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SYNTHESIS OF SUBSTITUTED 2-ANTHRAQUINONESUCCINAMIC ACID AMIDES AND STUDY OF THEIR PHARMACOLOGICAL ACTIVITY

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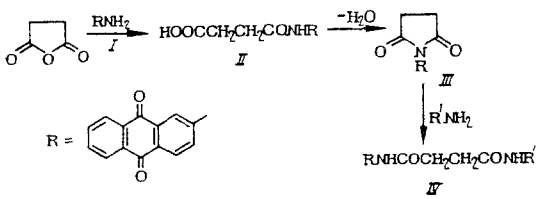
The problem of pharmacotherapeutic correction of liver diseases still remains unsolved because of the polyetiology of the mechanisms of the defects of the liver, and the variety of disturbances of its function [1]. Analysis of the data shows that a favorable clinical effect is observed when drugs with anti-inflammatory, anti-oxidant and membrane-stabilizing action are used [4]. However, there is no information on any research trend on new hepatoprotectors combining the above mentioned types of activity.

We have previously established [2] the presence of antioxidant and membrane-stabilizing activity in several anthraquinone-succinamic acid derivatives. In continuation of this investigation, we synthesized substituted amides of 2-anthraquinonesuccinamic acid and examined their pharmacological activity. The reaction of 2-aminoanthraquinone (I) with succinic anhydride in a glacial acetic acid medium gave 2-anthraquinonesuccinamic acid (II), which was cyclized with Ac_2O to form 2-anthraquinonesuccinimide (III). In the reaction of III with fatty amines, substituted amides of anthraquinonesuccinamic acid (IV a-j) were formed.



These compounds are in the form of yellow crystalline substances, which are soluble in dioxane, DMFA and insoluble in water. The structure and purity of the compounds was controlled by means of elemental analysis, TLC, and IR and UV spectral data.

The structures of the R^1 substituents and the physicochemical characteristics of compounds IVa-j are given in Table 1.

Compounds IVa-j were examined for anti-inflammatory, antioxidant, membrane-stabilizing, and choleretic activity.

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TABLE 1. Characteristics of Compounds IVa-j

Compound	R′	Yield, %	mp, °C	R_f	Empirical formula	IR spectra		
						ν_{NH}	$\nu_{C=O}$	δ_{NH}
IVa	H	80	282—284	0,13	$C_{18}H_{14}N_2O_4$	3450	1685	1530
IVb	Me	74	262—264	0,43	$C_{19}H_{16}N_2O_4$	3350	1690	1530
IVc	C_2H_4OH	97	234—236	0,17	$C_{20}H_{18}N_2O_5$	3340	1685	1515
IVd	Pr	79	252—254	0,53	$C_{21}H_{20}N_2O_4$	3360—3320	1693	1520
IVe	i-Pr	78	273—275	0,40	$C_{21}H_{20}N_2O_4$	3300	1690	1510
IVf	Bu	77	241—243	0,48	$C_{22}H_{22}N_2O_4$	3340	1690	1520
IVg	$PhCH_2$	95	251—253	0,59	$C_{25}H_{20}N_2O_4$	3330	1700	1520
IVh	$PhCH_2CH_2$	76	266—268	0,68	$C_{26}H_{22}N_2O_4$	3373—3346	1693	1520
IVi	Cyclo-C_6H_{11}	94	298—300	0,66	$C_{24}H_{24}N_2O_4$	3340	1700	1527
IVj	$(CH_2)_{17}CH_3$	83	230—232	0,88	$C_{36}H_{50}N_2O_4$	3373—3333	1707	1533

Note. The results of the elemental analyses correspond to the calculated values.

EXPERIMENTAL (CHEMICAL)

The IR spectra were run in KBr tablets (concentration 1%), on a "Specord IR-75" spectrophotometer.

The R_f of the compounds was determined on "Silufol UV-366" plates in a benzene–MeOH–methyl ethyl ketone–acetone system (70:10:5:1).

2-Anthraquinonesuccinamic Acid (II). A 1.1 g portion (0.011 mole) of succinic anhydride was added to a solution of 2.23 g (0.01 mole) of 2-aminoanthraquinone in 20 ml of glacial acetic acid, and the mixture was heated for 1 h. The reaction mixture was cooled, the precipitate was filtered off, dried, and recrystallized from dioxane. Yield 2.81 g (87%), mp 228-230°C.

2-Anthraquinonesuccinimide (III). A mixture of 3.23 g of acid II and 10 ml of Ac_2O was heated for 30 min, and then was cooled. The precipitate that separated out was filtered off, dried, and recrystallized from dioxane. Yield, 2.81 g (92%), mp 289-291°C.

General Method for the Preparation of 2-Anthraquinonesuccinamic Acid Amides (IVa-l). A 3.05 g portion (0.01 mole) of imide III was dissolved at 30-50°C in 30 ml of dry dioxane, and 0.011 mole of a fatty amine was added. After 12-14 h, the mixture was diluted with water acidified with HCl (1:1). The precipitate that separated out was filtered off, washed, dried and recrystallized from dioxane.

EXPERIMENTAL (PHARMACOLOGICAL)

The pharmacological activity of the compounds was studied on 168 white rats. The cholagogic activity was determined by collecting portions of bile every hour by canulation of the common bile duct [6]. The compounds in a dose of 50 mg/kg and the reference preparation oxaphenamide in an ED_{50} (150 mg/kg) were introduced intraduodenally. The anti-oxidant and membrane protecting activity was studied on a model of acute fat dystrophy of the liver, simulated by the subcutaneous administration of a 50% oily solution of tetrachloromethane in a dose of 0.8 ml per 100 g for 2 days. The compounds in a dose of ED_{50} of Silibor (25 mg/kg) were administered intragastrically 2 h before and 2 h after the injection of hepatotoxin. The content of malonic dialdehyde (MDA) was determined in liver homogenates [5], and the activity of alanine aminotransferase (AlAT) in the blood serum [7]. The anti-inflammatory activity was evaluated using a model of carrageenan-induced edema of the paw in rats. The compounds were introduced intragastrically in a dose of ED_{50} of indomethacin (5 mg/kg) 2 h before the subplantary injection of carrageenan. The anti-exudative action was determined oncometrically 2.5 h after the action of the phlogogenic factor [3].

The results of the investigations show (Table 2) that compounds IVa, IVc, IVe, IVi, IVd display a significant choleretic effect, increasing the rate of intact bile secretion by 33-50%. In compounds IVa and IVd, this activity is only slightly inferior to that of oxaphenamide. The ability to inhibit the peroxy oxidation of lipids, induced by the prooxidant tetrachloromethane is most characteristic for compounds IVd, IVa, IVg, IVh: the content of the peroxidation end product (MDA) in the liver homogenates is reliably decreased by 34-57%. In compounds IVd, IVh, IVa, the antioxidant effect was clearly a manifestation of a membrane-stabilizing action, since the hypertransaminasemia became normalized: when the compounds were introduced, the activity of the marker enzyme of cytolysis of hepatocytes (AlAT) decreased by 50% on the average. It should be noted that the antioxidant activity of compound IVd was more pronounced than that of vitamin E, equally as the membrane-protecting action of compounds IVa,c,

TABLE 2. Cholagogic, Antioxidant, and Membrane-Protecting Activity of 2-Anthraquinonesuccinamic Acid Derivatives IVa-j

Compound	Activity, %			
	cholagogic	antioxidant	membrane protecting	anti-inflammatory
IVa	41,6*	48,3*	47,4*	38,4*
IVb	0	0	51,2*	11,6
IVc	37,5*	27,6	44,4*	28,1*
IVd	50,0*	57,0*	42,7*	15,2
IVe	33,3	0	0	18,3
IVf	0	4,7	42,1*	5,5
IVg	0	35,6*	26,4*	12,2
IVh	0	33,7*	51,9*	20,7
IVi	37,5*	0	0	11,6
IVj	0	0	19,4	0
Vitamin E	—	48,5*	21,7	—
Oxaphenamide	58,3*	—	—	—
Silibor	27,3	0	37,3*	—
Indomethacin	—	—		50,5

*Significant at $P \leq 0.05$.

h, b, f, d surpassed the activity of the hepatoprotector silibor. Compounds IVc, IVc [sic], IVb, and IVf also have membrane protecting activity, but this is not caused by antiradical activity and is due to other mechanisms.

The anti-inflammatory action found among the 2-anthraquinonesuccinamic acid amides is characteristic for compounds IV, IVc and IVh.

Analysis of the data obtained makes it possible to identify compounds in the series of 2-anthraquinonesuccinamic acid amides, which combine anti-oxidant, membrane-stabilizing, anti-inflammatory and cholagogic action, and therefore are prospective in the production of new hepatoprotectors. The amide and monoethanolamide of 2-anthraquinonesuccinamic acid (IVa and IVc) belong to the group of compounds which are reliably known to combine these four types of activity.

The propylamide of 2-anthraquinonesuccinamic acid (IVd) combines three types of hepatotropic action; IVe and IVi are potential choleretic preparations, since the dose in which they increase the bile secretion by 30% is one third the ED_{50} of oxaphenamide.

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