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Synthesis of 4-Antipyryl Alkamine Ethers *

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A number of basic ethers have been prepared by the reaction of 4-hydroxyantipyrine with alkamine halides commonly used for the production of antihistamines.

Only a few ethers of 4-hydroxyantipyrine are reported in the literature. Of these, two alkyl ethers (a methyl and an ethyl ether) are described by Knorr and Pschorr [1]. The rest are nitrophenyl and substituted nitrophenyl ethers prepared by Kaufmann *et al.*[2] In all these cases, the method of etherification was the same. 4-Hydroxyantipyrine was allowed to react with the requisite alkyl or nitrophenyl halide in the presence of sodium methoxide or ethoxide.

In the hope of obtaining compounds with a simultaneous antipyretic and antihistaminic effect, some alkamine ethers of 4-hydroxyantipyrine were prepared for pharmacologic evaluation. The present paper is concerned with the synthesis of these compounds.

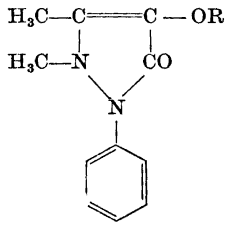
An attempt to use 4-bromoantipyrine for the etherification failed, obviously owing to the poor reactivity of the "aromatically" substituted bromine atom. After reflux with dimethylaminoethanol or its sodium compound in dry toluene for 24 h, the 4-bromoantipyrine was recovered unchanged.

The method used by Knorr and Pschorr [1], with 4-hydroxyantipyrine as starting material, although successfully employed by us for the preparation of 4-antipyryl benzyl ether, did not work with alkamine halides. In spite of the markedly phenolic character of the 4-hydroxyantipyrine, the formation of N,N,N′,N′-tetra-alkylpiperazinium dihalides quite outbalanced the etherification reaction. An attempt to carry out the condensation of 4-hydroxyantipyrine with an alkamine halide in the presence of pyridine was also unsuccessful. In this case, an alkamine pyridinium halide hydrohalide was formed, as observed already by Kratzl and Berger [3] when studying the corresponding condensation with 4-aminoantipyrine.

The etherification could be effected satisfactorily, if the sodium compound of 4-hydroxyantipyrine was prepared by means of sodium amide in dry toluene and the condensation carried out under anhydrous conditions (method A).

* New features disclosed in this paper are covered by a pending Finnish patent application.

Table 1. Alkamine ethers of 4-hydroxyantipyrine



R	Free amine	Mono-oxalate								
		Formula	Yield[e] %	M.P. °C	Analyses					
					Calc.			Found		
					C	H	N	C	H	N
$(CH_3)_2NCH_2CH_2$-	M.p.65°C[a,b]	$C_{17}H_{23}O_6N_3$	84	153[c]	55.88	6.35	11.50	55.47	6.44	11.57
$(C_2H_5)_2NCH_2CH_2$-	Oil	$C_{19}H_{27}O_6N_3$	66	123[d]	58.00	6.92	10.68	57.81	7.08	10.68
$(CH_3)_2NCH_2CH(CH_3)$-	Low melting solid[a]	$C_{18}H_{25}O_6N_3$	74	170[d]	56.98	6.64	11.08	56.57	6.76	10.86
$(CH_3)_2NCH_2CH_2CH_2$-	Oil	$C_{18}H_{25}O_6N_3$	71	158[d]	56.98	6.64	11.08	56.70	6.94	10.99
$H_2C(CH_2—CH_2)N—CH_2CH_2$-	Oil	$C_{20}H_{27}O_6N_3$	69	156[c]	59.24	6.71	10.37	59.01	6.98	10.25

[a] From petroleum ether. [b] From this compound a dihydrochloride, m.p. 180° (from ethanol), was also obtained. [c] From ethanol. [d] From acetone-methanol. [e] Calculated on the basis of 4-hydroxyantipyrine.

It turned out, however, that the best results in regard to both the yield and purity of the products could be obtained simply by refluxing 4-hydroxyantipyrine with the appropriate alkamine halide hydrohalide in dry acetone in the presence of anhydrous potassium carbonate (method B).

The ethers obtained were viscous liquids or low-melting solids, which were difficult to purify. For analysis they were converted into their mono-oxalates. Some data relating to these new compounds, all prepared according to method B, are presented in Table 1.

For further characterization, ultraviolet absorption spectra of the ethers were determined. These are represented in Fig. 1. For comparison, the corresponding spectra of 4-hydroxy-, -ethoxy- and -benzyloxyantipyrine are included.

One of the ethers, 4-antipyryl 2-dimethylaminoethyl ether, was allowed to react with methyl iodide at room temperature to give the corresponding quaternary ammonium salt. It has been shown by Knorr [4] that at 60° antipyrine also reacts with methyl iodide to form 1-phenyl-2,3-dimethyl-5-methoxypyrazolium-2 iodide. In order to decide, which of these two courses the reaction had taken, a test was made with antipyrine for comparison. It turned out that under the same reaction conditions, no iodide formation was observed

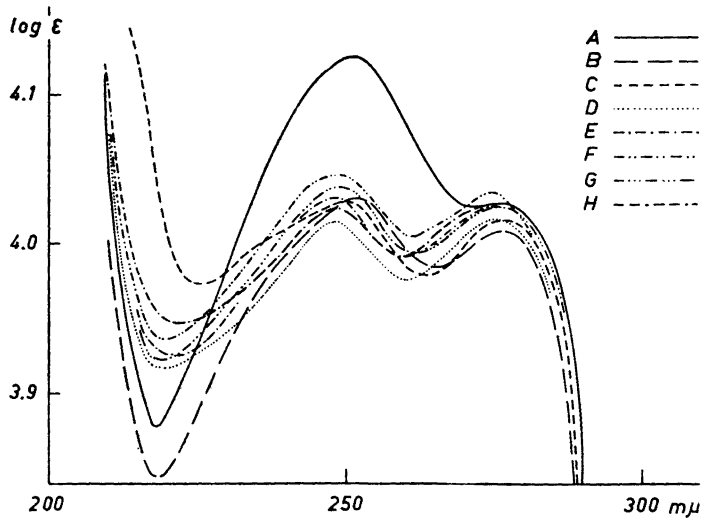


Fig. 1. Ultraviolet absorption spectra of 4-hydroxyantipyrine (A) and the following of its ethers: ethyl (B), benzyl (C), 2-dimethylaminoethyl (D), 2-diethylaminoethyl (E), 3-dimethylaminopropyl (F), 2-dimethylamino*iso*propyl (G) and 2-(N-piperidino)ethyl (H).

between antipyrine and methyl iodide after 3 days at room temperature, while from 4-antipyryl 2- dimethylaminoethyl ether an almost quantitative yield of the salt was obtained within one day. Accordingly, the salt in question must be β-(4-antipyryloxy)ethyltrimethylammonium iodide.

EXPERIMENTAL

All melting points were determined on a Kofler hot stage and are corrected. The microanalyses were performed by the Microanalytisches Laboratorium im Max-Planck-Institut, Mülheim (Ruhr), Germany. The ultraviolet data, from the Analytical Laboratory of Lääketehdas Orion Oy, are for solutions in ethanol (concentration 0.010—0.025 g per liter).

4-Hydroxyantipyrine. This was prepared from 4-dimethylaminoantipyrine (pyramidon) by the general route devised by Bockmühl [5]. Because no detailed information is to be found in the literature, a description of the procedure used by us is given:

Pyramidon (0.5 mole) was dissolved in a mixture of 200 ml of conc. hydrochloric acid (37.8 %) and 85 ml of water. This solution was added dropwise and with continuous agitation to a solution of sodium nitrite (2.0 mole) in 250 ml of water, while the temperature was kept below 0°. After the addition, the mixture was allowed to stand in the refrigerator overnight to complete the crystallization of the resultant intermediate, 1-diketobutyryl-1-phenyl-2-methyl-2-nitrosohydrazide monohydrate. This was filtered off, washed with 200 ml of cold water and then added to a solution of 130 g of sodium bisulfite in 700 ml of water. The mixture was allowed to stand at room temperature overnight. The crystallized 4-hydroxyantipyrine was filtered, washed with water and dried. The yield was 92 %, m. p. 182°.

4-Antipyryl alkamine ethers. Method A: 4-Hydroxyantipyrine (0.1 mole) and sodium amide (0.1 mole) in 300 ml of anhydrous toluene were heated and stirred for 4 h at 80°, all moisture being excluded. To this mixture a carefully dried solution of the appropriate

alkamine chloride (0.12 mole) in toluene was added. The mixture was heated at 80° for 25 h. The residue, after evaporation of the solvent *in vacuo*, was dissolved in chloroform, washed with dilute sodium hydroxide and water and dried over anhydrous sodium sulfate. After evaporation of the solvent, the ether remained as a viscous liquid. This was dissolved in ethanol, oxalic acid was added and the resulting oxalate was precipitated from the solution with ethyl ether.

Method B: A mixture of 4-hydroxyantipyrine (0.1 mole), an alkamine chloride hydrochloride (0.1 mole) and freshly ignited, fine-ground potassium carbonate (0.3 mole) was added to 350 ml of dry acetone. The mixture was refluxed for 2 days with continuous agitation. After cooling, the anorganic salts were filtered off. The filtrate was evaporated *in vacuo*, after which the remainder was worked up as in A.

4-Benzyloxyantipyrine. To a solution of 0.01 mole of sodium ethoxide in ethanol 0.01 mole of benzyl chloride and 0.01 mole of 4-hydroxyantipyrine were added. The mixture was refluxed for 4 h, after which it was evaporated to dryness and the remainder worked up as in the case of alkamine ethers. The yield was 79 %, m. p. 71—72° (from a mixture of petroleum ether and acetone). With method B, a yield of 72 % was obtained. (Found: C 73.63; H 6.29; N 9.71. Calc. for $C_{18}H_{18}N_2O_2$: C 73.45; H 6.16; N 9.71.)

4-Ethoxyantipyrine. To a solution of 0.25 mole of 4-hydroxyantipyrine in an equivalent amount of 0.1 N aqueous sodium hydroxide, 0.25 mole of diethyl sulfate was added gradually with shaking. After half an hour's heating at 60—70°, the mixture was extracted with chloroform and the chloroform solution worked up as in method A. The yield was 65 %, m. p. 53—54° (from a mixture of petroleum ether and acetone)(lit[1]. m. p. 60).

β-(4-Antipyryloxy)ethyltrimethylammonium iodide. To a solution of 2.75 g (0.01 mole) of 4-antipyryl 2-dimethylaminoethyl ether in 30 ml of absolute ether was added 1.42 g (0.01 mole) of methyl iodide. After one day standing at room temperature, the crystals formed were filtered off, washed with 10 ml of absolute ether and dried. The theoretical yield was obtained, m. p. 187°. After recrystallization from a mixture of acetone and methanol the salt was analyzed. (Found: C 45.90; H 5.73; N 10.12; I 30.38. Calc. for $C_{16}H_{24}O_2N_3I$: C 46.05; H 5.80; N 10.07; I 30.42.)

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