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BENZOXAZOLE DERIVATIVES. II. 2-DIALKYLAMINO-ALKYLMERCAPTOBENZOXAZOLES

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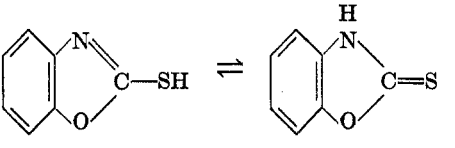
In an earlier investigation the preparation of a series of 2-mercaptobenzoxazoles was described (1) some of which possessed significant antibacterial action.

To further our knowledge with regard to the microbiological and pharmacological properties of benzoxazoles, the dialkyaminoalkyl side chain which is known to be an important factor in the action of many known drugs was incorporated into the 2-mercaptobenzoxazole molecule.

The phenomenon of tautomeric mobility in benzoxazolone, 2-aminobenzoxazole, and 2-mercaptobenzoxazole is well known through the studies of Desai, Hunter, and Khaladi (2). As a consequence of this prototropic mobility, substitution of an alkyl group into the 2-mercaptobenzoxazoles could occur at either the nitrogen or the sulfur atom depending upon whether the molecule existed in the thiol (IA) or thione (IB) configuration.



IA IB

Although ring nitrogen substitution has been conclusively demonstrated in 2-aminobenzoxazole and benzoxazolone (2), some variance of opinion exists concerning the nature of the product obtained by the alkylation of 2-mercaptobenzoxazole. Desai, *et al.* (2) reported that the methylation of IA ⇌ IB with dimethyl sulfate gave rise to no well defined substance, which leads one to suspect that both S and N alkylation had occurred. On the other hand Hoggarth (3) and Kendall (4) prepared the 2-methylmercapto compound under essentially the same conditions.

The alkylation of a number of benz-substituted 2-mercaptobenzoxazoles with 2-diethylaminoethyl chloride produced a pure mono-alkylated derivative which was isolated and crystallized as the hydrohalide salt. However, through the loss of hydrogen halide or other less obvious decomposition, some of the crystalline hydrohalides failed to provide carbon-hydrogen analyses within the prescribed limits. The quaternary ammonium derivatives, prepared by treating the free base with gaseous methyl bromide, invariably led to crystalline substances whose analyses were acceptable. The hydrohalide and methonium salts prepared are listed in Table A as shown in the Flow Sheet.

Although most of the hydrohalides isolated melted sharply and gave evidence

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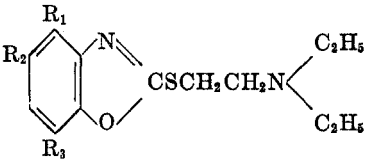
TABLE A

HYDROHALIDE AND METHONIUM SALTS OF 2-DIETHYLAMINOETHYLMERCAPTOBENZOXAZOLE



No.	R_1	R_2	R_3	YIELD, %	M.P.,[a] °C.	EMPIRICAL FORMULA	ANALYSES					
							C		H		X[m]	
							Calc'd	Found	Calc'd	Found	Calc'd	Found
1	H	H	H	88	159–160[c]	$C_{11}H_{15}N_2OS{\cdot}HCl$					12.36	12.50
2	H	H	H	87	154–155[d]	$C_{11}H_{15}N_2OS{\cdot}CH_3Br$					23.14	22.95
3	H	Cl	H	97	187–189[e]	$C_{11}H_{17}N_2OS{\cdot}HCl$	48.59	48.56	5.65	5.46		
4	H	Cl	H	76	219–220[f]	$C_{11}H_{17}N_2OS{\cdot}CH_3Br$	44.27	44.30	5.31	5.21		
5	H	H	Cl	63	228–230[g]	$C_{11}H_{17}N_2OS{\cdot}HCl$	48.59	49.57	5.62	5.72		
6	H	H	Cl	85	213–214[g]	$C_{11}H_{17}N_2OS{\cdot}CH_3Br$	44.27	44.49	5.31	5.14		
7	H	NO_2	H	88	223–224[f]	$C_{11}H_{17}N_3O_3S{\cdot}HCl$	47.00	47.02	5.45	5.43		
8	H	NO_2	H	98	203–204[h]	$C_{11}H_{17}N_3O_3S{\cdot}CH_3Br$					20.46	20.16
9	H	*t*-Bu	H	90	184–185[h]	$C_{17}H_{26}N_2OS{\cdot}HCl$					10.34	10.64
10	H	*t*-Bu	H	94	[b]	$C_{17}H_{26}N_2OS{\cdot}CH_3Br$	53.85	53.70	7.28	7.34		
11	H	Cl	Cl	97	233–235[f]	$C_{11}H_{14}Cl_2N_2OS{\cdot}HCl$	43.89	44.49	4.82	4.48		
12	H	Cl	Cl	93	200–201[i]	$C_{11}H_{14}Cl_2N_2OS{\cdot}CH_3Br$	40.59	41.28	4.62	5.06		
13	H	CH_3	CH_3	74	220–222[f]	$C_{15}H_{22}N_2OS{\cdot}HCl$	57.21	56.63	7.33	7.53		
14	H	CH_3	CH_3	92	180–182[h]	$C_{15}H_{22}N_2OS{\cdot}CH_3Br$	51.48	51.20	6.70	6.59		
15	H	*t*-Bu	Cl	95	241–242[j]	$C_{17}H_{25}ClN_2OS{\cdot}HCl$	54.10	54.79	6.95	6.96		
16	H	*t*-Bu	Cl	98	169–171[k]	$C_{17}H_{25}ClN_2OS{\cdot}CH_3I$	44.77	44.65	5.84	5.89		
17	H	*t*-Bu	Cl	78	202–203[h]	$C_{17}H_{25}ClN_2OS{\cdot}CH_2Br$	49.59	48.87	6.47	6.62		
18	Cl	Cl	Cl	91	268–269[l]	$C_{11}H_{13}Cl_3N_2OS{\cdot}HCl$	40.02	40.19	4.13	3.76		
19	Cl	Cl	Cl	88	232–233[h]	$C_{11}H_{14}Cl_3N_2OS{\cdot}CH_3Br$	37.42	37.43	4.05	4.33		
20	CH_3	Cl	*i*-Pr	93	269–270[f]	$C_{17}H_{25}ClN_2OS{\cdot}HBr$	48.34	48.69	6.16	6.49		
21	CH_3	Cl	*i*-Pr	82	212–213[h]	$C_{17}H_{25}ClN_2OS{\cdot}CH_3Br$	49.59	49.81	6.47	6.42		

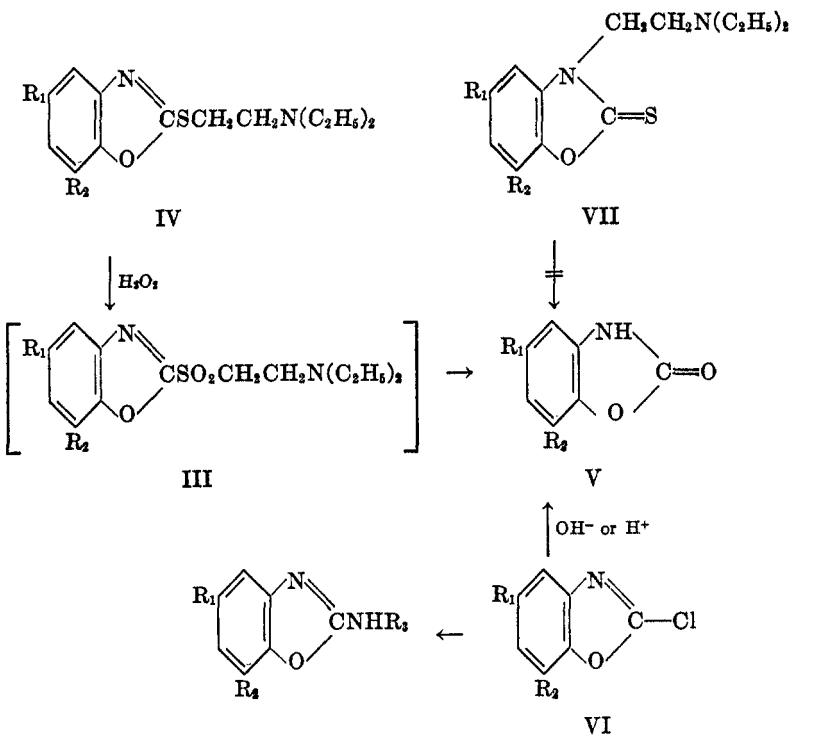
[a] All m.p.'s are uncorrected. [b] M.p. indistinct. [c] From ethyl acetate as a white powder. [d] From benzene-methanol as white rods. [e] From methyl ethyl ketone as a white powder. [f] From isopropyl alcohol as a white powder. [g] From methanol-isopropyl ether as a white powder. [h] From isopropyl alcohol-isopropyl ether as a white powder. [i] From ethylene chloride as a white powder. [j] From hot water as white needles. [k] From benzene-methylcyclohexane as a white powder. [l] From methanol as short white rods. [m] X is halogen.

of homogeneity, conclusive proof that the isolated product was the S-alkylated substance was lacking. The question was decisively settled by an oxidation reaction originally employed for the purpose of preparing the sulfone III from IV (R = *tert*-butyl; R_2 = Cl).

Instead of the anticipated sulfone III, a white crystalline substance was isolated possessing the solubility characteristics of a weak acid. In addition, an elementary analysis revealed the absence of sulfur. The new compound was shown to be V (R_1 = *tert*-butyl; R_2 = Cl), by its carbon-hydrogen analysis and also by its synthesis through the hydrolysis of VI (R_1 = *tert*-butyl; R_2 = Cl). Had the alkylation reaction given rise to the N-alkylated derivative VII (R_1 = *tert*-butyl; R_2 = Cl), oxidation would not have yielded V.

A number of attempts were made to prepare the sulfone III (R_1 = *tert*-butyl; R_2 = Cl) through the use of varying proportions of oxidant. In every case the sole product isolated was the benzoxazolone. Hoggarth (3) had shown that

FLOW SHEET



R_1 = *tert*-butyl; R_2 = Cl
VIII; R_3 = $CH_2CH_2N(C_2H_5)_2$
VIIIA; R_3 = H
VIIIB; R_3 = $C_6H_5CH_2$

2-methylsulfonylbenzoxazole was converted to benzoxazolone merely on recrystallization from hot water and it is assumed that the instability of III precluded its isolation under these experimental conditions.

The preparation of 2,7-dichloro-5-*tert*-butylbenzoxazole was required for the structure proof of V and also for the preparation of the nitrogen isoster VIII [R_3 = $CH_2CH_2N(C_2H_5)_2$]. McCoy (5) had described the preparation of 2-chlorobenzoxazole by the action of chlorine on the 2-mercapto compound. When this reaction was extended to 5-*tert*-butyl-7-chloro-2-mercaptobenzoxazole, the yield of product was 15%. An alternative method in which McCoy heated the mercapto compound with an equivalent of phosphorus pentachloride showed little improvement. It was found that the yield could be increased markedly through the use of a large excess of phosphorus pentachloride. Although the hydrogen halide released during the reaction is capable of forming a hydrochloride salt with the 2-chloro compound, this salt was found to be unstable; 2,7-dichloro-5-*tert*-butylbenzoxazole (VI) was distilled directly from the reaction mixture *in vacuo* in 56% yield. The chloro compound was converted to the 2-amino (VIIIA) and 2-benzylamino (VIIIB) compound for other studies. An attempt

to substitute an alkylamino group directly for the mercapto group by fusion of the 2-mercapto compound with the corresponding amine gave rise to mixtures of products which could not in most instances be successfully purified. In two cases, however, a fair yield of 2-benzylamino compound was obtained by heating 2-mercapto-4,5,7-trichlorobenzoxazole and 2-mercapto-5-nitrobenzoxazole with benzylamine in refluxing trichlorobenzene and *o*-dichlorobenzene respectively.

Pharmacology. All of the methonium derivatives exhibited a modicum of antispasmodic activity as evidenced by their ability to reduce intestinal motility in the anesthetized dog. The greatest activity was encountered with compounds 17 and 21, Table A. These derivatives were as effective as Banthine at a dose level of 0.25 mg./kg.

EXPERIMENTAL[3]

2-(2'-Diethylaminoethylmercapto)-4,5,7-trichlorobenzoxazole hydrochloride. The following is illustrative of the method used to prepare all the 2-(2'-diethylaminoethylmercapto)-benzoxazoles and their quaternary salts which are tabulated in Table A. Into a flask fitted with a mechanical stirrer and a reflux condenser were added 10.2 g. (0.04 mole) of 4,5,7-trichloro-2-mercaptobenzoxazole, 7.7 g. (0.056 mole) of potassium carbonate, 6.5 g. (0.048 mole) of 2-diethylaminoethyl chloride hydrochloride, 40 ml. of water, and 60 ml. of toluene. The two phase system was heated under reflux with stirring for 14–16 hours. At the end of this period the mixture was cooled and the organic layer was separated. The aqueous layer was extracted with two 20-ml. portions of ether and these ethereal extracts were combined with the toluene phase. After washing with water and drying over magnesium sulfate, the product was precipitated by the addition of ethereal hydrogen chloride. There was obtained 14.2 g. (91%) of a white powder; m.p. 268–270°. Recrystallization from methanol gave short white rods with essentially the same melting point.

2-(2'-Diethylaminoethylmercapto)-4,5,7-trichlorobenzoxazole methobromide. A stream of gaseous methyl bromide was introduced into a solution of 4.5 g. (0.018 mole) of 2-(2'diethylaminoethylmercapto)-4,5,7-trichlorobenzoxazole in 100 ml. of ethyl acetate. An initial heat of reaction and heat of solution took place as the white crystalline product precipitated from solution. The passage of methyl bromide through the solution was discontinued as soon as the temperature began to fall. After standing at room temperature overnight, the product was collected, and washed with excess ethyl acetate. The white needles weighed 6.1 g. (88%) and melted at 231–232°. Recrystallization from isopropyl alcohol-isopropyl ether gave little change in the melting point.

2-(3'-N-morpholinopropylmercapto)-5-tert-butyl-7-chlorobenzoxazole hydrochloride. Into a flask equipped with a mechanical stirrer and a reflux condenser was added 5.0 g. (0.021 mole) of 5-*tert*-butyl-7-chloro-2-mercaptobenzoxazole, 1.2 g. (0.008 mole) of potassium carbonate, 3.6 g. (0.022 mole) of 3-N-morpholinopropyl chloride, 30 ml. of water, and 30 ml. of toluene. The two phase system was heated under reflux overnight, cooled, and the layers were separated. The aqueous phase was extracted with two 20-ml. portions of ether and the ethereal solutions were combined with the toluene phase. The solvent was removed *in vacuo* leaving a light tan oil, 7.0 g. (90%). A portion of this oil was dissolved in ether and ethereal hydrogen chloride was added. The white powder which precipitated, m.p. 212–213°, was recrystallized from methyl ethyl ketone to give short white rods whose melting point was virtually unchanged.

Anal. Calc'd for $C_{18}H_{26}Cl_2N_2O_2S$: C, 53.33; H, 6.46.
Found: C, 53.40; H, 6.60.

2-(3'-N-Morpholinopropylmercapto)-5-tert-butyl-7-chlorobenzoxazole methiodide. A solu-

[3] All melting points are uncorrected. Microanalyses by the Clark Microanalytical Laboratory, Urbana, Illinois.

tion of 2.20 g. (0.06 mole) of 2-(3′-N-morpholinopropylmercapto)-5-*tert*-butyl-7-chlorobenzoxazole and 1.0 ml. of methyl iodide in 25 ml. of heptane and 25 ml. of ethyl acetate was heated under reflux for 24 hours. The product which was collected, 2.9 g. (94%), melted to a semi-solid at 135° and then to a clear melt at 210°. Repeated crystallization resulted in no improvement of the melting point.

Anal. Calc'd for $C_{19}H_{28}ClIN_2O_2S$: C, 44.67; H, 5.52.

Found: C, 44.54; H, 5.29.

5-tert-Butyl-7-chlorobenzoxazolone. A solution was prepared containing 1.0 g. (0.003 mole) of 2-(2′-diethylaminoethylmercapto)-5-*tert*-butyl-7-chlorobenzoxazole and 10 ml. of 30% hydrogen peroxide in 20 ml. of acetic acid. After standing for three days, the reaction mixture was poured into 100 ml. of water. The solid which separated was collected, washed with water, and dried. There was obtained 0.5 g. (74%) of white needles; m.p. 166–171°. Recrystallization from aqueous acetic acid raised the melting point to 171–173°. The same product, m.p. 171–173° and mixture m.p. 170–172°, was obtained when 2,7-dichloro-5-*tert*-butylbenzoxazole was heated for a few minutes with either 6 *N* hydrochloric acid or 20% sodium hydroxide.

Anal. Calc'd for $C_{11}H_{12}ClNO_2$: C, 58.53; H, 5.32.

Found: C, 58.70; H, 5.57.

2,7-Dichloro-5-tert-butylbenzoxazole. A mixture of 19.3 g. (0.08 mole) of 5-*tert*-butyl-7-chloro-2-mercaptobenzoxazole and 29.2 g. (0.14 mole) of phosphorus pentachloride was heated at 160–170° under reflux for three hours. The flask was then fitted with a distilling head and the oil was distilled *in vacuo*. The first fraction, unreacted phosphorus pentachloride and some phosphorus oxychloride, was discarded. The product, b.p. 122–123°/7 mm., solidified in the receiving flask and weighed 11.0 g. (57%). Vacuum sublimation of a small portion of this material gave white prisms, m.p. 36–38°, which possessed the characteristic odor of an acid chloride.

Anal. Calc'd for $C_{11}H_{11}Cl_2NO$: C, 54.09; H, 4.51.

Found: C, 53.69; H, 4.46.

2-(2′-Diethylaminoethylamino)-5-tert-butyl-7-chlorobenzoxazole. A mixture of 4.9 g. (0.02 mole) of 2,7-dichloro-5-*tert*-butylbenzoxazole and 4.6 g. (0.04 mole) of N,N-diethylethylenediamine was heated to 120° after the initial exothermic reaction had subsided. After one-half hour the thick oil was cooled, poured into 25 ml. of water, and extracted with 50 ml. of ether. The ethereal solution was washed, dried, and then the ether was evaporated. The residual oil was distilled *in vacuo* to give 2.5 g. (38%) of thick yellow oil, b.p. 214°/5 mm., which did not form a crystalline hydrochloride or hydrobromide salt. The product was characterized as the *dipicrate* salt m.p. 180–182°, obtained as yellow crystals from alcohol.

Anal. Calc'd for $C_{17}H_{26}ClN_3O \cdot 2C_6H_3N_3O_7$: C, 44.54; H, 4.11.

Found: C, 45.12; H, 4.22.

2-Amino-5-tert-butyl-7-chlorobenzoxazole. A slurry consisting of 2.4 g. (0.01 mole) of 2,7-dichloro-5-*tert*-butylbenzoxazole and 20 ml. of concentrated ammonium hydroxide was shaken for one hour. The solid was then dissolved in hot methyl alcohol and water was added to the cloud point. Upon cooling, crystals formed which were collected, washed with water, and dried. The product, 1.9 g. (85%) m.p. 170–175°, was dissolved in 25 ml. of warm 1 *N* hydrochloric acid, filtered and then reprecipitated by the addition of sodium bicarbonate. After washing and drying, it was recrystallized from cyclohexane and gave tiny white crystals; m.p. 184–186°.

Anal. Calc'd for $C_{11}H_{13}ClN_2O$: C, 58.80; H, 5.79.

Found: C, 58.76; H, 6.04.

2-Benzylamino-5-tert-butyl-7-chlorobenzoxazole. A mixture of 2.4 g. (0.01 mole) of 2,7-dichloro-5-*tert*-butylbenzoxazole and 2.40 g. (0.22 mole) of benzylamine was heated at 120° for one-quarter hour after the initial exothermic reaction. When the reaction mixture had cooled to room temperature, 25 ml. of water was added containing enough acetic acid to give an acid test with Hydrion paper. The solid which separated was collected, washed

with dilute acetic acid, and recrystallized from aqueous propanol-2 to give 2.8 g. (90%) of short white needles; m.p. 129.5–130.5°. Subsequent recrystallization did not alter the melting point.

Anal. Calc'd for $C_{18}H_{19}ClN_2O$: C, 68.68; H, 6.03.

Found: C, 68.58; H, 6.06.

2-Benzylamino-4,5,7-trichlorobenzoxazole. Five grams (0.020 mole) of 4,5,7-trichloro-2-mercaptobenzoxazole and 2.25 g. (0.021 mole) of benzylamine were heated at reflux in 12 ml. of trichlorobenzene for four hours. Hydrogen sulfide gas was evolved rapidly at first, but at the end of the reflux period its odor was negligible. The solution was cooled and the crystals which separated were collected and washed with benzene. There was obtained 1.5 g. (23%) of 2-benzylamino-4,5,7-trichlorobenzoxazole; m.p. 200–203°. Repeated crystallization from benzene gave cream-colored crystals; m.p. 205–205.5°. A primary contaminant in the reaction was the benzylamine salt of 2-mercapto-4,5,7-trichlorobenzoxazole; m.p. 203–205°.

Anal. Calc'd for $C_{14}H_9Cl_3N_2O$: C, 51.32; H, 2.77.

Found: C, 51.87; H, 2.90.

2-Benzylamino-5-nitrobenzoxazole. A mixture of 5.0 g. (0.026 mole) of 2-mercapto-5-nitrobenzoxazole, 2.9 g. (0.027 mole) of benzylamine, and 15 ml. of *o*-dichlorobenzene was heated under reflux for 2½ hours. The evolution of hydrogen sulfide gas had subsided by this time and the solution was cooled to room temperature. When the reaction mixture was poured into 250 ml. of petroleum ether (b.p. 30–60°) a yellow solid, which weighed 6.3 g. but melted poorly, separated. One crystallization from aqueous methanol gave 4.9 g. (70%) of yellow platelets; m.p. 149–150°. Recrystallization did not alter the melting point.

Anal. Calc'd for $C_{14}H_{11}N_3O_3$: C, 62.65; H, 4.12.

Found: C, 62.55; H, 4.15.

SUMMARY

A number of 2-mercaptobenzoxazoles have been shown to undergo S-alkylation. Replacement of the mercapto group by alkylamino and halogen groups has also been described.

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