.92	0.92
322	1470	1207	1.22	1.07
−314	9133	9988	0.91	0.95
411	235	346	0.68	0.75
412	1946	2208	0.88	0.91
−412	1652	1499	1.10	1.07
−514	1612	1763	0.91	0.92

Results and discussion

A perspective view of the molecular structure showing the absolute configuration as determined from this X-ray analysis is presented in Fig. 1. The chirality at C(15), according to the Cahn–Ingold–Prelog system of notation (9), with the priority sequence HO > CH_2NH_2 > C_6H_5 > H is *S*(−) as shown in **3***a*. The arbitrarily-selected atomic numbering system and the bond lengths, not corrected for thermal vibration, are presented in Fig. 2. The valence angles and some selected torsion angles are given in Fig. 3 and Table 4, respectively.

The geometry of the piperazinyl ring in this compound is very similar to that of the corresponding rings in the psychoactive agents loxapine and

[3]The structure factor table and anisotropic thermal parameters of the non-hydrogen atoms are available, at a nominal charge, from the Depository of Unpublished Data, CISTI, National Research Council of Canada, Ottawa, Ont., Canada K1A 0S2.

TABLE 2. Fractional coordinates ($\times 10^4$; $\times 10^5$ for Br) and the equivalent isotropic temperature factors (Å^2) for the heavier atoms ($B_{eq} = \frac{8}{3}\pi^2 \Sigma_i \Sigma_j U_{ij}\, a_i^*\, a_j^*\, \mathbf{a}_i \cdot \mathbf{a}_j$)

Atom	x	y	z	B_{eq}
Br	71559(5)	−50000	−4692(4)	9.22(2)
C(1)	8693(4)	−7999(8)	5857(3)	4.8(1)
C(2)	9745(5)	−8684(10)	6419(3)	6.4(2)
C(3)	10759(5)	−7805(12)	6709(3)	6.9(2)
C(4)	11138(4)	−5851(10)	6539(3)	5.8(2)
C(5)	10538(4)	−4440(10)	6030(3)	5.3(2)
C(6)	9406(4)	−4525(8)	5540(3)	4.7(1)
C(7)	8573(4)	−5978(7)	5428(2)	4.0(1)
N(8)	7502(3)	−5512(6)	4927(2)	4.5(1)
C(9)	7195(4)	−3342(8)	4707(3)	5.3(2)
C(10)	5944(4)	−3118(9)	4448(3)	5.7(2)
N(11)	5429(3)	−4427(7)	3747(2)	4.2(1)
C(12)	5698(4)	−6626(8)	3978(3)	4.7(1)
C(13)	6950(4)	−6955(9)	4257(3)	4.9(1)
C(14)	4218(3)	−4040(9)	3397(3)	4.7(1)
C(15)	4033(3)	−2120(8)	2865(2)	4.1(1)
C(16)	2827(3)	−1450(8)	2524(2)	3.9(1)
C(17)	2072(3)	−2614(8)	1914(3)	4.0(1)
C(18)	963(3)	−1991(8)	1588(2)	4.1(1)
C(19)	602(3)	−168(9)	1872(2)	4.3(1)
C(20)	1341(4)	947(8)	2485(3)	4.9(1)
C(21)	2449(3)	313(9)	2800(2)	4.7(1)
C(22)	5400(3)	−1700(9)	2189(3)	4.5(1)
C(23)	5819(3)	−2600(9)	1556(3)	4.6(1)
C(24)	5405(4)	−4428(10)	1145(3)	5.9(2)
C(25)	5805(4)	−5129(11)	541(3)	6.6(2)
C(26)	6636(4)	−4040(11)	374(3)	6.0(2)
C(27)	7078(4)	−2275(13)	778(3)	7.4(2)
C(28)	6668(4)	−1565(11)	1375(3)	6.3(2)
C(29)	560(4)	−4616(11)	573(3)	6.0(2)
C(30)	−904(4)	2271(10)	1744(3)	6.0(2)
O(1)	7859(3)	−9153(6)	5753(2)	6.2(1)
O(2)	180(2)	−3009(6)	987(2)	5.0(1)
O(3)	−501(2)	377(6)	1501(2)	5.4(1)
O(4)	4465(2)	−2635(5)	2211(2)	4.4(1)
O(5)	5878(3)	−331(7)	2637(2)	7.0(1)

TABLE 3. Fractional coordinates ($\times 10^3$) and isotropic temperature factors (Å^2) for the H atoms

Atom	x	y	z	B_{iso}
H(2)	955(4)	−1023(10)	665(3)	7.5(13)
H(3)	1133(4)	−869(9)	705(3)	6.9(14)
H(4)	1196(5)	−557(13)	685(4)	11.5(20)
H(5)	1095(4)	−303(9)	593(3)	6.5(12)
H(6)	925(3)	−337(8)	522(2)	5.1(11)
H(9,1)	747(4)	−278(9)	520(3)	6.9(13)
H(9,2)	752(3)	−300(8)	427(2)	5.3(11)
H(10,1)	556(4)	−321(11)	489(3)	8.6(17)
H(10,2)	577(5)	−175(11)	423(3)	9.9(17)
H(12,1)	544(3)	−714(8)	442(2)	5.0(11)
H(12,2)	528(3)	−736(8)	349(2)	5.3(10)
H(13,1)	717(3)	−846(7)	446(2)	4.2(09)
H(13,2)	721(3)	−673(7)	378(2)	4.9(10)
H(14,1)	386(3)	−383(8)	384(3)	6.2(11)
H(14,2)	391(3)	−527(8)	306(2)	4.9(10)
H(15)	441(3)	−91(7)	314(2)	4.0(10)
H(17)	233(3)	−395(7)	173(2)	4.5(10)
H(20)	110(4)	216(9)	266(3)	7.1(13)
H(21)	294(3)	107(6)	323(2)	3.6(09)
H(24)	485(4)	−508(11)	125(3)	7.8(13)
H(25)	550(4)	−636(10)	28(3)	9.0(17)
H(27)	757(4)	−174(9)	67(3)	7.5(14)
H(28)	690(4)	−51(10)	166(3)	8.5(15)
H(29,1)	117(3)	−402(7)	40(2)	4.4(09)
H(29,2)	92(4)	−574(9)	97(3)	6.9(13)
H(29,3)	−8(5)	−480(12)	18(3)	8.8(15)
H(30,1)	−43(4)	327(9)	165(3)	6.3(12)
H(30,2)	−85(4)	212(10)	242(3)	8.6(15)
H(30,3)	−163(4)	236(10)	142(3)	7.9(15)

amoxapine (10). It has a distorted chair form with its four C atoms slightly non-planar ($\chi^2 = 27.3$, deviations from mean plane ±0.013(5) Å). N(8) and N(11) lie on opposite sides at significantly different distances (−0.642(3) and 0.708(4) Å, respectively) from the mean plane of the C atoms. While the endocyclic angles are approximately tetrahedral, 108.0(4)–111.0(4)°, the exocyclic angles are well above tetrahedral values with the angles of 119.3(4) and 119.7(4)° at N(8) considerably larger than those of 112.5(4) and 113.2(4)° at N(11). The flattening of the ring at N(8) was interpreted for loxapine and amoxapine (10) as indicative of some electron delocalization into the bond corresponding to N(8)–C(7), although its length in those structures, as in the present work, was 1.388 Å, i.e. within the range expected for C(sp^2)—N(sp^3) bonds (11). The other C—N bonds have a mean length of 1.466(11) Å in the present structure and 1.462(8) Å in the other two structures.

The cycloheptatriene ring is nearly planar, with $\chi^2 = 31.6$ for the seven C atoms. However, excluding C(1), the other six C atoms are coplanar ($\chi^2 = 1.8$) while C(1) is off that plane by −0.036(5) Å, resulting in a slight bend of 2.8(5)° between the plane C(2)—C(1)—C(7) and that of the six atoms. O(1) lies at 0.034(4) Å from the C(2)—C(1)—C(7)

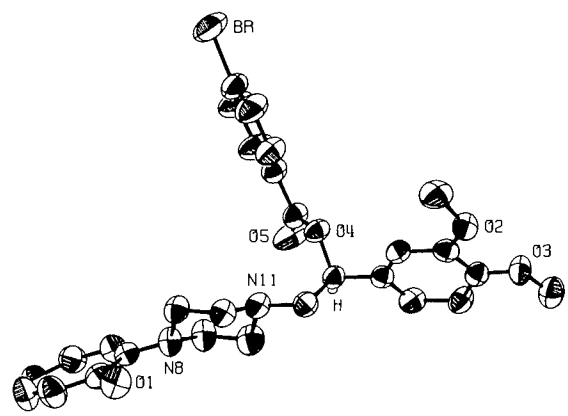


FIG. 1. A perspective view of the molecular structure showing its absolute configuration.

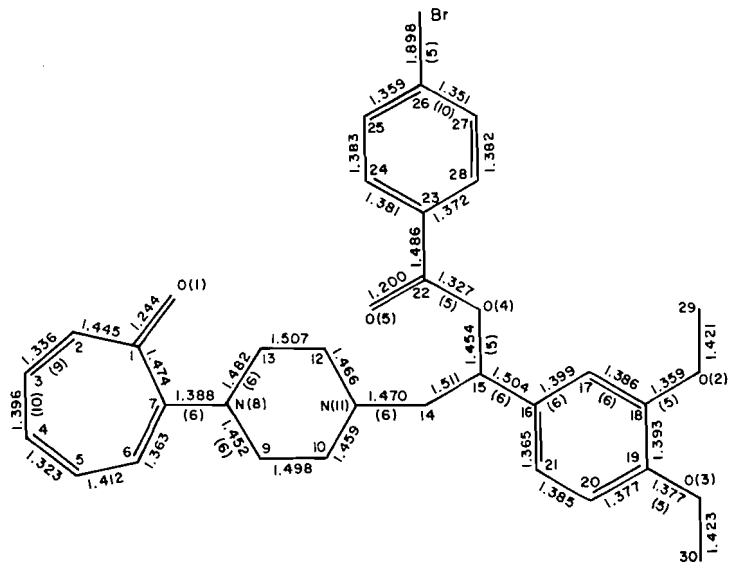


FIG. 2. Bond lengths (Å). The estimated standard deviations are 0.007–0.008 Å except for those given in parentheses.

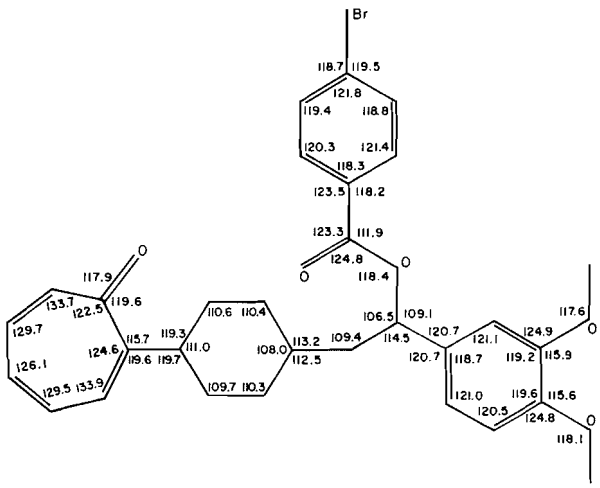


FIG. 3. Valence angles (deg). The estimated standard deviations are 0.4–0.6°.

TABLE 4. Selected torsion angles

Atoms	Torsion angle (deg)
N(11)—C(14)—C(15)—C(16)	−175.1(4)
N(11)—C(14)—C(15)—O(4)	64.1(4)
C(15)—O(4)—C(22)—O(5)	−5.9(7)
C(15)—O(4)—C(22)—C(23)	172.1(4)
C(17)—C(18)—O(2)—C(29)	−10.9(6)
C(19)—C(18)—O(2)—C(29)	167.7(4)
C(20)—C(19)—O(3)—C(30)	2.5(7)
C(18)—C(19)—O(3)—C(30)	−177.5(4)
C(14)—C(15)—O(4)—C(22)	−109.4(4)
C(16)—C(15)—O(4)—C(22)	126.5(4)

plane. The three C=C double bonds have a mean value 1.341 Å which is comparable to the average value (12) of 1.337(6) Å.

The C atoms of the *p*-bromobenzoic group are coplanar ($\chi^2 = 15.3$) with deviations within ±0.013 Å, but the substituents Br and C(22) are at distances 0.059(2) and 0.052(5) Å from the plane of the ring. The Br—C(26) distance of 1.898(5) Å is comparable to the value 1.902(10) Å for *p*-bromobenzoic acid (13).

The remaining aromatic ring C(16) to C(21) is planar ($\chi^2 = 15.2$) with the substituents C(15), O(2), and O(3) in the plane of the ring. The two methyl groups C(29) and C(30) lie on the same side of the ring plane but at unequal distances of 0.260(6) and 0.123(6) Å, respectively. This imbalance is reflected in the corresponding torsion angles in Table 4. The average C—C length in the two aromatic rings is 1.378(14) Å and the average C—H length is 0.97(8) Å. The molecules are separated by normal van der Waals contacts.

In summary, the above assigns the chirality of β-C-atom of **2** as *S*. In turn the chirality of that carbon in AY-27110 follows. The biological activity thus resides with the *S*(−) enantiomer.

Acknowledgements

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