SYNTHESIS AND PROPERTIES OF A FLUORESCENT DERIVATIVE OF QUINOLINE – N-[N-(6-AMINOHEXYL)-5-DIMETHYLAMINO-1-NAPHTHYLSULFONAMIDO]-8-(N-METHYL-N-2-PROPYNYL)AMINOMETHYLQUINOLINE-5-CARBOXAMIDE

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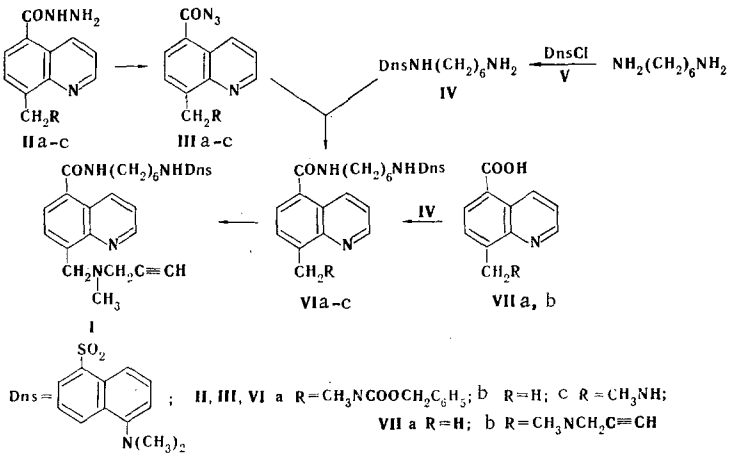
The synthesis of quinoline derivatives that contain a fluorogenic grouping by condensation of 8-(N-methyl-N-carbobenzoxy)aminomethylquinoline-5-carboxylic acid azide with N-(6-aminohexyl)-5-dimethylaminonaphthalenesulfonamide is described. The resulting carboxamide was subjected to hydrogenolysis, and subsequent reaction with propargyl bromide led to the title compound.

Fluorescent organic compounds of various classes are used in the study of biological membranes [1] and enzymes such as monoamine oxidase [2].

For similar purposes associated with the study of this enzyme we synthesized a new fluorescent compound of the quinoline series, viz. N-[N-(6-aminohexyl)-5-dimethylamino-1-naphthylsulfonamido]-8-(N-methyl-N-2-propynyl)aminomethylquinoline-5-carboxamide (I), on the basis of 8-(N-methyl-N-2-propynyl)-aminoethylquinoline [3], which contains the 5-dimethylamino-1-naphthylsulfonyl (dansyl) grouping bonded to the heterocyclic ring by means of a hexamethyldenediamine bridge as a fluorogen.



As the starting compound we used the previously synthesized 8-(N-methyl-N-carbobenzoxy)aminomethylquinoline-5-carboxylic acid hydrazide (IIa) [4], which was converted to the corresponding azide (IIIa) by the standard method. Both azide IIIa itself and model 8-methyl- and 8-(N-methyl)aminomethylquinoline-5-carboxylic acid azides (IIIa,b) are completely stable during storage. N-(6-Aminohexyl)-5-dimethylamino-1-naphthylsulfonamide (IV), which does not have a fluorogenic grouping, was synthesized by sulfonylation of hexamethylenediamine (taken in a sixfold excess) with dansyl chloride (V) by our modified method [5]. The yield of dansyl derivative IV ranged from 30 to 69%, depending on the quality of the hexamethylenediamine.

N-[N-(6-Aminohexyl)-5-dimethylamino-1-naphthylsulfonamido]-8-(N-methyl-N-carbobenzoxy)aminomethylquinoline-5-carboxamide (VIa) was obtained in analogy with [6] by condensation of azide IIIa with dansylated amine IV in dry pyridine. The reaction does not take place in chloroform or ethyl acetate, while only

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formylation of amine IV, as in the case of aliphatic amines [7], occurs in dimethylformamide (DMF). Hydrogenolysis of derivative VIa in the presence of palladium gave amine VIc, which was converted without isolation to propynylated compound I by reaction with propargyl bromide in methanol in the presence of potassium carbonate. Attempts to synthesize key amine VIc by other methods did not give positive results. Thus azide IIIc did not react with dansylamine IV. Attempts to synthesize I by activation of 8-(N-methyl-N-2-propynyl)aminomethylquinoline-5-carboxylic acid (VII) through the chloride, by the carbodiimide method, by the method of mixed anhydrides, and other methods were also unsuccessful. Reaction with the amine did not occur in these cases evidently as a consequence of the zwitter-ion character of acid VIIb. At the same time, model compound N-[N-(6-aminohexyl)-5-dimethylamino-1-naphthylsulfonamido]-8-methylquinoline-5-carboxamide (VIb) was synthesized from 8-methylquinoline-5-carboxylic acid (VIIa) activated by N,N'-carbonyldiimidazole [8].

The structures of I and model dansyl derivatives IV and VIa were confirmed by their PMR and IR spectra, which unambiguously demonstrate the presence in the molecules of a hexamethylene chain bonded to the quinoline ring by means of a CONH bond and, in the case of I, a propynyl grouping.

The fluorescence spectrum of final dansylated compound I has a λ_{max} band at 515 nm in the case of excitation with UV light with λ_{max} 355 nm; there is virtually no difference between its fluorescence characteristics and those of starting amine IV, model amide VIb, and dansylated N-methyl-N-2-propynylbenzylamine [2].

EXPERIMENTAL

The IR spectra of KCl pellets and solutions of the compounds in chloroform (in a KBr cuvette) were recorded with a Unicam SP-1000 spectrophotometer. The fluorescence spectra were recorded with a PMQ spectrometer. The UV spectra of solutions of the compounds in ethanol (10^{-4}-10^{-5} M) were recorded with a Specord UV-vis spectrophotometer. The PMR spectra were recorded with a Varian XL 100 A-12 spectrometer at 27°C with tetramethylsilane as the internal standard. The systems for thin-layer chromatography (TLC) on Silufol UV-254 and preparative chromatography on LS 5/40 μ silica gel were as follows: chloroform–methanol–25% NH_4OH–water (100:50:8:1) (A), benzene–ethyl acetate–acetic acid (100:50:1) (B), acetonitrile–25% NH_4OH (10:1) (C), benzene–ethyl acetate–acetic acid (50:50:1) (D), and acetonitrile–25% NH_4OH (6:1) (E).

8-(N-Methyl-N-carbobenzoxy)aminomethylquinoline-5-carboxylic Acid Azide (IIIa). A 350-mg (5 mmole) sample of sodium nitrite was added with ice cooling to a solution of 780 mg (2.1 mmole) of hydrazide IIa in 4 ml of 5 N HCl, after which it was stirred for 20 min, treated with 40% K_2CO_3 solution to pH 7, and extracted with chloroform. The extract was washed with water and dried with Na_2SO_4, and the solvent was evaporated to give 500 mg (62%) of azide IIIa (a viscous oil). IR spectrum: 2172 cm^{-1} ($\bar{N}\equiv\overset{+}{N}=N-$). Similarly, 140 mg (82%) of 8-methylquinoline-5-carboxylic acid azide (IIIb), with mp 82-84°C (dec.), was obtained from 160 mg (0.07 mmole) of hydrazide IIb and 60 mg (0.9 mmole) of $NaNO_2$ in 2.5 ml of 1 N HCl. IR spectrum: 2172 cm^{-1} ($\bar{N}\equiv\overset{+}{N}=N-$). Found: N 26.6%. $C_{11}H_8N_4O$. Calculated: N 26.4%. Similarly, 70 mg (47%) of 8-(N-methyl)aminomethylquinoline-5-carboxylic acid azide (IIIc) (an oil) was obtained from 140 mg (0.6 mmole) of hydrazide IIc and 50 mg (0.7 mmole) of $NaNO_2$ in 5 ml of 5 N HCl. IR spectrum. 2172 cm^{-1} ($\bar{N}\equiv\overset{+}{N}=N-$).

N-(6-Aminohexyl)-5-dimethylamino-1-naphthylsulfonamide (IV). A solution of 1.1 g (3 mmole) of dansyl chloride in 30 ml of chloroform was added gradually in the course of 2 h to a mixture of 2.2 g (19 mmole) of hexamethylenediamine* and 0.6 ml (10 mmole) of triethylamine in 50 ml of chloroform. After 1 h, the precipitate was separated, washed with 10% $NaHCO_3$ solution and water, and dried with Na_2SO_4. The residue obtained after evaporation was subjected to preparative TLC in system C to give 1 g (69%) of derivative IV (an oil that crystallized after standing for a long time) with mp 106-110°C (mp 105-110°C [5]). IR spectrum: 3357 cm^{-1} (NH_2). UV spectrum, λ_{max} (log ε): 244 (3.79) and 400 nm (4.76). PMR spectrum (d_6-DMSO): 8.05-8.6, 7.1-7.7 (6H, m, naphthalene ring); 3.65 (4H, broad m, NCH_2, CH_2N); 2.9 (6H, s, CH_3N); 1.06 ppm [8H, broad m, $-(CH_2)_4$]. Fluorescence spectrum, λ_{max}: 355 (excitation) and 515 nm (emission). The substance was homogeneous in systems A, C, and E.

N-[N-(6-Aminohexyl)-5-dimethylamino-1-naphthylsulfonamide]-8-(N-methyl-N-carbobenzoxy)aminomethylquinoline-5-carboxamide (VIa). A mixture of 500 mg (1.3 mmole) of freshly prepared azide IIIa and 600 mg (1.7 mmole) of amine IV in 5 ml of dry pyridine was stirred at ~20°C for 3 days, after which the solvent was evaporated, and the residue was treated with toluene and evaporated. The treatment was repeated three times, after which preparative TLC in system D gave 540 mg (58%) of VIa (an oil). IR spectrum: 1680 cm^{-1} (CONH). PMR spectrum ($CDCl_3$): 7.1-8.3 (16H, m, aromatic rings), 5.2 (2H, m, NHCO, $NHSO_2$), 4.7

*The hexamethylenediamine was distilled three times in vacuo immediately before the experiment.

(4H, t, NCH_2, CH_2N), 2.9 (9H, s, CH_3N), 2.7 (2H, s, $CH_2OC=O$), 2.1 (2H, s, CH_2N), and 0.9 ppm [8H, m, $-(CH_2)_4$]. The substance was homogeneous in systems A and D. Found: C 67.2; H 6.9; N 9.7%. $C_{38}H_{43}N_5O_5S$. Calculated: C 67.6; H 6.3; N 10.0%.

N-[N-(6-Aminohexyl)-5-dimethylamino-1-naphthylsulfonamido]-8-methylquinoline-5-carboxamide (VIb). A 120-mg (0.75 mmole) sample of N,N'-carbonyldiimidazole was added gradually to a mixture of 140 mg (0.65 mmole) of acid VIIa in dry THF. After CO_2 evolution ceased, 250 mg (0.7 mmole) of amine IV was added, and the mixture was heated at 60°C for 8 h. It was then evaporated, and the residue was subjected to preparative TLC in system D to give 150 mg (45%) of VIb (an oil). IR spectrum: 1652 cm^{-1} (CONH). UV spectrum, λ_{max} (log ε): 285 (3.907) and 400 nm (726). Fluorescence spectrum, λ_{max}: 355 (excitation) and 515 nm (emission). The substance was homogeneous in systems A and D. Found: C 67.0; H 6.4; N 10.1%. $C_{29}H_{34}N_4O_3S$. Calculated: C 67.2; H 6.6; N 10.1%.

8-(N-Methyl-N-2-propynyl)aminomethylquinoline-5-carboxylic Acid (VIIb). A mixture of 288 mg (1 mmole) of 8-(N-methyl)aminomethylquinoline-5-carboxylic acid hydrochloride [4], 1.2 ml of propargyl bromide, and 80 mg of sodium hydroxide in 50 ml of methanol was refluxed for 6 h, and the precipitate was separated and washed with methanol. The filtrate was evaporated, the residue was dissolved in chloroform–methanol (1:1), and the precipitate was separated. This procedure was repeated two times. Evaporation of the filtrate gave 200 mg (83%) of acid VIIb (a hygroscopic oil). The acid was treated with a solution of HCl in methanol, the mixture was evaporated to dryness, and the residue was dissolved in 5 ml of methanol–chloroform (5:1). Evaporation of the filtrate gave 200 mg of the hydrochloride of acid VIb with mp 134-136°C. IR spectrum: 1717 (COOH) and 2043 cm^{-1} (C≡C). PMR spectrum of the Na salt (d_6-DMSO): 7.6-8.3 (5H, m, quinoline ring), 4.6 (2H, s, CH_2C), 3.1 (2H, s, CH_2N), 2.4 (3H, s, CH_3N), and 2.2 ppm (1H, s, ≡CH). The substance was homogeneous in system A. Found: C 45.8; H 7.13; N 7.4%. $C_{15}H_{14}N_2O_2 \cdot 2HCl \cdot 3H_2O$. Calculated: C 45.1; H 8.80; N 7.1%.

N-[N-(6-Aminohexyl)-5-dimethylamino-1-naphthylsulfonamido]-8-(N-methyl-N-2-propynyl)aminomethylquinoline-5-carboxamide (I). A) A solution of 500 mg (0.8 mmole) of derivative VIa in 30 ml of methanol was hydrogenated for 3 days in the presence of 1 g of Pd black, after which the catalyst was removed by filtration. A 0.5-ml (4 mmole) sample of propargyl bromide was added to the filtrate, and the mixture was refluxed for 4 h. The solvent was evaporated, and the residue was subjected to preparative TLC in system E to give 50 mg (10%) of I (an oil). IR spectrum: 2130 (C≡C), 3208 (C≡CH), and 1680 cm^{-1} (CONH). UV spectrum, λ_{max} (log ε): 244 (3.792) and 476 nm (4.657). Fluorescence spectrum, λ_{max}: 355 (excitation) and 510 nm (emission). PMR spectrum ($CDCl_3$): 7.2-8.9 (11H, m, aromatic rings), 6.5 (1H, broad m, NH), 5.2 (1H, broad m, NH), 4.3 (2H, s, CH_2C), 3.4 (4H, m, NCH_2, CH_2N), 3.3 (2H, M, $\equiv C-CH_2N$), 2.9 (9H, 2, CH_3N), 2.4 (1H, s, ≡CH), and 1.25 ppm [8H, m, $(CH_2)_4$]. The substance was homogeneous in system D. Found: C 67.7; H 7.7; N 10.7%. $C_{35}H_{49}N_5O_3S$. Calculated: C 67.8; H 8.0; N 11.3%.

B) A 0.5-g sample of thionyl chloride was added to 205 mg (0.8 mmole) of acid VIIIb in 10 ml of DMF, and the mixture was stirred for 20 min. A 280-mg (0.8 mmole) sample of amine IV was added, and the mixture was heated at 60°C for 3 h. The solvent was evaporated in vacuo at 40°C, and 250 mg of starting amine IV was extracted from the residue with chloroform.

C) A mixture of 205 mg (0.8 mmole) of acid VIIb, 280 mg (0.8 mmole) of amine IV, and 185 mg (0.8 mmole) of N,N'-dicyclohexylcarbodiimide in 10 ml of DMF was stirred at 20°C for 3 days, after which the solvent was evaporated, and the residue was extracted with chloroform to give 260 mg of starting amine IV.

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