subjecting the solution to chromatography on Florisil (350 g.). The first seven fractions contained the most product and were combined and were rechromatographed starting with methylene chloride as the eluting solvent and adding ethyl acetate. Two fractions, obtained in 25 and 50% ethyl acetate in methylene chloride, contained 4.12 g. of approximately 60% purity. Trituration of the two fractions rich in XIX with ethyl acetate gave yellow crystals. Two recrystallizations from ethyl acetate afforded an analytical sample; m.p. 161–167°, λ_{max} 237 mμ (16,400), $[\alpha]_D$ +75°.

Anal. Calcd. for $C_{22}H_{26}O_5F_2$: C, 64.69; H, 6.42. Found: C, 65.05; H, 6.54.

A solution of 8 mg. of XIX and 2.37 mg. of *o*-phenylenediamine in 1.5 ml. of ethanol was heated at reflux for 0.5 hr. Addition of water caused the precipitation of a solid, weighing 5 mg., λ_{max}^{alc} 238 mμ ($E_{1\,cm}^{1\%}$ 708) and 320 mμ ($E_{1\,cm}^{1\%}$ 108).

21-Methyl-6α,9-difluoro-11β,17,21α$_F$-trihydroxypregna-1,4-diene-3,20-dione (XVII).—A solution of 10 g. of crude α-diketone XIX in 1200 ml. of ethanol was added to a mixture of 2850 g. of sucrose and 77 g. of active dry yeast in 21.2 l. of tap water. The mixture was stirred slowly for 15 days with daily additions of 60 g. of yeast and 320 g. of sucrose. The reaction mixture was filtered through Super Cel and the product isolated from the filtrate by extraction with ethyl acetate as described above for XIV. Concentration of the washed ethyl acetate extract to 150 ml. gave 6.3 g. of crude crystalline product (66% pure by paper chromatographic assay), which was purified by acetylation with acetic anhydride (12.5 ml.) in pyridine (25 ml.). The crystalline acetate XVIIa was precipitated by the addition of water and recrystallized twice from ethyl acetate. This treatment afforded 3.0 g. of 6α,9-difluoro-11β,17,21α$_F$-trihydroxy-21-methylpregna-1,4-diene-3,20-dione 21-acetate (XVIIa), which had m.p. 256–257° dec., λ_{max} 237.5 mμ (16,200), $[\alpha]_D$ +95°.

Anal. Calcd. for $C_{24}H_{30}O_6F_2$: C, 63.70; H, 6.68. Found: C, 63.51; H, 6.91.

Saponification of a 778-mg. sample of XVIIa with methanolic potassium carbonate in the usual way and recrystallization twice from ethyl acetate afforded an analytical sample which had m.p. 211–211.8°, λ_{max} 237 mμ (15,500), $[\alpha]_D$ +102°. The infrared spectrum of XVII showed that it retained ethyl acetate of crystallization despite drying at 135° for 16 hr. The following analysis also indicates the presence of solvent of crystallization.

Anal. Calcd. for $C_{22}H_{25}O_5F \cdot {}^1/_2\ CH_3COOC_2H_5$: C, 63.44; H, 7.05. Found: C, 63.47; H, 7.13.

Treatment of 21-Methyl-6α,9-difluoro-11β,17,21α$_F$-trihydroxypregna-1,4-diene-3,20-dione with Periodic Acid.—Treatment of 64 mg. of XVII with periodic acid (55 mg.) in 2 ml. of dioxane and 1.5 ml. of water overnight at room temperature afforded 32 mg. of an acid, m.p. 257–260° dec., identical to the etio acid obtained from 6α,9-difluoroprednisolone[34] under the same conditions.

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Proton Magnetic Resonance and Stereochemistry of 1-Ethynyl-2-tolylcyclohexanols[1]

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The diastereoisomers 1-ethynyl-*cis*-2-tolylcyclohexanol and 1-ethynyl-*trans*-2-tolylcyclohexanol, for the *o*-, *m*-, and *p*-tolyl compounds, were separated by gas chromatography and characterized by n.m.r. The n.m.r. spectra of all six isomers are consistent with structures in which the cyclohexane ring is in a chair conformation with the aromatic ring in an equatorial orientation. The long-range shielding effect of the aromatic ring causes different chemical shifts of the acetylenic hydrogen in *cis* and *trans* isomers. The aromatic *o*-hydrogen of each *o*-tolyl isomer exhibits a downfield chemical shift. Upon reduction of the ethynyl group to an ethyl group this downfield shift persists in the *cis* isomer (OH axial) and disappears in the *trans* isomer (OH equatorial).

The synthesis of 1-ethynyl-2-tolylcyclohexanols was reported in an earlier publication.[2] The separation of the resulting mixtures of *cis* and *trans* diastereoisomers has now been accomplished by gas chromatography for each of the *o*, *m*- and *p*-tolyl compounds. The components have been characterized and their stereochemistry established by nuclear magnetic resonance.

The n.m.r. spectra of the six isomers are consistent with structures in which the cyclohexane ring has the chair conformation with the aromatic ring in an equatorial orientation when measured in carbon tetrachloride. This conformation is indicated for each isomer by the quartet given by the signal of the hydrogen on C-2, which, from first-order approximation, becomes the X component of an ABX system; the two hydrogens on C-3 making up the A and B components. Figure 1 shows this signal at τ = 7.06 for 1-ethynyl-*trans*-2-*o*-tolylcyclohexanol and at τ = 6.92 for 1-ethynyl-*cis*-2-*o*-tolylcyclohexanol. The other four isomers give analogous quartets. First-order treatment of the quartets give axial–axial (*a*,*a*) splitting of 11.5 c.p.s. and axial–equatorial (*a*,*e*) splitting of 3.5 c.p.s. for every isomer with the ethynyl group in equatorial orientation. For the compounds with the ethynyl group in axial orientation the splittings are as follows: *a*,*a* = 10 c.p.s. and *a*,*e* = 4 c.p.s. for the *p*-tolyl isomer; *a*,*a* = 10.5 c.p.s. and *a*,*e* = 3.9 c.p.s. for the *m*-tolyl isomer; *a*,*a* = 10.7 c.p.s. and *a*,*e* = 3.5 c.p.s. for the *o*-tolyl isomer. In every isomer it is necessary that the hydrogen at C-2 be in an axial orientation to account for the observed splitting pattern. This interpretation has been described earlier for related compounds.[3–5] Selectively deuterated compounds are being prepared to determine if the observed splittings are true measures of the coupling constants because of the inherent danger of assigning coupling constants from first-order treatment.[6–8]

Configurations were established from the chemical shifts of the acetylenic hydrogens and the chemical

(1) This investigation was supported in part by PHS research grants no. H-3843 (C2) and no. HE-03843-04, from the National Heart Institute, Public Health Service.

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(3) A. C. Huitric and J. B. Carr, *ibid.*, **26**, 2648 (1961).

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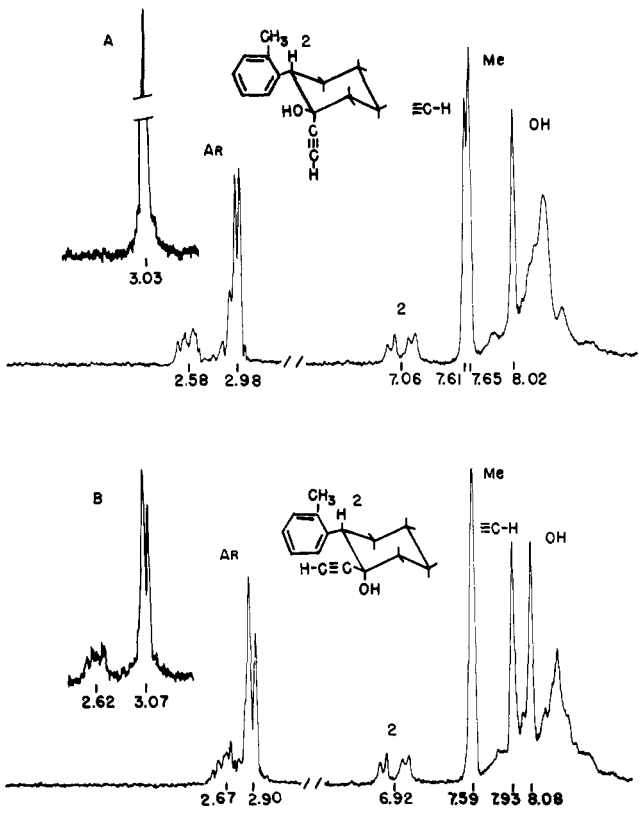


Fig. 1.—N.m.r. spectra of 1-ethynyl-*trans*-2-*o*-tolylcyclohexanol (upper curve) and 1-ethynyl-*cis*-2-*o*-tolylcyclohexanol (60 Mc.; about 1 *M* in carbon tetrachloride at 23°). Curves A and B show the signals of the aromatic hydrogens of the corresponding compounds where the ethynyl group has been reduced to an ethyl group.

shifts of the hydrogens on C-2. The chemical shifts of the hydroxyl hydrogens give additional supporting evidence for the assigned configurations. There is a significant difference in the chemical shift of the acetylenic hydrogen of the *cis* and *trans* components of each pair of diastereoisomers of the 1-ethynyl-2-tolylcyclohexanol series (see Fig. 1 and Table I), but this is not the case for the *cis* and *trans* isomers of 1-ethynyl-4-*t*-butylcyclohexanol. The difference is attributed to the long-range shielding effects of the aromatic ring, the largest effect being a shielding of the acetylenic hydrogen in those isomers having the ethynyl group equatorial. It can be shown with molecular models that in the 1-ethynyl-*cis*-2-tolylcyclohexanols the equatorial ethynyl group hinders rotation of the tolyl group preventing coplanarity of the rings and causing the average time orientation of the aromatic ring to be more closely one in which the plane of the aromatic ring is perpendicular to the cyclohexane ring. With this orientation of the aromatic ring the equatorial acetylenic hydrogen is located in a region of shielding resulting from the magnetic anisotropy of the aromatic ring. The magnetic anisotropy of the benzene ring has been discussed elsewhere,[9-11] and regions and extent of positive and negative shielding have been mapped for the benzene ring by Johnson and Bovey.[11] Calculations from Dreiding models, using the "Nuclear Shielding Values Table" of Johnson and Bovey,[11] give a shielding value of 0.27 τ units for the acetylenic hydrogen of 1-ethynyl-*cis*-2-tolylcyclohexanols (ethynyl group equatorial) when the rings are perpendicular to each other. Counterclockwise rotation[12] of the aromatic ring by about 15° from perpendicular would increase the shielding to a maximum of about 0.4 τ units, and further rotation would result in a gradual decrease of the shielding effect. Rotation in a clockwise direction would cause a decrease of the shielding effect. The observed shielding values of about 0.2 p.p.m. for the *para* and *meta* tolyl isomers and 0.24 p.p.m. for the *ortho* isomers, compared to *cis*- and *trans*-1-ethynyl-4-*t*-butylcyclohexanol (τ = 7.69), are in good agreement with expected values. The greater shielding for the *o*-tolyl isomer is as expected because the additional steric hindrance of the *o*-methyl group will restrict the limits of oscillation of the aromatic ring.

In the 1-ethynyl-*trans*-2-tolylcyclohexanol series the axial ethynyl hydrogen is in a region of deshielding when the rings are perpendicular to each other (calculated deshielding of about 0.2 p.p.m.), but it can be brought into a region of shielding by slight rotation of the aromatic ring in a clockwise direction, while counterclockwise rotation would increase the deshielding effect. The effects appear to cancel out in the *para* and *meta* tolyl isomers, but, as expected, there is a deshielding effect in the *ortho* isomer where clockwise rotation would be hindered to a greater extent by the *o*-methyl group.

The signal of the acetylenic hydrogen was differentiated from that of the hydroxyl hydrogen for each isomer by measuring the n.m.r. spectrum at half the original concentration and also at increased temperature. Under these conditions the signal of the hydroxyl group was shifted to higher field because of decrease in intermolecular hydrogen bonding, while that of the acetylenic hydrogen remained essentially constant. The same was true for the 1-ethynyl-4-*tert*-butylcyclohexanols.

The configurations assigned on the basis of the long-range shielding effects of the aromatic ring on the acetylenic hydrogens are substantiated by the larger chemical shift of the hydrogen at C-2 for the isomer with the hydroxyl group axial in each diastereoisomeric pair. This difference cannot be explained by inductive effect through bonding orbitals. The same phenomenon has been observed in *cis*- and *trans*-2-*o*-tolylcyclohexanol[3] and in the three diastereoisomeric pairs of 2-(chlorophenyl)cyclohexanols,[4] where it was pointed out that this is consistent with the magnetic anisotropy of the C–O bond deshielding the hydrogen at C-2 when the hydroxyl group is axial and shielding it when the hydroxyl group is equatorial. In the 1-ethynyl-*cis*-2-tolylcyclohexanols the steric repulsion between the equatorial ethynyl group and the aromatic ring should cause a greater deshielding of the hydrogen on C-2 by the aromatic ring. In the 1-ethynyl-*trans*-2-tolylcyclohexanols the additional long-range effect resulting from the magnetic anisotropy of the ethynyl group must be considered. The long-range effects of

(9) L. M. Jackman, "Application of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, 1959, Chap. 2 and 7.

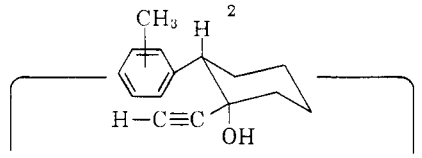
(10) J. A. Pople, W. G. Schneider, and H. J. Bernstein, "High-Resolution Nuclear Magnetic Resonance," McGraw-Hill Book Co., Inc., New York, N. Y., 1959, Chap. 7.

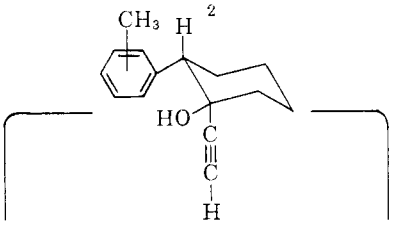
(11) C. E. Johnson, Jr., and F. A. Bovey, *J. Chem. Phys.*, **27**, 1012 (1958).

(12) The terms "clockwise" and "counterclockwise" rotation refer to the structures shown in Fig. 1. For the mirror images rotation would be in opposite direction to produce the same effect.

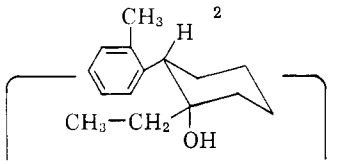
TABLE I

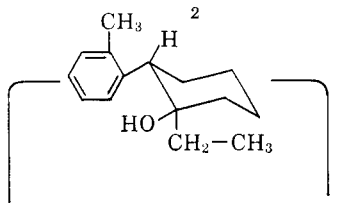
CHEMICAL SHIFTS[a]

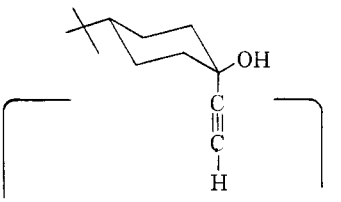


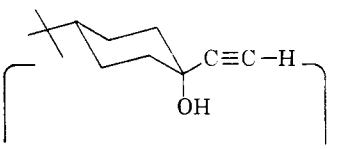


isomer	≡C—H	2	OH	CH_3	AR	≡C—H	2	OH	CH_3	AR
p-Methyl	7.88	7.38	8.15	7.73	2.92	7.72[b]	7.50	8.06	7.72	2.92
m-Methyl	7.88	7.36	8.23	7.69	2.91	7.67	7.49	7.92	7.67	2.86
o-Methyl	7.93	6.92	8.08	7.59	2.90; 2.67	7.61	7.06	8.02	7.65	2.98; 2.58









2	CH_3	AR	2	CH_3	AR	≡C—H	OH	*t*-Bu	≡C—H	OH	*t*-Bu
7.26	7.75	3.07; 2.62	6.98[c]	7.64	3.03	7.70	7.77	9.15	7.68	7.17	9.14

[a] The chemical shifts are expressed as τ values (p.p.m.) referred to tetramethylsilane used as internal reference. [b] The signal of this hydrogen is completely overlapped with the signal of the hydrogens of the methyl group. [c] The signal of the hydrogen at C-2 of this isomer is an unresolved multiplet.

the ethynyl triple bond give conical regions of shielding along the longitudinal axis at both ends of the ethynyl group, and deshielding elsewhere.[13] If the magnetic anisotropy of the ethynyl group exerts any effect on the hydrogen on C-2 through space it must be one of shielding when the group is axial. The shielding effect of the axial ethynyl group is therefore in the same direction as that of the equatorial hydroxyl group. The extent and direction of the shielding effect on the hydrogen at C-2 resulting from the magnetic anisotropy of an equatorial ethynyl group is less certain but the effect is probably small. All factors affecting the chemical shift of the hydrogen on C-2 are consistent with the observed chemical shifts and with the assigned configurations.

The larger downfield shift of the signal of the hydroxyl hydrogen when the hydroxyl group is equatorial, compared to the corresponding isomer where it is axial, is in agreement with similar observations for the *cis*- and *trans*-2-*o*-tolylcyclohexanol[3] and the three diastereoisomeric pairs of 2-(chlorophenyl)cyclohexanols.[4] The same phenomenon is observed for 1-ethynyl-4-*tert*-butylcyclohexanols (Table I). This could result from differences in degree of intermolecular hydrogen bonding.

The n.m.r. spectra of 1-ethynyl-2-*o*-tolylcyclohexanols (Fig. 1) show a significant downfield shift of the signal of one aromatic hydrogen for each isomer, the effect being larger for the isomer with the ethynyl group in axial orientation. This effect does not occur in any of the isomers with the methyl group *meta* or *para*. Furthermore, the phenomenon does not occur in either *cis*- or *trans*-2-*o*-tolylcyclohexanol.[3] The *ortho* methyl group in the isomeric 1-ethynyl-2-*o*-tolylcyclohexanols must cause the *ortho* hydrogen to be located in a region of long-range negative shielding and the ethynyl group must play a role in both isomers. Molecular models show that for both isomers the least hindered position of the aromatic ring is one where the two rings are essentially perpendicular to each other with the methyl group on top. Oscillation from this position is allowed, but clockwise rotation is hindered by repulsion of the methyl group and the equatorial substituents, especially the equatorial ethynyl group, and counterclockwise rotation is hindered by the repulsion of *ortho* hydrogen and the axial ethynyl group in the other isomer. In the favored conformation of the isomer with the ethynyl group axial the *ortho* hydrogen is located in close proximity to the ethynyl group about midway between the two *sp* carbon atoms, a region of negative shielding resulting from the magnetic anisotropy of the ethynyl group.[13] In the isomer with the ethynyl group equatorial the *ortho* hydrogen comes closer to the no. 1 carbon atom of the ethynyl group and in relationship to the ethynyl group it appears to fall more closely in the line of demarcation between regions of shielding and de-

(13) Ref. 9, pp. 17 and 112; ref. 7, p. 179.

shielding of the ethynyl group. The *ortho* hydrogen, however, is in very close proximity of the axial hydroxyl group and it seems likely that the downfield shift of the *ortho* hydrogen in this isomer results from a deshielding effect of the axial hydroxyl group, while the effect in the other isomer results from a deshielding of the *ortho* hydrogen by the axial ethynyl group. The long-range deshielding effect of the hydroxyl group is a recognized phenomenon.[14-16] This interpretation was tested by measuring the n.m.r. spectra of the hydrogenation product of the two ethynyl isomers and found to be correct. If the interpretation is correct the downfield shift of the *ortho* hydrogen should persist in 1-ethyl-*cis*-2-*o*-tolylcyclohexanol (ethyl group equatorial) and disappear in 1-ethyl-*trans*-2-*o*-tolylcyclohexanol (ethyl group *cis* to the tolyl group). Curves A and B of Fig. 1 show that this is exactly what takes place. Actually the paramagnetic shift of the *ortho* hydrogen is greater with the equatorial ethyl group than with the equatorial ethynyl group. The signal of the hydrogen on C-2 of 1-ethyl-*cis*-2-*o*-tolylcyclohexanol gives the typical quartet with *a,a* splitting of 11.2 c.p.s. and *a,e* splitting of 3.5 c.p.s. Indicating the chair conformation with the aromatic group in equatorial orientation as expected, while the signal of the C-2 hydrogen of 1-ethyl-*trans*-2-*o*-tolylcyclohexanol gives a broad unresolved multiplet. This could result from an equilibrium between the two possible chair conformations in this isomer where the tolyl and ethyl groups are *cis* to each other; but it could also possibly result from the difference in long-range shielding effects of the axial ethyl group compared to the axial ethynyl group on the axial hydrogen on C-3. This point will be clarified by the preparation of selectively deuterated compounds.

Experimental

The separation of the liquid mixtures of 1-ethynyl-2-tolylcyclohexanols[2] into their *cis* and *trans* components was accomplished with a Beckman GC-2 gas chromatograph using a 10 ft. × 5/8 in. column packed with 18% Dow Corning Silicone QF-1 on acid-washed Chromosorb W[17] at 160°.

1-Ethyl-*cis*-2-*o*-tolylcylohexanol and 1-Ethyl-*trans*-2-*o*-tolylcyclohexanol.—These compounds were obtained by catalytic hydrogenation of the corresponding 1-ethynyl-2-*o*-tolylcyclohexanols in ethyl acetate using 10% palladium on carbon under 20 pounds pressure. The calculated amount of hydrogen was picked up rapidly. The products were purified by gas chromatography at 160° using the same column used to separate the ethynyl compounds. The products were also obtained by reduction of the mixture of ethynyl compounds and subsequent separation of the isomers by gas chromatography with a 10-ft. column of 18% Carbowax 20M on acid-washed Chromosorb W at 196°.

Anal. Calcd. for $C_{15}H_{22}O$: C, 82.51; H, 10.16. Found for the *cis* isomer: C, 82.64; H, 10.21. Found for the *trans* isomer: C, 82.53; H, 10.29.

TABLE II

PHYSICAL CONSTANTS AND ANALYSES[a]

Compound	M.p., °C.[b]	Found, % C	Found, % H
1-Ethynyl-*cis*-2-*p*-tolylcyclohexanol	36–37	83.95	8.16
1-Ethynyl-*trans*-2-*p*-tolylcyclohexanol	65.5–66.5	83.95	8.73
1-Ethynyl-*cis*-2-*m*-tolylcyclohexanol	56–56.5	84.03	8.39
1-Ethynyl-*trans*-2-*m*-tolylcyclohexanol	[c]	84.06	8.23
1-Ethynyl-*trans*-2-*o*-tolylcyclohexanol	56–57	84.29	8.40
1-Ethynyl-*cis*-2-*o*-tolylcyclohexanol	81–82	83.91	8.50

[a] Calcd. for $C_{15}H_{18}O$: C, 84.07; H, 8.47. [b] Melting points were determined with a Kofler micro hot stage. [c] This compound was obtained as a viscous, colorless liquid.

1-Ethynyl-*trans*-4-*t*-butylcyclohexanol and 1-Ethynyl-*cis*-4-*t*-butylcyclohexanol.—These two isomers were obtained by the method of Hennion and O'Shea.[18] The configurations assigned by these authors on the basis of kinetics of saponification of the *p*-nitrobenzoate esters are in agreement with the observed chemicals shifts of the hydroxyl protons of these two isomers when compared to the relative chemical shifts of axial and equatorial hydroxyl protons of other cyclohexanols (Table I and ref. 3 and 4). Because of the variability in the chemical shifts of hydroxyl protons this observation does not constitute proof of conformation.

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(17) Wilkens Instrument and Research, Inc., Walnut Creek, Calif.
(18) G. F. Hennion and F. X. O'Shea, *J. Am. Chem. Soc.*, **80**, 614 (1958).

4-(*p*-Tolyl)-1-pentanol in Douglas Fir Pulping Products[1]

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An optically active alcohol has been isolated from the product of pulping Douglas fir *via* the kraft process. This has been identified by degradation and synthesis as 4S-4-(*p*-tolyl)-1-pentanol. It is suggested that this alcohol is formed during the pulping process from γ-curcumene, a terpene not previously identified in Douglas-fir extractives.

Among the organic products derived from the pulping of wood of the Douglas fir, *Pseudotsuga menziesii*, [Mirb. (Franco)] by the kraft process are some with a considerable biological activity. In particular the toxicity of the by-product toward a number of species of fish has been thoroughly established. Recent work on this campus[2] established that one or more of these toxic substances could be steam distilled. It occurred to us that some of the biologically active materials could be related chemically to the furocoumarin fish

(1) This project was supported by a research grant, no. WPOO79-5 from the Division of Water Supply and Pollution Control, Public Health Service.

(2) Robert A. McHugh, "Preliminary report on a study of the factors responsible for the toxicity of waste from a modern kraft pulp mill," Oregon State University, 1954.