Acta Cryst. (1983). C**39**, 304–306

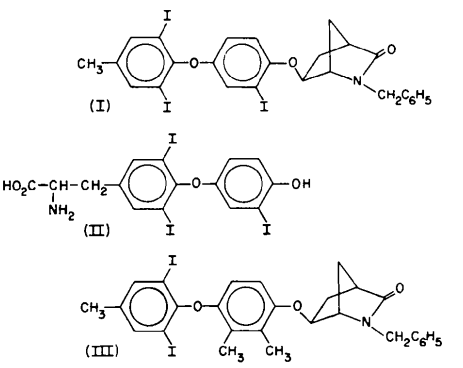
Structure of 2-Benzyl-6-*exo*-[2,3-dimethyl-4-(2,6-diiodo-4-methylphenoxy)phenoxy]-2-azabicyclo[2.2.1]heptan-3-one, $C_{28}H_{27}I_2NO_3$

BY HERMAN L. AMMON, SOVAN K. BHATTACHARJEE, PRASAD S. RAVI AND STEVEN J. POTLOCK

Department of Chemistry, University of Maryland, College Park, MD 20742, *USA*

(*Received* 28 *June* 1982; *accepted* 27 *October* 1982)

Abstract. $M_r = 679{\cdot}3$, triclinic, $P\bar{1}$, $a = 7{\cdot}386\ (2)$, $b = 13{\cdot}572\ (3)$, $c = 14{\cdot}701\ (6)$ Å, $\alpha = 66{\cdot}68\ (2)$, $\beta = 86{\cdot}53\ (2)$, $\gamma = 75{\cdot}68\ (2)°$, $V = 1310\ (1)$ Å^3, $D_x = 1{\cdot}722$ Mg m^{-3}, $Z = 2$, $\lambda(\text{Cu } K\alpha) = 1{\cdot}5418$ Å, $\mu = 19{\cdot}87$ mm^{-1}, $T = 294$ K. Final $R = 0{\cdot}062$ for 3271 observed reflections. The bicyclo[2.2.1]heptane portion of the molecule is similar to that found in several other molecules. The diphenyl ether fragment adopts a semi-perpendicular *distal* conformation with an angle of 79·9° between the two benzene rings. The dimethylphenyl ring is planar, and the only bond-angle distortion is associated with the O—C—C regions.



Introduction. We are developing a molecular system designed to use nuclear magnetic resonance–lanthanide shift reagents (NMR–LSR) for the determination of the *distal/proximal* conformation ratios of the diphenyl ether moieties in various thyroid-hormone analogs. The system basically consists of a bicyclic lactam linked to an appropriately substituted diphenyl ether, which serves as a model for an analogous region in the thyroid hormone being mimicked. For example, the diphenyl ether section in compound (I) should mirror the conformational properties of the aromatic region in triiodothyronine (T3, II). To calibrate our NMR results, it was necessary to study several bicyclic analogs which can exhibit only the *distal* or *proximal* conformation by virtue of the substituent pattern in the inner ring of the bicyclic compound. One such substance is (III), which is forced to adopt only the *distal* conformation because of the steric effects of the 3′-methyl substituent. A search of the crystallographic literature revealed that only one 2,3-dimethylbenzene-1,4-dioxy-containing structure had been reported *viz* 3,5-diiodo-2′,3′-dimethyl-D,L-thyronine (Fawcett, Camerman & Camerman, 1976). We felt that the bond angles in this section of (III) might deviate substantially from 120° or that the methyl groups might appreciably deviate from the benzene ring plane, and thus we have determined the structure of (III) to provide another estimate of these parameters needed for the construction of an atomic-coordinate model for the subsequent NMR–LSR calculations.

Experimental. Prepared from 2,3-dimethyl-4-(2,5-diiodo-4-methylphenoxy)phenol and 2-benzyl-6-*exo*-tosyloxy-2-azabicyclo[2.2.1]heptan-3-one according to the general procedures described by Mazzocchi, Ammon, Liu, Colicelli, Ravi & Burrows (1981); recrystallization from a toluene–pentane mixture gave transparent trapezoids, 0·30 × 0·15 × 0·05 mm; cell parameters determined and intensity measurements made with a Picker FACS-I diffractometer, graphite-monochromated Cu radiation; unit-cell parameters determined by least squares from 2θ values of 18 reflections obtained by manual centering at $\pm 2\theta$ (average $|2\theta_o - 2\theta_c| = 0{\cdot}009°$); intensities measured with θ–2θ scan technique, scan rate 2° min^{-1} and 10 s backgrounds, 2θ scan width calculated from 1·8° + 0·3° tan θ, four standards measured at 100-reflection intervals to monitor intensity fluctuations, total of 4825 reflections measured to $2\theta_{max} = 127°$, 4274 unique, 3271 3σ above background; data corrected for absorption with the Gaussian quadrature method (8 × 8 × 8 grid), minimum and maximum transmission factors 2·23 and 8·84 respectively; the two I positions located from a Patterson map; electron and difference density maps revealed 27 of the 32 C, N and O atoms, remaining atoms appeared in subsequent maps; structure refined by full-matrix least squares with anisotropic temperature factors applied to C, N, O, and I atoms; many of the H atoms could not be located in a difference map therefore non-methyl H atoms were fixed at geometrically reasonable locations while a

0108-2701/83/020304-03$01.50

rotationally disordered model (consisting of appropriately positioned circles of ten 0·3 weight atoms) was assumed for methyl H atoms, H-atom B values set to 10 Å^2; quantity minimized $\sum w(F_o - F_c)^2$, $w = [1/\sigma(F)]^2$, scattering factors for C,N,O and I atoms calculated from analytical expressions of Cromer & Mann (1968), H terms interpolated from tabulated values of Stewart, Davidson & Simpson (1965), $F(000) = 664$, final $R_w = 0{\cdot}071$; all calculations performed on a Univac 1108 computer at the University of Maryland's Computer Science Center with the XRAY system (Stewart, Machin, Dickinson, Ammon, Heck & Flack, 1976) of crystallographic programs.

Discussion. Atomic coordinates and temperature factors are listed in Table 1.*

An *ORTEP* drawing (Johnson, 1971) of the molecule is shown in Fig. 1, and bond lengths and angles are given in Table 2. The bicyclic lactam portion of (III) is similar to the corresponding fragment in several other recently reported structures (Ammon, Mazzocchi, Liu, Colicelli, Doherty & Stewart, 1982). For example, a

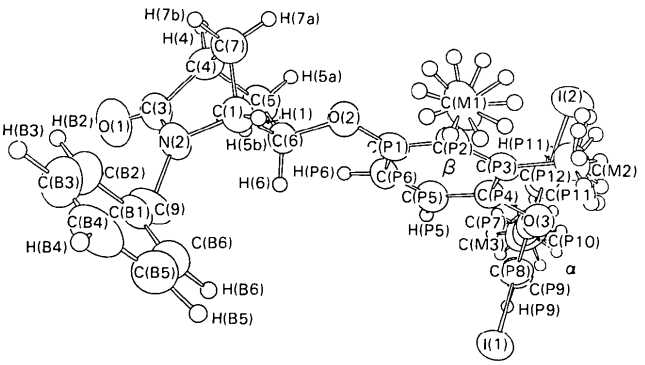


Fig. 1. An *ORTEP* drawing of (I) with the C, N, O and I atoms depicted as 50% probability boundary ellipses. H atoms are shown as 0·1 Å radius circles. The atom numbering adopted is consistent with our previously reported 2-azabicyclo[2.2.1]-heptane work (Ammon *et al.*, 1982). The following conversions in the diphenyl ether fragment would be consistent with the standard thyroid-hormone-analog numbering: C(*P*1)–C(*P*4) = C(4′), C(3′), C(2′), C(1′); C(*P*7), C(*P*8), C(*P*10), C(*P*12) = C(4), C(3), C(1), C(5).

* Lists of structure factors, anisotropic temperature factors and H-atom parameters have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 38203 (20 pp.). Copies may be obtained through the Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

Table 1. *Fractional coordinates and equivalent isotropic temperature factors* (Å^2)

The U_{ij} values have been deposited. The e.s.d of the last significant digit is given in parentheses. $U_{eq} = \frac{1}{3}\sum_i\sum_j U_{ij} a_i^* a_j^* \mathbf{a}_i.\mathbf{a}_j$.

	x	y	z	U_{eq}
C(1)	−0·167 (1)	0·5383 (8)	−0·2283 (7)	0·03 (4)
C(3)	−0·463 (2)	0·6271 (9)	−0·2052 (8)	0·03 (4)
C(4)	−0·311 (2)	0·6237 (8)	−0·1351 (7)	0·03 (4)
C(5)	−0·247 (1)	0·4984 (8)	−0·0650 (7)	0·03 (4)
C(6)	−0·150 (1)	0·4424 (7)	−0·1299 (6)	0·03 (4)
C(7)	−0·143 (2)	0·6303 (8)	−0·2010 (8)	0·03 (4)
C(9)	−0·452 (2)	0·5302 (9)	−0·3184 (7)	0·02 (4)
C(*B*1)	−0·370 (1)	0·5586 (8)	−0·4217 (6)	0·02 (1)
C(*B*2)	−0·401 (2)	0·6656 (8)	−0·4902 (8)	0·04 (2)
C(*B*3)	−0·339 (2)	0·6880 (8)	−0·5840 (8)	0·05 (2)
C(*B*4)	−0·247 (2)	0·610 (1)	−0·6107 (8)	0·03 (2)
C(*B*5)	−0·206 (2)	0·502 (1)	−0·545 (1)	0·04 (1)
C(*B*6)	−0·275 (2)	0·4775 (8)	−0·4500 (8)	0·031 (8)
C(*P*1)	0·104 (1)	0·2937 (7)	−0·0308 (6)	0·02 (3)
C(*P*2)	0·294 (1)	0·2437 (7)	−0·0305 (6)	0·02 (3)
C(*P*3)	0·368 (1)	0·1374 (7)	0·0440 (7)	0·02 (3)
C(*P*4)	0·247 (1)	0·0875 (7)	0·1136 (6)	0·02 (3)
C(*P*5)	0·061 (1)	0·1401 (7)	0·1123 (6)	0·03 (3)
C(*P*6)	−0·012 (1)	0·2436 (7)	0·0413 (7)	0·03 (3)
C(*P*7)	0·244 (1)	−0·0567 (7)	0·2712 (6)	0·04 (3)
C(*P*8)	0·119 (1)	−0·1243 (7)	0·2908 (7)	0·03 (3)
C(*P*9)	0·058 (2)	−0·1691 (8)	0·3855 (7)	0·04 (3)
C(*P*10)	0·107 (2)	−0·1438 (8)	0·4617 (8)	0·05 (3)
C(*P*11)	0·232 (2)	−0·0771 (9)	0·4421 (7)	0·03 (3)
C(*P*12)	0·304 (2)	−0·0351 (7)	0·3488 (7)	0·03 (2)
C(*M*1)	0·412 (1)	0·3029 (9)	−0·1045 (7)	0·05 (4)
C(*M*2)	0·567 (1)	0·0821 (8)	0·0488 (7)	0·04 (2)
C(*M*3)	0·040 (2)	−0·190 (1)	0·5634 (8)	0·10 (3)
N(2)	−0·364 (1)	0·5761 (6)	−0·2621 (5)	0·03 (4)
O(1)	−0·632 (1)	0·6601 (7)	−0·2034 (6)	0·06 (4)
O(2)	0·0464 (9)	0·3981 (5)	−0·1051 (4)	0·04 (4)
O(3)	0·3256 (9)	−0·0214 (5)	0·1805 (4)	0·04 (2)
I(1)	0·0360 (1)	−0·16151 (6)	0·17830 (5)	0·03 (2)
I(2)	0·4992 (1)	0·05973 (6)	0·32384 (6)	0·03 (2)

Table 2. *Bond lengths* (Å) *and angles* (°) *with e.s.d.'s in parentheses*

C(1)–N(2)	1·46 (1)	C(*P*1)–C(*P*6)	1·39 (1)
C(1)–C(6)	1·50 (1)	C(*P*1)–O(2)	1·383 (9)
C(1)–C(7)	1·51 (2)	C(*P*2)–C(*P*3)	1·42 (1)
C(3)–C(4)	1·55 (2)	C(*P*2)–C(*M*1)	1·46 (1)
C(3)–N(2)	1·36 (2)	C(*P*3)–C(*P*4)	1·39 (1)
C(3)–O(1)	1·22 (1)	C(*P*3)–C(*M*2)	1·47 (1)
C(4)–C(5)	1·57 (1)	C(*P*4)–C(*P*5)	1·38 (1)
C(4)–C(7)	1·52 (2)	C(*P*4)–O(3)	1·408 (9)
C(5)–C(6)	1·49 (2)	C(*P*5)–C(*P*6)	1·37 (1)
C(6)–O(2)	1·44 (1)	C(*P*7)–C(*P*8)	1·40 (2)
C(9)–N(2)	1·47 (2)	C(*P*7)–C(*P*12)	1·40 (2)
C(9)–C(*B*1)	1·54 (1)	C(*P*7–O(3)	1·38 (1)
C(*B*1)–C(*B*2)	1·37 (1)	C(*P*8)–C(*P*9)	1·38 (1)
C(*B*1)–C(*B*6)	1·35 (2)	C(*P*8)–I(1)	2·08 (1)
C(*B*2)–C(*B*3)	1·37 (2)	C*P*9)–C(10)	1·39 (2)
C(*B*3)–C(*B*4)	1·30 (2)	C(*P*10)–C(*P*11)	1·39 (2)
C(*B*4)–C(*B*5)	1·37 (2)	C(*P*10)–C(*M*3)	1·48 (2)
C(*B*5)–C(*B*6)	1·40 (2)	C(*P*11)–C(*P*12)	1·39 (1)
C(*P*1)–C(*P*2)	1·40 (1)	C(*P*12)–I(2)	2·09 (1)
C(6)–C(1)–C(7)	103·1 (9)	C(*P*3)–C(*P*2)–C(*M*1)	121·7 (8)
C(6)–C(1)–N(2)	107·7 (8)	C(*P*2)–C(*P*3)–C(*P*4)	118·3 (8)
C(7)–C(1)–N(2)	101·7 (8)	C(*P*2)–C(*P*3)–C(*M*2)	120·9 (8)
C(4)–C(3)–N(2)	103·2 (9)	C(*P*4)–C(*P*3)–C(*M*2)	120·8 (7)
C(4)–C(3)–O(1)	128 (1)	C(*P*3)–C(*P*4)–C(*P*5)	121·5 (7)
N(2)–C(3)–O(1)	129 (1)	C(*P*3)–C(*P*4)–O(3)	113·8 (7)
C(3)–C(4)–C(5)	103·7 (9)	C(*P*5)–C(*P*4)–O(3)	121·1 (8)
C(3)–C(4)–C(7)	101·5 (9)	C(*P*4)–C(*P*5)–C(*P*6)	120·8 (9)
C(5)–C(4)–C(7)	98·3 (8)	C(*P*1)–C(*P*6)–C(*P*5)	118·9 (8)
C(4)–C(5)–C(6)	105·0 (7)	C(*P*8)–C(*P*7)–C(*P*12)	119·0 (8)
C(1)–C(6)–C(5)	101·4 (7)	C(*P*8)–C(*P*7)–O(3)	121 (1)
C(1)–C(6)–O(2)	106·4 (8)	C(*P*12)–C(*P*7)–O(3)	119·5 (9)
C(5)–C(6)–O(2)	112·5 (9)	C(*P*7)–C(*P*8)–C(*P*9)	120 (1)
C(1)–C(7)–C(4)	92·9 (9)	C(*P*7)–C(*P*8)–I(1)	119·7 (7)
C(*B*1)–C(9)–N(2)	109·3 (9)	C(*P*9)–C(*P*8)–I(1)	120·5 (9)
C(9)–C(*B*1)–C(*B*2)	121 (1)	C(*P*8)–C(*P*9)–C(*P*10)	122 (1)
C(9)–C(*B*1)–C(*B*6)	120·5 (8)	C(9)–C(*P*10)–C(11)	118 (1)
C(*B*2)–C(*B*1)–C(*B*6)	117·9 (9)	C(9)–C(*P*10)–C(*M*3)	123 (1)
C(*B*1)–C(*B*2)–C(*B*3)	120 (1)	C(11)–C(*P*10)–C(*M*3)	119 (1)
C(*B*2)–C(*B*3)–C(*B*4)	121·5 (9)	C(*P*10)–C(*P*11)–C(*P*12)	122 (1)
C(*B*3)–C(*B*4)–C(*B*5)	121 (1)	C(*P*7)–C(*P*12)–C(*P*11)	120 (1)
C(*B*4)–C(*B*5)–C(*B*6)	118 (1)	C(*P*7)–C(*P*12)–I(2)	120·1 (7)
C(*B*1)–C(*B*6)–C(*B*5)	121·3 (9)	C(*P*11)–C(*P*12)–I(2)	120·3 (9)
C(*P*2)–C(*P*1)–C(*P*6)	121·7 (7)	C(1)–N(2)–C(3)	109·0 (9)
C(*P*2)–C(*P*1)–O(2)	112·0 (8)	C(1)–N(2)–C(9)	124·6 (9)
C(*P*6)–C(*P*1)–O(2)	117·1 (8)	C(3)–N(2)–C(9)	123 (1)
C(*P*1)–C(*P*2)–C(*P*3)	118·7 (8)	C(6)–O(2)–C(*P*1)	118·2 (7)
C(*P*1)–C(*P*2)–C(*M*1)	119·6 (7)	C(*P*4)–O(3)–C(*P*7)	116·4 (7)

comparison of the two (seven-atom) bicyclic lactam portions in (III) and 2-benzyl-6-*exo*-phenoxy-2-azabicyclo[2.2.1]heptan-3-one (IV) (Ammon *et al.*, 1982) with Nyburg's (1974) best-molecular-fit program gave r.m.s. and maximum differences of 0·029 and 0·052 Å, respectively. Similar comparisons between (IV) and three other bicyclic lactams gave values in the range of 0·008–0·046 and 0·015–0·076 Å (Ammon *et al.*, 1982). The dimensions of the diphenyl ether portion of (III) are similar to the values found in a number of thyroactive structures reported over the last ten years by Cody, the Camermans and others (many of these structures are listed by Cody, 1978).

The diphenyl ether moiety is in the *distal* conformation. The torsion angles C(*P*4)–O(3)–C(*P*7)–C(*P*12) and C(*P*5)–C(*P*4)–O(3)–C(*P*7) (called φ and φ' by Cody, 1978) of −87 (1) and −29 (1)° are within the ranges observed for thyroactive compounds. The corresponding values reported for 3,5-diiodo-2′,3′-dimethyl-D,L-thyronine (Fawcett *et al.*, 1976) are very similar at 85 and 23°.

There are no angle or out-of-plane effects associated with the methyl groups linked to the β-ring in (III), and it would appear that the methyl groups are not inordinately crowded. The exocyclic angles at C(*P*1) and C(*P*4) are unexpected, however, in that the O–C–C angles nearest to the neighboring methyl groups are smaller than the angles furthest away. One might have anticipated finding just the opposite trend to that observed, as a result of steric effects between the methyls and the ether O atoms. We note, however, that a similar angle trend occurs in 3,5-diiodo-2′,3′-dimethyl-D,L-thyronine where the [C(*P*6)–C(*P*1)–O(2), C(*P*2)–C(*P*1)–O(2)] and [C(*P*3)–C(*P*4)–O(3), C(*P*5)–C(*P*4)–O(3)] angle differences are 5·0 and 7·3°, respectively; the corresponding differences in (III) are 9·2 and 7·8°. O–C–C angle differences of several degrees have been observed in other compounds containing the diphenyl ether fragment [*e.g.* an 8° difference was reported for 3,5-diiodothyropropionic acid (Cody & Hazel, 1977)].

The torsion angles C(*P*1)–O(2)–C(6)–C(5) = 85·4, C(*P*2)–C(*P*1)–O(2)–C(6) = −21·2, C(*B*1)–C(9)–N(2)–C(3) = 137·8 and C(*B*6)–C(*B*1)–C(9)–N(2) = −66·7° in (III) are similar to the corresponding values reported in other [2.2.1] and [2.2.2]bicyclic lactams (Ammon *et al.*, 1982). Differences between (III) and the other structures involving the first two torsion angles may be attributable to the methyl group linked to C(*B*2) and steric interactions with the C(7) region in the bicyclic lactam. The larger values of the C(9)–N(2) and C(*B*1)–C(9) angles may be due to crystal-packing effects.

There are no unusual features in the molecular packing arrangement.

This work was supported in part by the NIH (AM-17458), and through the facilities of the University of Maryland's Computer Science Center.

References

AMMON, H. L., MAZZOCCHI, P. H., LIU, L., COLICELLI, E. C., DOHERTY, R. & STEWART, J. M. (1982). *Acta Cryst.* B**38**, 540–547.

CODY, V. (1978). *Recent Progress in Hormone Research*, Vol. 34, edited by R. O. GREEP, 437–475. New York: Academic Press.

CODY, V. & HAZEL, J. (1977). Abstr. Am. Crystallogr. Assoc. No. PB1.

CROMER, D. T. & MANN, J. B. (1968). *Acta Cryst.* A**24**, 321–324.

FAWCETT, J. K., CAMERMAN, N. & CAMERMAN, A. (1976). *Can. J. Chem.* **54**, 1317–1321.

JOHNSON, C. K. (1971). *ORTEP*-II. Report ORNL-3794. Oak Ridge National Laboratory, Tennessee.

MAZZOCCHI, P. H., AMMON, H. L., LIU, L., COLICELLI, E., RAVI, P. & BURROWS, E. (1981). *J. Org. Chem.* **46**, 4530–4536.

NYBURG, S. C. (1974). *Acta Cryst.* B**30**, 251–253.

STEWART, J. M., MACHIN, P. A., DICKINSON, C. W., AMMON, H. L., HECK, H. S. & FLACK, H. (1976). The XRAY system–version of 1976. Tech. Rep. TR-446. Computer Science Center, Univ. of Maryland, College Park, Maryland.

STEWART, R. F., DAVIDSON, E. R. & SIMPSON, W. T. (1965). *J. Chem. Phys.* **42**, 3175–3187.