Syntheses and Conformational Analyses of Some 3-Amino-2,5-dioxo-2,3,4,5-tetrahydro-1*H*-1-benzazepine Derivatives: X-Ray Crystal Structure of 3*S*-3-[[(1,1-Dimethylethoxy)carbonyl]amino]-2,5-dioxo-2,3,4,5-tetrahydro-1*H*-1-benzazepine

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The constrained dipeptide mimic **1** was synthesized from **2** in three steps with 65% overall yield. Analyses of the ^{1}H nmr data of a number of 3-amino-2,5-dioxo-2,3,4,5-tetrahydro-1*H*-1-benzazepine derivatives led to the conclusion that these compounds adopt a similar conformation and that this ring system is rigid. X-ray crystallography was used to define the structure of **3**, and computer-aided energy minimization of **6** gave a preferred conformation similar to that observed in the crystal of **3**.

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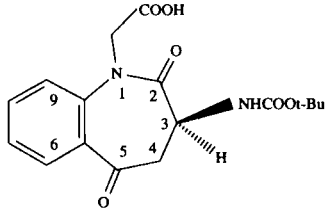
As part of a study of the syntheses of conformationally constrained peptide analogues, we chose the amino acid derivative **1** as a constrained dipeptide mimic. Structurally related mimics have been used successfully in the preparation of a number of potent ACE-inhibitors [1,2]. It was envisaged that **1** could be smoothly incorporated into a Merrifield-type solid phase peptide synthesis [3].



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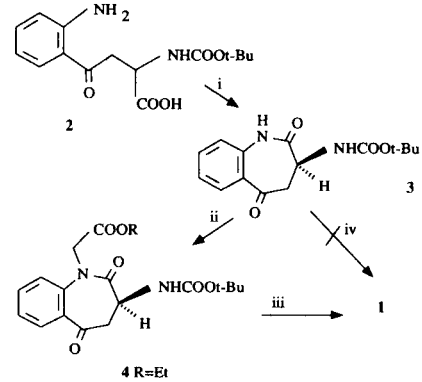
Few 3-amino-2,5-dioxo-2,3,4,5-tetrahydro-1*H*-1-benzazepines have been documented in the literature [4-11] and there have been scant nmr, infrared, or mass spectral data reported to date [4,5]. Also, there have not been any nmr, computational or X-ray studies on any previously reported 2,5-dioxo-2,3,4,5-tetrahydro-1*H*-1-benzazepines [4-23]; such an analysis of **1** is of primary importance for its use as a conformational constraint of bioactive peptides. Moreover, it was anticipated that the synthesis of **1** would be readily achieved using chemistry developed for similar systems [5,6].

We now report an efficient synthesis of the 2-(3-amino-2,5-dioxo-2,3,4,5-tetrahydro-1*H*-1-benzazepin-1-yl)ethanoic acid derivative **1** and the first nmr, computational and X-ray conformational studies on the 2,5-dioxo-2,3,4,5-tetrahydro-1*H*-1-benzazepine ring system.

The carboxylic acid **1** was synthesized in three steps from the *N*-protected L-kynurenine derivative **2** [5] (Scheme 1) in 65% overall yield. Cyclization of **2** using dicyclohexylcarbodiimide and *N*-hydroxybenzotriazole furnished the colourless lactam **3** in 70% yield. This was accompanied by the appearance in the ^{1}H nmr spectrum of an exchangeable one-proton singlet at δ 8.21 ppm (assigned to the anilide NH proton), and an amide carbonyl absorption band in the infrared spectrum at 1668 cm^{-1}. Alkylation of the anilide nitrogen atom with ethyl or benzyl bromoacetate and hydrated potassium carbonate proceeded smoothly in acetone in the presence of a catalytic amount of tetrabutylammonium bromide; this quantitatively yielded the esters **4** and **5**, respectively, as yellow

Scheme 1



4 R=Et

5 R=Bzl=benzyl

i) Dicyclohexylcarbodiimide/*N*-Hydroxybenzotriazole

ii) K_2CO_3 (hydrate)/ Bu_4N Br/ Et- or $BzlO_2CCH_2Br$

iii) NH_4CO_2H / Pd-C (5 %)

iv) $BrCH_2CO_2H$ / OH^- (2 eq)

glasses. All attempts to alkylate **3** directly to **1** with bromoacetic acid in the presence of base, failed. This was attributed to the less electrophilic nature of a methylene group adjacent to a carboxylate anion relative to one adjacent to an ester.

Base hydrolysis of the ester substituent in **4** or **5** unexpectedly gave a complex mixture of ring-opened products [24], resulting from an unusual intramolecular nucleophilic catalysis. However, catalytic transfer hydrogenation [25] of the benzyl ester **5** furnished the free carboxylic acid **1** after a few minutes [26] as a colourless glass in 95% yield after purification. Extension of the reaction time led to the reduction of the aryl carbonyl to the alcohol [24]. It was interesting to note that each lactam had an ultraviolet absorption maximum at a significantly shorter wavelength than that of **2**, in agreement with previous findings [5,27].

Crystallographic, computational and nmr data for this ring system indicate a high degree of rigidity. The evidence for this is discussed below:

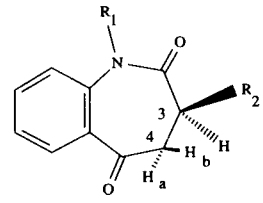
The room temperature T_1 relaxation times of C3 and C4 in **3** were within 10% of those of the phenyl carbons (NT_1 = 0.5-0.6), which suggests a great deal of rigidity in this ring system. Flexing of the dioxoazepine ring would be reflected by an increase in the NT_1 values of these carbons over those in the aromatic ring [28].

In the ^1H nmr spectrum of **5**, each benzylic proton gave rise to a doublet [δ 5.16 ppm and δ 5.10 ppm (^2J = 12.1 Hz)], possibly as a result of the hindrance of free rotation by the nearby bulky *t*-butyl group.

The *N*-methylene protons in **4**, **5** and **1** are chemical shift inequivalent and gave rise to characteristic, very well separated (100 Hz) doublets near δ 4.7 ppm and δ 4.4 ppm. This observation is indicative of a certain rigidity, as flexing of the ring would lead ultimately to the merging of these signals.

The signals ascribed to H4a and H4b in the N-protected lactams **1**, **3-5**, and **7-9** (Figure 1) are typical of a rigid ring system and all have very similar chemical shifts and coupling constants (see Table 1). In **3**, these were doublets of doublets at δ 3.31 ppm (^2J = 19.1, ^3J = 2.8 Hz) and δ 3.00 ppm (^2J = 19.0, ^3J = 13.0 Hz), respectively. The consistently large difference in the vicinal (^3J) coupling constants for these lactams implies rigidity since an averaged vicinal coupling constant of 5-8 Hz would be expected in a flexible system [30]. H4a and H4b were assigned on the following basis:

The Karplus equation [29,30] was applied to the solid-state conformation of **3** (see Table 2) to estimate the vicinal coupling constants expected for H4a and H4b (with use of constants derived for amino acids [31]). The resulting calculated ^3J values for H4a and H4b (1.8, 9.7 Hz in **3a** and 3.9, 12.0 Hz in **3b**) were compared with those observed in the ^1H nmr spectrum for **3**. Hence, the assignment of the doublet of doublets at δ 3.31 ppm to H4a and those at δ 3.00 ppm to H4b in **3** was made. Analogous assignments in the other lactams were justified on the basis of the similar nature of the signals for these protons, both in chemical shift and vicinal coupling constants (Table 1).



	R_1	R_2 [a]
1	CH_2CO_2H	NH-Boc
3	H	NH-Boc
4	CH_2CO_2Et	NH-Boc
5	CH_2CO_2Bzl	NH-Boc
6 [b]	H	NH_2
7 [4]	H	NHCOPhF
8 [24]	Bzl	NH-Boc
9 [24]	CH_2CO_2Me	NH-Boc

[a] Boc = "t-butyloxycarbonyl". [b] **6** was prepared as the hydrochloride salt by treatment of **3** with 4M HCl/dioxan.

Figure 1. The structures of the dioxobenzazepines studied in this paper.

Table 1

A comparison of the vicinal coupling constants (^3J) observed [a] for the 4-CH_2,3-CH fragment in lactams **1**,**3**,**4**,**5**,**7**,**8** and **9** with those calculated from the torsion angles [b] in this fragment for crystal structures **3a** and **3b** [c].

	δ_{Ha}[d]	^3J(Hz)	δ_{Hb}[d]	^3J(Hz)
3a	-	1.8	-	9.7
3b	-	3.9	-	12.0
1	3.26	3.6	2.99	12.7
3	3.31	2.8	3.00	13.0
4	3.27	4.2	2.95	12.8
5	3.24	4.0	2.91	12.7
7 [4]	3.45	3.1	3.05	13.0
8 [24]	3.24	4.1	2.83	12.8
9 [24]	3.29	4.1	2.98	12.7

[a] From the ^1H nmr spectra run on a Bruker AM-300 (300 MHz) spectrometer. [b] The relationship between vicinal coupling constants and torsion angles has been well documented [29-31]. [c] See Table 2 for crystal data. [d] In ppm relative to tetramethylsilane (chloroform-d_1).

Table 2

Selected dimensions in the 2,5-dioxo-2,3,4,5-tetrahydro-1*H*-1-benzazepine system. The values for **3** are for the X-ray structure (e.s.d.'s in parentheses) and for **1** and **6** for their AM1-optimized structures [33]. Distances (Å) and angles (degrees).

Atoms	**3a**	**3b**	**1**	**6**
N1-C2	1.358(3)	1.357(3)	1.39	1.39
C2-C3	1.514(5)	1.507(3)	1.54	1.54
C3-C4	1.533(4)	1.535(3)	1.54	1.53
C4-C5	1.510(5)	1.497(4)	1.50	1.51
C5-C5a	1.486(5)	1.488(4)	1.48	1.48
C5a-C9a	1.409(4)	1.408(3)	1.41	1.41
C9a-N1	1.418(3)	1.421(3)	1.43	1.40
C2-O2	1.227(4)	1.219(3)	1.25	1.25
C5-O5	1.207(4)	1.209(4)	1.24	1.23
N1-C2-C3	117.5(2)	116.2(2)	118	115
C2-C3-C4	108.7(2)	110.0(2)	106	108
C3-C4-C5	114.6(2)	116.6(2)	114	119
C4-C5-C5a	121.0(2)	122.2(2)	119	125
C5-C5a-C9a	126.0(2)	125.0(2)	124	123
C5a-C9a-N1	125.7(2)	124.0(2)	122	124
C9a-N1-C2	130.4(2)	129.1(2)	121	122
N1-C2-O2	119.8(2)	120.6(2)	120	119
C3-C2-O2	122.7(2)	123.1(2)	122	122
C4-C5-O5	119.1(2)	118.2(2)	120	118
C5a-C5-O5	119.9(2)	119.4(2)	121	120
N1-C2-C3-C4	−56.7(3)	−67.9(3)	−74	−69
C2-C3-C4-C5	86.1(3)	73.6(3)	71	71
C3-C4-C5-C5a	−37.9(4)	−8.9(4)	5	−2
C4-C5-C5a-C9a	−12.3(5)	−32.4(4)	−51	−45
C5-C5a-C9a-N1	0.3(5)	−0.9(4)	1	3
C5a-C9a-N1-C2	41.4(4)	43.6(4)	47	47
C9a-N1-C2-C3	−14.6(4)	−4.3(4)	−7	−8
O2-C2-N1-C9a	167.1(3)	178.2(2)	173	172
O2-C2-C3-N10	−1.6(4)	−13.5(3)	−16	−14
O5-C5-C5a-C6	−8.1(5)	−25.0(4)	−46	−38
C5-C4-C3-N10	−152.4(3)	−165.1(2)	−166	−163
N1-C2-C3-N10	−179.8(2)	169.1(2)	164	167
H1-N1-C2-O2	14	4	−17	7
H1-N1-C9a-C9	10	33	61	29
H3-C3-C4-H4a	85	62	74	75
H3-C3-C4-H4b	−155	−179	−169	−167
H4a-C4-C5-O5	25	47	61	54
H4b-C4-C5-O5	−89	−69	−55	−61

The absolute molecular structure of **3** (Figure 2) was assigned by comparison with that of L-kynurenine [32]. There are two independent molecules, **3a** and **3b**, of similar conformation in the crystal. Although the bond lengths and angles in the two molecules are in good agreement with each other, there are some significant differences in the torsion angles of the 2,5-dioxoazepine ring. Table 2 lists the dimensions of **3a** and **3b** as well as those determined for the AM1-optimized [33] structures of **1** and **6**.

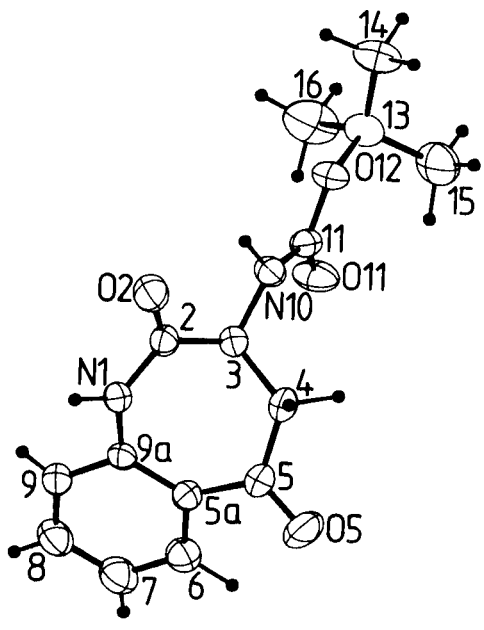


Figure 2. ORTEP drawing of **3a**. Thermal ellipsoids are scaled to the 50% probability level. Hydrogen atoms are spheres of arbitrary radii.

In the crystal structure of **3**, the phenyl ring carbons together with N1 and C5 are coplanar to within ± 0.04(1) Å in each molecule. The carbonyl bonds C5-O5 *ortho* to the phenyl ring are rotated from the ring plane by differing amounts (8° in **3a** and 25° in **3b**). However, the essentially identical C5a-C5 bond lengths (Table 2) indicated a similar extent of π-character for the C(phenyl)-C(carbonyl) bonds. These results support the finding of Chattopadhyay and Mazumdar [34] that the π-overlap between the phenyl ring and the acetyl group in acetophenones cannot be correlated with the torsion angle between their planes. The C9a-N1 bonds of mean length 1.419(3) Å are substantially shorter than the C(sp^2)-N(sp^2) single bond length of 1.470 (5) Å proposed by Camerman [35], indicating significant π-character. For the C(phenyl)-C(carbonyl) and C(phenyl)-N(amide) bonds in both the AM1-optimized structures of **1** and **6**, there is a similar degree of π-character. However, the extent of delocalization of the electron clouds of the carbonyl bonds of the 2,5-dioxoazepine moieties is less in **1** and **6** than in **3** (see Table 2). For the amide groups in **3**, the delocalization is comparable with that in acetanilide [36] in which the C-O bond length

Table 3

Dimensions of the urethane moiety in crystals of **3**. Distances (Å), angles (degrees) with e.s.d.'s in parentheses.

Atoms	**3a**	**3b**	Atoms	**3a**	**3b**
C3-N10	1.439(3)	1.444(3)	O12-C13	1.477(4)	1.483(3)
N10-C11	1.340(4)	1.344(3)	C13-C14	1.522(5)	1.519(5)
C10-O11	1.202(3)	1.215(3)	C13-C15	1.503(5)	1.529(5)
C11-O12	1.351(3)	1.342(3)	C13-C16	1.522(5)	1.506(6)
C3-N10-C11	121.5(2)	119.2(2)	C11-C12-C13	120.3(2)	120.1(2)
N10-C11-O12	109.5(2)	110.9(2)	O12-C13-C14	102.5(2)	102.6(2)
N10-C11-O11	124.3(2)	124.1(2)	O12-C13-C15	110.1(2)	109.4(2)
O12-C11-O11	126.1(2)	125.0(2)	O12-C13-C16	109.2(2)	109.9(2)
C2-C3-N10-C11	−127.0(3)	−144.5(2)	C13-O12-C11-O11	0.6(4)	8.9(4)
C3-N10-C11-O11	−4.0(4)	−7.1(4)	C11-O12-C13-C14	176.4(3)	175.2(2)
C3-N10-C11-O12	176.0(2)	174.7(2)	C11-O12-C13-C15	−65.0(4)	−68.9(3)
N10-C11-O12-C13	−179.3(2)	−172.9(2)	C11-O12-C13-C15	60.1(4)	56.7(3)

Table 4

Hydrogen bonding in **3**. Distances (Å) and angles (degrees). Atoms in molecule **3b** are primed.

Atoms	N.....O	N-H	H...O	<N-H...O	Symmetry Operation
N10.....O2′ [a]	2.983(4)	0.79	2.25	155	none
N1′.....O2	2.839(3)	0.90	2.04	147	none
N1.....O11′	2.859(3)	0.97	1.94	158	½−x, 2−y, ½+z
N10′.....O5 [a]	3.136(3)	1.06	2.23	142	½−x, 1−y, −½+z
N10.....O2 [a,b]	2.681(4)	0.79	2.60	87	none
N10′.....O2′ [a,b]	2.678(4)	1.06	2.09	112	none

[a] Bifurcated interaction. [b] Intramolecular hydrogen bond.

of 1.219(3) Å is similar to the mean length 1.223(4) Å in **3**.

The main difference in the conformations of the 2,5-dioxoazepine moieties in the AM1-optimized structures of **1** and **6** and the crystal structure **3** is reflected in the torsion angles C4-C5-C5a-C9a and O5-C5-C5a-C6 (Table 2). The slightly lesser planarity in **1** compared with **6** could be a consequence of alkylation at the ring nitrogen.

The downfield shift of the signal ascribed to H4a relative to H4b in the ^{1}H nmr spectrum of **3** could be caused by deshielding due to its synclynal relationship with the aryl carbonyl. A similar disposition of these signals was observed in all the other *N*-protected lactams, further supporting the supposition of a common conformation.

The equatorial N-Boc substituents at C3 are extended and their linear chains are nearly orthogonal to the benzene ring (torsion angle, approx. 71°). The urethane moieties adopt the *trans-trans* conformation (type *b*) as is generally observed for urethanes containing a secondary nitrogen atom [37]; the torsion angles N10-C11-O12-C13 and C3-N10-O11-C12 have the respective values −179.3(2), 176.0(2)°, in **3a** and −172.9(2), 174.7(2)° in **3b**. The NH of the *trans* planar NH-CO moiety in each molecule forms an intramolecular hydrogen bond with the lactam oxygen O2 of the dioxoazepine ring (Table 3). The dimensions of the urethane group are similar to those observed in others with the *b* type conformation [37] (see Table 3).

In the crystal, intermolecular hydrogen bonds link the molecules into layers parallel to the *bc* plane (Figure 3). Four unique interactions link each molecule to three adjacent molecules (Table 4). The interactions with the urethane nitrogens are bifurcated; each of the latter also form an intramolecular hydrogen bond. All intermolecular interactions are between **3a** and **3b**.

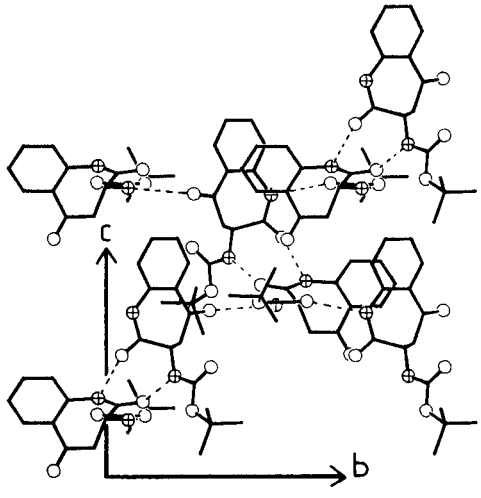


Figure 3. Crystal packing of **3**. Oxygen atoms are represented by open circles whilst nitrogen atoms are represented by circles containing an 'X'.

The insertion of **1** into CCK-5, and a study of the resulting induced conformation(s) and pharmacology is currently being undertaken in our laboratory.

Table 5

Crystal Data for **3**.

Formula	$C_{15}H_{18}N_2O_4$
Formula weight	290.3
Crystal system	orthorhombic
Space group	$P2_12_12_1$
a(Å)	24.327(2)
b(Å)	10.976(1)
c(Å)	11.073(2)
V(Å^3)	2956.6(1)
Z	8
D_m(g cm^{-3})	1.31(1)
D_c(g cm^{-3})	1.304
F(000)	1232
λ(Å)	1.5418
μ(Cu Kα) (cm^{-1})	7.03
Crystal size (mm)	0.37 x 0.34 x 0.45
T(K)	288(1)

EXPERIMENTAL

General Methods.

Elemental analyses were carried out by the Australian Microanalytical Service, Melbourne, on samples which had been dried under vacuum over phosphorus pentoxide at 60° for 24 hours. Melting points were determined on a Reichert Micro-melting point apparatus and are uncorrected. Mass spectra were determined on a Jeol JMS-DX300 mass spectrometer operating at 70eV with a source temperature of 200° (direct insertion). Peak intensities, in brackets, are expressed as a percentage of the base peak. The nmr spectra were recorded on a Bruker AM-300 (300 MHz) spectrometer, using tetramethylsilane as the internal standard. Assignments with the same superscript may be interchanged. Infrared spectra were recorded on a Hitachi 270-30 spectrometer. Ultraviolet spectra were recorded on a Hitachi 150-20 Spectrophotometer using a Hitachi 150-20 Data Processor. All evaporations of organic solvents were done under reduced pressure.

3*S*-3-[[(1,1-Dimethylethoxy)carbonyl]amino]-2,5-dioxo-2,3,4,5-tetrahydro-1*H*-1-benzazepine (**3**).

A solution of **2** [5] (1.80 g, 5.84 mmoles) and *N*-hydroxybenzotriazole (0.788 g, 5.84 mmoles) in tetrahydrofuran (30 ml) at 0° was treated with dicyclohexylcarbodiimide (1.22 g, 5.84 mmoles) and, following stirring for 1 hour, was allowed to warm to room temperature. After stirring overnight, the solvent was removed, and the residue triturated with ethyl acetate (50 ml). After filtering off the solid by-product, the organic layer was washed with

Table 6

Final atomic coordinates and equivalent isotropic temperature factors for the non-hydrogen atoms of **3**. The estimated standard deviations are given in parentheses. See Figure 1 for atom numbering.

Atoms	**3a**				**3b**			
	10^4x	10^4y	10^4z	B_{eq}†	10^4x	10^4y	10^4z	B_{eq}†
N1	1335(1)	8054(2)	12207(2)	3.21(4)	1688(1)	9506(2)	8505(2)	2.88(4)
C2	1173(1)	7751(3)	11073(2)	2.71(4)	2062(1)	8648(2)	8184(2)	2.70(4)
O2	1017(1)	8548(2)	10375(2)	3.62(4)	1967(1)	7569(2)	8343(2)	3.83(4)
C3	1210(1)	6422(3)	10716(2)	2.97(5)	2578(1)	9107(2)	7584(2)	2.71(4)
C4	1804(1)	5991(3)	10889(3)	3.72(6)	2441(1)	9626(3)	6332(2)	3.44(5)
C5	1938(1)	5557(3)	12149(3)	3.44(5)	154(1)	10832(3)	6304(3)	3.48(5)
O5	2236(1)	4687(2)	12276(3)	5.46(5)	2131(2)	11372(3)	5353(2)	7.53(7)
C5a	1705(1)	6178(3)	13226(3)	3.26(5)	1936(1)	11421(3)	7416(2)	2.79(4)
C6	1789(2)	5612(4)	14346(3)	4.79(7)	1922(1)	12690(3)	7421(3)	3.67(5)
C7	1622(2)	6113(5)	15409(3)	5.99(9)	1715(1)	13336(3)	8391(3)	4.25(6)
C8	1353(2)	7223(4)	15403(3)	5.67(8)	1500(1)	12716(3)	9361(3)	4.09(6)
C9	1262(1)	7822(3)	14326(3)	4.37(6)	1500(1)	11458(3)	9371(3)	3.33(5)
C9a	1434(1)	7312(3)	13232(2)	2.95(5)	1726(1)	10795(2)	8425(2)	2.48(4)
N10	1024(1)	6274(3)	9491(2)	3.92(5)	2971(1)	8123(2)	7516(2)	2.78(4)
C11	633(1)	5465(2)	9203(2)	2.78(4)	3509(1)	8369(2)	7648(2)	2.67(4)
O11	428(1)	4765(2)	9906(2)	4.19(4)	3698(1)	9392(2)	7713(2)	4.15(4)
O12	510(1)	5565(2)	8017(2)	3.64(4)	3806(1)	7339(1)	7663(2)	2.93(3)
C13	84(1)	4780(3)	7473(3)	3.71(5)	4402(1)	7383(3)	7943(3)	3.26(5)
C14	55(2)	5251(4)	6182(3)	6.01(9)	4559(1)	6044(3)	7973(4)	4.37(6)
C15	263(2)	3470(4)	7510(5)	7.25(10)	4707(1)	8010(4)	6908(4)	5.42(7)
C16	−462(2)	5006(5)	8106(4)	6.06(8)	4491(2)	7977(4)	9153(4)	6.06(8)

† Calculated from refined anisotropic thermal parameters: $B_{eq} = (8\pi^2/3)\ \Sigma_i\ \Sigma_j\ U_{ij}\ a_i^*a_j^*a_i.a_j$.

saturated aqueous sodium hydrogen carbonate (3 x 20 ml), dried (sodium sulfate), and evaporated. The residue was recrystallized twice from ethanol, to give **3** (1.18 g, 70%) as colourless plates, mp 212-213° (lit [5] 209-210°); ms: m/z 290 ($M^{+\cdot}$, 1%; accurate mass 290.1239; $C_{15}H_{18}N_2O_4$ requires $M^{+\cdot}$, 290.1265), 234 (67), 146 (63); uv: λ max 314 (w) nm (lit [5] 315 nm); ir (potassium bromide disc): ν cm^{-1} 3380 w (NH), 3244 w (NH), 1702 m (PhC=O), 1682 s (NHC=O), 1668 s (NHC=O); ^1H nmr (chloroform-d_1): δ 1.44 (9H, s, 3 x Me), 3.00 (1H, dd, H4b, ^2J = 19.0, ^3J = 13.0 Hz), 3.31 (1H, dd, H4a, ^2J = 19.1, ^3J = 2.8 Hz), 4.8-5.0 (1H, m, H3), 5.68 (1H, d, 3-NH, ^3J = 6.1 Hz), 7.00 (1H, d, H9, ^3J = 7.7 Hz), 7.28 (1H, t, H7, ^3J = 7.6 Hz), 7.53 (1H, t, H8, ^3J = 7.2 Hz), 7.85 (1H, d, H6, ^3J = 7.0 Hz), 8.21 (1H, s, H1); ^{13}C nmr (chloroform-d_1): δ 29.0 (3 x Me), 48.2 (C3), 48.6 (C4), 81.0 (O-C), 122.9 (C9), 126.6 (C7), 130.4 (C5a), 131.5 (C6), 135.0 (C8), 136.4 (C9a), 155.5 (3-NHC), 173.0 (C2), 197.8 (C5).

Benzyl 2-(3*S*-3-[[(1,1-Dimethylethoxy)carbonyl]amino]-2,5-dioxo-2,3,4,5-tetrahydro-1*H*-1-benzazepin-1-yl)-ethanoate (**5**).

To a stirred mixture of **3** (580 mg, 2.0 mmoles), powdered potassium carbonate trihydrate (1 g, 3 mmoles) and tetrabutylammonium bromide (65 mg, 0.2 mmoles) in acetone (20 ml), was added benzyl bromoacetate (460 mg, 2.0 mmoles). After stirring overnight, the solvent was removed and the product partitioned between ether (30 ml) and water (20 ml). The separated organic layer was washed with saturated aqueous potassium hydrogen sulfate (3 x 10 ml), dried (sodium sulfate) and evaporated, to give **5** (857 mg, 98%) as a yellow glass. This was used without further purification in subsequent reactions; ms: m/z 438 ($M^{+\cdot}$, 2%; accurate mass 438.1774; $C_{24}H_{26}N_2O_6$ requires $M^{+\cdot}$, 438.1791), 382 (49), 175 (48), 146 (18), 132 (53); uv: λ max 296 (w) nm; ir (potassium bromide disc): ν cm^{-1} 3448 w (NH), 1746 m (OC=O), 1720 m (PhC=O), 1700 m (NHC=O), 1680 s (NHC=O); ^1H nmr (chloroform-d_1): δ 1.41 (9H, s, 3 x Me), 2.91 (1H, dd, H4b', ^2J = 19.4, ^3J = 12.7 Hz), 3.24 (1H, dd, H4a', ^2J = 19.3, ^3J = 4.0 Hz), 4.36 (1H, d, H2, ^2J = 17.3 Hz), 4.68 (1H, d, H2, ^2J = 17.1 Hz), 4.9-5.0 (1H, m, H3'), 5.10 (1H, d, CH_2Ar, ^2J = 12.1 Hz), 5.16 (1H, d, CH_2Ar, ^2J = 12.1 Hz), 5.69 (1H, d, NH, ^3J = 6.7 Hz), 7.1-7.3 (9H, m, 9 x ArH); ^{13}C nmr (chloroform-d_1): δ 29.1 (3 x Me), 49.0 (C3'), 49.6 (C4'), 51.9 (C2), 68.3 (CH_2Ar), 81.0 (*C*(Me)$_3$), 124.7 (C9'), 128.5 (C7'), 129.3 (5 x ArCH), 130.2 (C6'), 134.4 (C8'), 135.4 (^{A}C5a'), 135.7 (^{A}ArC), 140.1 (C9a'), 155.5 (NH-C), 168.8 (^{B}C1), 171.5 (^{B}C2'), 200.4 (C5').

Anal. Calcd. for $C_{24}H_{26}N_2O_6$: C, 65.7; H, 6.4; N, 6.4. Found: C, 65.5; H, 6.2; N, 6.3.

Ethyl 2-(3*S*-3-[[(1,1-Dimethylethoxy)carbonyl]amino]-2,5-dioxo-2,3,4,5-tetrahydro-1*H*-1-benzazepin-1-yl)-ethanoate (**4**).

The title compound **4** was made from **3** (300 mg, 1.03 mmoles) by the above procedure using ethyl bromoacetate instead of benzyl bromoacetate, furnishing **4** (377 mg, 97%) as a yellow glass; ms: m/z 376 ($M^{+\cdot}$, 1%; accurate mass 376.1642; $C_{19}H_{24}N_2O_6$ requires $M^{+\cdot}$, 376.1634), 320 (19), 234 (38), 175 (19), 146 (52); uv: λ

max 306 (w) nm; ir (potassium bromide disc): ν cm^{-1} 3400-3500 w, 1746 m, 1710 m, 1690 s, 1680 s; ^1H nmr (chloroform-d_1): δ 1.21 (3H, t, CH_2CH_3, ^3J = 7.2 Hz), 1.40 (9H, s, 3 x Me), 2.95 (1H, dd, H4b', ^2J = 19.4, ^3J = 12.8 Hz), 3.27 (1H, dd, H4a', ^2J = 19.4, ^3J = 4.2 Hz), 4.15 (2H, q, CH_2CH_3, ^3J = 7.1 Hz), 4.29 (1H, d, H2, ^2J = 17.4 Hz), 4.66 (1H, d, H2, ^2J = 17.2 Hz), 4.9-5.0 (1H, m, H3'), 5.70 (1H, d, NH, ^3J = 6.9 Hz), 7.2-7.6 (4H, m, 4 x ArH); ^{13}C nmr (chloroform-d_1): δ 14.0 (CH_2CH_3), 28.3 (CMe_3), 48.2 (^{A}C3'), 48.8 (^{A}C4'), 51.2 (C2), 61.9 (OCH_2), 80.3 (CMe_3), 124.0 (C9'), 127.9 (C7'), 129.4 (C6'), 133.6 (C8'), 135.4 (C5a'), 139.3 (C9a'), 154.8 (NH-C), 167.6 (^{B}C1), 170.7 (^{B}C2'), 200.0 (C5').

Due to varying degrees of solvation in the purified product, none of the several microanalyses performed were satisfactory.

2-(3*S*-3-[[(1,1-Dimethylethoxy)carbonyl]amino]-2,5-dioxo-2,3,4,5-tetrahydro-1*H*-1-benzazepin-1-yl)-ethanoic Acid (**1**).

To a stirred solution of **5** (249 mg, 0.568 mmole) and anhydrous ammonium formate (44 mg, 0.7 mmole) in methanol (5 ml) under nitrogen, was added 5% palladium/carbon (50 mg). After stirring at room temperature for 5 minutes [26], the reaction mixture was filtered through celite, and the filtrate evaporated. The crude product was taken up into dichloromethane (30 ml) and extracted with saturated aqueous sodium hydrogen carbonate (3 x 30 ml). The separated aqueous layer was acidified with saturated aqueous potassium hydrogen sulfate and the product extracted with dichloromethane (3 x 15 ml). The organic layer was dried (sodium sulfate) and evaporated, to give the crude product as a pale yellow glass. Chromatotron separation using dichloromethane/methanol/acetic acid (192.5:5:2.5) gave **1** (177 mg, 95%) as a colourless glass; ms: m/z 348 ($M^{+\cdot}$, 20%; accurate mass 348.1326; $C_{17}H_{20}N_2O_6$ requires $M^{+\cdot}$, 348.1322), 292 (46), 275 (22), 248 (16), 204 (17), 175 (20), 160 (15), 146 (31), 132 (41); uv: λ max 298 (w) nm; ir (potassium bromide disc): ν cm^{-1} 3400-3200 w (NH), 1740 m (OC=O), 1720 m (PhC=O), 1700 s (NHC=O), 1680 s (NHC=O); ^1H nmr (chloroform-d_1): δ 1.42 (9H, s, 3 x Me), 2.99 (1H, dd, H4b', ^2J = 19.4, ^3J = 12.7 Hz), 3.26 (1H, dd, H4a', ^2J = 19.4, ^3J = 4.0 Hz), 4.37 (1H, d, H2, ^2J = 17.6 Hz), 4.67 (1H, d, H2, ^2J = 17.5 Hz), 4.9-5.1 (1H, m, H3'), 5.79 (1H, d, NH, ^3J = 6.9 Hz), 7.2-7.6 (4H, m, 4 x ArH), 8.89 (1H, bs, CO_2H); ^{13}C nmr (chloroform-d_1): δ 28.3 (3 x Me), 48.3 (^{A}C4'), 48.6 (^{A}C3'), 51.0 (C2), 80.4 (CMe_3), 124.1 (C9'), 127.8 (C7'), 129.5 (C6'), 133.8 (C8'), 134.5 (C5a'), 139.3 (C9a'), 155.0 (NH-C), 171.0 (^{B}Cl), 172.3 (^{B}C2'), 200.0 (C5').

Anal. Calcd. for $C_{17}H_{20}N_2O_6$: C, 58.6; H, 5.8; N, 8.0. Found: C, 58.2; H, 6.1; N, 8.3.

X-Ray Crystal Structure Analysis.

Compound **3** crystallized as colourless prisms from ethanol. The crystal data are given in Table 5. The setting angles for 25 reflections were used to determine the cell parameters. Intensities were measured at 288(1) K on a Rigaku-AFC diffractometer with Cu Kα radiation (graphite-crystal monochromator, λ = 1.5418 Å). The data were recorded by a ω - 2θ scan with a scan range ($\Delta\omega$) of 1.2° + 0.5° tan θ and scan rate of 2° min^{-1}. Three standard reflections monitored every 50 reflections showed no significant variation in intensity during the data collection. Data to a 2θ (max) of 130° yielded 2822 unique terms. The integrated intensities were corrected for Lorentz and polarization effects and for absorption (transmission factors ranged from 0.709 to 0.844).

The structure was solved by direct methods with SHELXS-86 [38]. The non-methyl H-atom sites were located on difference maps but their coordinates were not refined; the methyl H atoms were included in the analysis at idealized positions. Refinement with SHELX-76 [39] on 2723 data ($I \geq \sigma I$) with anisotropic temperature factors given to the C, N and O atoms and isotropic for H, converged at R = 0.041 and R_w = 0.052. An isotropic extinction correction of the form $F_c = F[1 - (2.64 \times 10^{-6} \mid F \mid^2/\sin\theta)]$ was applied to the calculated structure amplitudes. The function minimized in the refinement was:

$\Sigma w(\mid F_o \mid - \mid F_c \mid)^2$ with $w = (\sigma^2 \mid F_o \mid + 0.0006 \mid F_o \mid^2)^{-1}$ and the largest peaks on the final difference map were of heights +0.22 and −0.21 e $Å^{-3}$. Scattering factors were taken from the International Tables for X-ray Crystallography [40].

The final atomic parameters for the non-hydrogen atoms are given in Table 6. Figures have been prepared from the output of ORTEP-II [41]. Anisotropic thermal parameters, hydrogen atom coordinates short intermolecular contacts and observed and calculated structure amplitudes are available as supplementary material.

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