Hydrogenation of 4-(3,5-Dimethyl-4-isoxazoylmethyl)-7,7a-dihydro-1β-hydroxy-7aβ-methyl-5(6*H*)-indanone

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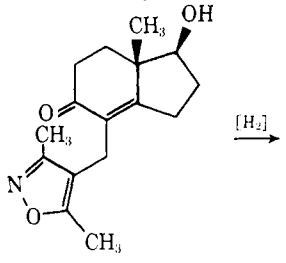
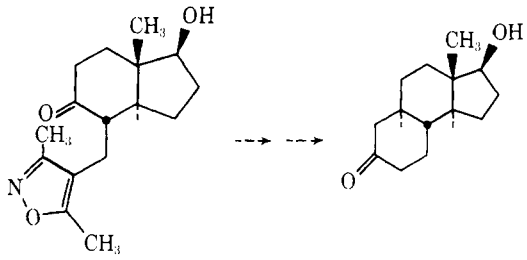
The hydrogenation of the title compound was reinvestigated and the major product was reassigned the trans configuration. The structure assignment was based on a single-crystal X-ray study of 6α-bromo-4α-(3,5-dimethyl-4-isoxazoylmethyl)-1β-hydroxy-7aβ-methyl-3aα,6,7,7a-tetrahydro-5(4*H*)-indanone (**3**). The bromo compound **3** crystallizes in the tetragonal space group $P4_2/nbc$ with $a = b = 15.6134$ and $c = 27.8258$ Å. The structure was solved by the heavy atom method and refined to an *R* index of 11.2%. A rationalization of the stereochemical outcome of the hydrogenation of hydrindanones is offered.

The production of a trans CD ring juncture has been a serious problem in the efficient total synthesis of steroids. While studying the utility of the isoxazole annelation sequence[2] for steroid synthesis we hoped to overcome this problem by hydrogenating the hydrindanone isoxazole **1**. If the enone **1** could be stereospecifically reduced to the trans bicyclic ketone **2**, then the isoxazole ring could easily be converted into the B ring of a de-A steroid with the natural configuration.



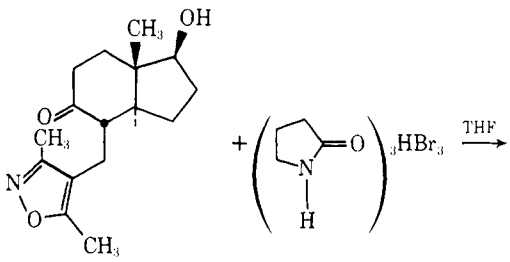
1



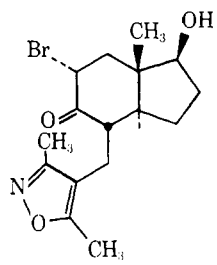
2

Hydrogenation of **1** over palladium on charcoal in acidic ethanol gave an 85:15 mixture of two reduced ketones, **2a** and **2b**. These two ketones exhibited angular methyl group resonances at δ 1.09 and 1.25, respectively, in the nmr. This hydrogenation had been studied previously by McMurry,[3] and he had assigned ketone **2b**, the δ 1.25 compound, to the trans series on the basis of the half-width of its angular methyl group signal in the nmr.[4] This assignment seemed unlikely because the Zürcher[5] rules predict that the trans ketone should exhibit an angular methyl resonance δ 0.091 upfield from that of the cis ketone and because there was precedent which suggested that 4-substituted hydrindanones should give 30–80% trans product.[6]

In fact, both reduced ketones, **2a** and **2b**, exhibited similar, wide, angular methyl group resonances in the nmr ($\Delta W_h/2$ = 0.75 and 0.65 Hz, respectively). Stereochemistry could be assigned, with confidence, only after the X-ray crystal structure of the bromo ketone **3** had been completed. The bromo ketone **3** was prepared by PHT bromination[7] of **2a**, which in turn was isolated from the hydrogenation mixture by repeated fractional crystallization.



2a

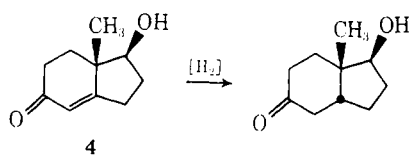


3

The X-ray data from **3** were collected with nickel-filtered Cu Kα radiation to a spacing of 0.94 Å. The structure was solved by the Patterson method and refined by full-matrix least-squares refinement with anisotropic temperature factors of all nonhydrogen atoms. The *R* index is 11.2%. A view of the molecule is shown in Figure 1 and reveals that bromo ketone **3** and therefore **2a** have the trans configuration and not the cis assigned by McMurray.

Discussion

The effect of a substituent at C-4 on the stereochemistry of hydrindanone hydrogenation is a curious phenomenon. The parent enone without a side chain at C-4 (**4**) gives largely the cis product upon reduction,[8] while substituted hydrindanones (**5**) give considerably more of the trans product. The amount of trans product is roughly[6] correlated with the size of the side chain.



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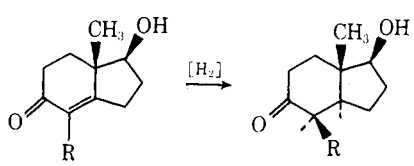


5

The classical Horiuti-Polanyi[9] mechanism of hydrogenation requires that the two hydrogen atoms add to the

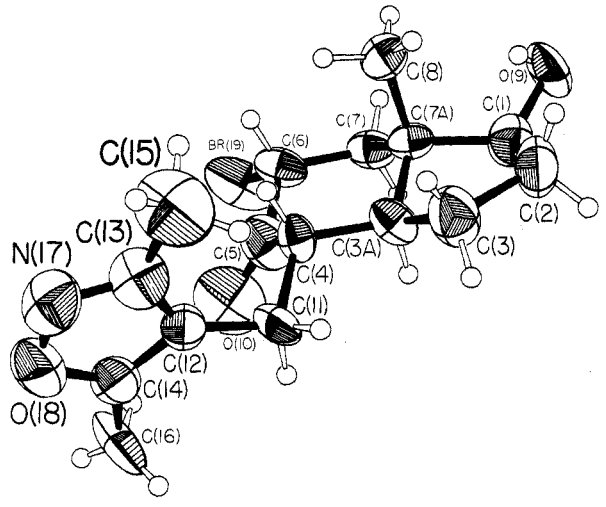
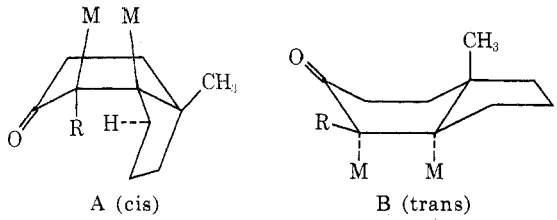


Figure 1. ORTEP drawing of the bromo ketone **3**.

same side of an olefin. In the case of a substituted hydrindanone **5** this means that the side chain must become axial in the trans product unless there is a prereduction double-bond equilibration. We did not observe any axial product under our acidic hydrogenation conditions, but Baggaley[10] has reported that hydrogenation of a hydrindanone with a methoxy group at C-4 (**5**, R = OCH_3) under neutral, nonequilibrating conditions did give a trans product with an axial methoxy group. The question, then, is why a side chain at C-4 leads to the production of more of the product with the least stable ring junction, especially when this requires the side chain to become axial.

Part of the answer is that the hydrogenation of **4** and **1** may have different product-determining steps. Unlike **4**, the hydrogenation of **1** exhibits no pressure effect on the stereochemistry of the product.[9c] This suggests that the slow step in the hydrogenation of **1**, the tetrasubstituted olefin, is the formation of the adsorbed olefin[11] and not the formation of the half-hydrogenated state. The stereochemical results than can be rationalized in terms of a boat-like complexed olefin.[12]

There are two plausible boat complexes, A and B, each leading to a different product. Addition of hydrogen in some fashion[13] to the cis boat A will give a cis saturated ketone. However, if the R group is large, steric repulsion between the side chain and the 3α hydrogen atom in the cis boat A will favor the trans boat B. Transfer of hydrogen and desorption of B gives a trans boat saturated ketone with an equatorial side chain. Ring inversion then gives the trans chair axial product. In the case of **1**, the first-formed trans chair axial product is presumably equilibrated under the acidic reaction conditions to the observed trans chair equatorial product.



A (cis) B (trans)

M stands for a metal surface atom

The boat intermediate may well be a consequence of the stereoelectronic requirement that the two carbon–metal bonds be eclipsed and coplanar in the olefin complex.[14] Hussey[15] has pointed out that this eclipsing of carbon–metal bonds during the hydrogenation of simple, isolated, cyclohexene double bonds implies a boat intermediate, and he has offered some evidence that is consistent with this suggestion, at least for simple cyclohexenes hydrogenated over a platinum catalyst.

Experimental Section

Preparation of 4α-(3,5-Dimethyl-4-isoxazolylmethyl)-1β-hydroxy-7aβ-methyl-3aα,6,7,7a-tetrahydro-5-(4*H*)-indanone (2a). A solution of 50 mg (0.182 mmol) of isoxazole alcohol **1** in 0.01 *M* perchloric acid in ethanol and 15 mg of 10% palladium on charcoal was stirred for 48 hr under 1 atm of hydrogen. Solid sodium bicarbonate was added, and the mixture was swirled for 5 min. Filtration and evaporation gave 49 mg (0.177 mmol, 97.5% yield) of a semisolid material identified as an 85:15 mixture of trans and cis hydrindanone. Recrystallization from hexane–isopropyl ether gave a purer sample of **2a**: mp 146–149°; nmr ($CDCl_3$) δ 3.73 (m, 1 H), 2.73 (s, 3 H), 2.21 (s, 3 H), 1.09 (s, 3 H); ir ($CHCl_3$) 3.03, 5.89, 6.10, 9.02, 11.18 μ; mass spectrum (25 eV) *m/e* (rel intensity) 277 (9.5), 150 (5.1), 110 (100).

Preparation of 6α-Bromo-4α-(3,5-dimethyl-4-isoxazolylmethyl)-1β-hydroxy-7aβ-methyl-3aα,6,7,7a-tetrahydro-5(4*H*)-indanone (3). A solution of 22.5 mg (0.081 mmol) of ketone **2a** and 46.8 mg (0.094 mmol) of pyrrolidone 2-hydrotribromide (PHT) in 4 ml of THF was allowed to stand at room temperature for 4 hr. The solution was filtered from the precipitate which had formed, and the filtrate was evaporated at reduced pressure to give 47 mg of crystalline material. The crude product was chromatographed on a 10 × 20 × 0.2 cm silica gel plate, developed with 60:40 ethyl acetate–chloroform (R_f 0.35) to yield 9.4 mg (0.026 mmol, 32.6%) of colorless crystals. Recrystallization from acetone–hexane gave crystals suitable for X-ray: mp 161–164°; nmr ($CDCl_3$) δ 2.42 (s, 3 H), 2.23 (s, 3 H), 1.18 (s, 3 H); ir ($CHCl_3$) 2.77, 5.77, 6.10 μ.

X-Ray Structure of 3. Unit cell dimensions were obtained from least-squares refinement of the 2θ angles of 31 reflections measured on a Datex automated General Electric diffractometer. Unit cell parameters are $a = b = 15.6134 \pm 0.0002$ Å; $c = 27.8258 \pm 0.0004$ Å.

The absence of *hk*0 reflections for $h + k$ odd, 0*kl* reflections for k odd, and *hhl* reflections for l odd indicated that the space group is $P4_2/nbc$. The crystal density was found to be 1.41 ± 0.01 g cm^{-3}. The calculated density is 1.40 g cm^{-3} for 16 molecules of molecular weight 356.261 per unit cell.

Intensity data were collected by the θ–2θ scan method with nickel-filtered Cu Kα radiation (λ = 1.5418 Å). Reflections were collected to a maximum value of 2θ = 110° with a scan rate in 2θ of 2° min^{-1}. Three reflections, the 201, 224, and 220, monitored at regular intervals during the data collection, decayed in intensity by 5.3, 7.9, and 3.4 standard deviations, respectively.

The intensities of 2140 reflections were measured. The intensities of 339 of these were observed to be less than one standard deviation above background and were assigned a value of zero with zero weight throughout the refinement. The data were corrected for Lorentz-polarization effects and for crystal decay but not for absorption (μ = 37 cm^{-1}). The data were placed on an absolute scale by Wilson's method.[16] A Howells, Phillips, and Rogers plot[17] confirmed that the crystal is centrosymmetric.

Approximate coordinates of the nonhydrogen atoms were obtained by the Patterson–Fourier process. Least-squares refinement of coordinates and anisotropic temperature factors converged at an R index of 11.2%. The weighted R index was 4.7%, and the goodness of fit was 4.2. The average standard deviation in atomic position is 0.01 Å, the average standard deviation in bond length is 0.02 Å, and the average standard deviation in bond angle is 1°.[18]

Acknowledgment. The author wishes to thank Professor Gilbert Stork for encouragement and guidance. The financial support of the National Institutes of Health is gratefully acknowledged.

Registry No.—**1**, 50323-79-0; **2a**, 50323-80-3; **3**, 50323-81-4.

Supplementary Material Available. Tables I–V, containing the observed and calculated structure factors, the heavier atom parameters, the hydrgen atom coordinates, the bond distances and angles, and the least-square plane of the isoxazole ring, respectively, will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the supplementary

material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D. C. 20036. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche, referring to code number JOC-74-629.

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(12) There is a second possible explanation for the stereochemical results. Hydrindanone **4** may undergo a prereduction α,β–β,γ double bond equilibration and the β,γ unsaturated ketone could undergo fast reduction to give predominantly a cis product. At higher hydrogen pressure this isomerization would be intercepted, resulting in formation of more of the trans product. In the case of C-4 substituted hydrindanones like **1** the α,β double bond isomer would be significantly more stable than the β,γ isomer and again more of the trans product would be formed. That the β,γ isomer does not give predominantly the cis product was shown by reducing **4** with deuterium and exchanging all the lable hydrogens with H_2O. Mass spectra showed that the separated cis and trans products had equal amounts of retained deuterium.
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Quinoxaline Studies. XXI.[1a] 1,4-Bis(*p*-toluenesulfonyl)-2-hydroxymethyl-1,2,3,4-tetrahydroquinoxaline

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The alcohol originally reported by Acheson as 1,4-bis(*p*-toluenesulfonyl)-2-hydroxymethyl-1,2,3,4-tetrahydroquinoxaline (**1**) is 1,5-bis(*p*-toluenesulfonyl)-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepin-3-ol (**4a**). Alcohol **1** has been prepared by condensation of *N,N'*-bis(*p*-toluenesulfonyl)-*o*-phenylenediamine with methyl 2,3-dibromopropionate to give 1,4-bis(*p*-toluenesulfonyl)-2-carbomethoxy-1,2,3,4-tetrahydroquinoxaline (**14**), which was reduced with lithium aluminum hydride to give authentic **1**. Detosylation of alcohol **1** with sulfuric acid gave 2-hydroxymethyl-1,2,3,4-tetrahydroquinoxaline (**6**), identical with that obtained by lithium aluminum hydride reduction of 2-carboethoxy-1,2,3,4-tetrahydroquinoxaline (**15**). Similarly, detosylation of diazepinol **4a** with sulfuric acid gave 2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepin-3-ol (**5a**), which could be retosylated to give diazepinol **4a**.

Substituted tetrahydroquinoxalines are of interest as models for tetrahydrofolic acid.[2,3] Therefore, the reported[4] synthesis of 1,4-bis(*p*-toluenesulfonyl)-2-hydroxymethyl-1,2,3,4-tetrahydroquinoxaline (**1**) was extensively studied, for the 2-hydroxymethyl group of **1** would be an easy source of various functional groups on a reduced quinoxaline ring *via* routine oxidation, reduction, and displacement reactions.

Condensation of the disodium salt of *N,N'*-bis(*p*-toluenesulfonyl)-*o*-phenylenediamine (**2**) with 2,3-dibromo-1-propanol (**3**) by the procedure of Acheson[4] gave ditosyl alcohol **4a**, mp 194–195°, reported[4] mp 193° for supposed 1,4-bis(*p*-toluenesulfonyl)-2-hydroxymethyl-1,2,3,4-tetrahydroquinoxaline (**1**). Detosylation of alcohol **4a** with sulfuric acid gave alcohol **5a**, mp 139–140°, reported[4] mp 140–141° for supposed 2-hydroxymethyl-1,2,3,4-tetrahydroquinoxaline (**6**). Oxidation of alcohol **5a** by a variety of agents was unsuccessful; however, oxidation of ditosyl alcohol **4a** with Jones reagent[5-7] gave a carbonyl compound (**7**), mp 179–180°, which readily formed an oxime, a hydrazone, a tosylhydrazone, and a 2,4-dinitrophenylhydrazone, and which was stable to Tollens and Benedict solutions. The nmr spectrum of **7** showed, in addition to the tosyl methyl and aromatic signals, only a sharp singlet at δ 4.06 for four protons, thus indicating a very symmetrical molecule, to which was assigned the structure 1,5-bis(*p*-toluenesulfonyl)-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepin-3-one (**7**). Mertes and Lin[3] have also reported this ketone. They concluded that alcohol **1** rearranged to ketone **7** during oxidation with dicyclohexylcarbodiimide in dimethyl sulfoxide. We conclude, however, that the reported[4] structure of **1** is incorrect and, in fact, is 1,5-bis(*p*-toluenesulfonyl)-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepin-3-ol (**4a**), and Acheson's detosylated alcohol is 2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepin-3-ol (**5a**), not 2-hydroxymethyl-1,2,3,4-tetrahydroquinoxaline (**6**) as reported.[4] The *O*-mesylate (**4b**) and *O*-tosylate (**4c**) derivatives of **4a** and the *N,N'*-diacetyl (**5b**) and *N,N'*-dinitroso (**5c**) derivatives of **5a** have also been prepared and have properties consistent with the benzodiazepine structure.

Sodium borohydride reduction of ketone **7** gave material identical (melting point, mixture melting point, ir) to diazepinol **4a**, thus ruling out formation of ketone **7** from alcohol **1** by rearrangement during oxidation. Retosylation of diazepinol **5a** with tosyl chloride in a variety of media (pyridine, aqueous potassium bicarbonate, or acetic acid–sodium acetate–tetrahydrofuran[8]) generally resulted in noncrystallizable oils. However, the oil from tosylation of **5a** in the acidic medium crystallized from ethanol after standing at 0° for several weeks to give a 6% yield of solid