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INVESTIGATIONS OF INDOLO[3,2-*b*]QUINOLINES

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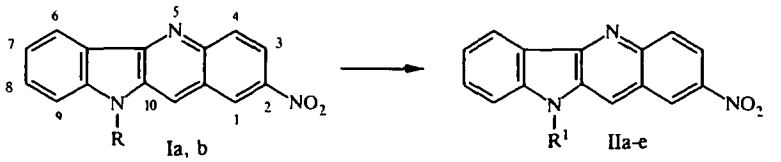
A number of 10-γ-aminoalkyl derivatives based on 2-nitroindolo[3,2-b]quinoline have been synthesized. A preparative method has been developed for quaternary salts of 2-acetylaminoindolo[3,2-b]quinoline.

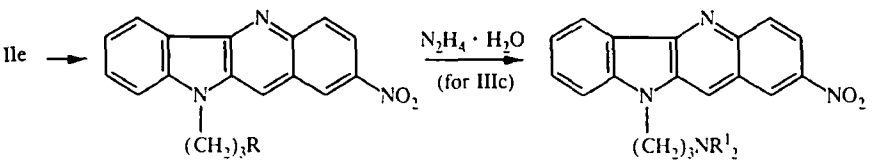
Vilsmeier formylation of 3-arylaminoindoles occurs via an intramolecular cyclization to give substituted indolo[3,2-*b*]quinolines [1]. Derivatives of this planar heteroaromatic system can be of interest as potential intercalators, having antiviral and antitumor activity [2]. Our work concerns a study of the possible synthesis of different derivatives of this heteroocyclic system, including those which have short chain alkyl(dialkyl, acyl)aminoalkyl substituents at the indole nitrogen atom. The first stage of the investigation was a study of the alkylation of 2-nitroindolo[3,2-*b*]quinoline (Ib) in DMSO in the presence of base (which generates conditions for the efficient formation of the corresponding anion). In these conditions, reaction of Ib with dimethylsulfate, benzyl chloride, diethylamino- and dimethylaminoethyl chlorides readily gives the corresponding 10-alkyl derivatives IIa-d. The reaction with bromochloropropane occurs easily and this gives an additional possibility for the synthesis of novel 10-γ-aminopropyl substituted



Ia, b IIa-e

I a R = $COCH_3$, b R = H; a R^1 = Me, b R^1 = CH_2Ph, c R^1 = $(CH_2)_2NEt_2$,
d R^1 = $(CH_2)_2NMe_2$, e R^1 = $\overset{\alpha}{CH_2}\overset{\beta}{CH_2}\overset{\gamma}{CH_2}Cl$

compounds. In fact, 10-γ-chloropropylindolo[3,2-*b*]quinoline (IIe) readily reacts with piperidine and morpholine to give the corresponding 10-piperidino- and morpholinopropyl derivatives IIIa, b. The reaction of IIe with potassium phthalimide also occurs smoothly. The phthalimido derivative IIIc readily reacts with hydrazine hydrate under Gabriel conditions and the γ-aminopropyl derivative IVa obtained is identified by its N-acetylation to form 2-nitro-10-γ-diacetylaminopropylindolo[3,2-*b*]quinoline IVb.



IIIa-c IVa, b

III a R = morpholino, b R = piperidino, c R = phthalimido;
IV a R^1 = H, b R^1 = COMe

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TABLE 1. PMR Spectral Data for IIa-c, e, IIIa, IVa, b, V, VIIa-c, VIIIb, and IX in DMSO-D_6

Compound	Chemical shift, δ, (ppm)								
	1-H (split s)	3-H (q)†	4-H (d)	6-H (d)	7-H (t)	8-H (t)	9-H (d)	11-H (s)	2-H, 10-H
IIa*	9,04	8,25	8,30	8,37	7,32	7,71	7,66	8,61	3,91 (s, 3H, 10-CH_3)
IIb*2	9,15	8,35	8,38	8,45	7,40	7,75	7,81	8,88	5,76 (s, 2H, $\underline{CH_2}$Ph), 7,29 (narrow m), 5H, Ph)
IIc	9,19	8,33	8,36	8,42	7,36 (split .)	7,76 (narrow m)		8,80	0,72 (t, 6H, N($CH_2\underline{CH_3}$)$_2$), 2,47 (q, 4H, N($\underline{CH_2}CH_3$)$_2$), 2,82 (t, 2H, β-CH_2), 4,52 (t, 2H, α-CH_2)
IIe*	9,11	8,32	8,35	8,42	7,39 (split .)	7,76 (narrow m)		8,73	2,37 (qn, 2H, β-CH_2), 3,70 (t, 2H, γ-CH_2), 4,61 (t, 2H, α-CH_2)
IIIa	9,11	8,31	8,35	8,41	7,37 (split .)	7,76 (narrow m)		8,75	1,33 (m, 2H, δ-CH_2), 1,42 (m, 4H, 2δ-CH_2), 2,01 (qn, 2H, β-CH_2), 2,16 (m, 6H, γ-CH_2 + 2δ-CH_2), 4,49 (t, 2H, α-CH_2)
IVa	9,14	8,32	9,36	8,42	7,37	7,78 (narrow m)		8,81	1,93 (qn, 2H, β-CH_2), 2,58 (t, 2H, γ-CH_2), 4,53 (t, 2H, α-CH_2)
IVb	9,15	8,35	8,38	8,44	7,40	7,80 (narrow m)		8,84	2,10 (br. m 2H, β-CH_2), 2,22 (s, 6H, N($COCH_3$)$_2$), 3,70 (br. t, 2H, γ-CH_2), 4,55 (t, 2H, α-CH_2)
V*	6,89	7,06	7,83	8,16	7,15 (m)	7,43 (narrow m)		7,77	5,25 (br. s, 2H, 2-NH_2), 10,82 (br. s, 1H, 10-NH)
VIIa	8,47	7,66	8,10	8,29	7,26	7,58	7,53	8,14	2,13 (s 3H, 2-NHCO$\underline{CH_3}$), 10,20 (br. s, 1H, 2-$\underline{NH}$COCH$_3$), 11,30 (br. s, 1H, 10-NH)
VIIb	8,17	7,69	8,25	8,39	7,55	7,75	8,38	9,06	2,26 (s, 6H, 2-N($COCH_3$)$_2$), 2,95 (s, 3H, 10-$COCH_3$)
VIIc	8,53	7,76	8,08	8,30	7,50	7,67	8,34	8,80	2,15 (s, 3H, 2-NHCO$\underline{CH_3}$), 10,30 (br. s, 1H, 2-$\underline{NH}$COCH$_3$), 2,97 (s, 3H, 10-$COCH_3$)
VIIIb	8,82	8,02	8,64	8,72	7,47	7,87	7,77	9,12	2,14 (s, 3H, 2-NHCO$\underline{CH_3}$), 10,52 (s, 1H, 2-$\underline{NH}$COCH$_3$), 4,96 (s, 3H, 5-CH_3), 12,70 (s, 1H, 10-NH)
IX	8,68	7,98	7,92	8,37	7,18	7,47	7,55	–	2,09 (s, 3H, 2-NHCO$\underline{CH_3}$), 10,20 (s, 1H, 2-$\underline{NH}$COCH$_3$), 4,35 (s, 3H, 5-CH_3), 11,88 (br. s 1H, 10-NH)

*Scan temperature +90°C.

*2As in Russian original; footnote is omitted — Publisher.

†q) Quartet; qn) quintet.

TABLE 2. Physicochemical Parameters for Synthesized IIa-e, IIIa-c, IVb, V, VIa, VIIa, b

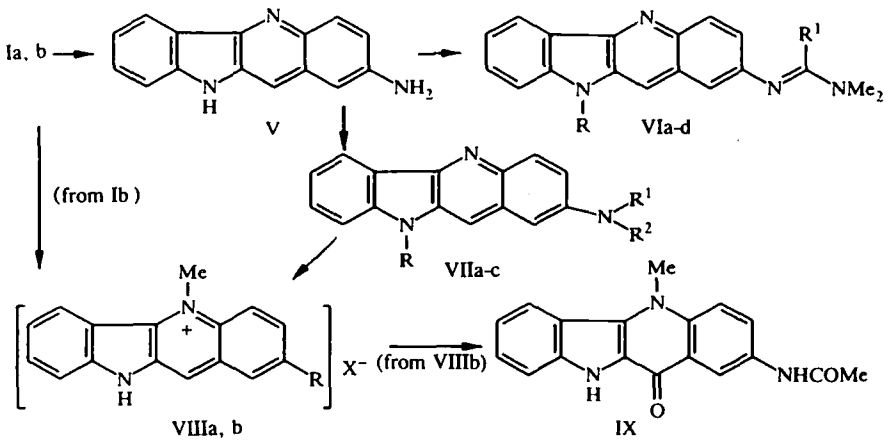
Compound	Empirical formula	Found, % / Calculated, % C	H	N	mp, °C (recrystallization solvent)	$M^{+\cdot}$	Yield, %
IIa	$C_{16}H_{11}N_3O_2$	69,51 / 69,31	4,12 / 3,97	15,22 / 15,16	254...256 (DMF)	277	100
IIb	$C_{22}H_{15}N_3O_2$	74,80 / 74,79	4,28 / 4,25	11,83 / 11,90	246...248 (DMF-methanol)*	353	100
IIc	$C_{21}H_{22}N_4O_2$	69,62 / 69,61	5,98 / 6,08	15,35 / 15,47	136...138 (methanol)	362	77
IId	$C_{19}H_{18}N_4O_2$	68,44 / 68,26	5,33 / 5,39	16,59 / 16,77	170...171 (methanol)	334	100
IIe	$C_{18}H_{14}N_3ClO_2$	63,50 / 63,62	4,24 / 4,12	12,44 / 12,37	223...225 (DMF-methanol)*	353	100
IIIa	$C_{23}H_{24}N_4O_2$	71,35 / 71,13	6,14 / 6,19	14,46 / 14,43	135...137 (methanol)	388	60
IIIb†	$C_{22}H_{22}N_4O_2$	65,31 / 65,51	5,79 / 5,67	13,85 / 13,73	115...116 (methanol)	390	96
IIIc	$C_{26}H_{18}N_4O_4$	69,42 / 69,33	4,02 / 4,00	12,60 / 12,44	312...314 (DMF)	450	93
IVb	$C_{22}H_{20}N_4O_4$	65,49 / 65,35	4,94 / 4,95	13,75 / 13,86	114...115 (methanol)	404	63
V	$C_{15}H_{11}N_3$	77,35 / 77,25	4,96 / 4,72	17,93 / 18,03	300 (DMF)	233	73
VIa	$C_{18}H_{16}N_4$	74,93 / 75,00	5,65 / 5,56	19,56 / 19,44	289...292 (methanol)	288	71
VIIa†	$C_{17}H_{13}N_3O$	72,71 / 72,52	4,85 / 4,87	14,80 / 14,93	341...343 (ethyl acetate)	275	100 (A) 92 (B)
VIIb	$C_{21}H_{17}N_3O_3$	69,99 / 70,19	4,77 / 4,74	11,58 / 11,70	235...237 (ethyl acetate)	359	65

*Ratio of solvents 14:10 for IIb and 1:1 for IIe.

†Compounds IIb [sic] and VIIa exist as crystalline hydrates: IIIb ($C_{22}H_{22}N_4O_3 \cdot 0.7\ H_2O$), water content found, %: 3.22, calculated, %: 3.12; VIIa ($C_{17}H_{13}N_3O \cdot 0.35\ H_2O$), water content found, %: 2.67, calculated, %: 2.24.

An alternative route to synthesis of these compounds is based on the reduction of the 2-nitro group to give the 2-aminoindoloquinoline V. It was found that both compound Ib and its 10-acetyl derivative Ia are smoothly reduced by hydrazine hydrate in the presence of Raney nickel, and high yields of V are obtained. In the case of the acetyl substituted Ia there also occurs a 10-desacetylation during the reduction process. Condensation of the 2-amino V with dimethylformamide diethylacetal yields the amidine VIa. Mass spectrometric analysis of the compound contained in the mother liquor showed that there occur both the basic amidine synthesis process and an N-alkylation to give the 10-ethyl derivative VIb (the latter could not, however, be separated). This kind of N-alkylation is characteristic of amide acetals and is well documented in the literature [3]. A more complex picture emerges for the reaction of V with dimethylacetamide diethylacetal. In this case, a many component mixture is obtained which PMR and mass spectrometry show to contain the desired amidine together with N-alkylation and polymeric products.

Acetylation of V under different conditions leads to the formation of all possible N-acetylation products. Treatment with acetic anhydride under mild conditions gives an almost quantitative yield of the 2-N-acetyl derivative VIIa but refluxing in Ac_2O gives basically the 2-bisacetylamino-10-acetylindolo[3,2-*b*]quinoline VIIb with the 2-bisacetylamino derivative VIIc separated and identified as a minor product. Hence, the results discussed above demonstrate the possible uses of a functional substituent at position 2 and a reaction at the indole 10-NH position in the synthesis of various derivatives of indolo[3,2-*b*]quinolines.



VI a R = R^1 = H, b R = Et, R^1 = H, c R = R^1 = Me, d R = Et, R^1 = Me;
VII a R = R^1 = H, R^2 = COMe, b R = R^1 = R^2 = COMe, c R = R^1 = COMe, R^2 = H;
VIII a R = NO_2, X = I^- or $MeSO_4^-$, b R = NHCOMe, X = I^-

Another feature of the system studied is the presence of the pyridine nitrogen atom at position 5. Initially we tried to introduce the nitro derivative Ib into the alkylation reaction (in the absence of the basic agent). However, all attempts to achieve an easy and preparative method for synthesizing a quaternary salt through use of either methyl iodide or dimethylsulfate did not give the expected result. Refluxing in toluene gave a complex mixture containing 40% starting Ib and only 15% of the quaternary salt VIIIa and heating in DMF a 60:40 mixture of Ib and VIIIa. The data obtained show that the quaternization process at the pyridine nitrogen occurs extremely slowly (and, possibly, reversibly) and this is evidently linked to the strong electron acceptor effect of the nitro group. Based on this proposal, we selected the 2-acetylamino derivative VIIa as the starting material in the next step. Prolonged contact of VIIa with methyl iodide and DMF at room temperature gives a quantitative yield of the quaternized compound VIIIb. As expected, the PMR proton signals in the spectrum of salt VIIIb were shifted to low field when compared with those of the base VIIa (see Table 1). The quaternary salt VIIIb prepared is a promising starting compound for generating a novel functional group in the indoloquinoline system. Within the limits of our work, this possibility was studied via treatment of salt VIIIb with base by heating in DMSO. As a result, 2-acetylamino-5-methylindolo[3,2-*b*]quinolin-11-one (IX) was synthesized in 36% yield. The developed method opens up extremely interesting synthetic possibilities and the investigation of novel derivatives in the studied heterocyclic system.

EXPERIMENTAL

Mass spectra were obtained on a Finnigan MAT SSQ-710 mass spectrometer with direct introduction of the sample into the ion source. The electron ionization energy was 70 eV and the temperature of the ionization chamber 150°C. ^{1}H NMR spectra were taken on a Varian Unity-400 instrument with TMS as internal standard. Monitoring of the reaction course and compound purity was performed on Silufol UV-254 TLC plates using chloroform–methanol (10:1) solvent and visualization in UV light.

2-Nitro-10-methylindolo[3,2-*b*]quinoline (IIa). Compound Ib (1 g, 4 mmole) was added to a suspension of KOH (0.9 g, 16 mmole) in DMSO (8 ml). The mixture was stirred for 30 min at 20°C. Dimethylsulfate (2.4 g, 16 mmole) was added in 0.6 g portions over 1.5 h at 20°C until disappearance of starting material on chromatography. The precipitate was filtered and washed with water to pH 7 and then methanol to give compound IIa (1 g).

2-Nitro-10-benzylindolo[3,2-*b*]quinoline (IIb) was obtained similarly to IIa from Ib (1 g, 4 mmole) and benzyl chloride (1 g, 8 mmole) in 1.35 g yield.

2-Nitro-10-diethylaminoethylindolo[3,2-*b*]quinoline (IIc). Ib (2 g, 8 mmole) was added to a suspension of NaOH (1.28 g, 32 mmole) in DMSO (15 ml). The mixture was stirred for 30 min at 20°C. Diethylaminoethyl chloride hydrochloride (2.8 g, 16 mmole) was added and the product stirred for 4 h at 20°C. Methanol (40 ml) was then added to the reaction mixture and the crystalline product filtered and washed with water to pH 7 to give IIc (2.12 g).

2-Nitro-10-dimethylaminoethylindolo[3,2-*b*]quinoline (IId) was prepared from Ib (1.1 g, 4 mmole), NaOH (1.28 g, 32 mmole) and dimethylaminoethyl chloride hydrochloride (2.28 g, 16 mmole) in the conditions for synthesizing IIc. The reaction product was poured into water and the precipitate was filtered and washed with water to give IId (1.4 g).

2-Nitro-10-chloropropylindolo[3,2-*b*]quinoline (IIe) was prepared from Ib (6.3 g, 24 mmole), NaOH (3.84 g, 96 mmole), and 1-chloro-3-bromopropane (7.56 g, 48 mmole) under the conditions for synthesis of IIc. The reaction was exothermic. The precipitated product was filtered and washed with methanol and water to pH 7 to give IIe (7.55 g).

2-Nitro-10-piperidinopropylindolo[3,2-*b*]quinoline (IIIa). A solution of the chloro derivative IIe (2 g, 5.9 mmole) in piperidine (10 ml) was refluxed for 20 min and cooled to 20°C. Water (150 ml) was added to the precipitate and the whole was filtered and washed with water to give IIIa (1.37 g)

2-Nitro-10-morpholinopropylindolo[3,2-*b*]quinoline (IIIb) was prepared from IIe (2 g, 5.9 mmole) and morpholine (10 ml) using the conditions for synthesis of IIIa to give IIIb (2.2 g).

2-Nitro-10-phthalimidopropylindolo[3,2-*b*]quinoline (IIIc). A suspension of IIe (3.55 g, 10 mmole), potassium phthalimide (3.05 g, 16 mmole), and DMF (15 ml) was stirred for 40 min at 100°C. After cooling to 20°C, water (100 ml) was added, and the precipitate was filtered off and washed with water to give IIIc (4.35 g).

2-Nitro-10-γ-aminopropylindolo[3,2-*b*]quinoline (IVa). Hydrazine hydrate (7.5 ml) was added to a suspension of IIIc (6 g, 13 mmole) in ethanol (60 ml) and the product was stirred for 2.5 h under reflux. It was cooled to 20°C and ethanol (100 ml) and aqueous ammonia (25%, 50 ml) were added. The suspension obtained was stirred for 10 min, filtered, and washed with ethanol to give IVa (4.2 g).

2-Nitro-10-γ-diacetylaminopropylindolo[3,2-*b*]quinoline (IVb). A mixture of IVa (0.5 g, 1.6 mmole) and acetic anhydride (2 ml) was refluxed for 1.5 h. Methanol (10 ml) was added to the cooled reaction mass and the precipitate was filtered and washed with methanol to give IVb (0.4 g)

2-Nitro-10H-indolo[3,2-*b*]quinoline (V). A. Hydrazine hydrate (52 ml) was added to a suspension of Ia (9.15, 30 mmole) in 2-propanol (200 ml) and stirred for 15 min at 20°C. A suspension of Raney nickel in 2-propanol (8 g in 25 ml) was added in portions with slow heating and stirring until evolution of hydrogen ceased. The reaction mass was stirred for 3 h at 85-90°C and held for 20 h at 20°C. Catalyst was filtered off. The filtrate was evaporated to give V (0.25 g). The catalyst was refluxed in DMF (3 × 180 ml) and the catalyst filtered off. The filtrate was evaporated to give a further 4.85 g of V.

B. Prepared from Ib (0.79 g, 3 mmole) similarly to method A. The melting temperature of a sample mixed with one prepared by method A was not depressed.

2-Dimethylaminomethyleneimino-10-indolo[3,2-*b*]quinoline (VIa) and 2-Dimethylaminomethyleneimino-10-ethylindolo[3,2-*b*]quinoline (VIb). A mixture of V (2 g, 8.6 mmole), dimethylformamide acetal (70%, 3 ml), and DMF (10 ml) was stirred under gentle reflux for 10 min and then held at 20°C for 20 h (monitoring by TLC). The reaction product crystallized. DMF (2 ml) and DMF acetal (70%, 1 ml) were further added and the product held for 48 h at 20°C. The precipitate was filtered off and washed with methanol to give VIa (1.75 g). The filtrate from the reaction mixture was poured into water and the precipitate filtered off to give a mixture of VIa,b (0.45 g) (M_1^+ 316, M_2^+ 288).

2-Acetylamino-10H-indolo[3,2-*b*]quinoline (VIIa). A. Acetic anhydride (0.19 g, 1.9 mmole) was added to a suspension of V (0.3 g, 1.3 mmole) in glacial acetic acid (3 ml). An exotherm was observed. The reaction mixture was held for 30 min at 40°C and for 40 min at 90°C (monitoring by TLC). It was then cooled to 20°C and methanol (15 ml) was added. The precipitate was filtered off and washed with ethyl acetate to give VIIa (0.36 g).

B. Obtained similarly to A with the difference that the reaction mixture was held for 1 h at 20°C. The melting temperature of a sample mixed with that prepared by method A was not depressed.

2-Diacetylamino-10-acetylindolo[3,2-*b*]quinoline (VIIb) and 2-Acetylamino-10-acetylindolo[3,2-*b*]quinoline (VIIc). A suspension of V (0.3 g, 1.3 mmole) and acetic anhydride (5 ml) was refluxed for 3.5 h. The filtered precipitate from the hot reaction mixture was washed with ethyl acetate to give VIIc (0.03 g, 7%) with mp 290°C (with decomp.). M^+ 317, Found, %: N 13.15. $C_{18}H_{15}N_3O_2$. Calculated, %: N 13.25. Cooling the filtrate gave VIIb (0.3 g).

2-Acetylamino-5-methyl-10H-indolo[3,2-*b*]quinoline Iodide (VIIIb). Methyl iodide (5 ml) was added in 1 ml portions at 20°C over 10 days to a solution of VIIa (0.3 g, 2 mmole) in DMF (7 ml) (monitoring by TLC). The precipitate was filtered and washed with methanol to give salt VIIIb (0.45 g, 100%) with mp 320-325°C (with decomp.). M^+ 289 (128). Found, %: N 9.83. $C_{18}H_{16}N_3IO$. Calculated, %: N 10.07.

2-Acetylamino-5-methyl-10H-indolo[3,2-*b*]quinolin-11-one (IX). Salt VIIIb (0.3 g, 1 mmole) was added to a suspension of NaOH (0.4 g, 10 mmole) in DMSO (5 ml) and stirred for 4.5 h at 60°C. Methanol (20 ml) was added to the

reaction mixture and the precipitate filtered off and washed with methanol to give IX (0.08 g, 36%) with mp > 350°C (from DMF). $M^{+\cdot}$ 305. Found, %: N 14.01. $C_{18}H_{15}N_3O_2$. Calculated, %: N 13.77.

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