SYNTHESIS AND BIOLOGICAL ACTIVITY OF N-PHENYLANTHRANILIC ACID DERIVATIVES

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Substituted derivatives of N-phenylanthranilic acid are of practical interest as compounds with different biological activities [8, 9]. The Ullmann reaction [2, 15] is used for their preparation. This is based on the reaction of o-halobenzoic acid derivatives with arylamines in n-amyl alcohol medium in the presence of potassium carbonate and copper powder as a catalyst. To increase the yield of the N-phenylanthranilic acids, the reaction is sometimes carried out in high-boiling solvents, such as nitrobenzene and glycerin [6, 13, 14]. The disadvantages of these methods consist in low yields of the reaction products in several cases, the use of toxic solvents, and also the complexity of designing the process flow diagram.

It is known that the rate of the Ullmann reaction in the synthesis of diarylamines is considerably influenced by the nature of the solvent [2]; substitution of the halogen bound to the aromatic ring is considerably facilitated by using polar aprotic solvents, such as DMFA and DMSO; these solvents appreciably increase the nucleophilicity of arylamines [5]. We took this into consideration, and reproduced the preparation of several N-phenylanthranilic acids [1, 3, 4, 12], and synthesized derivatives of 4-chloro- and 4-nitro-N-phenylanthranilic acids (I-XII) in the DMFA medium, in the presence of potassium carbonate and a catalyst at a temperature of 140-150° (see Table 1).

$$2\text{-}(RR^1C_6H_3NH)\text{-}4\text{-}R^2C_6H_3COOH$$

I — XII

I — X: $R^1 = H$, $R^2 = Cl$; I: R = OMe-2; II: R = OMe-3; III: R = Me-2; IV: R = Me-3; V: R = Me-4; VI: R = Cl-2; VII: R = Cl-3; VIII: R = Cl-4; IX: R = Br-3; X: R = = Br-4; XI: R = Me-3, R^1 = Me-4, $R^2 = NO_2$; XII: R = Me-3, R^1 = Me-5, $R^2 = NO_2$.

By carrying out the reaction in the DMFA medium, the yield of the already described phenylanthranilic acids could be increased by 5-30%, depending on the substituents, and also the isolation of the end products could be simplified. It was found that the formation of substituted derivatives of 5-nitro-N-phenylanthranilic acid proceeds in the absence of a catalyst [10]. The reaction with 2-chlorobenzoic, 2,4-dichlorobenzoic, and 2-chloro-4-nitrobenzoic acids with arylamines proceeds only in the presence of a catalyst (copper powder). It is clear that the reaction of 2-chloro-5-nitrobenzoic acid with arylamines in the absence of a catalyst involves an inductive effect of the nitro group at the p-position with respect to the chlorine atom. In the case of 4-substituted o-halobenzoic acids, the inductive effect of the substituent has less influence on the carbon—halogen bond, and therefore the presence of the catalyst is necessary to increase the electrophilicity of the reaction center.

Compounds I-XII are colored crystalline substances, which are insoluble in water but solube in alcohol, acetone, DMFA, and aqueous solutions of alkalies. Their structure was confirmed by the data of elemental analysis, IR spectroscopy and their individuality by the TLC method.

The IR spectra of compounds I-XII are characterized by several intense absorption bands. In the 1660-1650 cm^{-1} region, bands are observed corresponding to the stretching vibrations of the carbonyl group. They are shifted somewhat to the low frequencies region, because of the formation of a hydrogen bond with proton-donor groups (OH, NH). The presence of the

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TABLE 1. Derivatives of N-Phenylanthranilic Acid I-XII

Compound	Yield, %	mp, °C	Found N, %	Empirical formula	Calculated N, %	pKa	R_{f_1}	R_{f_2}
I	95	209	5,03	$C_{14}H_{12}ClNO_3$	5,04	6,60	0,56	0,73
II	92	164—5	5,13	$C_{14}H_{12}ClNO_3$	5,04	6,57	0,60	0,77
III	98	206	5,31	$C_{14}H_{12}ClNO_2$	5,35	6,65	0,60	0,77
IV	95	198	5,46	$C_{14}H_{12}ClNO_2$	5,35	6,59	0,67	0,78
V	99	240—1	5,42	$C_{14}H_{12}ClNO_2$	5,35	6,62	0,63	0,78
VI	84	236—7	4,91	$C_{13}H_9Cl_2NO_2$	4,96	6,31	0,64	0,78
VII	95	194—5	4,81	$C_{13}H_9Cl_2NO_2$	4,96	6,26	0,67	0,78
VIII	96	179	4,83	$C_{13}H_9Cl_2NO_2$	4,96	6,29	0,65	0,79
XI	68	247—8	4,31	$C_{13}H_9BrClNO_2$	4,29	6,35	0,64	0,79
X	72	220	4,37	$C_{13}H_9BrClNO_2$	4,29	6,34	0,69	0,78
XI	78	237—8	9,69	$C_{15}H_{14}N_2O_4$	9,78	5,62	0,64	0,76
XII	82	140—1	10,01	$C_{15}H_{14}N_2O_4$	9,78	5,60	0,63	0,74

Note. R_{f_1} was determined in $CHCl_3$—acetone—AcOH (90:20:12) system, R_{f_2} in $CHCl_3$—propanol (100:50) system.

hydrogen bonds is also confirmed by a somewhat broadened stretching vibrations band of the NH group in the 3340-3305 cm^{-1} region. In the region of approximately 2900 cm^{-1}, these compounds show the blurred maximum of very broad resonance band, corresponding to the stretching vibrations of the hydrogen-bonded OH group. The presence of intense absorption bands in the 1580-1540 cm^{-1} range is explained by deformational vibrations of the NH group. The bands at 1520-1505 cm^{-1} for compounds XI, XII correspond to asymmetric and symmetric stretching vibrations of the nitro group.

The ionization constants of the compounds obtained, determined by potentiometric titration in a 60% aqueous dioxane, indicate that the pKa values are inappreciably influenced by substituents at the phenyl radical which does not contain a carboxylic group.

The biological investigation of I-XII showed that compounds I and II have an antifungal activity towards test culture of *Trichophyton rubrum* (minimal inhibiting concentration 500 μg/ml). Compounds XI and XII inhibit the growth of *Trichophyton rubrum*, *Trichophyton gypseum*, and *Microsporum canis* fungi (minimal inhibiting concentration 62.5 μg/ml). An antiexudative effect was observed in compounds II, IV, VII, XI (a 9-16% suppression of inflammation); the dichloro- and nitro derivatives of N-phenylanthranilic acid were found to be most active.

EXPERIMENTAL CHEMICAL PART

The IR spectra were run on the "Specord" spectrophotometer (GDR) in KBr tablets (concentration of compounds 1%). The TLC was carried out on the Silufol UV-254 plates.

N-(2-Methoxyphenyl)-4-chloroanthranilic Acid (I). A mixture of 4.8 g (0.025 mole) of 2,4-dichlorobenzoic acid, 12.3 g (0.1 mole) of o-anisidine, 4.8 g of anhydrous potassium carbonate, and 0.1 g of copper powder in 50 ml of DMFA is heated in a round-bottomed flask under reflux condenser for 10-12 h at 140-150°C. After the reaction mixture has been heated, it is diluted with 500 ml of water and acidified by concentrated HCl to pH 3.0. The precipitate is filtered in a warm state, washed on the filter with hot water, and dried. It is then crystallized from AcOH. Yield 95%.

Compounds II-XII are obtained in a similar way.

EXPERIMENTAL BIOLOGICAL PART

The method of dilution in dense culture medium — Subbaraud agar with glucose [11] was used for determining the antifungal activity. The final concentrations of the compounds studied were 500, 400, 300, 200, 100, and 50 μg per ml of the medium. Weighed samples of the compounds were dissolved in DMSO. The incubation was carried out in a thermostat at 28°C to complete development of the test cultures of the fungi in test tubes containing the solvent at the same concentration as in the experiments. Clinical strains of dermatophytes were used as test cultures of the fungi. The antiinflammatory activity was determined on a model of a formalin-induced edema by the method of Yu. E. Strel'nikov [7]. The experiments were carried out on white mice weighing 18-20 g each. The inflammation was induced by injection of 0.1 ml of a 2.5% formalin solution into the femural muscle of one of the paws of the animals. The compounds studied were introduced intragastrically in an amount of 100 mg per kg body weight of the animal 2 h before injection of formalin, and then 5 and 18 h after

introduction of the phlagogenic compounds. The degree of expression of the inflammation edema was judged from increase in weight of the inflamed and noninflamed paws of the animals of the experimental groups in comparison with the control. Six animals were used in each experiment.

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SYNTHESIS AND RADIOPROTECTIVE PROPERTIES OF CERTAIN DIOL LIPIDS

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It is known that lipid antioxidants maintain a constant level of oxidizing reactions in membranes of healthy cells [1]. On irradiation of a living organism, pathological changes occur in the cell membranes: peroxidation of the lipids, increase in permeability, etc. It seemed to be desirable to study the radioprotective properties of certain diol lipids, including those with the fragment of an antioxidant, since diol lipids can be considered as modified structural elements of the membranes [3].

In the present work, the synthesis of O,O-diacylated diols (IV-VI), containing the residue of gallic acid, is described, and the results of a comparison of their radioprotective activity with the activity of diol lipids (I, II), with no antioxidizing fragments, are given. Comparative data are also given on the radioprotective activity of O-acyl- and O-alkyldiols to clarify the influence of the nature of both the diol itself and its lipophilic residues. Since alkyl esters of polyols (VIII-XI) undergo enzymatic hydrolysis with more difficulty than the acyl derivatives of I and II, differences could also be expected in the biological properties of these compounds.

$$RO(CH_2)_nOR'$$

I — VI, VIII

I, II: R = H; III, IV: R = $COC_{15}H_{31}$; V, VI, VIII: R = $COC_6H_2(OMe)_3$-3,4,5; I—III: R′—$COC_{15}H_{31}$; IV: R′ = $COC_6H_2(OAc)_3$-3,4,5; V, VI: R′—$COC_6H_2(OMe)_3$-3,4,5; VIII: R′ = $C(=NC_6H_{11})NHC_6H_{11}$; I, V, VIII: $n = 2$; II — IV, VI: $n = 4$.

Monopalmitoylethylene glycol I was obtained from sodium palmitate and ethylene chlorohydrin [4]. In the reaction of butane-1,4-diol with palmitoyl chloride in benzene in the pres-

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