Synthesis of Pharmacologically Active Nitrogen Analogs of the Tetrahydrocannabinols

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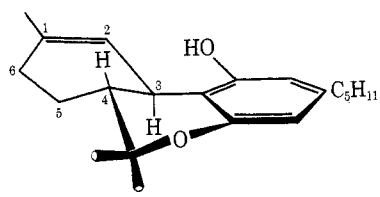
The synthesis of a nitrogen analog of $\Delta^{1(6)}$-*trans*-tetrahydrocannabinol, a psychoactive component of *Cannabis sativa* L, is described. The condensation of 2,6-dimethoxy-4-*n*-amylbenzylidenemethylamine (**9**) with glutaric anhydride in refluxing xylene provided *trans*-1-methyl-5-carboxy-6-(2,6-dimethoxy-4-*n*-amylphenyl)-2-piperidone (**11**). Subsequent transformations yielded the desired tricyclic system **27** in which the C-2 methylene of $\Delta^{1(6)}$-*trans*-tetrahydrocannabinol is replaced by an *N*-methyl moiety. Configurational and conformational assignments of the intermediates were made by nmr spectroscopy. The diastereomeric mixture of amines **4** and **5** obtained on catalytic reduction of **27** possesses both antidepressant and anticonvulsant activity.

Two psychoactive constituents of Cannabis have been shown, Δ^1-*trans*-tetrahydrocannabinol (Δ^1-THC, **1**)[2] and $\Delta^{1(6)}$-*trans*-tetrahydrocannabinol ($\Delta^{1(6)}$-THC, **2**).[3] We recently reported the synthesis of a series of model nitrogen analogs of the THC's, including **3**.[4] Since a phenolic group and an alkyl side chain have been demonstrated to be structural requirements for pharmacologic activity,[5,6] our model compounds did not appear to be promising candidates for biologic evaluation. We now wish to report the successful extension of our studies to the preparation of the nitrogen analog of $\Delta^{1(6)}$-THC, compound **27**. Catalytic reduction of **27** gave a diastereomeric mixture of amines **4** and **5**. Preliminary pharmacologic tests[7] indicate that this mixture possesses both antidepressant (modified dopa test in mice; marked activity at 5 mg/kg) and anticonvulsant (audiogenic seizure in mice; 60% protection at 30 mg/kg) activity.



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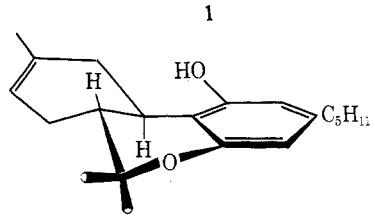

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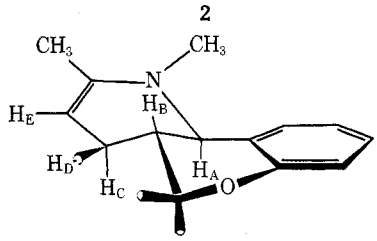

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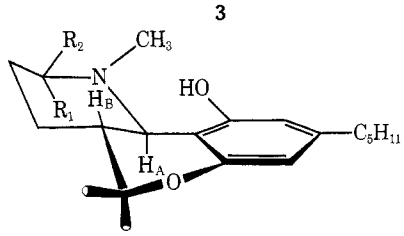
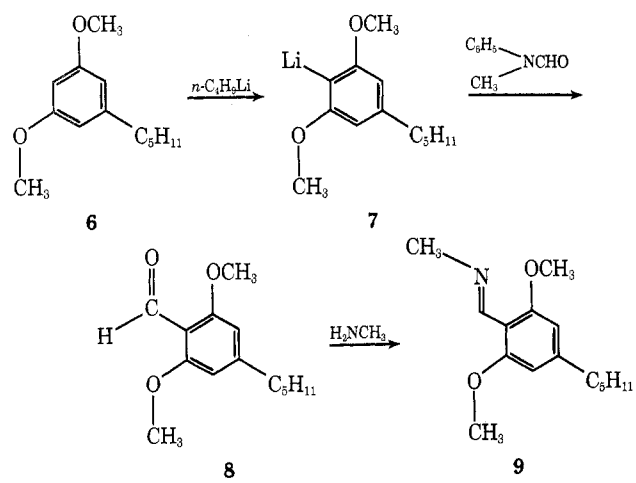


4, $R_1 = CH_3$; $R_2 = H$
5, $R_1 = H$; $R_2 = CH_3$

Metalation of olivetol dimethyl ether (**6**) with *n*-butyllithium provided the phenyllithium intermediate **7**, which was converted to 2,6-dimethoxy-4-*n*-amylbenzaldehyde (**8**) with *N*-methylformanilide.[8] The Schiff base **9** was obtained by stirring a solution of the aldehyde **8** and methylamine in benzene over molecular sieves.

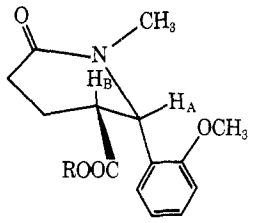


6 **7** **8** **9**

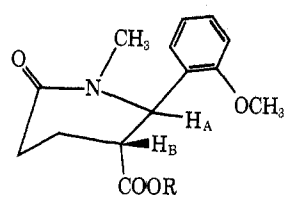
Condensation of the Schiff base **9** with glutaric anhydride in refluxing xylene gave an 86% yield of the diastereomeric mixture of piperidones **10** and **11**, which was separated by fractional crystallization. The minor cis diastereomer **10** produced the expected axial–equatorial coupling constant J_{AB} = 5 Hz, which is identical with that of the model cis diastereomer **12**. The major diastereomer was isolated in 45% yield and displayed an nmr coupling constant J_{AB} = 7 Hz. Since vicinal diaxial protons show coupling constants of 8–13 Hz and vicinal diequatorial protons 1–5 Hz in six-membered rings,[9] evidently the trans diastereomer **11** spends more time in the diequatorial conformation than the model trans compound **13** (J = 2.5 Hz), which appears to exist largely in the diaxial conformation. This change in conformational equilibrium of the trans diastereomer **11** relative to **13** is also reflected in the chemical shift value for the methoxycarbonyl proton signal of the trans ester **14** (δ 3.61 ppm) relative to the model trans ester **15** (δ 3.75 ppm). This is expected, since the methoxycarbonyl protons can experience the shielding effect of the aromatic π cloud in the diequatorial conformation but cannot in the diaxial conformation. The corresponding values in the cis methyl ester **16** and cis model methyl ester **17** were δ 3.51 and 3.56, respectively.

Finally, the trans dimethyl ether **11** was demethylated to the diphenol **18** with boron tribromide in methylene chloride.[10] Subsequent cyclodehydration to the rigid di-

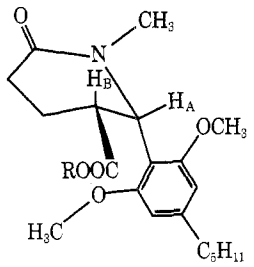
equatorial lactone 19 (J_{AB} = 13 Hz) was accomplished with dicyclohexylcarbodiimide in tetrahydrofuran.



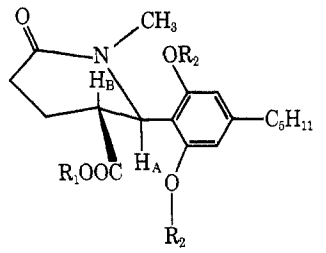
12, R = H
17, R = CH_3



13, R = H
15, R = CH_3



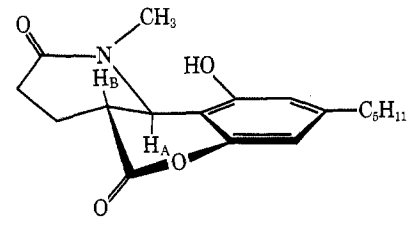
10, R = H
16, R = CH_3



11, R_1 = H; R_2 = CH_3
14, R_1 = R_2 = CH_3
18, R_1 = R_2 = H

Methylation of the trans ester 14 with methylmagnesium bromide in ether gave the corresponding tertiary alcohol 20 in 83% yield, which was demethylated with boron tribromide in methylene chloride to form the tertiary bromide 21. The crude bromide was dehydrohalogenated in boiling ethanol solution to form the terminal olefin 22, which was obtained as a glass.[11] Although 22 could be isolated as a crystalline solid in 29% yield from 20, higher overall yields of the desired tricyclic lactam 25 were realized when the glass was used without further purification.

We anticipated from our model studies that the terminal olefin 22 could be cyclized to the trans tricyclic compound 25 in the presence of trifluoroacetic acid. However,



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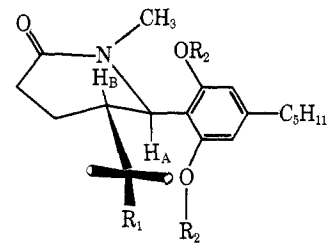
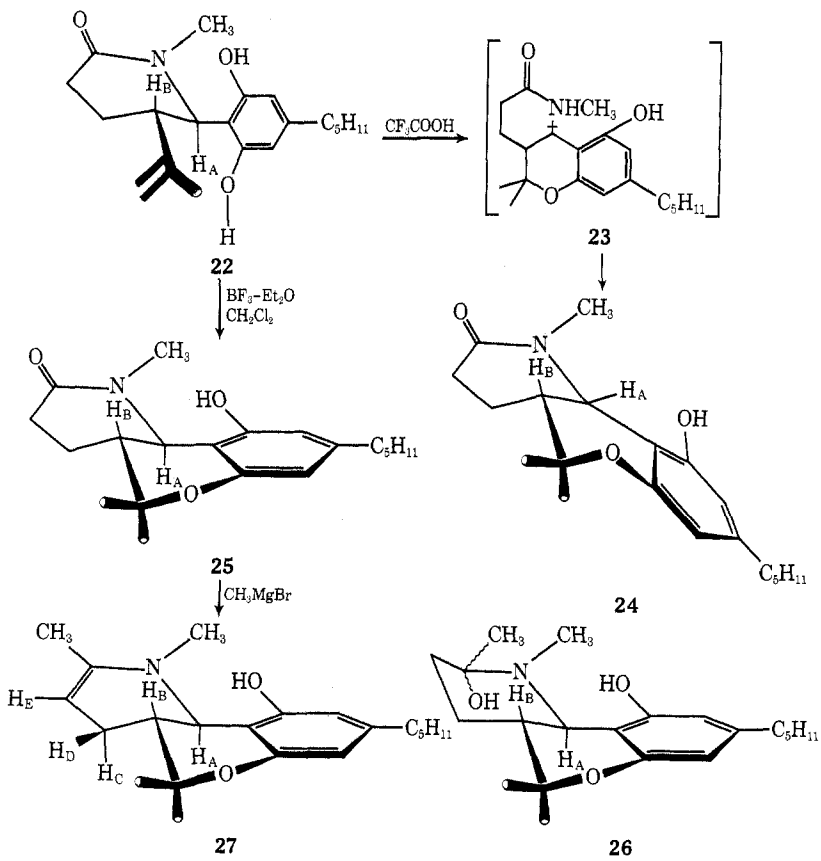


20, R_1 = OH; R_2 = CH_3
21, R_1 = Br; R_2 = H

treatment of 22 with trifluoroacetic acid at reflux for 1 hr gave exclusively the cis diastereomer 24 (J_{AB} = 5 Hz) and none of the trans isomer 25 could be detected when the reaction was followed by nmr. From our model studies it was apparent that the transformation of 22 to the cis tricyclic system 24 proceeds *via* the resonance-stabilized benzylic carbonium ion species 23. The much greater rate of isomerization of 22 to 24 relative to the case of the corresponding model compounds must reflect the stabilization of species 23 by the electron-donating phenolic and alkyl substituents, and supports our earlier view that the principal pathway for the trans to cis conversion in this series involves epimerization at the benzylic carbon atom rather than at the allylic center.[4] It seemed reasonable to anticipate that the formation of charged species 23 would be discouraged by employing a less polar solvent. Therefore, in an attempt to promote formation of the desired trans lactam 25, cyclization of the terminal olefin was ef-



fected in methylene chloride containing boron trifluoride etherate. Overall yields of the trans lactam **25** (J_{AB} = 10 Hz) of 25% from **20** were thus realized.

The nmr signal for proton H_A of **22** in $CDCl_3$ appears as a doublet at δ 5.00 ppm, whereas for **24** it appears at δ 4.63 and for **25** at δ 4.45. Proton H_A of the bicyclic system **22** is forced into the plane of the aromatic ring owing to steric interactions between the two phenolic substituents and the *N*-methyl and isopropenyl groups, and is therefore deshielded relative to the tricyclic systems **24** and **25** in which H_A cannot be in the plane of the ring. Similar variations in field effects were observed in the cyclization of cannabidiol to Δ^1-THC.[2]

Methylation of the trans lactam **25** with methylmagnesium bromide in tetrahydrofuran led to a mixture of the carbinolamine **26** and enamine **27**. The carbinolamine **26** could be isolated in 14% yield. The corresponding amino aldehyde and "enamine plus water" structures were ruled out owing to the absence of aldehyde or enamine double-bond absorbance in the solid-state ir spectrum. The spontaneous dehydration of **26** in $CDCl_3$ to give **27** could be followed by nmr. This facile dehydration was also evident in the electron impact mass spectrum of **26**, which was essentially identical with that of the enamine **27**. Pure **27** in practice was obtained by stirring the mixture of **26** and **27** in methylene chloride over molecular sieves. In this way, the enamine **27** was prepared in 81% yield. Addition of D_2O to $CDCl_3$ solutions of **27** resulted in the disappearance of the olefinic proton H_E and olefinic methyl group in the nmr spectrum.

The enamine **27** was subjected to catalytic hydrogenation in acetic acid over 5% palladium on carbon. The nmr spectrum, high-resolution chemical ionization mass spectrum, and combined gas chromatography–electron impact mass spectrum indicated that the isolated oil was a 3:1 mixture of diastereomeric amines **4** and **5**. The signals for the *C*-methyl, *N*-methyl, and H_A protons of the major diastereomer appeared upfield in the nmr spectrum relative to the minor diastereomer. However, the relative configurations of the major and minor diastereomers were not assigned. The ratio of the major to minor diastereomer increased after crystallization from methanol, but complete separation was not attempted.

Experimental Section

All reactions were performed under a nitrogen atmosphere, and solvents were evaporated on a rotary evaporater under vacuum. Melting points were taken on a Thomas-Hoover apparatus and are uncorrected. Nmr spectra were recorded on a JEOL JNM-4H-100 100-MHz instrument and, except where noted, in $CDCl_3$ solvent. Chemical shift values are reported in parts per million relative to TMS as internal standard. Ir spectra were recorded on a Perkin-Elmer Model 337 spectrophotometer. Glpc analyses were performed on a Varian Aerograph Model 2100 gas chromatograph equipped with a flame ionization detector using a 6 ft × 0.125 in. column of 3% SE-30 on Chromosorb W, 100–120 mesh. The electron impact mass spectra were recorded on an AEI MS-12 instrument at 70 eV and the chemical ionization mass spectrum was recorded on an AEI MS-901 spectrometer modified for chemical ionization. Microanalyses were performed by the Microanalytical Laboratory, University of California, Berkeley.

Olivetol Dimethyl Ether (6). A solution of CH_2N_2 (*ca.* 12 g, 0.29 mol) in EtOH–Et_2O (800 ml) was added to a solution of olivetol (18.02 g, 0.10 mol) in Et_2O (50 ml). After standing at room temperature overnight, additional CH_2N_2 (*ca.* 6 g, 0.14 mol) in EtOH–Et_2O (400 ml) was added to the solution. The reaction progress could be followed by glpc analysis (3% SE-30 on Chromosorb W, 100–120 mesh, 150°, 37 ml/min) of the solution, which gave the following retention times: olivetol dimethyl ether, 1 min 59 sec; olivetol monomethyl ether, 2 min 34 sec; olivetol, 3 min 13 sec. The solution was allowed to stand for 3 days before it was concentrated to 100 ml by evaporation of solvent and unreacted CH_2N_2. The solution was washed with 5% NaOH (100 ml) and the aqueous layer was extracted with Et_2O (50 ml). The combined organic layers were washed with H_2O (50 ml) and dried ($MgSO_4$) and the solvent was evaporated. The residue was distilled at 103° (0.05 mm)–105° (0.06 mm) to yield olivetol dimethyl ether (15.16 g, 73%): ir ($CDCl_3$) 2920, 1605 (shoulder), 1595, 1460, 1200, 1148, 1067 cm^{-1}; nmr ($CDCl_3$) δ 6.30 (m, 3 aromatics), 3.71 (s, 2 OCH_3), 2.52 (br t, benzylic CH_2), 1.72–1.15 (m, 6 methylene), 0.88 (br t, terminal CH_3).

2,6-Dimethoxy-4-*n*-amylbenzaldehyde (8).[8] *n*-Butyllithium (9 ml of a 9.7 *M* solution in hydrocarbon, 87 mmol) was added dropwise to an ice-cold, stirred solution of olivetol dimethyl ether (13.54 g, 65 mmol) in Et_2O (45 ml). After stirring at room temperature for 16 hr a solution of *N*-methylformanilide (14.87 g, 110 mmol) in Et_2O (45 ml) was added dropwise to the ice-cold reaction mixture. The mixture was stirred at room temperature for 2 hr before dropwise addition of 3% aqueous H_2SO_4 (45 ml) to the suspension. The organic phase was separated and the aqueous phase was washed with Et_2O (2 × 45 ml). The solvent was evaporated from the combined, dried (Na_2SO_4) organic layers and the residue was distilled. The aldehyde was collected at 149–153° (0.2 mm) [lit.[8] bp 148–152° (0.3 mm)] as a yellow oil (12.78 g, 83%): ir ($CDCl_3$) 2950, 1675 cm^{-1} (C=O); nmr δ 10.44 (s, CHO), 6.39 (s, 2 aromatics), 3.87 (s, 2 OCH_3), 2.60 (br t, benzylic CH_2), 1.80–1.10 (m, 6 H, amyl methylene), 0.92 (br t, terminal CH_3).

2,6-Dimethoxy-4-*n*-amylbenzylidenemethylamine (9). Methylamine (4.29 g, 0.138 mol) was dissolved in a solution of the aldehyde **8** 29.48 g, 0.125 mol) in benzene (50 ml) in the presence of molecular sieves (3A, 20 g) with occasional stirring. After 30 min, the sieves were filtered off and washed with benzene (2 × 50 ml). Evaporation of solvent from the filtrate left the imine (31.07 g, 100%) as a pale yellow oil. The analytical sample was prepared by evaporative distillation at 80° (3 μ): ir (thin film) 2915, 1645 cm^{-1} (C=N); nmr δ 8.58 (q, J = 1.5 Hz, imino H), 6.38 (s, 2 aromatics), 3.82 (s, 2 OCH_3), 2.58 (br t, benzylic CH_2), 2.52 (d, J = 1.5 Hz, NCH_3), 1.80–1.10 (m, 6 H, amyl methylene), 0.90 (br t, terminal CH_3).

Anal. Calcd for $C_{15}H_{23}NO_2$: C, 72.25; H, 9.30; N, 5.62. Found: C, 71.99; H, 9.16; N, 5.53.

***trans*-1-Methyl-5-carboxy-6-(2,6-dimethoxy-4-*n*-amylphenyl)-2-piperidone (11).** The imine **9** (15.91 g, 63.8 mmol) and glutaric anhydride (7.28 g, 63.8 mmol) were heated in refluxing xylene (15 ml) for 30 min. The reaction mixture was cooled to room temperature and extracted with 5% aqueous $NaHCO_3$ (200 + 100 ml). The combined aqueous layers were acidifed to pH 1 with concentrated H_2SO_4 and the resulting suspension was extracted with Et_2O (2 × 100 ml). The combined, dried ($MgSO_4$) Et_2O layers were concentrated to 100 ml and the suspension was stored at 1° overnight before filtration of the colorless solid (11.20 g, 48%). The only detectible (by nmr) impurity proved to be a trace of Et_2O which could not be completely removed at 25° (0.04 mm) overnight. The analytical sample was prepared by heating a sample (36.5 mg) at 98° for 10 min, during which time the sample melted, Et_2O vapor evolved, and the pure solid (34.8 mg) crystallized from the melt: mp 144–145°; ir ($CDCl_3$) 2925, 1710 (carboxyl C=O) 1610 cm^{-1} (lactam C=O); nmr ($CDCl_3$) δ 9.68 (s, COOH, exchangeable with D_2O), 6.36 (s, 2 aromatics), 5.44 (d, J = 7 Hz, H_A), 3.76 (s, 2 OCH_3), 3,13 (m, H_B), 2.67 (s, NCH_3), 2.58 (m, benzylic CH_2 and $COCH_2$), 2.13 (m, $COCH_2CH_2$), 1.80–1.16 (m, 6 H, amyl methylene), 0.91 (br t, terminal CH_3); electron impact mass spectrum m/e (rel intensity) 363 (19), 318 (12), 307 (28), 261 (14), 260 (58), 250 (22), 249 (20), 248 (100), 234 (10), 219 (16).

Anal. Calcd for $C_{20}H_{29}NO_5$: C, 66.09; H, 8.04; N, 3.85. Found: C, 65.89; H, 7.94; N, 3.81.

***cis*-1-Methyl-5-carboxy-6-(2,6-dimethoxy-4-*n*-amylphenyl)-2-piperidone (10).** The solvent was evaporated from the solution left after filtration of the trans diastereomer **11** and the residue was recrystallized four times from Me_2CO–Et_2O to yield the pure *cis* diastereomer (0.12 g, 0.5%): mp 155–155.5°; ir (KBr) 2910, 1735 (carboxylic acid C=O), 1625 cm^{-1} (lactam C=O); nmr ($CDCl_3$) δ 10.28 (s, COOH, exchangeable with D_2O), 6.32 (s, 2 aromatics), 5.40 (d, J = 5 Hz, H_A), 3.68 (s, 2 OCH_3), 3.18 (m, H_B), 2.74 (s, NCH_3), 2.70–2.02 (m, benzylic CH_2 and $COOCH_2CH_2$), 1.90–1.20 (m, 6 H, amyl methylene), 0.91 (br t, terminal CH_3); electron impact mass spectrum m/e (rel intensity) 363 (20), 307 (28), 261 (21), 260 (83), 250 (24), 249 (25), 248 (100), 234 (10), 219 (14).

Anal. Calcd for $C_{20}H_{29}NO_5$: C, 66.09; H, 8,04; N, 3.85. Found: C, 66.27; H, 7.88; N, 3.95.

***trans*-1-Methyl-5-methoxycarbonyl-6-(2,6-dimethoxy-4-*n*-amylphenyl)-2-piperidone (14).** An excess of CH_2N_2 in EtOH–Et_2O was added to the trans acid **11** (3.64 g, 10 mmol). Evapora-

tion of solvent from the solution left the ester as a viscous oil (3.78 g, 100%). The analytical sample was prepared by evaporative distillation at 110° (75 μ): ir ($CDCl_3$) 2945, 1735 (ester C=O), 1625 cm^{-1} (lactam C=O); nmr ($CDCl_3$) δ 6.38 (s, 2 aromatics), 5.36 (d, J = 8 Hz, H_A), 3.78 (s, 2 OCH_3), 3.61 (s, $COOCH_3$), 3.13 (m, H_B), 2.63 (s, NCH_3), 2.49 (m, benzylic CH_2 and $COCH_2$), 2.09 (m, $COCH_2CH_2$), 1.82–1.29 (m, 6 H, amyl methylene), 0.91 (br t, terminal CH_3); electron impact mass spectrum m/e (rel intensity) 377 (30), 321 (24), 318 (14), 260 (35), 250 (21), 249 (18), 248 (100), 192 (23).

Anal. Calcd for $C_{21}H_{31}NO_5$: C, 66.82; H, 8.28; N, 3.71. Found: C, 66.77; H, 8.22; N, 3.49.

***cis*-1-Methyl-5-methoxycarbonyl-6-(2,6-dimethoxy-4-*n*-amylphenyl)-2-piperidone (16).** An excess of CH_2N_2 in EtOH–Et_2O was added to the cis acid **10** (727 mg, 2 mmol). Evaporation of solvent from the filtered solution left the cis ester as a colorless, viscous oil (640 mg, 85%). The analytical sample was obtained by evaporative distillation at 110° (10 μ): ir ($CDCl_3$) 2915, 1735 (ester C=O), 1650 cm^{-1} (lactam C=O); nmr ($CDCl_3$) δ 6.36 (s, 2 aromatics), 5.35 (d, J = 5 Hz, H_A), 3.74 (s, 2 OCH_3), 3.51 (s, $COOCH_3$), 3.19 (m, H_B), 2.73 (s, NCH_3), 2.53 (m, benzylic CH_2 and $COCH_2CH_2$), 1.92–1.20 (m, 6 H, amyl methylene), 0.92 (br t, terminal CH_3); electron impact mass spectrum m/e (rel intensity) 377 (30), 321 (25), 318 (10), 261 (14), 260 (63), 250 (28), 249 (19), 248 (100), 235 (10), 219 (15), 192 (35).

Anal. Calcd for $C_{21}H_{31}NO_5$: C, 66.82; H, 8.28; N, 3.71. Found: C, 66.52; H, 8.26; N, 3.78.

***trans*-1-Methyl-5-carboxy-6-(2,6-dihydroxy-4-*n*-amylphenyl)-2-piperidone (18).** A solution of the trans acid **11** (6.00 g, 16.5 mmol) in CH_2Cl_2 (60 ml) was added dropwise to a stirred solution of BBr_3 (25.10 g, 100 mmol) in CH_2Cl_2 (80 ml) at 0°. After stirring for 48 hr at room temperature, H_2O (250 ml) and Et_2O (600 ml) were added slowly to the solution at 0°. The organic phase was separated and dried (Na_2SO_4) and the solvent was evaporated. The residue (6.24 g) was dissolved in acetone (10 ml), and Et_2O (20 ml) was added to the filtered solution. The diphenol **18** crystallized from the solution as a colorless solid (2.10 g, 38%), mp 195° dec. The analytical sample was recrystallized from aqueous EtOH: mp 203° dec; ir (KBr) 2910, 1700 (carboxyl C=O), 1585 cm^{-1} (lactam C=O); nmr ($CDCl_3$–pyridine-d_5, 3:1) δ 6.41 (s, 2 aromatics), 5.64 (d, J = 7 Hz, H_A), 3.55 (m, H_B), 2.88 (s, NCH_3), 3.20–2.00 (m, $COCH_2CH_2$), 2.40 (br t, benzylic CH_2), 1.85–1.10 (m, 6 H, amyl methylene), 0.80 (br t, terminal methyl); electron impact mass spectrum m/e (rel intensity) 335 (15), 317 (20), 291 (22), 260 (14), 259 (38), 258 (100), 235 (10), 232 (14), 230 (14), 219 (20), 218 (18), 217 (26), 204 (21), 202 (42), 124 (88).

Anal. Calcd for $C_{18}H_{25}NO_5$: C, 64.46; H, 7.51; N, 4.18. Found: C, 64.53; H, 7.50; N, 4.24.

1-Methyl-2,5-dioxo-1,2,3,4,4a,10b-hexahydro-8-*n*-amyl-10-hydroxy-*trans*-5*H*-[1]benzopyrano[4,3-*b*]pyridine (19). A mixture of the diphenol **18** (1585 mg, 4.73 mmol) and DCC (976 mg, 4.73 mmol) was heated in refluxing THF (20 ml) with stirring for 2.5 hr. The suspension was stirred under nitrogen for an additional 24 hr before filtration of the DCU. Evaporation of the solvent from the filtrate left the lactone as a colorless solid (1343 mg, 89%), mp 177–180°. The analytical sample was recrystallized once from benzene and twice from Me_2CO: mp 174–175°; ir ($CDCl_3$) 2920, 1775 (lactone C=O), 1620 cm^{-1} (lactam C=O); nmr ($CDCl_3$) δ 8.66 (br, OH), 6.65 (d, J = 1.5 Hz, 1 aromatic), 6.51 (d, J = 1.5 Hz, 1 aromatic), 4.60 (d, J = 13 Hz, H_A), 3.25 (m, H_B), 3.20 (s, NCH_3), 3.05–2.10 (m, $COCH_2$), 2.55 (t, benzylic CH_2), 1.92 (m, $COCH_2CH_2$), 1.80–1.12 (m, 6 H, amyl methylene), 0.91 (br t, terminal CH_3); electron impact mass spectrum m/e (rel intensity) 317 (31), 259 (34), 258 (100), 202 (35), 201 (11), 188 (24).

Anal. Calcd for $C_{18}H_{23}NO_4$: C, 68.12; H, 7.30; N, 4.41. Found: C, 68.35; H, 7.24; N, 4.62.

***trans*-1-Methyl-5-(2-hydroxyisopropyl)-6-(2,6-dimethoxy-4-*n*-amylphenyl)-2-piperidone (20).** A solution of the trans ester **14** (7.28 g, 19.3 mmol) in Et_2O (100 ml) was added dropwise to a stirred solution of CH_3MgBr (26 ml of a 3 M solution, 78 mmol) in Et_2O at 0°. The mixture was allowed to stand at room temperature for 2 hr before it was again cooled in an ice bath, following which saturated aqueous NH_4Cl (100 ml) was added to the suspension. The white solid was filtered from the organic layer, the organic layer was separated, and the aqueous layer was extracted with Et_2O (2 × 100 ml). The white solid was added to the combined organic layers and the volume of the suspension was reduced to 25 ml. The suspension was stored at 0° overnight before filtration of the tertiary alcohol **20**, obtained as a colorless solid (6.07 g, 83%), mp 111–113°. The analytical sample was recrystallized from Me_2CO–Et_2O: mp 114–114.5°; ir ($CDCl_3$) 2930, 1625 cm^{-1} (lactam C=O); nmr ($CDCl_3$) δ 6.38 (s, 2 aromatics), 4.97 (d, J = 8 Hz, H_A), 3.81 (s, 2 OCH_3), 2.90–2.38 (m, benzylic CH_2 and $COCH_2$), 2.55 (s, NCH_3), 2.27 (s, OH, exchangeable with D_2O), 2.05 (m, $COCH_2CH_2$), 1.80–1.15 (m, 6 H, amyl methylene), 1.20 (s, *gem*-dimethyl), 0.90 (br t, terminal CH_3); electron impact mass spectrum m/e (rel intensity) 377 (15), 349 (20), 344 (39), 330 (99), 328 (79), 323 (16), 321 (19), 318 (29), 316 (15), 274 (20), 261 (22), 260 (100), 250 (32), 248 (58), 219 (18), 200 (19).

Anal. Calcd for $C_{22}H_{35}NO_4$: C, 69.99; H, 9.34; N, 3.71. Found: C, 69.84; H, 9.12; N, 3.76.

***trans*-1-Methyl-5-isopropenyl-6-(2,6-dihydroxy-4-*n*-amylphenyl)-2-piperidone (22).** A solution of BBr_3 (12.53 g, 50 mmol) in CH_2Cl_2 (40 ml) was added dropwise to a stirred solution of the trans dimethyl ether **20** (3.77 g, 10 mmol) in CH_2Cl_2 (40 ml) at 0°. After stirring for 2 days at room temperature, H_2O (150 ml) was added dropwise followed by Et_2O (300 ml). The organic layer was separated and the aqueous layer was extracted with Et_2O (2 × 150 ml). The solvent was evaporated from the combined, dried ($MgSO_4$) organic layers to leave a glassy residue (4.52 g) containing the tertiary bromide **21**. This residue was boiled in EtOH (50 ml) for 30 min. The solution was cooled to room temperature before addition of H_2O (50 ml) and Et_2O (50 ml). The organic layer was separated and the aqueous layer was extracted with Et_2O (50 ml). Evaporation of solvent from the combined, dried ($MgSO_4$) organic layers left the crude olefin **22** as a glassy residue (3.05 g). Crystallization from Et_2O–pentane (15 + 5 ml) afforded a solid (0.96 g, 29%), mp 177–183°. The analytical sample was recrystallized from aqueous EtOH: mp 193–194°; nmr ($CDCl_3$–pyridine-d_5, 1:1) δ 9.58 (br, 2 OH, exchangeable with D_2O), 6.45 (s, 2 aromatics), 5.31 (d, J = 9 Hz, H_A), 4.83 (s, 1 olefinic H), 4.73 (s, 1 olefinic H), 3.41 (m, H_B), 2.93 (s, NCH_3), 2.64 (m, $COCH_2$), 2.41 (br t, benzylic CH_2), 1.95 (m, $COCH_2OH_2$), 1.83 (s, olefinic CH_3), 1.72–1.10 (m, 6 H, amyl CH_2), 0.79 (br t, terminal CH_3); electron impact mass spectrum m/e (rel intensity) 331 (65), 317 (12), 316 (50), 259 (18), 258 (10), 246 (29), 245 (14), 231 (20), 222 (100), 221 (62), 220 (19).

Anal. Calcd for $C_{20}H_{29}NO_3$: C, 72.47; H, 8.82; N, 4.23. Found: C, 72.32; H, 8.44; N, 4.10.

1,5,5-Trimethyl-2-oxo-1,2,3,4,4a,10b-hexahydro-8-*n*-amyl-10-hydroxy-*cis*-5*H*-[1]benzopyrano[4,3-*b*]pyridine (24). A solution of the olefin **22** (332 mg, 1 mmol) in CF_3COOH (5 ml) was heated at reflux for 1.5 hr. Evaporation of solvent left an orange oil which was dissolved in Et_2O (20 ml). The solution was washed with 5% aqueous $NaHCO_3$ (20 ml). Evaporation of solvent from the dried ($MgSO_4$) organic layer left a glass, which crystallized on trituration with Et_2O (2 ml) as a colorless solid (113 mg, 34%), mp 158–160°. Recrystallization from MeOH (1 ml) provided the analytical sample as colorless needles: mp 169–170°; ir (KBr) 2920, 1625 cm^{-1} (lactam C=O); nmr δ 8.88 (s, OH), 6.37 (d, J = 1.5 Hz, 1 aromatic), 6.22 (d, J = 1.5 Hz, 1 aromatic), 4.63 (d, J = 5 Hz, H_A), 3.00 (s, NCH_3), 2.62–1.90 (m, benzylic CH_2 + $COCH_2CH_2$), 1.80–1.15 (m, 6 H, amyl methylene), 1.33 (s, CH_3), 1.19 (s, CH_3), 0.87 (br t, terminal CH_3); electron impact mass spectrum m/e (rel intensity) 331 (14), 317 (22), 316 (100).

Anal. Calcd for $C_{20}H_{29}NO_3$: C, 72.47; H, 8.82; N, 4.23. Found: C, 72.43; H, 8.73; N, 4.42.

1,5,5-Trimethyl-2-oxo-1,2,3,4,4a,10b-hexahydro-8-*n*-amyl-10-hydroxy-*trans*-5*H*-[1]benzopyrano[4,3-*b*]pyridine (25). To a solution of the crude, glassy olefin **22** [3.05 g, prepared from 3.77 g (10 mmol) of **20**] in CH_2Cl_2 (150 ml) was added BF_3–Et_2O (30 ml). The solution was left standing in a sealed flask for 21 hr before addition of H_2O (150 ml). The organic layer was separated, washed with 5% aqueous $NaHCO_3$ (150 ml), and then dried ($MgSO_4$). Evaporation of solvent left a solid residue (3.00 g), mp 157–168°, containing **22** and **25** in a 1:4 ratio, respectively. The solid was dissolved in 5% aqueous NaOH (150 ml) and the purple solution was added to Et_2O (150 ml) in a separatory funnel. The mixture separated into three phases. The deep purple, oily middle layer was separated and dissolved in H_2O (50 ml), and the solution was acidified (pH 1) with concentrated H_2SO_2. The solid precipitate was filtered off and recrystallized from MeOH (8 ml) to yield analytically pure product (0.82 g, 25% from **20**): mp 227–228°; ir (KBr) 2910, 1625 cm^{-1} (lactam C=O); nmr ($CDCl_3$) δ 9.27 (s, OH, exchangeable with D_2O), 6.38 (d, J = 1.5 Hz, 1 aromatic), 6.29 (d, J = 1.5 Hz, 1 aromatic), 4.45 (d, J = 10 Hz, H_A), 2.86 (s, NCH_3), 2.68 (m, H_B, $COCH_2$), 2.47 (br t, benzylic CH_2), 1.96 (m, $COCH_2CH_2$), 1.78–1.10 (m, 6 H, amyl methylene), 1.36 (s, CH_3), 0.88 (br t, terminal CH_3); electron impact mass spectrum m/e (rel intensity) 331 (13), 317 (22), 316 (100); high resolution chemical ionization mass spectrum, 332.2219 (calcd for $C_2OH_{30}NO_3$, 332.2226).

Anal. Calcd for $C_{20}H_{29}NO_3$: C, 72.47; H, 8.82; N, 4.23. Found: C, 72.61; H, 9.02; N, 4.21.

1,2,5,5-Tetramethyl-2,10-dihydroxy-1,2,3,4,4a,10b-hexahydro-8-*n*-amyl-*trans*-5*H*-[1]benzopyrano[4,3-*b*]pyridine (26). Methylmagnesium bromide (2 ml of a 3 *M* solution in Et_2O, 6 mmol) was added slowly to a solution of **25** (332 mg, 1 mmol) in THF (10 ml). The solution was heated at reflux for 24 hr. The solution was cooled to 0° before addition of saturated aqueous NH_4Cl (10 ml). The organic phase was separated and the aqueous phase was washed with Et_2O (2 × 10 ml). Evaporation of solvent from the combined organic layers left a semisolid residue which was triturated with Et_2O (2 ml). The colorless carbinolamine (49 mg, 14%) was filtered and washed with H_2O (2 × 1 ml) and Et_2O (1 ml): mp 101° dec; nmr ($CDCl_3$) δ 6.23 (d, J = 1 Hz, 1 aromatic), 6.18 (d, J = 1 Hz, 1 aromatic), 4.67 (br, H_A), 2.47 (br t, benzylic CH_2), 2.25 (s, NCH_3), 2.15–1.05 (br, H_B, $COCH_2CH_2$, 6 amyl methylene), 1.58 (s, C-2 CH_3), 1.38 (s, C-5 CH_3), 1.17 (s, C-5 CH_3), 0.88 (br t, terminal CH_3); electron impact mass spectrum *m/e* (rel intensity) 329 ($M^+ - H_2O$, 98), 328 (12), 315 (23), 314 (88), 301 (19), 283 (18), 259 (13), 243 (15), 232 (12), 231 (69), 174 (19), 150 (22), 84 (100).

Anal. Calcd for $C_{21}H_{33}NO_3$: C, 72.58; H, 9.57; N, 4.03. Found: C, 72.85; H, 9.81; N, 4.24.

Evaporation of solvent from the filtrate left the crude enamine **27** (199 mg, 60%) as a light amber oil.

1,2,5,5-Tetramethyl-1,4,4a,10b-tetrahydro-8-*n*-amyl-10-hydroxy-*trans*-5*H*-[1]benzopyrano[4,3-*b*]pyridine (27). Methylmagnesium bromide (10 ml of a 3 *M* solution in Et_2O, 30 mmol) was added slowly to a solution of **25** (1.66 g, 5 mmol) in THF (50 ml). The solution was heated at reflux for 24 hr. The clear solution was cooled to 0° before addition of saturated aqueous NH_4Cl (50 ml). The organic phase was separated and the aqueous phase was extracted with Et_2O (3 × 50 ml). Evaporation of solvent from the combined, dried (Na_2SO_4) organic phases left a semisolid residue (1.65 g), which was dissolved in CH_2Cl_2 (50 ml). The solution was stirred over molecular sieves (3A, 10 g), for 4 hr. The sieves were filtered off and washed with CH_2Cl_2 (10 ml). Evaporation of solvent from the filtrate left the enamine as a light amber oil (1.34 g, 81%). The analytical sample was evaporatively distilled at 108° (0.1 mm): $n^{24}D$ 1.5379; ir (thin film) 1660 cm^{-1} (enamine C=C); nmr ($CDCl_3$) δ 6.28 (d, J = 1.5 Hz, 1 aromatic), 6.23 (d, J = 1.5 Hz, 1 aromatic), 5.05 (m, H_E, $t_{1/2}$ for D_2O exchange *ca.* 11 hr), 3.92 (d, J = 10 Hz, H_A), 2.49 (br t, benzylic CH_2), 2.25 (s, NCH_3), 1.99 (m, $H_{B,C,D}$), 1.84 (s, C-2 CH_3, $t_{1/2}$ for D_2O exchange *ca.* 40 min), 1.72–1.17 (m, 6 H, amyl methylene), 1.40 (s, C-5 CH_3), 1.13 (s, C-5 CH_3), 0.89 (br t, terminal CH_3); electron impact mass spectrum *m/e* (rel intensity) 329 (88), 328 (13), 315 (19), 314 (70), 301 (10), 300 (22), 283 (14), 259 (15), 243 (13), 232 (12), 231 (68), 174 (19), 150 (22), 84 (100).

Anal. Calcd for $C_{21}H_{31}NO_2$: C, 76.55; H, 9.48; N, 4.25. Found: C, 76.64; H, 9.34; N, 4.26.

1,2,5,5-Tetramethyl-1,2,3,4,4a,10b-hexahydro-8-*n*-amyl-1-hydroxy-*trans*-5*H*-[1]benzopyrano[4,3-*b*]pyridine (4 and 5). A solution of the enamine **27** (637 mg, 1.93 mmol) in acetic acid (90 ml) was hydrogenated over 5% Pd/C (150 mg) at 35 psi for 24 hr. The catalyst was filtered off and the solvent was sublimed at 16° (0.1 mm) from the frozen solution; aqueous 5% NaOH (30 ml) and Et_2O were added to the residue. The organic layer was separated and the aqueous layer was extracted with Et_2O (30 ml). Evaporation of solvent from the combined, dried (Na_2SO_4) organic layers left a diastereomeric mixture of amines **4** and **5** as an oil (537 mg, 84%). The ratio of major to minor diastereomer was 3:1 (by nmr). Recrystallization from MeOH (2 ml) gave a solid (380 mg, mp 72–81°). The ratio of major to minor diastereomer in the solid was 6:1 (by nmr). On glpc analysis (3% SE-30 on Chromosorb W, 155°, 37 ml/min), the solid produced two peaks with retention times of 42.5 (minor) and 45.0 min (major). When subjected to glpc–mass spectrum, these glpc peaks corresponded to the following mass spectra: minor diastereomer *m/e* (rel intensity) 331 (100), 316 (38), 314 (19), 285 (19), 275 (35), 260 (19), 259 (92), 245 (37), 231 (67); major diastereomer *m/e* (rel intensity) 331 (99), 316 (38), 314 (22), 285 (22), 275 (27), 260 (22), 259 (100), 245 (36), 231 (60); high resolution chemical ionization mass spectrum, 322.2581 (calcd for $C_{21}H_{34}NO_2$, 322.2589).

Registry No.—**4**, 51014-90-5; **5**, 51064-86-9; **6**, 22976-40-5; **8**, 3410-84-2; **9**, 51015-16-8; **10**, 51014-91-6; **11**, 51014-92-7; **14**, 51014-93-8; **16**, 51014-94-9; **18**, 51014-95-0; **19**, 51014-96-1; **20**, 51014-97-2; **22**, 51014-98-3; **24**, 51014-99-4; **25**, 51015-00-0; **26**, 51015-17-9; **27**, 51015-01-1; olivetol, 500-66-3.

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D-Homoandrostanes. I. Preparation and Properties of *D*-Homo-5α-androstan-1-, -2-, -3-, and -4-ones[1a]

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The synthesis of the four *D*-homo ketones from commercially available 17-oxo steroids is described. A key step in an alternate synthesis of the 1-ketone is a selective silver carbonate oxidation of a 17β-hydroxyl group in the presence of 1-hydroxyl groups in the 5α-androstane series. Sodium borohydride reduction of the ketones gives similar results to the analogs, while the almost exclusive 1α-alcohol formation can be explained in terms of "steric intermediate control."

Previous studies on monofunctional *D*-homoandrostanes have been concerned with those possessing functional groups in the expanded terminal ring.[2] In connection with other work we required the title compounds, thus excluding many *D*-homo rearrangements[3] as potential synthetic methods, as the products contain undesired groupings, such as alkyl groups, in the D ring. The earlier method[4] of expanding androstan-17-ones (**1**) has several disadvantages, discussed previously,[5] such as the reversible formation of cyanohydrins **2**, using potentially hazardous cya-