Regiospecific Synthesis and Structural Studies of 3,5-Dihydro-4H-pyrido[2,3-b][1,4]diazepin-4-ones and Comparison with 1,3-Dihydro-2H-benzo[b][1,4]diazepin-2-ones

David Núñez Alonso, Marta Pérez-Torralba,* Rosa M. Claramunt, M. Carmen Torralba, Patricia Delgado-Martínez, Ibon Alkorta, José Elguero, and Christian Roussel

ABSTRACT: Nine 3,5-dihydro-4H-pyrido[2,3-b][1,4]diazepin-4-ones (17–25), some of which contain fluoro-substituents, have been regiospecifically prepared by reaction of 2,3-diaminopyridines with ethyl arylacetates. In two cases, open intermediates have been isolated and these are related to the reaction pathway. The X-ray crystal structure of 1-methyl-4-phenyl-3,5-dihydro-4-(2-methyl-4-phenyl-1,5-benzodiazepin-2-one (1) has been solved (formula, C_{15}H_{13}N_{3}O; crystal system, monoclinic; space group, C2/c). This is an asymmetric unit constituted by a single nonplanar molecule and its conformational enantiomer due to the presence of the seven-membered diazepin-2-one moiety, which introduces a certain degree of torsion in the adjacent pyridine ring. The 1H, 13C, 15N, and 19F NMR spectra were obtained and the chemical shifts, together with bond was also calculated and its dynamic properties were discussed.

INTRODUCTION

Benzo[b][1,4]diazepin-2-ones are much less important in medicinal chemistry than benzo[e][1,4]-diazepin-2-ones such as diazepam and, for this reason, they have been less studied. However, there are some important drugs that contain the benzo[b][1,4] structure, for instance, the anxiolytic clobazam (7-chloro-1-methyl-5-phenyl-1,5-benzodiazepine-2,4-dione)\(^1\) and the atypical antipsychotic olanzapine ((2-methyl-4-(4-methyl-1-piperaziny1)-10H-thieno[2,3-b][1,5]-benzodiazepine)).\(^2\) Note that there are compounds like nevirapine that are both [b] and [e] [1,4]diazepines.\(^3\) We have previously published some results in the field of benzo[b][1,4]diazepines (Figure 1).\(^5,7\)

Figure 1. Structures of some benzo[b][1,4]diazepinones.

Several papers on benzo[b][1,4]diazepinones have been published and these encompass new synthetic methodologies\(^8–10\) and reactivity studies, including a comprehensive review\(^11\) and a more recent reference.\(^12\) The biological properties of benzo[b][1,4]diazepinones closely related to our work have been reported and the compounds are potent noncompetitive metabotropic glutamate receptor antagonists.\(^13\) Finally, the ESIPT (excited-state intramolecular proton transfer) mechanism has been observed in the photochemistry of benzo[b][1,4]diazepinones.\(^14\)

The biological importance of these compounds contrasts with the paucity of their structural studies. In this work, we present the regiospecific synthesis, X-ray crystallography data, and NMR (static and dynamic) properties of nine pyrido[2,3-b][1,4]-diazepin-4-ones, together with NMR data from our previous work concerning a series of sixteen benzo[b][1,4]diazepin-2-ones. Moreover, theoretical calculations of absolute shieldings.
(\(\sigma\), ppm) and their transformation into chemical shifts (\(\delta\), ppm) have been carried out at the GIAO/B3LYP/6-311++G(d,p) level to assign all NMR active nuclei (\(^1\)H, \(^13\)C, \(^15\)N, and \(^19\)F) and enable the structures to be unambiguously identified. Moreover,
related theoretical calculations have been carried out to
determine the inversion barriers of the diazepinone seven-
membered ring in the gas phase.

**RESULTS AND DISCUSSION**

The structures of the compounds under study are depicted in
Figure 2. Pyrido[2,3-b][1,4]diazepin-4-ones 17 to 25 have been
synthesized for the first time in this work, and compounds 1–16
were described in our previous publications or elsewhere, a
citation being provided in the corresponding tables.

**Regiospecific Synthesis and Structural Studies of 3,5-
Dihydro-4H-pyrido[2,3-b][1,4]diazepin-4-ones.** The
standard procedure to obtain 1,3-dihydro-2H-benzo[b][1,4]-
diazepin-2-ones involves a condensation reaction in xylene at
120 °C between benzene-1,2-diamines and β-oxoesters, ethyl
acetate, or ethyl aroylacettes. This method was used for the
preparation of the N-unsubstituted 1,3-dihydro-4H-pyrido[2,3-
b][1,4]diazepin-4-ones 17–22 starting from 2,3-diaminopyridines;
in all cases, only one regioisomer was formed (Scheme 1).

Open intermediates resulting from the condensation of the
pyridine 2-amino group with the ester counterpart were isolated
in two cases, 26 and 27, as detailed in Experimental Section.
Compounds 23–25 were obtained by subsequent N-alkylation
under basic conditions.15

Our results differ from those of Israel et al.16,17 who described
the formation of two regioisomers I and II in the reaction of 2,3-
diaminopyridine with ethyl acetate. However, the results are
consistent with those of Barchet and Merz18 on the reaction of
2,3-diaminopyridine with ethyl acetate, or ethyl aroylacetates. This method was used for the
preparation of the N-unsubstituted 1,3-dihydro-4H-pyrido[2,3-
b][1,4]diazepin-4-ones 17–22 starting from 2,3-diaminopyridines;
in all cases, only one regioisomer was formed (Scheme 1).15
Open intermediates resulting from the condensation of the
pyridine 2-amino group with the ester counterpart were isolated
in two cases, 26 and 27, as detailed in Experimental Section.
Compounds 23–25 were obtained by subsequent N-alkylation
under basic conditions.15

Our results differ from those of Israel et al.16,17 who described
the formation of two regioisomers I and II in the reaction of 2,3-
diaminopyridine with ethyl acetate. However, the results are
consistent with those of Barchet and Merz18 on the reaction of
2,3-diaminopyridine with ethyl acetate, or ethyl aroylacetates. This method was used for the
preparation of the N-unsubstituted 1,3-dihydro-4H-pyrido[2,3-
b][1,4]diazepin-4-ones 17–22 starting from 2,3-diaminopyridines;
in all cases, only one regioisomer was formed (Scheme 1).15
Open intermediates resulting from the condensation of the
pyridine 2-amino group with the ester counterpart were isolated
in two cases, 26 and 27, as detailed in Experimental Section.
Compounds 23–25 were obtained by subsequent N-alkylation
under basic conditions.15

Note that the multiplicity of H3 in tautomomer b differs between
17, a triplet of \( J = 2.2 \) Hz, and 18, a doublet of \( J = 2.3 \) Hz.
The triplet corresponds to two identical coupling constants of 2.2 Hz
between H3 and H1 and H5. The doublet of 2.3 Hz is probably
due to the fact that, in 18, one of the coupling constants is much
smaller than the other, although an NH to ND proton exchange
in DMSO-\( d_6 \) cannot be excluded.

**Crystal Structure of Compound 23.** Crystals of 5-methyl-
2-phenyl-3,5-dihydro-4H-pyrido[2,3-b][1,4]diazepin-4-one (23)
were grown from ethanol; the compound crystallizes in the
C2/c space group belonging to the monoclinic system.
The asymmetric unit is constituted by a single molecule that is not
planar due to the presence of the seven-membered diazepin-2-
one moiety, which introduces a certain degree of torsion in the
adjacent pyridine ring. In this sense, the defined dihedral angle
between the pyridine and phenyl rings is 49.8(2)° (Figure 4).
The N1 atom is flat and the sum of the angles around it is 359.3°.
Both \( M \) conformational enantiomers are present in the unit cell
and these correspond to rotation about the C9A–N1 bond
(−177.97° and +177.97° corresponding to \( M \) and \( P \) conformational
enantiomers); the same angles calculated theoretically
(gas phase) are ±174.9°.

However, a certain planarity is observed in the molecule in the
pyridine-N1N5 fragment on the one hand and in the 4-phenyl-
C3C4N5 unit on the other. The C2 carbonyl carbon points away
from these two moieties and the distances to the aforementioned
planes are 0.719(3) and 1.451(3) Å, respectively. This result,
along with the electronic distribution observed, is consistent
with the crystallographic angle and bond length data obtained
for this compound, which corresponds to tautomomer a with a
C4=NN5 double-bonded imino group. Molecules of 23 can be
considered to be crystallographically isolated since there are no
notable interactions between them, probably due to the
presence of the methyl group on the N1 nitrogen atom, which
prevents the formation of hydrogen bonds. The packing along
the \( b \) axis is provided in Figure S1 (Supporting Information).

The structure obtained for pyrido[2,3-b][1,4]diazepin-4-one
(23) has similar characteristics to those previously determined
in benzo[b][1,4]diazepin-2-ones,6,7 but less distortion is

---

**Scheme 2. Regioisomers Formed in the Reaction of β-
Oxoesters with 2,3-Diaminopyridine and Application of a
Thermal Rearrangement Reaction to Establish Their
Structure**

![Scheme 2. Regioisomers Formed in the Reaction of β-
Oxoesters with 2,3-Diaminopyridine and Application of a
Thermal Rearrangement Reaction to Establish Their
Structure](image-url)

The synthesis of 17 was also described by Martins et al.29
from the cyclocondensation reaction of 2,3-diaminopyridine with
1,1,1-trichloro-4-phenyl-4-methoxybut-3-en-2-one under basic
conditions. The same group later isolated and characterized the
open intermediate formed by addition of the 3-amino pyridine
group to the β-olefinic carbon of the vinyl ketone, cyclization of
which led to compound 17 (Scheme 3).21

**Characterization and Imino/Enamine Tautomerism.** Characterization of 3,5-dihydro-4H-pyrido[2,3-b][1,4]-
diazepin-4-ones 17–25 was achieved by elemental analysis and
multinuclear NMR spectroscopy. All classical 2D techniques,
including spin–spin coupling constants, were used to
assign the chemical shifts and these are consistent with the
results of GIAO calculations (vide infra).

The \( ^1H, ^13C, ^15N, \) and \( ^19F \) NMR spectroscopic data in DMSO-
\( d_6 \) or CDCl\(_3\) solution (Table S1) confirmed that even if five
tautomeric forms are possible (Scheme 4), they exist as the oxo-
imino form a with, in some cases, small amounts of form b, as
previously observed in compounds 1–16.6,7

The presence of the oxo-enamin form b was detected in
compounds 17 and 18 in proportions of 7 and 9%, respectively
(Figure 3). The most relevant NMR features allowing the
identification of both tautomeric forms are as follows: oxo-imino
form, \( \delta \) of 3-CH\(_3\) around 3.60 ppm, \( \delta \) of 3-CH\(_2\) at around 40
ppm; oxo-enamin form, \( \delta \) of 3-CH around 4.70 ppm, \( \delta \) of 3-
CH\(_3\) at around 96 ppm. Note that the atom numbering scheme
used in Figure 3 differs from the IUPAC system but allows
comparison between 3,5-dihydro-2H-benzo[b][1,4]diazepin-2-
one and 3,5-dihydro-4H-pyrido[2,3-b][1,4]diazepin-4-ones
since, in both cases, the NH and NR nitrogen atom is N1 and
the C=O group is on C2.
observed in the latter, where the dihedral angle between the benzo and phenyl rings lies in the range of 4.6(1)–25.8(1)° depending on the substituents, cf. a value of 49.8(2)° observed for 23 (Figure 5).

Comparison of Experimental and Calculated NMR Chemical Shifts. The experimental and calculated chemical shifts of compounds 1 to 25 (two calculated rotamers of the benzyl group of 25) are gathered in Table S1 of the Supporting Information. The chemical shifts and coupling constants of compounds 17–25 are provided in Experimental Section.

The data for all the nuclei (1H, 13C, 15N, and 19F) in all the reported solvents (CDCl3, DMSO-d6, acetone-d6, and THF-d8) were analyzed using simple and multiple regressions. The following multivariate equation was obtained

\[ \text{experimental(ppm)} = (0.9999 \pm 0.001)\text{calculated(ppm)}, n = 544, R^2 = 0.9993, \text{RMS residual} = 2.7 \text{ ppm} \]  

(1)

An examination of the residuals shows some systematic deviations. The compounds that present these deviations have NH protons and C−Br and C−Cl carbons. On introducing them as dummy variables (1, presence; 0, absence), the following multivariate equation was obtained

\[ \text{experimental(ppm)} = (0.9998 \pm 0.0009)\text{calculated} \]
\[ + (3.7 \pm 0.6)\text{NH} - (18.2 \pm 1.6)\text{C} - \text{Br} \]
\[ - (9.9 \pm 1.1)\text{C} - \text{Cl}, n = 544, R^2 = 1.000, \text{RMS residual} = 2.3 \text{ ppm} \]

(2)

The new coefficients show that the 1H NMR signal of the NH is shifted in different solvents by +3.7 ppm (on average for the four solvents) and that the C atoms bearing a Br or, to a lesser extent, a Cl atom, are not well calculated by GIAO because of relativistic effects, a well-known fact that we and others have already reported.22–25

Inversion Barriers of the Seven-Membered Rings. An interesting phenomenon was observed in compounds 23–25 and this concerns the appearance of the two enantiotopic protons, endo (H3A)/exo (H3B) (see Figure 4) or axial and equatorial, Hax and Heq, or of the methylene group at position 3 in tautomer a at room (300 K) and low temperatures. These signals were used to determine the inversion barrier of 5-benzyl-2-phenyl-3,5-dihydro-4H-pyrido[2,3-b][1,4]diazepin-4-one (25) by recording the 1H NMR spectra in THF-d8 at different temperatures (Figure 7). The difference in the chemical shifts of the methylene protons depends on the structure of the compound and on the temperature; for instance, this signal is not observed in compounds 17 and 18 at room temperature.

The inversion process of the seven-membered ring of [1,4]diazepinones is similar to that of cycloheptatriene (inversion barrier, 26 kJ·mol−1)26 and 7H-benzo[7]annulene. We determined the barrier for compound 25 (see Figure 7 and experimental part) and added other barriers from the literature and from our previous works (Table 1).

Table 1 is completed by calculating compounds 28 to 33 (Figure 8), for which experimental values are not available. Derivatives 28 to 32 were selected to cover complementary situations not found in the studied compounds, and quaternary salt 33 contributes to the discussion of the barriers.

Our goal is not to achieve precision but proportionality as the barriers often contain significant errors and various solvents have been used. An attempt to differentiate the solvents indicated that dimethyl sulfoxide and tetrahydrofuran increase the barrier by around 5 kJ·mol−1 with respect to chloroform, acetone, and toluene. In the discussion, solvent effects will not be considered. With the data of Table 1, different models were considered, giving rise to eqs 3–5 (units in kJ·mol−1, Se = standard error)

\[ \text{exp.} = (7.1 \pm 6.2) + (1.06 \pm 0.11)\text{calc.}, n = 13, R^2 = 0.900, \text{Se} = 2.3 \]

(3)

\[ \text{exp.} = (3.3 \pm 3.3) + (0.95 \pm 0.05)\text{calc.} \]
\[ +(8.8 \pm 1.9)\text{tetraF}, n = 13, R^2 = 0.970, \text{Se} = 2.8 \]

(4)

\[ \text{exp.} = (1.00 \pm 0.02)\text{calc.} + (9.8 \pm 1.6)\text{tetraF}, n = 13, R^2 = 0.998, \text{Se} = 2.8 \]

(5)

The most important conclusion is that a correction term was necessary for 6,7,8,9-tetrafluoro-substituted compounds, i.e., 9–16 and 32. Therefore, eq 4 was used to calculate the fitted and predicted values in Table 1. Since the intercept of eq 4 is not significant, it was imposed to be 0 to give eq 5.

In the case of compounds 23 and 24, the proton signals of the methylene group at position 3 in DMSO-d6 are lost in the baseline, meaning that the coalescence occurs at around 300 K; however, the signals can be observed in CDCl3 at 300 K (Figure 9). The fitted values reported in Table 1 (52.8 and 53.6 kJ·mol−1) are related to the experimental Δυ values (see Figure 9 and Table S1, 400.13 and 468.15 Hz, respectively) through the
Eyring equation; the corresponding coalescence temperatures should be 301 K for $23$ and 305 K for $24$, i.e., not far from 300 K (Figure 7) but indicating that the predicted values are underestimated by eq 4.

Figure 3. $^1$H NMR spectra of (a) 2-phenyl-3,5-dihydro-4$H$-pyrido[2,3-b][1,4]diazepin-4-one (17) and (b) 8-fluoro-2-phenyl-3,5-dihydro-4$H$-pyrido[2,3-b][1,4]diazepin-4-one (18). The atom numbering is shown in the structures.
The data in Table 1 (fitted and predicted) were used to calculate the differences related to the structures of compounds (see Figure S2 of the Supporting Information) and these are provided in Table 2. There are six main primary effects: replacing N1H by N1Me and then replacing N1Me by N1Bn, replacing C2=O by C2=S, replacing C4-Me by C4-Ph, replacing CH6,7,8,9 by CF6,7,8,9, and replacing C9H by N9. These primary effects are discussed assuming that they are independent, even if we are aware that, in empirical modeling, the action of secondary and even tertiary effects is apparent from the extreme values for some effects, e.g., −18.5/−43.7 for NH to NMe, +4.4/−11.6 for CO to CS, and +5.4/+13.9 for C9H to N9.

The calculations were performed on the CH2 tautomer and the calculated barriers to inversion quantitatively associate a barrier in kJ·mol⁻¹ to a single combination of R, X, Y, and R′ (Figure 10), covering a wide range of values. Qualitatively, the interconversion barrier arises from rotation around the C9a−N1 axis through a quasi-planar transition state (TS) in which R is facing Y, with the cyclic structure imposing some special features during the rotation. For instance, the C2=O bond is pointing outward throughout the whole rotation process and, thus, the well-documented large change in the steric requirement upon going from C2=O to C2=S is not operating.31 Replacing C2=O by C2=S increases the barrier by 5.5 kJ·mol⁻¹ and the origin of that weak change is due to the stiffening of the N1−C2 bond upon going from amide to thioamide. The stiffening of the N1−C2 bond peaks in salt 33 (Figure 8) yields a barrier of 84.3 kJ·mol⁻¹.

As one would expect, a large increase of the barrier (28.1 kJ·mol⁻¹) is observed upon going from R = H to R = Me. A further increase of the barrier (6.5 kJ·mol⁻¹) occurs upon going from R = Me to R = Bn. These changes result from the frontal interaction between Y = CH and R in the TS.

In the case of the 9-aza derivatives (Y = N), for R = H, the decrease of the barrier is 11.5 kJ·mol⁻¹ on average. For N1 = H (3/17 pair), the effect is +5.4 kJ·mol⁻¹; for N1 = Me (4/23 pair), the effect is +12.4 kJ·mol⁻¹; and for N1 = Bn (5/25 pair), the effect is +13.2 kJ·mol⁻¹. These results seem reasonable, bearing in mind the lower steric demand of the N atom and the possibility of forming HBs with the CH of Me and Bn groups. The lower steric demand and the H-bonding ability of Y = N is not the only contribution to the decrease of the barrier as the electron-attracting character of pyridine is prone to stabilizing of the almost planar transition state through cross-conjugation of the (thio)amide nitrogen atom.

A similar cross-conjugation is possibly at work when four desaturating F atoms were introduced on the aromatic part and this more than compensates for the small but significant steric effect of the fluorine atom in position 9.32,33 The introduction of

![Figure 4. ORTEP plot (20% probability) of compound 23 showing the labeling of the corresponding asymmetric unit. The N bearing the methyl group is numbered N1.](image)

![Figure 5. Comparative views of the molecular distortion in 23 and 13.](image)

![Figure 6. Plot of experimental versus calculated chemical shifts (ppm) for compounds 1 to 25.](image)
four F atoms increases the barrier by 18.3 kJ·mol⁻¹ (or by 7.9 kJ·mol⁻¹, excluding compounds 14 and 32) (Table 2). One must consider the electron-attracting effects of the pyridine nitrogen and the perfluoro substitution, which may stabilize the planar TS and thus contribute to the lowering of the barrier.34,35

A more complete approach that would include all interaction terms (primary, secondary, and tertiary) is possible and this involves the use of complete factorial designs. We will discuss only the case of compound 14 because 32 is a perturbation of 14 with increasing effects, which has a third-order interaction involving three terms NMe/tetraF/4Ph. The corresponding 2³ matrix is provided in Table 3.

The resulting equation is as follows

$$\Delta G = a_0 + a_1\text{NMe} + a_2\text{tetraF} + a_4\text{4Ph}$$

$$+ a_{12}\text{NMe/tetraF} + a_{13}\text{NMe/4Ph}$$

$$+ a_{23}\text{tetraF/4Ph} + a_{123}\text{NMe/tetraF/4Ph}$$

(6)

where the reference compound is 1.

Since the matrix has eight independent variables and eight dependent ones, the correlation coefficient is 1. The results of the multiregression are as follows: $a_0 = 43.7$ (compound 1); $a_1 = 20.4$; $a_2 = 0.0$; $a_3 = -4.0$; $a_{12} = 7.6$; $a_{13} = 5.1$; $a_{23} = 8.1$; $a_{123} = 10.6$.

The primary interactions are 20.4 (NMe), 0.0 (tetraF), and $-4.0$ kJ·mol⁻¹ (4Ph) in which, when compared with the results of Table 2, 25.9, 7.9, and 1.7 kJ·mol⁻¹, respectively (excluding 14 and 32), they are different, although the order is the same (shifted by 6–8 kJ·mol⁻¹). This finding stresses the danger of neglecting interaction terms.

Of the secondary interactions, it should be noted that NMe and tetraF on the one hand and 4Ph and tetraF on the other are in proximity, but NMe and 4Ph appear to be more remote. One possible explanation for this result is that the $a_{13}$ interaction is transmitted through the four F atoms (Figure 11). Finally, it is worth highlighting the high values of the tertiary effect, NMe/tetraF/4Ph, $a_{123} = 10.6$ kJ·mol⁻¹. The structures of the minimum and the TS of 14 are provided in Figure 12 to show the conformational changes that occur in the TS.

**Rotational Barriers of the N-Benzyl Group of Compound 25.** Note that the signals of the enantiotopic methylene protons of the N-benzyl group at 5.44 ppm (Figure 7) are only broadened at 220 K, but the coalescence should occur far below 200 K. On comparison of the appearance of the two methylene signals, it is reasonable to assume that the $T_c$ for the benzyl CH₂ protons is about 170 K. The different behavior of these two methylene groups is related to the difference in the chemical shifts. According to the calculated values (Table S2), the difference for C(3)H₂ is 1.60 ppm (experimental, 1.23 ppm), while for the benzyl group, it is only 0.34 ppm.
Table 1. Experimental (tw = This Work, nm = Not Measured) and Calculated Barriers of Benzo- and Pyrido[1,4]diazepinones in kJ·mol−1d

| comp. | ref. | Solvent        | T_C (K), CH_2 ring | exp.  | calc. | fitted & predicted |
|-------|------|----------------|--------------------|-------|-------|-------------------|
| 1     | 6, 27| "              | 203                | 39.8  | 42.4  | 43.7              |
| 2     | 6, 28| nm             | 203                | 39.8  | 42.4  | 43.7              |
| 3     | 6, 28| acetone        | 268.5              | 65.3  | 65.0  | 65.2              |
| 4     | 6, 28| acetone        | 267                | 67.0  | 71.7  | 71.6              |
| 5     | 28   | acetone        | 206                | 46.9  | 41.9  | 43.2              |
| 6     | 28   | acetone        | 306                | 79.5  | 77.1  | 76.8              |
| 7     | 28   | DMSO-^d_6      | 306                | 82.5  | 80.1  | 79.6              |
| 8     | 28   | DMSO-^d_6      | >373               | 83.3  | 81.5  |                   |
| 9     | 6    | toluene-^d_6   | 230                | 42.6  | 42.4  | 43.7              |
| 10    | 6    | toluene-^d_6   | 263                | 69.9  | 61.9  | 71.7              |
| 11    | 7    | THF-^d_6       | 263                | 48.9  | 37.5  | 47.8              |
| 12    | 7    | THF-^d_6       | 251                | 47.7  | 38.4  | 48.7              |
| 13    | 7    | THF-^d_6       | 245                | 47.3  | 35.8  | 46.2              |
| 14    | 7    | DMSO-^d_6      | >373               | 83.3  | 81.5  |                   |
| 15    | 7    | toluene-^d_6   | >373               | 79.7  | 88.0  |                   |
| 16    | 7    | DMSO-^d_6      | >373               | 81.1  | 89.4  |                   |
| 17    | tw   | DMSO-^d_6      | 300 K              | 32.5  | 34.3  |                   |
| 18    | tw   | DMSO-^d_6      | 300 K              | 33.6  | 35.3  |                   |
| 19    | tw   | DMSO-^d_6      | 300 K              | 37.0  | 38.6  |                   |
| 20    | tw   | DMSO-^d_6      | 300 K              | 36.2  | 37.8  |                   |
| 21    | tw   | DMSO-^d_6      | 300 K              | 37.7  | 39.2  |                   |
| 22    | tw   | DMSO-^d_6      | 300 K              | 39.0  | 40.5  |                   |
| 23    | tw   | CDCl_3         | 300 K (broad)      | 51.9  | 52.8  |                   |
| 24    | tw   | CDCl_3         | 300 K (broad)      | 52.8  | 53.6  |                   |
| 25    | tw   | THF-^d_6       | 303                | 56.6  | 57.8  | 58.4              |
| 26    | tw   |                   |                    |       | 28.9  | 30.9              |
| 27    | tw   |                   |                    |       | 49.2  | 50.2              |
| 28    | tw   |                   |                    |       | 37.8  | 38.3              |
| 29    | tw   |                   |                    |       | 75.6  | 75.3              |
| 30    | tw   |                   |                    |       | 95.0  | 102.6             |
| 31    | tw   |                   |                    |       | 85.0  | 84.3              |

# CONCLUSIONS

Taddei et al.28 discussed the possibility that the coalescence of the methylene ring signals was due to a N_1−R pyramidal inversion, but they rejected this proposal by analogy with results obtained with benzo[1,e][1,4]diazepin-2-ones. In fact, the N_1 atom is planar as in amides; for the three N-benzyl derivatives, the sum of the angles around N1 is 359.9^° for compounds 5, 8, and 25. Experimentally, the sum of these angles for the N-methyl compound 23 is 359.3^° (Figure 4).

We calculated the rotation profile of the N-benzyl substituent of compound 25. The dihedral is defined as C_{\alpha1}−C(H_2)−N1−C_{\alpha9} (Figure 13).

From 0^° to 360^°, there are two minima and two TSs: 1st TS, \( \phi = 26.8^\circ \), \( E_{rel} = 32.7 \text{ kJ\cdot mol}^{-1} \); 1st minimum, \( \phi = 105.9^\circ \), \( E_{rel} = 6.1 \text{ kJ\cdot mol}^{-1} \); 2nd TS, \( \phi = 175.4^\circ \), \( E_{rel} = 35.8 \text{ kJ\cdot mol}^{-1} \); 2nd minimum, \( \phi = 281.8^\circ \), \( E_{rel} = 0.0 \text{ kJ\cdot mol}^{-1} \). The TSs are much lower in energy than those of the ring inversion, which means that they do not contribute to the broadening of the signals. Furthermore, rotation cannot exchange the benzylic protons. As a consequence, the observed broadening of the benzyl methylene proton signals is due to the ring inversion (\( \Delta G = 51,700 \text{ J\cdot mol}^{-1} \)) and the much lower \( T_C (170 \text{ K vs 303 K}) \) to the marked decrease in \( \Delta G / H_8 / H_9 \) separation.

The differences in energy between the two rotamers is 6100 J·mol−1, which corresponds to 92% of the most stable one at 303 K and to 98% of the most stable one at 170 K. It was decided to ascertain whether the differences in calculated chemical shifts (Table S1, mainly affecting signals of the N-benzyl group) compared with the experimental ones could be sufficient to determine the structure of the most stable conformer, i.e., the principal minimum vs secondary minimum. To this end, we carried out a statistical analysis of the data using simple regressions. The results are reported in Table 4.

The differences are not dramatic, but all of them point in the same direction, namely, the largest square correlation coefficient, slope closer to 1, and intercept closer to 0, thus indicating that the rotamer present in solution is indeed that of lower energy (1st minimum).

The main conclusions of this work are as follows:

1. Nine new 3,5-dihydro-4H-pyrido[2,3-b][1,4]diazepin-4-ones, 17 to 25, have been prepared regiospecifically.
2. Two new examples of oxo-imino/oxo-enamino tautomerism have been reported in the family of pyrido[2,3-b][1,4]diazepin-4-ones.
3. A large series of experimental chemical shifts, 544 values, has been successfully correlated with those calculated at the GIAO/B3LYP/6-311++G(d,p) level and this allows the prediction of those values that were not determined.
4. The inversion barriers, measured or estimated, of the seven-membered ring have been compared with those calculated at the B3LYP/6-311+G(d,p) level. The total set has been successfully analyzed, taking into account several structure effects.
5. The effects on the inversion barriers have been discussed (a) considering the properties of atoms, bonds, and steric effects and (b) using a complete factorial design that includes primary, secondary, and tertiary effects. This
model shows the importance of secondary and tertiary interactions that were not previously taken into account.

6. In the case of the N-benzyl derivative 25, the rotation of the benzyl group has been calculated and discussed in relation to the experimental evidence.

**EXPERIMENTAL SECTION**

**General Information.** All chemicals used in the synthetic procedures were commercial compounds. Melting points were determined by DSC with a DSC 220 C instrument (SEIKO Instruments Inc., Torrance, CA, USA) connected to a model SSCS200H disk station. Thermograms (sample size, 0.003–0.005 g) were recorded at a scan rate of 5.0 °C/min. Column chromatography was performed on silica gel (Merck 60, 70–230 mesh) and elemental analyses were carried out on a LECO-CHNS-932 apparatus.

**NMR Parameters and DNMR.** Solution spectra were recorded on a 9.4 T spectrometer (400.13 MHz for 1H, 79.50 MHz for 19F, 100.62 MHz for 13C, and 40.56 MHz for 15N) at 300 K with a 5 mm inverse detection H-X probe equipped with a z-gradient coil or with a QNP 5 mm probe. Signals were characterized as s (singlet), d (doublet), t (triplet), and m (multiplet).

2D experiments (1H-1H) gs-NOESY, (1H-13C) gs-HMQC, (1H-15N) gs-HMQC, (1H-19F) gs-HMQC, and (1H-19F) gs-COSY were carried out with the standard pulse sequences to assign the 1H, 13C, 15N, and 19F signals. The numbering system used in the NMR assignments is provided in Figure 14.

Variable temperature spectroscopy was performed using a Bruker BVT3000 temperature unit to control the temperature of the cooling gas stream and an exchanger to achieve low temperatures. To avoid problems at low temperatures caused by air moisture, pure nitrogen was used as the bearing, driving, and cooling gas. The procedure for calculating the barrier of compound 25 is reported in Table S2 (Supporting Information).

**Synthetic Procedures.** Compounds 1–10 and 11–16 were prepared as previously described.

1-Phenyl-3,5-dihydro-4H-pyrido[2,3-b][1,4]diazepin-4-one (17). 2,3-Diaminopyridine (0.15 g, 1.39 mmol) and ethyl benzoxyacetate (0.25 mL, 1.45 mmol) in anhydrous xylene (8 mL) were heated at 120 °C for 24 h. The mixture was cooled down and a solid precipitated. This residue was washed with ethyl ether to give compound 17 (0.20 g, 61%) as a pale yellow solid; mp 267.2 °C (EtOH); lit. mp 264–266 °C.18 258 °C, 250–252 °C;11 1H NMR (400.13 MHz, DMSO-d6) δ 10.95 (s, 1H, H1), 8.34 (dd, 3JH1 = 6.6, 3JH1s = 1.7 Hz, 1H, H8), 8.08 (dd, 3JH1 = 7.3, 3JH8 = 1.8 Hz, 1H, H6), 7.55 (m, 3H, Hm, Hp, H7), 7.32 (dd, 3JH6 = 7.3, 3JH7 = 1.8 Hz, 1H, H7), 3.60 (s, 2H, H3); 13C NMR (100.62 MHz, DMSO-d6) δ 166.2 (C2), 159.4 (C4), 146.1 (C8), 141.5 (C9), 136.9 (C5), 136.5 (C6), 134.7 (C8a), 131.1 (Cp), 128.8 (Cm), 127.8 (Cg), 120.1 (C7), 40.3 (C3); 15N NMR (40.54 MHz, DMSO-d6) δ = –231.3 (N1), n.o. (N5), –84.8 (N9); anal. calcld for C14H11N3O: C, 70.87; H, 4.67; N, 17.71. Found: C, 70.44; H, 4.59; N, 17.69.

8-Fluoro-2-phenyl-3,5-dihydro-4H-pyrido[2,3-b][1,4]diazepin-4-one (18). 5-Fluoro-2,3-diamino-pyridine (0.50 g, 2.52 mmol) and ethyl benzoxyacetate (0.71 mL, 4.07 mmol) in anhydrous xylene (8 mL) were heated at 120 °C for 24 h. The mixture was cooled down and a solid precipitated. This residue was washed with ethyl ether to give compound 18 (0.54 g, 54%) as a pale yellow solid: mp 270.7 °C (EtOH);19 mp 262.7 °C (EtOH);19 1H NMR (400.13 MHz, DMSO-d6) δ 11.03 (s, 1H, H1), 8.39 (dd, 3JH1s = 2.8 Hz, 1H, H8), 8.08 (dd, 3JH1 = 6.9, 3JH1s = 1.7 Hz, 2H, Hs), 7.82 (dd, 3JH1 = 9.2, 3JH8 = 2.8 Hz, 1H, H6), 7.55 (m, 3H, Hm, Hp, H7), 3.64 (s, 2H, H3); 13C NMR (100.62 MHz, DMSO-d6) δ = 165.4 (C2), 160.6 (C4), 155.2 (C7, 3JF7 = 250.9), 133.9 (C9a), 136.4 (C6), 134.9 (C5a, 3JF7 = 7.3), 133.4 (C8, 3JF7 = 25.2), 131.1 (Cp), 128.3 (Cm), 127.4 (C6, 3JF7 = 20.0), 140.1 (C3), 15N NMR (40.54 MHz, DMSO-d6) δ = –232.6 (N1), n.o. (N5), –80.4 (N9); 19F NMR (376.50 MHz, DMSO-d6) δ = –133.2 (d, 3JF8 = 9.3 Hz, 1F, F7); anal. calcld for C14H10FN3O: C, 70.44; H, 3.95; N, 17.69. Found: C, 70.5; H, 3.95; N, 17.69.

2-Phenyl-3,5-dihydro-4H-pyrido[2,3-b][1,4]diazepin-4-one (21). 2,3-Diaminopyridine (0.15 g, 1.39 mmol) and ethyl benzoxyacetate (0.71 mL, 4.07 mmol) in anhydrous xylene (8 mL) were heated at 120 °C for 24 h. The mixture was cooled down and a solid precipitated. This residue was washed with ethyl ether to give compound 21 (0.20 g, 61%) as a pale yellow solid; mp 270.7 °C (EtOH); lit. mp 264–266 °C.18 258 °C, 250–252 °C;11 1H NMR (400.13 MHz, DMSO-d6) δ 10.95 (s, 1H, H1), 8.34 (dd, 3JH1 = 6.6, 3JH1s = 1.7 Hz, 1H, H8), 8.08 (dd, 3JH1 = 7.3, 3JH8 = 1.8 Hz, 1H, H6), 7.55 (m, 3H, Hm, Hp, H7), 7.32 (dd, 3JH6 = 7.3, 3JH7 = 1.8 Hz, 1H, H7), 3.60 (s, 2H, H3); 13C NMR (100.62 MHz, DMSO-d6) δ = 166.2 (C2), 159.4 (C4), 146.1 (C8), 141.5 (C9), 136.9 (C5), 136.5 (C6), 134.6 (C8a), 131.1 (Cp), 128.8 (Cm), 127.8 (Cg), 120.1 (C7), 40.3 (C3); 15N NMR (40.54 MHz, DMSO-d6) δ = –231.3 (N1), n.o. (N5), –84.8 (N9); anal. calcld for C14H11N3O: C, 70.87; H, 4.67; N, 17.71. Found: C, 70.44; H, 4.59; N, 17.69.
Table 2. Differences Corresponding to Six Effects (in kJ·mol⁻¹)¹

| number of effects | effect        | pair of compounds | ∆ΔG (kJ·mol⁻¹)  | mean value | difference | mean value excluding 14 and 32 (in italics) |
|-------------------|---------------|-------------------|------------------|------------|------------|--------------------------------------------|
| 8                 | N₁H to N₁Me  | 1 → 2             | −20.4            | −28.1      | +7.7       | −25.9                                      |
|                   |               | 3 → 4             | −25.5            | +2.6       |            |                                            |
|                   |               | 6 → 7             | −33.6            | −5.5       |            |                                            |
|                   |               | 9 → 10            | −28.0            | +0.1       |            |                                            |
|                   |               | 17 → 23           | −18.5            | +9.6       |            |                                            |
|                   |               | 28 → 29           | −19.3            | +8.8       |            |                                            |
|                   |               | 30 → 31           | −36.0            | −7.9       |            |                                            |
|                   |               | 11 → 14           | −43.7            | −15.6      |            |                                            |
| 4                 | N₁Me to N₁Bn | 4 → 5             | −6.4             | −6.5       | +0.1       | −4.9                                       |
|                   |               | 7 → 8             | −2.8             | +3.7       |            |                                            |
|                   |               | 23 → 25           | −5.6             | +9.0       |            |                                            |
|                   |               | 14 → 32           | −11.1            | −4.6       |            |                                            |
| 4                 | C₆O to C₆S   | 1 → 30            | +4.4             | −5.5       | −9.9       | −5.5                                       |
|                   |               | 2 → 31            | −11.2            | −5.7       |            |                                            |
|                   |               | 3 → 6             | −3.5             | +2.0       |            |                                            |
|                   |               | 4 → 7             | −11.6            | −6.1       |            |                                            |
|                   |               | 4 → 7             | −11.6            | −6.1       |            |                                            |
| 7                 | 4Me to 4Ph    | 1 → 3             | +4.0             | −4.3       | +8.3       | −1.7                                       |
|                   |               | 2 → 4             | −1.1             | +3.2       |            |                                            |
|                   |               | 9 → 11            | −4.1             | +0.2       |            |                                            |
|                   |               | 28 → 17           | −3.4             | +0.9       |            |                                            |
|                   |               | 30 → 6            | −4.0             | +0.3       |            |                                            |
|                   |               | 31 → 7            | −1.5             | +2.8       |            |                                            |
|                   |               | 10 → 14           | −19.8            | −15.5      |            |                                            |
| 4                 | tetrafluoro   | 2 → 10            | −7.6             | −18.3      | +10.7      | −7.9                                       |
|                   |               | 3 → 11            | −8.1             | +10.2      |            |                                            |
|                   |               | 4 → 14            | −26.3            | −8.0       |            |                                            |
|                   |               | 5 → 32            | −31.0            | −12.7      |            |                                            |
| 5                 | C₆H to N₆     | 1 → 28            | +12.8            | +11.5      | +1.3       | +11.5                                      |
|                   |               | 2 → 29            | +13.9            | +2.4       |            |                                            |
|                   |               | 3 → 17            | +5.4             | −6.1       |            |                                            |
|                   |               | 4 → 23            | +12.4            | +0.9       |            |                                            |
|                   |               | 5 → 25            | +13.2            | +1.7       |            |                                            |

¹∆ΔG values were calculated from the fitted and predicted ∆G values of Table 1.

4.06 mmol) and ethyl benzoyleacetate (0.72 mL, 4.16 mmol) in anhydrous xylene (8 mL) were heated at 120 °C for 24 h. The mixture was cooled down and a solid precipitated. This residue was washed with ethyl ether to give compound 19 (0.29 g, 28%) as a pale yellow solid: mp 280.3 °C (EtOH); ¹H NMR (400.13 MHz, DMSO-d₆) δ 10.80 (s, 1H, H₁), 8.20 (d, 3JH₂ = 4.7 Hz, 1H, H₈), 8.11 (dd, 3JHH = 7.6, 3JHH = 2.0 Hz, 2H, H₀), 7.56 (m, 3H, H₃M, H₃P), 7.20 (d, 3JHH = 4.7 Hz, 1H, H₇), 3.57 (s, 2H, H₃), 2.44 (s, 3H, Me); ¹³C NMR (100.62 MHz, DMSO-d₆) δ 166.3 (C₂), 157.9 (C₄), 145.6 (C₆), 145.4 (C₈), 142.0 (C₉a), 137.0 (Cᵢ), 133.4 (C₅a), 131.2 (C₆), 128.8 (C₇m), 127.6 (C₇o), 121.5 (C₇), 40.4 (C₃), 17.8 (Me), ¹⁵N NMR (40.54 MHz, DMSO-d₆) δ −230.4 (N₁), n.o. (N₅), −81.0 (N₉); anal. calcd for C₁₄H₁₁N₃O (251.29): C, 71.70; H, 5.21; N, 16.72. Found: C, 71.16; H, 5.15; N, 16.60. 9-Chloro-2-phenyl-3,5-dihydro-4H-pyrido[2,3-b][1,4]-diazepin-4-one (20). 4-Chloro-2,3-diamino-pyridine (0.50 g, 3.48 mmol) and ethyl benzoyleacetate (0.62 mL, 3.59 mmol) in anhydrous xylene (8 mL) were heated at 120 °C for 24 h. The mixture was cooled down and a solid precipitated. This residue was washed with ethyl ether to give compound 20 (0.24 g, 25%) as a pale yellow solid: mp 261.6 °C (EtOH); ¹H NMR (400.13 MHz, DMSO-d₆) δ 11.16 (s, 1H, H₁), 8.29 (d, 3JH₂ = 5.1 Hz, 1H, H₈), 8.12 (d, 3JHₘ₁ = 7.4 Hz, 2H, H₀), 7.57 (m, 3H, H₃M, H₃P), 7.51 (d, 3JH₁ = 5.1 Hz, 1H, H₇), 3.69 (s, 2H, H₃); ¹³C NMR (100.62 MHz, DMSO-d₆) δ 166.2 (C₂), 160.3 (C₄), 146.3 (C₆), 143.7 (C₉a), 141.1 (C₆), 136.5 (Cᵢ), 131.7 (C₅a), 128.9 (C₇m), 128.0 (C₇o), 120.9 (C₇), 40.8 (C₃); ¹⁵N NMR (40.54 MHz, DMSO-d₆) δ −230.4 (N₁), n.o. (N₅), −89.1 (N₉); anal. calcd for C₁₄H₁₀ClN₃O (271.70): C, 61.89; H, 3.71; N, 15.47. Found: C, 61.45; H, 3.72; N, 15.47.
Table 3. Matrix Corresponding to eq 6

| comp. | NMe, a₁ | tetraF, a₂ | 4Ph, a₃ | NMe/tetraF, a₁₂ | NMe/4Ph, a₁₅ | tetraF/4Ph, a₂₃ | NMe/tetraF/4Ph, a₁₂₅ | ΔG |
|-------|---------|-----------|---------|----------------|---------------|----------------|---------------------|-----|
| 1     | 0       | 0         | 0       | 0              | 0             | 0              | 0                   | 43.7|
| 2     | 1       | 0         | 0       | 0              | 0             | 0              | 0                   | 64.1|
| 3     | 0       | 1         | 0       | 0              | 0             | 0              | 0                   | 39.7|
| 4     | 1       | 0         | 1       | 1              | 1             | 1              | 1                   | 65.2|
| 9     | 0       | 1         | 0       | 0              | 0             | 0              | 0                   | 43.7|
| 10    | 1       | 1         | 0       | 1              | 0             | 0              | 0                   | 71.7|
| 11    | 0       | 1         | 1       | 1              | 1             | 1              | 1                   | 47.8|
| 14    | 1       | 1         | 1       | 1              | 1             | 1              | 1                   | 91.5|

*ΔG values are the fitted and predicted values from Table 1.

**Figure 11.** Primary and secondary interactions in compound 14.

**Figure 12.** Two views of the minimum and TS of the inversion of the seven-membered ring of 14.

8-Bromo-9-chloro-2-phenyl-3,5-dihydro-4H-pyrido[2,3-b][1,4]diazepin-4-one (21). S-Bromo-4-chloro-2,3-diaminopyridine (0.5 g, 2.25 mmol) and ethyl benzoylecetate (0.44 mL, 2.55 mmol) in anhydrous xylene (8 mL) were heated at 150 °C for 48 h. Purified by column chromatography using hexanes and ethyl acetate in a 15:1 ratio as eluent to give compound 22 (0.29 g, 35%) as a pale yellow solid: mp 290.4 °C (EtOH); 1H NMR (400.13 MHz, DMSO-d₆) δ 10.98 (s, 1H, H1), 8.44 (s, 1H, H8), 8.11 (dd, J_H6 = 4.6, J_H6 = 1.8 Hz, 1H, H6), 7.57 (m, 3H, Hm, Hp), 3.62 (s, 2H, H3), 2.53 (s, 3H, Me); 13C NMR (100.62 MHz, DMSO-d₆) δ 166.3 (C2), 159.3 (C4), 146.4 (C8), 144.4 (C6), 141.4 (C9a), 136.6 (C5a), 131.6 (Cp), 128.9 (Cm), 127.8 (Ca), 117.5 (C7), 40.5 (C3), 16.1 (Me); 19F NMR (40.54 MHz, DMSO-d₆) δ −232.0 (N1), n.o. (NS), −87.6 (N9); anal. calc'd for C₁₅H₁₂BrN₃O (330.19): C, 54.56; H, 3.66; N, 12.73. Found: C, 54.50; H, 3.71; N, 12.77.

5-Methyl-2-phenyl-3,5-dihydro-4H-pyrido[2,3-b][1,4]diazepin-4-one (23). Iodomethane (0.062 mL, 1.00 mmol), K₂CO₃ (0.13 g, 0.94 mmol), and a catalytic amount of KI were added to a solution of 17 (0.21 g, 0.89 mmol) in DMF (1.2 mL), and the mixture was heated at 110 °C for 4 h. After cooling, the mixture was treated with cold water and extracted with ethyl acetate (3 × 3 mL). The organic solvent was evaporated to afford compound 23 (0.19 g, 85%) as a pale yellow solid: mp 142.7 °C (EtOH); 1H NMR (400.13 MHz, CDCl₃) δ 8.42 (dd, J_H7 = 4.6, J_H6 = 1.8 Hz, 1H, H8), 8.14 (m, 2H, H2, H3), 7.82 (dd, J_H6 = 7.9, J_H6 = 1.8 Hz, 1H, H6), 7.51 (m, 3H, Hm, Hp), 7.26 (dd, J_H6 = 7.9, J_H6 = 4.6 Hz, 1H, H7), 4.12 (vb, 1H, H3), 3.52 (s, 3H, Me), 3.12 (vb, 1H, H3); 13C NMR (100.62 MHz, CDCl₃) δ 166.0 (C2), 161.2 (C4), 145.8 (C8), 146.1 (C9a), 136.9 (C1), 136.6 (C5a), 136.2 (C6), 131.5 (Cp), 128.8 (Cm), 127.9 (Co), 120.5 (C7), 40.1 (C3), 33.0 (Me); 19F NMR (40.54 MHz, CDCl₃) δ −239.1 (N1), n.o. (NS), −85.8 (N9); anal. calc'd for C₁₅H₁₁BrN₃O (251.29): C, 71.70; H, 5.21; N, 16.72. Found: C, 71.58; H, 5.57; N, 15.75.

8-Fluoro-1-methyl-2-phenyl-3,5-dihydro-4H-pyrido[2,3-b][1,4]diazepin-4-one (24). Iodomethane (0.054 mL, 0.86 mmol), K₂CO₃ (0.13 g, 0.94 mmol), and a catalytic amount of KI were added to a solution of 18 (0.20 g, 0.78 mmol) in DMF (1.2 mL) and the mixture was heated at 110 °C for 3 h. After cooling, the mixture was treated with cold water and extracted with ethyl acetate (3 × 3 mL). The organic solvent was evaporated to afford compound 24 (0.17 g, 82%) as a pale yellow solid: mp 144.7 °C (EtOH); 1H NMR (400.13 MHz, CDCl₃) δ 8.28 (d, J_H6 = 2.8 Hz, 1H, H8), 8.14 (m, 2H, H2, H3), 7.52 (m, 4H, H6, Hm, Hp), 4.21 (vb, 1H, H3), 3.34 (s, 3H, Me), 3.04 (vb, 1H, H3); 13C NMR (100.62 MHz, CDCl₃) δ 165.6 (C2), 156.2 (C7), 152.2 (C4), 142.5 (C9a), 137.3 (C5a), 136.6 (C1), 133.9 (C8), 131.9 (Cp), 128.9 (Cm), 128.8 (Co), 121.9 (C6), 40.2 (C3), 33.2 (Me); 19F NMR (40.54 MHz, CDCl₃) δ n.o. (N1), n.o. (NS), −79.2 (N9); 17F NMR (376.50 MHz, CDCl₃) δ −239.1 (F7); anal. calc'd for C₁₅H₁₁BrF₁₁N₃O (461.04): C, 57.87; H, 3.80; N, 14.33. Found: C, 57.78; H, 3.77; N, 14.26.
Table 4. Comparison of Experimental and Calculated Chemical Shifts for the Two Rotomers of Compound 25

| minimum     | nuclei | no. of points | intercept | slope       | R²   |
|-------------|--------|---------------|-----------|-------------|------|
| first minimum | all    | 30            | +0.0690   | 0.9997      | 0.99973 |
| second minimum | all    | 30            | −0.1048   | 1.0030      | 0.99956 |
| first minimum | only 13C | 17            | +0.1954   | 0.9986      | 0.99782 |
| second minimum | only 13C | 17            | −4.2266   | 1.0343      | 0.99771 |

\[ \text{C}_{19}\text{H}_{19}\text{FN}_{2}\text{O} (293.28): \text{C}, 66.91; \text{H}, 4.49; \text{N}, 15.60. \text{Found: C, 65.60; H, 4.49; N, 15.36.} \]

5-Benzyl-2-phenyl-3,5-dihydro-4H-pyrido[2,3-b][1,4]-diazepin-4-one (25). Benzyl chloride (0.13 mL, 1.16 mmol), K₂CO₃ (0.175 g, 1.26 mmol), and a catalytic amount of KI were added to a solution of 17 (0.25 g, 1.05 mmol) in DMF (2.5 mL) and the mixture was heated at 110 °C for 5 h. After cooling, the mixture was treated with cold water and extracted with ethyl acetate (3 × 3 mL). The organic solvent was evaporated to afford compound 25 (0.28 g, 80%) as a pale yellow solid: mp 140–142 °C (EtOH); ¹H NMR (400.13 MHz, CDCl₃) δ 8.39 (dd, ¹JH₇ = 4.6, ¹JH₈ = 1.8 Hz, 1H, H₇), 7.79 (dd, ¹JH₈ = 7.9, ¹JH₆ = 1.8 Hz, 1H, H₆), 7.52 (m, 3H, H₅, H₆), 7.13 (m, 5H, H₀-Bn, H₅-Bn, H₆-Bn, H₇-Bn), 4.30 (s, 2H, CH₂-Bn), 3.07 (s, 2H, H₇, H₈; ¹C NMR (100.62 MHz, CDCl₃) δ 165.1 (C₂), 161.4 (C₄), 145.8 (C₉), 144.9 (C₉a), 137.7 (C₁-Bn), 137.2 (C₁), 137.0 (C₅a), 136.3 (C₆), 126.9 (C₉, C₁-Bn), 128.8 (C₇), 127.9 (C₉a), 127.4 (C₇-Bn), 120.7 (C₁-Bn), 40.3 (C₁-Bn), 48.0 (CH₂); ¹⁵N NMR (40.54 MHz, CDCl₃) δ n.o. (N₁), n.o. (N₅), −83.6 (N₉); anal. calcd for C₁₉H₁₇N₃O (327.39): C, 77.04; H, 5.23; N, 12.84. Found: C, 76.99; H, 5.31; N, 13.00.

N-(3-Aminopyridin-2-yl)-3-phenyl-3-oxopropanamide (26, Enol Form). 2,3-Diaminopyridine (0.15 g, 1.39 mmol) and ethyl benzoyleacetate (0.25 mL, 1.45 mmol) in anhydrous xylene (8 mL) were heated at 120 °C for 6 h. The mixture was cooled down and a solid precipitated. This residue was washed with ethyl ether to give compound 26 (0.07 g, 19%) as a brown solid: mp 159.4 °C (EtOH); ¹H NMR (400.13 MHz, DMSO-d₆) δ 9.39 (s, 1H, NH), 8.01 (d, ¹JH₆ = 7.7, 2H, H₆), 7.80 (dd, ¹JH₇ = 4.7, ¹JH₈ = 1.7, 1H, H₇), 7.67 (t, ¹JH₆ = 7.4, 1H, H₆), 7.57 (m, 2H, H₅), 7.48 (m, 1H, H₄), 6.55 (m, 1H, H₃), 5.81 (s, 2H, NH₂), 4.16 (s, 2H, H₈); ¹³C NMR (100.62 MHz, DMSO-d₆) δ 195.1 (C⁹), 166.0 (C₇), 153.7 (C₂), 144.6 (C₆), 136.2 (C₈), 133.7 (C₉), 132.0 (C₄), 128.8 (C₈m), 128.3 (C₈o), 118.0 (C₃), 112.1 (C₅), 47.4 (C₈); ¹⁵N NMR (40.54 MHz, DMSO-d₆) δ −310.7 (NH₃), −256.21 (NH, n.o. (N₁)); anal. calcd for C₁₉H₁₇N₃O (255.28): C, 65.87; H, 5.13; N, 16.46. Found: C, 65.28; H, 5.09; N, 16.50.

N-(3-Amino-5-bromo-4-methylpyridin-2-yl)-3-phenyl-3-oxopropanamide (27, Enol Form). 5-Bromo-4-methyl-2,3-diaminopyridine (0.50 g, 2.48 mmol) and ethyl benzoyleacetate (0.44 mL, 2.55 mmol) in anhydrous xylene (8 mL) were heated at 120 °C for 24 h. The mixture was cooled down and a solid precipitated. This residue was washed with ethyl ether to give compound 27 (0.73 g, 85%) as a pale yellow solid: ¹H NMR (400.13 MHz, DMSO-d₆) δ 9.48 (s, 1H, NH), 8.02 (d, ¹JH₆ = 7.6, 2H, H₆), 7.95 (s, 1H, H₇), 7.69 (t, ¹JH₆ = 7.1, 1H, H₆), 7.57 (m, 2H, H₅), 6.05 (s, 2H, NH₂), 4.20 (s, 1H, H₈); ¹³C NMR (100.62 MHz, DMSO-d₆) δ 195.7 (C⁹), 166.1 (C₇), 156.0

Figure 13. Rotation profile of compound 25 together with Newman projections.

Figure 14. Atom numbering used in the NMR assignments of compounds 1–27.
Calculations were carried out with the Gaussian-16 package.41 Frequency calculations were carried out at the same computational level to verify that the structures obtained correspond to energetic minima (0) or to transition states (TS) (1). These geometries were used for the calculations of the absolute chemical shielldings with the GIAO method.39,40 All calculations were carried out with the Gaussian-16 package.41 The following equations were used to transform absolute shielldings into chemical shifts:

\[ \delta^1H = 31.0 - 0.97*\delta^1H \text{ (reference TMS, 0.00 ppm)} \]

\[ \delta^{13}C = 175.7 - 0.963*\delta^{13}C \text{ (reference TMS, 0.00 ppm)} \]

\[ \delta^{15}N = -152.0 - 0.946*\delta^{15}N \text{ (reference MeNO}_2, 0.00 \text{ ppm)} \]

\[ \delta^{19}F = 162.1 - 0.959*\delta^{19}F \text{ (reference CFCl}_3, 0.00 \text{ ppm)} \]

X-ray Crystallography. Data collection for 23 was carried out at 298 K on a Bruker Smart CCD diffractometer using graphite-monochromated Mo-Kα radiation (\( \lambda = 0.71073 \) Å). The system was operated at 50 kV and 35 mA with an exposure time of 20 s in omega. A summary of the fundamental crystal and refinement data is given in Table 5. The structures were solved by direct methods and refined by full-matrix least-squares procedures on \( F^2 \) using SHELXS and SHELXL programs, respectively,48 with the aid of the program Olex2.56 All nonhydrogen atoms were refined anisotropically. The hydrogen atoms were included in their calculated positions and refined as riding on the respective atoms. CCDC 2003929 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via https://www.ccdc.cam.ac.uk/structures/.

### Table 5. Crystal Data and Structure Refinement for 23

| Crystal Data | Value |
|--------------|-------|
| Crystal Data | 23    |
| CCDC code   | 2003929 |
| Empirical formula | C15H13N3O |
| Formula weight | 251.28 |
| Temperature (K) | 296.15 |
| Crystal system | monoclinic |
| Space group | C2/c |
| \( a \) (\( Å \)) | 21.088(3) |
| \( b \) (\( Å \)) | 8.6190(13) |
| \( c \) (\( Å \)) | 17.432(3) |
| \( \alpha \) (\( ° \)) | 90 |
| \( \beta \) (\( ° \)) | 126.527(2) |
| \( \gamma \) (\( ° \)) | 90 |
| Volume (\( Å^3 \)) | 2546.0(7) |
| Z | 8 |
| \( \rho_{calc} \) (g/cm\(^3\)) | 1.311 |
| \( \mu \) (mm\(^{-1}\)) | 0.085 |
| \( F(000) \) | 1056.0 |
| 2\( \theta \) range for data collection (\( ° \)) | 4.800 to 57.61 |
| Index ranges | \(-28 \leq h \leq 28, -11 \leq k \leq 11, -22 \leq l \leq 22\) |
| Reflections collected | 12,819 |
| Independent reflections | 3127 [0.0390] |
| Data/restraints/parameters | 3127/0/173 |
| Goodness-of-fit on \( F^2 \) | 1.072 |
| \( R \) (reflns obsd) \[ I \geq 2\sigma(I) \] | 0.0526 (1858) |
| \( wR \) [all data] | 0.1559 |
| Largest diff. peak/hole (e \( Å^{-3} \)) | 0.17/−0.20 |

**Notes**

The authors declare no competing financial interest.

**ACKNOWLEDGMENTS**

This work was carried out with financial support from the Spanish Ministerio de Ciencia, Innovacion y Universidades (project PGC2018-094644-B-C2). We thank Prof. Pedro Cintas, Universidad de Extremadura, for his useful comments.
REFERENCES

(1) Sankar, R. GABA(A) receptor physiology and its relationship to the mechanism of action of the 1,5-benzodiazepine clozapam. CNS Drugs 2012, 26, 229–244.

(2) Mendoça Júnior, F. J. B.; Scotti, L.; Ishiki, H.; Botelho, S. P. S.; Da Silva, M. S.; Scotti, M. T. Benzo- and thienobenzodiazepines: Multitarget drugs for CNS disorders. Mini-Rev. Med. Chem. 2015, 15, 630–647.

(3) Heinisch, G.; Huber, E.; Leitner, C.; Matusczasz, B.; Maurer, A.; Pachler, S.; Prillinger, U. Pyridazino[3,4-b]1,5-benzodiazepin-5-ones: Synthesis and biological evaluation. Antiviral Chem. Chemother. 1997, 8, 371–379.

(4) Burke, E. W. D.; Morris, G. A.; Vincent, M. A.; Hillier, I. H.; Clayden, J. Is nevirapine atropisomeric? Experimental and computational evidence for rapid conformational inversion. Org. Biomol. Chem. 2012, 10, 716–719.

(5) Clarumunt, R. M.; Alkorta, I.; Elguero, J. A theoretical study of the conformation and dynamic properties of 1,5-benzodiazepines and their derivatives. Comput. Theor. Chem. 2013, 1019, 108–115.

(6) Pérez-Torralla, M.; Clarumunt, R. M.; García, M. A.; López, C.; Torralba, M. C.; Torres, M. R.; Alkorta, I.; Elguero, J. Structure of 1,5-benzodiazepinones in the solid state and in solution: Effect of the fluorination in the six-membered ring. Beilstein J. Org. Chem. 2013, 9, 2156–2167.

(7) Martín, O.; Pérez-Torralla, M.; García, M. Á.; Clarumunt, R. M.; Torralba, M. C.; Torres, M. R.; Alkorta, I.; Elguero, J. Static and dynamic properties of fluorinated 4-aryl-1,5-benzodiazepinones. ChemistrySelect 2016, 1, 861–870.

(8) Abdel-Ghany, H.; El-Sayed, A. M.; Sultan, A. A.; El-Shafei, A. A. A novel synthesis of pyrano[2,3-c][1,5]benzodiazepines. Synth. Commun. 1990, 20, 893–900.

(9) Chintit, S.; Nisra, A.; Khouaja, S.; Mechria, A.; Gharbi, R.; Al-Mureekh, M.; Leouve, M. Highly diastereoselective synthesis of rigid 3-enamin-1,5-benzodiazepines. ARKIVOC 2018, 2018, 283–295.

(10) Mansour, H.; El-Hendawy, M. M. Mechanistic perspectives on piperidine-catalyzed synthesis of 1,5-benzodiazepin-2-ones. Mol. Catal. 2010, 484, 110774.

(11) Gaponov, A. A.; Anishchenko, A. A. Chemical properties of 2,3-dihydro-1H-1,5-benzodiazepin-2-ones: A review. J. Chem. Technol. 2013, 21, 59–78.

(12) Mitraoui, H.; Renault, K.; Sanselme, M.; Msaddek, M.; Renard, P. Y.; Sabot, C. Metal-free oxidative ring contraction of benzodiazepinones: An entry to quinoxalinoines. Org. Biomol. Chem. 2017, 15, 3060–3068.

(13) Woltering, T. J.; Wichmann, J.; Goetschi, E.; Knoedlach, F.; Ballard, T. M.; Huwyler, J.; Gatti, S. Synthesis and characterization of 1,3-dihydro-benzo[b][1,4]diazepin-2-one derivatives: Part 4. In vivo active potent and selective non-competitive metabotropic glutamate receptor 2/3 antagonists. Bioorg. Med. Chem. Lett. 2010, 20, 6969–6974.

(14) Mitraoui, H.; Gharbi, R.; Msaddek, M.; Bretonnie, Y.; Andraud, C.; Sabot, C.; Renard, P. Y. 1,5-Benzodiazepin-2-ones: Investigation of a family of photoluminescent materials. J. Org. Chem. 2016, 81, 4720–4727.

(15) Meanwell, N. A.; Sit, S. Y.; Gao, J.; Wong, H. S.; Gao, Q.; Laurent, D. R. S.; Balasubramanian, N. Regioselective functionalization of 1,3-dihydro-2H-benzimidazo-2-one and structurally related cyclic urea derivatives. J. Org. Chem. 1995, 60, 1565–1582.

(16) Israel, M.; Jones, L. C.; Modest, E. J. Synthesis and tautomeric behavior of dihydropyrido[2,3-b][1,4]diazepinones. J. Heterocycl. Chem. 1967, 4, 659–661.

(17) Israel, M.; Jones, L. C. On the reactions of β-ketoesters with 2,3-diaminopyridine and its derivatives. J. Heterocycl. Chem. 1973, 10, 201–207.

(18) Barchet, V. R.; Merz, K. W. Uber kondensation von nicotinoylessigester mit aminativen diaminen. Tetrahedron Lett. 1964, 5, 2239–2244.

(19) Israel, M.; Jones, L. C. Application of a thermal rearrangement Reaction to questions of structure of condensed dihydrazepinones.
(39) London, F. Quantum Theory of Interatomic Currents in Aromatic Compounds. *J. Phys. Radium* 1937, *8*, 397–409.

(40) Ditchfield, R. Self-consistent Perturbation Theory of Diamagnetism. I. A Gauge-Invariant LCAO (Linear Combination of Atomic Orbitals) Method for NMR Chemical Shifts. *Mol. Phys.* 1974, *27*, 789–807.

(41) Frisch, M. J., Trucks, G. W., Schlegel, H. B., Scuseria, G. E., Robb, M. A., Cheeseman, J. R., Scalmani, G., Barone, V., Petersson, G. A., Nakatsuji, H., Li, X., Caricato, M., Marenich, A. V., Bloino, J., Janesko, B. G., Gomperts, R., Mennucci, B., Hratchian, H. P., Ortiz, J. V., Izmaylov, A. F., Sonnenberg, J. L., Williams-Young, D., Ding, F., Lipparini, F., Egidi, F., Goings, J., Peng, B., Petrone, A., Henderson, T., Ranasinghe, D., Zakrzewski, V. G., Gao, J., Rega, N., Zheng, G., Liang, W., Hada, M., Ehara, M., Toyota, K., Fukuda, R., Hasegawa, J., Ishida, M., Nakajima, T., Honda, Y., Kitao, O., Nakai, H., Vreven, T., Throssell, K., Montgomery, Jr., J. A., Peralta, J. E., Ogliaro, F., Bearpark, M. J., Heyd, J. J., Brothers, E. N., Kudin, K. N., Staroverov, V. N., Keith, T. A., Kobayashi, R., Normand, J., Raghavachari, K., Rendell, A. P., Burant, J. C., Iyengar, S. S., Tomasi, J., Cossi, M., Millam, J. M., Klene, M., Adamo, C., Cammi, R., Ochterski, J. W., Martin, R. L., Morokuma, K., Farkas, O., Foreman, J. B., Fox, D. J. Gaussian 16, Revision A.03, Gaussian, Inc., Wallingford CT 2016.

(42) Silva, A. M. S.; Sousa, R. M. S.; Jimeno, M. L.; Blanco, F.; Alkorta, I.; Elguero, J. Experimental measurements and theoretical calculations of the chemical shifts and coupling constants of three azines (benzalazine, acetophenoneazine and cinnamaldehyde). *Magn. Reson. Chem.* 2008, *46*, 859–864.

(43) Blanco, F.; Alkorta, I.; Elguero, J. Statistical analysis of $^{13}$C and $^{15}$N NMR chemical shifts from GIAO/B3LYP/6-311++G** calculated absolute shieldings. *Magn. Reson. Chem.* 2007, *45*, 797–800.

(44) Fresno, N.; Pérez-Fernández, R.; Jimeno, M. L.; Alkorta, I.; Sánchez-Sanz, G.; Elguero, J.; Del Bene, J. E. Multinuclear NMR characterization of cyanuric fluoride (2,4,6-trifluoro-1,3,5-triazine). *J. Heterocycl. Chem.* 2012, *49*, 1257–1259.

(45) (a) Sheldrick, G. M. Crystal structure refinement with SHELXL. *Acta Crystallogr.*, Sect. C: Struct. Chem. 2015, *71*, 112–118. (b) Sheldrick, G. M. SHELXT - Integrated space-group and crystal-structure determination. *Acta Crystallogr.*, Sect. A: Found. Adv. 2015, *71*, 3–8.

(46) Dolomanov, O. V.; Bourhis, L. J.; Gildea, R. J.; Howard, J. A. K.; Puschmann, H. OLEX2: a complete structure solution, refinement and analysis program. *J. Appl. Crystallogr.* 2009, *42*, 339–341.