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REVIEW ARTICLE

Preparation and Properties of 2-Benzoxazolinones

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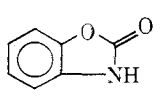
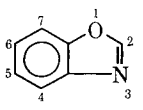
2-Benzoxazolinone (I) is a heterocyclic compound comprised of a benzene ring which is fused to a five-membered ring containing oxygen and nitrogen as the hetro atoms. The numbering of 2-benzoxazolinone is derived from the parent benzoxazole (II). Prior to 1936, *Chemical Abstracts* employed the numbering system shown in III. Under this system, I was referred to as benzoxazolone rather than as 1-benzoxazolinone. Frequently in chemical literature which originated before 1900, *o*-oxycarbanil and carbonyl-*o*-aminophenol were used to designate I.

Benzoxazolinones have been investigated extensively primarily for their medicinal value as central nervous system (CNS) depressants which exhibit analgesic, antipyretic, anticonvulsant, hypnotic, and skeletal muscle relaxant activity.



I



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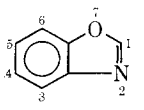
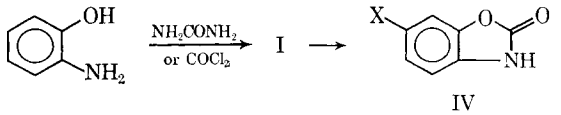


III

One review article concerning the preparation and limited reactions of 2-benzoxazolinone (1), and another dealing with structure-activity relationships of 2-benzoxazolinones with minor emphasis on the preparation and physical properties of 2-benzoxazolinones (2) have appeared. The present article, although containing some material previously reviewed, primarily provides supplemental information.

SYNTHESIS OF 2-BENZOXAZOLINONES

Cornforth (1) has covered the literature amply prior to 1946 with regard to the synthesis of I. Cain and Roszkowski (2) have presented additional methods. The methods presented by Cornforth for the formation of I are of classical interest only, due to poor yields and extreme difficulties encountered in purification procedures. The synthesis of I now is accomplished readily and practically through the reaction of urea or phosgene with *o*-aminophenol under appropriate conditions.



IV

von Chelmicki (3) demonstrated that a solution of *o*-aminophenol in benzene or chloroform treated with phosgene gives I in low yields. Jacoby (4) showed that I could be obtained in 50% yield by shaking *o*-aminophenol in benzene with phosgene. In 1915 von Meyer (5) obtained I in 82% yield by dissolving *o*-aminophenol in pyridine, and then adding phosgene, also in pyridine, and warming the mixture slightly. Close *et al.* (6) increased the yield of I to 90% by conducting the reaction of phosgene with *o*-aminophenol in ethyl acetate in the presence of potassium acetate.

The fusion of urea with *o*-aminophenol hydrochloride was first described by Sandmeyer (7). This method remained unexploited because of the poor yield, until Bywater *et al.* (8) were able to obtain I in a 35% yield. Subsequent work by Williams (9), MacDonald and Chechak (10), Takahashi and Yoneda (11), and Close *et al.* (6) showed that I could be obtained in yields of 76–90% by moderating the temperature and time of reaction.

The reaction of phosgene with *o*-aminophenols and the fusion of *o*-aminophenols with urea are the methods of choice for obtaining most 2-benzoxazolinones which have substituents other than the 6-position on the benzene ring. Close *et al.* (6) advocated this procedure and obtained yields of 55–70%. Sam *et al.* (12, 13) also have used this procedure in obtaining yields of 60–90%.

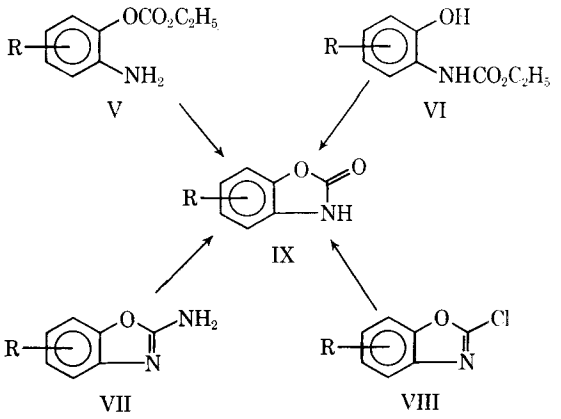
Substitution on the benzene moiety of 2-benzoxazolinone is influenced by the hetero nitrogen atom, *i.e.*, 2-benzoxazolinones react to substitution as does N-acyl aniline. Thus halogenation of I results in a 6-halo-2-benzoxazolinone (IV) (6, 12, 14). Jacoby (4) and Bender (15*a*) proposed that bromination of I yields 6-bromo-2-benzoxazolinone. Desai *et al.* (16) likewise postulated that bromination occurs in the 6-position and later (14) demonstrated this *via* acid hydrolysis of IV (X = Br) to 5-bromo-2-aminophenol.

Similarly Close *et al.* (6) noted that chlorination of I in acetic acid using sulfuryl chloride gives 6-chloro-2-benzoxazolinone melting at 189–194°. Earlier, Jacoby (4) had reported treating I with chlorine in acetic acid and obtaining a trichloro-2-benzoxazolinone melting at 184–186°. The treatment of I with potassium chlorate and hydrochloric acid also was observed to produce either a monochloro or a trichloro derivative depending upon the reaction conditions. Subsequent to the work of Jacoby (4), Bender (15*b*), and von Chelmicki (3) showed that the action of phosphorus pentachloride on I produced a monochloro derivative. Since adequate evidence was not provided, the chlorination product obtained by each of the groups of investigators above most likely is the same, *i.e.*, 6-chloro-2-benzoxazolinone.

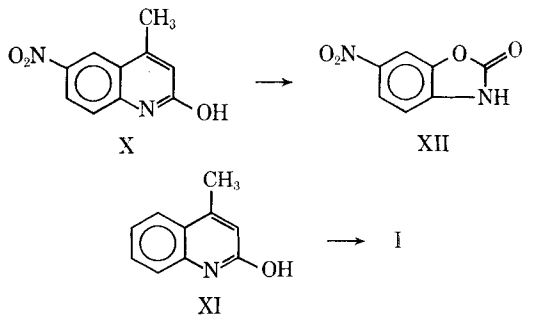
The nitration of I gives 6-nitro-2-benzoxazolinone (XII) (15*a*, 17–22). The position of the nitro group was substantiated by an unequivocal synthesis (14) of the latter compound by the pyrolysis of *N*-(2-hydroxy-4-nitrophenyl)urethane (VI, R = 4-NO_2). Moreover, Beech (19) demonstrated that the nitration occurs in the 6-position of related 2-benzoxazolinones *via* the conversion of the latter to known substituted phenols. The chlorosulfonation (23) and sulfonation (19) of I are analogous to the reactions described above and also occur in the 6-position.

The preparation of 6-substituted derivatives regardless of other nuclear substituents is accomplished readily by either halogenation or nitration. The 6-nitro-2-benzoxazolinone thereafter can be reduced either chemically (14, 19) or catalytically (20, 24) to the corresponding amino derivative which *via* the Sandmeyer reaction (19, 21) yields other 6-substituted derivatives. The Sandmeyer reaction performed on the appropriate 5-amino-2-benzoxazolinone (13) likewise permits formation of other 5-substituted derivatives not readily accessible *via* a reaction of appropriate *o*-aminophenols with phosgene or urea. Various derivatives of the amino group at Position 5, 6 or 5 and 6 have been prepared (14, 20, 21, 25, 26).

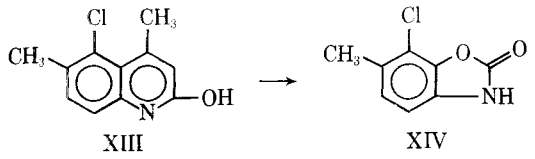
Harsanyi and Toffler (27) synthesized various 2-benzoxazolinones by reacting appropriate *N*-(*o*-hydroxyphenyl)urethans (VI) with various catalysts (NaOEt, Na, NaOH, or NaCN) in tetralin (1,2,3,4-tetrahydronaphthalene). Sam *et al.* (13) obtained 5-trifluoromethyl-2-benzoxazolinone (IX, R = 5-CF_3) by treating 2-amino-5-trifluoromethylphenylethyl carbonate (V, R = 5-CF_3) with hydrochloric acid. 2-Benzoxazolinones (IX) also can be obtained either by the action of acid upon 2-aminobenzoxazoles (VII) (12, 28) or warm water upon 2-chlorobenzoxazoles (VIII) (12, 28).



Balaban (29) has reported that oxidation of 6-nitro-2-hydroxy-4-methylquinoline (X) with hot neutral aqueous potassium permanganate gives 6-nitro-2-benzoxazolinone (XII). The same condition on 2-hydroxy-4-methylquinoline (XI) reportedly provides 2-benzoxazolinone (I). Other substituted 2-benzoxazolinones also were prepared in this manner. Both I and XII were found to be identical with authentic samples prepared from the appropriate aminophenol and phosgene. In an attempt to repeat this work, Marais and Backeberg (30) found that no oxidation could be effected. Attempts

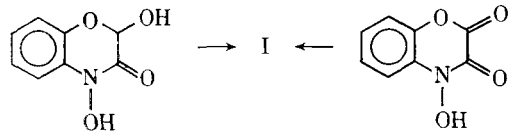


also were unsuccessful when the nitro group was replaced by a chloro group. A small yield of compound, believed to be 6-methyl-7-chloro-2-benzoxazolinone (XIV), was obtained by treating 2-hydroxy-4,6-dimethyl-5-chloroquinoline (XIII) with an aqueous pyridine solution containing potassium hydroxide and potassium permanganate. Unequivocal identification of XIV, however, was not provided.



XIII XIV

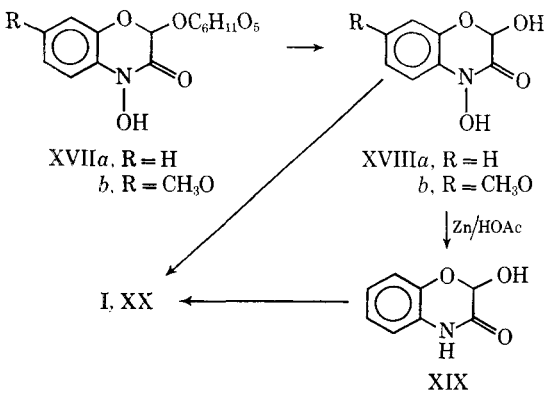
The preparation of I by the rearrangement of either 2,4-dihydroxy-2H-1,4-benzoxazine-3-one (XV) or 4-hydroxy-1,4-benzoxazine-2,3-dione (XVI) by refluxing in water also has been reported (31).



XV XVI

Isolation of 2-Benzoxazolinones from Natural Sources—Virtanen and Hietala (32) first reported the isolation of 2-benzoxazolinone from "Oiva," a variety of rye. The 2-benzoxazolinone proved to be a resistance factor to the fungus *Fusarium nivale* which is responsible for the overwintering of rye in snow-covered fields. The isolation of I was accomplished first from crushed rye seedlings and later from crushed rye seeds (33). Furthermore, Virtanen *et al.* (33) found that the amount of I present in the seedlings was dependent upon whether growth occurred in the light. The absence of light during the growth period of the seedlings inhibited the formation of I.

A point of early perplexity for Virtanen *et al.* was the fact that I could be isolated only from crushed seeds or seedlings. This problem, however, was resolved when the percursors of I were isolated from intact seedlings (34–39). The primary precursor proved to be a glycoside (XVII) of 2,4-dihydroxy-2H-1,4-benzoxazine-3-one (XVIII*a*) which through enzymatic hydrolysis formed a second precursor upon crushing the plant (36). The formation of I from the aglucone then occurred *via* chemical transformations. With this information Virtanen and Hietala (39) were able to propose probable structures for the glycoside (XVII*a*) and the aglucone (XVIII*a*). Additional studies demonstrated that reduction of the aglucone gave a compound (XIX) which could not be converted to I. Later Honkanen and Virtanen (40, 41) synthesized both the aglucone and its reduction product. Subsequently it was shown through labeling studies on the aglucone that the carbon in the 2-position was lost in the process of forming I (31).



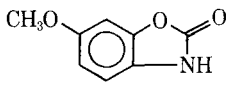
XVII*a*, R = H
b, R = CH_3O

XVIII*a*, R = H
b, R = CH_3O

I, XX

XIX

The isolation of a benzoxazolinone also was accomplished from the roots of *Coix lachrymajobi* and was called coixol (42). Subsequently coixol was identified as 6-methoxy-2-benzoxazolinone (XX) (43). Shortly thereafter, Virtanen *et al.* (44) isolated XX from wheat and corn while Smissman *et al.* (45, 46) isolated and



XX

synthesized XX showing their identical nature. The work of Smissman *et al.* was based on a finding by Loomis *et al.* (47) that extracts from corn were inhibitory to *Pyrausta nubilalis* (European corn borer). Hietala and Wahlroos (48) also had succeeded in synthesizing XX prior to Smissman *et al.* although both groups used different synthetic pathways. Subsequently, Wahlroos and Virtanen (49, 50) isolated precursors of XX from maize seedlings. The precursors (XVII*b*, XVIII*b*) were shown to be identical to those isolated from rye seedlings save for the methoxy group (51). The isolation of XX was accomplished by several workers (52–54) from the fungus *Ustilago maydis* collected from infected corn plants and from *Zea mays* (field corn), and the causal organism of bacterial wilt, *Xanthomonas stewartic*, respectively.

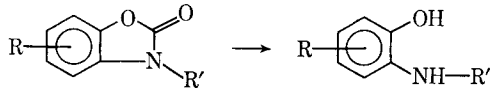
Beck and Smissman (55) prepared and tested fifty compounds against *Pyrousta nubilalis* and *Penicillium chrysoyenium* among which were several nuclear substituted derivatives of 2-benzoxazolinone. The conclusion of this study was that the oxazole ring was important for activity against *Pyrousta nubilalis*.

Whether XX is an *in vivo* constituent of the corn or an artifact caused by chemical manipulations upon the corn tissue has been the subject of much discussion (51, 56, 57). A recent finding (58), however, that XX is not a primary factor in chemical resistance to the corn borer lends credence to the theory (51, 57) that XX is an artifact.

Reaction and Physical Properties of 2-Benzoxazolinones—Jacoby (4) was the first to show that I could be hydrolyzed to the parent *o*-aminophenol using hydrochloric acid under sealed tube conditions (160-170°). Graebe and Rostovzeff (59) confirmed Jacoby's original observation. Desai *et al.* (14) showed that 6-bromo-2-benzoxazolinone could be hydrolyzed by refluxing in concentrated hydrochloric acid for 14 hr. Koyama (43) noted that 6-methoxy-2-benzoxazolinone is hydrolyzed in concentrated hydrochloric acid using stannous chloride. Less rigorous acid conditions do not cause hydrolysis (32, 60). Acid hydrolysis of 3-methyl-2-benzoxazolinone has been reported using concentrated hydrochloric acid under sealed tube conditions (61) and concentrated hydrochloric acid under reflux conditions (16). Other attempts (62) to hydrolyze various 2-benzoxazolinones using dilute or concentrated acid conditions were unsuccessful. (Certain 3-substituents will make the oxazolinone portion of the hetero ring system more labile to acid hydrolysis as will be discussed in a following section.) Hewitt and King (17) likewise found acid hydrolysis of 6-nitro-2-benzoxazolinone to occur with

difficulty; an extremely low yield of 5-nitro-2-aminophenol was obtained.

Basic hydrolysis of various 2-benzoxazolinones (XXI) to *o*-aminophenols (XXII) was reported to occur readily in dilute aqueous base (14, 19, 59, 63–66). Close *et al.* (6) noted the cleavage of the oxazolinone ring of 6-chloro-2-benzoxazolinone using sodium hydroxide but gave no solvent or conditions. The basic hydrolysis of 3-substituted-2-benzoxazolinones also was observed (62) to occur in aqueous medium but the yields of the *o*-aminophenol were low. This was attributed to the relative insolubility of the 3-substituted-2-benzoxazolinones in water. A more effective hydrolysis medium is ethyl cellosolve (2-ethoxyethanol) and a two to one ratio of base to 2-benzoxazolinone (62).

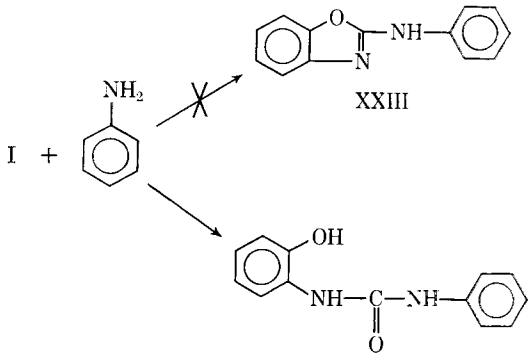


XXI XXII

Certain substituents in the 3-position will facilitate hydrolysis of the oxazolinone moiety. Takahashi and Yoneda (11) reported the hydrolysis of 3-benzyl-2-benzoxazolinone to 2-benzylaminophenol using an alcoholic potassium hydroxide solution. Eckstein and Zukowski (21) demonstrated that some 6-substituted-3-acetyl-2-benzoxazolinones are soluble in warm dilute sodium hydroxide. This fact was attributed to the loss of an acetyl group. Similar results were observed (62) when 3-benzoyl-2-benzoxazolinone is placed in cold dilute sodium hydroxide.

From literature reports one encounters considerable difficulty in determining whether or not 2-benzoxazolinone forms typical carbonyl derivatives (*e.g.*, phenylhydrazones). Bender (15) reported that condensation of equal molar amounts of 2-benzoxazolinone and phenylhydrazine yields a compound with a melting point of 208° which was considered to be 2-phenylhydrazinobenzoxazole. Koshimura *et al.* (67) reported the preparation of a 2-phenylhydrazinobenzoxazole with a melting point of 208° but gave no indication as to the method utilized. Bayer *et al.* (68) noted the preparation of 2-hydrazinobenzoxazole, m.p. 154–155°; however, the report is not clear as to whether the derivative was formed from 2-benzoxazolinone or 2-chlorobenzoxazole. Katz (69) prepared 2-hydrazinobenzoxazole, m.p. 150–152°, from 2-chlorobenzoxazole and hydrazine. Bower and Stephens (70) demonstrated that the action of hydrazine on 6-nitro-2-benzoxazolinone yields a hydrazine salt of 4-(2-hydroxy-4-nitrophenyl) semicarbazide which upon treatment with acetic acid gives 4-(2-hydroxy-4-nitrophenyl)semicarbazide. Similar results were obtained with 2-benzoxazolinone. The action of hydrazine on 3-methyl-6-nitro-2-benzoxazolinone also was reported to give 2-methylamino-5-nitrophenol. Seefelder and Reppe (71) reported that the action of hydrazine on the imine of 3-methyl-2-benzoxazolinone gives 3-methyl-2-hydrazinobenzoxazole. Work by Henry and Dehn (72) confirmed the original observation of von Meyer (5) that 2-benzoxazolinone reacts with a phenylisocyanate. The product, however, was not identified conclusively.

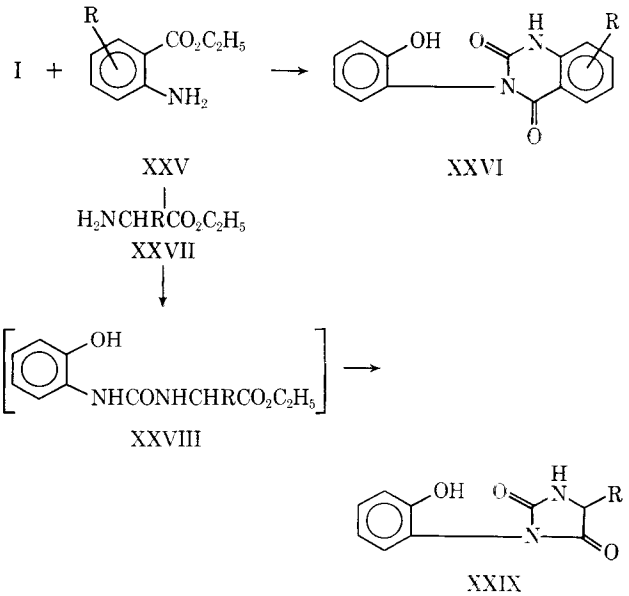
von Chelmicki (3) heated aniline and 2-benzoxazolinone in a sealed tube at 200–210° and reported the formation of 2-anilinobenzoxazole (XXIII). Later Young and Dunstan (73) demonstrated that the product obtained by von Chelmicki was *N*-phenyl-*N'*-(2-hydroxyphenyl)-urea (XXIV).



XXIII XXIV

Similar results were noted by using *p*-toluidine in place of aniline. Other primary and secondary amines (including heterocyclic compounds) (62) effect ring cleavage and form ureas. The formation of a urea was readily detected by the appearance of a 1650 $cm.^{-1}$ carbonyl band in the IR spectrum.

The reaction of aminoacid esters (XXV, XXVII) with 2-benzoxazolinone follows a similar course with concomitant ring closure to quinazolidine-2,4-diones (XXVI) and imidazolidine-2,4-diones (XXIX), respectively. Esters such as methyl benzoate fail to react with the potassium salt of 2-benzoxazolinone. This evidence supports the course of reaction *via* intermediate XXVIII (62). Moreover, ureas containing an appropriate carbethoxy group are known to spontaneously form cyclic structures (74).



XXV XXVI

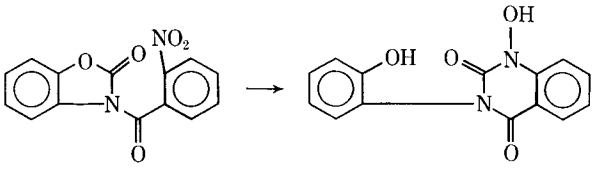
XXVII

XXVIII

XXIX

Sam and Richmond (75) reported that catalytic hydrogenation of 3-(2-nitrobenzoyl)-2-benzoxazolinone (XXX) in the presence of 5% palladium on carbon and an equivalent amount of hydrochloric acid yields

1-hydroxy-3-(2-hydroxyphenyl)quinazoline-2,4-dione (XXXI). It was speculated that partial reduction of the nitro group to a hydroxylamino group occurs; the

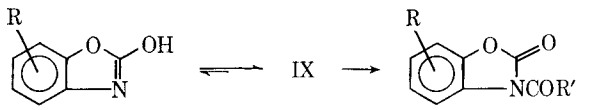


XXX XXXI

latter then attacks the carbonyl group of the benzoxazolinone portion of the molecule, causing rearrangement to XXXI.

Gaylord and Kay (76) showed that reduction of I with lithium aluminum hydride gives *o*-methylaminophenol. Zinner and Herbig (77) used the same reagent to demonstrate that the Mannich bases were formed at the 3-position. Mustafa *et al.* (78) demonstrated that the action of phenylmagnesium bromide on I followed by hydrolysis gives *N*-benzoyl-*o*-aminophenol.

2-Benzoxazolinone can be considered as a potential tautomeric substance whose corresponding tautomer is 2-benzoxazolol(2-hydroxybenzoxazole) (XXXII). Seidel (79) was the first to propose that 2-benzoxazolinone could exist in either a lactam (I) or a lactim (XXXII) form. Similarly, von Meyer (5) was cognizant of this potential of 2-benzoxazolinone. Because of this possible tautomerism there has been a great deal of confusion in the literature with regards to which form is produced upon synthesis from various materials.



XXXII XXXIII

Applegath and Franz (80) proposed that XXXII was formed by treating *o*-aminophenol with carbon monoxide in the presence of sulfur, at 80 p.s.i. and 100° for 2 hr. Caronna and Palazzo (81) reported the formation of XXXII by the action of sodium azide on *o*-hydroxybenzoic acid (Schmidt reaction). In 1961, Harsanyi *et al.* (82) described the preparation of XXXII by alkali treatment of *N*-(2-hydroxyphenyl)urethan (VI, R = H) in tetralin. Nagano *et al.* (83) reported the synthesis of various 2-hydroxybenzoxazoles from urea and appropriate *o*-aminophenols. The syntheses of other 2-benzoxazolinones (Table I) have reportedly given the lactam form. From the chemical and spectral data presented later, it is unlikely that XXXII was obtained as the sole product in any of the reactions above.

Hartley *et al.* (84) have shown through UV absorption data that the lactam form predominates in solution. Tautomeric forms were suspected since several different melting points had been observed for I (7, 15, 85). However, when I and 3-ethyl-2-benzoxazolinone (which can exist only in the lactam form) were prepared, similar UV absorption curves were noted, thus showing that only the lactam form existed. Furthermore, Hartley *et al.* (84) observed no color change when I was placed in a ferric chloride solution. Lucas and Vantu (86) obtained the same spectral data as did Hartley *et al.* (84).

Zinner *et al.* (63–65) utilized the reaction of diazomethane with various 2-benzoxazolinones in an effort to determine the presence of either the lactam or lactim form. These workers demonstrated that when I or various nitro derivatives of 2-benzoxazolinone are treated with diazomethane only the *N*-methyl derivatives are formed. The presence of the lactim would have resulted in *O*-methylation. Hydrolysis of the methylated benzoxazolinones yielded in each case only an *N*-methylaminophenol which reverted to the *N*-methyl-2-benzoxazolinones upon reaction with phosgene. Zinner and Wigert (24) later showed that a number of amine and hydroxyl derivatives of 2-benzoxazolinone (Table I; 28–31, 40, 41) all give *N*-methyl derivatives with diazomethane except 4-amino-2-benzoxazolinone (Table I, 38) which gives *O*-methylation. Prior to the foregoing work Koyama *et al.* (87) demonstrated that various methoxy-2-benzoxazolinones (Table I, 18–22) when reacted with diazomethane give a six to four ratio of *N*-methyl to *O*-methyl derivative. The 2,6-dimethoxybenzoxazole was identified on the basis of an unequivocal synthesis from 2-chloro-6-methoxybenzoxazole and sodium methoxide. Furthermore, these investigators demonstrated that the reaction of methyl iodide with the potassium salt of 6-methoxy-2-benzoxazolinone gives only the 3-methyl (*N*-substituted) derivative.

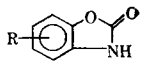
Synthesis of N-Substituted-2-Benzoxazolinones (XXI, XXXIII)—Lespagnol and Cannesson (88) reported in 1944 that *N*-substituted-2-benzoxazolinones possess greater anesthetic activity than do the 2-benzoxazolinones which are unsubstituted on the nitrogen atom. This study stimulated other work in search of *N*-substituted-2-benzoxazolinone derivatives which might be of medicinal value.

Prior to 1944 few references are available which describe the preparation of *N*-substituted-2-benzoxazolinones. The formation of 3-benzoyl-2-benzoxazolinone from I and benzoyl chloride in a pyridine solution was described by von Meyer (5). Raiford and Inman (89) used the same reaction parameters to prepare other 3-substituted derivatives (XXXIII, R′ = OR′′) by the condensation of 5-methyl-7-bromo-2-benzoxazolinone with various alkyl chloroformates.

Ransom (61) was the first to describe the preparation of *N*-alkyl derivatives of I by the use of an alkyl halide in methanolic potassium hydroxide. This method was used for the synthesis of 3-ethyl-2-benzoxazolinone by Lucas and Vantu (86). Similarly, Lespagnol (90) prepared a number of 3-substituted derivatives. The aforementioned method resulted in very poor yields. In 1949, Close *et al.* (6) modified Ransom's original procedure by substituting the higher boiling ethyl cellosolve for methanol, thus obtaining 80–95% yields. This remains the method of choice for preparing 3-substituted derivatives.

Sam *et al.* (13) prepared a number of 3-aminoalkyl-2-benzoxazolinones by *in situ* condensation of the potassium salt of various 2-benzoxazolinones with appropriate aminoalkyl halides in ethyl cellosolve. Similarly,

Table I—Literature References to Synthesis and Pharmacology of Various 2-Benzoxazolinones

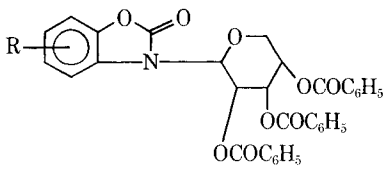


No.	R	Refs. to Synthesis	Pharmacol. Activity	Refs.
1	H	6–10, 80–82	Hypnotic, analgesic, anticonvulsant, anesthetic, antibacterial, anthelmintic	6, 88, 110, 111, 113–116
2	5-Cl	82, 117	Fungicide, muscle relaxant	2, 12, 118–123
3	6-Cl	3, 4, 6, 12, 15(*b*), 21	Muscle relaxant, fungicide	2, 12, 21
4	5,6-diCl	12, 124, 125, 127	Fungicide, germicide	2, 12, 60, 118, 124, 126
5	4,5,7-tri Cl	118, 127, 128, 129	Fungicide	2, 118, 120
6	4,5,6,7-tetra Cl	127, 128	Fungicide	118, 126
7	5-Br	12, 13, 89	Muscle relaxant	2, 12
8	6-Br	4, 14, 15(*a*), 16, 21	Muscle relaxant, fungicide	2, 12, 21
9	5,7-diBr	12, 89, 128, 129	Muscle relaxant	2, 12
10	4,5,7-tri Br	118	Fungicide	118
11	5-Cl-6-Br	12, 93	Fungicide, antifertility	2, 12, 93, 130
12	5-F	13		
13	6-F	21		
14	5-I	13		
15	6-I	21		
16	5-CF_3[a]	13, 91		91
17	5-F-6-Cl	13		
18	4-OCH_3	87, 131		
19	5-OCH_3[a]	6, 12, 19, 131		2, 6, 12
20	6-OCH_3	42, 46, 87, 131		
21	7-OCH_3	87, 131		
22	5-Cl-6-OH[a]	108		2, 108
23	5-Cl-6-OCH_3[a]	108		2, 108
24	5-Br-6-OCH_3	132	Hypotensor	132
25	5-OCH_3-6-Cl	132	Hypotensor	132
26	5-OCH_3-6-Br	132	Hypotensor	132
27	6-CN	21	Fungicide	2
28	4-OH	24		
29	5-OH	24		
30	6-OH	24		
31	7-OH	24		
32	4-NO_2	63	Fungicide	63
33	5-NO_2	20, 63, 82, 133	Anticonvulsant, fungicide	20, 63
34	6-NO_2	14, 15(*a*), 18, 20, 21, 63	Anticonvulsant, fungicide	20, 21, 63
35	7-NO_2	63	Fungicide	63
36	5,7-diNO_2	65		
37	5,6-diNO_2	20	Anticonvulsant	20
38	4-NH_2	24		
39	5-NH_2	12, 20, 24, 133	Anticonvulsant	2, 12, 20
40	6-NH_2	14, 20, 21, 24	Anticonvulsant	20
41	7-NH_2	24		
42	6-$NHCOCH_3$	14, 26		
43	5-$NHCONH_2$	20	Anticonvulsant	20
44	6-$NHCONH_2$	20, 21, 25	Anticonvulsant	20, 25
45	6-N_2BF_4	21		
46	5-CO_2H	20, 83	Anticonvulsant	20
47	5-$CO_2C_4H_9$	83		
48	5-*t*-butyl	20	Anticonvulsant	20
49	5-*n*-octyl	20	Anticonvulsant	20
50	6-$NHCSNH_2$	20	Anticonvulsant	20
51	6-$NHCON(C_6H_5)_2$	20	Anticonvulsant	20
52	5,6-ureido	20	Anticonvulsant	20
53	5-CH_3[b]	6	Analgesic	6
54	5-*n*-C_3H_7[b]	6	Analgesic	6
55	5-*n*-C_5H_{11}[b]	6	Analgesic	6
56	5,6-diCH_3	6	Analgesic	6
57	4,5,7-tri Cl-6-Br	127, 128		
58	5-*t*-butyl-7-Cl	134		
59	5-CH_3-7-Br	89, 135		
60	4-$COCH_3$	136		
61	5-CO_2CH_3	137		
62	5-SOMe	138		
63	5-SMe	138		
64	5-AsO_3H_2	133, 139		
65	6-AsO_3H_2	140	Antispirochetes	140
66	5-CH_3-6-AsO_3H_2	116, 141		
67	5-Cl-6-AsO_3H_2	116, 141		
68	5-AsO_3H_2-7-Cl	143		
69	5-AsO	142, 143	Antispirochetes	142, 143
70	6-AsO	142, 143	Antispirochetes	142, 143
71	7-Cl-5-AsO	143	Antispirochetes	143
72	5-AsO-6-Cl	142	Antispirochetes	142, 143
73	5-AsO-6-CH_3	143	Antispirochetes	142, 143
74	5-CH_3-6-AsO	142, 143	Antispirochetes	142, 143
75	5-CH_3-6-NO_2	116		
76	5-CH_3-6-NH_2	116		
77	5-Cl-6-NO_2	116		
78	5-Cl-6-NH_2	116		
79	4-NO_2-5-CH_3	29		
80	7-Cl-6-CH_3	30		
81	5-OCH_3-6-SO_3H	19		
82	5-Cl-7-SO_3H	19		
83	5-Cl-6-NO_2-7-SO_3H	19		
84	5-Cl-6-NH_2-7-SO_3H	19		
85	5,6-diCl-7-SO_3H	19		
86	5-CH_3-6-NO_2-7-SO_3H	19		
87	5-CH_3-6-NH_2-7-SO_3H	19		
88	5-CH_3-6-Cl-7-SO_3H	19		

[a] Only LD_{50} data reported. [b] Tested for analgesic activity but showed little or no activity.

Sam *et al.* (91) prepared a number of 3-alkyl-2-benzoxazolinones and 3-chloroalkyl-2-benzoxazolinones; the latter serve as intermediates in an alternate route to 3-aminoalkyl-2-benzoxazolinones. Toyoshima and Morishita (92–94) reported the preparation of a number of 3-substituted-2-benzoxazolinones by reacting an appropriate alkyl iodide with either 5-chloro-, 5,6-dichloro-, or 5-chloro-6-bromo-2-benzoxazolinone in a sodium ethoxide solution. The low yields reported by these authors are attributable (62) to the selection of solvent. *Chemical Abstracts* (92) erroneously reports the formation of 3-substituted-5-chloro-2-benzoxazolinones by reacting an alkyl iodide with 6-chloro-2H-1,4-benzoxazine-3-one.

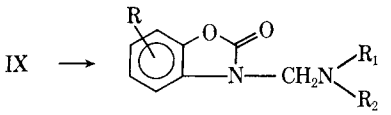
Recently Advani and Sam (95) reported the preparation of a number of riboside derivatives (XXXIV) of 2-benzoxazolinone for their evaluation as anticancer and antiviral agents. The riboside derivatives were prepared by reacting the sodium, chloromercuric, or silver salts of various 2-benzoxazolinones with tri-*O*-benzolyl-β-D-ribopyranosyl bromide.



XXXIV

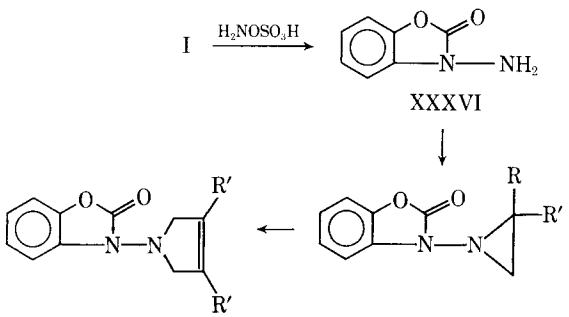
2-Benzoxazolinones can be considered to be weak acids in the Lowry-Bronsted sense, due to their ability to give up a proton. This acidic character facilitates formation of Mannich bases (XXXV) (63, 96–100).

Atkinson and Rees (101) noted that amination of I with hydroxylamine-*O*-sulfonic acid readily produces 3-amino-2-benzoxazolinone (XXXVI). Oxidation of the latter with lead tetraacetate produces a nitrene which



XXXV

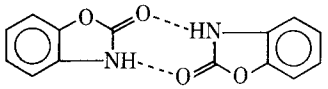
when reacted with various mono or dieneophiles produces ethyleneimine derivatives (XXXVII). Two unsaturated derivatives (XXXVII) undergo thermal re-



XXXVIII XXXVII*a*, R = $CHCH_2$, R′ = H
b, R = $C(CH_3)CH_2$, R′ = CH_3

arrangement (102) to the 3-pyrrolino compounds (XXXVIII, R′ = H, CH_3), whereas others produce 3-unsaturated aliphatic amino-2-benzoxazolinones (103).

Spectral Properties of 2-Benzoxazolinones—As discussed earlier, Hartley *et al.* (84) and Lucas and Vantu (86) investigated the UV absorption of I. O'Sullivan (104) reported that I exhibits strong IR carbonyl absorption at 1770 and 1725 cm.$^{-1}$ in potassium bromide disks. The observed doublet was attributed to dimer links between the C=O and N—H groups (XXXIX). Smissman *et al.*



XXXIX

(46) observed only a singlet carbonyl band for XX at 5.7 μ. Examination of IR spectra of various nuclear substituted 2-benzoxazolinones (62) likewise has shown that some 2-benzoxazolinones give doublet carbonyl bands whereas others give only singlet bands. More recently (91, 100) IR absorption data was reported for a number of 3-substituted-2-benzoxazolinones. Only a singlet carbonyl band in the region of 1800–1730 cm.$^{-1}$ was noted in the compounds studied. According to Gompper (105) this is indicative of *N*-substitution, exclusively.

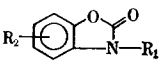
NMR data was reported for 5-trifluoromethyl-2-benzoxazolinone (91). This compound like other mono- or di-nuclear substituted 2-benzoxazolinones gives multiplet aromatic absorptions (62). The N—H proton has no characteristic chemical shift associated with different aromatic substituents; in some instances this shift is obscured by other absorption patterns.

Pharmacological Properties of 2-Benzoxazolinones—The pharmacological properties of various 2-benzoxazolinones are noted briefly in Tables I and II. Since the observation of Lespagnol and Cannesson (88) that 3-substituted-2-benzoxazolinones possess anesthetic properties, many reports containing accounts of other effects of 2-benzoxazolinones have appeared. For the most part, these are reviewed by Cain and Roszkowski (2). One of the most notable compounds in this area is 5-chloro-2-benzoxazolinone which possesses useful muscle relaxant properties. Other 2-benzoxazolinones possess analgesic, antipyretic, hypnotic, anticonvulsant, antibacterial, anthelmintic, and antihistaminic properties when administered to experimental animals.

Several groups of workers have demonstrated that 2-benzoxazolinones are metabolized in part through hydroxylation of the aromatic ring (106–108) and that the ring essentially remains intact.

Patane and Arcerito (109) recently demonstrated that sodium phenobarbital has the ability to produce induction into the enzyme which is responsible for metabolism of 5-chloro-2-benzoxazolinone. Presumably, this is the enzyme which is responsible for the 6-hydroxylation of 2-benzoxazolinones.

Table II—Literature References to Synthesis and Pharmacology of 3-Substituted-2-Benzoxazolinone



No.	R_1	R_2	Refs. to Synthesis	Pharmacol. Activity	Refs.
1	CH_3	H	6, 61, 64, 113	Anticonvulsant, anthelmintic, hypnotic	110, 113, 114, 145
2	CH_3	5-Cl	12, 28, 92	Muscle relaxant	12
3	CH_3[a]	6-Cl	6	Analgesic	6
4	CH_3	5,6-diCl	93	Antibacterial, antifungal	93
5	CH_3	5-Cl-6-Br	93	Antibacterial, antifungal	93
6	CH_3	4-NO_2	63	Fungicide	63
7	CH_3	5-NO_2	63	Fungicide	63
8	CH_3	6-NO_2	20, 63, 144	Antimicrobial	144
9	CH_3	7-NO_2	63	Fungicide	63
10	CH_3	5,7-diNO_2	65		
11	CH_3	4-NH_2	24		
12	CH_3	5-NH_2	4		
13	CH_3	6-NH_2	20, 24, 144	Anticonvulsant, antimicrobial	20, 144
14	CH_3	7-NH_2	2		
15	CH_3	4-$NHCOCH_3$	24		
16	CH_3	5-$NHCOCH_3$	24		
17	CH_3	6-$NHCOCH_3$	24		
18	CH_3	7-$NHCOCH_3$	24		
19	CH_3	6-N=CH-C_6H_5	144	Antimicrobial	144
20	CH_3[a]	5-$(CH_2)_4CH_3$	6	Analgesic	6
21	CH_3	4-OCH_3	24		

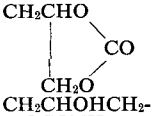
(*continued on next page*)

Table II (*continued*)

No.	R_1	R_2	Refs. to Synthesis	Pharmacol. Activity	Refs.
22	CH_3	5-OCH_3	24		
23	CH_3	6-OCH_3	24		
24	CH_3	7-OCH_3	24		
25	CH_3	6-$NHCONH_2$	20	Anticonvulsant	20
26	CH_2CH_3	H	3,113	Anticonvulsant	113
27	CH_2CH_3	5,6-diCH_3	6	Analgesic	6
28	CH_2CH_3	5-Cl	12,92	Muscle relaxant	12
29	CH_2CH_3	5-Cl-6-Br	93	Antibacterial, antifungal	93
30	CH_2CH_3	5,6-diCl	93	Antibacterial, antifungal	93
31	$(CH_2)_2CH_3$	H	91		
32	$(CH_2)_2CH_3$	5-Cl	92		
33	$(CH_2)_2CH_3$	5,6-diCl	93	Antibacterial, antifungal	93
34	$(CH_2)_2CH_3$[a]	5-Cl-6-Br	93	Antibacterial, antifungal	93
35	$(CH_2)_2CH_3$	5-$(CH_2)_4CH_3$	6	Analgesic	6
36	$CH(CH_3)_2$	6-Cl	6	Analgesic	6
37	CH_2CHCH_2	H	6	Anticonvulsant, hypnotic, anthelmintic	110, 114, 145
38	CH_2CHCH_2	5-Cl	12	Muscle relaxant	12
39	CH_2CHCH_2[b]	5-Cl-6-Br	91		91
40	CH_2CCH	H	91	Hypnotic	91
41	$(CH_2)_3CH_3$[a]	H	6	Analgesic	6
42	$(CH_2)_3CH_3$	5-CH_3	6	Analgesic	6
43	$(CH_2)_3CH_3$	5-$(CH_2)_2CH_3$	6	Analgesic	6
44	$(CH_2)_3CH_3$[a]	5,6-diCH_3	6	Analgesic	6
45	$CH_2CH(CH_3)_2$[a]	H	6	Analgesic	6
46	$CH_2CH(CH_3)_2$[a]	5-CH_3	6	Analgesic	6
47	$CH_2CH(CH_3)_2$	5-$(CN_2)_2CH_3$	6	Analgesic	6
48	$CH_2CH(CH_3)_2$	5-$(CH_2)_4CH_3$	6	Analgesic	6
49	$CH_2CH(CH_3)_2$	5-OCH_3	6	Analgesic	6
50	$(CH_2)_4CH_3$	H	6	Analgesic	6
51	$(CH_2)_4CH_3$[a]	5-CH_3	6	Analgesic	6
52	$(CH_2)_4CH_3$[a]	5-$(CH_2)_2CH_3$	6	Analgesic	6
53	$(CH_2)_4CH_3$[a]	5-$(CH_2)_4CH_3$	6	Analgesic	6
54	$(CH_2)_4CH_3$	5-OCH_3	6	Analgesic	6
55	$(CH_2)_2CH(CH_3)_2$	H	6	Analgesic	6
56	$(CH_2)_2CH(CH_3)_2$[a]	5-CH_3	6	Analgesic	6
57	$(CH_2)_2CH(CH_3)_2$	6-Cl	6	Analgesic	6
58	$(CH_2)_2CH(CH_3)_2$[a]	5-$(CH_2)_2CH_3$	6	Analgesic	6
59	$(CH_2)_2CH(CH_3)_2$	5,6-diCH_3	6	Analgesic	6
60	$CH_2CH(CH_3)$-CH_2CH_3	H	6	Analgesic	6
61	$CH_2CH(CH_3)$-CH_2CH_3[a]	5-CH_3	6	Analgesic	6
62	$CH_2CH(CH_3)$-CH_2CH_3[a]	5-$(CH_2)_2$-CH_3	6	Analgesic	6
63	$COCH_3$[a]	H	5,6,96	Analgesic	6,112
64	$COCH_3$	6-Cl	21		
65	$COCH_3$	6-F	21		
66	$COCH_3$	6-Br			
67	$COCH_3$	6-I	21		
68	$COCH_3$	6-CN	21		
69	$COCH_3$	5-Br	146		
70	$COCH_3$	5,7-diBr	89,146		
71	$COCH_3$	5,7-diNO_2	65		
72	$COCH_3$	5-CH_3	146		
73	$COCH_3$	6-CH_3	146		
74	$COCH_3$	7-CH_3	146		
75	$COCH_3$	5-OCH_3	6	Analgesic	6
76	$COCH_3$	4-$NHCOCH_3$	24		
77	$COCH_3$	5-$NHCOCH_3$	24		
78	$COCH_3$	6-$NHCOCH_3$	20,24	Anticonvulsant	20
79	$COCH_3$	7-$NHCOCH_3$	24		
80	$COCH_3$	5-CH_3-7-Br	89		
81	$COCH_3$	4-O_2CCH_3	24		
82	$COCH_3$	5-O_2CCH_3	24		
83	$COCH_3$	6-O_2CCH_3	24		
84	$COCH_3$	7-O_2CCH_3	24		
85	$CONH_2$	H	91		
86	$CON(CH_3)_2$	H	91	Muscle relaxant	91
87	COC_6H_5	H	5		
88	COC_6H_5	5-CH_3-7-Br	89		
89	COC_6H_5	6-OCH_3	46		
90	CO-*p*-$NO_2C_6H_4$	H	64		
91	$COC_7H_2NO_2$[c]	H	96		
92	$(CO)_2C_7H_4NO_2$[c]	H	96		
93	$COCH_2COC_7H_4$-NO_2[c]	H	96		
94	$CO(CH_2)_2COC_7$-H_4NO_2[c]	H	96		
95	$C_7H_3ClNO_2$[d]	5-Cl	28		
96	COC_4H_3O[e]	H	147		
97	$COCH(C_6H_5)_2$	6-$NHCOCH$-$(C_6H_5)_2$	20		
98	CO_2CH_3	5-CH_3-7-Br	89		
99	$CO_2CH_2CH_3$	5-CH_3-7-Br	89		
100	$CO_2(CH_2)CH_3$	5-CH_3-7-Br	89		
101	$CO_2(CH_2)_3CH_3$	5-CH_3-7-Br	89		
102	$CO_2C_6H_5$	5-CH_3-7-Br	89		
103	CO_2-*o*-$CH_3C_6H_4$	5-CH_3-7-Br	89		
104	CO_2-*m*-$CH_3C_6H_4$	5-CH_3-7-Br	89		
105	CO_2-*p*-$CH_3C_6H_4$	5-CH_3-7-Br	89		
106	CO_2-2-$NO_2C_6H_4$	5-CH_3-7-Br	89		
107	CO_2-2,4-di-ClC_6H_3	5-CH_3-7-Br	89		
108	CO_2-2,4,6-tri-BrC_6H_2	5-CH_3-7-Br	89		
109	CO_2-3-CH_3-6-$CH(CH_3)_2$-C_6H_3	5-CH_3-7-Br	89		
110	CO_2-3-CH_3-4-Cl-6-CH-$(CH_3)_2C_6H_5$	5-CH_3-7-Br	89		
111	CO_2-3-CH_3-4-Br-6-CH-$(CH_3)_2C_6H_2$	5-CH_3-7-Br	89		
112	CO_2-4-$C_6H_4C_6H_5$	5-CH_3-7-Br	89		
113	CO_2-α-$C_{10}H_7$[f]	5-CH_3-7-Br	89		
114	CO_2-β-$C_{10}H_7$[f]	5-CH_3-7-Br	89		
115	SO_2CH_3	H	64		
116	SO_2CH_3	5-NO_2	63		
117	SO_2CH_3	6-NO_2	63		
118	SO_2CH_3	7-NO_2	63		
119	$SO_2C_6H_5$	H	64		
120	$SO_2C_6H_5$	5-NO_2	63		
121	$SO_2C_6H_5$	6-NO_2	63		
122	$SO_2C_6H_5$	7-NO_2	63		
123	$SO_2C_6H_5$	5-CH_3-7-Br	89		
124	$SO_2C_6H_5$	6-OCH_3	46		
125	SO_2-*p*-$NH_2C_6H_4$	H	64		
126	SO_2-*p*-NH-$COCH_3C_6H_4$	H	64		
127	SO_2-*p*-$CH_3C_6H_4$	H	64		
128	SO_2-*p*-$CH_3C_6H_4$	5-NO_2	63		
129	SO_2-*p*-$CH_3C_6H_4$	6-NO_2	63		
130	SO_2-*p*-$CH_3C_6H_4$	7-NO_2	63		
131	$CH_2N(CH_3)_2$	H	96,100	Antimicrobial	100
132	$CH_2N(CH_2CH_3)_2$	H	96		
133	$CH_2N[(CH_2)_3$-$CH_3]_2$	H	96		
134	$CH_2C_5H_{10}N$[g]	H	96	Antimicrobial	100
135	$CH_2C_5H_{10}N$[g]	5-NO_2	63		
136	$CH_2C_5H_{10}N$[g]	6-NO_2	63		
137	$CH_2C_5H_{10}N$[g]	5-Cl	100	Antimicrobial	100
138	CH_2-2-CH_3-$C_5H_{10}N$[g]	H	100	Antimicrobial	100
139	CH_2-3-CH_3-$C_5H_{10}N$[g]	H	100	Antimicrobial	100
140	CH_2-3-CH_3-$C_5H_{10}N$[g]	5-Cl	100	Antimicrobial	100

(*continued on next page*)

Table II (*continued*)

No.	R_1	R_2	Refs. to Synthesis	Pharmacol. Activity	Refs.
141	CH_2-4-CH_3-$C_5H_{10}N$[g]	H	100	Antimicrobial	100
142	CH_2-4-$CH_3C_5H_{10}N$[g]	5-Cl	100	Antimicrobial	100
143	CH_2-4-$(CH_2)_3C_6H_4$-$C_5H_{10}N$[g]	H	100	Antimicrobial	100
144	CH_2-4-$(CH_2)_3C_6H_4$ $C_5H_{10}N$[g]	5-Cl	100	Antimicrobial	100
145	CH_2-4-C_6H_5-$C_5H_{10}N$[g]	H	100	Antimicrobial	100
146	CH_2-4-C_6H_5-$C_5H_{10}N$[g]	5-Cl	100	Antimicrobial	100
147	CH_2-4-$(CH_2)_3$-4′$C_5H_{10}N$-1-$(CH_2)_2OHC_5H_{10}N$[g]	H	100	Antimicrobial	100
148	CH_2-4-$(CH_2)_3$-4′-$C_5H_{10}N$-1′-$(CH_2)_2OHC_5H_{10}N$[g]	5-Cl	100	Antimicrobial	100
149	$CH_2C_6H_5N$[h]	H	100	Antimicrobial	100
150	$CH_2C_4H_6N$[h]	5-Cl	100	Antimicrobial	100
151	$CH_2C_4H_8NO$[h]	H	100	Antimicrobial	100
152	$CH_2C_4H_8NO$[i]	5-Cl	100	Antimicrobial	100
153	$CH_2C_4H_8NO$[i]	5-NO_2	63	Antimicrobial	100
154	$CH_2C_4H_8NO$[i]	6-NO_2	63	Antimicrobial	100
155	$CH_2C_4H_8NO$[i]	7-NO_2	63	Antimicrobial	100
156	$CH_2C_6H_{12}N$[j]	H	100	Antimicrobial	100
157	$CH_2C_8H_{12}N$[j]	5-Cl	100	Antimicrobial	100
158	CH_2-2,6-diCH_3-C_4H_8NO[i]	H	100	Antimicrobial	100
159	$CH_2C_8H_{14}N$[k]	H	100	Antimicrobial	100
160	$CH_2C_8H_{14}N$[k]	5-Cl	100	Antimicrobial	100
161	$CH_2C_7H_4NO_2$[l]	H	96		
162	$CH_2NHC_6H_5$	H	97		
163	CH_2NH-*o*-CH_3-C_6H_4	H	97		
164	CH_2NH-*m*-$CH_3C_6H_4$	H	97		
165	CH_2NH-*p*-$CH_3C_6H_4$	H	97		
166	CH_2NH-*o*-ClC_6H_4	H	97		
167	CH_2NH-*m*-ClC_6H_4	H	97		
168	CH_2NH-*p*-ClC_6H_4	H	97		
169	CH_2NH-*o*-$OCH_3C_6H_4$	H	97		
170	CH_2NH-*p*-$OCH_3C_6H_4$	H	97		
171	CH_2NH-*p*-OCH_2-$CH_3C_6H_4$	H	97		
172	CH_2NH-*m*-BrC_6H_4	H	97		
173	CH_2NH-*p*-BrC_6H_4	H	97		
174	CH_2NH-*p*-$NHOCH_3$-C_6H_4	H	97		
175	CH_2NH-3,4-di$CH_3C_6H_3$	H	97		
176	CH_2NH-2,4,5-tri$CH_3C_6H_2$	H	97		
177	CH_2NH-2,4,6-tri$CH_3C_6H_2$	H	97		
178	CH_2NH-2-$C_{10}H_7$[f]	H	97		
179	CH_2NH-2-C_5H_4N[l]	H	97		
180	CH_2NH-2,4-diClC_6H_3	H	97		
181	CH_2NH-*o*-NH-$C_6H_4CH_2$-$C_7H_4NO_2$[c]	H	97		
182	CH_2NH-*p*-NH-$C_6H_4CH_2C_7H_4NO_2$[c]	H	97		
183	$CH(NHC_6H_5)$-C_6H_5	H	97		
184	$CH_2(NHC_6H_5)_2$-$CH_2C_7H_4NO_2$[c]	H	97		
185	$CH(C_6H_5)CH_2$-COC_6H_5	H	97		
186	$CH_2N(CH_2CH_2Cl)_2$	H	99	Antitumor	99
187	$CH_2C_7H_4NOS$[m]	H	77(*b*)		
188	$CH_2C_5H_{10}$[n]	5-Cl	92		
189	CH_2OH	H	96		
190	CH_2CCOCH_3	H	96		
191	$(CH_2)_2C_2CCH_3$	H	90,148		
192	$(CH_2)_2C_2CCH$-$(C_6H_5)_2$	H	90,148		
193	C_6H_5	H	90,148		
194	$(CH_2)_2O_2C$-*p*-$NO_2C_6H_4$	H	90,148		
195	$(CH_2)_2O_2C$-*p*-$NH_2C_6H_4$	H	90,148		
196	$(CH_2)_2OH$	H	90,113,148	Anticonvulsant	113
197	$(CH_2)_3OH$	H	91		
198	$CH_2CHOHCH_2OH$	H	91	Muscle relaxant	91
199		H	91		
200	$CH_2CHOHCH_2OCONH_2$	H	91		
201	$(CH_2)_3OCONH_2$	H	91	Muscle relaxant	91
202	$(CH_2)_3OCH_3$	5,6-diCl	91	CNS depressant	91
203	CH_2CO_2H	H	90,113	Anticonvulsant	113
204	$CH_2C(Br)CH_2$	H	90,148		
205	$(CH_2)_2Br$	H	90,148		
206	9-$C_5H_3N_5O_2$[o]	H	90		
207	$(CH_2)_2$-3-$C_7H_4NO_2$[c]	H	96		
208	$(CH_2)_3$-3-$C_7H_4NO_2$[c]	H	96		
209	$(CH_2)_4$-3-$C_7H_4NO_2$[c]	H	96		
210	$(CH_2)_5$-3-$C_7H_4NO_2$[c]	H	96		
211	$(CH_2)_6$-3-$C_7H_4NO_2$[c]	H	96		
212	CH_2Cl	H	96		
213	$(CH_2)_2Cl$	H	90,148	Analgesic	112
214	$(CH_2)_2Cl$	5-Cl	92		
215	$(CH_2)_2Cl$	5,6-diCl	93		
216	$(CH_2)_2Cl$	5-Cl-6-Br	93		
217	$(CH_2)_3Cl$	H	91		
218	$(CH_2)_3Cl$	5-CF_3	91		
219	$(CH_2)_3Cl$[b]	5,6-diCl	91		
220	$(CH_2)_3Cl$[b]	5-Cl-6-Br	91		
221	$(CH_2)_2N(CH_3)_2$	H	149		
222	$(CH_2)_2N(CH_2CH_3)_2$	H	11,90,113,149,150	Anticonvulsant, Hypnotic, antihistaminic, local anesthetic	113,150
223	$(CH_2)_2N(CH_2CH_3)_2$	5-F	13		

(*continued on next page*)

Table II (*continued*)

No.	R_1	R_2	Refs. to Synthesis	Pharmacol. Activity	Refs.
224	$(CH_2)_3N(CH_3)_2$	H	11		
225	$(CH_2)_3N(CH_3)_2$	5-CF_3	91		
226	$(CH_2)_3C_5H_{11}N_2$[p]	5-F	13		
227	$(CH_2)_3C_5H_{11}N_2$[p]	5-Cl	13		
228	$(CH_2)_3C_5H_{12}N_2$[p]	H	13		
229	$(CH_2)_3C_6H_{13}N_2O$[q]	H	13		
230	$(CH_2)_3C_6H_{13}N_2O$[q]	5-Cl	13		
231	$(CH_2)_3C_6H_{13}N_2O$[q]	5-F	13		
232	$(CH_2)_3C_8H_4NO_2$[r]	H	91		
233	$(CH_2)_3C_8H_4NO_2$[r]	5-Cl-6-Br	91		
234	$(CH_2)_3C_8H_4NO_2$[r]	5,6-diCl	91		
235	$CH_2SP(S)(OCH_3)_2$	H	151	Insecticide, fungicide	151
236	$CH_2SP(S)(OCH_2CH_3)_2$	H	151	Insecticide, fungicide	151
237	$CH_2SP(S)(OCH_3)_2$	6-Cl	151	Insecticide, fungicide	151
238	$CH_2SP(S)(OCH_3)_2$	6-Br	151	Insecticide, fungicide	151
239	$CH_2SP(O)(OCH_3)_2$	H	151	Insecticide, fungicide	151
240	$SC(Cl)_3$	H	152, 153	Fungicide	152
241	$SC(Cl)_3$	6-Br	152, 153	Fungicide	152
242	$SC(Cl)_3$	6-NO_2	152, 153	Fungicide	152
243	$SC(Cl)_3$	5-$C(CH_3)_3$	152, 153	Fungicide	152
244	$SC(Cl)_3$	6-Cl	152, 153	Fungicide	152
245	$SC(Cl)_3$	5,7-diCl	152, 153	Fungicide	152
246	$SC(Cl)_3$	5,6-diCH_3	152	Fungicide	152
247	$SC(Cl)_3$	5,7-diCH_3	152	Fungicide	152
248	$SC(Cl)_3$	7-CH_3	153		
249	$SC(Cl)_3$	6-OCH_3	153		
250	$SC(Cl)_3$	6-F	153		
251	$SC(Cl)_3$	5-Br	153		
252	$SC(Cl)_3$	6-I	153		
253	$SO_2C_6H_4SO_2$-CH_2Cl-*p*-	H	153		
254	$HgCH_3$	H	154	Fungicide	154
255	$HgCH_3$	6-Cl	154	Fungicide	154
256	$HgCH_2CH_3$	H	154	Fungicide	154
257	$HgCH_2CH_3$	6-Cl	154	Fungicide	154
258	$Hg(CH_2)_2CH_3$	H	154	Fungicide	154
259	$Hg(CH_2)_2CH_3$	6-Cl	154	Fungicide	154
260	$Hg(CH_2)_3CH_3$	H	154	Fungicide	154
261	$Hg(CH_2)_3CH_3$	6-Cl	154	Fungicide	154
262	$Hg(CH_2)_3CH_3$	6-Br	154	Fungicide	154
263	$Hg(CH_2)_3CH_3$	6-I	154	Fungicide	154
264	$Hg(CH_2)_4CH_3$	H	154	Fungicide	154
265	$Hg(CH_2)_4CH_3$	6-Cl	154	Fungicide	154
266	HgC_6H_5	H	154	Fungicide	154
267	HgC_6H_5	6-Cl	154	Fungicide	154
268	$CH_2C_6H_5$	H	11		
269	$C_{26}H_{21}O_7$[s]	H	95		
270	$C_{26}H_{21}O_7$[s]	5,6-diNO_2	95		
271	$C_{26}H_{21}O_7$[s]	5-Cl	95		
272	$C_{26}H_{21}O_7$[s]	5-I	95		
273	$C_{26}H_{21}O_7$[s]	5-NO_2	95		
274	$C_{26}H_{21}O_7$[s]	6-NO_2	95		
275	$C_{26}H_{21}O_7$[s]	6-Cl	95		
276	$C_{26}H_{21}O_7$[s]	5,6-diCl	95		
277	$C_{26}H_{21}O_7$[s]	5-NO_2-7-Cl	95		
278	$C_{26}H_{21}O_7$[s]	5-Cl-6-Br	95		
279	$C_{26}H_{21}O_7$[s]	5-F	95		
280	$C_{26}H_{21}O_7$[s]	5-CF_3	95		
281	$(CH_2)_2NC_5H_{10}$[q]	H	150	Local anesthetic	150

[a] Tested for analgesic activity but showed little or no activity. [b] Only LD_{50} data reported. [c] $C_7H_4NO_2$ = 2-benzoxazolinone. [d] $C_7H_3ClNO_2$ = 5-chloro-2-benzoxazolinone. [e] C_4H_3O = 2-furyl. [f] $C_{10}H_7$ = naphthyl. [g] $C_5H_{10}N$ = piperidino. [h] C_4H_8N = pyrrolidino. [i] C_4H_8NO = morpholino. [j] $C_6H_{12}N$ = hexamethyleneimino. [k] $C_8H_{14}N$ = azabicyclo-[3.2.2]nonanyl. [l] C_5H_4N = pyridyl. [m] C_7H_4NOS = 2-benzoxazolthion-d-yl and 2-benzoxazolylmercapto. [n] C_5H_{10} = cyclopentyl. [o] $C_5H_3N_5O_2$ = xanthenyl. [p] $C_5H_{11}N_2$ = 4-methylpiperazino. [q] 4-(2-Hydroxyethyl)piperazine. [r] Phthalimido. [s] Tri-*O*-benzoyl-β-D-ribopyranoside.

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