assay of other products and drugs as well as the use of other thin-layer media is indicated and will be reported at a later date.

REFERENCES

(1) Comer, J. P., and Comer, I., *J. Pharm. Sci.*, **56**, 413(1967).
(2) Rangone, R., *Farmaco (Pavia) Ed. Prat.*, **21**, 275 (1966).
(3) Derry, P. D., Holden, M., and Newburger, S. H., *Proc. Sci. Sect. Toilet Goods Assoc.*, **36**, 25(1961).
(4) Gänshirt, H., and Morianz, K., *Arch. Pharm.*, **293**, 1065(1960).
(5) Donato, S. J., *J. Pharm. Sci.*, **54**, 917(1965).
(6) Recent minutes of the PMA Quality Control Section, April 1967 and October, 1967.
(7) Schriftman, H., and Kondritzer, A. A., *J. Am. Pharm. Assoc., Sci. Ed.*, **46**, 173(1957).
(8) Schriftman, H., *ibid.*, **48**, 111(1959).
(9) Schriftman, H., and Shultz, R., *J. Pharm. Sci.*, **50**, 332(1961).
(10) Schriftman, H., *ibid.*, **55**, 985(1966).

Keyphrases

Parabens in gels, creams—analysis
UV densitometry on TLC—analysis
UV light, phototube detector—scanning

3-Substituted-2-benzoxazolinones

By JOSEPH SAM, J. L. VALENTINE, and C. W. RICHMOND

The preparation of 2-amino-5-trifluoromethylbenzoxazole, 5-trifluoromethyl-2-benzoxazolinone and their chemical precursors are described. The reaction of appropriately substituted 2-benzoxazolinones with substituted alkyl halides provided the 3-substituted 2-benzoxazolinones.

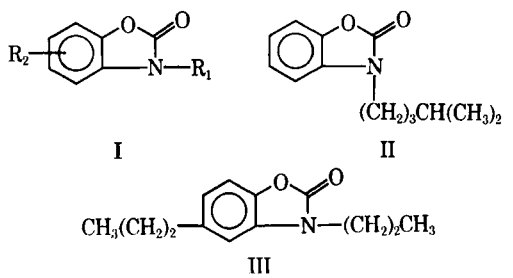
PREVIOUS INVESTIGATIONS (1–4) on the medicinal value of 3-substituted-2-benzoxazolinones (I, Table I) prompted the present work on other 3-substituted derivatives. Lespagnol and co-workers (5, 6) studied the time required for 2-benzoxazolinone and some 3-substituted derivatives to produce immobilization in fish. Swinyard and associates (7) demonstrated that the 3-substituted derivatives prepared by Lespagnol were active in antagonizing maximal electroshock states. Subsequently, Close and co-workers (2) studied a number of 3-substituted derivatives for their analgesic activity. Two of these derivatives (II and III) were tested clinically and proved to be less active than indicated by the animal studies

The 2-benzoxazolinones (XI) utilized in this study were prepared according to procedures described in earlier reports; however, additional studies were conducted on the preparation of 5-trifluoromethyl-2-benzoxazolinone (VI).

Previously, the preparation of VI *via* two routes was reported (1). One of these routes involved the condensation of phosgene with 2-amino-4-trifluoromethylphenol (V), whereas the alternate route involved the use of the intermediates 2-nitro-4-trifluoromethylphenyl ethyl carbonate (VII) and the corresponding amino derivative (VIII) *in situ*. Compounds VII and VIII now have been isolated and the structures elucidated. (Scheme I.)

The preparation of VII was accomplished by condensing IV with ethyl chloroformate. Catalytic reduction of VII gave VIII which upon treatment with aqueous hydrochloric acid yielded VI.

The pronounced biological properties of 5-chloro-2-aminobenzoxazole (8) prompted the authors to investigate the preparation of 5-trifluoromethyl-2-aminobenzoxazole (X). The con-



I II III

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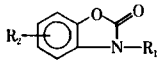
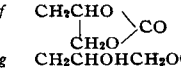
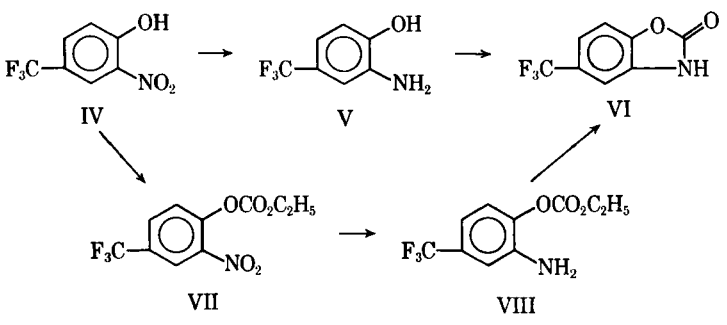
TABLE I—3-SUBSTITUTED-2-BENZOXAZOLINONES



No.	R_1	R_2	Recryst. From[a]	Method	Yield, %	M.p., °C.	Formula	Anal. Calcd.	Anal. Found
I*a*	$CH_2CH_2SCH_3$	5-F	W	A	56	71–72	$C_{10}H_{10}FNO_2S$	C, 52.9 H, 4.4 N, 6.2	C, 53.2 H, 4.6 N, 6.5
I*b*	$CONH_2$	H	E–W	D	84	144–146	$C_8H_6N_2O_3$	C, 53.9 H, 3.4 N, 15.7	C, 54.2 H, 3.6 N, 15.0
I*c*	$CON(CH_3)_2$	H	W	E	53	68–69	$C_{10}H_{10}N_2O_3$	C, 58.2 H, 4.9 N, 13.6	C, 58.3 H, 5.2 N, 13.6
I*d*	$(CH_2)_3OH$	H	—	A	81	—	$C_{10}H_{11}NO_3$[b]		
I*e*	$CH_2CHOHCH_2OH$	H	B	A	70	73–75	$C_{10}H_{11}NO_4$	C, 57.4 H, 5.3 N, 6.7	C, 57.5 H, 5.5 N, 6.7
I*f*		H	E	F	68	184–185	$C_{11}H_9NO_5$	C, 56.2 H, 3.7 N, 6.0	C, 56.4 H, 3.7 N, 5.9
I*g*	$CH_2CHOHCH_2OCONH_2$	H	W	G	50	136–137	$C_{11}H_{12}N_2O_5$	C, 52.4 H, 4.8 N, 11.1	C, 52.1 H, 4.7 N, 10.7
I*h*	$(CH_2)_3OCONH_2$	H	E–W	H	50	142–143	$C_{11}H_{12}N_2O_4$	C, 55.9 H, 5.1 N, 11.9	C, 56.2 H, 5.2 N, 11.8
I*i*	$CH_2CH(CH_3)_2$	H	E–W	A	60	63–64	$C_{11}H_{13}NO_2$	C, 69.1 H, 6.9 N, 7.3	C, 69.2 H, 6.9 N, 7.5
I*j*	CH_2CCH	H	E–W	A	70	97–98	$C_{10}H_7NO_2$	C, 69.4 H, 4.1 N, 8.1	C, 69.2 H, 4.0 N, 8.2
I*k*	$(CH_2)_2CH_3$	H	—	A	72	—	$C_{10}H_{11}NO_2$[c]	C, 67.8 H, 6.3 N, 7.9	C, 67.8 H, 6.2 N, 8.0
I*l*	CH_2CHCH_2	5-Cl-6-Br	M	A	72	70–71	$C_{10}H_7BrClNO_2$	C, 41.6 H, 2.4 N, 4.9	C, 41.6 H, 2.4 N, 4.7
I*m*	$(CH_2)_3OCH_3$	5,6-diCl	E	I	82	90–91	$C_{11}H_{11}Cl_2NO_3$	C, 47.8 H, 4.0 N, 5.1	C, 47.7 H, 4.0 N, 4.9
I*n*	$(CH_2)_3N(CH_3)_2$	5-CF_3	E	A	68	180–181	$C_{19}H_{18}F_3N_5O_9$[d]	C, 44.8 H, 3.5 N, 13.5	C, 44.2 H, 3.3 N, 13.6
I*o*	$(CH_2)_3Cl$	H	M	B	89	64–65	$C_{10}H_{10}ClNO_2$	C, 56.7 H, 4.8 N, 6.7	C, 56.6 H, 4.7 N, 6.4
I*p*	$(CH_2)_3Cl$	5,6-diCl	E	B	82	135–136	$C_{10}H_8Cl_2NO_2$	C, 42.7 H, 2.9 N, 5.0	C, 42.5 H, 3.0 N, 5.1
I*q*	$(CH_2)_3Cl$	5-Cl-6-Br	B	B	91	130–131	$C_{10}H_8BrCl_2NO_2$	C, 37.0 H, 2.5 N, 4.3	C, 37.2 H, 2.6 N, 4.1
I*r*	$(CH_2)_3Cl$	5-CF_3	M–W	B	90	47–48	$C_{11}H_8F_3ClNO_2$	C, 47.3 H, 3.2 N, 5.0	C, 47.2 H, 3.1 N, 5.2
I*s*	$(CH_2)_3NC_8H_4O_2$	H	D–W	C	81	179–181	$C_{18}H_{14}N_2O_4$[e]	C, 67.1 H, 4.4 N, 8.7	C, 67.4 H, 4.5 N, 8.7
I*t*	$(CH_2)_3NC_8H_4O_2$	5-Cl-6-Br	C	C	81	214–215	$C_{18}H_{12}BrClN_2O_4$[e]	C, 49.6 H, 2.8 N, 6.4	C, 49.4 H, 2.9 N, 6.2
I*u*	$(CH_2)_3NC_8H_4O_2$	5,6-diCl	C	C	81	219–220	$C_{18}H_{12}Cl_2N_2O_4$[e]	C, 55.3 H, 3.1 N, 7.2	C, 55.1 H, 3.2 N, 7.1

[a] W = water, E–W = ethanol–water, E = ethanol, B = benzene, M = methanol, D–W = dioxane–water, C = ethyl cellosolve, M–W = methanol–water. [b] B.p. 135–140°/0.05 mm., analysis as I*h*. [c] B.p. 122–124°/0.05 mm., n_D^{25} 1.5365. [d] Picrate, free base, b.p. 138–142°/2.5 mm., n_D^{26} 1.4892. [e] Phthalimido.



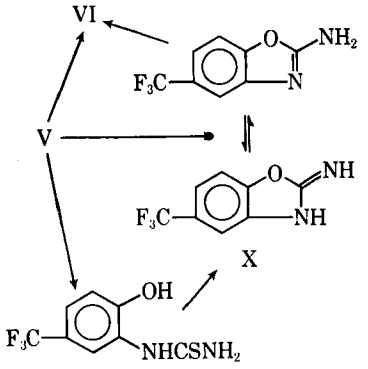
Scheme I

TABLE II—ACUTE INTRAPERITONEAL TOXICITY

No.[a]	LD_{50}, mg./kg.
I*a*	>1,000
I*c*	>1,000
I*e*	>1,000
I*h*	>1,000
I*j*	400–800
I*l*	400–800
I*m*	>1,000
I*n*	100–300
I*p*	>1,600
I*q*	>1,600
I*s*	>1,000
I*t*	>1,000
IV	800–1,600
V	>1,000
VI	200–400
VII	800–1,600
VIII	>1,000
IX	>1,000

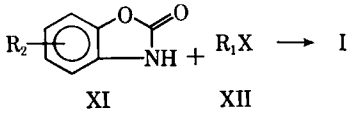
[a] Refers to compound numbers found in Table I and in the text.

densation of V with ammonium thiocyanate yielded 2-hydroxy-5-trifluoromethylphenyl thiourea (IX) which upon treatment with yellow lead oxide gave X. The preparation of X also was accomplished *via* condensation of V with cyanogen bromide. Refluxing X in dilute acid provided an alternate route to VI. (Scheme II.)



Scheme II

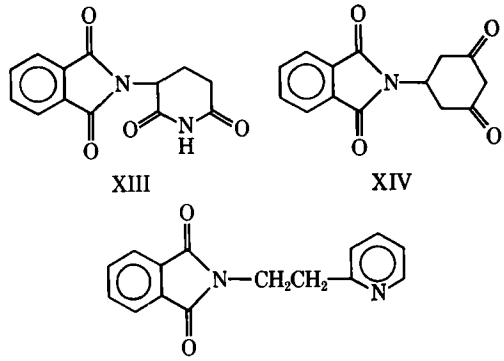
The 3-substituted-2-benzoxazolinones (I, Table I) were obtained from the condensation of the potassium salt of the requisite 2-benzoxazolinone (XI) with an appropriately substituted alkyl halide (XII). (Scheme III.)



Scheme III

The treatment of I*e* with phosgene gave I*f* which upon subsequent reaction with ammonia yielded I*g*. The opening of carbonates such as I*f* with ammonia to give the primary carbamate (*e.g.*, I*g*) has been rigorously demonstrated (9). The reaction of I*p* with sodium methoxide and I*o*, I*p*, and I*q* with potassium phthalimide provided the corresponding methoxy (I*m*) and phthalimido (I*s*, I*t*, and I*u*) derivatives, respectively, whereas the reaction of I*d* with phosgene, followed by ammonia gave the corresponding carbamate (I*h*).

The phthalimide derivatives are structurally related to the medicinally active thalidomide (XIII) (10), *d,l*-3-phthalimidoglutarimide (XIV) (11), and *N*-(2-pyridyl)ethylphthalimide (XV) (12).



PHARMACOLOGICAL RESULTS[1]

Fasted female Pharmakon mice (19–28 g.) were used for this study. The test animals were observed for 4 hr. posttreatment for signs of toxicity and for observable pharmacological effects. Thereafter, the animals were observed daily for 3 days. All compounds were administered intraperitoneally. Table II summarizes the acute intraperitoneal toxicity.

Compounds I*a*, I*c*, I*e*, I*h*, I*j*, I*n*, and I*t* showed good muscle relaxation at 1,000 mg./kg. accompanied by less motor activity, slow respiratory rate, and depression. The degree of muscle relaxation was less at 300 and 100 mg./kg. with all the above compounds exclusive of I*e* which exhibited these properties only at 1,000 mg./kg. Compounds V, VIII, and IX showed good depression at 100 mg./kg. with less muscle tone and motor activity; however these activities reached a minimum at 30 mg./kg. Compound I*m* had weak depressant properties at 100 mg./kg. but depressant activity was abolished at 30 mg./kg. Compound I*s* exhibited depression, catatonia, and reduced motor activity at 1,000, 300, 100, and 30 mg./kg.

[1] The authors are grateful to Dr. John Ward, A. H. Robins Co., Richmond, Va., for the pharmacological data.

TABLE III—INFRARED SPECTRAL DATA OF 3-SUBSTITUTED-2-BENZOXAZOLINONES[a]

No.[b]	Methylene[c]	Carbonyl	Other Groups
Ia	2,925, 1,470	1,775	—CH_3; 1,460, 1,380; —SCH_3; 1,325
Ib	—	1,800, 1,750	—$CONH_2$; 3,500, 3,300
Ic	—	1,775, 1,700	—$CON(CH_3)_2$; 1,145
Id	2,925, 1,480	1,750	—OH; 1,175, 1,095
Ie	2,925, 1,480	1,750	di-OH; 1,100, 1,085
If	2,900, 1,480	1,775	—OCOO—; 1,180, 1,090
Ig	2,950, 1,480	1,775, 1,680	—$OCONH_2$; 1,125; —OH; 1,100
Ih	1,490	1,775, 1,725	—$OCONH_2$; 1,110
Ii	2,975, 1,480	1,775	—CH_3; 1,380, 1,360, 1,145
Ij	2,900, 1,480	1,760	—$CH_2C{\equiv}CH$; 1,430
Ik[d]	2,900, 1,470	1,750	—CH_3; 3,000, 1,460, 1,350
Il	1,470	1,775	—$CH_2CH{=}CH_2$; 1,430
Im	2,925, 1,470	1,775	—CH_3; 1,450, 1,380; —OCH_3; 1,350
In[d]	2,925, 1,470	1,775	—CH_3; 2,750, 1,460;, —$N(CH_3)_2$; 1,160, 1,120
Io	2,850, 1,480, 725	1,775	—CH_2Cl; 680
Ip	2,900, 1,470, 725	1,775	—CH_2Cl; 675
Iq	2,900, 1,480, 720	1,775	—CH_2Cl; 675
Ir	2,925, 1,480, 725	1,775	—CH_2Cl; 680
Is	2,925, 1,480, 725	1,775, 1,710	—
It	2,925, 1,480, 710	1,775, 1,700	—
Iu	2,950, 1,480, 725	1,775, 1,710	—

[a] The compounds in this table all exhibit characteristic aromatic absorptions, single peak from 1,630–1,600, multiplet peaks in regions of 1,225–950 and 900–700. [b] Refers to compound numbers found in Table I. [c] Absorption at 2,975–2,900 of weak intensity. [d] Liquid film.

EXPERIMENTAL[2]

Syntheses—5-Fluoro-2-benzoxazolinone (1), 2-benzoxazolinone (13), 5-chloro-6-bromo-2-benzoxazolinone (14), 5,6-dichloro-2-benzoxazolinone (14), and 2-nitro-4-trifluoromethylphenol (15) were prepared according to reported procedures.

3-Substituted-2-benzoxazolinones—*Method A*—A modification of the procedure described by Close *et al.* (2) was followed. A solution of 0.05 mole of KOH in 200 ml. of ethyl cellosolve was treated with 0.05 mole of an appropriate 2-benzoxazolinone (Table I) and thereafter stirred at room temperature for 2 hr. In one portion was added 0.05 mole of an appropriate alkyl halide. The entire mixture was stirred and refluxed for 4 hr. The solid was removed by filtration and the filtrate concentrated under reduced pressure on a steam bath. The residue was distilled and the resultant distillate was recrystallized from an appropriate solvent (Table I).

3-(3-Chloropropyl)-2-benzoxazolinones—*Method B*—The procedure used in Method A was followed using 0.05 mole of an appropriate 2-benzoxazolinone, 0.05 mole of KOH, and 0.4 mole of 1-bromo-3-chloropropane.

3-(3-Phthalimidopropyl)-2-benzoxazolinones—*Method C*—A warm solution of 0.05 mole of a requisite 3-(3-chloropropyl)-2-benzoxazolinone in 200 ml. of ethyl cellosolve was stirred and treated, in one portion, with 9.26 g. (0.05 mole) of potassium phthalimide and thereafter refluxed for 4 hr. The resulting precipitate (KCl) was removed by filtration and the filtrate concentrated under reduced pressure on a steam bath. The residual solid was then recrystallized from a suitable solvent (Table I).

3-Carbamyl-2-benzoxazolinone — *Method D*—A modification of the procedure described by Mooradian (16) was followed. A solution of 5.4 g. (0.04 mole) of 2-benzoxazolinone and 7.5 g. (0.05 mole) of *N,N*-diethylaniline in 40 ml. of chloroform was added dropwise at room temperature to a solution of 5.0 g. (0.05 mole) of phosgene in 75 ml. of toluene. The reaction mixture was stirred for 24 hr., saturated with ammonia gas, and filtered. The filtrate was washed with 5% HCl and water, respectively, and then concentrated under reduced pressure. The residual solid was recrystallized.

3-(N,N-Dimethylcarbamoyl)-2-benzoxazolinone—*Method E*—To a stirred solution of 6.75 g. (0.05 mole) of 2-benzoxazolinone in 50 ml. of pyridine at 0–5° was added dropwise 5.35 g. (0.05 mole) of *N,N*-dimethylcarbamoyl chloride. The mixture was stirred for 1 hr. at 0–5° and then refluxed for 1 hr. The solution was cooled to room temperature and thereafter treated with 50 ml. of anhydrous ether. The solid which separated was removed by filtration; the filtrate was concentrated under reduced pressure and the residual solid recrystallized.

4-(2-Benzoxazolinon-3-yl)methyl-1,3-dioxolan-2-one—*Method F*—A modification of the procedure described by Lunsford *et al.* (17) was followed. To a cooled solution (5–10°) of 10.45 g. (0.05 mole) of *Ie* in 300 ml. of anhydrous benzene and 200 ml. of diethylene glycol was added dropwise a solution of 5.0 g. (0.05 mole) of phosgene in 100 ml. of anhydrous benzene. The resulting solution was stirred and maintained at 5–10° for 1 hr. The solution, after being allowed to attain room temperature, was treated with 7.95 g. (0.1 mole) of pyridine and stirred for an additional 10 hr. The reaction mixture was washed three

[2] All melting points were taken on a Fisher-Johns melting point apparatus and are corrected. IR spectra (Table III) were obtained with a Perkin-Elmer model 137B Infracord spectrophotometer using KBr pellets; values are recorded as cm.$^{-1}$. The NMR spectra were determined on a Varian A-60A spectrometer using Me_4Si as an internal standard; chemical shifts are recorded as δ values.

times with water, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residual solid was recrystallized.

3 - (2 - Benzoxazolinon - 3 - yl) - 2 - hydroxypropyl Carbamate—*Method G*—To 100 ml. of concentrated ammonium hydroxide solution at 0° was added 8 g. (0.02 mole) of *If*. The solution was stirred at 0° for 1 hr. and then concentrated under reduced pressure. The resultant solid was recrystallized.

3 - (2 - Benzoxazolinon - 3 - yl)propyl Carbamate—*Method H*—A solution of 3.5 g. (0.035 mole) of phosgene and 5.5 g. of *N,N*-diethylaniline in 100 ml. of benzene was treated dropwise with a solution of 6.0 g. (0.03 mole) of *Id* in 100 ml. of anhydrous benzene. The solution was maintained at 5–10° for 4 hr., then allowed to warm to room temperature and thereafter saturated with ammonia. The benzene was distilled under reduced pressure; the resultant solid was washed with water and then recrystallized.

3 - (3 - Methoxypropyl) - 5,6 - dichloro - 2 - benzoxazolinone—*Method I*—A solution of 1.2 g. (0.05 mole) of sodium ribbon and 14.0 g. (0.05 mole) of *Ip* in 200 ml. of methanol was refluxed for 30 min. The solution was concentrated to one-fourth the original volume and treated with 250 ml. of water. The precipitate was filtered and recrystallized.

2-Amino-4-trifluoromethylphenol (V)—The procedure described by Pettit and Tatlow (15) was modified by using 0.1 g. of platinum oxide. From 20.7 g. (0.1 mole) of 2-nitro-4-trifluoromethylphenol there was obtained 17.3 g. (98%) of product, m.p. 126.5–127° after recrystallization from water [lit. (15) m.p. 121–122°]; $\nu_{max.}$ 3,000 (NH_2), 1,150, 1,200 (phenolic OH); NMR (in d_2-DMSO), 3-proton singlet at 6.8 (aromatic CH), 2-proton singlet at 7.0 (NH_2), 1-proton singlet at 3.2–3.4 (phenolic OH).

2-Nitro-4-trifluoromethylphenyl Ethyl Carbonate (VII)—A modification of the procedure described by Sam *et al.* (1) was followed. A cooled solution (5–10°) of 2.94 g. (0.062 mole) of NaOH and 17.5 g. (0.089 mole) of IV in 40 ml. of water was treated with 7.96 g. (0.074 mole) of ethyl chloroformate and thereafter maintained at 5–10° with stirring for 1 hr. The solid was removed by filtration and recrystallized from ethanol–water to give 16.6 g. (95%) of product, m.p. 87.5–88°; $\nu_{max.}$ 1,750 (C=O); NMR (in d_5-pyridine), 3-proton multiplet at 7.75–8.0 (aromatic CH), 2-proton multiplet at 4.15–4.4 (CH_2), 3-proton multiplet at 1.2–1.4 (CH_3).

Anal.—Calcd. for $C_{10}H_8F_3NO_5$: C, 43.02; H, 2.88; N, 5.01. Found: C, 43.15; H, 2.72; N, 5.24.

2-Amino-4-trifluoromethylphenyl Ethyl Carbonate (VIII)—A solution of 13.9 g. (0.05 mole) of VII in 100 ml. of ethanol was hydrogenated at 40 p.s.i. using 0.1 g. of platinum oxide catalyst until the theoretical amount of hydrogen had been absorbed (*ca.* 2 hr.). The catalyst was removed by filtration and the ethanol distilled under reduced pressure. The residual dark yellow solid was recrystallized from benzene to give 13.0 g. (93%) of product, m.p. 194–195°; $\nu_{max.}$ 3,200 (NH_2), 1,675 (C=O); NMR (in d_5-pyridine), 3-proton triplet at 7.1–7.3 (aromatic CH), 2-proton multiplet at 4.1–4.5 (CH_2), 3-proton multiplet at 1.05–1.35 (CH_3), 2-proton singlet at 8.83 (NH_2).

Anal.—Calcd. for $C_{10}H_{10}F_3NO_3$: C, 48.20; H, 4.05; N, 5.62. Found: C, 48.44; H, 4.24; N, 5.83.

2-Hydroxy-5-trifluoromethylphenyl Thiourea (IX)—The procedure described by Sam and Plampin (14) was followed. From 17.8 g. (0.1 mole) of V and 9.2 g. (0.12 mole) of ammonium thiocyanate there was obtained 12.2 g. (68%) of product, m.p. 151–152°, after recrystallization from water; $\nu_{max.}$ 3,200 (NH, NH_2), 1,625 (C=O), 1,175, 1,125 (phenolic OH); NMR (in d_2-DMSO), 3-proton multiplet at 7.16–7.73 (aromatic CH), 2-proton singlet at 8.66 (NH_2), 1-proton singlet at 9.25 (NH), 1-proton broad singlet at 10.73–10.96 (phenolic OH); upon D_2O exchange the absorptions at 8.66, 9.25, and 10.73–10.96 were absent.

Anal.—Calcd. for $C_8H_7F_3N_2OS$: C, 40.67; H, 2.99; N, 11.89. Found: C, 40.78; H, 3.17; N, 11.73.

2-Amino-5-trifluoromethylbenzoxazole (X)—*Method J*—The method described by Sam and Plampin (14) for the preparation of 2-aminobenzoxazoles was followed using 11.8 g. (0.05 mole) of IX and 22.2 g. (0.1 mole) of yellow lead oxide. The product (9.3 g., 67%) was recrystallized from water, m.p. 146–147°; $\nu_{max.}$ 3,200 (NH_2 or 2NH); NMR (in d_2-DMSO), 5-proton multiplet at 7.33–7.83 (aromatic CH, NH_2, or 2NH); D_2O exchange showed that two protons were exchanged.

Anal.—Calcd. for $C_8H_5F_3N_2O$: C, 47.53; H, 2.49; N, 13.86. Found: C, 47.59; H, 2.23; N, 13.74.

Method K—The method described by Sam and Plampin (14) for the preparation of 2-aminobenzoxazoles was followed using 16.9 g. (0.15 mole) of cyanogen bromide and 17.7 g. (0.1 mole) of V. The product (12.5 g., 71%) was recrystallized from water, m.p. 146–147°. A mixture of the products obtained from Methods *J* and *K* showed no depression of the melting point. The IR and NMR spectra were identical.

5-Trifluoromethyl-2-benzoxazolinone (VI)—*Method L*—The method described by Sam and Plampin (14) was followed using 15.0 g. (0.07 mole) of X. The product (13.5 g., 82%) was recrystallized from water, m.p. 169–170° [lit. (1) 169–170°]; $\nu_{max.}$ 1,750 (C=O); NMR (in *d*-$CHCl_3$), 3-proton multiplet at 7.2–7.5 (aromatic CH), 1-proton singlet at 10.29 (NH).

Method M—A solution of 5 g. (0.018 mole) of VIII in 250 ml. of 20% aqueous HCl was refluxed for 18 hr. and then cooled to room temperature. The precipitate was filtered and recrystallized from water to give 2.0 g. (45%) of product, m.p. 169–170°. A mixture with the product obtained in Method *L* showed no depression of the melting point. The IR and NMR spectra were identical.

REFERENCES

(1) Sam, J., Richmond, C. W., and Valentine, J. L., *J. Med. Chem.*, **10**, 408(1967).
(2) Close, W. J., Tiffany, B. D., and Spielman, M. A., *J. Am. Chem. Soc.*, **71**, 1265(1949).
(3) Lespagnol, A., Mercier, J., and Lespagnol, C., *Arch. Intern. Pharmacodyn.*, **94**, 212(1953); through *Chem. Abstr.*, **48**, 10003(1954).
(4) Varma, R. S., and Nobles, W. L., *J. Pharm. Sci.*, **57**, 39(1968).
(5) Lespagnol, A., Durbet, G., and Mongy, E., *Compt. Rend. Soc. Biol.*, **135**, 1255(1941); through *Chem. Abstr.*, **38**, 5587(1944).
(6) Lespagnol, A., and Lefebvre-Cannesson, Mme.,

Compt. Rend. Soc. Biol., **138**, 529(1944); through *Chem. Abstr.*, **40**, 131(1946).

(7) Swinyard, E. A., Toman, J. E. P., and Goodman, L. S., *J. Neurophysiol.*, **9**, 47(1946).

(8) Cain, C. K., and Roszkowski, A. P., "Psychopharmacological Agents," Vol. I, Gordon, M., Ed., Academic Press, New York, N. Y., 1964, p. 344.

(9) Baizer, M. M., Clark, J. R., and Swidinsky, J., *J. Org. Chem.*, **22**, 1595(1957).

(10) Williams, R. T., and Parke, D. V., "Annual Review of Pharmacology," Vol. 4, Cutting, W., Ed., Annual Review, Palo Alto, Calif., 1964, p. 90.

(11) Misiti, D., Rosnati, V., Bignami, G., Bovet-Nitti, F., and Bovet, D., *J. Med. Chem.*, **6**, 464(1963).

(12) Lewis, J. R., *Arch. Intern. Pharmacodyn.*, **88**, 142 (1951); through *Biol. Abstr.*, **27**, 9727(1953); through *Chem. Abstr.*, **46**, 2680(1952).

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

(14) Sam, J., and Plampin, J. N., *J. Pharm. Sci.*, **53**, 538(1964).

(15) Pettit, M. R., and Tatlow, J. C., *J. Chem. Soc.*, **3853**(1954).

(16) Mooradian, A., Brit. patent 850,003, Sept. 28, 1960; through *Chem. Abstr.*, **55**, 11311(1961).

(17) Lunsford, C. D., Mays, R. P., Richman, J. A., and Murphey, R. S., *J. Am. Chem. Soc.*, **82**, 1166(1960).

Keyphrases

3-Substituted-2-benzoxazolinones—synthesis
2-Amino-5-trifluoromethylbenzoxazole—synthesis
5-Trifluoromethyl-2-benzoxazolinone—synthesis
Pharmacological screening—3-substituted-2-benzoxazoles
IR spectrophotometry—structure
NMR spectroscopy—structure

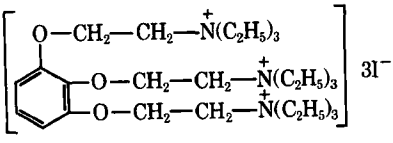
Drug Standards

Quantitative Determination of Gallamine Triethiodide

By PETER P. ASCIONE, JOHN B. ZAGAR, and GEORGE P. CHREKIAN

A nonaqueous method for the determination of crystalline gallamine triethiodide was developed. The titration utilized a mixture of *N,N*-dimethylformamide (DMF)–*p*-dioxane as the solvent, bromophenol blue as an indicator, and 0.1 *N* perchloric acid as the titrant. Also a colorimetric acid-dye extraction was developed for the determination of gallamine triethiodide in the injectable dosage form. This technique involved the extraction of an acid-dye complex, gallamine triethiodide and bromocresol green buffered to pH 5.3, with chloroform.

A SURVEY of literature revealed that gallamine triethiodide (I), a muscle relaxant, was synthesized and introduced in 1946 by Bovet (1). Its structure, although much simpler, was based on that of *d*-tubocurarine, and it owes its high potency as a relaxant to the three triethylammonium groups of its molecule (2).



I

Pharmaceutical dosage form and the crystalline powder are currently being assayed by the procedure outlined in the NF XII (3). This procedure is based on the Volhard volumetric titration of the iodide present in the molecule. However this procedure is capable of measuring halogens other than the iodide portion of the molecule, thereby lacking specificity for gallamine. A spectrophotometric determination was investigated but it was found to be a function of the iodide portion of the molecule rather than the active triethylammonium groups.

The purpose of this investigation was to develop a rapid and more specific procedure which could be employed in quality control laboratories for analyzing gallamine triethiodide both in

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