The *tert*-Amino Effect in the Synthesis of Hetaryl- and Arylsulfonyl-Substituted Pyrrolo- and Pyrido[1,2-α]quinoline Derivatives and their Pyrazolo Annulated Analoueges

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Abstract: 4-Hetaryl and 4-tosyl-1,2,3,3a,4,5-hexahydropyrrrolo[1,2-α]quinoline-4-carbonitriles were prepared in two steps by the condensation of 2-(1-pyrrolidinyl)benzaldehydes with substituted acetocnitriles $X\text{CH}_2\text{CN}$ ($X$ = hetaryl, tosyl), followed by the thermal cyclization of the corresponding aryldiene derivatives. Similarly, starting from 2-(1-piperidinyl)benzaldehydes 5-hetaryl and 5-tosyl-2,3,4,4a,5,6-hexahydro-1H-pyrazolo[1,2-α]quinoline-5-carbonitriles were obtained. For the hetaryl-substituted derivatives the cyclization step was found to be assisted by protons. In addition were obtained. For the hetaryl-substituted derivatives the cyclization step was found to be assisted by protons. In addition were obtained. For the hetaryl-substituted derivatives the cyclization step was found to be assisted by protons. In addition were obtained. For the hetaryl-substituted derivatives the cyclization step was found to be assisted by protons. In addition were obtained. 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Pyrazolo[1,2-α]quinoline derivatives are attracting chemists’ attention because their skeleton often appears in marine alkaloids (for reviews see 1). In particular, the derivatives with partially or completely hydrogenated hetereocyclic rings are of great interest. Moreover, certain tetrahdydropyrido[1,2-α]quinolines, 2 the homologues of pyrroloquinolines, have shown high biological activity. In the eighties Verboom and Reinhoudt developed an efficient method 1 for the preparation of hexahdyropyrrrolyl- and pyrido[1,2-α]quinolines 2 (Scheme 1) using the so called tert-amino effect. (The term was coined 4 to describe this type and related cyclizations.) Thus upon heating cinnamonitriles 1 in high-boiling polar solvents the target derivatives 2 were isolated in good yields. 3 The starting materials 1 were obtained easily by condensation of the corresponding aminodehydes ($R^{1} = H$) or ketones ($R^{1} = \text{CH}_3$, $\text{Ar}$) with malonodinitrile. Furthermore, the method was extended to the preparation of various heterocycles by varying widely the tert-amino framework. 5 stereochecmistry and mechanistic aspects of the tert-amino effect were thoroughly investigated. 3c-f The authors assumed a sigmatropic hydrogen shift occurred from the canonic structure 3, this was the rate-determining step, a further fast cyclization of the bipolar intermediate 4 then occurred. The stereochecmical studies on the cyclization of derivatives of type 1, with substituted and chiral tert-amino moieties, revealed the high regio- and stereoselectivity of the reaction and revealed that the hydrogen shift occurred suprafacially. 3d-f However, kinetic measurements indicated that in fact it was not a sigmatropic rearrangement, but rather a hydride transfer, 5 so a mixed mechanism was suggested. 3c-f Also, it should be noted that all research on the tert-amino effect and its synthetic applications was carried out with malonodinitrile derivatives and, therefore, yielded products like 2 symmetrically substituted at the 3-position of the quinoline moiety. 3d-f To the best of our knowledge a sole example based on ethyl cyanoacetate has been reported. 2 All the previously known syntheses of hydrogenated pyrrolo- and pyrido[1,2-α]quinolines gave predominantly unsubstituted adducts. 3c-f Apart from dinitriles 2 only a few examples of 4-substitued pyrrolo[1,2-α]quinolines were reported in the literature. 3c-f Continuing our research 11 on the utility of
hetarylacetonitriles 7 and 8, and their derivatives in heterocyclic synthesis, we have studied their behavior in the tert-amino effect reactions and report the results herein.

Thus cinnamonitrile derivatives 10–13 (Scheme 2) were obtained as single stereoisomers in 80–90% yields by condensation of the appropriate aldehydes 5 or 6 with hetarylacetonitriles 7 or 8 in ethanol in the presence of triethylamine, under the typical conditions for the condensations of compounds 7 and 8. Since nitriles 7 and 8 were known to give adducts with an E-configuration with substituted benzaldehydes 12c,d the same stereochemistry was assigned to the products 10–13. Usually the tert-amino effect cyclization was effected by refluxing the dinitriles 1 in tert-butanol or DMF. Since derivatives 10–13 were hardly soluble in alcohols their heating in DMF was examined. It resulted in the formation of the expected compounds 16–19 within seven to ten hours when heated at reflux, but in only moderate yields. Contrary to the dinitriles 1, the substituent X in compounds 10–13 exhibits basic properties; this prompted us to inspect the possibility of the proton-assisted cyclization. Although the tert-amino effect is strongly facilitated by polar solvents acetic acid was reported to give poor results (slow reaction and low yields), probably due to protonation of the tert-amine moiety. Nevertheless, upon refluxing in acetic acid compounds 10–13 were found to undergo cyclization to derivatives 16–19 in high yields (ca. 80%). Moreover, the reaction was completed in four to seven hours, i.e. considerably faster compared to DMF in spite of the lower boiling point. Perhaps formation of the salt 22a (Scheme 3) increases the contribution of the canonic structure 22b, which would favorably undergo a hydrogen shift. Furthermore the positively charged intermediate 23 seems to be more stable than the bipolar intermediate 4, thus facilitating the hydrogen transfer. The final ring-closure of the intermediate 23 is achieved by interaction of the electrophilic iminium and nucleophilic enamine moieties. Of course it is slower than the bond formation between oppositely charged carbons in 4, but it is not the rate-determining step.3c,d

It is noteworthy that the nitro-substituted benzimidazole derivatives 12c and 13c were not transformed into their corresponding compounds 18 and 19 either in acetic acid or in DMF. Instead, both compounds underwent an intramolecular nucleophilic substitution of the tert-amine yielding the same product 24 (Figure 1) described previously.13

According to the literature pyrrolo- and pyrido[1,2-a]quinolines bearing sulfur containing substituents are very rare.14 Except for a few dithiane and dithiolane derivatives14c,d of appropriate carbonyl compounds only 4-methylthio- and 3-phenylthiopyrrolo[1,2-a]quinoline derivatives were reported,14a,b both in low yields via multistep sequences. Nothing is published concerning sulfonyl substituted derivatives of these heterocycles. For this reason reaction of aldehydes 5 and 6 with the readily avail-
able tosylacetonitrile \(9\) (Scheme 2) was examined. Corresponding arylidene derivatives of \(9\) turned out to be more reactive towards cyclization. Thus, only nitro-substituted compounds \(14c\) and \(15c\) could be isolated. For the remaining aldehydes \(5a,b\) and \(6a,b\) mixtures of arylidene derivatives and compounds \(20a,b\) and \(21a,b\) were formed even after short reaction times. Prolonged heating of the aldehydes \(5a,b\) and \(6a,b\) with nitrile \(9\) in ethanol in the presence of triethylamine furnished pure compounds \(20a,b\) and \(21a,b\) in excellent yields. The derivatives \(14c\) and \(15c\) also cyclized smoothly by heating in DMF. Similar behavior was noted for certain malonodinitrile derivatives.\(^{3a,d,e}\) As expected there was no proton assistance for tosyl derivatives \(14c\) and \(15c\) and acetic acid was ineffective for their cyclization.

Further efforts were directed towards extending this reaction to heterocyclic analogues of aldehydes \(5\) and \(6\), several examples have been reported previously.\(^{15}\) Thus successful tert-amino effect cyclizations were described based on pyridine-derived aminoaldehydes.\(^{15a,b}\) On the other hand, thiophene analogues of \(1\) were prepared by the reaction of pyrrolidino- and piperidino-substituted thiophenes and benzothiophenes with methoxymethylene-malonodinitrile.\(^{15c}\) However, their cyclization was not so clear and depended on the substitution pattern. Even so, an apparently insignificant factor, the position of the methyl group, turned out to be crucial for the cyclization.\(^{15c}\) Hence, the behavior of five-membered heterocycles that have a lesser degree of aromaticity and more definite bond alternations with respect to the tert-amino effect is scarcely predictable. Amazingly, aldehydes \(25\) and \(26\) (Scheme 4) readily available from the corresponding chloroaldehydes\(^{16}\) had not previously been employed in the tert-amino effect. Their condensation with nitriles \(7–9\) under standard conditions afforded propenenitriles \(27\) and \(28\) as single \(E\)-isomers. Generally compounds \(27\) and \(28\) turned out to be less reactive compared to the benzo analogues \(10–15\). Nevertheless, they were converted into derivatives \(29\) and \(30\) in 50–70% yields by heating in DMF for one to two days. Similarly, within the pyrazole series the tosyl derivatives \(29c\) and \(30c\) were more reactive requiring shorter reaction times and giving higher yields. Also, it is noteworthy that the proton-assisted tert-amino effect was not observed for compounds \(27a,b\) and \(28a,b\), probably because of competitive unfavorable protonation of the pyrazole moiety. Furthermore, a literature search revealed compounds \(30a–c\) to be representatives of a hitherto unknown heterocyclic system, namely pyrazolo[4,3-c]quinolizine. Among the quinolizines fused at the c-side with five-membered rings the thieno,\(^{15c,17a}\) cyclopenta\(^{17b–d}\) and fur\(^{17b}\) derivatives have been reported to date. At the same time derivatives of the pyrazolo[3,4-e]indolizine framework present in compounds \(29a–c\) were described earlier.\(^{18}\)

The structures of the prepared heterocycles \(16–21, 29,\) and \(30\) were confirmed by \(^1H,\) \(^13C,\) and 2D NMR (COSY, NOESY, HMBC, and HSQC experiments) data. Particularly, the disappearance of the methylene proton singlet (8.0–8.5 ppm) of the arylidene derivatives \(10–15, 27,\) and \(28\), and the presence of two doublets, each representing a single proton, with geminal coupling (\(J = 14–18\) Hz) in the region of 2.8–3.9 ppm in the \(^1H\) NMR spectra of compounds \(16–21, 29,\) and \(30\) were especially remarkable attributes of the tricyclic system formation. However, the spectral data did not allow us to make conclusions in relation to the stereochemistry. It should be emphasized that both compounds \(16–21\) and their pyrazole analogues \(29\) and \(30\) were obtained as single stereoisomers, the relative configuration of the bridgehead hydrogen and the cyano group could be determined. A small amount (5–10%) of another stereoisomer was detected by NMR for only a number of pyridine derivatives (\(n = 2\)), but it was removed by simple recrystallization of the product. Verboom and Reinhoudt established\(^{3b,k}\) that the tert-amino effect cyclization occurs from the conformation where the double bond points away from the tert-amino substituent (as shown in the Schemes 1 and 3) and further addition of the negatively charged carbon atom to the iminium moiety in the bipolar intermediate \(4\) proceeds from the same face from where the hydrogen has migrated. Following this mechanism and considering the \(E\)-configuration of the starting materials \(10–15, 27,\) and \(28\) the cyano group and the bridgehead hydrogen should occupy a trans position in the products \(16–21, 29,\) and \(30\). Therefore the prepared compounds \(16–21, 29,\) and \(30\) should be formulated as racemates of the structure \(31a\) and its mirror image \(31b\) (Figure 2). To check this and to determine unambiguously the relative configuration of the obtained heterocycles an X-ray crystallographic study was carried out for derivative \(29c\) (Figure 3). It confirmed the trans arrangement of
the hydrogen and the cyano group thus indicating clearly the cyclization of compounds 10–15, 27, and 28 proceeds in complete agreement with the mechanism proposed by Verboom and Reinhoudt.3c–e By analogy the same relative configuration (Figure 2) was assigned throughout the series of compounds 16–21, 29, and 30. The formation of another stereoisomer could be explained by either partial stereomutation of the double bond in the starting materials 10–15, 27, and 28 or stereomutation of the already formed products 16–21, 29, and 30. The latter seems to be more plausible since the Lewis acid induced stereomutation was noted for derivatives like 2,3f

In conclusion, the substituted acetonitriles 7–9 have been employed in the tert-amino effect reactions resulting in the synthesis of hetaryl and arylsulfonyl derivatives of pyrrolo- and pyrido[1,2-a]quinolines 16–21, compounds of potential biological interest.1,2 The new stereochemical aspect arisen has been studied and the cyclization has been shown to proceed according to the previously proposed mechanism.3c–e Furthermore, the proton-assisted ring closure has been ascertained and rationalized for hetaryl derivatives 10–13. The method has been successfully extended to the pyrazole-derived aldehydes 25 and 26; as a result, derivatives of novel heterocyclic system 30 as well as of known, but rare,3f heterocyclic framework 29 have been obtained.

The starting aminomaledehydes 5, 6id,19 and 25, 26b as well as the 2-benzothiazoleacetonitrile 7b2a were prepared as reported. The nitriles 8 and 9 were commercially available. All melting points were determined in open capillary tubes in a Thiele apparatus and are uncorrected. 1H NMR spectra were recorded on a Mercury 400 (400 MHz) spectrometer in DMSO-d6 solutions. Chemical shifts (δ) are given in ppm downfield from the internal standard TMS. J values are in Hz.13c and 2D NMR experiments were performed on a Bruker Avance 500 (500 MHz for 1H and 125 MHz for 13C) spectrometer. The purity of all compounds prepared was checked by 1H NMR and LC/MS on an Agilent 1100 instrument.

Propenenitriles 10a,b, 11a,b, 12a,b, 13a,b, 27a–c, 28a–c; General Procedure
A solution of the corresponding aldehyde 5a, 5b, 6a, 6b, 25, 26 (5 mmol), nitrile 7–9 (5 mmol) and Et3N (0.1 mL in EtOH (10 mL) was refluxed for 1–1.5 h. After cooling, the mixture was poured into H2O (20 mL), the precipitated solid was filtered and recrystallized from an appropriate solvent.

2-(Benzothiazol-2-yl)-3-[2-(1-pyrrolidinyl)phenyl]-2-propenenitrile (10a)

Yield: 1.34 g (82%); mp 92 °C (i-PrOH).

1H NMR: δ = 1.99 (m, 4 H, CH2CH2), 3.39 (m, 4 H, NCH2), 6.91 (m, 2 H, 3,5-HAr), 7.33 (t, J = 8.4, 1 H, 4-HAr), 7.42 (t, J = 7.6, 1 H, HX), 7.51 (t, J = 7.6, 1 H, HX), 7.85 (d, J = 7.2, 1 H, 6-Ha), 7.99 (m, 2 H, HAr), 8.42 (s, 1 H, 3-H).

Anal. Calcd for C21H18FN3S: C, 69.40; H, 4.99; N, 11.56; S, 8.82.

2-(Benzothiazol-2-yl)-3-[2-fluoro-6-(1-pyrrolidinyl)phenyl]-2-propenenitrile (10b)

Yield: 1.55 g (89%); mp 92 °C (i-PrOH).

1H NMR: δ = 1.97 (t, J = 6.0, 4 H, CH2CH2), 3.30 (t, J = 6.0, 4 H, NCH2), 6.60 (t, JH = JHF = 9.2, 1 H, 3-H), 6.75 (t, J = 9.2, 1 H, HX), 7.29 (m, 1 H, 4-HAr), 7.45 (t, J = 7.6, 1 H, HX), 7.95 (d, J = 7.6, 1 H, HX), 8.03 (m, 2 H, HAr), 8.27 (s, 1 H, 3-H).

Anal. Calcd for C21H19N3S: C, 73.00; H, 5.54; N, 12.16; S, 9.67.

2-(Benzothiazol-2-yl)-3-[2-(1-pyrrolidinyl)phenyl]-2-propenenitrile (10c)

Yield: 1.65 g (96%); mp 137 °C (EtOH).

1H NMR: δ = 1.64 (m, 2 H, CH2), 1.71 (m, 4 H, 2CH2), 2.89 (m, 4 H, NCH2), 6.85 (m, 2 H, 3,5-HAr), 7.30 (t, J = 8.5, 1 H, 4-HAr), 7.46 (t, J = 7.8, 1 H, HX), 7.51 (t, J = 7.8, 1 H, HX), 7.82 (d, J = 8.0, 1 H, 6-Ha), 8.03 (m, 2 H, HAr), 8.35 (s, 1 H, 3-H).

Anal. Calcd for C21H19N3S: C, 73.00; H, 5.60; N, 12.35; S, 9.30.

2-(Benzothiazol-2-yl)-3-[2-(1-piperidinyl)phenyl]-2-propenenitrile (11a)

Yield: 1.54 g (85%); mp 159 °C (i-PrOH).

1H NMR: δ = 1.60 (m, 2 H, CH2), 1.73 (m, 4 H, 2CH2), 2.98 (m, 4 H, NCH2), 6.94 (m, 2 H, 3,5-HAr), 7.48 (m, 2 H, 4-HAr, HX), 7.56 (t, J = 7.8, 1 H, HX), 8.06 (m, 3 H, 3-H, HAr).

Anal. Calcd for C21H19FN: C, 73.00; H, 4.99; N, 11.56; S, 8.82.

2-(Benzothiazol-2-yl)-3-[2-(1-piperidinyl)phenyl]-2-propenenitrile (11b)

Yield: 1.30 g (83%); mp 204 °C (EtOH).

1H NMR: δ = 1.98 (t, J = 6.0, 4 H, CH2CH2), 3.38 (t, J = 6.0, 4 H, NCH2), 6.90 (m, 2 H, 3,5-HAr), 7.16 (m, 2 H, HAr), 7.30 (t, J = 7.5, 1 H, HAr), 8.03 (m, 2 H, HAr), 8.27 (s, 1 H, 3-H).
H, 4-HAr), 7.47 (m, 1 H, H2), 7.60 (m, 1 H, H3), 7.79 (d, J = 9.0, 1 H, 6-HAr), 8.43 (s, 1 H, 3-H), 12.70 (s, 1 H, NH).


2-(Benzimidazol-2-yl)-3-[2-(1-piperidinyl)phenyl]-2-propenenitrile (13a)

Yield: 1.49 g (91%); mp 241 °C (EtOH).
1H NMR: δ = 1.79 (m, 6 H, CH2), 3.14 (t, J = 6.7, 4 H, NCH2), 4.48 (s, 2 H, 2-H), 7.47–7.56 (m, 7 H, Ph, HX), 7.96 (d, J = 8.4, 1 H, H2), 8.19 (d, J = 8.4, 1 H, H3), 8.45 (s, 1 H, 3-H).

Anal. Calcd for C20H16N4O2S: C, 63.81; H, 4.28; N, 14.71; S, 8.59. Found: C, 63.80; H, 4.40; N, 14.71; S, 8.59.

5-Nitrocinnamamides 10c–15c; General Procedure

A few drops of Et3N were added to a solution of the aldehyde 5c, 6c (5 mmol) and nitrile 7–9 (5 mmol) in EtOH (10 mL) and the resulting mixture was refluxed for 0.5–1.0 h. After cooling the precipitate formed was filtered and washed with EtOH to yield compounds 10c–15c, which were of sufficient purity for further use. Analytical samples were additionally purified by recrystallization from dioxane.

2-(Benzothiazol-2-yl)-3-[5-nitro-2-(1-pyrrolidinyl)phenyl]-2-propenenitrile (10c)

Yield: 1.75 g (93%); mp 195 °C (dioxane).
1H NMR: δ = 2.18 (t, J = 5.9, 4 H, CH2CH2), 3.26 (m, 4 H, NCH2), 4.47 (s, 2 H, 2-H), 7.61 (t, J = 7.6, 1 H, H4), 7.66 (d, J = 7.6, 1 H, H5), 7.80 (dd, J = 9.0, 4.5, 1 H, H6), 8.73 (s, 1 H, 3-H).

Anal. Calcd for C22H16N6O2S: C, 68.31; H, 4.28; N, 14.88; S, 8.52. Found: C, 68.30; H, 4.40; N, 14.71; S, 8.59.

2-(Benzoazolizol-2-yl)-3-[5-nitro-2-(1-pyrrolidinyl)phenyl]-2-propenenitrile (11c)

Yield: 1.68 g (86%); mp 216 °C (dioxane).
1H NMR: δ = 1.63 (m, 2 H, CH2), 1.74 (m, 4 H, CH2CH2), 2.60 (m, 4 H, NCH2), 2.80 (dd, J = 9.2, 1 H, H3), 7.54 (t, J = 8.0, 1 H, H4), 7.60 (t, J = 8.0, 1 H, H5), 8.09 (s, 1 H, 3-H), 8.11 (d, J = 8.0, 1 H, H6), 8.20 (dd, J = 9.2, 2.3, 1 H, 4-H4), 8.38 (s, 1 H, 3-H).

Anal. Calcd for C22H16N6O2S: C, 64.60; H, 4.65; N, 14.35; S, 8.21. Found: C, 64.64; H, 4.39; N, 14.58; S, 8.30.
2-(Benzimidazol-2-yl)-3-[5-nitro-2-(1-pyrrolidinyl)phenyl]-2-propenitrile (12c)
Yield: 1.54 g (86%); mp 264 °C (dioxane).

1H NMR: δ = 1.94 (m, 4 H, CH2CH2), 3.58 (m, 4 H, NCH2), 6.95 (d, J = 11.7, 1 H, 3-H), 7.26 (d, 2 H, H3), 7.55 (d, J = 7.2, 1 H, H4), 7.71 (d, J = 7.2, 1 H, H2), 8.13 (dd, J = 11.7, J = 16.4, 1 H, H4-α), 8.53 (m, 2 H, 3- H, 6-H), 13.07 (s, 1 H, NH).

Anal. Calcd for C20H19N3O4S: C, 60.44; H, 4.82; N, 10.57; S, 8.07. Yield: 1.67 g (86%); mp 282 °C (dioxane).

1H NMR: δ = 1.61 (m, 2 H, CH2), 1.71 (m, 4 H, 2 × CH2), 3.20 (m, 4 H, NCH2), 7.27 (m, 3 H, 2 H2, 3-H), 7.57 (d, J = 7.5, 1 H, H3), 7.72 (d, J = 7.5, 1 H, H1), 8.18 (s, 1 H, 3- H), 8.28 (dd, J = 8.4, J = 16.4, 1 H, H4-α), 8.78 (d, J = 1.8, 1 H, 6-H), 13.26 (s, 1 H, NH).


2-(Benzimidazol-2-yl)-3-[5-nitro-2-(1-piperidinyl)phenyl]-2-propenitrile (13c)
Yield: 1.60 g (86%); mp 282 °C (dioxane).

1H NMR: δ = 1.61 (m, 2 H, CH2), 1.71 (m, 4 H, 2 × CH2), 3.20 (m, 4 H, NCH2), 7.27 (m, 3 H, 2 H2, 3-H), 7.57 (d, J = 7.5, 1 H, H3), 7.72 (d, J = 7.5, 1 H, H1), 8.18 (s, 1 H, 3- H), 8.28 (dd, J = 8.4, J = 16.4, 1 H, H4-α), 8.78 (d, J = 1.8, 1 H, 6-H), 13.26 (s, 1 H, NH).

Anal. Calcd for C20H19N3O4S: C, 60.44; H, 4.82; N, 10.57; S, 8.07. Yield: 1.81 g (88%); mp 143 °C (dioxane).

1H NMR: δ = 1.66 (m, 2 H, CH2), 1.73 (m, 4 H, 2 × CH2), 2.45 (s, 3 H, CH3), 3.17 (t, J = 4.8, 4 H, CH2), 7.30 (d, J = 12.0, 1 H, 3-H), 7.57 (d, J = 8.0, 2 H, H2), 7.88 (d, J = 8.0, 2 H, H2), 8.26 (s, 1 H, 3-H), 8.30 (dd, J = 12.0, J = 2.0, 2 H, 1-H), 8.64 (d, J = 2.0, 1 H, 6-H).


Pyrryl- and Pyridin-1,2-quinolines 16a–c, 17a–c, 18a,b, 19a,b; General Procedure
A solution of arylidine derivative 10–13 (3 mmol) in AcOH (10 mL) was refluxed for 4–7 h. After cooling, H2O (15 mL) was added and the solid formed was collected by suction and recrystallized from an appropriate solvent to give compounds 16–19. When the reaction was carried out with derivatives 12c and 13c the precipitate separated from the AcOH solution after cooling. It was filtered off and identified as the known compound 24.13

4-Benzo(benzo-2-yl)-1,2,3,3a,4,5-hexahydropyrido[1,2-a]quinoline-4-carbonitrile (16a)
Yield: 0.81 g (82%); mp 169 °C (toluene).

1H NMR: δ = 2.02–2.23 (m, 4 H, 2,3-H), 3.45 (m, 2 H, 1-H, 5-H), 3.62 (dd, J = 8.0, J = 6.8, 1 H, 1-H), 3.77 (d, J = 16.4, 1 H, 5-H), 4.07 (dd, J = 8.0, J = 5.2, 1 H, 3a-H), 6.61 (d, J = 8.8, 1 H, 9-H), 6.67 (t, J = 8.8, 1 H, 7-H), 7.10 (d, J = 8.8, 1 H, 6-H), 7.17 (t, J = 8.8, 1 H, 8-H), 7.50 (t, J = 7.6, 1 H, H8), 7.57 (t, J = 7.6, 1 H, H8), 8.05 (m, 2 H, 6-H).

13C NMR: δ = 22.5 (2-C), 29.1 (3-C), 39.9 (5-C), 44.4 (4-C), 47.4 (1-C), 64.2 (3a-C), 111.2 (7-C), 115.9 (9-C), 117.0 (5a-C), 118.3 (CN), 122.5 (4-C), 123.1 (7-C), 125.9 (6-C), 126.8 (5-C), 128.2 (6-C), 128.7 (8-C), 134.3 (7a-C), 142.4 (9a-C), 152.3 (3a-C), 167.1 (2-C).


5-(Benzoimidazol-2-yl)-2-(4-fluoro-1,2,3,4,5,6-hexahydro-pyrido[1,2-a]quinoline-5-carbonitrile (17b)
Yield: 0.95 g (87%); mp 193 °C (i-PrOH–H2O).

1H NMR: δ = 1.46–1.85 (m, 6 H, 2,3-H), 2.83 (m, 1 H, 1-H), 3.48 (d, J = 16.4, 1 H, 6-H), 3.61 (d, J = 16.4, 1 H, 6-H), 3.70 (m, 1 H, 1-H), 4.10 (m, 1 H, 4a-H), 6.51 (t, J = 8.8, 1 H, 8-H), 6.78 (d, J = 8.8, 1 H, 10-H), 7.13 (m, 1 H, 9-H), 7.46 (t, J = 8.0, 1 H, H8).
5-(Benzothiazol-2-yl)-8-nitro-2,3,4,4a,5,6-hexahydro-1H-pyrido[1,2-a]quinoxine-5-carbonitrile (17c)

Yield: 0.98 g (84%); mp 217 °C (dioxane).

1H NMR: δ = 8.05 (m, 1 H, 1-H), 7.13–7.18 (m, 1 H, 7-H), 7.00 (d, J = 7.2, 1 H, 8-H), 6.98 (d, J = 8.4, 1 H, 10-H), 6.79 (d, J = 8.4, 1 H, 9-H), 6.71 (t, J = 7.2, 1 H, 6-H).

13C NMR: δ = 123.5 (3-C), 123.3 (7-C), 123.7 (5-C), 123.5 (9-C), 123.8 (5-Cx), 126.7 (6-Cx), 127.5 (7-Cx), 127.5 (7a-Cx), 135.7 (7a-C), 137.6 (8-C), 150.3 (10a-C), 152.5 (4a-Cx), 167.3 (2-Cx).

Anal. Calcd for C20H18N4: C, 76.41; H, 5.77; N, 17.82. Found: C, 76.54; H, 5.62; N, 17.82.

5-(Benzimidazol-2-yl)-7-fluoro-2,3,4,4a,5,6-hexahydro-1H-pyrido[1,2-a]quinoxine-5-carbonitrile (19b)

Yield: 85 g (82%); mp 220 °C (i-PrOH).

1H NMR: δ = 7.66 (d, J = 8.4, 1 H, 9-H), 7.01 (d, J = 8.4, 1 H, 10-H), 6.79 (d, J = 8.4, 1 H, 8-H), 6.77 (d, J = 8.4, 1 H, 7-H), 7.09–7.19 (m, 3 H, 9-H, 2-Hx, 8-Hx).

Found: C, 68.04; H, 5.53; N, 16.18.


Tosyl-Substituted Pyrrolo- and Pyrido[1,2-a]quinolines 20a, 21a,b; General Procedure

Et2N (0.1 mL) was added to a solution of aldehyde 5a, 6a (4 mmol) and tosylation reagent (9 0.78 g, 4 mmol) in EtOH (10 mL) and the resulting mixture was refluxed for 1 d. After cooling it was poured into H2O (20 mL) and the precipitated solid was filtered and recrystallized from an appropriate solvent to yield compounds 20a and 21a,b.

4-[4-(Methylphenyl)sulfonyl]-1,2,3,3a,4,5-hexahydropyrrolo[1,2-a]quinoline-4-carbonitrile (20a)

Yield: 1.24 g (88%); mp 189 °C (EtOH).

1H NMR: δ = 7.42 (d, J = 8.0, 2 H, Hx), 7.30 (d, J = 8.0, 2 H, Hx), 7.28 (m, 5 H, 3-7-H), 7.08 (d, J = 8.4, 1 H, 9-H), 6.99 (d, J = 16.0, 1 H, 1-H).

Found: C, 76.48; H, 6.02; N, 17.98.

6-Fluoro-1,2,3,3a,4,5-hexahydropyrrolo[1,2-a]quinoline-4-carbonitrile (20b)

Yield: 1.36 g (92%); mp 175 °C (dioxane).

1H NMR: δ = 8.07 (m, 2 H, 2-H, 7-H), 7.25 (m, 4 H, 1-H, 3-H, 4-H, 5-H), 6.99 (d, J = 8.4, 1 H, 9-H), 6.90 (d, J = 8.4, 1 H, 8-H), 6.69 (d, J = 8.4, 1 H, 10-H), 6.81 (d, J = 8.4, 1 H, 11-H).

Anal. Calcd for C33H29N3OS: C, 76.18; H, 5.67; N, 13.87. Found: C, 75.79; H, 5.57; N, 13.78.

6-Fluoro-4-[4-(methylphenyl)sulfonyl]-1,2,3,3a,4,5-hexahydropyrrolo[1,2-a]quinoline-4-carbonitrile (20b)

Yield: 1.36 g (92%); mp 175 °C (dioxane).

Anal. Calcd for C33H29N3OS: C, 76.18; H, 5.67; N, 13.87. Found: C, 75.79; H, 5.57; N, 13.78.
5-[(4-Methylphenyl)sulfonyl]-2,3,4,4a,5,6-hexahydro-1H-pyrido[1,2-a]quinoline-5-carbonitrile (21a)

Yield: 1.20 g (82%); mp 184 °C (dioxane).

1H NMR: δ = 1.30 (3 mmol) in DMF (10 mL) was heated at 150 °C for 1–2 d.

30a–c and Tosyl-Substituted Derivatives 20c, 21c; General Procedure

A solution of the corresponding arylidene derivative 14c, 15c, 27a–c, 28a–c (3 mmol) in DMF (10 mL) was heated at 150 °C for 1–2 d. After cooling, H2O (15 mL) was added and precipitate formed was filtered and recrystallized from dioxane to yield compounds 20c, 21c, 29a–c, and 30a–c.

4-(4-Methylphenyl)sulfonyl]-7-nitro-1,2,3,3a,4,5-hexahydropyrido[1,2-a]quinoline-4-carbonitrile (20c)

Yield: 0.92 g (77%); mp 215 °C (dioxane).

Anal. Calcd for C34H22N5O4S: C, 69.90; H, 4.06; N, 12.99; S, 7.96. Found: C, 69.90; H, 4.10; N, 12.95; S, 7.95.
**References**


(22) Sheldrick, G. M. SHELXL97 Program for the Refinement of Crystal Structures; University of Gottingen: Germany, 1997.