Acta Cryst. (1989). B45, 172–178

Structure–Activity Relationships of Antiarrhythmic Agents: Crystal Structure of Amiodarone Hydrochloride and Two Derivatives, and Their Conformational Comparison with Thyroxine

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(*Received* 8 *April* 1988; *accepted* 1 *November* 1988)

Abstract

Amiodarone.HCl (I), 2-butyl-3-benzofuranyl 4-[2-(diethylamino)ethoxy]-3,5-diiodophenyl ketone hydrochloride, $C_{25}H_{30}I_2NO_3^+.Cl^-$, $M_r = 680{\cdot}78$, monoclinic, $P2_1/c$, $a = 17{\cdot}124$ (2), $b = 17{\cdot}079$ (2), $c = 9{\cdot}162$ (1) Å, $\beta = 98{\cdot}37°$, $V = 2651{\cdot}2$ Å^3, $Z = 4$, $D_x = 1{\cdot}71$ g cm^{-3}, λ(Mo $K\alpha$) = 0·7107 Å, $\mu = 24{\cdot}73$ cm^{-1}, $F(000) = 1332$, $T = 294$ K, $R = 6{\cdot}6\%$ for 5515 data; desethylamiodarone.HCl (II), 2-butyl-3-benzofuranyl 4-[2-(ethylamino)ethoxy]-3,5-diiodophenyl ketone hydrochloride, $C_{23}H_{26}I_2NO_3^+.Cl^-$, $M_r = 654{\cdot}74$, monoclinic, $P2_1/c$, $a = 23{\cdot}867$ (2), $b = 10{\cdot}134$ (1), $c = 10{\cdot}287$ (2) Å, $\beta = 93{\cdot}91$ (2)°, $V = 2482{\cdot}5$ Å^3, $Z = 4$, $D_x = 1{\cdot}75$ g cm^{-3}, λ(Mo $K\alpha$) = 0·07107 Å, $\mu = 26{\cdot}37$ cm^{-1}, $F(000) = 1276$, $T = 294$ K, $R = 5{\cdot}7\%$ for 5916 data; benziodarone (III), 2-ethyl-3-benzofuranyl 4-hydroxy-3,5-diiodophenyl ketone, $C_{17}H_{12}I_2O_3$, $M_r = 518{\cdot}09$, monoclinic, $P2_1/n$, $a = 17{\cdot}564$ (2), $b = 8{\cdot}294$ (1), $c = 11{\cdot}587$ (2) Å, $\beta = 93{\cdot}20$ (2)°, $V = 1685{\cdot}55$ Å^3, $Z = 4$, $D_x = 2{\cdot}04$ g cm^{-3}, λ(Mo $K\alpha$) = 0·7101 Å, $\mu = 36{\cdot}99$ cm^{-1}, $F(000) = 976$, $T = 294$ K, $R = 6{\cdot}2\%$ for 4311 data. The molecular conformations of these three benzofuran structures are similar: the carbonyl oxygen is *s-trans* to the benzofuran C(2)–C(3) double bond, the phenyl ring is in a twist conformation about the carbonyl bridge to the benzofuran ring system, the ethoxy side chain is perpendicular to the phenolic ring, the *n*-butyl side chain is folded back over the iodophenyl ring and the amine is protonated in amiodarone and its desethyl analogue. There is a change from *+gauche* (amiodarone) to *–gauche* (desethylamiodarone) in the 2-side chain and *N*-ethylamino group, which causes these two structures to have different overall conformations.

Introduction

Cardioactive agents are compounds which can selectively control either the rate or strength and rhythm of the heart beat. Antiarrhythmic drugs are those which control heart-beat rhythm and are classified on the basis of their chemical structure and intracellular electrophysiological properties (Singh & Vaughan Williams, 1970; Singh, Opie, Harrison & Marcus, 1987). Amiodarone is a potent antiarrhythmic agent which acts by lengthening repolarization in the myocardium. It has been shown to have many diverse effects on thyroid-hormone metabolism, transport and action causing reduced peripheral conversion of thyroxine (T_4) to 3,5,3′-triiodothyronine (T_3) owing to impaired hepatic deiodinase activity (Sogol, Hershman, Reed & Dillmann, 1983; Aanderud, Sundsfjord & Aarbakke, 1984; Kannan, Ookhtens, Chopra & Singh, 1984). In addition, there is a reduction in heart rate and cardiac Ca^{2+}-activated myosin ATPase activity. These findings are consistent with the hypothesis that amiodarone blocks some of the effects of thyroid hormone on the heart. However, amiodarone has no effect on circulating thyroxine-binding globulin levels, although there is a fall in prealbumin and serum albumin levels, and also in basal serum thyroid-stimulating hormone (Franklyn, Davis, Gammage, Littler, Ramsden & Sheppard, 1985; Venktesh, Al-Sarraf, Hershman & Singh, 1986). The principal metabolite of amiodarone, *N*-desethylamiodarone, is produced primarily in the liver and has the same effects on thyroid function as amiodarone (Latini, Connolly & Kates, 1983; Young & Mehendale, 1986).

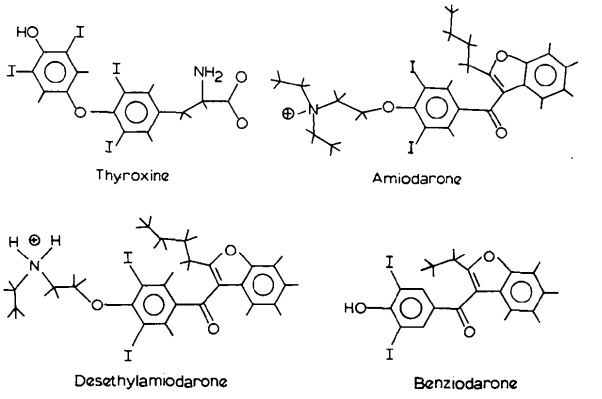

Fig. 1. Schematic figure comparing the structures of thyroxine, amiodarone, desethylamiodarone and benziodarone.

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0108-7681/89/020172-07$03.00

Structure–activity data on amiodarone and two analogues (*N*-desethylamiodarone and benziodarone), measured in a human red cell Ca^{2+}-ATPase assay system, showed that amiodoarone is a potent inhibitor of both basal and thyroid-hormone-stimulable Ca^{2+}-ATPase activity. However, desethylamiodarone had no effect on either enzyme activity. Benziodarone, on the other hand, was shown to be stimulatory at low concentrations and inhibitory at high concentrations (Cody, Galindo, Davis, Davis & Blas, 1987).

Therefore, to further understand the mechanisms of actions of amiodarone and its analogues, the crystal and molecular structures of this antiarrhythmic agent and its derivatives, *N*-desethylamiodarone and benziodarone, have been determined and their conformations compared with those of thyroxine (Fig. 1).

Experimental

Crystals of amiodarone.HCl, desethylamiodarone.HCl and benziodarone (Sanofi, Montpellier, France) were grown from ethanolic solutions. Crystal data are described in Table 1. Data were collected in the automated θ–2θ scan mode with a 2θ range of 4–50° on a Syntex/Nicolet *P*3 four-circle diffractometer at room temperature. In each case, accurate cell dimensions were obtained from least-squares refinement of 25 reflections with 2θ values between 25·10 and 30·01°. Six standard reflections were measured every 92 [crystal (I)] or 138 [crystals (II) and (III)] reflections. There was no deterioration of intensities during data collection. Data were corrected for Lorentz and polarization effects, but not absorption. The structures were determined by multisolution procedures (Main, Lessinger, Woolfson, Germain & Declercq, 1977; DeTitta, Edmonds, Langs & Hauptman, 1975) and the non-H atoms refined anisotropically by full-matrix least-squares methods on F, minimizing $\sum[w(F_o - F_c)^2]$, where $w = 1/\sigma^2(F_o)$. H-atom coordinates were located in Fourier difference maps for amiodarone (I) and benziodarone (III) and refined isotropically and were calculated for desethylamiodarone (II), and their isotropic thermal parameters derived from their attached C parameters. Scattering factors were taken from *International Tables for X-ray Crystallography* (1974) and refinements carried out using the Nonius suite of programs on VAX 11/780 and VAX 8600 computers. Tables 2–4 contain the atomic coordinates and equivalent isotropic thermal parameters for compounds (I)–(III), respectively. Tables 5–7 contain the geometric data for these compounds.*

*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 51443 (121 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

Table 1. *Crystallographic data*

	(I)	(II)	(III)
Compound	Amiodarone	Desethylamiodarone	Benziodarone
Molecular formula	$C_{25}H_{30}I_2NO_3^+.Cl^-$	$C_{23}H_{26}I_2NO_3^+.Cl^-$	$C_{17}H_{12}I_2O_3$
Formula weight	681·78	654·74	518·09
Space group	$P2_1/c$	$P2_1/c$	$P2_1/n$
a (Å)	17·124 (2)	23·867 (2)	17·564 (2)
b (Å)	17·079 (2)	10·134 (1)	8·294 (1)
c (Å)	9·162 (1)	10·287 (2)	11·587 (2)
β (°)	98·37 (2)	93·91 (2)	93·20 (2)
Z	4	4	4
V (Å^3)	2651·2	2482·5	1685·55
D_x (g cm^{-3})	1·71	1·75	2·04
Crystal size	0·05 × 0·3 × 0·5	0·2 × 0·4 × 0·4	0·1 × 0·3 × 0·3
λ (Å)	0·7107	0·7107	0·7107
μ (cm^{-1})	24·73	26·37	36·99
hkl range	−21→21, 0→21, −1→11	−21→21, 0→10, −1→14	−29→29, 0→13, −1→13
No. of reflections	5515	5916	4311
Max. Δ/σ	0·01	<0·01	0·02
R (%)	6·6	5·7	6·2
wR (%)	7·2	6·2	6·7
Estimated unit weight	3·2	2·3	3·3
$\Delta\rho_{max}$ (e Å^{-3})	1·49	1·87	1·64
$\Delta\rho_{min}$ (e Å^{-3})	−2·60	−2·40	−1·50

Results and discussion

As illustrated (Fig. 2, Table 7), the molecular conformations of amiodarone and its derivatives, as well as that of the previously reported structure of benzbromarone (Fontaine, Dideberg & Dupont, 1975) are similar. The results of these crystal structure analyses show that the C(3)–C(8)–C(1′) ketone bridge angle is 120° and the conformation of the two ring systems is twist, similar to that observed in other ketone bridge structures (Van der Heijden, Chandler & Robertson, 1975).

Even though the 2-*n*-butyl side chain in amiodarone and *N*-desethylamiodarone both fold back over the phenolic ring, the change in torsion angle around the C(2)–C(21) bond and the ±*gauche* orientation of the terminal side-chain atom, causes the *n*-butyl group to have different conformations (Fig. 3). The 2-ethyl side-chain orientations in benziodarone and benzbromarone are both similar to the desethyl analogue and point away from the phenolic ring. The 4′-ethoxy group is extended and perpendicular to the iodophenolic ring, and the amine is protonated in both amiodarone and desethylamiodarone. Again, because of the ±*gauche* orientation of the amine, the local conformation of the *N*-ethyl substituents is different. The net effect of these conformational changes is demonstrated in Fig. 3(*b*) which shows the van der Waals surface of amiodarone (dark net) not shared with that of desethylamiodarone (dashed net), and *vice versa*. As illustrated, the side chains of each molecule lie on one side of the molecular surface.

The orientation of the carbonyl oxygen and furan-ring double bond can be either *s-cis* or *s-trans*. Infrared studies of benzbromarone indicate a high degree of conjugation and suggest a preference for *s-cis* coplanar ring structure in solution. Semiempirical calculations carried out on a series of 2-substituted benzbromarone derivatives (Brasseur, Ruysschaert & Chatelain, 1986)

Table 2. *Atomic coordinates and equivalent isotropic thermal parameters* (Å²) *for amiodarone*.HCl (I) *with e.s.d.'s in parentheses*

	x	y	z	B_{eq}*
I(3')	−0·3530 (1)	−0·0675 (1)	0·1645 (1)	3·48 (1)
I(5')	−0·1252 (1)	0·0132 (1)	−0·2691 (1)	3·49 (1)
Cl(1)	0·4989 (1)	0·3686 (1)	0·1783 (2)	3·82 (4)
O(1)	−0·0247 (3)	0·2915 (3)	0·2742 (6)	3·84 (13)
C(2)	−0·0675 (4)	0·2260 (4)	0·2332 (7)	3·01 (16)
C(3)	−0·0398 (3)	0·1632 (4)	0·3152 (6)	2·51 (14)
C(3a)	0·0273 (4)	0·1915 (4)	0·4183 (7)	2·74 (15)
C(4)	0·0815 (4)	0·1585 (4)	0·5280 (7)	3·41 (17)
C(5)	0·1398 (4)	0·2073 (5)	0·6018 (9)	4·29 (21)
C(6)	0·1429 (5)	0·2866 (5)	0·5676 (11)	5·18 (25)
C(7)	0·0894 (5)	0·3198 (5)	0·4603 (9)	4·36 (21)
C(7a)	0·0331 (4)	0·2707 (4)	0·3878 (8)	3·42 (18)
C(8)	−0·0760 (4)	0·0862 (4)	0·3259 (6)	2·67 (15)
O(8)	−0·0668 (3)	0·0510 (3)	0·4404 (5)	4·00 (14)
C(1')	−0·1282 (4)	0·0516 (4)	0·1968 (6)	2·56 (14)
C(2')	−0·1975 (4)	0·0156 (4)	0·2255 (6)	2·73 (15)
C(3')	−0·2487 (3)	−0·0170 (4)	0·1092 (7)	2·67 (15)
C(4')	−0·2295 (3)	−0·0159 (3)	−0·0338 (7)	2·54 (14)
C(5')	−0·1594 (4)	0·0170 (4)	−0·0592 (7)	2·66 (15)
C(6')	−0·1082 (4)	0·0522 (4)	0·0567 (7)	2·73 (15)
C(21)	−0·1389 (4)	0·2414 (4)	0·1200 (7)	3·26 (17)
C(22)	−0·2120 (4)	0·2575 (5)	0·1900 (8)	3·82 (19)
C(23)	−0·2860 (5)	0·2683 (5)	0·0775 (10)	4·98 (24)
C(24)	−0·3146 (5)	0·1931 (6)	0·0016 (10)	5·11 (25)
O(4'1)	−0·2790 (3)	−0·0519 (3)	−0·1474 (5)	2·90 (11)
C(4'2)	−0·3362 (4)	0·0003 (4)	−0·2251 (8)	3·36 (18)
C(4'3)	−0·3710 (4)	−0·0370 (4)	−0·3708 (8)	3·49 (18)
N(4'4)	−0·4186 (3)	−0·1086 (3)	−0·3578 (6)	3·33 (14)
C(4'5)	−0·4841 (5)	−0·0960 (5)	−0·2678 (10)	4·65 (23)
C(4'6)	−0·5519 (6)	−0·1510 (6)	−0·3007 (12)	6·58 (32)
C(4'7)	−0·3727 (5)	−0·1818 (4)	−0·3145 (9)	4·20 (20)
C(4'8)	−0·3135 (5)	−0·1990 (5)	−0·4118 (11)	5·66 (27)

* $B_{eq} = \frac{4}{3}\sum_i\sum_j\beta_{ij}(a_i a_j)$.

Table 3. *Atomic coordinates and equivalent isotropic thermal parameters* (Å²) *for desethylamiodarone*.HCl (II) *with e.s.d.'s in parentheses*

	x	y	z	B_{eq}*
I(3')	0·8057 (1)	0·5277 (1)	0·2797 (1)	4·53 (1)
I(5')	0·8394 (1)	1·1023 (1)	0·4148 (1)	4·21 (1)
Cl(1)	0·0617 (1)	0·8257 (1)	0·9927 (1)	4·51 (3)
O(1)	0·5635 (1)	1·1209 (3)	0·4579 (3)	4·14 (8)
C(2)	0·6023 (2)	1·0300 (4)	0·4228 (4)	3·41 (10)
C(3)	0·6144 (2)	0·9414 (4)	0·5205 (4)	3·14 (9)
C(3a)	0·5816 (2)	0·9802 (4)	0·6270 (4)	3·22 (10)
C(4)	0·5776 (2)	0·9377 (5)	0·7565 (5)	4·04 (12)
C(5)	0·5427 (2)	1·0107 (6)	0·8326 (5)	5·10 (15)
C(6)	0·5136 (2)	1·1203 (5)	0·7860 (6)	5·15 (15)
C(7)	0·5166 (2)	1·1634 (5)	0·6599 (6)	4·84 (14)
C(7a)	0·5518 (2)	1·0915 (4)	0·5835 (5)	3·79 (11)
C(21)	0·6195 (2)	1·0467 (5)	0·2862 (4)	4·22 (12)
C(22)	0·6527 (2)	1·1760 (6)	0·2691 (5)	4·88 (14)
C(23)	0·6693 (3)	1·1985 (8)	0·1296 (6)	6·59 (20)
C(24)	0·7149 (4)	1·1147 (9)	0·0922 (8)	8·55 (29)
C(8)	0·6493 (2)	0·8229 (4)	0·5186 (5)	3·63 (11)
O(8)	0·6349 (2)	0·7224 (4)	0·5729 (5)	6·28 (13)
C(1')	0·7027 (2)	0·8239 (4)	0·4510 (4)	3·16 (9)
C(2')	0·7224 (2)	0·7065 (4)	0·3997 (4)	3·19 (9)
C(3')	0·7732 (2)	0·7058 (4)	0·3443 (4)	2·99 (9)
C(4')	0·8057 (2)	0·8202 (4)	0·3391 (4)	3·14 (9)
C(5')	0·7870 (2)	0·9371 (4)	0·3947 (4)	3·14 (9)
C(6')	0·7355 (2)	0·9384 (4)	0·4492 (4)	3·29 (10)
O(4'1)	0·8569 (1)	0·8157 (3)	0·2867 (3)	3·48 (7)
C(4'2)	0·8552 (2)	0·8553 (5)	0·1508 (4)	3·95 (11)
C(4'3)	0·9092 (2)	0·8178 (5)	0·0968 (4)	3·84 (11)
N(4'4)	0·9576 (1)	0·9041 (4)	0·1397 (4)	3·53 (9)
C(4'5)	0·9768 (2)	0·8967 (5)	0·2809 (5)	4·41 (13)
C(4'6)	1·0232 (3)	0·9925 (7)	0·3121 (7)	6·58 (20)

* $B_{eq} = \frac{4}{3}\sum_i\sum_j\beta_{ij}(a_i a_j)$.

showed that the two most probable structures, present in equal populations, correspond to the *s-cis* and *s-trans* conformations. The conformation of unsubstituted

Table 4. *Atomic coordinates and equivalent isotropic thermal parameters* (Å²) *for benziodarone* (III) *with e.s.d.'s in parentheses*

	x	y	z	B_{eq}*
I(3')	0·8580 (1)	0·4089 (1)	0·8236 (1)	4·33 (1)
I(5')	0·6224 (1)	0·3289 (1)	0·4258 (1)	4·11 (1)
O(1)	0·3705 (2)	0·3711 (5)	0·8299 (4)	3·16 (9)
C(2)	0·4476 (3)	0·3672 (6)	0·8252 (5)	2·68 (11)
C(3)	0·4789 (2)	0·5144 (6)	0·8482 (4)	2·27 (10)
C(3a)	0·4157 (3)	0·6213 (6)	0·8734 (4)	2·56 (10)
C(4)	0·4082 (4)	0·7828 (7)	0·9016 (5)	3·53 (14)
C(5)	0·3347 (4)	0·8418 (9)	0·9115 (7)	4·73 (19)
C(6)	0·2709 (4)	0·7430 (10)	0·8937 (6)	4·85 (19)
C(7)	0·2774 (3)	0·5842 (9)	0·8662 (6)	3·98 (15)
C(7a)	0·3509 (3)	0·5262 (7)	0·8571 (4)	2·88 (11)
C(21)	0·4786 (3)	0·2040 (7)	0·8036 (6)	3·67 (15)
C(22)	0·4494 (5)	0·1337 (11)	0·6889 (10)	5·96 (26)
C(8)	0·5588 (3)	0·5646 (6)	0·8537 (4)	2·30 (10)
O(8)	0·5796 (2)	0·6806 (4)	0·9139 (3)	3·06 (9)
C(1')	0·6147 (3)	0·4835 (6)	0·7819 (4)	2·35 (10)
C(2')	0·6899 (3)	0·4696 (6)	0·8246 (4)	2·58 (10)
C(3')	0·7458 (3)	0·4132 (6)	0·7540 (5)	2·64 (10)
C(4')	0·7276 (3)	0·3707 (6)	0·6400 (4)	2·44 (10)
C(5')	0·6521 (3)	0·3850 (6)	0·5978 (4)	2·56 (10)
C(6')	0·5960 (3)	0·4397 (6)	0·6683 (4)	2·41 (10)
O(4'1)	0·7785 (2)	0·3194 (5)	0·5646 (3)	3·37 (9)

* $B_{eq} = \frac{4}{3}\sum_i\sum_j\beta_{ij}(a_i a_j)$.

Table 5. *Bond distances* (Å) *for amiodarone* (I), *desethylamiodarone* (II) *and benziodarone* (III)

	(I)	(II)	(III)
C(3)–C(2)	1·356 (9)	1·363 (6)	1·360 (7)
C(3)–C(3a)	1·460 (8)	1·443 (6)	1·463 (7)
C(3)–C(8)	1·462 (9)	1·463 (6)	1·461 (6)
C(2)–O(1)	1·361 (8)	1·371 (5)	1·359 (6)
C(2)–C(21)	1·506 (9)	1·501 (7)	1·485 (8)
O(1)–C(7a)	1·375 (8)	1·374 (6)	1·373 (7)
C(7a)–C(3a)	1·387 (10)	1·391 (6)	1·389 (7)
C(7a)–C(7)	1·374 (10)	1·394 (7)	1·388 (8)
C(7)–C(6)	1·365 (12)	1·375 (9)	1·361 (11)
C(6)–C(5)	1·394 (13)	1·379 (8)	1·394 (10)
C(5)–C(4)	1·396 (10)	1·393 (8)	1·393 (10)
C(4)–C(3a)	1·385 (9)	1·410 (7)	1·387 (8)
C(8)–O(8)	1·200 (8)	1·222 (6)	1·232 (6)
C(8)–C(1')	1·497 (8)	1·492 (6)	1·484 (7)
C(1')–C(2')	1·396 (9)	1·396 (6)	1·390 (6)
C(1')–C(6')	1·375 (9)	1·401 (6)	1·387 (7)
C(2')–C(3')	1·393 (8)	1·375 (6)	1·393 (7)
C(3')–C(4')	1·396 (9)	1·398 (6)	1·387 (7)
C(3')–I(3')	2·111 (6)	2·091 (4)	2·087 (5)
C(4')–C(5')	1·409 (9)	1·402 (6)	1·393 (7)
C(4')–O(4'1)	1·387 (7)	1·369 (5)	1·353 (6)
C(5')–C(6')	1·409 (8)	1·385 (6)	1·390 (7)
C(5')–I(5')	2·091 (7)	2·092 (4)	2·085 (5)
O(4'1)–C(4'2)	1·435 (8)	1·452 (5)	—
C(4'2)–C(4'3)	1·520 (10)	1·487 (7)	—
C(4'3)–N(4'4)	1·484 (9)	1·490 (6)	—
N(4'4)–C(4'5)	1·500 (11)	1·496 (6)	—
N(4'4)–C(4'7)	1·500 (9)	—	—
C(4'5)–C(4'6)	1·491 (13)	1·491 (9)	—
C(4'7)–C(4'8)	1·473 (13)	—	—
C(21)–C(22)	1·513 (11)	1·547 (8)	1·514 (13)
C(22)–C(23)	1·524 (10)	1·532 (9)	—
C(23)–C(24)	1·508 (13)	1·452 (12)	—

benzofurans is coplanar. The observation in this study of the approximately equal torsion angles and equivalent bond lengths about the ketone bridge (Table 7), and the *s-trans* conformation of the ketone, shows that there is little conjugation between the ketone bridge and either the benzofuran or phenolic rings of these antiarrhythmic agents.

Structural data for diphenyl ketone bridge systems show that a twist conformation is preferred and that the

Table 6. *Bond angles* (°) *for amiodarone* (I), *desethylamiodarone* (II) *and benziodarone* (III)

	(I)	(II)	(III)
C(2)–C(3)–C(3a)	106·0 (4)	106·4 (3)	106·3 (3)
C(2)–C(3)–C(8)	129·2 (5)	128·5 (3)	129·9 (4)
C(8)–C(3)–C(3a)	123·7 (5)	124·9 (3)	123·8 (4)
C(3)–C(2)–O(1)	111·5 (4)	111·2 (3)	111·3 (3)
C(3)–C(2)–C(21)	134·6 (5)	135·0 (3)	134·7 (4)
O(1)–C(2)–C(21)	113·4 (5)	113·8 (3)	113·8 (4)
C(2)–O(1)–C(7a)	107·2 (4)	106·6 (3)	107·1 (3)
O(1)–C(7a)–C(3a)	109·9 (5)	110·3 (3)	110·4 (4)
O(1)–C(7a)–C(7)	125·8 (5)	125·9 (4)	126·1 (4)
C(7)–C(7a)–C(3a)	124·3 (5)	123·8 (4)	123·5 (4)
C(7a)–C(7)–C(6)	116·4 (6)	116·0 (4)	116·4 (5)
C(7)–C(6)–C(5)	121·4 (6)	121·7 (4)	121·8 (5)
C(6)–C(5)–C(4)	121·3 (6)	122·6 (4)	121·5 (5)
C(5)–C(4)–C(3a)	117·7 (5)	116·8 (4)	117·4 (5)
C(4)–C(3a)–C(3)	135·8 (5)	135·2 (3)	135·7 (4)
C(4)–C(3a)–C(7a)	118·8 (5)	119·1 (3)	119·5 (4)
C(3)–C(3a)–C(7a)	105·4 (5)	105·6 (3)	104·7 (4)
C(3)–C(8)–C(1′)	120·8 (5)	120·4 (3)	120·7 (3)
C(3)–C(8)–O(8)	120·5 (4)	120·0 (3)	120·1 (3)
C(1′)–C(8)–O(8)	118·6 (4)	119·6 (3)	119·1 (3)
C(8)–C(1′)–C(2′)	122·3 (5)	119·4 (3)	119·0 (4)
C(8)–C(1′)–C(6′)	116·8 (5)	120·5 (3)	121·5 (4)
C(2′)–C(1′)–C(6′)	120·8 (5)	119·8 (3)	119·1 (4)
C(1′)–C(2′)–C(3′)	119·3 (5)	119·4 (3)	120·4 (4)
C(2′)–C(3′)–C(4′)	120·3 (5)	121·2 (3)	120·8 (4)
C(2′)–C(3′)–I(3′)	120·7 (4)	119·6 (3)	117·3 (4)
C(4′)–C(3′)–I(3′)	118·7 (4)	119·0 (3)	121·8 (4)
C(3′)–C(4′)–C(5′)	119·6 (5)	119·5 (3)	118·5 (4)
C(3′)–C(4′)–O(4′1)	119·8 (4)	120·0 (3)	124·7 (4)
C(5′)–C(4′)–O(4′1)	120·4 (4)	120·4 (3)	116·8 (3)
C(4′)–C(5′)–C(6′)	120·6 (5)	119·3 (3)	120·9 (4)
C(4′)–C(5′)–I(5′)	116·1 (4)	121·2 (3)	119·9 (4)
C(6′)–C(5′)–I(5′)	123·6 (4)	119·0 (3)	119·2 (4)
C(5′)–C(6′)–C(1′)	119·3 (5)	120·7 (3)	120·4 (4)
C(4′)–O(4′1)–C(4′2)	113·2 (4)	113·9 (3)	—
O(4′1)–C(4′2)–C(4′3)	109·1 (5)	108·8 (3)	—
C(4′2)–C(4′3)–N(4′4)	115·1 (5)	114·4 (3)	—
C(4′3)–N(4′4)–C(4′5)	112·9 (5)	116·0 (3)	—
C(4′3)–N(4′4)–C(4′7)	115·8 (5)	—	—
C(4′5)–N(4′4)–C(4′7)	112·2 (5)	—	—
N(4′4)–C(4′5)–C(4′6)	115·0 (6)	110·5 (4)	—
N(4′4)–C(4′7)–C(4′8)	112·7 (6)	—	—
C(2)–C(21)–C(22)	112·3 (5)	112·2 (4)	112·9 (5)
C(21)–C(22)–C(23)	113·1 (6)	113·6 (4)	—
C(22)–C(23)–C(24)	113·0 (6)	114·1 (5)	—

Table 7. *Selected torsion angles* (°) *for amiodarone* (I), *desethylamiodarone* (II) *and benziodarone* (III)

	(I)	(II)	(III)
C(2)–C(3)–C(8)–C(1′)	31·3 (10)	39·8 (7)	30·0 (7)
C(3)–C(8)–C(1′)–C(6′)	45·6 (9)	33·9 (6)	40·5 (7)
C(8)–C(3)–C(2)–C(21)	−3·9 (9)	−2·7 (6)	4·1 (7)
C(2′)–C(1′)–C(8)–O(8)	40·5 (9)	28·3 (6)	35·9 (7)
O(8)–C(8)–C(3)–C(2)	−145·8 (7)	−140·4 (5)	−153·7 (5)
C(3)–C(2)–C(21)–C(22)	80·0 (10)	−116·3 (5)	−123·1 (7)
C(2)–C(21)–C(22)–C(23)	−176·5 (6)	−178·1 (5)	—
C(21)–C(22)–C(23)–C(24)	71·4 (9)	−74·0 (7)	—
C(3′)–C(4′)–O(4′1)–C(4′2)	92·9 (7)	87·5 (4)	—
C(4′)–O(4′1)–C(4′2)–C(4′3)	164·0 (5)	−167·2 (4)	—
O(4′1)–C(4′2)–C(4′3)–N(4′4)	66·1 (7)	−74·9 (5)	—
C(4′2)–C(4′3)–N(4′4)–C(4′5)	54·9 (8)	67·4 (5)	—
C(4′2)–C(4′3)–N(4′4)–C(4′7)	−76·5 (8)	—	—
C(4′3)–N(4′4)–C(4′5)–C(4′6)	155·6 (7)	−177·1 (4)	—
C(4′3)–N(4′4)–C(4′7)–C(4′8)	−54·1 (9)	—	—
C(4′6)–C(4′5)–N(4′4)–C(4′7)	−71·3 (7)	—	—
C(4′8)–C(4′7)–N(4′4)–C(4′5)	174·2 (9)	—	—

bridge bond lengths are equal. However, solution NMR data for di-*ortho*-substituted structures indicate a preference for a skewed conformation (Van der Heijden, Chandler & Robertson, 1975; Van der Heijden, Griffith, Chandler & Robertson, 1975). The structure of an *ortho*-diiodo ketone bridge thyroid-hormone analogue (Cody, Cheung & Jorgensen, 1982), has a skewed conformation and unequal bridge bond lengths; the bond to the iodo ring is longer than the phenolic bridge bond (1·52/1·46 Å, respectively), suggesting conjugation between the phenolic ring and the ketone. The bridge bond lengths are also equal (1·52 Å) for a skewed *ortho*-diiodo hydroxy methylene bridge hormone analogue (Cody, 1981*a*). These data suggest that the *ortho*-iodo substituents force a skewed conformation rather than the preferable twist conformation. The average bridge bond lengths in these phenyl–benzofuran amiodarone structures are also shorter than those observed in diphenyl ring systems (Table 7).

The analysis of the crystal packing in these structures shows that in amiodarone there is a short I···O contact distance (3·04 Å) as observed in many of the thyroid-hormone structures (Cody, 1980) and the protonated amine forms a hydrogen bond with the chloride ion (3·08 Å). In the structure of desethyl-

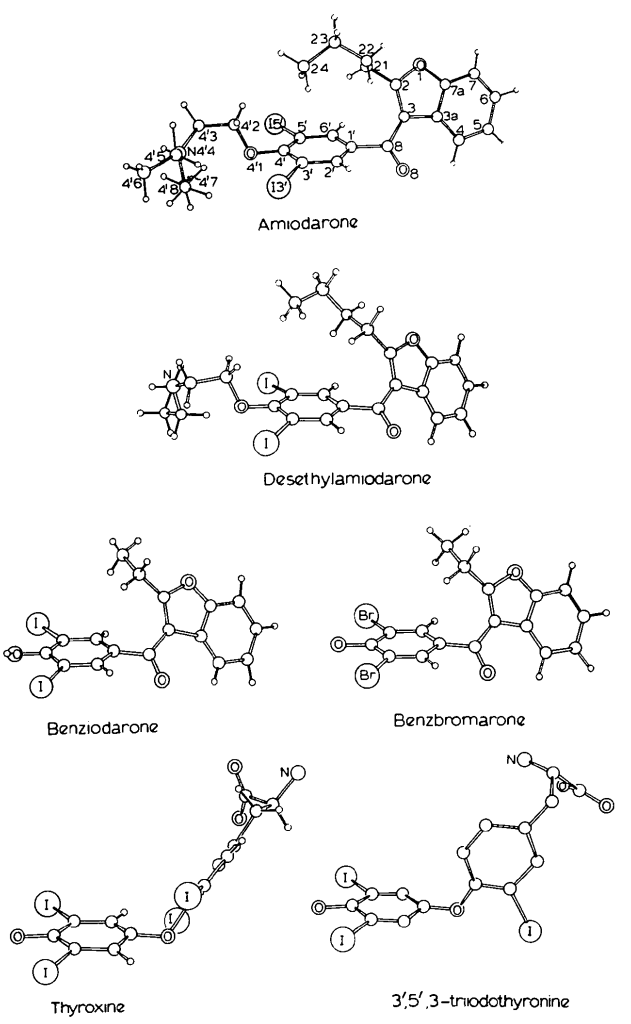


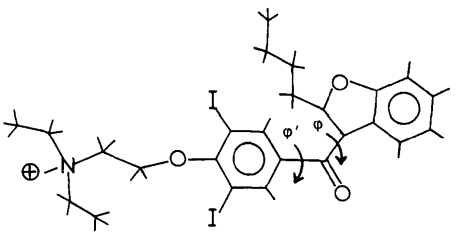
Fig. 2. Molecular conformation of amiodarone, desethylamiodarone, benziodarone, benzbromarone, thyroxine and 3′,5′,3-triiodothyronine (rT_3).

amiodarone, there is a short I···I (4·10 Å) and a short I···Cl (3·36 Å) contact, but no short I···O contacts. The chloride ion also forms a hydrogen bond to the amine (3·10 Å). In benziodarone there is hydrogen bonding between the phenolic hydroxyl and the bridging ketone (2·74 Å), but no short iodine contacts.

In order to understand how these antiarrhythmic agents might act as inhibitors of thyroid-hormone-responsive enzymes, computer graphics modeling studies were also carried out to compare their molecular structures (Table 8). Because the bulky *ortho*-tyrosyl iodines in T_4 restrict its conformational flexibility, only the skewed conformation has been observed (Fig. 2) (Cody, 1981*b*). On the other hand, rT_3, which has only a single tyrosyl substituent, has more flexibility, and has been observed in an antiskewed conformation (Fig. 2) (Okabe, Fujiwara, Yamagata & Tomita, 1982). These are the only conformations observed for thyroid-hormone structures and are in contrast to the twist conformations found for these amiodarone analogues.

In seeking the best structural homology between these classes of compounds, the iodophenolic ring of the amiodarone can be matched with either the tyrosyl ring or the phenolic ring of the skewed conformation of thyroxine or the antiskewed conformation of rT_3. After comparing several orientations of these molecules, the best fit with thyroxine is made by superposition of the hormone phenolic ring on that of the antiarrhythmic agent. As illustrated, when the twist conformation of amiodarone is matched to either skewed thyroxine (Fig.

Table 8. *Conformation comparison*



Structure	φ (°)	φ' (°)	Conformation
Thyroxine	−113	33	Skewed
RT_3	8	86	Antiskewed
Amiodarone	31	46	Twist
Desethylamiodarone	40	34	Twist
Benziodarone	30	41	Twist
Benzbromarone	31	41	Twist

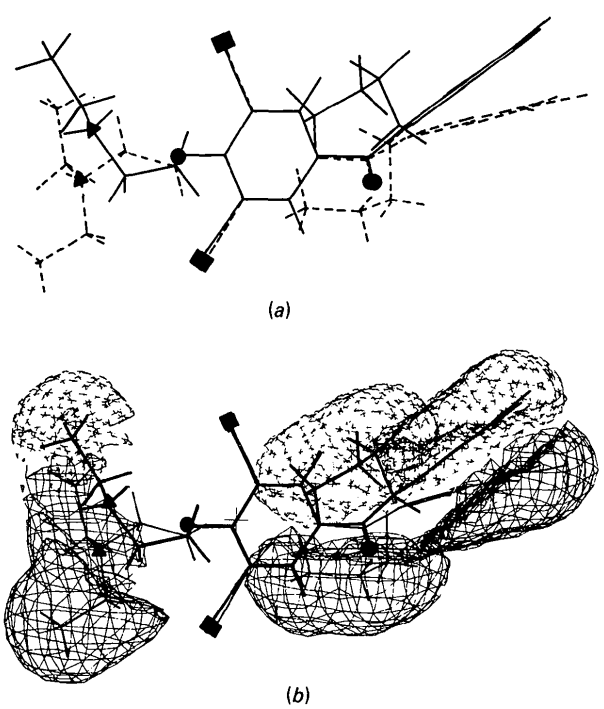


Fig. 3. (*a*) Superposition of amiodarone (dashed lines) and *N*-desethylamiodarone (solid lines) illustrating the ±*gauche* conformation of the 2-butyl and *N*-ethyl side chains. (*b*) Comparison of amiodarone and *N*-desethylamiodarone as in (*a*) showing the van der Waals surface of amiodarone (dark net) not shared by the structure of *N*-desethylamiodarone (dashed net), and *vice versa*.

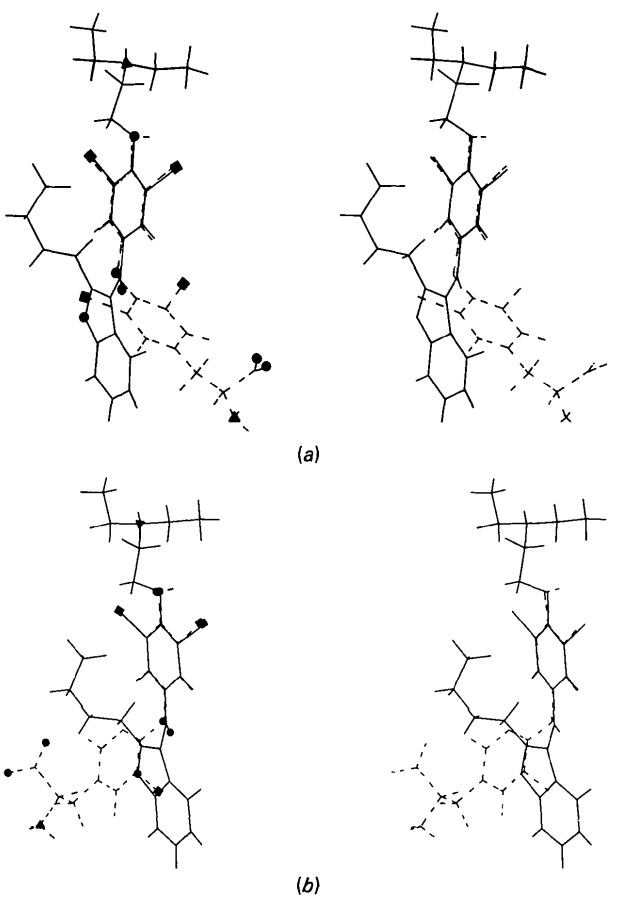


Fig. 4. (*a*) Stereosuperposition of twist amiodarone (solid line) and skewed T_4 (dashed line), with iodophenolic rings matched. (*b*) Stereosuperposition of twist amiodarone (solid line) and antiskewed rT_3 (dashed line), with iodophenolic rings matched. Squares are I, circles O and triangles N.

4*a*) or antiskewed rT_3 (Fig. 4*b*), the benzofuran ring does not occupy much of the tyrosyl conformational space. However, if the amiodarone bridge bonds are rotated to fit the skewed conformation of T_4 (Fig. 5*b*), which is energetically accessible (Brasseur *et al.*, 1986; Cody, 1980), there is good homology between the ring systems and the 2-butyl group points away from the iodophenyl ring. A similar comparison with an antiskewed conformation (Fig. 5*b*) shows that the 2-butyl side chain maintains the same relative orientation; folded back over the iodophenolic ring. These studies would suggest that amiodarone and its derivatives can also adopt the thyroid-hormone conformations.

Thus, these structural studies have described the molecular conformation of three members of the antiarrhythmic cardioactive drug amiodarone and show that their conformations are similar and that the *N*-ethyl and 2-alkyl side chains are flexible. Although the mechanism of the antiarrhythmic effect of amiodarone has not yet been established, it has been postulated that either by interfering with myocardial 5′-deiodinase or blocking nuclear binding in the heart, amiodarone may induce a local antithyroid (and antiarryhthmic) state. In the case of the Ca^{2+}-ATPase data, the thyromimetic actions of benziodarone may result from its structural homology with thyroxine while the inhibitory action of amiodarone in this assay may be due to the steric hinderance of the *N*-diethylethoxy substituent. However, these studies do not explain the lack of effect by the desethyl metabolite.

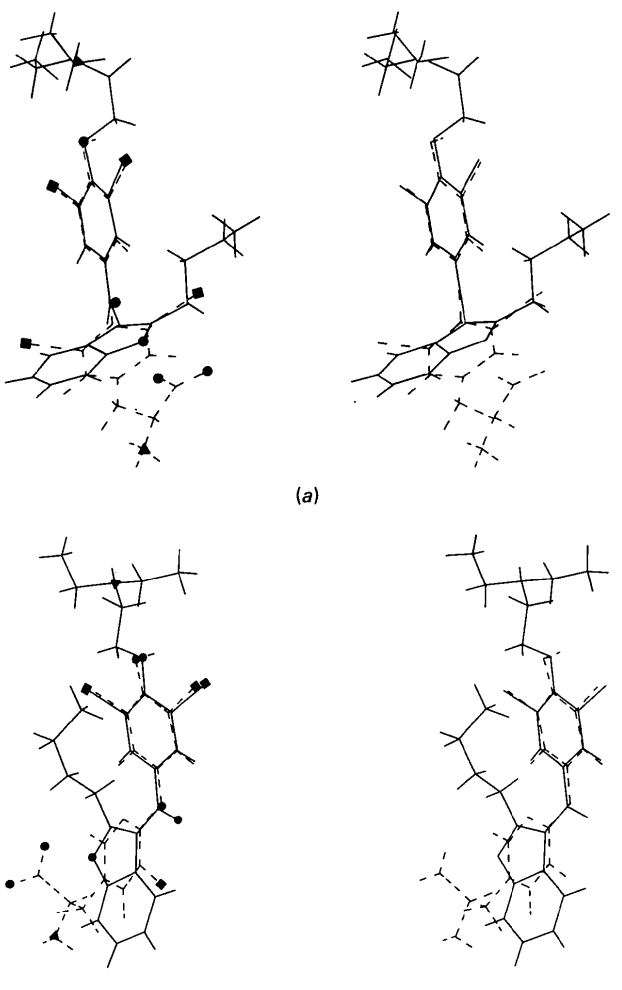


Fig. 5. (*a*) Stereosuperposition of amiodarone, modeled in a skewed conformation (solid line), and T_4 (dashed line), with iodophenolic rings matched. (*b*) Stereosuperposition of amiodarone, modeled in an antiskewed conformation (solid line), and rT_3 (dashed line), with iodophenolic rings matched. Squares are I, circles O and triangles N.

The authors thank Dr Walter Pangborn for collection of diffraction data. The MMS-X computer graphics display system, designed and fabricated by the Computer Systems Laboratory, Washington University, St Louis, was used for the conformational comparison. This system was made possible by a grant (RR-00396) from the Division of Research Resources, NIH, under their Biotechnology Resource Program.

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Structural Influence of the *Ortho-Peri*-Condensed Cycloalkane Rings on the Conformation of 2-(Hydroxyalkyloxy)indanone Cyclization Products*

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(*Received* 27 *July* 1988; *accepted* 26 *October* 1988)

Abstract

Benzocyclobutenols, obtained by arynic condensation of 1,2-diketone monoketal enolates, can transpose to give alkoxyindanones that undergo cyclization to 1,4-dioxa heterocyclic derivatives. The X-ray crystal structure analysis of these products, carried out using Cu $K\alpha_1$ radiation ($\lambda = 1{\cdot}540562$ Å) at room temperature [293 (2) K], gave the following data: 2,3,4a,-9b-tetrahydro-4a,5-butano-5*H*-indeno[1,2][1,4]dioxin (I,3), $C_{15}H_{18}O_2$, $M_r = 230{\cdot}3$, monoclinic, $P2_1/c$, $a = 13{\cdot}033$ (8), $b = 10{\cdot}293$ (5), $c = 9{\cdot}267$ (4) Å, $\beta = 90{\cdot}94$ (2)°, $V = 1243$ (1) Å^3, $Z = 4$, $D_x = 1{\cdot}231$ Mg m^{-3}, $\mu = 0{\cdot}598$ mm^{-1}, $F(000) = 496$, $R = 0{\cdot}0493$ for 671 observed reflections; 3,3-dimethyl-3,-4,5a,10b-tetrahydro-5a,6-butano-2*H*,6*H*-indeno[1,2-*b*]-[1,4]dioxepin (III,3), $C_{18}H_{24}O_2$, $M_r = 272{\cdot}4$, monoclinic, $C2/c$, $a = 28{\cdot}683$ (8), $b = 6{\cdot}446$ (1), $c = 18{\cdot}451$ (8) Å, $\beta = 116{\cdot}19$ (2)°, $V = 3061$ (2) Å^3, $Z = 8$, $D_x = 1{\cdot}182$ Mg m^{-3}, $\mu = 0{\cdot}553$ mm^{-1}, $F(000) = 1184$, $R = 0{\cdot}0712$ for 2544 observed reflections; 2,3,4a,9b-tetrahydro-4a,5-pentano-5*H*-indeno[1,2]-[1,4]dioxin (I,4), $C_{16}H_{20}O_2$, $M_r = 244{\cdot}3$, monoclinic, $P2_1/c$, $a = 7{\cdot}716$ (1), $b = 17{\cdot}474$ (4), $c = 10{\cdot}362$ (1) Å, $\beta = 106{\cdot}44$ (1)°, $V = 1322$ (4) Å^3, $Z = 4$, $D_x = 1{\cdot}227$ Mg m^{-3}, $\mu = 0{\cdot}588$ mm^{-1}, $F(000) = 528$, $R = 0{\cdot}0617$ for 1348 observed reflections; 3,4,5a,10b-tetrahydro-5a,6-pentano-2*H*,6*H*-indeno[1,2-*b*][1,4]dioxepin (II,4), $C_{17}H_{22}O_2$, $M_r = 258{\cdot}4$, triclinic, $P\bar{1}$, $a = 9{\cdot}766$ (2), $b = 14{\cdot}622$ (7), $c = 10{\cdot}404$ (4) Å, $\alpha = 105{\cdot}15$ (2), $\beta = 96{\cdot}95$ (8), $\gamma = 101{\cdot}57$ (1)°, $V = 1381$ (1) Å^3, $Z = 4$, $D_x = 1{\cdot}243$ Mg m^{-3}, $\mu = 0{\cdot}588$ mm^{-1}, $F(000) = 560$, $R = 0{\cdot}0459$ for 4032 observed reflections; 2,3,4a,9b-tetrahydro-4a,5-hexano-5*H*-indeno[1,2][1,4]dioxin (I,5), $C_{17}H_{22}O_2$, $M_r = 258{\cdot}4$, $P2_1/n$, $a = 11{\cdot}012$ (1), $b = 6{\cdot}989$ (1), $c = 37{\cdot}644$ (6) Å, $\beta = 92{\cdot}44$ (1)°, $V = 2894$ (7) Å^3, $Z = 8$, $D_x = 1{\cdot}186$ Mg m^{-3}, $\mu = 0{\cdot}561$ mm^{-1}, $F(000) = 1120$, $R = 0{\cdot}0300$ for 3188 observed reflections; 2.3,4a,9b-tetrahydro-4a,5-octano-5*H*-indeno[1,2][1,4]dioxin (I,7), $C_{19}H_{26}O_2$, $M_r = 286{\cdot}4$, orthorhombic, *Pbca*, $a = 19{\cdot}721$ (4), $b = 18{\cdot}801$ (4), $c = 8{\cdot}542$ (2) Å, $V = 3167$ (1) Å^3, $Z = 8$, $D_x = 1{\cdot}201$ Mg m^{-3}, $\mu = 0{\cdot}556$ mm^{-1}, $F(000) = 1248$, $R = 0{\cdot}0498$, for 1789 observed reflections; 2,3,4a,9b-tetrahydro-4a,5-nonano-5*H*-indeno[1,2][1,4]dioxin (I,8), $C_{20}H_{28}O_2$, $M_r = 300{\cdot}4$, triclinic, $P\bar{1}$, $a = 5{\cdot}752$ (1), $b = 13{\cdot}238$ (5), $c = 11{\cdot}724$ (3) Å, $\alpha = 108{\cdot}48$ (3), $\beta = 99{\cdot}05$ (4), $\gamma = 89{\cdot}40$ (1)°, $V = 835{\cdot}4$ (4) Å^3, $Z = 2$, $D_x = 1{\cdot}194$ Mg m^{-3}, $\mu = 0{\cdot}548$ mm^{-1}, $F(000) = 328$, $R = 0{\cdot}0478$ for 2462 observed reflections. The stereochemistry at the junctions of the dioxa and polymethylene rings with the pentaatomic indan ring is influenced by the number of C atoms of the alkane ring. Comparison of the conformations of the puckered rings shows that, in the case of the fused 11-membered cycloalkane, significant conformational changes are present. The endocyclic angles in the benzo ring are deformed in a systematic way which was found to be peculiar to the fused indan system.

* An account of this research was communicated at the XIth European Crystallographic Meeting, Vienna, 28 August–2 September 1988.

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0108-7681/89/020178-12$03.00