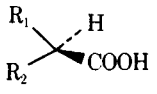
clearly demonstrates that for each sample the ratio of the diastereomeric esters produced is identical to the ratio of enantiomers present in the original sample. If, however, enantiomerically impure (*S*)-(+)-II were used, the slope of the line in Fig. 2 would be less than 0.5 and could be calculated from:

$$\text{slope} = \frac{\text{enantiomeric purity of (S)-(+)-II}}{200} \qquad \text{(Eq. 3)}$$

Table I shows the results of the liquid chromatographic analysis of five samples of (*S*)-(+)-I (80% enantiomerically pure). The data clearly demonstrate the excellent reproducibility of the method. This result is expected since the measurement is not dependent on quantitative recovery of III but rather involves comparison of relative peak areas of two closely eluting diastereomers. The applicability of this method to other



A

carboxylic acids of this type (Structure A) can only be speculative but is perhaps not unlikely if $R_1$ and $R_2$ are sufficiently dissimilar.

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# Stability of E-Type Prostaglandins in Triacetin


**S. H. YALKOWSKY** ˣ **and T. J. ROSEMAN**



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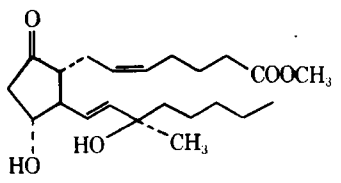
**Abstract** □ A drug delivery system for E-type prostaglandins is described. In this system, consisting of drug dissolved in triacetin and filled into soft gelatin capsules, normally unstable prostaglandins show excellent stability at room temperature.



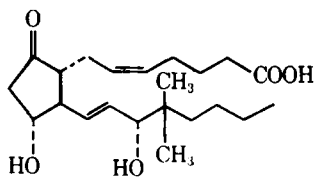
**Keyphrases** □ Prostaglandins, E type—stability in triacetin drug delivery system □ Stability—E-type prostaglandins in triacetin drug delivery system □ Delivery, drug—E-type prostaglandins in triacetin system, stability


Prostaglandins are a class of biologically active compounds with a wide spectrum of pharmacological responses. Their application in human reproduction (1) and antiulcer therapy (2) demonstrates their clinical usefulness. The general instability of prostaglandins has resulted in the arduous task of developing stable formulations for biological, toxicological, and clinical testing.

The number of asymmetric carbon centers in the molecule can result in the formation of stereoisomers through various degradative pathways. For example, in the F series, dinoprost (prostaglandin $F_{2\alpha}$) undergoes acid-catalyzed epimerization to form the 15-epi derivative (3). Prostaglandins of the E series [*e.g.*, prostaglandin $E_1$ and prostaglandin $E_2$ (dinoprostone)] are more labile due to the facile dehydration of the 11-$\beta$ hydroxyl group in the cyclopentanone ring, forming prostaglandins of the A series; in some cases, subsequent isomerization to B series prostaglandins occurs (4). Recently (5), a more detailed kinetic scheme was elucidated for the decomposition of prostaglandins $E_1$ and $E_2$ to include other degradative steps leading to the formation of 8-iso, 15-epi, and 13,15-rearrangement products of the respective prostaglandins.



I



II

**Table I—Stability of II in Triacetin**

| Time | Temperature | Triacetin Solution, % label[a] | Soft Elastic Capsule[b], % label |
|---|---|---|---|
| Initial | 4° | 102 | 100 |
| 1 month | 4° | 102 | 108 |
| 3 months | 4° | 103 | 98.8 |
| 6 months | 4° | 105 | 91.1 |
| 9 months | 4° | 108 | 105 |
| 12 months | 4° | 98.7 | 106[c] |
| Initial | 25° | 102 | 100 |
| 1 month | 25° | 98.8 | 95.3 |
| 3 months | 25° | 103 | 93.5 |
| 6 months | 25° | 102 | 87.9 |
| 9 months | 25° | 103 | 100 |
| 12 months | 25° | 94.7 | 94.5 |
| Initial | 40° | 102[d] | 100 |
| 1 month | 40° | 99.1[d] | 101 |
| 3 months | 40° | 87.7[d] | 91.5 |
| 6 months | 40° | 87.3[d] | 70.3 |

[a] Average values from theoretical concentrations of 0.5 and 2.2 mg/ml unless otherwise indicated. [b] Theoretical concentration was 0.85 mg/ml. [c] Value was for 11 months. [d] Value from a theoretical concentration of 2.2 mg/ml.

This paper reports the use of triacetin for stabilizing stock solutions of (15*R*)-15-methyl prostaglandin $E_2$ methyl ester (I) and 16,16-dimethyl prostaglandin $E_2$ (II) for experimental studies and in dosage form design. Nonaqueous solvents usually are employed for solubilizing water-insoluble drugs (6, 7). With prostaglandins, a variety of solvent vehicles also was employed to enhance stability (8) and to provide a milieu for rapid drug dissolution.

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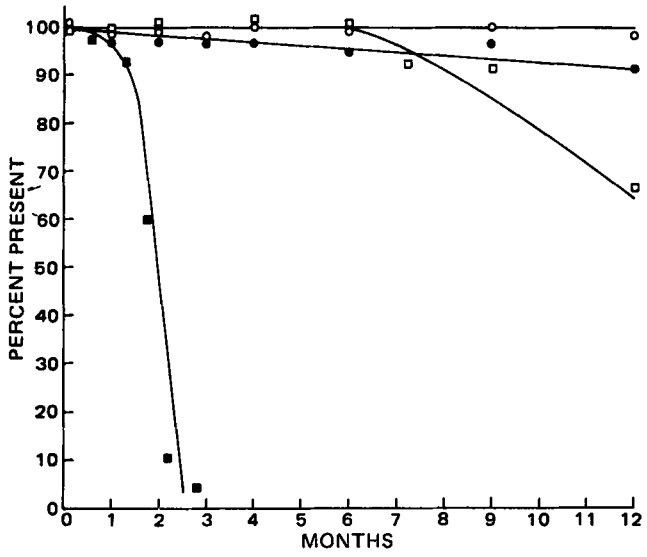


**Figure 1**—*Stability of I in the solid state and triacetin solutions. Data for solutions are average values for theoretical concentrations from 0.10 to 12 mg/ml. Key: □, 25° bulk drug; ■, 47° bulk drug; ○, 25° triacetin solution; and ●, 47° triacetin solution.*

## EXPERIMENTAL

**Materials**—Compounds I (9) and II (10) were synthesized[1] as described previously. Triacetin[2] was purchased.

**Stability Studies**—Both I and II were tested for stability as bulk drug and in triacetin solution. Stability[3] was monitored at 4, 25, and 47° for up to 12 months (Table I and Fig. 1).

[1] At The Upjohn Co.
[2] Aldrich Chemical Co. or Union Carbide Chemicals Co., New York, N.Y.
[3] Analyses were performed by the Control Division, The Upjohn Co., using high-pressure liquid chromatography.

## RESULTS AND DISCUSSION

The solid-state stability of I is shown in Fig. 1. Degradation occurred at 47 and 25°. At these temperatures, the drug was stable at early times and then rapidly decomposed. As the prostaglandin degraded, a physical transformation of the solid resulted, producing an oil phase. The marked change in the slopes at 25 and 47° may have been due to subsequent catalysis by the decomposed liquid phase. In sharp contrast to the stability of bulk drug, I was quite stable in triacetin solutions at 25°, and there was a marked improvement of stability at the elevated temperature of 47° (Fig. 1).

Table I shows the stability of another E series prostaglandin drug in triacetin. Analysis of these data further substantiates the stability-enhancing property of this solvent. Triacetin dosage forms prepared with II were clinically effective as inhibitors of simulated gastric secretion in humans, indicating that the drug is bioavailable from these dosage forms (11).

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# Fluorinated Phenytoin Anticonvulsant Analogs

**WENDEL L. NELSON ˣ, YOUNG G. KWON, GARY L. MARSHALL, JAMES L. HOOVER, and GARY T. PFEFFER**

Received March 20, 1978, from the *Department of Pharmaceutical Sciences, School of Pharmacy, University of Washington, Seattle, WA 98195.* Accepted for publication June 8, 1978.

**Abstract** □ Six ring-fluorinated phenytoin analogs were synthesized, and their anticonvulsant activity in the maximal electroshock seizure and subcutaneous pentylenetetrazol assays was determined. 5-(4-Fluorophenyl)-5-phenylhydantoin, 5-(3-fluorophenyl)-5-phenylhydantoin, and 5,5-bis(4-fluorophenyl)hydantoin were active in the maximal electroshock seizure assay. The compounds were much less potent than phenytoin but showed an extremely long duration of action.

**Keyphrases** □ Phenytoin analogs, fluorinated—synthesized, evaluated for anticonvulsant activity in mice □ Anticonvulsant activity—fluorinated phenytoin analogs evaluated in mice □ Fluorinated phenytoin analogs—synthesized, evaluated for anticonvulsant activity in mice □ Structure-activity relationships—fluorinated phenytoin analogs evaluated for anticonvulsant activity in mice

Phenytoin (5,5-diphenylhydantoin) has been used as an effective agent for the treatment of many different seizure disorders for about 40 years. The principal route of metabolism in humans and dogs is *para*-hydroxylation, affording optically active 5-(4-hydroxyphenyl)-5-phenylhydantoin (1, 2). This compound is eliminated as a urinary conjugate, making up 60–70% of the daily dose (2). Other metabolites of aromatic hydroxylation also have been reported, including 5-(3-hydroxyphenyl)-5-phenylhydantoin (3), 5-(3-dihydroxyphenyl)-5-phenylhydantoin (4, 5), 5,5-bis(4-hydroxyphenyl)hydantoin (6), 5-(3-methoxyphenyl)-5-phenylhydantoin (4, 5), and the dihydrodiol 5-(3,4-dihydroxy-1,5-cyclohexadienyl)-5-phenylhydantoin (7). Further oxidized phenytoin conjugates, a trihydroxyphenytoin glucuronide and a dihydroxymethoxyphenytoin glucuronide, were identified as metabolites of 5,5-bis(4-hydroxyphenyl)hydantoin (6).

Since the primary route of metabolism, aromatic hydroxylation in the *para*-position, provides inactive me-

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