A MECHANISTIC SUGGESTION FOR PUMMERER REARRANGEMENT OF CYCLIC β-KETO SULFOXIDES
SYNTHESIS OF 3-METHOXY-16-THIA-D-HOMOESTRA-1,3,5(10),8,14-PENTAENE-17,17a-DIOLS[1]

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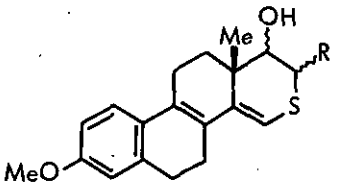
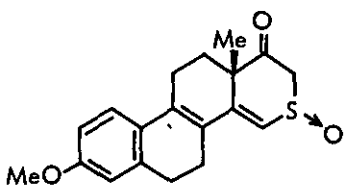
Synthesis of the title compound via Pummerer rearrangement of corresponding β-keto sulfoxides is reported. The mechanism and stereochemistry of the rearrangement are also discussed.

In connection with biological activities[2] of 3-methoxy-16-thia-D-homoestra-1,3,5(10),8,14-pentaen-17a-ols 1, we were interested in introduction of an additional hydroxy group at the 17-position. To this end, we investigated the Pummerer reaction of β-keto sulfoxides 2 and 3. The present communication discloses the synthesis of the title steroids (4) and the mechanistic aspect of the Pummerer rearrangement.

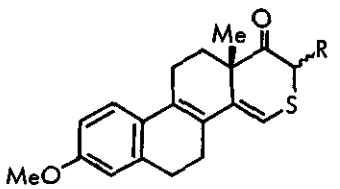
The above sulfoxides have already been prepared, though in low isolated yields.[3] We now found that this fact was due to successive Pummerer rearrangement of the sulfoxides,



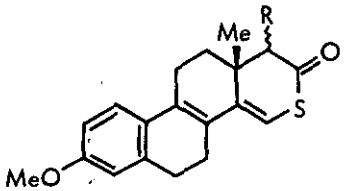
1, R = H
4, R = OH



2, α-oxide
3, β-oxide



5, R = H
7, R = OCOPhCl(m)
9, R = α-OAc
10, R = β-OAc



6, R = β-OH
8, R = OCOPhCl(m)
11, R = β-OAc

which occurs during chromatographic separation through silica gel. After the keto sulfide 5 was oxidized with an equivalent of m-chloroperbenzoic acid (0°, CH_2Cl_2), the mixture was usually worked up by washing with aqueous alkali. When the crude product was chromatographed on wet silica gel, an unexpected ketol 6 (mp 203-206°; 38.4%)[4] was isolated together with isomeric sulfoxides 2 (23.8%) and 3 (32.5%). We further observed that chromatography of the similar products obtained without alkaline treatment, which probably contained m-chlorobenzoic acid, no longer afforded any sulfoxides. The compounds separated were the ketol 6 (19.5%) and a keto ester 7 (viscous syrup; 27.4%);[5] the latter proved to be the primary

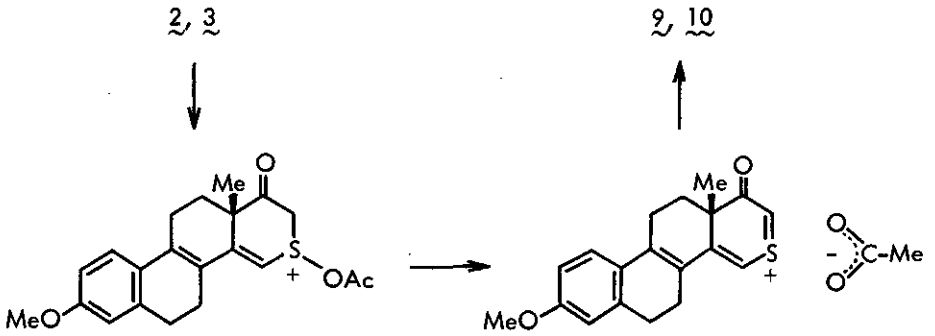
Pummerer product. Alkaline hydrolysis (K_2CO_3, THF-aq CH_3OH) of 7 readily led to 6. This conversion presumably involved isomerization of 7 to 8, in which acyl migration evidently proceeded through the cyclic ortho ester. Indeed, 7 was hydrolyzed under mild conditions ($KHCO_3$) yielding 8 (mp 208-209.5°)[6] accompanied by 6. The structures of 6, 7, and 8 were compatible with their spectral data. The above experiments implied that the reaction sequence can be a convenient preparative route to 4.

In order to establish the stereochemistry of the rearrangement, the reaction of sulfoxides 2 and 3 with excess acetic anhydride was further examined under various conditions. The results are given in Table I. In all cases, the reaction afforded (80-90%) both epimeric 17-acetoxy derivatives 9 (mp 126.5-128°)[7] and 10 (mp 142-145°).[8] Their configurations were unequivocally established using the

TABLE I. Pummerer reaction of 2 and 3 with acetic anhydride

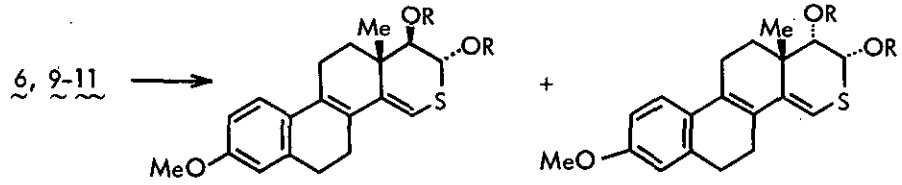
	Reagent	Conditions	Product ratio 9 : 10
2	Ac_2O	80°, 1.3 hr	1.8-2.0 : 1
	Ac_2O	140°, 15 min	1.8-1.9 : 1
	Ac_2O-HOAc (5:4)	rt, overnight	2.5 : 1
3	Ac_2O	rt, 94 hr	1 : 1.2
	Ac_2O	80°, 50 min	1 : 1.2-1.3
	Ac_2O	140°, 15 min	1 : 1.3-1.4
	Ac_2O-HOAc (5:4)	rt, 16 hr	1.7 : 1

nuclear Overhauser effect (NOE). A 20% NOE (100 MHz, C_6D_6) was observed between the 13-methyl group and the 17-hydrogen only in the case of 9. On treatment with sodium acetate in acetic acid (reflux, 2 hr) 10 underwent epimerization, resulting in a 1.3:1 mixture of 9 and 10. The product stability was consistent with the above assignment. On the other hand, we also confirmed that no epimerization occurred under the Pummerer conditions employed. Based on this fact, our data suggested that the reaction proceeded with a slight but definite degree of stereoselectivity when only acetic anhydride was used as the reagent. In contrast, addition of acetic acid consistently predominated the formation of the 17α-acetate, independent of the stereochemistry of sulfoxides.



According to recent studies[9] of the Pummerer reaction, stereoselective migration of the acetoxy group can best be accounted for by an intramolecular process, possibly proceeding via the ion pair (ii) from the acetoxysulfonium ion (i). The ion pair character, which subtly varies with the nature of

the Pummerer reagent and the solvent used, may be responsible for the degree of stereoselectivity. The observed low stereoselectivity appears to suggest that under these experimental conditions, the ion pair must be loose to some extent, allowing competitive intervention of the intermolecular process. The presence of acetic acid in the reaction media serves to enhance the separated ion character. Then the intermolecular process probably favors introduction of an acetoxy group from the less hindered α-side of the ring. Prolonged heating of 9 in boiling pyridine (24 hr) led to an equilibrated mixture which contained more of a different acetate 11 (viscous oil)[10] than 9 and 10 (9:10:11 = 1:1.4:1.5); hence the new isomer proved to be thermodynamically the most stable. The structure was identified by acetylation of ketol 6. This ketol was again obtained on saponification of the above ketol acetates. The favorable β-configuration of the hydroxy group of 6, supported by its ir spectrum, was consistent with succeeding transformations.

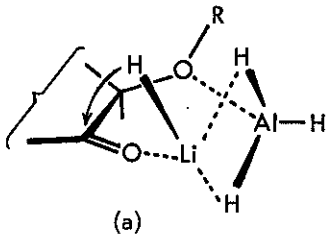


12, R = H
14, R = Ac

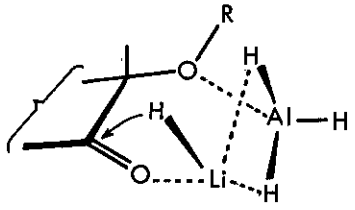
13, R = H
15, R = Ac

When the ketol 6 was reduced with either lithium aluminum hydride (THF, rt) or sodium borohydride (CH_3OH-THF, rt), the trans diol 12 (mp 190-193°)[11] was exclusively formed.

Noteworthy is that lithium aluminum hydride reduction of ketol acetates 9-11 consistently gave identical two diols, the trans 12 and cis diols 13 (mp 195-197°);[12] no other possible epimers were obtained. The product ratio of 12 to 13 was very different between the hydride reduction of 9 (1:8.8) and 10 (1:1.2) and that of 11 (6.3:1). These diols were also converted into the corresponding diacetates 14 (mp 184-186°)[13] and 15 (mp 148-150°).[14] The 17α,17aβ- and 17α,17aα-structures for both compounds were deduced from nmr analysis of the coupling pattern of the related hydrogens and confirmed by NOE observation. In the case of 14, NOE occurred between the 17-hydrogen and the 13-methyl group, while additional NOE was observed between the 17a-hydrogen and the 13-methyl group in the case of 15.



(a)



(b)

To interpret the stereochemistry of the above hydride reduction, we may suppose the formation of cyclic complexes (a) and (b) as transient intermediates, similar to those postulated by Lattes et al.[15] in the reduction of 2-amino cyclohexanones. Participation of the preferred complex (a) would account for the preponderant cis addition of hydride in the reduction of 6 and 11. These results parallel those for

analogous 2-amino cyclohexanones. On the other hand, the steric course in the reduction of 9 would rather favor the trans addition via the complex (b) presumably due to spatial requirement, as judged from Dreiding models. Alternatively, the observed stereochemistry may be explained without considering any cyclic complex in analogy with the reduction of 5 predominantly forming the 17aα-ol. The formation of 13 in the reduction of both 10 and 11 appears to be puzzling. Nevertheless, the experimental fact may suggest a possibility of a reduction mechanism which partly allows isomerization or epimerization through enolization of the ketol derivatives probably in their metal chelate forms.

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REFERENCES AND NOTES

1 Totally Synthetic Steroid Heterocycles Part 5. — Part 4, T. Terasawa and T. Okada, J.C.S. Perkin I, 1979, in press.

2 U.S. Patent 4,083,852 (1978).

3 T. Terasawa and T. Okada, J.C.S. Perkin I, 1978, in press.

4 m/e 328 (M^+); $\nu_{max.}$ (dilute CCl_4) 3510 cm^{-1} (bonded OH); δ($CDCl_3$-CD_3OD) 1.05 (3H, s, 13-Me), 3.80 (3H, s, OMe), 6.23 (1H, s, 15-H).

5 m/e 466 (M^+); $\nu_{max.}$ ($CHCl_3$) 1740 (OCO), 1725 cm^{-1} (CO); δ($CDCl_3$) 1.47 (s), 1.53 (s) (13-Me), 3.85 (3H, s, OMe),

6.22 (bs), 6.44 (s) (15-H), 6.42 (s), 6.68 (s) (17-H).

6 m/e 466 (M^+); $\nu_{max.}$ ($CHCl_3$) 1733 (OCO), 1696 cm^{-1} (SCO); δ($CDCl_3$) 1.31 (3H, s, 13-Me), 3.80 (3H, s, OMe), 5.70 (1H, s, 17a-H), 6.22 (1H, s, 15-H).

7 $\nu_{max.}$ ($CHCl_3$) 1755 (OAc), 1726, 1712 cm^{-1} (CO); δ($CDCl_3$) 1.45 (3H, s, 13-Me), 2.16 (3H, s, OAc), 3.81 (3H, s, OMe), 6.10 (1H, s, 17β-H), 6.37 (1H, s, 15-H).

8 $\nu_{max.}$ ($CHCl_3$) 1759 (OAc), 1725 cm^{-1} (CO); δ($CDCl_3$) 1.41 (3H, s, 13-Me), 2.21 (3H, s, OAc), 3.80 (3H, s, OMe), 6.09 (1H, s, 17α-H), 6.31 (1H, s, 15-H).

9 S. Glue, I. T. Kay, and M. R. Kipps, Chem. Comm., 1970, 1158; B. Stridsberg and S. Allenmark, Acta Chem. Scand. (B), 1974, 28, 591.

10 $\nu_{max.}$ ($CHCl_3$) 1752 (OAc), 1696 cm^{-1} (SCO); δ($CDCl_3$) 1.17 (3H, s, 13-Me), 2.22 (3H, s, OAc), 3.80 (3H, s, OMe), 5.45 (1H, s, 17aα-H), 6.17 (1H, bs, 15-H).

11 $\nu_{max.}$ (dilute CCl_4) 3613 (free OH), 3592, 3553 cm^{-1} (bonded OH).

12 $\nu_{max.}$ (dilute CCl_4) 3538 cm^{-1} (bonded OH).

13 $\nu_{max.}$ ($CHCl_3$) 1747 cm^{-1} (OAc); δ($CDCl_3$) 1.14 (3H, s, 13-Me), 2.07 (3H, s, 17-OAc), 2.12 (3H, s, 17a-OAc), 3.78 (3H, s, OMe), 5.34 (1H, d, J 9 Hz, 17aα-H), 6.00 (1H, s, 15-H), 6.08 (1H, d, J 9 Hz, 17β-H).

14 $\nu_{max.}$ ($CHCl_3$) 1745 cm^{-1} (OAc); δ($CDCl_3$) 1.17 (3H, s, 13-Me), 2.07 (3H, s, 17-OAc), 2.15 (3H, s, 17a-OAc), 3.79 (3H, s, OMe), 5.31 (1H, d, J 3 Hz, 17aβ-H), 6.11 (1H, s, 15-H), 6.45 (1H, d, J 3 Hz, 17β-H).

15 C. Bénard, M-T. Maurette, and A. Lattes, Bull. Soc. chim. France, 1976, 145; E. Costes, C. Bénard, and A. Lattes, Tetrahedron Letters, 1976, 1185.

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