STUDY OF THE NUCLEOPHILIC SUBSTITUTION REACTIONS OF 2,4,10-TRICHLOROPYRIMIDO[5,4-b]QUINOLINE

N. E. Britikova, L. A. Belova, and A. S. Elina

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A number of pyrimido[5,4-b]quinoline derivatives were synthesized. It is shown that in the reaction of 2,4,10-trichloropyrimido[5,4-b]quinoline (II) with strong nucleophilic reagents ($O\overline{C}H_3$ and $\overline{S}H$) both of the halogens of the pyrimidine ring are replaced, while with amines substitution of the halogens of the pyrimidine ring proceeds successively; under more severe conditions, all three halogen atoms of II are replaced by amine residues.

We have previously described the snythesis and properties of a number of 2,4,10-trioxo and 2,4-dioxo derivatives of hexahydro- or, respectively, tetrahydropyrimido[5,4-b]quinolines. In order to synthesize a completely aromatized pyrimido[5,4-b]quinoline system and obtain a number of mono-, di-, and trisubstituted derivatives of this heterocycle, which seem of interest for biological study, we obtained 2,4,10-trichloropyrimido[5,4-b]quinoline (II) from 2,4-dioxo-10-chloropyrimido[5,4-b]quinoline (I) by heating it with PCl_5 and $POCl_3$ and studied its reactions with nucleophilic reagents. The reaction of II with strong nucelophilic reagents (CH_3ONa or NaSH) proceeds with replacement of two halogens by methoxy or mercapto groups; we were unable to obtain the corresponding monomethoxy or monomercapto derivatives even when we used molar ratios of the reagents and carried out the reaction under mild temperature conditions. Inasmuch as the halogens in the 4- and 2-positions in II should have higher reactivities than the halogen in the 10-position, the structures of the dimethoxy and dimercapto derivatives obtained probably correspond to III and IV; this was confirmed by hydrolysis of III to the starting 2,4-dioxo derivative of I.

The purification of IV presented considerable difficulty, and it was therefore identified as the S-methylated derivative (V).

The appreciable difference in the reactivities of the halogens in the 2- and 4-positions was manifested in the reactions of chloro derivative II with weaker nucleophilic reagents. On reaction with concentrated ammonium hydroxide, II underwent replacement of only one chlorine atom by an amino group; the reactions of II with primary or secondary amines proceed similarly. In analogy with halogen derivatives of pyrimidine and condensed pyrimidine systems [2-4], for which the reactivity order is 4-Cl > 2-Cl, we suppose that we obtained a number of 4-amino derivatives of pyrimido[5,4-b]quinoline (VIa-f).

In the reaction of II with an excess of the corresponding amine we observed replacement of both chlorine atoms (VIIa, b). Monoamino derivatives VIa react with amines to give pyrimido[5,4-b]quinolines (VIIIa-c) that are substituted in the 4- and 2-positions by different amine residues. In VIIa, aminolysis of the chlorine in the 10-position is realized only under more severe conditions. Thus, IX was obtained by prolonged refluxing of VIIa or II with excess piperidine in dimethylformamide (DMF).

A certain amount of antibacterial activity was detected in vitro in the case of VIc and VIIb.

EXPERIMENTAL

2,4,10-Trichloropyrimido[5,4-b]quinoline (II). A mixture of 6 g (24 mmole) of I, 20 ml of phosphorous oxychloride, and 17.4 g (83 mmole) of phosphorus pentachloride was refluxed for 8 h, after which the $POCl_3$

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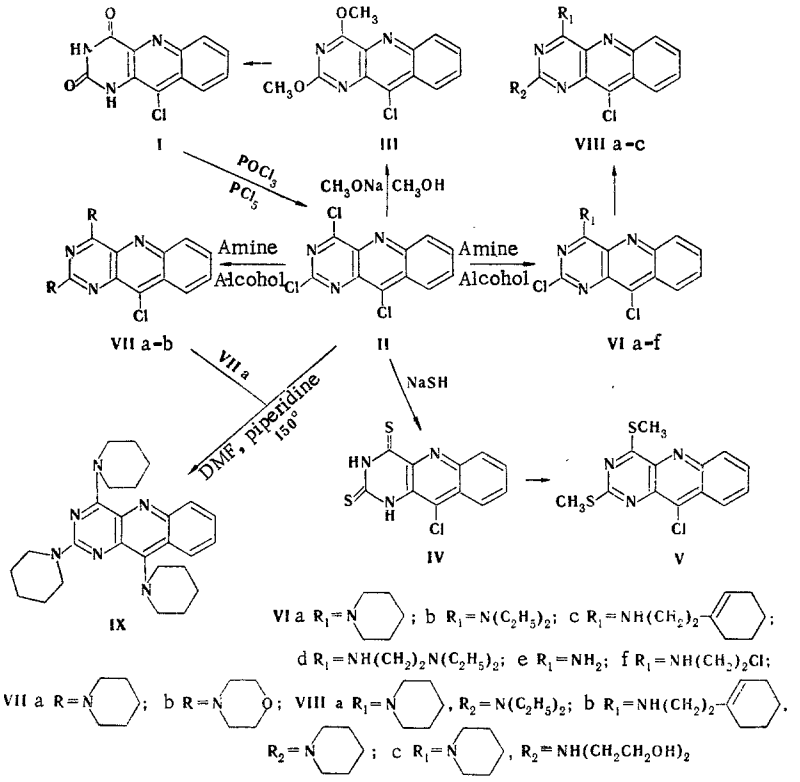

was removed by vacuum distillation. Ice was added to the residue, and the mixture was filtered after 1-2 h. The filtrate was extracted with chloroform, and the chloroform was evaporated to give 4.6 g (66.5%) of II with mp 226° (from ethyl acetate). Found: C 46.6; H 1.6; Cl 37.1; N 14.5%. $C_{11}H_4N_3Cl_3$. Calculated: C 46.4; H 1.4; Cl 37.4; N 14.8%.

2,4-Dimethoxy-10-chloropyrimido[5,4-b]quinoline (III). A 0.6-g (2 mmole) sample of II was added to a solution of sodium methoxide, obtained from 0.13 g (5.6 mmole) of Na and 40 ml of CH_3OH, and the reaction mixture was stirred at 20-25° for 4 h. The precipitate was then removed by filtration to give 0.4 g (66.5%) of III with mp 240° (from alcohol). Found: C 56.3; H 3.8; Cl 12.7; N 15.3%. $C_{13}H_{10}N_3O_2Cl$. Calculated: C 56.6; H 3.7; Cl 12.9; N 15.2%.

2,4-Dimethylthio-10-chloropyrimido[5,4-b]quinoline (V). A 1.2-g (4.2 mmole) sample of II in 60 ml of chloroform was added gradually with stirring to 6 ml (11 mmole) of 10% aqueous NaSH solution. After 2 h, the chloroform was decanted, and the residue was dissolved in 500 ml of water. The solution was acidified to pH 4-5 with acetic acid, and the mixture was filtered to give 1.2 g (4.3 mmole) of 2,4-dimercapto-10-chloro-1,2,3,4-tetrahydropyrimido[5,4-b]quinoline (IV), to which a solution of 0.5 g (9 mmole) of KOH in 60 ml of water was added. A 1.4-ml (15 mmole) sample of dimethyl sulfate was added gradually at 20-25° to the resulting solution, and the mixture was stirred at 20-25° for 2.5 h. Workup of the mixture gave 1 g (61.8%) of V with mp 187° (from acetone). Found: C 50.7; H 3.5; Cl 11.6; N 13.3; S 20.8%. $C_{13}H_{10}N_3ClS_2$. Calculated: C 50.7; H 3.3; Cl 11.5; N 13.6; S 20.8%.

4-Piperidino-2,10-dichloropyrimido[5,4-b]quinoline (VIa). A 0.2-g (2.3 mmole) sample of piperidine was added to 0.3 g (1 mmole) of II in 10 ml of alcohol, and the mixture was stirred at 20-25° for 4 h. It was then filtered to give 0.3 g (87.0%) of VIa with mp 156° (from alcohol). Found: C 57.9; H 4.2; Cl 21.0; N 16.9%. $C_{16}H_{14}Cl_2N_4$. Calculated: C 57.7; H 4.2; Cl 21.3; N 16.8%.

Compounds VIb-d were similarly obtained.

Compound VIb (65.7%) had mp 141° (from alcohol). Found: C 56.2; H 4.3; Cl 21.7; N 17.3%. $C_{15}H_{14}Cl_2N_4$. Calculated: C 56.1; H 4.4; Cl 22.1; N 17.4%. Compound VIc (60%) had mp 183° (from alcohol). Found: C 59.8; H 5.0; Cl 18.7; N 14.5; H_2O 2.1%. $C_{19}H_{18}N_4Cl_2 \cdot 0.5H_2O$. Calculated: C 59.7; H 5.0; Cl 18.6; N 14.6; H_2O 2.4%. Compound VId (52.6%) had mp 160° (from alcohol). Found: C 55.8; H 5.0; Cl 19.1; N 19.0%. $C_{17}H_{19}N_5Cl_2$. Calculated: C 56.0; H 5.2; Cl 19.5; N 19.2%.

4-Amino-2,10-dichloropyrimido[5,4-b]quinoline (VIe). A 0.2-g (0.7 mmole) sample of II was allowed to stand in 10 ml of ammonium hydroxide at 20-25° for 4 days, after which the precipitate was removed by

filtration to give 0.1 g (55.0%) of VIe with mp 305-308° (from aqueous DMF). Found: C 49.4; H 2.1; Cl 26.5; N 21.0%. $C_{10}H_6N_4Cl_2$. Calculated: C 49.8; H 2.3; Cl 26.8; N 21.1%.

4-(β-Chloroethylamino)-2,10-dichloropyrimido[5,4-b]quinoline (VIf). An aqueous solution of 0.23 g (2.7 mmole) of $NaHCO_3$ in 5 ml of H_2O was added gradually with stirring to a mixture of 0.3 g (1 mmole) of II and 0.15 g (1.3 mmole) of β-chloroethylamine hydrochloride in 15 ml of chloroform. After 1 h, the chloroform was separated and evaporated, and the residue was treated with water. The aqueous mixture was filtered to give 0.1 g (28.6%) of VIf with mp 170° (dec., from ethyl acetate). Found: C 47.6; H 2.9; Cl 32.3; N 17.5%. $C_{13}H_9N_4Cl_3$. Calculated: C 47.6; H 2.7; Cl 32.2; N 17.1%.

2,4-Dipiperidino-10-chloropyrimido[5,4-b]quinoline (VIIa). A mixture of 0.6 g (2.1 mmole) of II, 20 ml of alcohol, and 1.2 g (14 mmole) of piperidine was refluxed for 2 h, after which the precipitate was removed by filtration to give 0.5 g (60.6%) of VIIa with mp 155° (from alcohol). Found: C 66.9; H 6.3; Cl 9.1; N 17.7%. $C_{22}H_{24}N_5Cl$. Calculated: C 66.8; H 6.1; Cl 9.0; N 17.8%.

2,4-Dimorpholino-10-chloropyrimido[5,4-b]quinoline (VIIb). A mixture of 1 g (3.5 mmole) of II, 25 ml of DMF, and 3.3 g (38 mmole) of morpholine was heated at 140° for 6 h. It was then cooled, and the crystalline precipitate was removed by filtration to give 0.6 g (44.5%) of VIIb with mp 198° (from aqueous DMF). Found: C 59.0; H 5.0; Cl 8.8; N 17.9%. $C_{19}H_{20}N_5O_2Cl$. Calculated: C 59.1; H 5.2; Cl 9.2; N 18.1%.

2-Diethylamino-4-piperidino-10-chloropyrimido[5,4-b]quinoline (VIIIa). A 0.6-g (1.8 mmole) sample of VIa was allowed to stand in 10 ml of diethylamine at 20-25° for 48 h, after which the diethylamine was vacuum evaporated, and the residue was triturated with acetone. The mixture was filtered to give 0.3 g (45%) of VIIIa with mp 108° (from alcohol). Found: C 65.4; H 6.6; Cl 9.4; N 18.9%. $C_{20}H_{24}N_5Cl$. Calculated: C 65.0; H 6.5; Cl 9.6; N 18.9%.

2-Piperidino-4-cyclohexenylethylamino-10-chloropyrimido[5,4-b]quinoline (VIIIb). A mixture of 1 g (2.7 mmole) of VIc and 0.46 g (5.4 mmole) of piperidine in 35 ml of alcohol was stirred at 20-25° for 5 h, after which the precipitate was removed by filtration to give 0.5 g (44.3%) of VIIIb with mp 140° (from alcohol). Found: C 68.2; H 6.6; Cl 8.0; N 16.4%. $C_{24}H_{28}N_5Cl$. Calculated: C 68.3; H 6.6; Cl 8.4; N 16.6%.

2-Diethanolamino-4-piperidino-10-chloropyrimido[5,4-b]quinoline (VIIIc). A mixture of 0.3 g (0.9 mmole) of VIa and 0.2 g (1.8 mmole) of diethanolamine was heated at 100-110° for 3 h. The reaction mixture was treated several times with water, and the water was decanted. The solid material was triturated with acetone, and the mixture was filtered to give 0.2 g (55.0%) of VIIIc with mp 187° (from alcohol). Found: C 60.2; H 5.9; Cl 8.6%. $C_{20}H_{24}O_2N_5Cl$. Calculated: C 59.8; H 6.0; Cl 8.8%.

2,4,10-Tripiperidinopyrimido[5,4-b]quinoline (IX). A 0.3-g (0.76 mmole) sample of VIIa was refluxed with 0.34 g (4 mmole) of piperidine in 10 ml of DMF for 3 h, and the precipitate was removed by filtration to give 0.2 g (61%) of IX with mp 118° (from alcohol). Found: C 72.4; H 7.9%. $C_{26}H_{34}N_6$. Calculated: C 72.5; H 7.9%. Compound IX was similarly obtained in 55% yield from 1.8 mmole of II and 18 mmole of piperidine.

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