Anal.—Calcd. for $C_{15}H_{12}O_2S_2$: C, 62.47; H, 4.19. Found: C, 62.22; H, 4.37.

5-Methyl-5-dimethylaminomethylthiaindan-6-ol.—A modification of the procedure outlined by Chaikin and Brown (9) for the reduction of aldehydes and ketones was employed. To a solution of 18.9 Gm. (0.5 mole) of sodium borohydride in 400 ml. of 50% methanol, cooled to 20°, was added dropwise, with stirring, a solution of 5-methyl-5-dimethylaminomethylthiaindan-6-one (prepared from 56 Gm. (0.23 mole) of the hydrochloride) in 100 ml. of ethanol. The rate of addition of the ketone was controlled in order to maintain a reaction temperature of about 30°. The mixture, following the addition of the ketone, was heated for 2 hours at 50°. Thereafter, the mixture was concentrated *in vacuo* to a solid, treated with 200 ml. of water, and extracted with three 150-ml. portions of ether. The combined ether extracts were dried over anhydrous sodium sulfate, separated from the drying agent by filtration, and concentrated *in vacuo*. The residual solid (23 Gm., 47.5%) was recrystallized from ethanol, to give product, m.p. 110–111°. The infrared spectrum of the product in carbon tetrachloride showed absorption at 3600 cm.$^{-1}$ characteristic of hydroxyl groups, and the absence of the carbonyl absorption at 1660 cm.$^{-1}$.

Anal.—Calcd. for $C_{11}H_{17}NOS$: C, 62.56; H, 7.49; S, 5.17. Found: C, 62.39; H, 7.75; S, 15.00.

5-Methyl-5-dimethylaminomethyl-6-benzylthiaindan-6-ol.—The method of Gilman and Catlin (10) was used in the preparation of benzylmagnesium chloride. In a 1-L. three-necked flask fitted with a stirrer, dropping funnel, and a condenser provided with a drying tube containing calcium chloride and soda lime, were placed 9.5 Gm. (0.4 Gm. At.) of magnesium turnings, 25 ml. of dry ether, 5 ml. of a solution of 49.34 Gm. (0.3 mole) of benzyl chloride in 200 ml. of dry ether, and a crystal of iodine. Stirring was begun, and the remaining ethereal solution of benzyl chloride was added over a period of 30 minutes and then refluxed for an additional 30 minutes.

The method of Pohland and Sullivan (5) was used for the Grignard reaction. To the Grignard reagent, prepared as described above, was added a solution of 16.1 Gm. (0.08 mole) of 5-methyl-5-dimethylaminomethylthiaindan-6-one in 200 ml. of dry ether over a period of 30 minutes. The reaction mixture was decomposed by the dropwise addition of a saturated solution of ammonium chloride. The ether was decanted from the solid and dried over anhydrous magnesium sulfate.

The ether solution was evaporated on a steam bath to give a red oil which partially crystallized on cooling in a dry ice–acetone bath. The solid substance (10 Gm., 44%) was removed by filtration and after several recrystallizations from ethanol melted at 113–115°. The infrared spectrum showed hydroxyl absorption at 3600 cm.$^{-1}$ and the absence of the characteristic carbonyl maximum between 1600 and 1700 cm.$^{-1}$.

Anal.—Calcd. for $C_{18}H_{23}NOS$: C, 71.76; H, 7.64. Found: C, 71.61; H, 7.71. A white methiodide salt was prepared by the usual procedure and recrystallized from ethanol, m.p. 228° dec., darkening at 220°.

Anal.—Calcd. for $C_{19}H_{26}INOS$: C, 51.46; H, 5.85. Found: C, 51.63; H, 5.95.

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Benzoxazoles: Potent Skeletal Muscle Relaxants

By JOSEPH SAM* and JAMES N. PLAMPIN

The synthesis of a number of substituted 2-aminobenzoxazoles and benzoxazolinones is described. The majority of the compounds exhibit marked muscle relaxant activity, two of the most potent being 2-amino-5-chlorobenzoxazole[1] and 5-chlorobenzoxazolinone.[2]

As early as 1943 Goodman and associates (1) reported that benzimidazole produced a reversible flaccid paralysis in various species of laboratory animals. However, it was not until 1952 when Domino and co-workers (2) investigated a series of benzazoles that more than a passing interest was expressed in this class of compounds.

The interesting pharmacological properties of the benzazoles mentioned above and the marked central nervous system depressant activity of substituted benzoxazolinones (3, 4) prompted

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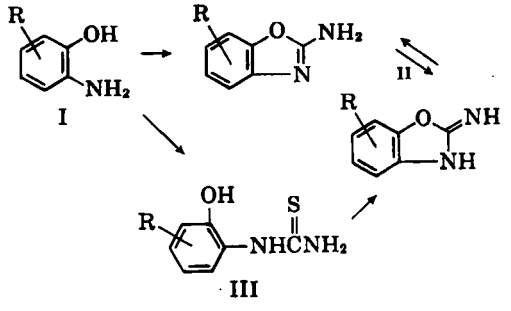
[1] Zoxazolamine. Marketed as Flexin by McNeil Laboratories.
[2] Chlorzoxazone. Marketed as Paraflex by McNeil Laboratories.

us to investigate various substituted benzoxazoles further.

Initial efforts were directed toward the preparation of substituted 2-aminobenzoxazoles, inasmuch as few such derivatives were described. In addition, these compounds would serve as intermediates to more complex compounds. Other investigators (5–7) have described the preparation of similar compounds.

2-Aminobenzoxazoles (II) may be prepared conveniently from *o*-aminophenols (I) either by reaction with cyanogen bromide (7) to give the desired product directly or by first converting to the thiourea (III) with ammonium thiocyanate followed by cyclization (8).

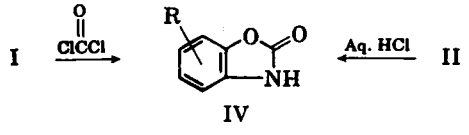


The conversion of thioureas to 2-aminobenzoxazoles is accelerated by maintaining an alkaline pH and by adding metallic oxide which results in the formation of the insoluble sulfide that is removed by filtration.

The use of ammonium thiocyanate for the preparation of thioureas unfortunately did not always yield crystalline or easily purified products. In the course of our work it was found convenient to convert the crude thiourea to the desired benzoxazole without loss in yield. The thioureas that were isolated and identified are listed in Table I.

The observation that 2-amino-5-chlorobenzoxazole (V) is a potent spinal cord depressant agent (9) stimulated our interest in other halogenated 2-aminobenzoxazoles. In addition to the thiourea and cyanogen bromide methods, halogenation of 2-aminobenzoxazole and 5-substituted-2-aminobenzoxazole was employed for the preparation of the corresponding 6-halo-2-aminobenzoxazoles. Halogenation proceeded to give the 6-halo derivatives. This was verified by comparison of the products with the 6-halo derivatives obtained by the unequivocal synthesis *via* the thiourea and cyanogen bromide methods. The results were in agreement with the observation made by Desai and associates (8) on the bromination of 2-aminobenzoxazole.

In the course of our studies it was observed that the 2-aminobenzoxazoles could be hydrolyzed readily to the corresponding benzoxazolinones (IV) which also exhibited marked muscle relaxant activity.



A number of benzoxazolinones was prepared (Table III) either by the hydrolysis of the corresponding 2-aminobenzoxazoles (II) or by treatment of the requisite 2-aminophenol (I) with phosgene (10).

As with 2-aminobenzoxazoles, halogenation of benzoxazolinone and substituted benzoxazolines proceeded to give the corresponding 6-halobenzoxazolinones.

The reaction of 2-amino-5-chlorobenzoxazole (V) with methyl iodide and ethyl β-bromopropionate gave 5-chloro-2-imino-3-methylbenzoxazoline (VI) and 5-chloro-3-(2-ethoxycarbonylethyl)-2-iminobenzoxazoline (VII), respectively. The methylation and proof of structure of all *N*-methylated derivatives is the subject of a previous publication (11).

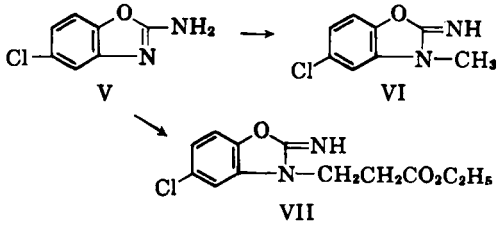
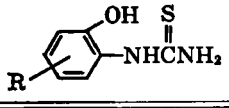


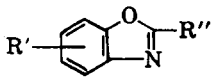
TABLE I.—SUBSTITUTED *o*-HYDROXYPHENYLTHIOUREAS



R	Recrystd. From	M.p., °C.	Formula	N Analyses, % Calcd.	N Analyses, % Found
4-Cl	Ethyl acetate-heptane	157 to 157.5 dec.	$C_7H_7ClN_2OS$	13.8	13.5
4-CH_3O	Methanol	174–175	$C_8H_{10}N_2O_2S$	14.1	13.8
5-Cl	Ethyl acetate	173–174	$C_7H_7ClN_2OS$[a]	13.8	13.6
4-CH_3	Ethyl acetate	156–157	$C_8H_{10}N_2OS$	15.4	15.0

[a] Calcd.: C, 41.5; H, 3.5. Found: C, 41.5; H, 3.6.

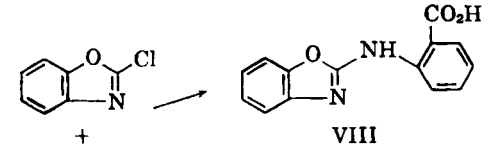
TABLE II.—BENZOXAZOLES



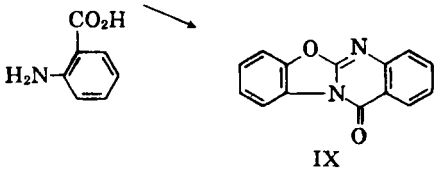
R′	R″	Recrystd. From	Method	M.p., °C.	Formula	N Analyses, % Calcd.	N Analyses, % Found
H	$NHCOCH_2Cl$	Benzene	...	180–180.5	$C_9H_7ClN_2O_2$	13.3	13.5
5-Cl	NH_2	Benzene	*A, B*	183–184	$C_7H_5ClN_2O$[a]	...	...
5-Cl	$NHCOCH(CH_3)_2$	Heptane	...	182–183	$C_{11}H_{11}ClN_2O_2$	11.7	11.6
5-CH_3O	NH_2	Benzene	*A, B*	165–166	$C_8H_8N_2O_2$	17.1	16.8
6-Cl	NH_2	Benzene	*E*	184–185	$C_7H_5ClN_2O$	16.6	16.4
5-CH_3	NH_2	Benzene	*A,B*	141–142	$C_8H_8N_2O$	18.9	18.6
H	*o*-$NHC_6H_4CO_2H$	Methanol	...	304–305	$C_{14}H_{10}N_2O_3$	11.0	10.9
5-Cl	H	Petroleum ether	...	37–37.5	C_7H_4ClNO	9.1	8.7
5-F	NH_2	Benzene	*A, B*	148–149	$C_7H_5FN_2O$	18.4	18.3
5-Br	NH_2	Acetone-water	*B*	177–178	$C_7H_5BrN_2O$	13.1	12.7
5-I	NH_2	Acetone-water	*B*	196–197	$C_7H_5IN_2O$	10.7	10.6
5-Cl	$NH(CH_2)_3N(CH_3)_2$	...	...	78–79	$C_{12}H_{16}ClN_3O$	16.6	16.5
5-Cl	SCH_3	Methanol-water	...	87–89	C_8H_6ClNOS	7.0	7.0
5-Cl	NC_5H_{10}[b]	Acetone-water	...	106–107	$C_{12}H_{13}ClN_2O$	11.8	12.1
5-Cl-6-Br	NH_2	Methanol-water	*E*	237	$C_7H_4BrClN_2O$	11.3	11.3
7-Cl	NH_2	Acetone-benzene	*B*	218–219	$C_7H_5ClN_2O$	16.6	16.7
5-Cl	$NHCH_2C_6H_5$	Acetone-water	...	136–139	$C_{14}H_{11}ClN_2O$	10.8	10.7
4-Cl	NH_2	Acetone-water	*B*	200–201	$C_7H_5ClN_2O$	16.6	16.6
5,6-diCl	NH_2	Acetone-water	*E*	239–240	$C_7H_4Cl_2N_2O$	13.8	13.6
5-Cl	$NHNH_2$	Methanol-water	...	196–197	$C_7H_6ClN_3O$[c]	22.9	22.8
5-Cl-7-SO_3H	NH_2	Water	*B*	300	$C_7H_5ClN_2O_4S$	11.3	11.3
5-Cl	OCH_3	Acetone-water	...	80.5–81.5	$C_8H_6ClNO_2$	7.6	7.6
5-NH_2	NH_2	Methanol-ether	...	300 dec.	$C_7H_8ClN_3O$[d]	22.6	22.1
5-NO_2	NH_2	Cellosolve-water	*B*	300	$C_7H_5N_3O_3$	22.4	23.0
5-Cl	$NHCOCH_3$	Methanol	...	220–221	$C_9H_7ClN_2O_2$	13.3	13.3
5,7-diBr	NH_2	Acetone-Benzene	*E*	253–254	$C_7H_4Br_2N_2O$	9.6	9.6
4,5,7-triCl	NH_2	2-Butanone	*B*	296–297	$C_7H_3Cl_3N_2O$	11.8	11.9

[a] *Reference 7.* [b] Piperidino. [c] Calcd.: C, 45.8; H, 3.3. Found: C, 45.9; H, 3.4. [d] Hydrochloride.

A representative arylaminobenzoxazole was prepared from 2-chlorobenzoxazole and anthranilic acid (6). The reaction, when performed in methanol, gave predominantly *N*-(2-benzoxazolyl) anthranilic acid (VIII) and some 12-benzo(d)quinazo(2,3-b)oxazole-12-one(IX). The same reaction when conducted in glacial acetic acid yielded predominantly the ring compound (IX). Neither of the compounds above exhibited significant muscle relaxant properties when tested in experimental animals.



VIII



IX

EXPERIMENTAL[3]

Syntheses

2-Aminophenol, 2-amino-4-chloro and 3-amino-5-chloro-2-hydroxybenzenesulfonic acid are available commercially. 2-Amino-6-chlorophenol (5), 2-amino-4-fluorophenol (12), 2-amino-4-methoxyphenol (10), 2-amino-4-methylphenol (10), 2-amino-4-nitrophenol (13), 2-amino-5-chlorophenol (14), 2-amino-4-bromophenol (15), 2-amino-4-iodophenol (16), 2-amino-4,6-dibromophenol (16), 2-amino-3-chlorophenol (17), and 2-amino-3,4,6-trichlorophenol (18) were prepared according to procedures described in the literature.

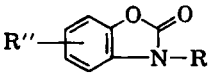
Thioureas (Table I).—To a solution of 0.3 mole of the 2-aminophenol in 300 ml. of water containing 34 ml. (14.6 Gm., 0.4 mole) of concentrated hydrochloric acid was added 30.4 Gm. (0.4 mole) of ammonium thiocyanate. The resulting solution was placed in a porcelain evaporating dish and heated on steam bath for 3 hours. Water (300 ml.) was added to the cooled mixture and the product removed by filtration. The filtrate was heated again on a steam bath for 3 hours and the additional product removed by filtration. Purification was accomplished by recrystallization from a suitable solvent (Table I). Yield, 50–60%.

2-Aminobenzoxazoles (Table II).—*Method A.*—A solution of 0.3 mole of the *o*-hydroxyphenylthiourea in 1 L. of methanol was treated with 100 Gm. (0.45 mole) of lead monoxide and the resulting mixture refluxed with stirring for 4 hours. The lead sulfide and excess lead monoxide were removed by filtration and washed thoroughly with hot methanol. Evaporation of the solvent and recrystallization of the residue, using charcoal as a clarifying agent, gave 70–90% of the 2-aminobenzoxazoles (Table II). In general, a crude thiourea was employed, the yield of product ranged from 45–60% based on the aminophenol.

Method B.—A stirred solution of 1.1 moles of cyanogen bromide (19) in 200 ml. of 70% methanol

[3] All melting and boiling points are uncorrected.

TABLE III.—BENZOXAZOLINONES



R′	R″	Recrystd. From	Method	M.p., °C.	Formula	N Analyses, % Calcd.	N Analyses, % Found
H	6-Cl	Methanol-water	*E*	195–196	$C_7H_4ClNO_2$[a]	...	...
H	5-Br	Methanol-water	*C*	214–216	$C_7H_4BrNO_2$[b]	...	...
H	5,7-diBr	Ethyl acetate	*E, D*	260–261	$C_7H_3Br_2NO_2$[c]	...	...
H	5-CH_3O	Ethyl acetate	*D*	169–170	$C_8H_7NO_3$[d]	...	...
H	5-Cl-6-Br	Methanol-water	*E, D*	204–205	$C_7H_3BrClNO_2$	5.6	5.7
H	5-NH_2	Water	*D*	227–229	$C_7H_6N_2O_2$	18.7	18.7
H	5,6-diCl	Methanol-water	*E, D*	205	$C_7H_3Cl_2NO_2$	6.9	6.8
C_2H_5	5-Cl	Heptane	*F, G*	73–75	$C_9H_8ClNO_2$	7.1	6.8
CH_3	5-Cl	Methanol	*F*	133–135	$C_8H_6ClNO_2$	7.6	7.7
CH_2=$CHCH_2$	5-Cl	Petroleum ether	*G*	62–64	$C_{10}H_8ClNO_2$	6.7	6.7

[a] *Reference 10.* [b] *Reference 20.* [c] *Reference 21.* [d] *Reference 22.*

was treated with a solution of 1 mole of the substituted *o*-aminophenol in the minimum amount of methanol at room temperature. The solution was allowed to stand for 40 minutes, then neutralized with concentrated sodium hydroxide solution. Most of the methanol was distilled *in vacuo*, and the residual material was treated with water. The solid was removed by filtration and recrystallized from a suitable solvent (Table II) after treatment with charcoal. Yields of 50–70%, based on the aminophenol, were obtained.

Benzoxazolinones (Table IV).—*Method C.*—The method of Close, *et al.* (10), was followed. A suspension of 0.1 mole of substituted *o*-aminophenol and 0.2 mole of sodium acetate in 300 ml. of ethyl acetate was stirred and treated with a solution of 0.11 mole of phosgene in 200 ml. of ethyl acetate. After refluxing briefly, the solution was cooled and washed with water and 5% hydrochloric acid, respectively. The ethyl acetate solution was dried over anhydrous magnesium sulfate and evaporated to dryness. The residue was recrystallized to give 60–90% of product (Table III).

Method D.—A solution of 0.1 mole of substituted 2-aminobenzoxazole in 200–300 ml. of 1*N* hydrochloric acid was refluxed for 3 to 5 hours. The mixture was cooled, and the solid was removed by filtration. Recrystallization gave 50–70% of product (Table III).

Halogenation of 2-Aminobenzoxazoles and Benzoxazolines.—*Method E.*—A solution of 1.4 moles of the 2-aminobenzoxazole or benzoxazolinone in 2 L. of a suitable solvent (chloroform, ethyl acetate, etc.) was cooled to 5° and treated with a solution of 1.6 moles of the halogen in the same solvent. The temperature was maintained at 10–15° during the addition and stirring was continued for 1 to 2 hours. The solid was removed by filtration, suspended or dissolved in water, and neutralized with ammonia. The solid was removed by filtration and recrystallized to give 60–80% of product (Tables II, III).

5-Chloro-3-substitutedbenzoxazolinones (Table III).—*Method F.*—A solution of 0.1 mole of 5-chlorobenzoxazolinone in 200 ml. of water containing 4.3 Gm. of sodium hydroxide was stirred and treated with 0.12 mole of dimethyl or diethyl sulfate. The mixture was warmed on a steam bath until it became neutral and then cooled. The solid was removed by filtration and recrystallized to give 65–70% of product.

Method G.—The procedure described by Close, *et al.* (10), (*Method B*), with minor modifications, was followed. A solution of 0.055 mole of potassium hydroxide and 0.05 mole of 5-chlorobenzoxazolinone in 120 ml. of cellosolve was stirred for 1 hour, then treated with 0.05 mole of alkyl bromide or iodide. After refluxing for 3 hours, the solvent was distilled and the residue recrystallized to give 70–80% of product.

5-Chloro-2-hydrazinobenzoxazole.—The method described by Sam, *et al.* (11), for the preparation of 5-chloro-2-dimethylaminobenzoxazole was followed using 9.4 Gm. (0.05 mole) of 2,5-dichlorobenzoxazole, 5 Gm. (0.1 mole) of hydrazine hydrate, and 100 ml. of water. Six grams (67%) of product was obtained after recrystallization from a methanol and water mixture, m.p. 196–197°.

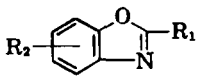
N,N-Bis [2-(5-chlorobenzoxazolyl)]-N′,N′-dimethyl-1,3-propanediamine and 5-Chloro-2-(3-dimethylaminopropylamino)benzoxazole.—A solution of 18.8 Gm. (0.1 mole) of 2,5-dichlorobenzoxazole(11) in 100 ml. of chloroform was treated with 10.2 Gm. (0.1 mole) of 3-dimethylaminopropylamine. After the initial reaction had subsided, the solution was refluxed briefly and cooled. A precipitate of 3-dimethylaminopropylamine hydrochloride was removed by filtration, and the chloroform was distilled *in vacuo*. The oily residue solidified and was recrystallized from dilute methanol to give 10 Gm. of solid, m.p. 140–144°. Repeated recrystallization of the solid from dilute methanol gave 5.5 Gm. (27%) of *N,N*-bis[2-(5-chlorobenzoxazolyl)]-*N′,N′*-dimethyl-1,3-propanediamine, m.p. 146–148°.

Anal.—Calcd. for $C_{19}H_{18}Cl_2N_4O_2$: N, 13.8. Found: N, 13.6.

The dilute methanol solutions were combined and concentrated *in vacuo*. The residual oil was extracted with chloroform and dried over anhydrous magnesium sulfate. Distillation of the chloroform solution gave 8 Gm. (32%) of 5-chloro-2-(3-dimethylaminopropylamino)benzoxazole, b.p. 168–170° (0.4 mm.), m.p. 78–79°.

5-Chloro-2-methylmercaptobenzoxazole.—A solution of 37 Gm. (0.2 mole) of 5-chloro-2-mercaptobenzoxazole (5) and 12 Gm. of sodium hydroxide in 200 ml. of water was treated with 25.2 Gm. (0.2 mole) of dimethylsulfate and stirred for 2 hours. The solid (32 Gm., 82%) was removed by filtration, washed with water, and recrystallized from dilute methanol, m.p. 87–89°.

TABLE IV.—PARALYZING AND LETHAL DOSES OF BENZOXAZOLES ON INTRAPERITONEAL ADMINISTRATION TO MICE



	R_1	R_2	PD_{50}[a]	LD_{50}[b]	Index[c]
(A)	CHLORINATED 2-AMINOBENZOXAZOLES				
	NH_2	4-Cl	36	54	1.5
	NH_2[d]	5-Cl	81	376	4.6
	NH_2	6-Cl	66	347	5.3
	NH_2	7-Cl	85	180	2.1
	NH_2[e]	6-Br[f]	103	294	2.9
(B)	5-SUBSTITUTED 2-AMINOBENZOXAZOLES				
	NH_2	F	115	450	3.9
	NH_2	Br	144	189	1.3
	NH_2	I	150	150	1.0
	NH_2	CH_3	103	360	3.5
	NH_2	CH_3O	220	432	2.0
	NH_2	NO_2	[g]	350	...
	NH_2	NH_2	1500	2000	1.3
	NH_2[h]	H	99	392	4.0
(C)	5-CHLORO-2-SUBSTITUTED BENZOXAZOLES				
	H	Cl	230	530	2.3
	$NHCOCH_3$	Cl	250	1500	6.0
	$NHCOCH_2Cl$	H[f]	400	450	1.0
	$NHCOCH(CH_3)_2$	Cl	350	1200	4.0
	$NHCH_3$[i]	Cl	180	230	1.3
	$N(CH_3)_2$[i]	Cl	280	280	1.0
	SCH_3	Cl	350[j]	350	1.0
	NC_5H_{10}[k]	Cl	1000[j]	1000	...
	$NHNH_2$	Cl	[g]	80	...
	OCH_3	Cl	750	1450	1.9
	$NH(CH_2)_2N(CH_3)_2$	Cl	[g]	230	...
	$NHCH_2C_6H_5$	Cl	[g]	1280	...
	SH[l]	Cl	100	120	1.2
(D)	DI AND TRI SUBSTITUTED 2-AMINOBENZOXAZOLES				
	NH_2	5-Cl-6-Br	105	240	2.3
	NH_2	5,6-diCl	132	300	2.3
	NH_2	5-Cl-7-SO_3H	1440[j]	1440	...
	NH_2	5,7-diBr	420	780	1.9
	NH_2	4,5,7-triCl	1750	2000	1.1

[a] Dose in mg./Kg. which causes a loss in righting reflex in 50% of the animals. [b] Dose in mg./Kg. which causes death in 50% of the animals. [c] Ratio of LD_{50} to PD_{50}. [d] *Reference 7.* [e] *Reference 8.* [f] Included here for convenience. [g] Stimulant. [h] *Reference 23.* [i] *Reference 11.* [j] No acute loss in righting reflex. [k] Piperidino. [l] *Reference 24.*

5-Chloro-2-piperidinobenzoxazole.—A solution of 8 Gm. (0.04 mole) of 5-chloro-2-methylmercaptobenzoxazole in 40 ml. of piperidine was refluxed for 22 hours. The solution was cooled and diluted with 250 ml. of water. The precipitate was collected and dissolved in dilute hydrochloric acid. A small amount of acid-insoluble material was removed by filtration and the product was precipitated with sodium hydroxide solution. After recrystallization from dilute acetone, there was obtained 8.7 Gm. (92%) of product, m.p. 106–107°.

2-Benzylamino-5-chlorobenzoxazole.—A solution of 23 Gm. (0.12 mole) of 5-chloro-2-mercaptobenzoxazole (5) and 26.6 Gm. (0.25 mole) of benzylamine in 100 ml. of xylene was refluxed for 6 hours. The product was removed by filtration and dissolved in hot methanol. The solution was made alkaline with sodium hydroxide, and the product was precipitated by dilution with water. The solid was collected and recrystallized from dilute acetone to give 20 Gm. (65%) of product, m.p. 136–139°.

5-Chloro-2-methoxybenzoxazole.—A cold, stirred solution of 2.1 Gm. of sodium in 50 ml. of anhydrous methanol was treated rapidly with a cold solution of 15 Gm. (0.08 mole) of 2,5-dichlorobenzoxazole (11) in 150 ml. of methanol. The reaction mixture was immediately poured into 1 L. of ice water. The white precipitate (14 Gm., 96%) was removed by filtration, washed with water, and recrystallized from dilute acetone, m.p. 80.5 to 81.5°.

N-(2-Benzoxazolyl)anthranilic Acid.—To a solution of 13.8 Gm. (0.1 mole) of anthranilic acid in 150 ml. of ethanol was added dropwise 15.4 Gm. (0.1 mole) of 2-chlorobenzoxazole. The resulting solution was refluxed on a steam bath for 3 hours and the precipitated 12-benzo(d)quinazo(2,3-b)oxazole-12-one (3 Gm.) removed by filtration. The filtrate was concentrated *in vacuo* and the residue extracted with 200 ml. of 10% sodium hydroxide solution. Neutralization of the solution with dilute hydrochloric acid gave 10 Gm. of product which was recrystallized from methanol, m.p. 304 to 305°.

12-Benzo(d)quinazo(2,3-b)oxazole-12-one.—To a warm solution of 13.8 Gm. (0.1 mole) anthranilic acid in 100 ml. of glacial acetic acid was added dropwise 15 Gm. (0.1 mole) of 2-chlorobenzoxazole. After the initial reaction subsided, the solution was refluxed for 30 minutes. The acetic acid was

distilled *in vacuo* from the precipitated product. After washing with water, 10% sodium hydroxide solution, and water, respectively, the product was recrystallized from 2 L. of isopropanol. Ten grams of product were obtained, m.p. 253 to 253.5°.

Anal.—Calcd. for $C_{14}H_8N_2O_2$: N, 11.86. Found: N, 11.80.

5-Chlorobenzoxazole.—A mixture of 28 Gm. (0.2 mole) of 2-amino-4-chlorophenol and 50 ml. of formamide was heated for 2 hours at 170–180°. The black solution was distilled *in vacuo* at 30 mm. The distillate was redistilled to give 13 Gm. of product, b.p. 112–114° (30 mm.), m.p. 37 to 37.5°.

N-(2-benzoxazolyl)-α-chloroacetamide.—To a solution of 13.4 Gm. (0.1 mole) of 2-aminobenzoxazole and 7.9 Gm. (0.1 mole) of pyridine in 300 ml. of dry benzene was added gradually with stirring at room temperature 9.3 Gm. (0.1 mole) of α-chloroacetyl chloride. The resulting mixture was stirred at room temperature for 2 hours. The benzene was distilled *in vacuo;* the residue was washed with water and recrystallized from methyl ethyl ketone and then benzene to give 7 Gm. of product, m.p. 180 to 180.5°.

N-[2-(5-Chlorobenzoxazolyl)]isobutyramide.—The above procedure was followed using 8.5 Gm. (0.05 mole) of 2-amino-5-chlorobenzoxazole, 4 Gm. (0.05 mole) of pyridine, and 5.3 Gm. (0.05 mole) of isobutyryl chloride. The mixture was refluxed with stirring for 3 hours. Water (300 ml.) was added to the mixture and the layers separated. The organic layer was washed with dilute hydrochloric acid and water. Evaporation of the solvent gave 8 Gm. of product which was recrystallized from heptane, m.p. 182–183°.

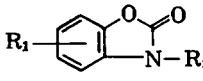
N-[2-(5-Chlorobenzoxazolyl)]acetamide.—The procedure for the preparation of the isobutyramide above was followed using 3.9 Gm. (0.05 mole) of acetyl chloride. After recrystallization from methanol, 8 Gm. of product, m.p. 220–221°, was obtained.

2,5-Diaminobenzoxazole Hydrochloride.—A suspension of 34 Gm. (0.19 mole) of 2-amino-5-nitrobenzoxazole in methanol was treated with Pd-C catalyst and hydrogenated at room temperature. After the required amount of hydrogen was absorbed (2 hours), the catalyst was removed by filtration and the solution diluted with 2 vol. of ether. Conversion of the resulting solid to the hydrochloride and subsequent recrystallization from a methanol-ether mixture gave 28 Gm. (79%) of product, m.p. 300° dec.

3-(2-Ethoxycarbonylethyl)-2-imino-benzoxazoline Hydrobromide.—A mixture of 15 Gm. (0.11 mole) of 2-aminobenzoxazole, 19 Gm. (0.11 mole) of ethyl β-bromopropionate, and 50 ml. of dry toluene was heated on a steam bath for 9 hours. The toluene was decanted from the semisolid residue. The latter was triturated with methyl ethyl ketone and the solid (10 Gm.) removed by filtration. Recrystallization from isopropanol gave product melting at 181 to 181.5°.

Anal.—Calcd. for $C_{12}H_{15}BrN_2O_3$: N, 8.9. Found: N, 8.6.

TABLE V.—PARALYZING AND LETHAL DOSES OF BENZOXAZOLINONES ON INTRAPERITONEAL ADMINISTRATION TO MICE



R_1	R_2	PD_{50}[a]	LD_{50}[b]	Index[c]
5-Cl[d]	H	86	210	2.4
6-Br[e]	H	237	445	1.9
6-Cl[f]	H	215	435	2.0
5-Br[g]	H	109	262	2.4
5,7-diBr[h]	H	420	392	0.8
4,5,7-triCl[i]	H	61	61	1.0
5-OCH_3[j]	H	250	650	2.6
5-Cl-6-Br	H	194	222	1.2
5-NH_2	H	420[k]	420[l]	2.6
5,6-diCl	H	150	263	1.8
5-Cl	C_2H_5	220	505	2.3
5-Cl	CH_3	800	2000	2.5
5-Cl	CH_2=$CHCH_2$	160	320	2.0

[a] Dose in mg./Kg. which causes a loss in righting reflex in 50% of the animals. [b] Dose in mg./Kg. which causes death in 50% of the animals. [c] Ratio of LD_{50} to PD_{50}. [d] *Reference 7, 25.* [e] *Reference 26.* [f] *Reference 10.* [g] *Reference 20.* [h] *Reference 21.* [i] *Reference 27.* [j] *Reference 22.* [k] No acute loss of righting reflex. [l] Delayed death.

TABLE VI.—COMPARATIVE LOSS OF RIGHTING REFLEX AND TOXICITY OF MUSCLE RELAXANTS ON INTRAPERITONEAL INJECTION TO MICE (28)

	PD_{50}[a]	LD_{50}[b]	Index[c]
Zoxazolamine	81	376	4.6
Chlorzoxazone	86	210	2.4
Mephenesin	130	471	3.6
Meprobamate	195	710	3.6

[a] Dose in mg./Kg. which causes a loss in righting reflex in 50% of the animals. [b] Dose in mg./Kg. which causes death in 50% of the animals. [c] Ratio of LD_{50} to PD_{50}.

Pharmacological Results[4]

The paralyzing action and lethal doses of the compounds described in this report are summarized briefly in Tables IV, V, and VI. A more extensive report of the pharmacological properties of the compounds will be the subject of another communication.

Of the various chloro-2-aminobenzoxazoles (Table IV), positions 5 and 6 provided compounds with similar activity. In the 2-amino-5-substituted benzoxazole series, the chloro, fluoro, and methyl substituted derivatives as well as the unsubstituted benzoxazole (R_2 = H) were the most active. Variation of the substituent in the 2-position of 5-chlorobenzoxazole by groups other than the primary amino, in general, results in a decrease in activity. Only the amides possess muscle relaxant activity comparable to 2-amino-5-chlorobenzoxazole (zoxazolamine). Muscle relaxant activity also is present in disubstituted and trisubstituted 2-aminobenzoxazoles; the activity, however, is less than that of the corresponding 2-amino-5-chlorobenzoxazole. Most of the benzoxazolinones that were evaluated possessed some degree of muscle relaxant activity (Table V). Several of the compounds listed in Table V possess muscle relaxant activity comparable to that of 5-chlorobenzoxazolinone (chlorzoxazone). Table VI is included for comparative purposes.

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[4] The pharmacological data was obtained by the staff of the Department of Pharmacology, McNeil Laboratories.

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Interactions Between Orange II and Selected Long Chain Quaternary Ammonium Salts

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The interactions between the dye, sodium *p*-(2-hydroxy-1-naphthylazo)benzenesulfonate (orange II) and four long chain quaternary ammonium salts—1-hexadecylpyridinium chloride, dodecylquinolinium bromide, (2-phenoxyethyl)dodecyldimethylammonium bromide, and (diisobutylphenoxyethoxyethyl)dimethylbenzylammonium chloride—have been investigated. The stoichiometry of these interactions has been determined to be 1:1 at pH values ranging from 0.73 to 12.91, except for the reaction involving the hexadecylpyridinium ion above pH 12.34, where the stoichiometry of dye to quaternary ammonium ion is 1:2. The solubility of the various solid compounds has been determined at 25, 30, 35, and 40°. From these data, the thermodynamic functions, $\Delta H°$, $\Delta S°$, and $\Delta F°$ have been calculated. Marked solubilization of these compounds has been observed in the presence of excess common quaternary ammonium ion at or near the critical micelle concentration of the particular long chain ion. The significance of these results is discussed.

IN RECENT YEARS the diverse properties of surface-active agents have led to an increased utilization of these substances in pharmaceutical preparations. Such uses include emulsification, wetting, solubilization, and disinfection. An important group of surface-active agents are the long chain quaternary ammonium compounds which have been shown to exhibit a high degree of activity against bacteria and fungi (1).

Because of the positive charge on the quaternary nitrogen, these compounds are extremely incompatible with substances such as soaps and anionic dyes, generally forming insoluble compounds. In view of this, many studies concerned with the introduction of quaternary ammonium compounds into pharmaceuticals and the subsequent incompatibilities, have been reported (2–4). Lachman, *et al.* (5), studied the interaction of 1-hexadecylpyridinium chloride, dodecyldimethyl(2-phenoxyethyl)ammonium bromide, and benzalkonium chloride with several anionic certified dyes. It was found that for equal quantities of the three quaternary ammonium salts, the amount of any dye which can be added without producing turbidity increases in the order: benzalkonium chloride, dodecyldimethyl (2-phenoxyethyl)ammonium bromide, and hexadecylpyridinium chloride. They concluded that this order of reactivity can be assigned to the electropositive center and the steric configuration of the molecule.

It was the purpose of this investigation to gain more insight into the nature of these interactions by isolating the compounds formed from each dye-detergent[1] combination, measuring their

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[1] The general term, detergent, is used throughout this paper to refer to the quaternary ammonium salts; it should not necessarily be implied that they are useful as detergents.