Crystallography (1974), locally written or locally modified versions of standard computer programs, final $R = 0.034$, $wR = 0.037$ for 670 reflections with $I \geq 3\sigma(I)$, $S = 1.319$, 96 parameters, isotropic type I extinction, $g = 0.7\,(1) \times 10^4$, $R = 0.098$ for all 1255 reflections, $\Delta/\sigma = 0.003$ (mean), 0.011 (maximum), maximum final difference density −0.25 to 0.29 e Å^{-3} (all large peaks near Cl atoms).

Discussion. Final positional and equivalent isotropic thermal parameters ($U_{eq} = \frac{1}{3}$ trace of diagonalized U) are given in Table 1, and geometrical data appear in Table 2.* A stereoview of the molecule is shown in Fig. 1.

The compound (3) is evidently formed through a complex series of reactions with resorcinol (1). A possible mechanism involves cyclization and dehydration of the intermediate chlorinated acid (2).

The five-membered ring is planar to within experimental error but the molecule as a whole deviates slightly from planarity, the maximum displacements from the weighted mean molecular plane being −0.08 (5) Å for H(3) and +0.063 (2) Å for Cl(3). The molecular geometry (Table 2) is normal, with mean distances: C(sp^2)—Cl = 1.707 (8), C=O = 1.187 (6), C(sp^2)—O = 1.381 (8), C=C = 1.327 (8), and C(sp^2)—C(sp^2) = 1.450 (4) Å. The shortest intermolecular distance between non-hydrogen atoms is Cl(2)···O(2) $(x-\frac{1}{2}, \frac{1}{2}-y, \frac{1}{2}+z) = 3.001$ (4) Å.

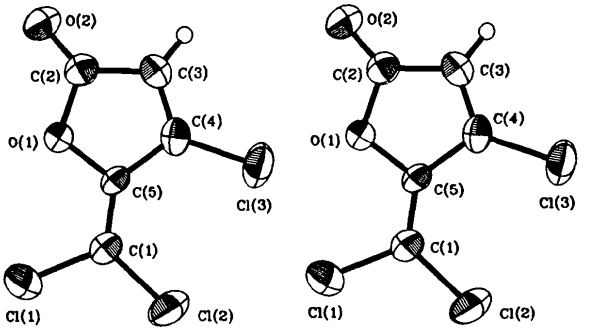

Fig. 1. Stereoscopic view of the molecule: 50% probability thermal ellipsoids are shown for the non-hydrogen atoms.

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* Lists of anisotropic thermal parameters, torsion angles, and structure factors have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 44990 (9 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

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Structure of the (+)-Tartrate of the Selective 5-HT$_2$ Antagonist Irindalone

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(*Received* 1 *March* 1988; *accepted* 28 *April* 1988)

Abstract. (+)-(1*R*,3*S*)-*trans*-1-[2-[4-[3-(4-Fluorophenyl)-1-indanyl]-1-piperazinyl]ethyl]-2-imidazolidinone, (+)-(2*R*,3*R*)-tartrate. $C_{28}H_{35}FN_4O_7$, $M_r = 558.6$, monoclinic, $P2_1$, $a = 24.716$ (9), $b = 8.457$ (10), $c = 6.290$ (3) Å, $\beta = 93.21$ (3)°, $V = 1313$ (3) Å^3, $Z = 2$, D_m(295 K) = 1.39 (1), D_x(105 K) = 1.413 Mg m^{-3}, λ(Mo $K\alpha$) = 0.71073 Å, μ(Mo $K\alpha$) = 0.10 mm^{-1}, $F(000) = 592$, $T = 105$ (1) K. $R = 0.041$ for 3885 observed [$I \geq 3.0\sigma(I)$] reflections. The absolute configuration is 1*R*,3*S*, opposite to the expected configuration. The ions are connected into infinite chains *via* hydrogen bonds from piperazine N atoms to tartrate ions.

Introduction. The selective 5-HT$_2$* antagonist irindalone was developed by systematic variations of structural components (Bøgesø, 1988). The structure

* Abbreviations used: DA, dopamine; 5-HT$_2$, 5-hydroxotryptophan (serotonine); NE, norepinephrine.

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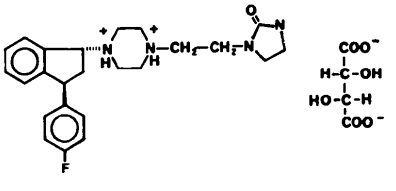
Table 1. *Final positional and thermal parameters for non-hydrogen atoms*

$U_{eq} = \frac{1}{3}\sum_i\sum_j U_{ij} a_i^* a_j^* \mathbf{a}_i.\mathbf{a}_j$.

	x	y	z	$U_{eq} \times 10^2$ (Å^2)
O011	0·66516 (7)	0·6472	0·3432 (2)	1·07
O012	0·62305 (7)	0·5594 (2)	0·6270 (3)	1·23
C01	0·65136 (9)	0·6572 (3)	0·5358 (3)	0·84
C02	0·67216 (9)	0·8021 (3)	0·6592 (3)	0·83
O02	0·70085 (8)	0·9064 (2)	0·5283 (3)	1·44
C03	0·70921 (9)	0·7457 (3)	0·8485 (3)	0·88
O03	0·74917 (7)	0·6404 (2)	0·7794 (3)	1·33
C04	0·73505 (9)	0·8876 (3)	0·9657 (3)	0·96
O041	0·78367 (8)	0·9129 (3)	0·9523 (3)	2·04
O042	0·70210 (7)	0·9722 (2)	1·0698 (3)	1·21
C1	0·80428 (9)	0·2327 (3)	0·2507 (3)	0·98
C2	0·82475 (10)	0·0949 (3)	0·3943 (4)	1·19
C3	0·84754 (10)	0·1669 (3)	0·6093 (4)	1·30
C4	0·87374 (11)	0·4603 (4)	0·6903 (5)	2·19
C5	0·87378 (12)	0·6149 (4)	0·6139 (6)	2·69
C6	0·85286 (11)	0·6503 (3)	0·4103 (6)	2·48
C7	0·82992 (11)	0·5325 (3)	0·2790 (5)	1·85
C8	0·82799 (10)	0·3789 (3)	0·3585 (4)	1·23
C9	0·85043 (9)	0·3420 (3)	0·5600 (4)	1·33
N11	0·63466 (8)	0·3666 (2)	0·2156 (3)	0·89
C12	0·66237 (10)	0·3334 (3)	0·0154 (3)	1·07
C13	0·72312 (10)	0·3486 (3)	0·0572 (3)	1·14
N14	0·74299 (8)	0·2340 (2)	0·2246 (3)	0·85
C15	0·71526 (9)	0·2674 (3)	0·4254 (3)	0·86
C16	0·65452 (9)	0·2528 (3)	0·3848 (3)	0·96
C17	0·57412 (9)	0·3609 (3)	0·1769 (4)	1·25
C18	0·55322 (9)	0·5167 (3)	0·0768 (4)	1·23
N31	0·50367 (8)	0·4956 (3)	−0·0527 (3)	1·13
C32	0·45409 (9)	0·4815 (3)	0·0342 (4)	1·03
O32	0·44383 (8)	0·5233 (3)	0·2147 (3)	1·85
N33	0·41869 (8)	0·4179 (3)	−0·1166 (3)	1·24
C34	0·44234 (9)	0·4088 (3)	−0·3234 (3)	1·28
C35	0·50327 (10)	0·4207 (3)	−0·2628 (4)	1·38
C21	0·90117 (10)	0·0942 (3)	0·6865 (4)	1·37
C22	0·94667 (11)	0·1098 (4)	0·5660 (5)	2·40
C23	0·99538 (12)	0·0371 (5)	0·6296 (5)	2·84
C24	0·99803 (11)	−0·0483 (4)	0·8156 (5)	2·22
C25	0·95473 (12)	−0·0642 (4)	0·9431 (4)	2·04
C26	0·90602 (10)	0·0074 (3)	0·8751 (4)	1·54
F24	1·04551 (8)	−0·1222 (3)	0·8761 (3)	3·48

determination was undertaken in order to establish the absolute configuration of irindalone and thereby of a whole class of related compounds for which the biological effects are highly stereospecific (Bøgesø, Hyttel, Christensen, Arnt & Liljefors, 1986).



Experimental. Title compound synthesized by K. P. Bøgesø, H. Lundbeck & Co A/S. Transparent plate-like crystals grown from DMF and water, kept in a desiccator containing P_2O_5. M.p. (hot stage microscope) 490–492 K. D_m by flotation. Crystal size for data collection 0·1 × 0·2 × 0·3 mm. Enraf–Nonius CAD-4 diffractometer and low-temperature device, graphite-monochromatized Mo $K\alpha$ radiation. Temperature recorded with a thermocouple, variation within 1 K. Cell parameters and orientation matrix from 16 reflections ($18 \le \theta \le 21°$). No corrections for absorption or secondary extinction. Three intensity control reflections measured every 10^4 s; no systematic variation. Intensity data measured by ω–2θ scan, $\theta_{max} = 32·5°$; $-37 \le h \le 37$, $0 \le k \le 12$, $0 \le l \le 9$. 5010 unique reflections measured, 1112 unobserved, 13 removed due to measuring errors. $R_{int} = 0·038$, for $\pm h00$. Non-hydrogen atoms localized by direct methods using *MULTAN*80 (Main, Fiske, Hull, Lessinger, Germain, Declercq & Woolfson, 1980). All H atoms were placed in calculated positions, except the hydroxyl H atoms which were placed in positions found in a $\Delta\rho$ map; no refinement of H atoms ($U_{iso} = 0·025$ Å^2). Structure refinement by least squares minimizing $\sum w(|F_o| - k|F_c|)^2$, $w = 1$ if $F_o \le 15·0$, otherwise $w = 15^2 F_o^{-2}$. Programs of the *XRAY* system (Stewart, Machin, Dickinson, Ammon, Heck & Flack, 1976). Atomic scattering factors as implemented in *XRAY*76. Final $R = 0·041$, $wR = 0·058$. $\Delta/\sigma \le 0·21$. Features in final $\Delta\rho \le \pm 0·2$ e Å^{-3}.

Discussion. Final atomic coordinates and equivalent isotropic thermal parameters for non-hydrogen atoms are given in Table 1.* The atom-numbering scheme is shown in Fig. 1. The configuration of the tartrate ion was known to be *R,R*, and it thus follows that the configuration of irindalone is 1*R*,3*S*. This was not as expected (Bøgesø, 1983), and therefore a series of resolved *trans*-1-piperazino-3-phenylindan derivatives of biological interest was examined by use of CD spectra (Jensen, H. P., Technical Univ. of Denmark) which showed that the configuration of the more active enantiomer invariably is 1*R*,3*S* for derivatives with

* Lists of structure factors, anisotropic thermal parameters and H-atom parameters have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 44997 (17 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

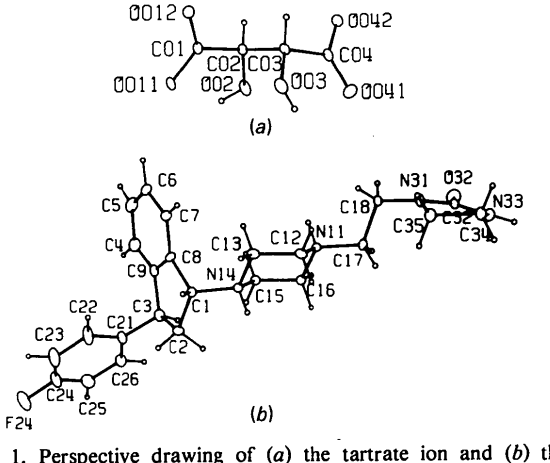


Fig. 1. Perspective drawing of (*a*) the tartrate ion and (*b*) the irindalone ion. Atom numbering is shown. Non-hydrogen atoms are represented by their thermal ellipsoids drawn at the 50% probability level and hydrogen atoms as spheres of an arbitrary radius (Johnson, 1971).

Table 2. *Bond lengths* (Å), *valency angles* (°), *selected torsion angles* (°) *and interplanar angles* (°)

C01–O011	1·280 (2)	C13–N14	1·494 (3)
C01–O012	1·244 (3)	N14–C15	1·497 (3)
C01–C02	1·524 (4)	C15–C16	1·514 (3)
C02–O02	1·423 (3)	N11–C16	1·497 (3)
C02–C03	1·537 (3)	N11–C17	1·503 (3)
C03–O03	1·416 (3)	C17–C18	1·537 (4)
C03–C04	1·529 (4)	C18–N31	1·443 (3)
C04–O041	1·228 (3)	N31–C32	1·375 (3)
C04–O042	1·290 (3)	C32–O32	1·229 (3)
C1–C2	1·542 (4)	C32–N33	1·364 (3)
C2–C3	1·559 (4)	N33–C34	1·458 (3)
C3–C9	1·515 (4)	C34–C35	1·536 (3)
C9–C8	1·390 (4)	C35–N31	1·465 (3)
C8–C1	1·512 (4)	C3–C21	1·516 (4)
C4–C9	1·397 (4)	C21–C22	1·397 (4)
C4–C5	1·393 (5)	C22–C23	1·391 (4)
C5–C6	1·387 (5)	C23–C24	1·373 (5)
C6–C7	1·394 (4)	C24–C25	1·379 (4)
C7–C8	1·394 (4)	C25–C26	1·393 (4)
N14–C1	1·515 (3)	C26–C21	1·395 (4)
N11–C12	1·493 (3)	C24–F24	1·365 (4)
C12–C13	1·515 (4)		

O011–C01–C02	115·8 (2)	C12–C13–N14	110·5 (2)
O012–C01–C02	118·8 (2)	C13–N14–C15	108·9 (2)
O011–C01–O012	125·4 (2)	N14–C15–C16	109·8 (2)
C01–C02–C03	108·3 (2)	C15–C16–N11	110·5 (2)
C01–C02–O02	111·6 (2)	C16–N11–C12	109·3 (2)
C03–C02–O02	110·3 (2)	C12–N11–C17	110·9 (2)
C02–C03–O03	110·7 (2)	C16–N11–C17	112·2 (2)
C04–C03–O03	111·2 (2)	N11–C17–C18	110·3 (2)
C02–C03–C04	110·2 (2)	C17–C18–N31	112·3 (2)
C03–C04–O041	119·2 (2)	C18–N31–C32	122·2 (2)
C03–C04–O042	114·9 (2)	C18–N31–C35	121·7 (2)
O041–C04–O042	125·9 (3)	C32–N31–C35	111·1 (2)
C1–C2–C3	107·7 (2)	N31–C32–O32	125·2 (2)
C2–C3–C9	102·9 (2)	N33–C32–O32	126·7 (2)
C3–C9–C8	112·6 (2)	N31–C32–N33	108·0 (2)
C9–C8–C1	110·5 (2)	C32–N33–C34	111·6 (2)
C8–C1–C2	104·4 (2)	N33–C34–C35	102·2 (2)
C3–C9–C4	127·0 (2)	C34–C35–N31	102·1 (2)
C8–C9–C4	120·3 (3)	C2–C3–C21	112·7 (2)
C9–C4–C5	118·6 (3)	C9–C3–C21	114·3 (2)
C4–C5–C6	120·9 (3)	C3–C21–C22	120·3 (2)
C5–C6–C7	120·7 (3)	C3–C21–C26	121·2 (2)
C6–C7–C8	118·3 (3)	C21–C22–C23	120·8 (3)
C7–C8–C9	121·1 (2)	C22–C23–C24	118·5 (3)
C7–C8–C1	128·4 (2)	C23–C24–C25	123·0 (3)
C8–C1–N14	113·7 (2)	C24–C25–C26	117·7 (3)
C2–C1 N14	111·2 (2)	C25–C26–C21	121·4 (2)
C1–N14–C13	111·6 (2)	C26–C21–C22	118·5 (2)
C1–N14–C15	114·3 (2)	C23–C24–F24	118·5 (3)
N11–C12–C13	109·5 (2)	C25–C24–F24	118·4 (3)

C01–C02–C03–C04	175·0 (2)	C1–C8–C9–C3	3·0 (3)
O011–C01–C02–O02	3·9 (3)	C8–C9–C3–C2	5·8 (3)
O012–C01–C02–O02	−176·3 (2)	C9–C8–C1–C2	−10·6 (3)
O02–C02–C03–O03	−70·8 (2)	C9–C3–C2–C1	−12·1 (2)
O041–C04–C03–O03	14·0 (3)	C8–C1–C2–C3	13·9 (2)
O042–C04–C03–O03	−166·8 (2)		

Plane I C4, C5, C6, C7, C8, C9
Plane II N31, C32, O32, N33
Plane III C21, C22, C23, C24, C25, C26
∠ I–II 76°; ∠ I–III 84°

receptor blocking properties (DA and/or $5HT_2$ antagonist), while the opposite configuration is found in derivatives with antidepressant activity (DA and NE uptake inhibitors) (Bøgesø, Hyttel, Christensen, Arnt & Liljefors, 1986).

Bond lengths, valency angles, torsion angles and interplanar angles are given in Table 2. Dimensions of hydrogen bonds are shown in Table 3, and a stereoview of a fragment of the packing is shown in Fig. 2. The tartrate ion adopts the normal conformation with the two hydroxy groups *gauche* and the carboxylate groups *trans* to each other. O02 has a distance of only

Table 3. *Inter- and intramolecular hydrogen bonds*

X–H···*Y*	*X*···*Y* (Å)	*X*–H···*Y* (°)
N11–H11···O011	2·603 (3)	173
N14–H14···O042^{i}	2·600 (3)	163
N33–H33···O042^{ii}	3·051 (3)	143
O02–H020···O042^{iii}	2·939 (3)	130
O02–H020···O011	2·612 (3)	126
O03–H030···O041	2·668 (4)	118

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

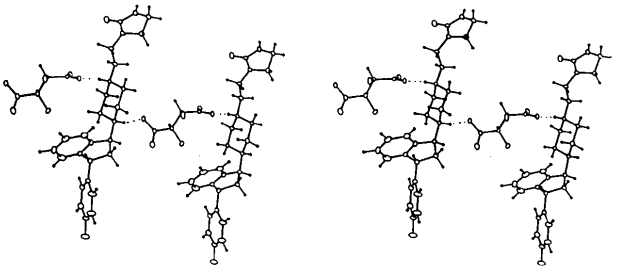


Fig. 2. A fragment of the packing pattern. Hydrogen bonds N–H···O interlink the ions in chains.

0·086 (2) Å to the best plane through O011, O012, C01 and C02 while O03 has a distance of 0·306 (2) Å to the best plane through C03, C04, O041 and O042. Both of the hydroxy groups seem to be engaged in *intra*molecular hydrogen bonds, as the hydroxyl H atoms are found very close to the plane of the adjacent carboxylate groups (*cf.* Fig. 1*a*). The C–O bond lengths in the carboxylate groups are far from being equal, with variations from 1·228 (3) to 1·290 (3) Å. This is a result of the strong hydrogen bonds from the piperazine nitrogen atoms N11 and N14 and possibly of the weaker contacts from a hydroxy atom O02 and an amide nitrogen atom N33 (*cf.* Table 3).

The imidazolidinone ring adopts a twist conformation with C34 and C35 removed 0·22 (1) and 0·15 (1) Å, respectively, in either direction from the best plane through N31, C32, O32 and N33. The dimensions found for the irindalone ion are very similar to corresponding values found for the related compound tefludazine (Jensen, 1983). The five-membered ring of the indane system is a little flatter in the present structure, a deformation which was predicted by *MM*2 calculations (Allinger, 1977) to demand very little energy (Jensen, 1983; Liljefors & Bøgesø, 1988). The relative orientations of the rings in crystals of irindaline tartrate are very similar to that found in crystals of tefludazine. For example, the torsion angles C22–C21–C3–C2 and C2–C1–N14–C13 are 62·7 (3) and −170·1 (2)°, respectively, in the present structure and 57·8 (5) and −176·2 (5)° in tefludazine. The values found for the torsion angle C22–C21–C3–C2 correspond to the conformation for which *MM*2 calculations find the lowest energy minimum. The same calculations indicate that the values found for the torsion angle C2–C1–N14–C13 correspond to an energy minimum 0·5 kcal mol^{-1} (1 kcal mol^{-1} ≡

4·2 kJ mol^{-1}) above the global minimum found for a conformer, in which C2–C1–N14–C13 is −60°. The energy barriers between the conformers do not exceed 4 kcal mol^{-1}, and both of the conformers – as well as others – will no doubt be accessible in solution (Liljefors & Bøgesø, 1988).

The author thanks Mr Flemming Hansen for collecting the data for the structure determination. The diffractometer and X-ray generator were acquired by means of Grants 11-1837, 11-2360 and 11-3531 from the Danish Natural Science Research Council.

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Redetermination of the Crystal and Molecular Structure of the Antimalarial Chloroquine Bis(dihydrogenphosphate) Dihydrate

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Abstract. N^4-(7-Chloro-4-quinolinyl)-N',N'-diethyl-1,4-pentanediamine bis(dihydrogenphosphate) dihydrate, $C_{18}H_{28}ClN_3^{2+}.2H_2PO_4^-.2H_2O$, $M_r = 551{\cdot}8$, monoclinic, $P2_1/c$, $a = 9{\cdot}830$ (2), $b = 16{\cdot}879$ (3), $c = 15{\cdot}783$ (4) Å, $\beta = 105{\cdot}51$ (2)°, $V = 2523{\cdot}2$ Å^3, $Z = 4$, $D_x = 1{\cdot}452$ g cm^{-3}, Mo $K\alpha$, $\lambda = 0{\cdot}71073$ Å, $\mu = 2{\cdot}78$ cm^{-1}, $F(000) = 1168$, room temperature, final $R = 5{\cdot}5\%$ for 2431 reflections with $|F_o| > 3\sigma$. The chloroquine molecule is a dication with a hydrogen atom from each of the phosphate moieties residing on the quinoline and the terminal chain nitrogen atoms. Neighboring phosphate chains are bridged by chloroquine molecules *via* hydrogen bonding. Each hydrogen atom on each nitrogen atom, on each phosphate oxygen atom, and in each water molecule participates in hydrogen bonding. The helical manner in which the side chains of the chloroquine molecules wrap around phosphate chains and the stacking interval of the quinoline rings between the phosphate groups may be indicative of the interaction of chloroquine molecules with cellular constituents important to antimalarial action.

Introduction. Chloroquine (Fig. 1), first developed for human use during World War II, was the drug of choice for the treatment of *Plasmodium falciparum* (Webster, 1985). However, in the 1960's resistant strains of *P. falciparum* appeared in Asia and South America which have now spread across all of the

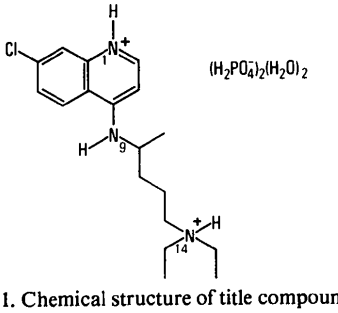

Fig. 1. Chemical structure of title compound.

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