SYNTHESIS OF 4H-1,3-BENZOXAZIN-4-ONIUM SALTS AND 4-H-1,3-BENZOXAZIN-4-ONES

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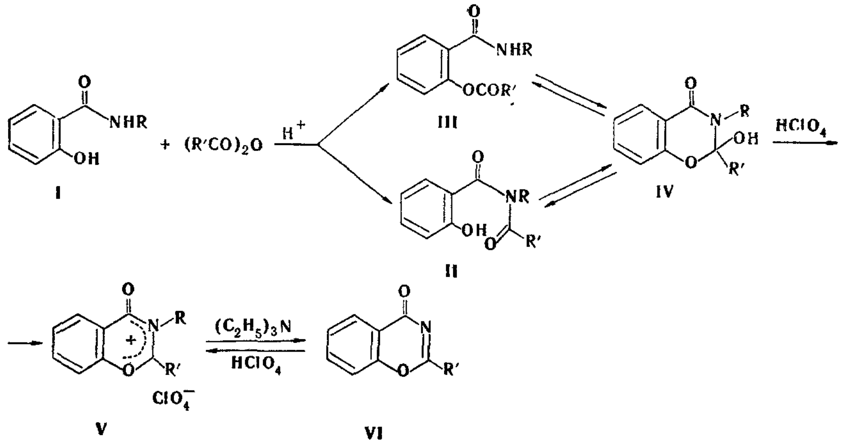
UDC 547.867.2.07

Salicylamide and its substituted derivatives react with aliphatic carboxylic acid anhydrides and perchloric acid to give 4H-1,3-benzoxazin-4-onium salts. These same compounds were obtained by acidic cyclization of O- and N-acylsalicylamides. The synthesized salts are converted to 2-substituted 4H-1,3-benzoxazin-4-ones by the action of triethylamine and are hydrolyzed by water to N-acylsalicylamides. The probable reaction scheme is examined.

In the present paper we propose a simple method for the synthesis of the previously unknown 4H-1,3-benzoxazin-4-onium salts from amide I (salicylamide, N-methylsalicylamide, and salicylanilide), an alkanecarboxylic acid anhydride, and perchloric acid.

Both N- and O-acylsalicylamides (II, III), which undergo tautomerization to 2,3-dihydro-2-hydroxy-2-R-4H-1,3-benzoxazin-4-ones (IV), which are converted to oxazinonium salts V by the action of acids, may be intermediates in this reaction:



The proposed scheme is confirmed by the fact that salicylamide is capable of giving O- and N-acyl derivatives under acid catalysis conditions [12] and by the possibility of conversion of the latter to cyclic tautomer IV [3]. In addition, we have shown that salicylamide in acetic anhydride is converted to a mixture of II and III when catalytic amounts of perchloric acid are added; the mixture of II and III reacts with molar amounts of perchloric acid to give oxazinonium salts V, which may be of interest within the framework of independent methods for the synthesis of these salts. However, for preparative purposes, it is more convenient to use amides II, which are more stable than the O-acyl derivatives. Cyclization of II in glacial acetic acid makes it possible to obtain oxazinonium salts V with practically any substituents in the 2 position of the heteroring.

Rostov State University. Scientific-Research Institute of Physical and Organic Chemistry, Rostov-on-Don. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 4, pp. 460-464, April, 1975. Original article submitted May 27, 1974.

TABLE 1. 4H-1,3-Benzoxazin-4-onium Perchlorates (V)

Compound	R	R′	mp, °C*	Empirical formula	Found, %				Calc., %				IR spectra (principal frequencies), cm⁻¹	Yield, %
					C	H	Cl	N	C	H	Cl	N		
Va	H	CH_3	208	$C_9H_8ClNO_6$	41,2	3,3	13,0	5,2	41,4	3,1	13,6	5,4	1766 1633 1598 1580 1532	98
Vb	H	C_2H_5	183—185	$C_{10}H_{10}ClNO_6$	43,1	3,5	12,3	4,8	43,6	3,6	12,9	5,1	1768 1630 1591 1573 1525	70
Vc	H	C_3H_7	211	$C_{11}H_{12}ClNO_6$	45,7	4,6	11,7	4,8	45,7	4,2	12,3	4,8	1755 1630 — 1580 1530	96
Vd	H	C_4H_9	212—214	$C_{12}H_{14}ClNO_6$	47,7	5,0	11,4	4,7	47,5	4,6	11,6	4,6	1758 1632 — 1580 1530	92
Ve	H	C_5H_{11}	103—106†	$C_{13}H_{16}ClNO_6$	48,9	5,2	10,8	4,7	49,2	5,0	11,2	4,4	1755 1633 — 1580 1530	91
Vf	H	C_6H_5	247	$C_{14}H_{10}ClNO_6$	52,2	3,3	11,3	4,0	52,0	3,1	11,0	4,2	1766 1630 1600 1570 1513	75
Vg	H	$CH{=}CHC_6H_5$	232	$C_{16}H_{12}ClNO_6$	55,0	3,7	9,8	4,4	55,3	3,5	10,2	4,0	1760 1633 — 1578 1506	76
Vh	CH_3	CH_3	200—202	$C_{10}H_{10}ClNO_6$	43,0	3,6	12,3	4,8	43,6	3,6	12,9	5,1	1760 1633 1604 1574 —	97
Vi	C_6H_5	CH_3	dec. >185	$C_{15}H_{11}ClNO_6$	53,2	3,8	11,0	4,0	53,4	3,6	10,5	4,2	1770 1664 1635 1618 1596 1563 1528	93
Vj	CH_3	C_3H_7	183—185	$C_{12}H_{14}ClNO_6$	47,7	4,9	11,4	4,7	47,5	4,6	11,7	4,6	1759 1631 — 1570 —	98

*Crystallization from glacial acetic acid.

†Reprecipitated from glacial acetic acid solution by the addition of ether.

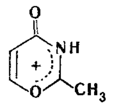
However, when N-benzoylsalicylamide is cyclized in acetic anhydride, 2-methylbenzoxazinonium salt Va is formed instead of the expected 2-phenylbenzoxazinonium salt Vf because of transacylation.

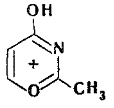
In order to confirm the structure of oxazinonium salts V, we obtained the latter by alternative synthesis by protonation of 4H-1,3-benzoxazin-4-ones (VI).

The synthesized salts are colorless crystalline substances that can be used for synthetic purposes without additional purification. The individuality of the compounds obtained was confirmed by chromatography. Data on the yields and properties of perchlorates V are presented in Table 1.

The IR spectra of the 4H-1,3-benzoxazin-4-onium salts (V) contain an intense absorption band at 1755-1766 cm^{-1}, which is due to the stretching vibrations of the C=O group of the heterocyclic cation, and two strong bands at 1630-1633 and 1525-1532 cm^{-1}, which we assigned to vibrations of the $\underline{O\cdots\overset{+}{C}\cdots N}$ fragment. Absorption bands characteristic for the phenyl ring and the ClO_4^- anion are also present in the IR spectra of salts V.

Calculation of the total energy of the pseudoaromatic 2-methyl-4H-1,3-benzoxazin-4-onium cation (VII) showed that this structure is 60 kcal/mole more advantageous than the possible tautomeric 2-methyl-4-hydroxy-1,3-azapyrylium cation (VIII) (E = −840.916 eV),* despite the genuine aromatic character of the latter.


VII


VIII

The presence of an absorption band in the IR spectra of synthesized salts V at 1755-1766 cm^{-1} (C=O) is in good agreement with the calculated values, which constitutes evidence that the 4H-1,3-benzoxazin-4-onium salts exist in the keto form rather than in the hydroxy form.

When the synthesized perchlorates V (where R = H) are treated with dry triethylamine, perchloric acid is split out to give the corresponding benzoxazinones (VI). The previously proposed methods for the synthesis of 4H-1,3-benzoxazin-4-ones, which are based on cyclization of N- or O-acylsalicylamides [4] or acylation of salicylamide with aromatic acid chlorides in the presence of tertiary amines as catalysts [5], are considerably more laborious than the method described in the present paper.

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*We thank V. I. Minkin and R. M. Minyaev for the quantum-chemical calculations.

TABLE 2. N-Acylsalicylamides (II)

Compound	R	R′	mp, °C*	Empirical formula	Found, %			Calc., %		
					C	H	N	C	H	N
IIa	H	C_2H_5	122—123	$C_{10}H_{11}NO_3$	62,0	5,5	6,9	62,2	5,7	7,3
IIb		C_3H_7	124—125	$C_{11}H_{13}NO_3$	63,3	6,0	6,6	63,8	6,3	6,8
IIc		C_4H_9	125—126	$C_{12}H_{15}NO_3$	64,6	6,9	6,8	65,1	6,8	6,3
IId		C_5H_{11}	120—121,5	$C_{13}H_{17}NO_3$	66,9	7,4	6,3	66,4	7,2	6,0
IIe	CH_3	CH_3	92,5—94	$C_{10}H_{11}NO_3$	62,5	5,9	7,0	62,2	5,7	7,3
IIf	C_6H_5	CH_3	124—126	$C_{15}H_{13}NO_3$	71,2	5,5	5,9	70,6	5,1	5,5

*Compounds IIa-c were recrystallized from benzene, IId,f were recrystallized from benzene—petroleum ether, and IIe was recrystallized from ether—petroleum ether.

The oxazinonium salts react readily with water with opening of the heteroring to give quantitative yields of N-acylsalicylamides (II) (see Table 2).

EXPERIMENTAL METHODS

The PMR spectra were recorded with a Tesla BS 487C spectrometer (80 MHz). The IR spectra of mineral-oil suspensions were recorded with a UR-20 spectrometer.

2-Methyl-4H-1,3-benzoxazin-4-onium Perchlorate (Va). A) A 5-ml (0.05 mole) sample of 70% perchloric acid was added to a mixture of 6.85 g (0.05 mole) of salicylamide and 30 ml of acetic anhydride. The mixture, which began to crystallize on standing, was diluted with ether, and the precipitate was removed by filtration and washed with ether to give 12.8 g (98%) of a salt with mp 208° (dec., from glacial acetic acid), PMR spectrum (in CF_3COOH): 2.75 (s,* CH_3) and 7.38-8.02 ppm (m, phenyl).

Perchlorates Vb-e were similarly obtained (see Table 1). Absolute ether was used to isolate and purify salts Vb,c,e.

B) A 0.5-ml sample of 70% perchloric acid was added to a mixture of 1.20 g (0.005 mole) of N-benzoylsalicylamide and 10 ml of acetic anhydride, after which the mixture was allowed to stand for 30 min. It was then treated with ether, and the mixture was filtered to give 0.6 g (46%) of a salt with mp 208°.

C) A solution of 1 ml of 70% perchloric acid in 3 ml of acetic anhydride was added to a mixture of 1.79 g (0.01 mole) of O-acetylsalicylamide and 4 ml of glacial acetic acid, after which the mixture was heated to the boiling point, cooled, and diluted with ether to give 1.4 g (54%) of a salt with mp 280°.

2,3-Dimethyl-4H-1,3-benzoxazin-4-onium Perchlorate (Vh). A 1-ml sample of 70% perchloric acid was added dropwise to a mixture of 1.51 g (0.01 mole) of N-methylsalicylamide and 6 ml of acetic anhydride, and the mixture was heated to the boiling point, cooled, and diluted with ether to give 2.65 g (97%) of a salt with mp 200-202° (dec., from glacial acetic acid). PMR spectrum (in CF_3COOH): 2.72 (s, CH_3), 3.48 (s, N-CH_3), and 7.25-7.94 ppm (m, phenyl).

Perchlorates Vi,j were similarly obtained (see Table 1).

2-Phenyl-4H-1,3-benzoxazin-4-onium Perchlorates (Vf). A) A solution of 1 ml of 70% perchloric acid in 3 ml of acetic anhydride was added to a mixture of 2.41 g (0.01 mole) of N-benzoylsalicylamide and 25 ml of glacial acetic acid, after which the mixture was heated rapidly until the solids had dissolved, and the solution was refluxed until crystals began to form. The mixture was diluted with ether and filtered, and the crystals were washed with ether to give 2.42 g (75%) of a salt with mp 247° (dec., from glacial acetic acid—nitromethane).

Perchlorates of Va,g were similarly obtained in 97 and 76% yields, respectively (see Table 1).

B) A 0.25-ml sample of 70% perchloric acid was added to a solution of 0.56 g of benzox-

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*Here and subsequently, s is singlet and m is multiplet.

azinone VI ($R' = C_6H_5$) in 5 ml of glacial acetic acid, after which the mixture was heated to the boiling point. It was then cooled, and the resulting crystals were removed by filtration and washed with ether to give 0.56 g (70%) of a product with mp 247°.

Perchlorate Va was similarly obtained in 70% yield.

2-Methyl-4H-1,3-benzoxazin-4-one (VI, $R' = CH_3$). A mixture of 2.61 g (0.01 mole) of perchlorate Va with 1.01 g (0.01 mole) of dry freshly distilled triethylamine was allowed to stand overnight, after which it was extracted with benzene—chloroform (5:1). The extract was evaporated to give 1.53 g (95%) of a crystalline substance with mp 217° (from benzene) (mp 217° [6]).

2-Phenyl-4H-1,3-benzoxazin-4-one (VI, $R' = C_6H_5$). This compound, with mp 100-102° (from cyclohexane) (mp 100-102° [7]), was similarly obtained from perchlorate Vf in 100% yield.

2-Styryl-4H-1,3-benzoxazin-4-one (VI, $R' = CH = CHC_6H_5$). This compound, with mp 150° [from benzene—petroleum ether (1:1)], was similarly obtained from perchlorate Vg in 98% yield. IR spectrum cm^{-1}: 1681, 1634, 1545. Found %: C 77.5; H 4.5; N 5.9. $C_{16}H_{11}NO_2$. Calculated %: C 77.1; H 4.4; N 5.6.

N-Acetylsalicylamide (II, R = H, $R' = CH_3$). Water (20 ml) was added to 2.61 g (0.01 mole) of Va, and the mixture was heated to the boiling point. The resulting solid was removed by filtration and dried to give 1.79 g (100%) of amide II with mp 143-144° (from benzene) (mp 143-144° [8]).

Amides IIa-f were similarly obtained (see Table 2).

The IR spectra of the N-acylsalicylamides contain absorption bands of a bonded NH amide group at 3200-3300 cm^{-1} and two bands at 1720-1760 and 1640-1660 cm^{-1}, which correspond to carbonyl absorption.

Compounds IIa-f react with an alcohol solution of ferric chloride to give an intense violet coloration.

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