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Preparation of Benzoxazolones from Halogenosalicylhydroxamic Acids and Ethyl Chloroformate

by

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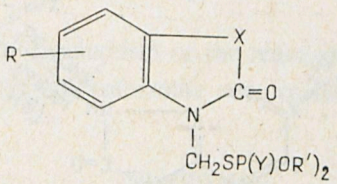
Summary. Benzoxazolones were prepd. in a convenient method in high yield by the treatment of halogeno substituted hydroxamic acids with ethyl chloroformates.

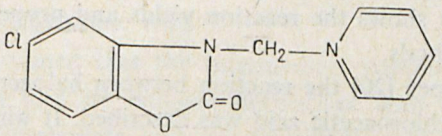
Forty years ago attention was drawn to the physiological activity of benzoxazolone and its derivatives [1]. They were found to possess a spasmodic and somniferous action as well as an activity on central nervous system.

Benzoxazolone and 5-bromobenzoxazolone which were prepared by Urbański and Lewenstein [2] exhibited tuberculostatic activity. 6-Methoxybenzoxazolone was prepared as a fungicide by Japanese workers [3]. Many benzoxazolone derivatives were synthesized by Eckstein [4] and were tested as fungicides.

Derivatives of benzoxazolone and benzothiazolone of the general formula



were patented as pesticides [5] and in the case where X=O or S, R=H, and the substituent at nitrogen atom is $CH_2SP(S)(OMe)_2$ they can be used as agents to cure skin mycoses of animals [6] (*Hypoderma bovis*, *Dermatobia gastrophilus*, and *Dermatobia hominus*). Antibacterial activity of 3-substituted derivative of 5-chlorobenzoxazolone was published.

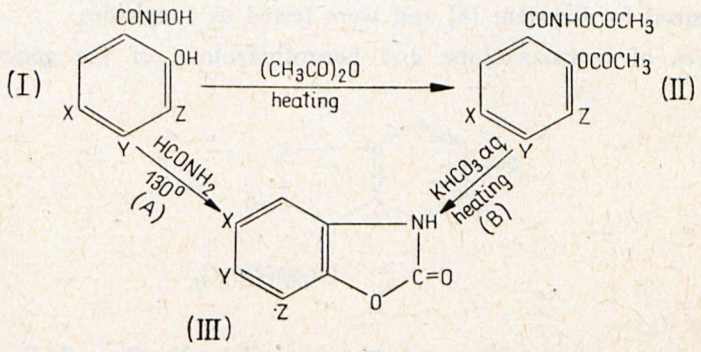


Among many methods of preparation of benzoxazolone and its derivatives the following are most common: Condensation of *o*-aminophenol and its derivatives with urea [8, 9] or ethyl chloroformate [10]; reaction of phosgene with *o*-aminophenol and its derivatives in ethylacetate solution [11]; reaction of sodium hypochlorite with salicylamide [12]; heating of high temperature of 2-hydroxyphenyl urea over a catalyst [13]; reaction of salicylic acid with ammonia and subsequent with sulphuric acid [14]. Benzoxazolones can be prepared also by Lossen rearrangement of salicylhydroxamic acid and its derivatives.

Benzoxazolone was obtained by Marquis [15] in the reaction of thionyl chloride with salicylhydroxamic acid and by Scott [16] from potassium salt of the benzoyl derivative of salicylhydroxamic acid. Hershenson *et al.* [18] prepared benzoxazolone by the reaction of benzenesulphonyl chloride with salicylhydroxamic acid. They suggested that as an intermediate compound *o*-sulphonyl derivative of salicylhydroxamic acid is formed which, after transformation into the isocyanate, undergoes cyclization to the benzoxazolone.

For preparation of benzoxazolone from salicylhydroxamic acid Eckstein [17] used formamide and proposed a convenient method for carrying out Lossen rearrangement of monoacetyl derivatives of salicylhydroxamic acids.

It was found in our previous work [19] that halogen derivatives of salicylhydroxamic acid when treated with acetic anhydride gave diacetyl derivatives which, upon heating to boiling in aqueous potassium hydrogen carbonate, gave benzoxazolone derivatives identical with those obtained by heating of the parent halogen hydroxamic acids with formamide, respectively.



Therefore it appeared that the diacetyl derivatives of halogensalicylhydroxamic acids undergo Lossen rearrangement with simultaneous hydrolysis of the acetyl group attached to the phenolic hydroxyl, which enables the cyclization reaction to the benzoxazolone.

The following table shows the reaction yields and properties of benzoxazolone obtained by both methods.

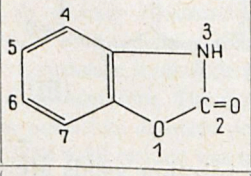
In our previous paper [20] the reaction between halogen derivatives of salicylhydroxamic acid and chloroacetic acid was described. It was found then that ana-

logous products were obtained when ethyl bromoacetate was used i.e. derivatives of ethyl salicylhydroxamoacetate. It was expected that with the use of ethyl chloroformate derivatives of salicylhydroxamic acid and carbonic acid could be obtained.

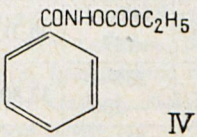
However, it was found now that the products isolated from the reaction were derivatives of benzoxazolone.

TABLE I

Properties of benzoxazolones obtained by both methods; Method A — hydroxamic acid and formamide, Method B — diacetyl derivative of hydroxamic acid heated in $KHCO_3$ solution

No.		Yield, %		m.p. °C	Analysis, %					
		Method			C		H		N	
		A	B		Calc.	Found	Calc.	Found	Calc.	Found
1	5-fluoro-7-chloro-	59	80.2	210.5—212	44.80	44.62	1.60	1.49	7.47	7.55
2	5-fluoro-7-bromo-	55	65	221—222	36.21	36.50	1.36	1.40	6.36	6.31
3	5-chloro-7-bromo-	52	63	235—236	33.80	33.68	1.21	1.50	5.63	5.64
4	5-bromo-7-chloro-	51	61	221—222	33.80	33.56	1.21	1.29	5.63	5.52
5	5-iodo-7-bromo-	28	59	260—261	24.71	24.95	0.88	1.12	4.12	4.15
6	5-chloro-7-iodo-	32	65	248—249	28.43	28.71	1.02	1.12	4.74	4.53

In order to elucidate the mechanism of the reaction the condensation of benzohydroxamic acid with ethyl chloroformate was carried out to give ethyl benzohydroxamocarbonate

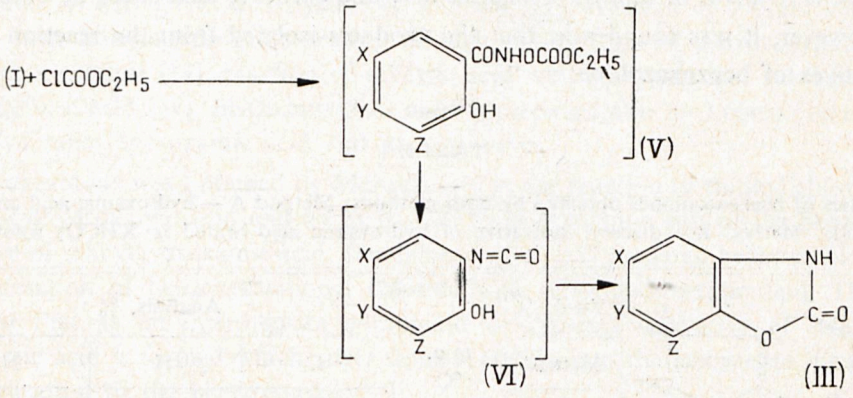


IV

Compound IV, when heated in aqueous alcoholic solution decomposed and yielded carbon dioxide and *N,N'*-diphenyl urea which is a characteristic product of Lossen rearrangement of benzhydroxamic acid.

It was therefore assumed that the intermediate compound in the reaction of salicylhydroxamic acid and its halogen derivatives with ethyl chloroformate is ethyl salicylhydroxamocarbonate and its derivatives (V). These compounds are

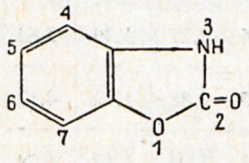
unstable in the reaction conditions and undergo Lossen rearrangement through the izocyanates (VI) resulting in the formation of benzoxazolone derivatives (III).



Benzoxazolone obtained by this method are pure and the reaction yields are very good.

TABLE II

Properties of benzoxazolones obtained with the aid of ethylchloroformate promoting the Lossen rearrangement

No.		Yield %	m.p. °C	Analysis, %					
				C		H		N	
				Calc.	Found	Calc.	Found	Calc.	Found
1	Benzoxazolone [2,18]	89,0	141	62.22	62.43	3.70	3.91	10.37	10.38
2	6-fluoro- [4]	91.5	186	54.90	54.93	2.61	2.67	9.15	9.20
3	-5-bromo- [2,17]	93.5	214—214.5	39.25	39.49	1.87	1.92	6.54	6.83
4	5-bromo-6-fluoro-	90.8	146—147	36.21	36.58	1.36	1.66	6.36	6.51
5	5-chloro-7-bromo-	92	235—236	33.80	34.27	1.21	1.42	5.63	5.55
6	5-bromo-7-chloro-	90.3	221—222	33.80	33.87	1.21	1.37	5.63	5.46
7	5-chloro-7-iodo-	76.4	248	28.43	28.58	1.02	1.09	4.74	4.81
8	5-iodo-7-bromo-	67	260—261	24.71	25.50	0.88	0.96	4.12	4.20
9	5,7-dibromo-6-fluoro-	90	220 decomp. >180°	27.01	27.45	0.64	0.71	4.50	4.47

Experimental

Preparation of 5-chloro-7-bromobenzoxazolone

a) *By heating the hydroxamic acid in formamide.* 3-Bromo-5-chlorosalicylhydroxamic acid (5.0 g) was heated in formamide (10 ml) at 80° and distilled water (20 ml) was added after 20 min. Brown solid precipitate was filtered, disolved in aqueous 5% potassium carbonate, decolorized with charcoal and reprecipitated with dilute sulphuric acid. 5-chloro-7-bromobenzoxazolone (2.4 g; 52% yield) recrystallized from benzene (m.p. 235—6°C).

b) *By rearrangement of the diacetyl derivative of hydroxamic acid in aqueous potassium hydrogen carbonate solution.* The diacetyl derivative of 3-bromo-5-chlorosalicylhydroxamic acid (2.5 g, 0.007 mol) was suspended in aqueous (100 ml) potassium hydrogen carbonate (1.4 g) solution and heated to boiling for 10 min. 5-chloro-7-bromobenzoxazolone (1.1 g, 63% yield) separated on cooling m.p. 235—6°C.

c) *By heating 3-bromo-5-chlorosalicylhydroxamic acid with ethylchloroformate in methanolic solution.* 3-Bromo-5-chlorosalicylhydroxamic acid (2.7 g, 0.01 mol) was disolved in methanolic (50 ml) potassium hydroxide (1.2 g, 0.02 mol) solution to which ethyl chloroformate was added at room temperature. The reaction mixture was heated on water bath during 1 hour and after cooling potassium chloride precipitate was filtered off. The filtrate was evaporated to dryness *in vacuo*. The solid residue was treated with water and acidified with dilute sulphuric acid. 5-chloro--7-bromobenzoxazolone (2.3 g, 92% yield) precipitated, after recrystallization from benzene had m.p. 236°C.

Reaction of benzhydroxamic acid with ethyl chloroformate

Benzhydroxamic acid (2.8 g, 0.02 mol) was disolved in methanolic 50 ml potassium hydroxide (1.2 g, 0.02 mol) solution and after carrying the procedure described in part 1 c ethyl benzhydroxamocarbonate m.p. 76—7° (4.0 g, 96% yield) was obtained.

Found: C 57,44; H 5.55; N 6.76%;

Required for $C_{10}H_{11}O_4N$: C 57.42; H 5.26; N 6.70%.

Heating the ethyl benzhydroxamocarbonate in aqueous alcohol leads to the formation of diphenyl urea accompanied by evolution of carbon dioxide.

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А. Осташиньски, Г. Пленкевич, Т. Урбаньски, **Получение бензоксазолонов из галогеносалицилгидроксамовых кислот и этилхлорформиата**

Содержание. В настоящей работе описан удобный синтез бензоксазолонов, получаемых воздействием этилхлорформиата на галогенозамещенные гидроксамовые кислоты. Упомянутый выше метод отличается чистотой получаемых продуктов и высоким выходом.