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Tetrahedron

Fused isoquinolines: 3-aryl-2,3,4,5-tetrahydro-1*H*-pyrrolo[2,3-*c*]-isoquinoline-1,5-dione-2-spiro-4′-(1′-alkyl-1′,4′-dihydropyridine)s

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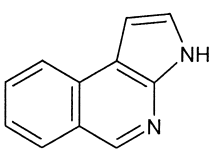
Abstract—Previously unknown 3-arylamino-1,2-dihydro-1-isoquinolones were obtained by condensation of 2-cyanomethylbenzoic acid with arylamines. Isonicotinoylation of the compounds was shown to proceed at the carbon atom in the 4-position to give 3-arylamino-4-isonicotinoyl-1,2-dihydro-1-isoquinolones which were quaternized with alkylating agents and formed the corresponding pyridinium salts. Deprotonation of the latter induced intramolecular conjugated addition with the pyrrole ring closure and formation of spiro compounds. The structure of the products was confirmed by NMR, IR and UV spectroscopy and by synthesis of the model compound, 3-(4-tolyl)-2,3,4,5-tetrahydro-1*H*-pyrrolo[2,3-*c*]isoquinoline-1,5-dione.

The preparative access to 1,4-dihydropyridines via the addition of nucleophilic agents to pyridinium salts was first developed by Kröhnke in 1967.[1] This idea, in its intramolecular version, was used later in the synthesis of the alkaloid nauclefine[2] involving cyclization of quaternized nicotinamides and isonicotinamides induced by coupled addition. Such a cyclization process is of the *exo-trig* type[3] and can be considered as an intramolecular modification of the Michael reaction. Additional examples of the cyclization of similar substrates have been reported.[4,5] This heterocyclization method was extended further, using 4-aryl-substituted pyridinium salts.[6,7] We have shown that quaternary salts of hetaryl 4-pyridyl ketones can also undergo the heterocyclization.[8]

Continuing the study into the *exo-trig* ring closure, we surmised that 3-arylamino-4-isonicotinoyl-1,2-dihydro-1-isoquinolones (**4**) may be appropriate substrates for this purpose.

Using the method proposed earlier for preparation of 3-anilino-1,2-dihydro-1-isoquinolone (2, R=H),[9] we introduced *p*-toluidine, ethyl 4-aminobenzoate, 4-bromoaniline or 4-nitroaniline into reaction with 2-cyanomethylbenzoic acid and obtained the previously unknown 3-arylamino-1,2-dihydro-1-isoquinolones (**2a**–**d**) in good yields.

In their ^{1}H NMR spectra, compounds **2a**–**d** exhibit signals of two exchangeable NH protons, at 10.66–11.35 and 7.78–9.20 ppm, referring to $N^{(2)}H$ and $N^{(3*)}H$, respectively. This assignment is based on the correlation of ^{1}H NMR spectra of **2a**–**d** and their transformation products. Among other spectroscopic peculiarities of compounds **2a**–**d**, there should be intimated the paramagnetic shift (ca. 0.5 ppm)



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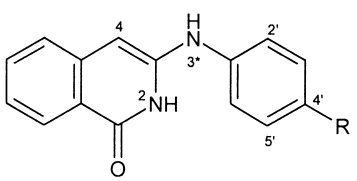
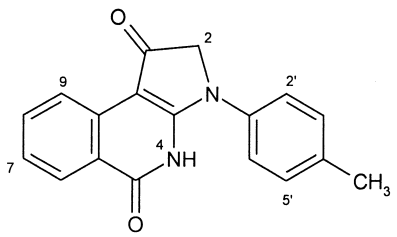


2 a-d

2a : R = Me
2b : R = COOEt
2c : R = Br
2d : R = NO_2



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Keywords: Acylation; Quaternization; 1,4-Dihydropyridines; Spiro compounds.
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of the doublet signal from the $C^{(8)}H$ proton and the diamagnetic shift (by more than 1 ppm) of the singlet from the $C^{(4)}H$ proton relative to the corresponding signals in isoquinoline. In the first case, this is due to magnetic anisotropy of the neighboring C═O group and in the second—to quasi-aromaticity of the pyridone ring.

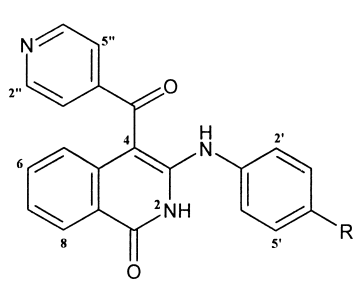
The acylation of 3-anilino-1,2-dihydro-1-isoquinolone was not studied earlier. Since isoquinolones **2a**–**d** have several nucleophilic centers, the acylation, in principle, may proceed at different sites. To determine the main direction of the reaction, we studied first isonicotinoylation of the substrates with isonicotinoyl chloride. The products are formed generally in good yields (60–85%). Based on ^1H NMR spectra, they were identified as 3-arylamino-4-isonicotinoyl-1,2-dihydro-1-isoquinolones (**4a**–**d**), that is, the acylation takes place at the C-4 atom. In the ^1H NMR spectra of compounds **4a**–**d**, the signal of the $C^{(4)}H$ proton, observed in the starting substrates **2a**–**d** at 5.91–6.42 ppm, is absent, but both exchangeable NH protons remain in the molecules and resonate as singlets in the region of 11.52–12.00 and 8.60–9.66 ppm. It should be noted that the effect of the acyl residue at the C-4 atom in **4a**–**d** on chemical shifts is much stronger for the NH than for $C^{(5)}H$ protons. IR spectra of compounds **4a**–**d** show an additional band between 1660 and 1725 cm^{-1} which is absent in starting **2a**–**d** and can be assigned to stretching vibrations of the ketone carbonyl group. Its position in the spectra points to a considerable conjugation of this function with both N-2 and N-3* atoms as is also evidenced in the ^1H NMR spectra. The introduction of the acyl group into molecules **2** causes only a small bathochromic shift (Δ 13 nm) of their long-wave absorption bands in UV spectra. Such a shift as well as a small hyperchromic effect observed are quite predictable for a benzoyl (isonicotinoyl in our case) substituent in the conjugated system.[10] 3-Arylamino-4-isonicotinoyl-1,2-dihydro-1-isoquinolones (**4a**–**d**) are smoothly quaternized in acetonitrile solutions. Although the compounds have several nucleophilic centers, the electrophilic agents attack exclusively the pyridine nitrogen atom to form quaternary salts **5a**–**d** as evidenced by ^1H NMR spectra.

The influence of the acyl residue on the heterocyclic system is more distinct in the salts than in the free bases. Primarily proton-containing groups closest to the substituent suffer considerable paramagnetic shifts: the NMR signals of the $N^{(2')}H$, $N^{(3'*)}$ and $C^{(5')}H$ protons in **5a**–**d** appear already at lower field, in the region of 11.5–12.2, 9.4–9.8 and 7.9–8.3 ppm (as against 11.8–12.0, 8.6–9.3 and 6.8–7.8 ppm in **4a**,**b**), respectively. At the same time, the stretching vibration frequency of the ketone carbonyl in salts **5a**–**d** (near 1670 cm^{-1}) remains unchanged. The color of the solid quaternary salts **5a**–**d** is deeper as compared to the starting compounds **4a**,**b** and **2a**,**b**.

Solutions of **5a**–**d** are instantly decolorized when treated with bases (e.g. triethylamine, piperidine, morpholine or pyridine) and, after dilution with water, easily-crystallizable from DMF precipitates can be isolated. The ^1H NMR and IR spectra of the properly purified products give grounds to suggest that they have the structure of spiro-annelated 1,4-dihydropyridines **7**. The signal of the isoquinoline NH proton remains in structures **7** at 11.51–11.96 ppm, but the proton $N^{(3*)}H$ disappears and a new characteristic pattern corresponding to four α- and β-protons of the 1,4-dihydropyridine moiety arises as two doublets at 6.38–6.59 and 4.33–4.51 ppm. In all cases the coupling constants for these protons are equal to 8 Hz that is typical of olefin *cis*-protons. In the ^{13}C NMR spectra of **7a** and **7c** taken in DMSO-d_6, the signals of the spiro carbon atoms are observed at 88.8 and 88.7 ppm, respectively. The enamine character of the dihydropyridine moiety is reflected in chemical shifts of its C-2′,6′ and C-3′,5′ atoms, i.e. 96.5 and 79.1 ppm for **7a** and 96.8 and 76.0 ppm for **7c**.

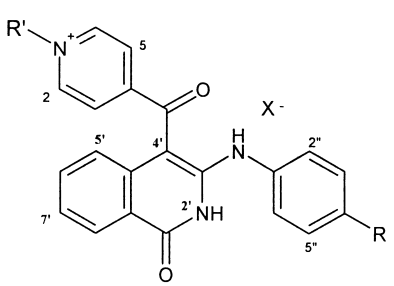
The transformation of quaternary salts **5** into spiro compounds **7** evidently proceeds via intermediates of type **6** which are formed upon deprotonation of the starting salts and then undergo cyclization through intramolecular addition to the electrophilic site in the 4-position of the pyridinium group. It is significant that the sequential transformations **5**→[**6**]→**7** run easily. For example, the contour of the electronic absorption spectrum taken for salt **5a** in methanol reproduces in detail that of spiro compound **7a** but differs in band shape from the spectrum of ketone **4a**. This suggests that the spiro structure is thermodynamically more favorable as compared to the structure of the quaternary salt because even such a weak base as the methanol solvent is able to deprotonate the latter (Scheme 1).

There is no need for preliminary preparation of salts **5** in



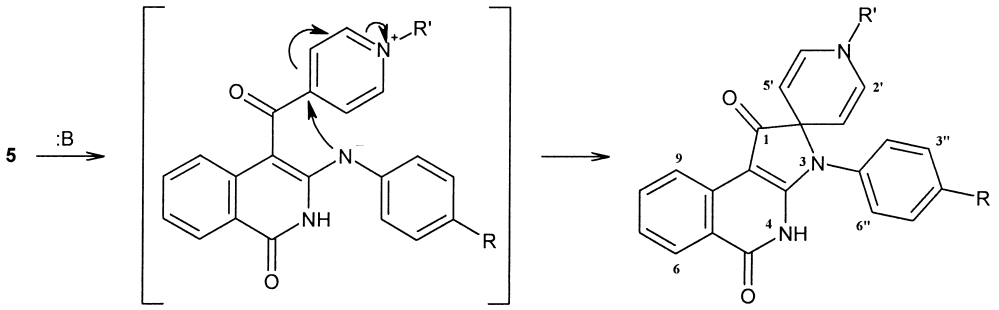
4a-d

4a : R = Me
4b : R = COOEt
4c : R = Br
4d : R = NO_2



5a-d

5a : R = R' = Me , X = TsO
5b : R = Me , R' = Et , X = I
5c : R = COOEt , R' = Et , X = I
5d : R = COOEt , R' = Me , X = I



7a : R = R' = Me
7b : R = Me, R' = Et
7c : R = Me , R' = $PhCH_2$
7d : R = Me , R' = Bz
7e : R = COOEt , R' = Et
7f : R = COOEt , R' = $PhCH_2$
7g : R = Br , R' = Et
7h : R = NO_2 , R' = Me
7i : R = NO_2 , R' = Et

Scheme 1.

order to obtain spiro compounds **7**. It is possible first to treat the isonicotinoylated derivatives **4a–d** with alkylating agents and then, without isolation of the salts **5a–d**, to treat the reaction mixture with a base. In this way compounds **7c** and **7f–i** were obtained in sufficiently high yields. Of particular interest is the one-pot preparation of **7d**, were benzoyl chloride was used in place of the alkylating agent. The benzoyl substituent in the resulting structure **7d** has the strongest effect just on the dihydropyridine ring whose enamine protons exhibit considerable paramagnetic shift in the ^{1}H NMR spectrum.

The basis for the spiro structure **7** is the heterocyclic 3*H*-pyrrolo[2,3-*c*]isoquinoline system (**1**) which is poorly studied. It is known that its derivatives are formed in the reactions of 3-amino-2-methyl-1,2-dihydro-l-isoquinolone with oxalyl chloride[11] and 3-aminoisocarbostyril with *p*-bromophenacyl bromide.[12] In the last case the product is 2-(4-bromophenyl)-4,5-dihydro-3*H*-pyrrolo[2,3-*c*]isoquinolin-5-one which was studied as a selective inhibitor of *c*AMP-dependent proteinkinase.[13] In order to verify the spiro structure of **7**, we synthesized 3-(4-tolyl)-2,3,4,5-tetrahydro-1*H*-pyrrolo[2,3-*c*]isoquinoline-1,5-dione (**3**) as a model compound by the classical method, that is, by reacting 3-(4-toluidino)-1,2-dihydro-l-isoquinolone (**2a**) with chloroacetyl chloride. The comparison of ^{1}H NMR spectra shows a close similarity between chemical shifts of protons in the fused heterocyclic systems of compounds **3** and **7a**. The methylene group $C^{(2)}H_2$ in **3** gives a singlet signal at 4.24 ppm which is absent in **7a**. Also IR spectra of **3** and **7a** are very similar in shapes of absorption bands and vibrational frequencies in the region of 1700–1400 cm^{-1}. The structure similarity of **3** and **7a** having the same chromophore also follows from likeness of their electronic spectra between 250 and 400 nm.

1. Experimental

Melting points of compounds were determined on a Boëtius-type apparatus and are uncorrected. IR spectra were measured with a Pye Unicam SP3-300 instrument in KBr or CsI disks. Electronic spectra of 5×10^{-5} M solutions of **2a**, **3**, **4a**, **5a** and **7a** in methanol were obtained on a Specord M40 spectrophotometer. ^{1}H NMR spectra were taken on a Mercury 400 (Varian) spectrometer (400 MHz) in DMSO-d_6. ^{13}C NMR spectra were measured in DMSO-d_6 on the same instrument at 100 MHz. Chemical shifts are reported in ppm (δ) vs. TMS used as the internal standard. The assignment of signals from aromatic protons was confinned by the COSY HH correlation performed for **7e** and **7h**. In all cases the vicinal coupling constants of aromatic protons are in the range of 7.4–8.4 Hz. TLC on Silufol UV-254 plates was used to monitor the progress of the reactions and to check the purity of the compounds prepared. 2-Cyanomethylbenzoic acid was obtained by the reported procedure.[14]

1.1. General procedure for preparation of 3-arylamino-l,2-dihydro-1-isoquinolones (2a–d)

A suspension of 2-cyanomethylbenzoic acid (10.0 mmol) and the equimolar amount of *p*-toluidine (for **2a**), ethyl 4-aminobenzoate (for **2b**), 4-bromoaniline (for **2c**), or 4-nitroaniline (for **2d**) in chlorobenzene (5 mL) was heated at reflux for 5 h, after which time the solvent was evaporated and the residue was triturated with 2-propanol, filtered, washed with a small amount of 2-propanol, dried, and purified by crystallization from appropriate solvents.

1.1.1. 3-(4-Toluidino)-1,2-dihydro-1-isoquinolone (2a). A colorless solid; (1.5 g, yield 60%); mp 181 °C (from glacial AcOH); [Found: C, 76.68; H, 5.59; N, 11.31. $C_{16}H_{14}N_2O$: requires C, 76.78; H, 5.64; N, 11.19%]; λ_{max} (log ε): 210 (4.37), 370 (3.79) nm; ν_{max} (KBr): 3270 (N–H), 3080, 2959 (C–H), 1650 (C=O), 1600 cm^{-1} (C=C); δ_H: 10.71 (1H, s, NH-2), 7.98 (1H, d, *J*=8.0 Hz, H-8), 7.78 (1H, s, NH-3*), 7.48 (1H, t, *J*=8.0 Hz, H-6), 7.35 (1H, d, *J*=8.0 Hz, H-5), 7.15 (2H, d, *J*=8.2 Hz, H-3′, H-5′), 7.14 (1H, t, *J*=8.0 Hz, H-7); 7.10 (2H, d, *J*=8.2 Hz, H-2′, H-6′), 5.91 (1H, s, H-4), 2.32 (3H, s, CH_3).

1.1.2. 3-(4-Ethoxycarbonylanilino)-1,2-dihydro-1-isoquinolone (2b). A colorless solid; yield (2.22 g, 72%); mp

243 °C (from 2-propanol); [Found: C, 69.98; H, 5.11; N, 8.98. $C_{18}H_{16}N_2O_3$ requires C, 70.12; H, 5.23; N, 9.09%]; ν_{max} (KBr): 3050 (N–H), 2970 (C–H), 1630 cm^{-1} (C═O); δ_H: 11.10 (1H, s, NH-2), 8.65 (1H, s, NH-3*), 8.07 (1H, d, J=8.2 Hz, H-8), 7.87 (2H, d, J=8.4 Hz, H-3′, H-5′), 7.58 (1H, t, J=8.2 Hz, H-6), 7.51 (1H, d, J=8.2 Hz, H-5), 7.29 (1H, t, J=8.2 Hz, H-7), 7.16 (2H, d, J=8.4 Hz, H-2′, H-6′), 6.31 (IH, s, H-4), 4.26 (2H, q, J=7.6 Hz, OCH_2), 1.30 (3H, t, J=7.6 Hz, CH_3).

1.1.3. 3-(4-Bromoanilino)-1,2-dihydro-1-isoquinolone (2c). A colorless solid; (2.55 g, yield 81%); mp 233 °C (from glacial AcOH); [Found: C, 55.13, Br 25.17; N, 8.72. $C_{15}H_{11}BrN_2O$ requires C, 57.16, Br 25.35; N, 8.89%]; ν_{max} (KBr): 3140 (N–H), 2950 (C–H), 1660 (C═O), 1600, 1560, 1540 cm^{-1}; δ_H: 10.66 (1H, s, NH-2), 8.01 (1H, d, J=8.0 Hz, H-8), 7.93 (1H, s, NH-3*), 7.46 (1H, t, J=8.0 Hz, H-6), 7.40 (2H, d, J=8.4 Hz, H-3′, H-5′), 7.30 (1H, d, J= 8.0 Hz, H-5), 7.14 (1H, t, J=8.0 Hz, H-7), 7.12 (2H, d, J=8.4 Hz, H-2′, H-6′), 5.99 (1H, s, H-4).

1.1.4. 3-(4-Nitroanilino)-1,2-dihydro-1-isoquinolone (2d). A colorless solid; (2.39 g, yield 85%); mp 286 °C (from glacial AcOH); [Found: C, 63.9; H, 4.23; N, 14.08. $C_{15}H_{11}N_3O_3$ requires C, 64.05; H, 3.94; N, 14.94%]; ν_{max} (KBr): 3380 (N–H), 1655 (C═O), 1600, 1560, 1505 cm^{-1} (C═C); δ_H: 11.35 (1H, s, NH-2), 9.20 (1H, s, NH-3*), 8.11 (IH, d, J=8.0 Hz, H-8), 7.64 (IH, t, J=8.0 Hz, H-6), 7.58 (1H, d, J=8.0 Hz, H-5), 7.40 (2H, d, J=8.4 Hz, H-3′, H-5′), 7.14 (1H, t, J=8.0 Hz, H-7), 7.12 (2H, d, J=8.4 Hz, H-2′, H-6′), 6.42 (1H, s, H-4).

1.1.5. Preparation of 3-(4-tolyl)-2,3,4,5-tetrahydro-1*H*-pyrrolo[2,3-*c*]isoquinoline-1,5-dione (3). A suspension of isoquinolone **2a** (0.5 g, 2.0 mmol) in anhydrous dioxane (50 mL) was heated under reflux until it became homogeneous. Chloroacetyl chloride (0.2 mL, 2.5 mmol) was then added to the resultant solution and the mixture was refluxed for 4H, and concentrated. The residue was treated with a concentrated soda solution and the solid was filtered off, washed with water, and crystallized from 2-propanol to give **3** as a light yellow solid. Yield (0.33 g, 58%); mp 285 °C; [Found: C, 73.90; H, 4.83; N, 9.58. $C_{18}H_{14}N_2O_2$ requires C, 74.47; H, 4.86; N, 9.65%]; ν_{max} (log ε): 238 (4.46), 247 (4.45), 284 (4.25), 316 (4.15), 370 (3.91) nm; ν_{max} (KBr): 3140, 3060 (N–H), 1670 infl., 1645 (C═O), 1625, 1580, 1525, 1505, 1445, 1400 cm^{-1}; δ_H: 11.91 (1H, s, NH-4), 8.31 (1H, d, J=7.6 Hz, H-9), 8.02 (1H, d, J=7.6 Hz, H-6), 7.61 (1H, t, J=7.6 Hz, H-8), 7.27 (2H, d, J=8.0 Hz, H-3′, H-5′), 7.23 (2H, d, J=8.0 Hz, H-2′, H-6′), 7.22 (1H, 1, J=7.6 Hz, H-7), 4.24 (2H, s, CH_2), 2.37 (3H, s, CH_3).

1.2. General procedure for preparation of 3-arylamino-4-isonicotinoyl-l,2-dihydro-1-isoquinolones (4a–d)

A mixture of the appropriate isoqiunolone **2a**–**d** (5.0 mmol) and isonicotinoyl chloride (5.1 mmol) in anhydrous dioxane (20 mL) was heated at reflux for 3 h. After evaporation of the solvent in vacuum, the residue was treated with a saturated soda solution, filtered off, washed with water and 2-propanol, and recrystallized from dimethylformamide.

1.2.1. 4-Isonicotinoyl-3-(4-toluidino)-1,2-dihydro-l-isoquinolone (4a). Obtained from **2a** as a light yellow solid; (1.08 g, yield 61%); mp 278 °C; [Found: C, 72.70; H, 4.78; N, 10.89. $C_{22}H_{17}N_3O_2$ requires C, 74.35; H, 4.82; N, 11.82%]; ν_{max} (log ε): 293 (4.34), 383 (4.06) nm; ν_{max} (KBr): 3180, 3050 (N–H), 1675, 1620 (C═O), 1575, 1530 cm^{-1}; δ_H: 11.96 (1H, s, NH-2), 8.69 (2H, d, J=4.4 Hz, H-2″, H-6″), 8.60 (1H, s, NH-3*), 8.15 (1H, d, J=7.4 Hz, H-8), 7.42 (2H, d, J=4.4 Hz, H-3″, H-5″), 7.32 (2H, d, J=7.4 Hz, H-3′, H-5′), 7.22 (1H, t, J=7.4 Hz, H-6), 7.21 (2H, d, J=7.4 Hz, H-2′, H-6′), 7.17 (1H, t, J=7.4 Hz, H-7), 6.83 (1H, d, J=7.4 Hz, H-5), 3.00 (3H, s, CH_3).

1.2.2. 3-(4-Ethoxycarbonylanilino)-4-isonicotinoyl-l,2-dibydro-1-isoquinolone (4b). Obtained from **2b** as a colorless solid; (1.45 g, yield 70%); mp 261 °C; [Found: C, 69.68; H, 4.61; N, 10.11. $C_{24}H_{19}N_3O_4$ requires C, 69.72; H, 4.63; N, 10.16%]; ν_{max} (CsI): 3000 (N–H), 1725, 1670, 1610 (C═O), 1570 cm^{-1}; δ_H: 11.82 (1H, s, NH-2), 9.28 (1H, s, NH-3*), 8.40 (2H, d, J=3.6 Hz, H-2″, H-6″), 8.22 (1H, d, J=7.4 Hz, H-8), 7.79 (1H, d, J=7.4 Hz, H-5), 7.68 (2H, d, J=7.6 Hz, H-3′, H-5′), 7.57 (1H, t, J=7.4 Hz, H-6), 7.38 (1H, t, J=7.4 Hz, H-7), 7.38 (2H, d, J=3.6 Hz, H-3″, H-5″), 6.79 (2H, d, J=7.6 Hz, H-2′, H-6′), 4.24 (2H, q, J= 7.8 Hz, OCH_2); 1.34 (3H, t, J=7.8 Hz, CH_3).

1.2.3. 3-(4-Bromoanilino)-4-isonicotinoyl-1,2-dihydro-1-isoquinolone (4c). Obtained from **2c** as a colorless solid; (1.34 g, yield 64%); mp 305 °C; [Found: C, 59.97; H, 3.32, Br 18.96; N, 9.96. $C_{21}H_{14}BrN_3O_2$ requires C, 60.02; H, 3.36, Br 19.1; N, 10.00%]; ν_{max} (CsI): 3180, 3100 (N–H),1670, 1610 (C═O), 1570, 1505 cm^{-1}; δ_H: 11.52 (1H, s, NH-2), 9.66 (1H, s, NH-3*), 8.47 (2H, d, J=4.0 Hz, H-2″, H-6″), 8.14 (1H, d, J=8.4 Hz, H-8), 7.53 (1H, d, J=8.4 Hz, H-5), 7.42 (1H, t, J=8.4 Hz, H-6), 7.38 (2H, d, J=4.0 Hz, H-3″, H-5″), 7.28 (2H, d, J=8.4 Hz, H-3′, H-5′), 7.27 (1H, t, J=8.4 Hz, H-7), 6.90 (2H, d, J=8.4 Hz, H-2′, H-6′).

1.2.4. 4-Isonicotinoyl-3-(4-nitroanilino)-1,2-dihydro-1-isoquinolone (4d). Obtained from **2d** as a sandy-colored solid; (1.64 g, yield 85%); mp 282 °C; [Found: C, 65.26; H, 3.60; N, 14.47. $C_{21}H_{14}N_4O_4$ requires C, 65.28; H, 3.65; N, 14.50%]; ν_{max} (KBr): 3090 (N–H), 1660, 1640 (C═O), 1595, 1515 cm^{-1}; δ_H: 12.00 (1H, s, NH-2), 9.37 (1H, s NH-3*), 8.42 (2H, d, J=4.8 Hz, H-2″, H-6″), 8.26 (1H, d, J=8.4 Hz, H-8), 7.93 (2H, d, J=8.4 Hz, H-3′, H-5′), 7.84 (1H, d, J=8.4 Hz, H-5), 7.64 (1H, t, J=8.4 Hz, H-6), 7.46 (1H, t, H 8.4 Hz, H-7), 7.44 (2H, d, J=4.8 Hz, H-3″, H-5″), 6.79 (2H, d, J=8.4 Hz, H-2′, H-6′).

1.3. General procedure for preparation of 1-alkyl-4-(3-arylamino-1-oxo-1,2-dihydro-4-isoquinolinoyl)-pyridinium salts (5a–d)

A mixture of isoquinolone **4a** or **4b** and an excess of the appropriate alkylating agent in anhydrous acetonitrile (15–20 mL) was refluxed for 10 h. The volatiles were removed in vacuum and the residue was triturated with 2-propanol and washed on a filter with the same solvent.

1.3.1. 1-Methyl-4-[1-oxo-3-(4-toluidino)-1,2-dihydro-4-isoquinolinoyl]pyridinium tosylate (5a). Obtained from

isoquinolone **4a** (0.7 g, 2.0 mmol) and methyl tosylate (0.42 g, 2.2 mmol) as a bright red solid; yield (0.81 g, 75%); mp 230 °C (from AcOH); [Found: C, 66.48; H, 4.98; N, 7.73. $C_{30}H_{27}N_3O_5S$ requires C, 66.53; H, 5.02; N, 7.76%]; λ_{max} (log ε) 238 (4.66); 247 (4.55); 284 (4.40); 316 (4.25); 370 (3.93) nm; ν_{max} (KBr): 3480, 3080 (N–H), 1675, 1630 (C=O), 1555, 1525 cm^{-1}; δ_H: 11.50 (1H, s, NH-2′), 9.78 (1H, s, NH-3′*), 8.89 (2H, d J=6.4 Hz, H-2, H-6), 8.16 (1H, d, J=8.4 Hz, H-8′), 8.04 (2H, d, J=6.4 Hz, H-3, H-5), 7.88 (1H, d, J=8.4 Hz, H-5′), 7.53 (1H, t, J=8.4 Hz, H-6′), 7.46 (2H, d, J=8.0 Hz, H-3″, H-5″), 7.33 (1H, t, J= 8.4 Hz, H-7′), 7.06 (4H, m, $C_6H_4SO_3$), 6.85 (2H, d, J= 8.0 Hz, H-2″, H-6″), 4.25 (3H, s, NCH_3), 2.31 (6H, s, 4″-CH_3+$CH_3C_6H_4SO_3$.

1.3.2. 1-Ethyl-4-[1′-oxo-3′-(4″-toluidino)-1′,2′-dihydro-4′-isoquinolinoyl] pyridinium iodide (5b). Obtained from isoquinolone **4a** (1.06 g, 3.0 mmol) and ethyl iodide (0.62 g, 4.0 mmol); yield (1.22 g, 80%); mp 246 °C (from DMF); [Found: C, 56.30; H, 4.29; N, 8.19. $C_{24}H_{22}IN_3O_2$ requires C, 56.37; H, 4.34; N, 8.22%]; ν_{max} (KBr): 3500, 3050 (N–H), 1675, 1615 (C=O), 1560, 1525 cm^{-1}; δ_H 11.69 (1H, s, NH-2′), 9.44 (1H, s, NH-3′*), 8.94 (2H, d, J=6.4 Hz, H-2, H-6), 8.18 (1H, d, J=8.4 Hz, H-8′), 8.10 (1H, d, J=8.4 Hz, H-5′), 8.05 (2H, d, J=6.4 Hz, H-3, H-5), 7.60 (1H, t, J= 8.0 Hz, H-6′), 7.37 (1H, t, J=8.0 Hz, H-7′), 7.00 (2H, d, J=8.4 Hz, H-3″, H-5″), 6.75 (2H, d, J=8.4 Hz, H-2″, H-6″), 4.50 2H, (q, J=7.8 Hz, NCH_2), 2.27 (3H, s, 4″-CH_3), 1.31 (3H, t, J=7.8 Hz, CH_2CH_3).

1.3.3. 4-[3-(4-Ethoxycarbonylanilino)-1-oxo-l,2-dihydro-4-isoquinolinoyl]-1-ethylpyridinium iodide (5c). Obtained from isoquinolone **4b** and ethyl iodide taken in the same mole ratio as in Section 1.3.2; (1.02 g, yield 60%); mp 295 °C (from DMF); [Found: C, 54.82; H, 4.22; N, 7.33. $C_{26}H_{24}IN_3O_4$ requires C, 54.85; H, 4.25; N, 7.38%]; ν_{max} (KBr): 3510, 3000 (N–H), 1720, 1675, 1610 (C=O), 1560, 1530 cm^{-1}; δ_H: 12.18 (1H, s, NH-2′), 9.37 (1H, s, NH-3′*), 8.92 (2H, d, J=6.4 Hz, H-2, H-6), 8.34 (1H, d, J=8.4 Hz, H-8′), 8.27 (1H, d, J=8.4 Hz, H-5′), 8.09 (2H, d, J=6.4 Hz, H-3, H-5), 7.72 (1H, t, J=8.4 Hz, H-6′), 7.71 (2H, d, J=8.8 Hz, H-3″, H-5″), 7.49 (1H, t, J= 8.4 Hz, H-7′); 6.75 (2H, d, J=8.8 Hz, H-2″, H-6″), 4.43 (2H, q, J=7.8 Hz, NCH_2), 4.27 (2H, q, J=7.8 Hz, OCH_2), 1.34 (3H, t, J=7.8 Hz, OCH_2CH_3), 1.19 (3H, t, J=7.8 Hz, NCH_2CH_3).

1.3.4. 4-[3-(4-Ethoxycarbonylanilino)-1-oxo-l,2-dihydro-4-isoquinolinoyl]-1-methylpyridinium iodide (5d). Obtained from isoquinolone **4b** (0.5 g, 1.2 mmol) and methyl iodide (0.3 g, 2.1 mmol) added in two equal portions 5H, apart; yield (0.48 g, 72%); mp 228 °C (from AcOH); [Found: C, 54.02; H, 3.93; N, 7.52. $C_{25}H_{22}IN_3O_4$ requires C, 54.07; H, 3.99; N, 7.57%]; ν_{max} (KBr): 3500, 3030 (N–H), 1725, 1670, 1610 (C=O), 1575, 1525 cm^{-1}; δ_H: 12.06 (1H, s, NH-2′), 9.41 (1H, s, NH-3′*), 8.86 (2H, d, J=6.0 Hz, H-2, H-6), 8.26 (1H, d, J=7.8 Hz, H-8′), 8.23 (1H, d, J=7.8 Hz, H-5′), 8.09 (2H, d, J=6.0 Hz, H-3, H-5), 7.75 (2H, d, J= 8.0 Hz, H-3″, H-5″), 7.68 (1H, t, J=7.8 Hz, H-6′), 7.47 (1H, t, J=7.8 Hz, H-7′), 6.82 (2H, d, J=8.0 Hz, H-2″, H-6″), 4.29 (2H, q, J=8.0 Hz, OCH_2), 4.18 (3H, s, NCH_3), 1.36 (3H, t, J=8.0 Hz, CH_2CH_3).

1.4. General and typical procedures for preparation of 3-aryl-2,3,4,5-tetrahydro-1*H*-pyrrolo[2,3-*c*]isoquinoline-1,5-dione-2-spiro-4-[1-alkyl(acyl)-1,4-dihydropyridine]s (7a–i)

Method A (for **7a**, **7b**, **7e**). The appropriate pyridinium salt **5a**, **5b** or **5c** (5 mmol) was dissolved on heating in anhydrous pyridine (about 2 mL) and, after cooling, the resultant solution was diluted with water (30 mL). The precipitate formed was separated by filtration, washed with water, dried, and crystallized from dimethylformamide.

Method B (for **7c**, **7f**–**i**). A mixture of the appropriate isoquinolone **4a**–**d** (5 mmol) and alkylating agent (6 mmol) was refluxed in anhydrous acetonitrile (30 mL) for 6H, and concentrated under a reduced pressure. The residue was dissolved in pyridine (10 mL) on heating and after cooling the resulting solution was diluted with water (30 mL). The precipitate formed was filtered off, washed with water, dried, and crystallized from dimethylformamide.

Method C (for **7d**). To isoquinolone **4a** (1.78 g, 5 mmol) dissolved on heating in anhydrous pyridine (30 mL) was added dropwise benzoyl chloride (1.4 g, 10 mmol). The mixture was heated at reflux for 1H, and concentrated under a reduced pressure. The solid residue was triturated with a saturated solution of soda, washed with water and 2-propanol on a filter, dried, and crystallized from dimethylformamide.

1.4.1. 3-(4-Tolyl)-2,3,4,5-tetrahydro-1*H*-pyrrolo[2,3-c]-isoquinoline-1,5-dione-2-spiro-4′-(1′-methyl-1′,4′-dihydropyridine) (7a). Obtained by Method A from salt **5a** as light yellow crystals; (1.48 g, yield 80%); mp 270 °C; [Found: C, 74.70; H, 5.12; N, 11.32. $C_{23}H_{19}N_3O_2$: requires C, 74.78; H, 5.18; N, 11.37%]; λ_{max} (log ε): 238 (4.72), 247 (4.63), 284 (4.44), 316 (4.20), 370 (4.01) nm; ν_{max} (KBr): 3500, 3140, 3050 (N–H), 1650, 1620 (C=O), 1575, 1518, 1400 cm^{-1}; δ_H: 11.65 (1H, s, NH-4), 8.30 (1H, d, J=8.0 Hz, H-9), 8.05 (1H, d, J=8.0 Hz, H-6); 7.65 (1H, t, J=8.0 Hz, H-8), 7.22 (1H, t, J=8.0 Hz, H-7), 7.20 (2H, d, J=8.0 Hz, H-3″, H-5″), 7.09 (2H, d, J=8.0 Hz, H-2″, H-6″), 6.44 (2H, d, J=7.2 Hz, H-2′, H-6′), 4.33 (2H, d, J=7.2 Hz, H-3′, H-5′), 2.90 (3H, s, NCH_3), 2.39 (3H, s, 4″-CH_3); δ_C,: 96.5 (C-2′.6′), 88.8 (spiro-C), 79.1 (C-3′.5′).

1.4.2. 3-(4-Tolyl)-2,3,4,5-tetrabydro-1*H*-pyrrolo[2,3-*c*]-isoquinoline-1,5-dione-2-spiro-4′-(1′-ethyl-1′,4′-dibydropyridine) (7b). Obtained by Method A from salt **5b**; (1.57 g, yield 82%); mp 331 °C; [Found: C, 75.11; H, 5.48; N, 10.91. $C_{24}H_{21}N_3O_2$ requires C, 75.18; H, 5.52; N, 10.96%]; ν_{max} (KBr): 3510, 3150, 3060 (N–H), 1655, 1625 (C=O), 1585, 1525 cm^{-1}; δ_H: 11.51 (1H, s, NH-4), 8.30 (1H, d, J=7.8 Hz, H-9), 7.99 (1H, d, J=7.8 Hz, H-6), 7.58 (1H, t, J=7.8 Hz, H-8), 7.17 (1H, t, J=7.8 Hz, H-7), 7.14 (2H, d, J=8.0 Hz, H-3″, H-5″), 7.03 (2H, d, J=8.0 Hz, H-2″, H-6″), 6.38 (2H, d, J=7.6 Hz, H-2′, H-6′), 4.34 (2H, d, J= 7.6 Hz, H-3′, H-5′), 3.20 (2H, q, J=7.8 Hz, NCH_2), 2.36 (3H, s, 4″-CH_3), 0.95 (3H, 1, J=7.8 Hz, CH_2CH_3).

1.4.3. 3-(4-Tolyl)-2,3,4,5-tetrahydro-1*H*-pyrrolo[2,3-*c*]-isoquinoline-1,5-dione-2-spiro-4′-(1′-benzyl-1′,4′-dihydropyridine) (7c). Obtained by Method B from

isoquinolone **4a** and benzyl chloride; (1.74 g, yield 78%); mp 340 °C; [Found: C, 78.14; H, 5.11; N, 9.39. $C_{29}H_{23}N_3O_2$ requires C, 78.18; H, 5.20;N, 9.43%]; ν_{max} (KBr): 3490, 3140, 3060, 2950 (N–H), 1645, 1620 (C═O), 1580, 1525, 1495, 1435, 1405 cm^{-1}; δ_H: 11.65 (1H, s, NH-4), 8.30 (1H, d, *J*=7.6 Hz, H-9), 7.99 (1H, d, *J*=7.6 Hz, H-6), 7.64 (1H, t, *J*=7.6 Hz, H-8), 7.22 (1H, t, *J*=7.6 Hz, H-7), 7.19 (2H, d, *J*=8.0 Hz, H-3″, H-5″), 7.09 (2H, d, *J*=8.0 Hz, H-2″, H-6″), 6.83–7.21 (5H, m, Ph), 6.50 (2H, d, *J*=7.8 Hz, H-2′, H-6′), 4.43 (2H, d, *J*=7.8 Hz, H-3′, H-5′), 4.41 (2H, s, NCH_2), 2.38 (3H, s, 4″-CH_3); δ_C,: 96.8 (C-2′.6′), 88.7 (spiro-C), 79.0 (C-3′.5′).

1.4.4. 3-(4-Tolyl)-2,3,4,5-tetrahydro-1*H*-pyrrolo[2,3-*c*]-isoquinoline-l,5-dione-2-spiro-4′-(1′-benzoyl-1′,4′-dihydropyridine) (7d). Obtained by Method C; (1.68 g, yield 73%); mp 250 °C; [Found: C, 75.75; H, 4.58; N, 9.10. $C_{29}H_{21}N_3O_3$ requires C, 75.80; H, 4.61; N, 9.14%]; ν_{max} (KBr): 3130, 3060, 2950 (N–H), 1670 infl., 1660, 1625 (C═O), 1585, 1525, 1455 cm^{-1}; δ_H: 11.88 (1H, s, NH-4), 8.28 (1H, d, *J*=8.2 Hz, H-9), 8.02 (1H, d, *J*=8.0 Hz, H-6), 7.63 (1H, t, *J*=8.0 Hz, H-8), 7.37–7.56 (5H, m, Ph), 7.24 (2H, d, *J*=7.2 Hz, H-2′, H-6′), 7.23 (2H, d, *J*=8.0 Hz, H-3″, H-5″), 7.19 (1H, t, *J*=8.0 Hz, H-7), 7.16 (2H, d, *J*=8.0 Hz, H-2″, H-6″), 5.03 (2H, d, *J*=7.2 Hz, H-3′, H-5′), 2.38 (3H, s, 4″-CH_3).

1.4.5. 3-(4-Ethoxycarbonylphenyl)-2,3,4,5-tetrahydro-1*H*-pyrrolo[2,3-*c*]isoquinoline-1,5-dione-2-spiro-4′-(1′-ethyl-1′,4′-dihydropyridine) (7e). Obtained by Method A from salt **5c**; (1.74 g, yield 79%); mp 238 °C; [Found: C, 70.70; H, 5.21; N, 9.47. $C_{26}H_{23}N_3O_4$ requires C, 70.74; H, 5.25; N, 9.52%]; ν_{max} (KBr): 3510, 3130, 3010 (N–H), 1730, 1670 infl., 1650, 1620 (C═O), 1588, 1550, 1520, 1500, 1405 cm^{-1}; δ_H: 11.94 (1H, s, NH-4), 8.32 (1H, d, *J*=8.0 Hz, H-9), 8.02 (1H, d, *J*=8.0 Hz, H-6), 7.91 (2H, d, *J*=8.0 Hz, H-3″, H-5″), 7.60 (1H, t, *J*=8.0 Hz, H-8), 7.28 (2H, d, *J*=8.0 Hz, H-2″, H-6″), 7.22 (1H, t, *J*=8.0 Hz, H-7), 6.44 (2H, d, *J*=7.2 Hz, H-2′, H-6′), 4.39 (2H, d, *J*=7.2 Hz, H-3′, H-5′), 4.34 (2H, q, *J*=7.8 Hz, OCH_2), 3.24 (2H, q, *J*=7.8 Hz, NCH_2), 1.37 (3H, t, *J*=7.8 Hz, OCH_2CH_3), 1.03 (3H, t, *J*=7.8 Hz, NCH_2CH_3).

1.4.6. 3-(4-Ethoxycarbonylphenyl)-2,3,4,5-tetrahydro-1*H*-pyrrolo[2,3-*c*]isoquinoline-1,5-dione-2-spiro-4′-(1′-benzyl-1′,4′-dihydropyridine) (7f). Obtained by Method B from isoquinolone **4b** and benzyl chloride; (1.79 g, yield 71%); mp 301 °C; [Found: C, 73.91; H, 4.96; N, 8.29. $C_{31}H_{25}N_3O_4$: requires C, 73.94; H, 5.00; N, 8.34%]; ν_{max} (KBr): 3500, 3140, 3020 (N–H), 1728, 1670 infl., 1650, 1620 (C═O), 1580, 1540, 1520, 1405 cm^{-1}; δ_H 11.85 (1H, s, NH-4), 8.33 (1H, d, *J*=8.2 Hz, H-9), 8.02 (1H, d, *J*=8.2 Hz, H-6), 7.90 (2H, d, *J*=8.2 Hz, H-3″, H-5″), 7.63 (1H, t, *J*=8.2 Hz, H-8), 7.28 (2H, d, *J*=8.2 Hz, H-2″, H-6″), 7.23 (1H, 1, *J*=8.2 Hz, H-7), 6.907.21 (5H, m, Ph), 6.53 (2H, d, *J*=7.2 Hz, H-2′, H-6′), 4.43 (2H, s, NCH_2), 4.39 (2H, d, *J*=7.2 Hz, H-3′, H-5′), 4.37 (2H, q, *J*=7.8 Hz, OCH_2), 1.42 (3H, t, *J*=7.8 Hz, CH_3).

1.4.7. 3-(4-Bromopbenyl)-2,3,4,5-tetrahydro-1*H*-pyrrolo-[2,3-*c*]isoquinoline-1,5-dione-2-spiro-4′-(1′-ethyl-1′,4′-dihydropyridine) (7g). Obtained by Method B from isoquinolone **4c** and ethyl iodide; (1.91 g, yield 85%); mp 291 °C; [Found: C, 61.59; H, 4.01, Br 17.73; N, 9.32. $C_{23}H_{18}BrN_3O_2$: requires C, 61.62; H, 4.05; Br 17.82; N, 9.37%]; ν_{max} (KBr): 3505, 3150, 3060, 3000 (N–H), 1670 infl., 1650, 1620 (C═O), 1580, 1505, 1435, 1405 cm^{-1}; δ_H: 11.73 (1H, s, NH-4), 8.29 (1H, d, *J*=8.0 Hz, H-9), 7.99 (1H, d, *J*=8.0 Hz, H-6), 7.59 (1H, t, *J*=8.0 Hz, H-8), 7.49 (2H, d, *J*=8.2 Hz, H-3″, H-5″), 7.20 (1H, t, *J*=8.0 Hz, H-7), 7.11 (2H, d, *J*=8.2 Hz, H-2″, H-6″), 6.43 (2H, d, *J*=7.2 Hz, H-2′, H-6′), 4.35 (2H, d, *J*=7.2 Hz, H-3′, H-5′), 3.23 (2H, q, *J*=7.8 Hz, NCH_2), 0.97 (3H, t, *J*=7.8 Hz, CH_3).

1.4.8. 3-(4-Nitrophenyl)-2,3,4,5-tetrahydro-1*H*-pyrrolo-[2,3-*c*]isoquinoline-1,5-dione-2-spiro-4′-(1′-methyl-1′,4′-dihydropyridine) (7h). Obtained by Method B from isoquinolone **4d** and dimethyl sulfate as an ocher-colored solid; (1.38 g, yield 69%); mp 319 °C; [Found: C, 65.97; H, 3.99; N, 13.92. $C_{22}H_{16}N_4O_4$ requires C, 66.00; H, 4.03; N, 13.99%]; ν_{max} (KBr): 3500, 3420, 3120 (N–H), 1670 infl., 1645, 1620 (C═O), 1575, 1485, 1415 cm^{-1}; δ_H: 11.96 (1H, s, NH-4), 8.30 (1H, d, *J*=8.2 Hz, H-9), 8.18 (2H, d, *J*=8.2 Hz, H-3″, H-5″), 8.04 (1H, d, *J*=8.2 Hz, H-6), 7.61 (1H, t, *J*=8.2 Hz, H-8), 7.46 (2H, d, *J*=8.2 Hz, H-2″, H-6″), 7.25 (1H, t, *J*=8.2 Hz, H-7), 6.55 (2H, br.s, H-2′, H-6′), 4.52 (2H, br.s, H-3′, H-5′), 3.06 (3H, s, NCH_3).

1.4.9. 3-(4-Nitrophenyl)-2,3,4,5-tetrahydro-1*H*-pyrrolo-[2,3-*c*]isoquinoline-l,5-dione-2-spiro-4′-(1′-ethyl-1′,4′-dihydropyridine) (7i). Obtained by Method B from isoquinolone **4d** and ethyl iodide; (1.76 g, yield 85%); mp 291 °C; [Found: C, 66.58; H, 4.31; N, 13.47. $C_{23}H_{18}N_4O_4$ requires C, 66.66; H, 4.38; N, 13.52%]; ν_{max} (KBr): 3500, 3140, 3040 (N–H), 1670 infl., 1655, 1625 (C═O), 1585, 1535, 1510, 1440, 1405 cm^{-1}; δ_H: 11.96 (1H, s, NH-4), 8.31 (1H, d, *J*=8.2 Hz, H-9), 8.15 (2H, d, *J*=8.2 Hz, H-3″, H-5″), 8.04 (1H, d, *J*=8.2 Hz, H-6), 7.62 (1H, t, *J*=8.2 Hz, H-8), 7.46 (2H, d, *J*=8.2 Hz, H-2″, H-6″), 7.26 (1H, t, *J*=8.2 Hz, H-7), 6.59 (2H, br.s, H-2, H-6(′), 4.51 (2H, br.s, H-3′, H-5′), 3.35 (2H, q, *J*=7.8 Hz, NCH_2), 1.08 (3H, t, *J*=7.8 Hz, CH_3).

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