SOME METHOXY DERIVATIVES OF 9-AMINO-6-NITROACRIDINE

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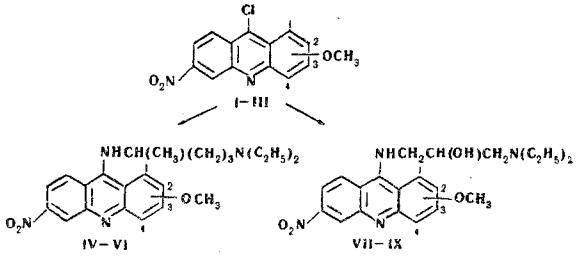
The reaction of the 2-, 3-, and 4-methoxy derivatives of 9-chloro-6-nitroacridine with δ-diethylamino-α-methylbutylamine and with γ-diethylamino-β-hydroxypropylamine in phenol has given the 2-, 3-, and 4-methoxy derivatives of 9-(δ-diethylamino-α-methylbutylamino)-6-nitroacridine and of 9-(γ-diethylamino-β-hydroxypropylamino)-6-nitroacridine, respectively.

9-Amino-6-nitroacridine [1] and its derivatives [2, 3] are known as substances with powerful antibacterial action. In order to seek new active compounds, we have synthesized a number of methoxy-substituted 9-amino-6-nitroacridines containing aliphatic side chains in position 9. The synthesis was carried out in the following way:



The initial 2-, 3-, and 4-methoxy derivatives of 9-chloro-6-nitroacridine (I–III) have been described by two of us previously [4]. When compounds I–III were heated with δ-diethylamino-α-methylbutylamine and with γ-diethylamino-β-hydroxypropylamine in phenol, the 2-, 3-, and 4-methoxy derivatives of 9-(δ-diethylamino-α-methylbutylamino)-6-nitroacridine IV–VI) and of 9-(γ-diethylamino-β-hydroxypropylamino)-6-nitroacridine (VII–IX) were obtained, respectively, and these are characterized in the table in the form of their dihydrochlorides.

Preliminary tests carried out by Docent O. V. Chuiko have revealed antimicrobial activity for all six substances IV–IX. Compounds VII–IX are the most active. Detailed results of the biological tests will be published separately.

EXPERIMENTAL

Dihydrochlorides of the 2-, 3-, and 4-methoxy derivatives of 9-(δ-diethylamino-α-methylbutylamino)-6-nitroacridine (IV–VI). 2.88 g (0.01 mole) of the appropriate 9-chloroacridine (I–III) was dissolved in 7.5 ml of phenol at 70° C and, with stirring, 2.37 g (0.015 mole) of δ-diethylamino-α-methylbutylamine was added dropwise over 10 min. Stirring was continued at 100° C for 1 hr. After cooling, the mixture was treated with 10% sodium hydroxide, and the resulting oil was separated off, washed with water, and dissolved in benzene. The benzene solution was dried with potassium carbonate and filtered, and a current of dry HCl was passed through the filtrate. The benzene was decanted off from the oil that had deposited and this was then dissolved in absolute ethanol, ether was added, and the mixture was left 1–2 days for crystallization. The crystals of the product (one of the dihydrochlorides of IV–VI) was separated off, washed with dry ether, and dried in the air. When aqueous solutions of the compounds obtained were made alkaline with ammonia, the bases IV–VI separated in the form of dark oils which crystallized only in the case of the 2-methoxy derivative IV, which formed red-brown plates with mp 97–98° C. Found, %: N 12.75, 12.82. Calculated for $C_{23}H_{30}N_4O_3 \cdot 2H_2O$, %: N 12.56. On drying in vacuum over P_2O_5, the substances lost 8.19% of water, which corresponds to 1 molecule (calculated, %: H_2O 8.07).

Dihydrochlorides of the 2-, 3-, and 4-methoxy derivatives of 9-(γ-diethylamino-β-hydroxypropylamino)-6-nitroacridine (VII–IX). 2.88 g (0.01 mole) of one of compounds I–III was dissolved in 7.5 g of phenol at 70° C and, with stirring, 2.19 g (0.015 mole) of γ-diethylamine-β-hydroxypropylamine (prepared by the method of Gilman et al. [5]) was added in drops. The temperature was raised to 85–90° C and stirring was continued for 1.5 hr. The mixture was cooled, treated with 50 ml of anhydrous ethanol, and filtered. The filtrate was made acid to Congo Red with concentrated HCl, and 200 ml of dry ether was added. The ethereal layer was drawn off from the dark oil and this was then dissolved in 150 ml of water and the solution was mixed with 150 ml of ethanol, filtered, made alkaline with 10% ammonia, and diluted with 300 ml of water. The oil formed (one of the bases VII–IX) crystallized on standing, and the crystals were separated off, washed with water, and dried in the air. VII—dark red needles, mp 88° C. Found, %: N 12.65, 13.10. VIII—dark yellow prisms, mp 65°C. Found,

Characteristics of the Compounds Obtained

Compound	Mp, °C	Color and form of the crystals	Found, %*		Yield, %
			N	Cl	
IV	221 (decomp.)	Red needles	10.50 10.54	13.55 13.46	83
V	220 (decomp.)	Dark yellow needles	10.45 11.03	13.60 13.72	79
VI	198 (decomp.)	Red prisms	11.10 10.96	13.39 13.50	69
VII	212—214	Red needles	10.92 10.87	13.75 13.92	80
VIII	178—180	Yellow needles	11.34 11.28	13.80 13.69	84
IX	118—120	Red needles	11.32 11.35	13.90 14.09	67

*For compounds IV-VI, calculated for $C_{23}H_{30}N_4O_3 \cdot 2HCl \cdot 2H_2O$, %: N 10.79, Cl 13.68; for VII-IX, calculated for $C_{21}H_{26}N_4O_4 \cdot 2HCl \cdot 2H_2O$, %: N 11.05, Cl 14.00.

%: N 13.17, 13.00. IX—red needles, mp 80° C (decomp). Found,% N 12.96, 12.71. On being dried in vacuum over P_2O_5, the substances lost water: VII—8.38%; VIII—8.42%; IX—8.21%. Formula for all the compounds $C_{21}H_{26}N_4O_4 \cdot 2H_2O$. Calculated, %: N 12.90; H_2O 8.29.

The bases VII and IX were suspended in the minimum amount of water and the suspension was acidified with hydrochloric acid (1:1) to Congo Red, after which acetone was added to the solution. The oils that separated (the dihydrochlorides of VII and IX) crystallized on standing. In the case of compound VIII, to obtain the salt the dried base was dissolved in absolute ethanol, the solution was acidified with concentrated HCl and dry ether was added; the salt crystallized in a day.

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