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CONVERSIONS OF POLYFUNCTIONAL 3-AMINO-1(2H)ISOQUINOLINES

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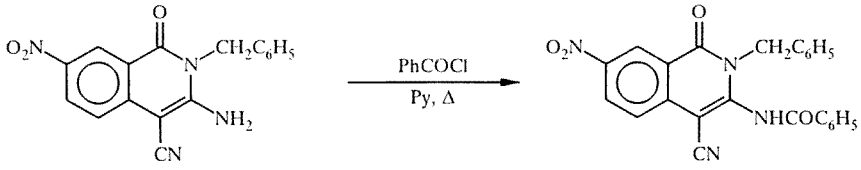
The acylation of 3-amino-4-cyano-1(2H)isoquinolines with benzoyl chloride leading to the formation of 1,3-oxazino[4,5-c]isoquinoline-6-ones has been studied. Previously undescribed 1-aminopyrimido[4,5-c]isoquinolin-6-ones have been obtained by the reaction of the appopriate 3-amino-1(2H)isoqinolones with formamide. Nucleophilic replacement has been carried out with 3-amino-1-chloroisoquinoline by the action of sodium hydroxide, primary alcohols, hydrazine hydrate, and various amines. 1,2,4-Triazino[2,3-b]isoqinolone has been synthesized by condensing 2,3-diamino-1(2H)isoquinolone with mesoxalic acid ethyl ester.

Many isoquinoline derivatives are used widely as highly effective drugs [1]. The synthesis and study of the properties of new compounds of this series is therefore a timely problem.

We synthesized previously [2-4] the polyfunctional 3-amino-1(2H)isoquinolones (I)-(III) which possess high biological activity (antimicrobial, analeptic, and sedative). The polyfunctional character of these compounds raises the possibility of further purpose-directed modification of their structure in the search for new substances possessing a set of useful properties.

The reactivity of 3-amino-4-cyano-1(2H)isoquinolones (I) [1] is determined primarily by their basicity, which depends on the electron density on the nitrogen atom of the amino group, its steric accessibility, and is sensitive even to small changes of structure.

It is known [5-7] that 3-aminoisoquinoline (pK_a = 5.0) is the least basic of the isomeric aminoisoquinolines. The presence of electron-accepting substituents, particularly nitrile and carbonyl groups, in the 3-aminoquinolines (I) studied by us leads to a further reduction in the basic properties of the amino group. In practice, acylation of the amino group occurs under forcing conditions, on boiling the reactants in pyridine for 10-40 h. Only 3-amino-2-benzyl-4-cyano-1(2H)isoquinolone (Ia) gives a benzoylamino derivative (IV) on boiling with an excess of benzoyl chloride in pyridine solution for 10 h.



Ia IV

The stretching vibrations of the amide group are represented by bands at 3200 and 1680 cm^{-1}, the band near 2210 cm^{-1} belongs to the nitrile group. In the PMR spectrum in DMSO-D_6 the signal for the amide group proton is observed at low field at 11.45 ppm. Addition of deuterated water to the sample leads to disappearance of this singlet. The signals of the amino group protons in the initial 3-aminoisoquinol-1-one are displayed at 8.05 ppm.

The proximity of the amino and nitrile groups leads to the acylation reaction continuing after the first step. The excess of acylating agent in the reaction mixture provokes further acylation of the amine and the formation of derivatives of a new

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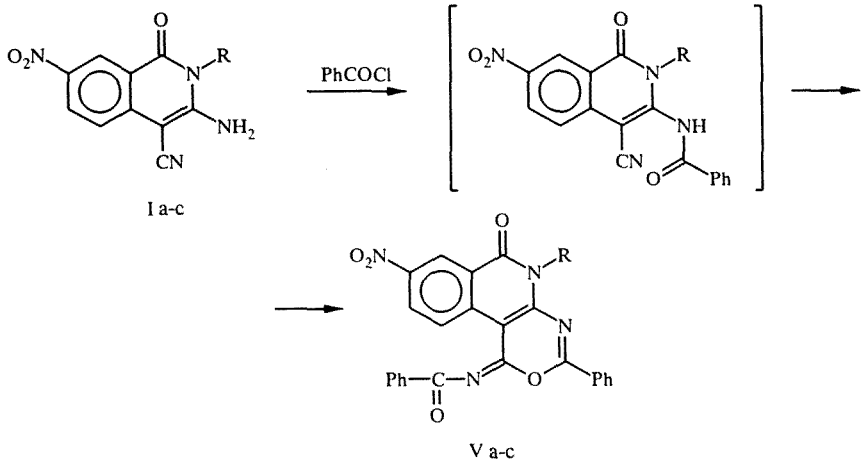
heterocyclic system, viz. 1,3-oxazino[4,5-c]isoquinoline. In reality the 3-amino-1(2H)isoquinolones (Ia-c) form the 1,3-oxazino-[4,5-c]isoquinol-6-ones (Va-c) under these conditions.

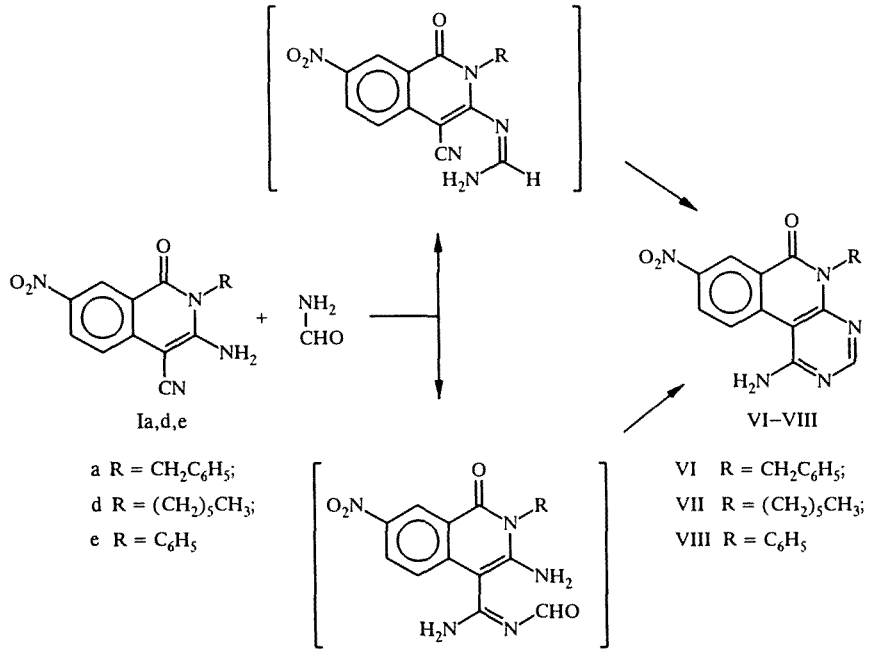


I, V a $R = CH_2C_6H_5$; b $R = CH_3$; c $R = CH(CH_3)_2$

There is no absorption characteristic of the stretching vibrations of a nitrile group in the IR spectra of compounds (Va-c). The following signals were present in the PMR spectrum of compound (Vc) in CF_3CO_2D: a weak doublet at 9.41 for the 7-H proton, the signal at 8.7 belongs to the 9-H and 10-H protons, the doublet of the methyl groups of the isopropyl substituent is observed at 1.92 (J = 6.84 Hz), and the methine proton gives a heptet at 6.18 ppm.

Compounds (I) are, in essence, heterocyclic enaminonitriles. 1-Aminopyrimido[4,5-c]isoquinolin-6-ones are formed readily and in good yield on brief boiling of compounds (Ia, d, e) in formamide. Two pathways are possible for the conversion leading to the same compounds (VI)-(VIII) (see below).

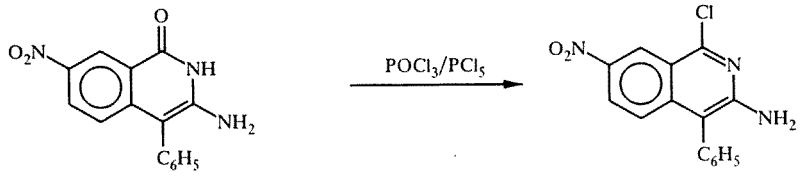
This reaction is fine for vicinal aminonitriles and has been well studied previously for many structurally related azines [8]. The following data point in favor of the formation of compounds (VI)-(VIII). In the IR spectra there is a band near 3300 cm^{-1} for the stretching vibration of the N–H bond of a primary amino group and the band for the nitrile group vibration is absent. Study of the PMR spectra showed that the amino group protons are displayed as two signals at 7.49-7.51 and 10.61-10.63 ppm which disappear on addition of heavy water. A singlet for the 3-H proton at 8.29-8.32 ppm is a characteristic of these products.



a $R = CH_2C_6H_5$;
d $R = (CH_2)_5CH_3$;
e $R = C_6H_5$

VI $R = CH_2C_6H_5$;
VII $R = (CH_2)_5CH_3$;
VIII $R = C_6H_5$

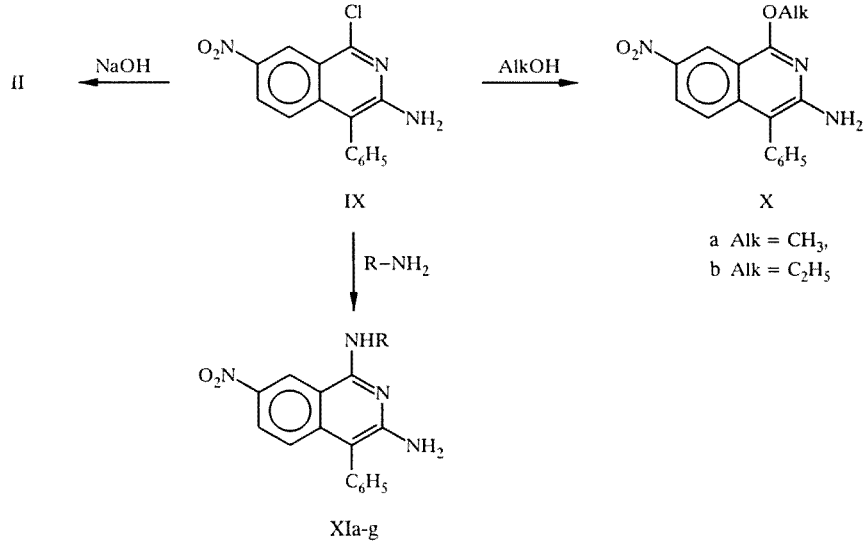
Treatment of 3-amino-1(2H)isoquinolone (II) [2] with a mixture of $POCl_3$ and PCl_5 leads to the formation of the chloro derivative (IX).



II IX

Data of elemental analysis and the absence from the IR spectrum of compound (IX) of absorption characteristic of the stretching vibrations of the carbonyl group confirm the formation of the 3-amino-1-chloroisoquinoline (IX). The following signals were observed in the PMR spectrum of the chloro derivative in DMSO-D_6: a two-proton singlet at 6.50, which disappeared on treating the sample with heavy water, corresponds to the protons of the amino group, a weak doublet at 8.84 for the 8-H proton, and also a doublet for the 5-H proton which falls into the region of diamagnetic shielding by the π-electron ring currents of the phenyl substituent and absorbs at 7.18 ppm.

The chlorine atom in compound (IX) is in conjugation with the nitrogen of the isoquinoline ring; it is labile and is readily substituted by various nucleophilic groups. Boiling alcoholic solutions of the chloro derivative in the presence of potassium carbonate leads to the formation of the alkoxy derivatives (Xa, b), but treatment of the chloro derivative with NaOH in aqueous dioxan is accompanied by hydrolysis and leads to the initial 3-amino-1(2H)isoquinolone (II). Nucleophilic replacement of the chlorine atom occurs under the action of primary amines or hydrazine hydrate on the chloro derivative and the amino derivatives (XIa-g) are formed.



IX

X

a Alk = CH_3,
b Alk = C_2H_5

XIa-g

a R = NH_2, b R = $(CH_2)_3CH_3$, c R = $(CH_2)_3OH$, d R = $CH_2C_6H_5$, e R = $(CH_2)_3N(CH_3)_2$,
f R = 2-(3,4-dimethoxyphenyl)ethyl, g R = 2-piperidinoethyl

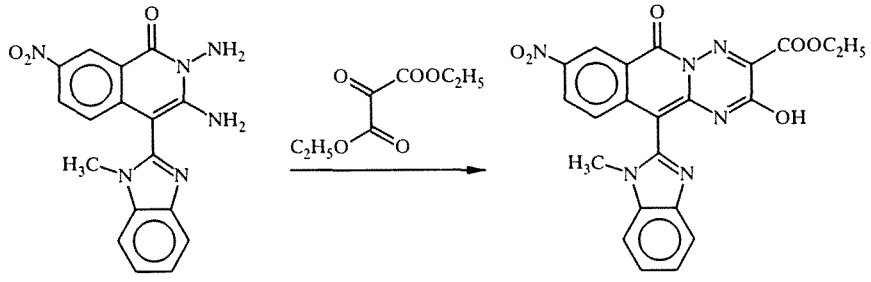
The amino derivatives (XIa-g) obtained are crystalline substances, brownish red in color, containing a long wave maximum in the visible region of the UV spectrum at 485-500 nm (log ε = 4.01-4.1). In the PMR spectrum in DMSO-D_6 the signals of the protons of the primary amino group were represented by a two-proton singlet at 5.52-5.65, the N−H proton is displayed as a broad triplet at 8.07-8.10 ppm. The aliphatic protons of compound (XI) are represented by characteristic signals at 1.8-4.8 ppm.

The 2,3-diamino-1(2H)isoquinolone (III) [4] reacts with α-dicarbonyl compounds. The 1,2,4-triazino[2,3-b]isoquinolin-6-one (XII) is formed on reaction with mesoxalic acid ethyl ester (see top of the following page).

A one-proton singlet is present in the PMR spectrum of compound (XII) in DMSO-D_6 at 10.14 ppm which disappears on treatment of the sample with D_2O. We assigned it to the proton of the hydroxyl group. The protons of the ester group are

TABLE 1. Characteristics of the Compounds Synthesized

Compound	Empirical formula	mp, °C	Solvent for recrystallization	Yield, %
IV	$C_{24}H_{16}N_4O_4$	282	DMF	82
Va	$C_{31}H_{20}N_4O_5$	>300	DMF	60
Vb	$C_{25}H_{16}N_4O_5$	296	DMF	80
Vc	$C_{27}H_{20}N_4O_5$	274	DMF	75
VI	$C_{18}H_{13}N_5O_3$	294	Dioxan	62
VII	$C_{17}H_{19}N_5O_3$	244	Dioxan	60
VIII	$C_{17}H_{11}N_5O_3$	>300	Dioxan	60
IX	$C_{15}H_{10}ClN_3O_2$	195	Dioxan	82
Xa	$C_{16}H_{13}N_3O_3$	175	Benzene	62
Xb	$C_{17}H_{15}N_3O_3$	168	Dioxan	62
XIa	$C_{15}H_{13}N_5O_2$	250	Dioxan	70
XIb	$C_{19}H_{20}N_4O_2$	152	Acetonitrile	75
XIc	$C_{18}H_{18}N_4O_3$	157	Toluene	75
XId	$C_{22}H_{18}N_4O_2$	162	Benzene	70
XIe	$C_{20}H_{23}N_5O_2$	170	Benzene	60
XIf	$C_{25}H_{24}N_4O_4$	218	Toluene	55
XIg	$C_{22}H_{25}N_5O_2$	204	Benzene	55
XII	$C_{22}H_{16}N_6O_6$	260	DMF	78



III XII

displayed as a triplet at 1.32 and a quartet at 4.37, the aromatic protons give a complex multiplet at 7.6-8.2 ppm. The OH group stretching vibrations form a broad band at 3400-3600 cm^{-1} in the IR spectrum. The ester group carbonyl is represented by an intense absorption band at 1725 cm^{-1}.

EXPERIMENTAL

The IR spectra were drawn on a Pye Unicam SP 3-300 instrument in KBr disks. The PMR spectra were taken in DMSO-D_6 and in deuterotrifluoroacetic acid with a Bruker WP-100 spectrometer with an operating frequency of 100.13 MHz using TMS as internal standard. The homogeneity of all the substances was checked chromatographically on Silufol UV 254 plates. Eluent was chloroform–methanol, 9:1.

The data of elemental analysis for C, H, N, and Cl of the compounds synthesized corresponded to calculated values.

3-Benzoylamino-2-benzyl-4-cyano-7-nitro-1(2H)isoquinolone (IV). Benzoyl chloride (0.73 g: 0.005 mole) was added to a solution of compound (Ia) (0.8 g: 0.0025 mole) in pyridine (30 ml) and the mixture boiled for 10-15 h. A check on the progress of the reaction was effected by TLC. The solvent was evaporated in vacuum, water (30 ml) was added to the residue, the solid was filtered off, and dried.

1,3-Oxazino[4,5-c]isoquinolin-6-ones (Va-c). Benzoyl chloride (0.005 mole) was added to a solution of the appropriate 3-amino-4-cyano-1(2H)isoquinolone (Ia-c) (0.0025 mole) in pyridine (30 ml) and the mixture was boiled for 30-40 h. A check

on the course of the reaction was effected by TLC. The solvent was evaporated in vacuum, water (40 ml) was added to the residue, the solid filtered off, and dried.

Pyrimido[4,5-c]isoquinolin-6-ones (VI)-(VIII). A solution of the appropriate 3-amino-1(2H)isoquinolone (Ia, d, e) (0.0025 mole) in formamide (30 ml) was boiled for 2 h. The formamide was evaporated in vacuum down to 10 ml, water (30 ml) added, the precipitate was filtered off, washed with water, and dried.

3-Amino-1-chloro-7-nitro-4-phenylisoquinoline (IX) was obtained on boiling 3-amino-7-nitro-4-phenyl-1(2H)isoquinolone (II) (1.4 g: 0.005 mole) in $POCl_3$ (50 ml) in the presence of PCl_5 (0.5 g: 0.0025 mole) for 2 h. The $POCl_3$ was evaporated in vacuum, water (50 ml) was added to the residue, the solid was filtered off, and dried.

Hydrolysis of compound (IX) was carried out in an aqueous solution of dioxan in the presence of NaOH for 4 h. The solvent was evaporated in vacuum, water (20 ml) was added, the solution neutralized to pH 7 with acetic acid, the solid filtered off, and dried. The yield of compound (II) was 0.56 g (80%).

1-Alkoxy-3-amino-7-nitro-4-phenylisoquinolines (Xa, b). A solution of the chloro derivative (IX) (0.75 g: 0.0025 mole) in the appropriate alcohol (50 ml) was boiled in the presence of K_2CO_3 (0.35 g: 0.005 mole) for 2 h. The alcohol was evaporated in vacuum, water (30 ml) was added, the solution neutralized to pH 7 with acetic acid, the precipitate filtered off, washed with water, and dried.

Amino Derivatives (XI). Hydrazine hydrate (0.005 mole) was added to a solution of the chloro derivative (IX) (0.75 g: 0.0025 mole) in dioxan (50 ml). When making compounds (XIb-g) an amine (0.0025 mole) and K_2CO_3 (0.0025 mole) were used. The mixture was boiled for 1-3 h, the solvent evaporated in vacuum, the residue triturated with water (50 ml), the solid filtered off, and dried.

1,2,4-Triazino[2,3-b]isoquinoline (XII). Mesoxalic acid ethyl ester (0.38 ml: 0.0025 mole) was added to a solution of compound (III) (0.88 g: 0.0025 mole) in DMF (30 ml). The mixture was boiled for 3 h, the solvent evaporated in vacuum, water (30 ml) was added, the precipitate filtered off, washed with water, and dried.

The characteristics of the compounds synthesized are given in Table 1.

REFERENCES

1. Merck Index, An Encyclopedia of Chemicals, Drugs, and Biologicals, Merck, Rahway (1983).
2. A. G. Nemazanii, Yu. M. Volovenko, T. A. Silaeva, and F. S. Babichev, Dokl. Akad. Nauk UkrSSR Ser. B, No. 12, 36 (1989).
3. A. G. Nemazanii, Yu. M. Volovenko, T. A. Silaeva, and M. Yu. Kornilov, Khim. Geterotsikl. Soedin., No. 3, 378 (1991).
4. A. G. Nemazanii, Yu. M. Volovenko, T. A. Silaeva, M. Yu. Kornilov, and F. S. Babichev, Khim. Geterotsikl. Soedin., No. 1, 86 (1992).
5. J. A. Joule and G. F. Smith, Heterocyclic Chemistry, Van Nostrand Reinhold, New York (1972).
6. J. Elliott and S. F. Mason, J. Chem. Soc., July-August, 2352 (1959).
7. E. V. Brown and S. R. Mitchell, J. Org. Chem., **37**, 1053 (1972).
8. S. K. Robev, Tetrahedron Lett., **21**, 2097 (1980).