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Structure of 3,5,3′-Triiodothyronamine* Bis(salicylato)borate (1:1) Salt, T_3AM.BSA, $C_{14}H_{13}I_3NO_2^+.C_{14}H_8BO_6^-$

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(*Received* 24 *November* 1983; *accepted* 24 *February* 1984)

Abstract. $M_r = 891{\cdot}0$, monoclinic, $P2_1/c$, $a = 14{\cdot}886\ (4)$, $b = 14{\cdot}514\ (4)$, $c = 15{\cdot}870\ (4)$ Å, $\beta = 108{\cdot}92\ (2)°$, $V = 3243{\cdot}4\ (3)$ Å^3, $Z = 4$, $D_x = 1{\cdot}82$ g cm^{-3}, $\lambda(\text{Mo } K\alpha_1) = 0{\cdot}71069$ Å, $\mu = 29{\cdot}7$ cm^{-1}, $F(000) = 1696$, $T = 298$ K. Final $R = 0{\cdot}064$ for 8316 unique significant reflections. This is the first structural report of both molecules. T_3AM is *cisoid*, the 3′-iodine proximal, the protonated side chain extended, and the diphenyl ether conformation twist-skewed, an observation previously found only for the parent thyroid hormone containing an amino-acid side chain. BSA has tetrahedral B coordination with the planes of each salicylate moiety bisecting one another.

Introduction. It has been shown that the activity of the thyroid hormones (tetra-, triiodothyronines: T_4, T_3) and their metabolites depends primarily on specific structural requirements for optimal binding to their serum and nuclear-binding proteins. Thyroid-hormone conformational preferences have been delineated from analogue structural studies (Cody, 1980, 1981) in order to define the contribution of each hormone substituent to its overall activity. Decarboxylation of the thyronine amino acid to a thyronamine is one analogue type that has had little study.

Recent studies have shown that 3,5,3′-triiodothyronamine (T_3AM), the decarboxylation product of the active hormone T_3, has no thyromimetic activity at the nuclear receptor level, but does show adrenergic and dopaminergic effects (Meyer & Hesch, 1982, 1983). These data show that T_3AM specifically inhibits β-adrenergic receptor binding in turkey erythrocytes and α-adrenergic receptor binding in human platelets. These effects are not observed for the thyroid hormones themselves.

* Systematic name: 4-(4-hydroxy-3-iodophenoxy)-3,5-diiodophenethylamine.

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Table 1. *Atomic coordinates* ($\times 10^4$) *and equivalent isotropic thermal parameters* ($\times 10$) *with e.s.d.'s in parentheses*

	x	y	z	B_{eq}*(Å^2)
Molecule (I)				
I(3)	5028 (1)	1772 (1)	2586 (1)	50·0 (1)
I(5)	7382 (1)	−1691 (1)	3558 (1)	56·2 (1)
I(3′)	4440 (1)	−1438 (1)	−280 (1)	59·4 (1)
C(1)	7934 (3)	1085 (3)	2819 (3)	34 (1)
C(2)	7078 (4)	1531 (3)	2704 (3)	37 (1)
C(3)	6312 (3)	1055 (4)	2796 (3)	35 (1)
C(4)	6374 (3)	135 (3)	3034 (3)	31 (1)
C(5)	7234 (3)	−312 (3)	3159 (3)	34 (1)
C(6)	8006 (3)	153 (3)	3049 (3)	36 (1)
O(4)	5631 (2)	−317 (2)	3176 (2)	36 (1)
C(1′)	4888 (3)	−599 (3)	2434 (3)	30 (1)
C(2′)	5021 (3)	−797 (3)	1630 (3)	33 (1)
C(3′)	4243 (3)	−1098 (3)	924 (3)	34 (1)
C(4′)	3367 (3)	−1211 (4)	1025 (3)	38 (1)
C(5′)	3257 (3)	−1001 (4)	1841 (3)	37 (1)
C(6′)	4008 (3)	−700 (3)	2540 (3)	34 (1)
O(4′)	2634 (3)	−1534 (3)	321 (3)	55 (1)
C(7)	8751 (4)	1588 (4)	2668 (3)	41 (2)
C(8)	8700 (4)	1508 (3)	1707 (3)	37 (1)
N(8)	9469 (3)	2067 (3)	1528 (3)	37 (1)
Molecule (II)				
C(1)	−1249 (4)	−1081 (4)	−281 (4)	44 (2)
C(2)	−2215 (4)	−1078 (4)	−433 (4)	54 (2)
C(3)	−2530 (4)	−1140 (5)	282 (5)	63 (2)
C(4)	−1921 (4)	−1189 (5)	1151 (5)	58 (2)
O(5)	−349 (2)	−1148 (3)	2166 (2)	41 (1)
B(6)	583 (4)	−796 (4)	2307 (4)	34 (2)
O(7)	963 (2)	−1065 (2)	1586 (2)	36 (1)
C(8)	405 (3)	−1172 (3)	757 (3)	35 (1)
C(9)	−618 (3)	−1115 (3)	592 (3)	32 (1)
C(10)	−951 (3)	−1156 (3)	1316 (4)	37 (2)
O(11)	1205 (3)	−1162 (2)	3147 (2)	41 (1)
C(12)	2706 (4)	−1123 (4)	4284 (4)	49 (2)
C(13)	3478 (4)	−623 (5)	4789 (4)	52 (2)
C(14)	3569 (4)	298 (5)	4641 (4)	54 (2)
C(15)	2864 (4)	752 (4)	3980 (4)	47 (2)
C(16)	1285 (4)	743 (4)	2806 (4)	40 (2)
O(17)	560 (2)	228 (2)	2320 (2)	38 (1)
C(18)	2065 (3)	260 (4)	3461 (3)	35 (1)
C(19)	1991 (4)	−670 (4)	3619 (3)	38 (1)
O(20)	1264 (3)	1568 (2)	2692 (3)	57 (1)
O(21)	770 (3)	−1331 (3)	182 (2)	52 (1)

* $B_{eq} = \frac{4}{3}\sum_i\sum_j\beta_{ij}(\mathbf{a}_i.\mathbf{a}_j)$ (Hamilton, 1959).

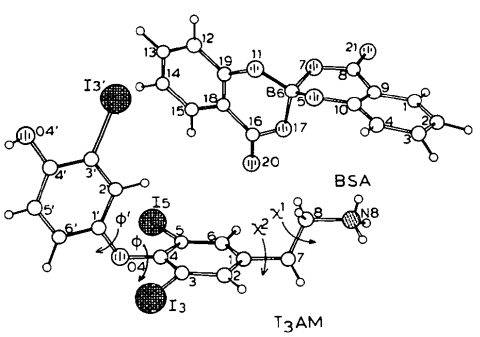

Fig. 1. Molecular conformation and numbering scheme for 3,5,3′-triiodothyronamine bis(salicylato)borate (1:1) salt. The torsion angles in T_3AM are: φ [C(5)–C(4)–O(4)–C(1′)] −104·3 (5); φ' [C(4)–O(4)–C(1′)–C(2′)] 27·6 (6); χ^2 [C(6)–C(1)–C(7)–C(8)] 89·0 (6); χ^1 [C(1)–C(7)–C(8)–N(8)] 175·7 (4)°.

To compare the relative influence of the amine side chain on thyroid-hormone conformation and intermolecular interactions, the crystal and molecular structures of T_3AM were analyzed and are reported here as the bis(salicylato)borate salt (Fig. 1). This is the first structural report of both the iodothyronamine and the bis(salicylato)borate molecules.

Experimental. Single crystals of the 1:1 salt of triiodothyronamine (H. Rokos, Henning Co., Berlin) and bis(salicylato)borate were grown from a methanol solution containing salicylic acid (Aldrich) at room temperature. Accurate cell dimensions determined by least-squares analysis of 25 2θ values (25·2–26·9°); Nicolet $P3$ diffractometer, Zr-filtered Mo $K\alpha$ radiation, θ–2θ scan mode up to $\theta = 60°$ ($-20 \le h \le 20$, $0 \le k \le 20$, $0 \le l \le 21$), crystal size 0·16 × 0·16 × 0·50 mm; four standard reflections monitored every 100 reflections, no crystal decay observed during data collection; 10629 reflections recorded, 8316 with $I \ge 2\sigma(I)$ (Stout & Jensen, 1968) used in refinement; no extinction or absorption corrections made. Heavy-atom procedures, refinement on F by full-matrix least squares with anisotropic thermal parameters; H atoms located from difference Fourier syntheses, refined isotropically; final $R = 0{\cdot}064$ for 8316 reflections and 0·103 for all data, statistical weights, $w = 1/[\sigma^2(F) + (0{\cdot}02F)^2]^{1/2}$; max. shift/error 0·03; final difference Fourier map showed no peaks >0·20 e Å^{-3}; atomic scattering factors from *International Tables for X-ray Crystallography* (1974); all calculations performed on a VAX 11/780 computer using the Enraf–Nonius (1979) least-squares package.

Discussion. The final fractional coordinates and equivalent B values are listed in Table 1.* The molecular conformation of the 3,5,3′-triiodothyronamine bis(salicylato)borate salt is shown in Fig. 1 along with the numbering scheme used. T_3AM is *cisoid,* the 3′-iodine proximal, the diphenyl ether conformation twist-skewed and the protonated amine side chain extended. Although these general features have been reported for the parent thyroid hormones, thyroxine (T_4) and 3,5,3′-triiodothyronine (T_3) (Cody, 1980, 1981), this is the first observation of a twist-skewed conformation in a thyroid-hormone analogue without the full amino-acid side chain. The deaminated metabolites of T_4 and T_3 (*e.g.* thyroacetic or thyropropionic acid) adopt a skewed conformation with the bridging torsion angles φ [C(5)–C(4)–O(4)–C(1′)] and φ' [C(4)–O(4)–C(1′)–C(2′)] nearly 90 and 0°

* Lists of structure factors, anisotropic thermal parameters and H parameters have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 39295 (47 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

respectively (Cody, Hazel, Langs & Duax, 1977). These results suggest that the amine is of key importance in the selection of this conformation. The T_3AM geometry (Fig. 2) is in agreement with that reported for other thyroid-hormone structures (Cody, 1980).

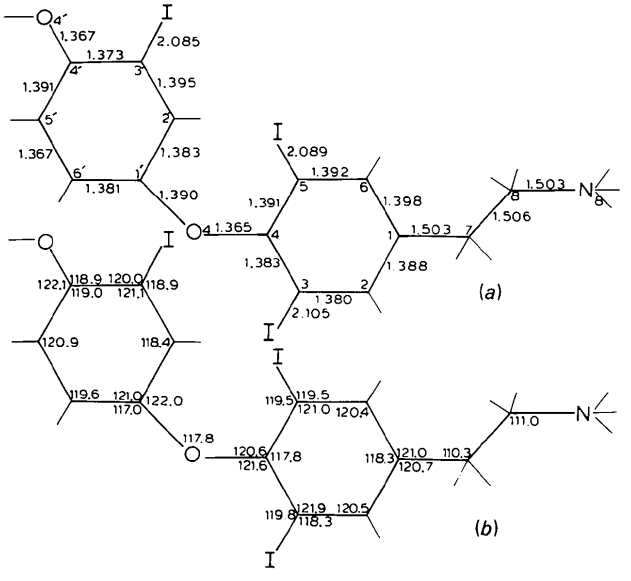

Fig. 2. (*a*) Bond lengths (Å) and (*b*) bond angles (°) for T_3AM. The e.s.d.'s for bonds and angles are 0·005–0·007 Å and 0·3–0·5° respectively.

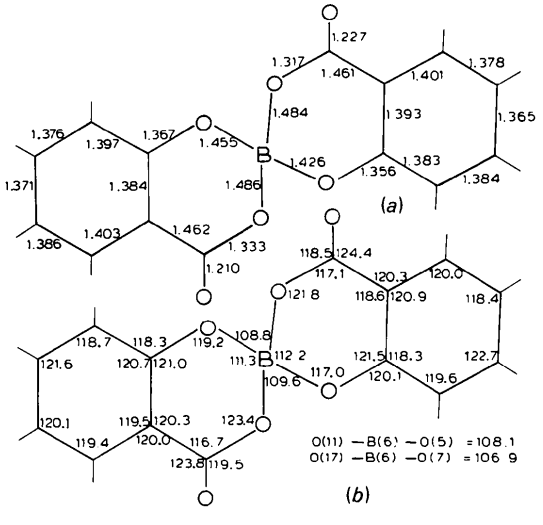

Fig. 3. (*a*) Bond lengths (Å) and (*b*) angles (°) for BSA. The e.s.d.'s for bonds and angles are 0·007–0·016 Å and 0·4–0·6° respectively.

Table 2. *Hydrogen-bond geometry for the T_3AM.BSA salt*

E.s.d.'s are 0·01 Å and 4·0° for bond distances and angles respectively.

D—H···*A*	*D*···*A*	*D*—H	H···*A*	∠*D*—H···*A*
N(8)—H(*A*)···O(20)	2·81 Å	1·03 Å	1·80 Å	166°
—H(*B*)···O(21)	2·83	0·74	2·11	165
—H(*C*)···O(11)	2·87	1·15	1·79	154
O(4′)—H···O(21)	2·73	0·66	2·11	158

The geometry of the bis(salicylato)borate anion is shown in Fig. 3. It has been shown that boric acid forms tetrahedral boron complexes in the presence of α-hydroxy acids such as salicylic acid (Boeseken, Vermaas & Kuchlin, 1930; Jones, 1933). The boron is tetrahedrally bonded at the intersection of the two salicylate moieties. The ring junction in each salicylate moiety is 7·3 (4) and 2·2 (4)° about the C(9)—C(10) and C(18)—C(19) bonds respectively. The dihedral angle between the two boron-containing rings is 82·5 (10)°.

The average B—O distance is 1·463 Å, in agreement with the results of other tetrahedral borate structures (Merlino & Sartori, 1972; Mariezcurrena & Rasmussen, 1973; Dunitz, Hawley, Miklos, White, Berlin, Marusic & Prelog, 1971; Grainger, 1981). However, as noted for most borates, there is significant variation in the individual B—O bonds. The variation shown in BSA is similar to that observed for bis(malato)borate (Mariezcurrena & Rasmussen, 1973), which is an analogous boric-acid complex. In each of these structures the boron—hydroxyl—oxygen distances are significantly shorter than the boron—carboxy—oxygen distances (Fig. 3).

These observed bond-length variations have been explained in terms of electrostatic valence principles (Pauling, 1929) to relate bond strength to B—O bond length (Zachariasen, 1963). In an analysis of tetrahedral B—O coordination (Grainger, 1981), it was shown that the sum of the bond strengths is close to 3·000, the valence of B. The sum of the B—O bond strengths in BSA is 3·110 using these formulations, which is larger than the values reported by Grainger (3·065).

The protonated amine and 4′-OH of T_3AM are involved in an extended network of hydrogen bonds with the O atoms of the bis(salicylato)borate anion (Table 2). There is one close (4·01 Å) I···I contact, as is frequently observed in other thyroid-hormone structures (Cody, 1980), and no short I···O contacts.

This research was supported in part by Grant No. AM-15051 from the National Institute of Arthritis, Metabolism and Digestive Diseases, DHEW. The author thanks Drs R. D. Hesch and H. Rokos for providing the sample, and Dr D. C. Swenson, E. De Jarnette, M. Tugas, G. Del Bel and Q. Bright for their technical assistance.

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Acta Cryst. (1984). C**40**, 1217–1219

N-{(1*R**,5*S**,7*R**)-6-Oxobicyclo[3.2.0]hept-2-en-7-yl}phthalimide, $C_{15}H_{11}NO_3$

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(*Received* 1 *December* 1983; *accepted* 5 *March* 1984)

Abstract. $M_r = 253{\cdot}25$, orthorhombic, *Pcab*, $a = 7{\cdot}434$ (1), $b = 13{\cdot}163$ (2), $c = 24{\cdot}684$ (4) Å, $Z = 8$, $V = 2415{\cdot}3$ Å^3, $D_x = 1{\cdot}39$ Mg m^{-3}, λ(Cu $K\alpha$) = 1·5418 Å, $\mu = 0{\cdot}716$ mm^{-1}, $F(000) = 1056$, $T = 293$ K, $R = 0{\cdot}082$ for 1300 unique observed reflections [$F_o \geq 3\sigma(F_o)$]. The cyclobutanone and cyclopentene rings of the bicyclohept-2-en-6-one moiety are *cis* fused; the phthalimide system is essentially planar. Bond lengths and angles are normal.

Introduction. The β-lactam antibiotics such as penicillin are thought to owe their action to their ability to inhibit the *trans*-peptidase enzyme necessary for bacterial wall synthesis (Ghuysen, Frère & Leyh-Boille, 1981). Bacterial resistance to β-lactam antibiotics is primarily due to the ability of the bacteria to make the enzyme β-lactamase which catalyses the hydrolysis of the β-lactam ring (Charnas & Knowles, 1981; Orlek, Sammes, Knott-Hunziker & Waley, 1979).

We have suggested (Gensmantel, McLellan, Morris, Page, Proctor & Randhawa, 1981; Proctor, Gensmantel & Page, 1982; Page, 1984) that the β-lactam ring is not an essential feature required for the drug to exhibit antibacterial activity. A potential class of new inhibitors of both classes of enzymes are therefore the carbocyclic analogues of penicillin in which the β-lactam ring is replaced by a cyclobutanone. We report here details of the structure of such a carbocyclic analogue of penicillin.

Experimental. The material was prepared by M. I. Page. Tabular crystal 0·44 × 0·18 × 0·09 mm. Enraf–Nonius CAD-4F diffractometer. Non-standard setting of space group *Pbca* used [equivalent positions ±(x, y, z; $\frac{1}{2}-x$, y, $\frac{1}{2}+z$; $\frac{1}{2}+x$, $\frac{1}{2}-y$, z; x, $\frac{1}{2}+y$, $\frac{1}{2}-z$)]. No correction for absorption. $2\theta_{max} = 120°$, h 0 to 8, k −14 to 14, l −27 to 27; 7804 reflections measured. Check reflection: average count 238, calculated σ (of the distribution) = 17·6. Cell dimensions from θ measurements of 48 reflections. Data merged using *SHELX* (Sheldrick, 1976) giving 1673 unique reflections, 1300 considered observed [$F_o \geq 3\sigma(F_o)$], merging $R_{int} = 0{\cdot}0532$. *MULTAN*80 (Main *et al.*, 1980) used to solve the structure. Least-squares refinement with *SHELX*76; positional parameters of all atoms and anisotropic thermal parameters for non-H atoms refined; $\sum w(\Delta F)^2$ minimized; unit weights. H atoms from difference Fourier syntheses. In the final cycle max. Δ/σ 0·450 (H) and 0·142 (non-H), average 0·035. $\Delta\rho$ final difference Fourier map within +0·46 and −0·53 e Å^{-3}. Scattering factors from *International Tables for X-ray Crystallography* (1974). Anisotropic scaling factor (Shakked & Rabinovich, 1977) applied. $R = 0{\cdot}082$ for 1300 observed reflections.

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