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Vinyl Polymerization. 272. Synthesis and Polymerization of 9-*O*-Methacryloylquinine

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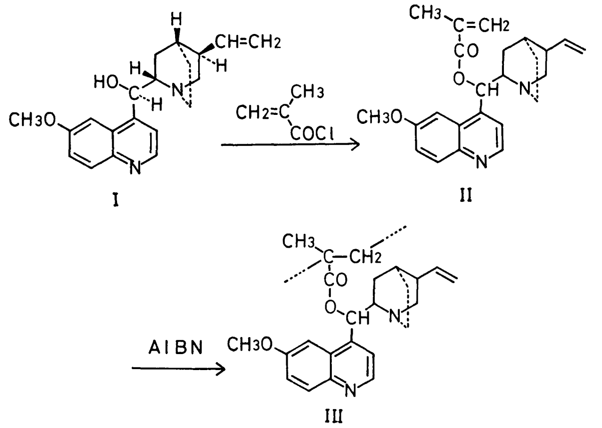
There have been various studies aimed at incorporating drugs into polymeric materials.[1] The most challenging aspect of the problem has been the search for systems, in which the polymer might receive advantages, such as increased pharmacological activities and reduced undesirable side effects.

The present study was undertaken for the synthesis and the polymerization of 9-*O*-methacryloylquinine (II) with the hope that the polymer (III) derived from II might show an increased effectiveness against the usual quinine (I) formulations, such as antifebrile and antimalarial activities.[2]

Further, III would be useful as an optically active resin, since quinine holds four asymmetric carbons. Grubhofer and Schleith[3] performed a resolution of manderic acid, using the reaction product of Amberlite XE 64 reisn with thionyl chloride and then with I (16% content of I). The polymer (III), which we wish to discuss in this paper, might be attractive in this field, too, since it contains one resolving agent per monomer unit.

The synthesis of II was performed by the reaction of I with methacryloyl chloride; it was obtained in a 70% yield. The stereospecific configuration of the quinine part was not altered during the esterification, since an alkaline hydrolysis of II reproduced I in a good yield.

The ester (II) could be converted into a water-soluble dihydrochloride quantitatively, during which time a racemization and a fission of the ester bond of II had not taken place. The compound (II) was also optically stable toward heating in benzene. On the basis of these chemical properties of II, the polymerization was carried out in benzene at 80°C, using AIBN as an initiator. The polymer (A) obtained in the lower concentration of II was soluble in chloroform, benzene, and pyridine, whereas the polymer (B) produced in the higher concentration was insoluble in most organic solvents, but swelled in DMF and DMSO. The difficulty in solubility may be caused by cross-linking through the participation of the vinyl group on the quinuclidinyl ring, and a coupling of radicals produced by chain-transfer reactions.



For the studies of the pharmacological activities of the polymer, it would be desirable to modify the polymer into a water-soluble one. This was performed by converting III to its hydrochloride. The introduction of dry hydrogen chloride gas into a benzene solution of polymer (A) generated a hygroscopic salt, and it became very soluble in water, as expected. On the other hand, the salt formation of polymer (B) was difficult because of the lack of appropriate solvents.

The use of the polymer as a high-molecular-weight drug and as an optical-active resin is now being studied; the studies will be described later.

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[1] G. W. Hastings, *Angew. Chem.*, **82**, 367 (1970).

[2] "The Merck Index of Chemicals and Drugs," 7th ed., Merck and Co., Inc., New Jersey (1960), p. 888.

[3] N. Grubhofer and L. Schleith, *Hoppe Seylers Z. Physiol. Chem.*, **296**, 262 (1954).

Table 1. Physical constants and analytical data

Compd.	Mp °C	$[\alpha]_D^{19}$ (c)	λ_{max} mμ (ε)	Formula		Analyses (%)			
						C	H	N	Cl
II	125.5—126.5	+29.7 (1.6)a) +30.4 (9.5)b)	335.0 (4600)a)	$C_{24}H_{28}N_2O_3$	Calcd Found	73.44 73.22	7.19 7.22	7.14 7.00	
polymer (A)	>250	−32.2 (1.6)a)	336.1 (5500)a)	$(C_{24}H_{28}N_2O_3)_n$	Calcd Found	73.44 72.65	7.19 7.30	7.14 6.87	
Polymer (B)	>300	——	——	$\begin{pmatrix}C_{24}H_{28}N_2O_3\\1.5H_2O\end{pmatrix}_n$	Calcd Found	68.70 68.93	7.44 6.94	6.67 6.61	
II-HCl*	170 (decomp)	−16.0 (4.0)c)	335.0 (5000)c)	$C_{24}H_{28}N_2O_3$ $2HCl\cdot 2H_2O$	Calcd Found	57.48 57.64	6.83 6.52	5.58 5.69	14.14 14.31
Polymer (A)-HCl*	235 (decomp)	+ 9.1 (7.3)c)	336.0 (5300)c)	$\begin{pmatrix}C_{24}H_{28}N_2O_3\\2HCl\cdot 3H_2O\end{pmatrix}_n$	Calcd Found	55.48 54.54	6.96 6.39	5.36 5.45	13.65 13.95
Poylmer (B)-HCl*	>300	——	——	$\begin{pmatrix}C_{24}H_{28}N_2O_3\\2HCl\cdot 2H_2O\end{pmatrix}_n$	Calcd Found	57.48 57.70	6.83 6.09	5.58 6.14	14.14 13.13

Solvent: a, chloroform; b, benzene; c, water.

* Hygroscopic properties of samples were taken into account for calculation of analytical data.

Experimental

The melting points were uncorrected. The infrared spectra (IR) were run on a Jasco Model IR-G Spectrometer. The ultraviolet absorption spectra (UV) were measured with a Hitachi Recording Spectrometer, Model EPS-3T. The optical rotations were recorded with a Yanagimoto Photo-Magnetic Polarimeter, Model OR-10. The molecular weight was determined using a Hitachi Vapor Pressure Osmometer, Model 115. The physical constants and analytical data of the compounds are listed in Table 1.

9-O-Methacryloylquinine (II). A mixture of quinine monohydrochloride dihydrate (13.0 g, 0.032 mol) and chloroform (60 m*l*) was treated with 4N sodium hydroxide to transfer quinine into the chloroform layer, which, after dring with anhydrous sodium sulfate, was mixed with methacryloyl chloride (3.3 g, 0.032 mol) and triethylamine (3.2 g, 0.032 mol). After the reaction mixture had been kept at room temperature for one day, it was washed with 10% sodium bicarbonate and dried over anhydrous sodium sulfate. The organic solution was concentrated and then chromatographed on alumina (2 cm × 70 cm, 300 mesh, neutral). Elution with ethyl acetate gave 9.2 g of crystalline 9-*O*-methacryloylquinine, which was recrystallized from ether to afford 9.0 g (70%) of the pure product.

IR (KBr); 2960, 1710, 1620, 1590, 1500, 1225, and 1150 cm^{-1}.

The optical rotation of II was not changed after heating at 80°C for ten hours in benzene; $[\alpha]_D^{19}$+30.4° (c 10, benzene).

Hydrolysis of II. A mixture of II (0.39 g, 1 mmol), methanol (10 m*l*), and 4N potassium hydroxide (10 m*l*) was allowed to stand for two hours at room temperature. Subsequent extraction with chloroform and evaporation of the solvent gave 0.27 g (76%) of a white solid, the optical ratation of which showed $[\alpha]_D^{19}$−104° (c 1.5, chloroform). An authentic sample had $[\alpha]_D^{19}$−108° (c 1.5, chloroform). The solid gave only one spot in thin layer chromatography in several solvent systems. IR, UV, and NMR spectra were all identical with those of quinine (I); mp 176°C (lit,2) 177°C).

Polymerization of II. Polymer (A): The ester (II) (2.00 g, 5.1×10^{-3} mol), AIBN (4.5×10^{-3} g, 2.8×10^{-5} mol), and benzene (12 m*l*) were placed in a glass tube, which was then degassed and sealed. The tube was immersed in a waterbath thermostatted at 80°C and shaken for eight hours, after which it was opened; the reaction mixture was then poured into diethyl ether to precipitate a white polymer, 0.98 g (49%).

The polymer is soluble in chloroform, benzene, DMF, DMSO, and conc. hydrochloric acid, and insoluble in water, methanol, and acetone. Mw=4380 (benzene, 30°C).

Polymer (B): A mixture of II (0.84 g, 2.1×10^{-3} mol), AIBN (2.1×10^{-3} g, 1.3×10^{-5} mol), and benzene (1.6 m*l*) was treated in a manner similar to that used for polymer (A), producing 0.78 g (93%) of a yellow solid which had an identical IR spectrum with that of polymer (A).

The polymer did not dissolve in any organic solvents and concentrated hydrochloric acid, but swelled in DMF and DMSO.

Preparation of Hydrochloride. II-HCl: Dry hydrogen chloride gas was passed through a benzene solution of II (0.69 g) to produce 0.63 g (70%) of the white hydrochloride. The salt is hygroscopic, and is soluble in water, methanol, and pyridine, but insoluble in tetrahydrofuran and ether.

IR (KBr): 3400, 2500, 1723, 1615, 1500, 1250, and 1135 cm^{-1}.

The ester (II) was recovered from II-HCl (0.30 g) by mixing it with 10% sodium bicarbonate and extracting it with chloroform; 0.21 g (83%), $[\alpha]_D^{19}$+29.7° (c 9.0, chloroform), mp 125—126°C.

Polymer (A)-HCl: The introduction of hydrogen chloride gas into a mixture of polymer (A) (0.10 g) and benzene yielded 0.11 g (85%) of the salt. The product is hygroscopic and is soluble in water and methanol, but insoluble in ether, chloroform, and acetic acid.

IR (KBr): 3400, 2600, 1735, 1620, 1600, 1500, 1250, 1140, and 1110 cm^{-1}.

Polymer (B)-HCl: Polymer (B) (0.1 g) in benzene afforded 0.1 g (83%) of the hygroscopic hydrochloride, which was insoluble in any organic solvents and water. Its IR spectrum was similar as that of polymer (A)-HCl.