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SYNTHESIS OF DERIVATIVES OF 7-IODO-4-AMINOQUINOLINES

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7-Iodo- and 7,8-diiodo-4-(3-dimethylaminopropylamino)quinolines and 7-iodo-4-(3)dipropylaminopropylamino)- and 7-iodo-4-(3-diallylaminopropylamino)quinoline were obtained by the reaction of 7-iodo- and 7,8-diodo-4-chloroquinolines with the corresponding diamines. The catalytic hydrogenation of 7-iodo-4-(3-diallylaminopropylamino)quinoline at normal pressure leads to 7-iodo-4-(3-dipropylaminopropylamino)quinoline.

The biological activity of substituted 4-aminoquinolines has been the subject of intensive studies (for example, see [1-6]). A study of the distribution of these compounds in individual organs and tissues of organisms made it necessary to synthesize radioisotope-labeled aminoquinolines. For example, 7-^{131}I-4-(3-dimethylaminopropylamino)quinoline and its analogs are localized in malignant tumors [1-4].

The aim of the present research was to synthesize 7-iodo-4-(3-dimethylaminopropylamino)quinoline (I) and the analogous II-VI, in the molecules of which iodine or hydrogen radioisotopes can be easily introduced.

4-Aminoquinolines I-VI were obtained in analytically pure form by heating mixtures of 4-chloroquinolines VII or VIII and the corresponding diamines (Table 1). A similar previously known method for the synthesis of quinoline I [1] was poorly reproduced and did not make it possible to obtain significant amounts of a preparation with a high degree of purity. We established that quinolines I-VI can be obtained only when thoroughly purified starting 4-chloroquinolines VII and VIII and diamines were used.

4-Chloro-7,8-diiodoquinoline (VIII) was obtained from 4-chloro-7-iodoquinoline (VII). The nitration of quinoline VII with excess fuming nitric acid at 100°C gives 4-chloro-7-iodo-8-nitroquinoline (IX), which is reduced by stannous chloride to 4-chloro-7-iodo-8-aminoquinoline (X) with admixed 4-chloro-8-aminoquinoline. Aminoquinoline X was converted to diiodoquinoline VIII via the Sandmeyer reaction.

The results of elementary analysis and data from thin-layer chromatography (TLC) and the PMR and UV spectra (Tables 1 and 2) confirm the individuality and structures of quinolines I-X. The expected quinoline II is formed in 53% yield in the catalytic hydrogenation of quinoline IV at normal pressure in the presence of 10% platinum on silica gel. Virtually no hydrogenolysis of the C–N bond occurs under these conditions.

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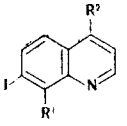
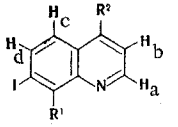
TABLE 1.



Compound	R¹	R²	mp, °C	Found, %				Empirical formula	Calculate, %				Yield,* %
				C	H	I	N		C	H	I	N	
II	H	$NHCH_2CH_2CH_2NPr_2$	79,2—80,4	52,6	6,6	30,9	10,4	$C_{18}H_{26}IN_3$	52,6	6,4	30,9	10,2	36
III	H	$NHCH_2CH(Me)CH_2NMe_2$	141,7—142	48,7	5,1	34,6	11,4	$C_{15}H_{20}IN_3$	48,8	5,5	34,4	11,4	65
IV	H	$NHCH_2CH_2CH_2N(CH_2CH=CH_2)_2$	81,6—82,2	53,5	5,4	31,0	10,0	$C_{18}H_{22}IN_3$	53,1	5,4	31,2	10,3	44
V	I	$NHCH_2CH_2CH_2NMe_2$	135,6—136	34,6	3,6	52,5	8,7	$C_{14}H_{17}I_2N_3$	34,9	3,6	52,8	8,7	48
VI	I	$NHCH_2CH(Me)CH_2NMe_2$	148,2—149	36,5	3,8	51,4	8,6	$C_{15}H_{19}I_2N_3$	36,4	3,9	51,3	8,5	72
VIII	I	Cl	161—161,5	25,7	1,0	61,2	3,0	$C_9H_4CII_2N$	26,0	1,0	61,1	3,4	69
IX	NO_2	Cl	158,4—159	32,3	1,2	37,2	8,4	$C_9H_4ClIN_2O_2$	32,3	1,2	37,9	8,4	66
X	NH_2	Cl	78,5—79,5	35,3	1,9	41,4	9,3	$C_9H_6ClIN_2$	35,5	2,0	41,7	9,2	44

*These are the yields of the analytically pure preparation.

TABLE 2. PMR and UV Spectra of Quinolines



Compound	δ, ppm						J, Hz				UV spectrum (hexane), λ_{max}, nm (log ε)
	H_A	H_B	H_C	H_D	R¹	R²	AB	CD	DR*	solvent	
I	8,31	6,18	7,28	7,51	8,28	1,84 m (2H), 2,30 s (6H), 2,49 m (2H), 3,28 m (2H)	5,0	8,7	1,6	CCl_4*	228 (4,47), 263 (4,28), 329 (3,85)
II	8,30	6,17	7,36	7,62	8,27	0,85 t 1,48 m (10H, J=7,5 Hz), 1,83 m (2H), 2,36—2,65 m (6H), 3,27 m (2H)	5,5	8,5	1,5	CCl_4*	231 (4,37), 266 (4,31), 333 (4,05)
III	8,28	6,09	7,18	7,48	8,24	0,94 d (3H, J=6,2Hz), 2,30 s (6H), 1,8—3,3 m (5H), 7,94 s (1H)	5,0	8,7	1,6	CCl_4*	230 (4,42), 263 (4,35), 325 (4,01)
IV	8,42	6,18	7,40	7,52	8,30	1,83 m (2H), 2,60 t (2H), 3,10 d (4H, J=7 Hz), 3,27 m (2H), 5,16 d, 5,18 d and 5,84 m (3H, J=9,7 and 17,5Hz)	4.5	9,0	1,6	CCl_4	220 (4,53), 257 (4,33), 322 (3,94)
V	8,37	6,30	7,37	7,77		1,90 m (2H), 2,34 s (6H), 2,52 m (2H), 3,35 m (2H), 8,10 s (1H)	5,6	9,2		CH_2Cl_2	243 (4,45), 261 (4,26), 336 (4,05)
VI	8,29	6,15	7,25	7,89		0,95 d (3H, J=6Hz), 2,28 s (6H), 1,8—3,3 m	5,0	8,5		CH_2Cl_2	242 (4,47), 261 (4,28), 336 (4,08)

*Hexamethyldisiloxane was used as the external standard.

EXPERIMENTAL

The IR and UV spectra were obtained with UR-20 and Perkin–Elmer-402 spectrometers, respectively. The PMR spectra of quinolines I-IV and VII were obtained with a Varian HA-100 spectrometer, while the spectra of the remaining quinolines were obtained with a Varian EM-360 spectrometer with hexamethyldisiloxane as the internal standard. The individuality of the compounds obtained was verified on Silufol UV-254 plates.

4-Chloro-7-iodoquinoline (VII). A mixture of 135 g (0.5 mole) of 7-iodo-4-hydroxyquinoline and 1.5 g of phosphorus oxychloride was refluxed for 10 h, after which the excess phosphorus oxychloride was removed, and the residue was poured over ice. The solid material was removed by filtration, and the aqueous solution was added carefully to a mixture of ice and ammonium hydroxide (the final pH of the medium should be greater than seven). The precipitate was removed by filtration, washed with water, dried, and distilled twice in vacuo to give 110 g (77%) of quinoline VII with mp 102.3-102.7°C and bp 174-175°C (4 mm) (mp 97-98°C [1]). PMR spectrum (CCl_4–CH_2Cl_2): δ 7.38 and 8.64 (d, J = 4.8 Hz, 2H), 7.77 (m, 2H), and 8.43 ppm (m, 1H).

4-Chloro-7-iodo-8-nitroquinoline (IX, Table 1). A 37-ml (0.87-mole) sample of nitric acid (sp. gr. 1.50) was added dropwise at −10°C in the course of 30 min to a solution of 25 g (87 mmole) of quinoline VII in 100 ml of concentrated sulfuric acid, and the mixture was heated to room temperature. It was then heated at 100°C for 1 h, after which it was cooled to room temperature and poured over 250 g of ice. The aqueous mixture was neutralized with a 20% solution of sodium hydroxide, and the precipitate was removed by filtration, washed with water and ethanol, and recrystallized from alcohol to give 19 g of quinoline IX. IR spectrum (CCl_4): 1565 and 1370 cm^{-1} (ν_{NO_2}). PMR spectrum (acetone): δ 7.85 and 8.80 (d, J.= 5 Hz, 2H); 8.17 ppm (s, 2H).

4-Chloro-7-iodo-8-aminoquinoline (X, Table 1). A 20-g (0.06-mole) sample of nitroquinoline IX was added in portions with stirring to a heated (to 33°C) solution of 76 g (0.34 mole) of stannous chloride in a mixture of 69 ml of concentrated hydrochloric acid and 69 ml of ethanol in such a way that the temperature did not exceed 37°C. After 2 h, 50 g of ice was added, and the mixture was treated dropwise with a 30% solution of sodium hydroxide up to pH 10. The precipitated aminoquinoline X was removed by filtration, washed with water, dried, and recrystallized from heptane to give 11.8 g of quinoline X. IR spectrum (CCl_4): 3490, 3380 cm^{-1} (ν_{NH_2}). PMR spectrum (CCl_4): δ 5.42 (s, 2H), 7.02 and 7.57 (d, J = 9 Hz, 2H), and 8.33 and 7.28 ppm (d, J = 5 Hz, 2H). The residue from the mother liquor was separated by column chromatography on aluminum oxide (elution with a mixture of hexane and ether with increasing polarity) to give 6.1 g of quinoline X, with mp 77-78°C, and 0.24 g of 4-chloro-8-aminoquinoline with mp 97.3-98.5°C (from heptane) (mp 99-100°C [7]). IR spectrum (CCl_4): 3500 and 3400 cm^{-1} (ν_{NH_2}). PMR spectrum (CCl_4): δ 4.87 (s, 2H), 6.67 and 7.1-7.3 (m, 3H), and 7.23 and 8.38 ppm (d, J = 4.6 Hz, 2 H).

4-Chloro-7,8-diiodoquinoline (VIII, Table 1). A solution of 1.69 g (25 mmole) of sodium nitrite in 11 ml of water was added dropwise at no higher than −5°C to a stirred mixture of 6.2 g (20 mmole) of aminoquinoline X in 3.3 ml of concentrated sulfuric acid and 17 ml of water, after which a solution of 6.7 g of potassium iodide in 10 ml of water was added, and the mixture was heated at 100°C for 1 h. It was then cooled, and the precipitate was removed by filtration, washed with a 10% solution of sodium hydroxide, a 25% solution of sodium thiosulfate and water, and dried. Purification by column chromatography on 200 g of activity II aluminum oxide (elution with chloroform) gave 4.5 g of diiodoquinoline VIII.

7-Iodo-4-(3-diallylaminopropylamino)quinoline (IV, Tables 1 and 2). A mixture of 7.93 g (27 mmole) of quinoline VII and 12.6 g (82 mmole) of diallylaminopropylamine (bp 199.5-199.8°C, n_D^{20} 1.4688) was heated with stirring with a stream of nitrogen at 135-138°C for 4.5 h, after which it was cooled and dissolved in 45 ml of 18% hydrochloric acid. The solution was extracted with ether, and the aqueous layer was treated with a 15% solution of sodium hydroxide to pH 10. The liberated oil began to crystallize after washing with ice water. Recrystallization from octane gave 6.9 g of quinoline IV.

A similar procedure was used to synthesize 7-iodo-4-(3-dipropylaminopropylamino)quinoline (II, Tables 1 and 2) and 7-iodo-4-(3-dimethylaminopropylamino)quinoline (I), with mp 104.5°C (from heptane) (mp 101-103°C [1]), in 47% yield. An analytically pure sample of quinoline I was obtained by repeated decantation of a hot saturated solution of I in heptane from the precipitated impurities.

7,8-Diiodo-4-(3-dimethylaminopropylamino)quinoline (V, Tables 1 and 2). A 5.3-g (52-mmole) sample of 3-dimethylaminopropylamine (bp 134.0-134.2°C) was added to 7.1 g (17 mmole) of quinoline VIII, and the mixture was heated with stirring with a stream of nitrogen at 135-137°C. The resulting black mass was dis-

solved in 120 ml of 18% hydrochloric acid at 75°C, and the solution was cooled to 0°C and treated with a cold 20% solution of sodium hydroxide (up to pH 10). The precipitate was washed with water, dried, and purified by chromatography on 400 g of activity II aluminum oxide (elution with acetone). The product was recrystallized successively from 65% ethanol, 75% acetone, and heptane to give 4.0 g of quinoline V.

7,8-Diido-4-(3-dimethylamino-2-methylpropylamino)quinoline (VI, Tables 1 and 2). A mixture of 0.69 g (1.7 mmole) of quinoline VIII and 0.59 g (5 mmole) of 3-dimethylamino-2-methylpropylamine (bp 143-144°C, n_D^{20} 1.4348) was heated at 140°C in a stream of nitrogen, and the light-yellow viscous mass was dissolved in 25 ml of 18% hydrochloric acid at 80°C. The solution was cooled, and the precipitate was washed with alcohol to give 0.85 g of the hydrochloride of quinoline VI. A 20% solution of sodium hydroxide was added to a solution of the hydrochloride in water, and the precipitate was recrystallized from ethanol to give 0.6 g of quinoline VI.

7-Iodo-4-(3-dimethylamino-2-methylpropylamino)quinoline (III) was similarly obtained.

Reduction of 7-Iodo-4-(3-diallylaminopropylamino)quinoline (IV). A flask was charged with 0.77 g of a catalyst containing 10% platinum dioxide on L 40/100 silica gel, 0.77 g (1.9 mmole) of quinoline IV, and 30 ml of ethyl acetate, after which 112 ml of hydrogen was absorbed by the mixture with vigorous stirring at room temperature in the course of 40 min. The catalyst was removed by filtration, and the solvent was removed in vacuo. The residue was separated by preparative TLC on activity II aluminum oxide (elution with ether). Workup of the upper zone gave 0.41 g (53%) of quinoline II with mp 72.3-73.5°C (from 75% alcohol); according to the data from TLC and the IR, PMR, and UV spectra, this product was identical to the preparation obtained by the reaction of 4-chloro-7-iodoquinoline (VII) with 3-dipropylaminopropylamine.

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