The identified compounds were benzoic acid (0.16%), *m*-chloronitrobenzene (1.7%), *m*-chlorobenzoic acid (0.85%), *m*-nitrobenzoic acid (2.0%), and 3-chloro-5-nitrobenzoic acid (27.9%).

(b) This fraction was extracted by acetone, and it was a mixture of unidentified substances, whose average equivalent weight was 225: yield 62.1%; ir (KBr) 1690 (-C=O), 1515 and 1351 cm^{-1} ($-NO_2$).

(c) This fraction resulted in a black powder insoluble in all the above-mentioned solvents. It does not melt up to 500° and has an equivalent weight of 530. The equivalent weight of this material was obtained by boiling it for 30 min with a standard solution of NaOH (in N_2 atmosphere) and then determining the NaOH consumed with a standard solution of HCl: ir (KBr) 1690 (-C=O), 1515 and 1351 cm^{-1} ($-NO_2$).

(3) **3-Carboxy-4-nitrobenzenediazonium chloride** (**7**) exploded at 116° with light emission. The residue, a microcrystalline black powder, was worked up in the same form of diazonium salt (**6**). Three fractions were obtained.

Fraction a was extracted by benzene, and glpc (Table VI) indicated the presence of *p*-chloronitrobenzene (0.55%), benzoic acid (0.07%), *o*-nitrobenzoic acid (0.15%), 5-chloro-2-nitrobenzoic acid (1.7%), and *m*-chlorobenzoic acid (0.05%).

Fraction b was extracted by acetone and methanol, affording a complex mixture of unidentified substances with an average equivalent weight of 230: ir (KBr) 1695 (-C=O), 1515 and 1333 cm^{-1} ($-NO_2$).

Fraction c, the remaining residue after the successive extractions with the indicated solvents, was a black powder infusible up to 500° with an equivalent weight of 1840. In the ir spectrum the principal absorption band occurred at 1575 cm^{-1}, characteristic of aromatic nitro group. The absence of fine structure in the spectrum may possibly result from a high degree of orientation involving the polymer chains as has been reported.[1,18]

Thermal Decomposition Reaction of 7 in the Presence of Hydrogen Chloride.—The diazonium salt **7** was placed in the reaction flask as indicated in ref 1. To the evacuated apparatus was added pure, dry hydrogen chloride, until the pressure indicated in Table III was reached. Once the desired pressure was obtained, the diazonium salt in the flask (**6**) was heated until the product exploded. The temperature of the bath at the moment of the explosion was taken and the residue was washed with different boiling solvents (benzene, acetone, and methanol) until the extraction was complete. The following products were determined: *p*-chloronitrobenzene and 5-chloro-2-nitrobenzoic acid (glpc) and P_2 (insoluble in all above-mentioned solvents) (Table III).

Registry No.—**5**, 25116-40-9; **6**, 25116-41-0; **7**, 25116-42-1; **14**, 25116-43-2.

Acknowledgment.—This research was supported by the Air Force Office of Scientific Research, Office of Aerospace Research, U. S. Air Force, under Grant No. AFOSR-68-1425.

(18) (a) P. Kovacic and A. Kyriakys, *J. Amer. Chem. Soc.*, **85**, 454 (1963); (b) J. Dale, *Acta Chem. Scand.*, **11**, 640 (1957).

Resin Acids. XX. The Structure of Levopimaric Acid Dioxide[1,2]

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The reaction of levopimaric acid transannular peroxide (**1a**) with triphenylphosphine affords a monoxide whose structure has been shown to be 8α,14α-oxidoabiet-12-en-18-oic acid (**8a**). Since epoxidation of **8a** affords levopimaric acid dioxide, the structure of the latter is revised to 8α(14α),12α,13α-dioxidoabietan-18-oic acid (**2a**). Other transformations of **1a** are described.

The transannular peroxide **1a** of levopimaric acid can be isomerized[5,6] to a dioxide for which structures **2a** or **3a** may be written. Expression **3a** has been given preference on the basis of limited chemical studies,[6] but this interpretation has been questioned,[7] largely because a similar ambiguity of long standing concerning the structure of isoascaridole or pseudoascaridole,[8] the thermal rearrangement product of ascaridole (**4**), has now been settled in favor of **5**.[9,10] In the present paper we present conclusive proof that levopimaric acid dioxide possesses structure **2a** and that its formation presents no departure from other thermal transannular peroxide rearrangements.

Doubts about the structure previously[6] assigned to the dioxide arose when attempts to correlate it with the potassium permanganate oxidation product **7**[11] of levopimaric acid ended in failure.

In an effort to prepare the dioxide by an unambiguous route, the transannular peroxide **1b** was refluxed with triphenylphosphine in hexane, a treatment which resulted in formation of a new monoxide. This reaction when originally applied to ascaridole was reported[12] to yield a 1,4-oxide. However, recent reinvestigation while our work was in progress has shown that the product from ascaridole is 3,4-epoxy-1-menthene (**6**).[10]

The monoxide from **1b** was eventually shown to have the analogous structure **8**. The nmr spectrum exhibited a one-proton multiplet (H-12) at 5.47 and a narrow one-proton doublet (H-14) at 3.02 ppm whose splitting (2 Hz) was reasonable for allylic coupling. These observations seemed to rule out a structure based on **3b**. However, efforts to confirm the location of the oxide ring by chemical methods failed. Attempts to rearrange the epoxide by treatment with

(1) From Florida State University. Previous paper: W. Herz and M. G. Nair, *J. Org. Chem.*, **34**, 4016 (1969).

(2) Work at Florida State University supported in part by a grant from the National Science Foundation (GP-12582).

(3) National Research Council–Agricultural Research Service Postdoctoral Research Associate, 1968.

(4) One of the laboratories of the Southern Utilization Research and Development Division, Agricultural Research Service, U. S. Department of Agriculture.

(5) W. H. Schuller, J. C. Minor, and R. V. Lawrence, *Ind. Eng. Chem., Prod. Res. Develop.*, **3**, 97 (1964).

(6) H. Kanno, W. H. Schuller, and R. V. Lawrence, *J. Org. Chem.*, **31**, 4138 (1966).

(7) J. Hudec and R. S. A. Kelly, *Tetrahedron Lett.*, 3175 (1967).

(8) For literature citations, see ref 6.

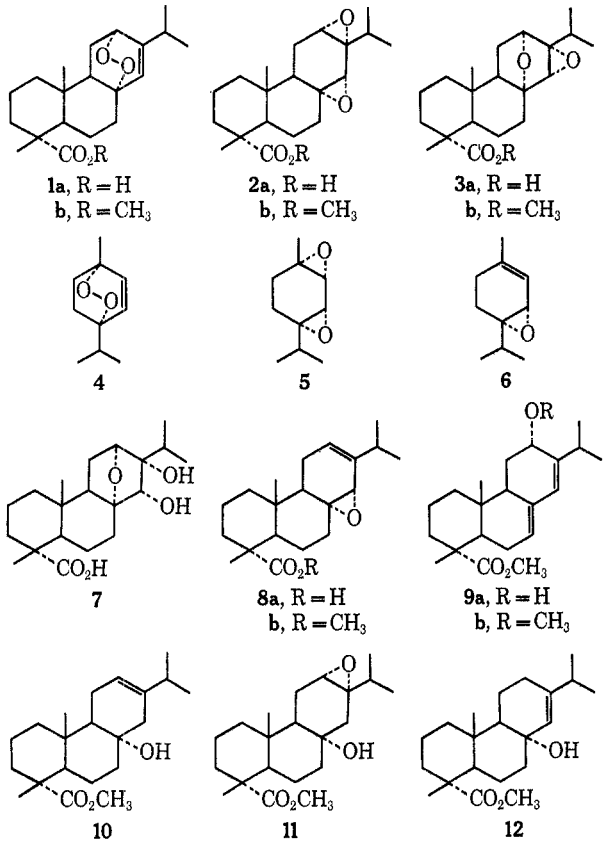
(9) J. Boche and O. Runquist, *J. Org. Chem.*, **33**, 4285 (1968).

(10) G. O. Pierson and O. Runquist, *ibid.*, **34**, 3654 (1969).

(11) W. Herz and R. Ligon, unpublished results.

(12) L. Horner and W. Jurgeleit, *Justus Liebigs Ann. Chem.*, **591**, 138 (1955).

Lewis acids led to complex mixtures. Perchloric acid catalyzed epoxide ring opening in methanol led to methyl 12-methoxyabietate (**9b**), identified by comparison of its nmr spectrum with that of **9a**,[13] and oxidation with BF_3–DMSO[14] gave a quantitative yield of methyl dehydroabietate.



Attempted hydrogenation of the monoxide (platinum oxide catalyst, ethanol) resulted quite unexpectedly in hydrogenolysis of the allylic carbon–oxygen bond and formation of an unsaturated alcohol which had to be formulated as **10**.[15] In the nmr spectrum of this substance the signal of the vinylic proton appeared as a multiplet at 5.52 ppm; its locus therefore was not likely to be C-14 and must be C-12. That the BC ring fusion was cis was indicated by the relatively high-field position (0.83 ppm) of the C-10 methyl signal.[16]

Further evidence for the structure assigned to **10** was its conversion by epoxidation to **11**. The infrared spectrum of this compound indicated the presence of a weak intramolecular hydrogen bond (narrowly split hydroxyl band, $\Delta\nu = 12$ cm^{-1}, which did not change on dilution) between the α-oriented hydroxyl and epoxide groups as suggested by the model. The nmr spectrum of **11** displayed the epoxidic proton as a multiplet, not as a singlet, at 3.18 ppm. Now the H-14 signal of $\Delta^{13(14)}$- or $\Delta^{8(14)}$-abietanes is broadened by long-range coupling; hence the multiplet character of the vinylic proton signal of **10** could not be used to dismiss quite unequivocally formulas such as **12** and **13**, the latter of which should also exhibit somewhat shielded C-10 methyl signals. On the other hand, it was difficult to see how an epoxy alcohol derived from **12** or **13** could give rise to a complex H-14 multiplet of the type observed, even if some W-type coupling were present.[17]

Convincing evidence for the formulation of the monoxide as **8b** was finally obtained from spin-decoupling experiments at 90 MHz.[18] Irradiation of **8b** at a frequency corresponding to the vinyl proton resonance collapsed the signal assigned to H-14 to a singlet still slightly broadened by allylic coupling to H-15.[19] Conversely, irradiation of the H-14 signal converted the signal at 5.47 ppm to a triplet ($J_{11\alpha,12} = J_{11\beta,12} = 3$ Hz) slightly broadened by allylic coupling to H-15 also.[19] These results which confirm that the only significant coupling experienced by the epoxidic proton is allylic coupling to the vinyl proton are consistent only with fromula **8b** and not with **14** or **15**.

Epoxidation of **8b** led to a substance identical in all respects with the dioxide obtained by rearrangement of methyl levopimarate transannular peroxide **1b**. Hence the structure of the dioxide is **2b** The glycol produced[6] from **2b** by the action of sulfuric acid (formula **8b** of ref 6) can now be assigned formula **16** because of the nmr spectrum which displays a somewhat deshielded C-10 methyl signal at 1.10 ppm. The α orientation of the C-14 hydroxyl group then follows from the usual trans-diaxial mode of epoxide ring opening. By analogy the chlorohydrin obtained from **2b** by action of hydrogen chloride (formula **7b** of ref 6) which can be reconverted to **2b** by treatment with base[6] is **17**.

In the following we report briefly the results of other transformations of **1b** and related experiments undertaken in the course of this work. Epoxidation of **1b** gave **18** whose nmr spectrum (multiplet at 4.30, H-12, singlet at 3.31 ppm, H-14) was in accord with the postulated formula. Treatment of **18** with base resulted in the isolation of two compounds **20** and **21** whose formation can be understood as proceeding through a Favorskii rearrangement of the intermediate not isolable, hydroxyepoxy ketone **19**.[20] The more soluble product **20** was transformed into **21** by lengthening the reaction time.

Structures were assigned to these substances on the basis of the following evidence. The dihydroxy diester **20** (strongly bonded hydroxyl band, two carbonyls at 1727 and 1690 cm^{-1} identified as carbomethoxy functions by the nmr spectrum) contained one secondary hydroxyl group (nmr doublet at 3.38 ppm which collapsed to a singlet on deuterium exchange) and the usual two methyl singlets and isopropyl doublets. The other hydroxyl group was apparently tertiary and, because of the convertibility to **21**, necessarily γ to the newly introduced ester function. That the two hy-

(13) W. Herz, H. J. Wahlborg, W. D. Lloyd, W. H. Schuller, and G. W. Hedrick, *J. Org. Chem.*, **30**, 3190 (1965).

(14) L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis," Wiley, New York, N. Y., 1967, p 304.

(15) Inspection of the models of **8** and **10** does not afford an obvious explanation for our failure to effect reduction of the C-12, C-13 double bond under these and other (low pressure) conditions.

(16) J. W. Huffman, T. Kamiya, L. H. Wright, J. J. Schmid, and W. Herz, *J. Org. Chem.*, **31**, 4128 (1966).

(17) *Cf.* the nmr spectrum of **25b** (*vide infra*) where H-14 appears as a sharp singlet.

(18) The Bruker 90-MHz nmr spectrometer use in this study was purchased with the aid of an NSF grant to Florida State University. We wish to thank Mr. A. L. Hall for performing the decoupling experiments.

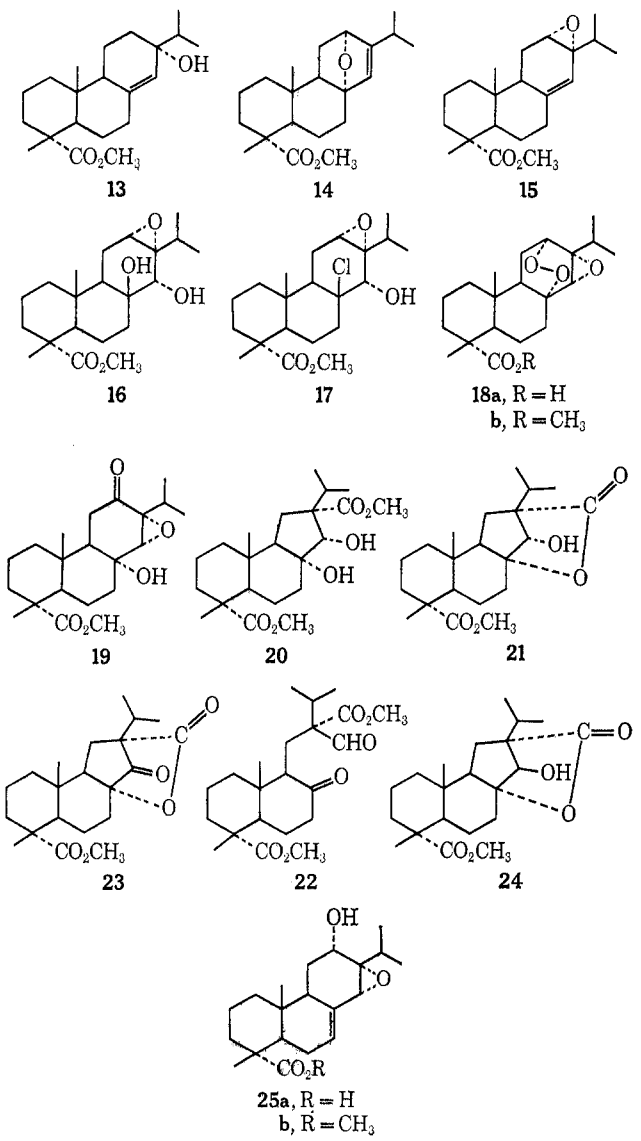
(19) The H-15 signal could be located at 2.29 ppm by irradiating at the frequency of the isopropyl methyl doublet.

(20) The formation of **19** from **18** is characteristic of peroxides containing at least one hydrogen α to the peroxidic linkage.[21] For other examples of Favorskii rearrangements involving α-epoxy ketones, see W. Herz and M. G. Nair, *J. Org. Chem.*, **34**, 4016 (1969).

(21) N. Kornblum and P. De La Mare, *J. Amer. Chem. Soc.*, **73**, 880 (1951).

droxyl groups of **20** were vicinal was shown by lead tetraacetate oxidation which gave a noncrystalline ketoaldehyde **22** characterized as a dinitrophenylhydrazone.

Analysis and physical properties of **21** (ir bands at 3438, 1734, and 1718 cm^{-1}, one methoxyl signal in the nmr) indicated that it was the lactone of **20** and contained a secondary hydroxyl group flanked by quaternary carbon atoms (singlet at 4.07 ppm after D_2O exchange). Oxidation of **21** with Jones reagent afforded a ketolactone ester **23** whose ir spectrum indicated the presence of a γ-lactone function (band at 1818 cm^{-1}, high frequency shift due to strain imposed by ketone group), strained cyclopentanone (band at 1764 cm^{-1}), and one ester function (band at 1720 cm^{-1}, nmr signal at 3.71 ppm). The absence of other low-field protons confirmed that the second hydroxyl group of the precursor **20** was tertiary.



Sodium borohydride reduction of **23** furnished a monohydroxy compound **24** (new nmr singlet at 3.81 ppm), presumably by attack from the less hindered α side (model). Consequently the secondary hydroxyl group of **20** and **21** was deduced to be α. This is in accord with the ease of lead tetraacetate oxidation of **20**.

Reaction of **18a** with triphenylphosphine resulted in formation of an unsaturated epoxy alcohol. This was formulated as **25a** on the basis of the nmr spectrum which exhibited a multiplet at 5.9 whose shape and chemical shift was characteristic of vinylic H-7,[22] a multiplet at 4.0 obviously associated with hydrogen on carbon carrying the hydroxyl because it underwent simplification on D_2O exchange and which, because of its complexity, had to be attached to C-12, and a singlet due to epoxidic hydrogen at C-14. The formation of **25a** which implies attack by triphenylphosphine on **18a** in a sense opposite to that favored by the same reagent in the case of **1a** or **1b** is difficult to understand. Models suggest that the oxygen atom removed from **1a** as triphenylphosphine oxide, *i.e.*, the one attached to C-12, is somewhat less encumbered than the oxygen atom attached to C-8 which is not removed. This situation is exacerbated rather than relieved in the case of **18a**, yet the considerably more hindered oxygen atom attached to C-8 of **18a** is removed preferentially. It is possible that the polar effect of the epoxidic oxygen atom, which from the model appears to be somewhat closer to the peroxydic oxygen at C-8 than to the one at C-12, is responsible for directing the attack of triphenylphosphine.

Experimental Section[23]

8α(14α),12α,13α-Dioxidoabietan-18-oic Acid and Methyl Ester (2a and 2b).—The preparation of **2a** was generally carried out as described earlier using ferrous sulfate.[7] The methyl ester **2b** was prepared from **1b** in the same manner.

Methyl 8α,14α-Oxidoabiet-12-en-18-oate (8b). A.—A solution of 2.84 g of **1a** in 980 ml of *n*-heptane was allowed to stand with 6.7 g of triphenylphosphine for 8 days until the optical rotation had leveled off at $[\alpha]^{25}D$ −27°. The mixture was filtered and evaporated *in vacuo*. The residue was mixed with 0.9 g of cyclohexylamine. The salt which precipitated weighed 1.6 g (45%). When recrystallized to constant rotation $[\alpha]^{25}D$ −60° (*c* 0.6), it had mp 187–188° dec; no uv absorption in the range 220–320 nm.

Anal. Calcd for $C_{26}H_{43}NO_3$: C, 74.78; H, 10.38; N, 3.35; O, 11.49. Found: C, 74.67; H, 10.21; N, 3.48; O, 11.28.

The acid **8a** was formed by suspending 11.3 g of the salt in ether and washing with a slight excess of dilute phosphoric acid. The crude acid, wt 8.65 g (100%), was converted to the methyl ester **8b** by treatment with diazomethane. The product was recrystallized from methanol–water to constant rotation, $[\alpha]^{25}D$ −77.0° (*c* 0.87), and had mp 104–106°; ir bands at 1727, 1387, 1362, and 990 cm^{-1}; nmr signals at 5.47 m (H-12), 3.71 (methoxyl), 3.02 d (J = 2 Hz, H-14), 1.20 (C-4 methyl), 1.09 d (J = 7 Hz, isopropyl methyls), and 0.81 ppm (C-10 methyl); mass spectrum (70 eV) 332 (molecular ion, intensity 17.8 compared with base peak at 239).

Anal. Calcd for $C_{21}H_{32}O_3$: C, 75.86; H, 9.70; O, 14.44. Found: C, 75.65; H, 9.71; O, 14.47.

B.—The following procedure for preparing **8b** was more convient and gave better yields. A solution of 1.0 g of **1b** and 0.8 g of triphenylphosphine in 150 ml of *n*-hepane was refluxed for 3 hr, cooled, filtered, and evaporated. The residue (**8b**) was recrystallized from methanol–water, yield 0.7 g (70%), mp 104–106°.

Epoxidation of 2.25 g of **8b** in 165 ml of ethylene dichloride with 1.6 g of *m*-chloroperbenzoic acid at reflux temperature for 2.5 hr, cooling, washing, and drying followed by evaporation at reduced pressure afforded 2.59 g of crude **2b**. After recrystallization from aqueous methanol there was obtained 1.9 g (81%) of **2b**: mp 120–121°; $[\alpha]^{25}D$ −72° (*c* 0.7), mmp (with **2b** from rearrangement of **1b**) 120–121°; nmr and ir spectra superimposable.

(22) H. J. Wahlborg, Ph.D. Dissertation, Florida State University, 1965.

(23) Melting points are uncorrected. Nmr spectra were run on a Varian A-60 nmr spectrometer in deuteriochloroform solution, unless otherwise specified, using tetramethylsilane as internal standards. Ultraviolet spectra and rotations were determined in 95% ethanol solution. Infrared spectra were run as KBr pellets unless otherwise specified.

Treatment of 8b with Acid. A.—A solution of 1.0 g of **8b** and 0.5 ml of BF_3-etherate in 25 ml of dimethyl sulfoxide was stirred mechanically. The process of the reaction was followed by tlc and nmr analysis. After 20 hr, quantitative conversion to methyl dehydroabietate had occurred.

B.—A solution of 1.0 g of **8b** in tetrahydrofuran-methanol was cooled in an ice bath and stirred for 1 hr with 0.5 ml of 60% perchloric acid solution. The mixture was poured into brine and extracted with ether. The washed and dried ether extract was evaporated and the residue was recrystallized from methanol-water. Pure **9b**, yield 0.46 g (50%), had mp 110–112°; $[\alpha]^{25}D$ −4.9°; ir bands at 1714 cm^{-1}; nmr signals at 6.01 (H-14), 5.75 m (H-7), 3.88 m (H-12), 3.73 (methoxyl), 3.46 (methoxyl), 1.19 (C-4 methyl), 1.10 d, 1.08 d (J = 7 Hz, isopropyl methyls), and 0.84 ppm (C-10 methyl).

Anal. Calcd for $C_{22}H_{34}O_3$: C, 76.26; H, 9.89; O, 13.85. Found: C, 76.14; H, 9.78; O, 13.97.

Methyl 8α-Hydroxyabiet-12-en-18-oate (10).—A solution of 2.0 g of **8b** was hydrogenated in ethanol solution with platinum oxide at 15 psi for 20 hr. The solution was filtered and evaporated at reduced pressure. The crude **10** was recrystallized from hexane, yield 1.3 g (65%), and had mp 132–133°; $[\alpha]^{25}D$ −49.4° (c 0.79); ir bands at 3560 and 1720 cm^{-1}; nmr signals at 5.52 m (H-12), 3.70 (methoxyl), 2.05 (-OH, disappears on D_2O exchange), 1.17 (C-4 methyl), 1.00 d (J = 6 Hz, isopropyl methyls), and 0.83 ppm (C-10 methyl).

Anal. Calcd for $C_{21}H_{34}O_3$: C, 75.41; H, 10.25; O, 14.35. Found: C, 74.92; H, 10.03; O, 14.65.

Methyl 8α-Hydroxy-12α,13α-oxidoabietan-18-oate (11).—A solution of 1.3 g of **10** and 0.9 g of *m*-chloroperbenzoic acid in 50 ml of chloroform was allowed to stand at room temperature for 2 hr and then extracted thoroughly with saturated sodium bicarbonate solution. The washed and dried organic layer was evaporated. The residue was recrystallized from hexane: yield of **11**, 1.1 g (79%); mp 142.5–143.5°; $[\alpha]^{25}D$ +4.9° (c 0.82); ir bands at 3460–3440 and 1718 cm^{-1}; nmr signals at 4.50 (-OH, disappears on D_2O exchange), 3.67 (methoxyl), 3.18 m (H-12), 1.15 (C-4 methyl), 0.99 d and 0.96 d (J = 7 Hz, isopropyl methyls), and 0.87 ppm (C-10 methyl).

Anal. Calcd for $C_{21}H_{34}O_4$: C, 71.96; H, 9.78; O, 18.26. Found: C, 72.06; H, 9.84; O, 17.82.

Methyl 8β,14α-Dihydroxy-12α,13α-oxidoabietan-18-oate (16).—This substance, prepared by the literature method,[6] had nmr signals at 3.68 (methoxyl), 3.41 t (J = 2 Hz, H-12), 3.22 d (J = 9.5 Hz, H-14, collapses to singlet on D_2O exchange), 2.52 d (J = 5 Hz, -OH, disappears on D_2O exchange), 1.21 (C-4 methyl), 1.10 (C-10 methyl), and 1.03 d and 0.96 d (J = 6 Hz, isopropyl methyls).

Epoxidation of 1a. Formation of 18.—A solution of 20 g of **1a** and 16 g of *m*-chloroperbenzoic acid in ethylene dichloride was refluxed on the steam bath for 4 hr, allowed to stand overnight, washed thoroughly with saturated sodium bicarbonate solution, water, and brine, and dried. Removal of solvent furnished crude **18a**, wt 19.8 g (95%), which was purified to constant rotation, $[\alpha]^{25}D$ +121° (c 1.1), by recrystallization from *n*-heptane: yield of pure **18a** 6.22 g (78%); mp 165–167° dec; nmr signals at 4.40 m (H-12), 3.36 (H-14), 1.20 (C-4 methyl), 1.14 d and 0.84 d (J = 7 Hz, isopropyl methyls), and 0.87 ppm (C-10 methyl).

Anal. Calcd for $C_{20}H_{30}O_5$: C, 68.54; H, 8.63; O, 22.83. Found: C, 68.70; H, 8.70; O, 23.01.

Methylation of **18a** with diazomethane afforded **18b** in quantitative yield. It melted unsharply in the range 175–188° dec, presumably due to thermal decomposition, but tlc and spectrometric analysis indicated homogeneity: $[\alpha]^{25}D$ +98.5° (c 0.79); ir bands 1724, 1391, and 1251 cm^{-1}; nmr signals at 4.30 m (H-12), 3.66 (methoxyl), 3.31 (H-14), 1.15 (C-4 methyl), 1.10 and 0.80 d (J = 7 Hz, isopropyl methyls), and 0.81 ppm (C-10 methyl).

Anal. Calcd for $C_{21}H_{32}O_5$: C, 69.20; H, 8.85; O, 21.95. Found: C, 69.08; H, 8.77; O, 22.22.

Base Treatment of 18b. Formation of 20 and 21.—A solution of 5 g of **18b** in 700 ml of 95% ethanol and 75 ml of 1 M sodium hydroxide in ethanol was refluxed for 20 min, cooled, filtered, and acidified with dilute phosphoric acid. The acid fraction was isolated in the usual manner and methylated with ethereal diazomethane. The solution was concentrated to ~50 ml and chilled in the refrigerator for 2 hr. This resulted in separation of **21** (2.8 g). Concentration to 30 ml and chilling produced an additional 0.3 g of **21**. The mother liquor was evaporated to dryness *in vacuo* and the residue was recrystallized from aqueous methanol. This resulted in separation of 1.6 g of **20**. When the hydrolysis mixture was refluxed for 40 min or longer, only **21** was isolated in ~90% yield.

Ester **20** was recrystallized from aqueous methanol and had mp 106–107°; $[\alpha]^{25}D$ −16.6° (c 0.75); ir bands at 3480–3280 (broad, hydrogen bonded), 1727, and 1690 cm^{-1}; nmr signals at 4.56 d (J = 9 Hz, C-13, -OH, disappears on D_2O exchange), 3.74 and 3.68 (two methoxyls), 3.38 d (J = 9 Hz, H-13, collapses to singlet on D_2O exchange), 1.25 (C-4 methyl), 1.00 d and 0.93 d (J = 6 Hz, isopropyl methyls), and 0.83 ppm (C-10 methyl).

Anal. Calcd for $C_{22}H_{36}O_6$: C, 66.74; H, 9.15; O, 24.21. Found: C, 66.75; H, 9.03; O, 24.19.

Ester **21** was recrystallized from ether and had mp 242–244°; $[\alpha]^{25}D$ +61.7° (c 0.78); ir bands at 3438, 1734, and 1718 cm^{-1}; nmr signals at 4.07 d (J = 7 Hz, H-13, collapses to singlet on D_2O exchange), 3.70 (methoxyl), 2.22 d (J = 7 Hz, -OH, disappears on D_2O exchange), 1.18 (C-4 methyl), 1.12 d (J = 7 Hz, isopropyl methyls), and 0.91 ppm (C-10 methyl).

Anal. Calcd for $C_{21}H_{32}O_5$: C, 69.20; H, 8.85; O, 21.95. Found: C, 69.31; H, 8.81; O, 21.97.

Lead Tetraacetate Oxidation of 20.—A solution of 0.45 g of **20** and 0.5 g of lead tetraacetate was stirred overnight, filtered, and evaporated. The residue (**22**) was taken up in hexane, but could not be induced to crystallize. The nmr spectrum had signals at 11.33 (-CHO), 3.69 (two methoxyls), 1.17 (C-4 methyl), 1.08 d and 0.91 d (J = 7 Hz, isopropyl methyls), and 0.70 ppm (C-10 methyl). The material was converted to a crystalline bis-2,4-dinitrophenylhydrazone which was recrystallized from ethanol and then decomposed at 135°.

Anal. Calcd for $C_{34}H_{42}N_8O_{12}$: C, 55.15; H, 5.88. Found: C, 55.36; H, 5.60.

Oxidation of 21.—Oxidation of 1.0 g of **21** with Jones reagent in acetone solution by stirring overnight, pouring into water, extracting with ether, washing and drying the ether extract, and removal of solvent afforded crude **23** which was recrystallized from methanol-water. The product, wt 0.95 g (95%), had mp 94–95.5°; $[\alpha]^{25}D$ +77.8° (c 0.76); ir bands at 1818, 1763, and 1720 cm^{-1}; nmr signals at 3.71 (methoxyl), 1.20 (C-4 methyl), 1.12 d (J = 7 Hz, isopropyl methyls), and 0.78 ppm (C-10 methyl).

Anal. Calcd for $C_{21}H_{30}O_5$: C, 69.59; H, 8.34; O, 22.07. Found: C, 69.63; H, 8.39; O, 22.08.

Reduction of 23 to 24.—A solution of 0.3 g of **23** in 4:1 methanol–water containing sufficient ether to dissolve the substrate was stirred overnight with 23 mg of $NaBH_4$, poured into 15% phosphoric acid solution, and extracted with ether. The washed and dried extract was evaporated and the residue (**24**) recrystallized from methanol–water: yield 240 mg (80%); mp 225–227°; $[\alpha]^{25}D$ +120° (c 0.23); ir bands at 3465, 1743, and 1724 cm^{-1}; nmr signals at 3.8 br (H-13, sharpens to singlet on D_2O exchange), 3.71 (methoxyl), 2.92 br (-OH, disappears on D_2O exchange), 1.20 (C-4 methyl), 1.11 d and 1.08 d (J = 7 Hz, isopropyl methyls), and 1.09 ppm (C-10 methyl).

Anal. Calcd for $C_{21}H_{32}O_5$: C, 69.20; H, 8.85; O, 21.95. Found: C, 69.51; H, 8.80; O, 21.62.

12α-Hydroxy-13α,14α-oxidoabiet-7-en-18-oic Acid and Methyl Ester (25a and 25b).—A solution of 9.5 g of **18a** and 7.08 g of triphenylphosphine in 380 ml of benzene was allowed to stand at room temperature until the optical rotation became constant (45 hr). The solution was evaporated at reduced pressure; the residue was dissolved in 23 ml of acetone and mixed with 3.23 g of cyclohexylamine. The salt, wt 10 g, was recrystallized from acetone: yield 8.5 g (73%); $[\alpha]^{25}D$ +15.7° (c 0.8), mp 208° dec; ir bands at (Nujol mull) 3580, 1625, 1240, 1048, 885, and 765 cm^{-1}.

Anal. Calcd for $C_{26}H_{43}NO_4$: C, 72.01; H, 10.00; N, 3.23; O, 14.75. Found: C, 71.96; H, 9.88; N, 3.55; O, 14.83.

The free acid was regenerated from the salt by shaking an ether suspension with an excess of 1 M phosphoric acid. Recrystallization from acetonitrile afforded **25a** in 84% yield: mp 142–144° dec; $[\alpha]^{25}D$ +25.7° (c 0.8); no characteristic uv absorption in the range 220–320 nm; ir bands ($CHCl_3$) at 3510, 1690, and 885 cm^{-1}.

Anal. Calcd for $C_{20}H_{30}O_4$: C, 71.82; H, 9.05; O, 19.14; neut equiv, 334. Found: C, 71.86; H, 9.07; O, 19.15; neut equiv, 335.

Treatment of **25a** with ethereal diazomethane and recrystallization from aqueous acetonitrile afforded a 94% yield of **25b**:

mp 128–130°; $[\alpha]^{25}D$ +23.8° (c 1.0); ir bands ($CHCl_3$) at 3510 and 1715 cm^{-1}; nmr signals (CCl_4) at 5.9 m (H-7), 4.0 m (H-12, simplifies on D_2O exchange), 3.51 (methoxyl), 3.25 (H-14), 2.25 d (J = 10 Hz, -OH, disappears on D_2O exchange), 1.21 (C-4 methyl), 1.01 d and 0.94 d (J = 7 Hz, isopropyl methyls), and 0.74 ppm (C-10 methyl); mass spectrum 348 (molecular ion).

Anal. Calcd for $C_{21}H_{32}O_4$: C, 72.38; H, 9.26; O, 18.37. Found: C, 72.13; H, 9.18; O, 18.43.

Registry No.—**2a**, 23160-61-4; **8a** cyclohexylamine salt, 25859-58-9; **8b**, 25859-59-0; **9b**, 25236-84-4; **10**, 25859-61-4; **11**, 25859-62-5; **16**, 25859-63-6; **18a**, 25859-64-7; **18b**, 25859-65-8; **20**, 25859-66-9; **21**, 25859-67-0; **22** bis-2,4-DNP, 25907-93-1; **23**, 25859-68-1; **24**, 25907-94-2; **25a**, 25859-69-2; **25a** cyclohexylamine salt, 25859-70-5; **25b**, 25859-71-6.

Electrophilic Substitution in Highly Substituted Diphenyl Ethers[1]

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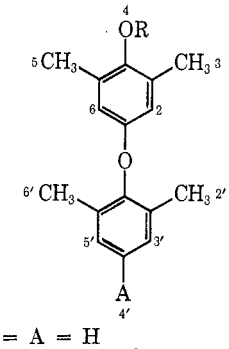
Derivatives of 4-hydroxy-3,5,2′,6′-tetramethyldiphenyl ether (1) have been of interest for some time as analogs of thyroxine in which the iodo groups have been replaced with methyls. These products have been obtained by electrophilic substitution on 1 or its methyl ether (2), which, in each case, is reported to occur in the 4′ position. For example, 1 is reported to give 4′-bromo-4-hydroxy-3,5,2′,6′-tetramethyldiphenyl ether (8) on bromination in acetic acid. We have repeated all of the reported substitution reactions and obtained products identical with those prepared earlier. However, we have shown by pmr and ir spectral analyses that each of these products is substituted in the 2 position. Thus 1 is brominated to give 2-bromo-4-hydroxy-3,5,2′,6′-tetramethyldiphenyl ether (10). We have explained this result on the basis of the steric effect of the two methyl groups *ortho* to the aryl ether linkage which interfere with resonance forms that activate the 4′ position for substitution, but which do not interfere with resonance forms that activate the 2 position. This hypothesis is supported by additional substitution data and ultraviolet spectra, which show that there is little or no electronic interaction between the aryl ether oxygen "p" electrons and the hindered aryl ring. These results show that no authentic tetramethyl analogs of thyroxine have been prepared, and that conclusions regarding bioactivity based on compounds prepared by electrophilic substitution of 1 and 2 are in error.

Electrophilic substitution products of 4-hydroxy-3,5,2′,6′-tetramethyldiphenyl ether (1) and its methyl ether (2) have been used as intermediates for the preparation of tetramethyl analogs of thyroxine. In this connection, Bruice, Kharasch, and Winzler in 1954 reported that nitration of 2 in acetic anhydride resulted in 4′-nitro-4-methoxy-3,5,2′,6′-tetramethyldiphenyl ether (3).[3] This product was subsequently converted to the amino derivative of 1, reported to have structure 4, which was tested for biological activity.[4] Later, Bielig and Lützel reported that bromination and chloromethylation experiments with 2 resulted in the derivatives 5 and 6 which are substituted in the 4′ position of the phenoxy ring.[5] The product obtained by chloromethylation was converted to an amino acid derivative of 1 which was reported to be 7, the structural analog of thyroxine in which all of the iodines have been replaced with methyl groups. This product has since been used in several biological studies designed to determine the effect of methyl relative to that of other substituents on the thyroxine nucleus.[6] More recently, Van Heyningen has brominated 1 in acetic acid and reported the 4′-bromo derivative 8.[7] This product was converted by metal exchange and carbonation to a carboxylic acid. This product, reported to have structure 9, has also been used in biological studies.[8] In none of the above cases did the authors offer structural proofs for their products, nor did they discuss the possibility of alternative structures.



1, R = A = H
2, R = CH_3; A = H
3, R = CH_3; A = NO_2
4, R = H; A = NH_2
5, R = CH_3; A = Br
6, R = CH_3; A = CH_2Cl
7, R = H; A = CH_2CHNH_2COOH
8, R = H; A = Br
9, R = H; A = COOH

Because of our interest in obtaining 8 for use in another connection, we have repeated the bromination reactions of Van Heyningen[7] and Bielig and Lützel[5] and obtained products which are identical with those reported. However, we have determined by proton magnetic resonance (pmr) spectral data that the products are substituted in the 2 position of the phenolic ring rather than the 4′ position of the phenoxy ring as previously reported. These results have led us to repeat other electrophilic substitution reactions of 1 and 2 and to determine the structures of the products. This paper describes the results of these experiments and the structural identifications and includes a discussion of the unexpected substitution pattern.

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