Mass spectral data were obtained with a CEC 21-104 mass spectrometer utilizing a direct-introduction probe and an Associated Electronics Industries high-resolution mass spectrometer (70 eV ionizing voltage) with perfluorotributylamine (mol wt 671) as a reference standard. Exact mass measurements were not made. Infrared spectra of KBr pellets of **3** were obtained with Perkin-Elmer Model 221 and 621 spectrophotometers. Ultraviolet spectra of cyclohexane (spectroquality) solutions of **3** were taken with a Cary Model 11 spectrophotometer.

^{13}C nuclear magnetic resonance spectra were obtained with a Varian CFT-20 spectrometer modified with a switchable carbon/proton probe and a frequency synthesizer/broadband amplifier. It was necessary to use chromium(III) 2,4-pentanedionate (CrAcAc, ~0.1 M) as a paramagnetic relaxation agent.[21] The shortened spin-lattice relaxation time (T_1) allowed rapid, repetitive excitation and provided an observable spectrum of **3** even though its solubility was low. The spectra were collected at ~40 °C with a 90° pulse and an ~2.9-s repetition rate, thus allowing ~5 T_1 for relaxation. For natural-abundance ^{13}C–^{13}C coupling constants for **1**, 24–72-h data acquisitions were necessary with CrAcAc as a relaxation agent. Tetramethylsilane was used as an internal standard in $CDCl_3$ solvent.

Acknowledgment. We express deep appreciation to Professor W. H. Urry and the late Dr. R. H. Campbell for securing some of the spectral data and for extremely useful discussions.

Registry No. 1, 77-47-4; 3, 79357-50-9.

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Stereospecific Formation of Equatorial Diacetylimides from the Stereoisomers of Six-Membered Carbocyclic Amines

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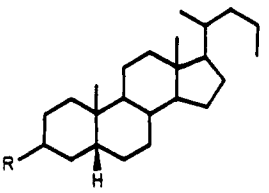
We report here that in varied six-membered carbocyclic primary amines, diacetyl imide derivatives could only be obtained from the equatorial stereoisomers.

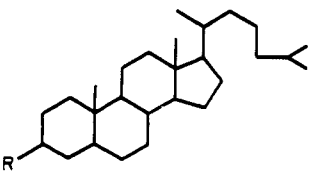
Reduction of the oxime derivatives of 3-oxocholane[1] (series **1**, Chart I), 3-oxocholestane[2] (series **2**), and 4-*tert*-butylcyclohexanone (series **3**) utilizing lithium aluminum hydride for the steroids and catalytic hydrogenation for the cyclohexane served to produce the mixtures of isomeric amines. After acylation with acetic anhydride and pyridine, chromatography yielded two extremely easily separable materials. In each case (series **1–3**) the faster moving material was shown by mass spectrometry, proton NMR, and elemental analysis to be the imides, which were isolated as pure substances (**1a–3a**).[3] Similar analysis indicated the slower moving material to be, in each case (series **1–3**), a mixture of the epimeric acetyl amides. Further acetylation of these mixtures produced more of the previously encountered imides (**1a–3a**) and, after a single crystallization, the isomerically pure amides of the axial amine in each case (**1b–3b**).

Chart I



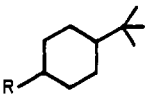
series 1

1a, R = (3α)-N(COCH$_3$)$_2$
b, R = (3β)-NH(COCH$_3$)
c, R = (3α)-NH(COCH$_3$)



series 2

2a, R = (3β)-N(COCH$_3$)$_2$
b, R = (3α)-NH(COCH$_3$)
c, R = (3β)-NH(COCH$_3$)
d, R = (3α)-NCO
e, R = (3β)-NCO



series 3

3a, R = *trans*-N(COCH$_3$)$_2$
b, R = *cis*-NH(COCH$_3$)
c, R = *trans*-NH(COCH$_3$)

In each case the imides **1a–3a** could be easily hydrolyzed in alcoholic NaOH to yield the isomerically pure equatorial acetyl amides **1c–3c**.

In the cholestanes[2] and the *tert*-butylcyclohexanes[4] the epimeric amides are known materials.[2,4] In the cholanes we characterized the epimeric amides here as well as the imides which have not been previously reported in any of these systems.

In another attempt to prepare the axial imide we subjected **1b** and **3b** to refluxing acetyl chloride. Evaporation of the solvent yielded a solid material in which no imide could be detected by proton NMR (absence of a signal near δ 2.4[3]) or by thin-layer chromatography (no spot near the positions for **1a** and **3a** in each case). We also subjected 3α- and 3β-isocyanatocholestane (**2d** and **2e**) to refluxing acetic anhydride.[5] The equatorial isomer (**2e**) yielded a mixture of the amide **2c** and the imide **2a** in low yield and a great deal of tar while the axial isocyanate **2d** gave only the amide **2b** in a similar low yield.

Our inability to isolate an axial imide in all three systems could arise from an insuperable kinetic barrier or from a highly unfavorable equilibrium. The imide of 3β-aminocholestane (**2a**) does yield a mixture of **2a** and the amide **2c** in refluxing acetic anhydride–pyridine which favors the imide (**2a**). This is consistent with reports that imides and amides can equilibrate.[6] Earlier work has shown that the acetyl imide could not be isolated from tertiarybutyl amine and that the yield of imide compared to amide decreases with increasing steric size of the *N*-alkyl group.[7] Equilibrium processes could explain the formation of the amide **2b** from the axial isocyanate **2d** in refluxing acetic anhydride. The reagent, present in large excess as the solvent, could contain enough acetic acid to supply the necessary protons. Although the imide **2a** is formed from the equatorial isomer **2e**, the amide **2c** is also isolated here. The proposed mechanism of imide formation from isocyanates[8] could not lead to amide, but others have also

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(2) C. W. Shoppee, D. E. Evans, H. C. Richards, and G. H. R. Summers, *J. Chem. Soc.*, 1649 (1956).

(3) Imides have been reviewed by (a) O. H. Wheeler and O. Rosado in "The Chemistry of Functional Groups (Amides)", S. Patai, Ed., Interscience, NY, 1970, Chapter 7, pp 335–381. (b) See also B. C. Challis and J. A. Challis, "Comprehensive Organic Chemistry", Vol. 2, D. Barton and W. D. Olles, Eds., Pergamon Press, London, 1978, Section 9.9.

(4) W. Hückel and K. Heyder, *Chem. Ber.*, **96**, 220 (1963).

(5) This procedure is known to yield the imide in model acyclic systems. See C. D. Hurd and A. G. Prapas, *J. Org. Chem.*, **24**, 388 (1959).

(6) H. J. Meyer, C. Nolde, I. Thomsen, and S.-O. Lawesson, *Bull. Soc. Chim. Belg.*, **87**, 621 (1978), and references therein.

(7) R. P. Mariella and K. H. Brown, *J. Org. Chem.*, **36**, 735 (1971). See also: J. T. Edward and C. Jitrangsri, *Can. J. Chem.*, **53**, 3339 (1975); G. G. Trigo, C. Avendaño, E. Santos, J. T. Edward, and S. C. Wong, *ibid.*, 57, 1456 (1979).

(8) See ref 3a pp 347–348 and references therein.

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isolated amide in this reaction nevertheless.[9]

Both acetyl groups in imides are believed to participate in resonance stabilization with the nitrogen lone-pair electrons, and this manifests itself in the planarity of this system.[10] NMR studies on model imides demonstrate that increased steric bulk on the *N*-alkyl or carbonyl alkyl group causes a decrease in the activation energy necessary for rotation about the nitrogen to carbonyl bond.[11] The groups studied were smaller than cyclohexyl, which suggests the systems here would be subject to this stress on conjugation.

This can be seen independently by inspection of Stuart–Briegleb models. Both the axial and equatorial cyclohexyl acetyl imides experience severe van der Waals repulsion with the hydrogens on C-2 and C-6. The equatorial imide may escape this problem by swinging into a plane perpendicular to the ring, but the axial imide must choose between two undesirable paths: swing one acetyl arm over the ring; rotate around the carbonyl to nitrogen bond.[12]

It is reasonable that the acetyl group pushed out of the resonance plane will find a lower energy of activation to be removed. This could also account for the equilibrium process and the expectation that this process would strongly disfavor the axial imide. There are reports of transacylations in *N*-alkyldiacetamides, and the rate for this process increases with the steric size of the *N*-alkyl group.[13]

Although an initial formation of axial imide followed by equilibration strongly favoring amide is therefore certainly possible, we cannot exclude a kinetic barrier to formation of the axial acetyl imides.

An axial cyclic imide has been reported in the reaction of 3-aminocholestane with 1,2-diphenylmaleic anhydride.[14] The Stuart–Briegleb models do show an easing of the steric problem because the cis carbonyl oxygens are pulled away from the C-2 and C-6 hydrogens. However, we could only produce reaction with the solvent dimethylformamide to form the formamide derivative when we conducted the closely related reaction[14] of 3α-aminocholestane with maleic anhydride. We have not explored the cyclic imide reactions further.

Experimental Section

Proton NMR spectra were taken on a Varian-A60A instrument in deuteriochloroform with Me_4Si as a standard. Mass spectra were taken on a Hitachi RMU-6L instrument. Analyses were carried out by Schwarzkopf Microanalytical Laboratory.

Acylation of 3-Aminocholestane Isomers. A 1-g sample of a mixture of 3α- and 3β-aminocholestane[2] was refluxed with 20 mL of acetic anhydride (distilled) and 2 mL of pyridine (dried over kOH and distilled) for 2 h. The brown solution with solid crystallizing out was poured onto ice and stirred, yielding 1 g of a dirty white solid which was filtered, washed with water, and dried. Chromatography on 50 g of silica gel (J. T. Baker) with benzene as the eluant yielded 400 mg of a fast-moving material (**2a**). This was crystallized from pentane: mp 136–137 °C; mass spectral mol wt 471; ^{1}H NMR, steroid envelope in the hydrocarbon region and a sharp singlet at δ 2.33 (6 H). Anal. Calcd for $C_{31}H_{53}NO_2$: C, 78.92; H, 11.32; N, 2.97. Found: C, 79.0; H, 11.63; N, 2.76.

A second material (400 mg) was obtained from the chromatography (see above) by elution with chloroform. NMR showed two unequal singlets near δ 2.0 which together integrated to ca. three hydrogens. The material is a broad-melting (ca. 195–240 °C) mixture of **2b** and **2c** (described below). A 100-mg sample of this mixture was acetylated as above. The solid product was triturated with pentane. The imide described above (**2a**) was obtained by evaporation of the pentane while the insoluble material (80 mg) was recrystallized from acetone to yield a solid (**2b**): mp 214–216 °C (lit.[2] mp 217–218 °C); NMR, steroid hydrocarbon envelope and singlet at δ 2.0 (3 H); mass spectral mol wt 429.

Acylation of 3-Aminocholane Isomers. 3-Oxocholane[1] (2 g) was converted to 2.04 g of the oxime with hydroxylamine hydrochloride and sodium acetate in 95% ethanol. This was reduced with 2 g of lithium aluminum hydride in refluxing dry ethyl ether for 6 h to yield 1.75 g of a mixture of amines which were not characterized. This material (1 g) was refluxed with acetic anhydride–pyridine, worked up, and subjected to chromatography exactly as above for the cholestane series. In this manner was obtained 390 mg of **1a** which was recrystallized from pentane–acetonitrile: mp 85–87 °C; mass spectral mol wt 429; ^{1}H NMR, steroid envelope in the hydrocarbon region and a sharp singlet at δ 2.40 (6 H). Anal. Calcd for $C_{28}H_{47}NO_2$: C, 78.26; H, 11.02; N, 3.26. Found: C, 78.7; H, 10.78; N, 3.41.

Chromatography yielded 840 mg of a mixture of **1b** and **1c** (described below) which on further acetylation, exactly as in the cholestane series (see above), gave 390 mg of **1b** which was recrystallized from chloroform–pentane: mp 127–128 °C; mass spectral mol wt 387; ^{1}H NMR, steroid envelope in the hydrocarbon region and singlet at δ 2.0 (3 H).

Acylation of (4-*tert*-Butylcyclohexyl)amine Isomers. A 1-g sample of the mixture of amine stereoisomers, obtained as described,[4] was treated in a manner identical with the procedures above to yield 200 mg of the imide **3a** which was recrystallized from acetonitrile: mp 77.5 °C (sharp); mass spectrum, no molecular ion but M – 43 at *m/e* 196; ^{1}H NMR δ 0.87 (s, 9 H), 2.35 (s, 6 H). Anal. Calcd for $C_{14}H_{25}NO_2$: C, 70.28; H, 10.46; N, 5.85. Found: C, 69.97; H, 10.82; N, 5.63.

Chromatography yielded 700 mg of **3b** and **3c** (described below) which was treated as above for the cholestane and cholane series to yield 350 mg of **3b** which was recrystallized from pentane–acetone: mp 168–169 °C (lit.[4] mp 170–171 °C); mass spectral mol wt 197; ^{1}H NMR δ 0.86 (s, 9 H), 2.01 (s, 3 H). Anal. Calcd for $C_{12}H_{23}NO$: C, 73.04; H, 11.75; N, 7.10. Found: C, 73.51; H, 12.26; N, 6.66.

Hydrolysis of 3β-(Diacetylamido)cholestane (2a). The imide **1a** (100 mg) was treated with 5 mL of 95% ethanol and 10 mL of 10% NaOH, and the heterogenious mixture was refluxed for 1 h, yielding a white solid (**2c**, 70 mg) which was recrystallized from acetone; mp 245–246 °C (lit.[2] mp 245–246 °C. The mass spectrum was almost identical with that of **2b** (see above) with a molecular weight of 429. The proton NMR hydrocarbon envelope was almost identical with that of **2b** with a different singlet of δ 1.97 (3 H).

Hydrolysis of 3β-(Diacetylamido)cholane (1a). This reaction was identical with the hydrolysis of **2a**, described above, and 1 g of the imide **1a** yielded 0.73 g of **1c** which was recrystallized from acetone; mp 212–214 °C. Anal. Calcd for $C_{26}H_{45}NO$: C, 80.57; H, 11.70; N, 3.60. Found: C, 80.49: H, 11.76; N, 3.53. The mass spectrum was almost identical with that for **1b** (see above) with a molecular weight of 387. The proton NMR hydrocarbon envelope almost identical with that of **1b** except for a singlet at δ 1.96 (3 H).

Hydrolysis of *trans*-4-*tert*-Butyl(diacetylamido)cyclohexane (3a). A 50-mg sample of the imide **3a** was dissolved in 2 mL of ethanol and 10 mL of 2.5% NaOH with stirring at room temperature for 10 min. This yielded 40 mg of **3c** which was recrystallized from pentane–acetone: mp 115–116 °C (lit.[4] mp 117–118 °C; mass spectrum almost identical with that for **3b**, mol wt 197; ^{1}H NMR δ 0.86 (s, 9 H), 1.96 (s, 3 H). Anal. Calcd for $C_{12}H_{23}NO$: C, 73.04; H, 11.75; N, 7.10. Found: C, 73.39; H, 12.00; N, 6.76.

Preparation and Acylation of 3α-Isocyanatocholestane. A 300-mg sample of 3α-aminocholestane obtained by chroma-

(9) See ref 5, p 391, experimental procedure for *N*-phenyldiacetamide.
(10) See ref 3 and especially Section 9.9.2.4 of ref 3b, and references therein.
(11) E. A. Noe and M. Raban, *J. Am. Chem. Soc.*, **97**, 5811 (1975). See also: G. Tetu, J.-C. Duplan, N. Pellissier, and E. Laurent, *J. Chem. Res. (S)*, 98 (1978).
(12) This overall analysis has parallels to that for phenylcyclohexane where the carbonyl carbons of the imide may be seen to occupy the ortho carbon positions in the phenyl ring. See: N. L. Allinger and M. T. Tribble, *Tetrahedron Lett.* 3259 (1971); B. L. Shapiro, M. J. Gattuso, N. F. Hepfinger, R. L. Shone, and W. L. White, *ibid.*, 219 (1971).
(13) See ref 3a, p 365 and references therein.
(14) U. Zehavi, *J. Org. Chem.*, **42**, 2819 (1977).

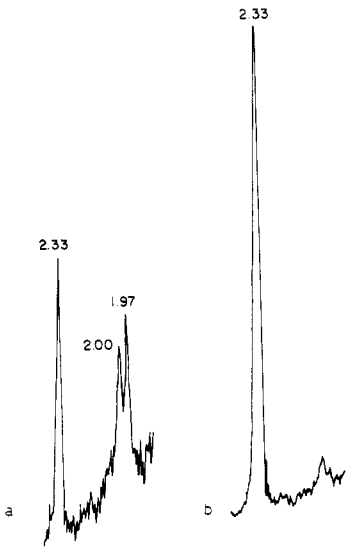

Figure 1. Proton NMR δ values shown of unseparated products from the acetylation of 3α- and 3β-aminocholestane (a) and their pentane-soluble fraction (b).

tography[2] was treated with phosgene (moderate bubbling) in boiling *o*-dichlorobenzene for 2 h. The workup yielded a solid residue which was recrystallized from ether–acetonitrile to give **2d**: 250 mg; mp 70–72 °C; mass spectral mol wt 413; IR showed the absence of NH_2 and a strong absorption at 2270 cm^{-1} (NCO). A 150-mg sample of this material (**2d**) was refluxed with 3 mL of acetic anhydride for 19 h (175 °C). Benzene followed by chloroform elution chromatography on 30 g of silica gel yielded 25 mg of a material identical with **2b** (see above) by melting point, TLC, and ^1H NMR. Starting material (15 mg) was also isolated in procedures known to yield imide if present.

Preparation and Acylation of 3β-Isocyanatocholestane. A 300-mg sample of 3β-aminocholestane was treated as above to yield 250 mg of **2e**: mp 81–83 °C; mass spectral mol wt 413; IR NH_2 absent, strong absorption at 2250 cm^{-1} (NCO). A 200-mg sample of **2e** was acylated as above to yield a brown residue which was purified by chromatography (as above) to give 15 mg of a material identical by melting point and ^1H NMR with **2a** and 5 mg of a material similarly identical with the amide **2c**.

Equilibration of 3β-(Diacetylamido)cholestane(2a). A 50-mg sample of **2a** was refluxed for 1 h in 1 mL of acetic anhydride with 3 drops of pyridine. The acetic anhydride showed a weak infrared absorption at near 3 μm. Solvent was removed under vacuum, and the ^1H NMR of the residue showed the characteristic singlets for **2a** and **2c** in a ratio of ca. 4:1 favoring the imide (**2a**).

Trituration Procedure for Separation of Isomers. A 1-g sample of the mixture of 3-aminocholestane isomers was acetylated as described above. This yielded a crude solid weighing 940 mg. The ^1H NMR in the region from ca. δ 2 to 2.5 is reproduced in Figure 1a. The singlet at low field is due to the imide **2a** while the doublet near δ 2.0 is due to the mixture of amides **2b** and **2c**. Pentane at room temperature was triturated (3 × 25 mL) with this solid and filtered by suction. Evaporation yielded 350 mg of a solid (**2a**) with a ^1H NMR in the same region, as exhibited in Figure 1b. Thin-layer chromatography on silica gel with chloroform showed only traces of amide in this sample. The insoluble residue weighed 580 mg and was subjected again to acetylation as above. The crude solid yield was again triturated with pentane as above to give another 200 mg of the soluble imide **2a**. The insoluble residue weighed 220 mg and was identified as the amide **2b** only slightly contaminated with the epimer **2c**. One crystallization gave pure **2b** as judged by its melting point, 215–216 °C.[2]

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Registry No. 1a, 79483-38-8; **1b**, 79499-33-5; **1c**, 79483-39-9; **2a**, 79483-40-2; **2b**, 40937-16-4; **2c**, 1912-64-7; **2d**, 24281-86-5; **2e**, 24281-87-6; **3a**, 79483-41-3; **3b**, 31023-35-5; **3c**, 31023-36-6; 3α-aminocholestane, 2206-20-4; 3β-aminocholestane, 2206-21-5; 3-oxocholane, 19443-04-0; 3-oxocholane oxime, 79483-42-4.

An Improved Yield Preparation of 3-Oxo-2,6,6-trimethylcyclohex-1-ene-1-carboxylic Acid, an Important Intermediate in the Synthesis of (±)-Strigol[1]

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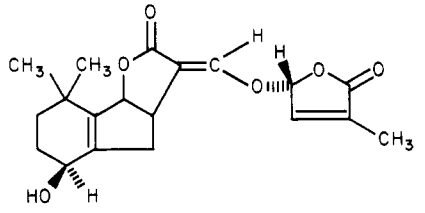
Witchweed [*Striga asiatica* (L.) Kuntze] is a parasitic plant whose seeds will not germinate unless they are stimulated by a chemical exuded from the roots of a host plant or some nonhost plants.[2] The active chemical in the root exudates was isolated in 1966[3] and identified in 1972[4] by Cook and co-workers. The compound 1 was given the trivial name strigol and it has been shown to be a very potent witchweed seed germination stimulant.



1

Total synthesis of (±)-strigol was reported in 1974 by Sih and co-workers,[5] and the details of their sequence and resolution of (±)-strigol was reported in 1976.[6] MacAlpine and co-workers reported the synthesis of strigol by a somewhat different method also in 1974 and 1976.[7]

Cook and co-workers suggested that strigol may be representative of a new class of plant hormones and that other biological effects should be examined.[4] In 1974, C. J. Sih provided the USDA with 4 g of (±)-strigol and 1 g of (±)-epistrigol. The data obtained from some of the experiments conducted with this limited amount of the germination stimulant have been very encouraging and emphasize the need for continuing studies on its biological activity.[8-10]

(1) Presented at the combined Southeast/Southwest Regional Meeting of the American Chemical Society, New Orleans, LA, Dec 10–13, 1980.
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