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The stereochemistry of isoquinoline Reissert compounds: a unique platform for observation of steric and electronic interactions

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This paper is dedicated to the memory of Professor Frank D. Popp, who pioneered the synthesis, study and use of Reissert compounds, and to the memory of Professor Ernest L. Eliel, an exemplary mentor in stereochemistry

Keywords: Isoquinolines Reissert compounds Stereochemistry Amide isomerism Atropisomerism

1. Introduction

ABSTRACT

Isoquinoline Reissert compounds (2-acyl-1,2-dihydroisoquinaldonitriles) with either 3-H (1) or 3-CH₃ (2) substituents and various *N*-acyl groups have been examined in detail by ¹H and ¹³C NMR spectroscopy and X-ray crystallography. In all cases the *trans* amide conformation, with reference to the carbonyl oxygen and the 3-position of the isoquinoline ring, predominates in solution. In the solid state the nitrile moieties are pseudo-axial and the amides exist almost exclusively in the *trans* form, except for the case of 2-isobutyryl-3-methyl-1,2-dihydroisoquinaldonitrile (**2c**), which exists exclusively as the *cis* amide form in the solid state. In *N*-aroyl 3-CH₃ compounds with two *ortho*-aroyl substituents both amide isomerism and hindered aryl/carbonyl rotation are observed by ¹H NMR spectroscopy. In other *N*-aroyl derivatives only hindered aryl/carbonyl rotations are observed by NMR and in *N*-alkanoyl compounds amide isomerism is observable only at very low temperatures. X-ray crystallography reveals the two rotamers in the solid state in four cases of *ortho*-substituted benzoyl compounds; with one exception, the rotamer with the larger *ortho*-aroyl substituent *syn* to the pseudo-axial cyano group is favored. Unusual solubility and reactivity patterns observed with these compounds are rationalized in terms of the interplay between steric and electronic factors.

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Reissert compounds are α -(acylamino)nitriles formed by the formal addition of acyl nitriles to imine bonds via *N*-acylium ions.¹ Isoquinoline Reissert compounds, 2-acyl-1-cyano-1,2-dihydroiso-quinolines, **1** and **2**, for example, are prepared by reaction of the isoquinolines and acid chlorides in the presence of a cyanide ion source.^{2–4} Aromatic and aliphatic acid chlorides and a variety of heterocycles and acyclic imines may be employed to make Reissert compounds.^{1,5} Proton H₁ of **1** and **2** is acidic and may be abstracted by a variety of bases and the resultant anions are excellent nucle-ophiles that undergo a number of reactions with proven utility in elaboration of nitrogen heterocycles.^{1,6} When an isoquinoline Reissert anion is treated with an aldehyde, the ester of a 1-(α -

hydroxyalkyl)isoquinoline forms. The anions likewise react with alkyl halides to produce derivatives such as **3** and **4**. Via these processes Reissert compounds have been employed in syntheses of novel monomers and polymers,⁷ and racemic isoquinoline alkaloids.^{8–12} Their application in stereoselective syntheses, an ongoing challenge,¹³ has now been reported,^{14–17} portending their increasing importance in this field. In spite of their wide synthetic application, the stereochemistry of the Reissert compounds themselves has received only scant attention.^{17,18} Our interest in the stereochemistry of 1-alkyl derivatives, e.g., **3** and **4**,¹⁹ and the necessity of synthesizing a series of new Reissert compounds^{20,21} for that effort led to this investigation of the stereochemistry of these parent compounds.

2. Results and discussion

It is known that the spatial requirement of the cyano group is somewhat greater than that of hydrogen.^{22,23} In analogous 1,2-dihydronaphthalene systems, the conformationally larger 1-substituent, cyano, occupies the pseudo-axial position.^{24,25} Thus, in Reissert compounds **1** and **2** the cyano moiety occupies the





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pseudo-axial position predominantly, if not exclusively, at room temperature, consistent²⁶ with the ~1 Hz coupling constants between the 1- and 3-protons of compounds 1 (Table 1), in agreement with previous work.¹⁸ Reissert compounds are tertiary amides and as such display amide isomerism, defined in Scheme 1 as s-cis and s-trans with respect to the R and H₁ moieties.²⁷ These isomers arise from the partial double bond character of the N-C(O) bond of the amide via resonance contribution from $N^+ = C - O^{-28,29}$ Additionally in compounds with unsymmetrically substituted N-aroyl moieties, there is hindered rotation around the aryl/carbonyl bond as shown in Scheme 1, yielding a total of four possible isomers, as known with other aromatic amides.^{28–31} The interactions between the 3-H or 3-CH₃ substituent and the substituents on the nitrogen atom may be considered in the sense of the classical allylic or A_{1-3} strain,³² and indeed these provide the steric driving forces that seem to control the stereochemistry of these compounds to great extent. These isomerization processes are elucidated in this work.

Table 1 ¹H NMR spectra of 2-acyl-1.2-dihydroisoguinaldonitriles (**1**) in CDCl₂ at 40 °C (60 or 80 MHz) unless otherwise noted

Cpd.	R	H ₁ (ppm)	H ₃ (ppm)	H ₄ (ppm)	J_{1-3} (Hz)
1a	CH₃	6.70	6.76	6.09	1
1b	C_2H_5	6.79	6.87	6.15	<1
1c ^a	$CH(CH_3)_2$	6.87	6.97	6.20	0.6
1d	(CH ₂) ₃ Cl	6.82	6.95	6.19	1
1e ^f	(CH ₂) ₂ Cl	6.63	6.74	6.15	0.8
1f ^{f,b}	C ₆ H ₅	6.63 ^g	6.60	6.11	1.0
1g	o-C ₆ H ₄ CH ₃	6.37 ^g	5.98	5.57	1.0
1i	p-C ₆ H ₄ CH ₃	6.61	6.73	6.10	_
1j	o-C ₆ H ₄ Cl	6.85	6.35	6.05	1
1k	p-C ₆ H ₄ Cl	6.62	6.68	6.15	1.2
1m ^{h,c}	α -C ₁₀ H ₇	6.88	6.30	5.88	_
10 ^{i,d}	2,6-C ₆ H ₃ (OCH ₃) ₂	5.67, 6.84 ^j	6.38, ^j 6.68	5.86, ^j 6.31	_
1r	OC_2H_5	6.43	7.03	6.07	_
1s	OCH ₂ C ₆ H ₅	6.43	7.03	6.08	0.8
6 ^{f,k,1}	_	6.61	6.61	6.08	1
7 ^e	_	6.27	6.80	6.16	1
10: R=H	—	—	7.37	6.27	—

See Supplementary data Fig. S1.

See Supplementary data Fig. S2.

See Supplementary data Fig. S5.

^d See Supplementary data Fig. S3a.

^e See Supplementary data Fig. S17.

^f In CD₃COOD.

^g Assignment verified by deuterium labeling, i.e., by taking the spectrum of analog **8**. 400 MHz. 22 °C.

ⁱ 500 MHz, 22 °C; methoxy signals at 3.67 (major), 3.70 (minor), 3.86 (major), and 3.89 (minor) ppm.

^j Major signal.

^k 25 °C.

Reported in CDCl₃: H₁: 6.61 ppm, H₃: 6.65 ppm, H₄: 6.11 ppm, J₁₋₃=1 Hz (Knabe, J.; Frie, A. Arch. Pharm. 1973, 306, 648-658).

2.1. Ambient temperature ¹H NMR spectra

The ¹H NMR spectra of the 2-acyl-1,2-dihydroisoquinaldonitriles (1 and 2) are summarized in Tables 1 and 2. The spectra of 6^{8,9} and 7^{33} (see Supplementary data Fig. S17 for the latter) are also given in Table 1. The signals due to H₁ were identified directly by substitution of deuterium for hydrogen; treatment of compound 1 or 2 with sodium hydride in dimethylformamide in the presence of carbon disulfide leads to formation of the orange dithiocarbamate anion (Scheme 2), which is unstable in water and reverts to starting $1.^{34}$ By quenching the anion with D₂O, 1-deutero-2-acyl-1,2dihydroisoquinaldonitriles (8 and 9) were prepared.³⁵ For example, from 1f, 8f was isolated in 92% yield. The signal present at 6.63 ppm (CDCl₃) in the spectrum of **1f** is absent in that of **8f**, while



Scheme 1. Isomers resulting from hindered rotation about the amide and carbonyl/ aryl bonds: **t**=*trans* amide; **c**=*cis* amide; **s**=larger group X *syn* to CN; **a**=larger group X *anti* relative to the cyano moiety.

all other signals are at the same positions (see Supplementary data Fig. S2). Likewise **1g** affords 100% of **8g**, which lacks the 6.55 ppm signal due to H_1 of **1g**. It is noteworthy that signals for H_1 and 3-CH₃ are broadened in the spectrum of **2i**.



2.2. Low temperature spectra

The ¹H NMR (80 MHz) spectra of the following compounds were examined in CDCl₃ solution down to -46 °C and underwent no significant changes: **1a**, **1c**, **1f**, **1k**. Likewise, compound **2f** did not exhibit any signal doubling, but significant peak broadening did occur. Compound **1i** showed no broadening or doubling of signals down to -62 °C in acetone- d_6 . Again the 3-methyl analog, **2i**, while not exhibiting signal doubling, did undergo significant broadening of the 3-methyl signal at -62 °C in acetone- d_6 (full width at half height 6.0 Hz). See Supplementary data Table S1. Not all compounds were examined at low temperatures, only the ones indicated here and in the following discussion.

However, the spectra of the following compounds revealed the presence of more than one stereoisomeric form as evidenced by doubling of NMR signals for certain protons: **2a**, **2c**, **1g**, **2g**, **2j**, **2l**, **2m**, **2n**, **2o**, and **2q**. The changes revealed in the spectra of **1g** and **2g** as a function of temperature (Fig. 1) are typical of some of the changes observed (see Supplementary data Table S1).

2.3. Determination of amide configuration

A diagnostic test for amide configuration is provided by aromatic solvent induced shifts (ASIS).³⁶ This technique involves comparison of chemical shifts of the compound when the solvent is changed from carbon tetrachloride to benzene. Groups *s*-*trans* to the carbonyl oxygen undergo large upfield (+) shifts; those *s*-*cis* undergo small downfield (-) shifts. These differential shifts originate in the anisotropy resulting from complexation of benzene to the carbonyl moiety.³⁶ In **5c** (Scheme 1) changing from carbon tetrachloride to benzene should cause a large upfield (+) shift in H₁ and a small downfield (-) in R₃ and H₄. Conversely in **5t**, R₃ and H₄ are predicted to shift upfield (+) significantly and H₁ is expected to

Table 2

 1H NMR spectra of 2-acyl-3-methyl-1,2-dihydroisoquinaldonitriles (2) in CDCl₃ at 40 °C (60 or 80 MHz) unless otherwise noted

Cpd.	R	H ₁ (ppm)	3-CH ₃ (ppm)	H ₄ (ppm)
2a	CH₃	6.75	2.31	6.35
2b	C_2H_5	6.82	2.36	6.44
2c ^a	$CH(CH_3)_2$	6.72 ^j	2.40	6.47
2d	(CH ₂) ₃ Cl	6.72	2.32	6.47
2f	C ₆ H ₅	6.53	1.81	6.47
2g	o-C ₆ H ₄ CH ₃	6.65 ^j	1.72	6.20
2h ^k	$m-C_6H_4CH_3$	6.43	1.80	6.15
2i	p-C ₆ H₄CH ₃	6.60	1.85	6.33
2j ^b	o-C ₆ H ₄ Cl	6.60 (br)	1.82 (br)	6.30
2k	p-C ₆ H ₄ Cl	6.60	1.85	6.36
21 ^{k,c}	o-C ₆ H ₄ F	6.31	1.80	6.01
2m ¹	$\alpha - C_{10}H_7$	6.75 (br)	1.58	6.20
2n ^{k,d}	2,6-C ₆ H ₃ (CH ₃) ₂	5.40, ^j 7.05 ^{j,m}	1.52, ^m 2.52	6.15, ^m 6.37
20 ^{k,e}	2,6-C ₆ H ₃ (OCH ₃) ₂	5.59, ^j 6.99 ^{j,m}	1.68, ^m 2.55	6.17, ^m 6.33
2p ^{k,n,f}	2,6-C ₆ H ₃ FCl	5.48, 5.50, ^j	1.72, 1.74, ^m	6.27, 6.29, ^m
		6.94, 6.96 ^{j,m}	2.54, 2.56	6.42, 6.45
2q ^{k,n,g}	2,6-C ₆ H ₃ ClCH ₃	5.41, 5.52, ^j	1.58, ^m 1.69,	6.25, ^{m,o} 6.41,
		7.09, 7.06 ^{j,m}	2.58, 2.60	6.46
2r ^h	OC_2H_5	6.43	2.34	6.17
2s ⁱ	OCH ₂ C ₆ H ₅	6.44	2.31	6.17
10: R=CH ₃	_	_	2.36	6.28

^a See Supplementary data Fig. S4.

^b For 600 MHz spectra at 25, -15, and -50 °C, see Supplementary data Fig. S18.

 c For 600 MHz spectra at 25, -15, and $-50\ ^\circ C,$ see Supplementary data Fig. S19. d See Supplementary data Fig. S9 for the 60 MHz spectrum and Fig. 2 for the

600 MHz spectrum.

^e See Fig. 3.

 $^{\rm h}$ 500 MHz spectrum@22 °C; H4 signal identified by COSY correlation with 3-CH3; see Supplementary data Fig. S10.

ⁱ 500 MHz spectrum@22 °C; H₄ signal identified by COSY correlation with 3-CH₃; see Supplementary data Fig. S11.

^j Assignment verified by deuterium labeling, i.e., by taking the spectrum of the analogous compound **9**.

^k At 25 °C.

¹ 600 MHz at 20 °C; see Supplementary data Figs. S6–S8.

^m Major signal.

ⁿ 500 MHz at 20 °C; see Fig. 5.

^o Two coincident signals.

undergo a small downfield (-) shift. Due to limited solubility of many of these compounds in CCl₄, CDCl₃ was used; it was demonstrated that the resultant differences are small and unambiguous, the chemical shifts in CDCl₃ being slightly upfield of those in CCl₄ (see Supplementary data Table S2, compounds 1c, 2c). ASIS were determined for several of the compounds at low temperature using chlorobenzene (C_6H_5Cl), or toluene- d_8 as the aromatic solvent so that solvent freezing was not a problem. The shifts were then those associated with the changes from CDCl₃ to C₆H₅Cl or toluene- d_8 (see Supplementary data Table S2). Included are results for compounds 10, which can only exist in the cis amide configuration; as a result the 3-H or 3-CH₃ (R) signal undergoes the expected small shift, while the methylene protons α to the 1-position and analogous to H₁ of **1** and **2** undergo large upfield shifts. In each instance the only or major signal for R₃ of the Reissert compounds 1 and 2 undergoes a large upfield shift; this means that the trans amides dominate in each case. This was previously observed with benzothiazole Reissert compounds.^{5d}



See Fig. 4.

^g See Fig. 5.



Scheme 2. Selective deuteration of isoquinoline Reissert compounds via reactions of their anions with CS2 and then D20.



Fig. 1. Methyl region of the ¹H NMR spectra (60 MHz) of (a) (left) 2-o-toluyl-1,2-dihydroisoquinaldonitrile (**1g**) and (**b**) (right) 2-o-toluyl-3-methyl-1,2-dihydroisoquinaldonitrile (**2g**) in CDCl₃ as a function of temperature.

2.4. Identification of isomerization processes with selected compounds

Compounds **1a**, **1c**, **1f**, **1i**, and **1k** at low temperature show no significant broadening or doubling of signals, indicating that for all five compounds the rate of interconversion of *cis* and *trans* amide isomers is rapid and in **1f**, **1i**, and **1k** rotation about the aryl/carbonyl bond is also rapid. In the 3-methyl series the simple benzoyl compound **2f** and the *para*-toluyl analog **2i** did not exhibit signal doubling, only peak broadening; in these compounds the barriers to rotation about the aryl/carbonyl and amide bonds are such as to be not observable at the lowest temperature accessed. This is expected, since the *N*-aroyl groups in these compounds are not *ortho*-substituted.

In considering the *N*-alkanoyl compounds the only possible observable dynamic process is amide isomerism. In **2a** and **2c** signal doubling is observed for 3-CH₃, H₁, H₄, and 2-alkanoyl groups at low temperatures and the *trans* amide isomers predominate (see Supplementary data Table S1).

As noted above a number of the N-aroyl compounds exhibit both amide and atropisomers; these will now be discussed in detail. The new 2',6'-dimethylbenzoyl-3-methyl compound 2n affords a good reference point for comparison of chemical shift data for the four possible individual isomers in ortho-substituted N-aroyl compounds. The presence of six methyl signals in the room temperature NMR spectrum of 2n (Fig. 2, Table 2, Scheme 3) indicated that there were two slow isomerization processes involved. The presence of four signals (1.7-2.6 ppm) for the N-aroyl methyl groups is due to restricted rotation about the arvl-carbonyl bond coupled with amide isomerism. The two signals for the 3-methyl group (identified by the 1 Hz coupling to H₄) and two signals for H₄ are attributed to slow amide isomerization. Accordingly, H₁ also displays two signals identified by examination of the deutero analog 9n (Fig. 2 inset), the major one at 7.08 ppm, the minor at 5.46 ppm. From integration of the 3-methyl and ortho-methyl signals in the ¹H NMR spectrum the trans/cis isomer ratio was found to be 71:29(\pm 1). The ¹³C NMR spectrum of **2n** (see Supplementary data Fig. S12) corroborates these results. Two signals at 44.58 and 49.62 ppm in intensity ratio 72:28, respectively, are assigned to the C_1 carbon of the isoquinoline ring. Matching these are two signals at 116.97 and 117.64 ppm in intensity ratio 72:28, respectively, assigned to the cyano carbons.

Clearly from the data for **2n**, amide isomerism leads to large chemical shift differences for the 3-substituent (R₃) (1 ppm) and H₁ (~1.6 ppm). However, only relatively small differences, ~0.1 ppm, are observed between *syn* methyl signals in the *cis* and *trans* amide isomers, and likewise for the *anti*-methyl groups (Scheme 3). However, the *syn* and *anti* positions lie in greatly different environments; for example, the chemical shifts of the two *ortho*-methyl groups of **2n** in the major *trans* amide forms vary by ~0.6 ppm (Scheme 3).

Molecular modeling indicates that the aryl ring of this and similar Reissert compounds cannot be coplanar with the carbonyl group; instead, it is rotated out of plane in such a way that the *ortho* substituents are projected above and below the plane of the isoquinoline nucleus as indicated in structures **5**. Because of the tilt of the aroyl moiety, the *syn-substituent* is tilted away from the cyano group and is less hindered than the *anti* position, which lies under the C_3 and C_4 positions of the isoquinolyl moiety. Thus, the *syn*substituent experiences a deshielding effect from the nearby carbonyl group, while the *anti*-substituent is shielded by the isoquinolyl nucleus. The solid state structure derived from X-ray crystallography, discussed below, is consistent with this analysis.

Turning now to the new 2',6'-dimethoxybenzoyl-3-methyl compound **20**, in CDCl₃ two signals are observed for the 3-methyl group (Fig. 3, Table 2, Scheme 4), along with four methoxy signals and two signals for H₁, identified by preparation of **90**. These results are again attributed to the combination of hindered aryl/carbonyl rotation and *cis/trans* amide isomerism, **5t** being the major (55%)



Fig. 2. ¹H NMR spectrum of 2-(2',6'-dimethylbenzoyl)-3-methyl-1,2-dihydroisoquinaldonitrile (**2n**) in CDCl₃ at 22 °C; the signals marked with asterisks (*) are due to ethyl acetate. Inset: partial spectrum of the 1-deuterio derivative **9n**; the arrows indicate the chemical shifts of the two H₁ signals in **2n**.



amide isomer. The ¹³C NMR spectrum of **20** (see Supplementary data Fig. S13) corroborates the ¹H NMR results. Signals at 45.07 and 49.56 ppm in intensity ratio 55:45, respectively, are assigned to the C₁ carbon of the isoquinoline ring. Matching these are two signals at 116.12 and 116.37 ppm in intensity ratio 53:47, respectively, assigned to the cyano carbons. Likewise the two carbonyl signals at 164.97 and 165.46 have a similar intensity ratio. There are two signals for the 3-methyl carbons at 20.49 and 20.59 ppm (intensity ratio 45:55, respectively) and four signals for the methoxy carbons at 55.37, 55.82, 55.96, and 55.97 (intensity ratios 25:20:27:28, respectively).

The only 3-H compound that displayed isomerism at room temperature was the new dimethoxy analog **10** (Table 1; also see

Supplementary data Fig. S3a); amide isomers with hindered aryl–carbonyl rotation were present in an 86:14 ratio in this case as proven by four signals for the methoxy protons, and two signals each for H_1 , H_3 , and H_4 . The ¹³C NMR spectrum (see Supplementary data Fig. S3b) confirmed the presence of two carbonyl peaks (164.7 and 165.8 ppm) with a height ratio of 1:9 and likewise four aromatic C(O) signals (156–158 ppm) in 1:1:9:9 peak height ratios, as well as other signals with the same relative intensities. Assignments were verified by ¹H COSY (correlation spectroscopy, see Supplementary data Fig. S3a) and HMBC (heteronuclear multiple bond correlation, see Supplementary data Fig. S3c) experiments.

Another 2',6'-disubstituted aroyl compound, the new 2'-chloro-6'-fluorobenzoyl-3-methyl derivative **2p** displays four 3-methyl signals in its 500 MHz ¹H NMR spectrum (Fig. 4, Table 2, Scheme 5), indicating the presence of all four isomers. The chemical shifts of the diagnostic 3-methyl group fall in line with the results for **2n**; in the *cis* isomer it appears at ~2.5 ppm and in the *trans* at ~1.7 ppm. The *trans* isomer predominates in a 79:21 ratio. From the four signals each for the 3-methyl protons, H₁ and H₄ (Table 2), the average ratio of the major to minor rotamers in the *trans* isomer was 56:44, as compared to 55:45 in the *cis* isomer (values good to ±2%). In the ¹³C NMR spectrum of **2p** (see Supplementary data Fig. S14) there are two peaks for the 3-methyl group (20.76 and 21.04 ppm), two for C₁ (45.15 and 49.69 ppm) and at least six signals in the range 155–162 ppm; the latter should include two carbonyl peaks and



Fig. 3. ¹H NMR spectrum (400 MHz) of 2-(2',6'-dimethoxybenzoyl)-3-methyl-1,2-dihydroisoquinaldonitrile (20) in CDCl₃ at 22 °C.



four doublets for C–F carbons with $J_{C-F} \sim 250$ Hz; however, only two such doublets are clearly observed, corresponding to major isomers **5ta** and **5ts**. In hopes of a clearer picture, we obtained the ¹⁹F NMR spectrum (see Supplementary data Fig. S15), which as expected contains four signals (at –113.43, –112.18, –111.99, and –111.52 ppm) in 37:10:11:42 proportion, in rough agreement with the proton NMR spectrum (Fig. 4) whose peaks overlapped to some extent, making precise determination of relative proportions difficult. The most upfield (–113.43 ppm) ¹⁹F signal constituted 37% and was assigned to F *anti* to the CN (**5ts** stereoisomer) based on the chemical shifts of the methyl protons of **2g** and **2n**. In the more



Fig. 4. ¹H NMR spectrum (400 MHz) of 2-(2'-chloro-6'-fluorobenzoyl)-3-methyl-1,2-isoquinaldonitrile (2p) in CDCl₃ at 22 °C.



Scheme 5. ¹H NMR (500 MHz, CDCl₃) and ¹⁹F (376 MHz, CDCl₃) results for 2p.

abundant *trans* amide isomer the signal was the most downfield (-111.52 ppm) and, therefore, assigned to F *syn* to the cyano group, i.e., isomer **5ta**. In the *cis* amide the F signal of the major (11%) rotational conformer was the downfield one (-111.99 ppm), corresponding to F *syn* to CN (**5ca**). The minor (10%) *cis* amide isomer with the F signal upfield (-112.18 ppm) thus corresponds to **5cs**, having the F *anti* to the CN. The slight preponderance of the **5ta** isomer over the **5ts** isomer may be due to the higher dipole associated with the C–Cl versus C–F bond;³⁷ having this dipole oppose the pseudo-axial C₁–CN dipole may lead to greater stability in the non-polar solvent. It is noteworthy, though, that in the crystalline state the **ts** isomer predominates greatly, as expected; see below.

These results prompted us to re-examine the ortho-halo compounds 2j and 2l at low temperatures at 600 MHz. Although a detailed study was not carried out in either case, at $-50\,^\circ\text{C}$ the presence of both amide isomers and rotamers was detected. In line with the results discussed above for **2p**, at that temperature the ortho-chloro compound 2j displayed two resolved signals at 1.57 and 1.65 (major, total 93%) and another at 2.56 ppm (minor, 7%) for the 3-methyl signals of the *trans* and *cis* amides, respectively, along with definite signals for individual rotamers in each of these; that is, similar to the room temperature spectrum of **2p** there are four clear signals each for H_1 and H_4 (see Supplementary data Fig. S18), indicative of all four isomers of **2i** in a ratio of 58:35:5:2 for **5ts/5ta**/ 5cs/5ca (X=Cl>Y=H). Similarly at -50 °C the ortho-fluoro compound **21** displayed two broad signals at 1.57 and 2.49 ppm for the 3-methyl protons of the *cis* and *trans* amides, along with definite signals for individual rotamers in that there are four clear signals each for H₁ and H₄ (see Supplementary data Fig. S19), indicative of all four isomers in a ratio of 49:41:9:1 for 5ts/5ta/5cs/5ca (X=H>Y=F).

A fourth new 2,6-disubstituted aroyl compound, 2'-chloro-6'methylbenzoyl-3-methyl derivative **2q**, displays four 3-methyl signals and four signals for H_1 and three for H_4 (Fig. 5, Table 2, Scheme 6). The H₁ signal assignments were verified by deuteration, producing 9q. The chemical shifts of the 3-methyl group are consistent with the above results, the upfield signals at \sim 1.6–1.7 ppm denoting the *trans* amide and \sim 2.6 ppm indicating the *cis* isomer. Moreover, the chemical shifts of the methyl group on the benzoyl ring are clearly indicative of its disposition relative to the cyano group: ~ 2.5 ppm if syn and 1.8–2.0 ppm if anti, in accord with the results for the methyl groups in **2n**. The *trans* isomer predominates in a 71:29 (± 1) ratio. Analysis of these signals indicates that the ratio of the major to minor rotamers in both the cis and trans amide isomers was 52:48 (values good to $\pm 1\%$). The larger chloro subtituent³⁸ preferentially occupies the syn position versus the methyl substituent, in agreement with other results. The ¹³C NMR spectrum of **2q** (see Supplementary data Fig. S16) corroborates the ¹H NMR results: four signals each for the 3-methyl group, C₁ and the benzoyl methyl group; analysis of their intensities in each case affords the following isomer ratios: 14:15:34:37 in excellent agreement with the ¹H results. This conclusion is consistent with the X-ray crystallographic results below.

The *ortho*-toluyl benzothiazole Reissert compound displays similar chemical shifts for the tolyl methyl group in the four isomers (1.87, 2.40, and 2.53, the latter overlapped), but the assignments made earlier for this compound are wrong,^{5d} in that case as in the present isoquinoline analogs the larger *ortho* substituent



Fig. 5. ¹H NMR spectrum (500 MHz) of 2-(2'-chloro-6'-methylbenzoyl)-3-methyl-1,2-isoquinaldonitrile (2q) in CDCl₃ at 22 °C. Inset: downfield region of deutero analog 9q.



Scheme 6. ¹H NMR results (500 MHz, CDCl₃) for 2q.

(CH₃) is *syn* to the cyano group in the major aryl/carbonyl isomers of both amide isomers.

In contrast to the behavior of these compounds, at low temperature (-46 °C) the doubled signals for H₃ and H₄ of **1g** are only slightly different (0.03–0.06 ppm) and H₁ is only broadened (see Supplementary data Table S1); moreover, the two tolyl methyl signals vary by only 0.32 ppm (Fig. 1a, Scheme 7). These results, in light of the



Scheme 7. ¹H NMR results (80 MHz, CDCl₃) for 1g and analog 2g.

above discussion, indicate that **1g** exists in the *trans* amide form exclusively, but undergoes slow aryl–carbonyl rotation in the low temperature range examined. The same conclusion may be drawn for **2g**: only the *trans* amide exists in solution; in fact the chemical shift difference for the tolyl methyls (0.6 ppm, Fig. 1b, Scheme 7) is about the same as for *trans*-**2n** (Scheme 3). These conclusions are supported by the low temperature results, which show the same sign of ASIS for each of the doubled signals for the H₃ in **1g** and the 3-methyl moiety (R₃) in **2g** (see Supplementary data Table S2).

For naphthoyl analog **2m** at room temperature only broad signals are observed (See Supplementary data Fig. S6); however, at low temperature four distinct isomers are detected, although the percentages of the *cis* amide isomers are quite low (Fig. 6, Scheme 8). Again the chemical shifts of the 3-methyl and H₁ moieties are diagnostic. The 3-methyl and H₄ signals were examined via a 600 MHz COSY experiment at -34 °C (see Supplementary data Fig. S7), taking advantage of the ~1 Hz allylic coupling between them to make the assignments. The H₁ signals were also verified at -34 °C by comparison to the deutero analog **9m** (see Supplementary data Fig. S8). The predominance of **5ts** isomer of **2m** is consistent with its X-ray structure (see below).

Based on the chemical shifts of the 3-methyl groups in urethane Reissert compounds **2r** and **2s** in comparison to those of compounds **2m**, **2n**, **2o**, **2p**, **2q**, and **10** it is apparent that these compounds both exist predominantly in the form of the *cis* isomers around the C(O)–N bond. Interestingly in **2r** the methylene protons



Fig. 6. ¹H NMR spectrum (600 MHz) of **2m** at -34 °C in CDCl₃. H₄ signals distinguished by COSY experiments to correlate with the 3-CH₃ signals via the ~1 Hz allylic coupling (see Supplementary data Fig. S7). H₁ signals verified with the deuterated analog **9m** at -34 °C in CDCl₃ (see Supplementary data Fig. S8).



Scheme 8. ¹H NMR results (600 MHz, CDCl₃) for 2m.

are diastereotopic as revealed by their classic ABX₃ signature (see Supplementary data Fig. S10); they differ in chemical shift by 0.07 ppm. Likewise the diastereotopic benzylic methylene protons of **2s** display a classic AB quartet and differ by 0.07 ppm (see Supplementary data Fig. S11).

The free energy differences (ΔG) between the stereoisomers of the various Reissert compounds were determined from the equilibrium constants evaluated by NMR. ΔG values range from near zero to 1.2 kcal/mol (see Supplementary data Table S1).

2.5. Single crystal X-ray structures

Single crystals of some of the Reissert compounds were examined by X-ray crystallography. Geometric factors derived from these analyses are gathered in Table 3. In general these results confirm that the *trans* amide isomers are preferentially formed in the solid state, that the rotamers with the larger *ortho* substituent *syn* to the 1-cyano group are favored and that the cyano moiety occupies a pseudo-axial position (dihedral angles with respect to the benzo plane: $82-96^{\circ}$).

The ortho-toluyl Reissert compound **1g** exists in the solid state entirely as the *trans* amide, as also determined from the solution NMR studies; the amide linkage is very nearly planar, only out by 0.4°. There are, however, two rotamers present in a ratio of 78:22 (Fig. 7). However, unlike the structure determined in solution (55% **ts**/45% **ta**), in the crystalline phase the rotamer with the orthomethyl group *anti* to the cyano moiety, i.e., **5ta**, is favored. The other noteworthy aspect of the solid state structure of the major rotamer is that the aryl/carbonyl dihedral angle (48°) is the lowest of any of the substituted *N*-aroyl Reissert compounds examined in the present work (Table 3). It is known that in some cases packing effects can cause solid state structures to differ from solution structures. This compound seems to fall into this category.

Table 3			
Structures of Reissert compounds from	X-ray	diffraction	on



Fig. 7. Two views of one enantiomer from the X-ray crystal structure of 2-(*o*-toluyl)-1,2-dihydroisoquinaldonitrile (**1g**) showing the pseudo-axial location of the cyano moiety, the *trans* orientation of the amide linkage and the twisted disposition of the tolyl group. In the major [78.2 (\pm 0.4)%] rotamer (top views) the *ortho*-methyl group is *anti* to the cyano group (**5ta**), while in the minor [21.8 (\pm 0.4)%] isomer (bottom views) it is *syn* to the cyano group (**5tb**). The 3-proton is 3.43 Å away from the centroid of the tolyl ring in the major rotamer and 3.15 Å away in the minor rotamer.

This result can be compared to the structure of the analogous 3-methyl compound **2g**, which exists solely in the *trans* amide form, but again with two aryl/carbonyl rotamers (Fig. 8). However, in this case, as in all of the other systems, the larger *ortho* substituent is preferentially *syn* to the cyano moiety, i.e., as in **5ts** and as determined in the solution phase to the extent of 69%. The amide linkage is out of planarity by 14° in this case, the largest variation in all of the *N*-aroyl compounds examined, and the pyridyl ring is the most distorted of the aroyl compounds in terms of N being out of the benzo plane (Table 3).

Cpd.	Conf of 5 maj/min	Ar/CO dihedral (°)	C ₁ -N-C-O amide dihedral (°)	Ar/benzo plane angle (°)	Benzo/C1–C(N) angle (°)	N out of benzo plane (Å)	C ₁ out of benzo plane (Å)	C ₃ out of benzo plane (Å)	3-Me H–Ar centroid (Å)
1a	trans	_	0.2	_	82.27	0.402	0.129	0.263	_
1f ⁴⁶	trans	45.0	1.7	41.24	72.50	0.373	0.009	0.125	_
1g	ts (minor)	56.2	0.45	50.9	83.28	0.517	0.060	0.291	3.15 ^a
1g	ta (major)	48.2	0.39	52.4	83.28	0.517	0.060	0.292	3.43 ^b
1m	ts only	49.7	3.6	47.5	86.44	0.642	0.017	0.372	_
2c	_	_	162.2	_	95.81	0.762	0.048	0.423	_
2g	ta (minor)	53.6	13.7	52.3	90.32	0.698	0.040	0.368	2.99
2g	ts (major)	56.0	13.7	55.6	90.32	0.698	0.040	0.368	2.99 ^c
2j	ts/ta	69.5	5.6	58.9	89.11	0.619	0.074	0.356	2.78
21	ts/ta	60.4	8.6	51.9	87.62	0.684	0.009	0.244	2.75
2m	ts only	57.4	10.1	48.8	85.44	0.602	0.050	0.232	2.87
2n	trans	67.5	12.6	54.7	90.28	0.680	0.058	0.392	2.79
2р	ts/ta	71.3	9.5	59.0	87.67	0.589	0.100	0.353	2.79
2q	ts/ta	69.6	12.5	56.0	89.66	0.636	0.092	0.411	2.82

^a 3-H to Ar centroid distance; 3-H to CH₃ distance 3.65 Å.

^b 3-H to Ar centroid distance; 3-H to CH₃ distance 2.72 Å.

^c CH₃ to CH₃ distance 2.60 Å.



Fig. 8. Two views of one enantiomer from the X-ray crystal structure of 2-(o-toluyl)-3methyl-1,2-dihydroisoquinaldonitrile (**2g**) showing the pseudo-axial location of the cyano moiety, the *trans* orientation of the amide linkage and the twisted disposition of the tolyl group. In the major [78.9 \pm 0.5)%] rotamer (top views) the ortho-methyl group is syn to the cyano group (**5ts**), while in the minor [21.1 \pm 0.5)%] isomer (bottom views) it is *anti* to the cyano group (**5ta**). In **5ts** a 3-Me proton is 2.99 Å away from the centroid of the tolyl ring but only 2.60 Å away from the closest *ortho*-methyl proton.

In the solid state 1'-naphthoyl Reissert compound **1m** (Fig. 9) exists totally in the *trans* amide form and there is a 50° rotation about the aryl/carbonyl bond, placing the benzo ring in the conformation described by **5ts**. However, the amide unit is very nearly coplanar, deviating only by 4°. The protons on the 3- and 2'-positions are in very close proximity, as deduced from the solution phase NMR results. Addition of the 3-methyl substituent in **2m** causes the amide bond to deviate more (10°) from planarity (Fig. 10), but the other aspects of the structure are very similar to those in **1m**. There is no evidence of disorder in either structure, indicating that only one aryl/carbonyl rotamer exists in the solid state; in both cases the benzo ring of the naphtho unit is *syn* to the cyano moiety. This establishes the distance between one of the 3-methyl protons of **2m** and the centroid of the closest naphtho



Fig. 9. Two views of one enantiomer from the X-ray crystal structure of 2-(1'-naph-thoyl)-1,2-dihydroisoquinaldonitrile (**1m**) showing the pseudo-axial location of the cyano moiety, the*trans*orientation of the amide linkage and the twisted disposition of the naphthoyl group and the location of the benzo ring*syn*to the cyano group (**5ts**). H₃ and the naphthyl 2'-proton are only 2.78 Å.



Fig. 10. Two views of one enantiomer from the X-ray crystal structure of 2-(1'-naphthoyl)-3-methyl-1,2-dihydroisoquinaldonitrile (**2m**) showing the pseudo-axial location of the cyano moiety, the *trans* orientation of the amide linkage, the twisted disposition of the naphthoyl group and the location of the benzo ring *syn* to the cyano group (**5t**). The closest 3-methyl proton is 2.87 Å away from the centroid of the A-ring of the naphthoyl moiety.

ring at 2.87 Å, a distance (2.7–2.9 Å) typically considered to indicate an ArCH– π interaction.⁴⁵

The X-ray structure for *ortho*-chlorobenzoyl-3-methyl derivative **2j** (Fig. 11), however, reveals the presence of two aryl/carbonyl rotamers in the form of disorder of the location of the chlorine atom in the *trans* amide isomer, which exists to the exclusion of the cis. In the most populated (92%) rotamer, the chlorine atom is *syn* to the cyano group, corresponding to isomer **5ts**, consistent with the general rule deduced from NMR results and in good agreement with the 93% **ts** observed in solution. It is noteworthy that one of the 3-methyl protons is 2.78 Å from the centroid of the chlorobenzoyl ring, once more indicative of a possible CH– π interaction.⁴⁵



Fig. 11. Two views of one enantiomer of each of the two C—O/aryl rotational isomers from the X-ray crystal structure of 2-(*o*-chlorobenzoyl)-3-methyl-1,2-dihydroisoquinaldonitrile (**2j**). In the major [92.3(\pm 0.2)%] rotamer (top) the chlorine atom (purple) is *syn* to the cyano group (**5ts**) and in the minor [7.7(\pm 0.2)%] isomer (bottom) it is *anti* (**5ta**), but otherwise the structure is the same. The cyano moiety is pseudo-axial, the amide linkage is *trans* and the aroyl group is twisted. The closest 3-methyl proton is 2.78 Å away from the centroid of the benzoyl moiety.

The X-ray crystal structure of the *ortho*-fluorobenzoyl compound **21** (Fig. 12) also reveals two rotameric forms of the *trans* amide. The 6'-proton is larger than the 2'-fluorine^{39a} and the major (69%) rotamer thus again corresponds to structure **5ts**, but the proportions

Fig. 12. Two views of one enantiomer of each of the two C=O/aryl rotational isomers from the X-ray crystal structure of 2-(o-fluorobenzoyl)-3-methyl-1,2-dihydroisoquinaldonitrile (**21**). In the major [$69.2(\pm 0.2)$ %] rotamer (top) the fluorine atom (green) is *anti* to the cyano group (**5ts**) and in the minor [$30.8(\pm 0.2)$ %] isomer (bottom) it is *syn* (**5td**), but otherwise the structure is the same. The cyano moiety is pseudo-axial, the amide linkage is *trans* and the aroyl group is twisted. The closest 3-methyl proton is 2.75 Å away from the centroid of the benzoyl moiety.

differ somewhat from those observed in solution (54% **tu**, 46% **ta**). Other features are similar to those of **2***j*, including a 2.75 Å distance from the centroid of the fluorobenzoyl ring to one of the 3-methyl protons, again consistent with a CH $-\pi$ interaction.⁴⁵

The X-ray results for the 2',6'-dimethylbenzoyl-3-methyl Reissert compound **2n** (Fig. 13) support the conclusion that the *trans* amide isomer is more stable than the *cis* isomer, since the latter is not observed in the solid state, even though it comprises 29% in solution; however, the amide unit is non-planar by 13°. Moreover, the influence of the two *ortho*-methyl substituents is clearly seen in the large twist about the aryl/carbonyl bond, amounting to 68°. Even with the twist, two of the *ortho*- and 3-methyl protons are still quite close to each other: 2.49 Å. And from the centroid of the dimethylbenzoyl ring to one of the 3-methyl protons the distance is only 2.79 Å, again suggesting CH– π interaction as one of the contributing forces in the solid state.



Fig. 13. Two views of one enantiomer from the X-ray crystal structure of 2-(2',6'-dimethylbenzoyl)-3-methyl-1,2-dihydroisoquinaldonitrile (**2n**) showing the pseudo-axial location of the cyano moiety, the *trans* orientation of the amide linkage (**5t**) and the highly twisted disposition of the aroyl group. The 3-methyl carbon and the upper *ortho*-methyl carbon are 3.84 Å apart, putting the hydrogens within 2.49 Å of each other. The closest 3-methyl proton is 2.79 Å away from the centroid of the aroyl moiety.

The X-ray structure of the 2-(2'-chloro-6'-fluorobenzoyl)-3methyl Reissert compound **2p** (Fig. 14) confirms the *trans* amide solely as opposed to 21% of the *cis* amide in solution. The amide unit in this case is non-coplanar by 71°, the largest such deviation observed. One of the 3-methyl protons is 2.79 Å from the centroid of the chlorofluorobenzoyl ring (CH $-\pi$ interaction). And again two



Fig. 14. Two views of one enantiomer of each of the two C=O/aryl rotational isomers from the X-ray crystal structure of 2-(2'-chloro-6'-fluorobenzoyl)-3-methyl-1,2-dihydroisoquinaldonitrile (**2p**). The cyano moiety is pseudo-axial, the amide is *trans* and the aroyl group is twisted. In the major $[67.6(\pm 0.5)\%]$ rotamer (top) the fluorine atom (green) is *anti* to the cyano group and the chlorine atom (purple) is *syn* to it (**5ts**). In the minor $[32.4(\pm 0.5)\%]$ isomer (bottom) the positions of the two halogens are reversed (**5ta**), but otherwise the structure is the same. The closest 3-methyl proton is 2.79 Å away from the centroid of the benzoyl moiety.

conformers about the aryl–carbonyl bond are present, in ~2:1 ratio. The more stable conformer is the one that places the chloro substituent *syn* to the cyano group and the smaller^{39a} fluoro moiety trans to it, a repetition of the pattern observed by NMR, but with different proportions (1.2:1) in solution.

In 2-(2'-chloro-6'-methylbenzoyl)-3-methyl-1,2-dihydroisoquinaldonitrile (**2q**) (Fig. 15) again only the *trans* amide form is observed, but out of planarity by 12.5° and accompanied by a 56° aryl/carbonyl rotation. The chloro moiety is sterically larger than the methyl group,³⁸ so the dominant (56%) structure corresponds to isomer **5ts**, consistent with the general rule that **5ts** predominates and remarkably similar to the solution result (52% **ts** vs 48% **ta**). Closer inspection reveals that in this case one of the *ortho*-methyl protons in **5ta** is quite close to a 3-methyl proton, 2.44 Å. In the predominant **5ts** rotamer the chlorine atom is 3.18 Å away from the same 3-methyl proton. As noted with the other compounds, a CH– π interaction⁴⁵ is indicated by the proximity (2.82 Å) of one of the 3-methyl protons to the centroid of the chloromethylbenzoyl ring.



Fig. 15. Two views of one enantiomer of each of the two C=O/aryl rotational isomers from the X-ray crystal structure of 2-(2'-chloro-6'-methylbenzoyl)-3-methyl-1,2-dihydroisoquinaldonitrile (**2q**). The cyano moiety is pseudo-axial, the amide is *trans* and the aroyl group is twisted. In the major $[56.0(\pm 0.2)\%]$ rotamer (top) the chlorine atom (green) is *syn* to the cyano group and the methyl group is *anti* to it (**5ts**). In the minor $[44.0(\pm 0.2)\%]$ isomer (bottom) the positions of the chlorine atom and the methyl group are reversed (**5ta**), but otherwise the structure is the same. The closest 3-methyl proton is 2.82 Å away from the centroid of the benzoyl moiety. Two Hs on the CH₃ groups are 2.44 Å apart in the minor isomer and >3 Å apart in the major isomer.

The aryl/carbonyl twist angles of **1m**, **2m**, **2n**, **2p**, and **2q**, i.e., 50° , 57° , 68° , 71° , and 70° , respectively (Table 3), can be compared to that of the analogous *N*-benzoyl compound, **1f**, in which the aryl and amide planes are situated at a 45° angle to each other,⁴⁶ reflecting the smaller steric interaction of the phenyl group with the 3-proton. In all of the Reissert compounds with unsymmetrically substituted benzoyl moieties, except for **1g**, in the solid state the larger *ortho*-substituent lies *syn* to the cyano group, as deduced from the NMR solution spectra.

Turning to the *N*-alkanoyl Reissert compounds, the X-ray crystal structure of the acetyl Reissert compound **1a** (Fig. 16) reveals the expected *trans* amide conformation and nearly planar isoquinoline ring system and amide linkages. On the other hand, the X-ray crystal structure of the isobutyryl Reissert compound **2c** (Fig. 17) demonstrates the result of the steric interactions brought about by the 3-methyl group and the bulky *N*-isobutyryl unit: (1) the amide linkage is now *cis*, (2) the dihydropyridyl ring is more puckered, and (3) the amide linkage is non-planar by 18°, the largest such



Fig. 16. Two views of one enantiomer from the X-ray crystal structure of 2-acetyl-1,2dihydroisoquinaldonitrile (**1a**) showing the pseudo-axial location of the cyano moiety and the *trans* orientation of the amide linkage. H_3 and the closest two acetyl protons are both 2.37 Å apart.



Fig. 17. Two views of one enantiomer from the X-ray crystal structure of 2-isobutyryl-3methyl-1,2-dihydroisoquinaldonitrile (**2c**) showing the pseudo-axial location of the cyano moiety and the *cis* orientation of the amide linkage. One of the 3-methyl protons and the carbonyl oxygen atom are 2.39 Å apart. H₁ is very close to the isopropyl methine proton, 1.94 Å. The origin of the chemical shift difference of the isopropyl methyl signals (0.17 ppm in CDCl₃, previously unpublished result) is obvious in this conformation.

deviation observed in this study. Note in contrast, however, that the *cis* amide structure is the minor isomer in solution, apparently a result of different intermolecular interactions in the solution versus solid states.

Considering the packing in these crystalline compounds, some display interesting close contacts. For example, in **1g** there are close in-plane contacts between the carbonyl oxygens and H_1 and H_8 of neighboring molecules (Fig. 18) in both the major and minor amide isomers. Moreover, the nitrogen atom of the cyano group is close to H_4 of a neighboring molecule, 2.54 Å at a C–H–N angle of 159.03°. The reported⁴⁶ packing of parent Reissert compound **1f** is very similar (see Supplementary data Table S3). In the 3-methyl analog



Fig. 18. Close contacts in the solid state of 1g. Distance/C–H–X angle (a): $2.52 \text{ \AA}/143.71^{\circ}$; (b): 2.53.

2g, however, there is no close contact of the oxygen atom with H₈; instead there is an H₅–N(\equiv C) interaction (2.73 Å/148.13°), but the H₁–O(=C) interaction remains (2.60 Å at a C–H–N angle of 147.81°). Indeed, while short H₁–O(=C) distances appear in many of these compounds, such an interaction is not universal; compounds **2j**, **2n**, **2p**, and **2q** with large aroyl substituents are exceptions (see Supplementary data Table S3). Other close contacts involve protons H₃, H₄, H₅, H₆, and H₇ of the isoquinolyl unit with the nitrogen atom of the nitrile, and the carbonyl oxygen with H₈.

2.6. Rationalization of structural effects

Increased steric hindrance due to *ortho N*-aroyl and 3-methyl substituents inhibits resonance of type **11a**, which requires coplanarity of the COAr group, tending to raise the amide isomerism barrier by increasing the contribution of resonance form **11b**. However, as the hindrance becomes more severe the coplanarity of the NCO group required for **11b** is also diminished and it becomes less important and the non-polar, less conjugated resonance structure **11c** becomes more important; moreover, the energy difference between the *cis* and *trans* isomers decreases as steric crowding increases.

While such arguments are known to be somewhat tenuous, melting point observations are consistent with the above amide resonance considerations. Four of the five highest melting Reissert compounds [**2p** (212 °C)>**2q** (208 °C)>**2n** (202 °C)>**2m** (199 °C)> **2o** (184 °C)] possess two bulky *ortho N*-aroyl substituents; the naphthoyl derivative **2m** is the exception. The high melting points [relative, e.g., to simple *N*-benzoyl analog **2f** (140 °C)], we believe, are indicative of increased solid state bonding due to the presence of stronger molecular dipoles arising from increased contributions of **11b** and **11c** at the expense of **11a** as the substituent size(s) increase(s). On the same basis the *ortho-*, *meta-*, and *para*-toluyl derivatives **2g**, **2h**, and **2i** are exemplary in terms of their lower trending melting points (146, 134, 130 °C, respectively).



Moreover, this view is consistent with the observed solubilities of these compounds. The 3-H/3-Me pairs of *ortho*- and *para*-chloro compounds **1j**/**2j** and **1k**/**2k**, respectively, reveal the decreased solubility behavior of the *ortho*-substituted *N*-aroyl derivatives: the *ortho*-chloro compound **1j** and its 3-methyl analog **2j** are soluble in chloroform to less than 1% by weight/volume as opposed to the *para*-chloro compounds **1k** and **2k**, which are soluble to the extent of ~20%. Again this is attributed to the increased contribution of polar resonance form **11b** for the *ortho*-substituted compounds **1j** and **2j** relative to the *para*-substituted compounds **1k** and **2k**.

2.7. Reactivity patterns

A number of rather puzzling reactivity patterns of Reissert compounds are now explicable in terms of their stereochemistry. For example, the deuterated 3-H *N*-benzoyl Reissert compound **8f** does not exchange its deuterium atom when recrystallized from boiling ethanol, whereas the deuterated 3-CH₃ *N*-(*o*-toluyl) Reissert compound **9g** undergoes nearly 100% exchange under such conditions. The latter compound would be expected to be less acidic on purely electronic grounds because of the electron donating

character of the methyl groups. Therefore, the unexpected difference in exchange must be due to some other factor.

The acidity of H₁ or D₁ is enhanced by greater contribution of resonance form **11b**, in which the positive charge resides upon the nearby N atom. Conversely, increased contribution of resonance structure **11a** causes diminished acidity due to the greater electron density on the N. **11a** requires coplanarity of the NCOAr moiety: **11b** does not. As shown above, the H_1 analog (1f) of 8f does not exhibit hindered aryl-carbonyl rotation, but in the analog (2g) of 9g aryl-carbonyl rotation is slow. Both compounds exist predominantly in the trans amide form. Therefore, the increased acidity of 2g and deutero analog 9g relative to 1f and 8f is attributed to increased contribution of non-coplanar (aryl) resonance form **11b** due to steric hindrance in **2g**; the positively charged nitrogen in **11b** enhances the acidity of H₁. This is clear in the solid state as the amide linkage is nearly planar in ${\bf 1f}$ (dihedral 1.7°), 46 indicating an enhanced contribution from **11b**, while in **2g** the dihedral angle is 14° (Table 3), signaling a decrease in the contribution of resonance structure **11b**.

Yet another anomalous reactivity pattern is observed in the rearrangement reactions^{1,20} of **1f** and **1g** in the presence of sodium hydride. Compound **1f** readily rearranges to **12a**, while **1g** does not rearrange, even though the red color due to its anion is observed. Similarly, in the corresponding 3-methyl analogs **2f** and **2g** a striking difference was observed. *N*-Benzoyl-3-methyl compound **2f** rearranges to ketone **12b** in 89% yield even in the presence of 2 equiv of

aroyl compounds 1g, 2g, 2j), which exchange most rapidly do not rearrange as rapidly, while those which exchange most slowly (unsubstituted or *para*-substituted aroyl compounds **1f**, **2f**, **2k**) rearrange rapidly. The rearrangement results are understandable on the same grounds as the exchange results, namely the variable contributions of resonance forms **11a**. **11b**. and **11c**. The rearrangement of Reissert compounds to the 1-acylisoquinolines 12 is an intramolecular reaction⁴⁷ involving attack of the C_1 carbanion on the amide carbonyl group. This attack must occur from the equatorial disposition of the carbanion as shown in Scheme 9. A prerequisite for the reaction is rotation about the N-CO bond to put the carbonyl carbon into a position favorable for attack in a cis amide conformation, leading to the anti-periplanar configuration required^{39b} for elimination of cyanide ion. This rotation is easier if the contribution from structure **11b** is minimized; rotation in **11a** and **11c** will be relatively more facile. As noted above, ortho N-aroyl substituents reduce contributions from **11a** and **11b**, thus facilitating the tendency to rearrange. Indeed the *cis* amide isomers of **1g** and **2g** were not observed. The tendency for 1g, 2g, and 2j to rearrange slowly relative to alkylation is attributable to a higher barrier for formation of the cis amide because of their ortho-substituents, relative to non-ortho-substituted 1f, 2f, and 2k, which possess much lower barriers for formation of the cis amide geometry.

The alkylation products **3** and **4** from alkanoyl Reissert compounds such as **1a**–**1c** and **2a**–**2c** upon treatment with base readily undergo cyclization to **14** by means of intramolecular attack of the



Scheme 9. The proposed mechanism for base-promoted conversion of isoquinoline Reissert compounds to 1-acylisoquinolines, involving isomerization of the trans amide to the cis isomer.

isopropyl iodide; in the presence of 8 equiv only 15% of the alkylated product **4f** was isolated.¹⁹ In contrast, even though it too tends to rearrange to ketone **12c**, *ortho*-toluyl-3-methyl compound **2g** in the presence of 8 equiv of isopropyl iodide afforded 70% of the isopropyl compound **3g**.²⁰ Thus, the apparent ratio of the rates of rearrangement to alkylation is 6 for **2f** and 0.5 for **2g**, a factor of 10 difference caused by the *ortho*-CH₃ moiety of **2g**. In part the lower propensity of **2g** for rearrangement might be attributed to the destabilization of the intermediate anion by the electron releasing tolyl methyl group. However, the results for the *o*-Cl- and *p*-Cl-benzoyl-3-methyl derivatives **2j** and **2k** also bear on this point. It was not possible to isolate the alkylation product of the *para*-chloro **2k**; even in the presence of 8 equiv of isopropyl iodide, the ketone **12d** was isolated in 93% yield.²⁰ *ortho*-Chloro **2j**, on the other hand, afforded 47% of the alkylated product **4j** under these conditions.²⁰

The rearrangement versus alkylation results parallel the deuterium exchange rate results; the compounds (mono-*ortho*-substituted enolate anion **13** on the equatorial cyano group (Scheme 10).^{19b,48} This reaction demands that the amide group exist in the *cis* form as shown in **13**. This is consistent with the observation of interconverting *cis* and *trans* amide isomers in **2a** and **2c** in solution and the *cis* structure of **2c** observed exclusively in the solid state.



Scheme 10. The proposed mechanism for base-promoted cyclization of 1-alkyl-2-alkanoyl-1,2-isoquinaldonitriles.

A similar situation exists in the conversion of **1d** and **2d** to **10**.²¹ The anion derived from *cis* amide isomer of **1d** and **2d** is required for effective ring closure, presumably. The high yields of this transformation are consistent with a mobile $cis \rightleftharpoons trans$ equilibrium in these *N*-alkanoyl Reissert compounds as noted in the present work.

3. Experimental

3.1. General

Melting points were taken in capillaries on a Thomas-Hoover apparatus and are corrected. Elemental analyses were carried out by Spang Microanalytical Laboratories, Ann Arbor, MI and Atlantic Microlabs, Norcross, GA. Some NMR spectra were recorded on Varian A-60-4, Jeolco C-60H, and Bruker WP-80 instruments, equipped with variable temperature probes, and the temperature was calibrated using methanol. Chemical shifts are relative to tetramethylsilane internal standard. Recent spectra were recorded on Varian Unity or Inova 400/100 MHz, IEOL Eclipse 500/125 MHz or Bruker Avance III 600/150 MHz instruments. The electrosprav ionization mass spectrometry (ESI MS) was carried out on an Agilent 6220 Accurate Mass TOF LC/MS Spectrometer. X-ray crystallography was done using an Oxford Diffraction SuperNova X-ray diffractometer. Molecular modeling was carried out over the years with several different commercial molecular mechanics software packages, including Serena Software PC Model (MMX), CambridgeSoft Chem 3D (MM2), CambridgeSoft ChemBioDraw 3D (MM3) and Wave Function Mac Spartan (MM2).

3.2. Reissert compounds (1 and 2)

Most of the Reissert compounds used in this work have been previously reported.^{1,3,20} However, several new compounds were prepared by the methylene chloride procedure,² as summarized below.

3.2.1. 2-(2',6'-Dimethoxybenzoyl)-1,2-dihydroisoquinaldonitrile (**10**). Yield 88%; mp 160.5–161.5 °C (ethanol); ¹H NMR (500 MHz, CDCl₃, 25 °C): δ 3.67 (s, 2.6H), 3.70 (s, 0.4H), 3.86 (s, 2.6H), 3.89 (s, 0.4H), 5.67 (br s, 0.14H), 5.86 (d, *J*=7, 0.86H), 6.31 (d, *J*=7, 0.14H), 6.38 (d, *J*=7, 0.86H), 6.56 (d, *J*=8, 0.86H), 6.61 (d, *J*=8, 0.86H), 6.69 (d, *J*=7, 0.14H), 6.84 (br s, 0.86H), 7.06 (d, *J*=8, 0.14H), 7.13 (d, *J*=8, 0.86H), 7.2–7.5 (m, 4.3H) ppm; ¹³C NMR (125 MHz, CDCl₃, 22 °C): δ 43.8, 48.4, 55.8, 55.9, 56.0, 56.2, 104.0 (two peaks: 103.98, 104.01), 109.2, 111.2, 112.2, 116.4 (two peaks: 116.39, 116.45), 125.1, 125.6, 126.8, 128.1, 129.9, 130.4, 132.0, 156.9, 157.2, 157.3, 157.7, 164.7, 165.8 (27 peaks; expected for two amide isomers: total of 38). Anal. Calcd: C, 71.24; H, 5.03; N, 8.74. Found: C, 71.43; H, 5.00; N, 8.66.

3.2.2. 2-(*m*-Toluyl)-3-*methyl*-1,2-dihydroisoquinaldonitrile (**2h**). Yield 69%, mp 132.5–134.5 °C (ethanol); ¹H NMR (500 MHz, CDCl₃, 23 °C): δ 1.82 (s, 3H), 2.38 (s, 3H), 6.26 (s, 1H), 6.51 (s, 1H), 7.2–7.5 (m, 8H) ppm; ¹³C NMR (125 MHz, CDCl₃, 22 °C): δ 21.3, 22.0, 115.5, 116.9, 125.2, 125.5, 125.8,126.2, 127.9, 128.5, 129.0, 130.0, 131.3, 132.8, 135.0, 135.5, 138.8, 169.0 (19 peaks, as required). Anal. Calcd: C, 79.14; H, 5.59; N, 9.72. Found: C, 79.14; H, 5.57; N, 9.71.

3.2.3. 2-(ortho-Fluorobenzoyl)-3-methyl-1,2-dihydroisoquinaldonitrile (**2l**). Yield 65%, mp 166.5–168.5 °C (ethanol); ¹H NMR (500 MHz, CDCl₃, 22 °C): δ 1.85 (br s, 3H), 6.28 (s, 1H), 6.57 (br s, 1H), 7.0–7.6 (m, 8H) ppm; ¹³C NMR (125 MHz, CDCl₃, 22 °C): δ 21.4, 46.6, 116.4, 116.6 (two peaks: 116.59, 116.64), 123.7, 124.7, 125.4, 125.7, 126.2, 128.0, 129.9, 130.1, 131.1, 133.4, 134.3, 158.3, 160.4, 164.5 (19 peaks, as required, including the doublet peaks at 158.3 and 160.4 for C–F). Anal. Calcd: C, 73.96; H, 4.48; N, 9.59. Found: C, 74.19; H, 4.58; N, 9.68.

3.2.4. 2-(2',6'-Dimethylbenzoyl)-3-methyl-1,2-dihydroisoquinaldonitrile (**2n**). Yield 47%, mp 201.0–202.5 °C (ethanol); ¹H NMR (400 MHz, CDCl₃, 22 °C): d 1.50 (d, *J*=1, 2.12H), 1.73 (s, 2.12H), 1.93 (s, 0.88H), 2.38 (s, 2.12H), 2.48 (s, 0.88H), 2.56 (d, *J*=1, 0.88H), 5.46 (s, 0.31H), 6.17 (q, *J*=1, 0.70H), 6.40 (q, *J*=1, 0.30H), 6.89 (d, *J*=4, 0.88H), 6.94 (d, *J*=7, 0.30H), 7.05–7.40 (m, 6.7H, including 7.08, 0.69H) ppm; ¹³C NMR (100.6 MHz, CDCl₃, 23 °C): δ 18.2, 18.9, 19.6, 20.6, 20.9, 116.2, 116.9, 116.9, 117.5, 124.8, 125.1, 125.5, 125.9, 127.6, 128.00, 128.1, 128.5, 129.8, 130.0, 130.3, 131.1, 134.2, 135.7, 135.8, 136.6, 169.1, 169.5 ppm (27 peaks; for two isomers total of 40 possible). Anal. Calcd: C, 79.44; H, 6.00; N, 9.27. Found: C, 79.42; H, 6.04; N, 9.26.

3.2.5. 2-(2',6'-Dimethoxybenzoyl)-3-methyl-1,2-dihydroisoquinaldonitrile (**20**). Yield 44%, mp 182.5–183.5 °C (ethanol); ¹H NMR (400 MHz, CDCl₃, 23 °C): δ 1.67 (s, 1.65H), 2.55 (s, 1.35H), 3.28 (s, 1.65H), 3.64 (s, 1.35H), 3.89 (s, 1.65H), 3.93 (s, 1.35H), 5.59 (s, 0.46H), 6.16 (br s, 0.54H), 6.33 (br s, 0.46H), 6.41 (d, *J*=8, 0.54H), 6.57 (d, *J*=8, 0.54H), 6.60 (d, *J*=8, 0.54H), 6.67 (d, *J*=8, 0.46H), 6.99 (s, 0.54H), 6.99 (d, *J*=8, 0.46H), 7.10–7.45 (m, 4.5H), including 7.40 (t, *J*=8, 0.54H) ppm; ¹³C NMR (100.6 MHz, CDCl₃, 23 °C): δ 20.59, 20.69, 45.1, 49.6, 55.4, 55.8, 56.0 (two peaks: 55.96, 55.97), 103.6, 104.0 (two peaks: 103.96, 104.03), 116.1, 116.4, 116.7, 117.3, 124.6, 124.8, 125.1, 125.9, 126.3, 126.7, 127.2, 127.6, 129.5, 129.8, 131.5, 132.0, 134.7, 137.1, 157.0, 157.3, 157.4, 157.8, 165.0, 165.5 ppm (35 peaks; for two isomers total of 40 possible). Anal. Calcd: C, 71.84; H, 5.43; N, 8.38. Found: C, 71.83; H, 5.39; N, 8.39.

3.2.6. 2-(2'-Chloro-6'-fluorobenzoyl)-3-methyl-1,2-dihydroisoquinal*donitrile* (**2p**). Yield 83%, mp 211.5–212.0 °C (ethanol); ¹H NMR (500 MHz, CDCl₃, 23 °C): δ 1.72 (br s, 1.4H), 1.74 (d, *J*=1, 1.0H), 2.54 (d, *J*=1, 0.37H), 2.56 (br s, 0.26H), 5.48 (br s, 0.09H), 5.50 (br s, 0.12H), 6.27 (br s, 0.34H), 6.29 (br s, 0.45H), 6.43 (br s, 0.12H), 6.45 (br s, 0.09H), 6.94 (s, 0.33H), 6.96 (s, 0.46H), 7.0–7.6 (m, 7H) ppm; ¹³C NMR (125 MHz, CDCl₃, 23 °C): δ 20.1, 20.3, 20.8, 21.0, 45.2, 49.7, 114.4, 114.6, 114.7, 114.9, 115.2, 115.4, 116.6 (two peaks: 116.59, 116.61), 116.6, 117.9, 118.0, 118.1, 118.2, 124.6, 124.7, 124.8, 124.9, 125.0, 125.3, 125.4, 125.5 (three peaks: 125.48, 125.51, 125.53), 125.6, 125.7, 126.0 (three peaks: 125.95, 126.00, 126.03), 126.2 (two peaks: 126.22, 125.25), 126.4, 128.0 (two peaks: 127.97. 128.01), 128.3, 130.1, 130.4, 130.5, 130.8, 130.9, 131.0, 132.1 (two peaks: 132.10, 132.14), 132.2, 132.3 (two peaks: 132.28, 132.31), 132.4, 132.5, 132.6, 133.6 (two peaks: 133.56, 133.60), 157.9, 158.9, 160.0, 160.9, 161.7, 161.8 (C-F doublets at 157.9/160.0 and 158.9/160.9) ppm (62 peaks; for four isomers total of 76 possible including C-F doublets); ¹⁹F NMR (376 MHz, CDCl₃, 23 °C): δ –113.43 (t, *J*=7, 0.37F), –112.18 (t, *J*=7, 0.10F), -111.99 (t, J=7, 0.11F), -111.51 (t, J=7, 0.42F). Anal. Calcd: C, 66.16; H, 3.70; N, 8.57. Found: C, 65.88; H, 3.84; N, 8.71. ESI MS: m/z 300.0605, 100% [M-CN]⁺; 327.0686 [M+H]⁺; calcd for M=C₁₈H₁₂ClFN₂O: m/z [M-CN]⁺, 300.0586, error 6.3 ppm; m/z[M+H]⁺, 327.0700, error 4.2 ppm.

3.2.7. 2-(2'-Chloro-6'-methylbenzoyl)-3-methyl-1,2-dihydroisoquinal*donitrile* (**2q**). Yield 88%; mp 207.4–208.1 °C (ethyl acetate); ¹H NMR (500 MHz, CDCl₃, 23 °C): δ 1.58 (d, *J*=1, 1.11H), 1.69 (d, *J*=1, 1.01H), 1.80 (s, 1.01H), 2.02 (s, 0.42H), 2.46 (s, 1.11H), 2.53 (s, 0.46H), 2.58 (d, *J*=1, 0.46H), 2.60 (d, *J*=1, 0.42H), 5.41 (br s, 0.14H), 5.52 (br s, 0.15H), 6.25 (br s, 0.72H), 6.41 (br s, 0.15H), 6.46 (br s, 0.13H), 6.98 (br s, 0.14H), 6.99 (s, 0.15H), 7.02 (br m, 0.34H), 7.04 (br m, 0.37H), 7.06 (b, 0.37H), 7.08 (br m, 0.46H), 7.09 (b, 0.34H), 7.1–7.5 (m, 7H) ppm; ¹³C NMR (125 MHz, CDCl₃, 23 °C): δ 18.4, 19.2, 19.3, 19.9, 20.2, 20.6 (two peaks: 20.59, 20.62), 21.0, 44.6, 44.9, 49.6 (two peaks: 49.56, 49.63), 115.8, 116.2, 116.6, 117.0, 117.5, 117.8 (three peaks: 117.79, 117.82, 117.83), 124.8, 125.2, 125.3, 125.5 (two peaks: 125.46, 125.47), 125.7, 125.9, 126.0, 126.1, 126.2, 127.2, 127.5, 127.8, 127.9 (two peaks: 127.87, 127.90), 128.2, 128.4, 128.7, 129.0, 129.1, 129.6, 130.0, 130.2, 130.3, 130.4, 130.8, 130.9 (two peaks 130.89, 130.90), 131.0 (two peaks: 130.97, 130.99), 131.3, 132.0, 133.1, 133.9, 135.3, 136.7, 138.4, 166.2, 166.3 ppm (59 peaks; for four isomers total of 76 possible). Anal. Calcd for C₁₉H₁₅ClN₂O: C, 70.70; H, 4.68; N, 8.68. Found: C, 70.67; H, 4.65; N, 8.81.

3.2.8. 2-*Ethoxycarbonyl*-3-*methyl*-1,2-*dihydroisoquinaldonitrile* (**2r**). Yield 36%, mp 46.5–49.0 °C (hexane); ¹H NMR (500 MHz, CDCl₃, 22 °C): δ 1.33 (t, *J*=7, 3H), 2.34 (d, *J*=1, 3H), 4.27 (16-line AB of ABX₃, *J*_{AB}=7.5, *J*_{Ax}=*J*_{Bx}=10, ν _A=4.24, ν _B=4.31, 2H), 6.17 (br s, 1H),

6.43 (s, 1H), 7.14 (d, *J*=8, 1H), 7.22–7.27 (m, 2H), 7.31–7.37 (m, 1H) ppm; 13 C NMR (125 MHz, CDCl₃, 23 °C): δ 14.4, 21.4, 47.5, 63.3, 114.6, 117.0, 125.0, 125.5 (two peaks: 125.48, 125.54), 127.5, 129.9, 131.3, 135.2, 152.7 (14 peaks, as required). Anal. Calcd: C, 69.40; H, 5.82; N, 11.57. Found: C, 69.48; H, 5.79; N, 11.63.

3.2.9. 2-Benzyloxycarbonyl-3-methyl-1,2-dihydroisoquinaldonitrile (**2s**). Yield 41%, mp 72.5–74.5 °C (ethyl acetate-hexane); ¹H NMR (500 MHz, CDCl₃, 22 °C): δ 2.31 (br s, 3H), 5.22 (AB q, J_{AB} =10, ν_A =5.19, ν_B =5.26, 2H), 6.17 (br s, 1H), 6.44 (s, 1H), 7.14 (d, *J*=8, 1H), 7.20–7.26 (m, 2H), 7.31–7.43 (m, 6H) ppm; ¹³C NMR (125 MHz, CDCl₃, 23 °C): δ 21.4, 47.6, 69.0, 114.9, 116.9, 125.1, 125.5, 127.6, 128.5, 128.7 (two peaks: 128.71, 128.74), 130.0, 131.2, 135.0, 135.1, 152.6 (16 peaks, 17 required). Anal. Calcd: C, 74.98; H, 5.30; N, 9.21. Found: C, 74.86; H, 5.26; N, 9.12.

3.3. Deuteration of Reissert compounds (9)

The following is a representative procedure. A solution of 1.30 g (5.00 mmol) of **1f** and 0.35 mL (5.8 mmol) of CS₂ in 10 mL of DMF was treated with 0.42 g (5.0 mmol) of 30% NaH in mineral oil. The solution turned red-orange. After it had been stirred for 45 min, the solution was poured into 18 mL (0.90 mol) of D₂O with stirring. The solid **8f** was filtered and dried (1.2 g, 92%) and recrystallized from ethanol, mp 126–128 °C (reported 124–125 °C,^{2d} 125–126 °C^{2c} for the H-analog **1f**). Note that some deuterated Reissert compounds revert to the protonated form upon recrystallization from ethanol; these compounds were recrystallized from hexane/ethyl acetate.

3.4. Growth of single crystals

Single crystals of the Reissert compounds suitable for diffractometry were grown by slowly cooling hot solutions in hexane/ ethyl acetate.

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Supplementary data

¹H NMR spectra of **1c**, **1f**, **1o**, **2c**, **1m**, **2m**, **2n**, **2r**, **2s**, **7**, **8f**, **9m**, and **9n**; low temperature ¹H NMR spectra of **2j**, **2l**, and **2m**; ¹³C NMR spectra of **1o**, **2n**, **2o**, **2p**, and **2q**; ¹⁹F NMR spectrum of **2p**; COSY results for **1o**, **2m**, and **2r**; HMBC results for **1o**; tables of ASIS results, low temperature ¹H NMR results and solid state packing parameters. Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2012.06.008.

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- Although in substituted cyclohexanes, the methyl group is 'larger',^{39a} because the longer C-Cl bond places the Cl atom further from neighboring pseudo-axial protons relative to the shorter C–C bond in the methyl analog, comparison of the rotational barriers of C-C bonds reveals that the chlorine atom exerts a larger impediment than the methyl group, e.g., *n*-propane (3.4 kcal/mol)^{39b} versus chloroethane (3.56 kcal/mol)⁴⁰ and 1-chloro-3,3-dimethylbutane versus 2,3,3-trimethylbutane (0,90 kcal/mol difference).⁴¹ Likewise, in terms of atropisomerism due to aryl-N rotation in N-arylsuccinimides⁴² and 3arylhydantoins the aryl-N rotational activation energy is higher (by 0.7-1. 5 kcal/mol⁴³) for the ortho-Cl compound than the ortho-methyl analog. Moreover, in diastereomeric (5S)-methyl-3-aryl-2,4-oxazlinediones the orthochloro compound produces 58.8% (ΔG =0.210 kcal/mol) of the major diastereomer, while the ortho-methyl analog yields 57.0% (ΔG =0.167 kcal/mol) of the analogous diastereomer.⁴⁴ On this basis Cl is considered to be 'larger' than methyl
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