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SYNTHESIS AND HETEROCYCLIZATION OF ALLYL DERIVATIVES OF 8-AMINOQUINOLINE

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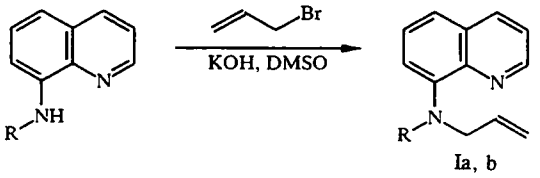
*We have shown that heterocyclization of N-tosyl- and N-acetyl derivatives of 8-(allylamino)quinoline with iodine occurs with formation of 3-iodomethyl-1-*p*-toluenesulfonyl-2,3-dihydropyrazino[3,2,1-i,j]quinolinium and 1-acetyl-3-iodomethyl-2,3-dihydropyrazino[3,2,1-i,j]quinolinium iodides.*

Some derivatives of 8-substituted quinolines exhibit biological activity, and also are convenient objects for constructing new heterocyclic systems [1-3]; in [4, 5], we investigated heterocyclization of 8-hydroxy- and 8-mercaptoquinolines. The goal of this work was synthesis of N-allyl derivatives of 8-aminoquinoline and study of their reaction with iodine. As the starting compounds, we used 8-(acetylamino)quinoline and 8-(tosylamino)quinoline. Allylation of these derivatives by allyl bromide in a superbasic medium (DMSO, KOH) quantitatively yields the corresponding allyl derivatives (I) [6].



Ia, b

I a R = Ac, b R = Ts

In the first step, we investigated the reaction of allylation of 8-aminoquinoline by allyl bromide, in particular allylation in the presence of tributylamine, sodium isopropylate, and also under phase transfer catalysis conditions with KF as the base and triethylbenzylammonium chloride as the phase transfer catalyst. We showed that in all cases, in the reaction a mixture of 8-(allylamino)quinoline (IIa) and 8-(diallylamino)quinoline (IIb) is formed. These data are consistent with the data in [7], where the authors used Na_2CO_3 as the base.

Better yields of the monoallyl derivative are obtained when using tributylamine as the base, and in the presence of potassium fluoride the major product is 8-(diallylamino)quinoline. The mixture of products formed was separated with the help of column chromatography on aluminum oxide (the eluent was a mixture of ether and hexane, 1:1). Due to the similar mobilities of the monoallyl and diallyl derivatives, their separation requires a considerable amount of solvent, so a more convenient method has been suggested. The mixture was treated with acetic anhydride and the 8-(N-allyl-N-acetylamino)quinoline formed in this case was easily isolated from the N,N-diallyl derivative on a chromatographic column (for the conditions, see above). The acetyl derivative isolated in this way was subjected to acid hydrolysis in order to obtain 8-N-(allylamino)quinoline. But the product formed did not correspond to the monoallyl derivative according to its characteristics. According to IR and PMR spectra, this product was assigned the structure of 2-methyl-2,3-dihydro-1H-pyrrolo[3,2-*h*]quinoline (III).

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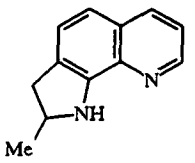
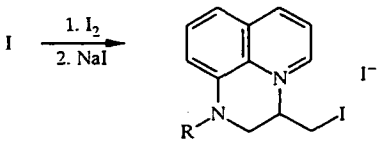


III

8-(N-allyl-N-tosylamino)quinoline was also subjected to acid hydrolysis. The compound obtained was also assigned the structure III.

In the next stage of our work, we investigated the behavior of allyl derivatives in the reaction of heterocyclization with iodine. We added a solution of two equivalents of iodine in diethyl ether to compound I dissolved in chloroform. The oil which fell out of solution after a day was dissolved in acetone, and to this solution we added a solution of sodium iodide in acetone. Bright yellow crystals of product (IV) precipitated almost immediately. The diallyl derivative IIb was isolated after the reaction without any change.



IVa, b

IV a R = Ac, b R = Ts

The structures of the compounds obtained were confirmed by PMR and IR spectra and elemental analysis results. The characteristics of the synthesized compounds are given in Tables 1 and 2.

Thus in this work we observed that derivatives of 8-(allylamino)quinoline in acid medium undergo rearrangement and cyclization with formation of 2-methyl-2,3-dihydro-1H-pyrrolo[3,2-*h*]quinoline, and heterocyclization with iodine occurs with formation of 1H-3-iodomethyl-2,3-dihydropyrazino[3,2,1-*i*,*j*]quinolinium iodide.

EXPERIMENTAL

The PMR spectra were recorded on a Bruker (250 MHz) spectrometer in the solvents $CDCl_3$ and DMSO-D_6. The IR spectra were taken on a Specord IR-75 in Vaseline oil and in CH_2Cl_2 solution. The course of the reaction was monitored and the purity of the compounds was assessed using thin-layer chromatography on Silufol UV-254 plates.

Allylation of 8-Aminoquinoline. A. Allyl bromide (2.3 ml, 0.028 moles) and 5.2 ml tributylamine were added to 3.2 g (0.022 mmoles) 8-aminoquinoline dissolved in 50 ml isopropyl alcohol. This was boiled with reflux for 5 h. The alcohol was driven off and the residue was treated with ether. The ether solution was washed 2-3 times with water in 30 ml portions. The ether layer was dried with anhydrous calcium chloride and evaporated. The oily residue was chromatographed on a column with aluminum oxide (ether–hexane, 1:1). Obtained: 1.6 g (40%) 8-(allylamino)quinoline (IIa) and 0.8 g (8%) 8-(diallylamino)quinoline (IIb).

B. Allyl bromide (2.5 ml, 0.03 moles) and an *i*-PrOH solution of sodium isopropylate (obtained from 0.6 g sodium) was added to 3.4 g (0.024 moles) 8-aminoquinoline in 50 ml isopropyl alcohol. This was boiled with reflux for 3 h. Then the mixture was treated as in the previous experiment. Obtained: 1.8 g (41%) 8-(allylamino)quinoline (IIa) and 1.1 g (21%) 8-(diallylamino)quinoline (IIb).

C. KF (1.2 g, 0.021 moles), 0.8 g (0.004 moles) triethylbenzylammonium chloride, and 0.7 ml (0.008 moles) allyl bromide were added to 1.0 g (0.007 moles) 8-aminoquinoline in 15 ml acetonitrile. This was boiled with reflux for 6 h. The solvent was driven off and the residue was treated as in methods A and B. Obtained: 0.1 g (10%) 8-(allylamino)quinoline (IIa) and 0.5 g (50%) 8-(diallylamino)quinoline (IIb).

8-(N-Allyl-N-acetylamino)quinoline (Ia). 8-Acetylaminoquinoline (1.8 g, 0.01 moles) was dissolved in 10 ml DMSO and, with cooling, 1.12 g (0.02 moles) KOH (dissolved in 5 ml water) and 0.9 ml (0.011 moles) allyl bromide were added. The mixture was then heated. After 2-2.5 h, 100 ml water was added to the solution. The precipitated crystals were filtered off and dried. The product was crystallized from benzene.

TABLE 1. Physicochemical Characteristics of Compounds I-IV

Compound	Empirical formula	Found % / Calculated %			mp, °C	IR spectra, cm^{-1}	Yield, %
		C	H	N			
Ia	$C_{14}H_{14}N_2O$	74,38 / 74,31	6,20 / 6,24	12,31 / 12,38	81...82	900, 970 δ (-C=CH₂), 1640 ν (-C=O)	83
Ib	$C_{19}H_{18}N_2O_2S$	67,27 / 67,43	5,17 / 5,36	8,23 / 8,28	89...89,5	920, 980 δ (-C=CH₂)	92
IIa	$C_{12}H_{12}N_2$	78,25 / 78,23	6,48 / 6,57	15,15 / 15,20	—	3340 ν (-NH), 920, 970 δ (-C=CH₂)	10...40
IIb	$C_{15}H_{16}N_2$	79,95 / 80,32	7,10 / 7,19	12,38 / 12,49	—	920, 970 δ (-C=CH₂)	8...50
III	$C_{12}H_{12}N_2$	78,07 / 78,23	6,46 / 6,57	15,07 / 15,20	86...87	3310 ν (-NH)	65
IVa	$C_{14}H_{14}N_2OI_2$	34,91 / 35,03	2,88 / 2,94	5,73 / 5,84	180...181	1650 ν (C=O)	85
IVb	$C_{19}H_{18}N_2O_2SI_2$	38,58 / 38,70	3,10 / 3,06	4,82 / 4,73	176...178	1360, 1160 ν (S=O)	85

TABLE 2. PMR Spectra of Compounds Ib, III, IVa, b

Compound	Protons		
	aliphatic	aromatic	
		tosyl	quinoline
Ib	2,30 (3H, s, CH_3), 4,60 (2H, d, > CH_2), 4,95 (2H, d, =CH_2), 5,85 (1H, m, CH)	7,15 (2H, d o-H), 7,6 (2H, d, m-H)	7,30 (1H, q, 3-H), 7,55 (1H, t, 6-H), 7,75 (1H, d, 7-H), 7,80 (1H, d, 5-H), 8,12 (1H, d, 4-H), 8,60 (1H, d, 2-H)
III	1,45 (3H, d, CH_3), 2,90 (1H, q, CH_2), 3,45 (1H, q CH_2), 4,30 (1H, m, CH), 5,00 (1H, s, NH)	—	7,20 (1H, d 6-H), 7,30 (1H, q, 3-H), 7,40 (1H, d, 5-H), 8,10 (1H, d, 4-H), 8,75 (1H, d, 2-H)
IVa	2,50 (3H, s, CH_3), 3,70 (2H, d, CH_2I), 4,10 (1H, d, CH_2), 5,10 (1H, d, CH_2), 5,65 (1H, m, CH)	—	8,05 (1H, t, 6-H), 8,35 (2H, m, 3-H, 7-H), 8,55 (1H, d, 5-H), 9,35 (1H, d, 4-H), 9,60 (1H, d, 2-H)
IVb	2,50 (3H, s, CH_3), 3,65 (2H, d, CH_2I), 4,20 (1H, d, CH_2), 5,10 (1H, d, CH_2), 5,65 (1H, m, CH)	7,5 (2H, d, o-H), 8,05 (2H, d, m-H)	7,95 (1H, t, 6-H), 8,25 (3H, m, 3-H, 5-H, 7-H), 9,35 (1H, d, 4-H), 9,60 (1H, д, 2-H)

8-(N-Allyl-N-*p*-toluenesulfonylamino)quinoline (Ib). 8-(*p*-Toluenesulfonylamino)quinoline (5.1 g, 0.017 moles) was dissolved in 20 ml DMSO and with cooling 1.92 g (0.034 moles) KOH (dissolved in 6 ml distilled water) and 2 ml (0.023 moles) allyl bromide were added. The mixture was then heated. The crystals precipitating after cooling were filtered off. The product formed was crystallized from benzene.

1-Acetyl-3-iodomethyl-2,3-dihydropyrazino[3,2,1-*i,j*]quinolinium iodide (IVa). 8-(N-Allyl-N-acetylamino)quinoline Ia (2.4 g, 0.01 moles) was dissolved in 10 ml chloroform. Iodine (5.2 g, 0.02 moles) iodine (dissolved in 40 ml ether) was added to the solution formed. A dark brown oil fell out of solution. The organic solvent was driven off and the oil was dissolved in acetone. Sodium iodide dihydrate (6.4 g, 0.02 moles) (dissolved in 50 ml acetone) was added. The precipitated yellow crystals were filtered off and washed several times with acetone and then dried.

1-*p*-Toluenesulfonyl-3-iodomethyl-2,3-dihydropyrazino[3,2,1-*i,j*]quinolinium iodide (IVb). Obtained by reaction of 2.3 g (0.007 moles) 8-(N-allyl-N-*p*-toluenesulfonylamino)quinoline Ib in 10 ml chloroform and 3.5 g (0.014 moles) iodine in 30 ml ether under the conditions of the previous experiment, followed by treatment with 3.2 g (0.01 moles) sodium iodide dihydrate in 25 ml acetone.

2-Methyl-2,3-dihydro-1H-pyrrolo[3,2-*h*]quinoline (III). A. 8-(N-allyl-N-*p*-toluenesulfonylamino)quinoline Ib (2.1 g, 0.006 moles) was dissolved in 30 ml 15% hydrochloric acid and boiled with reflux for 6 h. The cooled solution was alkalized with an aqueous solution of sodium hydroxide up to pH 9-10. Then this solution was treated three times with ether

in 30 ml portions. The ether extracts were combined and dried with anhydrous calcium chloride and purified using column chromatography, using diethyl ether as the eluent.

B. The reaction was carried out, as in experiment A, using 2.7 g (0.011 moles) 8-(N-allyl-N-acetylamino)quinoline Ia.

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