SOME DERIVATIVES OF PYRIMIDO[5,4-b]QUINOLINE

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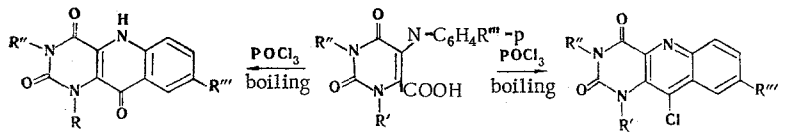
10-Chloro-2,4-dioxo derivatives of pyrimido[5,4-b]quinoline have been synthesized, and nucleophilic substitution reactions in these compounds have been studied.

Investigations in the field of little-studied [1, 2] derivatives of pyrimido[5,4-b]quinoline are of interest, since pyrimido[5,4-b]quinoline is a deaza analog of benzopteridine, and substances of natural origin are found in the benzopteridine series.

We have described the synthesis of pyrimido[5,4-b]quinolines from derivatives of orotic acid substituted in position 5 by aniline or p-methoxy- or p-chloroaniline residues (Ia-d) synthesized previously [3]. Ring closure with the formation of 1,2,3,4,5,10-hexahydropyrimido[5,4-b]quinoline-2,4,10-triones was performed by boiling compounds (Ia-d) with an excess of phosphorus oxychloride. At a higher temperature, in addition to ring closure the replacement of one of the hydroxy groups by chlorine took place. The monochloro derivative formed from the acid (Id) can have only structure (IIId), while in the monochloro derivatives obtained from the acids (Ia-c) the chlorine may be present in one of three possible positions: 2, 4, or 10.



II a-b I a-d III a-d

a $R'=R''=H$, $R'''=OCH_3$; b $R'=R''=R'''=H$; c $R'=R''=H$, $R'''=Cl$; d $R'=R''=CH_3$, $R'''=OCH_3$

To prove the structures of substances (IIIa-c), the halogen in (IIIb) was replaced by a piperidine residue, and the resulting compound (IV) was cleaved with aqueous alkali. This gave 3-amino-4-piperidinoquinoline-2-carboxylic acid (V), which was confirmed by its conversion into butyl 3-butylamino-4-piperidinoquinoline-2-carboxulate (VI).

Under fairly severe conditions, the chlorine in compounds (IIIa-d) reacts with amines. Thus, compound (IV) was obtained by heating substance (IIIb) with piperidine in dimethylformamide at a high temperature. Similarly, the amines (VII) and (VIII) were obtained from (IIIb). In the 8,10-dichloro derivative (IIIc), the mobility of the chlorine in position 10 was reduced, and to obtain compound (IX) it was necessary to heat the chloride (IIIc) with morpholine for a longer period. The reactivity of the chlorine in the derivative (IIIa) and (IIId) containing a methoxy group in position 8, is lowered to a particularly appreciable degree. Under the conditions mentioned above, these compounds did not take part in the reaction with amines. An attempt to replace the chlorine in (IIId) by piperidine by heating the reactants in phenol [4] led to the formation of the 10-phenoxy derivative (X). The reduction in the mobility of chlorine on the introduction of an electron-

*Deceased.

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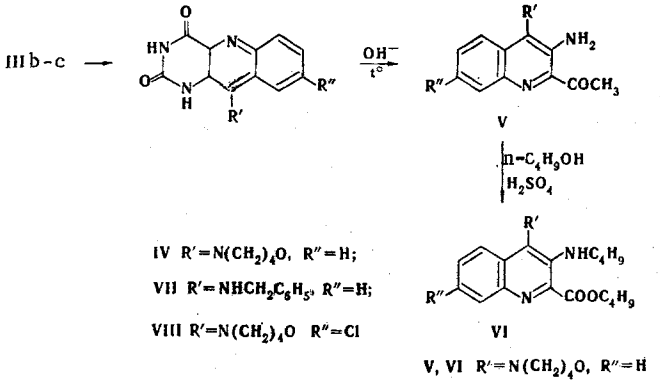
TABLE 1. Pyrimido[5,4-b]quinolines

Compound	Mp, °C (decomp.)	Empirical formula	Found, %				Calculated, %				Yield, %
			C	H	Cl	N	C	H	Cl	N	
IIIa	>350*	$C_{12}H_8ClN_3O_3$	52,2	3,0	12,4	14,9	51,9	2,9	12,8	15,1	40,0
IIIc	>340*	$C_{11}H_5Cl_2N_3O_2$	46,5	1,7	24,9	14,6	46,8	1,8	25,2	14,9	33,6
IIId	258*	$C_{14}H_{12}ClN_3O_3$	55,3	4,0	11,3	13,6	55,0	3,9	11,6	13,7	62,0
VII	334*	$C_{15}H_{14}N_4O_3$	60,5	4,8	—	19,1	60,4	4,7	—	18,8	55,5
VIII	278†	$C_{18}H_{14}N_4O_2$	68,0	4,7	—	18,0	67,9	4,4	—	17,6	66,1
IX	340†	$C_{15}H_{13}ClN_4O_3$	54,5	3,7	11,0	17,0	54,1	3,9	10,7	16,8	64,2

* From dimethylformamide.

† From aqueous dimethylformamide.

donating substituent into position 8 was also shown in the different stabilities of compounds (IIIa and b) to the action of acids. Thus, on being heated with dilute hydrochloric acid compound (IIIb) was converted comparatively readily into the corresponding 10-oxo derivative (IIb), while substance (IIIa) remained unchanged under the same conditions.



EXPERIMENTAL

8-Methoxy-1,2,3,4,5,10-hexahydropyrimido[5,4-b]quinoline-2,4,10-trione (IIa). A mixture of 3.5 mmoles of compound (Ia) and 10 ml of $POCl_3$ was heated at 80°C for 1 h and cooled, the precipitate was filtered off, it was treated with glacial acetic acid and again filtered off, and was then washed with dimethylformamide and with water. This gave 0.6 g (67%) of substance (IIa). It did not melt below 350°C. Found: C 55.0; H 3.4; N 16.6%. $C_{12}H_2N_3O_4$. Calculated: C 55.6; H 3.5; N 16.6%. IR spectra, cm^{-1}: 3240, 3140, 3080, 3000 (NH); 1730, 1690, 1640 (amide C = O).

10-Chloro-1,2,3,4-tetrahydropyrimido[5,4-b]quinoline-2,4-dione (IIIb). A mixture of 3.8 mmoles of compound (Ib) and 15 ml of $POCl_3$ was boiled for 3 h and cooled, the precipitate was filtered off and was treated with ice water and again filtered off; the filtrate was distilled in vacuum and the residue was worked up as is described above and was purified by crystallization from dimethylformamide and was then added to the main reaction product. This gave 0.52 g (56%) of compound (IIIb). Mp 320°C (decomp., from dimethylformamide). Found: C 53.6; H 2.4; Cl 14.0; N 16.9%. $C_{11}H_6ClN_3O_2$. Calculated: C 53.3; H 2.4; Cl 14.3; N 17.0%. IR spectrum, cm^{-1}: 3320, 3220, 3080 (NH); 1730, 1710, 1690 (amide C = O).

Compounds (IIIa), (IIIc), and (IIId) were obtained similarly (see Table 1). In the preparation of substance (IIId), the reaction time was 50 min.

3-Amino-4-piperidinoquinoline-2-carboxylic Acid (V). A mixture of 4 g (13.5 mmoles) of substances (IV) and 90 ml of 15% aqueous NaOH was heated in an autoclave at 160°C for 5 h. The precipitate was filtered off, treated with dilute hydrochloric acid to pH 3.4, again filtered off, and reprecipitated from aqueous alkaline solution with hydrochloric acid. This gave 2.7 g (74%) of substance (V). Mp 168°C (decomp., from water). Found: C 66.9; H 6.4; N 15.4%. $C_{15}H_{17}N_3O_2$. Calculated: C 66.7; H 6.3; N 15.5%. IR spectrum, cm^{-1}: 3400, 3240 (NH_2); 1660 (amino acid C = O with the possible superposition of δ NH_2). PMR spectrum (DMSO), ppm: 1.70 (β, γ-CH_2 of the piperidine substituent), 3.23 (α-CH_2 of the piperidine substituent), 7.44, 7.80 (multiplets of the benzene ring).

Butyl 3-Butylamino-4-piperidinoquinoline-2-carboxylate (VI). A mixture of 0.3 g of substance (V), 10 ml of n-butanol, and 0.5 ml of concentrated sulfuric acid was boiled for 5 h. Then the solution was evaporated in vacuum and the residue was treated with aqueous $NaHCO_3$ to pH 7 and was extracted with chloroform. This gave 0.2 g (48%) of (VI). Mp 78°C (decomp., from aqueous ethanol). Found: C 72.2; H 8.6; N 11.0%. $C_{23}H_{33}N_3O_2$. Calculated: C 72.1; H 8.6; N 11.0%. IR spectrum, cm^{-1}: 3440, 3330 (NH); 1690 (ester C = O).

10-Piperidino-1,2,3,4-tetrahydropyrimido[5,4-b]quinoline-2,4-dione (IV). A mixture of 2 g (8.1 mmoles) of (IIIb), 3.4 g (40 mmoles) of piperidine and 30 ml of dimethylformamide was boiled for 3 h and was then cooled, and the precipitate was filtered off and washed with water. This gave 1.3 g (54%) of the amine (IV). Mp 340°C (decomp., from dimethylformamide). Found: C 64.5; H 5.4; N 19.2%. $C_{16}H_{16}N_4O_2$. Calculated: C 64.9; H 5.4; N 18.9%. IR spectrum, cm^{-1}: 3260, 3190, 3070 (NH); 1730, 1700 (amide C = O). Compounds (VII), (VIII), and (IX) were obtained similarly (see Table 1). In the preparation of (VIII), the dimethylformamide was distilled off in vacuum and the residue was treated with aqueous dimethylformamide. In the preparation of (IX), the reaction time was 8 h.

8-Methoxy-1,3-dimethyl-10-phenoxy-1,2,3,4-tetrahydropyrimido[5,4-b]quinoline-2,4-dione (X). A mixture of 0.5 g (1.6 mmole) of the chloride (IIId), 2 g of phenol, and 0.6 g (7 mmoles) of piperidine was heated at 140°C for 2 h and was cooled and treated with 5% aqueous NaOH, and the precipitate was filtered off and washed with water. This gave 0.33 g (55%) of compound (X) with mp 296°C (decomp., from dimethylformamide). Found: C 66.5; H 4.9; N 11.6. $C_{20}H_{17}N_3O_4$. Calculated: C 66.1; H 4.7; N 11.6%.

1,2,3,4,5,10-Hexahydropyrimido[5,4-b]quinoline-2,4,10-trione (IIb). A mixture of 0.5 g of the chloride (IIIb) and 10 ml of dilute hydrochloric acid (1 : 1) was boiled for 3 h and was cooled, and the precipitate was filtered off and washed with water. This gave 0.4 g (87%) of the derivative (IIb). It did not melt below 350°C. Found: C 57.3; H 2.9; N 18.3%. $C_{11}H_7N_3O_3$. Calculated: C 57.6; H 3.0; N 18.3%.

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