RESEARCH ON NEW 4-AMINOANTIPYRINE ANTIPHLOGISTICS

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Khimiya Geterotsiklicheskikh Soedinenii, Vol. 3, No. 1, pp. 135–137, 1967

UDC 547.775

17 Acylalkyl derivatives of 4-aminoantipyrine (1-phenyl-2, 3-dimethyl-4-aminopyrazolone-5) are synthesized with a view to discovering antiphlogistics, febrifuges, and analgesics. The compounds were prepared by acylating 4-alkylaminoantipyrines with chlorides of substituted aromatic acids in benzene in the presence of aqueous potassium carbonate.

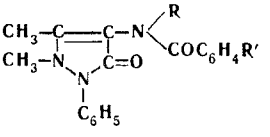
Use of 4-aminoantipyrine derivatives with antiphlogistic, febrifuge, and analgesic actions is widespread in medicine. Aminoantipyrine itself has febrifugal action, but because of its toxicity it has not come into extensive use. Dialkylation of this compound [1], and later monoalkylation [2], led to the preparation of actual medicinals, e.g., amidopyrine, analgin, melubrin, etc., which today play a leading part in the treatment of rheumatism. There has also been described preparation of a series of acyl derivatives of 4-aminoantipyrine, where it was acylated with aliphatic and aromatic acids in the presence of phosphorus trichloride, or else by the anhydrides of the acids or the acid halides [3–6]. Pharmacological tests on antipyrylamides showed that they have febrifugal and antiphlogistic action, and that some of them such as 4-(4'-aminobenzoyl)aminoantipyrine, 4-(2'-hydroxybenzoyl) aminoantipyrine, and 4-isovalerylaminoantipyrine, are better than butadione and amidopyrin, and have considerably lower toxicities.

Investigations [2] showed that introduction of an alkyl group into the amino group of aminoantipyrine greatly increases the analgesic action. For example isopropylaminoantipyrine has more than twice the analgesic action of antipyrine and 4-aminoantipyrine. Hence it was of interest to synthesize aminoantipyrine derivatives, with one hydrogen in the amino group substituted by an alkyl group, and the other by an acyl one. A small number of N-alkylacyl derivatives of 4-aminoantipyrine are known. Papers [8–10] describe a number of 4-alkylaminoantipyrine derivatives obtained by acylation with aliphatic acids. We previously acylated 4-methylaminopyrine with aromatic acids [11]. Pharmacological tests carried out at the Tomsk Medical Institute showed that almost all the N-methylantipyrylamides synthesized exceeded in antiphlogistic activity amidopyrine, and that some of them were better than butadione.

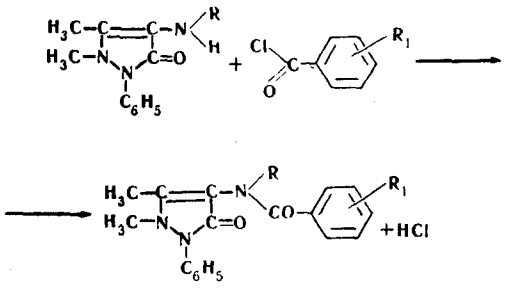
The present paper describes the synthesis of a number of N-alkylantipyrylamides of aromatic acids, the 4-alkylaminoantipyrines used being 4-methyl- and 4-ethylaminoantipyrine. 4-Methylaminoantipyrine was synthesized by a known route [12], dimethyl sulfate alkylation of the disodium salts of sulfaminoantipyrine. We successfully applied this method to the preparation of 4-ethylaminoantipyrine, alkylation being run in chlorobenzene and followed by hydrolysis of the sulfo group and isolation of the amine. The amines were purified by forming solutions of the hydrochlorides, then washing with organic solvents (chloroform, benzene).

N-Alkylantipyrylamides were prepared by reacting chlorides of aromatic acids with 4-alkylaminoantipyrine in benzene in the presence of aqueous potassium carbonate solution.

Aminoacyl Derivatives of 4-Alkylaminoantipyrines



Run number	R	R′	Mp, °C	Formula	N, % found	N, % calculated	Yield, %
1	CH_3	*o*-OH	199	$C_{19}H_{19}N_3O_3$	12.41	12.41	98
2	CH_3	*p*-Br	122	$C_{19}H_{18}BrN_3O_3$	10.76	10.50	96
3	CH_3	*o*-Br	138	$C_{19}H_{18}BrN_3O_2$	10.36	10.50	95
4	CH_3	*m*-Br	136	$C_{19}H_{18}BrN_3O_2$	10.25	10.50	94
5	CH_3	*o*-Cl	136	$C_{19}H_{18}N_3O_2Cl$	11.87	11.81	96
6	CH_3	*m*-Cl	131	$C_{19}H_{18}N_3O_2Cl$	11.52	11.81	96
7	CH_3	*o*-NH_2	176	$C_{19}H_{20}N_4O_2$	16.54	16.66	98
8	CH_3	*m*-NH_2	169	$C_{19}H_{20}N_4O_2$	16.92	16.66	98
9	C_2H_5	*p*-Cl	111	$C_{20}H_{20}N_3O_2Cl$	11.61	11.39	93
10	C_2H_5	H	147	$C_{20}H_{21}N_3O_2$	12.70	12.65	95
11	C_2H_5	*p*-NO_2	161	$C_{20}H_{20}N_4O_4$	14.73	14.86	96
12	C_2H_5	*o*-NO_2	165	$C_{20}H_{20}N_4O_4$	14.63	14.86	97
13	C_2H_5	*m*-NO_2	144	$C_{20}H_{20}N_4O_4$	14.68	14.86	96
14	C_2H_5	*p*-NH_2	207	$C_{20}H_{22}N_4O_2$	16.20	16.02	97
15	C_2H_5	*o*-NH_2	218	$C_{20}H_{22}N_4O_2$	16.25	16.02	97
16	C_2H_5	*m*-NH_2	172	$C_{20}H_{22}N_4O_2$	15.81	16.02	97
17	C_2H_5	*o*-OH	177	$C_{20}H_{21}N_3O_3$	12.13	11.96	98



Nitroacyl derivatives of 4-alkylaminoantipyrine were reduced to the corresponding aminoacyl derivatives with zinc dust in hydrochloric acid.

The N-alkylantipyrylamides are crystalline substances which are readily soluble in alcohols and ketones, less soluble in aromatic solvents, and almost insoluble in aliphatic hydrocarbons. They were purified by recrystallizing from ethanol or benzene.

The table gives the properties of the compounds prepared.

EXPERIMENTAL

4-Ethylaminoantipyrine. 0.05 mole diethyl sulfate was added to a suspension of 0.1 mole dry disodium salt of sulfaminoantipyrine in 50 ml dry chlorobenzene, and the mixture stirred and refluxed for 5 hr at 104–105°. The medium must be alkaline. Then the products were cooled to 60°, 50 ml 50% H_2SO_4 added, and the whole heated at 90° for 2 hr. After cooling the acid solution of 4-ethylaminoantipyrine was separated from the chlorobenzene, brought to pH 4–5 with alkali, treated with benzaldehyde to remove unreacted aminoantipyrine, and neutralized to give an oil which was the ethylaminoantipyrine, which was separated off after standing, yield 83–85%.

For purification 0.1 mole ethylaminoantipyrine was dissolved in 20 ml water, HCl added to bring the solution to pH 5, the solution shaken in a separatory funnel with 30 ml $CHCl_3$ in all in 2–3 lots, and the chloroform removed after standing. The aqueous solution was raised to pH 8 with acid. 4-Ethylaminoantipyrine was obtained as a slightly yellow oil, which crystallized on standing, mp 59°, yield 94.96%. 4-Methylaminoantipyrine was purified similarly. It formed colorless crystals mp 81°, yield 94–96%.

N-Alkylantipyrylamides. 0.07 mole K_2CO_3, as a 50% aqueous solution, was added to a solution of 0.1 mole 4-ethyl(methyl)aminoantipyrine in 100 ml benzene, the whole stirred, and 0.11 mole of the appropriate acid chloride in benzene added gradually. The temperature of the reaction mixture rose spontaneously to 40°, where it was held for 20 min. Then 50 ml water was added, the mixture stirred, the benzene solution separated off; on cooling the crystalline product separated from it.

Aminoacyl derivatives of 4-alkylaminoantipyrines. 120 ml conc. HCl was added gradually to a suspension of 0.1 mole of the appropriate nitroacyl derivative of the 4-alkylaminoantipyrine plus 0.3 mole Zn dust in 200 ml water. Reduction proceeded for 20 min, and the solution lost its color. Excess Zn dust was filtered off, and the aminoacyl derivative was precipitated from solution with a solution of NaOAc.

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