ference to the variation in the pre-exponential factor. The closely similar diene conversions (Table I) are also in accord with the possibility that these yields reflect equilibrium rather than rate values.

By the method of statistical thermodynamic functions, the free energy change for the butadiene-trifluoroacetonitrile reaction was calculated. Using the precise values[12,13] for butadiene, hydrogen, and trifluoroacetonitrile, and the methods[14] of group equations and group increments to estimate the functions for trifluoromethylpyridine and the heats of formation for CF_3CN and the latter, it was found that $\Delta F°$ was negative over the entire temperature range 300°–1000° K., being −9 kcal./mole at the upper limit. It is sufficient for the present discussion to refer only to the result at 400°. The standard free energy change, and the equilibrium S.T.Y. calculated from the well known equation:

$$\Delta F° = -RT \ln K_p \qquad (3)$$

at 400° were thus found to be −14 kcal./mole and 13×10^{-4} moles/hr./100 cc. reaction volume.

Comparison of the thermodynamically predicted value with the experimental S.T.Y., 6.1×10^{-4}, confirms that the present yields should be recognized as equilibrium yields, *i.e.* that thermodynamic control rather than kinetic control operates. It should be noted that the preceding results should be interpreted only qualitatively rather than giving a quantitative estimate of the nearness to equilibrium conditions in these experiments.

Extension of these studies is in progress at very short reaction times as well as very long periods, to evaluate the relative reactivities of the dienes and the reaction equilibria in the homogeneous gas phase at moderately high temperatures.

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Methyl Desoxypodophyllate and Its Methyl Ether

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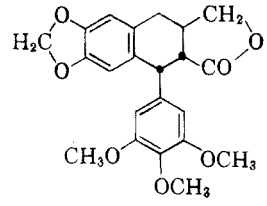
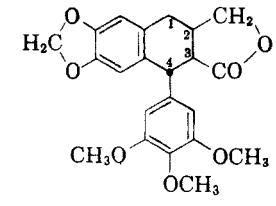
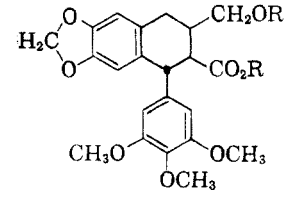
In a previous paper from this laboratory,[1] it was shown that anthricin (isolated by Noguchi and Kawanami[2] from *Anthriscus sylvestris* Hoffm.), hernandion (isolated by Hata[3] from *Hernandia ovigera* L.), and silicicolin [isolated by Hartwell, Johnson, Fitzgerald, and Belkin[4] from *Juniperus silicicola* (Small) Bailey] are all identical with desoxypodophyllotoxin (I),[5,6] a compound also obtained[7] from *Podophyllum peltatum* L. Base-catalyzed epimerization of I (at C_3) produces the *cis*-(2:3)-*trans*-(3:4) desoxypicropodophyllin (II),[5,6] which is identical[1] with isohernandion,[3] with silicicolin-B,[5] and also with cicutin (isolated by Marion[8] from *Cicuta maculata* L.[9]). Both I and II are saponified to the same hydroxy acid, desoxypodophyllic acid (IIIa), which in turn is lactonized to II.[5] Noguchi's isoanthricin[2] was probably[1] a mixture of this acid with some II.



I



II



IIIa: R = R′ = H
IIIb: R = CH_3; R′ = H
IIIc: R = H; R′ = CH_3
IIId: R = R′ = CH_3

In view of the identity of the various lactones with I or II, it is difficult to understand certain apparent discrepancies with regard to their reactions. Thus, Noguchi and Kawanami[2] reported that treat-

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(9) Cicutin is probably[1] an artifact, produced by epimerization of desoxypodophyllotoxin during its isolation, which included treatment with methanolic sodium hydroxide.

ment of isoanthricin with dimethyl sulfate in cold alkali yielded "isoanthricinic acid methyl ester" [*i.e.*, methyl desoxypodophyllate (IIIb)], $C_{19}H_{14}O_4(OCH_3)_4$, m.p. 173°, $[\alpha]_D$ −43.6° (chloroform), which was saponified to "isoanthricinic acid" [*i.e.*, desoxypodophyllic acid (IIIa)], $C_{19}H_{15}O_5(OCH_3)_3$, m.p. 205°, and which was regenerated from this acid with diazomethane. Hata[3] reported that reaction of silver desoxypodophyllate (prepared from isohernandion) with methyl iodide afforded a methyl ester, also $C_{19}H_{14}O_4(OCH_3)_4$, m.p. 173°, which thus appeared to be identical with Noguchi's ester.

Noguchi's results disagree with the observation[6] that desoxypodophyllic acid fails to form a methyl ester when treated with diazomethane, but is lactonized to II, even at 0°, in contrast to isodesoxypodophyllic acid[6] [IIIa, but *trans*-(2:3)-*trans*-(3:4)], which does yield the corresponding methyl ester. Moreover, Marion[8] reported that treatment of cicutin with dimethyl sulfate in hot alkali, followed by acidification, afforded an acid, $C_{19}H_{14}O_4(OCH_3)_4$, m.p. 194–195°, evidently desoxypodophyllic acid methyl ether (IIIc).

These contradictory findings could be reconciled only by the assumption that Noguchi's ester, m.p. 173°, was actually methyl dexoxypodophyllate methyl ether (IIId), which on saponification would yield IIIc, identical with Marion's acid. To determine whether this assumption was correct, potassium desoxypodophyllate (prepared from I) was methylated under conditions similar to those reported[2] by Noguchi. The neutral fraction was separated by chromatography into desoxypicropodophyllin (II) and methyl desoxypodophyllate methyl ether (IIId), $C_{19}H_{13}O_3(OCH_3)_5$, m.p. 173–174°, $[\alpha]_D$ −70° (chloroform). This compound depressed the melting point of methyl desoxypodophyllate (IIIb), m.p. 175–176°, $[\alpha]_D$ −66° (chloroform), prepared by Hata's[3] procedure. None of the latter ester could be isolated from the reaction with dimethyl sulfate. Methylation of desoxypicropodophyllin according to Marion[8] (*i.e.*, in hot alkali) yielded IIIc, m.p. 180–184° (foaming), in addition to unmethylated IIIa. Although the melting (or, rather, decomposition) point of IIIc was much lower than that reported by Marion, the substance was found to be analytically pure. Variable decomposition points of different samples have also been observed in the case of IIIa[5] and may be caused by the presence of trace impurities.

In summary, it appears that Noguchi's "isoanthricinic acid methyl ester" was actually methyl desoxypodophyllate methyl ether (IIId) and that his "isoanthricinic acid" was desoxypodophyllic acid methyl ether (IIIc).

EXPERIMENTAL[10,11]

Methyl desoxypodophyllate (IIIb). Silver desoxypodophyllate (0.9 g.), prepared from desoxypicropodophyllin[5] by Hata's procedure,[3] was stirred and refluxed with 7 ml. of methyl iodide for 1 hr. The mixture was extracted with hot ethanol and the filtrate concentrated. The solid thus obtained (0.57 g., m.p. 163–164°) afforded, after four recrystallizations from ethanol, small colorless needles, m.p. 175–176°, $[\alpha]_D^{22}$ −65.9° (*c* 0.99, chloroform), $[\alpha]_D^{22}$ −138° (*c* 0.50, pyridine), infrared maximum (in chloroform) at 1735 cm.$^{-1}$ (ester group). Prolonged heating with piperidine in ethanol caused partial conversion to II.

Anal. Calcd. for $C_{19}H_{14}O_4(OCH_3)_4$: C, 64.17; H, 6.09; OCH_3, 28.84. Found: C, 63.82; H, 5.92; OCH_3, 28.91.

Desoxypodophyllic acid methyl ether (IIIc). A hot solution of desoxypicropodophyllin in 3% sodium hydroxide was treated with dimethyl sulfate and 10% sodium hydroxide according to Marion's procedure.[8] The precipitate obtained after acidification was dissolved in sodium bicarbonate solution, which was then extracted with chloroform and reacidified at 0°. The gelatinous material, when recrystallized from methanol, formed tiny needles, m.p. 180–184° (foaming) (reported[8] m.p. 194–195°).

Anal. Calcd. for $C_{19}H_{14}O_4(OCH_3)_4$: C, 64.17; H, 6.09; OCH_3, 28.84. Found: C, 64.26; H, 6.02; OCH_3, 28.56.

The methanolic mother liquor, when diluted with water, yielded desoxypodophyllic acid (IIIa), m.p. 164–165° (foaming), which had an infrared spectrum (Nujol mull) identical with that of an authentic sample.[5]

Methyl desoxypodophyllate methyl ether (IIId). Following essentially Noguchi's procedure,[2] a chilled solution of 916 mg. of desoxypodophyllotoxin (I)[5] in 48 ml. of 40% potassium hydroxide was stirred magnetically and treated dropwise with 24.7 ml. (33.4 g.) of dimethyl sulfate during 15 min. It was then stirred at room temperature (with occasional immersion in cold water) for 3 hr., treated dropwise with another 18.7 ml. (25.3 g.) of dimethyl sulfate, and stirred for 3 more hr. The still alkaline mixture was then exhausted with ether in a continuous extractor. The extract was evaporated, the residue dissolved in chloroform, and the solution was washed with sodium bicarbonate solution and water, dried, and evaporated. The crude product was chromatographed on 18 g. of alumina (Alcoa, F-20) and eluted with 100 ml. of 1:1 benzene-chloroform, with 50 ml. of chloroform, and with 100 ml. of 9:1 chloroform-methanol. The last eluate left almost no evaporation residue.

The material eluted with benzene-chloroform was rechromatographed on neutral alumina (Woelm). Elution with 4:1 benzene-chloroform, followed by recrystallization from benzene-pentane provided rosettes of colorless needles, yield 50 mg., m.p. 173–174°, $[\alpha]_D^{26}$ −69.8° (*c* 0.84, chloroform), infrared maximum (in chloroform) at 1735 cm.$^{-1}$ (ester group). The compound and IIIb gave a mixed melting point depression and different infrared spectra.

Anal. Calcd. for $C_{19}H_{13}O_3(OCH_3)_5$: C, 64.85; H, 6.35; OCH_3, 34.91. Found: C, 65.00; H, 6.42; OCH_3, 35.05.

The material that was eluted with chloroform (113 mg.) crystallized from ethanol as electrified needles, m.p. 172–173°, $[\alpha]_D^{26}$ +35.8° (*c* 0.93, chloroform) (lit.[5,6] m.p. 172–173°, average $[\alpha]_D$ +34°). It was identified as desoxypicropodophyllin by the mixed melting point and infrared spectrum (lactone band in chloroform at 1770 cm.$^{-1}$).

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(10) Melting points are corrected and were determined in Pyrex capillaries with the Hershberg apparatus. Samples were dried for analysis at 78° and 0.01 mm. overnight. Optical rotations were measured in 10-dm. tubes.

(11) Microanalyses by Mrs. Evelyn Peake and Miss Paula M. Parisius in Dr. W. C. Alford's laboratory.

(12) National Institutes of Health, Public Health Service, U. S. Department of Health, Education and Welfare.