evaporation to dryness giving 1 g. (4.8%) of crude product, m.p. 118–121°. A small portion was converted smoothly to VII by reaction with ethyl acetoacetate in acetic acid. The product was recrystallized from benzene, m.p. and mixed m.p. with VII 214–215°. Compound VIII was purified by recrystallization from nitromethane and sublimation at 100° (0.1 mm.) giving a white crystalline product, m.p. 121–122.2°.

Anal. Calcd. for $C_4H_8N_4$: C, 42.84; H, 7.19. Found: C, 42.94, 42.94; H, 7.24, 7.09.

The organic material in the filtrate from the silver nitrate titration was isolated by a similar procedure giving 7.57 g. of oily liquid soluble in chloroform. Attempts to purify this material by sublimation gave a small amount of low melting solid and extensive decomposition. Several purifications by sublimation at 70° (0.1 mm.) gave a small amount of material, m.p. 80–90°, crude IX.

Anal. Calcd. for $C_4H_8N_4$: C, 42.84; H, 7.19. Found: C, 45.14, 45.19; H, 7.73, 7.80.

The crude IX was heated for 6 hr. with ethyl acetoacetate at 140°. A small amount of solid was recovered from the reaction mixture by sublimation at 200° (0.1 mm.). The solid was recrystallized from benzene, m.p. and mixed m.p. with IV 196.5–197.5°.

The products were tested for free amino groups by treatment with 5% sodium nitrite at 5° in 5% hydrochloric acid followed by addition of 5% β-naphthol in acetic acid. The starting material, 3-amino-1,2,4-triazole, gave a deep yellow dye solution and a precipitate of orange dye. The crude IX gave a deep orange dye solution; VIII gave a negative test.

3-Amino-5-*p*-benzyloxyphenyl-1,2,4-triazole (XI) was prepared by a modification of the method of Hoggarth.[11] In a 2-l. three-necked flask fitted with stirrer, azeotrope separator with reflux condenser and drying tube were placed 171 g. (0.75 mole) of *p*-benzyloxybenzoic acid,[12] 1 l. of benzene and 5 ml. of pyridine. The reaction mixture was dried by azeotropic distillation of benzene and water and then was cooled to 50° and stirred during the rapid addition of 119 g. (1.0 mole) of thionyl chloride. After completion of the addition, the mixture was slowly heated to reflux and finally under reflux for 2 hr. The resulting solution was evaporated to dryness at reduced pressure on a steam-bath and the residue dissolved in 450 ml. of pyridine at 50° and added rapidly with stirring to a solution of 102 g. (0.75 mole) of aminoguanidine bicarbonate in 800 ml. of pyridine at 0–6°. The resulting mixture was stirred and allowed to warm to room temperature overnight, and then evaporated to dryness on a steam-bath at reduced pressure. The residue was triturated with 800 ml. of 1.25 *N* sodium hydroxide and the solids separated by filtration. Recrystallization from alcohol separated some insoluble material. The alcohol-soluble portion was dissolved in a solution of 20 g. of sodium methoxide in 4 l. of methanol and precipitated by dilution with an equal volume of ice-water. The precipitate was separated by filtration and dried giving a solid, m.p. 178°, decomposing to a solid, m.p. 210–213°. Attempts to purify the aminoguanidine intermediate by recrystallization were unsuccessful and the solid was converted to the triazole by heating at 220° for 5 min. after melting. The product was cooled and recrystallized from ethanol and then from nitromethane giving 42 g. (21%), m.p. 220–220.5°.

Anal. Calcd. for $C_{15}H_{14}N_4O$: C, 67.55; H, 5.30. Found: C, 67.70, 67.51; H, 5.56, 5.35.

The product gave an orange-red azo dye when treated with sodium nitrite and then with β-naphthol in acetic and hydrochloric acids.

2-*p*-Benzyloxyphenyl-5-hydroxy-7-methyl-*s*-triazolo[2,3-a]pyrimidine (XII) was prepared from XI and ethyl acetoacetate by the method used in the synthesis of I. The product was recrystallized from acetic acid giving 11.5 g. (70%), m.p. 310–311° dec.

Anal. Calcd. for $C_{19}H_{16}N_4O_2$: C, 68.66; H, 4.85. Found: C, 68.57, 68.67; H, 4.90, 5.01.

2-*p*-Hydroxyphenyl-5-hydroxy-7-methyl-*s*-triazolo[2,3-a]-pyrimidine (XIII).—A suspension of 10 g. (0.03 mole) of XII and 0.2 g. of 10% palladium-on-charcoal catalyst in 200 ml. of absolute alcohol was placed in a Parr hydrogenation bottle and reduced with hydrogen with shaking at 50 p.s.i. at 68° overnight. The uptake of hydrogen was 2.6 p.s.i. (theory 2.4 p.s.i.). The product was separated by filtration, dissolved in hot 5% sodium hydroxide and the catalyst removed by filtration. The product was precipitated by addition of concentrated hydrochloric acid and the solid separated by filtration, washed with water and dried. The yield of white solid, m.p. 395° dec., was 6.45 g. (88%). A portion was recrystallized from dimethylformamide for analysis.

Anal. Calcd. for $C_{12}H_{10}N_4$: C, 59.50; H, 4.16. Found: C, 59.63, 59.44; H, 4.29, 4.30.

Infrared spectra of the triazolopyrimidines were obtained with the Perkin–Elmer model C-21 spectrophotometer. The samples were prepared in approximately 0.2% concentration in potassium bromide wafers. The curves so obtained are given in Fig. 1.

Ultraviolet spectra were obtained with the Cary recording spectrophotometer model 14. Samples were prepared in 5×10^{-5} *M* concentration in water. The maxima are given in Table II.

Apparent ionization constants were determined by titration of the samples in carbon dioxide free-water under nitrogen at 25 ± 0.5°. The *p*H values were obtained using the Beckman model G *p*H meter standardized against aqueous buffers. The pK_A and end-point values were obtained graphically. The results are given in Table I.

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[CONTRIBUTION FROM THE PHYSICS RESEARCH LABORATORY OF THE MASSACHUSETTS GENERAL HOSPITAL AND FROM THE RETINA FOUNDATION, DEPARTMENT OF OPHTHALMOLOGY OF THE MASSACHUSETTS EYE AND EAR INFIRMARY]

Benzoxazoles. I.[1,2]

BY EMERY NYILAS[3] AND JAMES L. PINTER

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The synthesis of a number of bis-2-benzoxazoles, representing a new class is reported. The connecting unit linking the two benzoxazole nuclei has been varied from simple alkane chains to aryl chains. Some of the compounds having a conjugated double bond system may be potential solutes in liquid scintillators.

Since 2,5-diphenyloxazole (PPO) was discovered by Hayes and co-workers[4] to act as an efficient solute in liquid phosphors, the class of organic scintillators containing heterocyclic rings has received much attention. Previous to that only organic solutions of isocyclic compounds, especially

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[2] This investigation was supported in part by research grant (A-1110) from the National Institute of Arthritis and Metabolic Diseases of the National Institutes of Health, U. S. Public Health Service.

[3] Recipient of the Sylvester Fellowship.

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Table I

No.	Compound	M.p., °C.[a]	Formula	Analyses,[b] % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
I	1,2-Bis-(2-benzoxazolyl)-ethane	192–193	$C_{16}H_{12}O_2N_2$	72.72	72.59	4.59	4.61	10.60	10.56
II	*trans*-1,2-Bis-(2-benzoxazolyl)-ethylene	244	$C_{16}H_{10}O_2N_2$	73.28	73.04	3.85	3.88	10.69	10.66
III	1,4-Bis-(2-benzoxazolyl)-butane	126–127	$C_{18}H_{16}O_2N_2$	73.96	74.08	5.53	5.84	9.59	9.65
IV	1,6-Bis-(2-benzoxazolyl)-hexane	96–98	$C_{20}H_{20}N_2O_2$	74.98	74.80	6.31	6.27	8.75	8.56
V	1,8-Bis-(2-benzoxazolyl)-octane	87–88	$C_{22}H_{24}O_2N_2$	75.84	75.58	6.96	6.84	8.04	7.99
VI	1,2-Bis-(2-benzoxazolyl)-cyclohexane	186	$C_{20}H_{18}O_2N_2$	75.45	75.30	5.71	5.61	8.80	8.83
VII	1,2-Bis-(2-benzoxazolyl)-4-cyclohexene	146–147	$C_{20}H_{16}O_2N_2$	75.94	76.15	5.11	5.31	8.86	8.71
VIII	2,2′-*o*-Phenylene-bis-benzoxazole	177	$C_{20}H_{12}O_2N_2$	76.92	76.92	3.88	3.86	8.97	8.95
IX	2,2′-*m*-Phenylene-bis-benzoxazole	229	$C_{20}H_{12}O_2N_2$	76.92	76.85	3.88	3.87	8.97	8.84
X	2,2′-*p*-Phenylene-bis-benzoxazole	355–356	$C_{20}H_{12}O_2N_2$	76.92	77.11	3.88	4.01	8.97	9.09

[a] Capillary, corrected. [b] Microanalyses by Schwarzkopf Microanalytical Laboratory, Woodside 77, N. Y.

that of *p*-terphenyl, were known to emit fluorescent light in a suitable yield upon excitation with high-energy electromagnetic radiation.[5–7] Series of 2,5-disubstituted oxazoles, oxadiazoles and thiazoles,[8] as well as 1,4-bis-phenyloxazolyl-benzenes and 1,4-bis-phenyloxadiazolyl-benzenes, have been prepared[9,10] and tested for scintillation efficiency[11,12] in the course of the liquid scintillator program of the Biomedical Research Group at the Los Alamos Scientific Laboratory. Some of these substances known as PBD, POPOP, etc., are now extensively used as primary and/or secondary solutes in organic liquid phosphors. Also, some substituted pyrazoline derivatives were found by Rosahl and co-workers[13,14] to be suitable organic scintillation solutes. Furthermore, a number of discussions have been published[10,11,14–16] regarding the correlation of scintillation efficiency and molecular structure.

More recently the field of heterocyclic scintillators is under extensive investigation in various laboratories. A wide variety of heterocyclic, potential liquid scintillation solutes, such as 3,6-diaryl-2-pyrones[17] and 3,6-diaryl-1,2,4,5-tetrazines,[18] being heterocyclic analogs of *p*-terphenyl, have been synthesized and screened for light output together with some substituted 4,7-phenanthrolines and benzo(f)quinolines,[19] mono- and disubstituted derivatives of pyridine, quinoline, benzoquinoline and isoquinoline,[20] and finally some N-arylated heterocycles.[21] However, as far as available scintillation data reveal, none of these new compounds was found to be more efficient than the systems designed earlier by Hayes and co-workers.[11,12]

In the present study a number of compounds described in Table I, representing a new class, the bis-benzoxazoles, have been prepared. This series of bis-benzoxazoles was synthesized in order to investigate the relationship between molecular structure and fluorescence or scintillation mechanism of heterocyclic scintillators.

The benzoxazole nuclei in these substances are connected through their 2-positions by saturated and unsaturated chains involving two or more carbon atoms. Some members of the series (compounds II, VIII and X) having a conjugated double bond system exhibited a strong photofluorescence in non-polar solvents. The capability for fluorescence of these substances was predicted on the basis of a hypothesis postulated as a mechanism for fluorescence or scintillation, and is discussed below. The theory is a modified extension of that developed by Sangster and Irvine[22] for the scintillation efficiency of crystalline isocyclic compounds.

In those substances having a conjugated double bond system, the possibility of high π-electron mobility, a prerequisite to efficient scintillation,[22] is established by large resonance interactions between the different portions of these molecules. Several resonant forms of these substances having comparable energies can be written. Certain types of possible resonant forms are quinoid structures with a single separation of charge as shown in Fig. 1. These forms may contribute to a smaller extent to the ground state of the respective molecular species but, as a condition of fluorescence, it is assumed that these singly-charged quinoid structures will be predominant in the excited state. This appears to be very probable, since scintillation efficiency has been related to the formation of a transient dipole moment[22] which necessarily is connected to electronic structures having a separation of charge. Secondly, it is well-known that only the lowest excited electronic states are usually involved in the emission of fluorescent light. It can be easily shown that such quinoid structures can make a predominant con-

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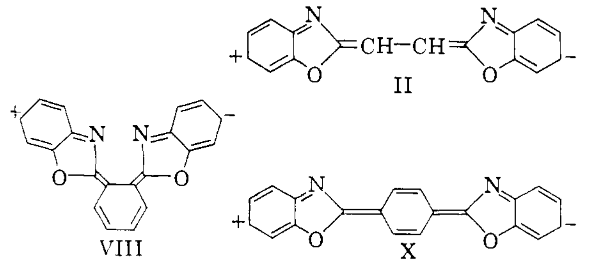

Fig. 1.

tribution to these states. Finally, the postulated existence of a quinoid form in the excited state may facilitate the presence of a planar type structure of the molecule. The approximately planar configuration of the excited molecule will then better favor a deactivation by the emission of fluorescence than by a radiationless transition to the ground state.[23,24] If the planar type configuration in the excited state cannot be retained, the absorbed energy can be easily consumed in part by the rotational motion of the different parts of the molecule or by the twisting motion of the two benzoxazole nuclei. In other words, the internal quenching occurs before the fluorescent photon can be emitted, since the thermal equilibrium in the excited state is established more rapidly (*ca.* 10^{-12} sec.) than the excited molecules return to the ground state (*ca.* 10^{-8} sec.).[10] However, in certain cases, no emission of fluorescence is observed despite the theoretical possibility of the formation of a quinoid-type structure. This can be accounted for by other factors, such as steric hindrance, interfering with the formation of the planar type configuration in the excited state.

In summary, as far as the mechanism of fluorescence or scintillation is concerned, we are postulating that in the bis-benzoxazoles having conjugated double bonds, the absorption of high-energy excitation and the emission of fluorescent light occurs *via* transient quinoid structures, as illustrated by the *trans*-1,2-bis-(2-benzoxazolyl)-ethylene in Fig. 2. As a consequence of our assumption, a failure of fluorescence might be related to any reason interfering with the formation of a quinoid type structure in the excited state.

The synthesis of the bis-benzoxazoles was performed in fair to excellent yields by intermolecular condensation of two molecules of *o*-aminophenol with one molecule of dicarboxylic acids or anhydrides in polyphosphoric acid[25] at temperatures ranging from 150 to 200°. The crude products were extracted with dioxane or pyridine.[26,27]

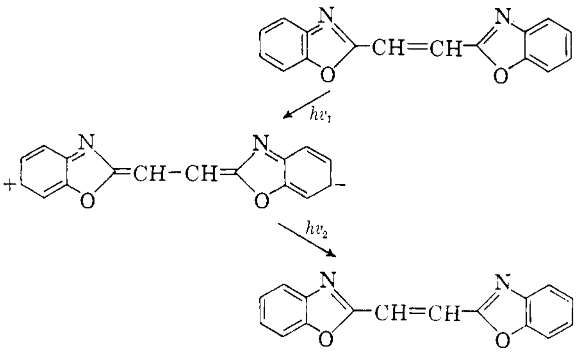

Fig. 2.

Experimental

The following procedure is illustrative of the preparation of bis-(2-benzoxazoles).

2,2′-*m*-Phenylene-bis-benzoxazole.—Five and forty-five hundredths g. of *o*-aminophenol (0.05 mole) and 4.15 g. of isophthalic acid (0.025 mole) were stirred to a paste in 110 g. of polyphosphoric acid (Victor Chemical Works) with gentle warming. When the mixture appeared to be homogeneous, it was heated slowly to 200° and stirred continuously for four hours at the same temperature. After allowing the reaction mixture to cool to about 100°, it was poured in a thin stream into 1.5 liters of stirred ice-water. After standing overnight at room temperature the precipitate was collected, washed successively with small amounts of water and sucked thoroughly. It was then suspended in an excess of 5% aqueous sodium carbonate solution, refiltered and washed with distilled water until the filtrate was alkali-free. The crude product was dried over concentrated sulfuric acid *in vacuo* yielding 7.45 g. (95.5%).

The crude product was extracted successively with three 100-ml. portions of boiling dioxane and filtered. Crystallization was initiated with the addition of a small amount of water to the hot filtrate. Crystallization overnight yielded 6.39 g. (81.8%) of the substance, m.p. 227°.

In general, a second recrystallization is required in order to obtain the compounds in a pure state; *viz.*, during the condensation reaction a small amount of colored material is formed, and some of it still contaminates the once-recrystallized substances.

In this case the second recrystallization was performed in 1-butanol with the addition of decolorizing carbon; yield 5.67 g. (74.2%), m.p. 229°. On further recrystallizations, no alteration was observed in the melting point.

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