ticles in the coprecipitated samples are in a fine state of subdivision and in intimate contact with urea. In such a solid dispersion system, the reduced particle size of aspirin, the concomitant increase in its surface area exposed to the suggested film layer of urea solution, and the resultant increase in its solubility appear to be the major factors responsible for the observed acceleration of aspirin degradation. Traces of alcohol in the coprecipitated sample also may play a part (22).

Aspirin–Povidone System—In the aspirin–povidone system, the effects of humidity, temperature, and aspirin solubilization by this water-soluble carrier seem to be operating in the microenvironment surrounding aspirin particles at the two storage conditions studied. The physically mixed and coprecipitated aspirin–povidone samples (curves C and D) exhibited decomposition rate constants of 0.069 and 0.077 $week^{-1}$, respectively (Fig. 2), which were comparable to those found with the aspirin–urea system. Possibly, the degradation-enhancing effect due to the high moisture sorption inherent to povidone (23), compared to that with urea, would be outweighed by the slight alkalinity imparted by urea.

However, for comparable times, the percent decomposition of both physically mixed and coprecipitated aspirin–povidone samples stored at 42% R.H.–65° was approximately one-seventh that observed with the same samples in the aspirin–urea system. This difference in aspirin stability could be attributed to the partial decomposition of urea at this high temperature. The apparent similarity between the stability of both physically mixed and coprecipitated aspirin–povidone samples stored at 42% R.H.–65° may be due to a complex reaction (24) that seems to be temperature dependent. This complex formation was reported for aspirin with other similar, structurally related compounds (25).

From these results, it can be concluded that the polar and perhaps the hygroscopic nature of urea and povidone tend to allow aspirin to degrade when incorporated into this type of carrier as physical mixtures or coprecipitates. Although the aspirin–povidone system exhibited lower degradation rates than those for the aspirin–urea system, the percent of decomposition in the former system was still prohibitively high. Consequently, the application of solid dispersion should be handled with care for drugs showing stability problems.

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Odoratin and Paucin: Cytotoxic Sesquiterpene Lactones from *Baileya pauciradiata* (Compositae)

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Abstract □ An ethanol extract of *Baileya pauciradiata* exhibited cytotoxic activity against the human epidermoid carcinoma of the nasopharynx and the lymphocytic leukemia test systems. Two constituents responsible for this activity were isolated and identified as odoratin and paucin. Their identities were proven by IR, PMR, and mass spectral data; elemental analysis; preparation of their acetates; and melting-point determinations. Odoratin was confirmed by comparison with an authentic sample.

Keyphrases □ *Baileya pauciradiata*—whole plant ethanol extract, odoratin and paucin isolated and identified □ Paucin—isolated and identified from whole plant ethanol extract of *Baileya pauciradiata* □ Odoratin—isolated and identified from whole plant ethanol extract of *Baileya pauciradiata* □ Cytotoxic sesquiterpene lactones—odoratin and paucin, isolated from whole plant ethanol extract of *Baileya pauciradiata*

In the continuing search for plants having antitumor properties, an ethanol extract of the whole plant of *Baileya pauciradiata* Harv. and Gray (Compositae)[1] exhibited cytotoxic activity against the human epidermoid carcinoma of the nasopharynx (KB) and lymphocytic leukemia (P-388) test systems[2].

[1] The plant was collected in California in March 1972. Identification was confirmed by Dr. Robert E. Perdue, Medicinal Plant Resources Laboratory, U.S. Department of Agriculture, Beltsville, Md., where a reference specimen (PR25375) is maintained.

[2] Data on the cytotoxic and *in vivo* activity were provided through the courtesy of the Division of Cancer Treatment, National Cancer Institute, National Institutes of Health, Bethesda, Md.

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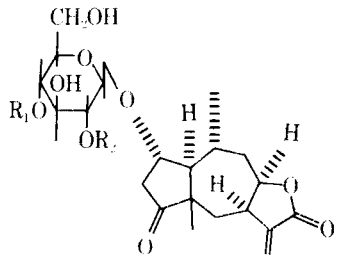

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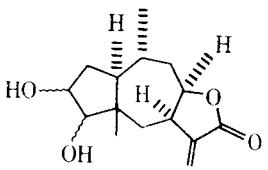

II

DISCUSSION

A literature search revealed that several sesquiterpene lactones have been isolated from various *Baileya* species. The germacranolide, baileyin, the closely related guaianolide, pleniradin, and the pseudoguaianolides, fastigilin C, radiatin, and baileyolin, were isolated from *B. multiradiata* and *B. pleniradiata* (1, 2). Plenolin was isolated from *B. pleniradiata* as was paucin, which also was isolated from *B. pauciradiata* (1, 3).

This paper reports the isolation of odoratin from *B. pauciradiata* and the fact that paucin is responsible for the high cytotoxic activity. Plenolin, paucin (I), and odoratin (II) are also pseudoguaianolides.

Paucin was isolated by a modification of the previously reported procedure (4). Its identity was confirmed by comparisons of the PMR, IR, and mass spectra and melting points of the parent compound and its triacetate with reported data and spectra (3, 4). Odoratin (5) was isolated from the mother liquor by column and preparative thick-layer chromatography. Its identity was verified by the mass spectrum, comparison of the PMR spectrum with the reported spectrum (6), preparation of its diacetate, and comparison with an authentic sample (mixed melting point and superimposable IR spectra).

Paucin exhibited cytotoxic activity at 0.016 and 0.4 μg/ml in the P-388 and KB test systems, respectively. Odoratin demonstrated an activity of 3.1 μg/ml in the KB test system. Activity in these test systems is defined[3] as an $ED_{50} \leq 4$ μg/ml. Paucin demonstrated *in vivo* activities of 135, 137, and 137% test/control (T/C) at dose levels of 35, 22, and 9.6 mg/kg, respectively, in the PS (lymphocytic leukemia) test system. Activity in the PS test system is defined[3] as an increase in the survival of treated animals over that of controls resulting in a T/C ≥ 130%.

EXPERIMENTAL[4]

Isolation Procedure—The whole plant (7 kg) of *B. pauciradiata* was ground to a powder and extracted exhaustively with 95% ethanol in a Lloyd-type extractor. The air-dried ethanol extract was partitioned between chloroform and water (1:1). The air-dried chloroform phase was taken up in hot ethanol, and two parts of hot water was added. After cooling, the resultant precipitate was removed by filtration and the filtrate was extracted with chloroform.

Isolation of Paucin—The air-dried chloroform phase (26 g) was taken up in 6% methanolic dichloromethane. The resultant residue was recrystallized from methanol and dichloromethane to yield a crystalline paucin, mp 172–173° [lit. (3) mp 171–173°].

Triacetylpaucin—Acetylation of paucin in pyridine with acetic anhydride yielded the triacetate, mp 240–242° [lit. (3) mp 241–243°].

Isolation of Odoratin—The mother liquor from the isolation was chromatographed on a silica gel 60[5] (600 g) column (7 × 40 cm) and was eluted with 6% methanolic dichloromethane. Fractions (30 ml each) 93–139 were combined and further fractionated on preparative TLC plates developed in chloroform–acetone (7:3). The major spot was further purified on preparative TLC plates developed in benzene–ether–methanol (5:10:1) and crystallized from acetone, methanol, and isopropyl ether to yield odoratin, mp 155°. Recrystallization from acetone yielded fine needles, mp 166° [lit. (5) mp 165–167°]. The mixed melting point with an authentic sample[6] showed no depression.

Anal.—Calc. for $C_{15}H_{22}O_4$: C, 67.64; H, 8.33; mol. wt. 266. Found: C, 67.29; H, 8.33; *m/e* 266 (M^+).

Diacetylodoratin—Acetylation of odoratin in pyridine with acetic anhydride yielded the diacetate, mp 132–133° [lit. (5) mp 132–133°].

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[5] Merck.

[6] Courtesy of J. Romo, Instituto de Quimica, Universidad Nacional Autónoma de México, Mexico 20, D.F., México.