

NEW SYNTHESIS OF STEROIDAL TETRAHYDROOXAZIN-2-ONES^{1, 2}

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ABSTRACT - In the DMSO/ NaHCO_3 system, 16 α -aminomethyl-, 16 α -benzylamino-methyl- and substituted benzylaminomethyl-3-methoxy-17 β -tosyloxyestra-1,3,5(10)-triene (3, 5a-k) do not undergo oxidation, but form a tetrahydrooxazin-2-one ring (7, 8a-k) via neighboring group participation. Under similar conditions, 16 β -aminomethyl-3-methoxy-17 β -tosylestra-1,3,5(10)-triene (4) decomposes into 16-methylene-3-methoxyestra-1,3,5(10)-trien-17-one (12).

The simplest way to prepare tetrahydrooxazin-2-one and its *N*-substituted derivatives is the cyclization of 1,3-aminoalcohols using phosgene.³⁻⁵ The thermal conversion of alicyclic azidoformates yields tetrahydrooxazin-2-one stereoisomers containing a condensed skeleton.⁶⁻⁸ The cyclization of 1-tosyl- or 1-halohydrin-2-carbaminic acid ester in alkaline media is also known.^{9,10} The conversion takes place via neighboring group participation,¹¹⁻¹³ characterized by the symbol (N^- -6).

The mechanism of the Kornblum oxidation¹⁴ of alkyltosylates in the presence of NaHCO_3 in DMSO was recently clarified.^{15,16} It was found that the alkyltosylates are transformed first into the alkyl carbonic acid halfester via an exchange reaction induced by NaHCO_3 . The product undergoes decomposition via 1,2-elimination to yield the corresponding carbonyl compound. The above mechanism was confirmed by the fact that in the presence of a hydroxy group beside the tosyl group a cyclic carbonate is formed as an intermediate and the oxidation step does not occur. In the case of sterane compounds we proved that the presence of a neighboring hydroxy group is a necessary, but not sufficient condition for the carbonate-forming reaction. Occurrence of the cyclization also requires an appropriate steric position of the hydroxy group.¹⁷

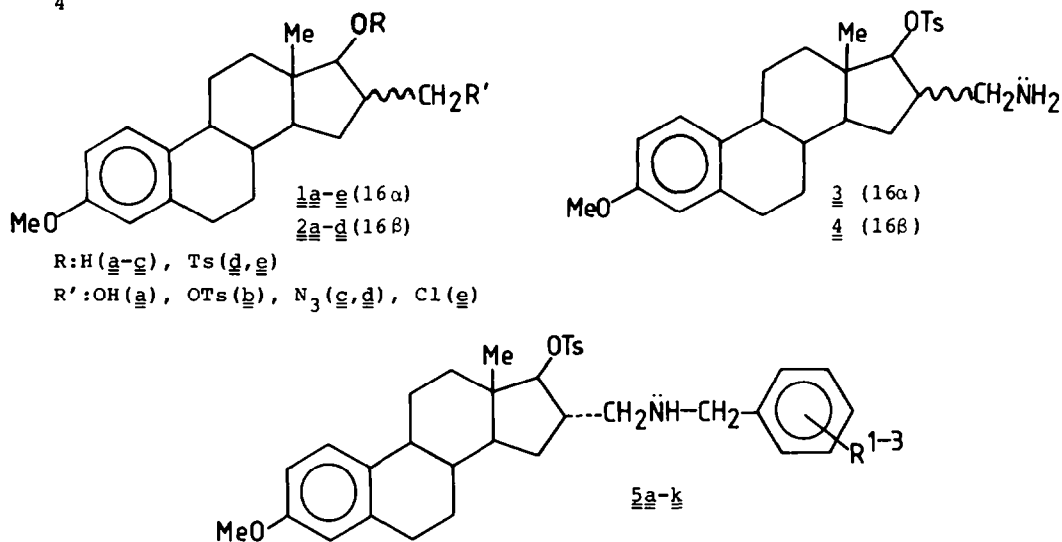
On the basis of the above mechanism, it can be expected that in the presence of an amino function in a favorable steric position in the vicinity of the tosyl group, the reaction will yield tetrahydrooxazin-2-one (7) or its *N*-substituted derivatives (8a-k) via the carbonic acid halfester intermediate.

We earlier reported on the preparation and structure elucidation of 16 α - and 16 β -hydroxymethyl-3-methoxyestra-1,3,5(10)-trien-17 β -ol epimers (1a, 2a).^{1, 18} Selective tosylation of 1a and 2a resulted in the 16 α - and 16 β -tosyloxymethyl derivatives 1b and 2b. Their exchange reaction with NaN_3 in DMF yielded the corresponding 16-azidomethyl compounds 1c and 2c. On repeated ester formation with tosyl chloride, the 16 α - and 16 β -azidomethyl-3-methoxy-17 β -tosyloxyestra-1,3,5(10)-

triene epimers (1d, 2d) were obtained. In the preparation of the 16 α -azidomethyl derivative (1d), a reaction observed only for the 16 α -,17 β -hydroxy epimer (1a) was also utilized. The diol 1a was allowed to react with a 4-fold excess of tosyl chloride to yield 16 α -chloromethyl-17 β -tosyl-3-methoxyestra-1,3,5(10)-triene (1e). The exchange reaction of the primary chlorine with NaN₃ resulted in the corresponding 16 α -azido-17 β -tosylate (1d).

In the ir spectra of 1c,d and 2c,d, the very intense, characteristic^{19a} azide band could be observed at 2143, 2100 (splitting), 2089, 2125 and 2102 cm⁻¹. For compounds 1c, 2c, 5h and 8h the ν OH bands of the C-17 alcoholic and the phenolic hydroxy groups in substituent R were found at 3485 and 3477 cm⁻¹ and at 3327 and 3070 cm⁻¹, respectively.

The 16 α - and 16 β -azidomethyl-17 β -tosylates (1d, 2d) obtained in this way were allowed to react with N₂H₄·H₂O in the presence of Raney Ni, and yielded the 16 α - and 16 β -aminomethyl-17 β -tosyl-3-methoxyestra-1,3,5(10)-triene epimers (3, 4) in satisfactory yields. The N-substituted derivatives of compound 3 were also prepared by forming Schiff bases with benzaldehyde and substituted benzaldehydes and reducing them *in situ*, to the corresponding benzylamino derivatives (5a-k) with NaBH₄.



R: H (a-c), Ts (d,e)

R': OH (a), OTs (b), N₃ (c,d), Cl (e)

R¹: H (a), pOMe (b), pCl (c), pNHAc (d), pNMe₂ (e), pNO₂ (f), mNO₂ (g), oOH (h), oOEt (i),
 R²=R³: H; R¹=R²: m, pCl₂, R³: H (j); R¹=R²=R³: m, p, m'OMe₃ (k)

The ir bands of the tosyl ester group in compounds 1d,e, 2d, 3, 4, 5a-k and 9 were found in the following intervals: 1335-1360, 1169-1175, 945-965, 810-875 (two bands), 665-685 and 530-573 cm⁻¹ (two bands). The ν NH band of compounds 3 and 5a-k could not be identified; the intermolecularly associated, relatively apolar group yielded a weak and diffuse band overlapped by the ν CH bands. The only exception was compound 2h: its sharp ν NH band of medium intensity was found at 3327 cm⁻¹. The sharp band indicates a monomeric NH group.^{19b} This can be attributed to the intramolecular N...H-O type hydrogen-bond with the phenolic hydroxy group (due to this, the N-H bond becomes polarized and the NH group is monomeric, since the six-membered intramolecular association sterically prevents the formation of intermolecular hydrogen-bonds). This explains the anomalous R_F value of compound 2h, which is higher than that for 5a or 5i, in contrast with the expected situation.

Solvolytic examinations. The 16 α -aminomethyl, 16 α -benzylaminomethyl and substituted benzylaminomethyl derivatives (3, 5a-k) were kept in DMSO in the presence of NaHCO₃ at 100 °C. TLC indicated that the conversion was complete after

6 h, and in all cases the products were more polar than the starting materials. Elemental analysis and the spectral data proved that the cyclization products were tetrahydrooxazin-2-ones (7, 8a-k) condensed to the sterane skeleton in the 16 α ,17 α -position.

The intense urethane carbonyl ir band appeared between 1695 and 1701 cm^{-1} for all the oxazinone derivatives. The ir bands due to the urethane or amide carbonyl groups could also be found for compound 9 (1718 cm^{-1}) and for the acetamino derivatives 5d and 8d ($\sim 1670 \text{ cm}^{-1}$), overlapping with the cyclic urethane band. The nitro bands of compounds 5f,g and 8f,g were found at 1522-1531 and 1348-1354 cm^{-1} .

In the ^1H nmr spectra (in CDCl_3 solution), the C-18 methyl singlet appeared at 0.84-0.86 ppm (1d,e, 3, 5a-i) and at 0.76-0.82 ppm (1c, 2c,d, 4, 7, 8a-k, 9), the $\text{OCH}_3(3)$ signal was found at 3.74-3.78 ppm, and the tosyl methyl signal was identified at 2.42-2.47 ppm for compounds 1d,e, 2d, 3, 4, 5a-i, and 9. For the latter compounds the AA'BB' multiplet of the tosyl group gave $\delta\text{H}-3',5'$: 7.25-7.38 ppm; $\delta\text{H}-2',6'$: 7.77-7.84 ppm, J_{ortho} : 8.1-8.3 Hz.

The ^1H nmr data for the AMX multiplet of aromatic ring A were as follows: $\delta\text{H}-1$: 7.10-7.20 ppm, d (J : 8.5-8.7 Hz); $\delta\text{H}-2$: 6.68-6.72 ppm, dd; $\delta\text{H}-4$: 6.60-6.63 ppm (J : 2.3-2.7 Hz).

The chemical shift of H-17 was 4.24-4.39 ppm, except for the two 17-hydroxy-derivatives (1c, 2c) and the 17 β -tosyloxy-16 -substituted compounds (2d, 4), where this value was 3.42, 3.84 and 4.52, 4.57 ppm, respectively. For the two former compounds, the upfield shift of the signal is due to the hydroxy group substituting the acyl group,²⁰ while in the second pair the 16 β ,17 β -configuration gives rise to the slight downfield shift.

In view of the configuration, the splitting of the H-17 doublet is of decisive importance. This varied between 5.7 and 6.3 Hz for the 16 α ,17 α -substituted series (7, 8), for the 16 α ,17 β compounds (1, 3, 5 and 9 series) it was 6.9-7.9 Hz, while for the derivatives 2c,d and 4 with the 16 β ,17 β -configuration it was ~ 10 Hz. All these data confirm the assumed configurations, as explained in detail earlier.^{1,18}

Due to the asymmetric molecular structure, the 16-methylene protons are not equivalent chemically; thus, they give two double doublets (AB part of an ABX type multiplet). The spectral parameters obtained were: δA : 2.44-2.60 (3, 4, 5), 2.95-3.15 (7, 8), 3.20-3.50 (1c-e, 2c,d, 9); δB : 2.58-2.80 (3, 5), 2.97 (4), 3.38-3.60 ppm (1c-e, 2c,d, 7, 8, 9); further, $\text{J}(\text{A,B})$: 11.5-12.7; $\text{J}(\text{A,X})$; and $\text{J}(\text{B,X})$: 7.4-8.2 and 4.6-5.3 (3, 5), 4.5-4.9 and 3.5-4.9 (7, 8), 5.4-6.8 and 3.4-3.8 (1c-e) and 7.1-10.0 and 5.4-7.3 Hz (2c,d, 4).

In the ^{13}C nmr spectra (Table 1), the difference in the chemical shifts C-1-11,14 and the $\text{OCH}_3(3)$ was less than 1.2 ppm for all compounds. The shielding of C-16,17,18 and $\text{CH}_2(16)$ atoms, however, differed significantly, in a manner characteristic of the isomeric 16,17-configurations, thereby confirming the assumed structures.

For compounds 1-5, with the 17 β -configuration, the C-18 signal appeared between 11.7 and 12.6 ppm, shifted upfield by 4.8 ppm on average as compared to 7 and series 8 with the 17 α -configuration (16.7-17.1 ppm), due to the field effect²¹ (steric compression shift) produced by the steric hindrance between the $\text{CH}_3(18)$ group and the 17 β -substituent in the *cis* position to it.

The shift of the C-16 line indicates increased shielding in compounds 7 and 8, as a result of the steric hindrance with the neighboring *cis* substituents (16 α ,17 α -configuration): the chemical shift (41.0-43.7 ppm) for the *trans* compounds with 16 α ,17 β -configuration (1, 3 and 5) was 8.2 ppm higher on average than for compounds 7 and 8 (33.6-34.8 ppm). For compounds with the 16 β ,17 β -configuration (2, 4) the field effect was somewhat less (6.6 ppm), corresponding to the lower steric hindrance.

Table 1. ^{13}C NMR chemical shifts ($\delta_{\text{rms}}=0$ ppm)^a of compounds 1c-e, 2c,d, 3, 4, 5a-c,e,f,h,i, 7 and 8a-h,j at 20.15 MHz.

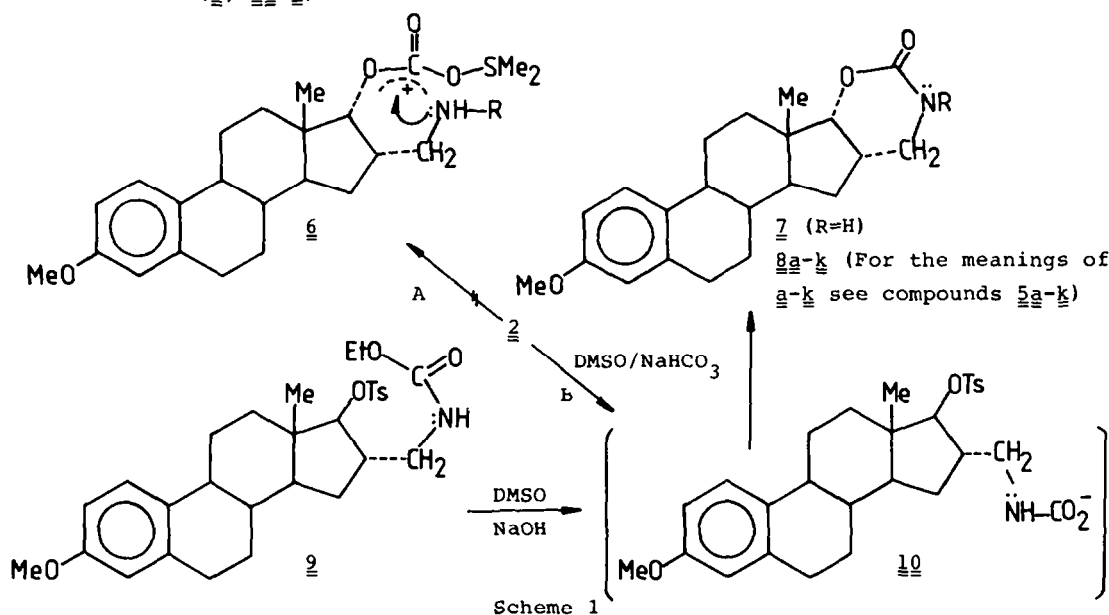
	C-1	C-2	C-3	C-4	C-5	C-6	C-7	C-8	C-9	C-10	C-11	C-12	C-13	C-14	C-15	C-16	C-17	C-18	OMe	CH ₂ (16)
1c	126.0	111.4	157.4	113.8	137.6	132.3	29.5	27.9 ^b	38.4	43.4 ^e	26.0	36.2	44.0	48.4	27.0 ^b	43.7 ^c	84.8	11.7	55.0	55.4
1d	126.1	111.5	157.6	113.8	137.6	132.0	29.5	27.8	38.4	43.4	25.9	36.1	44.1	48.0	26.9	41.2	90.5	12.4	55.1	53.1
1e	126.0	111.6	157.7	113.9	137.6	132.1	29.5	28.0	38.4	43.3 ^b	25.9	36.1	44.4	48.0	26.9	43.4 ^b	90.7	12.5	55.1	47.0
2c	126.1	111.4	157.4	113.8	137.6	132.4	29.6	27.3	38.0	43.7	26.2	37.5	44.1	48.7	30.3	40.0	81.2	12.1	55.0	53.3
2d	126.1	111.6	157.6	113.8	137.6	131.9	29.5	27.1	37.9	43.5	25.9	36.6	43.9	48.2	30.2	39.0	88.9	12.6	55.1	53.1
3	126.9	111.3	157.3	113.6	137.4	131.9	29.3	27.4	38.2	43.9 ^d	25.7	36.1	43.9 ^d	47.9	26.7	43.2	92.0	12.3	54.8	43.9 ^d
4	126.0	111.4	157.5	113.7	137.5	132.0	29.5	27.1	38.0	43.4	25.9	36.7	43.8 ^e	48.0	30.0	42.6	90.0	12.6	55.0	43.8 ^e
5a	126.0	111.4	157.5	113.7	137.5	132.0	29.5	28.2	38.4	43.4	25.9	36.3	44.0	48.0	26.8	41.5	92.9	12.4	55.0	53.9 ^d
5b	126.1	111.4	157.5	113.7 ^e	137.5	132.1	29.5	28.2	38.4	43.4	25.9	36.3	44.0	48.1	26.9	41.6	92.9	12.4	55.0 ^b	52.0 ^d
5c	126.2	111.6	157.6	113.9	137.7	132.2	29.6	28.4	38.6	43.6	26.0	36.4	44.2	48.2	27.0	41.7	93.0	12.6	55.2	52.2 ^c
5e	126.1	111.4	157.5	113.7	137.5	132.1	29.5	28.2	38.4	43.4	25.9	36.3	44.0	48.0	26.9	41.6	92.9	12.4	55.0	51.8 ^c
5f	126.1	111.4	157.5	113.8	137.5	132.0	29.5	28.3	38.4	43.4	25.9	36.3	44.1	48.1	26.9	41.6	92.8	12.4	55.0	52.2 ^c
5h	125.9	111.4	157.4	113.6	137.4	131.8	29.3	28.1	38.2	43.2	25.7	36.1	43.9	47.8	26.7	41.0	92.3	12.3	54.9	52.5 ^c
5i	126.1	111.4	157.5	113.8	137.6	132.1	29.5	28.2	38.5	43.4	26.0	36.3	44.0	48.1	26.9	41.6	92.9	12.5	55.0	51.8
7	126.2	111.5	157.5	113.8	137.7	132.5	29.7	27.9	39.1	43.2	25.9	31.0 ^b	47.4	48.8	30.6 ^b	33.6	89.3	17.1	55.1	42.5
8a	126.0	111.3	157.3	113.6	137.4	132.2	29.5	27.7	38.8	43.0	25.7	31.0 ^b	47.1 ^d	48.5	30.4 ^b	34.6	88.8	16.7	54.9	47.0 ^d
8b ^f	126.0	111.3	157.3	113.6	137.4	132.2	29.5	27.8	38.6	43.0	25.7	31.0 ^b	46.8	48.5	30.4 ^b	34.6	88.8	16.8	55.0 ^c	47.2
8c	126.1	111.4	157.4	113.7	137.5	132.3	29.6	27.9	38.9	43.1	25.8	31.0 ^b	47.4 ^c	48.6	30.6 ^b	34.7	89.0	16.8	55.0	47.3 ^c
8d	126.0	111.3	157.3	113.7	137.4	132.1	29.5	27.8	38.7	43.0	25.6	30.9 ^b	47.2 ^e	48.6	30.4 ^b	34.5	89.0	16.7	54.9	47.2 ^e
8e	126.0	111.2	157.3	113.6	137.4	132.3	29.5	27.8	38.8	43.0	25.7	31.0 ^b	47.1	48.5	30.4 ^b	34.7	88.7	16.8	54.9	46.5
8f	126.2	111.5	157.5	113.8	137.5	132.2	29.6	28.0	38.9	43.2	25.8	31.1 ^b	47.4	48.7 ^d	30.8 ^b	34.8	89.2	16.9	55.1	48.2 ^d
8g	126.0	111.3	157.3	113.6	137.4	132.1	29.5	27.7	38.8	43.0	25.7	30.9 ^b	47.2	48.5	30.5 ^b	34.5	89.0	16.7	54.9	47.9
8h	126.1	111.4	157.3 ^b	113.7	137.6	132.2	29.5	27.6	38.8	43.1	25.7	30.9 ^c	47.3	48.6	30.6 ^c	34.5	89.7	16.8	55.1	48.0
8j	126.2	111.4	157.5	113.8	137.6	132.3	29.6	27.9	38.9	43.1	25.8	31.1 ^b	47.7	48.7	30.7 ^b	34.7	89.0	16.9	55.1	47.4

Further signals: 17-OTs group in 1d,e, 2d, 3, 4 and 5c,e,f,h: CH₃= 21.1-21.6, C-1': 133.8-134.7, C-2',6': 127.5-127.8, C-3',5': 129.4-129.7, C-4': 144.1-144.8; NR group in 5a-c,e,f,h,i and 8a-h,j: CH₃ and CH₂ lines of the ethoxy group in 5i: 14.9 and 63.3, CH₃ and C=O lines of the acetyl group in 8d: 24.0 and 167.0, NCH₃: 40.5 (5e) and 40.3 (8e), NCH₂ (Assignments may be interchanged with 16-CH₂ for 5a-c,e,f,h): 49.4-53.4 OCH₃: 55.1^b (5b) and 54.9^c (8b), C-1'': 140.4 (5a), 132.6 (5b), 139.2 (5c), 128.3 (5e), 148.4 (5f), 122.4 (5h), 128.5 (5i), 136.7 (8a), 128.9 (8b), 135.5 (8c), 131.7 (8d), 124.3 (8e), 144.5 (8f), 139.2 (8g), 130.8 (8h), 137.3 (8j); C-2'': 158.0 (5h), 156.9 (5i), 122.6 (8g), 157.4 (8h), 130.1 (8j); C-2',6'': 127.9 (5a), 129.0 (5b), 128.4 (5c), 128.8 (5e), 128.4 (5f), 128.2^g (8a), 129.6 (8b), 129.7 (8c), 128.5 (8d), 129.4 (8e), 128.9 (8f); C-6'': 128.4 (5h), 127.9 (5i), 134.2 (8g), 130.1 (8h), 127.7 (8j); C-3'': 116.1 (5h), 111.1 (5i), 148.2 (8g), 117.7 (8h), 132.7 (8j), C-3',5'': 128.1 (5a), 113.7 (5b), 129.6 (5c), 112.6 (5e), 123.3 (5f), 128.3^g (8a), 113.8 (8b), 128.7 (8c), 120.0^b (8d), 112.3 (8e), 123.8 (8f); C-5'': 118.7 (5h), 120.2 (5i), 129.5 (8g), 119.4 (8h), 130.6 (8j); C-4'': 126.7 (5a), 158.5 (5b), 132.6 (5c), 149.7 (5e), 146.9 (5f), 128.1 (5h), 129.6 (5i), 127.4 (8a), 159.1 (8b), 133.5 (8c), 138.3 (8d), 150.0 (8e), 147.6 (8f), 122.5 (8g), 121.7 (8h), 131.8 (8j).

a In CDCl₃ solution; b,c,g Reversed assignments may also be possible; d Three overlapping lines; e Two overlapping lines; f Assignments were proved by DEPT measurements; h Broaden lines due to hindered rotation of the amide group

To a lesser extent, an analogous increased shielding could be observed for the C-17 and CH₂(16) atoms in series 8 and in compounds 2d, 4 and 7, as compared to the analogs of types 1, 3 and 5. If we neglect the C-17 shifts for 1c and 2c, where the α -effect²² of the substituent overcompensates the field effect (the substituent at C-17 is OH instead of OTs), the upfield shift is 3.3 ppm on average (the C-17 signal appeared in the intervals 88.7-89.7 and 92.0-93.0 ppm for 7, 8 and 3, 5 respectively). As concerns the CH₂(16) signal, comparison of the average value for series 5 (52.9 ppm) with that obtained for the analog of type 8 (47.3 ppm) showed a field effect of 5.5 ppm (for the pair 3-7 the difference was lower, since the substituent effect does not compensate the field effect to the same extent).

Two assumptions can be made as regards the mechanism of the cyclization (Scheme 1). In path A, the 17 β -tosyloxy group is replaced by the HCO₃⁻ ion *via* inversion, and the carbonic acid halfester formed is stabilized by the DMSO solvent. This unstable intermediate (6) undergoes cyclization with the amino function in a favorable steric position, and this reaction leads to the corresponding tetrahydrooxazin-2-ones (7, 8a-k).



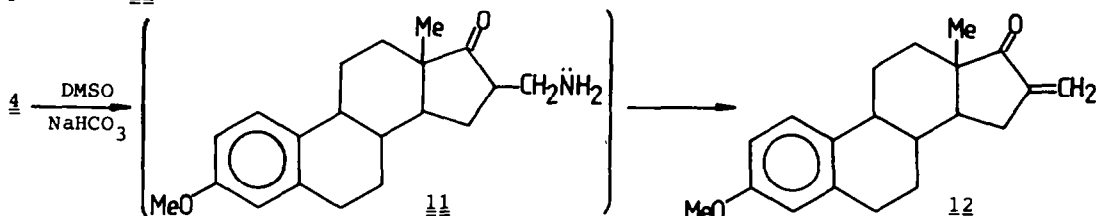
However, since 3-methoxy-17 β -tosyloxyestra-1,3,5(10)-triene undergoes oxidation only very slowly under similar experimental conditions, and the C-17 tosyl esters participate in nucleophilic exchange only under vigorous experimental conditions,²³ the possibility of another mechanism was also considered.

In path B, the formation of free carbaminic acid was assumed in the DMSO/NaHCO₃ system, and its cyclization *via* intramolecular catalysis yields the corresponding tetrahydrooxazin-2-one relatively rapidly.

In order to verify this assumption 16 α -ethoxycarbonylamino-17 β -tosyloxy-3-methoxyestra-1,3,5(10)-triene (2) was prepared. This was heated in DMSO in the presence of NaOH, hydrolysed into the free carbaminic acid (10) and then transformed to 7 in an intramolecular reaction. This mechanism conforms with the oxazolidone-forming reaction of 1,2-haloamines observed in the presence of Na₂CO₃/DMSO.²⁴

16 β -Aminomethyl-17 β -tosyloxy-3-methoxyestra-1,3,5(10)-triene (4), however, did not undergo cyclization under similar conditions. On prolonged reaction, significant amounts of unchanged starting material were detected, and the formation of a strongly apolar compound was observed, which proved to be 16-methylene-3-methoxyestra-1,3,5(10)-trien-17-one (12).^{25,26} The formation of compound 12 was explained by the fact that during the long reaction 16 β -aminomethyl-3-methoxyestra-1,3,5(10)-trien-17-one (11) was formed *via* oxidation of the 17 β -tosyl group, and then decom-

posed to 12 (Scheme 2).



Scheme 2

The strongly stereoselective conversion of the 16-aminomethyl-17 β -tosyl epimers 3, 4 and 5a-k in the presence of DMSO and NaHCO₃ indicated the neighboring group participation in the case of the 16 α -epimer. In the notation proposed by Winstein,²⁵ this process can be characterized by the symbol (R-NH-COO⁻-6).

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Experimental

Melting points were measured on a Kofler block and are uncorrected. The specific rotation values were determined in CHCl₃, *c* = 1, with a Polamat-A polarimeter. The ir spectra were recorded in KBr discs on a Bruker IFS-113v vacuum optic FT-spectrometer controlled by an Aspect 2000 computer.

The nmr spectra were recorded in CDCl₃ solution in 5 or 10 mm tubes at room temperature, on Bruker WM-250 (¹H) and WP-80SY (¹³C) FT-spectrometers controlled by an Aspect 2000 computer at 250.13 and 20.14 MHz, with the deuterium signal of the solvent as the lock and TMS as internal standard. The most important measuring parameters were as follows: sweep width 5 kHz, pulse width 1 (¹H) and 3.5 (¹³C) μ s ($\sim 20^\circ$ and $\sim 30^\circ$ flip angle), acquisition time 1.64 s, number of scans 16 or 32 and 1-4 K, computer memory 16 K. Lorentzian exponential multiplication for signal-to-noise enhancement [line broadening: 0.7 (¹H) and 1.0 (¹³C) Hz] and for the ¹³C NMR spectra complete proton noise decoupling (~ 1.5 W) was applied. The DEPT²⁶ spectra were run in a standard way,²⁷ using only the $\theta = 135^\circ$ pulse to separate CH/CH₃ and CH₂ lines phased "up and down", respectively. Typical acquisition data were: number of scans 128-12 K, relaxation delay for protons 3 s, 90 $^\circ$ pulse width 10.8 and 22.8 μ s for ¹³C and ¹H, respectively. The estimated value for $J(C,H)$ resulted in a 3.7 ms delay for polarization.

The TLC's were obtained on Kieselgel-G (Merck) layers 0.5 mm thick. The developing solvents were methanol-benzene mixtures: a) 2:98; b) 5:95. The chromatograms were sprayed with 50% aqueous phosphoric acid, and then heated at 100-120 $^\circ$ C for 15 minutes. The R_f values were determined in uv light of 365 nm. In the column chromatographic separation procedures, Al₂O₃ (standardized according to Brockmann) with an activity of III-IV was used.

The physical data on the compounds are listed in Table 2.

16 α - and 16 β -Azidomethyl-3-methoxyestra-1,3,5(10)-trien-17-ol (1c, 2c).

General method

16 α - or 16 β -Tosyloxymethyl-3-methoxyestra-1,3,4(10)-trien-17-ol¹⁸ (4.7 g, 0.01 mol) was dissolved in DMF (30 mL), NaN₃ (3.2 g, 0.05 mol) was added, and the mixture was heated at 100 $^\circ$ C for 6 h. It was then poured into water saturated with NaCl (250 mL), the oil separating out was extracted with benzene, the extract was evaporated to dryness, and the residue was subjected to chromatographic separation on Al₂O₃. The pure substance was eluted with a 1:1 mixture of benzene and petroleum ether.

16 α - and 16 β -Azidomethyl-3-methoxy-17 β -tosyloxyestra-1,3,5(10)-triene (1d, 2d).

General method

Compound 1c or 2c (3.41 g, 0.01 mol) was dissolved in anhydrous pyridine (50 mL) and tosyl chloride (3.8 g, 0.02 mol) was added in small portions. The reaction mixture was kept at 45 $^\circ$ C for 6 h, and was then poured onto a mixture of cc. H₂SO₄ (20 mL) and ice (500 g). The crystalline precipitate separating out was filtered off, washed until neutral and recrystallized from a mixture of acetone and water.

16 α -Chloromethyl-3-methoxy-17 β -tosyloxyestra-1,3,5(10)-triene (1e)

16 α -Hydroxymethyl-3-methoxyestra-1,3,5(10)-trien-17-ol¹⁸ (3.16 g, 0.01 mol) was dissolved in pyridine (50 mL), and tosyl chloride (7.6 g, 0.04 mol) was added. The reaction mixture was kept at 45 $^\circ$ C for 6 h, and then allowed to stand at room temperature overnight. It was diluted with water (500 mL), and the precipitate separating out was filtered off and recrystallized from methanol.

Table 2. Analytical data of compounds 1c-e, 2c,d, 3, 4, 5a-k, 7, 8a-k and 9

Com-pound	Formula	Mol. wt.	M. p. [°C]	α/β	R_f^a	Analysis (%)			Yield
						Calculated	Found		
						C	H	N	
1c	C ₂₀ H ₂₇ O ₂ N ₃	341.46	83-86	+54	0.70	70.35/70.54	7.97/8.05	12.30/12.06	96
1d	C ₂₇ H ₃₃ O ₄ N ₃ S	495.65	115-117	+16	0.90	65.42/65.37	6.71/6.80	8.47/8.12	87
1e	C ₂₇ H ₃₃ O ₄ SCl	489.08	150-154	+5	0.95	66.30/66.45	6.80/6.65	- / -	76
2c	C ₂₀ H ₂₇ O ₂ N ₃	341.46	134-135	+80	0.90	70.35/70.43	7.97/7.86	12.30/12.11	94
2d	C ₂₇ H ₃₃ O ₄ N ₃ S	495.65	115-116	+74	0.95	65.42/65.37	6.71/6.55	8.47/8.34	85
3	C ₂₇ H ₃₅ O ₄ NS	469.65	156-158	+13	0.20	69.05/69.18	7.51/7.45	2.98/3.05	70
4	C ₂₇ H ₃₅ O ₄ NS	469.65	155-158	+51	0.20	69.05/69.17	7.51/7.43	2.98/3.08	81
5a	C ₃₄ H ₄₁ O ₄ NS	559.77	144-147	+12	0.65	72.95/72.86	7.38/7.25	2.50/2.63	78
5b	C ₃₅ H ₄₃ O ₅ NS	589.80	144-146	+21	0.55	71.27/71.35	7.34/7.44	2.37/2.41	83
5c	C ₃₄ H ₄₀ O ₂ NSCl	594.22	145-149	+10	0.80	68.72/68.85	6.78/6.88	2.35/2.17	85
5d	C ₃₆ H ₄₄ O ₅ N ₂ Sb	653.29	198-203	+49	0.15	66.18/66.25	6.78/6.85	4.28/4.34	78
5e	C ₃₆ H ₄₆ O ₄ N ₂ S	602.85	93-95	+3	0.40	71.72/71.79	7.69/7.55	4.64/4.54	82
5f	C ₃₄ H ₄₀ O ₆ N ₂ S	604.77	144-147	+30	0.75	67.52/67.65	6.66/6.49	4.63/4.42	92
5g	C ₃₄ H ₄₀ O ₆ N ₂ Sb	641.23	153-158	+16	0.20	63.68/63.55	6.28/6.13	4.36/4.25	90
5h	C ₃₇ H ₄₇ O ₇ NS	649.85	137-139	+15	0.65	68.38/68.25	7.29/7.25	2.15/2.05	76
5i	C ₃₆ H ₄₅ O ₅ NS	613.91	132-134	+7	0.65	70.43/70.25	7.38/7.43	2.28/2.08	72
5j	C ₃₄ H ₃₈ O ₄ SCl ^b	635.13	197-202	+24	0.80	64.29/64.52	6.03/6.14	2.20/2.34	68
5k	C ₃₇ H ₄₇ O ₇ NS	649.85	75-77	+19	0.70	68.38/68.45	7.29/7.37	2.15/2.26	80
7	C ₂₁ H ₂₇ O ₃ N	341.45	265-270	+35	0.45	73.86/73.72	7.97/8.04	4.10/4.15	85
8a	C ₂₈ H ₃₃ O ₃ N	431.58	155-158	-23	0.85	77.92/78.03	7.70/7.65	3.24/3.40	82
8b	C ₂₈ H ₃₅ O ₄ N	461.60	176-178	-37	0.85	75.45/75.58	7.64/7.54	3.03/3.16	86
8c	C ₂₈ H ₃₂ O ₃ NCl	466.03	204-209	-44	0.80	72.16/72.34	6.92/7.05	3.00/3.21	84
8d	C ₃₀ H ₃₈ O ₄ N ₂	474.52	140-145	-36	0.40	73.74/73.56	7.42/7.52	5.73/5.45	73
8e	C ₃₀ H ₂₈ O ₃ N ₂	464.57	224-226	-47	0.90	77.56/77.40	6.07/6.23	6.03/5.96	78
8f	C ₂₈ H ₃₂ O ₅ N ₂	476.58	198-200	-11	0.80	70.56/70.43	6.76/6.79	5.87/5.65	85
8g	C ₂₈ H ₃₂ O ₅ N ₂	476.58	162-163	-33	0.80	70.56/70.34	6.76/6.58	5.87/5.91	82
8h	C ₂₈ H ₃₃ O ₄ N	447.58	191-193	-36	0.80	75.13/75.25	7.43/7.33	3.12/3.26	76
8i	C ₃₀ H ₃₇ O ₄ N	475.63	154-156	-29	0.80	75.75/75.60	7.84/7.67	2.94/2.70	68
8j	C ₂₈ H ₃₁ O ₃ NCl ₂	500.48	204-206	-8	0.95	67.19/67.30	6.24/6.15	2.79/2.92	82
8k	C ₃₁ H ₃₉ O ₆ N	521.66	75-77	-16	0.70	71.37/71.45	7.53/7.63	2.68/2.56	74
9	C ₃₀ H ₃₉ O ₆ NS	541.71	oil	+16	0.80	66.51/66.67	7.25/7.14	2.58/2.65	86

^a Methanol:benzene 2:98 (1c-e, 2c,d, 3, 4, 5a-k, 9) or 5:95 (7, 8a-k); ^b HCl salt

16 α -Azidomethyl-3-methoxy-17 β -tosyloxyestra-1,3,5(10)-triene (1d)

Compound 1e (4.89 g, 0.01 mol) was dissolved in DMF (30 mL), NaN₃ (3.2 g, 0.05 mol) was added, and the mixture was kept at 100 °C for 12 h. It was then poured into water saturated with NaCl (250 mL), and the precipitate separating out was filtered off and recrystallized from a mixture of acetone and water.

16 α - and 16 β -Aminomethyl-3-methoxy-17 β -tosyloxyestra-1,3,5(10)-triene (3, 4).

General method

Compound 1d or 2d (4.95 g, 0.01 mol) was dissolved in ethanol (150 mL), and N₂H₄·H₂O (5 mL, 72%) and Raney Ni (0.5 g) were then added. The mixture was allowed to stand at room temperature for 12 h, and was then gently refluxed for 2 h. The Raney Ni was filtered off, and the solution was concentrated to half volume and diluted with water (500 mL). The precipitate separating out was filtered off and dissolved in benzene, the benzene solution was evaporated to dryness and the crude product obtained was subjected to chromatographic separation on an Al₂O₃ column. The desired product was eluted in 1:1 mixture of benzene and petroleum ether, and was crystallized from a mixture of methanol and water.

16 α -(N-Benzyl- and substituted N-benzyl)-aminomethyl-3-methoxy-17 β -tosyloxyestra-1,3,5(10)-triene (5a-k). General method.

Compound 3 (4.96 g, 0.01 mol) was dissolved in anhydrous ethanol (50 mL), benzaldehyde (0.05 mol) or substituted benzaldehyde was added, and the reaction mixture was gently refluxed for 3 h. Ethanol (150 mL) was then added to the reaction mixture, the solution was cooled to 0 °C and NaBH₄ (7.56 g, 0.2 mol) was added in small portions. The reaction mixture was allowed to stand for 6 h, was then diluted with 2-fold volume of water, next saturated with (NH₄)₂SO₄, and the crystall-

ine precipitate separating out was filtered off. It was dissolved in benzene, the benzene solution was evaporated to dryness, and the crude product obtained was subjected to chromatographic separation on an Al_2O_3 column. Compounds 5a,c,e, were eluted with a 1:1 mixture of benzene and petroleum ether, while 5b,d,f,g,h,i,j,k were eluted with benzene. Compounds 5d,g,i are oils that crystallize only with difficulty. They were converted to the hydrochlorides with methanolic HCl and crystallized from a mixture of CHCl_3 and ether. The free bases were recrystallized from a mixture of acetone and petroleum ether.

3-Methoxyestra-1,3,5(10)-trien-3'-R-(16 α ,17 α -e)-4H-oxazin-2'-one (7, 8a-k).

General method

Compound 3, 5a-k (0.01 mol) was dissolved in DMSO (50 mL), and NaHCO_3 (8.4 g, 0.1 mol) was then added. The suspension was stirred at 100 °C for at least 6 h. The progress of the reaction was monitored by TLC. The reaction mixture was next diluted with water (500 mL), and the precipitate separating out was filtered off, dissolved in benzene and subjected to chromatographic separation on an Al_2O_3 column. Compounds 8b,c,f,g,i,j,k were eluted with benzene, while a 1:1 mixture of benzene and CHCl_3 was used for compounds 7, 8a,d,e,h,i. The products were crystallized from a mixture of CHCl_3 and petroleum ether.

16 α -Ethoxycarbonylaminomethyl-3-methoxy-17 β -tosyloxyestra-1,3,5(10)-triene (9)

Compound 3 (4.96 g, 0.01 mol) was dissolved in anhydrous pyridine (50 mL), and chlorocarbonic acid ethyl ester (1.8 g, 0.02 mol) was added during efficient cooling and stirring. The mixture was allowed to attain room temperature, and was then poured onto a mixture of cc. H_2SO_4 (20 mL) and ice (500 g). The oil separating out was extracted with benzene. The benzene fraction was evaporated to dryness and the crude product obtained was subjected to chromatographic separation on an Al_2O_3 column. The product was eluted with a 1:1 mixture of benzene and petroleum ether.

3-Methoxyestra-1,3,5(10)-trien (16 α -17 α -e)-4H-oxazin-2'-one (7)

Compound 9 (0.541 g, 0.001 mol) was dissolved in DMSO (10 mL), and finely-powdered NaOH (0.08 g, 0.002 mol) was added. The reaction mixture was kept at 100 °C for 2 h, and was then diluted with water (100 mL). The precipitate separating out was filtered off, dissolved in benzene and subjected to chromatographic separation on an Al_2O_3 column. The end-product was eluted with a 1:1 mixture of benzene and CHCl_3 , and yielded 0.230 g of 7 (67%).

Solvolysis of compound 4 in the DMSO/ NaHCO_3 system

Compound 4 (4.69 g, 0.01 mol) was dissolved in DMSO (50 mL), and NaHCO_3 (0.4 g, 0.1 mol) was added. The reaction mixture was kept at 100 °C for 48 h; the progress of the reaction was monitored by TLC. After 48 h, a significant amount of the starting material was still present in the reaction mixture. It was diluted with water (250 mL), the dark oily substance separating out was extracted with benzene, the extract was washed thoroughly with water and evaporated to dryness, and the substance obtained was subjected to chromatographic separation. A 1:1 mixture of benzene and petroleum ether eluted a strongly apolar substance, which proved to be compound 12 (1.35 g, 45.6%). M. p. 120-122 °C; $[\alpha]_D^{25} = +133$ ($c = 1$, CHCl_3). Lit. m. p. 121-122 °C; $[\alpha]_D^{29} = +133$.

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