SYNTHESIS OF 3-AMINO-4-HETARYL-1(2H)-ISOQUINOLONES FROM CONDENSED ISOQUINOLONES WITH A BRIDGEHEAD NITROGEN ATOM

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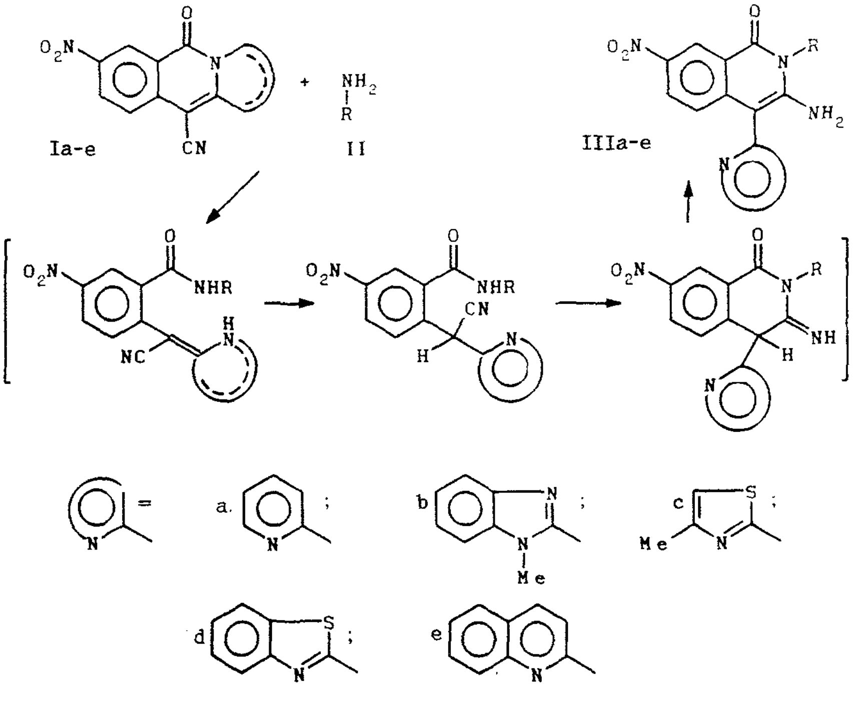
An alternative scheme for synthesis of 3-amino-4-hetaryl-1(2H)-isoquinolones is based on the reaction of condensed isoquinolones with a bridge nitrogen atom with amines.

We have previously developed a new approach to the synthesis of condensed isoquinolones with a bridgehead nitrogen atom, involving the reaction of α-azahetarylacetonitriles with 2-halobenzoate esters [1].

In this paper we show several possibilities for using condensed isoquinolones as synthons to obtain 3-amino-4-hetaryl-1(2H)-isoquinolones, which may find application in analytical chemistry [2, 3], as well as biologically active compounds or intermediate products of their synthesis [4]. The latter have been obtained from reaction of condensed isoquinolones I with primary aliphatic and aromatic amines II. The synthesis of 3-amino-4-hetaryl-1(2H)-isoquinolones III may be described as follows: first step, attack by the amine on the polarized carbonyl carbon and release of the isoquinoline nucleus; second step, intramolecular addition of the NH-amide fragment of the molecule to the nitrile triple bond with subsequent isomerization of the molecule. The second step of this transformation has been studied [5] using as an example the reaction of α-azahetarylacetonitriles with monosubstituted amides of 5-nitro-2-chlorobenzoic acid to give the same compounds III, whose formation was verified by the identity of the physicochemical characteristics (mixed mp, PMR, IR, and UV spectra) of the 3-amino-4-hetaryl-1(2H)-isoquinolones III obtained in the present study and described previously in [5].



$R = NH_2, CH_2CH_2CH_2CH_3, CH_2CH_2CH_2OH, CH_2C_6H_5, C_6H_5$

The IR spectra of III display a primary amino group absorption in the 3360-3470 cm^{-1} region, for compound III ($R = NH_2$), 3350-3500 cm^{-1}; the valence vibration of the conjugated carbonyl group is observed as an intense absorption band at 1645-1680 cm^{-1}. The electronic absorption spectra of isoquinolones III show a long-wave absorption in the 407-435 nm region (log ε 3.94-4.21) and agree well with those of the analogous structures in [5], indicating their isoelectronic structure.

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TABLE 1. Characteristics of the Synthesized Compounds

Compound	Elemental formula	R	T_{mp}, °C	PMR, δ, ppm			IR ν, cm^{-1}		Yield, % *
				8-H	6-H	5-H	C=O	NH_2	
IIIa	$C_{14}H_{11}N_5O_3$	NH_2	287	8,77	8,09	7,92	1660	3350	87
IVa	$C_{17}H_{16}N_4O_4$	$CH_2CH_2CH_2OH$	224	8,89	8,07	7,90	1645	3450	73
Va	$C_{21}H_{16}N_4O_3$	$CH_2C_6H_5$	208	8,82	8,10	7,91	1670	3360	84
VIa	$C_{18}H_{18}N_4O_3$	$CH_2CH_2CH_2CH_3$	195	8,79	8,14	7,87	1650	3450	78
VIIb	$C_{17}H_{14}N_6O_3$	NH_2	298	8,83	8,07	—**	1675	3360	73
IXb	$C_{23}H_{17}N_5O_3$	C_6H_5	239	8,75	—**	7,84	1665	3370	75
Xc	$C_{16}H_{16}N_4O_4S$	$CH_2CH_2CH_2OH$	241	8,83	8,21	7,60	1680	3470	81
XIId	$C_{16}H_{11}N_5O_3S$	NH_2	>300	8,52	8,27	8,11	1670	3500	83
XIIId	$C_{19}H_{16}N_4O_4S$	$CH_2CH_2CH_2OH$	224	8,85	—**	7,80	1665	3400	76

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*Compounds IIIa-VIa and Xc were recrystallized from dioxane, VIIb and IXb from acetonitrile, and XIId and XIIId from nitromethane.

**The signal is masked by the aromatic proton signal.

The PMR spectra in DMSO-d_6 of compounds III show the amino-group protons in the 3-position of the isoquinoline nucleus as broad singlets in the 7.27-8.29 (2H) and those in the 2-position (III, R = NH_2) in the 5.75-5.84 (2H) ppm region, disappearing upon treatment of the sample with D_2O. The chemical shifts of the isoquinoline protons of III appear in the same regions as described in [5] with the analogous effects of paramagnetic shielding (Table 1).

Thus, the proposed method affords not only the previously described 3-amino-4-hetaryl-1(2H)-isoquinolones, but also the 2-substituted molecules.

EXPERIMENTAL

IR spectra were made on a Specord UR in KBr disks, electronic spectra on a Specord UV-vis spectrophotometer in 2-propanol. PMR spectra were recorded on a Bruker WP-100Y in DMSO-d_6 with TMS as internal standard. The reaction progress and the purity of products were monitored by TLC on Silufol UV-254 plates with elution in chloroform—methanol 9:1 and UV visualization.

The characteristics of VIIIb, XIc, XIVd, and XVe (R = $CH_2C_6H_5$ for all of these) are given in [5]. Elemental analyses for N and S gave the expected values.

Condensed isoquinolones with a bridgehead nitrogen atom were obtained from the corresponding α-azahetarylacetonitriles and 5-nitro-2-chlorobenzoic esters [1].

10-Nitro-12-oxo-7-cyano(b, f)-dibenzoquinolizine (Ie, $C_{18}H_9N_3O_3$) were obtained by the method of [1]. Mp 202°C (from DMF). Yield 93%.

3-Amino-4-hetaryl-1(2H)-isoquinolones (III-XV). To a solution of 0.01 mole of the corresponding isoquinolone I in 50 ml DMF were added 0.01 mole of NaOH and 0.01 mole of the corresponding amine and the mixture was refluxed for 2 h. The solvent was removed under vacuum and the residue treated with 70 ml of water and acidified with acetic acid to pH 7. The precipitate was filtered off, washed with water, dried, and crystallized from the corresponding solvent. If the reaction was carried out with hydrazine hydrate, NaOH was not added to the reaction mixture.

Yields of VIIId, XIc, XIVd, and XVe (R = $CH_2C_6H_5$ for all of these) were 77-85%.

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