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THE OXIDATION OF 4-AZA-5-PREGNENE-3,20-DIONE WITH BENZENESELENINIC ANHYDRIDE. FORMATION AND DECOMPOSITION OF A SELENOXIDE INTERMEDIATE

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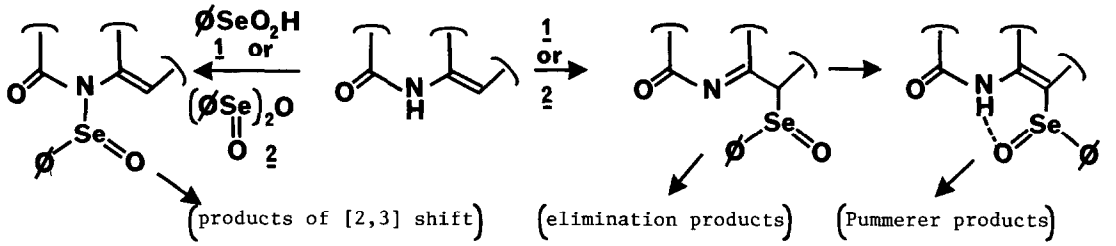
Abstract: The enamide moiety of the title azasteroid reacted with benzeneseleninic anhydride to afford products derived chiefly from a Pummerer-type reaction at C-6. The intermediate selenoxide was also prepared by oxidation of the corresponding selenide.

Benzeneseleninic acid (1) and benzeneseleninic anhydride (2) function as mild oxidants of various nitrogen nucleophiles, resulting in a number of synthetically useful transformations[1]. It occurred to us that enamides might prove interesting substrates for such oxidations, as introduction of new oxygen functions could occur either through [2,3] sigmatropic rearrangement of intermediate seleninamides[2] or *via* elimination or Pummerer-type reactions of initially formed selenoxides[3], followed by aqueous workup.

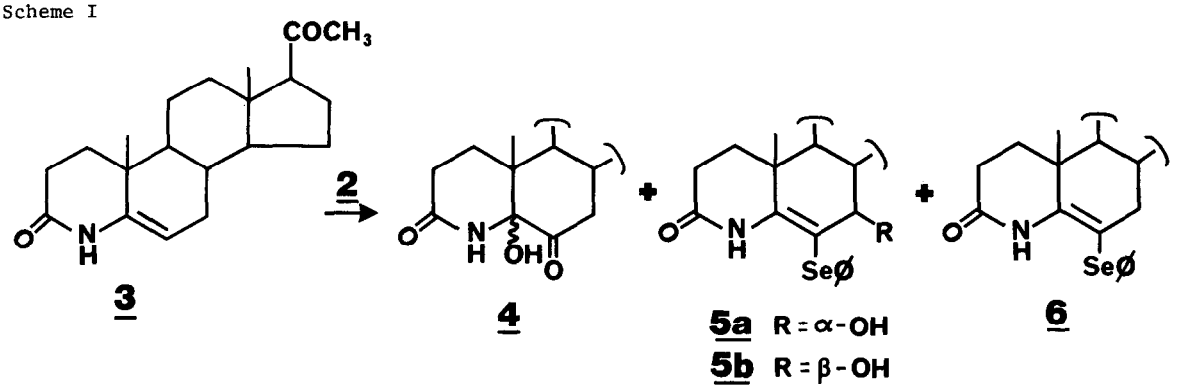


Certain azasteroids display biological activity and the synthesis of new derivatives is of consequent interest. We therefore chose 4-aza-5-pregnene-3,20-dione (3)[4] as the subject of our preliminary investigations. Herein we report the results.

Azasteroid 3 was treated with 1.1 molar equivalents of benzeneseleninic anhydride (2) in dichloromethane solution for 18 h at room temperature. The products were then separated by preparative t.l.c. (alumina) to afford, in order of increasing R_f, the keto carbinolamide 4[5] (40%), the epimeric 7-hydroxy enamidic selenides 5a and 5b[6,7] (28% and 12% respectively) and

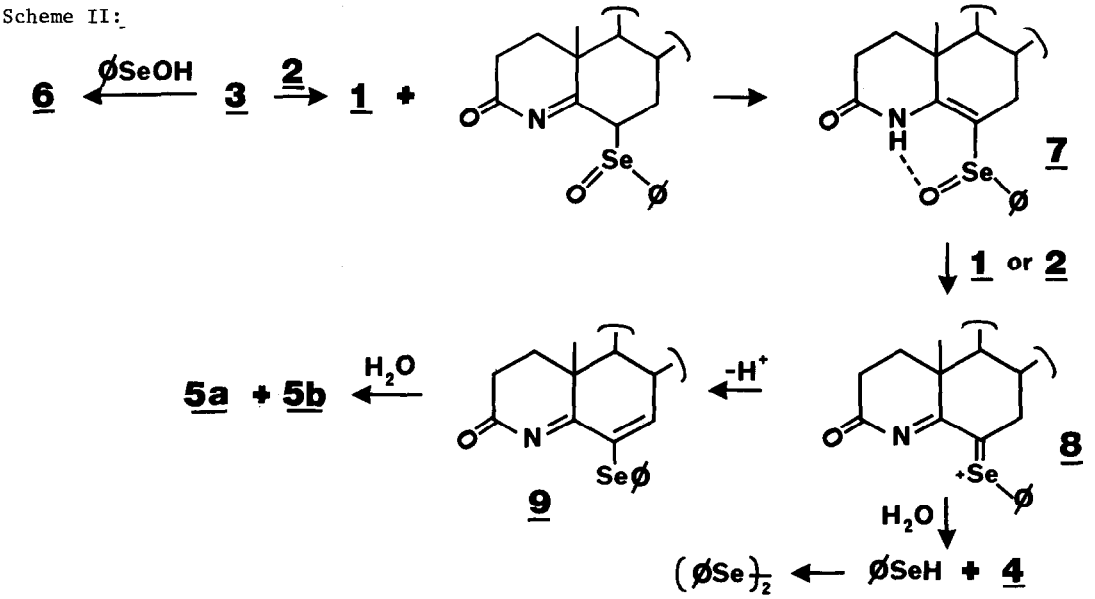
the selenide 6[8] (16%) (Scheme I).

Scheme I



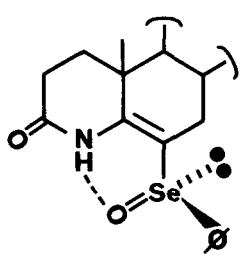
We believe that the azasteroid undergoes attack by the anhydride at C-6 to produce the corresponding selenoxide 7. The latter compound was not isolated from the reaction mixture, but reacted further to generate the Pummerer intermediate 8, which hydrolyzed with concomitant hydration of the N-acylimine moiety to afford the keto carbinolamide 4. Deprotonation of 8 at C-7 followed by 1,4 hydration of the resulting unsaturated N-acylimine 9 accounts for the formation of 5a and 5b. Furthermore, benzeneseleninic acid and diphenyl diselenide are expected byproducts of the preceding reactions. Their comproportionation[9] is known to generate benzeneselenenic acid[10], which in turn may react with azasteroid 3 at C-6. The formation of selenide 6 may thus be rationalized. (Scheme II).

Scheme II:



To verify the mechanism depicted in Scheme II, we prepared selenoxide 7 by an independent route. Treatment of azasteroid 3 with benzeneselenenyl chloride/pyridine furnished selenide 6, which gave the desired selenoxide upon oxidation with m-chloroperbenzoic acid (overall yield: quantitative). The selenoxide thus obtained is stable in the solid state or in dichloromethane solution at room temperature, but reacts readily in the presence of seleninic acid 1 or anhydride 2 to produce the same products 4, 5a and 5b in comparable yields to those obtained by the oxidation of azasteroid 3 with 2. Thus, the intermediacy of selenoxide 7 in the latter reaction is confirmed.

Finally, we note that the selenium atom of selenoxide 7 constitutes a chiral center. Consequently, the preparation of 7 from the oxidation of selenide 6 may, in principle, lead to the formation of a pair of diastereoisomers. We observed the formation of 7 as a mixture of two stereoisomers in a ratio of *ca.* 2:1 (nmr), from which the major isomer could be crystallized[11]. The two isomers decomposed with similar rates when treated with benzeneseleninic acid. Other diastereoisomeric steroid selenoxides have been reported[12], but were labile at or below room temperature because of facile elimination or sigmatropic shifts. The greater thermal stability of the enamidic selenoxide 7, where such reactions cannot occur, may render it a convenient substrate for stereochemical and chiroptical studies.



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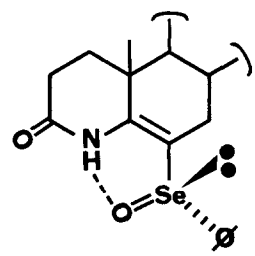

7 S-config.

Acknowledgements

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References and Notes

1. (a) T. G. Back and S. Collins, Tetrahedron Letters, 2661, (1979). (b) D. H. R. Barton, D. J. Lester and S. V. Ley, J.C.S. Chem. Comm., 276, (1978). (c) T. G. Back, *ibid*, p. 278. (d) D. H. R. Barton, D. J. Lester and S. V. Ley, J.C.S. Chem. Comm., 445, (1977). (e) M. R. Czarny, J.C.S. Chem. Comm., 81 (1976).

2. [2,3] Sigmatropic rearrangements of N-phenylseleninyl intermediates have been proposed in the oxidation of hydrazones with 2[1b,1d].

3. For reviews which describe the chemistry of selenoxides see: (a) H. J. Reich, Acc. Chem. Res., 12, 22, (1979). (b) D. L. J. Clive, Tetrahedron, 34, 1049, (1978). (c) K. B. Sharpless, K. M. Gordon, R. F. Lauer, D. W. Patrick, S. P. Singer and M. W. Young, Chem. Scripta, 8A, 9, (1975).

4. N. J. Doorenbos, C. L. Huang, C. R. Tamorria and M. T. Wu, J. Org. Chem., 26, 2546, (1961).

5. Compound 4: m.p. 232-234°; ν_{max} ($CHCl_3$) 3630, 3380, 1725, 1700 and 1660 cm^{-1}; ^1H nmr ($CDCl_3$) δ 7.00 (s, 1H, exchanged in D_2O), 3.80 (s, 1H, exchanged in D_2O); m/e 329 ($M^+ - H_2O$). A correct combustion analysis was obtained. Treatment with methanol and a trace of HCl effected exchange of OH for OCH_3.

6. Compound 5a: solid foam; $[\alpha]_D$ -132° (c 0.47, $CHCl_3$); ν_{max} ($CHCl_3$) 3580 and 3310 cm^{-1}; λ_{max} (CH_3OH) 249 nm (ε 15,400); ^1H nmr ($CDCl_3$) δ 4.05 (broad s, 1H, not exchanged in D_2O); ^{13}C nmr ($CDCl_3$) δ 70.3 (assigned to C-7); exact mass, Calculated for $C_{26}H_{33}NO_3{}^{80}Se$: 487.16257. Found: 487.1616. Compound 5b: solid foam; $[\alpha]_D$ +46° (c 0.17, $CHCl_3$); ν_{max} ($CHCl_3$) 3550 and 3310 cm^{-1}; λ_{max} (CH_3OH) 247 nm (ε 17,300); ^1H nmr ($CDCl_3$) δ 3.95 (d, J = 7 Hz, 1H, not exchanged in D_2O); ^{13}C nmr ($CDCl_3$) δ 74.8 (assigned to C-7); exact mass, Found: 487.1630.

7. The assignment of the 7α- and 7β-hydroxy structures to 5a and 5b is confirmed by the coupling constants of protons at C-7 and C-8. Product 5a has $J_{7,8}$ too small to measure while 5b has $J_{7,8}$ = 7 Hz. These values are most consistent with axial-equatorial and diaxial coupling respectively.

8. Compound 6: solid foam; $[\alpha]_D$ -107° (c 0.58, $CHCl_3$); λ_{max} (Et_2O) 252 nm (ε 17,000); m/e 471 (M^+). A correct combustion analysis was obtained.

9. (a) T. Hori and K. B. Sharpless, J. Org. Chem., 43, 1689, (1978). (b) H. J. Reich, S. Wollowitz, J. E. Trend, F. Chow and D. F. Wendelborn, *ibid*, p. 1697.

10. Phenylselenenylating species other than PhSeOH (e.g. PhSeOSePh, PhSe(O)OSePh) could also be involved in the formation of 6.

11. Compound 7: The mixture of diastereoisomers was a solid foam which gave a correct combustion analysis. ^1H nmr ($CDCl_3$) δ 11.80 (s) and 11.55 (s, total 1H, exchanged in D_2O), s at 1.20, 1.13, 0.67 and 0.60. The major diastereoisomer had m.p. 177-179.5°; $[\alpha]_D$ +70° (c 0.23, $CHCl_3$); λ_{max} (CH_3OH) 220 nm (ε 13,100) and 252 nm (ε 14,000); ^1H nmr ($CDCl_3$) δ 11.80 (s, 1H, exchanged in D_2O), s at 1.20 and 0.67; m/e 487 (M^+, faint) and 471 ($M^+ - O$).

12. (a) W. G. Salmond, M. A. Barta, A. M. Cain and M. C. Sobala, Tetrahedron Letters, 1683, (1977). (b) D. N. Jones, D. Mundy and R. D. Whitehouse, J.C.S. Chem. Comm., 86, (1970).

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