3-AMINO-4-ARYL-1(2H)-ISOQUINOLONES

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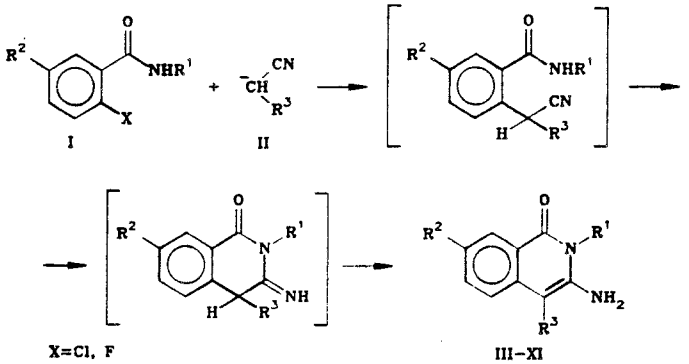
3-Amino-4-aryl-1(2H)-isoquinolones have been synthesized by treating 2-halobenzamides with arylacetonitriles. The angle of rotation of the 4-phenyl grop has been determined.

Among the isoquinolines there has been discovered a broad spectrum of physiological activity [1] and this has led to our interest in a search for methods of synthesizing polyfunctional isoquinolines. The first 3-amino-1(2H)-isoquinolones, synthesized from 2-cyanomethylbenzoic acids [2, 3], have been obtained recently. We have developed a method for the synthesis of the previously unknown 3-amino-4-aryl-1(2H)-isoquinolones by the reaction of monosubstituted 2-halobenzamides (I) with arylacetonitriles (II). Annelation of the heterocyclic nucleus can occur by the following reaction sequence:



X=Cl, F

III-XI

The IR spectra of III-IX show absorption bands at 3280-3330 (NH_2) and 1660-1680 cm^{-1} (CO). The UV spectra of the isoquinolines show a long wavelength maximum at 390-416 nm (log ε 4.06-4.23) for $R^2 = NO_2$ and 380 nm (log ε 3.87) for $R^2 = H$.

The PMR spectra of III-XI show amino group protons as a broadened singlet in the region 4.62-6.49 ppm (2H) and this disappears upon treatment with D_2O. The lowest field signal is the doublet for 8-H ($R^2 = NO_2$) at 8.76-8.83 ppm (J = 1.5 Hz). For XI, this signal appears at 8.06 ppm (J = 8.5 Hz).

The doublet for 5-H centered at 6.78 ppm is extremely prominent (J = 8.7 Hz). According to [4] this proton absorbs at 7.5-7.8 ppm in isoquinoline. The diamagnetic shift we see for this proton is due to it falling within the area of diamagnetic shielding by the π-electron ring current of the 4-phenyl substituent. This effect is typical of sterically hindered phenyl derivatives [5, 6].

To evaluate the contribution of the shielding σ by the phenyl ring current we have calculated by method [7] its angle of rotation φ relative to the plane of the heterocyclic nucleus as φ = 61°. The value of σ as a function of the torsional angle φ was made by the method of Johnson and Bovey [8]. For calculation of the angle φ the value of σ was 0.6 ppm, which was in agreement with the region given above for the 5-H absorption in the isoquinolone. It should also be mentioned that the 3-NH_2 group, in agreement with quantum chemical calculations, does not significantly affect the electron density at position 5 of the isoquinolone ring and thus has no significant effect on the chemical shift of the 5-H proton.

The above data do, in fact, confirm the presence of the phenyl substituent at position 4 in the isoquinolone molecule.

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TABLE 1. Parameters for the Synthesized Compounds

Compound	R¹*	R³	Empirical formula	mp., °C	PMR spectrum, δ, ppm			Yield, %**
					8-H, d	6-H, m	5-H, d	
III	H	C_6H_5	$C_{15}H_{11}N_3O_3$	228	8,76	7,92	6,78	83
IV	CH_3	C_6H_5	$C_{16}H_{13}N_3O_3$	259	8,80	7,99	6,71	74
V	CH_3	4-ClC_6H_4	$C_{16}H_{12}ClN_3O_3$	275	8,76	7,98	6,68	81
VI	C_6H_5	C_6H_5	$C_{21}H_{15}N_3O_3$	285	8,78	8,11	6,85	68
VII	$CH_2C_6H_5$	3-$CH_3OC_6H_4$	$C_{23}H_{19}N_3O_4$	193	8,83	8,05	6,74	78
VIII	CH_3	3,4-$(CH_3O)_2C_6H_3$	$C_{18}H_{17}N_3O_5$	269	8,80	8,00	6,79	65
IX	2- Pyridyl	C_6H_5	$C_{20}H_{14}N_4O_3$	202	8,74	8,11	6,83	67
X	$CH_2C_6H_5$	4-FC_6H_4	$C_{22}H_{16}FN_3O_3$	245	8,82	8,05	6,75	61
XI	C_6H_5	4-FC_6H_4	$C_{21}H_{15}FN_2O$	295	8,06	—***	6,80	72

*I–X $R^2 = NO_2$, XI R^2 = H.

**Compounds V and VII were recrystallized from 2-propanol and the rest from nitromethane.

***Signal hidden by the aromatic proton signals.

The above reaction occurs particularly readily (in the presence of K_2CO_3) when the chlorine atom is activated by the nitro group in 5-nitro-2-chlorobenzamides. Only when Cs_2CO_3 is used as base do the 2-fluoro- and 2-chlorobenzamides react with acrylacetonitriles.

EXPERIMENTAL

IR spectra were obtained on a Specord IR (in KBr tablets), electronic spectra on a Specord UV-vis (2-propanol solvent), and PMR spectra on a Bruker WP-100 (DMSO-d_6 solvent) with TMS as internal standard. The reaction course and product purities were monitored by TLC on Silufol UV-254 plates using chloroform—methanol (9:1) eluent and visualized by UV light.

For calculation of the effect of the ring current a molecular model for III-IX was used in which the lengths of the C—C and C—N bonds were taken the same and equal to 0.139 nm. The valence angles in the six-membered rings were 120° and the C—H bonds were placed along the bisector of the C—C—C valence angle. The effective radius for the hydrogen atom was taken as 0.12 nm.

The parameters and yields for the compounds synthesized are given in Table 1. Elemental analytical data for N and Cl agreed with those calculated.

3-Amino-4-aryl-1(2H)-isoquinolones (III-XI). Ignited K_2CO_3 (10 mmole) was added to a solution of the appropriate 2-halobenzamide (5 mmole) in DMF (70 ml) and refluxed for 1 h. The solvent was removed in vacuo and the residue poured into water (70 ml), acidified to pH 7 with acetic acid, and the precipitate filtered, washed with water, dried, and recrystallized from the corresponding solvent.

For the 2-fluoro- and 2-chlorobenzamides, the reaction was carried out in the presence of Cs_2CO_3 by refluxing in DMF for 3 h.

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