Synthesis and Antibacterial Activity of Certain 3-Substituted Benzoxazolinones

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The preparation of a series of 3-substituted 2-benzoxazolinones is described. These compounds were screened for their antibacterial properties; most compounds have shown significant antibacterial activity.

BENZOXAZOLINONES have been associated with various types of biological properties; Lespagnol and co-workers prepared and tested a number of derivatives of 2-benzoxazolinones for their anticonvulsive, hypnotic, antipyretic, and analgesic effects (1). 2-Benzoxazolinone and its 3-methyl, 3-ethyl, and 3-hydroxyethyl derivatives elicited the greatest anticonvulsant activity, whereas the 3-acetamido, 3-dihydroxyethyl, and 3-diethylaminoethyl derivatives exhibited marked analgesic activity. 2-Benzoxazolinone has also been reported to inhibit the growth of *Pseudomonas aeruginosa* (2), whereas its quaternary ammonium complexes have shown bactericidal properties (3).

The pronounced biological activity of many benzoxazole derivatives (4, 5) and the medicinal value of 5-chloro-2-benzoxazolinone (6) prompted the investigation of 3-substituted-2-benzoxazolinones. In this article the preparation of a number of 3-substituted-2-benzoxazolinones and their antibacterial activity are reported.

DISCUSSION

The compounds listed in Table I were prepared by the condensation of 2-benzoxazolinone, formaldehyde, and the appropriate secondary amine. The reaction usually occurred in the cold, but, in certain cases, warming for a few minutes resulted in improved yields. The source of formaldehyde was either formalin or paraformaldehyde; both gave satisfactory products. The condensations were performed in both ethanol or *p*-dioxane. Ethanol was usually preferred to *p*-dioxane.

Condensation of 2,6-dimethylpiperidine, as might be expected due to steric factors, with 2-benzoxazolinone did not yield the 2,6-dimethylpiperidinomethyl derivative, but gave instead a product whose analytical data, melting point, mixed melting point, and infrared spectra were identical with 3-hydroxymethyl-2-benzoxazolinone (XXIV). Under identical conditions 5-chloro-2-benzoxazolinone gave 3-hydroxymethyl-5-chloro-2-benzoxazolinone (XXV). While using 5-chloro-2-benzoxazolinone, 2,6-dimethylmorpholine also did not yield 3-(2,6-dimethylmorpholinomethyl)-5-chloro-2-benzoxazoline, but gave instead compound XXV.

The NMR spectrum (CCl_4) of compound III (Table I) was in complete agreement with the proposed structure. A multiplet representing protons (4H) of the aromatic ring and a singlet due to the $-N-CH_2-N-$ protons were observed at 6.9–7.2 δ and 4.5 δ, respectively. Four protons of the two methylene groups adjacent to the nitrogen were attributed to a doublet centered at 2.6 δ. A broad singlet observed at 1.5 was assigned to the methylene protons (6H) remote from the nitrogen.

Treatment of 2-benzoxazolinone with formaldehyde in the absence of amine furnished compound XXIV. The infrared spectrum of compound XXIV showed a band of medium intensity at 3400 cm.$^{-1}$ (OH, stretching) and a broad strong band at 1750 cm.$^{-1}$ (C=O, stretching). 5-Chloro-2-benzoxazolinone under identical conditions yielded compound XXV. The infrared spectrum of compound XXV exhibited a band of medium intensity at 3380 cm.$^{-1}$ (OH, stretching) and a strong band at 1755 cm.$^{-1}$ (C=O, stretching). In its NMR spectrum (CD_3CN) a complex multiplet was observed at 7 δ and a singlet at 5.16 δ which might be attributed to aromatic (3H) and methylene (2H) protons, respectively. The spectrum also showed a singlet at 4.18 δ which was assigned to the hydroxyl protons. The peak due to the hydroxyl group disappeared on D_2O exchange.

3-Hydroxymethyl-5-chloro-2-benzoxazolinone (XXV), on treatment with acetic anhydride, gave 3-acetoxymethyl-5-chloro-2-benzoxazolinone (XXVI). The infrared spectrum of this compound exhibited a doublet at 1785 cm.$^{-1}$ (ring carbonyl) and 1720 cm.$^{-1}$ (ester carbonyl). Compound XXV reacted with phosphorous tribromide to yield compound XXVII. Its infrared spectrum showed a strong band at 1780 cm.$^{-1}$ (C=O, stretching). The spectrum did not show hydroxyl absorption, thus indicating that the reaction has taken place. The NMR spectrum (CCl_4) of compound XXVII demonstrated singlets at 6.96 δ and 5.45 δ; these were assigned to aromatic (3H) and methylene (2H) protons, respectively.

The reaction of compound XXIV with 2-nitrophenylisocyanate furnished compound XXVIII. Its infrared spectrum showed characteristic absorptions at 3390 cm.$^{-1}$ (–NH–), 1790 cm.$^{-1}$ (ring carbonyl), and 1770 cm.$^{-1}$ (–C(=O)–NH–). Likewise compound XXV gave compound XXIX on treatment with 2-nitrophensyliocyanate. Its infrared

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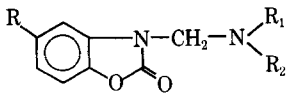
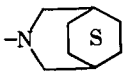
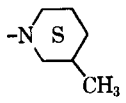
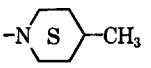
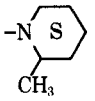
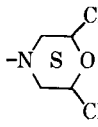
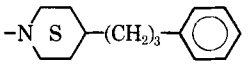
TABLE I—DIALKYLAMINOMETHYL-2-BENZOXAZOLINONES



R = H

Compd.	—N(R1)(R2)	Mol. Formula	Anal., % Calcd.	Anal., % Found	M.p., °C.	Yield, %[b]	Infrared cm.$^{-1}$ C=O
I[d,e]		$C_{16}H_{20}N_2O_2$	C, 70.56 H, 7.40 N, 10.29	70.80 7.53 10.17	159–160	94	1750
II[d,f]		$C_{10}H_{12}N_2O_2$	C, 62.49 H, 6.29 N, 14.57	...	125–126	76	1745
III[c,d,f]		$C_{13}H_{16}N_2O_2$	C, 67.22 H, 6.94 N, 12.06	66.93 6.85 12.26	139–140	60	1750
IV		$C_{14}H_{18}N_2O_2$	C, 68.27 H, 7.37 N, 11.37	68.52 7.55 11.47	150–152	62	1745
V[d]		$C_{14}H_{18}N_2O_2$	C, 68.27 H, 7.37 N, 11.37	68.55 7.50 11.59	107–108	67	1770
VI[d,]		$C_{12}H_{14}N_2O_3$	C, 61.53 H, 6.02 N, 11.96	...	148–150	83	1740
VII[d]		$C_{14}H_{18}N_2O_2$	C, 68.27 H, 7.37 N, 11.37	68.37 7.44 11.53	72–75	48	1765
VIII[d]	HMI[a]	$C_{14}H_{18}N_2O_2$	C, 68.27 H, 7.37 N, 11.37	68.50 7.50 11.42	110–111	73	1750
IX[d]		$C_{14}H_{18}N_2O_3$	C, 64.11 H, 6.92 N, 10.68	64.29 7.14 10.87	143–144	51	1765
X[d]		$C_{22}H_{26}N_2O_2$	C, 75.40 H, 7.48 N, 7.99	75.64 7.65 8.07	134–135	70	1745

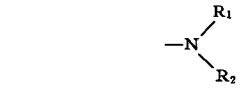
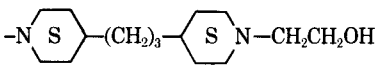
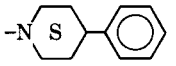
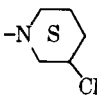
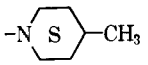
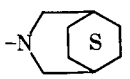
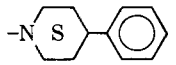
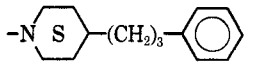
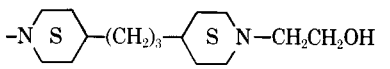
(*Continued on next page.*)

spectrum exhibited absorption bands at 3300 cm.$^{-1}$ (–NH–), 1790 cm.$^{-1}$ (ring carbonyl), and 1740 cm.$^{-1}$ (–C(=O)–NH–). Aniline in the presence of formaldehyde reacted with 5-chloro-2-benzoxazolinone to give compound XXX. Characteristic absorption bands were observed at 3380 cm.$^{-1}$ (–NH–) and 1750 cm.$^{-1}$ (C=O). 3,4,5-Trimethoxybenzoyl chloride in benzene solution successfully reacted with compound XXIV to yield compound XXXI. Its infrared spectrum showed a doublet at 1790 cm.$^{-1}$ (ring carbonyl) and 1720 cm.$^{-1}$ (ester carbonyl). Similarly, compound XXV yielded compound XXXII on treatment with 3,4,5-trimethoxybenzoyl chloride. A doublet was observed at 1800 cm.$^{-1}$ (ring carbonyl) and 1730 cm.$^{-1}$ (ester carbonyl) in the infrared spectrum of compound XXXII. The sequence of these reactions is described in Scheme I.

BIOLOGICAL DATA

All compounds reported here were subjected to preliminary antibacterial screening procedures except compounds XXIV, XXV, and XXVII. Filter paper disks (6.35 mm.), saturated with 2 drops of the solution or suspension of the test compound (20 mg./ml. in ethanol), were placed on the agar. The microbial spectrum consisted of four organisms: *Pseudomonas aeruginosa*, *Staphylococcus aureus* K257, *Mycobacterium smegmatis*, and *Klebsiella pneumoniae* ATCC8052. After 4 days of incubation, the zones of inhibition around the disks were measured. Out of the 29 compounds screened, 20 compounds inhibited the growth of *Ps. aeruginosa*, 19 compounds inhibited the growth of *S. aureus*

TABLE I—(*Continued.*)

Compd.		Mol. Formula	Anal., % Calcd.	Found	M.p., °C.	Yield, %[b]	Infrared cm.$^{-1}$ C—O
XI[d]		$C_{12}H_{14}N_2O_2$	C, 66.04 H, 6.47 N, 12.84	65.82 6.62 12.82	114–115	88	1750
XII[d]		$C_{22}H_{35}N_3O_3$	C, 68.80 H, 8.79 N, 10.46	68.50 8.90 10.60	107–108	56	1770
XIII[d]		$C_{19}H_{20}N_2O_2$	C, 74.00 H, 6.54 N, 9.08	74.17 6.73 9.08	174–175	84	1765
		R = Cl					
XIV[d]		$C_{12}H_{13}ClN_2O_2$	C, 58.53 H, 5.67 N, 10.51	58.76 5.84 10.31	108–109	56	1775
XV[d]		$C_{12}H_{13}ClN_2O_3$	C, 53.64 H, 4.88 N, 10.43	53.51 4.83 10.33	154–155	89	1775
XVI		$C_{14}H_{17}ClN_2O_2$	C, 59.88 H, 6.11 N, 9.98	60.04 6.28 10.02	89–90	48	1760
XVII[d]		$C_{14}H_{17}ClN_2O_2$	C, 59.88 H, 6.11 N, 9.98	60.01 6.23 10.04	91–93	60	1790
XVIII[d]		$C_{16}H_{19}ClN_2O_2$	C, 62.64 H, 6.24 N, 9.13	62.57 6.20 9.20	155	65	1780
XIX[d]	HMI[a]	$C_{14}H_{17}ClN_2O_2$	C, 59.88 H, 6.11 N, 9.98	59.73 5.91 9.81	68–69	53	1790
XX		$C_{19}H_{19}ClN_2O_2$	C, 66.57 H, 5.59 N, 8.17	66.76 5.70 7.96	173–174	70	1775
XXI[d]		$C_{22}H_{25}ClN_2O_2$	C, 68.64 H, 6.55 N, 7.28	68.48 6.41 7.15	87–88	73	1785
XXII[d]		$C_{12}H_{13}ClN_2O_2$	C, 57.12 H, 5.18 N, 11.09	57.02 5.32 10.86	74–78	40	1780
XXIII[d]		$C_{28}H_{34}ClN_3O_3$	C, 63.33 H, 7.86 N, 9.64	63.04 8.03 9.40	98–99	57	1780

[a] Hexamethyleneimino. [b] Yields are of the products obtained from first crystallization. [c] Prepared by method *A*. [d] Prepared by method *B*. [e] Prepared by method *C*. [f] Lit. (7) reports m.p. for II, III, VI, 126°, 110°, 148°, respectively.

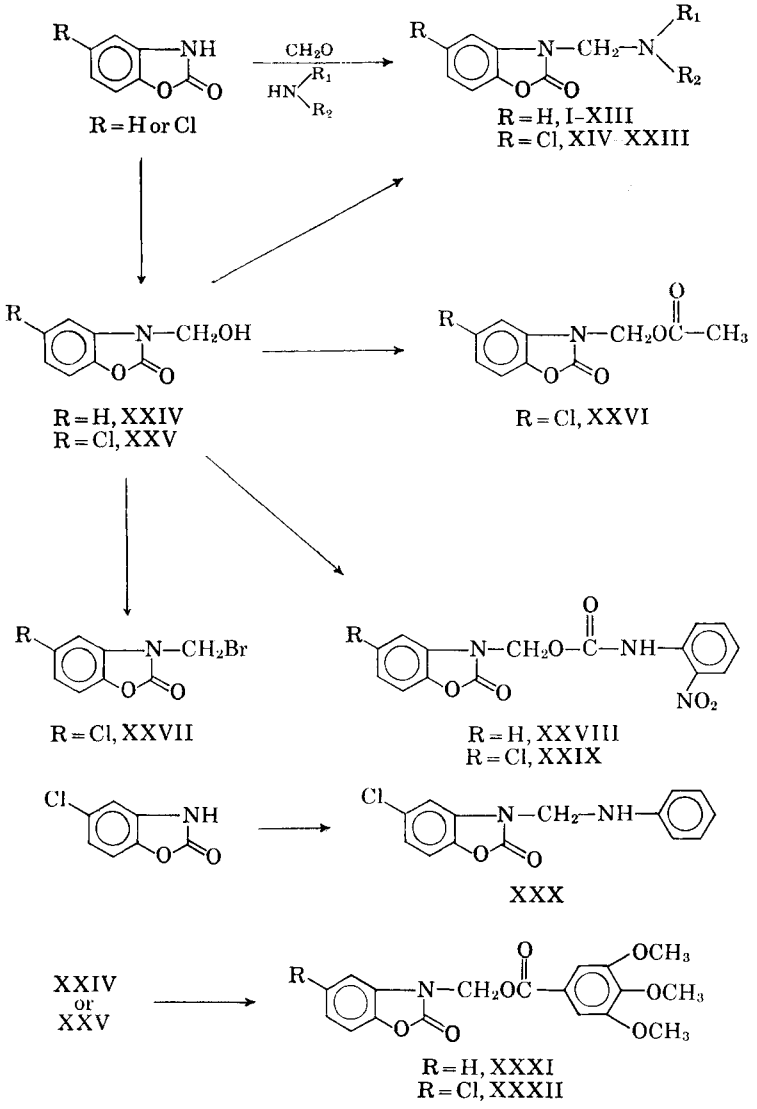
K257, 9 inhibited the growth of *M. smegmatis*, and 21 inhibited the growth of *K. pneumoniae* ATCC-8052. Zone sizes smaller than 6.35 mm. were considered to provide no inhibition of the growth of the organisms. A blank space indicates no activity.

The width of the zone of inhibition around a disk containing the compound depends to some extent on the rate of diffusion of the compound through the medium. A compound that diffuses very slowly through the agar may show a smaller zone of inhibition, but it might demonstrate a greater effect *in vivo* than another compound that showed a greater zone of inhibition *in vitro* because of the greater diffusion rate. This has been shown to be true with certain commercially available antibiotics. Because of this effect, even a narrow zone of inhibition *in vitro* may indicate a compound with potential usefulness. (See Table II.)

EXPERIMENTAL

Melting points were determined on a Thomas-Hoover apparatus and are uncorrected. Infrared spectra were determined on a Perkin-Elmer model 137 Infracord spectrophotometer in Nujol mull. NMR spectra were charted on a Varian A-60 spectrometer using tetramethylsilane as the internal standard. Microanalyses were performed by Galbraith Microanalytical Laboratories, Knoxville, Tenn.

N-Dialkylaminomethyl-2-benzoxazolinones (I–XXIII, Table I)—*Method A*—2-Benzoxazolinone



Scheme I

(0.05 mole), paraformaldehyde (2.25 Gm.), ethanol (25 ml.), and appropriate secondary amine (0.05 mole) were mixed thoroughly in a 100-ml. round-bottom flask. The reaction mixture was refluxed for 4 hr. At the end of this time, the contents were cooled in a refrigerator, and the product thus separated was collected on a filter.

Method B—To a suspension of 2-benzoxazolinone (0.05 mole) in 20 ml. of ethanol, were added 7.5 ml. of 37% formalin and appropriate secondary amine (0.05 mole). During addition of amine, the reaction mixture became warm. It was kept at room temperature for 30 min. and then heated for another 30 min. on a water bath. The reaction mixture upon cooling furnished the desired product.

Method C—A mixture of 3-hydroxymethyl-2-benzoxazolinone (0.02 mole), amine (0.02 mole), and ethanol (50 ml.) was refluxed for 4 hr. The reaction mixture was cooled, and the product thus separated was recrystallized from a suitable solvent.

Dimethylamine was used as a 25% aqueous solution. When a compound was prepared by more than one method, its identity was always established by comparison of melting points, mixed melting points, and infrared spectra.

3-Hydroxymethyl-2-benzoxazolinone (XXIV)—2-Benzoxazolinone (6.75 Gm., 0.05 mole) was suspended in 100 ml. of hot distilled water. To this suspension 7.5 ml. of aqueous 37% formaldehyde solution was added, and the reaction mixture was set aside for 24 hr. The product thus separated was recrystallized from chloroform–petroleum ether (60–80°), m.p. 135–136°. [Lit. (7), m.p. 110°.] Mixed melting point with 2-benzoxazolinone, 108–110°; IR: 3400 (OH), 1750 cm.$^{-1}$ (carbonyl).

Anal.—Calcd. for $C_8H_7NO_3$: C, 58.18; H, 4.27; N, 8.48. Found: C, 58.36; H, 4.46; N, 8.58.

3-Hydroxymethyl-5-chloro-2-benzoxazolinone (XXV)—Formalin (9 ml.) was added to a suspension of 10.17 Gm. (0.06 mole) of 5-chloro-2-benzoxazolinone in 100 ml. of hot water. The reaction mixture after keeping at room temperature overnight yields

TABLE II—ANTIBACTERIAL ACTIVITY OF 3-SUBSTITUTED-2-BENZOXAZOLINONES

Compd.	*Ps. aeruginosa*	*S. aureus* K257	*M. smegmatis*	*K. pneumoniae* ATCC8052
I	8[a]	13	...	...
II	13[a]	13[a]	...	16
III	11	...	...	9
IV	8[a]	10[a]	...	9
V	12[a]	16	...	9[a]
VI	10[a]	16	...	9
VII	14[a]	16[a]	...	10
VIII	12[a]	15[a]	...	8[a]
IX	12[a]	13[a]	...	13
X	...	...	20[a]	10[a]
XI	15[a]	12[a]	...	9
XII	9[a]	14	18	10[a]
XIII	...	...	...	...
XIV	13	8	11[a]	11
XV	13[a]	15	...	9
XVI	11[a]	10[a]	15[a]	9
XVII	10[a]	...	20[a]	9
XVIII	9[a]	8	9[a]	8[a]
XIX	12[a]	...	...	11
XX	...	...	...	...
XXI	13	9	30[a]	18
XXII	10[a]	...	...	9
XXIII	9[a]	12	14	8
XXVI	...	8	9[a]	7
XXVIII	...	...	...	...
XXIX	...	8	...	...
XXX	...	10[a]	...	...
XXXI	...	...	...	...
XXXII	...	...	...	...

[a] Partial inhibition.

11.8 Gm. (98%) of the desired product. It was crystallized from ethanol, m.p. 138–143°. IR: 3380 (OH), 1755 cm.$^{-1}$ (carbonyl); NMR: 7 δ (aromatic, 3H), 5.16 δ (-CH_2-), 4.18 δ (OH).

Anal.—Calcd. for $C_8H_6ClNO_3$: C, 48.14; H, 3.03; N, 7.02. Found: C, 48.39; H, 3.22; N, 7.16.

3 - Acetoxymethyl - 5 - chloro - 2 - benzoxazolinone (XXVI)—Acetic anhydride (6 Gm.) was refluxed with 2 Gm. (0.01 mole) of 3-hydroxymethyl-5-chloro-2-benzoxazolinone for 3 hr. and then the whole was poured on crushed ice while stirring. The product thus obtained was crystallized from ethanol, m.p. 76–80°. IR: 1785 (ring carbonyl), 1720 cm.$^{-1}$ (ester carbonyl).

Anal.—Calcd. for $C_{10}H_8ClNO_4$: C, 49.70; H, 3.34; N, 5.80. Found: C, 49.48; H, 3.18; N, 6.02.

3 - Bromomethyl - 5 - chloro - 2 - benzoxazolinone (XXVII)—3 - Hydroxymethyl - 5 - chloro - 2 - benzoxazolinone (3.99 Gm., 0.02 mole) was suspended in 150 ml. of dry ether and allowed to cool in ice. Three milliliters of phosphorous tribromide was then added to it dropwise while stirring. The reaction mixture was stirred for 1 hr. in cold and another 1 hr. at room temperature. During this time the hydroxy compound dissolved and the reaction mixture became clear. Ether was removed under vacuum. The product was crystallized from benzene, m.p. 108–110°, yield 4 Gm. (76%). IR: 1780 cm.$^{-1}$ (C=O); NMR: 6.96 δ (aromatic, 3H), 5.45 δ (-CH_2-).

Anal.—Calcd. for $C_8H_5BrClNO_2$: C, 36.61; H, 1.91; Br, 30.44. Found: C, 36.82; H, 2.09; Br, 30.24.

3 - (2 - Nitrophenylcarbamylmethyl) - 2 - benzoxazolinone (XXVIII)—2 - Nitrophenylisocyanate (1.64 Gm., 0.01 mole) was added to 1.64 Gm. (0.01 mole) of 3-hydroxymethyl-2-benzoxazolinone in 25 ml. of anhydrous benzene. The reaction mixture was heated under reflux for 8 hr. At the end of this time, the reaction mixture was diluted with 50 ml. of petroleum ether (b.p. 60–80°) and refrigerated overnight. The solid product thus obtained was filtered and recrystallized from benzene, m.p. 142–143° (softens at 123°); yield, 2 Gm. (60%). IR: 3390 cm.$^{-1}$ (-NH-); 1790 cm.$^{-1}$ (ring carbonyl); 1770 cm.$^{-1}$ (-C(=O)-NH-).

Anal.—Calcd. for $C_{15}H_{11}N_3O_6$: C, 54.72; H, 3.37; N, 12.76. Found: C, 54.94; H, 3.51; N, 12.59.

3 - (2 - Nitrophenylcarbamylmethyl) - 5 - chloro-2-benzoxazolinone (XXIX)—3-Hydroxymethyl-5-chloro-2-benzoxazolinone (2 Gm., 0.01 mole) and 2-nitrophenylisocyanate (1.64 Gm., 0.01 mole) were refluxed overnight in 50 ml. of dry benzene. Benzene was removed under vacuum and the product was recrystallized from benzene, m.p. 177–178° yield, 1.8 Gm. (50%). IR: 3300 cm.$^{-1}$ (-NH-), 1790 cm.$^{-1}$ (ring carbonyl), 1740 cm.$^{-1}$ (-C(=O)-NH-).

Anal.—Calcd. for $C_{15}H_{10}ClN_3O_6$: C, 49.56; H, 2.77; N, 11.55. Found: C, 50.55; H, 2.85; N, 11.31.

3 - Anilinomethyl - 5 - chloro - 2 - benzoxazolinone (XXX)—Aniline (1.86 Gm., 0.02 mole) was added with stirring to 5-chloro-2-benzoxazolinone (3.39 Gm., 0.02 mole) suspended in 10 ml. of ethanol containing 3 ml. of 37% formalin. The reaction mixture was stirred for 1 hr. and allowed to remain at room temperature overnight. The product thus obtained was recrystallized from ethanol–acetone, m.p. 174–175°, yield, 4.2 Gm. (68%). IR: 3380 cm.$^{-1}$ (-NH-), 1750 cm^{-1} (carbonyl).

Anal.—Calcd. for $C_{14}H_{11}ClN_2O_2$: C, 61.20; H, 4.04; N, 10.20. Found: C, 60.92; H, 4.03; N, 10.09.

3 - (3,4,5 - Trimethoxybenzoyloxymethyl) - 2 - benzoxazolinone (XXXI)—Freshly prepared 3,4,5-trimethoxybenzoyl chloride (4.6 Gm., 0.02 mole) and 3-hydroxymethyl-2-benzoxazolinone (2.47 Gm., 0.015 mole) were refluxed in 50 ml. of dry benzene for 4 hr. At the end of this time, benzene was distilled off and residual semisolid was washed repeatedly with 10% aqueous sodium bicarbonate solution. The product on crystallization from acetone gave 2 Gm. (37%) of the ester, m.p. 171°. IR: 1790 cm.$^{-1}$ (ring carbonyl), 1720 cm.$^{-1}$ (ester carbonyl).

Anal.—Calcd. for $C_{18}H_{17}NO_7$: C, 60.17; H, 4.77; N, 3.90. Found: C, 60.31; H, 4.90; N, 3.88.

3 - (3,4,5 - Trimethoxybenzoyloxymethyl) - 5 - chlorobenzoxazolinone (XXXII)—This compound was prepared in a manner similar to XXXI from 2 Gm. (0.01 mole) of 3-hydroxymethyl-2-benzoxazolinone and 3.45 Gm. (0.015 mole) of 3,4,5-trimethoxybenzoyl chloride. Recrystallization from ethanol–acetone gave 2 Gm. (50%) of the product melting at 159°. IR: 1800 cm.$^{-1}$ (ring carbonyl), 1730 cm.$^{-1}$ (ester carbonyl).

Anal.—Calcd. for $C_{18}H_{16}ClNO_7$: C, 54.90; H, 4.10; N, 3.56. Found: C, 55.06; H, 4.25; N, 3.43.

Amine Exchange Reaction—3-Dimethylaminomethyl-2-benzoxazolinone (1.02 Gm., 0.01 mole), 3-methylpiperidine (0.99 Gm., 0.01 mole), and 2 ml. of ethanol were heated on a water bath for 3 hr. The product obtained after cooling the reaction

mixture was recrystallized from ethanol, m.p. 150°, mixed melting point with compound IV, 150°. Infrared spectrum, of this product was identical with IV.

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Keyphrases

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Influence of Cyclodextrins on Ester Hydrolysis

By TING-FONG CHIN, PING-HONG CHUNG, and JOHN L. LACH

The hydrolysis of various ethyl esters of aminobenzoic acids, acetylsalicylic acid, and atropine in alkaline solution was shown to be either accelerated or decelerated in the presence of α and β-cyclodextrin. It is also shown that the stereochemistry of binding and the degree of ionization of cyclodextrin are primarily responsible for these catalytic and inhibitory effects observed.

THE FACT that the cycloamyloses (cyclodextrins) are capable of forming inclusion complexes with various compounds in solution especially with molecules containing aliphatic and aromatic groups has been known for some time and was recently reviewed by Thoma and Stewart (1). Although this aspect of inclusion formation has received considerable study, the present interest in cycloamylose chemistry has been in the kinetic aspect, since these cycloamyloses or cyclodextrins also have been shown to impose both rate accelerations and decelerations on various organic reactions.

Cramer and co-workers (2–4) have studied the cyclodextrin catalyzed decarboxylation of various organic acids and the fission of pyrophosphate. With respect to carboxylic acids, Cramer assumes that the carboxylic acids, after inclusion in the cavity of cyclodextrin, are activated by nucleophilic attack of the ether and hydroxyl O atoms at the carboxyl C atom and that their decarboxylation is consequently accelerated.

Bender and co-workers (5–8) reported that the cyclodextrins accelerated the hydrolysis of the various esters studied and that the accelerations are often large and are markedly substituent dependent. They also stated that this acceleration effect was due primarily to nucleophilic attack on the included ester by alkoxide ion of the cyclodextrin.

Lach and Chin (9) in their study dealing with hydrolysis of ethyl *p*-aminobenzoate in the presence of cyclodextrin, on the other hand, reported a deceleration effect. They attributed this deceleration in rate to a complete occlusion of the total ester in the void space of the cyclodextrin molecule and therefore shielding the ester linkage from hydroxyl ion attack and from alkoxide ion attack in the cyclodextrin molecules. They also stated that in this system the hydrolysis is due only to the free ester in solution resulting from the dissociation of the inclusion

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