standing yielded transparent crystals, mp 167–168 °C, in quantitative yield. Spectral properties of **4** were the following: IR ν_{max} (KBr) 3550, 1603, 920, 870, 830, 815 cm^{-1}; ^{1}H NMR (Me_2SO-d_6) δ 1.22 (3 H, t, J = 7 Hz, Ar–CH_2–CH_3), 2.25 (6 H, s), 2.6 (4 H, s), 2.74 (2 H, q, J = 7 Hz, Ar–CH_2–CH_3), 6.85 (1 H, s), 7.05 (1 H, d), 7.45 (1 H, d), 9.4 (2 H, s); mass spectrum, m/e 268 (M^+), and fragmentation at m/e 115, 119, 151, 164, 181, 195, 238, 268.

Dihydrojuncusol Diacetate (5). Acetylation of dihydrojuncusol (4) was carried out in pyridine and acetic anhydride in the usual way and the product was crystallized from benzene, mp 138 °C. Compound **5** gave the following spectral data: IR ν_{max} (KBr) 1750, 1603, 920, 870, 830, 815 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.3 (3 H, t), 2.4 (6 H, s), 2.5 (6 H, s), 2.8 (4 H, s), 2.9 (2 H, q), 6.9 (1 H, s), 7.4 (1 H, t), 9.4 (1 H, s). The mass spectrum gave fragmentation at m/e 238, 253, 268, and 310 and a parent peak at m/e 352 (M^+).

Anal. Calcd for $C_{22}H_{24}O_4$ (mol wt 352): C, 75.00; H, 6.81. Found: C, 75.16; H, 6.69.

CrO_3 Oxidation of Dihydrojuncusol Diacetate. Compound **5** (400 mg) was dissolved in glacial acetic acid (10 mL) and gradually added to a solution of CrO_3 (800 mg) in 80% aqueous acetic acid (5 mL), keeping the temperature below 5 °C. After the addition, the mixture was stirred at room temperature for 4 h. The resulting mixture was then poured onto ice water (100 mL), extracted thoroughly with $CHCl_3$, dried over anhydrous Na_2SO_4, and evaporated. The quinone **6** was crystallized from benzene as yellow needles (0.15 g): mp 210–215 °C dec; IR ν_{max} (KBr) 1750, 1650, 1603, 925, 915, 875, 180 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.35 (3 H, t, J = 7 Hz), 2.25 (3 H, s), 2.3 (6 H, s), 2.4 (3 H, s), 2.85 (2 H, q, J = 7 Hz), 7.26 (1 H, d, J = 5 Hz), 7.55 (1 H, s), 7.46 (1 H, d, J = 5 Hz). The mass spectrum gave a parent ion peak at m/e 380 (M^+) and fragmentation at m/e 181, 253, 268, 305, 337, 352, and 380.

Anal. Calcd for $C_{22}H_{20}O_6$ (mol wt 380): C, 69.47; H, 5.26. Found: C, 69.64; H, 5.20.

Reaction of Quinone 6 with *o*-Phenylenediamine. Compound **6** (0.04 g) was refluxed in glacial acetic acid (3 mL) with *o*-phenylenediamine (0.02 g) for 2.5 h. The reaction product was cooled and poured onto ice-cold water, at which time a yellow precipitate separated. The latter was extracted with chloroform, and the chloroform layer was washed with water, dried with anhydrous Na_2SO_4, and evaporated. The dark yellow mass was recrystallized from benzene to give short, fine yellow needles. Compound **7** shrinks at 250–255 °C and finally decomposes at 270 °C. The IR spectrum showed the disappearance of the carbonyl band of the quinone **6** at 1650 cm^{-1}.

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Registry No.—**1**, 62023-90-9; **2**, 62023-91-0; **3**, 67489-25-2; **4**, 64052-93-3; **5**, 64052-94-4; **6**, 67489-26-3; **7**, 67489-27-4; *o*-phenylenediamine, 95-54-5.

References and Notes

(1) (a) Contribution 4 in the series of antineoplastic agents. For part 3, refer to ref 7. (b) Part 7 in the series "Constituents of Marsh Grass."
(2) (a) Department of Chemistry, Mississippi State University. (b) The Institute for Natural Products Research and the Department of Chemistry, University of Georgia. (c) Partly taken from the Ph.D. Thesis of N. V. Mody, Mississippi State University. (d) Boll Weevil Research Laboratory, U.S. Department of Agriculture, Mississippi State, Miss.
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Convenient Synthesis of *N*-Noratropine[1]

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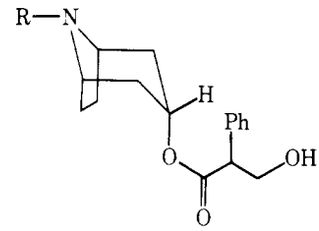
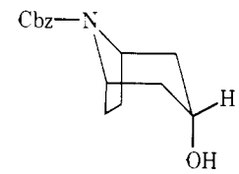
Due to their pronounced biological activities, compounds containing the tropane structure have been of interest for a number of decades.[2–4] Recently, derivatives of *N*-alkylnoratropine, especially the bronchodilator *N*-isopropyl-*N*-methylnoratropinium bromide[5–7] (Ipratropium bromide, Sch 1000), have commanded particular attention.

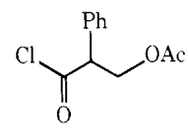
N-Noratropine (**1**) itself, long known as a constituent of various solanaceous plants,[8] was first synthesized by Nádor et al.[9,10] who reacted *N*-carbobenzyloxynortropine (**2**) with *O*-acetyltropic acid chloride (**3**) in the presence of pyridine,



1, R = H
4, R = Cbz
7, R = Me



2



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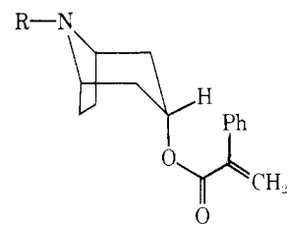
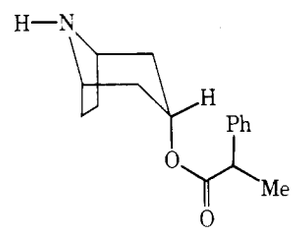
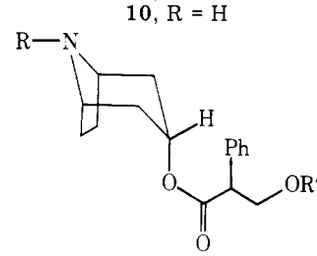


5, R = Cbz
10, R = H



6



8, R = Cl_3CCH_2OCO; R′ = H
9, R = R′ = Cl_3CCH_2OCO

followed by acid-catalyzed hydrolysis of the *O*-acetyl group. The resulting *N*-carbobenzyloxynoratropine (**4**) was subjected to hydrogenolytic cleavage to afford noratropine (**1**). However, Bertholdt et al.[11] claimed that under the acylation conditions mentioned above, the acrylate **5** was formed by elimination of AcOH. They conclusively proved that after hydrogenolysis, the phenyl propionate **6** was the final product. The same elimination reaction has also been observed by other workers[12] in a closely related series of compounds. Both groups of investigators pointed out that the desired tropate esters could be obtained in fair yields if the acylation step was carried out in the absence of basic catalysts. Nevertheless, it seemed worthwhile to examine the possibility of N-demethylating commercially available atropine (**7**), which would constitute a much simpler method of synthesizing noratropine.

It has already been shown that the simple bases tropine and tropinone can be demethylated with ethyl chloroformate,[13] but the strongly acidic conditions required for the hydrolysis of the resulting carbamate intermediates were deemed to be

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incompatible with the sensitive β-hydroxy ester functionality present in atropine. Demethylation with trichloroethyl chloroformate[14] seemed potentially more useful, since trichloroethyl carbamates can be cleaved under mild conditions with Zn in AcOH.

In a trial experiment, treatment of atropine with Cl_3CCH_2OCOCl under conditions similar to those employed for the PhOCOCl demethylation of morphine[15] resulted in the quantitative formation of two nonbasic, oily compounds (ratio ~9:1), which were separated by column chromatography and assigned structures **8** and **9** on the basis of NMR and IR spectroscopy. When treated with Zn dust in AcOH, both **8** and **9** were converted into the same polar product, presumed to be noratropine.

On a preparative scale, the reaction mixture consisting of **8** and **9** was directly treated with Zn dust in AcOH to produce crystalline noratropine (**1**) in 90.5% yield. Care had to be exercised during the workup, since concentration of the filtered AcOH solution containing noratropine on a rotary evaporator at 60 °C gave primarily the dehydration product **10** (oxalate mp 268–269 °C, NMR (Me_2SO-d_6) δ 6.32 [d, J = 28 Hz]), again demonstrating the sensitivity of this system. Therefore, the basification–extraction scheme described below was adopted.

Experimental Section

A mixture of 5.0 g (17.3 mmol) of atropine (**7**), 12 mL (87 mmol) of Cl_3CCH_2OCOCl, 17.28 g (173 mmol) of $KHCO_3$, and 250 mL of $CHCl_3$ was refluxed for 4 h. The cooled mixture was filtered, the solvent removed on a rotary evaporator, and the residue freed from excess Cl_3CCH_2OCOCl (kugelrohr setup, oil pump, 80 °C). The remaining mixture of carbamates was stirred with 10 g of activated Zn dust[16] in 100 mL of AcOH at 15 °C for 16 h. Inorganic matter was filtered off and the filter cake was washed with AcOH (50 mL). The filtrate was diluted with 150 mL of H_2O and cooled in an ice bath. Aqueous NH_3 (58%) was added dropwise (T < 10 °C) with stirring to pH ~6, at which point the mixture was extracted with ether to remove a small amount of neutral material. Addition of NH_3 to the aqueous phase was continued to pH ~10. Extraction with four 150-mL portions of $CHCl_3$, washing the combined extracts with brine, drying over anhydrous K_2CO_3, and evaporating afforded 4.3 g (90.5%) noratropine (**1**) as colorless crystals, mp 114 °C (lit. mp 114 °C),[11] homogeneous on TLC (silica gel, 50 CH_2Cl_2/50 MeOH/1 Et_3N).

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Registry No.—**1**, 16839-98-8; **7**, 51-55-8; **8**, 67393-86-6; **9**, 67393-87-7; Cl_3CH_2OCOCl, 17341-93-4.

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Side-Chain Extension of 17-Keto Steroids to 17α,22-Aldehydes

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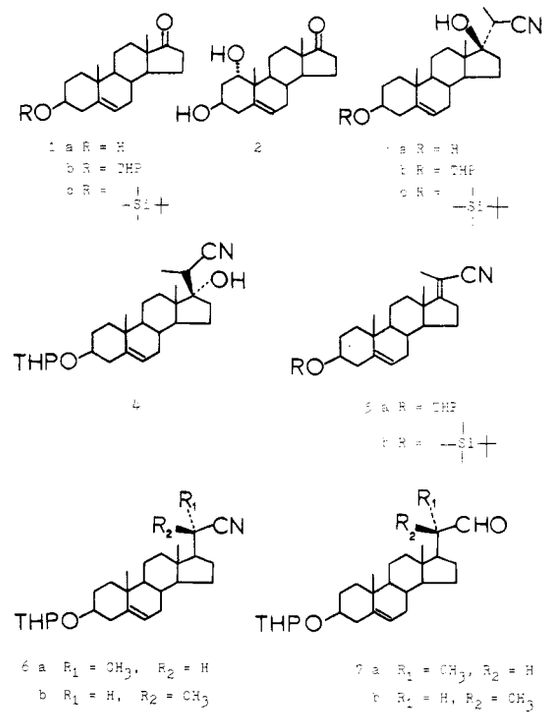
We wished to develop a method for side-chain extension of 17-keto steroids which could be applied to 1α,3β-dihydroxyandrost-5-en-17-one, readily available from 3β-hydroxyandrost-5-en-17-one by microbiological methods.[2] Thus an alternative route to the steroidal precursors of the clinically important 1α,25-dihydroxyvitamin D_3[3,4] and its analogues might become available. We now report a simple method of converting such 17-keto steroids into the 17α*H*-23,24-bisnorchol-5-en-22-al derivatives and related compounds.

3β-Hydroxyandrost-5-en-17-one (**1a**) was converted to the THP ether **1b**,[5] which upon treatment with excess propionitrile and lithium diisopropylamide (LDA)[6] at −78 °C for 90 min, followed by addition of the cold solution to water, gave a single product **3b** (88%). The 17β orientation of the hydroxyl in **3b** is assigned from mechanistic considerations and from the observed downfield shift of the C-18 methyl NMR signal (δ 0.88 in **1b**) to δ 0.95. The product was formed as a mixture of epimers at C-20, which was not resolvable by recrystallization or thin-layer chromatography. In the presence of $Eu(fod)_3$ (ca. 1 equiv), the originally sharp C-18 methyl singlet became shifted substantially downfield, and appeared as two singlets of nearly equal intensity at δ 1.18 and 1.21.[7]

When the propionitrile addition reaction was conducted by stirring the reactants at −78 °C for 20 min followed by stirring at 25 °C for 20 h before workup, a mixture of **3b** and an isomeric product assigned the structure **4** (ratio of **3b**–**4**, ca. 1:2) was obtained in very low yield, accompanied by recovered starting material (80%). After recrystallization of the **3b** + **4** mixture, the pure **4** was obtained. Product **4** closely



resembled **3b** in its IR and ^1H NMR spectra. The latter were practically superimposable in the region δ 3.0–6.0, and differed mainly in the chemical shifts of the C-20–H (**3b**, δ 2.74; **4**, δ 2.85), C-21 methyl (**3b**, 1.47; **4**, δ 1.42), and C-18 methyl (**3b**,

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