of *sec*-butyl 11-oxododecanoate. The yield of unsaturated methyl ester, b.p. 213–218°/1.5 mm., was 8.46 g. (79%). The purified acid was obtained in a yield of 5 g., m.p. 59–59.5°. Absorption in the ultraviolet showed ϵ_{210} 44, ϵ_{220} 24.

Anal. Calcd. for $C_{25}H_{50}O_2$: C, 78.55; H, 13.14; equiv. wt., 382.5. Found: C, 78.67; H, 13.37; equiv. wt., 377.

The *amide* had m.p. 82–82.5°.

Anal. Calcd. for $C_{25}H_{51}ON$: N, 3.67. Found: N, 3.64.

The *p-bromoanilide* had m.p. 72.5–73°.

Anal. Calcd. for $C_{31}H_{53}ONBr$: N, 2.60. Found: N, 2.43

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[CONTRIBUTION FROM MCNEIL LABORATORIES, INC.]

Methylated 2-Amino-5-chlorobenzoxazoles

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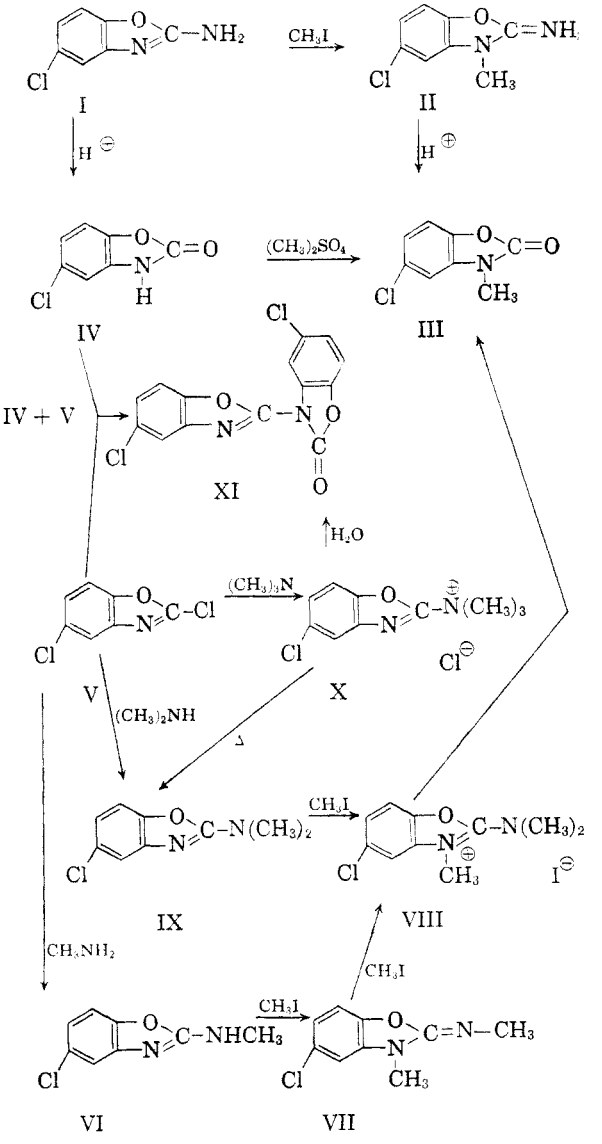
Preparation of all of the mono-, di-, and tri-methylated derivatives of 2-amino-5-chlorobenzoxazole is reported. Structure proofs, interconversions and spectral data of the methylated compounds are described. The two quaternary compounds (VIII and X) proved to be less stable than anticipated. The structures of the products resulting from reactions of the quaternary compounds under mild conditions were proved.

The discovery of the useful muscle-relaxant properties of 2-amino-5-chlorobenzoxazole (I)[1b] stimulated us to investigate compounds of related structure. One series of compounds, the six possible *N*-methylated derivatives of I, forms the subject of this communication.

As with the parent 2-aminobenzoxazole,[2] methylation of I with methyl iodide proceeded to give exclusively the 3-methyl derivative II. Analytical and spectral data were in accord with structure II which was confirmed by acid hydrolysis to 3-methyl-5-chloro-2-benzoxazolinone (III). An authentic sample of the latter compound was prepared for comparison by the dimethyl sulfate methylation of 5-chloro-2-benzoxazolinone (IV).

For the preparation of the other possible monomethyl derivative (VI), 2,5-dichlorobenzoxazole (V)[3] was treated with 25% aqueous methylamine solution.[4] The resultant base VI was isomeric with but different from II and was assigned the structure 2-methylamino-5-chlorobenzoxazole. When monomethyl derivative VI was treated with methyl iodide, there resulted 5-chloro-3-methyl-2-methyliminobenzoxazoline (VII) and further methylation of VII gave the quaternary salt 5-chloro-2-dimethylamino-3-methyl benzoxazolium iodide (VIII). The latter compound upon heating in methanol was transformed readily into 3-methyl-5-



(1) (a) Present address: E. I. du Pont de Nemours and Co., Inc., Camden, S. C.

(1) (b) Flexin® zoxazolamine, McNeil; R. T. Smith, K. M. Kron, W. P. Peak, and I. F. Hermann, *J. Am. Med. Assoc.*, **160**, 745 (1956); E. H. Abrahamsen and H. W. Baird III, *J. Am. Med. Assoc.*, **160**, 749 (1956); W. Amols, *J. Am. Med. Assoc.*, **160**, 742 (1956); M. Rodriguez-Gomez, A. Valdes-Rodriguez, and A. L. Drew, *J. Am. Med. Assoc.*, **160**, 752 (1956).

(2) R. D. Desai, R. F. Hunter, and A. R. K. Khalidi, *J. Chem. Soc.*, 1186 (1934).

(3) Prepared from 2-mercapto-5-chlorobenzoxazole by the method of H. N. McCoy, *Am. Chem. J.*, **21**, 111 (1899); *cf.* L. Katz and M. S. Cohen, *J. Org. Chem.*, **19**, 767 (1954).

(4) This method has been used to prepare substituted 2-aminobenzoxazoles; see, for example, P. Seidel, *J. prakt. Chem.* [2], **42**, 454 (1890).

TABLE I

SPECTRA OF COMPOUNDS

Compound	Ultraviolet Spectra[a] λ_{max} (mμ)	ϵ_{max}	Infrared Maxima, μ[b] N—H O—H Str.	C=N C=O Str.	C=C Str. (N—H Def.?)	C=C Str. (N—H Def.?)
I	243	12,800	2.90 (m)	5.91 (s)	6.17 (w)	6.24 (w)
	286	7,500	3.02 (vw)			
			3.09 (vw)	(6.00)[e]		
			3.33 (m)			
II	245	10,700	3.00 (m)	5.91 (s)	6.19 (s)	
	293	12,500		(5.90)[e]		
III	230[c]	7,350		5.58 (s)	6.17 (m)	
	283	5,500				
	289[c]	4,600				
IV	225[d]	5,800	3.16 (m)	5.60 (s)	6.15 (m)	
	282	5,400	3.25 (m)			
	288[d]	4,550				
VI	248	15,000	3.00 (w)	5.91 (s)	6.17 (m)	6.26 (m)
	289		3.16 (m)	(6.02)[e]		6.33 (m)
		9,500	3.25 (m)			
VII	250	8,750		5.75 (s)	6.19 (m)	
	297	10,200		5.90 (m)		
				(5.79)[e]		
VIII	249[c]	7,800		5.91 (s)	6.14 (m)	6.22 (m)
	295	5,500			6.18 (m)	
IX	252	15,000		6.03 (s)	6.17 (m)	6.34 (s)
	291	10,000		(6.02)[e]		
X	...	...	2.9-2.95[f]	6.03 (m)	6.14 (m)	6.36 (s)
XI	263	19,200		5.47 (s)	6.12 (m)	6.34 (s)
	312	23,300		5.52 (s)		

[a] Determined in methanol with Cary Model 11 Spectrophotometer. [b] Determined as mulls in mineral oil with Perkin-Elmer Model 21 Infrared Spectrophotometer: w = weak, m = medium, s = strong, v = very. [c] Shoulder, [d] Inflection. [e] Position of band in chloroform solution spectrum. [f] Undoubtedly from water due to the hygroscopic nature of this compound.

chloro-2-benzoxazolinone (III), identified by melting point, mixed melting point, and infrared spectra.

By reacting the dichlorobenzoxazole V with dimethylamine it was possible to obtain the isomeric dimethylated compound 2-dimethylamino-5-chlorobenzoxazole (IX). Quaternization of IX with methyl iodide led to the same quaternary compound (VIII) as was obtained from the isomeric dimethyl compound VII.

The remaining member of the series, trimethyl-(5-chloro-2-benzoxazolyl)ammonium chloride (X) precipitated when trimethylamine was passed into a benzene or ether solution of V. However, compound X proved to be even less stable than the isomeric quaternary VIII. When isolated directly, crystalline X was hygroscopic, showed a variable decomposition point on heating, and could not be purified for analysis by recrystallization. Upon boiling in benzene, trimethyl(5-chloro-2-benzoxazolyl)-ammonium chloride dissolved slowly and from the solution there was isolated dimethyl compound IX. Quaternary X was also found to have changed to tertiary amine IX after standing in a vacuum desiccator at room temperature for several days. Although tertiary amines have been prepared by the pyrolytic removal of methyl halide from methyl quaternaries, usually somewhat more vigorous conditions are required to bring about this reaction.[5]

Dissolution of quaternary X in water was rapid and was accompanied by the separation of reaction products from solution. The aqueous filtrate contained chloride ion. Separation of products by base solubility provided about 10% of an acidic compound shown to be 5-chloro-2-benzoxazolinone by melting points and spectra. From the neutral part there was separated about 25% of a high-melting new compound which gave analytical results in agreement with the formula $C_{14}H_6N_2O_3Cl_2$. Its ultraviolet spectrum in methanol showed maxima at 263 mμ (ϵ 19,200) and 312 mμ (ϵ 23,300) and the infrared spectrum was characterized by a lack of N—H or O—H absorption in the 3-μ region and a pair of strong carbonyl bands at 5.47 and 5.53 μ as well as multiple bands in the 6–7 μ region. Primarily on the basis of the very low wave length infrared carbonyl bands,[6] the benzoxazolylbenzoxazolinone structure XI was suggested for the compound. This structure was confirmed by the preparation of XI in excellent yield by the alkylation of 5-chloro-2-benzoxazolinone with 2,5-dichlorobenzoxazole in pyridine solution. The formation of

(5) See, for example, V. G. Ramsey, W. E. Baldwin, and R. S. Tipson, *J. Am. Chem. Soc.*, **69**, 67 (1947); N. R. Easton, L. R. Bartron, F. L. Meinholfer, and V. B. Fish, *J. Am. Chem. Soc.*, **75**, 2086 (1953).

(6) We have observed this split carbonyl band at about 5.5 μ in the spectra of several other 2-benzoxazolinones substituted on the nitrogen atom with a doubly bound carbon.

XI suggests that quaternary X is a good alkylating agent. When dissolved in water, a portion of X must be hydrolyzed to IV which in turn is rapidly alkylated to give the observed product XI.

Discussion of spectra. Ultraviolet absorption spectra and pertinent infrared absorption bands of compounds I–XI are given in Table I.

From an examination of the spectra, it appears that the compounds which can exist either as endocyclic or exocyclic carbon-nitrogen double bond tautomers prefer to have the double bond endocyclic in solution and exocyclic in the solid state.

The several compounds with fixed carbon-nitrogen double bonds are used for comparison. Thus, 3-monomethyl derivative II and dimethyl derivative VII show a more intense ultraviolet absorption maximum at higher wave length (293–297 mμ) and a less intense absorption maximum at lower wave length (245–250 mμ) and have a fixed exocyclic double bond. Conversely, the fixed endocyclic dimethyl isomer IX shows more intense absorption at lower wave length (252 mμ). All of the compounds which can tautomerize, *i.e.*, I, VI, and VIII, show the latter pattern and are assumed to have endocyclic double bonds in methanol solution.

In the infrared, strong bands in the 5.90–6.03 μ region are assigned to C=N stretching vibrations.[7] This band appears at 5.90–5.91 μ in the solid state for compounds I, VI, and VIII as well as for reference compound II and suggests an exocyclic bond position. However, when determined in chloroform solution, the position of the bands remained at 5.90 μ for II but shifted to 6.00 and 6.02 μ for I and VI, respectively. Referring to the fixed endocyclic dimethyl isomer IX again, the C=N absorption band is at 6.02–6.03 μ in both solution and solid state spectra.

The presence of anomalous split bands at 5.75 and 5.90 μ for compound VII in the solid state which combine to a single band at 5.79 μ in solution points up the difficulty of making accurate structural assignments based on the spectra of crystalline solids. Therefore, the data presented above can only be used to suggest that compounds I, VI, and VIII exist as the exocyclic double bond tautomers when in crystalline form.

Although some bands in the 6.1–6.4 μ region undoubtedly represent N—H deformation vibrations, we were unable to make satisfactory correlations of spectra and structures.

In the 3 μ region, the four compounds I, II, IV, and VI show expected N—H stretching vibrations. For II, the single sharp band at 3.00 μ can be assigned to non-bonded imino N—H[7] while with I, IV, and VI, multiple bands indicate a variable degree of hydrogen bonding for the N—H of the ring nitrogen and thus prevent definite assignment of imino N—H to the 3 μ bands of I.

(7) L. J. Bellamy, *The Infrared Spectra of Complex Molecules*, Methuen & Co., Ltd., London (1954), pp. 215, 226.

Pharmacological evaluation.—When tested in mice, rats, and hamsters, none of the methylated derivatives proved to be as potent a muscle relaxant as the parent 2-amino-5-chlorobenzoxazole in that an amount two or more times greater was necessary to cause a loss of righting reflex.

EXPERIMENTAL[8]

5-Chloro-2-imino-3-methylbenzoxazoline (II). A mixture of 8.4 g. (0.05 mole) of 2-amino-5-chlorobenzoxazole[9] and 4.2 g. (0.1 mole) of methyl iodide was heated in a bomb at 100° for 12 hr. The resulting product was treated with water and extracted with chloroform. The aqueous layer was chilled and neutralized with sodium bicarbonate. The white solid (8.0 g., 88%) was removed by filtration and dried, m.p. 148–150°. Recrystallization from cyclohexane gave 6.0 g. of crystalline product, m.p. 151.5–152°.

Anal. Calcd. for $C_8H_7ClN_2O$: N, 15.3. Found: N, 15.1.

5-Chloro-3-methyl-2-benzoxazolinone (III). *A. By hydrolysis of 5-chloro-2-imino-3-methylbenzoxazoline.* A solution of 100 mg. of 5-chloro-2-imino-3-methylbenzoxazoline (II) in 5 ml. of 2*N* hydrochloric acid was heated on a steam bath for 40 min. The solution on slow cooling deposited white needles which were separated, washed with water, and dried. The product melted at 133.5–134° alone or when mixed with III prepared as described below.

B. By Methylation of 5-chloro-2-benzoxazolinone. A solution of 16.9 g. (0.1 mole) of 5-chloro-2-benzoxazolinone[10] and 4.3 g. of sodium hydroxide in 200 ml. of water was stirred and treated with 15.1 g. (0.12 mole) of dimethyl sulfate. The white product precipitated and the mixture was stirred and heated until it was neutral to litmus paper. The mixture was cooled and the product was collected by filtration, washed, and dried. After recrystallization from methyl alcohol there was obtained 12.5 g. (68%) of III, m.p. 133–134°. Infrared spectra of samples of III prepared by the two methods were identical.

Anal. Calcd. for $C_8H_6ClNO_2$: C, 52.45; H, 3.30; N, 7.63. Found: C, 52.56; H, 3.35; N, 7.65.

2,5-Dichlorobenzoxazole (V). A suspension of 100 g. (0.54 mole) of 5-chloro-2-mercaptobenzoxazole[11] in 800 ml. of dry alcohol-free chloroform was cooled to 10–20° and was saturated with chlorine that had been dried by bubbling through sulfuric acid. The reaction mixture was poured into 4 l. of ice water. The chloroform layer was separated, washed with 2% sodium hydroxide, and with water. The solution was then dried over calcium chloride and was distilled. There was obtained 84.3 g. (82%) of V, b.p. 130–133°/25 mm., which crystallized readily below its melting point (44–46°).

5-Chloro-2-methylaminobenzoxazole (VI). A mixture of 10 g. (0.053 mole) of 2,5-dichlorobenzoxazole and 150 ml. of a 25% solution of methylamine in water was shaken occasionally for 1 hr. The resulting suspension of solid was filtered and recrystallized from benzene to give 6.0 g. (62%) of VI, m.p. 150.5–151°.

Anal. Calcd. for $C_8H_7ClN_2O$: C, 52.61; H, 3.86; N, 15.34. Found: C, 52.86; H, 3.83; N, 15.04.

5-Chloro-3-methyl-2-methyliminobenzoxazoline (VII). A mixture of 9.1 g. (0.05 mole) of 5-chloro-2-methylaminobenzoxazole and 14.2 g. (0.1 mole) of methyl iodide was

(8) Melting points are uncorrected. Nitrogen was determined by the semimicro Kjeldahl method. Carbon-hydrogen analyses by Huffman Microanalytical Laboratories, Wheatridge, Colo.

(9) T. Nagano, M. Itoh, and K. Matsumura, *J. Am. Chem. Soc.*, **75**, 2770 (1953).

(10) H. T. Upson, *Am. Chem. J.*, **32**, 13 (1904).

(11) A. Korczynski and S. Obarski, *Bull. soc. chim France*, [4] **33**, 1829 (1923)

sealed in a bomb and heated at 100° for 8 hr. The product was dissolved in hot methyl alcohol and the solution was neutralized with sodium hydroxide solution. The oily product was extracted into chloroform and distilled. There was obtained 7.5 g. (80%) of an oil (b.p. 120–123°/0.3 mm.) that solidified slowly on standing. A sample after sublimation *in vacuo* melted at 79.5–82°.

Anal. Calcd. for $C_9H_9ClN_2O$: C, 54.69; H, 4.59; N, 14.25. Found: C, 54.94; H, 4.53; N, 14.08.

5-Chloro-2-dimethylamino-3-methylbenzoxazolium iodide (VIII). *A. From 5-chloro-2-methylimino-3-methylbenzoxazoline.* A mixture of 1 g. of 5-chloro-2-methylimino-3-methylbenzoxazoline and 3 ml. of methyl iodide was heated in a bomb at 100° for 8 hr. The product was recrystallized from cold methyl alcohol–ether to give 1 g. of VIII, m.p. 242–244°.

Anal. Calcd. for $C_{10}H_{12}ClIN_2O$: C, 35.47; H, 3.57; N, 8.27. Found: C, 35.55; H, 3.51; N, 8.15.

B. From 5-chloro-2-dimethylaminobenzoxazole. A mixture of 6 g. (0.03 mole) of 5-chloro-2-dimethylaminobenzoxazole (IX, see preparation below) and 6 ml. of methyl iodide was heated in a bomb at 105° for 9 hr. The product was recrystallized from cold methyl alcohol by the addition of ether to give 3.5 g., m.p. 244–244.5°. A mixed melting point determination and infrared spectra proved this material identical with that prepared as described in section A above.

Hydrolysis of 5-chloro-2-dimethylamino-3-methylbenzoxazolium iodide. Hydrolysis was observed inadvertently in an attempt to recrystallize the crude quaternary salt VIII.

The product obtained from the quaternization of 10 g. (0.05 mole) of 5-chloro-2-dimethylaminobenzoxazole with 10 ml. of methyl iodide as described in the previous experiment (crude VIII, m.p. 239–244°) was dissolved in hot methanol, treated with charcoal, filtered, cooled, and diluted with ether but no crystals separated. The solution was evaporated to dryness under vacuum and the residue was crystallized by addition of methanol to give 6.0 g. of 5-chloro-3-methyl-2-benzoxazolinone (III), m.p. and mixed m.p. 133–135°; infrared spectrum identical with that of authentic III.

Concentration of the mother liquor to a small volume and dilution with ether provided 3.0 g. of 5-chloro-2-dimethylamino-3-methylbenzoxazolium iodide, m.p. 244–247°.

5-Chloro-2-dimethylaminobenzoxazole (IX). A mixture of 10 g. of 2,5-dichlorobenzoxazole and 50 ml. of 25% aqueous dimethylamine was heated on a steam bath for 30 min. with occasional stirring. The mixture was cooled and the solid product (12 g., m.p. 83–87°) was filtered. Recrystallization once from dilute acetone and twice from heptane gave pure IX, m.p. 92.5–94°.

Anal. Calcd. for $C_9H_9ClN_2O$: C, 54.97; H, 4.61; Cl, 18.03; N, 14.25. Found: C, 55.15; H, 4.66; Cl, 18.25; N, 14.05.

Preparation and behavior of trimethyl-(5-chloro-2-benzoxazolyl)ammonium chloride (X). *A. Isolation.* Excess trimethylamine was bubbled into a solution of 5.0 g. of 2,5-dichlorobenzoxazole in 150 ml. of dry ether. The resulting fluffy white precipitate was collected and washed with ether giving a rather unstable, hygroscopic white solid, m.p. 105–110°. The infrared spectrum was obtained on this material immediately after preparation. After standing in an evacuated desiccator at room temperature for several days, the melting point had changed to 92–94° and was not lowered on admixture with 5-chloro-2-dimethylaminobenzoxazole (IX).

B. Preparation and thermal decomposition. A solution of 5.0 g. of 2,5-dichlorobenzoxazole in 75 ml. of dry benzene was added to a solution of excess trimethylamine in 100 ml. of dry benzene. The initially formed white solid dissolved slowly as the mixture was stirred and heated under reflux for 2 hr. Evaporation of the resulting solution to dryness gave an acid-soluble residue free of ionic halogen. The material was recrystallized from heptane to give 5.0 g. of 5-chloro-2-dimethylaminobenzoxazole, m.p. and mixed m.p. 92–93°; infrared spectrum identical with authentic IX.

C. Preparation and reaction in water. A suspension of X in ether was prepared from 5.0 g. of V as described in section A. To the mixture was added 150 ml. of water with stirring. The white precipitate of X dissolved rapidly followed by the appearance of a new precipitate. The ether was evaporated and the resulting suspension of solid filtered. There was obtained 2.8 g. of a mixture which melted at 150–236°. Two grams of this material was slurried with 2% sodium hydroxide solution and the insoluble part separated, washed with water and acetone, and dried: 1.1 g., m.p. 236–237°. This product was identical by mixed melting point and infrared spectra with 3-(5-chloro-2-benzoxazolyl)-5-chloro-2-benzoxazolinone (XI) prepared as described below.

Acidification of the basic solution above gave 0.3 g. of 5-chloro-2-benzoxazolinone, m.p. 194–195°, identified by mixed melting point and infrared spectra.

3-(5-Chloro-2-benzoxazolyl)-5-chloro-2-benzoxazolinone (XI). A solution of 1.7 g. (0.01 mole) of 5-chloro-2-benzoxazolinone and 1.89 g. (0.01 mole) of 2,5-dichlorobenzoxazole in 15 ml. of pyridine was slowly heated to the reflux point. A crystalline solid separated and the mixture became dark. After 10 min. heating under reflux, the cooled mixture was diluted with water and the dark solid was washed with water and dried: 3.2 g., m.p. (190° change crystal form) 230–234°. Recrystallization from acetone gave 2.60 g. (83%) of fluffy yellow-green needles, m.p. 236–237°. A final recrystallization from ethyl acetate (charcoal) gave 2.02 g. of pure XI, m.p. 237–238°.

Anal. Calcd. for $C_{14}H_6Cl_2N_2O_3$: C, 52.36; H, 1.88; N, 8.73. Found: C, 52.65; H, 1.74; N, 8.68.

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