SYNTHESIS IN A SERIES OF QUINOLINE DERIVATIVES

VI. Synthesis of 8-Methacryloxyquinolines*

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Monomeric substances, 8-methacryloxyquinolines were synthesized with the object of obtaining preparations with prolonged action.

The synthesis of monomeric substances with biological activity is of great interest [2–3]. We have synthesized the esters of methacrylic acid, 8-oxyquinoline and its derivatives, from which a number of original substances (5-ethyloxymethyl-8-quinolinol, 5-allyloxymethyl-8-quinolinol, etc.) according to the data of those tested show fungicidal activity in relation to certain plant diseases comparable to the action of "Phygon" or exceeding the activity of the latter. The following methods were tested during the process of synthesis of esters of methacrylic acid.

a $ROH + NaOH + ClMAK(H_2O) \rightarrow ROMAK + NaCl + H_2O$,
b $ROH + NaOH + ClMAK(C_2H_5OH) \rightarrow ROMAK + NaCl + H_2O$,
c $ROH + ClMAK(C_5H_5N) \rightarrow ROMAK + C_5H_5N \cdot HCl$,
d $ROH + Na(C_6H_6) \rightarrow ROMAK + NaCl$

where R, quinolyl radical; ClMAK, acid chloride of methacrylic acid.

According to scheme **a** synthesis of the esters of methacrylic acid was successfully achieved for phenol, naphthol, and its derivatives [4], although by this pathway it was not possible to obtain the esters of 8-oxyquinoline and its derivatives. On conducting the reaction in alcoholic-alkaline medium (method **b**) the esters of 8-oxyquinoline and its 5-chloro- and 5-bromo derivatives are formed with a high yield. The esters of 5, 7-dichloro- and 5, 7-dibromo-8-oxyquinoline are obtained with an insignificant yield (20% or lower). An analogous picture was found during the reaction with 5-alkoxymethyl-8-quinolinols. The esters were not obtained by this method with the halogen derivatives of 5-alkoxymethyl-8-quinolinols.

According to the scheme **c** the esters of 8-oxyquinoline were successfully synthesized in the case of the acid chlorides of acids of the saturated and aromatic series [5]. In this case this method was not very effective, as on heating marked resinification of the reaction mass occurs, from which the individual products can only be separated with great difficulty.

The formation of esters of methacrylic acid by method **d** is a prolonged procedure, as the reaction of 8-oxyquinoline and its derivatives with metallic sodium in dry benzene proceeds slowly because of the heterogeneity of the medium and the passivation of the surface of metallic sodium by the precipitated sodium quinolate. Attempts to reduce the reaction time by exchange interaction of sodium alcoholate with the corresponding quinolinol with distillation of alcohol did not produce satisfactory results. A significant portion of the alcoholate remains in the reaction mass and on addition of the acid chloride of methacrylic acid a mixture of esters of methacrylic acid, quinolinol and ethyl, was obtained which was very difficult to separate on account of the tendency of the latter to polymerize. Certain characteristics of esters obtained according to scheme **d** are presented in Table 1.

During synthesis of the esters it was revealed that the substitutes in positions 5 and 7 of the quinoline ring have a significant effect on the yield of the final products. Thus, during synthesis of esters with 5, 7-dichloro- and 5, 7-dibromo-8-oxyquinoline, more resin formation is found than during the synthesis of esters with 5-chloro- and 5-bromo-8-oxyquinoline. 5-Iodo-8-oxyquinoline forms only resin-like products, and 5, 7-diiodo-8-oxyquinoline essentially does not react with metallic sodium and does not give rise to the corresponding ester. With increase in length of the alkyl radical in position 5, a marked decrease in the yields of the esters is also found (see Table 1). Very low yields of esters were obtained with 5-allyloxymethyl- and 5-propargyloxymethyl-8-quinolinols. These findings may probably be due to two causes: 1) the marked drawing away of electrons from methacryloyl by the halogen of the quinoline ring, as a result of which the double bond of methacryloyl must be more strongly polarized and the corresponding ester more apt to undergo polymerization; 2) the introduction of halogen atoms in position 7 of the quinoline ring (especially Br and I, the ionic radii of which are equivalent to 1.96 and 2.2 Å, respectively) leads to strong screening of the hydroxyl in position 8, i.e., creates steric hindrances. It is possible that this may be explained by the lack of reactivity of 5, 7-diiodo-8-oxyquinoline with metallic sodium in the studied reaction.

The resin-like products are also formed during the reaction with the acid chloride of methacrylic acid of such derivatives of 8-oxyquinoline as 5-propyl(isopropyl)oxymethyl-7-iodo-8-quinolinol, 5-β-chloroethyloxymethyl-7-bromo-8-quinolinol, and 5-propyloxymethyl-7-bromo-8-quinolinol.

The IR spectra of all compounds obtained were recorded. In the spectra bonds are found characteristic for the carboxyl group (1735–1740 cm^{-1}), and there are bonds at 1640, 1600, 1580, 1505 cm^{-1}, etc., characteristic for the quinoline ring, but there is no bond at 3420 cm^{-1} which would represent the valency oscillations of the hydroxyl group. The characteristic frequencies of IR spectra of typical ester compounds are presented in Table 2.

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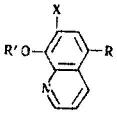
*For part V, see [1].

Table 1

Characteristics and Yield of Esters of Methacrylic Acid with Derivatives of 8-Oxyquinoline

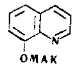
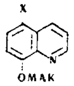
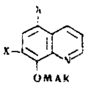
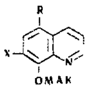
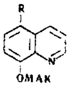


$R' = -COC(CH_3)=CH_2$

R	X	Mp, °C	Empirical formula	Found, %			Calculated, %			Yield, %
				C	H	N	C	H	N	
H	H	60—61	$C_{13}H_{13}NO_2$	72.84	5.18	6.93	73.21	5.20	6.57	60—70
CH_3OCH_2	"	74—75	$C_{15}H_{15}NO_3$	70.11	5.81	5.16	70.04	5.85	5.45	60—70
$C_2H_5OCH_2$	"	64—65	$C_{16}H_{17}NO_3$	70.63	6.25	5.22	70.84	6.29	5.17	60—70
$C_3H_7OCH_2$	"	48—50	$C_{17}H_{19}NO_3$	71.21	6.82	5.30	71.56	6.69	4.91	35—40
i-$C_3H_7OCH_2$	"	65—67	$C_{17}H_{19}NO_3$	72.03	6.95	5.12	71.56	6.69	4.91	20—25
$CH_2=CHCH_2OCH_2$	"	45—47	$C_{17}H_{17}NO_3$	71.71	5.94	5.02	72.07	6.02	4.95	10—15
$CH\equiv CCH_2OCH_2$	"	75—76	$C_{17}H_{15}NO_3$	72.25	5.78	—	72.59	5.35	—	10—15
$(CH_3)_2N\underset{\underset{S}{\Vert}}{C}SCH_2$	"	149—150	$C_{17}H_{18}NO_2S_2$	—	—	7.80	—	—	8.09	10—15
$(C_2H_5)_2N\underset{\underset{S}{\Vert}}{C}SCH_2$	"	142—143	$C_{19}H_{22}NO_2S_2$	61.51	6.10	7.23	60.91	5.92	7.48	30—40
$ClC_2H_4OCH_2$	"	53—54	$C_{16}H_{16}ClNO_3$	62.87	5.51	5.04	62.85	5.25	4.58	30—40
Cl	"	76—77	$C_{13}H_{10}ClNO_2$	63.49	4.39	5.73	63.04	4.07	5.65	60
Cl	Cl	80—81	$C_{13}H_9Cl_2NO_2$	55.68	3.09	—	55.34	3.21	—	50
Br	H	66—67	$C_{13}H_{10}BrNO_2$	53.15	3.60	4.49	53.44	3.45	4.79	60
Br	Br	74—75	$C_{13}H_9Br_2NO_2$	42.11	2.48	3.80	42.08	2.44	3.77	50
CH_3OCH_2	Br	77—78	$C_{15}H_{14}BrNO_3$	54.03	4.53	3.93	53.6	4.17	4.16	20—30
CH_3OCH_2	I	84—85	$C_{15}H_{14}INO_3$	47.30	4.03	3.41	47.03	3.66	3.65	10—15
$C_2H_5OCH_2$	Br	69—70	$C_{16}H_{16}BrNO_3$	54.68	4.76	—	54.88	4.58	—	50
$C_2H_5OCH_2$	I	68—70	$C_{16}H_{16}INO_3$	48.84	3.79	3.57	48.38	4.04	3.52	10—15
i-$C_3H_7OCH_2$	Br	77—78	$C_{17}H_{18}BrNO_3$	55.71	4.95	—	56.07	4.96	—	30—40

Table 2

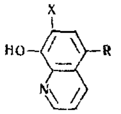
Characteristic Frequencies of IR Spectra of 8-Methacryloylquinolines, cm^{-1}

Types of compounds				
				
3000—3050Av.	3000—3030Av.	3010 W.	3000—3020Av.	3000—3030S.
2980 W. 2940 W.	2150 W.	2950	2930 2900, 2820 W.	2950Av. 2890S.
1735S. 1640Av. 1600Av. 1575 W. 1505S. 1470Av., 1450 W.	1735S. 1640Av. 1615 W. 1590Av. 1565Av. 1495S. 1460S.	1740S. 1640 W. 1605Av., 1590Av. 1560 W. 1490Av. 1460S.	1735S. 1640 W. 1600Av. 1500Av. 1460S.	1735S. 1640 W, 1620 W, 1600 W, 1580 W. 1505S. 1480Av., 1460Av.
1390Av. 1380Av., 1370Av.	1390 W. 1380 W., 1365Av.	1380Av., 1360Av.	1405 W. 1380 W. 1360Av.	1405Av. 1370— 1380Av. 1355Av.
1330S., 1310S. 1300S. 1240S.	1320S. 1295S. 1235Av., 1200 W.	1315Av. 1295Av. 1245 W., 1200S.	1320S. 1300S. 1270 W. 1236 W. 1200S.	1310S. 1300S. 1250S. 1240S.
1170S., 1145S., 1080S.	1150 W., 1135S. 1106Av.	1145 W., 1120S.	1165S. 1110—1120S.	1150S. 1125S. 1095S.
1060Av., 1030 W. 1005 W. 950S.	1060Av., 1040S. 1015 W., 1010 W. 950S.	1050Av. 1005 W. 960S.	1065 W. 1000—1030 W. 960S.	1070S. 1005 W 980 W 950Av.
910 W 885 W. 865Av. 820S.	920S. 880Av. 820S.	890S., 870Av. 810Av.	915 W. 880Av. 855Av. 820 W.	880Av. 825Av., 810 W.

***X, Cl, Br or I; R, alkoxymethyl ($-CH_2OCH_3$; $-CH_2OC_2H_5$, etc); MAK, residue of methacrylic acid. Note: W—weak, Av—average, S—strong.**

Table 3

Characteristics of the Original Derivatives of 8-Oxyquinoline



Substitutes		Mp, °C	Substitutes		TMp, °C
X	R		X	R	
H	H	74—75	H	$-CH_2OCH_2CH_2Cl$	90—91
H	Cl	124	H	$-CH_2S\underset{\underset{S}{\|}}{C}N(CH_3)_2$	177—178
H	Br	125	H	$-CH_2S\underset{\underset{S}{\|}}{C}N(C_2H_5)_2$	113—114
Cl	Cl	179—180	Br	$-CH_2OCH_3$	145—146
Br	Br	196	Br	$-CH_2OC_2H_5$	127—128
I	I	201—202	Br	$-CH_2OC_3H_7$	97
H	$-CH_2OCH_3$	82—83	Br	$-CH_2OC_3H_7$-*i*	98—99
H	$-CH_2OC_2H_5$	83	Br	$-CH_2OCH_2C\equiv CH$	95—96
H	$-CH_2OC_3H_7$	67—68	Br	$-CH_2OC_2H_4Cl$	103
H	$-CH_2OC_3H_7$-*i*	65—66	I	$-CH_2OCH_3$	143—144
H	$-CH_2OCH_2CH=CH$	80—81	I	$-CH_2OC_2H_5$	114—115
H	$-CH_2OCH_2C\equiv CH$	81—82	I	$-CH_2OC_3H_7$	89—90

The esters obtained do not produce a color reaction with a solution of ferric chloride characteristic for 8-oxyquinoline and its derivatives.

EXPERIMENTAL

The characteristics of the substances used in the synthesis of esters of methacrylic acid are presented in Table 3.

5-Methyloxymethylquinolinolyl-8-methacrylate. A 3.78 g (0.02 mole) quantity of 5-methyloxymethyl-8-quinolinol was dissolved in dry benzene and on stirring and heating 0.43 g (0.02 mole) sodium was added. The contents were boiled until the sodium was completely consumed which requires 20–30 hr. Hydroquinone (0.05 g) was added to the cooled solution and a solution of the acid chloride of methacrylic acid was added dropwise. The reaction mass was mixed until the residue of the quinolinolate disappeared over a period of 3–5 hr. The benzene solution was filtered, transferred to a separating funnel, and washed with a solution of soda, water, and dried with sodium sulphate.

After the benzene was removed by distillation under vacuum, the product was obtained with a yield of 80–85% and an mp 74–75° C (from petroleum ether). The other compounds indicated in Table 1 were obtained in an analogous manner.

8-Methacryloyl-5-bromoquinoline. A 4.48 g (0.02 mole) quantity of 5-bromo-8-oxyquinoline and 0.8 g (0.02 mole) sodium hydroxide were dissolved in 100 ml of ethanol and the contents were boiled with stirring for 30–60 min. A 2 ml (0.02 mole) quantity of the acid chloride of methacrylic acid was added to the cooled solution and the reaction mixture was stirred for 1–2 hr. Subsequently, the contents were transferred into water and the ester separating in the form of an oil and crystallizing on standing was removed by filtration, washed with water, and after drying was recrystallized from petroleum ether. Yield, 60%; mp 66–67° C. Found, %: C 53.15; H 3.60; N 4.49. Calculated for $C_{13}H_{10}BrNO_2$, %: C 53.44; H 3.45; N 4.79.

The esters of 5-chloro-8-oxyquinoline and the unsubstituted 8-oxyquinoline were obtained at high yields by this method.

The IR spectra of the compounds obtained were recorded in a UR-10 apparatus in a 5% solution of chloroform in the frequency region of 700–3600 cm^{-1}. The error was ±5 cm^{-1}.

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