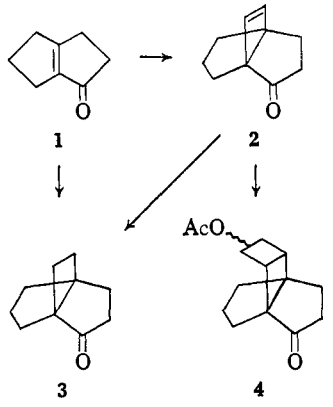
indicates the absence of intermolecular sensitization in the photoreduction.[5]

Photochemical cycloaddition of 1,2-dichloroethylene to bicyclo[3.3.0]oct-1(5)-en-2-one (**1**),[6] formation of the ethylene ketals, dechlorination with sodium in liquid ammonia, and hydrolysis of the ketal gave ketone **2**, semicarbazone mp 185°, in 67% yield from **1**.[7] The photoreduction product is identical with samples of ketone **3** obtained from hydrogenation of **2** and from photoaddition of ethylene to **1**; semicarbazones mp 200–202° dec and mmp 200–202° dec.

This photoreduction of a β,γ-unsaturated ketone[8] suggests that light-induced cycloaddition at the β,γ-double bond might be possible. Irradiation of ketone **2** in benzene solution containing vinyl acetate gave, after chromatography on alumina, a keto acetate in 30% yield, mol wt 234,[11] $\tilde{\nu}_{max}^{CCl_4}$ 1740 (very intense), 1415, 1380, and 1235 cm^{-1}; τ 4.88 ppm, broad (1 H), and two overlapping, unresolved multiplets centered at τ 7.54 and 8.18 ppm with a sharp singlet prominent at τ 8.00 ppm (17 H). The spectral evidence is compatible, but not exclusively so, with gross structure **4** for the 1:1 adduct. It is clear, however, that cycloaddition has occurred at a β,γ double bond.



(5) D. Scharf and F. Korte, *Tetrahedron Letters*, 821 (1963), found that norbornene underwent dimerization when irradiated in the presence of acetone or dicyclopropyl ketone.

(6) We are grateful to the Badische Anilin- und Soda-Fabrik for a generous gift of **1**.

(7) H. O. House and T. H. Cronin, *J. Org. Chem.*, **30**, 1061 (1965).

(8) The Büchi rearrangement[9] is the preferred path even in methylene chloride or ethanol for those β,γ-unsaturated ketones in which this path is not prevented for geometrical reasons.[10]

(9) G. Büchi and E. M. Burgess, *J. Am. Chem. Soc.*, **82**, 4333 (1960).

(10) R. L. Cargill, M. E. Beckham, A. E. Siebert, and J. Dorn, *J. Org. Chem.*, **30**, 3647 (1965), and references cited there.

(11) We are grateful to Professor A. L. Burlingame and Dr. H. K. Schnoes, University of California, Berkeley, for mass spectra of this adduct and of ketones **2** and **3**.

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1-Deamino-1,6-L-selenocystine-oxytocin, a Highly Potent Isolog of 1-Deamino-oxytocin[1]

Sir:

Recently we reported the synthesis and pharmacological properties of 6-hemi-L-selenocystine-oxytocin (6-seleno-oxytocin) and its deamino analog.[2] The present communication concerns the synthesis of 1-deamino-1,6-L-selenocystine-oxytocin (deamino-diseleno-oxytocin), the structure of which is shown in Figure 1. This molecule is identical with deamino-oxytocin[3] except that both sulfur atoms have been replaced by selenium atoms.

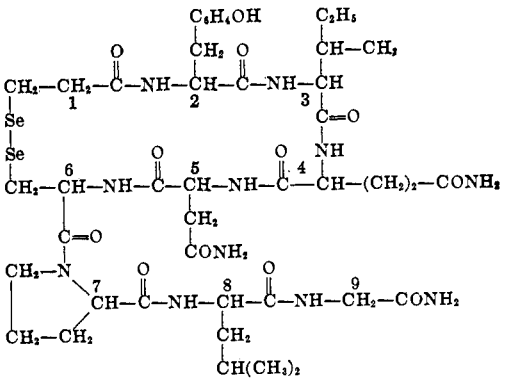

Figure 1. Structure of 1-deamino-1,6-selenocystine-oxytocin, with numbers indicating the positions of the component amino acid residues.

The protected tetrapeptide, N-carbobenzoxy-Se-benzyl-L-selenocysteinyl-L-prolyl-L-leucylglycinamide,[2] served as starting material for the synthesis of the deamino-diseleno-oxytocin. After removal of the carbobenzoxy group by hydrogen bromide–acetic acid the tetrapeptide was lengthened by the stepwise *p*-nitrophenyl ester procedure earlier employed in this laboratory for the synthesis of oxytocin[4] and deamino-oxytocin[3] to give the protected intermediate, Se-benzyl-β-selenopropionyl-L-tyrosyl-L-isoleucyl-L-glutaminyl-L-asparaginyl-Se-benzyl-L-selenocysteinyl-L-prolyl-L-leucylglycinamide.[5,6] The isolog was obtained after the cleavage of the protecting groups from this intermediate by sodium in liquid ammonia, followed by ring closure through treatment with ferricyanide. Subsequently, the ferrocyanide and ferricyanide ions were removed with the ion-exchange resin AG3X4 in the chloride form. The deamino-diseleno-oxytocin was isolated by countercurrent distribution in a 1-butanol–benzene–0.05% acetic acid system (3:2:5) in which it possessed a *K* value of approximately 1.5; $[\alpha]^{22}D$ −51.0° (*c* 0.25, 1 *N* acetic acid). *Anal.* Calcd for $C_{43}H_{65}N_{11}O_{12}Se_2$: N, 14.2. Found: N, 14.0. Upon thin layer chromatography in 1-butanol–acetic acid–water (4:1:5, upper phase) deamino-diseleno-oxytocin traveled as a single spot, although a trace of chromogenic material remained at the origin, as indicated by the platinic iodide reagent of Toennies and Kolb.[7]

Upon bioassay deamino-diseleno-oxytocin exhibited

(1) This work was supported in part by Grant HE-01675 from the National Heart Institute, U. S. Public Health Service.

(2) R. Walter and V. du Vigneaud, *J. Am. Chem. Soc.*, **87**, 4192 (1965).

(3) V. du Vigneaud, G. Winestock, V. V. S. Murti, D. B. Hope, and R. D. Kimbrough, Jr., *J. Biol. Chem.*, **235**, PC64 (1960); D. B. Hope, V. V. S. Murti, and V. du Vigneaud, *ibid.*, **237**, 1563 ((1962); B. M. Ferrier, D. Jarvis, and V. du Vigneaud, *ibid.*, **240**, 4264 (1965).

(4) M. Bodanszky and V. du Vigneaud, *J. Am. Chem. Soc.*, **81**, 5688 (1959).

(5) The *p*-nitrophenyl Se-benzyl-β-selenopropionate (mp 38–39°) was prepared by condensation of *p*-nitrophenol with Se-benzyl-β-selenopropionic acid in the presence of dicyclohexylcarbodiimide. *Anal.* Calcd for $C_{16}H_{15}NO_4Se$: C, 52.8; H, 4.15; N, 3.85. Found: C, 52.7; H, 4.31; N, 3.76. The Se-benzyl-β-selenopropropionic acid (mp 74–76°) was synthesized by the base-catalyzed β-addition of benzylselenol to acrylic acid. *Anal.* Calcd for $C_{10}H_{12}O_2Se$: C, 49.4; H, 4.98. Found: C, 49.4; H, 4.98.

(6) All intermediate peptides showed correct C, H, and N analyses, which were carried out by Galbraith Laboratories, Knoxville, Tenn.

(7) G. Toennies and J. J. Kolb, *Anal. Chem.*, **23**, 823 (1951).

approximately 850 units/mg of avian depressor activity[8] and 520 units/mg of oxytocic activity.[9] Thus the replacement of both sulfurs by selenium in deaminooxytocin yields a highly potent isolog. A further study of this isolog from various chemical, physical, and biological standpoints is indeed warranted.

Acknowledgments. The authors wish to thank the following members of this department for their cooperation: Dr. Theodore Mahowald and Mrs. Caroline Holzhauser for the amino acid analyses, and Dr. W. Y. Chan for the bioassays.

(8) R. A. Munsick, W. H. Sawyer, and H. B. van Dyke, *Endocrinology*, **66**, 860 (1960).

(9) Oxytocic assays were performed according to the method of P. Holton (*Brit. J. Pharmacol.*, **3**, 328 (1948)) on uteri from rats in natural estrus with the use of magnesium-free van Dyke–Hastings solution as employed by R. A. Munsick (*Endocrinology*, **66**, 451 (1960)).

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Chemistry of Conjugate Anions and Enols. VII. Rates of Formation and Equilibria of Enolate Anions[1,2]

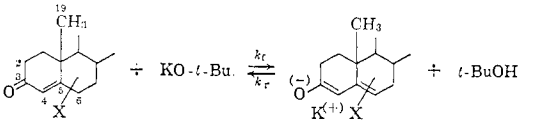
Sir:

Because of their high stability, solubility, and relatively fixed stereochemistry, the potassium enolate anions of Δ^4-3-keto steroids in *t*-butyl alcohol offer an ideal model for a systematic study of the factors that control the rate of formation and the stability of enolate anions as well as the nature of the transition state. Utilizing androst-4-ene-3,17-dione as primary substrate, the effects on enolization rate and equilibrium of alkyl and fluoro substitution have been measured and reveal a number of novel relationships not readily apparent in simple enolate systems.

The rate and extent of anion formation was best determined by quenching the *t*-butyl alcohol solution of steroid and potassium *t*-butoxide at various time periods with excess acetic anhydride.[3] Since only the enolate anion reacted under these conditions to form the $\Delta^{3,5}$-enol acetate, determination by gas chromatography of the ratio of enol acetate to unreacted ketone provided a semiquantitative measure of anion formation[4] that agreed well with values obtained by 4,4-dialkylation[5] or formation of the β,γ-unsaturated ketone by kinetically controlled protonation.[6] Table I lists the second-order rate constants for anion formation (k_f), the over-all equilibrium constants (K_{eq}), and the reverse rate (k_r) determined indirectly from K_{eq} and k_f.[7]

Entries 1 and 7 of the table, derived from a study of 6β-deuterioandrost-4-ene-3,17-dione *vs.* the nondeuterated compound, give the rates for axial and equatorial proton loss and gain from C-6 and demonstrate that 6β-(axial) proton loss is 53 times faster than 6α-(equatorial) loss ($k_{6\beta\text{-H},6\alpha\text{-H}}/k_{6\beta\text{-D},6\alpha\text{-H}} = 9$; 6$\beta$-deuterium loss 83% in enol acetate formation). The profound preference for axial proton loss despite greater steric hindrance from the β face strikingly emphasizes in a rigid system the importance of continuous $\sigma-\pi$ overlap of the departing (or entering) proton.[8] Since the C-19 angular methyl group is the major steric impediment to loss of the 6β proton to base, the 5- to 6-fold enhanced rate of protonation and of proton loss in the 19-nor compound (entry (4)) indicates an angular methyl *t*-butoxide interaction of *ca.* 1 kcal. Although the axial–equatorial preference has not been measured in (4) it is apparent that, in the absence of the angular methyl group, the true "stereoelectronic" axial preference should be approximately 300-fold, a magnitude much greater than previously suspected. In view of this preference, *cases of "equatorial" protonation in conformationally mobile systems must be considered in terms of axial protonation via nonchair conformations.*

Table I. Rates of Anion Formation and Reprotonation



		k_f,[a,b] l. mole^{-1} sec^{-1}	k_r,[c] l. mole^{-1} sec^{-1}	K_{eq} (27°)[a]
	Axial (6β) Proton Loss			
(1)	Androst-4-ene-3,17-dione	8.0×10^{-3}	1.6×10^{-5}	5.0×10^{2}
(2)	6α-Methyl-	2.9×10^{-3}	4.6×10^{-7}	6.3×10^{3}
(3)	6α-Fluoro	7.4×10^{-1}	3.1×10^{-5}	2.4×10^{4}
(4)	19-Nor-	4.0×10^{-2}	1.0×10^{-4}	4.0×10^{2}
(5)	4-Methyl-	1.8×10^{-3}	1.2×10^{-5}	1.5×10^{2}
(6)	2α-Methyl-	2.8×10^{-3}	5.6×10^{-5}	5.0×10^{1}
	Equatorial (6α) Proton Loss			
(7)	Androst-4-ene-3,17-dione	1.5×10^{-4} [d]	3.1×10^{-7}	5.0×10^{2}
(8)	6β-Methyl-	1.7×10^{-3}		
(9)	6β-Fluoro-	1.9×10^{-3}		

[a] Average value of three or more determinations. Average error *ca.* ±10%. [b] Forward rates are not corrected for the reverse reaction [c] Determined indirectly from k_f and k_{eq}. [d] Determined indirectly from $k_{6\beta\text{-H},6\alpha\text{-H}}/k_{6\beta\text{-D},6\alpha\text{-H}}$ and from 6β deuterium loss in enol acetate formation.

Entries (2) and (3) demonstrate that *either a 6-methyl or 6-fluoro substituent stabilizes the enolate anion* (13- and 48-fold, respectively). The 6α-fluorine effect is due primarily to a 90-fold increase in the rate of enolization, while the 6α-methyl group actually slows

(1) Supported by American Cancer Society Grant T-185.

(2) Previous paper in this series: T. D. J. D'Silva and H. J. Ringold, *Tetrahedron Letters*, 4487 (1965).

(3) H. J. Ringold and S. K. Malhotra, *J. Am. Chem. Soc.*, **84**, 3402 (1962); H. O. House and V. Kramer, *J. Org. Chem.*, **28**, 3362 (1963); S. K. Malhotra and F. Johnson, *J. Am. Chem. Soc.*, **87**, 5492 (1965).

(4) Product examination by thin layer chromatography showed only enol acetate and unreacted ketone except in the cases of the 6-fluoro derivatives where trace quantities of 6-dehydrosteroids were detected. The extent of dehydrohalogenation was not sufficient to significantly affect the results. The peak areas in gas chromatography were calibrated in each case with the authentic standard ketones and analytical specimens of the enol acetates which were prepared *via* the described anion quenching method.

(5) H. J. Ringold and S. K. Malhotra, *J. Am. Chem. Soc.*, **84**, 3402 (1962).

(6) H. J. Ringold and S. K. Malhotra, *Tetrahedron Letters*, 669 (1962).

(7) For rate and equilibrium determinations, the unsubstituted and methylated steroids were studied at concentrations of 0.033 *M*, the 6α-fluoro compound at 0.0021 *M*, and the 6β-fluoro compound at 0.0167 *M*. The concentrations of potassium *t*-butoxide varied from 1 to 5 equiv based on steroid while the reaction time allowed for equilibration ranged from 1 (6α-fluoro) to 72 hr for the 4-methyl compound. In order to prevent autoxidation, all reactions were carried out in an atmosphere of nitrogen.

(8) E. J. Corey and R. A. Sneen, *J. Am. Chem. Soc.*, 78, 6269 (1956).