Table III—Antifungal Activity [a]

Compound	*C. albicans*		*P. notatum*		*A. niger*	
	10 μg/ml	25 μg/ml	10 μg/ml	25 μg/ml	10 μg/ml	25 μg/ml
IV*a*	+	+	+	+	+	+
IV*b*	−	−	−	−	−	−
IV*c*	+	+	+	+	+	+
IV*d*	+	+	+	+	+	+
IV*e*	−	+	+	+	+	+
IV*g*	−	−	−	−	−	−
IV*h*	−	−	−	−	+	+
IV*j*	−	−	−	−	−	−
IV*k*	−	−	−	−	−	−
IV*l*	+	+	+	+	+	+
IV*m*	−	−	+	+	+	+
IV*o*	−	+	+	+	+	+
IV*p*	−	−	+	+	+	+
V*a*	+	+	+	+	+	+
V*b*	−	−	−	−	−	−
V*c*	−	−	−	−	−	−
Nystatin	+	+	+	+	+	+

[a] − = inactive.

lized from hot acetone to give 1.5 g (26.5%) of white needles, mp 147–151°; mass spectra: *m/e* 287 (M^+), 233 M − (SO_2), 195 M − (SO_2, N_2), and 180 M − (Se, N_2); NMR (deuteriochloroform): δ 5.1 (s, 2H, CH_2), 7.4–7.7 (m, 5H, C_6H_5), and 9.45 (s, 1H, CH) ppm.

4-Methyl-5-phenylsulfonyl-1,2,3-selenadiazole (IV*b*)—The mother liquor from the preparation of V*a* was diluted with an excess of water. After refrigeration, it gave 3.5 g of brownish crystals, which were recrystallized from diluted acetone to give 3.1 g (54%) of IV*b*, mp 76–78°; mass spectra: *m/e* 278 (M^+), 195 M − (SO_2,N_2) and 180 M − (Se, N_2); NMR (deuteriochloroform): δ 2.88 (s, 3H, CH_3) and 7.3–8.1 (m, 5H, C_6H_5) ppm.

The isomeric compounds V*b* and IV*c* were prepared similarly. The ratio of V*b* to IV*c* was 44:56 (Table I).

Photolysis of Disubstituted-1,2,3-selenadiazoles—p-*Toluenesulfonylpropyne* (*VI*a)—4-Methyl-5-*p*-toluenesulfonyl-1,2,3-selenadiazole (IV*c*), 3 g (0.01 mole), in 90 ml of dry benzene was photolyzed during 6 hr using a 100-w high-pressure mercury lamp. The solution was filtered and evaporated at low pressure, and the crystalline residue was recrystallized from petroleum ether to give 0.81 g (42%) of white crystals, mp 96–97° [lit. (7) mp 98–99°]; IR: λ_{max} 2200 (C≡C), 1328, 1291, 1152, 1087, 818, and 706 cm^{-1}.

Anal.—Calc. for $C_{10}H_{10}O_2S$: C, 61.85; H, 5.15. Found: C, 61.99; H, 5.17.

p-*Toluenesulfonylacetylene* (*VI*b)—Photolysis of IV*e* as indicated for the preparation of VI*a* afforded 64% of the desired compound, mp (petroleum ether) 79–81° [lit. (8) mp 80–81°]; IR: 2109 (C≡C) cm^{-1}.

Anal.—Calc. for $C_{15}H_{12}O_2S$: C, 70.31; H, 4.53. Found C, 70.22; H, 4.40.

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Effect of Dissolved Oxygen Levels on Oxidative Degradation of Pyrogallol

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Abstract □ Pyrogallol decomposition in aqueous systems with various dissolved oxygen levels was studied. The reduced dissolved oxygen levels were produced by deaeration *via* gas permeation. Dissolved oxygen levels were determined using a dropping mercury electrode polarograph. Degradation rates, T_{90}, and relative protection indexes are discussed. Even at dissolved oxygen levels of less than 0.05 ppm, some decomposition of pyrogallol occurred, indicating nonoxidative pathways or the necessity of total removal of dissolved oxygen to afford complete protection. Apparently, reducing the level of dissolved oxygen is a viable alternative to stabilization of aqueous pyrogallol solutions, since the T_{90} was increased from 1.9 days in water with dissolved oxygen levels of 9.05 ppm to 114.4 days in water with dissolved oxygen levels of less than 0.05 ppm.

Keyphrases □ Pyrogallol—oxidative degradation in aqueous systems, effect of dissolved oxygen levels □ Degradation, oxidative—pyrogallol in aqueous systems, effect of dissolved oxygen levels □ Oxidative degradation—pyrogallol in aqueous systems, effect of dissolved oxygen levels □ Antibacterials, topical—pyrogallol, oxidative degradation in aqueous systems, effect of dissolved oxygen levels

An important factor in drug stabilization is reduction of oxidative degradation. The sensitivity of several drugs to oxidative degradation was studied previously (1–5), and several techniques were used to inhibit this degradative pathway (6). Autoxidation of pharmaceuticals was described as a process mediated by free radicals: initiation, propagation *via* free radicals, and termination of the reaction to form inactive products (7).

If molecular oxygen, necessary for the propagation step, were substantially reduced, oxidative processes might be significantly reduced or eliminated. Therefore, the propagation step assumes major importance in free radical-

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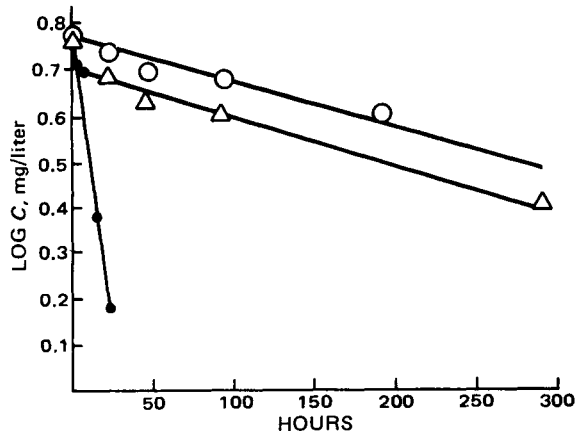

Figure 1—*Comparative degradation of pyrogallol at 30° in various dissolved oxygen levels. Key (dissolved oxygen level): ○, trace; △, 0.48 ppm; and ●, 9.05 ppm.*

mediated reactions for pharmaceutical systems such as pyrogallol decomposition.

The effect of dissolved oxygen concentration on the autoxidation reaction is not readily apparent. Shou (8) indicated that oxygen levels are not usually considered since it is difficult to alter the oxygen concentration with present equipment.

Because of its rapidity of oxidation, pyrogallol (1,2,3-trihydroxybenzene) was used as a model drug system to investigate the effect of a reduced molecular oxygen level of the solvent on the degradation process.

EXPERIMENTAL

Preparation of Deoxygenated Water—The method of reducing the dissolved oxygen levels of the water was described by Palmieri *et al.* (6). Essentially, distilled, deionized water was passed through a gas permeator[1] at various pressures and for various times to lower dissolved oxygen levels.

Dissolved oxygen levels (parts per million) were determined[2] on an average of 15–25 samples using a dropping mercury microelectrode polarograph with a rated sensitivity of ±0.01 ppm. Because of this sensitivity, any reading less than 0.05 ppm was considered to be a trace amount.

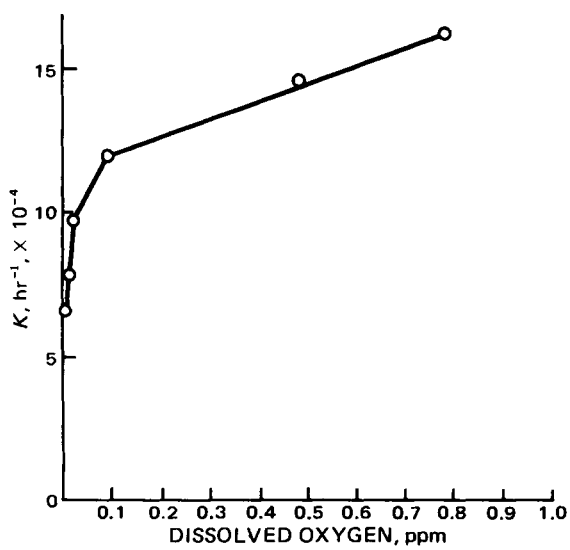

Figure 2—*Effect of oxygen concentration on degradation rate of pyrogallol at 30°.*

[1] Permasep, DuPont, Wilmington, Del.

[2] Model 106 dissolved oxygen analyzer, Delta Scientific Corp., Lindenhurst, N.J.

Table I—Comparative Degradation of Protected and Unprotected Systems of Pyrogallol at 30°

Dissolved Oxygen Level, ppm	K, mg/liter × 10^{-4} × days^{-1}	T_{90}, hr	Protection Index[a]
9.05	557.5	1.9	1.0
0.05–0.78	14.6	72.8	38.19
Trace	10.2	114.4	54.66

[a] Ratio of K rates relative to unprotected system.

Preparation and Analysis of Model Drug—Deoxygenated water prepared at various pressure ratings was employed as the solvent for the model drug system at an initial concentration of 6 mg of pyrogallol/liter. Distilled, deionized water was used to prepare the control sample. Each 30-ml vial was filled to capacity, capped with a polytef-coated screw cap, and sealed with six coats of a high melting wax to prevent oxygen intrusion. After labeling, the vials were stored in a dark, constant-temperature apparatus at 30° for the duration of the study. Unopened vials were removed periodically and assayed for pyrogallol content.

Pyrogallol was assayed according to the procedure of Grant and Patel (9). At preselected intervals, a 3-ml sample of pyrogallol solution was withdrawn, and 6 ml of a 1% vanillin solution in 70% H_2SO_4 was added. The absorbance was determined spectrophotometrically after 18 min against an appropriate blank at 520 nm. A control sample was assayed concurrently.

RESULTS AND DISCUSSION

Table I summarizes the data. There is a rank-order correlation of dissolved oxygen levels and degradation rates. Comparison of the time for 10% degradation (T_{90}) showed that systems with trace levels of dissolved oxygen had greatly increased protection. However, even systems of less than 1 ppm dissolved oxygen exhibited degradation. This result is explainable since pyrogallol may degrade by a nonoxidative process. Many chemicals having primarily oxidative pathways for degradation also degrade by other means. The degradation rates, however, were considerably less and appeared to "stabilize" or proceed at a slower rate after a slight initial degradation (Fig. 1).

Removal of most of the dissolved oxygen in the solvent should retard reaction kinetics since the molecular oxygen concentration affects the propagation step. However, because susceptible systems may degrade by a secondary pathway if oxygen is not readily available, the removal of molecular oxygen might not afford complete protection.

Figure 2 appears to substantiate the hypothesis of nonoxidative degradation of pyrogallol since even extremely low levels of dissolved oxygen (0.01 ppm) did not completely halt degradation. Apparently, with the total removal of molecular oxygen, only a minimum rate of degradation or maximum stability can be attained. The significant reduction in degradation may be due to the depletion of molecular oxygen in the reaction.

As seen in Table I, the relative protection index of deaerated systems was greater than that of the control. An indication of the protection afforded *via* gas permeation is the relative protection ratio. This 55-fold increase in stability is significant in that the drug solution might be stable enough for a commercially viable product.

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