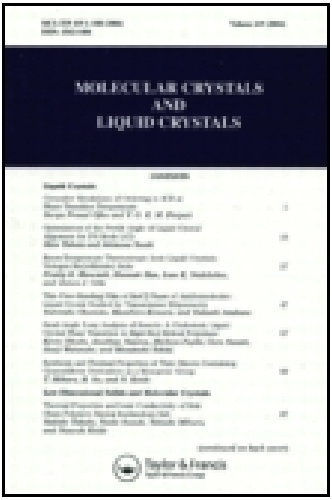

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Crystal and Molecular Structure of Synthetic Antidiabetic Compound: Derivatives of Tetrahydro Indoles-(1-N-Butyl-2,6,6′-Trimethyl-4-Oxo-4,5,6,7-Tetrahydro-3 Indole Acetic Acid) and Modeling Studies

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The crystal and molecular structure of (1-n-butyl-2,6,6'-trimethyl-4-oxo – 4,5,6,7 – tetrahydro – 3 indole acetic acid) with desirable anti hyperglycemic properties is reported. The title compound crystallises in orthorhombic space group Pbca with z =8. The unit cell dimensions are a=15.698(13)Å, b=11.639(2)Å, c = 18.506(3)Å, V =3381.2(29)Å^3, Dcal =1.145Mg/m^3. The cyclohexane ring adopts a sofa conformation. The structure is stabilized by C-H---O and O-H---O hydrogen bonds. Molecular modeling studies on this class of compounds and the classical antidiabetic agent tolbutamide reveal a structural basis for the similar biological activity exhibited by two totally structurally unrelated compounds.

Keywords: Anti diabetic compounds; modeling studies; Crystalstructure; Hypoglycemic agents; Tetrahydro indole derivatives

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INTRODUCTION

Among major endocrinal disorders in humans, non-insulin-dependent diabetes melitus(NIDDM) is assuming alarming global proportions, affecting 50–60 million people worldwide[1,2]. Of various factors related to the etiology of NIDDM, insulin deficiency has been identified to be the major cause which may be the result of insufficient secretion of insulin or desensitization of insulin receptors. Until recently, insulin secretagogues [2] like tolbutamide **1**and glibenclamide and to a lesser extent, biguanides (eg.metformin) have been used for the treatment of NIDDM. The former act by stimulating the release of insulin from the pancreas and the second persumably by extrapancreatic mechanisms[1]. In the last couple of years, insulin sensitizers belonging to the glitazone group have assumed importance among which troglitazone[3] and very recently rosiglitazone[4] have been introduced to clinical practice, but infrequent reports of liver disfunction have bedeviled some of the glitazones[2]. We had published earlier on a 4-oxo tetrahydroindole derivative, CGI 14600 as an insulin secretagogue with potency and profile similar to glibenclamide[5] and carried out modeling studies[6]. We had also synthesized [7] a class of 4-oxo-4,5,6,7-tetrahydroindole-3-acetic acids with hyperglycemic activity among which the 1-n-butyl **2(GO8778)** and 1-isobutyl **3(GO9001)** were the most potent with activity comparable to tolbutamide **1** in the normal fasted rat. Interestingly, unlike **1, 2** and **3** were also active in the streptozotocin-diabetic rat like metformin. Their profile included desirable features like no effect on blood lactate levels and decreasing liver glycogen level in the non- fasted rat and no inhibition of gluconeogenesis in rat[8]. Additinally they were relatively nontoxic in acute studies. In view of potential usefulness of new structural leads of this type in the treatment of diabetes, we have carried out crystallographic molecular modeling studies on **2** and **3** in relation to tolbutamide **1**. These could possibly help design newer antidiabetic molecules with useful profile and improved safety. The resuls are presented in this paper.

EXPERIMENTAL

2(GO8778) was synthesised from dimedone in three steps – addition to maleic acid, treatment of the adduct with acetic anhydride and reaction of the resultant triketoacid with n-butyl amine in acetic acid. Use of isobutyl amine in the last step in place of n-butyl gave **3(GO9001)**.

Crystals of **2** and **3** were obtained from toluene and benzene respectively. We have carried out single crystal X-ray studies on both the compounds. Details of the structure analysis of **3** have been published[9]. The results obtained for the crystal structure of **2** is reported here.

TABLE I Atomic cordinates ($\times 10^4$) and equivalent isotropic displacement parameters (Å $\times 10^3$) of non- hydrogen atoms with e.s. d's in paranthesis for **2**

Atom	*x*	*y*	*z*	*U(eq)*
N(1)	2102(2)	851(3)	3460(2)	87(1)
C(1)	−544(1)	1850(6)	4794(3)	151(2)
C(2)	−139(3)	1094(6)	4227(3)	123(2)
C(3)	789(3)	1317(5)	4167(3)	109(2)
C(4)	1229(3)	494(4)	3619(3)	98(2)
C(5)	2310(3)	1673(4)	2970(3)	82(1)
C(6)	3176(3)	1837(4)	3013(2)	76(1)
C(7)	3507(3)	1095(4)	3558(2)	80(1)
C(8)	2831(3)	496(4)	3824(3)	88(1)
C(9)	2808(3)	−402(5)	4401(3)	126(2)
C(10)	4413(3)	1001(4)	3817(3)	93(2)
C(11)	4900(4)	−2(6)	3521(5)	108(2)
C(12)	1711(3)	2310(4)	2503(2)	99(2)
C(13)	2166(3)	2829(4)	1856(2)	85(1)
C(14)	2376(4)	1886(5)	1312(3)	135(2)
C(15)	1588(3)	3695(5)	1484(3)	127(2)
C(16)	2975(3)	3411(4)	2103(3)	108(2)
C(17)	3583(4)	2683(4)	2569(3)	95(2)
O(1)	4358(2)	2885(3)	2577(2)	118(1)
O(2)	4842(9)	−243(13)	2924(6)	122(5)
O(3)	5382(12)	−550(15)	3950(5)	196(9)
O(2′)	4730(15)	−690(20)	3090(20)	229(18)
O(3′)	5589(14)	140(30)	3660(30)	330(20)

where $Ueq = 1/3\Sigma_i\Sigma_j a_i a_j a_i^* . a_j^*$

Crystal structure of 2

A colourless needle shaped crystal of dimension 0.45 × 0.075 x 0.125 mm was selected for X-ray data collection. All X-ray measurments were made at room temperature on an ENRAF-NONIUS (CAD-4 diffractometer)[13] using CuK_α radiation (λ=1.5418Å). The cell refinement and data reduction was done using CAD4-software[10]. The data were collected at 293K using ($\omega/2\theta$) scanning mode. Least-squres refinement of 25 well-centered reflection in the ranges $8° \leq \theta \geq 22°$ yielded a primitive orthorhombic cell. During data collection three standard reflections periodically monitored showed no significant intensity variation. Corrections for Lorentz and polarisation factors were applied to intensity value but no absorption correction was made. A total of 2996 intensities were collected in the range $4.78° \leq \theta \geq 69.87°$ of which 2994 were unique (R_{int} =0.039).

The structure was solved by means of direct methods SHELXS97 [11] and refined by full matrix least-squares method on $|F|^2$ using SHELXL97 [12]. Final refinement was carried out with anisotropic thermal parameters for all non H atoms. All the Hydrogens were geometrically fixed and allowed to ride on corresponding carbon atoms. The final cycle of full matrix refinement based on 2994 observed reflection($I>4\sigma I$) and 214 parameters converged to R =0.069 with goodness of fit= 0.956. The largest peak and the deepest hole in the final difference map were 0.217 and $-0.191 e.Å^{-3}$ respectively. The final positional co-ordinates of all atoms with equivalent isotropic thermal parameters, bond distances and bond angles for non-hydrogen atoms are listed in Tables I- II. Fig. 1 was plotted (displacement ellipsoids are drawn at 30% probabilty level) using ZORTEP Programme [16].

TABLE II Bond lengths (Å) and Bond angles (°) of non- hydrogen atoms with e.s. d's in paranthesis for **2**

Atoms	*Length*	*Atoms*	*Length*
N(1)-C(5)	1.358(5)	N(1)-C(8)	1.390(5)
N(1)-C(4)	1.463(5)	C(1)-C(2)	1.510(7)
C(2)-C(3)	1.483(6)	C(3)-C(4)	1.556(6)
C(5)-C(6)	1.375(6)	C(5)-C(12)	1.476(6)
C(6)-C(7)	1.426(6)	C(6)-C(17)	1.432(6)
C(7)-C(8)	1.361(6)	C(7)-C(10)	1.505(6)
C(8)-C(9)	1.495(6)	C(10)-C(11)	1.499(8)
C(11)-O(2)	1.143(12)	C(11)-O(3)	1.270(13)
C(12)-C(13)	1.520(5)	C(13)-C(16)	1.511(6)
C(13)-C(15)	1.520(6)	C(13)-C(14)	1.526(6)
C(16)-C(17)	1.541(6)	C(17)-O(1)	1.239(5)
C(5)-N(1)-C(8)	109.5(4)	C(5)-N(1)-C(4)	124.1(4)
C(8)-N(1)-C(4)	126.1(4)	C(3)-C(2)-C(1)	111.4(5)
C(2)-C(3)-C(4)	112.1(5)	N(1)-C(4)-C(3)	111.8(4)
N(1)-C(5)-C(6)	107.3(4)	N(1)-C(5)-C(12)	126.3(4)
C(6)-C(5)-C(12)	126.4(5)	C(5)-C(6)-C(7)	108.4(4)
C(5)-C(6)-C(17)	120.3(5)	C(7)-C(6)-C(17)	131.3(4)
C(8)-C(7)-C(6)	106.5(4)	C(8)-C(7)-C(10)	125.7(5)
C(6)-C(7)-C(10)	127.8(4)	C(7)-C(8)-N(1)	108.3(4)
C(7)-C(8)-C(9)	129.5(5)	N(1)-C(8)-C(9)	122.2(5)
C(11)-C(10)-C(7)	115.0(5)	O(2)-C(11)-O(3)	122.0(9)
O(3)-C(11)-C(10)	117.8(9)	C(5)-C(12)-C(13)	111.3(4)
C(16)-C(13)-C(12)	109.6(4)	C(16)-C(13)-C(15)	110.0(4)
C(12)-C(13)-C(15)	109.9(4)	C(16)-C(13)-C(14)	109.9(4)
C(12)-C(13)-C(14)	109.6(4)	C(15)-C(13)-C(14)	107.9(4)
C(13)-C(16)-C(17)	116.4(4)	O(1)-C(17)-C(6)	124.2(4)
O(1)-C(17)-C(16)	120.7(5)	C(6)-C(17)-C(16)	115.0(4)
O(2)-C(11)-C(10)	120.2(9)		

RESULTS AND DISCUSSIONS

The packing of the molecule is established by intermolecular O-H...O and C-H...O hydrogen bonds (Table III). The average e.s.d in bond lengths and bond angles are 0.006Å and 0.5° The fivemembered ring and carboxyl group are planar within experimental error. The cyclohexane ring is in the sofa conformation. The best plane passing through the five membered ring makes a dihedral angle of 4.3(2)° with the best plane passing through the cyclohexane ring. The carboxyl group oxygens are disordered with occupancies 0.6 and 0.4. This compound is known to loose carbon dioxide at room temperature if stored for a long period of time. The disorder of this group may be due to this phenomenon. Perspective view of **1,2** and **3** are shown in Figure 2 with the atom numbering schemes.

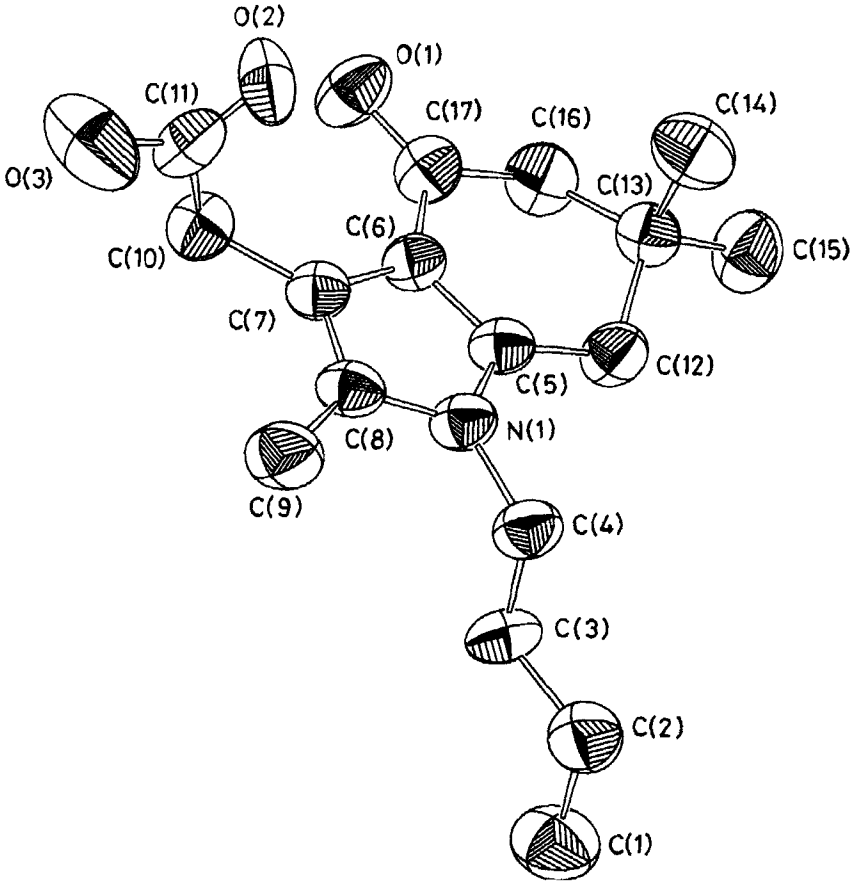

FIGURE 1 Zortep diagram of compound **2** with 50% probability displacement ellipsoids

TABLE III Hydrogen Bonds of **2**

Donor(D)	*Acceptor(A)*	*D...A(Å)*	*H...A(Å)*	*D-H...A(°)*	*Symmetry*
O(2)[a] -H(2)	H(2)...O(1)	2.7(1)	1.9(4)	152(4)	(4)
C(12)-H(12A)	H(12A)...O(2′)	3.4(4)	2.5(4)	155(1)	(2)
C(14)-H(14B)	H(14B)...0(3′)	3.5(5)	2.5(5)	165(1)	(3)
C(16)-H(16B)	H(16B)...O(3)[a]	3.5(4)	2.6(4)	152(1)	(1)
Equivalent positions	(1) -x+1, y+1/2, -z+1/2				
	(2) -x+1/2, y+1/2, z				
	(3) x-1/2, y, -z+1/2				
	(4) -x+1, y-1/2, z+1/2				

a. O2 and O3 are disordered, O2′ and O3′ are the alternate positions of O2 and O3. Hydrogens for O2 was fixed and not refined

Structure Activity correlation

As noted in our previous study of CGI 14600[6] the conformation observed in the crystal structure could be the only one or one of the possible bio-active conformation. Additionally we have carried out energy calculations for single bond rotations in **2** and **3**, using BIOSYM software [14] and CFF 91 forcefield. Thus in **2**, C8-N1-C4-C3 torsion angle (91.1°) was monitored. The energy value for the crystal structure, –5.15 Kcal/mole was nearly the same when this torsion was rotated through 180° (-5.17 Kcal/mole).

Likewise in **3** with C8-N1-C4-C3 angle (77.2°), the energy value of the crystal structure (4.4 Kcal/mole)was nearly the same. In both cases, the crystal conformations correspond very nearly to the minimum energy conformations of the isolated molecules. Thus although crystal structures are not always dependable indicators for determination of bio-active conformations, there is justification to believe that they may still represent rough approximations of the same. Hence these molecules were superimposed in their crystalline state conformations with tolbutamide **1**[15] inorder to determine the degree of overlap of marker groups. The best fit was obtained with superposition of N2-C5-O3-N1-C4 group in **1** with C7-C8-C9-N1-C4 framework of **2** and **3** with r.m.s deviation of 1.106Å and 1.107Å respectively. Table IV shows the relevent torsion angles of **1,2,3** in the superposed region. It can be seen that the hydrophobic and hydrophilic regions of **2** and **3** superpose very well with those of **1** (Figure 3) explainig their common biological activity. Thus the regions indicated in Figure 3. may be important for the receptor binding. The result agrees with our earlier comparison of another 4-oxo-1,2,3,4-tetrahydroindole with glibenclamide[6]. It appears in these cases

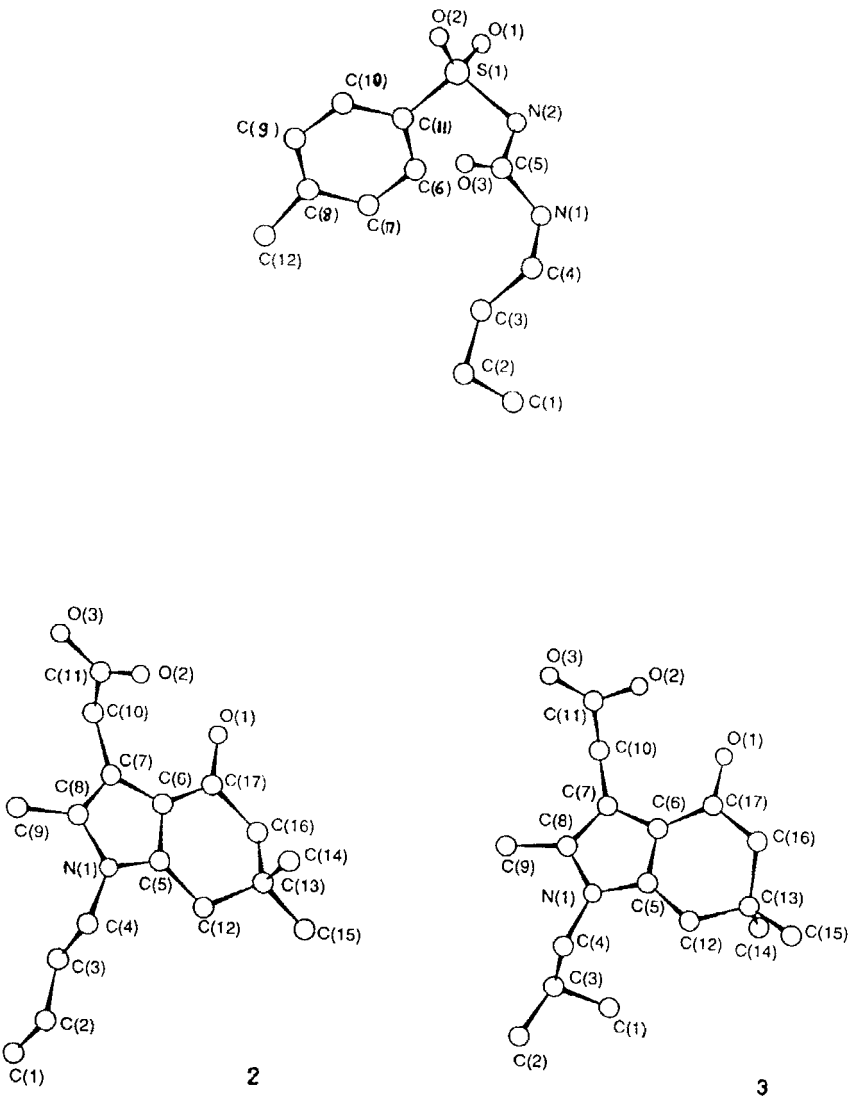

FIGURE 2 Perspective view of **1,2** and **3** with atom numbering schemes

that N-1, C-8 and C-7 of the indole moiety and NHCONH unit in **1** may serve as spacers. Additionally the cyclohexane ring of **2** and **3** may play an auxiliary role in binding to hydrophobic pocket in the receptor.

The study offers a plausible hypothesis for the common biological activity and relationships of the 2-substituted-4,5,6,7,-tetrahydroindole acetic acids **2** and **3**

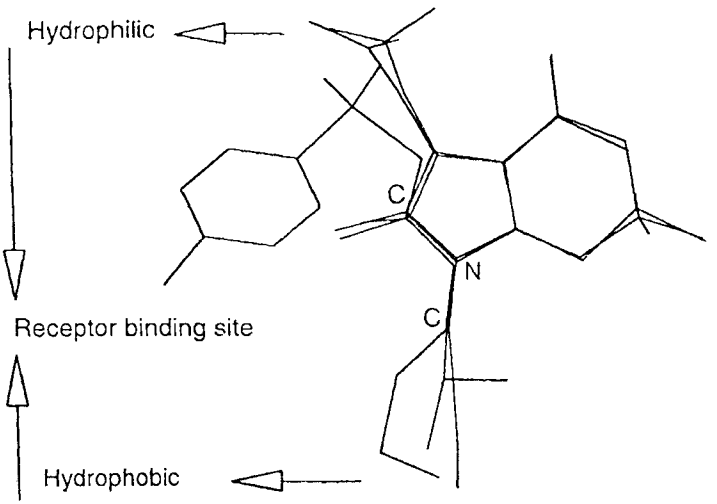

FIGURE 3 Superposition **1, 2** and **3** showing the probable receptor binding site

on the one hand and tolbutamide **1** on the other and offers some clues to the receptor topography. This approach may help design newer molecules with better activity profile and clinical utility.

TABLE IV Torsion angles of **1,2** and **3** (°) involving non- hydrogen atoms with e.s. d's in paranthesis

Bonds	***1***	***2***	***3***
C(1)-C(2)-C(3)-C(4)	−70.0(4)	176.4(2)	–
C(2)-C(3)-C(4)-N(1)	−178.2(3)	169.3(2)	−175.1(2)
C(3)-C(4)-N(1)-C(5)	88.3(3)	−82.5(2)	77.2(2)
C(4)-N(1)-C(8)-C(7) [C(4)-N(1)-C(5)-N(2)][a]	−178.0(2)	−174.8(2)	179.2(2)
N(1)-C(8)-C(7)-C(10) [N(1)-C(5)-N(2)-S(1)][a]	157.0(2)	178.0(2)	177.7(2)
C(8)-C(7)-C(10)-C(11) [C(5)-N(2)-S(1)-O(1)][a]	59.0(2)	81.1(2)	104.2(2)
C(7)-C(10)-C(11)-O(3) [C(5)-N(2)-S(1)-O(1)][a]	−171.0(2)	−138.7(2)	−108.8(3)
C(7)-C(10)-C(11)-O(2)	–	42.2(2)	71.2(3)

a. Tolbutamide numbering as given in Tolbutamide structure[15]

Acknowledgements

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