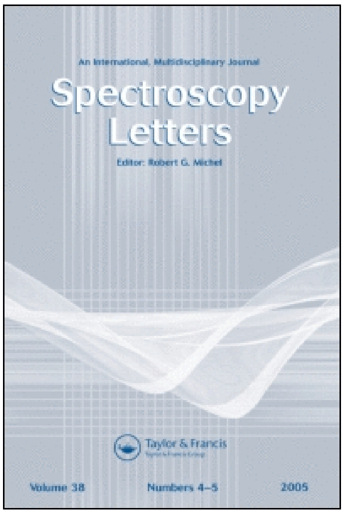

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Conformational Evaluation of Indol-3-yl-*N*-alkyl-glyoxalylamides and Indol-3-yl-*N,N*-dialkyl-glyoxalylamides

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Conformational Evaluation of Indol-3-yl-*N*-alkyl-glyoxalylamides and Indol-3-yl-*N,N*-dialkyl-glyoxalylamides

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ABSTRACT Restricted rotation in indol-3-yl-*N*-alkyl- and indol-3-yl-*N,N*-dialkyl-glyoxalylamides can in principle give the *syn*-periplanar and *anti*-periplanar rotamers. In asymmetrically disubstituted glyoxalylamides, steric effects lead to the occurrence of both rotamers, as observed by NMR spectroscopy. The predominant peak corresponds with the *anti* rotamer, in which the bulkier alkyl group is orientated *trans* to the amide carbonyl group. In monoalkylated glyoxalylamides, only one set of peaks is observed, consistent with the presence of only one rotamer. Crystal structures of 5-methoxyindole-3-yl-*N*-*tert*-butylglyoxalylamide, indole-3-yl-*N*-*tert*-butylglyoxalylamide, and indole-3-yl-*N*-isopropylglyoxalylamide reported here reveal a *syn* conformation held by an intramolecular N–H…O hydrogen bond.

KEYWORDS amides, crystal structure, glyoxalylamides, indole, intramolecular hydrogen bond, nuclear magnetic resonance, rotamers

INTRODUCTION

The method of Speeter and Anthony[1] is considered to be one of the most important synthetic routes to psychoactive tryptamines,[2] with indole-3-yl-*N*-alkyl-glyoxalylamides and 5-methoxyindole-3-yl-*N*-alkyl-glyoxalylamides being intermediates.[3] Acylation of the (substituted) indole moiety with oxalyl chloride followed by a substitution reaction with an amine yielded the indole-3-yl-glyoxalylamide intermediate. The final step is the reduction of the amide with lithium hydride to generate the desired tryptamine (Scheme 1).

Control of alkylation of the side-chain nitrogen can be achieved by altering the amine at the start of the synthesis. The degree of alkylation of the side-chain nitrogen is one of the most important factors that affect psychoactivity, and the convenience and versatility of this route make it attractive to illicit drug users.[4]

It is of interest to note that some indolyl-glyoxalylamide derivatives possess significant pharmacologic effects such as antidepressant,[5]

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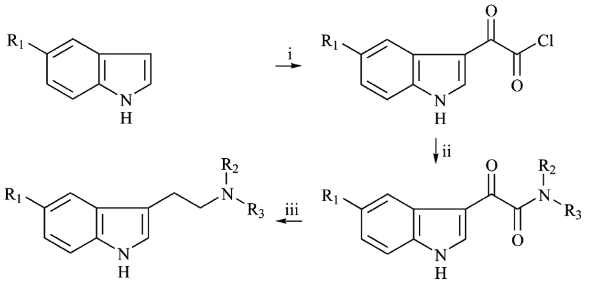


SCHEME 1 **Synthesis of *N,N*-disubstituted tryptamine derivatives *via* the Speeter and Anthony route i: Oxalyl chloride; ii: Primary or secondary amine; iii: LiAlH$_4$; R$_2$ = R$_3$ = alkyl or H; R$_1$ = H or OMe. For structures of disubstituted glyoxalylamides 1–14 and monosubstituted glyoxalylamides 15–23: see Table 1.**

anti-gastric-secretory,[6] and sleep potentiation.[7] Recently, indol-3-yl-*N*-benzyl-glyoxalylamides were reported as a novel class of benzodiazepine receptor (BzR) ligands,[8,9] the receptor playing a fundamental role in various neurologic functions such as anxiety, epilepsy, and amnesia.[10] The action of indol-3-yl-*N*-benzyl-glyoxalylamide derivatives at the benzodiazepine receptor was also found to induce positive cardioprotection effects on noise-induced mitochondrial damage in rats.[11] More recently, a series of *N*-alkyl-substituted indol-3-yl-glyoxalylamides, including two of the compounds reported in this paper (**16** and **18**), have demonstrated *in vitro* affinity for the BzR.[12] A number of 2-phenylindol-3-yl-*N,N*-dialkyl-glyoxalylamide derivatives also exhibit high specificity and affinity for peripheral benzodiazepine receptors (PBRS), the most potent of these stimulating steroid biosynthesis in rat C6 glioma cells.[13]

The indole glyoxalylamide motif is also present in an orally active anticancer agent, [1-(4-chlorobenzyl)-indol-3-yl]-*N*-(pyridin-4-yl)-glyoxalylamide (D-24851), exhibiting both *in vitro* and *in vivo* activity.[14,15] Furthermore, a number of *N*-heterocyclic indolyl-glyoxalylamides derived from the structure of D-24851 exhibited *in vitro* inhibition of the growth of cancer cells. When given orally, they demonstrated dose-dependent increased survival in animals.[16] A number of functionalized indole-3-glyoxalylamide derivatives have also been developed as potential inhibitors of hnps-PLA$_2$ (human nonpancreatic secretory phospholipase A$_2$),[17] increased levels of which have been detected in several pathologic conditions.[18] The most potent inhibitor was [[3-(aminooxoacetyl)-2-ethyl-1-(phenylmethyl-1*H*-indol-4-yl]oxy]acetate) (LY315920).[17]

The wide spectrum of pharmacologic actions displayed by the indol-3-yl-glyoxalylamides makes this structural research of high significance. Here, the rotamer conformation of the glyoxalylamides will be evaluated by NMR spectroscopy, X-ray crystallography, and molecular modeling.

MATERIALS AND METHODS

Materials

Anhydrous ether (99.8%), 5-methoxyindole (99%), indole (98%), anhydrous THF (99.9%), LiAlH$_4$ (95%), and all appropriate amines were from Aldrich UK. *N*-Ethyl-*N*-propylamine and *N*-ethyl-*N*-isobutylamine were from Alfar Aesar (Karlsruhe, Germany). Other solvents and reagents used were of analytical or HPLC grade. P$_2$O$_5$ (98%), silica gel (40–63 µm) and d$_6$-DMSO (Uvasol grade) were from VWR (Leicestershire, UK).

Instrumentation

NMR spectra were recorded using a Bruker Advance 300 at 300.1 MHz (^{1}H NMR) or 75.5 MHz (^{13}C NMR), unless stated otherwise (Bruker DPX 400) at 300 K. The solvent used was d$_6$-DMSO, and ^{1}H and ^{13}C NMR chemical shifts were calibrated on residual solvent at 2.51/39.6 ppm. *J* values are given in Hz. Melting points were determined using a SMP3 melting point apparatus (Stuart Scientific, Staffordshire, UK) and are uncorrected.

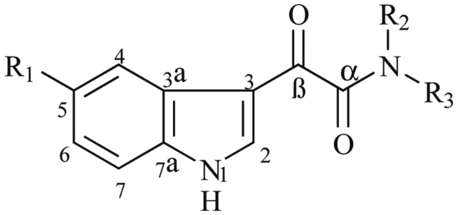
Procedures

Synthesis (Scheme 1)

The appropriate amine (15.65 mmol) was added dropwise to an ice-cold solution of 5-methoxyindole-3-yl-glyoxalyl chloride (1.24 g, 5.22 mmol) or indole-3-yl-glyoxalyl chloride (1.08 g, 5.22 mmol)[3] dissolved in 100 mL anhydrous THF. The mixture was stirred on ice for 4 h. The solvent was evaporated under reduced pressure and the crude solid purified by flash chromatography (DCM-MeOH, 9:1). The solvent was evaporated under reduced pressure, and all products (**1**–**23**) (Table 1) were recrystallized from aqueous ethanol, unless otherwise mentioned, and dried overnight under vacuum over P$_2$O$_5$.

Indole ^{1}H and ^{13}C NMR data for compounds **1**–**12** (disubstituted) and compound **17** (monosubstituted)

TABLE 1 Structures and Percentages of Major/Minor Rotamers of Asymmetrically *N,N*-Disubstituted Glyoxalylamides 1–12. Glyoxalylamides 13–23 Exist as Only One Rotamer in the NMR Spectrum



Compound	Rotamer	%	R^1	R^2	R^3	Compound	R^1	R^2	R^3
1	Major	70	MeO	Et	iPr	**13**	MeO	Me	tBu
	Minor	30				**14**	H	Me	tBu
2	Major	68	H	Et	iPr	**15**	MeO	H	tBu
	Minor	32				**16**	H	H	tBu
3	Major	55	MeO	Et	nPr	**17**	MeO	H	iPr
	Minor	45				**18**	H	H	iPr
4	Major	54	H	Et	nPr	**19**	MeO	H	Me
	Minor	46				**20**	H	H	Me
5	Major	58	MeO	Me	Et	**21**[a]	H	H	Me
	Minor	42				**22**	H	H	Et
6	Major	56	H	Me	Et	**23**	H	H	nPr
	Minor	44							
7	Major	52	MeO	Me	iBu				
	Minor	48							
8	Major	51	H	Me	iBu				
	Minor	49							
9	Major	67	MeO	Me	iPr				
	Minor	33							
10	Major	66	H	Me	iPr				
	Minor	34							
11	Major	53	MeO	Me	nPr				
	Minor	47							
12	Major	52	H	Me	nPr				
	Minor	48							

[a] For compound **21**, the ring is *N*-methylindole (N1 = Me).

are included in the supplementary data for Ref. 3.[3] The NMR data for compounds **16** and **18** have been reported at 200 MHz[12] and have therefore not been included here. The data for compounds **13–15** and **19–23** have not been previously reported at medium field strength and have therefore been included here.

*5-Methoxyindole-3-yl-N-methyl-N-tert-butylglyoxalylamide (**13**).* Yield: 997 mg (3.46 mmol, 66%). M.p. 200.5–201.5°C (from ethyl acetate). δ_H (300 MHz, d_6-DMSO) 7.86 (1H, H-2, s), 7.54 (1H, H-4, d, J 1.9), 7.44 (1H, H-7, d, J 9.0), 6.90 (1H, H-6, dd, J 8.9, J 2.5), 2.30 (3H, N-CH_3, s), 1.45 (9H, N-$C(CH_3)_3$, s). δ_C (75 MHz, d_6-DMSO) 186.8 (CO-β), 168.8 (CO-α), 156.0 (C-5), 135.9 (C-2), 131.7 (C-7a), 126.0 (C-3a), 113.6 (C-7), 113.5 (C-6), 112.7 (C-3), 102.8 (C-4), 56.6 (N-$C(CH_3)_3$), 55.5 (OCH_3), 32.6 (N-CH_3), 27.4 N-$C(CH_3)_3$).

*Indole-3-yl-N-methyl-N-tert-butylglyoxalylamide (**14**).* Yield: 851 mg (3.29 mmol, 63%). M.p. 190–191°C. δ_H (300 MHz, d_6-DMSO) 8.07 (1H, H-4, dd, J 5.7, J 2.0), 7.93 (1H, H-2, s), 7.56–7.51 (1H, H-7, m), 7.28 (1H, H-6, td, J 6.0, J 2.0), 7.24 (1H, H-5, td, J 5.7 Hz, 1.9), 2.80 (3H, N-CH_3, s), 1.45 (9H, N-$C(CH_3)_3$, s). δ_C (100 MHz, d_6-DMSO) 186.9 (CO-β), 168.7 (CO-α), 136.9 (C-7a), 135.9 (C-2), 125.1 (C-3a), 123.6 (C-6), 122.6 (C-5), 121.0 (C-4), 112.8 (C-3), 112.8 (C-7), 56.6 (N-$C(CH_3)_3$), 32.5 (N-CH_3), 27.4 (N-$C(CH_3)_3$).

*5-Methoxyindole-3-yl-N-tert-butylglyoxalylamide (**15**).* Yield: 952 mg (3.47 mmol, 64%). M.p. 187–188°C.

δ_H (300 MHz, d_6-DMSO) 8.60 (1H, H-2, s), 7.72 (1H, H-4, d, J 2.5), 7.43 (1H, H-7, d, J 8.9), 6.89 (1H, H-6, dd, J 8.8, J 2.5), 3.78 (3H, OCH_3, s), 1.37 (9H, N-$C(CH_3)_3$). δ_C (75 MHz, d_6-DMSO) 183.1 (CO-β), 163.8 (CO-α), 156.2 (C-5), 138.4 (C-2), 131.2 (C-7a), 127.4 (C-3a), 113.6 (C-7), 113.1 (C-6), 112.1 (C-3), 103.5 (C-4), 55.5 (OCH_3), 50.8 (N-$C(CH_3)_3$), 28.4 (N-$C(CH_3)_3$).

5-Methoxyindole-3-yl-N-methylglyoxalylamide (***19***). Yield: 859 mg (3.70 mmol, 71%). M.p. 202.0–202.5°C; lit.: 203–204°C.[19] δ_H (300 MHz, d_6-DMSO) 8.67 (1H, H-2, s), 7.72 (1H, H-4, br s), 7.43 (1H, H-7, d, J 8.7), 6.89 (1H, H-6, dd, J 8.9, J 1.1), 3.38 (3H, OCH_3, s), 2.73 (3H, N-CH_3, s). δ_C (100 MHz, d_6-DMSO) 182.1 (CO-β), 164.4 (CO-α), 156.2 (C-5), 138.8 (C-2), 131.2 (C-7a), 127.4 (C-3a), 113.6 (C-7), 113.2 (C-6), 112.3 (C-3), 103.6 (C-4), 55.5 (OCH_3), 25.8 (N-CH_3).

Indole-3-yl-N-methylglyoxalylamide (***20***). Yield: 837 mg (4.14 mmol, 79%). M.p. 220–222°C; lit.: 222–223°C.[20] δ_H (300 MHz, d_6-DMSO) 8.73 (1H, H-2, s), 8.24-8.16 (1H, H-4, m), 7.56–7.49 (1H, H-7, m), 7.27 (1H, H-6, td, J 6.9, J 1.8), 7.24 (1H, H-5, td, J 7.2, J 1.9), 2.73 (3H, N-CH_3, s). δ_C (75 MHz, d_6-DMSO) 182.2 (CO-β), 164.2 (CO-α), 138.6 (C-2), 136.3 (C-7a), 126.3 (C-3a), 123.5 (C-6), 122.6 (C-5), 121.4 (C-4), 112.6 (C-7), 112.2 (C-3), 25.6 (CH_3).

Methylindole-3-yl-N-methylglyoxalylamide (***21***). Yield: 836 mg (3.87 mmol, 74%). M.p. 209.0–209.5°C; lit.: 206–207°C.[7] δ_H (300 MHz, d_6-DMSO) 8.76 (1H, H-2, s), 8.22 (1H, H-4, dd, J 6.0, J 1.8), 7.58 (1H, H-7, br d, J 7.0), 7.38–7.25 (2H, H-5/6, m), 3.88 (3H, N-CH_3-1, s), 2.74 (3H, N-CH_3, s). δ_C (75 MHz, d_6-DMSO) 181.7 (CO-β), 164.1 (CO-α), 142.0 (C-2), 137.1 (C-7a), 126.8 (C-3a), 123.5 (C-6), 123.0 (C-5), 121.5 (C-4), 111.1 (C-7), 111.1 (C-3), 33.5 (NCH_3-1), 25.6 (N-CH_3).

Indole-3-yl-N-ethylglyoxalylamide (***22***). Yield: 870 mg (4.02 mmol, 77%). M.p. 203–204°C; lit.: 200–201°C.[20] δ_H (300 MHz, d_6-DMSO) 8.72 (1H, H-2, s), 8.26–8.16 (1H, H-4, m), 7.58–7.47 (1H, H-7, m), 7.31–7.20 (2H, H-5/6, m), 3.23 (2H, N-CH_2CH_3, q, J 6.8), 1.09 (3H, N-CH_2CH_3, t, J 7.1). δ_C (75 MHz, d_6-DMSO) 182.5 (CO-β), 163.5 (CO-α), 138.5 (C-2), 136.3 (C-7a), 126.3 (C-3a), 123.5 (C-6), 122.6 (C-5), 121.4 (C-4), 112.6 (C-7), 112.3 (C-3), 33.5 (CH_2), 14.6 (CH_3).

Indole-3-yl-N-propylglyoxalylamide (***23***). Yield: 852 mg (3.70 mmol, 71%). M.p. 183–184°C; lit.: 188–190°C.[21] δ_H (300 MHz, d_6-DMSO) 8.72 (1H, H-2, s), 8.27–8.17 (1H, H-4, m), 7.58–7.48 (1H, H-7, m), 7.33–7.20 (2H, H-5/6, m), 3.16 (2H, $CH_2CH_2CH_3$, t, J 7.1), 3.02 (2H, $CH_2CH_2CH_3$, sextet, J 7.2), 0.86 (3H, $CH_2CH_2CH_3$, t, J 7.3). δ_C (75 MHz, d_6-DMSO) 182.5 (CO-β), 163.7 (CO-α), 138.5 (C-2), 136.4 (C-7a), 126.3 (C-3a), 123.5 (C-6), 122.6 (C-5), 121.4 (C-4), 112.6 (C-7), 112.3 (C-3), 40.4 (N-$CH_2CH_2CH_3$), 22.3 (N-$CH_2CH_2CH_3$), 11.5 (N-$CH_2CH_2CH_3$).

X-ray Crystallographic Data

Crystal Structure Determination of (15): Crystal Data. $C_{15}H_{18}N_2O_3$, $M_r = 274.315\ \mathrm{g\,mol^{-1}}$, monoclinic, space group $P2_1$, $a = 6.9588(12)$, $b = 7.3364(12)$, $c = 14.226(3)$ Å, $\beta = 94.961(16)°$, $V = 723.6(2)$ Å^3, $Z = 2$, $D = 1.259\ \mathrm{Mg\,m^{-3}}$ (calc.), $\mu = 0.09\ \mathrm{mm^{-1}}$ at 293 K. A colorless, lath-shaped crystal with dimensions $0.65 \times 0.25 \times 0.05$ mm was measured on a 4-circle Enraf-Nonius diffractometer (Delft, The Netherlands) with Mo-K_α radiation. The structure was solved with SHELXS[22] and refined with SHELXL[22] to $R = 0.042$ for 849 reflections with $F_o > 4\sigma(F_o)$ and $wR2 = 0.130$ for all 1415 reflections. Hydrogen atoms attached to C were placed in calculated positions, but those attached to N were refined freely.

Crystal Structure Determination of (16): Crystal Data. $C_{14}H_{16}N_2O_2$, $M_r = 244.29\ \mathrm{g\,mol^{-1}}$, monoclinic, space group $P2_1/c$, $a = 23.957(5)$, $b = 5.974(3)$, $c = 19.678(3)$ Å, $\beta = 113.226(15)°$, $V = 2588.1(15)$ Å^3, $Z = 8$, $D = 1.254\ \mathrm{Mg\,m^{-3}}$ (calc.), $\mu = 0.09\ \mathrm{mm^{-1}}$ at 293 K. All crystals of this material that were examined gave weak diffraction. The best of them, a colorless, needle crystal with dimensions $0.60 \times 0.18 \times 0.05$ mm, was measured on a 4-circle Enraf-Nonius diffractometer with Mo-K_α radiation. The structure was solved with SHELXS[22] and refined with SHELXL[22] to $R = 0.070$ for 1978 reflections with $F_o > 4\sigma(F_o)$ and $wR2 = 0.250$ for all 4630 reflections. All hydrogen atoms were placed in calculated positions.

Crystal Structure Determination of (18): Crystal Data. $C_{13}H_{14}N_2O_2$, $M_r = 230.26\ \mathrm{g\,mol^{-1}}$, monoclinic, space group $P2_1/c$, $a = 5.1159(8)$ Å, $b = 25.880(4)$ Å, $c = 8.9785(11)$ Å, $\beta = 95.758(12)°$, $V = 1182.8(3)$ Å^3, $Z = 4$, $D = 1.293\ \mathrm{Mg\,m^{-3}}$ (calc.), $\mu = 0.09\ \mathrm{mm^{-1}}$ at 293 K. A colorless, triangular plate-shaped crystal with dimensions $0.2 \times 0.2 \times 0.03$ mm was measured on a 4-circle Enraf-Nonius diffractometer with Mo-K_α radiation. The structure was solved with SHELXS[22] and refined with SHELXL[22] to $R = 0.047$ for 1396 reflections with $F_o > 4\sigma(F_o)$ and $wR2 = 0.150$ for all 2105 reflections. Hydrogen atoms attached to C were placed in calculated positions, but those attached to N were refined freely.

RESULTS AND DISCUSSION

NMR Spectroscopy

Resonance through the amide bond of the glyoxalylamide results in the partial double-bond character of the C–N bond, and as a consequence, rotation about the bond is slow on the ^{1}H and ^{13}C NMR timescales.[23] The presence of the β-keto functional group in glyoxalylamides reduces the electron density on the amide group, increasing the rotational barrier when compared with simple amides.[24] Due to the restricted rotation of the amide bond, separate peaks are observed in the NMR spectra of the glyoxalylamide for each substituent in *syn* and *anti* rotamers (Fig. 1).[13,25] A similar phenomenon has been observed during the synthesis of psilocin analogues,[26,27] 5,6-methylenedioxyindole-3-yl-*N,N*-(disubstituted)-glyoxalylamides,[25] and *N,N*-diisopropyl-5-methoxy-tryptamine.[29,30]

Because the peak intensities are nonequivalent, there is clearly a preference toward one conformation. The relative abundance of each rotamer can be determined from the ratio of the peaks. Based on simple steric interactions, it has previously been suggested that the *anti*-periplanar conformation in which the large substituent is orientated *trans* to the amide carbonyl is preferred.[3] It was proposed that in a *syn*-periplanar conformation, the larger substituent is forced into the same plane as the amide carbonyl where it experiences a greater steric hindrance compared with the *anti*-periplanar conformation, in which it faces away from the amide carbonyl (Fig. 1).

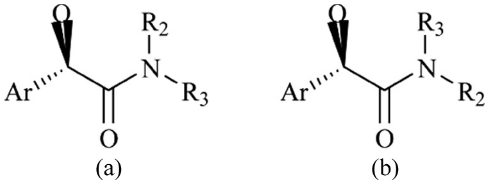


FIGURE 1 *syn*-Periplanar (a) and *anti*-periplanar (b) structures of glyoxalylamides 1–23 (R_2 = small substituent; R_3 = large substituent).

In a recent study by our group to characterize fully the Speeter and Anthony route, several symmetrically and asymmetrically *N,N*-disubstituted glyoxalylamides and their corresponding tryptamines were synthesized.[3] A detailed mass spectral characterization and NMR study of both amide intermediates and tryptamines was performed, providing information on the rotamer populations for the asymmetrically *N,N*-disubstituted glyoxalylamides.

Aymmetrically Substituted *N,N*-Dialkyl-glyoxalylamides 1–14

In the ^{1}H NMR and ^{13}C NMR spectra of glyoxalylamides **1–12**, sets of two unequal peaks were observed for each rotamer. Some of the indolic protons as well as the amide substituents were observed as two peaks. It is interesting to note, however, that for glyoxalylamides **13** and **14**, the presence of the *N-tert*-butyl group causes 100% population of one conformation. This effect is attributed to the bulk of the *N-tert*-butyl substituent, exemplified by the less dramatic impact of the primary (N–CH_2–C) substituents of the *N*-alkyl-*N*-n-propyl (**3**, **4**, **11**, **12**) and *N*-alkyl-*N*-iso-butyl (**7**, **8**) analogues. The major isomer was previously assigned as the *anti*-periplanar conformation.[3]

A review of amide NMR studies by Stewart and Siddall[25] contains a tabulation of the rotamer ratios in a series of unsymmetrically disubstituted alkylamides ($RC(O)NR_1R_2$). Here, electronic effects appear to be rather small. The most stable isomer seems in general to be that in which repulsion is minimized between the R group on the carbonyl carbon and the substituents on the nitrogen. This follows a study by LaPlanche and Rogers,[31] who demonstrated that when R = H, the preferred isomer is that in which the bulkier substituent is *trans* to the carbonyl oxygen (i.e., in an *anti*-periplanar conformation). However, when R > H, the preferred conformation is that in which the bulkier group is *cis* to the oxygen (i.e., in a *syn*-periplanar conformation). This was accounted for on the basis of the order of size of the groups (i.e., R (alkyl) > CH_3 > O > H), as a small rotation about the C–N bond (which would take the atoms attached to the carbon out of the plane formed by the C–N–R group) would lead to a reduction in the contribution of the resonance structures.[31] An increase in size of the R group and the concomitant interaction with the *N*-alkyl substituent would therefore result in a decrease in stability of the molecule.

If it is relevant, this preference would suggest that the preferred conformation for the glyoxalylamides **1–14** should be the *syn*-periplanar conformation, in which the bulkier substituent is orientated *trans* to the indolyl-carbonyl moiety. This contradicts our previous assignment, in which interaction between the larger N-alkyl substituent and the amide carbonyl group was suggested as the dominant factor influencing conformational stability. It was expected that rotation about the O=C–C=O bond would allow the indolyl-carbonyl moiety to evade steric clash with *N*-alkyl substituents, and consequently the *anti*-periplanar conformation was assumed to be preferred.[3] To settle this question, additional information is required.

Monosubstituted *N*-Alkylglyoxalylamides 15–23

In the ^{1}H NMR and ^{13}C NMR spectra of the monosubstituted glyoxalylamides **15–23**, only single peaks were observed for *N*-alkyl substituents, implying 100% population of one conformation. Comparison of the chemical shifts of the alkyl groups suggests that, if the major conformation in **1–14** is *anti*-periplanar, the sole conformation in **15–23** should be *anti*-periplanar. For example, in compound **17** ($R_1 = MeO$, $R_2 = H$, and $R_3 =$ isopropyl), the single peak for the isopropyl CH group occurs at a chemical shift of $\delta = 4.02$, which is close to the average chemical shift (δ 3.83) measured for *N,N*-dialkylamides where an isopropyl group constitutes the larger substituent assumed to be in the *anti* conformation (**1**, **2**, **9**, and **10**). The apparently logical assumption that the *N*-monoalkyl derivatives are 100% *anti* was previously attributed to unfavorable steric interaction in the *syn*-periplanar conformation, where the larger (bulkier) substituent is forced into the same plane as the amide carbonyl. The review of amide NMR studies by Stewart and Siddall[25] discusses the isomer ratios of a number of reported monosubstituted alkylamides (RC(O)NHR$_1$) in a variety of solvents. All of the examples favor the conformation in which the alkyl-substituent is located *cis* to the amide carbonyl (i.e., a *syn*-periplanar conformation). Significantly, all amides in which R > H exist completely in the *syn*-periplanar conformation, except where water is used as a solvent, which may be due to hydrogen bonding influencing the orientation of R$_1$. This phenomenon has been attributed to steric interactions between the *N*-alkyl substituent and the R group.[32] Despite our original conclusion, it is clear that the steric interaction between the alkyl group and the amide carbonyl is not the dominant factor influencing rotamer populations, and there must be a second effect operating that stabilizes the molecule in the *syn*-periplanar conformation.

Here, solid-phase X-ray structure determination is presented, along with molecular modeling data regarding rotamer preference against which the NMR data can be compared. The degree of intramolecular and intermolecular hydrogen bonding in the crystals and its impact on conformational stability and crystal packing will be discussed.

X-ray Crystallography

The molecules of three monosubstituted *N*-alkylglyoxalylamides in their crystal structures are displayed in Fig. 2: 5-methoxyindole-3-yl-*N*-*tert*-butylglyoxalylamide (**15**), indole-3-yl-*N*-*tert*-butylglyoxalylamide (**16**), and indole-3-yl-*N*-isopropylglyoxalylamide (**18**).

The preferred conformation for all three structures is *syn*-periplanar. The torsion angle O2–C9–N10–C11 measured in **18** is −0.4(4)°, indicating that the alkyl substituent is *cis* to the amide carbonyl with the two groups adopting a strictly eclipsed conformation. Even with the greater bulk of the *tert*-butyl substituent, there is little twisting of the amide C–N bond, O2–C9–N10–C11 being −3.9(8)° in **15** and −4.2(9)° and 3.5(8)° in the two independent molecules of **16**. Evidently, any significant rotation about the C9–N10 bond to mitigate the strain would sacrifice too much resonance stability. Instead, the torsional strain caused by electron repulsion between the eclipsed O2–C9 and N10–C11 bonds and the steric strain arising from interaction between O2 and C11 appear to be relieved by angle deformation. This leads to larger than expected O2–C9–N10 [123.1(2)°] and C9–N10–C11 [122.5(2)°] bond angles in **18**. Predictably, the bulkier *tert*-butyl group causes greater strain and consequently larger O2–C9–N10 [124.1(2)° in compound **15**; 125.6(5)° and 124.9(5)°

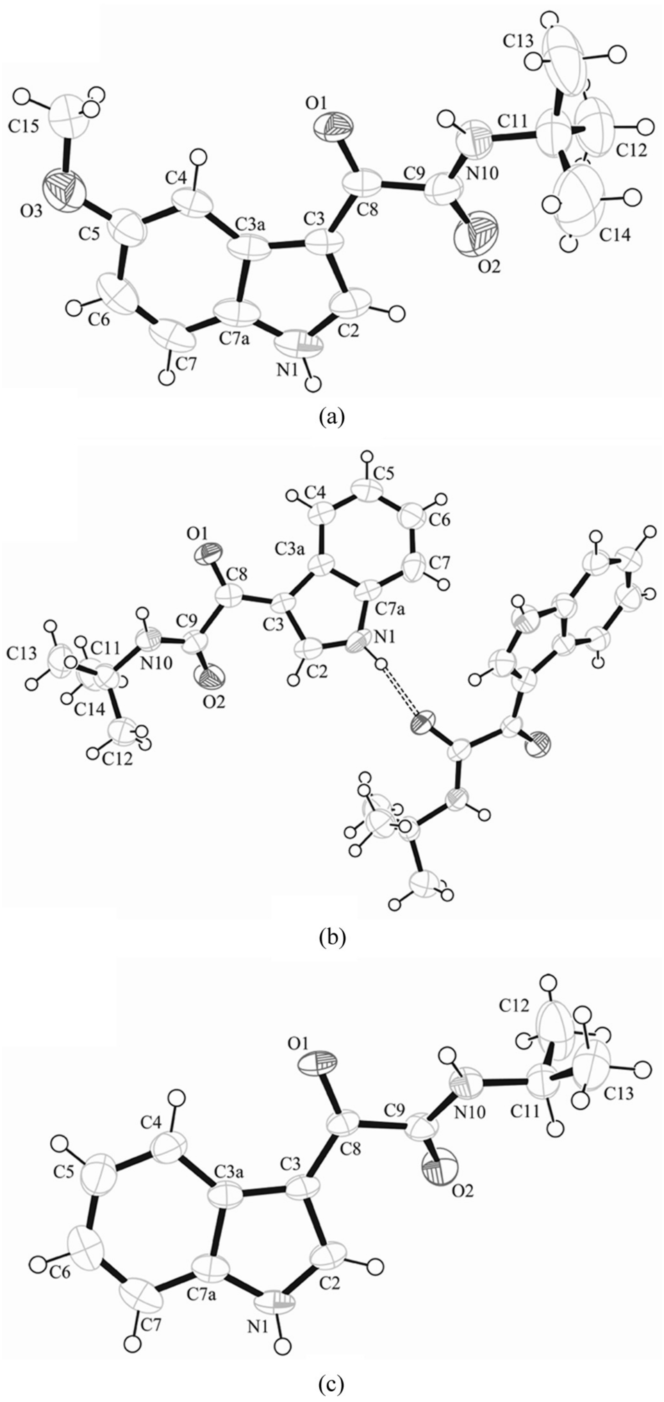


FIGURE 2 Molecular geometry taken from the crystal structures of (a) 15, (b) the two independent molecules of 16, and (c) 18.

TABLE 2 Hydrogen Bonds Identified in the Crystal Structures of Glyoxalylamides 15, 16, and 18

Compound	Atoms	Length (Å)	Angle (°)	Type
15	N1–H1…O1	1.93	156	Intermolecular
	N10–H10…O1	2.40	97	Intramolecular
	N10–H10…O3	2.69	157	Intermolecular
	C2–H2…O2	2.24	118	Intramolecular
16	N1–H1…O2′	1.92	168	Intermolecular
	N1′–H1…O2	1.95	168	Intermolecular
	N10–H10…O1	2.42	102	Intramolecular
	N10′–H10′…O1′	2.46	101	Intramolecular
	N10–H10…O1	2.36	155	Intermolecular
	N10′–H10′…O1′	2.28	157	Intermolecular
	C2–H2…O2	2.46	108	Intramolecular
	C2′–H2′…O2′	2.48	107	Intramolecular
18	N1–H1…O1	2.02	171	Intermolecular
	N10–H10…O1	2.45	106	Intramolecular
	N10–H10…O2	2.17	151	Intermolecular
	C2–H2…O2	2.43	112	Intramolecular

The crystal structure data confirm the presence of a weak intramolecular hydrogen bond between N10–H10 and O1 in each of the compounds (Table 2), forming a five-membered ring from the amide NH to the β-keto group with graph set S(5). Similar rings, many with closer H…O contacts, are known in the crystallographic literature (Fig. 3). The H10–N10–C9–C8=O1 system is bent in on itself with angles N10–C9–C8 in the range 114.2(4)° to 115.8(4)° and C9–C8=O1 117.5(4)° to 118.5(4)°. The reduction below 120° is consistent with the requirements of a five-membered ring. A similar pattern has also been observed in primary and secondary indol-2-yl-glyoxylylamides.[33] The hydrogen bond is angled sharply [compound **15** =97(3)°, in **16**] and C9–N10–C11 [127.2(5)° in compound **15**; 125.2(4)° and 124.4(4)° in **16**] bond angles.

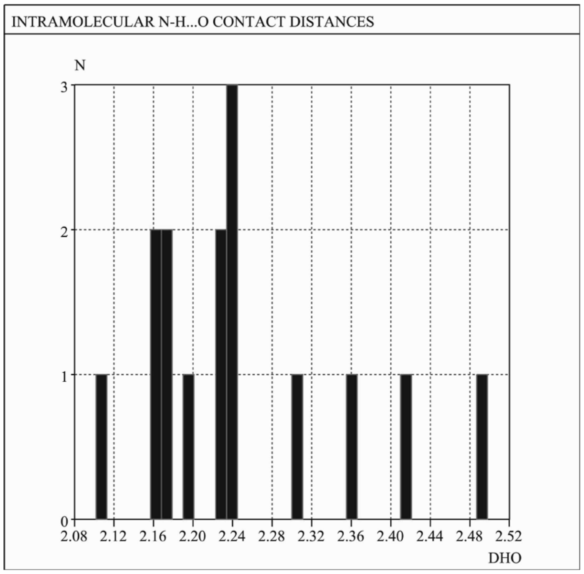


FIGURE 3 A histogram of the intramolecular N-H…O contact distances (DHO) for the hits of the CSD search.

16 = 102° and 101° based on calculated positions, **18** = 106(2)°] and therefore can only be viewed as a weak hydrogen bond.

In each case, the sharp angle of the intramolecular hydrogen bond makes room for N10–H10 to form a second, intermolecular hydrogen bond. The acceptors are the methoxy O3, albeit barely closer than a van der Waals contact, in compound **15** making a chain with graph set C(9); O1 and O1′ in **16** making rings with graph set $R_2^2(10)$; and O2 making a simple C(4) chain in **18**. In **15** and **16**, any intermolecular interaction between N10–H10 and O2, the amide O atom, appears to be obstructed by the methyl groups of the bulky *tert*-butyl substituent.

An intermolecular bond between the indole NH and an O1 of an adjacent molecule is observed for both **15** and **18** (Table 2). It is interesting to note that in the *anti*-periplanar conformation, the formation of this bond would be impeded; consequently, both crystal packing and hydrogen bonding may influence the conformational preference for the *syn* rotamer. Although the indole NH groups of **16** also form hydrogen bonds, these have O2′ and O2 as the acceptors. The combined effect of the intermolecular hydrogen bonding in **15** leads to chains of molecules running parallel to [0 1 0]; in **16**, the result is a three-dimensional network, whereas in **18** the molecules are linked into a two-dimensional sheet extending in the *x* and *z* directions.

The approximately *trans*-coplanar O=C–C=O geometry facilitates a close approach between the indole ring and O2. In compound **15**, the −162.9(5)° value of this torsion angle results in a strong intramolecular C–H…O hydrogen bond (H…O distance 2.24 Å) from C2 in the indole ring. Similar but longer hydrogen bonds occur in **16**, where the 149.0(5)° and −146.0(5)° torsion angles in the two independent molecules indicate greater twisting about the C–C bond, and in **18**, where the value of −143.1(2)° shows the greatest twist ever reported in this class. The close in-plane approach of a proton to an amide normally results in deshielding,[25] a phenomenon that has been observed for H2 in related compounds.[29] In compound **18**, with the isopropyl methine H atom only 2.46 Å from O2, deshielding would again be expected. This effect may explain the inversion of H-2 and H-4 signals in the ^{1}H NMR spectra and C-2 and C-7a signals in ^{13}C NMR spectra of the monosubstituted glyoxalylamides with respect to the disubstituted glyoxalylamides. The Cambridge Structural Database (CSD) study described below shows that the O=C–C=O torsion angles are invariably closer to *trans*-coplanarity, facilitating a close approach of H2 to O2, in the monosubstituted glyoxalylamides compared with the disubstituted glyoxalylamides (Fig. 4). The sizeable twist between carbonyl groups depicted in Fig. 1 appropriately represents the latter class of molecules. The inversion is perhaps also an indication that deshielding is more apparent in the *syn* conformation, adopted by the monosubstituted glyoxalylamides, than the *anti* conformation, adopted by the disubstituted glyoxalylamides. Interestingly, in the 5-methoxy derivatives, no signal inversion is observed when comparing monosubstituted *versus* disubstituted analogues. H-2 and H-4 are, however, shifted further downfield in the monosubstituted derivatives, particularly for H-2, which appears 1 ppm further downfield at ~9 ppm. This can be attributed to the deshielding effect of the 5-methoxy group on H-4, and hence both H-2 and H-4 appear further downfield.

The conformational preference for *syn* in the monosubstituted glyoxalylamides was confirmed by a substructure search of the CSD. A total of 13 hits comprising 15 observations of independent molecules was generated using the query $C(O)C(O)N_aHR$

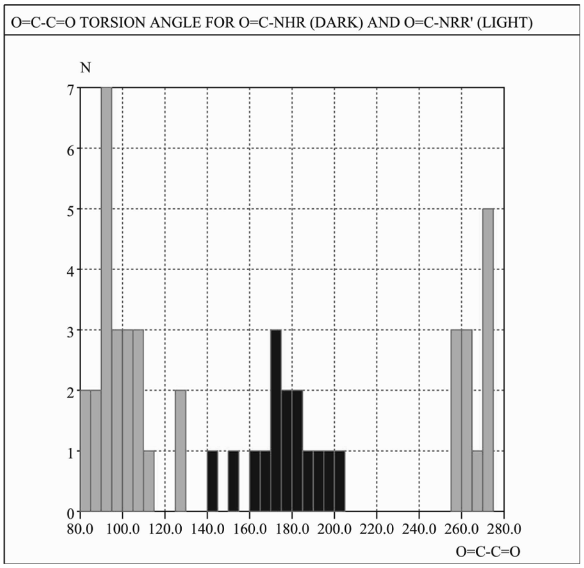


FIGURE 4 Comparison of the torsion angles for mono-substituted (O=C-NHR, dark) glyoxalylamides and di-substituted (O=C-NRR′, light) glyoxalylamides from the CSD. The mono-substituted glyoxalylamides are closer to *trans*-coplanarity than any of the disubstituted glyoxalylamides.

(compounds with cyclic amide substituents were avoided, and compounds with a carbonyl group as an amide substituent were manually removed because of the possible effect on conformation). All 15 occurrences in the CSD occupy the *syn*-periplanar conformation. The intramolecular S(5) ring observed in **15**, **16**, and **18** was observed in all cases and appears to be universal. The average H ... O contact distance is only 2.25 Å (Fig. 3). A distance of 2.30 Å or less has been taken as a definition of a significant hydrogen bond,[34] so most of these fall within that category. The average N ... O distance of 2.65 Å is respectably short, but the poor average N–H ... O angle of just 107° must limit the energetic contribution that this hydrogen bond can make. In this series, the mean absolute value of the O=C–C=O torsion angle (Fig. 4) is 167.5° with standard error 2.5° indicating that the geometry of this group is roughly coplanar and supporting the notion that this may facilitate the formation of the intramolecular N–H ... O hydrogen bond.

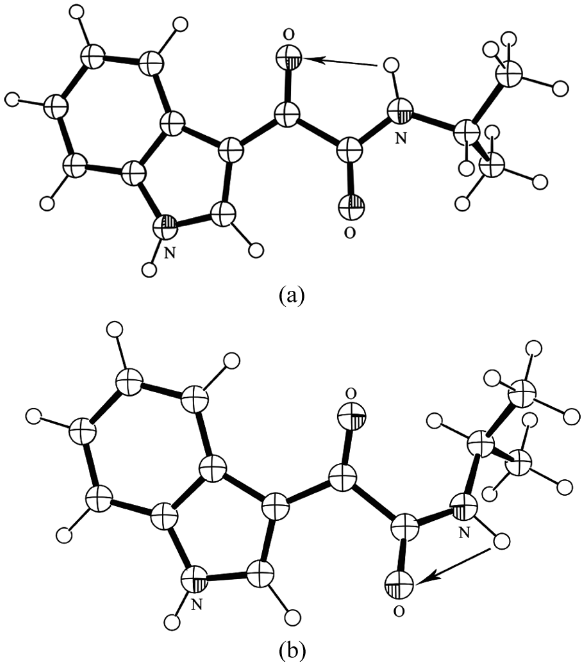
From a secondary indol-2-ylglyoxalylamide structure, Black and co-workers inferred that a set of three hydrogen-bonded rings, S(5) from amide H to β-O, $R_2^2(10)$ involving the same atoms intermolecularly, and S(6) from indole NH to α-O, could be a robust supramolecular synthon.[33] Analysis of all the available data for glyoxalylamides with one amide hydrogen atom provides only partial support for this hypothesis. The $R_2^2(10)$ ring occurs in five structures, but a simple C(4) chain linking amide NH to amide O occurs with similar frequency. The amide NH donates an intermolecular hydrogen bond to a keto oxygen atom in one case.

All of the other secondary indolyl-glyoxalylamides from the CSD are 3-indolyl rather than 2-indolyl, but the S(6) ring still forms in every case with the C2 hydrogen atom taking the place of NH. The average C ... O contact distance is 2.856 Å compared with the N ... O of 2.664 Å for the 2-indolyl compound, and the average H ... O contact of 2.30 Å is longer than the 2.00 Å observed for the 2-indolyl example, but still much shorter than a simple van der Waals contact. The average C–H ... O angle of 114° is bent a little more than the 121° for the 2-indolyl derivative. The geometric data for this C–H ... O hydrogen bond as well as its ubiquity suggest that this interaction could have some significance in facilitating coplanarity of the indole and amide moieties. For nonidentically disubstituted (NRR′) glyoxalylamides (R and R′ ≠ C=O), there is a total of six hits with six observations in the *anti*-periplanar conformation and one hit with two observations that adopt the *syn* conformation. There is a sufficient majority of *anti* conformations to suggest that the original assignment[3] of the major NMR peaks to the *anti* conformation was correct. The only exception, where the two independent molecules adopt a *syn* conformation, is a co-crystal containing *N*-ethyl-*N*-methylbenzoylformamide,[35] in which sterically undemanding methyl and ethyl groups are attached to the amide N atom. In a co-crystal with a different partner,[35] the same molecule exhibits the *anti* conformation. The keto oxygen atom undergoes repulsion from a substituent in every disubstituted glyoxalylamide instead of attraction to an amide hydrogen atom in the monosubstituted analogues. To mitigate such repulsion, the deviation of the O=C–C=O torsion angle from 180° is greater in the former series (Fig. 4).

Theoretical Molecular Orbital Energies and Charges

In order to gain further insight into the conformational stabilities of mono- and disubstituted glyoxalylamides, the *syn* and *anti* conformations of indole-3-yl-*N*-isopropylglyoxalylamide (**18**) and indole-3-yl-*N*-ethyl-*N*-methylglyoxalylamide (**6**) were optimized *in vacuo* by *ab initio* molecular orbital calculations at the HF/6-31G* level with the GAMESS program.[36] The results for **18** indicated that the *anti*-periplanar conformation is 29 kJ mol^{-1} higher in energy, and consequently less stable, than the *syn*-periplanar conformation. This suggests that the *syn*-periplanar conformation would be preferred, supporting the data collected by Stewart and Siddall[25] as well as the crystal structures.

To determine if hydrogen bond interactions are responsible for the increased stability of the *syn*-periplanar conformation, 3D diagrams (Fig. 5) of the atomic arrangement in the optimized structures were compared. In the *syn*-periplanar conformation, the hydrogen atom attached to the amide nitrogen points toward the nearby carbonyl group, and the H ... O contact distance is only 2.160 Å, which suggests that hydrogen bonding may be a factor driving the stability of the *syn*-periplanar conformation. The



(a)

(b)

FIGURE 5 *syn*-Periplanar (a) and *anti*-periplanar (b) conformations of indole-3-yl-*N*-isopropylglyoxalylamide (18) obtained by *ab initio* molecular orbital calculations at the HF/6-31G* level.

3D diagram of the *anti*-periplanar conformation shows that the hydrogen atom is more distant from its adjacent carbonyl oxygen atom (2.361 Å).

Molecular orbital calculations yield a Löwdin charge of +0.209 on the hydrogen atom attached to C2, and for **18** the calculated distance from H2 to O2 in the optimized *syn* conformation of 2.288 Å is very similar to the crystallographic value. This contact is significantly closer than the 2.669 Å found by a similar optimization procedure for the disubstituted 5-methoxyindol-*N*,*N*-diisopropyl-3-glyoxalylamide.[29] H2 is the most positive of all the C–H hydrogen atoms, though still less positive than the +0.310 on the indole N–H hydrogen atom. The expectation by Black and co-workers[33] that the amide carbonyl oxygen atom should be a better hydrogen bond acceptor than the keto carbonyl oxygen atom is substantiated by the Löwdin charges of −0.379 and −0.315, respectively.

The *syn*- and *anti*-periplanar conformations of indole-3-yl-*N*-ethyl-*N*-methylglyoxalylamide (**6**) were generated and optimized by similar procedures. Alternative orientations of the *N*-ethyl group governed by positive and negative values of the Cα–N–C–C torsion angle were explored, and the positive alternative (89.9° and 105.3°, respectively) gave lower energy for both *syn* and *anti* conformations. Structures of *N*-ethyl-*N*-methylbenzoylformamide[35] co-crystals similarly have positive values for this torsion angle, 108.3° and 111.1° when *syn*, and 104.4° when *anti*. Comparison of the lowest-energy optimized *syn* and *anti* forms of **6** showed that the latter conformation is more stable by 0.8 kJ mol^{-1}. Application of the factor $\exp(-\Delta E/RT)$ at a temperature of 300 K gives a *syn*:*anti* ratio of 0.72. This result for the molecules *in vacuo* is surprisingly close to the $0.44/0.56 = 0.79$ obtained by NMR in solution and provides some added support for the assignment[33] of *anti*-periplanar as the preferred conformation.

CONCLUSIONS

The ^{1}H and ^{13}C NMR spectra of asymmetrically disubstituted glyoxalylamides (**1**–**14**) show the duplication of peaks for the side chain due to restricted rotation within the amide group. Steric effects lead to the presence of major and minor rotamers, previously assigned as *anti*-periplanar and *syn*-periplanar conformations, respectively. Molecular orbital calculations and the occurrence of more *anti* than *syn* conformations in the crystallographic literature support this assignment. In the ^{1}H and ^{13}C NMR spectra of monosubstituted *N*-alkyl glyoxalylamides (**15**–**23**), single peaks are observed for the side-chain signals, indicating 100% population of one conformation. The crystal structures of 5-methoxyindole-3-yl-*N*-*tert*-butylglyoxalylamide (**15**), indole-3-yl-*N*-*tert*-butylglyoxalylamide (**16**), and indole-3-yl-*N*-isopropylglyoxalylamide (**18**) reveal that the preferred conformation for all structures is *syn*-periplanar. This is in agreement with the results of a CSD search, in which all 15 occurrences adopt the *syn* conformation. The stability of the *syn* conformation is attributed to the presence of two sets of intramolecularly hydrogen bonded rings, S(5) from amide NH to β-O and S(6) from CH-2 to α-O.

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