3-Aminoalkyl-2-benzoxazolinones[1]

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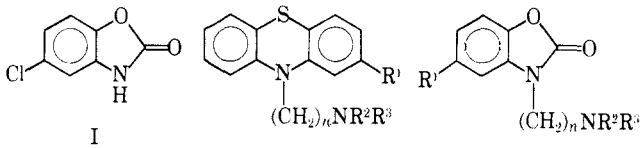
The preparations of some halogenated 2-benzoxazolinones are described. The reaction of 2-benzoxazolinones with aminoalkyl halides provided the corresponding 3-substituted 2-benzoxazolinones. Most of the compounds when tested in experimental animals exhibited CNS depressant properties.

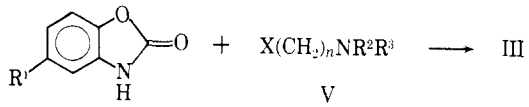
The useful medicinal value of 5-chloro-2-benzoxazolinone[3] (I) and many phenothiazines[4] (II) and the pronounced pharmacological activity of many benzoxazole derivatives[5,6] prompted us to investigate 3-substituted 2-benzoxazolinones (III). Lespagnol and coworkers[7] noted CNS depressant activity in 3-(2-diethylaminoethyl)-2-benzoxazolinone while Zinner and associates[8] described the preparation of a series of 3-



I II III

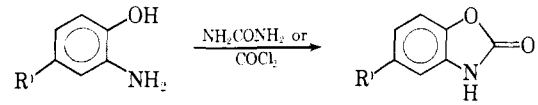
substituted aminomethyl-2-benzoxazolinones *via* the Mannich reaction. Recently[9] 2-benzoxazolinones have been isolated from natural sources.

The 3-substituted-2-benzoxazolinones (III) were prepared by the reaction of an appropriate 2-benzoxazolinone (IV) with an aminoalkyl halide (V).



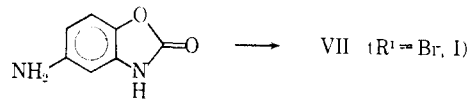
IV V

Several novel 2-benzoxazolinones (IV) containing the fluoro, trifluoromethyl, and iodo groups were investigated. For the most part the 2-benzoxazolinones described in this paper were substituted in the 5 position and were prepared from corresponding 4-substituted 2-aminophenol (VI) either by fusion with urea[10] or reaction with phosgene.[11]



VI VII

Although the 5-bromo- and 5-iodo-2-benzoxazolinones could be prepared by the methods described above, the Sandmeyer reaction[12] with 5-amino-2-benzoxazolinone (VIII) provided an alternate route and was preferred due to higher yields of products and limited availability of the parent aminophenols.

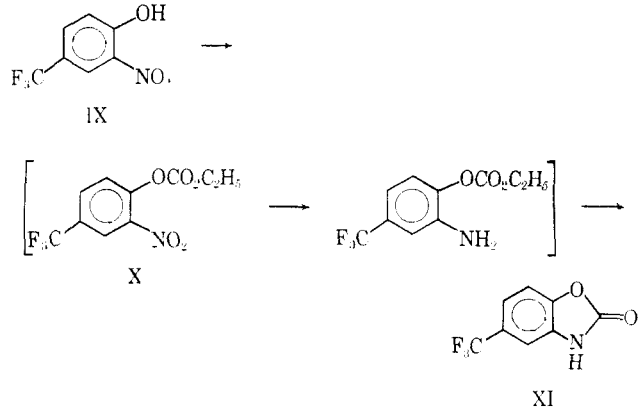


VIII

The chlorination of VII (R^1 = F) provided 6-chloro-5-fluoro-2-benzoxazolinone. Halogenation of other 2-benzoxazolinones and 5-substituted 2-benzoxazolinones is known to occur in the 6 position.[5,11]

A synthetic route utilizing benzoxazolethiones was investigated for the preparation of 5-fluoro- and 5-iodo-2-benzoxazolinone. This method, however, was discarded in favor of other methods because of low yields of products.

The preparation of 5-trifluoromethyl-2-benzoxazolinone (XI) was accomplished by reaction of IX with phosgene (method B) and also by the reduction of 4-trifluoromethyl-2-nitrophenyl ethyl carbonate (X).



IX X XI

Table I summarizes some physical characteristics and analyses of the 2-benzoxazolinones described in this paper.

(1) The authors are grateful to the A. H. Robins Company for financial support of the project.

(2) Abstracted in part from theses submitted by C. W. Richmond and J. L. Valentine to the Graduate School, The University of Mississippi, in partial fulfillment of Doctor of Philosophy and Master of Science degree requirements, respectively.

(3) W. Modell, "Drugs of Choice," The C. V. Mosby Company, St. Louis, Mo., 1964, p 305.

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(6) C. K. Cain and A. P. Roszkowski, "Psychopharmacological Agents," Vol. 1, M. Gordon, Ed., Academic Press Inc., New York, N. Y., 1964, p 327.

(7) C. Lespagnol, *Compt. Rend.*, **237**, 1164 (1953).

(8) H. Zinner, H. Herbig, and H. Wigert, *Chem. Ber.*, **89**, 2131 (1956).

(9) (a) A. I. Virtanen and P. K. Hietala, *Acta Chem. Scand.*, **9**, 1543 (1955); *Chem. Abstr.*, **50**, 8816 (1956); (b) A. I. Virtanen, P. K. Hietala, and O. Wahlroos, *Suomen Kemistilehti*, **29B**, 143 (1956); *Chem. Abstr.*, **51**, 5212 (1957); (c) E. E. Smissman, J. B. LaPidus, and S. D. Beck, *J. Org. Chem.*, **22**, 220 (1957); (d) O. Wahlroos and A. I. Virtanen, *Suomen Kemistilehti*, **32B**, 139 (1959); *Chem. Abstr.*, **54**, 2505 (1960); (e) S. D. Beck and E. E. Smissman, *Ann. Entomol. Soc. Am.*, **54**, 53 (1961); *Chem. Abstr.*, **57**, 16582 (1962); (f) E. E. Smissman, O. Kristiansen, and S. D. Beck, *J. Pharm. Sci.*, **51**, 292 (1962).

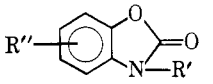
(10) W. G. Bywater, W. R. Coleman, O. Kamm, and H. H. Merritt, *J. Am. Chem. Soc.*, **67**, 905 (1945).

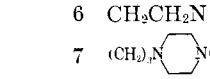
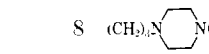
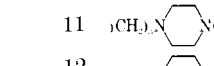
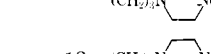
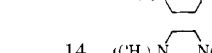
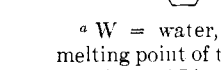
(11) W. J. Close, B. D. Tiffany, and M. A. Spielman, *J. Am. Chem. Soc.*, **71**, 1265 (1949).

(12) Z. Eckstein and E. Zokowski, *Przemysl Chem.*, **37**, 418 (1958); *Chem. Abstr.*, **53**, 5246 (1959).

TABLE I

SUBSTITUTED BENZOXAZOLINONES



No.	R'	R''	Method	Recrystn solvent[a]	Yield, %	Mp, °C	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
1	H	5-F	H	W	53	235–237	C_7H_4FNOS[b]	49.7	2.37	8.3	49.6	2.63	8.5
2	H	5-F	A, B, C	W	45, 25, 20	174–175[c]	$C_7H_4FNO_2$	54.9	2.61	...	55.1	2.94	...
3	H	5-CF_3	H	W	45	184–185	$C_8H_4F_3NOS$[d]	43.8	1.83	...	43.9	2.06	...
4	H	5-CF_3	B, I	W	89, 42	169–170[c]	$C_8H_4F_3NO_2$	47.4	1.98	6.9	47.6	2.05	7.0
5	H	5-F-6-Cl	G	W	48	207–209	$C_7H_3ClFNO_2$	44.8	1.61	7.5	44.9	1.47	7.4
6	$CH_2CH_2N(CH_2CH_3)_2$	5-F	J	E	20	173–174	$C_{13}H_{18}ClFN_2O_2$[e]	54.1	6.28	9.8	54.2	6.44	9.8
7		5-F	J	DMF	90	250 dec	$C_{15}H_{22}Cl_2FN_3O_2$[e]	49.2	6.06	11.5	48.8	6.05	11.4
8		5-Cl	J	DMF	80	240 dec	$C_{15}H_{22}Cl_3N_3O_2$[e]	47.1	5.79	11.0	47.1	6.13	11.1
9	H	5-Br	E	W–E	60	218–220[f]	$C_7H_4BrNO_2$	...	...	...	...	...	...
10	H	5-I	C, F	W–E	14, 34	241–242[c]	$C_7H_4INO_2$	32.2	1.54	5.4	32.3	1.43	5.3
11		H	J	E	75	230 dec	$C_{15}H_{25}Cl_2N_3O_2$[e,g]	49.2	6.88	11.4	49.3	7.05	11.5
12		5-F	J	W	55	104–105	$C_{16}H_{22}FN_3O_3$	59.4	6.86	13.0	58.9	6.96	12.9
13		5-Cl	J	W–E	81	140–141	$C_{16}H_{22}ClN_3O_3$	56.6	6.53	12.4	56.3	6.61	12.9
14		H	J	W	60	127–128	$C_{16}H_{23}N_3O_3$	62.9	7.59	13.8	63.0	7.65	13.8

[a] W = water, E = ethanol, DMF = dimethylformamide, W–E = water–ethanol. [b] 5-Fluoro-2-mercaptobenzoxazole. [c] Mixture melting point of the products from the different methods showed no depression. [d] 5-Trifluoromethyl-2-mercaptobenzoxazole. [e] Hydrochloride. [f] Lit.[5] and L. C. Raiford and G. O. Inmann (*J. Am. Chem. Soc.*, **56**, 1586 (1934)) give mp 214–216°. [g] Monohydrate.

Pharmacological Results.[13]—Compounds **3**, **11**, **13**, and **14** were each investigated in five mice for toxicity and for observable pharmacologic effects. The acute intraperitoneal LD_{50} ranges were as follows: **3** (62.5–75.0 mg/kg), **11** (100–200 mg/kg), **13** (33–109 mg/kg), and **14** (109–359 mg/kg). Compound **3** produced death with cyanosis, prostration, dyspnea, and apparent respiratory failure. With **11** sublethal symptoms were mild lacrimation, writhing, piloerection, and ataxia. Approaching lethality the mice showed ataxia, prostration, hyperpnea, and clonic convulsions. Symptoms with **13** and **14** were very similar: decreased mobility but easily arousable at lower dosage; tremors, Straub tail, and clonic convulsions preceding death from higher dosage.

Compounds **1–3**, **7**, and **11** were each studied in one anesthetized dog. A slight to moderate pressor effect and increased respiratory rate were seen with intraperitoneal doses of **1–3**. The pressor effect from 2.5 mg/kg of **3** was of long duration (>5 hr). None of these three compounds altered responses to acetylcholine, epinephrine, norepinephrine, or histamine. However, **3** showed a slight and **2** showed a moderate antagonism toward serotonin in the dog. The antiserotonin effect of 25 mg/kg of **2** lasted for more than 4 hr. Conversely, **7** and **11** showed a depressor effect with bradycardia after intravenous doses. Compound **11** at 4–16 mg/kg reduced blood pressure by 50–70%, and heart rate by 20%. Compound **7** at 4 mg/kg caused increased urinary flow despite a reduction in blood pressure, suggesting diuretic activity. At 32 mg/kg it caused severe hypotension with respiratory arrest. Both **7** and **11** reduced the blood pressure response to epinephrine. Additionally, **7** potentiated the response to acetylcholine and had no effect on responses to histamine or serotonin, while **11** blocked the response to histamine and had no effect on responses to acetylcholine and norepinephrine. Isoproterenol, atropine, or diphenhydramine did not antagonize the hypotension induced by **11**; this suggests that the cardiovascular effects of **11** may be accounted for by direct myocardial depression while those of **7** are more parasympathetomimetic.

(13) The authors are grateful to Dr. John Ward, A. H. Robins Company, Richmond, Va., for the pharmacological data.

Experimental Section[14]

Syntheses.—2-Benzoxazolinone,[10,11] 5-chloro-2-benzoxazolinone,[10] 5-nitro-2-benzoxazolinone,[15,16] 2-amino-4-fluorophenol,[17] 1-(3-chloropropyl)-4-methylpiperazine,[18] 1-(3-chloropropyl)-4-(2-hydroxyethyl)piperazine,[17] 2-nitro-4-trifluoromethylphenol,[19] and 2-amino-4-trifluoromethylphenol[19] were prepared according to reported procedures.

2-Benzoxazolinones. Method A.—A modification of the procedure described by Bywater, *et al.*,[10] was followed, using 0.1 mole of substituted 2-aminophenol and 7.2 g (0.12 mole) of urea. The mixture was fused at 145–150° for 4 hr in a preheated oil bath. The residue was recrystallized from a suitable solvent to give the desired product (Table I).

(14) All melting points were taken on a Fisher-Johns melting point apparatus and are uncorrected. Infrared spectra were obtained on all compounds with a Perkin-Elmer Model 137G infracord spectrophotometer using KBr pellets.

(15) R. L. Clark and A. A. Pessolano, *J. Am. Chem. Soc.*, **80**, 1664 (1958).
(16) H. Zinner, H. Herbig, I. Wistop, and H. Wigert, *Chem. Ber.*, **92**, 407 (1959).
(17) J. Corse and L. L. Ingraham, *J. Org. Chem.*, **16**, 1345 (1951).
(18) P. A. Barrett, A. G. Caldwell, and L. P. Walls, *J. Chem. Soc.*, 2404 (1961).
(19) M. R. Pettit and J. C. Tatlow, *ibid.*, 3853 (1954).

Method B.—A modification of the procedure described by Close, *et al.*,[10] was followed. A suspension of 0.1 mole of substituted 2-aminophenol and 16.4 g (0.2 mole) of sodium acetate in 300 ml of ethyl acetate was stirred and treated dropwise with a solution of 10.9 g (0.11 mole) of phosgene in 200 ml of ethyl acetate. After refluxing 15 min the solution was cooled and washed with water and 5% HCl, and the solvent was distilled under reduced pressure (water aspirator). The residue was recrystallized from a suitable solvent (Table I).

Method C.—To 0.05 mole of 5-halo-2-mercaptobenzoxazole (method H) was added 41.7 g (0.2 mole) of PCl_5. The mixture was refluxed for 7 hr and then distilled to remove $POCl_3$ and excess PCl_5. The residual material was treated with 100 ml of water, heated to boiling, and filtered. The filtrate was cooled; the solid was removed by filtration and recrystallized from either water or a mixture of water and alcohol. Mixture melting point with material obtained by methods A or B showed no depression.

5-Amino-2-benzoxazolinone. Method D.—A solution of 5-nitro-2-benzoxazolinone (14.5 g, 0.08 mole) in 150 ml of 70% ethanol was reduced at 2.8 kg/cm² using 0.1 g of 5% Pd-C catalyst. After the reduction was complete (~30 min), the catalyst was removed by filtration and the solvent was distilled *in vacuo*. The residual material was recrystallized from ethanol–water to give 11.0 g (92%) of product, mp 228–230° (lit.[15] mp 223°).

5-Bromo-2-benzoxazolinone. Method E.—A modification of the procedure described by Vogel[20] was followed. To a suspension of 11.0 g (0.073 mole) of 5-amino-2-benzoxazolinone in 40 ml of 48% HBr at 0–5° was added with shaking a solution of 5.55 g of $NaNO_2$ in 20 ml of water. This diazonium salt solution was added dropwise to a boiling solution of 6.5 g of Cu_2Br_2 in 10 ml of 48% HBr. After the complete addition of the diazonium salt, the reaction mixture was refluxed for 15 min and cooled, and the product precipitated by the addition of 300 ml of cold water. The solid was removed by filtration.

5-Iodo-2-benzoxazolinone. Method F.—A modification of the procedure described by Vogel[21] was followed. To a suspension of 9.2 g (0.066 mole) of 5-amino-2-benzoxazolinone in 20 ml of concentrated HCl and 20 ml of water at 0–5° was added with shaking a solution of 5.0 g of $NaNO_2$ in 15 ml of water. To this diazonium salt solution was added slowly a solution of 12.0 g of KI in 12 ml of water. The resulting solution was allowed to stand for 1 hr and thereafter was cautiously heated until the evolution of nitrogen was complete (~30 min) and then cooled. The product was precipitated by the addition of 300 ml of cold water. The solid was removed by filtration.

6-Chloro-5-fluoro-2-benzoxazolinone. Method G.—The procedure described by Katz and Cohen[22] was followed, using 9.0 g (0.058 mole) of 5-fluoro-2-benzoxazolinone and 15 g (0.072 mole) of PCl_5. The mixture was heated on a steam bath 12 hr and then treated with 200 ml of water. The solid which precipitated was removed by filtration.

5-Mercapto-5-substituted Benzoxazoles. Method H.—The general procedure described by Katz and Cohen[23] was followed.

5-Trifluoromethyl-2-benzoxazolinone. Method I.—A modification of the procedure described by Kinugawa, *et al.*,[24] was followed. To a cooled solution (0–5°) of 1.5 g (0.04 mole) of NaOH in 20 ml of water and 7.6 g (0.04 mole) of 2-nitro-4-trifluoromethylphenol was added with stirring 4.0 g (0.04 mole) of ethyl chloroformate. The reaction mixture was warmed gently to 70°, held constant for 30 min, and cooled. The solid was removed by filtration and placed in 20 ml of concentrated HCl. The solution was stirred vigorously and treated with 0.5 g of tin and thereafter stirred at room temperature for 2 hr. The solution was diluted with 100 ml of water and refluxed for 24 hr. The solution was filtered while still hot to remove traces of unreacted tin. The filtrate was cooled and the solid which precipitated was removed by filtration.

3-(Aminoalkyl)-2-benzoxazolinones. Method J.—A modification of the procedure described by Close, *et al.*,[10] was followed. To a solution of 0.04 mole of KOH in 75 ml of Ethyl Cellosolve was added 0.04 mole of requisite 2-benzoxazolinone. The aminoalkyl chloride (0.04 mole) or the corresponding hydrochloride (0.02 mole) was added and the mixture refluxed 2 hr. The solid was removed by filtration and the filtrate was evaporated *in vacuo* on a steam bath. The residue was taken up in benzene and washed with 5% NaOH and water. After distillation of the benzene *in vacuo*, the residue was dissolved in anhydrous ether and converted to the hydrochloride in the usual manner.

Pharmacological Procedures.[13]—Fasted female albino mice (19–28 g) were used. The animals were observed closely for signs of toxicity and pharmacologic effect during the first 4 posttreatment hr. They were observed daily, thereafter, for 3 days. Gross autopsies were performed on all animals that succumbed and on those that survived the observation period. All compounds were administered intraperitoneally.

Mongrel dogs of either sex were anesthetized by the intravenous administration of phenobarbital sodium, 125 mg/kg. A carotid artery was cannulated for recording arterial blood pressure, a jugular vein was cannulated for recording venous blood pressure, the trachea was cannulated for recording respiration, both ureters were cannulated for recording urinary flow, the urinary bladder was catheterized and connected to a closed system for recording urinary bladder activity, and needle electrodes were inserted under the skin of each limb for recording the electrocardiogram. Recordings were made with appropriate transducers on an 8-channel Grass polygraph.

The drugs were given intravenously into an exposed femoral vein, or intraperitoneally. The initial intravenous dose of each compound was 1 mg/kg and each subsequent dose was doubled until death occurred or it became impractical to increase the dosage further.

The responses to intravenous injections of standard compounds, *e.g.*, epinephrine (1 μg/kg), acetylcholine (10 μg/kg), and histamine (1 μg/kg), were obtained before and after each dose of an experimental compound.

(20) A. I. Vogel, "Practical Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1948, p 579.

(21) Reference 20, p 575.

(22) L. Katz and M. S. Cohen, *J. Org. Chem.*, **19**, 767 (1954).

(23) L. Katz and M. S. Cohen, *ibid.*, **19**, 758 (1954).

(24) J. Kinugawa, M. Oddai, and H. Yamamoto, *Yakugaku Zasshi*, **79**, 931 (1959); *Chem. Abstr.*, **54**, 497 (1960).