IMMUNOSTIMULANTS.

III. SYNTHESIS AND IMMUNOTROPIC ACTIVITY OF THE HYDROCHLORIDES OF BIS-BASIC ETHERS OF 4-SUBSTITUTED ALIZARINS

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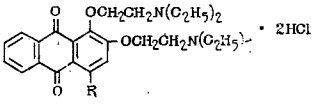
We have previously reported the synthesis [1-2] of several anthraquinone derivatives possessing immunostimulant and antitumor activity.

In continuation of the search for stimulants of immunity in malignant neoplasms amongst anthraquinones, based on a study of structure—activity relationships, we have synthesized compounds (I)-(III):



I: R=Br, II: R=Cl, III: R=NO_2

The starting material for the synthesis of these compounds was alizarin (IV). Reaction of this with toluene-p-sulphonyl chloride gave 2-toluene-p-sulphonylalizarin (V) [3]. Bromination or chlorination of (V) afforded 4-bromo-(VI) and 4-chloro-2-O-toluene-p-sulphonylalizarin (VII), which were hydrolyzed to 4-bromoalizarin (VIII) and 4-chloroalizarin (IX) [4].

Reaction of (IV) with benzoyl chloride afforded 1,2-dibenzoylalizarin (X) [5]. Nitration of (X) gave 0,0'-dibenzoyl-4-nitroalizarin (XI), which was hydrolyzed by boiling with sodium hydroxide solution to 4-nitroalizarin (XII) [4].

The position of the bromine in (VIII) was proven by conversion into 4-bromo-1-hydroxy-2-methoxyanthraquinone with dimethyl sulfate in alkali. A mixed melting point of this material with a sample obtained by brominating 1-hydroxy-2-methoxyanthraquinone [6] gave no depression.

The position of the chlorine in (IX) was proven by condensing (IV) with aniline in the presence of anhydrous sodium acetate at 190°C, followed by treatment of the reaction products with hydrochloric acid and isolation of 4-anilinoalizarin. We obtained 4-anilinoalizarin from compound VII. A mixed mp of both products did not give the depression temperature of the melt.

For compound XI the position of the nitrogen groups was revealed by condensation of XI with aniline in the presence of boric acid. When the reaction products were treated with an acidic saline solution, 4-anilinoalizarin was obtained. A mixed mp of this material with a sample synthesized from (VII) gave no depression.

Alkylation of (VIII), (IX), and (XII) was carried out in anhydrous media (toluene or xylene) in the presence of potassium hydroxide or sodium methoxide. The physicochemical properties of the aminoalkoxy-derivatives of the anthraquinones are shown in Table 1.

The structures of (I)-(III) were confirmed by IR spectroscopy. The IR spectra displayed the following absorption bands [7]: C=O at 1670-1665 cm^{-1}; C-O-C at 1000 cm^{-1}; and $CNHt_2$ at 1590-1560 cm^{-1}. The spectra of (I) and (II) displayed C-halogen absorption at 725-720 cm^{-1}, and bands due to asymmetrical and symmetrical vibrations of the nitro-group in (III) appeared at 1540 and 1345 cm^{-1}.

EXPERIMENTAL (PHARMACOLOGY)

The immunotropic effects of the drugs were studied in mice following immunodepression induced by 20-methylcholanthrene [8]. Compounds (I)-(III) were introduced in a single dose of 1/6 of the LD_{50}. On the fourth day following immunization by sheep erythrocytes, the hemolytic activity of the spleen cells and the blood serum were measured in comparison with the known immunostimulant tiloron [9]. The results are shown in Table 2, from which it will

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TABLE 1. Aminoalkoxy-derivatives of Anthraquinones

Compound	Melting point (°C)	Yield, %	Found, %				Molecular formula	Calculated, %			
			C	H	N	Hae		C	H	N	Hae
I	191—193	32	53,07	5,88	5,00	25,15	$C_{26}H_{33}BrN_2O_4 \cdot 2HCl$	52,89	5,99	4,74	25,54
II	207—209	35	57,38	6,22	5,11	18,91	$C_{26}H_{33}ClN_2O_4 \cdot 2HCl$	57,19	6,47	5,13	19,48
III	194—195	15	56,23	6,14	7,97	12,32	$C_{26}H_{33}N_3O_6 \cdot 2HCl$	56,11	6,39	7,55	12,74

TABLE 2. Effect of Aminoalkyl Derivatives of Anthraquinones on the Hemolytic Activity of Spleen Cells and Serum

Ep Experiment	Splenocytes		Serum	
	No. of lyzed erythrocytes x 10^6	%	No. of lyzed erythrocytes x 10^6	%
Control (methylcholanthrene)	4,30	100	1,10	100
Tiloron	5,30	123	1,30	118
Dihydrochloride I	3,83	89	1,09	99
II	3,27	76	1,07	97
III	5,55	129	1,57	143

Note: The compounds were administered following treatment with methylcholanthrene.

be seen that preliminary evaluation of (III) shows it to have greater immunostimulant activity than tiloron. It has previously been shown [1] that the activity of 3-nitro-1,2-bis/2-(diethylamino)ethoxy/anthraquinone dihydrochloride is somewhat lower than that of tiloron. It may therefore be concluded that the immunotropic activity of the above-mentioned compounds is associated with the presence of a nitro group in these molecules, and for this reason they are worthy of further study with respect to their immunostimulant properties.

Conversely, (I) and (II) intensify to some extent methylcholanthrene-induced depression.

EXPERIMENTAL (CHEMISTRY)

The IR spectra were recorded on a Perkin-Elmer-577 spectrometer (Sweden), in KBr disks.

The purity of the products was established by thin-layer chromatography on Silufol UV-254 plates (Czechoslovak SSR) using the solvent system benzene—chloroform—methanol (10:7:3). The benzene was previously saturated with ammonia.

2-Toluene-p-sulphonylalizarin (V). To a well-cooled mixture of 2.5 g (0.01 mole) of (IV) and 4 g (0.02 mole) of toluene-p-sulphonyl chloride in 15 ml of chloroform was added portionwise 4 ml of pyridine. The mixture was stirred for 1 h, and diluted with ethanol to give a yellow-orange precipitate which was filtered off, and recrystallized from alcohol—acetic acid (1:1). Recrystallization gave lustrous golden-yellow crystals of (V). Yield, 65-70%, mp 214-216°C. Found, %: S 8.05. $C_{21}H_{14}O_6S$. Calculated, %: S 8.1.

4-Bromo-2-O-toluene-p-sulphonylalizarin (VI). A mixture of 4 g (0.015 mole) of (V), 30 ml of glacial acetic acid, 2.4 g (0.03 mole) of anhydrous sodium acetate, and 5.52 g (0.07 mole) of bromine was boiled under reflux for $1^1/_2$ to 2 h. The solution was filtered hot, kept overnight, and the yellow acicular crystals which separated were crystallized from acetic acid. Yield, 88-90%, mp 177-178°C. Found, %: S 6.5 Br 16.0. $C_{21}H_{13}BrO_6$ S. Calculated, %: S 6.8, Br 16.9.

4-Chloro-2-O-toluene-p-sulphonylalizarin (VII). A mixture of 5 g (0.13 mole) of (V), 10 ml of nitrobenzene, 5 ml of sulphuryl chloride, and a crystal of iodine was heated on a water bath for 2 h. The nitrobenzene was removed by steam distillation, and the residue filtered off and recrystallized three times from acetic acid to give light yellow needles of (VII), mp 165-166°C. Yield 85-90%. Found, %: S 7.2, Cl 8.1. $C_{21}H_{13}ClO_6S$. Calculated, %: S 7.5, Cl 8.3.

4-Bromoalizarin (VIII). A solution of 1.5 g (0.003 mole) of (VI) in 30 ml of conc. H_2SO_4 was heated on a water bath for $1^1/_2$ to 2 h. The reaction mixture was poured into ice-water, and the light orange precipitate of (VIII) which separated was filtered off and crystallized from acetic acid. Mp 233-234°C, yield 90%. Found, %: Br 24.90. $C_{14}H_7BrO_4$. Calculated, %: Br 25.04.

IX was prepared similarly, mp 242-243°C, yield 80%. Found, %: Cl 12.7. $C_{14}H_7ClO_4$. Calculated, %: Cl 12.9.

1,2-Dibenzoylalizarin (X). A mixture of 15 g (0.062 mole) of (IV) and 82 ml of benzoyl chloride was heated under reflux in an oil bath at 200°C for 30 min. The reaction mixture was kept overnight, and the precipitate was filtered off and washed with light petroleum and hot ethanol. Recrystallization from methyl ethyl ketone gave yellow crystals of (X), mp 185-186°C, yield 90-95%.

O,O'-Dibenzoyl-4-nitroalization (XI). Three grams (0.006 mole) of finely ground (X) was added slowly with stirring to a mixture of 5.5 g of nitric acid (d 1.44 g/cm^3) and 8 ml of conc. H_2SO_4 at −5°C. The reaction mixture was stirred and further cooled for 2 h, and kept overnight. The contents of the flask were then poured onto ice, and the precipitate filtered off and recrystallized twice from acetic acid and once from ethanol. There was obtained (XI) as yellow needles, mp 230-231°C, yield 2 g (60%).

4-Nitroalizarin (XII). Three grams (0.003 mole) of (XI) was heated on a boiling water bath for 1 h with 70 ml of 10% NaOH. The mixture was cooled, weakly acidified with conc. HCl, and poured onto ice. The precipitate was filtered off and dried at 100°C to give 1.3 g (75%) of (XII), mp 289°C (sublimes). Found, %: N 4.7. $C_{14}H_7NO_6$. Calculated, %: N 4.9.

4-Bromo-1,2-bis-2-(diethylamino)ethoxyanthraquinone Dihydrochloride (I). Compound (VIII) (3.2 g, 0.01 mole) was suspended in 50 ml of xylene. A solution of 1.7 g (0.03 mole)

of KOH in 3.5 ml of water was added slowly, and the mixture boiled until all the water had been removed (Dean and Stark apparatus). The mixture was cooled to 50 to 60°C, and 2.8 g (0.02 mole) of diethylaminoethyl chloride in xylene was added. The mixture was boiled with stirring for 8 h, cooled, filtered, and the filtrate extracted repeatedly with 3 N HCl. The acid solution was neutralized with ammonia and extracted with ether. The ether extracts were dried over potassium hydroxide, the desiccant separated, and the extract acidified with ethereal hydrogen chloride. The precipitate of (XII) was separated and recrystallized 2-3 times from ethyl methyl ketone with the addition of ethanol.

II and III were similarly prepared, except that in the case of (III) the reaction was carried out by heating for 15 h in toluene in the presence of sodium methoxide. The products were crystallized from alcohol.

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SYNTHESIS OF DERIVATIVES OF PIPERIDINE AND DECAHYDROQUINOLINE AND THEIR ANALGESIC AND PSYCHOTROPIC PROPERTIES.

VII. N-SUBSTITUTED 2,3-DIMETHYL-4-PHENYL-4-HYDROXYPIPERIDINES AND THEIR PROPIONATES

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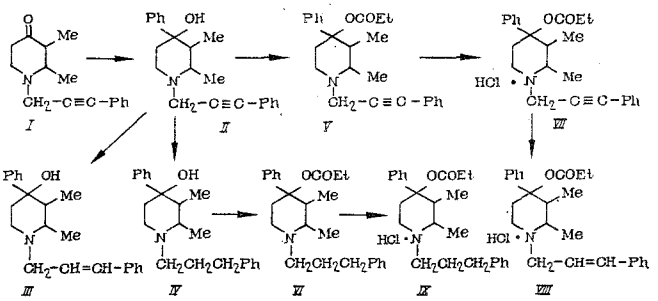
We have previously shown [1] that N-γ-phenylpropargyl (allyl- and propyl-)-2,3-dimethyl-4-phenyl-4-propionyloxypiperidines exhibit analgesic activity. To study the effect of the position of the methyl substituents in the piperidine ring on their physiological activity, we have synthesized analogous derivatives of 2,3-dimethylpiperidine [2, 3].

The starting material was N-γ-phenylpropargyl-2,3-dimethyl-4-piperidone (I) [4]. Reaction of this with phenyllithium afforded a mixture of two stereoisomers of N-γ-phenylprop-



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