REACTION OF PYRYLIUM SALTS WITH AMINES OF THE BENZIMIDAZOLE SERIES

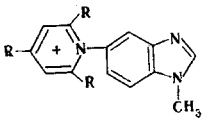
G. N. Dorofeenko, É. A. Zvezdina, M. P. Zhdanova, and I. A. Barchan

UDC 547.821.413'781.5

The reaction of pyrylium salts with primary amines of the benzimidazole series gives benzimidazolylpyridinium perchlorates. The bacteriostatic action of the synthesized preparations was investigated.

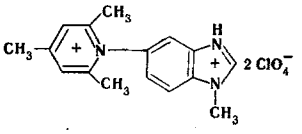
It is known that the reactivity of amino groups in the benzimidazole molecule is not equivalent. It seemed of interest to study the reaction of amines of the benzimidazole series with various pyrylium salts in order to obtain potentially biologically active compounds [1, 2].

The amino group in 1-methyl-5-aminobenzimidazole differs little from an aromatic amino group, and the latter, as in aniline [3], readily reacts with 2,4,6-trimethylpyrylium perchlorate (I) to give pyridinium salt IIa and its diperchlorate (IIc), which is formed by the reaction of IIa with unchanged I; this was confirmed by special experiments.



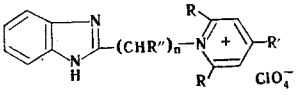
II a, b

II a R = CH_3; b R = C_6H_5



II c

A similar reaction with 2,4,6-triphenylpyrylium perchlorate (III) proceeds only in absolute dimethylformamide, and 2,4,6-triphenylpyridinium diperchlorate is not formed in this case. In view of the reduced basicity of the amino group, 2-aminobenzimidazoles do not form pyridinium salts with I but are converted to the perchlorates; this is accompanied by opening of the pyrylium ring. The pyridinium salt could not be obtained even in the reaction of the N-anion of 1-methyl-2-aminobenzimidazole, which has increased electron density, with I. On the other hand, 2-aminomethylbenzimidazole readily reacts with I [4] and other pyrylium salts. 2-β-Aminoethylbenzimidazole undergoes this reaction even more readily.



IV

IV a $n=1$, R = R′ = C_6H_5, R″ = H; IV b $n=1$, R = C_6H_5, R′ = R″ = H; IV c $n=2$, R = R′ = CH_3, R″ = H; IV d $n=2$, R = R′ = C_6H_5, R″ = H; IV e $n=1$, R = R′ = R″ = CH_3.

In contrast to IIa, IV do not form diperchlorates in the process of their formation from the appropriate aminobenzimidazoles and pyrylium salts. 2-α-Aminoethylbenzimidazole reacts with I to give the expected product (IIe), but the compound formed with III, possibly by virtue of the steric hindrance, decomposes, regardless of the reaction time, into 2,4,6-triphenylpyridine and 2-vinylbenzimidazolium perchlorate (V).

This transformation, which recalls the Hofmann degradation of quaternary ammonium bases [5], apparently proceeds via a similar mechanism. In fact, the hydrogen atom in the bridge carbon atom should be very labile under the influence of two strong electron-acceptor substituents and may split out a perchlorate

Rostov State University. Scientific-Research Institute of Physical and Organic Chemistry, Rostov-on-Don. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 12, pp. 1682-1685, December, 1973. Original article submitted June 27, 1972.

TABLE 1. Results of Microbiological Tests of Benzimidazolylpyridinium Perchlorates*

Compound	Salmonella typhosa	Flexner dysentery bacillus	Escherichia coli	Staphylococcus aureus
IIa	1 : 10000	1 : 10000	1 : 10000	—
IIb	1 : 10000	1 : 10000	1 : 10000	—
IIc	1 : 1000	1 : 1000	1 : 1000	—
IVa	1 : 10000	1 : 10000	1 : 10000	1 : 1000
IVc	—	—	—	—
IVd	1 : 100	1 : 100	1 : 100	1 : 1000
IVe	—	—	—	—

*The dashes in the table denote that the preparation is not active with respect to the indicated microorganism.

anion on heating to give perchloric acid. Of course, the molecules subsequently decompose to triphenylpyridine and 2-vinylbenzimidazole. The latter forms a perchlorate with the perchloric acid available in the reaction mixture.

The IR spectra of the compounds obtained (IIa-c and IVa-e) contain intense absorption bands of the pyridinium ring at 1620-1640 and 1555-1580 cm^{-1}, of the ClO_4 anion at 1100 cm^{-1}, and of the benzimidazole NH group at 3200-3400 cm^{-1}.

It is known [6] that pyrylium salts also react with secondary amines. However, 2,4,6-trimethylpyrylium perchlorate does not form aryl derivatives either at the pyrrole nitrogen atom of benzimidazole or with benzimidazoline and benzimidazolone.

We investigated the bacteriostatic action of the synthesized preparations by serial culture. The bacteriostatic action was studied with respect to Gram-negative and Gram-positive microorganisms. The bacterial cultures used in the experiments had the typical biochemical and serological properties. The data obtained are presented in Table 1.

Preparation IIa in vitro has a strong bacteriostatic effect on microorganisms of the enteric group in concentrations of 0.01 μg. Preparation IIb in the same concentration has a more moderate action. Preparation IIc is active with respect to the same group of microorganisms but in a concentration of 0.1 μg. Compound IVa is moderately active with respect to microorganisms of the enteric group at a concentration of 0.01 μg, and in larger doses has an effect on staphylococci. Preparations IVc and IVe are inactive, while IVd has a preferable effect on Staphylococcus aureus.

It is seen from the data presented that the most active preparations are those obtained from 5-aminobenzimidazole. Of the 2-aminoalkylbenzimidazole derivatives, only the compounds that contain phenyl substituents in the pyridinium ring are active.

EXPERIMENTAL

The IR spectra of mineral oil suspensions of the synthesized compounds were recorded with a UR-20 spectrometer.

Reaction of I with 1-Methyl-5-aminobenzimidazole. A mixture of 1.47 g (0.01 mole) of 1-methyl-5-aminobenzimidazole [7] and 2.23 g (0.01 mole) of I [8] in absolute alcohol was refluxed for 30 min. It was then cooled to precipitate 1.65 g (36%) of diperchlorate IIc with mp 278° (dec., from methanol). Found: C 42.6; H 4.2; Cl 15.4; N 9.1%. $C_{16}H_{18}ClN_3O_4 \cdot HClO_4$. Calculated: C 42.5; H 4.2; Cl 15.7; N 9.3%.

Ether was added to the mother liquor to precipitate 0.9 g (26%) of an oil that crystallized slowly to give perchlorate IIa with mp 128° (dec., from ethanol). Found: C 54.7; H 5.5; Cl 10.0; N 11.7%. $C_{16}H_{18}ClN_3O_4$. Calculated: C 54.6; H 5.2; Cl 10.1; N 11.9%.

Diperchlorate IIc was also obtained in quantitative yield by refluxing a solution of equimolecular amounts of monoperchlorate IIa and I in alcohol for 30 min.

1-(1-Methyl-5-benzimidazolyl)-2,4,6-triphenylpyridinium Perchlorate (IIb). This compound was similarly obtained by refluxing III [8] with 1-methyl-5-aminobenzimidazole in absolute dimethylformamide. The addition of ether precipitated an oily product, which formed solvates with ethanol and methanol on crystallization. Both solvates softened slightly on heating, after which they both solidified and melted identically

TABLE 2. 1-(2-Benzimidazolylalkyl)pyridinium Perchlorates (IV)*

Compound	mp, °C†	Recrystallization solvent	Empirical formula	Found, %				Calc., %				Yield, %
				C	H	Cl	N	C	H	Cl	N	
IVa	203	Ethanol	$C_{31}H_{24}ClN_3O_4$	69,7	4,8	6,9	7,6	69,2	4,5	6,6	7,8	68
IVb	213—214	Water	$C_{25}H_{20}ClN_3O_4$	64,7	4,6	8,0	9,4	65,0	4,4	7,7	9,1	44
IVc	170	Methanol	$C_{17}H_{20}ClN_3O_4$	55,3	5,8	9,5	11,5	55,8	5,5	9,7	11,5	72
IVd	128	Ethanol	$C_{32}H_{26}ClN_3O_4 \cdot 2H_2O$	65,1	5,2	6,3	7,0	65,4	5,1	6,0	7,1	83
IVe	174—175	Ethanol	$C_{17}H_{20}ClN_3O_4$	56,2	5,7	9,6	11,5	55,8	5,5	9,7	11,5	71

*All of the reactions were carried out in ethanol for 30 min.
†All of the compounds melted with decomposition.

at 294° (dec.). The yield was 61%. Found: C 67.0; H 5.8; Cl 5.5; N 6.2%. $C_{31}H_{24}ClN_3O_4 \cdot 2C_2H_5OH$. Calculated: C 66.7; H 5.8; Cl 5.6; N 6.7%. Found: C 66.1; H 5.1; Cl 5.6; N 6.8%. $C_{31}H_{24}ClN_3O_4 \cdot 2CH_3OH$. Calculated: C 65.8; H 5.4; Cl 5.9; N 7.0%. The dried product was very hygroscopic, and it was therefore not analyzed.

1-(2-Benzimidazolylmethyl)-2,4,6-triphenylpyridinium Perchlorate (IVa). 2-Aminomethylbenzimidazole, obtained by the action of an alcohol solution of sodium ethoxide [from 0.46 g (0.02 g-atom) of sodium] on 2.2 g (0.01 mole) of 2-aminomethylbenzimidazolium dihydrochloride, was refluxed in 25 ml of absolute ethanol for 30 min with 3.27 g (0.08 mole) of III. The mixture was cooled to precipitate 3.46 g (68%) of solvate $C_{31}H_{24}ClN_3O_4 \cdot 2C_2H_5OH$ with mp 147° (from ethanol). Prolonged drying in a pistol over P_2O_5 gave colorless crystals with mp 203° (dec.).

The remaining 2-substituted benzimidazoles (IVb-e) were similarly obtained.* Data on them are presented in Table 2. All of derivatives III gave solvates, while solvates were not formed with the other pyrylium salts.

Reaction of III with 2-(α-Aminoethyl)benzimidazole. 2-(α-Aminoethyl)benzimidazole, obtained by the action of an alcohol solution of sodium ethoxide [from 0.165 g (7.2 mg-atom) of sodium] on 0.84 g (3.6 mmole) of 2-(1-aminoethyl)benzimidazolium dihydrochloride, was refluxed for 30 min in 20 ml of absolute ethanol with 1.23 g (3 mmole) of III. The mixture was cooled and filtered to give a mixture of 2,4,6-triphenylpyridine [0.5 g (55%)] and unchanged III [0.17 g (14%)]. The filtrate was evaporated, and the residual oil was washed repeatedly with ether to separate an additional 0.27 g (29%) of 2,4,6-triphenylpyridine. The solidified oil contained 0.6 g (82%) of 2-vinylbenzimidazolium perchlorate (V) and apparently traces of the products of the polymerization of V. The mixture had mp 268° (dec., from glacial acetic acid). Found: C 44.4; H 3.9; Cl 14.2%. $C_9H_8N_2 \cdot HClO_4$. Calculated: C 44.2; H 3.7; Cl 14.5%.

Compound V was identical to 2-vinylbenzimidazolium perchlorate obtained from 2-vinylbenzimidazole, synthesized by the method in [11].

Reaction of I with 1,3-Dimethyl-2-benzimidazolinimine. A 1:2 mixture of the indicated compounds was refluxed for 2 h in ethanol. Cooling of the mixture precipitated 1,3-dimethyl-2-benzimidazolinimine perchlorate with mp 246° (from ethanol) in quantitative yield. Found: C 40.9; H 4.8; Cl 13.5%. $C_9H_{11}N_3 \cdot HClO_4$. Calculated: C 41.3; H 4.6; Cl 13.6%. The mother liquor contained excess imine and the product of opening of I.

LITERATURE CITED

1. C. H. Boehringer, Belgian Patent No. 621,344 (1963); Chem. Abstr., 60, 1712 (1964).
2. K. Thomae, British Patent No. 914,387 (1963); Chem. Abstr., 59, 13,955 (1963).
3. C. Toma and A. T. Balaban, Tetrahedron, 22, Supplement 7, 9 (1966).
4. G. N. Dorofeenko, A. N. Narkevich, Yu. A. Zhdanov, and T. G. Soroka, Khim. Geterotsikl. Soedin., 315 (1970).
5. H. J. Hagemeyer, J. Am. Chem. Soc., 71, 1119 (1949).
6. O. Diels and K. Alder, Ber., 60, 716 (1927).
7. F. Montanari, Gazz. Chim. Ital., 85, 981 (1955).
8. G. N. Dorofeenko, Yu. A. Zhdanov, V. I. Dulenko, and S. V. Krivun, Perchloric Acid and Its Compounds in Organic Synthesis [in Russian], Izd. Rostovsk. Univ. (1965), pp. 128, 131.

*The starting compounds were obtained by the methods in [9, 10].

9. L. Ceson and A. Day, J. Org. Chem., 27, 581 (1962).
10. B. Chatterjee, J. Chem. Soc., 2965 (1929).
11. C. G. Overgerger, B. Koster, and T. St. Pierre, J. Pol. Sci., 5, 1987 (1967)