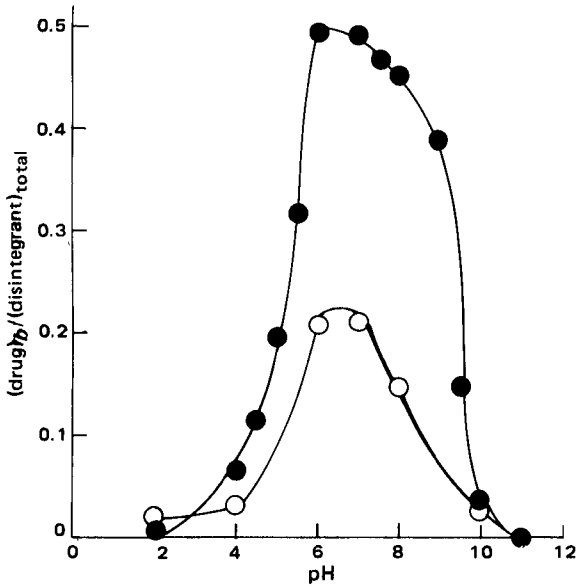

Figure 2—*Effect of solution pH on the interaction of oxymorphone derivative (I) with cross-linked carboxymethylcellulose sodium (●) and sodium starch glycolate (○).*

methylcellulose sodium and sodium starch glycolate at pH 6–7. However, the interaction of I with cross-linked carboxymethylcellulose sodium was twice that with sodium starch glycolate.

The interaction was believed to depend on the tertiary amine group at position 17 of I. Adsorption studies were extended to examine the interaction of cross-linked carboxymethylcellulose sodium with four derivatives of I, where substituents R_1, R_2, and R_3 varied and pKa values ranged from 7.9 to 8.7. Results indicated that the binding of I derivatives with cross-linked carboxymethylcellulose sodium can be described by the Freundlich adsorption isotherm as expressed by:

$$\log \frac{(\text{drug})_b}{(\text{disintegrant})} = \log k + \frac{1}{n} \log (\text{drug})_{eq} \qquad \text{(Eq. 1)}$$

where n and k are Freundlich adsorption constants that can be estimated from the slope and intercept of the linear portion of $\log[(\text{drug})_b/(\text{disintegrant})]$ *versus* $\log(\text{drug})_{eq}$ plots (Fig. 1); $(\text{drug})_{eq}$ is the equilibrium drug concentration in solution. Results obtained for the four I derivatives show n values of 1.43–1.75 and k values of 0.219–0.243. The data suggest that the structural variation of functional group R_1 at the tertiary amine group at position 17 of I does not greatly affect the Freundlich adsorption isotherm. All four I derivatives interacted with cross-linked carboxymethylcellulose sodium in a similar manner and to a significant extent.

The biological significance of these interactions is not known.

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Received January 19, 1981.
Accepted for publication March 23, 1981.

X-Ray Crystal Structure Analysis of 14-Hydroxycaryophyllene Oxide, a New Metabolite of (−)-Caryophyllene, in Rabbits

Keyphrases □ Caryophyllene—X-ray crystal structure analysis of 14-hydroxycaryophyllene in rabbits □ Metabolites—of caryophyllene by X-ray crystal structure analysis, 14-hydroxycaryophyllene □ Terpenoids—caryophyllene, new metabolite, X-ray crystal structure analysis of 14-hydroxycarophyllene

To the Editor:

The metabolic studies of diet or crude drugs containing potentially toxic terpenoids may have significant implications for human toxicology. (−)-Caryophyllene (I), a sesquiterpene hydrocarbon having a *gem*-dimethyl group on the four-membered ring, often is found in crude drugs. For toxicological evaluation, I, $[\alpha]_D$ −10.6° (*c*, 5.64 in chloroform) (12 g), was administered to six male rabbits by a previously described method (1). The neutral metabolites (2.37 g) obtained from urine were chromatographed directly on silica gel to give crude alcohols, followed by acetylation with acetic anhydride in pyridine. The crude acetates also were chromatographed on silica gel impregnated with 5% silver nitrate to yield a pure acetate (II) (48% for total acetates).

Compound II, mp 71.5–72.5°, $[\alpha]_D$ −36.5° (*c*, 2.74 in chloroform), $C_{17}H_{26}O_3$ (M^+, 278), showed the presence of an acetoxymethyl group [1730 and 1240 cm^{-1}; δ 2.08 (s, 3H)[1] and 3.85 (s, 2H)] and an exocyclic methylene group [895 cm^{-1}; δ 4.90 and 5.03 (each bs, 1H)]. The PMR spectrum also contained the signals of one proton [δ 2.80 (m)] and one tertiary methyl group [δ 1.22 (s)] on carbons bearing an ether oxygen. This spectral evidence indicated that one of the *gem*-dimethyl groups on the four-membered ring might be hydroxylated. This assumption was supported further by the ^{13}C-NMR spectrum of II, which showed the presence of two CH_3 groups (δ 17.0 and 17.2 ppm), five CH_2 groups (27.6, 28.8, 29.9, 30.3, and 34.8 ppm), two CH groups (45.8 and 48.1 ppm), a trisubstituted oxirane ring [59.4 (s) and 63.5 (d)], a tetrasubstituted sp^3 carbon (36.7), an exomethylene group [113.5 (t) and 151.4 (s) ppm], and an acetoxymethyl group [20.8 (q), 71.6 (t), and 170.9 (s) ppm].

Hydrolysis of II regenerated an alcohol, $[\alpha]_D$ −25.4° (*c*, 1.66 in chloroform); $C_{15}H_{24}O_2$ (M^+, 236); δ 1.07 and 1.25

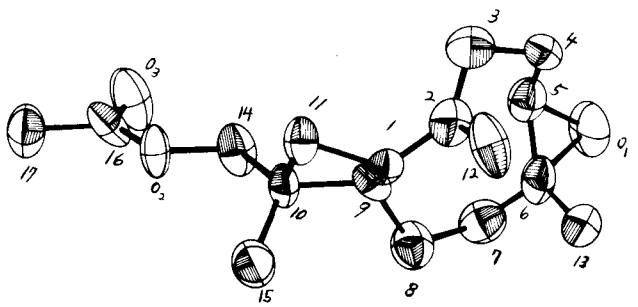

Figure 1—*X-ray structure of 14-acetoxycaryophyllene oxide (II).*

[1] s = singlet, bs = broad singlet, d = doublet, t = triplet, q = quartet, and m = multiplet.

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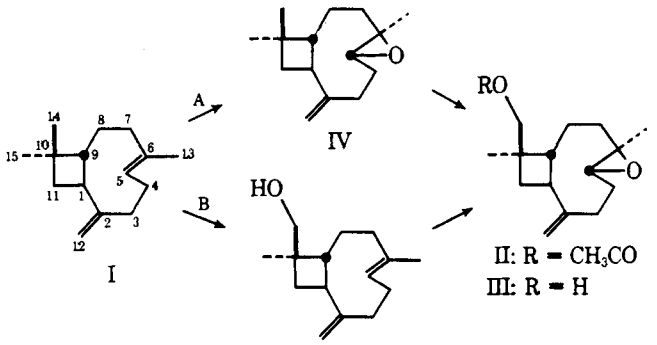

Scheme I

(each s, 3H), 2.92 (m, 1H, O–C–H), 3.55 (bs, 2H, CH_2OH), and 4.87 and 5.00 (each bs, 1H); 3450 cm^{-1} (OH). These results showed that the metabolic product and its acetate were represented best as III and II, respectively. The absolute configuration of the metabolized methyl group on a four-membered ring of I was established by X-ray study of II: [a = 9.624(4) Å, b = 8.599(4) Å, c = 10.214(4) Å, β = 105.47(3)°, space group $P2_1$, Dc = 1.13 g/cm^3, and z = 2]. The diffraction intensities were collected in the ω-scan mode, using graphite monochromated MoKα radiation on a diffractomer[2], and corrected for Lorenz polarization and background effects. The structure was resolved by direct methods using a Multan program (2) and was refined by full matrix least-squares calculations. The final R value was 0.092 for 1008 reflections. The relative stereostructure of II is shown in Fig. 1.

Two metabolic pathways may be present in the biotransformation of I (Scheme I). In this connection, (−)-caryophyllene oxide (IV), $[\alpha]_D$ −35.2° (*c*, 2.19 in chloroform), also was administered to rabbits by the method already described. After being acetylated, II was obtained as the major product from the neutral metabolites. Thus, route A was confirmed. Although the presence of route B remains to be clarified, route A may be more favorable than B since IV was found in some essential oils (3–5). According to biotransformation, the hydroxylation of the *gem*-dimethyl group on the three-, four-, five-, and six-membered rings was established for 3-carene (6, 7) and carane (7); caryophyllene; camphor (8) and fenchone (9); and retinoic acid (10), respectively. The stereoselective hydroxylation of *gem*-dimethyl on the four-membered ring in mammals was not reported previously.

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Received January 12, 1981.
Accepted for publication February 19, 1981.

Relationship between Flow Rates of Granular Powders through Stationary and Moving Orifices

Keyphrases □ Powders, granular—relationship between flow rates of granular powders through stationary and moving orifices □ Flow rates—of powder granulations, prediction of dynamic flow rate from static flow measurements □ Models, mathematical—prediction of dynamic flow rates of powder granulations from static flow measurements

To the Editor:

Since the compressed tablet is the most common dosage form manufactured, the ability to predict scale-up properties of tablet formulations for high-speed processing is needed. To manufacture tablets on a rotary tablet machine, flow of granular material through a stationary orifice (*i.e.*, efflux tube on the granulation hopper) followed by flow into moving orifices (*i.e.*, tablet dies) is required. Since little data have been reported (1, 2) that characterize the latter process of dynamic flow, data from static flow measurements have been used to predict dynamic flow properties of solids. Takieddin *et al.* (3) reported that dynamic flow rates were not predicted successfully from measurements of solid flow through a stationary orifice (static flow), noting that an apparatus suitable for the study of dynamic flow was not available.

An apparatus was constructed to study the dynamic flow of granular materials (4, 5). Although the instrument does not provide an exact duplication of events that occur within the feed frame of a tablet machine, it provides a reasonable means to obtain dynamic flow data. A slight modification of the apparatus also provides a means to study static flow rates.

Dynamic flow measurements of a lactose–cornstarch wet granulation (6) were reported (7). Six measurements were obtained for each combination of granulation mesh cut (20–40, 40–60, and 60–80), orifice size [3/16 (0.48), 1/4 (0.63), 5/16 (0.8), 3/8 (0.95), and 1/2 (1.3) in. (cm)], and five die ve-

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