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ORIGINAL PAPER

Crystal Structure of the Chiral Azomethine Imine, (Z)-(*S*)-4-*(tert*-Butylcarbonylamino)-2-(2-methoxybenzylidene)-5-oxopyrazolidin-2-ium-1-ide, Obtained by the Cyclization of *tert*-Butyl (*S*)-2-[2-(methoxybenzylidene)hydrazine]-1-(hydroxymethyl)-2-oxocarbamate

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Abstract

Further study of the cyclization reactions of (*S*)-t-BuOCH$_2$CONHCH(CH$_2$OH)CONHN = Ar, derived from (L)-serine, has found that reaction with MeI/K$_2$CO$_3$ in Me$_2$CO produces (Z)-(*S*)-4-*(tert*-butylcarbonylamino)-2-(benzylidene)-5-oxopyrazolidin-2-ium-1-ide, **3**. We now wish to report the crystal structure of the 2-methoxybenzylidene derivative, **3a**. While the pyrazolyl ring in **3a** exhibits an envelope shape, with the flap at C5, the displacement of C5 from the best plane through the ring, however, is only 0.053(5) Å. The dihedral angle between the phenyl and pyrazolyl rings is 12.14(16)°. The pyrazolyl ring has a betaine character with opposite charges on N1 and N2 atoms. The supramolecular arrangement is created from one classical N–H···O and weaker C–H···X (X = O, N) intermolecular hydrogen bonds, each of which generate chains of molecules. Combinations of the (i) C19–H19A···O1 and C11–H11···O2 hydrogen bonds generates sheets of molecules in the *ab* plane, containing $R^4_4(40)$ rings, (ii) C18–H18B···O1 and C11–H11···O2 hydrogen bonds produce a two molecule wide column, containing $R^3_3(26)$ rings, propagated in the *ac* plane and (iii) C19–H19A···O1 and C15–H15A···N2 hydrogen bonds generate a different two molecule wide column, containing $R^3_3(26)$ rings, propagated in the *ab* plane. The compound crystallises in the *orthorhombic* space group, $P2_12_12_1$, with $a = 6.5906(5)$ Å, $b = 10.9121(10)$ Å, $c = 22.2080(17)$ Å, and Z = 4.

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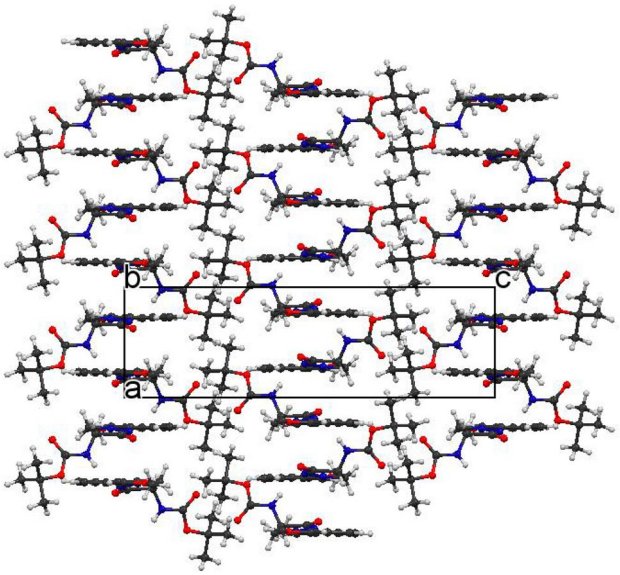
Graphical Abstract

The supramolecular array of the betaine compound, (*Z*)-(4*S*)-4-(*tert*-butyloxycarbonylamino)-3-oxo-1-(2-methoxybenzylidene)-pyrazolidinium inner salt, **3a**, is created from one classical N–H···O and weaker C–H···X (X = O, N) intermolecular hydrogen bonds.



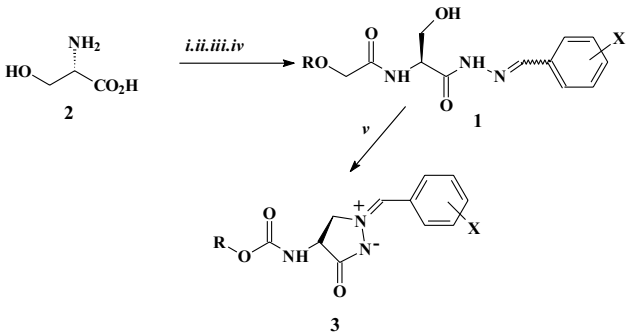
Keywords Azomethine imines · Cyclization reactions · Serine derivative · Hydrogen bonds

Introduction

Azomethine imines, R–N^+–N^-R = CHR/, are 1,3-dipoles of the aza-allyl type. Much use has been made in organic syntheses of their cycloaddition reactions, in particular [3 + 2] additions [1–3]. While many are transient intermediates and are used in situ, others have been found to be stable and isolatable. Cyclic derivatives with additional carbonyl substituents are more stable, due to increased conjugation. Further stabilization may arise from the presence of a benzylidene derivative.

Various preparations of azomethine imide derivatives have been reported with more accessible routes involving reactions of pyrazolidin-3-ones with substituted benzaldehydes or using substituted acylhydrazines, RCONHNHR as precursors [4–7].

In studies of the cyclisation reactions of alkyl (*S*)-2-[2-(benzylidene)hydrazine]-1-(hydroxymethyl)-2-oxocarbamates, **1**, prepared from *L*-serine, **2** [8], see Scheme 1, we have found that their treatment with mesityl chloride and triethylamine generates chiral azomethine imines derivatives (*Z*)-(4S)-4-(alkyloxycarbonylamino)-3-oxo-1-(benzylidene)-pyrazolidinium inner salts, **3**, see Scheme 1. We now wish to report the structure determination of (Z)-(4S)-4-(tert-butyloxycarbonylamino)-3-oxo-1-(2-methoxybenzylidene)-pyrazolidinium inner salt,



Scheme 1 Reagents and conditions: (i) MeOH, $SOCl_2$, rt; (ii) $PhCH_2Cl$, $NaHCO_3$, H_2O, rt or $(Bu^tOC)_2O$, Et_3N, THF, rt; (iii) N_2H_4. H_2O (80%), EtOH, rt; (iv) EtOH, XC_6H_4CHO, reflux, (v) $MeSO_2Cl$, Et_3N, CH_2Cl_2

also named (Z)-(S)-4-(tert-butylcarbonylamino)-2-(2-methoxybenzylidene)-5-oxopyrazolidin-2-ium-1-ide, (3a: R = tert-Bu, X = 2-MeO) The chirality of the compounds is derived from that of the (L)-serine precursor. The kinetic resolutions of 5-oxopyrazolidin-2-ium-1-ides using copper catalysts has been carried out [9].

The stability of compound **3a** is considered to be due, partially at least, to the presence of the 2-methoxybenzylidenyl substituent and its near planarity with the core of the

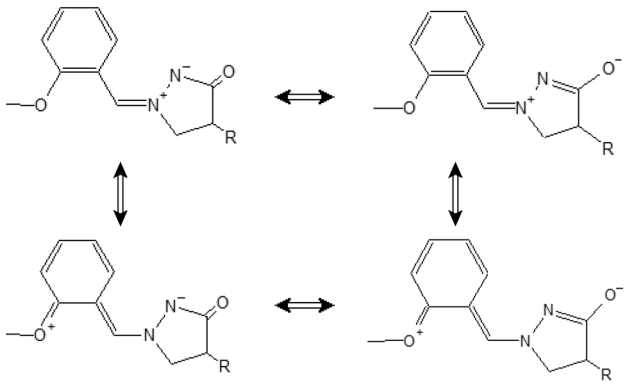


Fig. 1 Canonical forms for a (2-methoxybenzylidene)-pyrazolidinium inner salt

oxo-1-(benzylidene)-pyrazolidinium unit, which allows a very extensive conjugation to be set up, see Fig. 1.

The crystal structure of **3a** is compared to the reported structures of of other 3-oxo-1-pyrazolidinium inner salts.

General

Melting points were determined on a Buchi apparatus and are uncorrected. Infrared spectra were recorded on a Thermo Nicolet Nexus 670 spectrometer in potassium bromide discs. Mass spectra (ESI assay in solution of ammonium chloride) were recorded on a Micromass ZQ Waters mass spectrometer. Microanalysis data were obtained using a Perkin–Elmer 240 analyser, using a Perkin–Elmer AD-4 balance. NMR spectra were recorded on a Bruker Avance 500 spectrometer at room temperature. TLC was carried out on plates coated with silica gel, using ultraviolet light or ninhydrine (0.2% p/v in ethanol) to develop the plates.

Formation of 3a

tert-Butyl (*S*)-2-[2-(methoxybenzylidene)hydrazine]-1-(hydroxymethyl)-2-oxocarbamate, (**1a**: R = *tert*-Bu, X = 2-MeO) was prepared as previously reported [8]. A reaction mixture of **1a** (0.30 g, 0.9 mmol), methanesulfonyl chloride (0.1 mL, 1.35 mmol) and Et_3N (3.7 mL, 27 mmol) in dichloromethane (10 mL) was stirred at room temperature for 24 h. To the reaction mixture was added water (10 mL), the organic phase was collected and successively washed with aqueous hydrochloric acid (10%v/v, 2 × 20 mL) and water (2 × 20 mL), and dried over sodium sulfate. The residue, after rotary evaporation, was column chromatographed. The desired compound **3a** was obtained in 80% yield, 230 mg, mp 165-6 °C.

^{1}H NMR (500 MHz, DMSO-*d6*) δ (ppm): 8.97 (1H, d; *J* = 7.8 Hz, NHCH), 7.76 (1H. s, N = CH), 7.52 (1H, t, *J* = 7.8 Hz, H3), 7.29 (1H, d, *J* = 7.8 Hz; H5), 7.16 (1H, d, *J* = 7.8 Hz, H2), 7.10 (1H, t, *J* = 7.8 Hz, H4), 4.81 (1H, m, CH), 4.40–4.25 (2H, m, CH_2), 3.90 (3H, s, CH_3), 1.39 (9H, s, $(CH_3)_3C$).

^{13}C NMR (125 MHz, DMSO-*d6*) δ (ppm): 182.4 (COCH), 158.5 (C1), 155.8 (COO), 133.8 (N = CH), 131.8 (C3 or C5), 127.7 (C3 or C5), 121.0 (C4), 118.4 (C6), 111.8 (C2), 78.8 ($(CH_3)_3C-$), 62.4 (CH); 56.5 (CH_3), 50.2 (CH_2), 28.6 ($(CH_3)_3C-$).

ir (cm^{-1}; KBr): 1705 (COCH), 1662 (COO).

ms/esi: [M + Na]: 342.

Calcd. for $C_{16}H_{21}N_3O_4$: C: 60.18; H: 6.62; N: 13.15. Found: C: 60.31; H: 6.68; N: 13.03.

Crystal Structure Determination

Intensity data were obtained at 120(2) K with Mo-Kα radiation by means of a Bruker-Nonius Roper CCD on kappa-goniostat by the National Crystallographic Service, UK, based at the University of Southampton. Data collection was carried out under the control of the program COLLECT [10] and data reduction and unit cell refinement were achieved with the COLLECT [10] and DENZO [11] programs. Correction for absorption was achieved in each case by a semi-empirical method based upon the variation of equivalent reflections with the program SADABS 2007/2 [12]. The program MERCURY [13] was used in the preparation of the Figures. The structures were solved by direct methods using SHELXS-97 [14] and fully refined by means of the program SHELXL-97 [14]. The refinement was carried out as a 2-component inversion twin. The programs, SHELXL97 [14] and PLATON [15], were used in the calculation of molecular geometry. All hydrogen atoms were placed in calculated positions. Crystal data and structure refinement details are listed in Table 1.

Results and Discussion

As found for various acylhydrazone derivatives [16, 17], compound (**1a**: R = *tert*-Bu, X = 2-MeO) in solution is a mixture of (*E*)/(*Z*) isomers about the C=N bond, as shown by the doubling of certain NMR signals. In contrast, the ^{1}H and ^{13}C NMR spectra of **3a** indicated a single isomer in solution: considering the results of the X-ray structure determination, see below, this is shown to be the (*Z*)-isomer. As the formation of the five-membered ring does not involve reaction at the chiral cente in **1**, the stereochemistry is maintained in the product **3a**. The role of $MeSO_2Cl$ is to form a more effective leaving group on reaction with the hydroxyl group.

Table 1 Crystal data and structure refinement for **3a**

Empirical formula	$C_{16}H_{21}N_3O_4$
Formula weight	319.4
Temperature (K)	120(2)
Wavelength (Å)	0.71073
Crystal system, space group	*Orthorhombic*, $P2_12_12_1$
Unit cell dimensions (Å)	
a	6.5906(5)
b	10.9121(10)
c	22.2080(17)
Volume (Å^3)	1597.1(2)
Z	4
Density (calculated) (Mg/m^3)	1.328
Absorption coefficient (mm^{-1})	0.097
F(000)	680
Crystal size (mm)	0.36 × 0.04 × 0.03
Theta range for data collection (°)	3.22–27.57
Index ranges	−8 ≤ h ≤ 8, −4 ≤ k ≤ 14, −8 ≤ l ≤ 28
Reflections collected	28,434
Independent reflections	3688 [R(int) = 0.133]
Reflections observed (> 2sigma)	2490
Data completeness	1.00
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.7455 and 0.4497
Refinement method	Full-matrix least-squares on F2
Data/restraints/parameters	3688/0/212
Goodness-of-fit on F^2	1.07
Final R indices [I > 2sigma(I)]	R_1 = 0.077, wR_2 = 0.134
R indices (all data)	R_1 = 0.126, wR_2 = 0.149
Absolute structure parameter	0.00
Largest diff. peak and hole (e/Å^3)	0.223 and −0.243
CCDC No.	1426424

Crystal Structure of 3a

The crystals of **3a** used in the structure determination were grown by slow evaporation of a solution in methanol at room temperature. The betaine compound crystallizes in the chiral *orthorhombic* space group $P2_12_12_1$, with one molecule in the asymmetric unit. Figure 2a shows the numbering scheme and the atom arrangements, with a (*S*)-configuration at C4 and a (*Z*) arrangement about the exocyclic C=N bond. There are four weak intramolecular hydrogen bonds in five as listed in Table 1.

As indicated by the Puckering parameters [18], [Q(2) = 0.083(4) Å and Φ(2) = 147(3)°], the pyrazolyl ring exhibits a slight envelope shape, with the flap at C5. The displacement of C5 from the best plane through the ring, however, is only 0.053(5) Å, which for all intents and purposes indicates a very near planar ring. Sush a light deviation from planarity has been reported for other 5-oxopyrazolidin-2-ium-1-ides [19–22] The dihedral angle between the phenyl group and the complete oxopyrazolidinyl ring is 12.14(16)°: dihedral angle between the phenyl group and the N–N–C=O fragment of the oxopyrazolidinyl moiety moiety involved in the conjugation is just a little smaller at 10.82(16)°. A view of the conformation of **3a**, looking along the edge of the combined phenyl and pyrazolyl rings, is shown in Fig. 2b. There are four intramolecular hydrogen bonds in **3a**: two of which, C17–H17A···O1 and C18–H18B···O1, involve the *tert*-butyloxycarbonylamino substiuent and the other two, C6–H6···O4 and C18–H18C···N2, involve the 2-anisyl substiuent and the oxopyrazolidinyl ring. The latter two must be influential in keeping the dihedral angle small between the two components, thereby possibly aiding conconjugation between the two fragments.

The pyrazolyl ring has a betaine character with opposite charges on N1 and N2 atoms. The bond lengths and angles in the betaine ring are within the regions found for related compounds [4–6, 18–21]. The C7–C12 bond length, 1.429(6) Å, is noticeably longer than the other C–C bond lengths, 1.377(6)–1.399(6) Å, in the phenyl ring, which indicates a degree of bond fixation arising.

The PLATON analysis [15] indicated that the supramolecular arrangement is created from one classical N–H···O and weaker C–H···X (X = O, N) intermolecular hydrogen bonds [23], see Table 2 for symmetry operations. The strongest intermolecular interaction, the N3–H3···O2 hydrogen bond, generates zig-zag chains, C(5) [24], of molecules formed in the direction of the *a* axis, as illustrated in Fig. 3a. These chains are augmented by C3=O2···π(pyrazole) interactions. The four weaker intermolecular hydrogen bonds individually generate chains of molecules [23]: the C19–H19···O1 and the C15–H15A···N2 hydrogen bonds generate C(6) and C(8) chains, respectively, in the direction of the *a* axis, and the C11–H11···O2 and C18–H18B···O1 hydrogen bonds form C(9) and C(6) chains, respectively, in the direction of the *b* axis. Combinations of pairs of these individual hydrogen bonds create more elaborate structural sub-sets. Thus combinations (i) of the C19–H19A···O1 and C11–H11···O2 hydrogen bonds generate sheets of molecules in the *ab* plane, containing $R^4_4(40)$ rings [24], as illustrated in Fig. 3b, (ii) of the C18–H18C···O1 and C11–H11···O2 hydrogen bonds produce a two molecule wide column, containing $R^3_3(26)$ rings, propagated in the *ac* plane, see Fig. 3c, and (iii) of the C19–H19A···O1 and C15–H15A···N2 hydrogen bonds generate another two molecule wide column, containing $R^3_3(26)$ rings, propagated in the *ab* plane, see Fig. 3d. Overall, a 3-dimensional arrangement is formed.

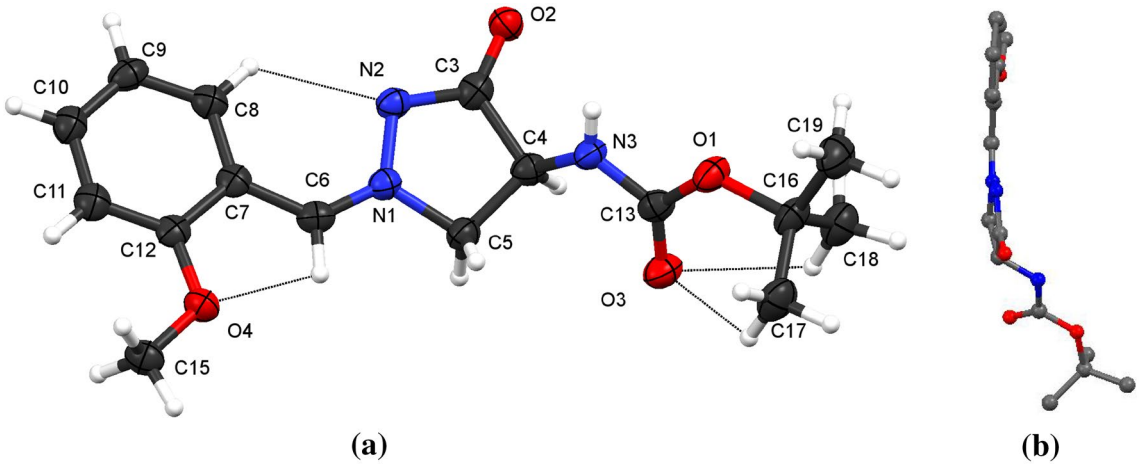


Fig. 2 **a** Atom numbering scheme and atom connectivity for **3a**. Probability ellipsoids are drawn at the 50% level, **b** view of the molecular conformation, looking along the edge of the phenyl and pyrazolyl rings

Table 2 Geometric parameters (Å, °) for intra- and intermolecular interactions

Intramolecular hydrogen bonds				
D–H···A	D–H	H···A	D···A	D–H···A
C6–H6···O4	0.95	2.20	2.631(5)	107
C8–H8···N2	0.95	2.38	2.987(5)	122
C17–H17A···O1	0.98	2.47	3.039(6)	116
C18–H18C···O1	0.98	2.40	2.947(6)	115
Intermolecular hydrogen bond				
D–H···A	D–H	H···A	D···A	D–H···A
N3–H3···O2^{i}	0.80	2.12	2.913(4)	173
C11–H11···O2^{ii}	0.95	2.52	3.453(5)	166
C15–H15A···N2^{iii}	0.98	2.60	3.503(6)	153
C18–H18B···O1^{iv}	0.98	2.59	3.407(6)	141
C19–H19A···O1^{v}	0.98	2.51	3.440(6)	158
Y–X···π interactions[a]				
Y–X···Cg[a]	X···Cg	X_{perp}	γ	Y–X···Cg	Y···Cg
C3 = O2···Cg1^{i}	3.367(3)	3.144	20.94	129.0(2)	4.258(5)

Symmetry codes: *i* = 1/2 + x, 3/2-y,-z; ii = x, − 1 + y, z; iii = − 1/2 + x, 1/2-y,-z; iv = x, 1/2 + y, 1/2-z; v = 1 + x, y, z

[a]Cg1 is the centroid of the pyrazolyl ring

Comparison of the structures

In Table 3, selected data are provided for a number of 5-oxopyrazolidin-2-ium-1-ide derivatives, 12 of which contained an arylidene sbstituent [4, 6, 19, 21, 25–29]. Featured are the $C_3 = O$ and $N^+ = C_{C5,C6}$ bond distances, which are taken as indicators of the conjugation of the N^+–N^- bond with the carbonyl group of the 5-oxopyrazolidin-2-ium-1-ide derivative and the R^5, $R^6CH =$ fragment, respectively: the values of the two bond lengths ranges for all 13 compounds are narrow being 1.226(2) to 1.242(11) (C–O) and 1.289(3) to 1.324(12) Å (C–N). No clear cut pattern w.r.t. to substituent effects emerges from these data regarding the interplanar angle between the aryl unit at R_5 and the 5-oxopyrazolidin-2-yl ring in compounds **3a, 4**–**15**. It is argued that the smaller this angle the greater possibilitythere will be for conjugation between the two fragments. It is apparent that the smallest angles are found for compounds having both electron releasing substituents in the benzylidene moiety and the absence of steric hindrance, arising from R^1 and R^2 substituents.

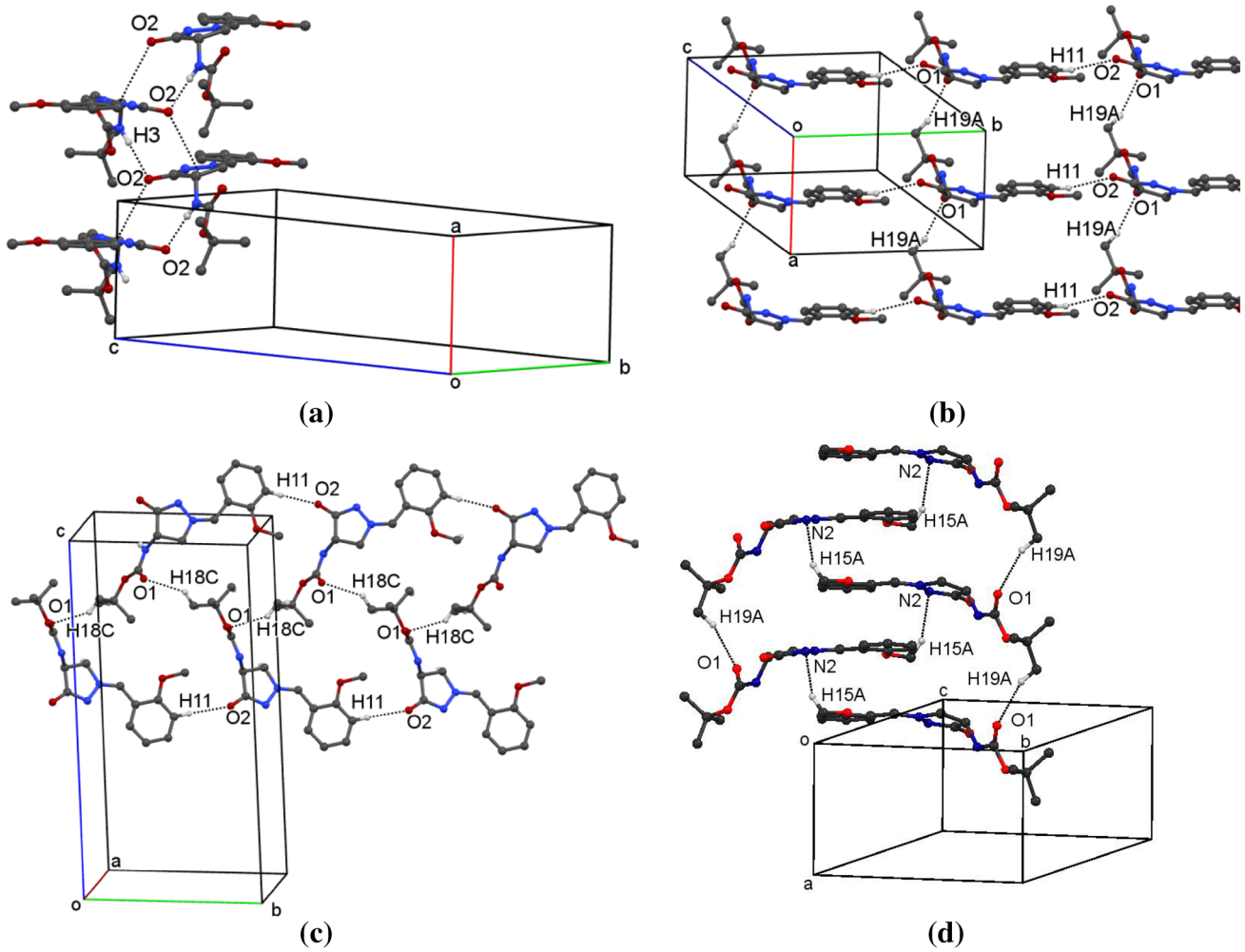


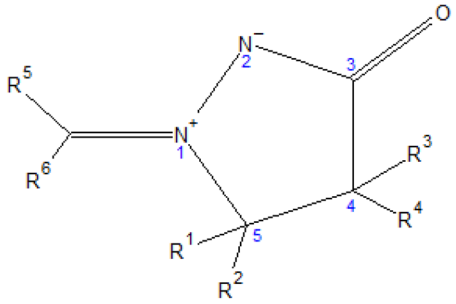
Fig. 3 **a** A part of a chain, C(5), of molecules generated from N3–H3···O2 intermolecular hydrogen bonds, augmented by C3–O2···π(pyrazole) interactions, **b** a sheet of molecules, with a network of rings, $R^4_4(40)$, obtained from C19–H19A···O1 and C11–H11···O2 intermolecular hydrogen bonds, **c** part of a two-molecule wide column of molecules, containing $R^3_3(26)$ rings, generated from C18–H18B···O1 and C11–H11···O2 intermolecular hydrogen bonds, **d** part of another two-molecular wide column, also containing rings, obtained from C19–H19A···O1 and C15–H15A···N2 intermolecular hydrogen bonds. Table 2 contains the symmetry operations. Intermolecular interactions are drawn as thin dashed lines

Thus compound **5**, with a 4-methoxyphenyl substituent and only hydrogens at R^1 and R^2, has a zero interplanar angle, while compounds **9** and **10**, each with 2,6-dichlorobenzylidene substituents and alkyl groups at R^1 and /or R^2 have large interplanar angles > 58°. Interestingly the presence of polynuclear aryl groups such as pyren-1-yl in **12**, anthracen-9-yl in **13** and 2-hydroxynaphenylen-1-yl in **4**, result in large interplanar angles, even in the absence of bulky substituents. In other cases, the lack of steric hindrance, even wth poorly electron releasing aryl substituents, e.g. 4-chlorophenyl in compounds **7** and **8**, can result in small interplanar angles, but on the contrary, a strong electronwithdrawing group, such as the 4-nitrophenyl group in **11**, even in the absence of steric effects, produces a significant interplanar angle of 19.4°.

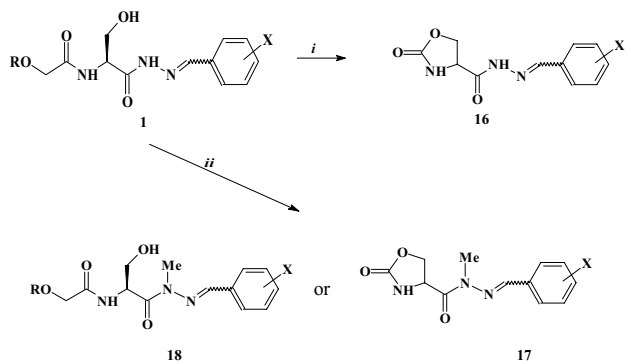
Other Cyclization Reactions of 1

In earlier articles [8, 30], we have reported on the formation of 2-oxo-1,3-oxazolidine 4-carbohydrazide derivatives from cyclization reactions of (**1**: $PhCH_2$ or Bu^t), see Scheme 2. Thus, reaction of **1** with NaH lead to the formation of 2-oxo-1,3-oxazolidine 4-carbohydrazide derivatives, **16** [8], while treatment with the weaker base, potassium carbonate, in the presence of methyl iodide, only the more reactive compounds **1** underwent cyclizations to *N*-methylated 2-oxo-1,3-oxazolidine 4-carbohydrazide derivatives, **17** [30, 31]. The *tert*-butyl esters, proved to be generally less susceptible to cyclizations and just provided the methylated products, alkyl *N*-[(*E*)-1-(2-benzylidene-1-methylhydrazinyl)-3-hydroxy-1-oxopropan-2-yl]carbamates, **18**, [30, 32]. The

Table 3 Selected geometric parameters for 5-oxopyrazolidin-2-ium-1-ides (Å, °)



	Substituents (non-hydrogen)	C_3=O	N^+=$C_{(C5,C6)}$	N–N	Interplanar angle aryl and oxopyrazolyl rings	Intramolecular hydrogen bonds involving aryl group and oxopyrazolyl moiety	References
4	R^5 = 2-HO-naphthalen-1-yl; R^2 = Ph	1.226(2)	1.2972(19)	1.3784(17)	42.22(7)	O–H(hydroxy)···N2	[25]
3a	R^5 = 2-$MeOC_6H_4$, R^3 = t-BuOC(O)NH	1.240(6)	1.296(5)	1.369(5)	12.1(2)	C–H(aryl)···O(OMe) and C–H(aryl)···N2	This study
5	R^5 = 4-$MeOC_6H4$	1.2297(5)	1.2890(6)	1.3677(6)	0.00	C–H(aryl)···N2	[26]
6	R^5 = Ph, R^1 = i-Pr, R^4 = $PhCH_2OC(O)NH$	1.243	1.297	1.379	5.12	C–H(aryl)···N2	[19]
7	R^5 = 4-ClC_6H_4, R^1 = R^2 = Me.	1.224(3)	1.296(3)	1.357(3)	1.64	C–H(aryl)···N2	[20]
8	R^5 = 4-ClC_6H_4, R^3 = 4-$MeOC_6H_4$	1.226(4)	1.295(4)	1.362(3)	4.83(17)	C–H(aryl)···N2	[5]
9	R^5 = 2.6-$Cl_2C_6H_3$, R^1 = R^2 = Me	1.234	1.292	1.361	58.13	No C–H(aryl)···N2	[6]
10	R^5 = 2,6-$Cl_2C_6H_3$, R^1 = i-Pr, R^4 = $PhCH_2OC(O)NH$	1.231(3)	1.297(3)	1.361(3)	62.40(12)	No C–H(aryl)···N2	[19]
11	R^5 = 4-$O_2NC_6H_4$	1.232(3)	1.301(3)	1.356(2)	19.4	C–H(aryl)···N2	[27]
12	R^5 = pyren-1-yl	1.229(11) 1.242(11)	1.325(12) 1.280(11)	1.342(9) 1.361(9)	29.6 23.7	C–H(aryl)···N2	[21]
13	R^5 = anthracen-9-yl	1.241(8)	1.288(7)	1.361(6)	65.4	C–H(aryl)···N2	[28]
14	R^5 = furan-2-yl, R6 = Me R^1, R^3 = –C(CH_2CH_2)(CH_2)C-	1.2378(14)	1.3097(15)	1.3757(14)	10.05(7)	C–H(aryl)···N2	[4]
15	R^5 = R^6 = Me, R^2 = 3-$O_2NC_6H_4$, R^3 = $PhCH_2OC(O)NH$	1.2303(19)	1.291(2)	1.384(2)	–	–	[29]



Scheme 2 Reagents : (i) NaH, THF; (ii) MeI, K_2CO_3, Me_2CO, 50 °C, 24–48 h

presence of the basic reaction media leads to racemisations in some cases.

Conclusions

The crystal structure determination of the title compound revealed similiarities with published structures of related compounds. A small interplanar angle between the 2-methoxyphenyl and the pyrazolidinyl ring allows extensive conjugation in the molecule. Compounds, (*S*)-$ROCH_2CONHCH(CH_2OH)CONHN$ = Ar are versatile precursors of different cyclized products, such as (Z)-(*S*)-4-(*tert*-butylcarbonylamino)-2-(benzylidene)-5-oxopyra-

zolidin-2-ium-1-ides as well as 2-oxo-1,3-oxazolidine 4-carbohydrazides, *N*-methylated 2-oxo-1,3-oxazolidine 4-carbohydrazides derivatives and alkyl *N*-[(*E*)-1-(2-benzylidene-1-methylhydrazinyl)-3-hydroxy-1-oxopropan-2-yl]carbamates.

Supplementary Material

Full details of the crystal structure determination in cif format are available in the online version, at doi: (to be inserted), and have also been deposited with the Cambridge Crystallographic Data Centre with deposition number 1426424. Copies can be obtained free of charge on written application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK (fax: +44 1223 336033); on request by e-mail to deposit@ccdc.cam.ac.uk or by access to http://www.ccdc.cam.ac.uk.

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