Synthesis, crystal and molecular structure of 1,3-dimethyl-10benzyl-2,4,9-trioxo-1,3,6,7,8,10-hexahydro-1,3-diazepino-[2,1-*f*]-purine

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The crystal and molecular structure of the title compound, obtained as a result of intramolecular cyclization of 4-(8-benzylaminotheophylline-7-yl)-butanoic acid, has been determined by X-ray diffraction. Two rings, (comprising the theophylline skeleton) are planar, but the 7-membered 1,3-diazepinon ring is undulated, with a twisted chair conformation.

Introduction

The central nervous system stimulatory properties of 1,3-dimethyl-2,8-dioxo purine (theophylline) are well known. Recently, we have found that anellation of the six-membered lactam ring at the 7,8-positions of theophylline changed the profile of its activity. The principal pharmacological effect of 1, 3-dimethyl-2, 4, 8trioxo - 1, 3, 6, 7 - tetrahydro - pirimido - [2, 1, -f] purine derivatives was a neurosedative action (Pawłowski et al., 1990). This unexpected result, due probably to the chemical properties of the third lactam ring, prompted us to extend the investigation in this field. We describe in this work a new tricyclic purine in which the sevenmembered lactam ring is fused in the 7,8-position of theophylline, and its physico-chemical and pharmacological properties. Incorporation of the seven-membered ring allows one to expect a higher lipophility and a better absorption by the central nervous system.

Experimental

Melting points are uncorrected. TLC: 0.25-mm layer of silica gel G 60 (Merck): solvent system: benzene + acetone 7 + 3; ¹H nmr spectra were recorded on Bruker AC 300 (300 MHz) using TMS as the internal standard. Protons exchangeable with D_2O are indicated by ^{ex}). The mass spectra were obtained using a Finnigan MATCH 7A spectrometer, operating at an ionizing energy of 70 eV. The samples were introduced into the source via a direct inlet system.

Ethyl-4-(8-benzylaminotheophylline-7-yl)-butanoate, 5

A mixture of the sodium salt of 2 (46 g; 0.15 mol) and ethyl 4-chlorobutanoate (45.2 g; 0.3 mol) in 50 cm³ of DMF was refluxed for 10 hr. After cooling, the precipitate was filtered off and washed with 2% NaOH and then with water. Recrystallization from EtOH results in 5. m.p. 148-149°C; yield 51; $R_f = 0.50$. Anal. Calc. for C₂₀H₂₅N₅O₄ (399.4): C = 60.13, H = 6.31, N = 17.53: Found: C = 60.18. H = 6.29, N = 17.90. MS (*m/e* rel. intensity): 399 (*M*⁺ 100), 354(18), 285(21), 234(20), 205(14), 194(11), 115(82), 91(88); ¹H nmr (CDCl₃): 1.24(3H, t, I = 7, CH₂CH₃), 2.00-2.09 (2H,

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m, CH₂CH₂C₂), 2.35 (2H, t, I = 7, CH₂CO), 3.37 (3H, s, N₁CH₃), 3.53 (3H, s, N₃CH₃), 4.05-4.13 (4H, m, N₇CH₂, CH₂CH₃), 4.68 (2H, d, I = 5.5, CH₂C₆H₅), 6.07 (1H, t, I-5.5NH CH₂^{2x}), 7.27-7.40 (5H, m, C₆H₅).

4-(8-benzylaminotheophylline-7-yl)butanoic acid, 6

To the solution of Na (6.0 g) in 240 cm³ of MeOH, 3 (7.0 g, 0.0175 mol) was added and the mixture was refluxed for 2 hr. Then the solvent was distilled off under reduced pressure. The crude residue was treated with 500 cm³ of water, and the solution was adjusted to *p*H 3 with 10% HCl. The product was filtered off, washed with water and recrystallized from EtOH; m.p. 217– 218°C; yield 95%; $R_f = 0.04$. Anal. Calc. for $C_{18}H_{21}N_5O_4$ (371.4); C = 58.21, H = 5.70, N = 18.86. Found: C = 58.17, H = 5.62, N = 19.37. Ms (*m*/*e* rel. intensity): 371 (M^+ 45), 285(12, 234(12), 194(13), 91(100), 82(15). ¹H nmr (DMSO); 1.84–1.93 (2H, m, CH₂CH₂CH₂), 2.22 (2H, t, I = 7, CH₂CO), 3.17 (3H, s, N₁CH₃), 3.33 (3H, s, N₃CH₃), 4.07 (2H, t, I = 7, N₇CH₂), 4.56 (2H, d, I = 5.5, CH₂C₆H₅), 7.23–7.38 (5H, m, C₆H₅), 7.60 (1H, t, I = 5.5, NHCH₂^{ex}), 12.14 (1H, brs, COOH^{ex}).

1,3-dimethyl-10-benzyl-2,4,9-trioxo-1,3,6,7,8,10hexahydro-1,3-diazepinol[2,1-f]-purine **7**

The mixture of 6 (10.0 g) and 100 cm³ of SOCl₂ was refluxed for 2 hr. The excess of SOCl₂ was distilled off under reduced pressure, the residue was treated with benzene (30 cm³) and then distilled off. The distillation with benzene was repeated several times. The residue after evaporation was crystallized from EtOH. m.p. 196–197°C; yield 86%; $R_f = 0.55$. Anal. cal. for C₁₈H₁₉N₅O₃ (353.4); C = 61.18, H = 5.42, N = 19.82. Found: C = 61.12, H = 5.31, N = 19.96. MS (rel. intensity): 353 (M^+ 44). 325(14), 234(21), 193(13), 91(100). ¹H nmr (CDCl₃): 2.40–2.47 (2H, m, CH₂CH₂CH₂), 2.55 (2H, t, I = 7, CH₂CO), 3.39 (3H, s, N₁CH₃), 3.59 (3H, s, N₃CH₃), 4.27 (2H, t, I = 7, N₅CH₂), 5.11 (2H, s, CH₂C₆H₅), 7.26–7.33 (5H, m, C₆H₅).

X-ray data collection of 7

Crystals of 7 were obtained in a hot box from ethanol (96%). One crystal was selected of size 0.3, 0.3, 0.4 mm and used on an Enraf-Nonius CAD4 single-crystal diffractometer, employing Cu $K\alpha$ ($\overline{\lambda}$ = 1.54178 Å) radiation and a graphite monochromator. The unit-cell dimensions were determined from the angular settings of 25 reflections (8 < θ < 30°). The intensity data of 3293 reflections were measured, using the $\omega - 2\theta$ technique. The intensity of the primary beam was checked throughout the data collection by monitoring three reference reflections every 70 reflections. The variation in the intensities over the course of the data collection was negligible. After Lorentz and polarization corrections, the data were reduced to $|F_0|$ values. The reflections were considered as "observed" if $|F_0|$ $> 4\sigma |F_0|$ and the number of the data were reduced to 3024 reflections.

Crystal data: $C_{18}H_{19}N_5O_3$; $M_r = 353.38$; monoclinic; $P2_1/a$; a = 14.3337(9), b = 8.7048(3), c = 15.0844(19)Å, $\beta = 116.517(72)^\circ$; V = 1684.11(6.03)Å³; $D_\beta = 1.394$; z = 4; $\mu = 7.69$ cm⁻¹; F(000) = 744; T = 293 K.

Structure determination and refinement

For the solution of the phase problem by direct methods the SHELXS package of computer programs was used [R(E) = 0.22, Karle *et al.*, 1966] (Sheldrick, 1986). Then, the structure was refined by full-matrix least-squares on $|F_0|$ values, using SHELX-76 (Sheldrick, 1976). Anisotropic temperature factors were applied to all non-H-atoms. Hydrogen atoms were located on an electron density difference map and their positional parameters refined with isotropic temperature parameters equal to 1.5 times those of the values for the respective parent carbon atoms. The scattering factors were taken from the International Tables for X-ray Crystallography (1974). The agreement factors R =0.0435 and $R_{\rm w} = 0.0432$ with w = $6.97/\delta^2(F)$ were calculated for 3024 reflections and 293 refined parameters. The maximum parameter change in the last cycle of refinement $\Delta/\sigma = 0.075$, and maximum and minimum electron densities in the final Fourier map were 0.09 and -0.09 e Å⁻³. The empirical correction of the secondary extinction with g = 0.01914 was applied. All calculation were performed on a PC Amstrad 1512 computer.

 Table 1. Nonhydrogen fractional atomic coordinates, equivalent temperature factors (A**2) with esd's in parentheses

Atom	x	у	Z.	U
N1	-405(1)	2174(2)	3966(1)	39(0)
N3	-1452(1)	256(2)	4178(1)	43(0)
N5	-38(1)	-1058(2)	2777(1)	37(0)
N10	1147(1)	-248(2)	2140(1)	36(0)
N12	510(1)	1395(2)	3026(1)	35(0)
02	-1325(1)	2673(2)	4825(1)	60(0)
04	-1606(1)	-2176(2)	3530(1)	65(0)
09	1406(1)	-1451(2)	949(1)	58(0)
C1	12(2)	3725(3)	4108(2)	55(1)
C2	-1076(1)	1759(2)	4354(1)	42(0)
C3	-2217(2)	-140(4)	4544(2)	64(1)
C4	-1214(2)	-900(2)	3651(1)	43(0)
C6	-13(2)	-2687(2)	2543(2)	47(0)
C7	-555(2)	-2947(2)	1432(2)	51(0)
C8	-305(2)	-1702(2)	854(1)	48(0)
C9	813(2)	-1166(2)	1303(1)	41(0)
C11	539(1)	47(2)	2627(1)	34(0)
C13	-131(1)	1113(2)	3452(1)	33(0)
C14	-492(1)	-362(2)	3317(1)	35(0)
C15	2194(1)	454(2)	2540(1)	40(0)
C16	2260(1)	1823(2)	1954(1)	37(0)
C17	2871(2)	1760(3)	1459(2)	49(0)
C18	2962(2)	3023(3)	941(2)	59(1)
C19	2446(2)	4354(3)	917(2)	60(1)
C20	1838(2)	4435(3)	1409(2)	61(1)
C21	1744(2)	3180(2)	1926(2)	49(0)

The final atomic parameters are listed in Tables 1, 2, and 3. The geometrical calculations were carried out with the CSU program (Vicković, 1988).

Results and discussion

The substrate for the synthesis of 1, 3-dimethyl-10benzyl-2, 4, 9-trioxo-1, 3, 6, 7, 8, 10-hexahydro-1, 3diazepino [2, 1-]purine was 8-benzylaminotheophylline 2 obtained earlier (Gorczyca et al., 1975). In the reaction of the sodium salt of 2 with methyl(ethyl)-4-chlorobutanoate in DMF only one product was separated. Its structure, as methyl(ethyl)-4-(8-benzyl-aminotheophylline-7-yl)butanoate 4 (5), was confirmed by spectrophotometrical analyses (MS, ¹H nmr) as well as by a chemical route. The same product 5 was also obtained in the reaction of ethyl-4-(8-bromotheophylline-7yl)butanoate with benzyloamine. Refluxing 4 with the excess of CH₃ONa, afforded 4-(8-benzylaminotheophylline-7-yl) butanoic acid 6, isolated after acidification of the reaction mixture to pH3. Intramolecular cyclization of the acid 6, via the corresponding chloride, to tricyclic lactam 7 was proposed on the basis of spectral data (¹H nmr, MS). In ¹H nmr spectrum of the acid 6, exchangeable with D_2O_1 , a triplet signal of NH group $(\delta = 7.60)$ in 8-position and a broad singled signal of COOH ($\delta = 12.14$) were observed. Disappearance of above described signals in the spectrum of 7 is evidence

 Table 2. Hydrogen fractional atomic coordinates, isotropic temperature factors (A**2) with esd's in parentheses

Atom	x	у	z	U
H11	16(2)	397(2)	351(2)	64
H12	64(2)	379(2)	478(2)	64
H13	-49(2)	450(3)	407(2)	64
H31	-233(2)	-128(3)	449(2)	76
H32	-285(2)	11(3)	413(2)	76
H33	-204(2)	47(3)	518(2)	76
H101	76(2)	-297(2)	284(2)	55-
H102	-40(2)	-321(2)	286(2)	55
H111	-34(2)	-398(2)	129(2)	59
H112	-137(2)	-297(2)	118(2)	59
H121	-76(2)	-72(2)	75(1)	55
H122	-50(2)	-203(2)	14(2)	55
H151	238(2)	79(2)	324(1)	49
H152	266(2)	-39(2)	253(1)	49
H17	320(2)	78(2)	143(2)	59
H18	337(2)	291(3)	58(2)	70
H19	248(2)	525(3)	51(2)	71
H20	146(2)	543(3)	139(2)	75
H2 1	129(2)	321(2)	226(2)	62

 Table 3. Nonhydrogen anisotropic temperature factors (A**2) with esd's in parentheses

Atom	U 11	U22	<i>U</i> 33	U12	<i>U</i> 13	U23
N1	45(1)	40(1)	40(1)	-1(1)	27(1)	-7(1)
N3	37(1)	62(1)	36(1)	-2(1)	22(1)	3(1)
N5	52(1)	30(1)	37(1)	-5(1)	27(1)	-3(1)
N10	42(1)	35(1)	38(1)	-2(1)	25(1)	-5(1)
N12	42(1)	33(1)	37(1)	-4(1)	24(1)	-5(1)
02	67(1)	71(1)	60(1)	14(1)	45(1)	-6(1)
04	80(1)	62(1)	68(1)	-32(1)	47(1)	-11(1)
09	76(1)	58(1)	64(1)	-3(1)	52(1)	-15(1)
C1	71(2)	41(1)	67(2)	-4(1)	44(1)	-16(1)
C2	39(1)	56(1)	35(1)	7(1)	20(1)	2(1)
C3	47(1)	99(2)	58(1)	-9(1)	35(1)	2(1)
C4	45(1)	52(1)	35(1)	-9(1)	21(1)	0(1)
C6	70(1)	29(1)	50(1)	-4(1)	33(1)	-1(1)
C7	65(1)	40(1)	53(1)	-11(1)	32(1)	-12(1)
C8	59(1)	49(1)	38(1)	-9(1)	23(1)	-8(1)
C9	58(1)	34(1)	40(1)	1(1)	30(1)	-3(1)
C11	41(1)	32(1)	33(1)	-1(1)	21(1)	-1(1)
C13	37(1)	36(1)	31(1)	-1(1)	19(1)	-3(1)
C14	42(1)	37(1)	33(1)	-4(1)	22(1)	-2(1)
C15	39(1)	41(1)	43(1)	1(1)	21(1)	2(1)
C16	38(1)	39(1)	36(1)	-4(1)	19(1)	-3(1)
C17	52(1)	54(1)	51(1)	-4(1)	33(1)	-4(1)
C18	63(1)	76(2)	50(1)	-20(1)	35(1)	-3(1)
C19	65(2)	60(1)	51(1)	-21(1)	21(1)	10(1)
C20	69(2)	41(1)	74(2)	-2(1)	34(1)	8(1)
C21	58(1)	41(1)	59(1)	0(1)	35(1)	2(1)

of the cyclization reaction of 6 to 7. Also, the results of X-ray analysis of 7 have confirmed the above suggested structure.

Bond lengths and bond angles date for the structure are given in Tables 4 and 5, and a PLUTO (Motheweel, 1976) diagram of the molecule is given in Fig. 1. Figure 2 shows the packing of the molecules in the unit cell. A

	Table 4.	Bond lengths (A) with esd's	in parenth	eses
N1	C1	1.453(3)	04	C4	1.221(3)
N1	C2	1.379(2)	O9	C9	1.214(3)
N1	C13	1.371(2)	C4	C14	1.418(3)
N3	C2	1.395(2)	C6	C7	1.517(4)
N3	C3	1.472(4)	C7	C8	1.530(3)
N3	C4	1.415(3)	C8	C9	1.508(4)
N5	C6	1.466(3)	C13	C14	1.365(2)
N5	C11	1.352(2)	C15	C16	1.512(2)
N5	C14	1.388(3)	C16	C17	1.383(4)
N10	C9	1.386(2)	C16	C21	1.384(3)
N10	C11	1.392(3)	C17	C18	1.388(4)
N10	C15	1.477(2)	C18	C19	1.366(4)
N12	C11	1.328(2)	C19	C20	1.376(5)
N12	C13	1.358(2)	C20	C21	1.383(4)
02	C2	1.221(2)			

Table 5.	Bond angles	(deg)	with esd	's	in	parenthese	es
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C1	N1	C2	120.0(2)	N10	C9	09	119.6(2)
C1	N1	C13	120.4(2)	N10	C9	C8	116.9(2)
C2	N1	C13	119.6(1)	09	C9	C8	123.5(2)
C2	N3	C3	116.0(2)	N5	C11	N10	122.1(1)
C2	N3	C4	127.2(2)	N5	C11	N12	114.1(1)
C3	N3	C4	116.8(2)	N10	C11	N12	123.8(2)
C6	N5	C11	124.4(2)	N1	C13	N12	124.8(2)
C6	N5	C14	129.2(2)	N1	C13	C14	122.2(1)
C11	N5	C14	105.7(1)	N12	C13	C14	113.0(1)
C9	N10	C11	123.0(2)	N5	C14	C4	132.2(2)
C9	N10	C15	119.0(2)	N5	C14	C13	104.6(1)
C11	N10	C15	118.0(1)	C4	C14	C13	123.1(2)
C11	N12	C13	102.7(1)	N10	C15	C16	113.9(1)
N1	C2	N3	116.7(1)	C15	C16	C17	120.3(2)
N1	C2	O2	121.1(2)	C15	C16	C21	121.2(2)
N3	C2	O2	122.2(2)	C17	C16	C21	118.4(2)
N3	C4	O4	121.4(2)	C16	C17	C18	120.9(2)
N3	C4	C14	111.2(2)	C17	C18	C19	120.0(3)
04	C4	C14	127.4(2)	C18	C19	C20	119.7(3)
N5	C6	C7	110.8(2)	C19	C20	C21	120.6(3)
C6	C7	C8	112.9(2)	C16	C21	C20	120.4(2)
C7	C8	C9	115.8(2)				



a)



Fig. 1. Structure of molecule 7: (a) with atom numbering system, (b) stereoview.



Fig. 2. Unit-cell packing.

 Table 6. Torsional angle values in the 7-membered ring (deg)

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N5-C6-C7-C8	41.1(3)	C6-C7-C8-C9	40.7(3)
C7-C8-C9-N10	-73.0(3)	C11-N5-C6-C7	-72.7(3)
C8-C9-N10-C11	7.1(3)	N10-C11-N5-C6	6.4(3)
C9-N10-C11-N5	41.2(3)		
C8-C9-N10-C11 C9-N10-C11-N5	7.1(3) 41.2(3)	N10-C11-N5-C6	6.4

remarkable feature of the structure is the orientation of the benzyl group relative to the fused tricyclic system [torsional angles C9–N10–C15–C16 = 76.4(2)°, N10–C15–C16–C21 = 67.4(2)°]. An examination of the space filling model shows that this orientation minimizes the interaction between the phenyl ring, the C9=O9 group and the imide nitrogen N12. Intermolecular packing effects may also contribute to the observed geometry of the molecule.

Both rings from the fused system, which comprise the theophylline skeleton, are planar. The maximum deviations of the C14 atom from the planes of respective rings are -0.017(1) in the six-membered ring and 0.004(1)Å in the five-membered ring. These two rings are inclined each to each other at 1.6(1)°. All bond lengths and angles in this part of the molecule are similar to those reported for the other structures with theophylline skeleton (Blythin et al., 1986; Brown et al., 1977; Rosen et al., 1971; Takashi et al., 1987). The third ring from this system, 7-membered 1, 3-diazepinon ring, is undulated. In this ring, on the basis of the torsional angle values (Table 6), we observed the twisted chair conformation with an axis of symmetry bisecting the N10-C11 bond and the atom C7. The respective asymmetry parameter $\Delta C_2(C7) = 0.56$ (Griffin et al., 1984).

We are planning to use the structure described as a model compound for searching the relationships between purines with six- and seven-membered rings in respect of their influence on pharmacological activity.

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Structure factor data have been deposited with the British Library, Boston Spa, Wetherby, West Yorkshire, UK as supplementary publication No. 60680 (19 pages).