AMIDES AND ANILIDES OF ANTHRANILIC ACID DERIVATIVES

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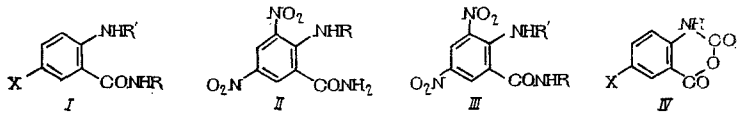
The synthesis and examination of biological activity of anthranilic acid derivatives is of justified interest. Amides of 3,5-dinitroanthranilic acid (IIa) and its N-alkyl-substituted derivatives are effective in treating coccidiosis of chickens [1]. N-Arylanthranilic acids display a tuberculostatic effect [2]. Substituted diphenylamines, similar in structure to N-arylanthranilic acids, possess an expressed anthelminthic activity [3, 4].

The preparation of amides and anilides of anthranilic acids (I-III) is described in this paper, and results are presented of the examination of these materials during coccidiosis of chickens and mice helminthoses.



I: a) X=R=R'=H; b) X=R'=H; R=C_6H_5; c) X=NO_2; R=R'=H; d) X=NO_2; R=C_6H_5; e) X=R=H; R'=C_6H_5

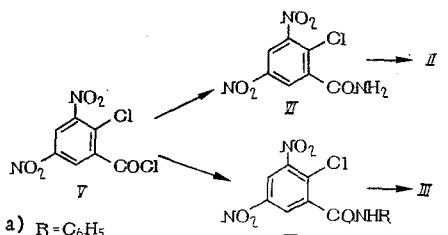
II: a) R=H; b) R=C_6H_5; c) R=4-$CH_3OC_6H_4$; d) R=4-ClC_6H_4; e) R=2-ClC_6H_4; f) R=2,4-$Cl_2C_6H_3$; g) R=3,4-$Cl_2C_6H_3$; h) R=2,5-$Cl_2C_6H_3$

III: a) R=R'=C_6H_5; b) R=C_6H_5; R'=H; c) R=4-$NO_2C_6H_4$; R'=H; d-g) everywhere R=2-Cl-4-$NO_2C_6H_3$; R'=d) H, e) CH_3, f) C_6H_5, g) 4-$CH_3OC_6H_4$

IV: a) X=H; b) X=NO_2

Compounds (Ia) and the main intermediate products in their synthesis, anhydrides (IV), were obtained by known methods [5-8], the use of which required further improvement. Anhydride (IVa) was synthesized by boiling anthranilic acid with ethyl chlorocarbonate and subsequent cyclization of N-carbethoxyanthranilic acid (without its isolation in a pure form) by reaction with acetyl chloride. Anhydrides were transformed into anthranilic acid derivatives (Ia-d) by heating with the corresponding amines. Amide (Ig) was isolated after treatment of N-phenylanthranilyl chloride [9] with ammonia.

The starting compound for synthesis of amides (II, III) was 3,5-dinitro-o-chlorobenzoyl chloride (V), which we obtained by boiling 3,5-dinitrosalicylic acid [10] with thionyl chloride in the presence of dimethylformamide.



V → II (via VI); V → III (via VII)

a) R=C_6H_5; b) R=4-$NO_2C_6H_4$; c) R=2-Cl-4-$NO_2C_6H_3$

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The amide of 3,5-dinitro-o-chlorobenzoic acid (VI) was transformed into anthranylamides (II) by boiling with an alcohol solution of an equimolecular amount of the corresponding aniline in the presence of potassium acetate (method A) or by heating with excess aromatic amine in dioxane solution (method B). The latter method was also used to obtain anilides (VII) from (V) and an equimolecular amount of substituted aniline. Anilides (VII) were transformed into anilides (IIIb-e) by reaction with an aqueous or aqueous alcoholic solution of ammonia or methylamine.

N-Arylanilides (IIIa, f, g) were synthesized from anilides (VII) by method A. N-Phenylanilide (IIIa) was also obtained by reaction of (V) with aniline. Samples of (IIIa), obtained by various methods, melted at the same temperature (203-204°C) and did not give a depression in a mixed sample. The authors of [11] gave an mp of 160-161° for (IIIa), synthesized earlier from N-phenyl-3,5-dinitroanthranilyl chloride and aniline. Analytical data and IR spectra indicate that structure (IIIa) corresponds to the compound with mp 203-204°.

Amides of 2-phenoxy- and 2-p-chlorophenoxy-3,5-dinitrobenzamides (VIII and IX) [12] were synthesized for comparative examinations. The properties of the synthesized compounds are presented in Table 1; their purity was confirmed by thin layer chromatography, and the structure was confirmed by IR spectral data. The frequency of stretching vibrations of the carbonyl group of anthranylamides and anthranylanilides lies in the usual range of 1665-1690 cm^{-1}. The frequency shifts to 1710-1720 cm^{-1} for certain nitroanilides (IIIf, g, VIIb). Absorption bands in the region of 3000-3500 cm^{-1} correspond to the free and bonded hydrogen bond of the NH groups. A decrease in frequency of antisymmetrical and symmetrical stretching vibrations of the nitro group correspondingly to 1500-1525 and 1320-1335 cm^{-1} is characteristic for nitro- and dinitroanthranylanilides. All compounds have an absorption band in the interval of 735-755 cm^{-1}, which should possibly be associated with the presence of the nitro group [13].

The coccidiostatic effect of the preparations was confirmed on four-week-old chicks, infected with a mixed E. tenella (96%) and E. necatrix (4%) culture in an amount of 70,000 cocci per chick. The preparations were fed once per day in a dose of 200 mg per 1 kg of feed for 10 days from the moment of infection. The majority of compounds do not possess coccidiostatic activity in the used dose. 4'-Nitroanilide of 3,5-dinitroanthranilic acid (IIc) protects 60% of the chicks from loss at 100% mortality in the control.

The anthelminthic activity of compounds (I-III), (VI-IX) was studied on mice infected with laboratory strains of helminths H. nana and G. spumosa. The preparations were introduced per os in doses of 100-2000 mg per 1 kg of weight at one time as a suspension prepared in starch. All of the examined compounds do not affect nematode G. spumosa; however, many of them posses a certain activity in relation to cestode H. nana. 2'-Chloro-4'-nitroanilide of 3,5-dinitroanthranilic acid (IIId) was found to be most effective; in doses of 500-1000 mg/kg it expels 85-100% of helminths. Substitution of the amino group in this compound by a methylamino group leads to a decrease in the used dose to 200 mg/kg; however, the effectiveness of preparation (IIIe) decreases slightly in this case. It is possible that the anthranilic acid structure is not necessary for the appearance of an anthelminthic activity. The anilide of 3,5-dinitro-o-chlorobenzoic acid (VIIa, d) and amides (VIII) and (IX) are similar to (IIId) in anthelminthic effect. Compounds not containing two nitro groups (Ia-e) or the carboxamide group, for example, 2,4-dinitrodiphenylamine, are inactive. In contrast to all of the examined preparations, anilide (IIIf) was found to be highly toxic. In a dose of 5 mg/kg it caused loss of 30% of the test animals.

EXPERIMENTAL

IR spectra of the obtained materials were taken in suspensions in mineral oil on a UR-10 spectrophotometer. Chromatography was achieved in a mobile thin layer of silica gel in a hexane–chloroform–acetone (3:1:1) solvent system.

Isatoic Anhydride (IVa). A mixture of 2.75 g of anthranilic acid and 8.1 g of ethyl chlorocarbonate was boiled for 4 h, cooled, diluted with 15 ml of acetyl chloride, and boiled again for 14 h. The precipitate, separating out upon cooling, was separated, washed with alcohol, and recrystallized from acetone. Yield 1.8 g (5.5%), mp 239-240°; literature data [7], mp 240°.

Nitroisatoic Anhydride (IVb). In portions 1 g of (IVa) was added to 4 ml of nitric acid (d 1.48). The reaction mass was held for 2 days at 20° and poured into 50 g of an ice–water mixture. The precipitate was separated, washed carefully with water and a small amount of alcohol, and dried at 100°. Yield 1 g (78%), mp 244-245° (from alcohol); literature data [5, 14], mp 220-230, 244°.

TABLE 1. Amides and Anilides of Substituted Benzoic Acids

Compound	Length of reaction (h)	Yield (%)	Mp (deg)†	Found (%) C	Found (%) H	Found (%) N	Empirical formula	R_f	Calc (%) C	Calc (%) H	Calc (%) N
Ie	0,5	30*	126—7	73,40 73,32	5,81 5,96	13,01 12,99	$C_{13}H_{12}N_2O$	—	73,56	5,70	13,20
IIb	0,5	86	215—6	51,70 51,90	3,36 3,44	18,40 18,48	$C_{13}H_{10}N_4O_5$	0,41	51,65	3,33	18,54
IIc	1	72	218—9	50,70 50,33	3,65 3,49	17,14 17,32	$C_{14}H_{12}N_4O_6$	0,30	50,60	3,64	16,87
IId	1	80	236—7	46,75 46,89	2,66 2,87	16,45 16,52	$C_{13}H_9ClN_4O_5$	0,41	46,37	2,69	16,64
IIe	10	72	242—3	46,47 46,38	2,94 2,79	16,42 16,67	$C_{13}H_9ClN_4O_5$	0,38	46,37	2,69	16,64
IIf	6	79	214—5	42,29 42,29	2,54 2,66	14,41 14,67	$C_{13}H_8Cl_2N_4O_5$	0,41	42,07	2,17	15,10
IIg	3	59	213—4	42,04 42,07	2,21 2,15	15,13 15,30	$C_{13}H_8Cl_2N_4O_5$	0,41	42,07	2,17	15,10
IIh	35	75	211—2	41,70 41,68	2,27 2,28	14,83 14,88	$C_{13}H_8Cl_2N_4O_5$	0,40	42,07	2,17	15,10
IIIa	2	81	203—4	60,41 60,39	3,91 3,97	14,98 14,97	$C_{19}H_{14}N_4O_5$	0,74	60,31	3,73	14,81
III c	24	80	297—8	45,21 45,04	2,79 2,81	20,40 20,39	$C_{13}H_9N_5O_7$	0,64	44,96	2,61	20,17
III d	48	70	265—6	41,03 41,27	2,19 2,49	18,32 18,20	$C_{13}H_8ClN_5O_7$	0,64	40,90	2,11	18,35
III e	24	68	220—1	42,73 42,74	2,76 2,80	17,55 17,63	$C_{14}H_{10}ClN_5O_7$	0,60	42,49	2,55	17,70
III f	2	73	202—3	50,23 50,07	2,43 2,97	15,23 15,15	$C_{19}H_{12}ClN_5O_7$	0,68	49,85	2,64	15,30
III g	1	64	228—9	49,28 49,48	3,06 2,85	14,07 14,02	$C_{20}H_{14}ClN_5O_8$	0,65	49,24	2,89	14,36
VII a	3	69	177—8	48,36 48,21	2,87 2,79	13,38 13,41	$C_{13}H_8ClN_3O_5$	0,76	48,54	2,51	13,07
VII b	3	70	218—9	42,09 42,11	2,07 1,99	15,34 15,67	$C_{13}H_7ClN_4O_7$	—	42,58	1,93	15,28
VII c	5	78	203—4	38,75 38,76	1,96 1,82	13,38 13,56	$C_{13}H_6Cl_2N_4O_7$	—	38,92	1,51	13,97
VIII	1	45*	155—6	51,79 51,56	3,00 3,17	13,65 13,94	$C_{13}H_9N_3O_6$	—	51,49	2,99	13,86

*Yield is indicated from calculation based on the starting acid.
†Compounds (Ie) and (VIII) were crystallized from a 1:1 alcohol–water mixture; (IIb) was crystallized from a 5:1 acetone–water mixture; (IIc) and (IIIa), from a 1:1 acetone–alcohol mixture; (IId), from a 3:1 acetone–water mixture; (IIe), (IIIe, g), from acetone; (II*f*, g, h), from a 1:2 acetone–alcohol mixture; (IIIc, d), from dioxane; (IIIf), (VIIa, c), from ethyl acetate; (VIIb), from a 6:1 ethyl acetate–acetone mixture.

Upon mixing (IVa, b) with a tenfold amount by weight of 25% ammonia for 5 h at 50° the amide of anthranilic acid (Ia) in a yield of 62%, mp 109-110° (from chloroform) (literature data [5], mp 108°) and the amide of 5-nitroanthranilic acid (Ic) in a yield of 59%, mp 210-212° (from alcohol and acetone) were correspondingly obtained; literature data [5, 15], mp 200-210, 230°.

Reaction under the same conditions of (IVa, b) with a twofold amount by weight of aniline, instead of a 25% ammonia solution, yielded the anilide of anthranilic acid (Ib) in a yield of 59%, mp 128-129° (from benzene); literature data [5], mp 130°, and the anilide of 5-nitroanthranilic acid (Id) in a yield of 73%, mp 202-203° (from acetic acid); literature data [6], mp 201-203°.

3,5-Dinitro-o-chlorobenzoyl chloride (V). A mixture of 60 g of 3,5-dinitrosalicylic acid [10], 145 g of thionyl chloride, 210 ml of dry toluene, and 3 ml of dimethylformamide was heated carefully to 80°, held for 1 h at this temperature, and for 1 h at 100°, cooled, and evaporated in vacuum at a temperature not above 80°. The solid residue was recrystallized from ether. Yield 50 g (71%), mp 64° literature data [16], mp 62°.

Amides of N-Aryl-3,5-dinitroanthranilic Acids (II). Method A. A solution of 2.46 g (0.01 mole of (VI) [2], 0.01 mole of aromatic amine, and 0.98 g (0.01 mole) of melted potassium acetate in 15 ml of anhydrous

alcohol was boiled for several hours, cooled, and poured into a threefold amount by volume of water. The residue was separated, washed carefully with water, dried at 100°, and crystallized. Amides (IIb-d) were obtained in this way; anilides (IIIf, g) were obtained from anilide (VIIc).

Method B. A solution of 2.46 g (0.01 mole) of (VI) and 0.02 mole of aromatic amine in 10 ml of anhydrous dioxane was mixed at 100-110°, cooled, and diluted with a 30-fold volume of a 10% hydrochloric acid solution. The residue was separated and treated as in method A. Amides (IIe-h) were obtained in this way. Anilides (VIIa-c) were synthesized in an analogous way from 2.65 g (0.01 mole) of (V) and 0.01 mole of aromatic amine.

Anilide of N-Phenyl-3,5-dinitroanthranilic Acid (III-a). A solution of 2.65 g (0.01 mole) of (V) and 2.8 g (0.03 mole) of aniline in 5 ml of dioxane was held for 2 h at 20° and for 15 min at 50°, cooled, and diluted with a double volume of 30% methanol. The residue was separated and washed with 5% hydrochloric acid and water. Yield 3.3 g (88%), mp 203-204° (from alcohol and acetone).

Anilides of 3,5-Dinitroanthranilic Acids (IIIb-e). Anilide (VII) was mixed with a 30-fold by weight amount of solution, obtained by mixing one volume of ammonia with two volumes of ethanol. The reaction mass was maintained for 1-2 days at 20° and treated by method A. Anilide (IIIb) was obtained in this way, yield 72%, mp 218°; literature data [11], mp 218°. Anilides (IIIc-e) were obtained analogously.

Amide of 3,5-Dinitro-o-phenoxybenzoic Acid (VIII). A suspension of 1.25 g of 3,5-dinitro-o-phenoxybenzoic acid [17] in 2.5 ml of thionyl chloride and 10 ml of dry benzene was boiled for 1 h. The solution was evaporated in vacuum at a temperature not above 60°. The residue was dissolved in 6 ml of absolute dioxane and poured with stirring into a mixture of 12 ml of 25% ammonia and 12 g of ice. After 30 min the precipitate was separated and treated as normally. The amide of N-phenylanthranilic acid (Ie) was synthesized analogously from the corresponding acid chloride [9].

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