ARTICLE

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Synthesis and conformational properties of 2,6-bis-anilino-3-nitropyridines†

Sylvia Schmid,[a] Martin Röttgen,[a] Ulf Thewalt[b] and Volkhard Austel*[a]

[a] *Universität Ulm, Abteilung Organische Chemie II, Albert-Einstein-Allee 11, 89081, Ulm, Germany. E-mail: volkhard.austel@chemie.uni-ulm.de*

[b] *Universität Ulm, Sektion Röntgen- und Elektronenbeugung, Albert-Einstein-Allee 11, 89081, Ulm, Germany*

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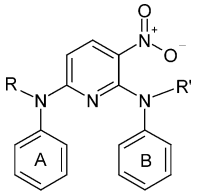
The synthesis of 2,6-bis-anilino-3-nitropyridines that are alkylated or acylated at the anilino nitrogen atoms is described. These derivatives show characteristic differences in the ^{1}H-NMR spectra compared with the unsubstituted parent compound. These differences are used to determine structure–conformation relationships of this type of compounds. The conclusions drawn from the ^{1}H-NMR spectra in this respect are supported by X-ray crystallographic data and by ^{1}H-NMR data of conformationally restricted analogues. Preliminary investigations indicate that these relationships can in principle be extended to other diarylamines.

Introduction

Molecular scaffolds from which molecules of diverse physical-chemical and conformational properties can be derived *via* convenient synthetic procedures are interesting for material science as well as for medicinal chemistry. In the former case they can serve as building blocks for oligomers with specific molecular architecture which, depending on the type and position of functional groups, allows them either to recognize guest molecules or to undergo self-assembly to form supramolecular structures. In medicinal chemistry, such molecular scaffolds are useful for creating spatial arrangements of structural moieties that are specifically recognized by biological targets.

Under these considerations we became interested in compounds of type **1** that are derived from 2,6-bis-anilino-3-nitropyridine as the basic scaffold.



1

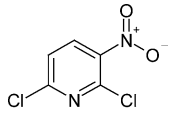
Functional groups that are needed for intermolecular interactions can be connected to this scaffold as part of the residues R and R′ or of substituents on the phenyl rings. Oligomers can be formed *via* diamino derivatives of **1** that carry one amino group in each of the phenyl rings.

As a basic requirement for applying this scaffold to the purposes mentioned above, suitable synthetic routes as well as the dependence of the conformational preferences on the substituents R and R′ have to be known. Both aspects are discussed in this paper.

Results and discussion

Synthesis

To our knowledge, only the parent 2,6-dianilino-3-nitropyridine (**2**) (along with the corresponding bis-(2-pyridyl)amino derivative) has so far been reported in the literature.[1] It was obtained as a side product from the reaction of 2,6-dichloro-3-nitropyridine (**3**) with aniline.

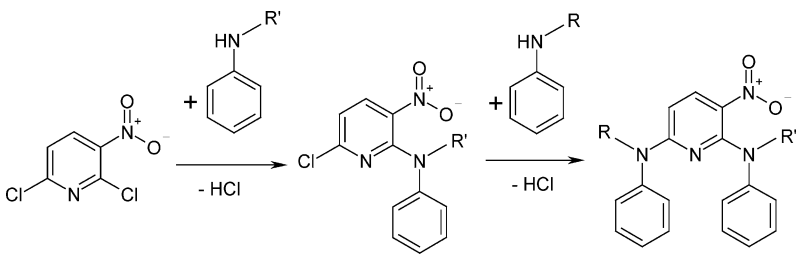


3

In principle, all compounds of type **1** in which R and R′ represent either H or alkyl substituents should be accessible from **3** following this procedure by using an excess of the corresponding aniline (for R = R′) or by introducing the corresponding *N*-substituted anilino groups in two consecutive steps (Scheme 1). The latter procedure should be viable without difficulty since a great preference for exchange of Cl-2 over Cl-6 was observed not only for primary[1] but also for secondary anilines.[2]

The first step of this sequence occurs readily and gives pure compounds in good yields.[1,2] The same does not apply to the second step except for R′ = H. In all cases which we have investigated harsh conditions such as using aniline as a solvent in addition to high temperatures were needed. The products were difficult to purify and were obtained at best in low yields. The

† Part of the PhD thesis of Sylvia Schmid, University of Ulm, 2005.



Scheme 1 Conceivable synthesis strategy for compounds of type **1**.

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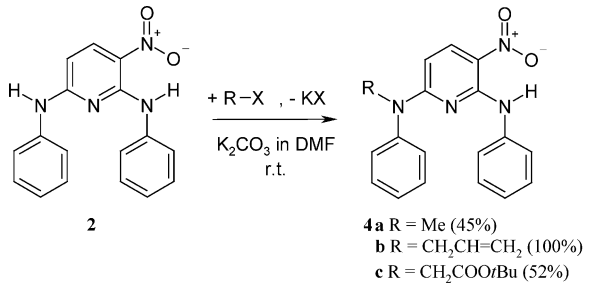
procedure failed completely if secondary anilines were used in the second step (even in the case of R′ = H).

Therefore, alternative syntheses had to be searched for. We found that **2** can be selectively alkylated at the nitrogen of the 6-anilino group (Scheme 2).



2

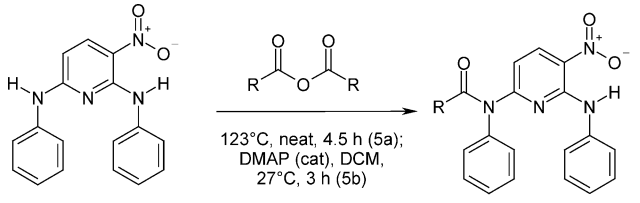
4a R = Me (45%)
b R = $CH_2CH{=}CH_2$ (100%)
c R = CH_2COO*t*Bu (52%)

Scheme 2 Mono-alkylation of **2**.

Using DMSO as a solvent in this reaction sometimes turned out to be problematic when alkyl bromides were used. For example, in experiments with *tert*-butyl bromoacetate we observed formation of significant amounts of products that were brominated in 5-position of the pyridine or in the anilino groups.[3]

The observed selectivity of the alkylation is explicable if one assumes the reactive species to be the anion derived from 2 by deprotonation of the 6-anilino nitrogen (*N*-6). This anion should be more favourable than the one formed on deprotonation of the 2-anilino nitrogen (*N*-2) because it does not require breaking of a hydrogen bond. Semi-empirical calculations (AM1, convergence limit = 0.01) support this view by showing that the *N*-6-derived anion is more favourable by 8 kcal mol^{-1}.

Acylation shows the same selectivity as alkylation: treating **2** with acetic anhydride or with di-*tert*-butyl dicarbonate and 4-*N*,*N*-dimethylaminopyridine (DMAP) yielded the corresponding *N*-6-acyl derivatives **5** (Scheme 3).



2

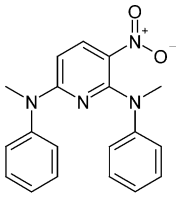
5a R = Me (59%)
b R = O*t*Bu (75%)

Scheme 3 Mono-acylation of **2**.

Since this acylation is probably a thermodynamically controlled process the selectivity has to be attributed to the higher stability of the *N*-6 acyl isomers which retain the hydrogen bond. In an AM1 calculation the *N*-6 acyl derivative **5a** is favoured over its *N*-2 isomer by 4 kcal mol^{-1}.

N-2 Mono alkylated derivatives can be prepared in two ways depending on whether the corresponding alkyl halide is stable towards strongly alkaline conditions or not. In the former case one starts from **2** which is selectively protected at *N*-6 by a *tert*-butoxycarbonyl group (**5b**) and subsequently alkylated at *N*-2 in the presence of strong base followed by deprotection (Scheme 4).

Compounds of type **1** in which *N*-2 and *N*-6 carry the same alkyl group can be synthesized directly from **2** using a stronger base. Thus the bis-methyl derivative **8** was prepared from **2** and methyl iodide in DMF with KO*t*Bu as an auxiliary base.



8

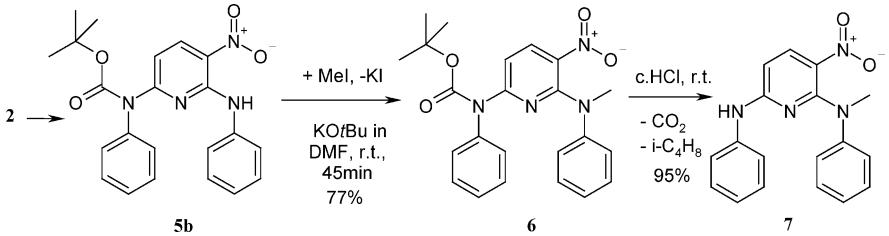
If the alkyl halide is unstable under such conditions (*e.g.* benzyl bromide) the 2-alkyl derivatives may be accessible from **9** and the corresponding *N*-alkyl aniline (Scheme 5).

However, due to the selectivity of the chlorine exchange mentioned above, **9** cannot be prepared directly from **3** and aniline. The selectivity may, however, be reversed if the attacking nucleophile is an anion.[4] Therefore, the sodium salt of *N*-*tert*-butoxycarbonyl-aniline (**11**) was reacted with **3**. An NMR spectrum of the crude product revealed that a 7 : 3 mixture of the 6-(**12**) and the 2-(**13**) substitution products was formed. After deprotection, we were able to separate the two isomeric anilino-3-nitropyridines (**9**, **14**) by column chromatography (Scheme 6).

Interestingly, under the conditions used for the nucleophilic replacement of the chlorine of **9**, compound **12** reacted considerably more slowly.

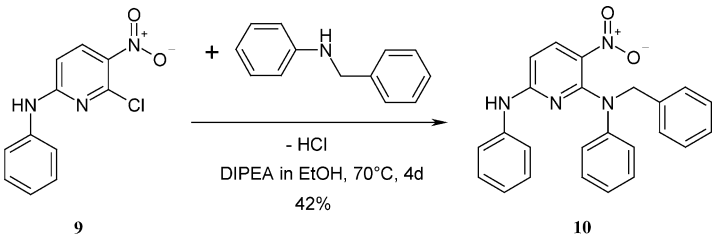
Conformational properties

On alkylation as well as on acylation of **2**, characteristic changes in the ^{1}H-NMR spectra were observed that differ for *N*-2



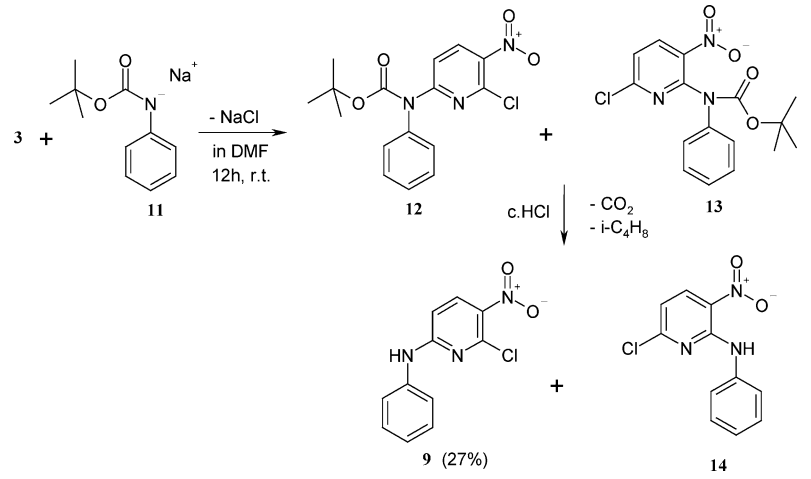
2 **5b** **6** **7**

Scheme 4 Synthesis strategy for *N*-2 mono-alkylation products of **2**.



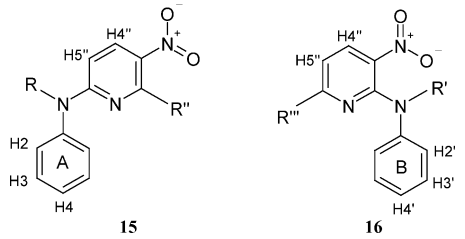
9 **10**

Scheme 5 Alternative synthesis strategy for *N*-2 mono-alkylation products of **2**.



Scheme 6 Synthesis strategy for 6-anilino-2-chloro-3-nitropyridine.

alkylation, *N*-6 alkylation, and *N*-6 acylation. These changes can be appreciated by inspection of the chemical shifts compiled in Table 1 for *N*-6 derivatives (general structure **15**) and in Table 2 for *N*-2 derivatives (general structure **16**).



Alkylation

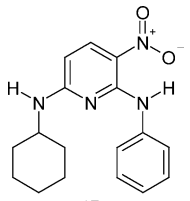
Alkylation of the parent 2,6-bis-anilino-3-nitropyridine (**2**) at *N*-6 shifts the signal of H5″ consistently up-field by approximately 0.4 ppm (compare **4a**, **4c**, **4d** with **2**, in Table 1). Concomitantly, the signals of H3 and H4 are shifted downfield by about 0.3 ppm and 0.4 ppm respectively whereas the *ortho* hydrogens (H2) experience a moderate up-field shift (around 0.15 ppm). These changes seem to be independent of the particular substituent R″ (compare **7** with **8** and **9** with **15a** in Table 1).

The pattern of changes of the phenyl signals are explicable if the conformational states that prevail in **2** are those in which the angle between the planes of the pyridine and the phenyl deviate at most moderately from co-planarity. In these conformations the H2 are shifted down-field by the anisotropy effect of the pyridine. Moreover, there is considerable conjugation of the *N*-6 lone electron pair with both the pyridine and phenyl A. On alkylation, phenyl A twists out of conjugation with the *N*-6 lone pair. The associated decrease in electron density is reflected in the observed down-field shift of the H3 and H4 signals. Since the pyridine ring remains in conjugation with the lone pair of *N*-6, the planes of the two rings prefer an approximately perpendicular orientation with respect to each other. Consequently, the H2 become shielded by the pyridine. Apparently, this latter effect more than compensates for the electronic effect and hence a moderate net up-field shift of these hydrogens remains.

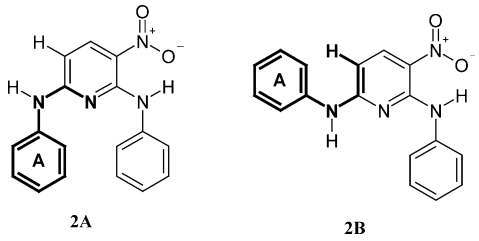
Regarding the discussed conformational change, the up-field shift of H5″ can have two conceivable causes:

1. an increase in conjugative electron release from *N*-6 to the pyridine,
2. a shielding by the phenyl, or combinations of these effects.

A major contribution from the first effect can be ruled out since exchanging the 6-anilino group of **2** for the much more electron releasing cyclohexylamino group (**17**) causes an up-field shift of H5″ of only 0.25 ppm (as compared to 0.39 ppm on *N*-6 methylation of **2**).

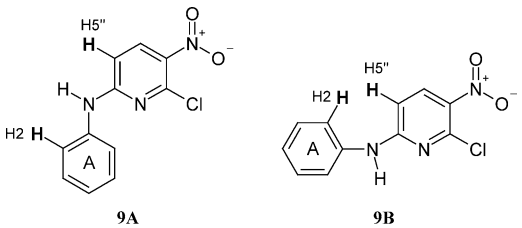


Therefore, the up-field shift of H5″ must be caused by a shielding effect from phenyl A. This would imply that in the parent compound **2** conformation **2A** (Scheme 7) in which phenyl A faces the ring nitrogen is preferred over **2B**.



Scheme 7 Conformational states of **2** with respect to the 6-anilino group.

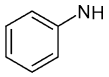
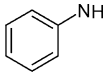
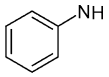
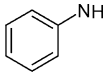
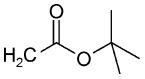
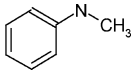
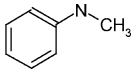
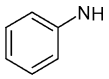
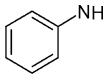
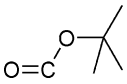
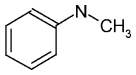
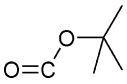
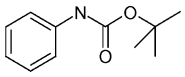
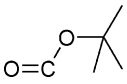
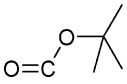
This conclusion is supported by a comparison of the chemical shifts of H5″ and H2 of **9** (Scheme 8). If the preferred conformation were to correspond to **9B** both protons would be subject to similar shielding effects and H5″ being bound to a more electronegative aromatic system ought to appear at lower field than H2. In reality the opposite is observed (H5″: 6.88 ppm; H2: 7.63 ppm).



Scheme 8 Conformational states of **9** with respect to the anilino group.

Therefore, the predominant conformation must be the one represented by **9A**. As discussed before, in this conformation H2 experiences a strong deshielding effect from the pyridine ring which is responsible for the considerable difference in chemical shift with respect to H5″. According to the observation that the changes in the pattern of chemical shifts and therefore in the conformational properties around position 6 do not depend on

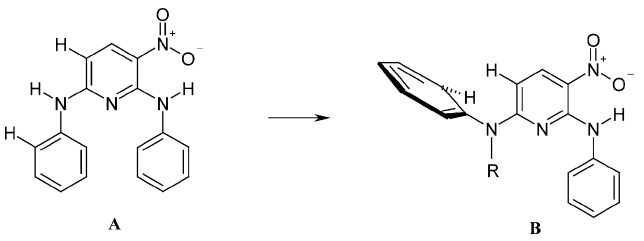
Table 1 Chemical shifts in ppm of the pyridine and anilino hydrogens of compounds of type **15**

No.	R″	R	H2	H3	H4	H4″	H5″
2		H	7.51	7.18	7.02	8.23	6.35
4a		CH_3	7.36	7.52	7.41	8.15	5.96
4b			7.33	7.50	7.40	8.15	5.90
4c			7.39	7.53	7.42	8.18	5.88
7		H	7.64	7.29	7.00	8.06	6.40
8		CH_3	7.40	7.51	7.36	7.93	5.94
9	Cl	H	7.63	7.37	7.10	8.31	6.88
15a	Cl	CH_3	7.40	7.54	7.40	8.18	6.36
5a			7.39	7.56	7.53	8.58	7.61
5b			7.25	7.49	7.45	8.56	7.51
6			7.25	7.42	7.32	8.20	7.40
15b			7.01	7.28	7.28	8.52	7.85
12	Cl		7.23	7.43	7.34	8.58	7.92

the substituent in position 2, structure **2A** in Scheme 7 must represent the preferred conformation of **2**.

On methylation of *N*-6, phenyl A is repositioned in such a way that H5″ becomes located directly above phenyl A and is therefore shifted to considerably higher field. Concomitantly, H2 moves from the deshielding zone into the shielding cone of the pyridine. However, because of the loss of electron density in phenyl A the observed net up-field shift is less than that for H5″.

In summary, alkylation of *N*-6 shifts the equilibrium between conformations of types **A** and **B** in the direction of the latter and thereby also changes the relative orientation of the pyridine and the phenyl rings from an approximately co-planar to a more perpendicular one (Scheme 9).



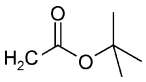
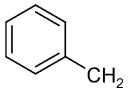
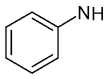
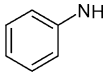
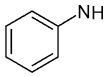
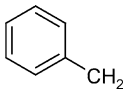
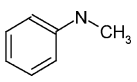
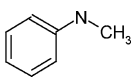
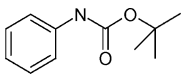
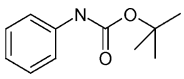
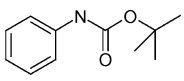
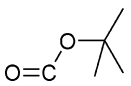
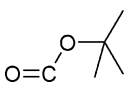
Scheme 9 Conformational changes on *N*-6 alkylation.

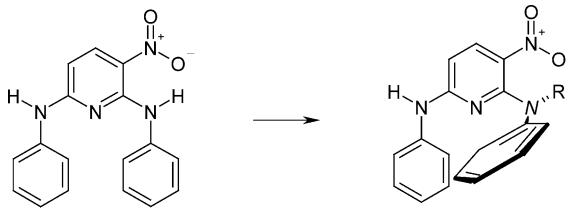
Table 1 shows that the NMR effects of *N*-6-alkylation hardly vary with the nature of the alkyl group (this even holds for aryl groups; unpublished results).

Alkylation of *N*-2 has quite different consequences. In this case the most significant change is an up-field shift of 0.45–0.58 ppm of the *ortho* hydrogens of phenyl B (H2′) (see Table 2). Significant up-field shifts are also observed for H4″. The remaining hydrogen atoms undergo smaller up-field shifts.

In the *N*-unsubstituted state, the 2-anilino group is hydrogen bonded to the nitro group as is demonstrated by a shift of δ = 10.59 ppm (in DMSO) for the 2-NH-hydrogen of **2**. Therefore, the phenyl ring must point towards the ring nitrogen. In addition, from the position of the H2′ signals (δ = 7.57 ppm in DMSO) it can be concluded that the phenyl and the pyridine rings are approximately co-planar (conformation **A** in Scheme 10). On alkylation, such a conformation is no longer possible because of repulsive forces between the alkyl and the nitro groups. The same would apply to a conformation analogous to **B** in Scheme 9 which is prevented by a repulsion between the nitro and the phenyl groups. Therefore, phenyl B must be located above (or below) the pyridine ring. As a consequence, the H2′ hydrogens could now be shielded instead of deshielded by the pyridine and therefore their signals are shifted up-field. But this shift is larger than that of the H2 hydrogens

Table 2 Chemical shifts in ppm of the pyridine and anilino hydrogens of compounds of type **16**

No.	R‴	R′	H2′	H3′	H4′	H4″	H5″
14	Cl	H	7.59	7.40	7.18	8.53	7.00
16a	Cl	CH_3	7.14	7.30	7.14	8.16	7.06
16b	Cl		7.14	7.31	7.16	8.20	7.11
16c	Cl		7.13	7.25	7.08	8.18	7.10
2		H	7.57	7.37	7.22	8.23	6.35
7		CH_3	7.08	7.29	7.08	8.06	6.40
10			7.01	7.23	7.06	8.06	6.40
4a		H	7.63	7.29	7.09	8.15	5.96
8		CH_3	7.05	7.26	7.05	7.93	5.94
5b		H	7.00	6.96	6.91	8.56	7.51
6		CH_3	6.97	7.23	7.05	8.20	7.40
15b			6.97	7.20	7.20	8.52	7.85
13	Cl		7.31	7.42	7.31	8.59	7.69



A **B**

Scheme 10 Conformational changes on *N*-2 alkylation.

on *N*-6 alkylation. Also unlike hydrogen atoms H3 and H4, H3′ and H4′ are not shifted down-field, indicating that the electron density in the phenyl ring does not change significantly. Apparently, the electron release from the *N*-2 lone pair remains more or less unaffected. This is probably a result of two opposing effects: in order to adopt the new spatial arrangement, both the pyridine and phenyl B rotate so that the overlap of their π-systems with the nitrogen lone pair decreases which would reduce the electron density in both rings. On the other hand the steric repulsion discussed above also twists the nitro group to a certain extent out of conjugation with the pyridine π-system. This effect reduces the electron withdrawing character of the pyridine ring and therefore its competition for the lone electron pair on *N*-2 which therefore becomes more available for phenyl B. The resulting increase in electron donation by *N*-2 apparently compensates for the effects of the reduced conjugation. A similar compensation seems to hold for the pyridine ring and would explain why the signal of H5″ is not shifted down-field. The twist of the nitro group makes itself also noticed by the significant up-field shift of H4″.

Taken together, the NMR data indicate that *N*-2 alkyl derivatives of **2** favour conformational states in which the plane of the phenyl group is positioned above the plane of the pyridine ring and in which both planes are twisted considerably with respect to each other (**B** in Scheme 10).

Acylation

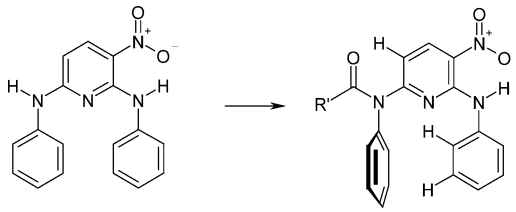
The effect of *N*-6 acylation (entries **5a** and **5b** in Table 1) on the hydrogen signals of phenyl A resembles that of *N*-6 alkylation. There is, however, a significant difference in the effects on the pyridine hydrogens. These are both shifted down-field, H5″ by as much as 1.2 ppm. Contrary to *N*-6 alkylation which leaves the signals of the hydrogen atoms of phenyl B virtually unaffected,

N-6 acylation leads to remarkable up-field shifts of these signals (0.57, 0.41, and 0.31 ppm for H2′, H3′, and H4′ respectively; compare entry **5b** in Table 2 with entries **2** and **4a**).

The down-field shift of H5″ may be attributed to an anisotropy effect of the newly introduced carbonyl group which therefore must be positioned in the plane of the pyridine ring and point towards H5″. This would place the phenyl ring next to the pyridine nitrogen. For steric reasons and because of the stronger conjugational interaction of the carbonyl and of the pyridine with the *N*-6 lone pair, phenyl A ought to adopt a more or less perpendicular position with respect to these two groups. The down-field shift of hydrogens H3 and H4 is a consequence of the corresponding loss of conjugation with the *N*-6 lone pair and the electronegative effect of the carbonyl group whereas the up-field shift of the H2 signal is due to an overcompensation of these effects by the loss of deshielding from the pyridine and a shielding from both the pyridine and the carbonyl group.

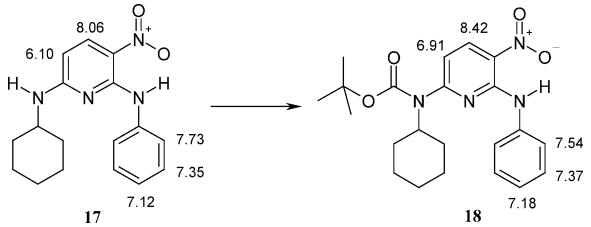
The spatial arrangement of the 6-*N*-acylanilino group also makes the unusual changes in the shift of the hydrogens of phenyl B understandable. As mentioned earlier, the conformational situation in position 2 of the 2-anilino-3-nitropyridines is largely independent of the substituents in position 6. Therefore, it can be safely assumed that phenyl B is approximately co-planar with the pyridine ring. Consequently, the H2′ and H3′ hydrogens lie in the shielding zone above the *N*-6 phenyl group. H4′ may still experience some of this shielding effect resulting in the observed up-field shift.

In conclusion, *N*-6-acylation of 6-anilino-3-nitropyridines affects almost exclusively the torsion around the bond from the nitrogen to phenyl A favouring a class of conformations in which the plane of this ring is approximately perpendicular to the plane of the pyridine (Scheme 11).



Scheme 11 Conformational changes on *N*-6 acylation.

In order to test the validity of these conclusions we compared the changes in chemical shifts on *tert*-butoxycarbonylation of the *N*-6 cyclohexyl analogue **17** of **2** yielding **18**, the corresponding analogue of **5b** (Scheme 12).



Scheme 12 Conformational changes on *N*-6 acylation of the *N*-6 cyclohexyl analogue of **2**.

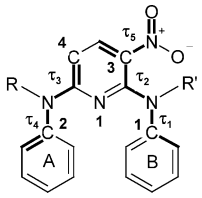
The changes in chemical shifts of the H4″ and H5″ signals of 0.36 ppm and 0.81 ppm respectively are comparable (0.33 and 1.16 ppm for **2** → **5b**) indicating that the *N*-acyl-cyclohexylamino group of **18** has the same spatial orientation as the *N*-acyl-anilino group of **5b**. However, the up-field shift of the phenyl B hydrogens is absent in **18** which supports the explanation for the up-field shifts in **5b** as being caused by a shielding effect from phenyl A.

Acylation of the 2-anilino nitrogen leads to a pronounced down-field shift of the H5″ signal whereas the H4″ signal is more or less unaffected. In the case of the 6-chloro derivative **13** the H2′ signals are shifted moderately up-field and the H3′ and H4′ signals slightly down-field (compare **14** and **13** in Table 2). With the *N*-6 *tert*-butoxycarbonylanilino derivative **15b**, the H2′ signal is virtually unaffected whereas the three remaining protons appear at somewhat lower field (compare **5b** and **15b** in Table 2). By analogy with the *N*-6 acyl derivatives, phenyl B is probably oriented perpendicular to the carbonyl group but the available data do not allow any significant further conclusions.

The structure–conformation relationships discussed so far were based only on solutions in DMSO. In order to test a possible dependence of these relationships on the solvent, a number of the DMSO spectra were compared with their counterparts in $CDCl_3$ solution. Tables 3 and 4 list the changes in chemical shifts in DMSO (upper entries) and in $CDCl_3$ (lower entries) observed on replacing a proton on one of the anilino nitrogens by an alkyl or an acyl group. A comparison shows that these changes go in the same direction in both solvents which suggests that the conformational properties are to a first approximation independent of the solvent.

X-Ray crystallography‡

The explanations given above for the changes in chemical shifts caused by substitution at the anilino-nitrogens of 2- and 6-anilino-3-nitropyridines are quite consistent. Nevertheless, additional support from independent experiments would be desirable. Therefore, we investigated the conformation of three representatives of general structure **19** by X-ray crystallography.



19

R = CH_2COO*t*Bu, R′ = H (**4c**);
R = H, R′ = Me (**7**);
R = COO*t*Bu, R′ = H (**5b**)

Even though the results may to some extent reflect packing effects, the observed conformations can at least be considered a realistic possibility.

Fig. 1 which shows a stereo view of compound **4c** demonstrates that the whole 2-anilino group, the pyridine ring, and the nitro group are virtually co-planar ($\tau_1 = 173°$, $\tau_2 = 180°$, $\tau_5 = -1°$) and that phenyl B points towards the ring nitrogen ($d_{C1–N1} = 2.95$ Å, $d_{C1–C3} = 3.79$ Å).

Phenyl A is oriented away from the ring nitrogen ($d_{C2–C4} = 2.86$ Å, $d_{C2–N1} = 3.64$ Å) and its plane is perpendicular to those of the pyridine ring ($\tau_4 = 92°$) and of the three atoms attached to *N*-6 whereas the pyridine ring remains in this plane ($\tau_3 = -2°$). The conformation in the crystal is therefore the same as that inferred from the NMR data.

A similarly good agreement is observed for compound **7** (Fig. 2).

As deduced from the NMR spectra for *N*-6 unsubstituted compounds, phenyl A points towards the ring nitrogen and does not deviate very much from co-planarity with the pyridine ring and the plane of the three atoms attached to *N*-6 ($d_{C2–N1} = 2.93$ Å, $d_{C2–C4} = 3.74$ Å, $\tau_3 = 174°$, $\tau_4 = 157°$). Both rings are therefore conjugated with the lone electron pair on *N*-6. Phenyl B points more to the side of the nitro group ($d_{C1–N1} = 3.57$ Å, $d_{C1–C3} = 3.03$ Å) and is positioned above (or below) the plane of the pyridine ring ($\tau_2 = -148°$). This orientation places one of the H2′ hydrogens above the pyridine ring and

‡ CCDC reference numbers 243005 (**4c**), 243006 (**7**), and 243007 (**5b**). See http://dx.doi.org/10.1039/b508819b for crystallographic data in CIF or other electronic format.

Table 3 Changes in chemical shifts in DMSO (upper entry) and $CDCl_3$ (lower entry) of the pyridine and anilino hydrogens of compounds of type **15** on replacing H by R

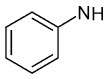
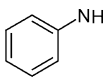
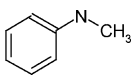
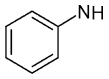
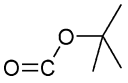
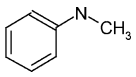
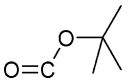
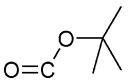
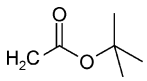
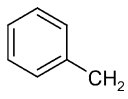
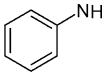
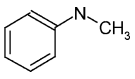
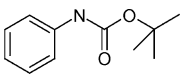
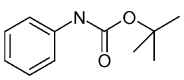
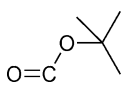
No.	R″	R	H2	H3	H4	H4″	H5″
4a		CH_3	−0.15	0.34	0.39	−0.08	−0.39
			−0.12	0.17	0.20	−0.20	−0.32
4d			−0.18	0.33	0.39	−0.06	−0.44
			−0.13	0.15	0.20	−0.19	−0.37
8		CH_3	−0.24	0.22	0.36	−0.13	−0.46
			−0.10	0.11	0.16	−0.16	−0.34
15a	Cl	CH_3	−0.23	0.17	0.31	−0.13	−0.52
			−0.09	0.06	0.13	−0.21	−0.46
5b			−0.26	0.31	0.43	0.33	1.16
			−0.19	0.16	0.26	0.17	1.43
6			−0.39	0.13	0.32	0.14	1.00
			−0.26	0.04	0.16	0.02	1.26
12	Cl		−0.40	0.06	0.24	0.27	1.04
			−0.20	−0.02	0.10	0.04	1.21

Table 4 Changes in chemical shifts in DMSO (upper entry) and $CDCl_3$ (lower entry) of the pyridine and anilino hydrogens of compounds of type **16** on replacing H by R′

No.	R‴	R′	H2′	H3′	H4′	H4″	H5″
16a	Cl	CH_3	−0.45	−0.10	−0.04	−0.37	0.06
			−0.60	−0.09	−0.05	−0.54	0.01
16b	Cl		−0.45	−0.09	−0.02	−0.33	0.11
			−0.53	−0.08	−0.02	−0.55	0.02
16c	Cl		−0.46	−0.15	−0.10	−0.35	0.10
			−0.62	−0.13	−0.07	−0.54	0.01
7		CH_3	−0.47	−0.07	−0.13	−0.17	0.05
			−0.49	−0.05	−0.07	−0.29	0.04
8		CH_3	−0.58	−0.03	−0.04	−0.22	−0.02
			−0.57	−0.05	−0.05	−0.25	0.02
6		CH_3	−0.03	0.27	0.14	−0.36	−0.11
			0.02	0.26	0.14	−0.44	−0.13
15b			−0.03	0.24	0.29	−0.04	0.34
			0.09	≈0.20	≈0.20	−0.22	0.35

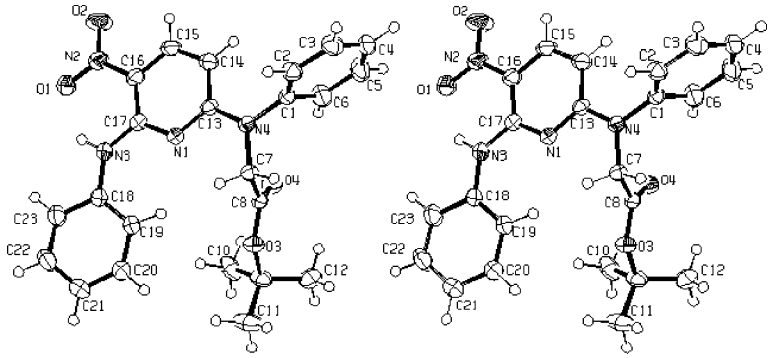


Fig. 1 ORTEP stereo view of compound **4c**.

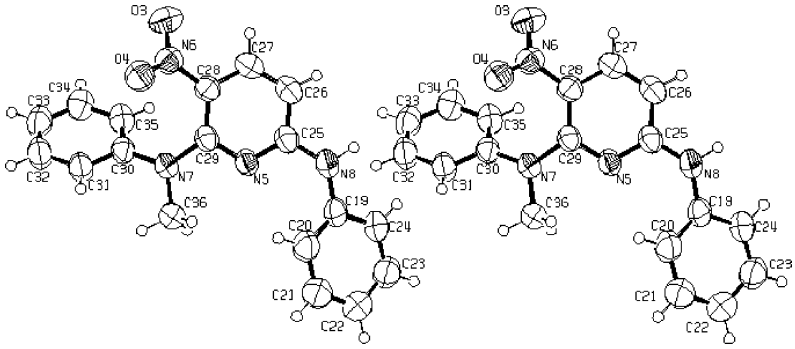


Fig. 2 ORTEP stereo view of compound **7**.

therefore supports the assumption of a shielding effect from this ring made above in the discussion of the NMR spectra. Phenyl B is moderately twisted out of the plane of the atoms attached to *N*-2 ($\tau_1 = 29°$), *i.e.* there is still significant resonance with the lone pair on *N*-2. The twists of the pyridine ring ($\tau_2 = 32°$) and the nitro group ($\tau_5 = 32°$) are both in accord with the conclusions drawn from the NMR spectra. Similarly, the mutual orientation of the planes of the pyridine and of phenyl B as discussed previously is corroborated (angle approximately 70°). It should be mentioned that one half of the molecules in the crystal adopt a slightly different conformation ($d_{C1–N1} = 3.56$ Å, $d_{C1–C3} = 2.96$ Å, $\tau_1 = 44.5°$, $\tau_2 = 33°$, $\tau_5 = 22°$, $d_{C2–N1} = 2.99$ Å, $d_{C2–C4} = 3.73$ Å, $\tau_3 = 174°$, $\tau_4 = 180°$) in which phenyl B is twisted more significantly out of the plane of the atoms attached to *N*-2 and where the nitro group is twisted slightly less out of the plane of the pyridine ring. The 6-anilino group is almost perfectly co-planar with the pyridine ring. The overall shape of both conformations is, however, still quite similar. Nevertheless, the NMR data, particularly with respect to the shifts of H3′, H4′, and H4″ seem to be more in accord with the first conformation

The X-ray structure of the *N*-6 acylated compound **5b** (Fig. 3) clearly confirms the conclusions drawn from the NMR data: the planes of the pyridine and phenyl A are more or less perpendicular to one another ($\tau_3 = 156°$, $\tau_4 = 101°$). Phenyl B remains co-planar with the pyridine ring and therefore one of each of the H2′ and H3′ hydrogens is held above phenyl A.

Similarly, the other conformational features suggested by the NMR data are corroborated by the crystal structure: approximate co-planarity of the pyridine ring with both the amide bond (torsion angle C7–N4–C12–N1 = 153°) and phenyl B ($\tau_1 = 167°$, $\tau_2 = 175°$).

Rigid analogues

In order to obtain further independent support for the conclusions drawn from the NMR spectra, the energy difference between conformations **2A** and **2B** as well as for the analogous conformations of **4a** were calculated. According to AM1 calculations **2A** is 0.5 kcal mol^{-1} more stable than **2B** whereas a difference of 0.7 kcal mol^{-1} in the opposite direction was found for **4a**, but both values are within the error limits of the method. Similarly, DFT calculations (B3LYP functional, 6–31G basis set) gave a non significant difference of 0.7 kcal mol^{-1}, this time in favour of **2B**. For the analogous conformation of **4a**, a significant preference of 2.1 kcal mol^{-1} was found in qualitative accord with the conclusions drawn above. Altogether, these results may not be very conclusive since they do not take the solvent into account. This is particularly relevant for **2** where the 6-NH group

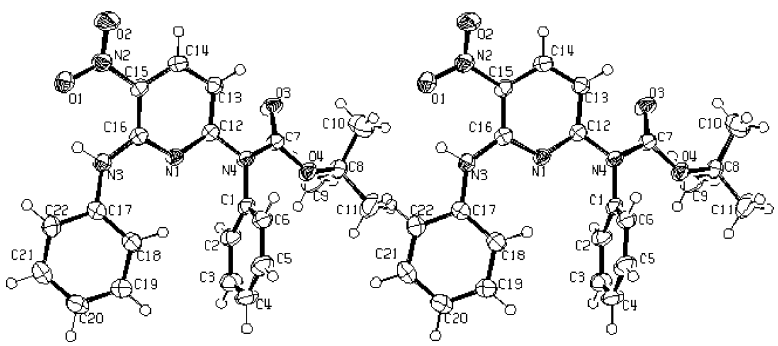
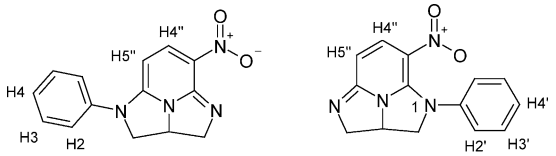


Fig. 3 ORTEP stereo view of compound **5b**.

serves as a hydrogen bond donor for the solvent DMSO. This hydrogen bond can be efficiently formed only in conformation **2A** which would explain its preference in DMSO as deduced from the NMR spectra.

Since these calculations were not suitable as an argument for or against our conclusions from the NMR spectra we tried to obtain more experimental evidence *via* rigid analogues of 2,6-bis-anilino-3-nitropyridines. For this purpose, we synthesized compounds **20** and **21**[5] which may be considered rigid analogues of **4a** and **7** respectively. These structures were selected because they were also interesting to us for a project in the field of new non-planar scaffolds for combinatorial chemistry.



20 **21**

The spatial position and orientation of the phenyl group in compound **20** should be comparable to the one in the supposedly preferred conformation of **4a** and therefore the chemical shifts of hydrogens H2, H3, and H4, should also be similar. Table 5 demonstrates the close correspondence between the two compounds with respect to these chemical shifts.

The considerable extra up-field shift of H5″ in **20** is most likely due to the lack of an equivalent of phenyl B of **2** and **4a**. A reasonable estimate for the actual shielding effect from the phenyl group in **20** may be obtained from the difference in chemical shifts of H5″ between **20** ($\delta = 5.54$ ppm) and **21** ($\delta =$ 5.88 ppm). This difference (−0.34 ppm) is reasonably close to the shift change on *N*-6 methylation of **2** (−0.39 ppm).

Contrary to the close relation between **20** and **4a**, the preferred conformation of compound **7** as derived from the ^{1}H-NMR data does not greatly resemble its rigid analogue **21**. Therefore, considerable differences in the ^{1}H-NMR spectra are to be expected. The most striking deviation refers to H4″ and H5″ which both appear at much higher field in **21** (see Table 6). This shift cannot be attributed solely to the absence of an equivalent of phenyl A as becomes clear from a comparison with the corresponding chemical shifts of the 6-cylohexylamino analogue **17** of **2** (see Table 6). In case of H5″ about half of the total shift difference must be caused by an additional effect, which resides most likely in the stronger electron donating ability of N^1 of **21**, the equivalent of *N*-2 of **7**. As pointed out earlier, in **7** phenyl B must still be significantly conjugated with the lone pair on the nitrogen. With compound **21**, steric repulsion with the nitro group should force the phenyl group into an orientation which at best allows a significantly reduced conjugation. The down-field shift of the phenyl hydrogens of **21** in relation to those of **7** indicates that this is indeed the case. On the other hand the pyridine ring of **21** is fixed in the ideal orientation for overlap of its π-system with the lone pair on N^1. Both effects increase the electron density in the pyridine and could translate into the observed additional up-field shift of H5″.

The unusually high up-field shift of the H4″ signal of **21** (compare the value for **20** in Table 5) is most likely caused by a more or less total twist of the nitro group out of the plane of the pyridine ring. All these differences between the ^{1}H-NMR spectra of **21** and of *N*-2 alkylated derivatives of **2** indicate clearly that in the preferred conformations of the latter the phenyl ring adopts a different position to that of **21** which may be viewed as indirect support for the conformational properties of **7** as derived from the ^{1}H-NMR spectra.

It should be pointed out that the present interpretation of these data assumes that possible effects from conformational distortions due to the steric strain of the tricyclic scaffold of **20** and **21** can be neglected to a first approximation.

Table 5 Comparison of the chemical shifts of the phenyl hydrogens of **2**, **4a**, and **20** in DMSO

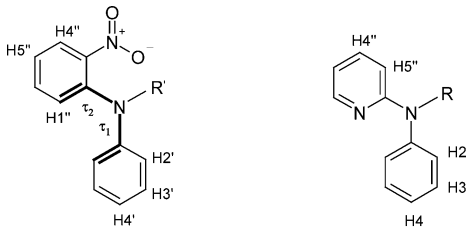
No.	H2	H3	H4	H4″	H5″
2	7.51	7.18	7.02	8.23	6.35
4a	7.36	7.52	7.41	8.15	5.96
20	7.32	7.48	7.28	8.08	5.54

Table 6 Comparison of the chemical shifts of the phenyl and the pyridine-5 protons of **2**, **7**, **17**, and **21**

No.	H2′	H3′	H4′	H4″	H5″
2a	7.51	7.18	7.02	8.32	6.35
17	7.73	7.35	7.12	8.06	6.10
7	7.08	7.29	7.08	8.06	6.40
21	7.22	7.35	7.25	7.74	5.88

Related *N*-aryl anilines

It is conceivable that the structure–conformation relationships derived above for 2,6-bis-anilino-3-nitropyridines could have a more general significance. In order to test this possibility we examined a few representative 2-nitro-diphenylamines **22** and 2-anilino-pyridines **23** that lack the nitro group. The chemical shifts (DMSO) of the aromatic hydrogens of these compounds are listed in Tables 7 and 8 respectively.



22 **23**

From Table 7 it becomes evident that the changes in chemical shifts on *N* alkylation of **22a** follow qualitatively the pattern observed on *N*-2 alkylation of the 2-anilino-3-nitropyridines except that the H3′ and H4′ hydrogens experience a significantly larger up-field shift. In addition, an inspection of the X-ray structure of **22a**[6] suggests that in this case shielding may not be a sufficient explanation for the up-field shift of H2′ because

Table 7 Shifts in ppm of the aromatic hydrogens of compounds of type **22**

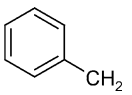
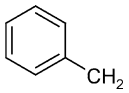
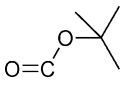
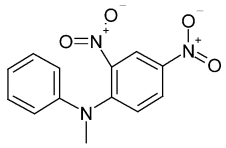
No.	R′	H2′	H3′	H4′	H4″	H5″	H1″
22a	H	7.31	7.40	7.19	8.10	6.86	7.18
22b	CH_3	6.64	7.15	6.77	7.91	7.41	7.50
22c		6.69	7.12	6.78	7.88	7.36	7.53

Table 8 Shifts in ppm of the aromatic hydrogens of compounds of type **23**

No.	R	H2	H3	H4	H4″	H5″
23a	H	7.66	7.24	6.86	7.53	6.81
23b	CH_3	7.27	7.41	7.21	7.40	6.50
23c		7.23–7.27	7.36	7.17	7.43	6.52
23d		7.15	7.33	7.21	7.83	7.51

the planes of the two rings form a rather large angle of 44°. A possible alternative reason is indicated by the torsion angles $\tau_1 = -32.9°$, and $\tau_2 = -19.5°$. The difference in the two torsion angles is largely due to the hydrogen bond between the nitro group and the amino group and indicates that the resonance between the nitrogen lone pair and the nitrophenyl group is considerably stronger than with the unsubstituted phenyl. Consequently, the electron density in the unsubstituted phenyl ring is lower as compared with its counterpart in the parent diphenylamine. The difference is reflected in the NMR chemical shifts (in DMSO): $\delta = 7.06$, 7.22, and 6.81 ppm for the *ortho*, *meta*, and *para* hydrogens respectively of diphenylamine *vs.* $\delta = 7.31$, 7.40, and 7.19 ppm for H2′, H3′, and H4′ of **22a**. *N* Alkylation not only abolishes the hydrogen bond but also introduces an additional steric repulsion which largely affects the nitrophenyl group. This becomes evident from an X-ray analysis of the dinitro analogue **24** of **22b**[7] in which τ_1 becomes 143.4° (in terms of conjugation, equivalent to −36.6°) and τ_2 143.8° (in terms of conjugation, equivalent to −36.2°) resulting in a considerable decrease in resonance and consequently electron withdrawal by the nitrophenyl group. Since τ_1 changes only slightly a redistribution of electron density into the unsubstituted phenyl ring is to be expected and could cause the up-field shift of protons H3′ and H4′ but seems insufficient as an explanation for the particularly large effect on H2′.



24

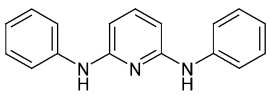
The new values of τ_1 and τ_2 reveal an interesting change in the orientation of the unsubstituted phenyl ring which moves from a position next to H1″ to one facing the nitro group. This new orientation places one of the *ortho* hydrogens above an edge of the nitrophenyl ring.

A similar repositioning in solution would expose the H2′ hydrogens of **22b** to a shielding effect from the nitrophenyl ring. This effect together with the increased electron density could cause the observed large up-field shift of the H2′ signals. It should be mentioned that this shielding effect corresponds to the one discussed above for the related nitropyridine derivative **7**.

The changes in shifts induced by *N* alkylation or *N* acylation of **23a** (Table 8) resemble those observed for 6-anilino-3-nitropyridines. This means that on alkylation the phenyl ring becomes twisted out of the conjugation with the anilino nitrogen and moves from a position pointing towards the pyridine nitrogen to one neighbouring H5″. Similarly, on acylation, the phenyl ring remains on the side of the ring nitrogen whilst the planes of the two ring systems adopt a mutually perpendicular position.

Altogether, these examples suggest that the structure–conformation relationships derived for 2,6-bis-anilino-3-nitropyridines are also valid for the closely related compounds of type **22** and **23**. It is therefore possible that similar relationships exist for diarylamines in general.

However, examination of X-ray analyses from the literature suggest that these relationships may depend on the specific environment of the molecules more significantly than observed for the examples investigated here. Thus, 2-anilinopyridine[8] and 2,6-bis-anilinopyridine (**25**)[9] adopt a conformation in which the phenyl rings are oriented away from the ring nitrogen. However, in *N*,*N*′-bis-2-pyridyl-*meta*-phenylenediamine (**26**) and the corresponding *para*-phenylenediamine (**27**) analogue the benzene ring faces the pyridine nitrogen on either side[10] but the latter also forms crystals with the opposite orientation.[10]



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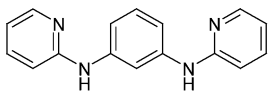

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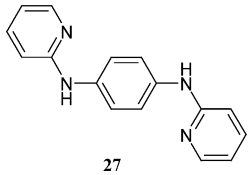
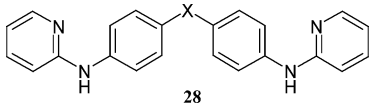


27

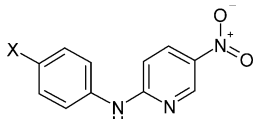
The same authors[10] have also investigated a number of compounds of general structure **28**.



28

For X = S the benzene rings are on the side of the ring nitrogens whereas in the diphenylmethane derivative (X = CH_2) they are oriented towards the ring carbons. The same is true for the 3,3′-diamino-diphenylmethane analogue, but in a crystal which also contains ethanol the opposite orientation occurs.

A similar situation is found with the 2-anilino-5-nitropyridines **29**.[11]



29

With X = H or $N(CH_3)_2$ the phenyl ring is oriented towards the CH in 3-position whereas in the corresponding chlorine derivative the phenyl faces the ring nitrogen.

Conclusions

The conformational properties of 2,6-bis-anilino-3-nitropyridines depend specifically on the nature of the substituents on the anilino nitrogens. The structure–conformation relationships are different for the 2- and the 6-anilino group but, to a first approximation, independent of the particular substituent in 6- or 2-position of the pyridine respectively. Even though alkylation and acylation of the anilino nitrogens give rise to different conformational preferences, the nature of the individual alkyl or acyl group does not seem to play a major role [preliminary experiments with *meta*-substituted anilines (unpublished results) indicate that at least *m*- (or *p*-)substituted anilino-nitropyridines behave like their unsubstituted counterparts]. For the compounds which we have investigated, these relationships were also invariant with respect to the environment of the compounds (DMSO, $CDCl_3$, crystal). Moreover, an exploratory investigation suggests that these structure–conformation relationships may have a more general significance even though the susceptibility to influences from the environment may differ depending on the specific type of structures.

The conclusions drawn from differences in chemical shifts in the ^{1}H-NMR spectra with respect to the conformational properties are not only consistent but are also corroborated by X-ray crystallography and by investigations on rigid analogues.

Based on the synthetic routes and the structure–conformation relationships which are reported here, it is possible to design 2,6-bis-anilino-3-nitropyridines with a preference for a specific shape. This makes them useful as scaffolds for biologically active compounds be it as potential drug molecules or as tools for biochemical investigations, *e.g.*, as specific conformational mimetics of small peptide sequences. In addition, the present compounds can serve as building blocks for oligomers with preferred conformational properties. Depending on the substitution of the individual monomers these oligomers can be used

to form specifically shaped supramolecular arrangements with predefined physical and chemical properties.

Experimental

General

For chromatography, silica gel 60 (230–400 mesh) from Fluka was used. Melting points were taken on a Büchi B-545 melting point apparatus and are uncorrected. ^{1}H and ^{13}C-NMR spectra were recorded on a Bruker Avance 400 spectrometer in d_6-DMSO. Chemical shifts are expressed in ppm with d_6-DMSO = 2.49 ppm for ^{1}H and 39.5 ppm for ^{13}C as internal standards; coupling constants are in Hz. Mass spectra were recorded on a Finnigan SSQ7000 mass spectrometer. Elemental analyses were done with an Elementar Analysensysteme Vario EL analyser.

2,6-Dichloro-3-nitropyridine (**3**) and purified Marathon-C resin were a gift from Boehringer Ingelheim Pharma GmbH & Co KG, **22a** was purchased from Merck, Darmstadt (now VWR International), NaH and **23a** from Aldrich.

16a[2] was prepared as described in ref. 2 by refluxing **3** with *N*-methylaniline in EtOH in the presence of $NaHCO_3$ (mp 76–77 °C, ref. 2: 75–77 °C).

X-Ray crystallography

The crystals used in this study were mounted onto the end of glass fibers. X-Ray data were collected on a STOE IPDS unit (Imaging Plate Diffraction System). Graphite monochromatized Mo–Kα radiation (λ = 0.71073 Å) was used. Crystal data are listed in Table 9 together with refinement details. Absorption corrections were not applied. The structures were solved by the direct Method with the SHELXS-86 program.[12] The atomic coordinates and anisotropic thermal parameters of the non-hydrogen atoms were refined using the SHELXL-97 program;[13] full matrix method, F^2 data. Hydrogen atoms were included in the final refinement cycles in a riding mode.‡

2,6-Bis-anilino-3-nitropyridine (2)[1]

3.86 g (20 mmol) of **3**, 5.60 g (5.47 mL, 60 mmol) of aniline and 5.04 g (60 mmol) of $NaHCO_3$ were heated in 40 mL of EtOH at 40 °C for 4 h. After cooling, the precipitated **2** was collected by filtration (5.51 g, 90%). Mp 190–191 °C (2× from *n*-hexane : EtOAc = 4 : 1, ref. 1: 175–177 °C); δ_H 10.59 (1 H, br s, NH(2)), 10.04 (1 H, vbr s, NH(6)), 8.23 (1 H, d, *J* 9.35, H4″), 7.55 (2 H, m, H2′), 7.51 (2 H, m, H2), 7.36 (2 H, m, H3′), 7.21 (1 H, m, H4′), 7.18 (2 H, m, H3), 7.02 (1 H, m, H4), 6.35 (1 H, d, *J* 9.35, H5″); δ_C 157.8, 151.9, 139.1, 138.0, 135.5, 128.6, 128.5, 124.8, 124.3, 123.3, 120.7, 119.3, 104.0.

General procedure for 2-anilino-6-(*N*-alkylanilino)-3-nitropyridines

To a solution of 153 mg (0.5 mmol) of **2** in 13 mL of DMF the appropriate amount of an auxiliary base and of the alkyl halide were added. The mixture was stirred at room temperature for 10 h. 40 mL of water were added and the mixture extracted twice with 50 mL of EtOAc. The organic layer was evaporated to dryness and the remaining product purified by column chromatography (silica gel, *n*-hexane : EtOAc = 4 : 1).

2-Anilino-6-(*N*-methylanilino)-3-nitropyridine (4a). MeI (142 mg or 0.063 mL; 1 mmol), K_2CO_3 (138 mg,1.0 mmol) (72 mg, 45%). Yellow crystals, mp 115–117 °C (from *n*-hexane : EtOAc = 4 : 1). Found: C 67.6, H 5.0, N 17.4. Calc. for $C_{18}H_{16}N_4O_2$: C 67.5, H 5.0, N 17.5%. δ_H 10.66 (1 H, s, NH), 8.15 (1 H, d, *J* 9.5, H4″), 7.63 (2 H, m, H2′), 7.52 (2 H, m, H3), 7.41 (1 H, m, H4), 7.36 (2 H, m, H2), 7.29 (2 H, m, H3′), 7.09 (1 H, m, H4′), 5.96 (1 H, br d, *J* 9.5, H5″), 3.44 (3 H, s, Me); δ_C 159.6, 150.3, 144.1, 138.1,136.0, 130.0, 128.6, 127.6, 127.1, 123.8, 121.9, 119.0, 100.9, 39.3; *m/z* (EI) 320 (M^+).

6-(*N*-Allylanilino)-2-anilino-3-nitropyridine (4b). Allyl bromide (121 mg or 0.084 mL; 1 mmol), K_2CO_3 (138 mg, 1.0 mmol). After evaporation of the organic layer the residue was dissolved in 6 mL of DMF and again treated with the same amounts of base and allyl bromide (174 mg, 100%). Yellow crystals, mp 104–105 °C (triturated with refluxing isopropanol). Found: C 69.3, H 5.3, N 16.05. Calc. for $C_{20}H_{18}N_4O_2$: C 69.35, H 5.2, N 16.2%. δ_H 10.60 (1 H, s, NH), 8.17 (1 H, d, *J* 9.5, H4″), 7.59 (2 H, m, H2′), 7.51 (2 H, m, H3), 7.41 (1 H, m, H4), 7.35 (2 H, m, H2), 7.28 (2 H, m, H3′), 7.09 (1 H, m, H4′), 5.91 (1 H, ddt, J_1 16.4, J_2 10.6, J_3 5.3, H2-allyl) 5.90 (1 H, br, H5″), 5.12 (1 H, dq, J_1 10.6, J_2 1.4, H3-*trans*-allyl), 5.11 (1 H, dq, J_1 16.4, J_2 1.4, H3-*cis*-allyl), 4.51 (1 H, dt, J_1 5.3, J_2 1.4, H1-allyl);

Table 9 Crystallographic data

	4c	7	5b
Empirical formula	$C_{23}H_{24}N_4O_4$	$C_{18}H_{16}N_4O_3$	$C_{22}H_{22}N_4O_4$
M_r	420.46	320.35	406.44
Crystal system	Monoclinic	Triclinic	Triclinic
Space group	$P2_1/c$	$P\bar{1}$	$P\bar{1}$
a/Å	7.607(2)	10.113(3)	8.595(2)
b/Å	24.695(4)	12.417(3)	9.790(2)
c/Å	11.851(3)	14.105(3)	13.308(2)
α/°	90	107.48(3)	75.57(2)
β/°	108.06(3)	95.21(3)	83.91(2)
γ/°	90	102.18(3)	75.36(2)
V/Å^3	2116.7(8)	1628.5(7)	1033.1(3)
Temperature/K	173(2)	293(2)	173(2)
Z	4	4	2
D(calculated)/g cm^{-3}	1.319	1.307	1.307
μ/mm^{-1}	0.092	0.089	0.092
Crystal size/mm^3	0.40 × 0.20 × 0.20	0.40 × 0.30 × 0.20	0.40 × 0.30 × 0.30
Θ range/°	2.45 to 25.97	2.38 to 26.08	2.24 to 26.01
Refl. collected	16630	14892	11455
Independent refl.	4066	5971	3763
R_{int}	0.0499	0.0460	0.0519
Observed Refl. [$I > 2\sigma(I)$]	2797	3473	3720
Goodness-of-fit on F^2	0.996	0.985	1.014
*R*1, *wR*2 [$I > 2\sigma(I)$]	0.0370, 0.0800	0.0415, 0.0870	0.0401, 0.1023
*R*1, *wR*2 (all data)	0.0595, 0.0849	0.0774, 0.0966	0.0588, 0.1090
Max./min. in $\Delta F(e^{-3})$	0.174 and −0.149	0.141 and −0.131	0.365 and −0.243

δ_C 159.3, 150.4, 142.7, 138.1, 136.3, 132.9, 130.0, 128.5, 127.8, 124.0, 122.2, 119.3, 117.3, 101.0, 53.6; *m/z* (EI) 346 (M^+).

2-Anilino-6-(*N*-*tert*-butoxycarbonylmethylanilino)-3-nitropyridine (4c). *tert*-Butyl bromoacetate (195 mg or 0.15 mL; 1 mmol), K_2CO_3 (138 mg, 1.0 mmol) (110 mg, 52%). Yellow crystals, mp 118–120 °C (from *n*-hexane : EtOAc = 4 : 1). Found: C 65.65, H 5.8, N 13.3. Calc. for $C_{23}H_{24}N_4O_4$: C 65.7, H 5.75, N 13.3%. δ_H 10.58 (1 H, s, NH), 8.18 (1 H, d, *J* 9.4, H4″), 7.64 (2 H, m, H2′), 7.53 (2 H, m, H3), 7.42 (1 H, m, H4), 7.39 (2 H, m, H2), 7.35 (2 H, m, H3′), 7.16 (1 H, m, H4′), 5.88 (1 H, br d, *J* 9.4, H5″), 4.55 (2 H, s, CH_2) 1.22 (9 H, s, *t*Bu); δ_C 168.0, 150.1, 146.9, 141.9, 137.9, 136.5, 130.1, 128.6, 128.0, 127.5, 124.6, 122.4, 119.7, 100.8, 81.2, 53.5, 27.4; *m/z* (EI) 420 (M^+).

2,6-Bis-(*N*-methylanilino)-3-nitropyridine (8). MeI (284 mg or 0.124 mL; 2.0 mmol), KO*t*Bu (224 mg, 2.0 mmol), after evaporation of the solvent the residue was triturated with boiling petroleum ether (139 mg, 83%). Yellow crystals, mp 138–140 °C. Found: C 68.1, H 5.5, N 16.6. Calc. for $C_{19}H_{18}N_4O_2$: C 68.25, H 5.4, N 16.8%. δ_H 7.93 (1 H, d, *J* 9.1, H4″), 7.51 (2 H, m, H3), 7.40 (2 H, m, H2), 7.36 (1 H, m, H4), 7.26 (2 H, m, H3′), 7.05 (1 H, m, H4′), 7.05 (2 H, m, H2′), 5.94 (1 H, d, *J* 9.1, H5″), 3.50 (3 H, s, Me(2)), 3.48 (3 H, s, Me(6)); δ_C 158.0, 151.7, 147.2, 144.3, 136.9, 129.9, 129.3, 127.1, 126.8, 124.5, 124.3, 121.7, 99.8, 40.2, 38.6; *m/z* (EI) 334 (M^+).

6-(*N*-Acetylanilino)-2-anilino-3-nitropyridine (5a). **2** (92 mg, 0.3 mmol) and acetic anhydride (3 mL) were heated at 123 °C for 4.5 h. The reaction mixture was stirred for 30 min with 120 mL of aqueous $NaHCO_3$. After extraction with 150 mL of dichloromethane (DCM), the organic phase was concentrated *in vacuo* (62 mg, 59%). Orange crystals, mp 180–181 °C (from acetone). Found: C 65.5, H 4.65, N 16.1. Calc. for $C_{19}H_{16}N_4O_3$: C 65.5, H 4.6, N 16.1%. δ_H 10.15 (1 H, s, NH), 8.58 (1 H, d, *J* 9.1, H4″), 7.61 (1 H, d, *J* 9.1, H5″), 7.56 (2 H, m, H3), 7.53 (1 H, m, H4), 7.39 (2 H, m, H2), 6.99–7.03 (4 H, m, H2′, H3′), 6.95 (1 H, m, H4′), 1.96 (3 H, s, Me); δ_C 167.0, 152.0, 150.5, 147.6, 141.5, 137.6, 133.6, 130.0, 129.4, 128.5, 128.4, 123.3, 120.6, 109.0, 26.0; *m/z* (CI) 349 ($[M + H]^+$).

2-Anilino-6-(*N*-*tert*-butoxycarbonylanilino)-3-nitropyridine (5b). A solution of **2** (1.48 g, 4.83 mmol), di-*tert*-butyl dicarbonate (1.20 g, 5.5 mmol) and a catalytic amount of DMAP in 30 mL of DCM was warmed at 27 °C for 3 h. The mixture was washed with 30 mL of 0.1 M citric acid and aqueous $NaHCO_3$ and the organic solvent evaporated (1.49 g, 75%). Orange crystals, mp 155–156 °C (from *n*-hexane : EtOAc = 4 : 1). Found: C 65.0, H 5.5, N 13.8. Calc. for $C_{22}H_{22}N_4O_4$: C 65.0, H 5.5, N 13.8%. δ_H 10.18 (1 H, s, NH), 8.56 (1 H, d, *J* 9.4 H4″), 7.51 (1 H, d, *J* 9.4, H5″), 7.49 (2 H, m, H3), 7.45 (1 H, m, H4), 7.25 (2 H, m, H2), 7.00 (2 H, m, H2′), 6.96 (2 H, m, H3′), 6.91 (1 H, m, H4′), 1.36 (9 H, s, *t*Bu); δ_C 159.4, 153.7, 152.3, 149.3, 142.2, 139.2, 138.9, 130.6, 130.0, 129.7, 128.8, 125.0, 121.6, 108.6, 83.9, 28.9; *m/z* (CI) 407 ($[M + H]^+$).

6-(*N*-*tert*-Butoxycarbonylanilino)-2-(*N*-methylanilino)-3-nitropyridine (6). To a solution of **5b** (899 mg, 2.2 mmol) in DMF (22 mL) were added KO*t*Bu (494 mg, 4.4 mmol) and MeI (625 mg, 0.28 mL, 4 mmol). The mixture was stirred at room temperature for 45 min. After addition of water the product was extracted with EtOAc, the organic layer evaporated and the residue purified by crystallization (650 mg, 77%). Yellow crystals, mp 164–165 °C (from *n*-hexane : EtOAc = 6 : 1). Found: C 65.5, H 5.7, N 13.2. Calc. for $C_{23}H_{24}N_4O_4$: C 65.7, H 5.75, N 13.3%. δ_H 8.20 (1 H, d, *J* 8.9, H4″), 7.42 (2 H, m, H3), 7.40 (1 H, d, *J* 8.9, H5″), 7.32 (1 H, m, H4), 7.25 (2 H, m, H2), 7.23 (2 H, m, H3′), 7.05 (1 H, m, H4′), 6.97 (2 H, m, H2′), 2.95 (3 H, s, Me), 1.39 (9 H, s, *t*Bu); δ_C 155.3, 152.5, 149.0, 146.2, 140.7, 137.6, 129.5, 128.8, 128.5, 127.1, 124.9, 121.8, 107.8, 82.1, 27.7; *m/z* (CI) 423 ($[M + H]^+$).

6-Anilino-2-(*N*-methylanilino)-3-nitropyridine (7). A suspension of **6** (300 mg, 0.71 mmol) in conc. HCl (6 mL) was stirred at room temperature. Immediately after complete dissolution the product precipitated. Water was added and the mixture extracted with DCM. The organic layer was washed with aqueous $NaHCO_3$ and concentrated in vacuum (216 mg, 95%). Orange crystals, mp 123–125 °C (from *n*-pentane : EtOAc = 3.2 : 1). Found: C 67.3, H 5.0, N 17.25. Calc. for $C_{18}H_{16}N_4O_2$: C 67.5, H 5.0, N 17.5%. δ_H 9.87 (1 H, s, NH), 8.06 (1 H, d, *J* 9.0, H4″), 7.64 (2 H, m, H2), 7.29 (4 H, m, H3′, H3), 7.08 (1 H, m, H4′), 7.08 (2 H, m, H2′), 7.00 (1 H, m, H4), 6.40 (1 H, d, *J* 9.0, H5″), 3.48 (3 H, s, Me); δ_C 156.0, 152.5, 147.2, 139.7, 136.8, 129.3, 128.7, 125.0, 124.5, 122.5, 122.3, 119.5, 102.9, 40.9; *m/z* (EI) 320 (M^+).

6-Anilino-2-chloro-3-nitropyridine (9). NaH (120 mg, 5 mmol) was added to a solution of *N*-*tert*-butoxycarbonylaniline (931 mg, 5 mmol) in DMF (20 mL) and stirred at room temperature for 10 min. This solution was added dropwise without cooling within 1 h to a solution of **3** (1447 mg, 7.5 mmol) in DMF (8 mL) and stirred for 12 h. This solution was added to 50 mL of 0.2 M aqueous citric acid, extracted with EtOAc and the organic layer washed with aqueous $NaHCO_3$ and water and evaporated (an NMR spectrum of a sample in DMSO showed that a 70 : 30 mixture of 6-(*N*-*tert*-butoxycarbonylanilino)-2-chloro-3-nitropyridine and 2-(*N*-*tert*-butoxycarbonylanilino)-6-chloro-3-nitropyridine had formed and that about 60% of the *N*-*tert*-butoxycarbonylaniline had reacted). The residue was stirred overnight at room temperature with 20 mL of conc. HCl. The mixture was diluted with 20 mL of water, brought to pH 6 with $NaHCO_3$, and extracted with EtOAc. The organic phase was dried with Na_2SO_4 and evaporated and the residue chromatographed on silica gradient from pure *n*-hexane to *n*-hexane : EtOAc = 1 : 1 (468 mg, 27% based on *N*-*tert*-butoxycarbonylaniline). Pale yellow crystals, mp 169–171 °C. Found: C 52.8, H 3.3, N 16. 9. Calc. for $C_{11}H_8ClN_3O_2$: C 52.9, H 3.2, N 16.8%. δ_H 10.34 (1 H, s, NH), 8.31 (1 H, d, *J* 9.0, H4″), 7.63 (2 H, m, H2), 7.37 (2 H, m, H3), 7.10 (1 H, m, H4), 6.88 (1 H, d, *J* 9.0, H5″); δ_C 156.5, 143.1, 138.8, 136.6, 133.9, 129.0, 123.7, 120.2, 109.2; *m/z* (CI) 250, 252 ($[M + H]^+$).

6-Anilino-2-(*N*-benzylanilino)-3-nitropyridine (10). A solution of **9** (125 mg, 0.5 mmol), *N*-benzylaniline (128 mg, 0.7 mmol), and DIPEA (90 mg, 0.11 mL, 0.7 mmol) in 3 mL of EtOH was heated at 70 °C for 4 d. The solvent was removed under vacuum, the residue dissolved in 1 mL of a 1 : 1 mixture of *n*-hexane and EtOAc and chromatographed on silica gel (*n*-hexane : EtOAc = 4 : 1) (85 mg, 42%). Orange crystals, mp 95 °C. Found: C 72.7, H 5.1, N 14.1. Calc. for $C_{24}H_{20}N_4O_2$: C 72.7, H 5.1, N 14.1%. δ_H 9.83 (1 H, s, NH), 8.06 (1 H, d, *J* 8.8, H4″), 7.42 (2 H, m, H2‴), 7.41 (2 H, m, H2), 7.30 (2 H, m, H3‴), 7.23 (2 H, m, H3′), 7.20 (1 H, m, H4‴), 7.15 (2 H, m, H3), 7.06 (1 H, m, H4′), 7.01 (2 H, m, H2′), 6.96 (1 H, m, H4), 6.40 (1 H, d, *J* 8.8, H5″), 5.36 (2 H, s, CH_2) (‴ refers to benzylic phenyl); δ_C 156.0, 151.3, 146.5, 139.4, 138.7, 136.8, 129.3, 128.5, 128.3, 126.7, 126.4, 125.4, 124.2, 122.6, 121.1, 119.5, 103.4, 55.2; *m/z* (CI), 397 ($[M + H]^+$).

6-(*N*-*tert*-Butoxycarbonylanilino)-2-chloro-3-nitropyridine (12). DMAP (62 mg, 0.5 mmol) was added to a solution of 100 mg (0.4 mmol) of **9** and 110 mg (0.5 mmol) of di-*tert*-butyl dicarbonate in 3.5 mL of DCM. The reaction mixture was stirred at room temperature for 4 h. After removal of the solvent the residue was purified by column chromatography (silica gel, *n*-hexane : EtOAc = 4 : 1) (100 mg, 71%). Colourless crystals, mp 101–103 °C (from *n*-hexane). Found: C 55.0, H 4.7, N 12.0. Calc. for $C_{16}H_{16}ClN_3O_4$: C 54.9, H 4.6, N 12.0%. δ_H 8.58 (1 H, d, *J* 8.8, H4″), 7.92 (1 H, d, *J* 8.8, H5″), 7.43 (2 H, m, H3), 7.34 (1 H, m, H4), 7.23 (2 H, m, H2), 1.38 (9 H, s, *t*Bu); δ_C 156.2,

152.2, 140.3, 140.1, 139.5, 137.4, 129.1, 128.3, 127.5, 117.4, 82.8, 27.5 *m/z* (CI) 350, 352 ([M + H]$^+$).

2-(*N*-*tert*-Butoxycarbonylanilino)-6-chloro-3-nitropyridine (13). A solution of **14** (250 mg, 1.0 mmol), di-*tert*-butyl dicarbonate (364 mg, 1.6 mmol), and DMAP (7 mg) in 2 mL of DCM was warmed at 38 °C for 15 h. The mixture was purified twice by column chromatography on silica gel (1. *n*-hexane, 2. *n*-hexane : EtOAc = 4 : 1) (245 mg, 70%, honey-coloured resin). Found: C 55.2, H 4.7, N 11.9. Calc. for $C_{16}H_{16}ClN_3O_4$: C 54.9, H 4.6, N 12.0%. δ_H 8.59 (1 H, d, *J* 8.6, H4″), 7.69 (1 H, d, *J* 8.6, H5″), 7.42 (2 H, m, H3′), 7.31 (1 H, m, H4′), 7.31 (2 H, m, H2′), 1.32 (9 H, s, *t*Bu); δ_C 151.8, 146.8, 140.9, 140.0, 138.0, 129.0, 127.5, 127.1, 123.5, 83.1, 27.3; *m/z* (CI) 350, 352 ([M + H]$^+$), 294, 296 ([(M + H)–$Me_2C{=}CH_2$]$^+$).

2-Anilino-6-chloro-3-nitropyridine (14)[1]. A mixture of **3** (2.50 g, 13 mmol), $NaHCO_3$ (1.18 g, 14 mmol), aniline (1.21 g = 1.18 mL, 13 mmol), and EtOH (30 mL) was stirred at room temperature for 1 d. The precipitate was collected, washed with EtOH and water and purified by column chromatography on silica gel (*n*-hexane : EtOAc = 4 : 1) (1.71 g, 53%). Mp 104 °C (ref. 1: 102–104 °C).

2-Chloro-6-(*N*-methylanilino)-3-nitropyridine (15a). To a solution of **9** (100 mg, 0.4 mmol) in DMF (2 mL) was added K_2CO_3 (70 mg, 0.5 mmol) and MeI (71 mg or 0.03 mL, 0.5 mmol) and the mixture stirred at 45 °C for 2 h. 10 mL of water was added and the mixture extracted with EtOAc. The organic phase was evaporated and the residue purified by column chromatography on silica gel (*n*-hexane : EtOAc = 4 : 1). (86 mg, 81%). Colourless crystals, mp 107 °C. Found: C 54.7, H 3.9, N 15.7. Calc. for $C_{12}H_{10}ClN_3O_2$: C 54.7, H 3.8, N 15.9%. δ_H 8.18 (1 H, d, *J* 9.1, H4″), 7.54 (2 H, m, H3), 7.41 (1 H, m, H4), 7.40 (2 H, m, H2), 6.36 (1 H, d, *J* 9.1, H5″), 3.47 (3 H, s, Me); δ_C 158.4, 143.6, 143.2, 136.6, 133.0, 130.3, 127.8, 126.7, 106.6, 39.2; *m/z* (CI) 264, 266 ([M + H]$^+$).

2,6-Bis-(*N*-*tert*-butoxycarbonylanilino)-3-nitropyridine (15b). A solution of **2** (140 mg, 0.45 mmol), di-*tert*-butyl dicarbonate (240 mg, 1.1 mmol), and DMAP (10 mg) in DCM (15 mL) was stirred at room temperature for 2 h. The solvent was removed and the residue purified by column chromatography on silica gel (*n*-hexane : EtOAc = 4 : 1) (114 mg, 50%). Mp 137 °C. Found: C 63.7, H 6.0, N 10.7. Calc. for $C_{27}H_{30}N_4O_6$: C 64.0, H 6.0, N 11.1%. δ_H 8.52 (1 H, d, *J* 9.1, H4″), 7.85 (1 H, d, *J* 9.1, H5″), 7.28 (3 H, m, H3, H4), 7.20 (3 H, m, H3′, H4′), 7.01 (2 H, m, H2), 6.97 (2 H, m, H2′), 1.33 (9 H, s, *t*Bu) 1.26 (9 H, s, *t*Bu); δ_C 161.4, 155.8, 151.8, 145.2, 140.0, 139.7, 136.5, 133.6, 128.8, 128.5, 128.2, 127.6, 127.0, 126.8, 115.7, 82.4, 82.3, 27.5, 27.4; *m/z* (CI) 507 ([M + H]$^+$).

2-(*N*-*tert*-Butoxycarbonylmethylanilino)-6-chloro-3-nitropyridine (16b). To a solution of **14** (225 mg, 0.9 mmol) in DMF (15 mL) were added K_2CO_3 (207 mg, 1.5 mmol) and subsequently *tert*-butyl bromoacetate (293 mg = 0.22 mL, 1.5 mmol). After stirring at rt for 16 h water was added and the mixture extracted with EtOAc. The organic layer was evaporated and the residue purified by column chromatography on silica gel (*n*-hexane : EtOAc = 4 : 1) (198 mg, 60%). Mp 163–165 °C (from *n*-hexane : EtOAc = 4 : 1). Found: C 56.1, H 5.1, N 11.4. Calc. for $C_{17}H_{18}ClN_3O_4$: C 56.1, H 5.0, N 11.55%. δ_H 8.20 (1 H, d, *J* 8.2, H4″), 7.31 (2 H, m, H3′), 7.16 (1 H, m, H4′), 7.14 (2 H, m, H2′), 7.11 (1 H, d, *J* 8.3, H5″), 4.54 (2 H, s, CH_2), 1.37 (9 H, s, *t*Bu); δ_C 168.0, 150.6, 149.1, 144.4, 138.6, 130.1, 129.5, 126.1, 123.5, 114.9, 81.0, 55.0, 27.7; *m/z* (EI) 363, 365 (M^+).

2-(*N*-Benzylanilino)-6-chloro-3-nitropyridine (16c). A solution of **3** (460 mg, 2.4 mmol), *N*-benzylaniline (457 mg, 2.5 mmol), and DIPEA (322 mg, 2.5 mmol) in 3 mL of toluene was heated at 80 °C for 4 d. The mixture was washed with 3 mL of 0.1 M citric acid and the solvent evaporated. The residue was dissolved in 10 mL of EtOAc, washed with saturated aqueous $NaHCO_3$ and the solvent evaporated. The residue was taken up in 20 mL of DCM and treated with 2 g of Marathon-C resin. After evaporation the residue was purified by column chromatography on silica gel (*n*-hexane : EtOAc = 4 : 1) (475 mg, 58%). Mp 108 °C. Found: C 63.8, H 4.2, N 12.3. Calc. for $C_{18}H_{14}ClN_3O_2$: C 63.6, H 4.15, N 12.4%. δ_H 8.18 (1 H, d, *J* 8.3, H4″), 7.35 (2 H, m, H2‴), 7.28 (2 H, m, H3‴) 7.25 (2 H, m, H3′), 7.20 (1 H, m, H4‴), 7.13 (2 H, m, H2′), 7.10 (1 H, d, *J* 8.3, H5″) 7.08 (1 H, m, H4′), 5.31 (2 H, s, CH_2) (‴ refers to benzylic phenyl); δ_C 150.9, 149.7, 144.3, 138.8, 137.6, 133.7, 129.6, 128.3, 127.4, 127.1, 122.3, 115.2, 55.0; *m/z* (CI) 340 ([M + H]$^+$).

2-Anilino-6-cyclohexylamino-3-nitropyridine (17). **14** (499 mg, 2 mmol), cyclohexylamine (238 mg = 0.274 mL, 2.4 mmol), and K_2CO_3 (332 mg, 2.4 mmol) in DMF (3 mL) were stirred at 50 °C for 1 d. Water was added, the precipitate collected by filtration, washed several times with water and dried (590 mg, 94%). Mp 170–181 °C. Found: C 65.3, H 6.5, N 17.8. Calc. for $C_{17}H_{20}N_4O_2$: C 65.4, H 6.45, N 17.9%. δ_H 10.86 (1 H, s, NH(2)), 8.24 (1 H, d, *J* 7.3, NH (6)), 8.06 (1 H, d, *J* 9.4, H4″), 7.73 (2 H, m, H2′), 7.35 (2 H, m, H3′), 7.12 (1 H, m, H4′), 6.10 (1 H, d, *J* 9.3, H5″), 3.75 (1 H, m, H1‴), 1.92 (2 H, m, H2‴e), 1.74 (2 H, m, H3‴e), 1.61 (1 H, m, H4‴e), 1.10–1.35 (5 H, m, H2‴a, H3‴a, H4‴a) (‴ refers to cyclohexyl); δ_C 159.3, 151.6, 138.3, 134.8, 128.5, 123.9, 121.9, 117.7, 103.4, 50.4, 32.0, 24.7, 25.2; *m/z* (CI) 313 ([M + H]$^+$).

2-Anilino-6-(*N*-*tert*-butoxycarbonyl-cyclohexylamino)-3-nitropyridine (18). A solution of **17** (93 mg, 0.3 mmol), di-*tert*-butyl dicarbonate (66 mg, 0.3 mmol), and DMAP (37 mg, 0.3 mmol) in DCM (3 mL) was stirred at room temperature for 1 d. The reaction mixture was fractionated as a whole on silica (*n*-hexane: EtOAc = 4 : 1). The fraction that contained the pure product was evaporated to dryness (27 mg, 22%). Mp 96 °C. Found: C 64.4, H 6.9, N 13.4. Calc. for $C_{22}H_{28}N_4O_4$: C 64.1, H 6.8, N 13.6%. δ_H 10.12 (1 H, s, NH), 8.42 (1 H, d, *J* 9.1, H4″), 7.54 (2 H, m, H2′), 7.37 (2 H, m, H3′), 7.18 (1 H, m, H4′), 6.91 (1 H, d, *J* 9.1, H5″), 4.19 (1 H, tt, J_1 12.1, J_2 3.5, H1‴), 1.79 (2 H, qd, J_1 12.4, J_2 3.3, H2‴a), 1.65 (2 H, m, H3‴e), 1.57 (2 H, m, H2‴e), 1.52 (1 H, m, H4‴e), 1.43 (9 H, s, *t*Bu), 1.12 (2 H, m, H3‴a), 0.92 (1 H, m, H4‴) (‴ refers to cyclohexyl); δ_C 158.2, 155.3, 152.7, 143.4, 138.0, 136.3, 128.6, 124.8, 124.1, 123.9, 81.7, 57.8, 30.1, 27.7, 25.9, 25.0; *m/z* (CI) 413 ([M + H]$^+$).

***N*-Methyl-2-nitrodiphenylamine (22b)[14].** To a solution of 624 mg (3 mmol) of **22a** in 6 mL of DMF was added K_2CO_3 (552 mg, 4 mmol) followed by 0.25 mL (548 mg, 4 mmol) of MeI. The mixture was stirred at room temperature for 2 h, poured onto water and extracted with EtOAc. The organic phase was evaporated and the remaining oily product purified by column chromatography on silica gel (*n*-hexane : EtOAc = 4 : 1) (380 mg, 64%; oily product). Found: C 68.5, H 5.3, N 12.3. Calc. for $C_{13}H_{12}N_2O_2$: C 68.4, H 5.3, N 12.3%. δ_H 7.91 (1 H, dd, J_1 8.1, J_2 1.5, H4″), 7.73 (1 H, ddd, J_1 8.1, J_2 7.3, J_3 1.5, H6″), 7.50 (1 H, dd, J_1 8.1, J_2 1.3, H1″), 7.41 (1 H, ddd, J_1 8.1, J_2 7.3, J_3 1.3, H5″), 7.15 (2 H, dd, J_1 8.8, J_2 7.3, H3′), 6.77 (1 H, tt, J_1 7.3, J_2 1.0, H4′), 6.64 (2 H, m, H2′), 3.24 (3 H, s, CH_3); δ_C 147.7, 146.3, 141.0, 134.6, 129.3, 129.0, 125.9, 125.3, 119.3, 114.9, 40.1; *m/z* (CI) 229 ([M + H]$^+$).

***N*-Benzyl-2-nitrodiphenylamine (22c).** To a solution of **22a** (570 mg, 2.7 mmol) in DMF (6 mL) was added KO*t*Bu (350 mg, 3.6 mmol) and subsequently benzyl bromide (616 mg, 0.43 mL, 3.6 mmol). The mixture was stirred at room temperature for 2 h. The solvent was removed under vacuum and the residue crystallized from EtOH under addition of enough 1,4-diazabicyclo[2,2,2]octane (DABCO) to remove unreacted benzyl bromide (as determined by an NMR spectrum of the crude reaction product) (560 mg, 69%). Mp 110 °C. Found: C 75.0, H 5.4, N 9.2. Calc. for $C_{19}H_{16}N_2O_2$: C 75.0, H 5.3, N 9.2%. δ_H 7.88 (1 H, dd, J_1 8.1, J_2 1.5, H4″), 7.68 (1 H, ddd, J_1 8.1, J_2 7.3, J_3 1.5, H6″), 7.53 (1 H, dd, J_1 8.1, J_2 1.0, H1″), 7.38 (2 H, m,

H2‴), 7.36 (1 H, ddd, J_1 8, J_2 7, J_3 1.3, H5″), 7.29 (2 H, m, H3‴), 7.21 (1 H, m, H4‴), 7.12 (2 H, m, H3′), 6.78 (1 H, m, H4′), 6.69 (2 H, m, H2′), 4.69 (2 H, s, CH_2) (‴ refers to benzylic phenyl); δ_C 147.2, 145.6, 140.2, 138.1, 134.5, 129.1, 128.7, 128.5, 127.0 (3C), 125.7, 125.5, 120.1, 116.6, 56.1; *m/z* (EI) 304 (M^+).

2-(*N*-Methylanilino)pyridine (23b)[15]. To a solution of 510 mg (3 mmol) of **23a** in 6 mL of DMF was added KO*t*Bu (369 mg, 3.3 mmol) followed by 0.21 mL (468 mg, 3.3 mmol) of MeI. The mixture was stirred at room temperature for 1.5 h, poured onto water and extracted with EtOAc. The organic phase was collected, evaporated and the remaining oily product purified by column chromatography on silica gel (*n*-hexane : EtOAc = 4 : 1) (525 mg, 95%, colourless oil). Found: C 78.2, H 6.6, N 15.3. Calc. for $C_{12}H_{12}N_2$: C 78.2, H 6.6, N 15.2%. δ_H 8.14 (1 H, ddd, J_1 5.1, J_2 2.0, J_3 1.0, H2″), 7.41 (2 H, m, H3), 7.40 (1 H, ddd, J_1 8.6, J_2 7.1, J_3 2.0, H4″), 7.27 (2 H, m, H2), 7.21 (1 H, m, H4), 6.65 (1 H, ddd, J_1 7.1, J_2 5.1, J_3 0.8, H3″), 6.50 (1 H, ddd, J_1 8.6, J_2 1.0, J_3 0.8, H5″), 3.37 (3 H, s, CH_3); δ_C 157.8, 147.2, 146.0, 136.7, 129.4, 125.6, 125.0, 113.0, 108.2, 37.8; *m/z* (CI) 185 ($[M + H]^+$).

2-(*N*-Benzylanilino)pyridine (23c). To a solution of 230 mg (1.35 mmol) of **23a** in 2 mL of DMF were added under argon 179 mg (1.5 mmol) of KO*t*Bu. After stirring for 10 min and cooling in an ice bath 230 mg (1.35 mmol) of benzyl bromide were added. The cooling was removed and the mixture stirred at room temperature for 1 d, poured onto 20 mL of water and extracted with EtOAc (25 mL). The organic phase was evaporated and the residue crystallized from 34 mL of EtOH under addition of 30 mg of DABCO. The product was then purified by column chromatography on silica gel (*n*-hexane : EtOAc = 4 : 1) (300 mg, 85%). Mp 71 °C. Found: C 83.0, H 6.3, N 10.7. Calc. for $C_{18}H_{16}N_2$: C 83.0, H 6.2, N 10.8%. δ_H 8.13 (1 H, ddd, J_1 5.1, J_2 2.0, J_3 0.8, H2″), 7.43 (1 H, ddd, J_1 8.8, J_2 7.1, J_3 2.0, H4″), 7.36 (2 H, m, H3), 7.23–7.27 (6 H, m, H2, H2‴, H3‴), 7.17 (2 H, m, H4, H4‴), 6.68 (1 H, ddd, J_1 7.1, J_2 5.1, J_3 0.8, H3″), 6.52 (1 H, dt, J_1 8.6, J_2 0.8, H5″), 5.22 (2 H, s, CH_2) (‴ refers to benzylic phenyl); δ_C 157.8, 147.7, 144.8, 139.3, 137.3, 129.7, 128.2, 127.1, 126.6, 126.2, 125.3, 113.8, 108.6, 52.5; *m/z* (CI) 261 ($[M + H]^+$).

2-(*N*-*tert*-Butyloxycarbonylanilino)pyridine (23d). A solution of **23a** (87 mg, 0.51 mmol), di-*tert*-butyl dicarbonate (141 mg, 0.65 mmol), and a catalytic amount of DMAP in DCM (2 mL) was stirred at room temperature for 5 h. The solvent was removed under vacuum and the residue purified by column chromatography on silica gel (*n*-hexane : EtOAc = 4 : 1) (115 mg, 84%). Mp 86 °C. Found: C 71.0, H 6.7, N 10.3. Calc. for $C_{16}H_{18}N_2O_2$: C 71.1, H 6.7, N 10.4%. δ_H 8.31 (1 H, ddd, J_1 4.8, J_2 2.0, J_3 0.8, H2″), 7.83 (1 H, ddd, J_1 8.1, J_2 7.3, J_3 2.0, H4″), 7.51 (1 H, dt, J_1 8.1, J_2 0.9, H5″), 7.33 (2 H, m, H3), 7.21 (2 H, m, H3″, H4), 7.15 (2 H, m, H2), 1.37 (9 H, s, *t*Bu); δ_C 154.8, 152.9, 148.2, 141.7, 138.0, 128.6, 127.4, 125.9, 121.3, 121.2, 80.8, 27.7; *m/z* (EI) 270 (M^+).

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