Reports of the Academy of Sciences of the USSR

CHEMISTRY

1964

SovietRxiv

Abstract

Full Text

Reports of the Academy of Sciences of the USSR
1964. Volume 154, No. 6

CHEMISTRY

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CATALYTIC SYNTHESIS OF ANTIPYRINE DERIVATIVES

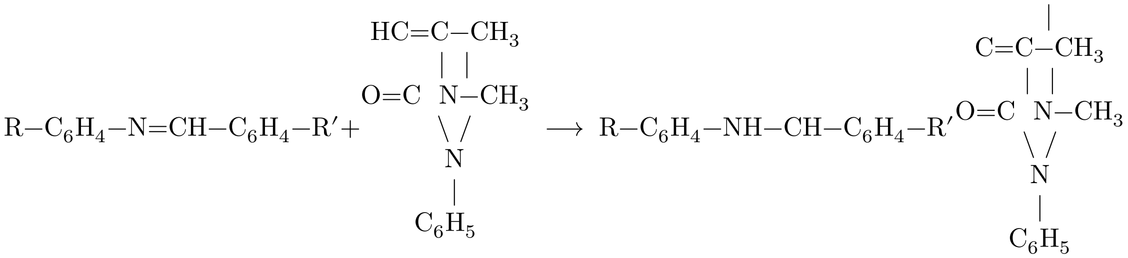
(Presented by Academician A. A. Balandin, 22 VIII 1963)

In recent years our laboratory has been studying the condensation reaction of Schiff bases with fatty-aromatic ketones in the presence of an acid catalyst. In the course of the reaction, fatty-aromatic ketones, as substances containing mobile hydrogen atoms at the α-carbon atom, add to the azomethine molecule, forming the corresponding β-arylaminoketones ($^{1-3}$).

In the present work, taking into account that the antipyrine molecule contains a mobile hydrogen at the fourth carbon atom, we decided to study the reaction of azomethines with antipyrine. Until now this reaction has not been described in the literature. At the same time, in studying this reaction it was expected that a variety of antipyrine derivatives could be obtained, which should be substances with potential physiological activity, since it is known that antipyrine itself is a substance with diverse physiological action. It is also appropriate to point out the broad use in modern medicine of such antipyrine derivatives as analgin and pyramidon (^{4,5}).

The latter also apparently explains why, in recent times, very great attention has been paid to the synthesis of new antipyrine derivatives (^{6,7}).

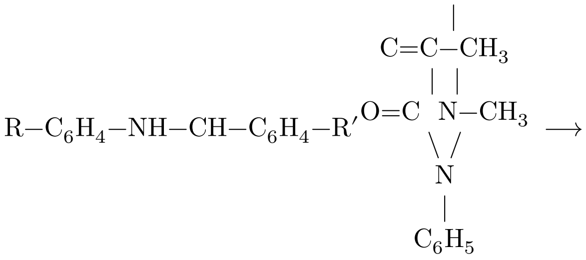
In the course of the investigation it proved possible to carry out the addition of antipyrine to the azomethine bond of a Schiff base, which may be expressed as follows:



$$R-C_6H_4-N=CH-C_6H_4-R' + \begin{array}{c} HC=C-CH_3 \\ |\quad | \\ O=C\quad N-CH_3 \\ \backslash\ / \\ N \\ | \\ C_6H_5 \end{array} \longrightarrow R-C_6H_4-NH-CH-C_6H_4-R' \begin{array}{c} | \\ C=C-CH_3 \\ |\quad | \\ O=C\quad N-CH_3 \\ \backslash\ / \\ N \\ | \\ C_6H_5 \end{array}$$

As the catalyst in this reaction we investigated the hydrochloride salt of the amine that is part of the azomethine molecule. Thus, in the course of the reaction we succeeded in developing a new method for the synthesis of arylamino derivatives of 4-methylantipyrine, compounds that have not been described at all in the contemporary literature.

Earlier ($^{1-3}$) it was indicated that β-arylaminoketones, when heated with concentrated hydrochloric acid, undergo hydramine cleavage into an amine and a chalcone. The 4-methylantipyrine derivatives synthesized in the present work, when heated with concentrated hydrochloric acid, also undergo cleavage, but only into benzylideneantipyrine derivatives, an aromatic amine, and an aromatic aldehyde:



[Reaction scheme showing formation of a bis-antipyrine derivative, with substituents *R* and *R*′, and liberation

Experimental Part

A reaction mixture consisting of 0.01 g-mol of the Schiff base and 0.01 g-mol of antipyrine in 15 ml of alcohol was heated to 50-60°, after which 0.5 g of the hydrochloride salt of the ester of *p*-aminobenzoic acid contained in the Schiff base was added. The reaction mixture was then placed in a refrigerator and kept there until crystals of the substance appeared. The solvent was filtered off, and the precipitate was treated with 5 ml of 25% aqueous ammonia. The products obtained were recrystallized from alcohol with benzene.

Cleavage with hydrochloric acid. 0.5 g of the substance, 4-(aminoaryl)-methylantipyrine, was dissolved in 5-7 ml of alcohol; 3 ml of concentrated hydrochloric acid was added, and the mixture was heated on a water bath for 10-15 min. The cooled solution was neutralized with 25% ammonia solution. The amine—the ester of *p*-aminobenzoic acid—was identified qualitatively, and the aromatic aldehyde by its characteristic odor.

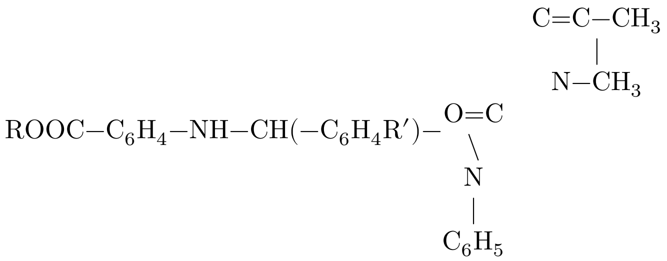
From compounds I-IV (Table 1), benzylidene-di-antipyrine was isolated. A mixed-melting-point test of benzylidene-di-antipyrine obtained upon cleav-

Table 1

Amino derivatives of antipyrine of the general formula A*; $R' = H$ (I-IV); Br (V–VIII)

No. of compound	R	Name of compound	Yield, %	M.p., °C	Empirical formula	N content, % calculated	N content, % found
I	CH_3	4-(*p*-carbomethoxyanilinophenyl)-methylantipyrine	54	175–176	$C_{26}H_{25}O_3N_3$	9.83	9.65; 9.70
II	C_2H_5	4-(*p*-carboethoxyanilinophenyl)-methylantipyrine	60	200–201	$C_{27}H_{27}O_3N_3$	9.52	9.40; 9.45
III	C_3H_7	4-(*p*-carbopropoxyanilinophenyl)-methylantipyrine	56	161–163	$C_{28}H_{29}O_3N_3$	9.23	9.15; 9.10
IV	C_4H_9	4-(*p*-carbobutoxyanilinophenyl)-methylantipyrine	58	152–154	$C_{29}H_{31}O_3N_3$	8.95	8.70; 8.75
V	CH_3	4-(*p*-carbomethoxyanilino-*p*-bromophenyl)-methylantipyrine	52	173–174	$C_{26}H_{24}O_3N_3Br$	8.30	8.15; 8.15
VI	C_2H_5	4-(*p*-carboethoxyanilino-*p*-bromophenyl)-methylantipyrine	55	164–165	$C_{27}H_{26}O_3N_3Br$	8.07	7.85; 7.89
VII	C_3H_7	4-(*p*-carbopropoxyanilino-*p*-bromophenyl)-methylantipyrine	59	148–150	$C_{28}H_{28}O_3N_3Br$	7.86	7.70; 7.66
VIII	C_4H_9	4-(*p*-carbobutoxyanilino-*p*-bromophenyl)-methylantipyrine	57	118–119	$C_{29}H_{30}O_3N_3Br$	7.66	7.48; 7.50

* General formula A:



$$\begin{array}{lll}
 & & \mathrm{C{=}C{-}CH_3} \\
 & & \quad\;| \\
 & & \mathrm{N{-}CH_3} \\
\mathrm{ROOC{-}C_6H_4{-}NH{-}CH({-}C_6H_4R'){-}} & \mathrm{O{=}C} & \\
 & \quad\backslash & \\
 & \;\mathrm{N} & \\
 & \;| & \\
 & \mathrm{C_6H_5} &
\end{array}$$

and synthesized (8) directly from benzaldehyde and antipyrine, no depression of the melting point was observed.

Analogously, from compounds V–VIII, *n*-bromobenzylideneantipyrine was obtained. The compounds obtained and their constants are given in Table 1.

In biological tests, a number of the compounds synthesized by us exhibited physiological activity.

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Received
14 VIII 1963

REFERENCES

1. N. S. Kozlov, A. D. Nikolaev, ZhOKh, **31**, 3894 (1961).
2. N. S. Kozlov, Z. A. Abramova, ZhOKh, **31**, 2236 (1961).
3. N. S. Kozlov, V. D. Pak, ZhOKh, **32**, 3386 (1962).
4. M. D. Mashkovskii, *Medicinal Agents*, Moscow, 1960, p. 73.
5. *State Pharmacopoeia of the USSR*, 1961, p. 60.
6. Ropp Frank, *J. Org. Chem.*, **26**, No. 5, 1565 (1961).
7. Takahashi Torizo, Konemotsu Ken, *Chem. and Pharmac. Bull.*, **6**, No. 1, 98 (1958).
8. F. Stolz, *Ber.*, **29**, 1826 (1896).

Note: Figure translations are in progress. See original paper for figures.

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