SYNTHESIS AND STRUCTURE OF 3-AMINO-4-HETARYL-1-(2H)-ISOQUINOLONES

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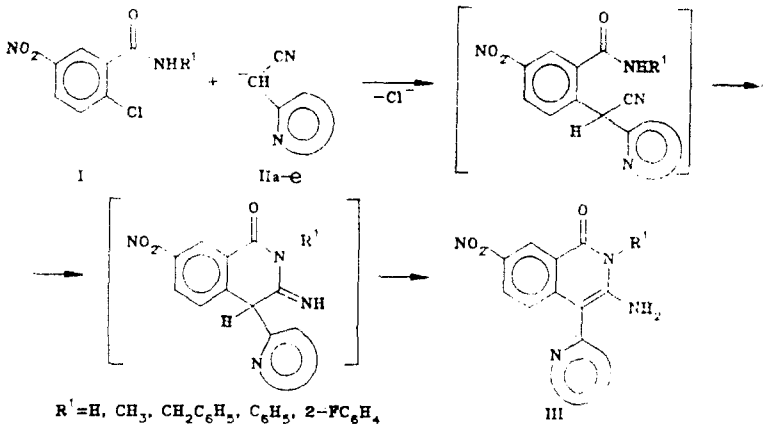
A one-step preparative method of synthesis of 3-amino-4-hetaryl-1(2H)-isoquinolones by reaction of 5-nitro-2-chlorobenzamides with α-azahetarylacetonitriles in the presence of base has been developed. It has been shown that benzimidazo[1,2-b]isoquinolones may be obtained in this way.

Continuing our work on the development of a new approach to the synthesis of polyfunctional isoquinolones [1, 2], we have investigated the preparation of 3-amino-4-hetaryl-1(2H)-isoquinolones, which constitute valuable synthons and potentially biologically active compounds [3]. An examination has been carried out of the reaction of monosubstituted 5-nitro-2-chlorobenzamides (I) with 2-cyanomethyl derivatives of pyridine (IIa), 1-methylbenzimidazole (IIb), quinoline (IIc), benzothiazole (IId), and 4-methylthiazole (IIe) in the presence of potassium carbonate. The synthesis of 3-amino-4-hetaryl-1(2H)-isoquinolones (III) involves replacement of chlorine by the carbanion formed from the α-azahetarylacetonitrile (II) in the presence of potassium carbonate, followed by intramolecular addition of the amide NH group to the nitrile group and isomerization of the product.



The IR spectrum of (III) showed no absorption for the nitrile group, but amino-group absorption was present as a broad band at 3300-3460 cm^{-1}, and stretching vibrations of the conjugated carbonyl group at 1645-1680 cm^{-1}. The UV spectra of (III) showed long-wavelength maxima at 395-435 nm (log ε 3.95-4.27).

The PMR spectra of (III) showed signals for the amino-group protons as a broadened singlet at 6.94-7.89 ppm (2H), which disappeared on treatment of the sample with D_2O. The presence of the isoquinoline ring was confirmed by the appearance in the PMR spectrum of a low-field signal for the 8-H proton at 8.78-9.26 ppm (d, J = 1.5 Hz), the high paramagnetic shift of which was due to the descreening effects of the adjacent carbonyl and nitro groups. The position of the signal for the 5-H proton (6.81-8.19 ppm, J = 8.7 Hz) was unusual. In previously-examined 3-amino-4-aryl-1(2H)-isoquinolines [2], the 5-H signal was seen as a doublet at 6.78 ppm. We attribute this shift to higher field, as reported in [4], to diamagnetic screening of the π-electron current of the phenyl substituent in the 4-position. This assumption was confirmed by calculation of the torsion angle of the aryl substituent with respect to the plane of the heterocyclic nucleus. In the present case, the opposite behavior is seen, as a result of hydrogen bonding between the amino-group and the nitrogen of the azaheterocycle, which results in flattening of the molecule. This in turn leads to a paramagnetic shift of the signal for the 5-H proton as a result of the descreening influence of the heterocycle in the 4-position of the isoquinolones (III).

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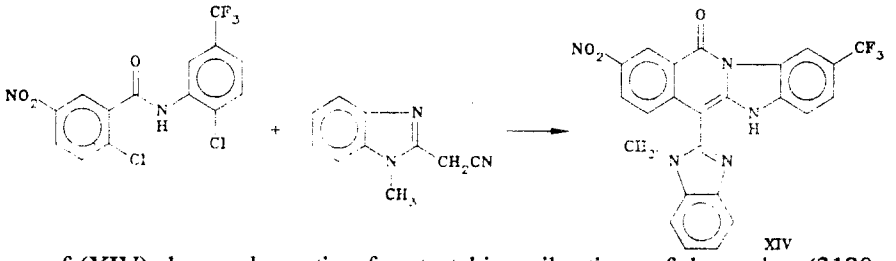
TABLE 1. Properties of Compounds Obtained

Compound	Empirical formula	R'	bp, °C	PMR spectrum, δ, ppm				IR spectrum, ν, cm^{-1}		Yield, %
				8-H	6-H	5-H	NH_2	C=O	NH_2	
IIIa	$C_{15}H_{12}N_4O_3$	CH_3	220	8,78	8,09	7,98	7,29	1655	3300	84
IVb	$C_{18}H_{15}N_5O_3$	CH_3	>300	8,82	8,07	7,67	7,10	1665	3300	93
Vb	$C_{24}H_{19}N_5O_3$	$CH_2C_6H_5$	>300	8,86	8,12	6,81	6,94	1650	3460	85
VIc	$C_{19}H_{14}N_4O_3$	CH_3	269	8,86	8,45	—**	7,60	1655	3350	73
VIIc	$C_{24}H_{15}FN_4O_3$	2-FC_6H_4	>300	9,26	8,66	8,19	—**	1680	3375	74
VIIIc	$C_{25}H_{18}N_4O_3$	$CH_2C_6H_5$	278	8,89	8,46	8,04	7,46	1660	3400	86
IXd	$C_{22}H_{14}N_4O_3S$	C_6H_5	263	8,82	8,32	—**	7,51	1673	3310	75
Xd	$C_{23}H_{16}N_4O_3S$	$CH_2C_6H_5$	258	8,83	8,27	—**	7,65	1650	3345	90
XIe	$C_{13}H_{10}N_4O_3S$	H	287	8,80	8,29	7,84	7,24	1653	3400	78
XIIe	$C_{14}H_{12}N_4O_3S$	CH_3	257	8,82	8,22	7,65	7,22	1645	3395	80
XIIIe	$C_{20}H_{16}N_4O_3S$	$CH_2C_6H_5$	233	8,87	8,24	7,69	7,89	1645	3380	83
XIV	$C_{24}H_{14}F_3N_5O_3$		>300							87

*Compounds (IIIa), (IVb), (VIa), (XIIe), and (XIIIe) were recrystallized from dioxane, (IXd) and (XIe) from acetonitrile, (XIIe) from nitromethane, and the remainder from DMF.

**Signals masked by aromatic proton absorption.

The reaction of 5-trifluoromethyl-2-chlorobenz-5-nitro-2-chloranilide with 1-methyl-2-cyanomethylbenzimidazole in the presence of potassium carbonate did not stop at the formation of the isoquinolone, intramolecular nucleophilic replacement of the chlorine in the N-phenyl ring (activated by the electron-acceptor CF_3 group) by the amino-group in the 3-position of the isoquinolone moiety occurring to give 11-(1-methylbenzimidazol-2-yl)-8-nitro-3-trifluoromethylbenzimidazo[1,2-b]isoquinol-6-one (XIV).



XIV

The IR spectrum of (XIV) shows absorption for stretching vibrations of the amino (3180 cm^{-1}) and carbonyl groups (1680 cm^{-1}). The PMR spectrum contains singlets for the 7-H and 9-H protons at 9.05 and 8.80 ppm, respectively, a doublet for the 10-H proton at 8.26 ppm (J = 9 Hz), a singlet for the methyl protons at 3.75 ppm, and signals for seven aromatic protons at 7.33-7.87 ppm.

A preparative route to 3-amino-4-hetaryl-1(2)-isoquinolones has thus been developed. These compounds could find application in analytical chemistry as extractants [5].

EXPERIMENTAL

IR spectra were obtained on a Pye-Unicam SP3-300 in KBr disks. UV spectra were recorded on a Specord UV-VIS in 2-propanol, and PMR spectra on a Bruker WP-100 in DMSO-D_6 with TMS as internal standard. The reactions were followed and the purity of the products established by TLC on Silufol UV-254 plates, visualized in UV, in the system chloroform—methanol (9:1).

The properties and yields of the products are shown in Table 1. The elemental analyses for N and S were in agreement with the calculated values.

3-Amino-4-hetaryl-1(2H)-isoquinolones (III-XIII). To a solution of 0.01 mole of the appropriate 5-nitro-2-chlorobenzamide in 80 ml of dry DMF were added 0.01 mole of the α-azahetarylacetonitrile and 0.01 mole of calcined potassium carbonate. The mixture was boiled for 2.5 h, the solvent removed under reduced pressure, and the residue treated with 70 ml of water, acidified with acetic acid to pH 7, and the precipitated solid filtered off, washed with water, and crystallized from the appropriate solvent.

11-(1-Methylbenzimidazol-2-yl)-8-nitro-3-trifluoromethylbenzimidazo[1,2-b]-isoquinol-6-one (XIV) was prepared by a previously-reported method.

LITERATURE CITED

1. A. G. Nemazanyi, Yu. M. Volovenko, T. A. Silaeva, and F. S. Babichev, *Dokl. Akad. Nauk UkrSSR, Ser. B*, No. 12, 36 (1989).
2. A. G. Nemazanyi, Yu. M. Volovenko, T. A. Silaeva, M. Yu. Kornilov, and F. S. Babichev, *Khim. Geterotsikl. Soedin.*, No. 3, 378 (1991).
3. *Merck Encyclopedia of Chemicals, Drugs, Biologicals*, Merck & Co., Inc. (1983), p. 1463.
4. T. J. Batterham, *NMR Spectra of Simple Heterocycles*, Wiley, New York (1973), p. 540.
5. F. S. Babichev, Yu. M. Volovenko, E. F. Gavrlova, L. L. Kolomiets, A. G. Pilipenko, and T. A. Silaeva, USSR Author's Certificate No. 4,669,042, December 12, 1989.

USE OF INTERPHASE CATALYSIS IN THE SYNTHESIS OF 2-ACYL-4-OXOPYRAZINO[2,1-*a*]ISOQUINOLINES AND 4-ACYL-2-PIPERAZINONES

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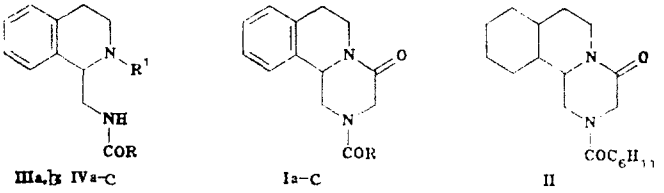
2-Acetyl-4-oxopyrazino[2,1-a]isoquinolines and 4-acyl-2-piperazinones have been synthesized, with interphase catalysis, by the intramolecular N-alkylation of the corresponding diamides.

In the synthesis of the high-efficiency antihelmintic Praziquantel (Ia), which has a tricyclic, pyrazinoisoquinoline structure, an intramolecular cyclization of diamide IVa is used. The cyclization takes place in an anhydrous medium on the action of such strong bases as potassium tert-butylate, sodium hydride, etc. [1].

We have synthesized praziquantel (Ia) and some of its analogs, Ib, c, by cyclization of the corresponding diacyl derivatives, IV, with interphase catalysis.



I a $R=C_6H_{11}$, b $R=C_6H_5$, c $R=CH_2Cl$; III a $R=C_6H_{11}$, $R^1=H$, b $R=C_6H_5$, $R^1=H$; IV a $R=C_6H_{11}$, b $R=C_6H_5$, c $R=CH_2Cl$, a–c $R^1=COCH_2Cl$

Starting materials IVa, b were prepared by acylation of the monoacyl derivatives, III, with chloroacetyl chloride. The conversion of diamides IVa, b to tricyclic Ia, b is carried out in a 50% aqueous solution of NaOH/organic solvent system in the presence of the interphase transfer catalyst TEBAC [triethylbenzylammonium chloride], as described in [2] (method **A**, see Experimental).

Tricyclic compounds Ia, b can be prepared from monoacyl derivatives IIIa, b even without isolating diamines IVa, b. In this case the acylation of compounds IIIa, b with chloroacetyl chloride leads the same system, and after the end of the reaction (monitored by TLC), TEBAC is added to the reaction mixture (method **B**, see Experimental). By the same method, starting from 1-cyclohexylcarbonylaminomethylperhydroisoquinoline, the hydrogenated analog of praziquantel, II, described by us earlier [3], has been synthesized.

In the synthesis of 2-chloroacetylpyrazinoisoquinoline, Ic, 1-aminomethyl-1,2,3,4-tetrahydroisoquinoline, converted to the bischloroacetyl derivative IVc by the action of chloroacetyl chloride, was used as the starting compound. Cyclization of IVc also takes place in the presence of the catalyst without the isolation of the IVc.

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