Epimeric 2-(*p*-Hydroxylhydrocinnamoyloxy)-4-(3-hydroxy-4-methoxyphenyl)(e)-*trans*-quinolizidines (19 and 20).—The appropriate benzyl ether (17 or 18, 0.3 g) in absolute ethanol were hydrogenated over 0.06 g of 5% Pd–C. The theoretical amount of hydrogen was taken up in 4 hr. Removal of the catalyst and the solvent gave the two phenols, 19 or 20 in essentially quantitative yields. Neither crystallized and both were characterized as glasses.

The axial epimer 20 showed a softening point of 70–85° and had the following spectral properties: ir (KBr) μ 3.00 (OH), 3.59, 3.64 (Bohlmann bands), 5.82 (C=O); nmr ($CDCl_3$) τ 3.33 (m, 7, aromatic), 5.0 (s, phenolic), 6.24 (s, 3, OCH_3), 7.20 (m, 7), 8.59 (m, quinolizidine); mass spectrum *m/e* (relative intensity) 426 (28), 425 (100), 424 (17), 260 (70), 259 (50), 258 (67), 177 (72), 150 (20), 137 (22), 136 (65), 117 (33), 110 (15), 107 (63), 84 (71), 55 (22); uv (ethanol) the spectrum was shifted to a higher wave length upon NaOH addition.

Anal. Calcd for $C_{25}H_{31}NO_5$: C, 70.57; H, 7.34; N, 3.29. Found: C, 70.03; H, 7.32; N, 2.91.

The equatorial isomer 19 had spectral properties qualitatively similar to those of 20. It liquified at 65–75°.

Anal. Found: C, 69.91; H, 7.35; N, 2.89.

Registry No.—**9**, 24807-37-2; **11**, 24807-38-3; **12**, 24807-39-4; **13**, 24806-75-5; **14**, 24806-76-6; **15**, 24806-77-7; **16**, 24806-78-8; **17**, 24806-79-9; **18**, 24806-80-2; **19**, 24806-81-3; **20**, 24806-82-4; **21**, 24807-40-7.

Acknowledgment.—We thank Dr. Shiroshi Shibuya for help in crystallizing compound 16 and repeating portions of the work.

Chemistry of *Ottonia vahlii* Kth. II.[1] Constitution of the Nonvolatile Component[2]

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The nonvolatile principle (piperovatine) of the leaves, roots, and stems of *Ottonia vahlii* Kth., has been shown, by spectral study and synthesis, to be N-isobutyl-6-*p*-methoxyphenylsorbamide (1).

In an earlier communication[1] we identified the volatile constituent of the shrub *Ottonia vahlii* [syn. *Piper ovatum* (Vahl)], native to the West Indies, as 1-butyl-3,4-methylenedioxybenzene. In this paper we are concerned with the chemical structure of the nonvolatile component of the same plant.

The sole chemical studies of this shrub were published over 70 years ago.[5] The isolation from the leaves of a crystalline "alkaloid," mp 123°, was described; it was named piperovatine, assigned a molecular formula $C_{16}H_{21}NO_2$, and found to be neutral in reaction and to have marked physiological properties. It proved to be a temporary nerve depressant, a heart poison, a local anesthetic, and a powerful sialagogue when applied to the tongue.

We have isolated from the leaves, roots, and stems of this plant what appears to be the same compound by a simplified mode of extraction. Some difficulty was experienced with its purification, owing to the fact that, as noted by the earlier workers, crystallization attempts were attended by a strong tendency towards gel formation in a variety of solvents. Eventually a combination of high-vacuum sublimation followed by crystallization from a critical volume of ether yielded a crystalline product of maximum mp 121°. A sample of the earlier workers' product was not available for comparison, but there seems little doubt, from the physical and physiological properties of our material, that it is identical with piperovatine.

Elemental analysis and molecular-weight determination by mass spectrometry necessitated an alteration of the molecular formula to $C_{17}H_{23}NO_2$, containing one methoxyl group. The presence of the latter was confirmed, and its aromatic character was revealed by nmr spectroscopy (singlet, 3.82 ppm, 3 H). The neutral character of the product suggested it might be amidic. This was confirmed by its ir spectrum (in CCl_4): maxima at 3460 (free NH), 3380 (H-bonded NH), and 1673 cm^{-1} suggested the carbonyl group is conjugated with two double bonds. Bands at 1461 and 1438, and 1178 and 1171 are assigned to a $>C(CH_3)_2$ group, at 1243 to an aromatic OCH_3 group, and at 991 cm^{-1} to a *trans,-trans* CH=CH—CH=CH system conjugated with the amide carbonyl group.[6] The uv spectrum (λ_{max}^{EtOH} 262 mμ, ϵ 26,500) confirms the presence of a diene system conjugated with the amidic carbonyl group and further supports the belief that the double bonds are both *trans* in geometry [compare sorbic acid, λ_{max}^{EtOH} 263 mμ, ϵ 25,800).[7] The nmr spectrum revealed the following features in the molecule: (a) a *para*-disubstituted benzene ring (A_2B_2 pattern, centered at 6.90, 4 H); (b) olefinic protons (4 H) attached to a conjugated diene system [multiplicity of signals in the range 5.6–6.4; of these a doublet centered at 5.87 (J = 15 Hz) is assigned to an α proton *trans* to the β proton on the α,β C=C bond (compare sorbic acid[8])]; (c) an aromatic methoxyl group singlet at 3.82, 3 H); (d) a benzylic CH_2 group (doublet, J = 5 Hz, centered at 3.45, 2 H); (e) an apparent triplet centered at 3.20, J = 5 Hz (2 H), assigned to a $-NHCH_2CH<$ grouping, is in reality a quartet in which the two innermost signals overlap ($J_{CH-NH} = J_{CH-CH}$). On deuteration these signals collapse to a doublet centered at 3.12 (J = 7 Hz) [several model compounds containing the grouping $R\cdot C(O)\cdot NH\cdot CH_2CH<\begin{matrix}R'\\R''\end{matrix}$, were synthesized;

(1) Part I: A. R. Pinder and S. J. Price, *J. Chem. Soc. C*, 2597 (1967).

(2) Presented at the Annual Meeting of the South Carolina Academy of Science, Columbia, S. C., April 1968; at the Southeastern Regional Meeting of the American Chemical Society, Tallahassee, Fla., Dec 1968, and at The Third National Products Symposium, Kingston, Jamaica, W. I., Jan 1970.

(3) Submitted by S. J. Price in partial fulfillment of the requirements for the Degree of M.S., Clemson University, May 1969.

(4) To whom inquiries should be addressed.

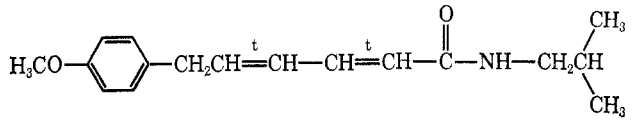
(5) W. R. Dunstan and H. Garnett, *J. Chem. Soc.*, **67**, 94 (1895). See also T. A. Henry, "The Plant Alkaloids," 4th ed, Churchill, London, 1949 p 2.

(6) For examples, see J. L. H. Allan, G. D. Meakins, and M. C. Whiting, *J. Chem. Soc.*, 1874 (1955).

(7) (a) U. Eisner, J. A. Elvidge, and R. P. Linstead, *ibid.*, 1372 (1953); (b) see also A. I. Scott, "Interpretation of the UV Spectra of Natural Products," Pergamon Press, New York, N. Y., 1964, p 81.

(8) Varian Associates NMR Spectral Catalog, Vol. 2, spectrum no. 462.

all had the N-CH_2 signal as an apparent triplet]; (f) a methine hydrogen in a grouping $CH_2CH(CH_3)_2$ (multiplet, 1 H, 1.1–2.2); and (g) an isopropyl group, the methyl hydrogens of which appeared as a doublet, J = 7.5 Hz (6 H), centered at 0.95 ppm.

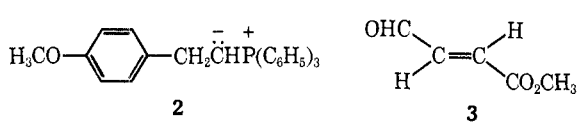


1

The information so far accumulated points to structure **1** for piperovatine. This formulation is supported by its mass spectrum, which has a parent ion peak at m/e 273. Fragmentation peaks at m/e 201, 173, 152, 121, and 100 are assigned to ions $[H_3COC_6H_4CH_2(CH{=}CH)_2CO]^+$, $[H_3COC_6H_4CH_2(CH{=}CH)_2]^+$, $[(CH{=}CH)_2CONHCH_2CH(CH_3)_2]^+$, $[H_3CO\text{-}C_6H_4\text{-}CH_2]^+$, and $[OCNHCH_2CH(CH_3)_2]^+$, respectively. A peak at 217 may be due to a McLafferty rearrangement to $[H_3COC_6H_4CH_2(CH{=}CH)_2CONH_2]^+$, with elimination of isobutene.[9]

Support is also provided by the facts that piperovatine on acid hydrolysis generates isobutylamine, and on quantitative catalytic hydrogenation takes up 2 mol of hydrogen.

The proposed structure was confirmed by the following synthesis. Reduction of ethyl *p*-methoxyphenylacetate with lithium aluminum hydride afforded *p*-methoxyphenethyl alcohol, converted by phosphorus pentabromide into the corresponding bromide.[10] Reaction of the latter with triphenylphosphine generated the expected *p*-methoxyphenethyltriphenylphosphonium bromide as a syrup which solidified on cooling. Attempts to purify this salt were unsuccessful; the solid mass was pulverized and converted into its ylide **2** by treatment with *n*-butyllithium. The ylide was treated with methyl *trans*-3-formylacrylate (**3**), obtained by selenium dioxide oxidation of methyl crotonate.[11] The product proved to be mainly the desired dienoic ester **4a**, contaminated with a geometrical isomer thereof, as indicated by its uv absorption (relatively wide λ_{max}^{EtOH} 260–265 mμ, with low ϵ 15,000–



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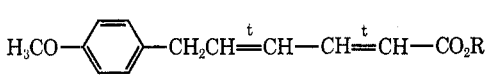
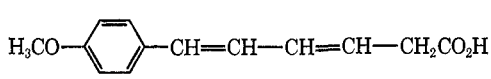
3



4a, R = CH_3
b, R = H



5

17,000),[7b] and by tlc analysis, which showed the presence of two major components, with similar R_f values. Recent studies on the stereochemical outcome of Wittig reactions[12] have shown that ylides enjoying resonance stabilization yield in the main *trans* alkenes, whilst ylides not so stabilized afford mixtures composed largely of *cis* alkenes. Ylide **2** is not resonance stabilized, and consequently it might have been anticipated that a mixture of isomers would result.

Treatment of a hexane solution of the product with a trace of iodine in sunlight[13] yielded a homogeneous all-*trans* ester **4a** (single spot on tlc), which crystallized easily. The all-*trans* configuration is assigned to it on spectral evidence: λ_{max}^{EtOH} 264 mμ (ϵ 25,500) and $\nu_{max}^{CCl_4}$ 1704, 1631, 1605, 994 cm^{-1}, both consistent with the presence of a CH=CH—CH=CH—CO grouping. The nmr spectrum showed a doublet (1 H, J = 15 Hz) centered at δ 5.87, which may be assigned to a proton α to the carbonyl group and *trans* to the β proton. The other features of the nmr spectrum were consonant with structure **4a**.

Hydrolysis of ester **4a** to the corresponding acid **4b** was first attempted with alkali, but it became clear on uv absorption measurement (λ_{max}^{EtOH} *ca.* 280–285 mμ, wide maximum) that the product was severely contaminated with the acid **5**, in which the double bonds have shifted into conjugation with the aromatic nucleus. This behavior was not unexpected, since analogous base-catalyzed isomerizations of compounds of the type $ArCH_2(CH{=}CH)_2CO_2CH_3$ (Ar = 2-thienyl, phenyl) have been described by Winterfeldt.[14] Fortunately, acid hydrolysis of **4a** furnished the corresponding acid, without isomerization (λ_{max}^{EtOH} 262 mμ). This acid did not react cleanly with thionyl chloride, but was smoothly converted by oxalyl chloride into its chloride.[13] The latter was not isolated but was condensed directly with isobutylamine to yield N-isobutyl-6-*p*-methoxyphenylsorbamide (**1**), which after high-vacuum sublimation and crystallization from ether had mp 121°, alone or mixed with an authentic sample of piperovatine, with which it was found to be identical in all respects. It will be evident that piperovatine must be reclassified as one of the increasing number of amides of vegetable origin.[15]

Experimental Section

Nmr measurements were made on a Varian A-60 instrument, with the assistance on occasion of a Varian C-1024 time-averaging computer, and using tetramethylsilane (TMS = 0) as internal reference. Thin layer chromatography (tlc) was effected on Merck silica gel plates (0.25 mm), with detection by iodine.

Isolation of Piperovatine.—Roots, leaves, and stems of dried *P. ovatum* plants were ground up finely, 600–650 g of this material being packed loosely into a linen bag and extracted with petroleum ether (bp 60–90°, 1500 ml) in a modified Soxhlet apparatus for 48 hr. The extract was concentrated to about 250 ml, filtered hot, and set aside at ambient temperature. The crystalline deposit was collected, washed with petroleum, and dried *in vacuo* (2.1 g). Attempts to recrystallize this product from a variety of solvents were unsuccessful, owing to gel formation.

(9) F. W. McLafferty, *Appl. Spectrosc.*, **11**, 148 (1957); *Anal. Chem.*, **31**, 82 (1959).
(10) J. B. Shoesmith and R. J. Connor, *J. Chem. Soc.*, 2230 (1927).
(11) F. Bohlmann and E. Inhoffen, *Chem. Ber.*, **89**, 1276 (1956).
(12) See, *inter al.*, L. D. Bergelson and M. M. Shemyakin, *Tetrahedron*, **19**, 149 (1963); L. D. Bergelson, L. I. Barsukov, and M. M. Shemyakin, *ibid.*, **23**, 2709 (1967); M. Schlosser and K. F. Christmann, *Justus Liebigs Ann. Chem.*, **708**, 1 (1967); W. P. Schneider, *Chem. Commun.*, 785 (1969).
(13) Compare P. E. Sonnet, *J. Org. Chem.*, **34**, 1147 (1969).
(14) E. Winterfeldt, *Chem. Ber.*, **96**, 3349 (1963).
(15) See, *inter al.*, A. Chatterjee and C. P. Dutta, *Sci. Cul.* (Calcutta), **29**, 568 (1963); *Tetrahedron Lett.*, 1797 (1966); *Tetrahedron*, **23**, 1769 (1967); C. K. Atal, K. L. Dhar, and A. Pelter, *Chem. Ind.* (London), 2173 (1967); K. L. Dhar and C. K. Atal, *Indian J. Chem.*, **5**, 588 (1967); C. K. Atal, P. N. Moza, and A. Pelter, *Tetrahedron Lett.*, 1397 (1968); J. W. Loder, A. Moorhouse, and G. B. Russell, *Aust. J. Chem.*, **22**, 1531 (1969).

It was purified by high-vacuum sublimation (0.05 mm), from an oil bath at 105–110°, to yield 60 mg of a white, microcrystalline product, mp 110–115°. A resublimation did not raise the melting point. Tlc of the twice-sublimed material, with development by ether–benzene (9:1), showed one major spot and a minor one of slightly lower R_f value. A careful crystallization of this product was effected by dissolving it in a fairly large volume of dry ether, then concentrating until, on slow cooling, crystallization rather than gel formation occurred. The matted needles (30 mg) so obtained had mp 120–121° (lit.[5] mp 123°) and showed a single spot on tlc. Spectral properties: λ_{max}^{EtOH} 262 mμ (ε 26,500); $\nu_{max}^{CCl_4}$ 3460, 3380, 3024, 2830, 1673, 1636, 1610, 1461, 1438, 1243, 1178, 1171, 1038, 991, and 939 cm^{-1}; nmr 0.95 (d, J = 7.5 Hz, 6 H), 1.10–2.20 (m, br, 1 H), 3.20 (t, J = 5 Hz, 2 H), 3.45 (d, J = 5 Hz, 2 H), 3.82 (s, 3 H), 5.6–6.3 (4 H), and 6.90 ppm (A_2B_2 pattern, 4 H).

The mass spectrum showed peaks at m/e 273 (parent ion), 217, 201, 174, 173, 158, 152, 139, 135, 128, 121, 115, 110, 101, 100, 96, 91, 83, 78, and 65.

Anal. Calcd for $C_{17}H_{23}NO_2$: C, 74.73; H, 8.42; N, 5.13; OCH_3, 11.34; mol wt, 273.4. Found: C, 74.41; H, 8.18; N, 4.99; OCH_3, 11.01; mol wt (mass spectrum), 273.

Later work showed that the product was more abundant in the roots or stems than in the leaves. In agreement with Dunstan and Garnett[5] the compound produces local anesthesia and a sharp burning sensation when rubbed on the tongue. It is insoluble in water, dilute aqueous alkali, and dilute acid, sparingly soluble in hydrocarbon solvents and ether, and readily soluble in methylene chloride, chloroform, and carbon tetrachloride.

Hydrolysis of Piperovatine.—Piperovatine (150 mg) and 4 N hydrochloric acid (25 ml) were boiled under reflux for 6 hr. The cooled, clear solution was rendered strongly alkaline with solid potassium hydroxide and then extracted continuously with ether for 48 hr. The ether solution was dried (KOH) and the solvent evaporated *via* a long Vigreux column to small bulk. The final solution was mixed with an excess of an ether solution of picric acid and the yellow precipitate which separated was collected, dried, and crystallized from ethanol, from which it separated in yellow prisms, mp 150–151°, alone or mixed with an authentic sample[16] of isobutylamine picrate, mp 150°.

Hydrogenation of Piperovatine.—Adams platinum oxide catalyst (25 mg) was prereduced in ethanol in a microhydrogenation apparatus. When no further hydrogen was absorbed, piperovatine (13.2 mg) was added and agitation resumed. Absorption of hydrogen was complete in 30 min and measured 2.40 ml at 740.9 mm and 24.3° (2.42 ml = $2H_2$).

***p*-Methoxyphenethyltriphenylphosphonium Bromide.**—Ethyl *p*-methoxyphenylacetate (61.4 g) in dry ether (100 ml) was added gradually, dropwise, to a stirred and cooled suspension of lithium aluminum hydride (6.5 g) in dry ether (150 ml) during 2 hr. After a further 2 hr of stirring Celite (2 g) was added, followed by the gradual addition of ice water until decomposition was complete. The ether was decanted and the inorganic residue was leached repeatedly with ether. The combined ether extracts were dried (Na_2SO_4) and the solvent was removed. The residual 2-*p*-methoxyphenylethanol distilled at 96–97° (0.15 mm) [lit.[17] bp 102–105° (0.3 mm)]: 32.2 g, 67%; ν_{max}^{film} 3230 cm^{-1}, no carbonyl band.

Phosphorus pentabromide (52.4 g) was suspended in dry benzene (150 ml) and stirred at 0° during the gradual (30 min) addition of the above alcohol (18.5 g) in dry benzene (50 ml). Dry air was drawn through the solution for 4 hr, and then it was washed with water, dried (Na_2SO_4), and concentrated. The residual *p*-methoxyphenethyl bromide distilled at 98–101° (0.2 mm) [lit.[10] bp 130–131° (11 mm)]: 15.2 g, 58%.

Triphenylphosphine (6.6 g) was dissolved in dry xylene (50 ml) along with the foregoing bromide (5.3 g), and the whole mixture refluxed in a bath at 170° for 6 hr. On cooling, an oily layer separated and quickly solidified. The xylene was decanted and the residue was rapidly ground to a fine powder and freed from solvent by keeping several hours *in vacuo*. The phosphonium bromide (8.8 g, 75%) had mp 80°, with sintering at 68°. It appeared to be amorphous, and attempts to purify it by crystallization from a variety of solvents failed, in part owing to its highly hygroscopic nature. It was stored *in vacuo* over phosphorus pentoxide.

Methyl *trans,trans*-6-*p*-Methoxyphenylhexa-2,4-dienoate (4a).—Methyl crotonate was oxidized with selenium dioxide in dioxane solution, as described by Bohlmann and Inhoffen.[11] The methyl *trans*-3-formylacrylate (**3**) so obtained distilled at 90–97° (25 mm) and crystallized easily on cooling. A suspension of *p*-methoxyphenethyltriphenylphosphonium bromide (12.9 g, 0.027 mol) in dry ether (400 ml) was stirred under nitrogen at room temperature during the gradual (5 min) addition of a 1.6 N hexane solution of *n*-butyllithium (20 ml). The resulting deep orange ylide solution was stirred for 1.5 hr, and then transferred under nitrogen to a pressure-equalized dropping funnel and added during 20 min, under nitrogen, to a stirred solution of methyl *trans*-3-formylacrylate (2.5 g, 0.025 mol) in dry ether (100 ml). The lighter-colored solution was stirred overnight at ambient temperature, and then freed from most of the triphenylphosphine oxide and lithium bromide by filtration. The filtrate was washed with dilute hydrochloric acid, aqueous sodium bicarbonate, and water, and dried and concentrated, finally *in vacuo*, yielding the crude dienoic ester (1.6 g, 28%) as a mixture of geometrical isomers. The product was dissolved in petroleum ether (bp 30–60°) and chromatographed on alumina (15 g) with elution with the same solvent, yielding a purified product (1.0 g) which showed two major spots on tlc, with R_f values of the same order, using petroleum ether (bp 30–60°)–ethyl acetate (4:1) for development. A solution of this product in hexane (250 ml) was kept under nitrogen, treated with a crystal of iodine, and exposed to direct sunlight for 10 min. The solution was washed with sodium thiosulfate solution and water, dried, and the solvent was removed. The residue (1.0 g) solidified readily and showed only one spot on tlc (conditions as above). Methyl *trans,trans*-6-*p*-methoxyphenylhexa-2,4-dienoate separated from hexane in prisms: mp 78–80°; bp 160° (bath) (0.07 mm); λ_{max}^{EtOH} 264 mμ (ε 25,500); $\nu_{max}^{CCl_4}$ 1704 (conjugated C=O), 1631, 1605 (two conjugated C=C), 1238 (aromatic ether), and 994 cm^{-1} (*trans,trans* CH=CH—CH=CH); nmr 3.50 (d, J = 6 Hz, 2 H, benzylic CH_2), 3.80, 3.85 (two s, each 3 H, aromatic and ester OCH_3), 5.70–6.35 (m, 4 H, olefinic H), and 7.05 ppm (A_2B_2 pattern, 4 H, aromatic H).

Anal. Calcd for $C_{14}H_{16}O_3$: C, 72.39; H, 6.94. Found: C, 72.68; H, 7.13.

***trans,trans*-6-*p*-Methoxyphenylhexa-2,4-dienoic Acid (6-*p*-Methoxyphenylsorbic Acid) (4b).**—The foregoing methyl ester (0.5 g), freshly distilled dioxane (25 ml), concentrated hydrochloric acid (7.5 ml), and water (5 ml) were heated under reflux on the steam bath for 16 hr. To the cooled mixture was added excess solid sodium bicarbonate. Neutral matter was removed by ether extraction, and the aqueous layer was acidified with 5 N hydrochloric acid. The semisolid material which separated was taken up in ether, and the solution was washed with water, dried, and concentrated. The oily residue (0.4 g) solidified readily; it was purified by vacuum distillation, bp 160–165° (bath) (0.04 mm), followed by crystallization from petroleum ether (bp 60–90°), from which it separated in clusters of feathery needles (0.4 g), mp 115°, λ_{max}^{EtOH} 262 mμ (ε 20,400).

Anal. Calcd for $C_{13}H_{14}O_3$: C, 71.54; H, 6.47; equiv, 218.2. Found: C, 71.67; H, 6.51; equiv, 218.5.

N-Isobutyl-6-*p*-methoxyphenylsorbamide (1).—The above acid (0.5 g) in dry ether (50 ml) was treated with oxalyl chloride (10 ml) and the mixture was kept at room temperature overnight with rigid exclusion of moisture. The solvent and excess oxalyl chloride were removed *in vacuo* and the residue was dissolved in dry ether (100 ml) and cooled in ice. A solution of isobutylamine (1.5 g) in dry ether (100 ml) was added gradually with agitation. After completion of the addition, the ethereal suspension was washed with dilute hydrochloric acid, water, and aqueous sodium bicarbonate, and then dried and concentrated. The solid residue (0.55 g) was purified by sublimation [105–110° (bath) (0.05 mm)] followed by crystallization from a critical volume of dry ether, from which it separated in matted needles or small prisms (0.35 g), mp 121°, alone or mixed with an authentic specimen of piperovatine. The spectral and tlc properties of the natural and synthetic materials were identical.

(16) "Organic Reagents for Organic Analysis," 2nd ed, Hopkin and Williams, Chadwell Heath, Essex, England, 1950, p 171.

(17) E. F. Jenny and S. Winstein, *Helv. Chim. Acta*, **41**, 807 (1958).

Registry No.—**1**, 25090-18-0; **4a**, 25090-19-1; **4b**, 25090-20-4.

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Side-Chain Transformations and Deuterium Labeling in the Steroidal Sapogenin Series[1]

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Synthetic transformations, notably through introduction of double bonds into rings E and F, have led to the preparation and characterization of a significant number of new derivatives of the basic nucleus of the steroidal sapogenin, (25*R*)-5α-spirostan, and to thirteen mono- or polydeuterated analogs. In the course of the work, it was possible to study the effect of acidic reagents on the spiroketal side chain, the ease of exchange proceeding in the order 23 >> 20 >>> 25. The availability of the various deuterium-labeled sapogenins proved of great value for many nmr assignments in this class of natural products.

In years past, synthetic work in the field of steroidal sapongenins has taken a number of directions. Characterization of unknown species either by direct chemical manipulation or by interconversion led Marker[4] and, more recently, others[5] to the identification of a wealth of these natural products. Degradation of the spiroketal side chain by modifications[6] of the original Marker procedure[7] afforded new and industrially important routes to such important hormones as the pregnanes,[7-9] cortisone,[8,9] and certain progestational agents.[8,9]

During the past 10 years, two groups[10,11] have reported total syntheses of members of this class; in addition, biosynthetic studies[12] and biodegradation experiments[13] have also appeared. Over the years the usual spectroscopic techniques, such as infrared,[14] ultraviolet,[15] nuclear magnetic resonance,[16] optical rotatory dispersion,[17] and mass spectrometry,[18] have been extensively applied with special reference to the spiroketal system of these sapogenins.

In this laboratory, in connection with a detailed study[18a] of the mass spectrometric behavior of steroidal sapogenins, it became necessary to introduce deuterium at numerous positions of the fundamental skeleton, namely (25*R*)-5α-spirostan or 3-deoxytigogenin (**1**).[19] We felt that such deuterium labeling, though laborious, would not only afford useful mass spectrometric information but would also aid in the interpretation of nuclear magnetic resonance spectra[16] by simplifying splitting patterns and by adding data to the Zürcher-type tables of Tori and Aono.[16e] With relatively few exceptions,[20] most of the chemical studies in this series have involved degradation of the spiroketal system rather than substitutions of the intact side chain. Consequently, our work was likely to contribute to this relatively scarcely studied aspect of sapogenin chemistry.

The problem which we faced may be stated as follows: starting with the basic sapogenin nucleus, **1**,

(1) Financial assistance from the National Institutes of Health (Grant No. AM 12758) is gratefully acknowledged.

(2) Taken, in most part, from the Ph.D. Thesis of W. H. F., National Institutes of Health Predoctoral Research Fellow, 1966–1970.

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