In an attempt to increase the efficiency of the regeneration process an experiment was carried out at 60° since it was believed that slow rates of equilibration might be in part responsible for the trailing edge in the sulfuric acid elution. Operation at higher temperature not only does not improve the regeneration but actually the removal of H_2SO_4 takes more water (*ca.* 32 column volumes) than at lower temperature indicating that the tailing in the elution band is not due to slow rates of equilibration. It probably arises from a pronounced nonlinearity of the adsorption isotherm. It is interesting to note that the copper band at 60° definitely showed some adsorption, the apparent elution constant E^4 being *ca.* 1 instead of the theoretical maximum *ca.* 2.5 when no adsorption takes place. At the lower temperature the copper band was less strongly adsorbed, but did not travel with elution constant as large as 2.5.

[4] *E* has been defined (K. A. Kraus and G. E. Moore, THIS JOURNAL, **73**, 9 (1951), as the distance (cm.) a band moves under equilibrium conditions, per cc. of eluent in a 1-cm.^{2} column.

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Preparation of Certain Derivatives of Benzoxazole

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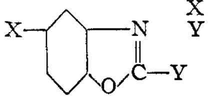
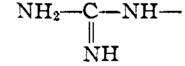
This note describes the preparation of several 2,5-disubstituted benzoxazoles, in the hope that they may be of therapeutic value.



X (5 position): Cl, $HO_2C—$, or $BuO_2C—$
Y (2 position): SH, OH, NH_2, or



$NH_2—C(=NH)—NH—$

Experimental

2-Benzeneazo-4-chlorophenol.—A modification of the method of Krause[1] was found to prevent the formation of tar. A solution of benzenediazonium chloride made from 0.1 mole (9.3 g.) of aniline was added at −3 to 0° with stirring over a period of two hours to a cold solution of 0.1 mole (12.9 g.) of *p*-chlorophenol, 4.0 g. of sodium hydroxide and 2.9 g. of sodium carbonate crystals in 100 ml. of 90% ethanol and 200 ml. of water. The stirring was maintained until there was no color reaction with alkaline β-naphthol, the solution then acidified with acetic acid, filtered, and the solid product (23 g. of orange yellow needles melting at 105–107°) washed with water. Recrystallization from 60% acetic acid gave orange prismatic needles melting at 110–111°.

2-Amino-4-chlorophenol.—To a stirred mixture of 4.64 g. of 2-benzeneazo-4-chlorophenol in 10 ml. of ethanol and 20 ml. of water was added 12.6 g. of sodium hydrosulfite during 15 minutes. Stirring was maintained until the mixture became colorless, and the ethanol was then removed on a water-bath. After standing overnight, the solution deposited 2.4 g. (83%) of colorless plates, melting at 138–140° with preliminary softening. Recrystallization from 50 ml. of hot water gave colorless rhombic plates melting at 140–141°. Popov[2] reported a melting point of 137–138°, and Korczynski and Obarski[3] a melting point of 185° for this product.

Anal. Calcd. for C_6H_6ClNO: N, 9.76. Found: N, 9.78.

The diacetyl derivative of 2-amino-4-chlorophenol gave colorless plates from benzene, melting at 173–175°. Korczynski and Obarski[3] reported a melting point of 201° for this derivative.

Anal. Calcd. for $C_{10}H_{10}ClNO_3$: N, 6.15. Found: N, 6.13.

The hydrochloride of 2-amino-4-chlorophenol gave colorless prisms from ethanol, melting at 258° with decomposition.

Butyl 4-Hydroxy-3-benzeneazobenzoate.—It has been found that the reaction of benzenediazonium chloride with 4-hydroxybenzoic acid gives only a small yield of 4-hydroxy-3-benzeneazobenzoic acid (the chief product being 2,4-bis-benzeneazophenol), but that substitution of the ethyl ester of the acid gives a good yield of ethyl 4-hydroxy-3-benzeneazobenzoate.[4] For this reason the butyl ester of 4-hydroxybenzoic acid was used in the present investigation.

A solution of benzenediazonium chloride made from 0.2 mole (18.6 g.) of aniline was added with stirring at −5 to −3° to a cold solution of 0.2 mole (38.8 g.) of butyl 4-hydroxybenzoate and 24 g. of sodium hydroxide in 400 ml. of water. After standing in the cold until there was no color reaction with alkaline β-naphthol, the solution was acidified with acetic acid, filtered and washed repeatedly with water. The product, crystallized from 100 ml. of 90% ethanol, weighed 46.0 g. (77%) and separated as orange yellow prisms (m.p. 75°), quite soluble in benzene and petroleum ether, and fairly soluble in warm ethanol and 80% hot acetic acid.

Anal. Calcd. for $C_{17}H_{18}N_2O_3$: N, 9.39. Found: N, 9.30.

The above coupling reaction also proceeds smoothly in sodium carbonate solution, although less rapidly than in sodium hydroxide.

Butyl 4-Hydroxy-3-aminobenzoate.—The reduction of butyl 4-hydroxy-3-benzeneazobenzoate, by the sodium hydrosulfite method outlined above, gave almost the theoretical yield of product melting at 72°. Recrystallization from glacial acetic acid gave colorless plates melting at 113°, but recrystallization from a chloroform–petroleum ether mixture gave colorless needles melting at 72°. Cavill[5] reported a melting point of 64–65° for this product.

Anal. (72°) Calcd. for $C_{11}H_{15}NO_3$: N, 6.70. Found: N, 6.69. *Anal.* (113°) Calcd. for $C_{11}H_{15}NO_3 \cdot C_2H_4O_2$: N, 5.20; $C_2H_4O_2$, 22.3. Found: N, 5.35, 5.10; $C_2H_4O_2$, 20.2 (titration).

Analysis indicated that crystallization from glacial acetic acid gives an acetate. Two recrystallizations of the acetate from chloroform–petroleum ether gave the substance melting at 72°.

The hydrochloride, prepared from the aminobenzoate and 10% hydrochloric acid, crystallized as colorless columns melting at 234° with decomposition.

4-Hydroxy-3-aminobenzoic acid was obtained by refluxing the ester with five times its weight of 20% hydrochloric acid for an hour. The acid separated as colorless rhombic plates melting at 202° with decomposition; the melting point is in agreement with that reported by Cavill,[5] and Auwers and Röhrig.[6] The hydrochloride of the free acid crystallized as colorless rhombic prisms melting at 250° with decomposition.

Hydrolysis of 5,5'-Dicarboxylic-dibenzoxazole-2,2'-disulfide.—A 400-mg. sample of the disulfide was dissolved in the calculated quantity of sodium carbonate solution, and the solution was immediately acidified with hydrochloric acid. Vigorous evolution of sulfur dioxide[7] (identified by odor and by a blue violet color with congo red paper) was followed by the separation of 300 mg. of solid melting at 265–271° with foaming. This material was separated into two fractions by recrystallization from 90% ethanol.

The more insoluble fraction, weighing 170 mg. and melting at 280° with foaming, separated as prismatic needles and was identified as 5-carboxylic-benzoxazole-2-thion by mixed melting point and analysis.

Anal. Calcd. for $C_8H_5NO_3S$: N, 7.18. Found: N, 7.55.

The more soluble fraction, weighing 110 mg. and melting at 248–249° with foaming, separated as prismatic needles

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[1] M. Krause, *Ber.*, **32**, 126 (1899).

[2] Popov, *Anilinokrasochnaya Prom.*, **3**, 391 (1933).

[3] Korczynski and Obarski, *Bull. soc. chim.*, [IV] **33**, 1823 (1923).

[4] Grandmougin and Freimann, *J. prakt. Chem.*, [2] **78**, 385 (1908).

[5] Cavill, *J. Soc. Chem. Ind.*, **64**, 212 (1945).

[6] K. Auwers and H. Röhrig, *Ber.*, **30**, 992 (1897).

[7] To our knowledge, the escape of sulfur dioxide has not heretofore been reported in similar reactions.

TABLE I

2,5-DISUBSTITUTED BENZOXAZOLES

Compounds 1, 5 and 8 were made by refluxing the corresponding aminophenol with ethanolic carbon disulfide for 60 hours. Compounds 2, 6 and 9 were made by fusion of the corresponding aminophenol hydrochloride with urea for two hours at 140–150°. Compounds 3, 7 and 10 were made by the reaction of the corresponding aminophenol with ethanolic cyanogen bromide for 50 hours at room temperature. Compound 4 and 11 were made from the corresponding aminophenol and dicyandiamide in ethanol–HCl by the method of Smith, *et al.* (THIS JOURNAL, 51, 2522 (1929)). The hydrochloride of butyl 4-hydroxy-3-aminobenzoate (490 mg.), refluxed for two hours with 170 mg. of dicyandiamide in 2 ml. of 90% ethanol, gave 150 mg. of a hydrochloride melting at 175–180°. The base set free from this hydrochloride, repeatedly recrystallized from ethanol and from benzene, melted at 182–183°, and gave a mixed melting point of 182–184° with a specimen of 2-amino-5-carbobutoxybenzoxazole (m.p. 186°). *Anal.* Calcd. for $C_{12}H_{14}N_2O_3$: N, 11.97. Found: N, 12.49, 12.59.

Cpd.	X	Y	Formula	Description[i]	Solvent	Solubility	Yield, %	M.p., °C.	Nitrogen, % Calcd.	Nitrogen, % Found
1	Cl	SH	$C_7H_4ClNOS^a$	Needles	90% al.	V.s., Na_2CO_3	70	268 d.[b]	7.55	7.57
2	Cl	OH	$C_7H_4ClNO_2$	Fibrous needles	80% al.	V.s., al., ether, Na_2CO_3	92	189–190[c]	8.26	8.24
3	Cl	NH_2	$C_7H_5ClN_2O^d$	Plates	50% al.	Sl.s., H_2O	88	182–183	16.62	16.55
4	Cl	$H_2N—\underset{\underset{NH}{\Vert}}{C}—NH—$	$C_8H_7ClN_4O^e$	Elongated plates	Benzene	I., al., acetone	40	228 d.	24.51	24.63
5	$BuO_2C—$	SH	$C_{12}H_{13}NO_3S$	Needles	Dil. al.	V.s., al., ether, Na_2CO_3	76	134	5.58	5.48
6	$BuO_2C—$	OH	$C_{12}H_{13}NO_4$	Needles	Benzene–petroleum	S., org. solvents	90	99–100	5.96	5.97
7	$BuO_2C—$	NH_2	$C_{12}H_{14}N_2O_3$	Prisms	Ether	I., H_2O, sl.s., C_6H_6, v.s., al.	74	186	11.97	12.01
8	$HO_2C—$	SH	$C_8H_5NO_3S^f$	Prisms	Water	V.s., al.	62	282 d.[g]	7.18	7.10
9	$HO_2C—$	OH	$C_8H_5NO_4$	Needles	Water	S., al.	70	>300	7.82	7.88
10	$HO_2C—$	NH_2	$C_8H_6N_2O_3$	Needles	90% al.	I., ether, C_6H_6 Sl.s., H_2O, al.	60	275 d.	15.73	15.68
11	$HO_2C—$	$H_2N—\underset{\underset{NH}{\Vert}}{C}—NH—$	$C_9H_8N_4O_3^h$	Needles	Abs. al.	Sl.s., al., ethyl acetate	60	280 d.	25.45	25.52

[a] Na salt, colorless plates from ethanol, soluble in water. [b] Deck and Dains (THIS JOURNAL, 55, 4989 (1933)) reported a melting point of 261–262°, and Korczynski and Obarski[3] reported a melting point of 283° for this substance. [c] Upson (*Am. Chem. J.*, 32, 25 (1905)) reported a melting point of 184–185°, and an English patent (240,969 (1925)) reported a melting point of 189–190° for this substance. [d] Hydrochloride: needles melting at 229° with decomposition; hydrolyzed by water. *Anal.* Calcd. for $C_7H_5ClN_2O\cdot HCl\cdot H_2O$: N, 12.56. Found: N, 12.70. Hydrobromide: plates melting at 240° with decomposition. [e] Hydrochloride: needles from alcohol, melting at 273° with decomposition; slightly soluble in water. [f] Disodium salt: flat needles, hygroscopic and quite soluble in alcohol or water. Mono-sodium salt: long colorless columns from absolute alcohol, soluble in water. [g] French patent (54,436 (1933)) reported a decomposition temperature of 283–284°. [h] Hydrochloride: columns from ethanol–HCl, melting at 280° with decomposition; hydrolyzed by water. Sodium salt: plates from water, soluble in alcohol. [i] All compounds are colorless.

TABLE II

5,5'-DISUBSTITUTED-DIBENZOXAZOLE-2,2'-DISULFIDES

These compounds were made from the monosodium salts of the corresponding mercaptans by reaction with 0.1 *N* iodine–potassium iodide solution in water; the yields were practically quantitative. Compounds a and b are soluble in the usual organic solvents. Compound c is practically insoluble in organic solvents, but soluble in the calculated quantity of sodium carbonate solution.

Cpd.	X	Formula	Description	Solvent	M.p., °C.	Nitrogen, % Calcd.	Nitrogen, % Found
a	Cl	$C_{14}H_6Cl_2N_2O_2S_2$	Prisms	Benzene	141–142	7.59	7.60
b	BuO_2C-	$C_{24}H_{24}N_2O_6S_2$	Needles	Benzene	115–116	5.60	5.62
c	HO_2C-	$C_{16}H_8N_2O_6S_2$	Prisms		237–238 d.	7.22	7.11, 7.31

and was identified as 5-carboxylic-benzoxazole by mixed melting point and analysis.

Anal. Calcd. for $C_8H_5NO_3\cdot H_2O$: N, 7.73. Found: N, 7.62.

5-Carboxylic-benzoxazole was independently synthesized by refluxing 300 mg. of 3-amino-4-hydroxybenzoic acid with an excess of formic acid for three hours, evaporating the excess formic acid, and finally heating the residue at 170° for three hours (94% yield). The product crystallized from dilute ethanol as prismatic needles melting at 249° with foaming, and gave no color with ferric chloride.

Anal. Calcd. for $C_8H_5NO_3\cdot H_2O$: N, 7.73. Found: N, 7.72.

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4,4',4''-Trinitrotriphenylamine[1]

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A trinitro compound prepared from triphenylamine by nitration with fuming nitric acid has been reported by Heydrich[2] and by Herz.[3] A substance having the same melting point, 280°, was subsequently described by Madelung, *et al.*,[4] who nitrated triphenylamine with nitrogen dioxide. None of these authors proposed a structure for his product, but Beilstein[5] lists the compound as 4,4',4''-trinitrotriphenylamine on the basis of a private communication from Piccard, who also claimed that the melting point was 396°. There are no data in the literature in support of this assignment of structure.

Attempts in this Laboratory to repeat the nitration of triphenylamine using Herz's procedure[3] resulted in a yellow powder which gave yellow crystals melting at 383° from nitromethane. In no case has the nitration resulted in a substance melting at 280°, nor have the recrystallization

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[1] This work was carried out at Rutgers University in connection with contract number N7-ONR-45403 of the Office of Naval Research.

[2] C. Heydrich, *Ber.*, **18**, 2156 (1885).

[3] R. Herz, *ibid.*, **23**, 2539 (1890).

[4] W. Madelung, E. Reiss and E. Herr, *Ann.*, **454**, 36 (1927).

[5] Beilstein, "Handbuch der Organischen Chemie," Fourth Edition, Vol XII, Springer Verlag, Berlin, 1929, p. 717.