11. V. B. Prozorovskii, Farmakol. Toksikol., No. 1, 115-118 (1962).
12. M. L. Belen'kii, Elements of the Quantitative Evaluation of Pharmacological Effects [in Russian], Riga (1959).

SYNTHESIS AND ANTIINFLAMMATORY ACTIVITY OF ACYL DERIVATIVES OF 4-AMINO- AND 4-(ISOPROPYLAMINO)ANTIPYRINE

E. V. Shmidt, T. P. Prishchep, A. M. Sedov,
N. A. Chernova, L. I. Alekseeva,
and V. M. Biryukova

UCC 615.276:547.77].0.12.1

In continuation of our investigations [1-4] on the synthesis of potential antiinflammatory preparations among the pyrazole group of compounds and establishment of a relationship between their structure and pharmacological properties, we synthesized N-protected aminoacylated (I-XI) and iodo-substituted benzoyl- and phenylacetyl derivatives (XII-XIX) of 4-aminoantipyrine and 4-(isopropylamino)antipyrine.

The reason for the synthesis of antipyrinyl amides of N-substituted amino acids of the fatty acid series was the presence of pronounced antiinflammatory properties in the 4-aminobenzoyl derivatives of 4-aminoantipyrine previously synthesized by us [1, 2], analgesic properties in certain derivatives of 4-aminoantipyrine acylated with N,N-dimethylamino acids of the fatty acid series [5, 6], and antipyretic properties of antipyrinylamide of aminoacetic acid [7]. The antiinflammatory activity of o- and p-iodo-substituted benzoic acid derivatives and their ammonium salts has been described in the literature [8]. We have already observed [2] a considerable increase in the antiinflammatory effect of N-antipyrinyl o-iodobenzamide, compared with that of a compound not substituted by iodine. Moreover, the isopropyl derivative of 4-aminoantipyrine has a higher antiphlogistic activity than 4-aminoantipyrine [9].

EXPERIMENTAL CHEMICAL PART

4-(Isopropylamino)antipyrine was prepared by reductive alkylation of 4-aminoantipyrine with acetone and zinc amalgam in an acid medium [10].

α-Amino acids were subjected to benzoyl and phthalyl protection by generally accepted methods [11, 12].

Iodine-substituted aromatic acids were synthesized by direct iodination or indirect introduction of iodine into the molecule of the corresponding carboxylic acid [11, 13-16].

The acylation of 4-amino- and 4-(isopropylamino)antipyrines was carried out in boiling dry benzene by free acids in the presence of phosphorus trichloride [4].

The IR spectra of the compounds were run on the UR-20 spectrophotometer (GDR) in the 400-4000 cm^{-1} region in mineral oil.

EXPERIMENTAL BIOLOGICAL PART

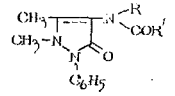
The antiinflammatory activity of the compounds was studied on rats of both sexes weighing 150-180 g each by determining their effect on the reactivity of capillaries [17], dextran edema [18], and on aseptic peritonitis induced by the introduction of silver nitrate [19], in comparison with butadione. To determine the permeability of the capillaries, the preparations were introduced 1 h before the injection of a dye. The intensity of the dextran edema was determined after the action of antipyrinylamides 3 h and 30 min after the administration of a proinflammatory agent.

The acute toxicity of antipyrinylamides was studied on noninbred male mice, weighing 18-20 g each, with single administration, and the rate of death of the animals was counted

Tomsk Polytechnic Institute. Tomsk Medical Institute. Translated from Khimiko-farmatsevticheskii Zhurnal, Vol. 16, No. 1, pp. 61-65, January, 1982. Original article submitted May 22, 1981.

0091-150X/82/1601-0051$07.50

TABLE 1. Acyl Derivatives of 2-Aminoantipyrine and 4-(Isopropylamino)antipyrine R = H (I-XIV), iso-C_3H_7 (XV-XIX), CH_3 (XX).



Compound	Name of acyl —COR'	Yield, %	mp, °C	Found, %			Empirical formula	Calculated, %		
				C	H	N		C	H	N
I	N-Benzoylaminoacetyl	50	189—90	65,63	5,53	15,45	$C_{20}H_{20}O_3N_4$	65,93	5,50	15,38
II	N-Benzoyl-α-amino-propionyl	60	167—9	67,09	6,00	14,46	$C_{21}H_{22}O_3N_4$	66,60	5,82	14,81
III	N-Benzoyl-α-amino-butyryl	60	200—2	67,67	6,64	14,20	$C_{22}H_{24}O_3N_4$	67,35	6,12	14,29
IV	N-Benzoyl-α-amino-isovaleryl	48	222—3	67,35	6,70	13,67	$C_{23}H_{26}O_3N_4$	67,98	6,40	13,80
V	N-Benzoyl-α-amino-capropyl	43	196—8	68,58	6,23	13,42	$C_{24}H_{28}O_3N_4$	68,57	6,66	13,33
VI	N-Benzoyl-α-amino-isocaproyl	60	197—9	68,59	6,73	13,44	$C_{24}H_{28}O_3N_4$	68,57	6,66	13,33
VII	N-Phthalyl-α-amino-propionyl	67	206—7	65,15	5,03	13,63	$C_{22}H_{20}O_4N_4$	65,35	4,95	13,86
VIII	N-Phthalyl-α-amino-butyryl	48	181—3	66,21	5,30	13,85	$C_{23}H_{22}O_4N_4$	66,03	5,26	13,46
IX	N-Phthalyl-α-amino-isovaleryl	58	209—10	66,70	5,50	12,84	$C_{24}H_{24}O_4N_4$	66,66	5,55	12,96
X	N-Phthalyl-β-phenyl-α-aminopropionyl	50	204,6	69,72	5,13	11,34	$C_{28}H_{24}O_4N_4$	70,00	5,00	11,70
XI	N-Acetyl-α-amino-butyryl	40	196—8	61,40	6,60	17,30	$C_{17}H_{22}O_3N_4$	61,82	6,66	16,97
XII	4-Iodobenzoyl	75	216—7	49,72	4,01	9,68	$C_{18}H_{16}O_2IN_3$	49,88	3,69	9,69
XIII	3-Iodo-4-methylbenzoyl	74	173—4	50,59	4,21	9,78	$C_{19}H_{18}O_2IN_3$	51,00	4,02	9,37
XIV	4-Iodophenylacetyl	87	210—1	50,88	4,10	9,55	$C_{19}H_{18}O_2IN_3$	51,00	4,02	9,37
XV	2-Iodobenzoyl	76	198—9	52,06	5,02	8,68	$C_{21}H_{22}O_2IN_3$	53,05	4,63	8,84
XVI	3-Iodobenzoyl	70	137—8	52,90	4,78	8,96	$C_{21}H_{22}O_2IN_3$	53,05	4,63	8,84
XVII	4-Iodobenzoyl	70	82—3	52,96	5,00	8,86	$C_{21}H_{22}O_2IN_3$	53,05	4,63	8,84
XVIII	3-Iodo-4-methylbenzoyl	60	161—2	53,82	5,24	8,91	$C_{22}H_{24}O_2IN_3$	53,98	4,90	8,58
XIX	4-Iodophenylacetyl	65	119—20	53,89	5,20	8,62	$C_{22}H_{24}O_2IN_3$	53,98	4,90	8,58
XX	4-Iodophenylacetyl	60	177—8	51,80	6,82	9,34	$C_{20}H_{20}O_2IN_3$	52,06	6,94	9,11

Note. Compounds VII-X, XII, were recrystallized from ethanol, XVII from aqueous ethanol, XIV from dilute acetic acid, and the remaining compounds from isopropanol.

TABLE 2. Antiinflammatory Activity and Toxicity of Acyl Derivatives of 4-Amino- and 4-(Isopropylamino)antipyrine (M ± m)

Compound	Reactivity of capillaries, min	Volume of exudate, ml	Increment in volume of inflamed extremity, % of initial			LD_{50}, mg/kg
			after 45 min	after 1 h 30 min	after 3 h	
I	4,11 ± 0,05 Pк 0,000	2,03 ± 0,31	206,0 ± 26,1	219,0 ± 19,8	122,0 ± 14,7	1,529 (1,318—1,774)
II	4,04 ± 0,03 Pк 0,000	2,13 ± 0,27	137,0 ± 19,2 Pк 0,061	169,0 ± 15,6 Pк 0,164	146,0 ± 21,8 Pк 0,01	2,483 (2,237—2,757)
III	3,20 ± 0,03 Pк 0,028	2,22 ± 0,39	125,0 ± 32,7 Pк 0,072	139,0 ± 31,3 Pк 0,099	128,0 ± 12,2 Pк 0,040	1,215 (0,799—1,847)
IV	5,21 ± 0,03 Pк 0,000	1,50 ± 0,43 Pк 0,350	54,0 ± 11,0 Pк 0,003 Pб 0,108	83,0 ± 17,2 Pк 0,007 Pб 0,241	100,0 ± 21,3 Pк 0,03	2,230 (1,806—2,676)
V	4,64 ± 0,05 Pк 0,000	1,50 ± 0,31 Pк 0,350	89,0 ± 15,1 Pк 0,018 Pб 0,269	91,0 ± 23,1 Pк 0,007 Pб 0,443	88,0 ± 19,3 Pк 0,009 Pб 0,579	3,500 (3,153—3,850)
VI	4,67 ± 0,03 Pк 0,000	1,52 ± 0,34 Pк 0,356	108,0 ± 11,4 Pк 0,019	127,0 ± 24,7 Pк 0,011	103,0 ± 17,7 Pк 0,02	2,210 (2,019—2,420)
VII	3,55 ± 0,03 Pк 0,000	2,30 ± 0,39	148,0 ± 15,1 Pк 0,042	177,0 ± 16,8 Pк 0,114	145,0 ± 10,5 Pк 0,031	3,285 (2,808—3,843)
VIII	3,70 ± 0,03 Pк 0,000	2,38 ± 0,29	208,0 ± 35,2 Pк 0,347	219,0 ± 47,0 Pк 0,394	196,0 ± 36,5 Pк 0,424	2,739 (2,323—3,232)
IX	3,31 ± 0,04 Pк 0,000	2,07 ± 0,64	151,0 ± 19,2 Pк 0,092	165,0 ± 10,5 Pк 0,016	130,0 ± 6,7 Pк 0,005	2,322 (1,903—2,336)
X	5,05 ± 0,09 Pк 0,000	1,65 ± 0,12 Pк 0,241	94,0 ± 10,5 Pк 0,007 Pб 0,313	98,0 ± 12,2 Pк 0,002 Pб 0,223	72,0 ± 9,4 Pк 0,001	1,935 (1,536—2,438)
XI	3,52 ± 0,05 Pк 0,000	2,08 ± 0,28	183,0 ± 8,4 Pк 0,184	186,0 ± 4,2 Pк 0,041	170,0 ± 6,3 Pк 0,08	2,182 (1,881—2,531)
XII	4,16 ± 0,19 Pк 0,000	2,13 ± 0,19	250,0 ± 31,4	216,0 ± 26,0 Pк 0,548	176,0 ± 31,8 Pк 0,315	2,665 (2,456—2,892)
XIII	3,21 ± 0,04 Pк 0,001	1,32 ± 0,30 Pк 0,211	207,0 ± 19,7 Pк 0,624	230,0 ± 13,9	166,0 ± 20,4 Pк 0,254	2,480 (2,292—2,683)
XIV	2,80 ± 0,5 Pк 0,002	1,70 ± 0,42 Pк 0,810	106,1 ± 14,3 Pк 0,054	120,1 ± 21,0 Pк 0,250	102,3 ± 18,9 Pк 0,250	1,359 (1,073—1,809)
XV	4,16 ± 0,10 Pк 0,000	1,05 ± 0,30 Pк 0,047	165,0 ± 28,9 Pк 0,193	191,0 ± 18,1 Pк 0,135	196,0 ± 13,3 Pк 0,335	1,830 (1,605—2,086)
XVI	3,75 ± 0,09 Pк 0,000	0,83 ± 0,09 Pк 0,000	114,0 ± 10,9 Pк 0,019	121,0 ± 3,3 Pк 0,000	116,0 ± 10,2 Pк 0,009	1,565 (1,423—1,722)
XVII	4,63 ± 0,07 Pк 0,001	0,95 ± 0,16 Pк 0,003	111,0 ± 21,0 Pк 0,027	128,0 ± 11,0 Pк 0,013	136,0 ± 18,0 Pк 0,009	1,029 (0,837—1,266)
XVIII	4,05 ± 0,11 Pк 0,000	1,43 ± 0,19 Pк 0,092	118,0 ± 27,2	131,0 ± 20,2 Pк 0,04	109, ± 15,1 Pк 0,006	2,550 (2,328—2,792)
XIX	2,98 ± 0,33 Pк 0,001	0,82 ± 0,36 Pк 0,000	100,1 ± 12,7 Pк 0,001 Pб 0,556	103,5 ± 10,6 Pк 0,003	93,5 ± 8,7 Pк 0,971	1,739 (1,527—2,001)
XX	3,33 ± 0,12 Pк 0,000	1,50 ± 0,42 Pк 0,370	93,5 ± 23,5 Pк 0,015 Pб 0,640	97,0 ± 12,6 Pк 0,002 Pб 0,372	78,0 ± 11,0 Pк 0,002	1,509 (1,271—1,903)
Butadione	5,01 ± 0,01 Pк 0,000	1,48 ± 0,13 Pк 0,018	114,0 ± 20,3 Pк 0,030	118,0 ± 11,6 Pк 0,001	98,0 ± 8,0 Pк 0,005	0,249 (0,206—0,301)
Control	2,81 ± 0,08	1,93 ± 0,08	229,0 ± 19,8	228 ± 13,7	206 ± 15,1	

Note. In brackets, the fluctuation limits are shown. [Meaning of Pк and Pб unknown — Publisher.].

for two days. In all the experiments, the preparations were administered intraperitoneally in the form of a suspension on a 1% potato starch mucilage in a dose of 1/10 LD_{50}, butadione in a dose of 100 mg/kg [20].

The experimental results were processed by the variation statistics method. The LD_{50} was calculated by the Litchfield and Wilcoxon method using the Roth modification [21].

Results and Discussion. The antipyrinylamides (Table 1) are crystalline colorless compounds, insoluble or sparingly soluble in water and in most organic solvents, and can be identified by melting points, elemental analysis, and IR spectra.

The IR spectra of antipyrinylamides are characterized by the presence of absorption bands corresponding to the stretching vibrations of the N—H bond of secondary amides (3290-3070 cm^{-1}), a band of amide I (1670-1650 cm^{-1}), amide II (1540-1490 cm^{-1}), amide III (1320-1200 cm^{-1}) of secondary amides, as well as an absorption band of the exocyclic carbonyl group of the heterocyclic ring (1730-1680 cm^{-1}).

The compounds studied have antiinflammatory activity (Table 2) whose expression is found in a definite dependence on the chemical structure. Thus, for the antipyrinylamides of protected amino acids, the nature of the protecting group is important: The phthalyl protection of the amino group (VII-IX), compared with that by the benzoyl group (IV-VI) leads to a lowering of the antiinflammatory effect. The activity of the derivatives of lower amino acids, containing 2-4 carbon atoms in the molecule (I-III) is inappreciable, irrespective of the nature of the protecting group. Derivatives of amino acids with 5 and 6 carbon atoms displayed an activity similar to that of butadione in the case of benzoyl protection (IV-VI).

The introduction of phenyl radical into the derivatives of α-alanine (transition from VII to X) intensifies the antiphlogistic action. The presence of the isopropyl radical in the 4-position of 4-aminoantipyrine leads to an increase in the antiflammatory effect of 4-(isopropylamino)antipyrinylamides of iodine-containing aromatic acids (XV-XIX) compared with nonalkylated analogs (XII-VIV). The position of the iodine atom in the aromatic ring (XV-XVII) and the transition from an aromatic to aliphatic acid (XVII, XIX) did not appreciably influence the antiphlogistic activity of the compounds. With respect to the effectiveness of action, 4-isopropylaminoantipyrinylamides of 3- and 4-iodobenzoic acids, 3-iodo-4-toluic acid and 4-iodophenylacetic acid closely resemble butadione.

There is a definite correlation between the ability of several acyl derivatives of substituted pyrazolone (IV-VI, X, XVI-XVII, XX) to effect the exudation process of genetically different experimental models and decrease the permeability of the vessels. This makes it possible to assume that these compounds act as inhibitors of biogenic compounds like histamine, serotonin, bradykinin, and active globulins [22-24] participating in the inflammation biogenesis.

Compared with butadione, antipyrinylamides have a lower acute toxicity. According to the factors studied, the antiinflammatory effect of the newly synthesized compounds is not superior to that of butadione, but the lower toxicity is advantageous; the last serves as a confirmation for the hypothesis that the toxicity of preparations becomes lower when the free amino group is acylated [3].

LITERATURE CITED

1. T. P. Prishchep, Farmakol. Toksokol., No. 1, 55-62 (1962).
2. A. S. Saratikov, G. M. Stepnov, E. V. Shmidt, et al., Izv. Sibirsk. Otd. Akad. Nauk SSSR, Ser. Biol. Nauk, No. 12, 84-90 (1965).
3. A. S. Saratikov, T. P. Prishchep, and V. E. Yavorovskaya, Antiinflammatory Agents of the Pyrazole Group [in Russian], Tomsk (1975), p. 197.
4. A. S. Saratikov, E. V. Shmidt, V. E. Yavorovskaya, et al., Khim.-farm. Zh, No. 8, 58-63 (1978).
5. W. Chiti, Farm. Ed. Sci., 15, 679-686 (1960).
6. M. Barattini, Minerva Med., 52, 3418-3420 (1961).
7. German Pat. No. 357752; Chem. Zbl., II, 575 (1922).
8. L. S. Salyamon, in: Handbook on Pharmacology [in Russian], N. V. Lazarev, ed., Vol. 2 Leningrad (1961), pp. 92-94.
9. A. Skita, F. Keil, and W. Stuhmer, Ber. Dtsch. Chem. Ges., 75, 1696-1698 (1942).
10. M. Erlenbach and A. Sieglitz, British Pat. No. 693249; Chem. Abstr., 49, No. 2521 (1955).
11. Weygand-Hilgetag, Experimental Methods in Organic Chemistry [Russian translation], Moscow (1965), pp. 301, 431.
12. J. Greenstein and M. Winitz, Chemistry of the Amino Acids, Wiley (1961).
13. W. Wachter, Ber. Dtsch. Chem. Ges., 26, 1744 (1893).
14. B. V. Tronov and A. N. Novikov, Zh. Obshch. Khim., 23, 1022 (1953).
15. B. T. Slusarchuk and A. N. Novikov, Izv. Tomsk. Politekh. Inst., 175, 38-39 (1971).
16. A. M. Sedov and S. A. Bebeshko, Ref. Zh. Khim., No. 5Zh 124DP (1978).
17. P. P. Golikov, Farmakol. Toksikol., No. 6, 742-743 (1964).
18. E. A. Usachev, in: Study Papers on Biologically Active Products of Organic Synthesis [in Russian], Perm' (1966), pp. 70-76.
19. S. S. Liberman and L. N. Yakhontov, Antiinflammatory Agents [in Russian], Moscow (1973), p. 68.
20. I. M. Sharapov, in: Butadione [in Russian], Moscow (1958), p. 23.
21. M. L. Belen'kii, Elements of Quantitative Evaluation of Pharmacological Effect [in Russian], 2nd Edition, Leningrad (1963), pp. 71, 81.
22. C. Lapiere and J. Lecomte, C. R. Soc. Biol., 153, 1088-1090 (1959).
23. J. Skidmore and M. Whitehouse, Biochem. Pharmacol., 16, 737-751 (1967).
24. B. V. Polushkin, "Allergy reactions," Doctoral dissertation, Novosibirsk (1971).