SYNTHESIS OF WATER-SOLUBLE POLYMERIC PHYSIOLOGICALLY ACTIVE SUBSTANCES

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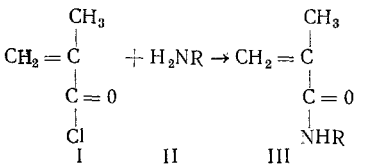
UDC 615.276.012.1

The present communication gives the results of the synthesis and study of polymeric physiologically active compounds with a primarily antiphlogistic action. These compounds were obtained by the copolymerization with methacrylic acid o-carboxyphenylamide of monomers described in the literature [1] and also of the monomers (III) which we have synthesized for the first time by the reaction between methacrylyl chloride (I) and an amino compound (II) by the reaction



The monomers obtained for the first time are given in Table 1.

The structure of the monomers was shown by the results of elementary analysis and by IR spectroscopy. As an example, Fig. 1 gives the IR spectra of 4-aminoantipyrine and the N-methacrylyl-4-aminoantipyrine obtained from it. It can be seen from Fig. 1 that the absorption bands characteristic for a free amino group at 1125, 1175, 1240, 3335, and 3440 cm^{-1} have disappeared in the spectrum of the monomer and bands have appeared in it which are characteristic for a nonaromatic double bond (940 cm^{-1}), together with bands characteristic for substituted amides —1520, 1680, and 3270 cm^{-1} [2].

The monomers obtained were subjected to radical polymerization with the o-carboxyphenylamide of methacrylic acid. The latter, in the form of the sodium salt, imparts water-soluble properties and a definite antiphlogistic activity to the copolymer.

TABLE 1. Monomers (III)

R	Melting point (°C)	Found (in %)			Empirical formula	Calculated (in %)		
		C	H	N		C	H	N
2,3-$(CH_3)_2C_6H_3$	115	76.54 76.38	7.99 8.02	7.56 7.42	$C_{12}H_{15}NO$	76.19	7.93	7.40
3,4-$(CH_3)_2C_6H_3$	100	76.42 76.69	7.45 7.90	7.38 7.28	$C_{12}H_{15}NO$	76.19	7.93	7.40
2,5-$(CH_3)_2C_6H_3$	88	76.14 76.48	7.71 7.95	7.41 7.40	$C_{12}H_{15}NO$	76.19	7.93	7.40
Antipyrin-4-yl	183—184	66.71 66.55	5.79 5.48	15.10	$C_{15}H_{17}N_3O_2$	66.42	5.53	15.49

Kiev Scientific-Research Institute of Pharmacology and Toxicology, Ministry of National Health of the Ukrainian SSR. Translated from Khimiko-Farmatsevticheskii Zhurnal, Vol. 7, No. 2, pp. 27-30, February, 1971. Original article submitted November 5, 1969.

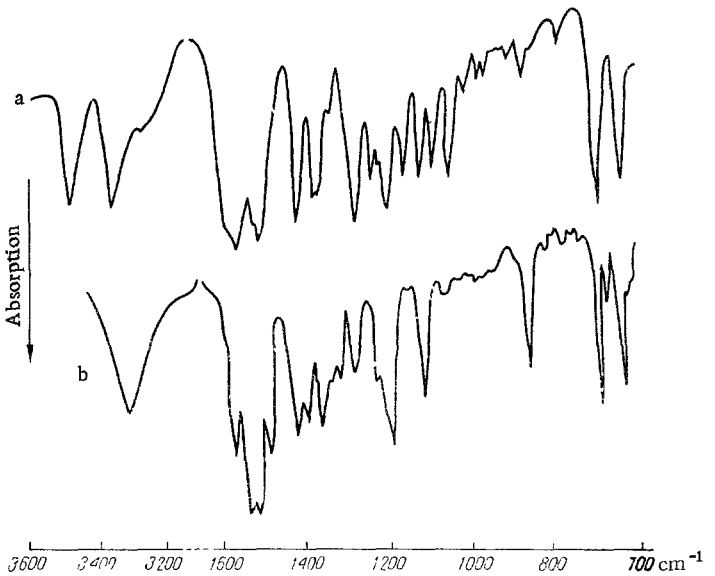


Fig. 1. IR spectra of 4-aminoantipyrine (a) and of N-methacrylyl-4-aminoantipyrine (b).

It has been found that the phenylmethacrylamides containing carboxy, ethoxy, and methoxy groups in the aromatic nucleus are highly active in copolymerization reactions, as they are in polymerization reactions [3]. Xylidine derivatives proved to be very unreactive in polymerization reactions, but they take part comparatively readily in copolymerization reactions, and the yields of copolymers are satisfactory. The reactivity of a xylidine derivative as monomer is affected by the position of the methyl residues: the further away they are from the amino group the higher it is, which is obviously due to steric factors [4, 5].

The compositions of the copolymers after careful purification (three reprecipitations with diethyl ether from solutions in ethanol, acetone, or dimethylformamide) were established by elementary analysis, IR spectroscopy, and acid number.

The copolymers are given in Table 2.

It can be seen from Table 2 that in some cases the acid number is higher than calculated for the given elementary unit (for example, for copolymers containing xylidine residues). This is explained by the higher reactivity of the o-carboxyphenylamide of methacrylic acid in this reaction. For example, the copolymerization constants r_1 and r_2 for the copolymer of o-carboxyphenylamide and the 2,3-dimethylphenylamide of methacrylic acid are, respectively, 0.85 and 0.15.

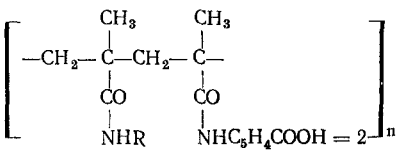
Nevertheless, the copolymers containing residues of anisidine or phenetidine have acid numbers close to those calculated for the given elementary unit, which is also confirmed by the copolymerization constants. For example, for the copolymer of the p-ethoxy- and o-carboxyphenylamides of methacrylic acid r_1 and r_2 are, respectively, 0.76 and 0.46.

As an example, Fig. 2 gives the IR spectra of the 2,3-dimethylphenylamide and the o-carboxyphenylamide of methacrylic acid and their copolymer. The bands at 700-770 cm^{-1} due to the aromatic ring and the amide bond are present in the spectra of both the monomers and their copolymer, but the bands in the 800-1000 cm^{-1} region characteristic for a nonaromatic double bond [2] are absent from the copolymer, which is explained by the conversion of the monomers into the copolymer.

The molecular weights of the copolymers obtained were determined osmometrically in ethanolic solutions [5-7], their mean value being 30,000-40,000. It must be mentioned that in our work we attempted to obtain copolymers with a low molecular weight so as to minimize the risk of precipitation within the organism. Experiments carried out in vitro have shown that the sodium salts of the copolymers obtained pass through biological membranes.

Biological studies carried out on white mice and rats have shown the comparatively low toxicity of the copolymers, which have a definite antiphlogistic activity. Thus, the sodium salt of the copolymer of

TABLE 2. Copolymers of the o-Carboxyphenylamide of Methacrylic Acid with Other N-Substituted Methacrylamides



R	Yield of copolymers (% with time) after 1 h	after 2 h	after 3 h	after 4 h	after 5 h	after 6 h	Acid No.	Found (in %)	Emprical formula	Calculated (in %)
2,3-$(CH_3)_2C_6H_3$	30	55	64	78	81	83	150	6,85 7,03	$(C_{23}H_{26}N_2O_4)_n$	7,12
3,4-$(CH_3)_2C_6H_3$	32	58	69	79	84	92	147	6,91 6,87	$(C_{23}H_{26}N_2O_4)_n$	7,12
2,5-$(CH_3)_2C_6H_3$	39	54	81	90	92	95	142	7,14 7,28	$(C_{23}H_{26}N_2O_4)_n$	7,12
Antipyrin-4-yl	48	60	85	93	97	—	120	11,58 11,43	$(C_{26}H_{28}N_4O_5)_n$	11,78
4-$C_2H_5OC_6H_4$	53	68	80	87	90	95	132	6,41 6,70	$(C_{23}H_{26}N_2O_5)_n$	6,83
4-$CH_3OC_6H_4$	60	68	79	81	88	93	135	6,94 7,09	$(C_{22}H_{24}N_2O_5)_n$	7,07
2-$CH_3OC_6H_4$	45	61	74	78	87	94	150	7,31 7,21	$(C_{22}H_{24}N_2O_5)_n$	7,07
2-$C_2H_5OC_6H_4$	67	87	91	93	95	97	130	6,80 6,73	$(C_{23}H_{26}N_2O_5)_n$	6,83

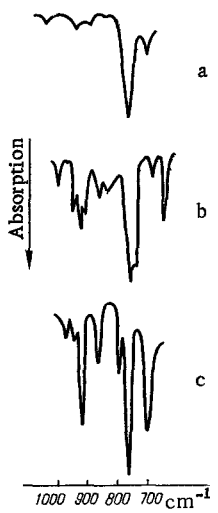


Fig. 2. IR spectra of the o-carboxydiphenylamide and the 2,3-dimethylphenylamide of methacrylic acid (b, c) and their copolymer (a).

the 2,3-dimethylphenylamide and o-carboxyphenylamide of methacrylic acid, on intraperitoneal administration at LD_{50} 720 mg/kg, suppresses an inflammatory process by 68% 4 h after administration and by 52% after 24 h, while the sodium salt of the copolymer of N-methacrylyl-4-aminoantipyrine and of methacrylic acid o-carboxydiphenylamide at LD_{50} 2300 mg/kg suppresses inflammation by 31% after 4 h. Under analogous conditions, widely used antiphlogistic preparations suppress the inflammatory process by 20-40%.

EXPERIMENTAL

Methacrylic Acid o-Carboxydiphenylamide (III, R = C_6H_4COOH-o) [4]. A solution of 0.1 mole of o-aminobenzoic acid in 100 ml of chloroform was treated with 0.2 mole of triethylamine and, with ice-water cooling, 0.1 mole of methacrylyl chloride was added dropwise. The reaction mixture was stirred at room temperature for about 2 h and was left overnight. After this, a 0.1 N solution of hydrochloric acid was added with stirring to pH 5.0-4.0, and the chloroform layer was separated off and evaporated in vacuum. The residue was recrystallized from dilute ethanol. Yield about 15 g (75%), mp 170°C. Found, %: N 6.65, 6.72. $C_{11}H_{11}NO_3$. Calculated, %: N 6.80.

The Anisidides, Phenetidides, and Xylidides of Methacrylic Acid [III, R = $CH_3OC_6H_4$, $C_2H_4OC_6H_4$, and $(CH_3)_2C_6H_3$]. A solution of 0.1 mole of the appropriate amino compound (o- or p-anisidine, o- or p-phenetidine, or 2,3-, 3,4-, or 2,5-xylidine) in 100 ml of chloroform was treated with a solution of 5.6 g of caustic potash in 100 ml of water and 0.5 g of sodium oleate, and with vigorous stirring at 0°C a solution of 0.1 mole of methacrylyl chloride [1] in 100 ml of chloroform was added. The reaction mixture was left for half an hour, and the chloroform layer was separated off, dried with anhydrous sodium sulfate, and evaporated in vacuum at a gentle heat. The residue was recrystallized from aqueous ethanol. Yield 80-90%.

N-Methacrylyl-4-aminoantipyrine. A solution of 20.3 g of 4-aminoantipyrine in 100 ml of anhydrous acetone was treated with 11 g of triethylamine and, with ice-salt cooling and vigorous stirring, 10.4 g of methacrylyl chloride in 50 ml of anhydrous acetone was added dropwise. The reaction mixture was stirred for 1 h, and the precipitate of triethylamine hydrochloride that formed was filtered off. The residue on

the filter was washed with acetone (3 ×20 ml). The filtrate was evaporated in vacuum, and the residue was recrystallized from benzene or xylene. Yield about 20 g (74%).

Copolymerization of the Monomers. This was carried out under standard conditions: molar ratio of the monomers 1:1, solvent dimethylformamide, initiator azobutyronitrile (1%), temperature 80°C, in sealed tubes.

The kinetics of the copolymerization was determined gravimetrically, and the constants r_1 and r_2 by the method of Mayo and Lewis (differential method) [8]. The sodium salts of the copolymers were obtained by neutralizing their ethanolic solutions with ethanolic caustic potash after determining their acid numbers.

LITERATURE CITED

1. T. A. Sokolova, Zh. Obshch. Khim., 27, 2205 (1957).
2. L. Bellamy, Infrared Spectra of Complex Molecules, 2nd edn., Methuen, London (1958) [Russian translation], Mir (1963).
3. T. A. Sokolova and T. M. Chetyrkina, Vysokomol. Soed., 1961, No. 3, 244.
4. M. M. Koton, T. A. Sokolova, M. N. Savitskaya, and T. M. Kiseleva, Zh. Obshch. Khim., 28, 417 (1958).
5. V. V. Korshak and K. K. Saltavskaya, Dokl. Akad. Nauk SSSR, 59, 497 (1948).
6. Ts'uan Jen-yüan, Determination of Molecular Weights of Polymers [in Russian], Moscow (1962).
7. I. P. Losev and O. Ya. Fedotova, Practical Work in the Chemistry of High-Molecular-Weight Compounds [in Russian], Moscow (1962).
8. G. P. Gladyshev, The Polymerization of Vinyl Monomers [in Russian], Alma-Ata (1964), p. 80.