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3,5,3'-Triiodo-4'-methoxythyropropionic Acid Methyl Ester

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Abstract. $C_{17}H_{15}I_3O_4$, m.p. 185°C, monoclinic, $P2_1/c$, $a = 9.736$ (2), $b = 7.510$ (1), $c = 28.387$ (5) Å, $\beta = 94.59$ (2)°, $Z = 4$, $M_r = 664.02$, $D_c = 2.13$ g cm^{-3}, observed data $R = 6.8\%$. The conformation of the iodine at the 3' position is proximal and the propionic acid side chain is fully extended. Both the methoxy and methyl ester carbons are coplanar with their respective functional groups. The torsion angles between the phenyl rings and the ether oxygen (φ and φ') are 103 and $-21°$, respectively, and the C—O—C angle is 117°.

Table 1. *Positional parameters for* 3,5,3'-*triiodo*-4'-*methoxythyropropionic acid methyl ester*

	x	y	z
I(3')	0.3378 (2)	0.2316 (2)	−0.15697 (6)
I(3)	0.9483 (2)	0.2130 (2)	−0.09156 (6)
I(5)	0.6282 (2)	0.8223 (2)	−0.01414 (8)
C(1)	0.7840 (20)	0.3235 (26)	0.04296 (68)
C(2)	0.8544 (20)	0.2465 (29)	0.00645 (82)
C(3)	0.8511 (22)	0.3351 (28)	−0.03665 (76)
C(4)	0.7833 (21)	0.4975 (27)	−0.04427 (72)
C(5)	0.7234 (23)	0.5725 (26)	−0.00636 (80)
C(6)	0.7175 (21)	0.4846 (27)	0.03722 (75)
O(41)	0.7933 (15)	0.5886 (19)	−0.08601 (52)
C(1')	0.6824 (23)	0.5803 (30)	−0.11917 (76)
C(2')	0.5860 (23)	0.4445 (28)	−0.11908 (82)
C(3')	0.4799 (23)	0.4368 (29)	−0.15525 (72)
C(4')	0.4670 (25)	0.5756 (32)	−0.18782 (82)
C(5')	0.5624 (30)	0.7087 (38)	−0.18763 (88)
C(6')	0.6660 (27)	0.7119 (23)	−0.15350 (89)
O(4'1)	0.3582 (19)	0.5626 (23)	−0.22148 (61)
C(4'2)	0.3406 (31)	0.6959 (43)	−0.25667 (103)
C(7)	0.7810 (26)	0.2241 (31)	0.08923 (94)
C(8)	0.8939 (25)	0.3002 (29)	0.12618 (80)
C(9)	0.9310 (24)	0.1838 (30)	0.16933 (71)
O(9)	0.9067 (24)	0.0315 (23)	0.17150 (67)
O(10)	0.9939 (19)	0.2786 (23)	0.20153 (66)
C(10)	1.0377 (34)	0.1877 (35)	0.24495 (118)

Introduction. 3,5,3'-Triiodo-4'-methoxythyropropionic acid methyl ester was prepared by methylation of triiodothyropropionic acid in methanol using diazomethane. Diazomethane in ether–alcoholic solution was prepared from *N*-methyl-*N*-nitroso-*p*-toluenesulfonamide by a commercial diazomethane generator (Aldrich Diazald Kit, Aldrich Chemical Co., Milwaukee, Wisconsin). A small crystal (0.02 × 0.36 × 0.38 mm) was selected for intensity data collection. The data showed the systematic absences for the space group $P2_1/c$ and the cell constants were determined by least-squares analysis of the angular settings of 45 reflections having $2\theta > 21°$ [at 20°C; λ(Mo $K\alpha$) = 0.7091 Å]. The intensities of 2885 (1202 reflections had $I > 2\sigma$) with $2\theta < 55°$ were measured on an Enraf–Nonius CAD-4 automated diffractometer. Reflections were measured in the θ–2θ scan mode using Zr-filtered Mo $K\alpha$ radiation and a sweep $= 1.1° + 0.1 \tan \theta$. No significant changes were observed in the intensities of the standard reflections measured daily during data collection. Intensities were corrected for Lorentz and polarization factors, but not for absorption. The structure was solved by application of heavy-atom techniques.

The positional and anisotropic thermal parameters for all non-hydrogen atoms were refined using full-matrix least-squares procedures. The weights used were the quantities $(1/\sigma_F^2)$ where σ_F is defined by Stout & Jensen (1968, equation H.14), and the instability correction was 0.06. This value increases σ_F for reflections with a large $|F|$ and prevents them from controlling the refinement. The R index, defined as $\sum ||F_o| - |F_c||/\sum |F_o|$, was 6.8% using 1202 data with $\sin \theta/\lambda < 0.55$ Å^{-1}. The Fourier and least-squares programs are part of the Nonius crystallographic package for the PDP 11/45. Scattering factors are from *International Tables for X-ray Crystallography* (1974).

The final refined positional parameters are given in Table 1.*

Discussion. The determination of the crystal structure of the thyroid hormone analogue 3,5,3'-triiodo-4'-methoxythyropropionic acid methyl ester (Fig. 1) is part of a comprehensive investigation of the crystallographic data of thyroid hormones, precursors and metabolites undertaken in this laboratory to explore their conformational flexibility and to investigate the structural requirements for thyromimetic activity.

The intramolecular bond lengths and angles for the title compound are shown in Fig. 2. The average standard deviations in bond distances and angles are 0·03 Å and 1·5° respectively. While there are no bond distances or angles which deviate by more than one standard deviation from their expected values, the C(7)—C(8) bond (1·57 Å) is longer than has been observed in the structure of 3,5-diiodothyropropionic

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* Lists of structure factors and anisotropic thermal parameters have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 33685 (6 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.
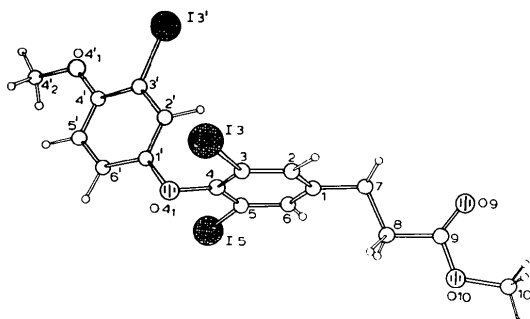

Fig. 1. 3,5,3'-Triiodo-4'-methoxythyropropionic acid methyl ester with numbering scheme.

Fig. 2. Bond distances (Å) and angles (°) in 3,5,3'-triiodo-4'-methoxythyropropionic acid methyl ester.

acid (1·41 Å) (Cody, Erman & De Jarnette, 1977) or 3,5,3'-triiodothyropropionic acid ethyl ester (1·46 Å) (Camerman & Camerman, 1974). The phenyl rings are planar and the maximum deviation of any C atom from the least-squares plane through its phenyl ring is 0·02 Å.

The 4'-methoxy C atom is coplanar with the phenyl ring, as measured by the torsion angle C(5')—C(4')—O(4'1)—C(4'2) = −2°, and points away from the 3'-iodine atom. The methyl ester is also *cis* coplanar with the carbonyl group [O(9)—C(9)—O(10)—C(10) = 0°]. The propionic acid side chain is nearly perpendicular to the inner ring as described by the torsion angle C(2)—C(1)—C(7)—C(8) = 99°. The side chain is also fully extended [C(1)—C(7)—C(8)—C(9) = −164°] as observed in the structures of 3,5-diiodothyropropionic acid (−177°) (Cody, Erman & De Jarnette, 1977) and 3,5,3'-triiodothyropropionic acid ethyl ester (169°) (Camerman & Camerman, 1974).

The conformation of the I at the 3' position is proximal as observed in the ethyl ester analogue (Camerman & Camerman, 1974). This is the first example of a proximal 3-iodo compound crystallized from neutral alcoholic solutions; the other proximal conformations were crystallized from HCl.

The overall conformation is transoid as shown in Fig. 1 where the outer phenyl ring and the propionic side chain are on opposite sides of the inner ring plane. The diphenyl ether conformation is twist-skewed as indicated by the ether bond torsion angles φ and φ' of 103 and −21° respectively.

Since both hydroxyl groups in this structure have been methylated there is no possibility of hydrogen bonding. However, there are short intermolecular interactions between I and O, the carbonyl O atom, O(9), forms two short intermolecular I···O contacts with I(3) (3·32 Å) and I(3') (3·0 Å) respectively. There is also one I···I (3·78 Å) intermolecular contact. The crystal packing is illustrated in Fig. 3.

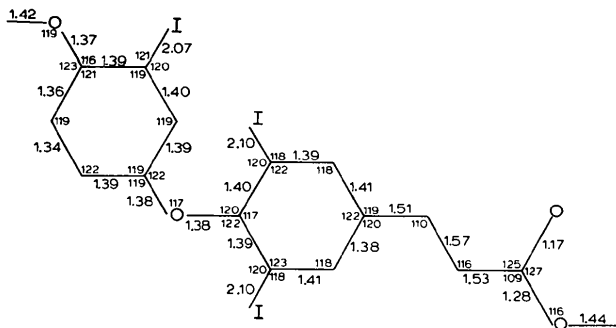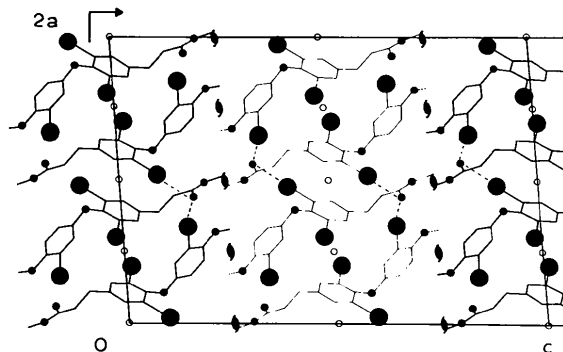Fig. 3. Packing diagram for 3,5,3'-triiodo-4'-methoxythyropropionic acid methyl ester. The dark molecules are above the light ones. The large circles are iodine and the small filled circles oxygen. The dashed lines indicate I···O interactions.

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6,7-Diphenyl[1,2,4]triazolo[5,1-c][1,2,4]triazine

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Abstract. $C_{16}H_{11}N_5$, $M_r = 273.304$, monoclinic, $P2_1/n$, $a = 12.846$ (11), $b = 7.664$ (7), $c = 13.610$ (12) Å, $\beta = 92.58$ (6)°, $Z = 4$, $V = 1338.56$ Å^3, $D_c = 1.36$, $D_m = 1.33$ g cm^{-3} (flotation). Direct phase determination and constrained full-matrix least-squares refinement reduced R to 0.072. The bicyclic system shows extensive delocalization, and is flat within ±0.03 Å. The phenyl rings are inclined to it at angles of 56.2 and 50.8°, and bent away from each other to reduce crowding.

Introduction. Interaction of 3-hydrazino-1,2,4-triazole and 1,2-diketones can afford entry to either the [1,2,4]-triazolo[5,1-c][1,2,4]triazine ring system (*Ia*) or the isomeric [1,2,4]triazolo[3,4-c][1,2,4]triazine series (*Ib*) (Gray & Stevens, 1976).

(*Ia*)   (*Ib*)
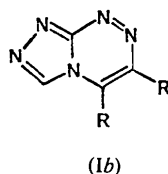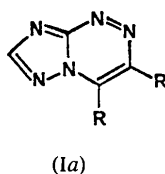
Since type (*Ib*) 1,2,4-triazoloazines undergo Dimroth rearrangement to type (*Ia*) (Daunis, Jacquier & Viallefont, 1969), fusion as in (*Ia*) appears thermodynamically more stable in agreement with CNDO calculations (Guerret, Jacquier & Maury, 1971). A case in point is

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the triazolotriazine formed by reacting 3-hydrazino-1,2,4-triazole and benzil, which was assigned structure (*Ia*) (R = Ph) on the scant evidence of the chemical shift of the triazole proton and the lack of rearrangement in acid or base (Gray & Stevens, 1976). We undertook a crystal structure determination to verify this assignment and investigate the stereochemical relationship of the rings.

Crystals of the title compound exhibited systematic absences $h0l$, $h + l = 2n + 1$, and $0k0$, $k = 2n + 1$, indicating space group $P2_1/n$. From a crystal $0.58 \times 0.46 \times 0.12$ mm mounted along b, 2540 reflexions were collected on a STADI-2 two-circle diffractometer (Mo $K\alpha$, $\mu = 0.0920$ mm^{-1}). Another crystal $0.72 \times 0.24 \times 0.20$ mm mounted along [10$\bar{1}$] was used for multiple-film Weissenberg photographs (Cu $K\alpha$, $\mu = 0.689$ mm^{-1}). Evaluation by microdensitometer of levels 0 to 4 yielded 411 reflexions. Upon merging of diffractometer and film data the R factor for 2475 unique data was 6.8%. This value of R was

$$\left(\left\{ \sum_{hkl} n \sum_{i=1}^{n} w_i [\bar{F}(hkl) - F_i(hkl)]^2 \right\} \middle/ \left[\sum_{hkl} (n-1) \sum_{i=1}^{n} w_i F_i(hkl)^2 \right] \right)^{1/2}$$

where the outer summations are over all unique hkl, each inner summation is over the n multiple observations, $\bar{F}(hkl)$ is the mean of these, and $F_i(hkl)$ and w_i are the individual observations and their weights. After elimination of reflexions with $F < 4\sigma(F)$ as well as three