SYNTHESES OF QUINOLINE DERIVATIVES

III. Bromination of 5-Alkoxymethyl- and 5-Aryloxymethyl-8-quinolinols*

L. I. Aristov and A. A. Shamshurin

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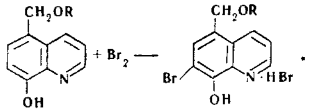
In order to study the relationship between structure and biological activity we have synthesized 5-alkoxymethyl- and 5-aryloxymethyl-7-bromo-8-quinolinols.

It is well known that the introduction of a halogen in phenols leads to a considerable rise in their bactericidal activity [2]. The introduction of a halogen into ethers and esters of 5-alkoxymethyl-8-quinolinols should also lead to substances with a more pronounced physiological action. For this purpose, we have obtained bromo derivatives of this series. For the compounds studied, the bromination reaction is a typical electrophilic substitution of position 7 of the quinoline ring in view of the orienting influence of the adjacent hydroxy group. It is interesting that the ether group in CH_2OAlk in the quinoline ring is not eliminated on bromination, while the bromination of 5-hydroxymethyl-8-quinolinol leads to 5,7-dibromo-8-quinolinol [3]. Bromination was carried out at room temperature in carbon tetrachloride or acid solution with the calculated amount of bromine in the same solvent. With equimolecular ratios of the reactants, the reaction yielded the hydrobromides or the monobromides in the form of yellow precipitates the production of which can be illustrated by the following scheme:



Differences exist in the infrared spectra of the initial and the brominated ethers. Characteristic for all the initial compounds are very narrow bands at 1240 and 1275 cm^{-1} ($V-CH_2OAlk$). In the spectra of the corresponding bromine derivatives these are less well-defined but there is a clear band at 1290 cm^{-1}. A weak narrow band appears at 1160 cm^{-1} which is characteristic for 1,2,4-substituted derivatives of a benzene ring. When the spectra were taken of the substances in a potassium bromide tablet, bands appeared at 550 cm^{-1} (w) and 660 cm^{-1} (m), which are characteristic for the C—Br bond.

In the spectrum of the brominated propargyl ether, the band at 3320 cm^{-1} that is characteristic for the deformation vibrations of the > CH— group is retained, which serves as an indication that substitution in the ring has taken place and not addition to the double bond. The bromo derivatives are sparingly soluble in CCl_4 and somewhat more soluble $CHCl_3$. Consequently, the latter was used as solvent. In the IR spectrum in chloroform, the band at 3400 cm^{-1} is split into two, at 3380 and 3600 cm^{-1}, which can be explained by a weakening of the OH . . . N hydrogen bond through interaction with the adjacent bromine atom. In the unbrominated ethers in the same solvent this splitting is not observed.

The compounds synthesized have been sent for testing for antihelminthic and fungicidal activity.

Some properties of the compounds obtained are given in Table 1. The characteristic frequencies of the IR spectra of some compounds are given in Table 2.

Bromination of the ethers at ratios of the initial ether and bromine of 1 : 2 and above led to dark orange precipitates which, in contrast to the hydrobromides or the monobromides, were sparingly soluble in water. The study of some of these compounds showed that in this case comparatively stable addition of bromine to the brominated ether took place.

These compounds may be called perbromides and their formation can be represented by the following schemes:

Table 1

Yields and Characteristics of the Ethers of 7-Bromo-5-hydroxymethyl-8-quinolinol

R	Mp,* °C	Nitrogen content, %		Yield, %
		found	calculated	
CH_3	145—146	5.26; 5.18	5.22	90
C_2H_5	127—128	4.96; 4.85	4.96	90
C_3H_7	95	4.69; 4.55	4.73	90
C_4H_9	95	4.54; 4.47	4.51	85
$—C_4H_9$	88—89	4.43; 4.55	4.51	85
C_2H_4Cl	103	4.44; 4.61	4.40	80
$CH_2C\equiv CH$	95—96	4.52	4.79	80
Cyclohexyl	110—112	4.56	4.13	80
Benzyl	114—115	4.00	4.07	80

*Solvent—petroleum ether + benzene.

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*For part II, see [1].

Table 2

Characteristic Frequencies of the IR Spectra of 5-Alkoxymethyl-7-bromo-8-quinolinols

R						
CH_3	C_2H_5	C_3H_7	C_4H_9	$CH_2C\equiv CH$	C_2H_4Cl	Cyclohexyl
3600 w	3600 w	3600 w	3600 w	3600 w	3600 w	3600 w
3380 m	3380 m	3380 m	3380 m	3380 m	3380 m	3400 m
3090 w	3090 w	3110 w	3100 w	3320 m	3100 w	3100 w
3020 m	3020 m	3020 m	3020 w	3100 m	2880 m	3000 m
2930 m	2930 m	2980 m	2980 m	1625 m	1625 m	2950 m
2830—	2830—	2940 m	2950 m	1580 m	1580 m	2880 m
2910 w	2910 w	2880 m	2880 m	1500 s	1500 s	1625 m
1620 m	1620 m	1625 m	1625 m	1465 s	1465 s	1580 m
1580 m	1580 m	1580 m	1580 m	1440 m	1445 m	1500 s
1500 s	1500 s	1500 s	1500 s	1420 m	1425 m	1470 s
1465 s	1480 m	1465 s	1470 s	1380 s	1410 w	1455 s
1420 m	1465 s	1440 m	1440 m	1350 s	1380 s	1425 m
1370 s	1420 m	1425 m	1420 m	1275 m	1350 s	1380 s
1350 s	1370 s	1380 m	1410 w	1235 m	1280 m	1360 m
1290 w	1355 s	1250 m	1380 s	1165 m	1235 m	1345 m
1260 m	1290 w	1280 m	1360 s	1090 s	1190 w	1290 m
1240 m	1265 m	1270 m	1280 m	1060 s	1165 m	1280 m
1195 m	1245 m	1260 m	1265 m	1000 w	1110 s	1265 s
1155 m	1195 m	1190 w	1235 m	980 m	1090 m	1235 s
1100 s	1155 m	1175 m	1190 w	950 w	1060 s	1165 m
1070 m	1135 w	1090 s	1155 m	890 w	980 m	1090 m
990 w	1100 s	1060 s	1090 m	865 w	890 m	1065 s
960 m	1060 m	980 m	1060 s	850 m	865 m	980 m
930 m	1040 w	970 w	980 m	805 s	850 m	850 s
915 w	950 w	890 w	890 w	690 s	805 s	805 s
880 m	930 m	865 m	865 w		690 s	690 s
865 m	915 w	850 m	850 m			650 m
820 m	818 m	820 m	820 w			
810 w	875 m	800 s	800 s			
650 s	820 m	690 s	690 s			
	810 m					
	650 s					

Table 3

Analytical Data for the Perbromides

Compound	R	Found, %				Calculated, %			
		C	H	Br	N	C	H	Br	N
						30.76	2.56	55.88	3.26
I	CH_3	26.58	2.44	61.72	3.03	25.93	2.16	62.86	2.75
						32.50	2.93	54.12	3.16
II	C_2H_5	27.87	2.57	60.64	2.75	27.53	2.52	61.18	2.57
						34.13	3.18	52.47	3.06
III	C_3H_7	29.49	2.83	59.71	2.83	29.05	2.79	59.59	2.60
						34.13	3.28	52.47	3.06
IV	i-C_3H_7	28.53	2.77	60.10	2.73	29.05	2.79	59.59	2.60
						35.66	3.60	50.90	2.97
V	C_4H_9	30.48	3.04	59.05	2.67	30.65	3.10	58.40	2.55
						30.15	2.51	50.21	2.93
VI	CH_2CH_2Cl	25.34	2.03	63.52	2.54	25.84	2.15	63.73	2.51

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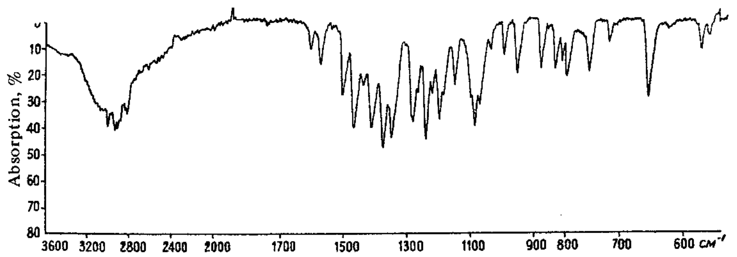
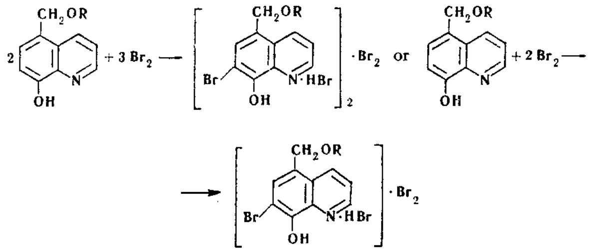
*The top series of figures were calculated for the empirical formula $(C_{10}H_7BrNO_2R\cdot HBr)_2\cdot Br_2$; and the lower series for the empirical formula $C_{10}H_7BrNO_2R\cdot HBr\cdot Br_2$.



IR spectrum of the methyl ether of 7-bromo-5-hydroxymethyl-8-quinolinol taken in a KBr tablet.



The formation of perbromides by the first scheme has been described in the literature for pyridine, although the bromine analyses of this perbromide show that this scheme does not accurately reflect the structure of the compounds obtained [4]. In our case, on the basis of a full elementary analysis, we give our preference to the formation of perbromides by the second scheme, although, in this case, also, we were unable to obtain accurately-agreeing analytical figures for all the perbromides, which is due to the difficulty of purifying the compounds obtained. The analytical figures for a number of perbromides are given in Table 3.

EXPERIMENTAL

7-Bromo-5-methoxymethyl-8-quinolinol. With stirring, 1.6 g of bromine in 5 ml of carbon tetrachloride was added to a solution of 1.89 g (0.01 mole) of 5-methoxymethyl-8-quinolinol in 10 ml of the same solvent. After some minutes, a yellow precipitate began to separate. The reaction mixture was kept for 1 hr and the precipitate was filtered off, dissolved in water acidified with hydrochloric acid, and neutralized with dilute ammonia solution. A colorless substance was obtained from a mixture of petroleum ether and benzene (8: 2) or from ethanol, mp 145–146° C. Found, %: N 5.26, 5.18. Calculated for $C_{11}H_{10}BrNO_2$, %: N 5.22.

The other bromo derivatives given in Table 1 were obtained similarly.

Perbromide of the hydrobromide of 7-bromo-5-ethoxymethyl-8-quinolinol. With stirring, a solution of 3.4 g (0.02 mole) of bromine in 5 ml of CCl_4 was added to a solution of 2.03 g (0.01 mole) of 5-ethoxymethyl-8-quinolino 10 ml of the same solvent. The bright yellow precipitate that deposited was filtered off, and was boiled with 15 ml of petroleum ether, in which the starting material is soluble. Yellow substance, mp 132–133° C. Found, %: C 27.87; H 2.57; Br 60.64; N 2.75. Calculated for $C_{12}H_{13}Br_4NO_2$, %: C 27.53; H 2.48; Br 61.18; N 2.67.

The other perbromides given in Table 3 were obtained similarly.

The infrared spectra were obtained in chloroform solution (5%) on a UR-10 instrument in the 700–3600 cm^{-1} region.

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Institute of Chemistry AS
Moldavin SSR, Kishinev