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### Vinyl Polymerization. 279. Synthesis and Polymerization of 9-Acryloxyquinine

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## Vinyl Polymerization. 279. Synthesis and Polymerization of 9-Acryloxyquinine

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### SUMMARY

The reaction of quinine with an equivalent molar amount of acryloyl chloride produced 9-acryloxyquinine in 80% yield. The radical polymerization of the ester was conducted in benzene using azobisisobutyronitrile as an initiator, and formed an oligomer consisting 6-7 monomeric units. The oligomer, which is soluble in organic solvents, became soluble in water upon conversion into the hydrochloride salt.

### RESULTS AND DISCUSSION

The use of polymeric materials which incorporate drugs has received considerable attention because such polymers might show

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increased pharmacological activities and reduced undesirable side effects. These advantages, for example, have been shown with *p*-aminosalicylic acid linked to polyvinyl alcohol [1], the condensation polymer of sulfapyridine with formaldehyde [2], etc. [3]. In view of the recent interest in this field, we wished to develop an improved antimalarial agent from quinine (I), which has still been used widely since its discovery, but which has toxic side effects toward the digestive organs. In a previous paper we have reported on the synthesis and polymerization of 9-methacryloxyquinine [4]. The present work shows renewed attempts in the preparation of a high molecular weight drug containing I, poly-9-acryloxyquinine (II).

The acrylate ester of I was prepared through the reaction of I with an equivalent molar amount of acryloyl chloride in chloroform at room temperature in 80% yield, and the crude reaction product was purified by a column chromatograph packed with alumina to afford a clear viscous oil in 77% yield. Though the product did not crystallize, it was found to be pure by thin-layer chromatography and an analysis of its hydrochloride. The stereospecific configuration of the quinine part of II was retained, since an alkaline hydrolysis of II reproduced I. The ester (II) was found to be optically stable toward heating in benzene.

The radical polymerization of II was conducted in a sealed glass tube using benzene as a solvent and azobisisobutyronitrile (AIBN) as an initiator. The polymerization product was precipitated from ether to give a light yellow powder. The reaction conditions and physical constants of the oligomeric powder are listed in Table 1. All oligomers obtained from Runs 1-3 had molecular weights of about 2300-3000,

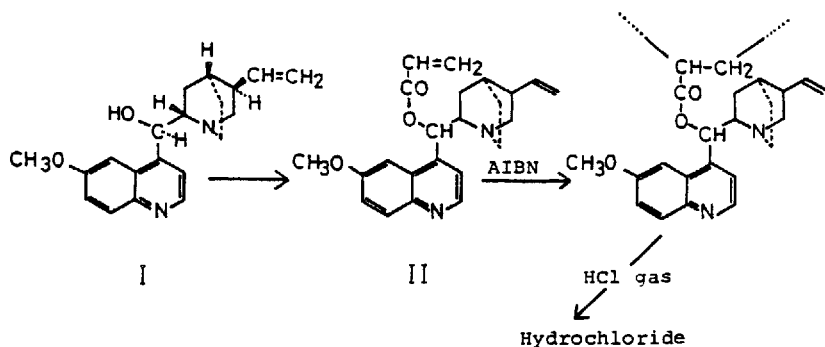


TABLE 1. Polymerization Condition and Physical Constants

Run	Monomer (mmole)	AIBN (mmole)	Temp (°C)	Benzene (ml)	Conversion (%)	$[\alpha]_D^{19}$ (C) (in CHCl <sub>3</sub> )	$\lambda_{\max}$ (ε) (in CHCl <sub>3</sub> )	MW
1	0.38	0.003	85	0.3	55	-19.0 (7.8)	337.0 (5300)	2420
2	0.38	0.008	75	2.1	35	-14.1 (9.8)	337.0 (5300)	2300
3	0.38	0.008	75	1.6	41	-19.8 (10.3)	337.0 (5300)	2650

corresponding to 6-7 monomeric units, and showed similar IR and UV spectra which are depicted in Figs. 1 and 2, respectively. The oligomer is soluble in only such organic solvents as chloroform, benzene, and dimethylformamide, but it becomes very soluble in water upon conversion to its hydrochloride. The water-soluble

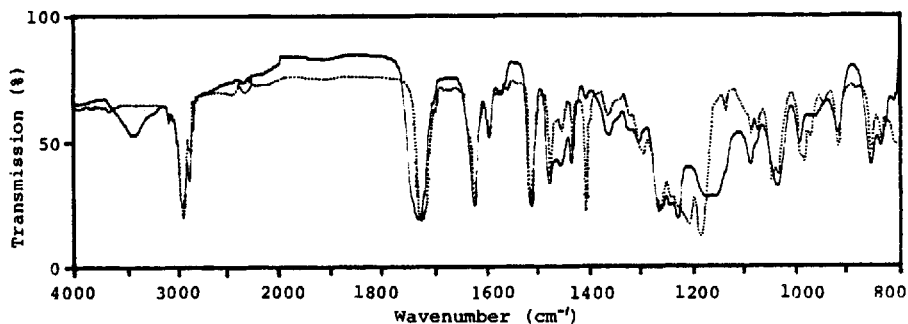


FIG. 1. Infrared spectra of 9-acryloxyquinine (· ·) and poly-9-acryloxyquinine (KBr pellet) (—).

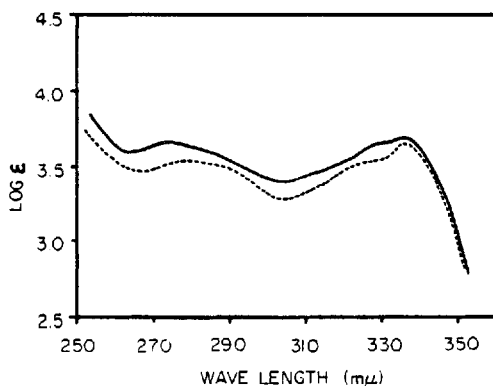


FIG. 2. Ultraviolet spectra of 9-acryloxyquinine (—) and poly-9-acryloxyquinine (—) in CHCl<sub>3</sub>.

property of the hydrochloride would be profitable for studies of its pharmacological activities, and accounts of this work now in progress, will be reported later.

## EXPERIMENTAL

Infrared and UV absorption spectra and optical rotations were measured with a JASCO model IR-G spectrometer, a Hitachi model EPS-3T spectrometer, and a Yanagimoto model OR-10 photomagnetic polarimeter, respectively. Molecular weights were measured with a Hitachi model 115 vapor pressure osmometer using benzene as a solvent at 30°C.

### 9-Acryloxyquinine (II)

A mixture of quinine hydrochloride dihydrate (7.26 g, 18.3 mmole), 4 N sodium hydroxide (20 ml), and chloroform (50 ml) was stirred vigorously at room temperature to extract quinine (I) into a chloroform layer. After washing with water and drying with anhydrous sodium sulfate, the chloroform layer was mixed with acryloyl chloride (1.70 g, 18.7 mmole) and stood at room temperature overnight. The reaction mixture was then washed with 10% sodium bicarbonate solution and the chloroform layer was dried over sodium sulfate, after which it was concentrated to about 15 ml and chromatographed with alumina (3 × 50 cm, 300 mesh). Elution with ethyl acetate gave II as a clear oil (5.53 g, 14.7 mmole, 80% yield). The ester (II) is soluble in chloroform, benzene, ether, and hot petroleum ether. Thin-layer chromatography of II gave only one spot by several solvent systems.  $[\alpha]_D^{19} = +13.3^\circ$  (CHCl<sub>3</sub>, C = 35.5). Infrared and UV spectra are shown in Figs. 1 and 2, respectively.

The optical rotation of II did not change before and after heating II (0.5 g) in benzene (10 ml) in a sealed tube at 85°C for 10 hr.  $[\alpha]_D^{19} = +3.1^\circ$  (benzene, C = 32.5). When dry hydrogen chloride gas was passed through the ether (20 ml) solution of II (1.0 g, 2.6 mmole), the hydrochloride was obtained as a white solid (1.15 g, 86%),  $\lambda_{\text{max}} = 335.2 \text{ m}\mu$  (H<sub>2</sub>O,  $\epsilon = 5200$ ).  $[\alpha]_D^{19} = -35.9^\circ$  (H<sub>2</sub>O, C = 9.1).

Analysis: Calculated for C<sub>23</sub>H<sub>26</sub>N<sub>2</sub>O<sub>3</sub>·2HCl·3H<sub>2</sub>O: C, 54.65; H, 6.58; N, 5.54; Cl, 14.05. Found: C, 54.08; H, 6.60; N, 5.51; Cl, 13.75.

### Hydrolysis of II

A mixture of II (1.0 g, 2.6 mmole), 4 N potassium hydroxide (15 ml), and methanol (15 ml) was kept at room temperature for a few hours, after which the reaction mixture was concentrated to about 10 ml under reduced pressure. An organic portion was extracted with chloroform, washed with water, and concentrated to dryness to give a white solid, 0.7 g (82%). Infrared, UV and NMR spectra and an optical rotation of the solid were all consistent to those of an authentic quinine.  $[\alpha]_D^{19} = -106^\circ$  ( $\text{CHCl}_3$ ,  $C = 1.5$ ). Authentic sample  $[\alpha]_D^{19} = -108^\circ$  ( $\text{CHCl}_3$ ,  $C = 1.3$ ). Thin-layer chromatography showed only one spot by several solvent systems.

### Polymerization of II

A glass tube was charged with a benzene solution of the ester (II), AIBN, and benzene. After cooling with a Dry Ice-methanol bath, the tube was flushed with nitrogen and degassed. After this procedure was repeated twice more, the tube was sealed. After polymerization the contents were poured into an excess of ether to precipitate the oligomer, which was filtered and dried under reduced pressure. Polymerization conditions and physical constants of the oligomer are listed in Table 1. The oligomer is soluble in chloroform, benzene, and dimethylformamide, and insoluble in water, methanol, and acetone.

### Hydrochloride of Oligomer

The hydrochloride of all oligomers from Runs 1-3 was prepared by passing hydrogen chloride through the solution of oligomer in benzene and gave similar results. For example, Oligomer A (0.10 g) was dissolved in benzene (10 ml) and dry hydrogen chloride gas was passed through the solution to precipitate the hydrochloride as a white solid (0.12 g, 90%). The salt was soluble in water, methanol, and pyridine, and insoluble in tetrahydrofuran, ether, and dioxane.

Analysis: Calculated for  $(\text{C}_{23}\text{H}_{26}\text{N}_2\text{O}_3 \cdot 2\text{HCl} \cdot 3\text{H}_2\text{O})_n$ : C, 54.65; H, 6.58; N, 5.54; Cl, 14.05. Found: C, 54.66; H, 6.41; N, 5.36; Cl, 13.66.  $[\alpha]_D^{19} = -14.3^\circ$  ( $\text{H}_2\text{O}$ ,  $C = 6.6$ ),  $\lambda_{\text{max}} = 337.8 \text{ m}\mu$  ( $\text{H}_2\text{O}$ ,  $\epsilon = 5500$ ).

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