$\beta/\gamma = 0$ is $K_{13}K_{24}$, and the value of $\beta/\gamma$ at the intercept at which $\alpha/\gamma = 0$ is $-K_{24}$. These values of $K_{13}$ and $K_{24}$ have been found to be concentration dependent; therefore, plots similar to those shown in Figs. 4A and B were made to obtain the thermodynamic values. In Table I, the results of these calculations for compounds I–IV are given.

A modification of method I was used to obtain the values of $K_{13}$ and $K_{24}$ of compound V. Since the two $pK_a$ values are far apart, the equilibria were assumed not to interact with each other; therefore, the equilibrium constants were determined by using the following expression for monoprotic compounds:

$$K_n = Z\frac{[H^+]([H^+] + [B] - [OH^-])}{[OH^-] + [A] - [H^+] - [B]} \qquad \text{(Eq. 16)}$$

where $Z$ is the activity coefficient ratio $Y_{(NRN)H^+}/Y_{(NRN)H_2^{2+}}$ for $K_{13}$ and $Y_{(NRN)}/Y_{(NRN)H^+}$ for $K_{24}$.

Figure 6 shows the titration curve obtained for compound V, and Figures 7A and B show the results of the calculated equilibrium constants *versus* percent neutralized. Precipitation was observed after the first equivalence point (Fig. 6), and therefore, consistent values should be obtained for $K_{13}$ (Fig. 7A). Conversely, a change in the calculated value for $K_{24}$ with respect to percent neutralized would be expected (Fig. 7B). The break in this latter curve at ~5% neutralization is due to the formation of a precipitate. The curve prior to precipitation should have a slope of zero (as in Fig. 7A), whereas the curve after precipitation will not necessarily be linear.

By knowing the value for $K_{24}$ and the pH at which precipitation occurs, the solubility of the base (uncharged) species of compound V was determined by:

$$[NRN]_s = \frac{[A]K_{24}}{[H] + K_{24}} \qquad \text{(Eq. 17)}$$

In Table I, the results of the calculations for compound V are given, along with those values for $K_{24}$ and $[NRN]_s$, as reported by Green (9) and determined by a spectrophotometric procedure. It can be seen there is excellent agreement among these data.

Since compounds I–IV are symmetrical molecules, it should be possible to calculate the microionization constants $K_1$, $K_2$, $K_3$, and $K_4$ of Scheme I. This is because $K_1$ should equal $K_3$, and $K_2$ should equal $K_4$. Furthermore, since the protonation sites are separated by large distances, it would be expected the $K_2$ and $K_4$ would be the same or only very slightly smaller than $K_1$ and $K_3$. The microionization constants were therefore calculated from Eqs. 1 and 2 and gave the results listed in Table II. It can be seen that there is very little difference in the calculated values, with $K_2$ and $K_4$ being slightly smaller.

For diprotic compounds with completely independent, equivalent sites of protonation, the ratio $K_{13}/K_{24}$ will equal 4, and $K_1/K_2$ will equal 1. From these ratios (Table II), it can be seen that the values are very close to the theoretical values.

From these results, it can be concluded that the equilibrium constants of slightly soluble compounds can be determined potentiometrically by extrapolation procedures and give results which are consistent with those reported in the literature. It would be expected that method II would be better to use with those compounds that have equilibrium constants close together, whereas method I would be better to use with those compounds that have equilibrium constants farther apart.

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# Degradation of Fenprostalene in Polyethylene Glycol 400 Solution


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Received March 14, 1983, from the *Institute of Pharmaceutical Sciences, Syntex Research, Palo Alto, CA 94304.* Accepted for publiction October 26, 1983.



**Abstract** □ The kinetics of degradation of fenprostalene (I) in polyethylene glycol 400 solution was examined using HPLC. The degradation of I at 80°C was shown to depend on the presence of oxygen and a large number of polar products were produced, as evidenced by using $^3H$-labeled I. Evidence that autoxidation of the polyethylene glycol 400 was concurrent with degradation of I was found from a drop in the apparent pH. Antioxidants were very effective in retarding the rate of degradation in the presence of oxygen. Degradation of I in polyethylene glycol 400 appears to arise from a reaction between the drug and reactive peroxide intermediates formed through air-oxidation of polyethylene glycol 400. This is supported by the finding that I reacts exclusively by a slow transesterification reaction in diethylene glycol, a solvent that is stable to autoxidation.

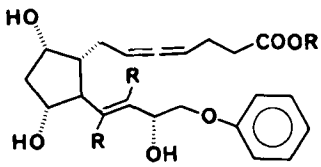


**Keyphrases** □ Degradation—fenprostalene in polyethylene glycol 400 □ Fenprostalene—autoxidation, degradation, kinetics □ Kinetics—fenprostalene in polyethylene glycol 400


Fenprostalene[1] (I), a PGF-type prostaglandin containing an aryloxy group at C-16 and an allene functionality at C-5 (1), is used as an abortifacient and for estrus synchronization in cattle (2). We have previously shown that in aqueous solution, I degrades exclusively through hydrolysis of the C-1 methyl ester under both acidic and basic conditions (3). No information is available, however, on the degradation of this family of prostaglandins in nonaqueous environments. Since an injectable formulation of fenprostalene (I) in polyethylene glycol 400 was chosen for development (4), we have investigated the chemical reactivity and degradation products of I in this solvent.

## EXPERIMENTAL SECTION

**Materials**—The fenprostalene[1] (I) used was 99% pure (HPLC). The radiochemical purity of fenprostalene labeled with tritium at C-13 and C-14 was 98%. The acetonitrile used was glass-distilled HPLC-grade, and the water




I, R = H, R′ = $CH_3$
[$^3H$]I, R = $^3H$, R′ = $CH_3$
II, R = H, R′ = $CH_2CH_2OCH_2CH_2OH$
III, R = R′ = H

[1] Fenprostalene is the generic name for methyl 7-[3,5-dihydroxy-2-(3-hydroxy-4-phenoxy-1-butenyl)cyclopentyl]-4,5-heptadienoate. Obtained from the Institute of Organic Chemistry, Syntex Research, Palo Alto, Calif. The synthesis of I is described in Ref. 1.

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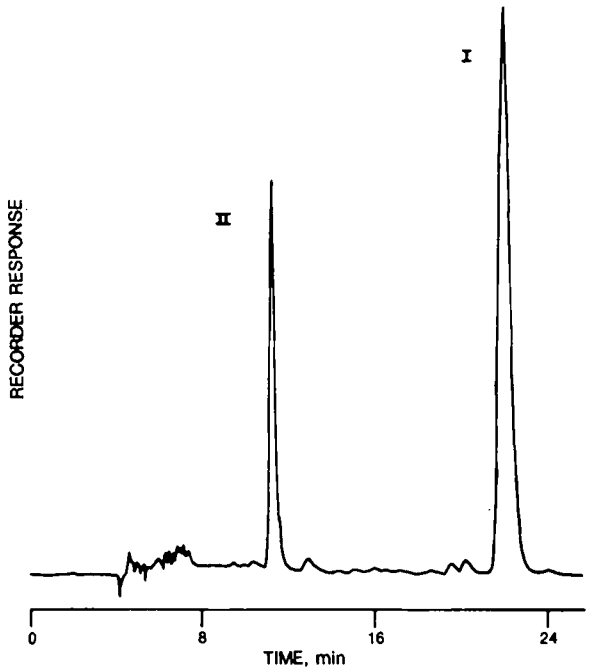


**Figure 1**—*Chromatogram of a solution of I after partial transesterification to II in diethylene glycol at 80°C.*

was purified through an ion-exchange and filtration system[2]. *dl*-α-Tocopherol was NF grade, propyl gallate and polyethylene glycol 400 were practical grade. All other chemicals were reagent grade.

**Kinetic Methods**—A mixture of 25 mg of I in 250 mL of polyethylene glycol 400 was stirred for 2 h and then filtered through a 0.7-μm glass membrane. This solution was used to prepare two other solutions, one containing 0.10% *dl*-α-tocopherol and another containing 0.006 M formic acid. The solutions were stored in either 10-mL ampules (5 mL of solution) or in 20-mL test tubes fitted with polytef-faced screw caps. These solutions were maintained at 80°C, 45°C, or 25°C. The samples stored in test tubes at 80°C were cooled, and the caps were removed for a few minutes each day to provide a relatively constant supply of oxygen to the solutions.

Solutions kept at 80°C were assayed by HPLC and compared with a control sample maintained at 4°C. The 45°C and 25°C samples were assayed by HPLC, and the chromatograms were compared to a freshly-prepared external standard of I. The polyethylene glycol 400 solutions of I were diluted 10-fold with water prior to HPLC analysis and 20-fold prior to pH measurements[3]. Diethylene glycol solutions of I were prepared and analyzed exactly as described above for the polyethylene glycol 400 solutions.

**Hydrolysis of Degradation Products**—A solution of I in polyethylene glycol 400 (100 μg/mL) was allowed to stand for 28 d at 80°C under air. After this period, HPLC assay showed 0.6% of I remaining. Concentrated HCl (41.5 μL) was added to a 5-mL aliquot of this solution and to a control solution of I. Both solutions were heated at 80°C for 3 h. Analysis of these solutions by HPLC showed that quantitative hydrolysis of I in the control solution occurred to give the free acid (III). None of this acid was found in the sample that had previously been degraded in polyethylene glycol 400.

**Liquid Chromatographic Method**—An HPLC system consisting of a pump[4], a variable-wavelength detector[5], and a 100-μL fixed-loop injector[6] was used. Separations were performed on columns packed with microparticulate bonded octyl material[7]. For analysis of I, a mobile phase of 35–45% acetonitrile in water was used. The eluant was monitored at 219 nm. Quantitation by integration of peak areas gave excellent linearity for I over the range of concentrations investigated in the kinetic studies. The presence of 10% polyethylene glycol 400 in the samples affected the quantitation of I when compared with an injection of a completely aqueous solution of I. The origin of this effect is unknown. To avoid this problem, standards of I were prepared in an aqueous solution containing 10% polyethylene glycol 400.

[2] Barnstead Nanopure System.

[3] Measurements of apparent pH were made on a Radiometer PHM 64 pH meter using a Radiometer combination electrode, type GK2401C. The polyethylene glycol 400 solutions were diluted with 0.01 M KCl solution.

[4] Altex model 110 A.

[5] Cecil model CE 212.

[6] Rheodyne model 70-10.

[7] For *analytical* use, an Ultrasphere 5-μm octyl 250 × 4.6-mm column by Altex was used. For semipreparative isolation of II, a 250 × 10-mm Ultrasphere 5-μm octyl column by Altex was used.

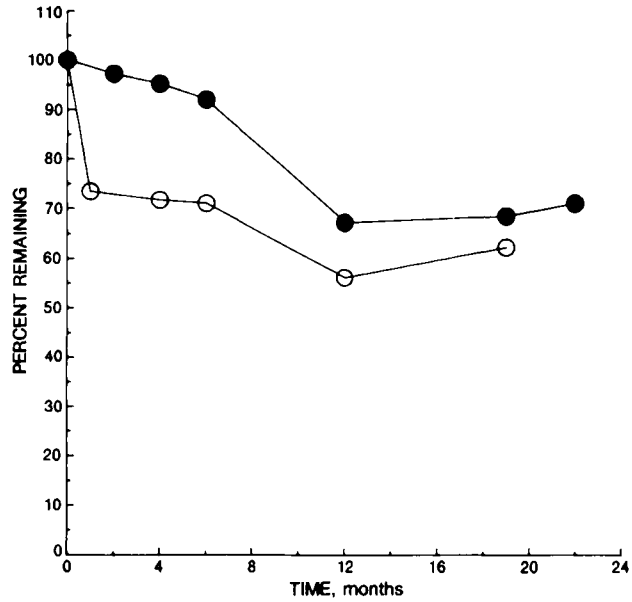


**Figure 2**—*Degradation rate of I in polyethylene glycol 400 at 25°C (●) and at 45°C (○). The solutions were sealed in ampules under air.*

Coincidentally, the diethylene glycol ester (II) and free acid (III) of fenprostalene (I) gave nearly the same retention time with the unbuffered mobile phase described above. Thus analysis of II in the presence of III was accomplished using a mobile phase of 35:65 acetonitrile–0.01 M aqueous phosphate buffer (pH 6). Under these conditions, III elutes near the solvent front while the retention of II is essentially unaffected by the pH change.

**Formation of II in Diethylene Glycol**—A solution containing 100 mg of I in 8 mL of diethylene glycol was prepared and sealed in a 10-mL ampule. The solution was allowed to stand at 80°C for 2 months and then was diluted fourfold with water and injected onto the semipreparative reverse-phase HPLC column. The fraction corresponding to the major degradation peak (Fig. 1) was collected and the mobile phase was removed by rotary evaporation to give a clear oil that was 98% pure (HPLC). $^1$H-NMR ($CDCl_3$)[8]: δ 1.62 (m, 1, CH-8β), 1.79 (m, 1, CH-10α), 2.1–2.4 (m, 6, $CH_2$-3,7, CH-10β,12α), 2.48 (m, 2, $CH_2$-2), 3.60 (t, 2, $J$ = 4.8 Hz, $CH_2$-4′), 3.74 (m, 3, CH-11β, $CH_2$-16), 4.28 (m, 3, CH-9β, $CH_2$-1′), 4.54 (m, 1, CH-15β), 5.1–5.2 (m, 2, allene CH),

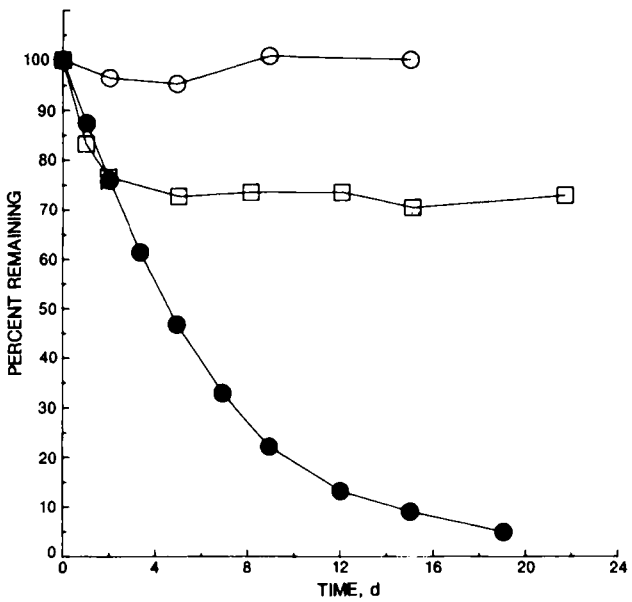


**Figure 3**—*Degradation rate of I in polyethylene glycol 400 at 80°C under various storage conditions. Key: (○) under nitrogen in a sealed ampule; (□) under air in a sealed ampule; (●) in a test tube exposed to air.*

[8] The NMR spectrum was determined at 300 MHz on a Bruker WM 300 FT spectrometer.

[9] The mass spectrum was obtained in the direct-inlet mode on a Varian MAT 112S system equipped with an SS-200 data system.

**Table I—Apparent pH of Fenprostalene (I) Solutions**

| Solvent | Additive | Initial pH | Apparent pH[a] |
|---|---|---|---|
| Polyethylene Glycol 400 | — | 5.2 | 3.5 |
| | $N_2$ | 5.2 | 5.0 |
| | *dl*-α-tocopherol | 5.2 | 4.5 |
| | formic acid | 3.9 | 3.5 |
| Diethylene Glycol | — | 5.8 | 5.2 |

[a] pH measured after a 20-fold dilution of the solution with 0.01 M KCl after 15 d at 80°C. [b] All solutions were stored in test tubes with a relatively constant supply of air except the sample stored under nitrogen, which was in a sealed ampule.

5.68 (m, 2, vinyl CH), and 6.9–7.3 ppm (m, 5, ArH). The mass spectrum was run at 90 eV in the CI mode with ammonia as the reagent gas[9]. The peak at *m/z* 476 was attributed to the $M\text{-}NH_4 - H_2O$ ion and a peak at *m/z* 459 to the $MH - H_2O$ ion. Other major peaks were at *m/z* 388, 259, and 241. The CI mass spectrum of the trimethylsilyl ether derivative gave an $MNH_4^+$ peak at *m/z* 782 with other prominent peaks at *m/z* 675, 581, 491, and 401.

*Anal.*—Calc. for $C_{26}H_{36}O_8$: C, 65.53; H, 7.62. Found: C, 65.70; H, 7.42.

Additional support for the structural assignment comes from observing that in 0.1 M HCl at 60°C, this diethylene glycol ester (II) hydrolyzes to give the free acid of I with a half-life of ~1 h. This rate is similar to that found for hydrolysis of fenprostalene under the same conditions (3).

**Degradation of $^3$H-Labeled I**—A polyethylene glycol 400 solution (1 mL) was prepared containing 500 μg/mL of I with a specific activity of ~130 μCi/mg [$^3$H]I. After an aliquot was removed, the solution was sealed in a glass ampule and stored for 64 h at 80°C. The polyethylene glycol 400 solution containing [$^3$H]I was analyzed by collecting and counting fractions from the reverse-phase HPLC method described above. A 0.040-g sample was accurately weighed and diluted to 1 mL with water. On injection of 108 μL[10] of this solution, fractions of the eluant were collected. A 100-μL aliquot of each fraction was mixed with 15 mL of scintillation fluid[11] and counted in a liquid scintillation counter[12]. A volume of sample equal to the loop volume (108 μL) was also diluted with 15 mL of scintillation fluid and counted[13].

**Incorporation of Tritium Into Polyethylene Glycol 400**—A 0.4-mL aliquot of the degraded polyethylene glycol 400 solution of [$^3$H]I was added to 5 mL of methanol in a flask equipped with a serum cap containing a needle attached to a source of nitrogen. The other neck was connected to a pear-shaped receiving flask through a vacuum adapter. The round-bottom flask was warmed to 45°C, and a stream of nitrogen was used to transfer the methanol to the receiving flask which was cooled to −78°C. The stream of nitrogen leaving the apparatus was scrubbed with water prior to its escape into the environment. A second 5-mL portion of methanol was added to the residue in the flask, and the procedure was repeated. An aliquot of the resulting methanol solution was diluted with scintillation fluid and the counts per minute were compared with that of the degraded polyethylene glycol 400 solution prior to methanol exchange.

## RESULTS AND DISCUSSION

The kinetics of the degradation of I in polyethylene glycol 400 in sealed ampules under air was followed by reverse-phase HPLC. Plots of percent remaining of I *versus* time for the degradation reactions at 25°C and 45°C are shown in Fig. 2. At 25°C a shelf-life of <8 months was observed. At 45°C the initial degradation rate is much faster than at 25°C, but surprisingly, the reaction abruptly stopped with ~60–70% of I remaining. The degradation at 25°C also shows a plateau in the rate profile, but more than 1 year is required for it to become apparent.

To evaluate the role oxygen plays in the above reaction, solutions of I in polyethylene glycol 400 were degraded at 80°C in sealed ampules containing either air or nitrogen in the head space and also in screw-capped test tubes that were opened each day to provide a relatively constant supply of oxygen. Figure 3 shows the dramatic differences observed under the three conditions. As was found at 25°C and 45°C, the degradation reaction at 80°C stopped with ~70% of I remaining unreacted in the ampules with air in the head space. When a constant supply of oxygen was permitted, however, the degradation reaction followed the first-order rate law[14] and nearly went to completion.

[10] The volume of the loop was calibrated using $^3$H-labeled water.
[11] Oxifluor by New England Nuclear.
[12] Beckman model LS 8100.
[13] The slight difference in final solvent compositions after dilution of 100 μL of either mobile phase or the 4% polyethylene glycol 400–water solution into 15 mL of scintillation fluid had no significant effect on the counting efficiency of [$^3$H]I.
[14] When the data for samples exposed to air (solid circles shown in Fig. 3) is plotted as log percent remaining *versus* time, excellent linearity through >3 half-lives is obtained.

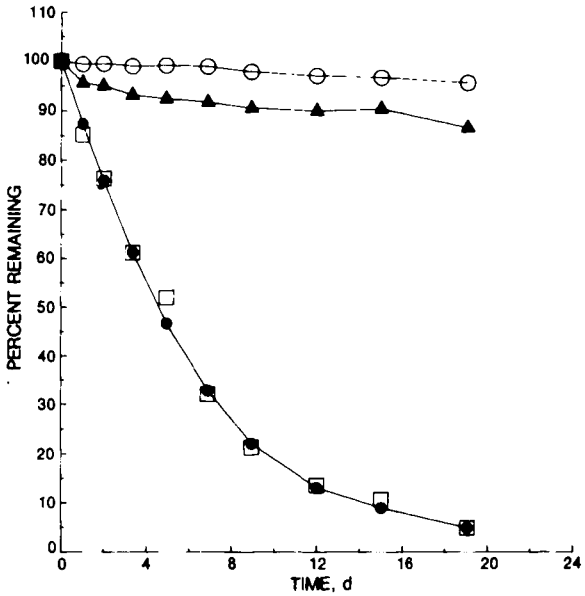


**Figure 4**—*Degradation rate of I at 80°C in diethylene glycol (▲) and in polyethylene glycol 400 solutions containing no additive (●), formic acid (□), and* dl*-α-tocopherol (○). All solutions were stored in test tubes exposed to air.*

Figure 3 also shows that no degradation of I was observed at 80°C when the solution was kept in an ampule containing nitrogen in the head space.

These results demonstrate that oxygen is required for the degradation of I in polyethylene glycol 400. The role oxygen plays in the degradation of I could be through direct reaction with the prostaglandin or through a reaction with the solvent, polyethylene glycol 400. The latter autoxidation reaction is known to produce peroxides and carboxylic acids (5–8). The highly reactive peroxide intermediates have been implicated in the degradation of several drugs in formulations containing polyethylene glycols (7, 8). Autoxidation of the solvent appears to occur during the degradation of I, which can be seen from the drop in apparent pH from 5.2 to 3.5 in the solution that contained a constant supply of air (Table I)[15]. The solution stored under nitrogen showed almost no pH change under the same conditions. When the initial pH of the solution exposed to air was lowered to 3.9 with formic acid, the rate of disappearance of I was identical to that of the pH 5.2 solution, as shown in Fig. 4. Thus, the pH drift in the solution has no apparent effect on the rate of degradation of I.

Autoxidation of the polyethylene glycol 400 provides a likely explanation for the incomplete reaction of I in sealed ampules containing air (Fig. 3). The autoxidation reaction consumes large amounts of oxygen resulting in the depletion of oxygen from solution; consequently, low peroxide levels are likely to occur as well.

The effect of 0.1% *dl*-α-tocopherol on the rate of degradation of I in polyethylene glycol 400 at 80°C is shown in Fig. 4. Although a constant supply of oxygen was present, the antioxidant prevented degradation of the prostaglandin under the reaction conditions[16]. The higher apparent pH of the solution after 15 d at 80°C compared with the solution without antioxidant (Table I) indicates that *dl*-α-tocopherol also appeared to prevent degradation of the solvent, thus reducing peroxide levels. Stabilization of fenprostalene (I) by the antioxidant is, in fact, likely to be a direct result of preventing peroxide accumulation in polyethylene glycol 400. One cannot, however, rule out the possibility that the antioxidant acts to inhibit reaction of I with oxygen directly.

The reverse-phase HPLC method used to follow the disappearance of I in polyethylene glycol 400 solutions under air did not provide any evidence of the formation of major degradation products. The only change noticed was an increase in the size of the already large solvent front. To unambiguously determine where the major degradation products of I eluted on reverse-phase HPLC, a solution of fenprostalene labeled with tritium at C-13 and C-14 in polyethylene glycol 400 was stored at 80°C for 64 h and analyzed. Fractions

[15] Addition of formic acid to polyethylene glycol 400 resulted in an apparent pH of 3.9 (Table I). This value is higher than that found for the degraded solution even though the concentration of formic acid ($6 \times 10^{-3}$ M) was 20-fold higher than the initial concentration of I ($2.5 \times 10^{-4}$ M). Thus, the pH drop in the degraded solution was due to formation of acidic decomposition products of polyethylene glycol 400, not fenprostalene (I).
[16] A similar effect was observed with 0.05% propyl gallate or 0.5% ascorbic acid as antioxidants.

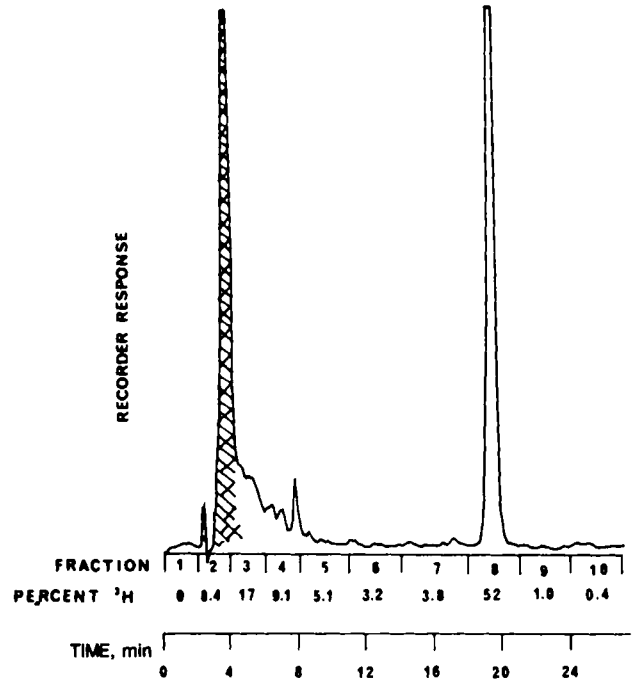


**Figure 5**—*Chromatogram of a partially degraded solution of [³H]I in polyethylene glycol 400. The percent of total radioactivity is shown for the 10 fractions collected. The hatched area in fraction 2 approximates the response due to the solvent front.*

of the HPLC eluant were collected and counted. The total cpm for all the fractions was 106% of the cpm determined directly by counting an aliquot of the degraded solution equal to the amount injected. Thus, no significant amount of radioactive material was bound to the column.

Both the analogue UV trace and the percent total radioactivity found in each fraction collected are presented in the chromatogram shown in Fig. 5. The peak area of each fraction appears to roughly correlate with the percent of total radioactivity found in that fraction, if the hatched area in fraction 2 is ignored. The large absorbance in fraction 2 is due predominantly to the solvent front. Most of the absorbance and counts in the chromatogram due to degradation products occurred near the solvent front, indicating that the products may be relatively polar compared with I[17]. Many peaks appear to be fused into aggregates, implying that many products are formed. The only evidence we have of their nature is that they are not due to transesterification with the solvent[18]. This was shown by treating a highly degraded (<1% of I remaining) solution of I in polyethylene glycol 400 with concentrated HCl at 80°C. No formation of the free acid (III) occurred under conditions which are known to completely hydrolyze fenprostalene.

The most likely reaction responsible for degradation of fenprostalene (I) in polyethylene glycol 400 is oxidation by reactive peroxides formed as a result of solvent autoxidation. However, the kinetic data described above does not exclude the possibility that oxygen reacts directly with the prostaglandin (as well as with the solvent) to account for at least part of the degradation reaction. Evidence that this pathway is not operating can be seen from the reaction of I in diethylene glycol under air at 80°C. Under conditions identical to those which result in rapid degradation of I in polyethylene glycol 400, the prostaglandin remains relatively stable in diethylene glycol (Fig. 4). The solvent also appears to be stable to autoxidation as evidenced by the small pH change after 15 d at 80°C (Table I)[19].

The slow degradation of I in diethylene glycol shown in Fig. 4 was not found to occur by oxidation, as suspected for the reaction of I in polyethylene glycol 400. Instead, the degradation product was identified as the diethylene glycol ester II of fenprostalene. Thus, while I undergoes a slow transesterification reaction in diethylene glycol, it undergoes a rapid oxidation reaction in polyethylene glycol 400[20]. This implies that fenprostalene (I) is intrinsically stable toward aerobic oxidation in nonaqueous solutions, but is susceptible to oxidation by peroxide intermediates formed during solvent decomposition. The success demonstrated by the use of antioxidants or nitrogen purging in stabilizing I in polyethylene glycol 400 is, therefore, due exclusively to the ability of these agents to prevent autoxidation of the solvent.

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[17] A significant amount of the tritium detected in the chromatogram in Fig. 5 was in or near the solvent front. Since polyethylene glycol 400 is weakly retained, if at all, on reverse-phase HPLC, the question of tritium exchange of I with solvent was examined. A 50-fold molar excess of methanol was added to the degraded polyethylene glycol 400 solution. The methanol was then recovered by evaporation using a cold trap. Any tritium present in the polyethylene glycol 400 as —O³H would be incorporated into the methanol and detected by liquid scintillation counting. Only 1.5% of the total tritium present in the sample was found in the methanol recovered. The tritium detected in and near the solvent front in Fig. 5 must, therefore, be a prostaglandin degradation product and not ³H-labeled polyethylene glycol 400.

[18] Both aspirin (10) and indomethacin (11) are reported to undergo transesterification with polyethylene glycols.

[19] Although diethylene glycol is known to undergo autoxidation, long induction periods have been reported (12) and may explain the apparent lack of degradation observed here. Addition of the free radical initiator 2,2′-azobisisobutyronitrile to a solution of I in diethylene glycol resulted in apparent oxidation of both I and the solvent at 80°C. The reaction rate, however, was very slow compared with that in polyethylene glycol 400. Formation of II was not observed under these conditions.

[20] In the presence of *dl*-α-tocopherol (or nitrogen) a slow transesterification reaction of I with polyethylene glycol 400 might be expected; however, no degradation of I was observed (Fig. 4). Thus, transesterification of I in diethylene glycol, while a slow reaction, was faster than in polyethylene glycol 400.