POLYMERIC COUMARIN DERIVATIVES

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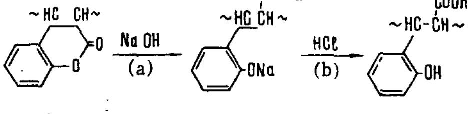
The chemical properties of coumarin, C, and its derivatives have been investigated fairly well, but information on the radical polymerization or copolymerization of C at the double bond of the α-pyrone ring is lacking. Alfrey, Lewis, et al., [1] studied the copolymerization of C with vinylidene chloride and came to the conclusion that C does not take part in copolymerization. Later, Lewis [2] stated that C is absolutely incapable of radical copolymerization. However, an analysis of information on the capacity of the double bond of the lactone ring for taking part in addition reactions (this bond is readily brominated [3] and reduced [4], while C reacts with mercuric acetate like styrene and other monomers of the vinyl type [5]) showed that this conclusion is inadequately substantiated. We have obtained copolymers of C, and also of a number of its derivatives, with N-vinylpyrrolidone (VP) and have shown that polymerization takes place at the expense of the 3,4 double bond of the lactone ring. The copolymerization of VP with coumarins was performed in bulk or in solution at 60–120°C using initiators of the radical type – azoisobutyronitrile (AIBN) or benzoyl peroxide (PB). Copolymers of various compositions and molecular weights (intrinsic viscosities [η] from 0.1 to 4 dl/g) were obtained. The dependence of the rate of polymerization and the composition of the copolymers on the reaction conditions and the composition of the initial mixture has been determined. It was found that C, like the majority of disubstituted ethylenes, is incapable of radical homopolymerization and therefore the number of coumarin links in the copolymers does not exceed 50 mole %. The copolymers obtained are white odorless powders soluble in ethanol, dioxane, chloroform, and dimethylformamide. With a small content of C in the copolymer (less than 10 mole %) the substances are soluble in water. The polymers melt in the range from 220 to 330°C. The structure of the copolymers was shown on the basis of their UV, IR, and NMR spectra and their compositions were determined by elementary analysis and also by their alkaline hydrolysis with the subsequent titration of the excess of alkali. We give the synthesis and the results of a study of the structure of copolymers of VP with coumarin (I), osthole (IV) and gosferol (XIV).

Table 1 gives the structures and compositions of copolymers of VP with coumarin C (I), umbelliferone (Umb) (II), esculetin (Esc) (III), osthole (Ost) (IV), ostholic acid (OstA) (V), meranzin hydrate (MH) (VI), isoimperatorin (IIm) (VII), oxypeucedanin (OP) (VIII), oxypeucedanin hydrate (OHP) (IX), isooxypeucedanin (IOP) (X), pranferol (PF) (XI), marmesin (M) (XII), pranchimgin (Pr) (XIII), and gosferol (GF) (XIV). As is well known [6], the UV spectrum of C has maxima at λ 275 and 325 nm (log ε 3.9 and 3.75), and the IR spectrum of C shows characteristic absorption bands at 1706 cm^{-1} (lactone C=O) and 1620 and 1596 cm^{-1} benzene ring), while in the UV spectra of copolymers of C two absorption maxima are found at λ 268 and 274 nm and in the IR spectra there are absorption bands at (cm^{-1}) 1765 (C=O of an α-dihydropyrone ring), 1675 (C=O in the ring of VP), and 1630 and 1580 (aromatic ring). The shift in the absorption band to 1765 cm^{-1} shows the disappearance of the 3,4 double bond of the lactone ring of the coumarins (in the IR spectrum of 3,4-dihydrocoumarin, likewise, the absorption band at 1765 cm^{-1} characteristic for the C=O grouping of an α-pyrone has disappeared). The copolymers of the coumarins readily undergo alkaline hydrolysis as the result of reaction *a*:



I XV XVI

Scheme 1

Leningrad Sanitary-Hygienic Medical Institute. Institute of Macromolecular Compounds, Academy of Sciences of the USSR. Translated from Khimiya Prirodnykh Soedinenii, No. 6, pp. 714–720, November–December, 1974. Original article submitted July 30, 1973.

TABLE 1

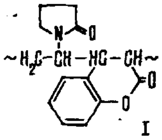
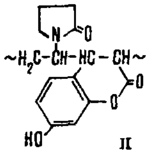
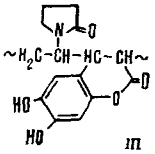
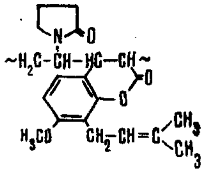
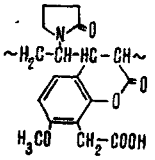
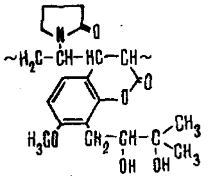
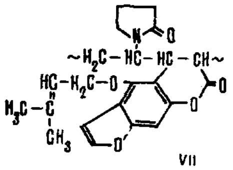
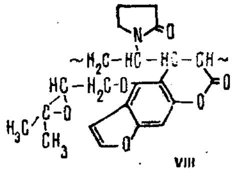
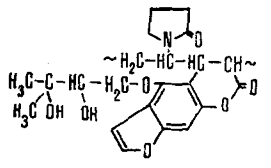
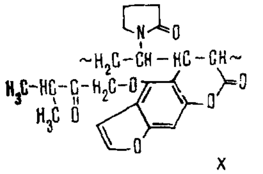
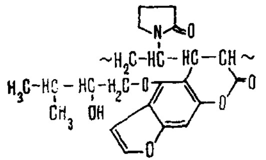
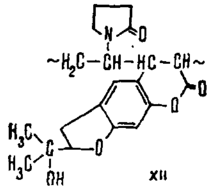
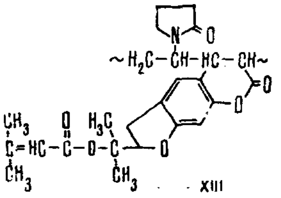
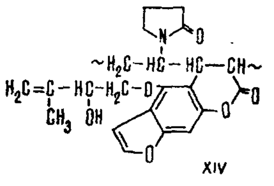
Structures of copolymers	Composition, %			Characteristic viscosity (DMFA, 25°C)	Yield,* %
	by weight		molar		
 I	VP C	51,4 48,6	58,1 41,9	0,80	85
 II	VP Umb	79 21	84,8 15,2	0,35	22
 III	VP Esc	76,6 23,4	84 16	0,16	26
 IV	VP Oct	78,6 21,4	89 11	0,32† 0,5 0,60 Fractions	9 12 20
 V	VP OctA	83,3 16,7	91,3 8,7	0,21	50
 VI	VP MH	82,5 17,5	92 8	0,67	36
 VII	VP IIm	77,7 22,3	89,5 10,5	0,64	44
 VIII	VP OP	71 29	86,3 13,7	1,4† 0,4 Fractions	7 5

TABLE 1. (Continued)

Structure of copolymers	Composition, %			Characteristic viscosity (DMFA, 20°C)	Yield*, %
	by weight		molar		
 IX	VP OPH	70,8 29,2	87 13	0,25† 1,42 Fractions	6 16
 X	VP IOP	77,7 22,3	90,0 10,0	1,20	38
 XI	VP PF	80,0 20,0	91,0 9,0	0,8	34
 XII	VP M	78,5 21,5	89,0 11,0	0,25‡	42
 XIII	VP PF	85,7 14,3	94,6 5,4	0,64‡	26
 XIV	VP GF	79,88 20,12	91,15 8,85	0,82	41

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*It is not the maximum possible yields that are shown but those which correspond to the values of the characteristic viscosities given in the preceding column.

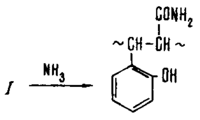
†The fractions were obtained by precipitation with ether from ethanolic solutions.

‡Viscosity measured in water at 25°C.

In substance (XV), the opening of the lactone ring of C is shown by the disappearance from the IR spectra of the band at 1765 cm^{-1} (lactone C = O), while in the UV spectra the bands at 268 and 274 nm are absent and a band has appeared at λ_{max} 276 nm. The occurrence of reaction *a* is also shown by the change in the physicochemical properties of the copolymer (the melting point and the intrinsic viscosity change, the previously water-insoluble copolymer becomes soluble, and so on). When compound (XV) was acidified (reaction c) no opening of the lactone ring took place (as was observed for the monomeric C) – in the IR spectrum of (XVI) there is no band at 1765 cm^{-1}, and in the UV spectrum there is only an absorption maximum at λ_{max} 276 nm.

The fact that coumarins take part in copolymerization through the 3,4 double bond of the lactone ring is shown by their behavior on reaction with ammonia and amines. As is well known, the initial C does not react with ammonia even at elevated temperatures and pressures [7]. At the same time, 3,4-dihydrocoumarin (in which there is no 3,4 double bond) readily reacts with ammonia and amines. The polymeric coumarins also react with amines, giving the corresponding amides.

This is shown by the increase of the nitrogen content in the amides obtained as compared with the initial polymers. Furthermore, the water-insoluble substances have become water-soluble, which shows the formation of amides.



XVII

Scheme 2

In the UV spectrum of (XVII) there is a strong absorption band with its maximum at λ_{max} 276 nm, and in the IR spectrum there is no absorption band at 1765 cm^{-1}. Since the copolymers investigated are hygroscopic and readily absorb water, their IR spectra show an absorption band at 3450 cm^{-1}. Copolymers with hydroxy groups (III, VI, IX, XI, XII, and XIV) and also the products of the hydrolysis and aminolysis of the copolymers (types XV, XVI, and XVII) adsorb more strongly at 3450 cm^{-1}.

In the NMR spectrum of compound (I) in the weak-field region there is a broad singlet with its center at 6.98 ppm due to aromatic protons. In the strong-field region there is a broad signal in the 2.02-2.06 ppm range due to the protons of the methylene groups of the pyrrolidone ring and to the –CH–CH– grouping in the dihydropyran ring. The signals from the protons of the 3,4 double bond of the α-pyrone ring usually observed in the spectra of monomeric coumarins at 6.0-6.45 and 7.40-8.20 ppm, respectively, are absent. This shows that the copolymerization of C with VP takes place at the 3,4 double bond of the lactone ring, which leads to the disappearance of the double bond in the α-pyrone ring.

In the region of aliphatic protons in the NMR spectrum of (IV), broadened singlets are observed at 1.62 and 1.74 ppm which are due to the protons of methyl groups on a double bond. A broad signal at 2.39 ppm belongs to the protons of the methylene groups in VP. A signal with its center at 3.29 ppm is due to the protons of the methylene groups attached to an aromatic ring. A singlet at 3.78 ppm is due to the protons of methoxy groups. In the weak-field region there are two broadened signals at 5.14 and 6.58 ppm, corresponding to olefinic and aromatic protons, respectively.

The NMR spectrum of (XIV) shows the signals of the protons of methyl groups on a double bond (1.86 ppm), of methylene groups in the ring of VP (2.06 ppm), and of hydroxy groups (3.36 ppm). A signal with its center at 4.26 ppm is due to the protons in a $Ar-O-CH_2-CH-$ grouping. The spectrum also shows the signals of methylene protons on a double bond (4.95 and 5.12 ppm), of the 4',5' protons of the furan ring (6.68 and 7.51 ppm), and of the protons in position 8 of the coumarin ring (6.88 ppm).

On the basis of the features of the NMR spectra of (IV) and (XIV), which also lack the signals from protons on the 3,4 double bond of an α-pyrone ring and from a comparison of the spectra of the monomeric and polymeric compounds it may be concluded that the double bonds of the side chains of osthole and gosferol do not take part in the copolymerization reaction, since all the signals due to the aliphatic protons of the monomeric coumarins are observed in the spectra.

With the production of polymeric derivatives, a series of new possibilities for the directed modification of their properties is opened up for the chemistry of coumarin compounds. For example, by regulating the composition of the copolymers it is possible to obtain water-soluble compounds which can be used as surfactants. The production of water-soluble copolymers of VP with coumarin derivatives also opens up possibilities for the broad pharmacological investigation of the latter. The solubility of the copolymers depends on the content of coumarin derivatives and their nature. The majority of the copolymers that we obtained, which contained about 10-15 mole % of substituted coumarins, proved to be readily soluble in water.

In a pharmacological study of the polymeric derivative, it was found that when the monomeric coumarins are copolymerized with VP their hypotensive and spasmolytic properties are completely retained, and the duration of their action on administration in equimolar doses increases 5- to 10-fold [8].

EXPERIMENTAL

The nitrogen contents were determined by the Dumas method and from the results obtained the weight and molar compositions of the copolymers were calculated. The intrinsic viscosities were determined with the aid of an Ubbelohde viscometer in DMFA at 25°C. The UV spectra were taken on a SF-4A spectrophotometer (in DMFA), the IR spectra on a UR-20 spectrometer (tablets with KBr), and the NMR spectra on Varian HA-100D (I, IV) and Bruker HX-90 (XIV) spectrometers (in $CDCl_3$ with HMDS as internal standard).

The Synthesis of a Copolymer of VP with Coumarin C (Copolymer I). A mixture of 2.22 g of VP, 1.46 g of C, 0.015 g of AIBN, and 2.5 ml of ethanol was charged into a 10-cm^3 tube. The tube was sealed in a current of argon and placed in a thermostat at 70°C. It was opened after 7 h, and the copolymer obtained was precipitated with diethyl ether. It separated out in the form of a fine white powder. The precipitate was filtered off, dissolved in ethanol, and reprecipitated with ether. The filtered-off material was washed with ether and dried in vacuum at 40°C. The yield of copolymer was 3.1 g (85%).

Synthesis of a Copolymer of VP with Osthole (Ost) (Copolymer IV). In a tube sealed in a current of argon a mixture of 31 g of VP, 3.44 g of Ost, 0.034 g of AIBN, and 30 ml of ethanol was heated in a thermostat at 70°C for 6 h. The fractional precipitation of an ethanolic solution of the copolymer with diethyl ether gave three fractions with a total yield of copolymer of 41%.

Synthesis of a Copolymer of VP with Gosferol (GF) Copolymer XIV. A mixture of 1.1 g of VP, 0.041 g of GF, 0.005 g of AIBN, and 1.1 ml of ethanol was heated in a sealed tube at 70°C for 50 min. The copolymer was precipitated with diethyl ether, and the precipitate was filtered off, washed with ether, and dried in vacuum. Yield 41%.

Alkaline Hydrolysis of Copolymer (I). A flask containing 500 ml of a 5% aqueous solution of caustic soda was charged with 40 g of a copolymer of VP with C (amount of C in the copolymer 50%). The solution was stirred in a current of argon at room temperature for 2 h. After this time, the whole of the copolymer had passed into solution, coloring it pink. The solution was acidified with 10% hydrochloric acid to pH 2. The copolymer was isolated in the form of a white precipitate, which was centrifuged off. The saponified copolymer was washed with water and acetone and dried in vacuum. Yield 99%. The amount of saponified coumarin in the chain (50%) was determined by direct titration of the free carboxy groups.

Reaction of the Copolymer I with Ammonia. A flask fitted with a stirrer and reflux condenser and containing 300 ml of a 10% solution of ammonia in dioxane was charged with 10 g of a copolymer of VP with C (37 mole % of C). The reaction was performed at room temperature under homogeneous conditions. The time of the reaction was 72 h. The product was purified by dialysis and was freeze-dried. Yield 96%. The percentage conversion of the copolymer was determined from its nitrogen content. After 72 h, the aminolysis reaction had taken place completely. The nitrogen content had increased from 7.2 to 9.96%.

SUMMARY

Copolymers of vinylpyrrolidone with coumarin, umbelliferone, esculetin, osthole, ostholic acid, meranzin hydrate, isoimperatorin, oxypeucedanin hydrate, isooxypeucedanin, gosferol, pranchimgin, and marmesin have been synthesized and their structures have been studied.

On the basis of a study of UV, IR, and NMR spectra, and also of chemical properties, it has been established that copolymerization takes place at the 3,4 double bond of the lactone ring and side chains do not participate in polymerization.

In a pharmacological study of monomeric coumarins and their copolymers it was found that they all possess well-defined spasmolytic and hypotensive properties.

LITERATURE CITED

1. T. Alfrey, Jr., J. Bohrer, H. Haas, and C. Lewis, J. Polymer Sci., 5, No. 6, 719 (1950).

2. C. W. Lewis, J. Polymer Sci., 6, 777 (1951).
3. M. G. Patel and S. Sethna, J. Ind. Chem. Soc., 37, 227 (1960).
4. M. E. Brokke and B. E. Christensen, J. Org. Chem., 23, 589 (1958).
5. T. R. Seshadri, Proc. Ind. Acad. Sci., 4A, 163, 630 (1931).
6. G. A. Kuznetsova, Natural Coumarins and Furocoumarins [in Russian] (1967), p. 67.
7. W. Michler, Ber., 14, 262 (1881).
8. I. V. Brodskii, V. A. Kropachev, O. S. Karchmarchik, A. Z. Abyshev, and P. P. Denisenko, Third Symposium on Physiologically Active Synthetic Polymers and Macromolecular Models of Biopolymers [in Russian], Riga (1971), p. 38.