COMMUNICATIONS TO THE EDITOR

SILICICOLIN, A NEW COMPOUND ISOLATED FROM *JUNIPERUS SILICICOLA*

Sir:

The finding[1] that an aqueous suspension of the pulverized dried needles of *Juniperus silicicola* (Small) Bailey[2] (Fam. *Pinaceae*) produced damage to Sarcoma 37 in mice, prompted a search for the active agent or agents. After a process involving successive extractions with different organic solvents and chromatography with activated alumina, similar to that described for other junipers,[3] a pure crystalline compound was obtained in 0.11% yield which was highly active against the tumor.

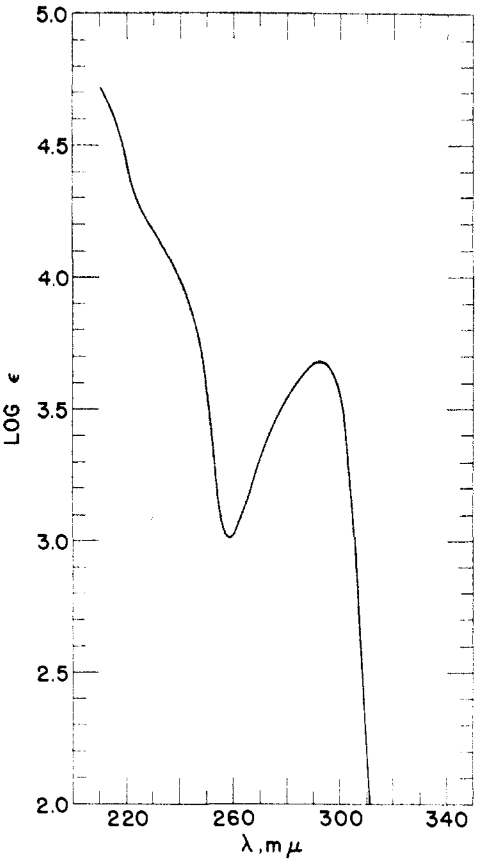

Fig. 1.—Ultraviolet absorption spectrum of silicicolin in 95% ethanol.

The new compound, for which we propose the name silicicolin, crystallizes from absolute ethanol in large, colorless, transparent prisms, m.p. 173.9–175.5° (cor.); $[\alpha]^{19}\text{D}$ −119° (*c*, 0.40, chloroform). *Anal.* Calcd. for $C_{22}H_{22}O_7$: C, 66.32; H, 5.57; 3-OCH_3, 23.37; mol. wt., 398.4. Found: C, 66.34; H, 5.52; OCH_3, 23.25; mol. wt. (Rast, camphor), 395. The Gaebel test[4] for the methylenedioxy group was positive.

The insolubility of silicicolin in water and cold 5% sodium hydroxide solution indicates the absence of acidic function such as carboxylic acid and phenolic hydroxyl groups. The slow solubility of the compound in boiling 5% sodium hydroxide solution, with separation of a white gelatinous precipitate on acidification, is strong evidence of a lactone group.

The ultraviolet spectrum (Fig. 1), showing $\lambda_{\text{max.}}^{\text{EtOH}}$ 293.5 mμ (log ε 3.68) and $\lambda_{\text{min.}}^{\text{EtOH}}$ 258.5 mμ (log ε 3.01), is similar to that of podophyllotoxin[5] [$\lambda_{\text{max.}}^{\text{EtOH}}$ 292 mμ (log ε 3.65) and $\lambda_{\text{min.}}^{\text{EtOH}}$ 260 (log ε 3.07)]. Bands in the infrared (Fig. 2) at 1780 cm.$^{-1}$ (γ-lactone) and 1593 cm.$^{-1}$ (aromatic ring) approximate closely the corresponding ones in podophyllotoxin (1785 cm.$^{-1}$ and 1595 cm.$^{-1}$)[5]. Hydroxyl group absorption around 3450 cm.$^{-1}$ is negligible.

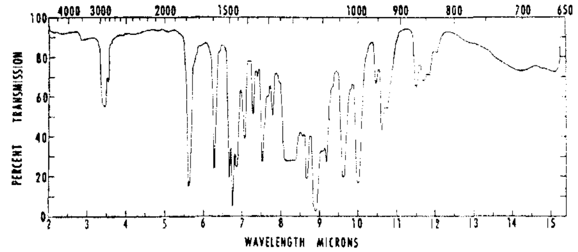

Fig. 2.—Infrared absortion spectrum of silicicolin in chloroform.

The available evidence is consistent with the assumption that silicicolin is a lignan, perhaps the previously unknown desoxypodophyllotoxin.[6]

Structural and biological studies are in progress.

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[1] D. B. Fitzgerald, M. Belkin, M. D. Felix and M. K. Carroll, to be published in *J. Nat. Cancer Inst.*

[2] Provided through the courtesy of Mr. R. A. Bonninghausen, Florida Board of Forestry, Tallahassee, Fla.

[3] J. L. Hartwell, J. M. Johnson, D. B. Fitzgerald and M. Belkin, THIS JOURNAL, in press.

[4] G. O. Gaebel, *Arch. pharm.*, **248**, 225 (1910).

[5] A. W. Schrecker and J. L. Hartwell, THIS JOURNAL, in press (1952). Podophyllotoxin itself was first suspected because of its isolation from other species of juniper.[3]

[6] Compounds of the same empirical formula, possibly structurally similar, have been isolated from plants of the family *Umbelliferae*, by K. Noguchi and M. Kawanami, *J. Pharm. Soc. Japan*, **60**, 629 (1940), and by L. Marion, *Can. J. Research*, **20B**, 157 (1942).

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11α-HYDROXYSTEROIDS. SYNTHESIS OF Δ^4-PREGNEN-11α,17α,21-TRIOL-3,20-DIONE 11,21-DIACETATE (11-EPI-COMPOUND F DIACETATE)

Sir:

We wish to report a general method for the reduction of the 11-carbonyl group in steroids to the

11α-hydroxy group.[1] This method, coupled with our observation that the 11α-hydroxyl group is not oxidized readily by N-bromoacetamide, has made possible the preparation of Δ^4-pregnen-11α,17α,-21-triol-3,20-dione 11,21-diacetate (11-epi-Compound F Diacetate).

Etiocholan-3α-ol-11,17-dione[2] was reduced with sodium in refluxing *n*-propyl alcohol in excellent yield to etiocholan-3α,11α,17β-triol (I), m.p. 245–247°, $[\alpha]^{25}$D +13° (0.5% in ethanol). *Anal.* Calcd. for $C_{19}H_{32}O_3$: C, 73.98; H, 10.46. Found: C, 73.82; H, 10.72. The configuration of the 11-hydroxyl group was inferred from the acetylation of I, which gave a triacetate, m.p. 161–162°, $[\alpha]^{25}$D −2° (0.9% in ethanol). *Anal.* Calcd. for $C_{25}H_{38}O_6$: C, 69.09; H, 8.81. Found: C, 69.31; H, 8.94. Oxidation of I with excess N-bromoacetamide (NBA) in aqueous methanol–acetone solution at room temperature gave, in good yield, etiocholan-11α-ol-3,17-dione (II), m.p. 143–144°, $[\alpha]^{25}$D +72° (1% in acetone). *Anal.* Calcd. for $C_{19}H_{28}O_3$: C, 74.96; H, 9.27. Found: C, 74.87; H, 9.24. The structure of II was established by independent synthesis from I. Oxidation of I with chromic anhydride in aqueous acetic acid at room temperature afforded etiocholan-3,11,17-trione (III),[3] m.p. 135–136°, $[\alpha]^{23}$D +151° (1% in acetone). Upon refluxing III with ethylene glycol and *p*-toluenesulfonic acid in benzene solution, there was obtained etiocholan-3,11,17-trione 3,17-bisdioxolane (IV), m.p. 122–123°, $[\alpha]^{26}$D +30° (1% in chloroform). *Anal.* Calcd. for $C_{23}H_{34}O_5$: C, 70.73; H, 8.77. Found: C, 70.75; H, 9.07. Reduction of IV with sodium in refluxing *n*-propyl alcohol, followed by hydrolysis of the product with methanol–hydrochloric acid, yielded II, identical in all respects with the sample from NBA oxidation of I.

Sodium and *n*-propyl alcohol reduction of pregnan-3α,17α-diol-11,20-dione 20-dioxolane[4] yielded the corresponding 11α-hydroxy compound (V), m.p. 213.2–214.0°, $[\alpha]$D −13° (1% in acetone). *Anal.* Calcd. for $C_{23}H_{38}O_5$: C, 70.01; H, 9.71. Found: C, 69.70; H, 9.74. Hydrolysis of V with aqueous methanol–hydrochloric acid gave pregnan-3α,11α,17α-triol-20-one (VI) as the monohydrate, $[\alpha]$D +25° (0.5% in acetone). *Anal.* Calcd. for $C_{21}H_{34}O_4 \cdot H_2O$: C, 68.44; H, 9.85. Found: C, 68.14; H, 10.07. Bromination of VI in chloroform at C-21 followed by acetoxylation according to the method of Gallagher[5] yielded an oil which was not further purified, but was oxidized at C-3 with NBA and then acetylated at C-11 to give pregnan-11α,-17α,21-triol-3,20-dione 11,21-diacetate (VII), m.p. 232–233° dec., $[\alpha]^{25}$D +44° (1% in dioxane). *Anal.* Calcd. for $C_{25}H_{36}O_7$: C, 66.94; H, 8.09. Found: C, 66.59; H, 8.29. Bromination at C-4 followed by semicarbazone formation, elimination of HBr and acid hydrolysis of the semicarbazone[6] gave Δ^4-pregnen-11α,17α,21-triol-3,20-dione 11,21-diacetate (11-epi-compound F diacetate), m.p. 223.0–225.8, $[\alpha]$D +116° (1% in dioxane), $\epsilon_{240}^{\text{alc}}$ 16,800. *Anal.* Calcd. for $C_{25}H_{34}O_7$: C, 67.24; H, 7.68. Found: C, 67.12; H, 7.85.

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[1] F. Sondheimer, R. Yashin, G. Rosenkranz and C. Djerassi (THIS JOURNAL, **74**, 2696 (1952)) noted that the carbonyl group and the double bond conjugated with it in Δ^8-22-isoallospirosten-3β-ol-11-one propionate are both reduced to yield the saturated 11α-ol with the aid of lithium, liquid ammonia and alcohol.

[2] L. H. Sarett, *ibid.*, **70**, 1454 (1948).

[3] S. Lieberman and K. Dobriner, *J. Biol. Chem.*, **166**, 773 (1946).

[4] The preparation of the various pregnane dioxolanes will be the subject of another paper.

[5] T. H. Kritchevsky, D. L. Garmaise and T. F. Gallagher, THIS JOURNAL, **74**, 483 (1952).

[6] V. R. Mattox and E. C. Kendall, *J. Biol. Chem.*, **188**, 287 (1951); B. Koechlin, T. Kritchevsky and T. F. Gallagher, *ibid.*, **184**, 393 (1950); E. B. Hershberg, *J. Org. Chem.*, **13**, 542 (1948).

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THE ION-EXCHANGE SEPARATION OF ISOMERIC DINITROTETRAMMINECOBALT(III) IONS[1]

Sir:

Recently it has been shown that the octahedral complex ions $Cr(H_2O)_6^{+++}$, $Cr(SCN)(H_2O)_5^{++}$, and $Cr(SCN)_2(H_2O)_4^{+}$ are readily separated by an ion-exchange technique.[2] The possibility of using this same technique to separate the isomeric *cis* and *trans* complexes having the general formula $MA_4B_2^{+n}$ was suggested at that time. The isomeric dinitrotetramminecobalt(III) ions have been prepared,[3] and their elution characteristics have been studied. An elution curve of a mixture of the two complex ions is shown in Fig. 1. Since the absorption spectra of these complex ions are different,[4] it is convenient to make use of the spectra in following the elution and identifying the eluted species. The more easily eluted ion is the *trans* complex.

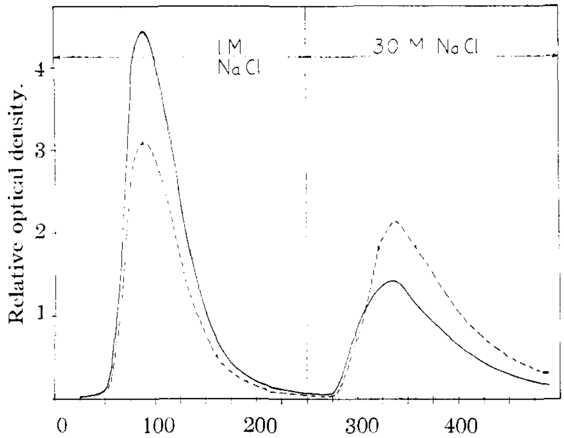

Fig. 1.—Relative optical density of eluant *versus* volume of eluant (in ml.). —350 mμ, - - - - - 325 mμ. For *trans* complex $\epsilon_{350} > \epsilon_{325}$. For *cis* complex $\epsilon_{325} > \epsilon_{350}$. Notice that the relative optical densities in the first part of the second peak indicate that the *trans* complex had not been completely eluted when the eluting agent was changed. Individual portions of eluant were 12.5 ml.

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[1] This work has been supported in part by a grant from the U. S. Atomic Energy Commission.

[2] E. L. King and E. B. Dismukes, THIS JOURNAL, **74**, 1674 (1952).

[3] *cis:* H. Biltz and W. Biltz, "Laboratory Methods of Inorganic Chemistry," John Wiley and Sons, New York, N. Y., 1928, p. 179. *trans:* S. M. Jorgensen, *Z. anorg. Chem.*, **17**, 469 (1898).

[4] F. Basolo, THIS JOURNAL, **72**, 4393 (1950).