

## Methyl 3,5-Diiodo-4-(3-isopropyl-4-methoxybenzoyl)benzoate

BY VIVIAN CODY\*

Medical Foundation of Buffalo, Inc., 73 High Street, Buffalo, NY 14203, USA

AND ELLEN CHEUNG AND EUGENE C. JORGENSEN†

Department of Pharmaceutical Chemistry, University of California at San Francisco, San Francisco, CA 94143, USA

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**Abstract.**  $C_{19}H_{18}I_2O_4$ , orthorhombic,  $Iba2$ ,  $a = 20.998$  (3),  $b = 24.002$  (4),  $c = 8.032$  (1) Å,  $Z = 8$ ,  $M_r = 564.2$ ,  $D_c = 1.85$  Mg m $^{-3}$ ; for 2281 observed data  $R = 6.6\%$ . The conformation of the diphenyl ketone bridge is skewed and the 3'-isopropyl group distally oriented, as is observed for many thyroid hormone analogue structures. There is a short  $I \cdots O$  intermolecular contact between I(5) and the carbonyl oxygen [3.17 (10) Å].

**Introduction.** Structural studies show that the thyroid hormones (Fig. 1a) are characterized by an oxygen bridging angle of  $120^\circ$  and diphenyl ether conformation that is either skewed (*i.e.* the phenyl ring planes are mutually perpendicular and bisecting) or twist-skewed (Cody, 1980). Either conformation minimizes the steric interactions between the bulky 3,5 inner-ring iodines and the *ortho* hydrogens of the outer phenyl ring. The observed biological activity and protein-binding affinity of non-oxygen-bridged ( $S,CH_2$ ) hormone analogues suggests that the requirement for oxygen is not absolute (Jorgensen, 1978).

As part of a program to study the effects of oxygen-bridge substitution, as well as to design hormone analogues that could be used as photo affinity probes of hormone-protein binding, a number of carbonyl-bridged thyroid hormone analogues were synthesized and their nuclear receptor protein-binding affinities measured. Here is reported the crystal structure of a ketone-bridged analogue (Fig. 1b), which is shown to possess significant nuclear binding affinity (Cheung, unpublished results).

Crystals were grown by slow evaporation at room temperature from an ethanol solution. Crystallographic data were measured from a  $0.07 \times 0.4 \times 0.9$  mm crystal on a Nicolet P3 automated diffractometer using Nb-filtered Mo  $K\alpha$  radiation. Cell dimensions were obtained by a least-squares refinement based on

\* To whom inquiries should be directed.

† Deceased.

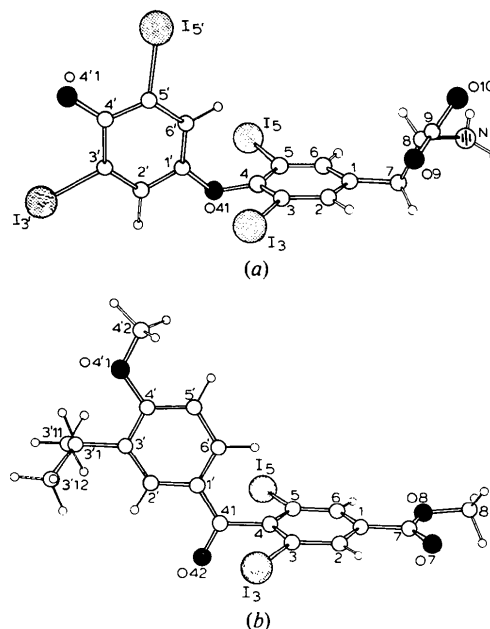


Fig. 1. (a) Thyroid hormone thyroxine ( $T_4$ ). (b) Methyl 3,5-diiodo-4-(3-isopropyl-4-methoxybenzoyl)benzoate with numbering scheme used.

the  $2\theta$  values of 25 reflections with  $2\theta > 25^\circ$  using Mo  $K\alpha$  radiation. The intensities of 3172 reflections (2330 with  $I > 2\sigma$ ) were measured in the  $\theta$ - $2\theta$  scan mode with a variable scan time to obtain counting errors in the range  $0.01 \leq \sigma(I)/I \leq 0.03$ . No significant changes were observed in the intensities of the standard reflections measured during data collection. Intensities were corrected for Lorentz and polarization factors, but no absorption correction was made. The structure was solved by heavy-atom techniques.

The positional and anisotropic thermal parameters for all non-hydrogen atoms were refined using full-matrix least-squares procedures on all data. Calculated H positions were included in the structure factor calculations but were not refined. The weights used

Table 1. Fractional coordinates ( $\times 10^4$ ) and equivalent isotropic thermal parameters ( $\times 10^3$ ; for I  $\times 10^4$ ) with e.s.d.'s in parentheses

|         | x         | y        | z         | $B_{eq}$ ( $\text{\AA}^2$ )* |
|---------|-----------|----------|-----------|------------------------------|
| C(1)    | 141 (4)   | 3403 (5) | 1639 (16) | 38 (2)                       |
| C(2)    | 408 (5)   | 3905 (5) | 1063 (18) | 45 (3)                       |
| C(3)    | 1079 (5)  | 3950 (5) | 977 (15)  | 39 (3)                       |
| C(4)    | 1464 (5)  | 3521 (5) | 1474 (16) | 40 (3)                       |
| C(5)    | 1187 (4)  | 3027 (4) | 2049 (16) | 38 (2)                       |
| C(6)    | 526 (5)   | 2969 (4) | 2094 (16) | 38 (2)                       |
| C(41)   | 2187 (5)  | 3565 (5) | 1369 (17) | 40 (3)                       |
| C(1')   | 2539 (4)  | 3762 (4) | 2803 (19) | 36 (2)                       |
| C(2')   | 3204 (4)  | 3791 (4) | 2752 (21) | 44 (3)                       |
| C(3')   | 3566 (5)  | 3973 (6) | 4049 (20) | 46 (3)                       |
| C(4')   | 3253 (5)  | 4132 (5) | 5523 (19) | 43 (3)                       |
| C(5')   | 2587 (5)  | 4095 (5) | 5658 (15) | 40 (3)                       |
| C(6')   | 2234 (4)  | 3913 (5) | 4266 (16) | 38 (3)                       |
| O(4'1)  | 3621 (5)  | 4302 (4) | 6818 (13) | 53 (3)                       |
| C(4'2)  | 3323 (9)  | 4483 (8) | 8249 (22) | 65 (5)                       |
| O(42)   | 2440 (4)  | 3457 (4) | -2 (13)   | 52 (2)                       |
| C(7)    | -566 (5)  | 3368 (6) | 1704 (18) | 48 (3)                       |
| O(8)    | -767 (3)  | 2901 (4) | 2285 (15) | 56 (3)                       |
| O(7)    | -910 (4)  | 3749 (5) | 1271 (20) | 75 (4)                       |
| C(3'1)  | 4290 (6)  | 3993 (9) | 3977 (22) | 68 (5)                       |
| C(3'11) | 4576 (7)  | 3433 (9) | 3958 (59) | 136 (14)                     |
| C(3'12) | 4526 (7)  | 4347 (8) | 2665 (63) | 122 (11)                     |
| C(8)    | -1453 (5) | 2823 (7) | 2523 (34) | 68 (5)                       |
| I(3)    | 1461 (1)  | 4707 (1) | 122       | 612 (3)                      |
| I(5)    | 1747 (1)  | 2342 (1) | 2687 (3)  | 508 (2)                      |

\*  $B_{eq} = \frac{4}{3} \sum_i \sum_j \beta_{ij} \mathbf{a}_i \cdot \mathbf{a}_j$ ; taken from Hamilton (1959), equation (18).

were the quantities  $(1/\sigma_F^2)$  where  $\sigma_F$  is defined by Stout & Jensen (1968), and the instability correction was 0.06. The  $R$  index,  $\sum ||F_o| - |F_c|| / \sum |F_o|$ , was 6.6% for 2281 data. The function minimized in the least-squares refinement was  $\sum w(|F_o| - |F_c|)^2$ . The Fourier and least-squares programs are part of the Nonius crystallographic package adopted for the VAX 11/780 computer. Scattering factors are from *International Tables for X-ray Crystallography* (1974). The final refined positional and isotropic thermal parameters are given in Table 1.\*

**Discussion.** The molecular conformation and geometry of the title compound are illustrated in Figs. 1(b) and 2. The two phenyl rings adopt a skewed conformation [ $C(3)-C(4)-C(41)-C(1') = 92.6(1.5)^\circ$  and  $C(4)-C(41)-C(1')-C(6') = 0.0(1.8)^\circ$ ] as observed in the structures of other thyro-active acids (Cody, Hazel, Langs & Duax, 1977). The 3'-isopropyl group is in the distal position. The only other similar 3'-iso-

\* Lists of structure factors, anisotropic thermal parameters and stereopacking diagrams have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 36769 (18 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

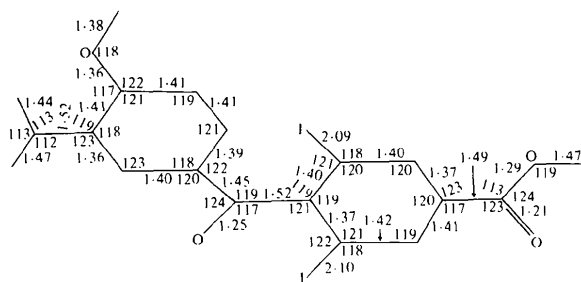


Fig. 2. Bond lengths ( $\text{\AA}$ ) and bond angles ( $^\circ$ ) for the title compound. The e.s.d.'s are 0.02  $\text{\AA}$  for bond lengths and 0.9 $^\circ$  for bond angles.

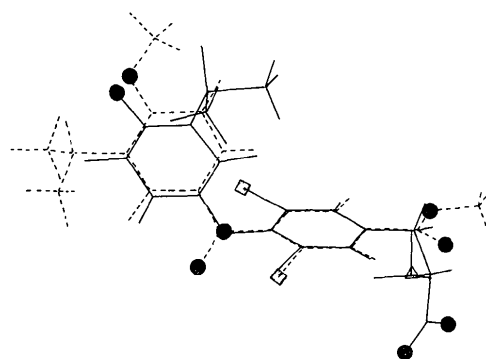


Fig. 3. Superposition of the title compound (dashed) with that of 3,5-diiodo-3'-isopropylthyronine (Fawcett, Camerman & Camerman, 1976). The squares are iodine, filled circles oxygen, open triangle nitrogen.

propyl compound, 3,5-diiodo-3'-isopropylthyronine (Fawcett, Camerman & Camerman, 1976), adopts a proximal 3'-isopropyl orientation (Fig. 3). Since the methoxycarbonyl group is coplanar [ $3.6(1.2)^\circ$ ] with the iodophenyl ring, the usual *cisoid/transoid* designation of the thyroid hormone conformations does not apply. The 4'-methoxy group is coplanar [ $-5.1(1.9)^\circ$ ] with the phenoxy ring and points toward the 5'-side of the ring. Since all the functional groups are blocked there is no hydrogen bonding in the structure, although there is a short intermolecular I...O contact between I(5) and the carbonyl oxygen [ $3.17(10) \text{\AA}$ ], similar to that observed in many of the thyroid hormone structures (Cody, 1980).

A comparison of this structure with those of the thyroid hormones shows that the geometries involving the atom linking the two phenyl rings are similar (Table 2). There is relatively little effect on conformation due to bridge lengthening [ $1.394 \text{\AA}$  versus  $1.523 \text{\AA}$ , Table 2, Fig. 4]. Further comparisons of this structure with those of other carbon-bridged diphenyl compounds (Cody, 1981) indicate that the bridging angle varies as a function of the bridge-atom substitution: the more fully substituted, the smaller the bridging angle (Gopal, Chandler & Robertson, 1979).

Table 2. Conformational effects of oxygen-bridge substitution

These values represent the averages of those structures reported by Cody (1980, 1981).

| C-X-C | 3,5-  | C(4)-X<br>(Å) | X-C(1')<br>(Å) | C(4)-X-C(1')<br>(°) | Conformation                   |
|-------|-------|---------------|----------------|---------------------|--------------------------------|
| O     | I     | 1.376         | 1.394          | 119.6               | Skewed,<br>twist-skewed        |
|       | Other | 1.380         | 1.377          | 120.0               | Skewed,<br>twist-skewed        |
| C     | I     | 1.484         | 1.523          | 116.3               | Skewed,<br>twist-skewed        |
|       | Other | 1.514         | 1.512          | 115.5               | Twist-skewed,<br>perpendicular |

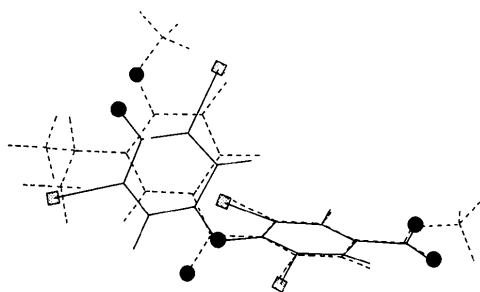


Fig. 4. Superposition of title compound (dashed) with that of 4-(4-hydroxy-3,5-diiodophenoxy)-3,5-diiodobenzoic acid (Cody & Strong, 1980). The squares are iodine and filled circles oxygen.

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### $\alpha,\alpha'$ -Dithiobisformamidinium Dinitrate, [(NH<sub>2</sub>)<sub>2</sub>CSSC(NH<sub>2</sub>)<sub>2</sub>]<sup>+</sup>[NO<sub>3</sub>]<sub>2</sub> at 110 K

BY GEOFFREY B. JAMESON,\* EVA BLAZSÒ, NIKOLAOS SEFERIADIS AND HANS R. OSWALD

*Institute of Inorganic Chemistry, University of Zürich, Winterthurerstrasse 190, CH-8057 Zürich, Switzerland*

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**Abstract.** C<sub>2</sub>H<sub>8</sub>N<sub>4</sub>S<sub>2</sub><sup>2+</sup>·2NO<sub>3</sub><sup>-</sup>, monoclinic, *C2/c*, *a* = 10.871 (5), *b* = 8.113 (4), *c* = 11.580 (5) Å,  $\beta$  = 100.32 (2)°, *V* = 1004.8 Å<sup>3</sup>, *Z* = 4. The structure was refined on *F* (including positional parameters for hydrogen atoms) to *R* = 0.038 and *R<sub>w</sub>* = 0.039 for 1055 reflections having *F<sub>o</sub>*<sup>2</sup> > 3σ(*F<sub>o</sub>*<sup>2</sup>). The dication has crystallographically imposed twofold symmetry with the following stereochemistry: C–N 1.311 (3) and 1.301 (3) Å; C–S 1.786 (2) Å; S–S 2.022 (1) Å;

The observation that these ketone-bridged thyroid hormone analogues have significant nuclear receptor binding affinity (Cheung, unpublished results) suggests that they could be used as photo-affinity probes of the active site on thyroid hormone-binding proteins.

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planar configuration around the carbon atom; C–S–S–C torsional angle 97.9 (1)°; S–S–C–N torsional angles 6.6 (2) and 6.8 (2)°. An extensive hydrogen-bonding network links nitrate oxygen atoms with hydrogen atoms [O...N 2.837 (3), 2.862 (3), 2.888 (3) and 2.970 (3) Å].

**Introduction.** In the course of studies on the interaction of metal(III) species with thiourea under acidic conditions colourless crystals of the title compound appeared as the result of redox reactions. Several possible structures exist for the cation.

\* Present address: Department of Chemistry, Georgetown University, Washington, DC 20057, USA.