PYRIDO[2,3-g]QUINOLINES

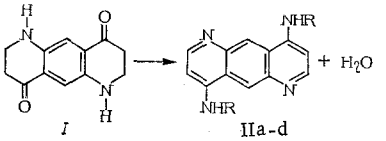
II. SYNTHESIS OF 4,9-DIAMINO SUBSTITUTED PYRIDO[2,3-g]QUINOLINES

A. F. Bekhli, F. S. Mikhailitsyn,
A. I. Krotov, S. A. Rabinovich,
and V. F. Gladkikh

UDC 615.283:547.831.].012.1

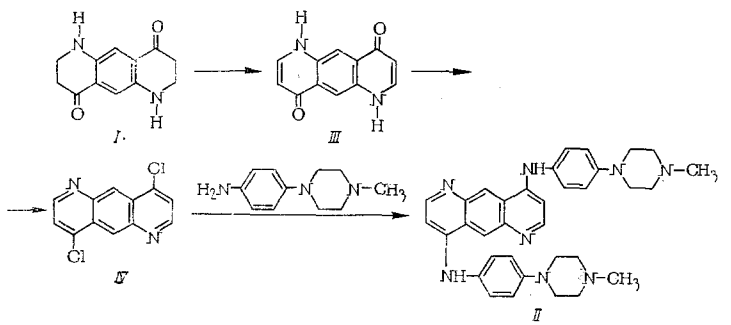
The biological properties of pyrido[2,3-g]quinoline derivatives have had extremely limited investigations. Of the compounds in this series, the anthelmintic activity (antischistosomiasis activity) for 2,7-dimethyl-3,8-bis-(diethylaminomethyl)-4,9-diethoxypyrido[2,3-g]quinoline has been reported [1]. The 4,9-diamino substituted pyrido[2,3-g]quinolines have remained unknown up to the present. They are of interest because they are structural analogs of the widely used antiparasitic preparations, the 4-aminoquinoline and 9-aminoacridine derivatives.

We synthesized the 4,9-diamino substituted pyrido[2,3-g]quinolines (IIa-d, see Table 1) by a method developed for similar systems [2-4]. 1,2,3,4,6,7,8,9-Octahydro-4,9-dioxopyrido[2,3-g]quinoline (I), which was converted into IIa-d by reacting it with alkyl(aryl)amines in boiling isoamyl alcohol in the presence of an oxidizing agent, served as the starting material. The reaction was accompanied by the splitting off of water, by the introduction of the amine substituents into the 4th and 9th positions, and by the complete aromatization of the partially hydrogenated pyridine rings of molecule I.



I IIa-d

In order to confirm the structure of IIa-d as compounds having an aromatic structure, one of the above (IId) was prepared by a different route: one using an aromatic derivative of pyrido[2,3-g]quinoline. For this purpose, I was dehydrogenated with palladium on carbon into pyrido[2,3-g]quinoline[1H,6H]-4,9-dione (III); the latter was converted into 4,9-dichloropyrido[2,3-g]quinoline (IV) by treatment with phosphorus oxychloride. Compound IId was obtained by reacting IV with 1-methyl-4-p-aminophenylpiperazine [5]; according to its physicochemical constants, IR, and UV spectra (see Fig. 1), it was identical to the IId sample obtained by the direct reaction of I with this same amine.



I III IV II

E. I. Martsinovskii Institute of Medicinal Parasitology and Tropical Medicine, Moscow. Translated from Khimiko-Farmatsevticheskii Zhurnal, Vol. 6, No. 3, pp. 24-26, March, 1972. Original article submitted October 19, 1970.

TABLE 1. 4,9-Diamino Substituted Pyrido[2,3-g]quinolines

Compound	R	Yield* (%)	M.p. (in deg)
IIa	$CH_3\ (CH_2)_3 - CH_3$	64	350—2 (from dimethylformamide)
IIb	$(C_2H_5)_2N\ (CH_2)_3CH -$	62	185-6 (from heptanonitromethane)
IIc	$H_3CO-C_6H_4-$	57	>360 (decomp., from methanol)
IId	$H_3C-N(CH_2CH_2)_2N-C_6H_4-$	68	>360 (decomp.)†

Compound	Color of reaction product	Found (%)			Empirical formula	Calc. (%)		
		C	H	N		C	H	N
IIa	Light-yellow plates	74,79	8,12	17,38	$C_{20}H_{26}N_4$	74,51	8,11	17,38
IIb	Yellowish-green powder	75,11	8,51	16,89	$C_{30}H_{48}N_6$	75,38	8,02	17,05
IIc	Reddish-orange powder	73,73	5,41	13,04	$C_{26}H_{22}N_4O_2$	73,92	5,25	13,26
IId	Light-green powder	73,12	7,14	19,78	$C_{34}H_{38}N_8$	73,09	6,86	20,06

*By method A.

†Method of purification is given in the Experimental section.

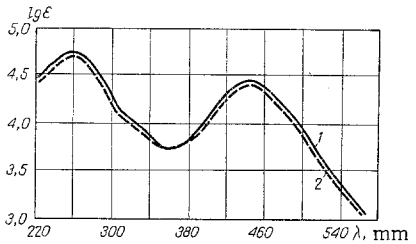


Fig. 1. UV spectra of IId. 1) IId obtained from I [λ_{max} (log ε) 258 and 446 nm (4.71; 4.41)]; 2) IId obtained from IV [λ_{max} (log ε) 258 and 446 nm (4.68; 4.39)], in a 0.1 N aqueous hydrochloric acid solution, SF-4 spectrophotometer.

The compounds synthesized were tested for their antimalarial and anthelmintic activity. In doses close to the maximum bearable, compounds IId (0.9 g/kg) and IIb (0.005 g/kg) do not have any effect on the asexual erythrocytic forms of Plasmodium berghei. Compound IId at a daily dose of 1 g/kg for four days was effective in 36% of the cases against trichocephaliasis of white mice (Trichocephalus muris). This same compound brought about the recovery of five out of six mice from hymenolepidiasis (Hymenolepis nana) at a dose of 0.7 g/kg, and possessed 100% activity at a dose of 1 g/kg. Compound IId of all the 4,9-diamino substituted pyrido [2,3-g]-quinolines we synthesized is the least toxic; doses of 10 g/kg of weight are well tolerated by the animals.

EXPERIMENTAL

4,9-Diamino substituted pyrido[2,3-g]quinolines (IIa-d). A. A mixture of 0.02 mole of I, 0.04 mole of amine, 0.01 mole of o-nitrophenol, and 20 ml of isoamyl alcohol was heated with agitation for 3 h at 150-170°C while azeotropically distilling off the water formed. After cooling the reaction mixture, the precipitate that formed was filtered off. The compounds were purified by reprecipitation and crystallization. Compounds IIa and b are highly soluble in the majority of organic solvents; IIc and d are poorly soluble (see Table 1).

B. A mixture of 0.25 g of IV and 0.38 g of 1-methyl-4-p-aminophenylpiperazine was boiled in 10 ml of 2 N hydrochloric acid for 1 h. The reaction mixture was treated with carbon, made alkaline, and the precipitate that formed was isolated. The product was purified by boiling it in dimethylformamide and reprecipitating it. The yield of IId was 0.43 g (77.2%), mp > 360°C. Found %: N 19.92. $C_{34}H_{38}N_8$. Calculated %: N 20.16.

Pyrido[2,3-g]quinoline-[1H,6H]-4,9-dione (III). A mixture of 1 g of I, 1 g of 20% palladium on carbon, and 100 ml of p-xylene was boiled 8 h. The residue was isolated and treated with 10% sodium hydroxide (10 ml) while heating; the insoluble products were removed. The filtrate was treated with concentrated hy-

drochloric acid until acid, the precipitate was isolated and washed with water. The yield of III was 0.62 g (63.2%), the powder was light-yellow, mp > 360°C (purified by reprecipitation), soluble in dilute alkaline solutions, poorly soluble in the majority of organic solvents. Found %: C 67.43; H 3.84; N 12.97. $C_{12}H_8N_2O_2$. Calculated %: C 67.92; H 3.80; N 13.20.

4,9-Dichloropyrido[2,3-g]quinoline (IV). A mixture of 0.42 g of III and 5 ml of phosphorus oxychloride was boiled 1 h and the excess phosphorus oxychloride was distilled off in vacuo. Ice was added to the remainder and, while cooling, it was treated with an aqueous ammoniacal solution until alkaline. The precipitate was filtered off and washed with water. Compound IV, 0.38 g (76%), was obtained. The product was purified by recrystallization from benzene followed by vacuum distillation (250°, 2 mm). White crystals with a greenish tinge, mp 310-312°C (in a sealed capillary), limited solubility in benzene, alcohol, hot dichloroethane, dimethylformamide, insoluble in water. Found %: C 58.11; H 2.52; Cl 28.40; N 10.04. $C_{12}H_6Cl_2N_2$. Calculated %: C 57.89; H 2.43; Cl 28.47; N 11.24.

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