Tumor Inhibitors. XLVIII.[1a] Taxodione and Taxodone, Two Novel Diterpenoid Quinone Methide Tumor Inhibitors from *Taxodium distichum*[1b]

S. MORRIS KUPCHAN,[2] AZIZ KARIM, AND CAROL MARCKS

Department of Pharmaceutical Chemistry, University of Wisconsin, Madison, Wisconsin 53706

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Evidence is presented for assignment of structure for two novel tumor-inhibitory diterpenoid quinone methides from *Taxodium distichum*, taxodione (**1**) and taxodone (**6**). The structures were deduced from studies of their infrared, ultraviolet, nmr, and mass spectra and confirmed by interrelation with a known diterpene. Both quinone methides were converted to 11,12-dihydroxyabieta-8,11,13-trien-6-one (**2**), which was methylated to 11,12-dimethoxyabieta-8,11,13-trien-6-one (**4**). Reduction of **4** with lithium aluminum hydride gave the 6β-alcohol **5**, which was dehydrated to 11,12-dimethoxyabieta-5,8,11,13-tetraene (**7**). Catalytic hydrogenation of **7** gave 11,12-dimethoxyabieta-8,11,13-triene (**8**), characterized by direct comparison with a sample prepared from sugiol (**9**). The third new compound isolated from *T. distichum*, taxoquinone, has been assigned the 7β-hydroxyroyleanone structure **13**. In addition, the isolation of the kn6wn diterpenes royleanone (**12**), sugiol (**9**), and Δ^5-dehydrosugiol (**15**) is described.

Taxodione and taxodone are novel tumor-inhibitory diterpenoid quinone methides from *Taxodium distichum* Rich (Taxodiaceae),[3] and their isolation and characterization have recently been reported in a preliminary communication.[4] It is the purpose of this paper to present in detail the fractionation of the active extract of *T. distichum* and the isolation and structural elucidation of the active constituents, taxodione and taxodone.[5] In addition, the isolation and characterization of the new diterpene, taxoquinone, and of the previously known diterpenes, royleanone, sugiol, and 5-dehydrosugiol, are described.[6]

Our investigation of the chemical constituents of *T. distichum* was undertaken as a part of our general search for tumor inhibitors of plant origin. An aqueous ethanol extract of the ground seeds showed significant activity *in vivo* against the Walker intramuscular carcinosarcoma 256 in rats and *in vitro* against cells derived from human carcinoma of the nasopharynx (KB). Partition of the concentrated aqueous ethanol extract between water and chloroform resulted in concentration of the cytotoxic principles in the chloroform phase. When the gold-colored residue from the chloroform layer was partitioned between 10% aqueous methanol and petroleum ether, the cytotoxicity was distributed evenly between both layers. This observation indicated that the cytotoxic principles were relatively nonpolar, and led to modification to the sequence in Chart I. Chromatography of fraction B gave six crystalline compounds (listed in order of decreasing R_f), two of which were readily identified as the known diterpenes royleanone[7] (**12**) and sugiol[9] (**9**). The structure of Δ^5-dehydrosugiol (**15**) was established by conversion to ferruginol (**16**) upon catalytic hydrogenation. Although Δ^5-dehydrosugiol has been described as a product of selenium dioxide dehydrogenation of sugiol,[10] the compound does not appear to have been isolated previously from natural sources. The three other crystalline compounds, taxodione (**1**),[11] taxodone (**6**),[11] and taxoquinone (**13**), appear to be new, and the sequel presents their structural elucidation in detail.

The molecular formula $C_{20}H_{26}O_3$ was assigned for taxodione (**1**) on the basis of elemental analysis and mass spectrometry (M^+ *m/e* 314). Addition of aqueous sodium hydroxide to a methanolic solution of taxodione gave a purple solution, which was decolorized by sodium dithionite. Treatment of a taxodione solution with titanium trichloride gave a red solution. These color reactions suggested the possible presence of a hydroxy quinonoid function.[12] The infrared spectrum of taxodione, with bands at 2.99 (enolic OH), 5.95 (quinonoid carbonyl), and 6.13 and 6.17 μ (doublet, hydrogen-bonded quinonoid carbonyl), supported the presence of a hydroxy-*p*-benzoquinone function.[13] However, the ultraviolet spectrum [λ_{max} 320 (ϵ 25,000), 332 (ϵ 26,000), and 400 mμ (ϵ 2000)] was more consistent with a quinone methide[14] functionality such as that in citrinin[15] and pulvilloric acid.[16] The nmr spectrum of taxodione in benzene-d_6 (see Table II) proved most informative. The two nonequivalent secondary methyl group signals at τ 8.96 and 9.03 (J = 7 Hz)

(1) (a) Part XLVII in the series: S. M. Kupchan, R. J. Hemingway, A. Karim, and D. Werner, *J. Org. Chem.*, **34**, 3908 (1969). (b) This investigation was supported by grants from the National Cancer Institute (CA-04500) and the American Cancer Society (T-275), and a contract with Chemotherapy, National Cancer Institute, National Institutes of Health (PH-43-64-551).

(2) Author to whom inquiries should be directed: Department of Chemistry, University of Virginia, Charlottesville, Va. 22901.

(3) Seeds were collected in Maryland in Oct 1966. The authors acknowledge with thanks the receipt of the dried plant material from Dr. Robert E. Perdue, Jr., U. S. Department of Agriculture (USDA), Beltsville, Md., in accordance with the program developed with the USDA by the Cancer Chemotherapy National Service Center (CCNSC).

(4) S. M. Kupchan, A. Karim, and C. Marcks, *J. Amer. Chem. Soc.*, **90**, 5923 (1968).

(5) Cytotoxicity [activity against human carcinoma of the nasopharynx carried in cell culture (KB)] and *in vivo* inhibitor activity (against the WM carcinosarcoma in rats) were assayed under the auspices of the CCNSC, by the procedures described in *Cancer Chemotherapy Rept.*, **25**, 1 (1962).

(6) For a recent review on constituents of the Taxodiaceae, see *Progr. Chem. Org. Nat. Prod.*, **24**, 207 (1966).

(7) O. E. Edwards, G. Feniak, and M. Los, *Can. J. Chem.*, **40**, 1540 (1962). We thank Dr. O. E. Edwards cordially for authentic samples of royleanone and hydroxyroyleanone ("horminone"[8]).

(8) M. Janot and P. Potier, *Ann. Pharm. Fr.*, **22**, 387 (1964).

(9) T. Sengupta, S. N. Choudhuri, and H. N. Khastgir, *Tetrahedron*, **10**, 45 (1960).

(10) J. B. Bredenberg, *Acta Chem. Scand.*, **11**, 932 (1957).

(11) Taxodione and taxodone showed significant inhibitory activity against the Walker intramuscular carcinosarcoma 256 (WM) in rats, at 25–50 and 25 mg/kg,[5] respectively (see Table I).

(12) F. Weygand and E. Csendes, *Chem. Ber.*, **85**, 45 (1952).

(13) B. W. Bycroft and J. C. Roberts, *J. Org. Chem.*, **28**, 1429 (1963).

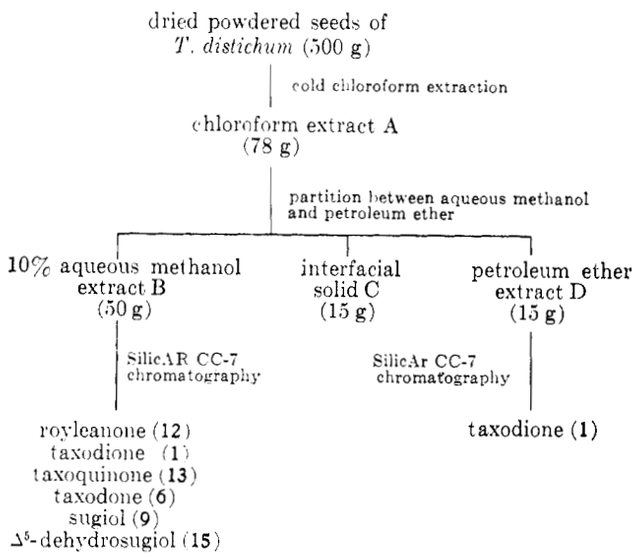
(14) For a recent review on naturally occurring quinone methides, see A. B. Turner, *Progr. Chem. Org. Nat. Prod.*, **24**, 288 (1966).

(15) J. P. Brown, A. Robertson, W. B. Whalley, and N. J. Cartwright, *J. Chem. Soc.*, 867 (1949).

(16) J. F. W. McOmie, A. B. Turner, and M. S. Tute, *ibid.*, 1608 (1966).

CHART I

FRACTIONATION OF THE CYTOTOXIC EXTRACT FROM *Taxodium distichum*



and the one-proton septet[17] centered at τ 7.05 (J = 7 Hz) in the 100-MHz spectrum were indicative of an isopropyl group,[18] whose presence in taxodione was further supported by a prominent peak at m/e 271 (M − 43) (due to loss of isopropyl group[19]) in its mass spectrum. Furthermore, irradiation at τ 7.05 collapsed the four peaks due to the isopropyl group into a broad signal.[20] The three singlets (3 H) at τ 8.62, 8.75, and 8.82 indicated three additional tertiary methyl groups. The one-proton singlet at τ 7.68 was assigned to a tertiary proton α to a carbonyl group. In the low-field region, three one-proton singlets appeared. The signal (exchangeable with D_2O) at τ 2.30 was assigned to the enolic hydroxyl group. The signals at τ 3.58 and 4.13 were attributed to protons on the quinone methide system; the breadth of the former signal could be attributed to allylic coupling.[21] The integration of the signals in the methylene region (τ 8.17–8.60) indicated the presence of five methylene protons and, in all, signals for 26 protons were found. The molecular formula ($C_{20}H_{26}O_3$, eight double-bond equivalents), the nmr data, and the cooccurrence with royleanone, sugiol, and 5-dehydrosugiol led to consideration of a tricyclic diterpene skeleton for taxodione.

In accord with the hypothetical quinone methide structure, reductive acetylation of taxodione (**1**, Scheme I) furnished a colorless diacetate ketone [**3**, $\lambda_{max}^{CHCl_3}$ 5.61 ($OCOCH_3$) and 5.79 μ (CO)], while catalytic hydrogenation gave a colorless dihydro derivative (**2**). The presence of two phenolic hydroxyl groups was indicated by two D_2O-exchangeable signals at τ 3.97 and 4.55 in the nmr spectrum. Furthermore, compound **2** was found to give a positive Gibbs reaction and to couple with diazotized *p*-nitroaniline to give an azo dye, indicative of the presence of an aromatic

(17) C. H. Brieskorn, A. Fuchs, J. B. Bredenberg, J. D. McChesney, and E. Wenkert, *J. Org. Chem.*, **29**, 2293 (1964).

(18) D. Karanatsios, J. S. Scarpa, and C. H. Eugster, *Helv. Chim. Acta*, **49**, 1151 (1966).

(19) W. L. Parker and F. Johnson, *J. Amer. Chem. Soc.*, **90**, 4716 (1968).

(20) We thank Miss Martha Petrie for the 100-MHz nmr decoupling studies.

(21) R. B. Bates, S. K. Paknikar, and V. P. Thalacker, *Chem. Ind.* (London), 1793 (1965).

TABLE I

BIOLOGICAL ACTIVITY

A. Cytotoxicity against Eagle's KB Strain of Human Carcinoma of the Nasopharynx

Fraction	ED_{50}, μg/ml
A	18.0
B	7.0
C	20.0
D	9.0
1	3.0
6	1.8
9	>100.0
12	80.0
13	73.0
15	>100.0

B. Tumor-Inhibitory Activity against the Walker 256 Intramuscular Carcinosarcoma in Rats[a]

Compd	Dose, mg/kg	Survivors	Animal wt change difference, g T − C	Tumor wt, mg, T/C	T/C × 100
1	50	3/4	−26	600/7600	7
	40	3/4	−13	1100/7600	14
	25	4/4	−13	2800/7600	36
	20	4/4	−7	4000/7600	52
6	50	1/4	...	...	Toxic
	25	3/4	−13	700/7600	9
	14	4/4	−5	3500/7600	46
	7	4/4	+3	8400/7600	110

[a] T, treated animals; C, control animals.

proton *para* to a phenolic hydroxyl group. This aromatic proton could be correlated with the signal at τ 3.60. Passage of a benzene solution of the dihydro derivative through a silica gel column packed in benzene resulted in quantitative reversion to taxodione. These results led to the tentative assignment of the structures **1** and **2** for taxodione and the dihydro derivative, respectively. Thus, the signals at τ 3.58, 4.13, and 7.68 could be assigned to protons at C-14, C-7, and C-5, respectively.

The spectral data of the second active compound, taxodone, showed a close similarity to those of taxodione. Elemental analysis and mass spectrometry (M^+ m/e 316) established the molecular formula as $C_{20}H_{28}O_3$. The ultraviolet absorption could again be attributed to a quinone methide chromophore. The main difference between the two compounds became apparent from comparisons of their infrared and nmr spectra. The infrared spectrum of taxodone (**6**) in carbon tetrachloride indicated the presence of two hydroxyl groups, one of which was *intramolecularly* hydrogen bonded (3.00 μ, enolic OH, no change on dilution) and the other *intermolecularly* hydrogen bonded [2.77 (sharp, nonbonded) and 2.86 μ (broad, bonded)]. The quinonoid carbonyl, hydrogen bonded to the hydroxyl group at C-11 (doublet at 6.14 and 6.18 μ), was still present, but the second quinonoid carbonyl absorption at 5.95 μ was absent. Instead, there was a strong diene absorption at 6.34 μ. The nmr spectrum established the presence of the C-15 H, the C-11 enolic hydroxyl group, the C-14 H, and the C-7 H. The one-proton singlet corresponding to the C-5 H at τ 7.68 in the nmr spectrum of taxodione was absent, but there was a one-proton broad signal at τ 5.30 ($W_{1/2}$ = 23 Hz), which was assigned to the C-6

TABLE II[a]
NUCLEAR MAGNETIC RESONANCE DATA FOR TAXODIONE, TAXODONE, AND RELATED COMPOUNDS

Compd	Solvent	C-5	C-6	C-7	C-10	C-14	C-15	C-11 and C-12 substituents	C-CH_3
1	Benzene-d_6	7.68 1 H, s		4.13 1 H, s		3.58 1 H, br s	7.05 1 H, septet	2.30[b] (1 H, s, C-11, OH)	8.62 (3 H, s), 8.75 (3 H, s), 8.82 (3 H, s), 8.96 (3 H, d, J = 7 Hz), 9.03 (3 H, d, J = 7 Hz)
2	$CDCl_3$	7.35 1 H, s		6.42, 6.55 2 H	8.65 3 H, s	3.60 1 H, br s	6.85 1 H, septet	3.97[b] and 4.55[b] (1 H, br s, C-11 and C-12 OH)	8.72 (6 H), 8.83 (3 H), 8.98 (3 H)
3	$CDCl_3$	7.40 1 H, s		6.40 2 H, m	8.67 3 H, s	3.10 1 H, s	7.08 1 H, s	7.69 (6 H, s, C-11 and C-12 $COCH_3$)	8.78 (3 H, s), 8.82 (3 H, d, J = 7 Hz), 8.84 (3 H, d, J = 7 Hz), 8.96 (3 H, s)
4	$CDCl_3$	7.41 1 H, s		6.42, 6.54 2 H	8.64 3 H, s	3.38 1 H, br s	6.85 1 H, septet	6.13 and 6.21 (3 H, s, C-11 and C-12 OCH_3)	8.72 (6 H), 8.89 (3 H), 8.99 (3 H)
5	$CDCl_3$		5.35 1 H, m $W_{1/2}$ = 8	7.00 2 H, m	8.31 3 H, s	3.35 1 H, br s	7.00 1 H, septet	6.14 and 6.23 (3 H, s, C-11 and C-12 OCH_3)	8.72 (6 H), 8.88 (3 H), 8.99 (3 H)
6	$CDCl_3$		5.30 1 H, m $W_{1/2}$ = 23	3.45 1 H, d J = 2.5 Hz		3.19 1 H, br s	7.00 1 H, septet	2.51[b] (1 H, s, C-11 OH)	8.78 (9 H), 8.83 (3 H), 8.90 (3 H)
7	$CDCl_3$		4.13 1 H, t sp = 4[c]	6.63, 6.72 2 H	8.53 3 H, s	3.33 1 H, br s	6.88 1 H, septet	6.12 and 6.22 (3 H, s, C-11 and C-12 OCH_3)	8.76 (6 H), 8.82 (3 H), 8.92 (3 H)
8	$CDCl_3$			7.00 2 H, m	8.68 3 H, s	3.33 1 H, br s	7.00 1 H, septet	6.13 and 6.22 (3 H, s, C-11 and C-12 OCH_3)	8.78 (3 H, d, J = 7 Hz), 8.81 (3 H, d, J = 7 Hz), 9.06 (6 H)
11	Acetone-d_6	7.15 1 H, s			8.70 3 H, s	2.33 1 H, s		2.0[b] (1 H, s, C-11 OH)	8.73 (3 H), 8.79 (3 H), 8.88 (6 H)
13	$CDCl_3$			5.20 1 H, m $W_{1/2}$ = 20	8.65 3 H, s		6.90 1 H, septet		8.73 (3 H), 8.85 (3 H), 9.05 (6 H)
14	$CDCl_3$			5.23 1 H, m W = 8	8.68 3 H, s		6.90 1 H, septet		8.75 (3 H), 8.82 (3 H), 9.00 (3 H), 9.08 (3 H)
15	Pyridine-d_5		3.32 1 H, s			1.55 1 H, s	6.33 1 H, septet	2.70 (1 H, s, C-11 H), 3.50[b] (1 H, C-12 OH)	8.52 (6 H), 8.65 (3 H), 8.78 (3 H), 8.82 (3 H)

[a] Values are given in τ units relative to tetramethylsilane as internal standard. Multiplicity of signals is designated as follows: s, singlet; br s, broad singlet; d, doublet; m, multiplet. [b] Signals exchangeable with D_2O. [c] *sp*, observed splitting in hertz.

β-axial methine proton.[22] Irradiation at τ 5.31 resulted in collapse of a doublet at τ 3.45 (C-7 H), confirming that this olefinic proton was coupled to the C-6 methine proton. The close relationship of taxodone (**6**) to taxodione (**1**) was confirmed by treatment of taxodone with methanolic hydrochloric acid, whereupon a high yield of **2** was obtained.

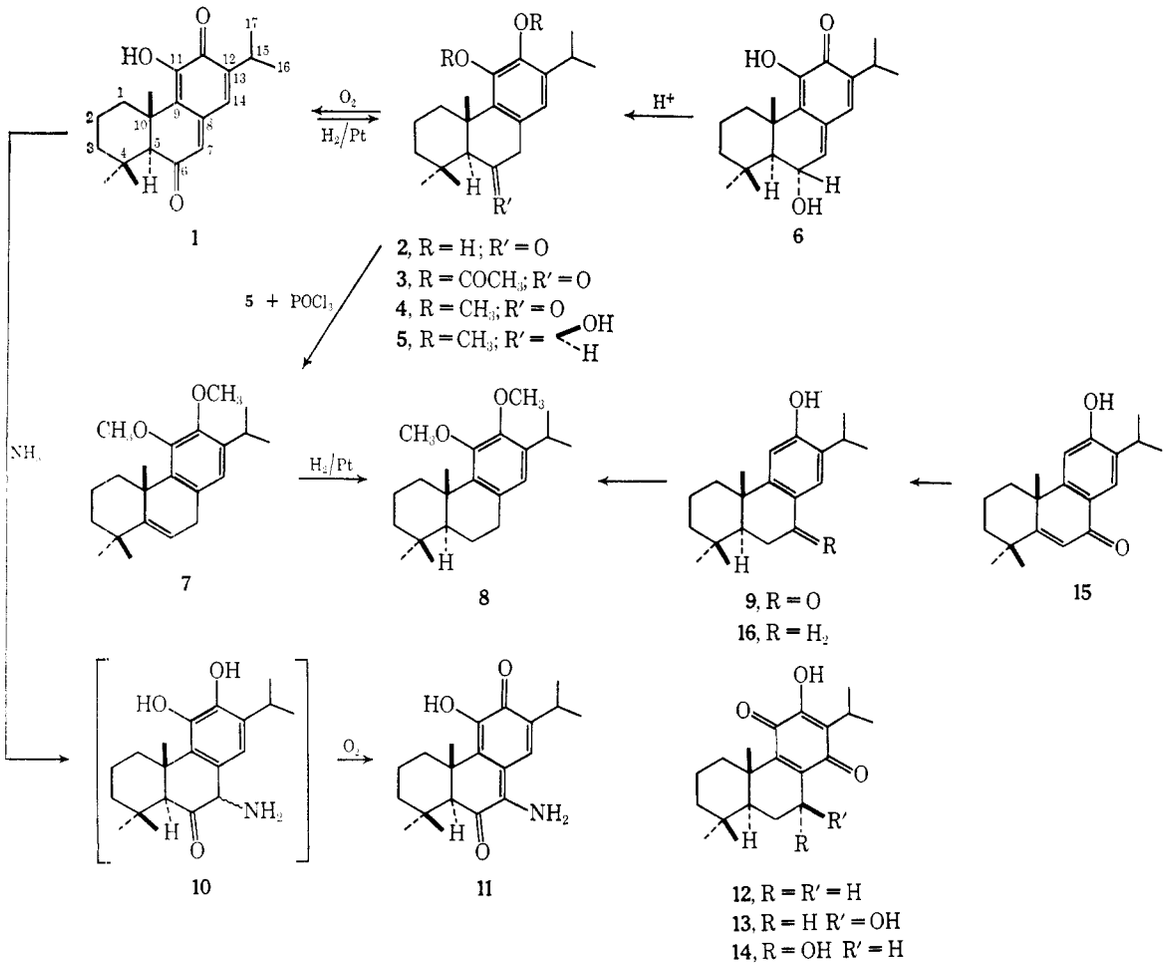
The carbon skeleton and the aromatic substitution pattern in **2** were completely confirmed by conversion to 11,12-dimethoxyabieta-8,11,13-triene (**8**) by the reaction sequence which follows. Methylation of **2** with dimethyl sulfate–potassium carbonate–acetone furnished 11,12-dimethoxyabieta-8,11,13-trien-6-one (**4**). The best yield of **4** was obtained when the methylation was carried out with rigorous exclusion of air. Attempted Clemmensen reduction of **4** resulted in a quantitative recovery of the starting material, and attempted Wolff–Kishner reduction yielded an intractable mixture. The resistance of ketone **4** toward Clemmensen reduction further supported its placement at C-6. Reduction of the ketone **4** with lithium aluminum hydride furnished an alcohol **5**. The configuration of the C-6 hydroxy group in **5** was assigned as β axial from its nmr spectrum, which indicated a methine signal ($W_{1/2}$ = 8 Hz) for the α-equatorial C-6 methine proton.[21] Furthermore, the signal due to the C-10 methyl group appeared downfield[23] by τ 0.33 relative to the corresponding signal for **4**. The rest of the C-methyl signals remained within 3 Hz of their positions in the spectrum of **4**. Assignment of the C-10 methyl group in 11-methoxyferruginol derivatives (and royleanones) has been based largely on the work of Wenkert and coworkers,[17] who have shown that the chemical shifts of the protons of the C-10 substituents in these compounds are *ca.* τ 0.3–0.4 downfield from the corresponding hydrogens in a saturated environment. Hydride reduction of a hindered 6 ketone to the β-axial alcohol has been reported earlier.[24] The alcohol **5** could be readily dehydrated with phosphorus oxychloride in pyridine to the olefin **7**, whose nmr spectrum showed a one-proton triplet with an observed splitting of 4 Hz at τ 4.13. These data established the presence of a $\Delta^{5,6}$ double bond in the olefin **7**. Catalytic hydrogenation of **7** gave an oil, which could not be induced to crystallize. The oil appeared to be homogeneous by tlc, but gas–liquid partition chromatography (glpc) indicated that a 60:40 mixture of two compounds was in hand. The mixture was separated by preparative glpc. The compound with a longer retention time was crystallized from methanol to give a product which was characterized by direct comparison with 11,12-dimethoxyabieta-8,11,13-triene (**8**) prepared from sugiol (**9**) by the procedure of Wenkert and coworkers.[17] Since the reaction sequence did not rigorously establish the stereochemistry at C-5, an attempt was made to remove the hydroxyl group in the alcohol **5** by reduction of its tosylate with lithium aluminum hydride. However,

(22) It is well established that an axial methine proton (equatorial alcohol) usually resonates at a higher field and shows a larger half-width ($W_{1/2}$ = 20–22 Hz) than an equatorial proton ($W_{1/2}$ = 7–10 Hz); see, *e.g.*, N. S. Bhacca and D. H. Williams, "Application of NMR Spectroscopy in Organic Chemistry," Holden-Day, Inc., San Francisco, Calif., 1964, pp 77–83.

(23) R. L. Clarke, S. J. Daum, P. E. Shaw, and R. K. Kulling, *J. Amer. Chem. Soc.*, **88**, 5865 (1966).

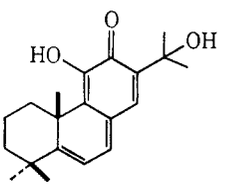
(24) J. S. E. Holker in "Terpenoids in Plants," J. B. Pridham, Ed., Academic Press, London, 1967, pp 34–35.

SCHEME I



the tosylate of the alcohol **5** could not be obtained, even under vigorous conditions. Attempted preparation of the mesylate of alcohol **5** resulted in the formation of olefin **7**. The assignment of α-axial configuration to the C-5 proton in taxodione (**1**), taxodone (**6**), and related compounds is supported by the facile dehydration of **5** to **7** and the failure of ketone **4** to epimerize under acid equilibrating conditions known to effect isomerization of 3β-acetoxy-4,4-dimethyl-5β-androstan-6-one.[25] The attempted equilibration of **4** was conducted in an atmosphere of hydrogen in order to prevent any aerial oxidation at the activated benzylic position.

Turner has pointed out that a common feature of naturally occurring quinone methides is the isolation of the quinone methide chromophore from labile hydrogen atoms, which prevents their tautomeric rearrangement to phenols.[14] In this respect, taxodone (**6**) is the first example of a naturally occurring quinone methide in which there is a labile hydrogen atom adjacent to the quinone methide chromophore. However, it is noteworthy that taxodone is very sensitive to acid treatment; under very mild acidic conditions, dienone–phenol rearrangement occurs to give phenol **2**. Another noteworthy feature of taxodone is the α (equatorial) configuration of the C-6 hydroxyl group. Presumably, a β (axial) hydroxy derivative would readily undergo facile *trans*-diaxial elimination of the hydroxyl group to give a quinone methide chromophore such as that found in fuerstione (**17**).[18]



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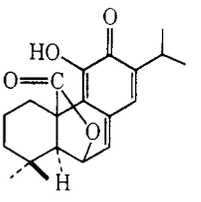
It has been shown by Wenkert, *et al.*,[26] that rosmaricine (**19**) is an artifact obtained by reaction of ammonia with a postulated quinone methide intermediate (**18**), derived from carnosic acid. In view



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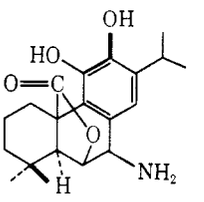

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of the close similarity between the reactive quinone methide intermediate **18** and taxodione (**1**), treatment of **1** with ammonia was deemed of interest. Under very mild conditions, addition of ammonia to taxodione

(25) T. G. Halsall, E. R. H. Jones, E. L. Tan, and G. R. Chaudhry, *J. Chem. Soc.*, 1374 (1966).

(26) E. Wenkert, A. Fuchs, and J. D. McChesney, *J. Org. Chem.*, 2931 (1965).

readily gave a purple-colored crystalline product (λ_{max} 265, 295, and 485 mμ) with elemental analysis and mass spectrum (M^+ m/e 329) indicative of a $C_{20}H_{27}O_3N$ empirical formula. The nmr spectrum indicated the presence of signals corresponding to C-11 enolic hydroxyl and C-14 H, but the signal due to the C-7 H in the precursor was absent. On the basis of the spectral data, structure **11** could be assigned to the product. The reaction can be visualized as having proceeded *via* the Michael adduct **10**, which would readily undergo aerial oxidation to give aminotaxodione (**11**).

The elemental analysis and mass spectrum (M^+ m/e 332) of taxoquinone (**13**) established the molecular formula $C_{20}H_{28}O_4$. The ultraviolet and infrared spectra of taxoquinone were similar to those of 7-hydroxyroyleanone (horminone),[7,8] suggesting the presence of a hydroxybenzoquinone unit and a secondary hydroxy group. Catalytic hydrogenation of taxoquinone (hydrogen consumption: 2 mol equiv), followed by silica gel chromatography of the product, gave royleanone (**12**).[7] These results indicated that taxoquinone differs from horminone only in the configuration of the C-7 benzylic hydroxyl group. The facile hydrogenolysis of this hydroxyl group has also been reported in horminone.[7] The configuration of this hydroxyl group in horminone has not yet been established. Edwards and coworkers[7] have pointed out that the nmr and infrared spectral data cannot be used in assigning configuration at C-7 because of the quasiaxial and quasiequatorial configuration of the C-7 substituents and the proximity of the quinone carbonyl. We have compared the nmr spectra of taxoquinone (**13**) and horminone (**14**) and have found that the C-7 methine proton signal in the former appears as a one-proton multiplet centered at τ 5.20 ($W_{1/2}$ = 20 Hz), whereas the C-7 methine proton signal in the latter is a one-proton broad signal at τ 5.23 ($W_{1/2}$ = 8 Hz). These results support assignment of β-equatorial[22] configuration to the C-7 hydroxyl group in taxoquinone and α-axial configuration to the C-7 hydroxyl in horminone.

The observed growth-inhibitory activity of taxodione (**1**) and taxodone (**6**) confirms and extends an earlier report of antitumor activity of quinone methides.[27] Investigations are in progress to determine the significance of the reactive quinone methide and of other structural features in relation to the tumor-inhibitory activity of taxodione and taxodone.

Experimental Section

Melting points were determined on a Fisher-Johns melting point apparatus and have been corrected. Ultraviolet absorption spectra were determined in methanol on a Beckman DK-2A ratio recording spectrometer. Infrared spectra were determined on Beckman IR-5A and IR-9 recording spectrophotometers. Optical rotations were recorded on a Zeiss–Winkel polarimeter. Nuclear magnetic resonance spectra were determined on a Varian Associates A-60A recording spectrometer at 60 MHz. The double resonance studies were performed on a Varian Associates HA-100 recording spectrometer at 100 MHz. Chemical shifts have been recorded in τ values. Thin layer chromatography (tlc) was run on silica gel G and developed with chloroform or 10% ethyl acetate in benzene. The spots were detected by spraying with $Ce(SO_4)_2$–H_2SO_4 solution followed by heating until colored spots appeared. Gas–liquid partition chromatography (glpc) was carried out on an F & M laboratory chromatograph Model 700, with flame ionization detector, employing a coiled stainless steel column, 2 m × 6 mm o.d., packed with 10% SE-30 silicone gum rubber on Chromosorb (66–80 mesh): column temperature, 240° isothermal; injection port temperature, 310°. Inlet pressure of carrier gas (N_2) was 2.76 × 10^6 dynes/cm^2, with a flow rate of 60 ml/min. Microanalyses were performed by Spang Microanalytical Laboratory, Ann Arbor, Mich. Petroleum ether refers to the fraction with bp 60–68°. Evaporations were carried out at reduced pressure below 40°.

Extraction and Preliminary Fractionation.—The dried ground seeds (500 g) were soaked in chloroform (3 l.) and stirred at room temperature for 28 hr. The suspension was filtered and the filtrate was evaporated to yield a golden brown, syrupy oil (A, 75 g). Fresh chloroform (2 l.) was added to the residue and extraction was continued for 24 hr. The second chloroform extract was evaporated to yield an additional golden oil (3 g). The combined chloroform extract (A) was partitioned between 10% aqueous methanol (2 l.) and four 500-ml portions of petroleum ether. Evaporation of the 10% aqueous methanol layer yielded a golden brown foam (B, 50 g). The combined petroleum ether extract was washed with water, dried (Na_2SO_4), and evaporated to yield a golden brown oil (D, 15 g). The interfacial solid was separated to give a brown semisolid material (C).

Fraction B was further fractionated by adsorption chromatography on silicAR CC-7 (Mallinckrodt, 200-325 mesh, 2 kg). Fraction B (50 g) was dissolved in benzene (200 ml) and applied to the column, which was eluted with benzene (20 l.). Fractions were collected and analyzed by tlc. The characteristic colors obtained with $Ce(SO_4)_2$–H_2SO_4 spray are listed in Table III.

TABLE III

Fraction	Wt, g	Color produced with $Ce(SO_4)_2$–H_2SO_4	Main component	Cytotoxicity ED_{50}, μg/ml
I	0.4	Gray	Royleanone	80
II	6.0	Brown	...	>100
III	2.2	Blue	Taxodione	8
IV	3.2	Gray	Taxoquinone	50
V	7.0	Green	Taxodone	6
VI	5.0	Yellow	Sugiol	80
VII	3.0	Light brown	Δ^5-Dehydrosugiol	80
IX	7.0	...	...	13
X	16.0	...	...	>100

Royleanone and taxoquinone gave a violet color before spraying. The benzene eluates were combined into nine main fractions from their tlc analysis. The cytotoxicity and weights of the residues are given in Table III. The column was finally eluted with methanol (2 l.) to give fraction X (16 g).

Isolation of Royleanone (12).—Fraction I (0.4 g) was rechromatographed on a silicAR CC-7 column (50 g) packed in petroleum ether. Elution with benzene (100 ml) gave a crystalline fraction, which was recrystallized from methanol to give pale orange needles (60 mg): mp 179–181°; $[\alpha]^{28}D$ +134° (c 1.00, $CHCl_3$). The melting point was not depressed by admixture with authentic royleanone,[7] and the infrared spectral ($CHCl_3$) and tlc behavior of the respective samples were identical.

Isolation of Taxodione (1).—Fraction III (2.2 g) was rechromatographed on a silicAR CC-7 column (100 g) packed in benzene. Elution with benzene (500 ml) gave a crystalline fraction (1.6 g) which was recrystallized from methanol to yield large golden plates of taxodione (1, 1.0 g): mp 115–116°; $[\alpha]^{28}D$ +56° (c 1.00, $CHCl_3$); uv λ_{max}^{MeOH} 320 (ϵ 25,000), 332 (ϵ 26,000), and 400 mμ (ϵ 2000); ir $\lambda_{max}^{CCl_4}$ 2.99, 5.95, 6.07, 6.13, 6.17, 7.01, 7.35, 7.99, 8.70, 9.43, and 10.99 μ; mass spectrum m/e 314 (M^+), 299, 286, 245, 232, and 231.

Anal. Calcd for $C_{20}H_{26}O_3$: C, 76.40; H, 8.34. Found: C, 76.18; H, 8.33.

Isolation of Taxodione from Fraction D.—Fraction D (15 g) was chromatographed on a silicAR CC-7 column (500 g) packed in petroleum ether. Elution with benzene (1 l.) gave two main crystalline fractions. Recrystallization of the first compound from methanol gave pale yellow plates (600 mg), mp 74–75°. This compound was not investigated further. Recrystallization of the second fraction from methanol gave taxodione (**1**), as golden plates (700 mg), mp 115–116°.

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Isolation of Taxoquinone (13).—Fraction IV (3.2 g) was rechromatographed on a silicAR CC-7 column (200 g) packed in benzene. Elution with 5% ethyl acetate in benzene (500 ml) gave a crystalline fraction (700 mg), which was recrystallized from ether to yield orange needles (500 mg): mp 212–214°; $[\alpha]^{28}D$ +340° (*c* 1.30, $CHCl_3$); uv λ_{max}^{MeOH} 276 (ε 12,000) and 408 mμ (ε 800); ir $\lambda_{max}^{CHCl_3}$ 2.81, 2.95, 5.95, 6.04, 6.14, 6.25, 7.14, 7.24, 7.69, 7.93, 8.69, and 9.35 μ; mass spectrum *m/e* 332 (M^+), 317, 314, 299, 289, 271, 261, and 195.

Anal. Calcd for $C_{20}H_{28}O_4$: C, 72.26; H, 8.49. Found: C, 72.20; H, 8.28.

Isolation of Taxodone (6).—Fraction V (7.0 g) was rechromatographed on a silicAR CC-7 column (500 g) packed in benzene. Elution with 5% ethyl acetate in benzene (1 l.) gave a crystalline fraction (4 g), which was recrystallized from petroleum ether–ether to yield yellow plates (3 g): mp 164–165°; $[\alpha]^{27}D$ +50° (*c* 2.50, $CHCl_3$); uv λ_{max}^{MeOH} 316 mμ (ε 20,000) (addition of 1 drop of dilute hydrochloric acid led to disappearance of this peak); ir $\lambda_{max}^{CCl_4}$ 2.77, 2.86, 3.00, 6.14, 6.18, 6.34, 6.82, 6.96, 7.31, 7.93, 9.48, 10.20, and 10.96 μ; mass spectrum *m/e* 316 (M^+), 314, 301, 273, 231, and 217.

Anal. Calcd for $C_{20}H_{28}O_3$: C, 75.91; H, 8.92. Found: C, 76.37; H, 9.08.

Isolation of Sugiol (9) and Δ⁵-Dehydrosugiol (15).—Fractions VI and VII were combined to give a crystalline residue (8 g), which was chromatographed on silicAR CC-7 column (500 g) packed in benzene. Elution with 5% ethyl acetate in benzene (1 l.) gave two crystalline fractions. Crystallization of the first fraction from aqueous methanol gave colorless needles (800 mg) of sugiol (9): mp 292–294°; $[\alpha]^{28}D$ +26° (*c* 1.00, EtOH); uv λ_{max}^{EtOH} 232 (ε 15,500) and 284 mμ (ε 13,200); $\lambda_{max}^{0.1\ N\ NaOH,\ EtOH}$ 251 (ε 3400) and 346 mμ (ε 26,000); ir λ_{max}^{KBr} 3.19, 6.06, 6.23, 6.29, 6.35, 7.59, 7.84, 9.30, and 11.43 μ [lit.[9] mp 292–294°; $[\alpha]D$ +26° (EtOH); uv λ_{max}^{EtOH} 232 (ε 15,500) and 284 mμ (ε 13,200); $\lambda_{max}^{0.1\ N\ NaOH,\ EtOH}$ 251 (ε 3400) and 346 mμ (ε 13,200); ir λ_{max}^{KBr} 3.2 and 6.05 μ]. Crystallization of the second fraction from acetone–petroleum ether gave colorless plates (500 mg) of Δ⁵-dehydrosugiol (15): mp 284–286°; $[\alpha]^{28}D$ +13° (*c* 1.00, EtOH); uv λ_{max}^{EtOH} 246 (ε 22,000) and 316 mμ (ε 13,000); ir λ_{max}^{KBr} 6.10, 6.19, 6.31, 6.39, 6.65, 6.85, 7.64, 11.27, and 11.55 μ [lit.[10] mp 288–290°; uv λ_{max}^{EtOH} 246 (ε 20,000) and 316 mμ (ε 15,000); ir λ_{max}^{KBr} 6.13, 6.21, 6.35, 6.43, 6.67, 6.85, 11.27, and 11.55 μ].

Catalytic Hydrogenation of Δ⁵-Dehydrosugiol (15).—A suspension of Δ⁵-dehydrosugiol (15, 100 mg) in methanol (30 ml) and perchloric acid (2 drops, 70%) was hydrogenated over platinum oxide (10 mg) at atmospheric pressure. The reduction was completed within 2 hr, after which the reaction mixture was worked up in the normal way to yield an oil (70 mg). The product was characterized as ferruginol (16) by tlc, infrared spectral, and glpc (trimethylsilyl derivative) comparison with a sample of ferruginol obtained by catalytic hydrogenation of sugiol (9) under the same conditions.

11,12-Dihydroxyabieta-8,11,13-trien-6-one (2). A. From Taxodione (1).—A solution of taxodione (100 mg) in methanol (20 ml) was hydrogenated at room temperature and atmospheric pressure over platinum oxide (10 mg) catalyst. After the consumption of hydrogen ceased (1 mol equiv absorbed in 30 min), the catalyst was removed by filtration and the filtrate was evaporated under nitrogen to yield a colorless crystalline residue (90 mg). Recrystallization from acetone–petroleum ether gave colorless plates (60 mg) of **2**: mp 176–177° (yellow on melting); ir λ_{max}^{KBr} 2.77, 2.84, 5.81, 6.14, 6.35, 6.67, 6.81, 6.92, 7.59, 7.75, 9.48, 9.71, 10.10, 10.31, 11.11, 11.37, 11.63, and 11.83 μ; mass spectrum *m/e* 316 (M^+), 314, 301, 273, and 231.

When the thin layer chromatogram was sprayed with methanolic KOH followed by Gibbs reagent, a deep brown spot was obtained. With diazotized *p*-nitroaniline, a red spot was obtained.

B. From Taxodone (6).—A solution of taxodone (50 mg) in methanol (20 ml) containing 2 drops of concentrated hydrochloric acid was warmed on the water bath for 15 min. Removal of the solvent under reduced pressure gave a crystalline residue (50 mg), which was recrystallized from acetone–petroleum ether to yield colorless plates, mp 176–177° (yellow on melting). The compound was identified as **2** by comparison of the respective infrared and mass spectra, melting point, mixture melting point, and tlc behavior.

Conversion of 2 to Taxodione (1).—A solution of **2** (25 mg) in benzene (25 ml) was adsorbed on a silica gel column (5 g) packed in benzene. The benzene solution turned deep brown upon coming into contact with silica gel. After 24 hr, elution with benzene (100 ml) gave a golden crystalline product, mp 115–116°, $[\alpha]^{28}D$ +56° (*c* 1.00, $CHCl_3$), whose identity with taxodione was confirmed by comparison of infrared and mass spectra, melting point, mixture melting point, and tlc behavior.

11,12-Diacetoxyabieta-8,11,13-trien-6-one (3).—A mixture of taxodione (1, 100 mg), anhydrous sodium acetate (20 mg), and zinc powder (100 mg) was suspended in acetic anhydride (2 ml) and heated on a water bath for 30 min, when the solution became colorless. The zinc was filtered off and the filtrate was worked up in the normal way to yield a colorless foam (100 mg). The foam was dissolved in chloroform (3 ml) and placed on a silica gel column (25 g) packed in chloroform. Elution with chloroform (50 ml) gave a colorless homogeneous (tlc) foam of **3**: ir $\lambda_{max}^{CHCl_3}$ 5.61, 5.79, 8.23, and 8.40 μ.

11,12-Dimethoxyabieta-8,11,13-trien-6-one (4).—To a solution of **2** (100 mg) in acetone (20 ml, distilled over anhydrous potassium carbonate), anhydrous potassium carbonate (5 g), and dimethyl sulfate (0.5 ml) were added and the reaction mixture was refluxed with continuous stirring for 24 hr. The solution was filtered and the filtrate was evaporated. Thin layer chromatography of the residue indicated two main products. The upper spot stained gray and the lower spot stained red with $Ce(SO_4)_2$–H_2SO_4 spray. The reaction product (100 mg) was dissolved in benzene (10 ml) and placed on a basic alumina column (50 g, Woelm activity I) packed in benzene. Elution with benzene gave two crystalline fractions. The compound of higher R_f was crystallized from methanol to give **4** (30 mg) as plates: mp 116–117°; $[\alpha]^{28}D$ +100° (*c* 1.00, $CHCl_3$); ir λ_{max}^{CHCl} 5.80, 6.23, 6.39, 6.80, 6.90, 7.11, 7.34, 7.61, 9.36, and 9.76 μ; mass spectrum *m/e* 344 (M^+), 329, 311, 301, and 259.

Anal. Calcd for $C_{22}H_{32}O_3$: C, 76.70; H, 9.36. Found: C, 77.12; H, 9.58.

The second crystalline fraction was crystallized from methanol to yield large plates (30 mg): mp 218–220°; ir $\lambda_{max}^{CHCl_3}$ 5.77, 6.23, 6.41, 6.80, 6.90, 7.14, 7.24, 7.31, 7.63, 8.21, 9.39, 9.76, and 10.00 μ; mass spectrum *m/e* 686–688 (M^+), 535, and 343.

When the methylation was repeated in an atmosphere of nitrogen with careful exclusion of air, only compound **4** was obtained in 80% yield.

Acid Equilibration of Ketone 4.—A solution of 11,12-dimethoxyabieta-8,11,13-trien-6-one (**4**, 50 mg) and toluene-*p*-sulfonic acid (50 mg) in dry benzene (5 ml) was heated under reflux for 4 hr in an atmosphere of hydrogen. Dilution with water and ether extraction gave unchanged **4**. When the equilibration was conducted without hydrogen, tlc indicated formation of a small amount of an unidentified polar compound.

11,12-Dimethoxyabieta-8,11,13-trien-6β-ol (5).—To a cooled solution of **4** (1.5 g) in tetrahydrofuran (100 ml, distilled over $LiAlH_4$), $LiAlH_4$ (100 mg) was added slowly and the reaction mixture was refluxed with constant stirring in an atmosphere of nitrogen for 6 hr and then left at room temperature for 12 hr. The excess of $LiAlH_4$ was destroyed by dropwise addition by ethyl acetate followed by methanol. After dilution with water (500 ml) and acidification with dilute hydrochloric acid, the reaction mixture was extracted with chloroform. Evaporation of the dried (Na_2SO_4) chloroform extract furnished a pale yellow oil (1.5 g), which was dissolved in benzene (10 ml) and placed on a silicAR CC-7 column (200 g) packed in benzene. Elution with benzene (1 l.) gave two crystalline fractions. Recrystallization of the first fraction (80 mg) from methanol yielded plates: mp 116–117°; $[\alpha]^{28}D$ +100° (*c* 1.00, $CHCl_3$). The melting point was undepressed by admixture with the starting material **4**, and the infrared spectra ($CHCl_3$) and tlc of the two samples were identical. Recrystallization of the second fraction (800 mg) from petroleum ether yielded **5** as large plates: mp 108–109°; $[\alpha]^{28}D$ +33° (*c* 1.20, $CHCl_3$); ir $\lambda_{max}^{CHCl_3}$ 2.75, 2.85, 6.23, 6.39, 6.80, 6.91, 7.12, 7.43, 7.52, 7.69, 7.93, 8.13, 9.13, 9.42, 9.48, 9.60, 9.71, 10.63, and 11.63 μ; mass spectrum *m/e* 346 (M^+), 331, 313, 271, 243, and 219.

Anal. Calcd for $C_{22}H_{34}O_3$: C, 76.26; H, 9.89. Found: C, 75.78; H, 10.16.

11,12-Dimethoxyabieta-5,8,11,13-tetraene (7).—To a solution of **5** (100 mg) in pyridine (10 ml), phosphorus oxychloride (three drops) was added and the reaction mixture was left at room temperature under nitrogen for 6 hr. Monitoring by tlc indicated that the starting material had reacted almost completely within 3 hr. The reaction mixture was worked up in the normal way, yielding a pale yellow oil (70 mg), which was dissolved in petro-

leum ether (5 ml) and placed on a neutral alumina column (10 g, Woelm, activity I) packed in petroleum ether. Elution with petroleum ether–benzene (1:1, 100 ml) gave a colorless oil (50 mg), which crystallized upon persistent rubbing. Recrystallization from methanol yielded fine needles of **7** (30 mg): mp 88–89°; ir $\lambda_{max}^{CCl_4}$ 6.23, 6.37, 6.80, 6.90, 7.09, 7.22, 7.33, 7.39, 7.52, 7.57, 7.68, 9.80, and 10.62 μ; mass spectrum *m/e* 328 (M^+), 313, 271, 265, 243, 228, and 201.

Anal. Calcd for $C_{22}H_{32}O_2$: C, 80.44; H, 9.83. Found: C, 80.27; H, 9.70.

Mesylation of Alcohol 5.—A solution of alcohol **5** (50 mg) in pyridine (10 ml) was cooled to 0–5° and treated with methanesulfonyl chloride (0.5 ml). After standing at room temperature, the reaction mixture was worked up in the normal way to afford a crystalline residue (30 mg), which was recrystallized from methanol to yield needles of **7**, mp 88–89°. The melting point was undepressed by admixture with **7** and the infrared spectra ($CHCl_3$) of the respective samples were identical. The two samples showed identical tlc and glpc behavior.

11,12-Dimethoxyabieta-8,11,13-triene (8).—A solution of **7** (25 mg) in ethyl acetate (10 ml) containing perchloric acid (60%, 1 drop) was hydrogenated in the presence of platinum oxide (5 mg) until the consumption of hydrogen ceased (1 mol equiv in 1 hr). The catalyst was removed by filtration and the filtrate was worked up in the normal way to yield an oil (23 mg). Although the oil appeared homogeneous by tlc (solvent: petroleum ether), glpc indicated a 60:40 mixture of two components. Alumina chromatography and preparative tlc (silica gel GF_{254}, 2 mm) failed to separate the mixture. The mixture was ultimately resolved by preparative glpc. Crystallization from methanol of the compound with longer retention time yielded **8** (3 mg) as fine needles, mp 87–88°. The identity of **8** with 11,12-dimethoxyabieta-8,11,13-triene prepared by the method of Wenkert and coworkers[17] was confirmed by comparison of infrared, nmr, and mass spectra, melting point, mixture melting point, and tlc and glpc behavior.

7-Aminotaxodione (11).—To a solution of taxodione (100 mg) in ethyl acetate (20 ml), concentrated ammonium hydroxide solution (5 drops) was added and the reaction mixture was stirred at room temperature for 30 min. Evaporation of the solvent yielded a purple crystalline residue (100 mg), which on crystallization from ether gave large plates of **11**: mp 208–210°; uv λ_{max}^{MeOH} 265 (ϵ 4200), 295 (ϵ 3800), and 485 mμ (ϵ 15,300); ir λ_{max}^{KBr} 2.99, 3.12, 5.85, 6.06, 6.34, 6.62, 7.15, 8.03, 9.35, 9.80, 10.36, and 11.05 μ; mass spectrum *m/e* 329 (M^+), 314, 301, 286, 260, 245, and 233.

Anal. Calcd for $C_{20}H_{27}O_3N$: C, 62.92; H, 8.26; N, 4.25. Found: C, 62.57; H, 8.44; N, 3.97.

Hydrogenation of Taxoquinone.—A suspension of taxoquinone (**13**, 100 mg) in glacial acetic acid (30 ml) was hydrogenated over platinum oxide (5 mg) at atmospheric pressure. The reduction was completed within 2 hr, after which the catalyst was removed by filtration and the filtrate was evaporated. The residue was dissolved in benzene and passed through a silica gel column (20 g) packed in benzene. Elution with benzene (100 ml) gave a crystalline product, mp 179–181°. The product was identical with an authentic sample of royleanone (**12**) by mixture melting point, tlc, and infrared spectral comparisons.

Registry No.—**1**, 19026-31-4; **2**, 21838-12-0; **3**, 21887-45-6; **4**, 21838-13-1; **5**, 21764-39-6; **6**, 19039-02-2; **7**, 21764-40-9; **8**, 7726-32-1; **11**, 21886-99-7; **13**, 21764-41-0; **14**, 21887-01-4; **15**, 21764-42-1.

Selective Reductions. XIV. The Fast Reaction of Aryl Bromides and Iodides with Lithium Aluminum Hydride in Tetrahydrofuran. A Simple, Convenient Procedure for the Hydrogenolysis of Aryl Bromides and Iodides

HERBERT C. BROWN AND S. KRISHNAMURTHY[1]

Richard B. Wetherill Laboratory, Purdue University, Lafayette, Indiana 47907

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Unactivated aromatic bromides are reduced quite rapidly and quantitatively to the corresponding hydrocarbons by lithium aluminum hydride in refluxing tetrahydrofuran. Iodides are reduced at a reasonable rate even at room temperature. The ease of reduction of the different halogens, as indicated by rate studies, follows the order I > Br > Cl > F. Iodo and bromo substituents can be selectively removed in the presence of chloro substituents. This provides a convenient synthetic procedure for debromination and deiodination of aryl halides where this is required in synthetic operations.

The inertness of nonactivated aromatic halides toward attack by nucleophilic reagents is generally recognized. However, Karabatsos and Shone recently reported that aromatic halides exhibit surprising reactivity toward lithium aluminum hydride in tetrahydrofuran.[2] Their results indicated that the reaction was less facile than dehalogenation of such halides with triphenylstannane.[3,4] Consequently, the latter substance was recommended as the reagent of choice.[2]

We had also been examining the reaction of lithium aluminum hydride with aromatic halides in tetrahydrofuran (THF). However, the rates that we observed are very much faster than those reported previously.[2] Indeed, they are considerably faster than the corresponding dehalogenations with triphenylstannane. Accordingly, we must question the conclusion that the latter substance should be considered as the preferred reagent for the hydrodehalogenation of unactivated aryl halogen.

Our interest in this problem arose in the course of a systematic comparison of the behavior of lithium aluminum hydride[5] and of aluminum hydride[6] toward representative organic compounds. We decided to extend these studies to organic halides. In the course of these studies, we noted that aromatic halides, such as bromobenzene and iodobenzene, are essentially inert toward aluminum hydride, but react relatively rapidly with lithium aluminum hydride. Moreover, the production of hydrocarbon is essentially quantitative.

$$ArX \xrightarrow[THF]{LiAlH_4} ArH\ (>90\%)$$

This was surprising in view of the commonly accepted position that aromatic halides are extremely

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