SYNTHESIS AND BIOLOGICAL ACTIVITY OF ANTIPYRIN-4-YLAMIDES OF ALKYL- AND ARALKYLOXAMOYLAMINOBENZOIC ACIDS

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Some acyl derivatives of 4-aminoantipyrine find use as medicinal preparations [1-5]. It has been shown previously [6] that on passing from 4-aminoantipyrine to its N-oxamoyl derivative the analgesic activity rises and the toxicity falls. It appeared of interest to study how the separation of the oxamoyl group (RNHCOCO) from the pyrazolone ring affects the biological activity. To solve this problem, we have synthesized antipyrin-4-ylamides of alkyl- and aralkyloxamoylaminobenzoic acids (VIII, IX) by the following route:

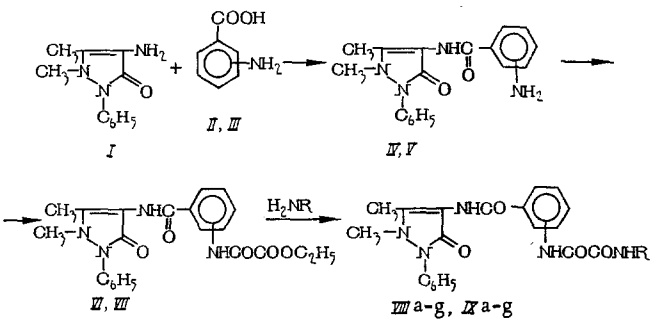

TABLE 1. Antipyrin-4-ylamides of Alkyl- and Aralkyloxamoylaminobenzoic Acids

Compound	Position of RNHCOCONH-	R	Yield (%)	Mp (°C)†	Found, %	Empirical formula	Calc., %
VIIIa	2	H	75,1	292—4	17,93	$C_{20}H_{19}5O_4$	17,80
VIIIb		CH_3	77,8	290	17,37	$C_{21}H_{21}5O_4$	17,19
VIIIc		n-C_4H_9	84,5	238—40	15,87	$C_{24}H_{27}5O_4$	15,59
VIIId		iso-C_4H_9	61,0	240	15,61	$C_{24}H_{27}5O_4$	15,59
VIIIe		n-C_5H_{11}	63,8	238—40	15,30	$C_{25}H_{29}5O_4$	15,10
VIIIf		$C_6H_5CH_2$	87,3	248	14,71	$C_{27}H_{25}5O_4$	14,48
VIIIg		$(CH_3)_2N(CH_2)_2^*$	63,9	214—5	18,71	$C_{24}H_{28}6O_4$	18,10
IXa	4	H	74,4	272—4	17,79	$C_{20}H_{19}5O_4$	17,80
IXb		CH_3	81,9	229—31	17,29	$C_{21}H_{21}5O_4$	17,19
IXc		iso-C_4H_9	66,7	224—6	15,71	$C_{24}H_{27}5O_4$	15,59
IXd		n-C_5H_{11}	79,0	200—2	15,35	$C_{25}H_{29}5O_4$	15,10
IXe		$C_6H_5CH_2$	69,0	214—6	14,62	$C_{27}H_{25}5O_4$	14,48
IXf		$(CH_3)_2N(CH_2)_2^*$	75,4	205—7	18,27	$C_{24}H_{28}6O_4$	18,10
IXg		$(C_2H_5)_2N(CH_2)_2^*$	52,7	200—2	17,23	$C_{26}H_{32}6O_4$	17,02

*Decomposition temperatures of the sulfates: (VIIIg) 140°C; (IXf) 155°C; (IXg) 140°C.

†All the compounds were crystallized from ethanol.

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The antipyrin-4-ylamide of p-aminobenzoic acid (V), under the name of "benzapyrine" is recommended for clinical trials as a fever-reducing and antiinflammatory agent [5]. However, the synthesis of this compound directly by the reaction of 4-aminoantipyrine (I) and p-aminobenzoic acid (III) in the presence of phosphorus oxychloride takes place only with a low yield [7]. For the reaction between (I) and the aminobenzoic acids (II, III) we used polyphosphoric acid; under these conditions the antipyrin-4-ylamides of aminobenzoic acids (IV, V) were obtained with a yield of about 74.5%. The reaction of (IV) and (V) with ethoxalyl chloride gave the antipyrin-4-ylamides of ethoxalylaminobenzoic acids (VI, VII). The latter were readily amidated with the formation of (VIII) and (IX) (see Table 1). These are water-insoluble crystalline substances; (VIIIg) and (IXf, g) possess basic properties and give readily water-soluble sulfates.

In contrast to the N-R-substituted amides of antipyrin-4-yloxamic acid (X), which possess analgesic is separated from it by an aminoaroyl residue. The results of pharmacological tests (Sangailo's method of mechanical stimulus) showed that in cases of 10-200 mg/kg substances (VIIIa-d) and (IXb) possess an analgesis activity comparable with the activity of amidopyrine; the derivatives of anthranilic acid (VIII) are more active than the derivatives of p-aminobenzoic acid (IX).

The LD_{50} of the substances tested amounted to 725-1450 mg/kg; i.e., they are 2-3 times less toxic than amidopyrine. The results obtained permit the assumption that the analgesic activity may be connected with spatial remoteness.

EXPERIMENTAL

Antipyrin-4-ylamide of Anthranilic Acid (IV). In small portions, a mixture of 20.5 g of anthranilic acid (II) and 30.5 g of (I) was added to 120 g of polyphosphoric acid, and the mixture was heated in a bath at 160-170°C for 2 h and cooled to 80-90°C, and, with stirring, 200 ml of water was carefully added to it. The solution was heated for 5 min with 3 g of activated carbon and was filtered, and the filtrate was made alkaline with 25% ammonia solution. The precipitate was filtered off and crystallized from ethanol. Yield 35 g, plates, mp 203-205°C. Found %: N 17.57. $C_{18}H_{18}N_4O_2$. Calculated %: N 17.39.

Antipyrin-4-ylamide of p-Aminobenzoic Acid (V). This was obtained similarly from (I) and (III). Yield 70%, plates, mp 279-280°C (from ethanol) [7].

Antipyrin-4-ylamide of p-(Ethoxalylamino)benzoic Acid (VII). To 9.6 g of (V) were added 40 ml of chloroform, 3 ml of triethylamine, and then 4.3 g (slight excess) of ethoxalyl chloride [the (V) passed into solution], and the mixture was heated to the boil, cooled, and shaken with 15 ml of water. The chloroform layer was separated off, dried, and evaporated on the water bath. Yield 12.7 g (≃ 100%), mp 235-237°C (from ethanol). Found %: N 13.56. $C_{22}H_{22}N_4O_5$. Calculated %: N 13.37.

Antipyrin-4-ylamide of N-Ethoxalylanthranilic Acid (VI). This was obtained similarly. Yield ≃ 100%; plates, mp 235-236°C (from ethanol). Found %: N 13.61. $C_{22}H_{22}N_4O_5$. Calculated %: N 13.37.

Antipyrin-4-ylamide of 2-Oxaloaminobenzoic Acid (VIIIa). A solution of 1 g of (VI) in 25 ml of ethanol was treated with 2 ml of ammonia solution. After 12 h, the bulk of the ethanol was distilled off, and the residue was filtered off and crystallized. Yield 0.7 g. Compounds (VIIIb-f) and (IXa-e) were obtained similarly.

Antipyrin-4-ylamide of 2-(β-Dimethylaminoethoxalylamino)benzoic Acid (VIIIg). A suspension of 2.5 g of (VI) in 10 ml of ethanol was treated with 0.5 g of N,N-dimethylethylenediamine and heated in the water bath. After 3 min, the solid matter passed into solution, and then heating was continued for another 12 min and the mixture was diluted in water, whereupon the reaction product precipitated in the analytically pure form. Yield 2.3 g. Compounds (IXf, g) were obtained similarly.

Sulfate of (VIIIg). A 0.1% ethanolic solution of sulfuric acid was added to a solution of 1 g of (VIII) in 5 ml of ethanol to give a pH of 7.0 (according to universal indicator paper). The salt was precipitated with ether. An amorphous mass deposited at first, and this rapidly changed into crystals; the precipitate was filtered off and washed with ether. The sulfates of (IXf, g) were obtained similarly.

LITERATURE CITED

1. Khronika VOZ [WHO Chronicle], 19, No. 11, 437 (1965).
2. P. A. Petyunin and L. A. Tetyueva, Med. Prom. SSSR, 1966, No. 3, 5.

3. M. Negwer, in: Organisch-chemische Arzneimittel und ihre Synonyma, Berlin (1967), pp. 412, 476, 516, 964.
4. T. P. Prishchep, Farmacol. i Toksikol., 1962, No. 1, 55.
5. A. S. Saranikov, Z. I. Voloshina. T. P. Prishchep, et al., Farmacol.i Toksikol, 1965, No. 3, 294.
6. T. P. Pastukhova, Farmacol. i Toksikol., 1967, No. 3, 326.
7. L. M. Semikolennyi, A. B. Solov'eva, G. M. Stepnova, et al., Zh. Vses. Khim. Obshchestva im. D. I. Mendeleeva, 8, 704 (1963).