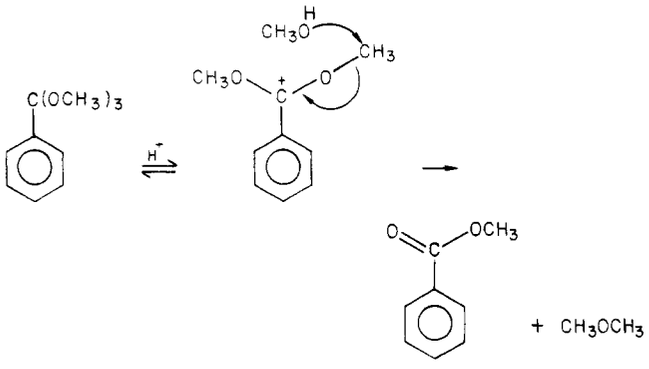
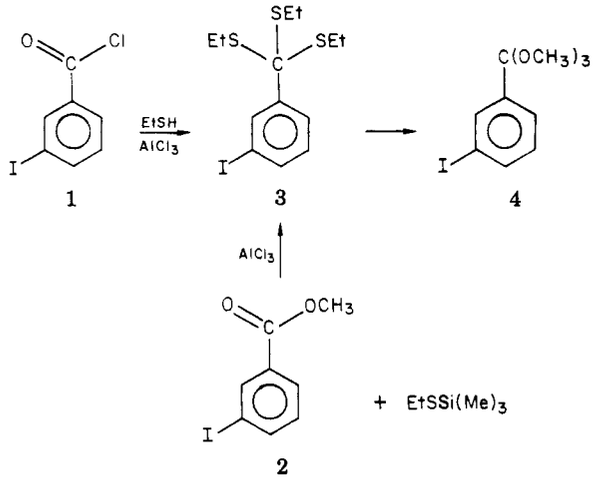
orthoesters,[2,3] the Pinner reaction of a nitrile, works very poorly for arylcarbonitriles.[4] As we have confirmed for *m*-iodobenzonitrile, it affords a difficultly separable mixture of the orthoester with (predominantly) the simple ester, from alkyl oxygen fission of the intermediate reversibly formed dimethoxybenzyl cation. Orthobenzoates



can also be prepared from benzotrichlorides, but chlorination of *m*-iodotoluene led to loss of iodine. Accordingly, we were forced to devise a new method for the synthesis of the desired orthoester, which produces the product in very good yield and excellent purity.

Our procedure is related to the report[3] that formate esters can be converted to orthothioformates with thiols and HCl and that the orthothioformates can then be converted to ethyl orthoformate with ethanol and $ZnCl_2$. We find that triethyl *m*-iodoorthothiobenzoate (3) can be



prepared in 90% yield[5] from *m*-iodobenzoyl chloride (1) with ethanethiol and $AlCl_3$ or directly in 70% yield from methyl *m*-iodobenzoate (2) with trimethylsilyl ethyl sulfide and $AlCl_3$. However, methanolysis of 3 with $AlCl_3$ catalyst led to a mixture of ester and orthoester, presumably again because of alkyl oxygen fission in a reversibly formed dimethoxyaryl carbocation. Thus, we needed reaction conditions for this methanolysis which would not affect the product orthoester, so we turned to silver-assisted solvolysis in a mildly basic medium. Treatment of the orthothioester 3 with $AgNO_3$ and collidine in methanol leads to rapid precipitation of silver mercaptide and the essentially quantitative formation of trimethyl *m*-iodoorthobenzoate (4). No other product can be detected by NMR, and the distilled crystalline product (4) is isolated in 85% yield.

In preliminary work we established that triethyl orthobenzoate could also be prepared from benzoyl chloride by our method. Thus it seems likely that this clean, high-yielding procedure will prove generally useful for the synthesis of aryl orthoesters.

Experimental Section

Triethyl *m*-Iodoorthothiobenzoate (3). Ethanethiol (25 mL) was added slowly to an anhydrous mixture of 8.0 g (30 mmol) of *m*-iodobenzoyl chloride (1) and 16.0 g of anhydrous $AlCl_3$. The homogeneous mixture was stirred and heated under reflux at 60 °C for 48 h, then cooled, and poured slowly with stirring into 150 mL of ice-cooled 4 N aqueous NaOH. Extraction with ether, washing, drying (Na_2SO_4, Na_2CO_3), and solvent evaporation afforded 12.0 g (100% of theoretical weight) of crude 3 which by NMR consisted of 90–95% of 3 contaminated with ethyl *m*-iodothiobenzoate. Chromatography[5] of 4.0 g of this oil on 200 g of basic alumina with ether–petroleum ether (20:80) afforded 3.6 g (90%) of pure 3 as the first fraction: bp 140 °C (0.3 mm); NMR (CCl_4) δ 1.15 (t, 9 H), 2.52 (q, 6 H), 7.00 (t, 1 H), 7.50 (d, 1 H), 7.75 (d, 1 H), 8.10 (s, 1 H).

Anal. Calcd for $C_{13}H_{19}S_3I$: C, 39.19; H, 4.81; S, 24.14; I, 31.86. Found: C, 38.95; H, 5.05; S, 23.88; I, 31.98.

This compound could also be prepared (in lower yield) by heating 3.5 g of (ethylthio)trimethylsilane[6] with 1.31 g of methyl *m*-iodobenzoate and 2.0 g of $AlCl_3$ at 110 °C for 24 h. Quenching and isolation as above yielded 1.8 g of crude 3, which afforded 1.40 g (70%) of pure 3 after chromatography.

Trimethyl *m*-Iodoorthobenzoate (4). To a solution of 2.0 g (5 mmol) of the orthothioester 3 and 2.50 g of collidine in 200 mL of anhydrous methanol was added 2.55 g (15 mmol) of $AgNO_3$ in 20 mL of acetonitrile. After 4 h of stirring at room temperature, the solid silver mercaptide was filtered away, the filtrate was taken to dryness, and the product was collected in ether (100 mL), which was filtered and evaporated. The crude product, 1.5 g (97%), was pure 4 by NMR. It was distilled to afford 1.30 g (85%) of pure crystalline 4: bp 110–115 °C (0.2 mm); mp 58–60 °C; NMR (CCl_4) δ 3.10 (s, 9 H), 7.05 (t, 1 H), 7.50 (d, 1 H), 7.65 (d, 1 H), 7.90 (s, 1 H).

Anal. Calcd for $C_{10}H_{13}O_3I$: C, 38.98; H, 4.25; I, 41.18. Found: C, 39.07; H, 4.42; I, 40.57.

Registry No. 1, 1711-10-0; 2, 618-91-7; 3, 72525-28-1; 4, 72525-29-2; ethanethiol, 75-08-1; (ethylthio)trimethylsilane, 5573-62-6.

(2) R. H. DeWolfe, "Carboxylic Ortho Acid Derivatives", Academic Press, New York, 1970.
(3) R. H. DeWolfe, *Synthesis*, 153 (1974).
(4) E.g., ref 2, p 4, reports an overall 27% yield from benzonitrile.
(5) The remainder is the thioester. On a moderate scale, as in the described procedure, this can be removed by simple chromatography. On a larger scale it would be more convenient to cleave the thioester with KOH hydrolysis. We find that in a few hours the thioester is completely hydrolyzed, while the orthothioester is inert and can be isolated by simple extraction. The thioester boils too close to the orthoesters 3 and 4 for easy removal by distillation.
(6) D. Evans, L. K. Truesdale, K. G. Grinn, and S. L. Nesbitt, *J. Am. Chem. Soc.*, **99**, 5009 (1977).

C(15) Configuration of Isopimaren-15,16-diols[1]

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The tricarbocyclic, pimaric diterpenes appear in nature mainly as dienes of the pimaradiene (1), sandaraco-

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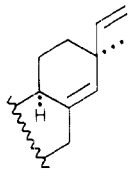
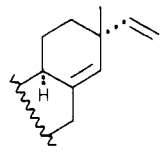
pimaradiene (**2**), and isopimaradiene (**3**) types as well as in the form of ene-15,16-diols **4**. A recent study of model and naturally occurring pimaren-15,16-diols revealed that ^{13}C NMR spectroscopy can be used for the determination of the heretofore unknown C(15) configuration of the latter compounds.[2] An earlier investigation on isopimaren-15,16-diols, substances not yet found in nature, is the subject of the present communication.



1



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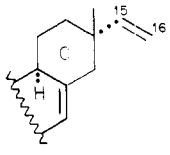
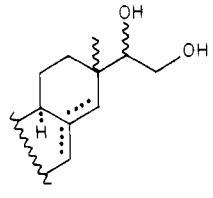


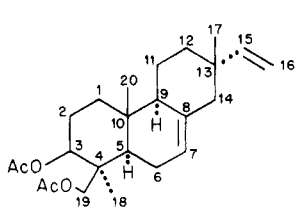
3



4

Virescenol B diacetate (**5**)[3] was used as a representative of the isopimaradienic diterpenes and was oxidized to a 15,16-diol isomer mixture with osmium tetraoxide. Neither the glycol mixture (**7a**) nor its diacetylated form (**7b**) could be separated, requiring all analyses to be executed on the mixture. The acetate mixture was also formed by the oxidation of diene **5** with potassium permanganate in acetic anhydride,[4] followed by the reduction of the resultant keto acetate **6** with lithium tri-*sec*-butylborohydride and subsequent acetylation. In view of only minimal carbon shift differences between the isomeric glycols **7a**—$\Delta\delta$(C-12) = $\Delta\delta$(C-17) = 0.8—and their esters **7b**—$\Delta\delta$(C-12) = 1.0 and $\Delta\delta$(C-17) = 0.5—the ^{13}C NMR spectral method of analysis is not applicable directly to the determination of the C(15) stereochemistry of natural, ring-C-saturated 15,16-diols. Apparently, a decreased difference of rotamer preference in the two C(15) epimeric dihydroxyethyl side chains results when both C(12) and C(14) are identically substituted, tetrahedral carbon sites, thus creating shift differences too small to be of diagnostic value. However, these differences were expected to be enhanced by the incorporation of the dioxygenated side chain in a rigid framework, a structural change which can be formulated readily by a variety of methods in the case of 7,8-unsaturated compounds, i.e., isopimaren-15,16-diols. The following procedure illustrates one example for the rigid fixation of the chiral side chain.

Oxidation of the photooxidation product 8 of virescenol B diacetate[5] with osmium tetraoxide and subsequent chromatography on silica led to an inseparable mixture of isomeric tetracycles **9a** and **9b**, whose oxidation with chromic acid yielded ketone **9c**. Wolff–Kishner reduction of the latter gave the tetrahydrofuran **9d**, while reduction



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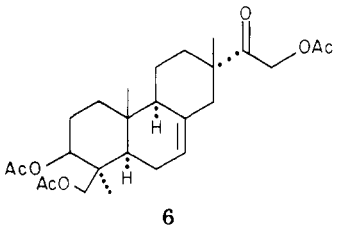

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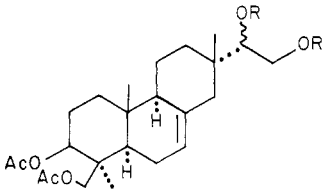
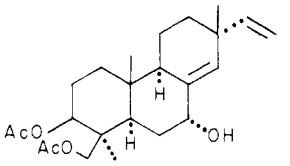
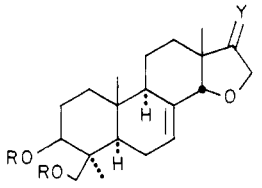


7a, R = H
b, R = Ac



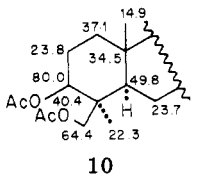
8

with lithium tri-*sec*-butylaluminum hydride afforded alcohol **9b**. The C(14) stereochemistry of compounds **9** is based on the ^{13}C NMR analysis of **9d** (vide infra), and the C(15) configuration of alcohols **9a** and **9b** is based on the same spectral analysis (vide infra) as well as on the expected steric course of the hydride reduction of ketone **9c**.



9a, Y = α-H, β-OH; R = Ac
b, Y = α-OH, β-H; R = Ac
c, Y = O; R = Ac
d, Y = H_2; R = H

The carbon shifts of ring A and its attachments in the diacetates **9a–c** are depicted to within ±0.1 ppm on formula **10**[6] and agree with the δ values for **6** and **7**. The chemical shifts of the ring C carbons and their attachments for tetrahydrofurans **9a–d** are shown on formulas **11–14**, respectively. The shielding of C(9) in the tetrahydrofurans (48.0 ± 0.3 ppm) compared with the δ(C-9) value (51.7 ± 0.4 ppm) of virescenol B[7] and compounds **6** and **7** and the upfield shift of C(12) in **9d** vs. the C(12) signal of virescenol B[7] indicate the axial disposition of the C(14)–oxygen bond toward ring C of the tetrahydrofurans and thus the cis attachment of the heterocycle to ring C. This stereochemistry is in agreement with the expected course of acid-induced ring closure of the 15,16-dihydro-15,16-diol derivatives of **8**.



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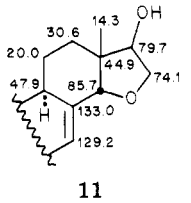

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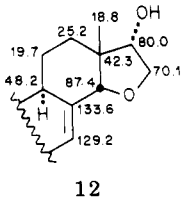

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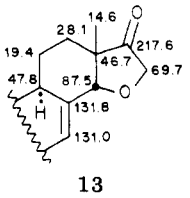

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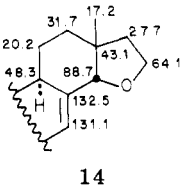

14

(1) "Carbon-13 Nuclear Magnetic Resonance Spectroscopy of Naturally Occurring Substances". 69. For the previous paper see N. Bellavita, J.-M. Bernassau, P. Ceccherelli, M. S. Raju, and E. Wenkert, *J. Am. Chem. Soc.*, in press.

(2) E. Wenkert, P. Ceccherelli, M. S. Raju, J. Polonsky, and M. Tingoli, *J. Org. Chem.*, **44**, 146 (1979).

(3) J. Polonsky, Z. Baskevitch, N. Cagnoli-Bellavita, and P. Ceccherelli, *Bull. Soc. Chim. Fr.*, 1912 (1970).

(4) K. B. Sharpless, R. F. Lauer, O. Repič, A. Y. Teranishi, and D. R. Williams, *J. Am. Chem. Soc.*, **93**, 3303 (1971); E. E. van Tamelen and S. A. Marson, *ibid.*, **97**, 5614 (1975).

(5) P. Ceccherelli, M. Curini, M. Tingoli, and R. Pellicciari, *Gazz. Chim. Ital.*, **108**, 129 (1978).

(6) The acetate shifts are δ Me = 20.9 ± 0.1 and δ CO = 170.4 ± 0.2.

(7) J. Polonsky, Z. Baskevitch, N. Cagnoli-Bellavita, P. Ceccherelli, B. L. Buckwalter, and E. Wenkert, *J. Am. Chem. Soc.*, **94**, 4369 (1972).

As expected at the initiation of the present study, the rigid tetrahydrofuranols **11** and **12** show dramatic shift differences for carbons in the vicinity of the 15-hydroxy group, thus making the identification of the C(15) configuration of a naturally occurring isopimaren-15,16-diol precursor an easy task. The γ effects induced by the hydroxy group on C(14) and C(17) in **11** and on C(12) in **12** caused characteristic shielding of these sites, thus revealing the indicated C(15) stereochemistry.

Experimental Section

Melting points were determined on a Reichert micro hotstage and are uncorrected. Infrared spectra of CCl_4 solutions were recorded on a Beckman IR5 spectrophotometer, and ^1H NMR spectra of $CDCl_3$ solutions (Me_4Si, $\delta = 0$) were obtained on JEOL IMN-C-60 HL and Varian EM390 spectrometers. Carbon-13 NMR spectra of $CDCl_3$ solutions were run on a Varian XL-100-15 spectrometer operating at 25.02 MHz in the Fourier transform mode.

15,16-Dihydro-15ξ,16-dihydroxyvirescenol B Diacetate (7a). A solution of 500 mg (0.200 mmol) of osmium tetraoxide in 10 mL of dioxane was added to a solution of 776 mg (0.200 mmol) of virescenol B diacetate (**5**) in 20 mL of dioxane, and the mixture was stirred at room temperature for 20 h. Hydrogen sulfide gas was bubbled through the mixture continuously for 1 h, the mixture filtered, and the precipitate washed exhaustively with methylene chloride. The filtrate and washings were evaporated and the residue (720 mg) chromatographed on silica gel. Elution with 9:1 benzene–ether yielded 680 mg (81%) of a gum whose crystallization from methanol gave diol mixture **7a**: mp 155–160 °C; ^1H NMR δ 0.75, 0.85, 0.98 (s, 3 each, 3 Me), 2.00 (s, 6, 2 Ac Me), 3.0–3.7 (m, 3, H-15, 2 H-16), 4.2–4.8 (m, 1, H-3), 4.20 (dd, 2, J = 9, 12 Hz, 2 H-19), 5.20 (m, 1, H-7); ^{13}C NMR δ major isomer 33.0 (C-12), 37.4 (C-13), 42.9 (C-14), 80.1 (C-15), 62.4 (C-16), 17.2 (C-17); ^{13}C NMR δ minor isomer 32.2 (C-12), 37.4 (C-13), 42.8 (C-14), 80.1 (C-15), 62.4 (C-16), 18.0 (C-17).

Anal. Calcd for $C_{24}H_{38}O_6$: C, 68.22; H, 9.07. Found: C, 68.00; H, 9.20.

15,16-Dihydro-16-acetoxy-15-oxovirescenol B Diacetate (6). Potassium permanganate (2.3 g) was added in small portions over a 45-min period to a stirring mixture, maintained below 6 °C, of 1.4 g (3.6 mmol) of virescenol B diacetate (**5**), 1.2 g of sodium carbonate, and 30 mL of acetic anhydride in 25 mL of 1,2-dimethoxyethane at 0 °C; stirring was continued for 2 h. Then there was added 15 mL of hexane, 15 mL of ethyl acetate, and 35 mL of a 10% aqueous solution of sodium bisulfite, and the mixture was extracted with hexane. The extract was washed with 400 mL of 1 N sodium hydroxide solution and water until it had become neutral, dried ($MgSO_4$), and evaporated under vacuum. Chromatography of the residue (1.2 g) on silica gel and elution with 19:1 benzene–ethyl acetate led to the recovery of 0.50 g of starting material (**5**) and to 0.50 g (47% on the basis of the recovery of **5**) of liquid keto ester **6**: IR C=O 1740 (s), 1730 (s), 1710 (s) cm^{-1}; ^1H NMR δ 0.90, 1.00, 1.06 (s, 3 each, 3 Me), 2.02, 2.02, 2.04 (s, 3 each, 3 Ac Me), 4.1–4.8 (m, 3, H-3, 2 H-19), 4.83 (s, 2, 2 H-15), 5.41 (m, 1, H-7); ^{13}C NMR δ 37.4 (C-1), 23.5 (C-2), 80.0 (C-3), 40.5 (C-4), 50.7 (C-5), 23.9 (C-6), 122.7 (C-7), 133.0 (C-8), 51.3 (C-9), 34.9 (C-10), 19.5 (C-11), 32.2 (C-12), 46.4 (C-13), 41.3 (C-14), 205.2 (C-15), 64.4 (C-16), 18.8 (C-17), 22.6 (C-18), 64.4 (C-19), 15.3 (C-20), 170.0, 170.2, 170.5 (Ac C=O), 21.1, 21.1 (Ac Me), 20.4 (16-OAc Me).

Anal. Calcd for $C_{26}H_{38}O_7$: C, 67.51; H, 8.28. Found: C, 67.68; H, 8.17.

15ξ,16-Diacetoxy-15,16-dihydrovirescinol B Diacetate (7b). A solution of 300 mg (0.71 mmol) of diol **7a** and 2 mL of acetic anhydride in 3 mL of pyridine was kept at room temperature for 24 h. The usual workup, chromatography of the crude product on silica gel and elution with 50:1 benzene–ethyl acetate, yielded 290 mg (80%) of gummy tetraacetate **7b**: ^1H NMR δ 0.85, 0.88, 1.02 (s, 3 each, 3 Me), 1.97, 1.99, 2.01, 2.05 (s, 3 each, 4 Ac Me), 3.8–5.0 (m, 6, H-3, H-15, 2 H-16, 2 H-19), 5.24 (m, 1, H-7); ^{13}C NMR δ major isomer 31.7 (C-12), 36.6 (C-13), 42.3 (C-14), 77.8 (C-15), 62.6 (C-16), 17.5 (C-17); ^{13}C NMR δ minor isomer 32.7 (C-12), 36.6 (C-13), 42.0 (C-14), 77.8 (C-15), 62.6 (C-16), 18.0 (C-17).

Anal. Calcd for $C_{28}H_{40}O_8$: C, 66.63; H, 7.99. Found: C, 66.75; H, 7.80.

A solution of lithium tri-*sec*-butylborohydride (0.5 M) in 12 mL of tetrahydrofuran was added dropwise at −30 °C to a stirring solution of 462 mg (1.00 mmol) of ketone **6** in 20 mL of tetrahydrofuran under nitrogen, and stirring was continued at −30 °C for 2 h. Sodium hydroxide solution (3 M, 5 mL) and 5 mL of 30% hydrogen peroxide were added, and the mixture was allowed to reach room temperature over a 0.5-h period, diluted with water, and extracted with chloroform. The extract was dried (Na_2SO_4) and evaporated under vacuum. The residue (0.4 g) was chromatographed on silica gel and eluted with 19:1 benzene–ethyl acetate. Acetylation of the resultant alcohol (350 mg) by the above procedure yielded 340 mg (67%) of tetraester **7b**, with spectra as above. (^{13}C NMR spectroscopy indicated the major isomer to be the minor product of the osmylation–acetylation process.)

8,14-Dehydro-7,8-dihydro-7α-hydroxyvirescenol B Diacetate (8). A solution of 1.00 g (2.50 mmol) of virescenol B diacetate (**5**) and 5 mg of eosine, through which a stream of oxygen was passed continuously, was irradiated by a 250-W tungsten lamp for 19 h. After vacuum removal of the solvent the residue (1.0 g) was chromatographed on silica gel and eluted with 19:1 benzene–ethyl acetate. The hydroperoxide eluate (0.8 g) was treated with a solution of 300 mg of sodium iodide and 50 mg of sodium thiosulfate in 50 mL of methanol. Water (150 mL) was added and the mixture extracted with chloroform. The extract was dried (Na_2SO_4) and evaporated under vacuum. Chromatography of the residue (0.7 g) on silica gel and elution with 9:1 benzene–ethyl acetate gave 650 mg (65%) of gummy hydroxy diester (spectra recorded in ref 5).

Anal. Calcd for $C_{24}H_{34}O_5$: C, 17.61; H, 8.51. Found: C, 71.58; H, 8.70.

15,16-Dihydro-15ξ-hydroxy-14α,16-oxidovirescenol B Diacetates (9a and 9b). A solution of 350 mg (1.40 mmol) of osmium tetraoxide in 20 mL of dioxane was added to a solution of 600 mg (1.50 mmol) of diene **8** in 30 mL of dioxane, and the mixture was stirred at room temperature for 20 h. After hydrogen sulfide gas had been bubbled through the mixture continuously for 1 h, the suspension was filtered and the residue washed exhaustively with methylene chloride. The combined filtrate and washings were evaporated, and the residue (560 mg) was chromatographed on silica gel. Elution with 19:1 chloroform–methanol yielded 500 mg (78%) of a gummy tetrahydrofuranol isomer mixture (**9a** and **9b**): ^1H NMR δ 0.83, 0.98, 0.98 (s, 3 each, 3 Me), 2.03, 2.06 (s, 3 each, 2 Ac Me), 3.1–4.8 (m, 6, H-3, H-15, 2 H-16, 2 H-19), 5.75 (m, 1, H-7).

Anal. Calcd for $C_{24}H_{36}O_6$: C, 68.54; H, 8.63. Found: C, 68.41; H, 8.72.

15,16-Dihydro-14α,16-oxido-15-oxovirescenol B Diacetate (9c). A solution of 1.00 g (1.88 mmol) of the **9a–9b** alcohol mixture was added to a solution of 1.80 g of chromic acid and 2.1 mL of pyridine in 20 mL of methylene chloride, and the mixture was stirred at room temperature for 0.5 h. It was poured into ice–water and extracted with methylene chloride. The extract was evaporated and the residue (900 mg) chromatographed on silica gel. Elution with chloroform gave 800 mg (80%) of semisolid ketone **9c**: IR C=O 1740 (s), 1770 (s) cm^{-1}; ^1H NMR δ 0.83, 1.00, 1.00 (s, 3 each, 3 Me), 2.02, 2.04 (s, 3 each, 2 Ac Me), 3.7–4.8 (m, 5, H-3, 2 H-16, 2 H-19), 5.90 (m, 1, H-7).

Anal. Calcd for $C_{24}H_{34}O_6$: C, 68.87; H, 8.19. Found: C, 68.91; H, 8.09.

15,16-Dihydro-14α,16-oxidovirescenol B (9d). A mixture of 800 mg (1.50 mmol) of ketone **9c** and 0.5 mL of hydrazine in 5 mL of diethylene glycol was stirred at 130 °C for 3 h during which time the water liberated was removed through a Dean–Stark trap. After 500 mg of finely powdered potassium hydroxide was added to the cooled mixture, it was heated at 130 °C for 1 h and then poured into ice–water and extracted with chloroform. The extract was dried (Na_2SO_4) and evaporated, and the residue (430 mg) was chromatographed on silica gel. Elution with 19:1 chloroform–methanol yielded 320 mg (53%) of semisolid **9d**: ^1H NMR δ 0.73, 1.03, 1.20 (s, 3 each, 3 Me), 3.1–4.7 (m, 5, H-3, 2 H-16, 2 H-19), 5.75 (m, 1, H-7).

Anal. Calcd for $C_{20}H_{32}O_3$: C, 74.96; H, 10.06. Found: C, 74.64; H, 9.80.

15,16-Dihydro-15α-hydroxy-14α,16-oxidovirescenol B Diacetate (9b). A stirring solution of 200 mg (0.375 mmol) of ketone **9c** in 5 mL of tetrahydrofuran under nitrogen at −5 °C was treated with lithium tri-*sec*-butylborohydride (1 M, 2.5 mL), and the mixture was allowed to reach room temperature and stirred for 3 h. After the addition of sodium hydroxide (3 M, 2 mL) and hydrogen peroxide solutions (30%, 2 mL), the mixture was stirred at room temperature for 0.5 h and then poured into ice-water. It was extracted with chloroform and the extract dried (Na_2SO_4) and evaporated. Chromatography of the residue (120 mg) on silica gel and elution with 19:1 chloroform–methanol gave 75 mg (38%) of the alcohol isomer **9b** (spectra given above).

Registry No. **5**, 11051-39-1; **6**, 72478-92-3; **7a**, isomer 1, 72478-93-4; **7a**, isomer 2, 72478-94-5; **7b**, isomer 1, 72522-14-6; **7b**, isomer 2, 72522-15-7; **8**, 68671-08-9; **9a**, 72478-95-6; **9b**, 72478-96-7; **9c**, 72478-97-8; **9d**, 72478-98-9.

Synthetic Applications and Mechanism of the Pyrolysis of Phenothiazine Carbamates

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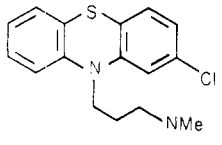
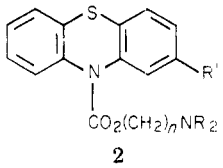
N-[(Dialkylamino)alkyl]phenothiazine derivatives such as chlorpromazine (**1**) have played an important role in the



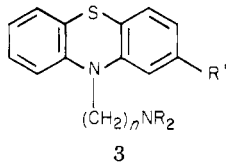
1

study and treatment of a variety of neurological disorders.[1] More recently, interest has developed in the phenothiazine psychotropic drugs as potential antitumor agents.[2] While a very large number of phenothiazines related to **1** have been prepared, nearly all have been synthesized by direct alkylation of the phenothiazine ring system with aminoalkyl halides.[3] We wish to report the results of our study of an alternative procedure starting with phenothiazine carbamates.

According to a German patent issued in 1956,[4] phenothiazine carbamates of type **2** (R = Et, R′ = H) decomposed upon distillation at 180–200 °C to afford the corresponding alkylated derivatives, **3**. The following year,



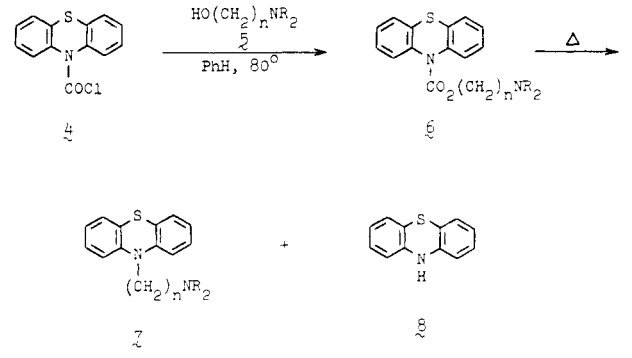
2



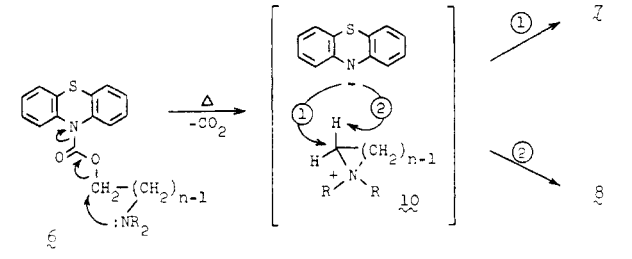
3

n = 2, 3

Scheme I

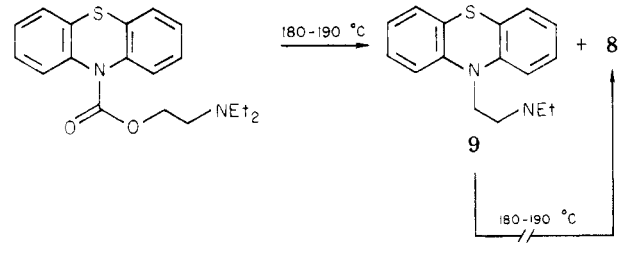


Scheme II



Schmitt and co-workers[5] reported that 3-substituted phenothiazine carbamates (**2**: R = Me, Et; R′ = COMe, COEt, OMe, etc.) could be pyrolyzed to their N-alkylated counterparts **3** in yields ranging from 45 to 80%.

To define the scope and synthetic utility of this reaction, we studied the carbamates **6a–i** listed in Table I. They were prepared from phenothiazine-10-carbonyl chloride (**4**) and either the appropriate amino alcohol or its sodium derivative (Scheme I). It was necessary to use the sodium aminoalkoxide in the preparation of **6h** and **6i**; the free amino alcohols were used in all other instances following literature procedures.[5] Pyrolysis experiments were carried out by heating the carbamates neat at about 10 °C above their decomposition temperatures for 30 min after cessation of gas evolution. Isolation of the products corresponding to **7** was readily accomplished by acid–base extractions. Invariably, the neutral layer from the workup contained phenothiazine (**8**) (Table I). We believe that the phenothiazine is not the result of thermal cracking of the N-alkylated products since, in the case of the pyrolysis of **6b**, no phenothiazine was formed when the product **9** was subjected to the same pyrolysis conditions.[6]



It was found that the ratio of the N-alkylated products to phenothiazine could be increased by employing carbamates purified via their hydrochloride salts. Thus, pyrolysis of "crude" (but devoid of phenothiazine) carbamate **6f** at 230 °C for 90 min afforded an oil whose NMR spectrum indicated a mixture of 84% N-alkylated product

(1) See, for example, A. Burger, Ed., "Medicinal Chemistry", 3rd ed., Wiley-Interscience, New York, 1970, pp 1428–37.

(2) J. S. Driscoll, N. R. Melnick, F. R. Quinn, N. Lomax, J. P. Davignon, R. Ing, B. J. Abbott, G. Congleton, and L. Dudeck, *Cancer Treat. Rep.*, **62**, 45 (1978), and references cited therein.

(3) For reviews on the chemistry of phenothiazine and its derivatives, see: (a) C. Bodea and I. Silberg, *Adv. Heterocycl. Chem.*, **9**, 321–460 (1968). (b) S. P. Massie, *Chem. Rev.*, **54**, 797 (1954). Recently the technique of phase-transfer catalysis has been reported to give improved yields for the direct alkylation of 2-chlorophenothiazines [J. Masse, *Synthesis*, 341 (1977)].

(4) H. H. Frederich, O. A. Grosskinsky, and A. Amann, German Offen. 939630 (1956); *Chem. Abstr.*, **53**, 8172e (1959).

(5) J. Schmitt, J. Biotard, P. Comoy, A. Hallot, and M. Suquet, *Bull. Soc. Chim. Fr.*, 938 (1957); J. Schmitt, A. Hallot, P. Comoy, M. Suquet, R. Fallard, and J. Boitard, *ibid.*, 1474 (1957).

(6) At higher temperatures, however, compound **9** does decompose to produce phenothiazine: heating at 260 °C for 2 h resulted in a 33% yield of **8** (58% of the starting material was recovered).

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