Tetrahedron Vol. 43, No. 17, pp. 3987 to 3995, 1987
Printed in Great Britain.

0040-4020/87 $3.00+.00
Pergamon Journals Ltd.

NEW SYNTHESIS OF STEROIDAL TETRAHYDROOXAZIN-2-ONES[1,2]

GYULA SCHNEIDER*, LÁSZLÓ HACKLER

Department of Organic Chemistry, József Attila University,
Dóm tér 8, H-6720 Szeged, Hungary

and

PÁL SOHÁR

Spectroscopic Department, EGIS Pharmaceuticals,
P.O.Box 100, H-1475 Budapest, Hungary

(*Received in UK 6 July* 1987)

ABSTRACT - In the DMSO/$NaHCO_3$ system, 16α-aminomethyl-, 16α-benzylaminomethyl- and substituted benzylaminomethyl-3-methoxy-17β-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, 16β-aminomethyl-3-methoxy-17β-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 oxidation[14] 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]

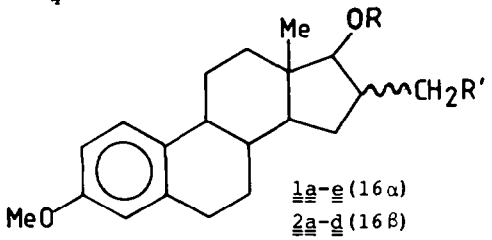
On the basis of the above mechanism, it can be expected that in the presence of an amino function in a favorable steric position in the vicinity of the tosyl group, the reaction will yield tetrahydrooxazin-2-one (7) or its N-substituted derivatives (8a-k) *via* the carbonic acid halfester intermediate.

We earlier reported on the preparation and structure elucidation of 16α- and 16β-hydroxymethyl-3-methoxyestra-1,3,5(10)-trien-17β-ol epimers (1a, 2a).[1,18] Selective tosylation of 1a and 2a resulted in the 16α- and 16β-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 16α- and 16β-azidomethyl-3-methoxy-17β-tosyloxyestra-1,3,5(10)-

triene epimers (1d, 2d) were obtained. In the preparation of the 16α-azidomethyl derivative (1d), a reaction observed only for the 16α-,17β-hydroxy epimer (1a) was also utilized. The diol 1a was allowed to react with a 4-fold excess of tosyl chloride to yield 16α-chloromethyl-17β-tosyl-3-methoxyestra-1,3,5(10)-triene (1e). The exchange reaction of the primary chlorine with NaN_3 resulted in the corresponding 16α-azido-17β-tosylate (1d).

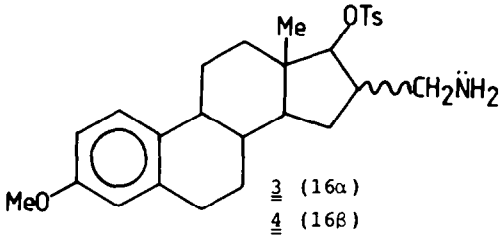
In the ir spectra of 1c,d and 2c,d, the very intense, characteristic[19a] azide band could be observed at 2143, 2100 (splitting), 2089, 2125 and 2102 cm^{-1}. For compounds 1c, 2c, 5h and 8h the νOH bands of the C-17 alcoholic and the phenolic hydroxy groups in substituent R were found at 3485 and 3477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

The 16α- and 16β-azidomethyl-17β-tosylates (1d, 2d) obtained in this way were allowed to react with $N_2H_4 \cdot H_2O$ in the presence of Raney Ni, and yielded the 16α- and 16β-aminomethyl-17β-tosyl-3-methoxyestra-1,3,5(10)-triene epimers (3, 4) in satisfactory yields. The N-substituted derivatives of compond 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 $NaBH_4$.

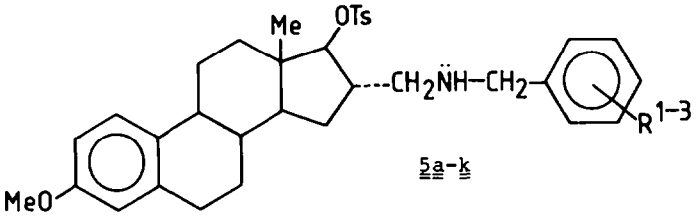


1a-e (16α)
2a-d (16β)

R:H(a-c), Ts(d,e)
R':OH(a), OTs(b), N_3(c,d), Cl(e)



3 (16α)
4 (16β)



5a-k

R^1:H(a), pOMe(b), pCl(c), pNHAc(d), $pNMe_2$(e), pNO_2(f), mNO_2(g), oOH(h), oOEt(i), $R^2=R^3$:H; $R^1=R^2$:m,pCl_2, R^3:H(j); $R^1=R^2=R^3$: m,p,m'OMe_3(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 νNH 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 νCH bands. The only exception was compound 2h: its sharp νNH 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 16α-aminomethyl, 16α-benzylaminomethyl and substituted benzylaminomethyl derivatives (3, 5a-k) were kept in DMSO in the presence of $NaHCO_3$ 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 16α,17α-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 (∿1670 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 ^{1}H nmr spectra (in $CDCl_3$ solution), the C-18 methyl singlet appeared at 0.84-0.86 ppm (1d,e, 3, 5a-j) and at 0.76-0.82 ppm (1c, 2c,d, 4, 7, 8a-k, 9), the 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 δH-3',5': 7.25-7.38 ppm; δH-2',6': 7.77-7.84 ppm, J_{ortho}: 8.1-8.3 Hz.

The ^{1}H nmr data for the AMX multiplet of aromatic ring A were as follows: δH-1: 7.10-7.20 ppm, d (J: 8.5-8.7 Hz); δH-2: 6.68-6.72 ppm, dd; δH-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 17β-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 16β,17β-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 16α,17α-substituted series (7, 8), for the 16α,17β compounds (1, 3, 5 and 9 series) it was 6.9-7.9 Hz, while for the derivatives 2c,d and 4 with the 16β,17β-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, J(A,B): 11.5-12.7; J(A,X); and J(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 OCH_3(3) was less than 1.2 ppm for all compounds. The shielding of C-16,17,18 and 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 17β-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 17α-configuration (16.7-17.1 ppm), due to the field effect[21] (steric compression shift) produced by the steric hindrance between the CH_3(18) group and the 17β-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 (16α,17α-configuration): the chemical shift (41.0-43.7 ppm) for the trans compounds with 16α,17β-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 16β,17β-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 ($\delta_{TMS}=0$ 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.

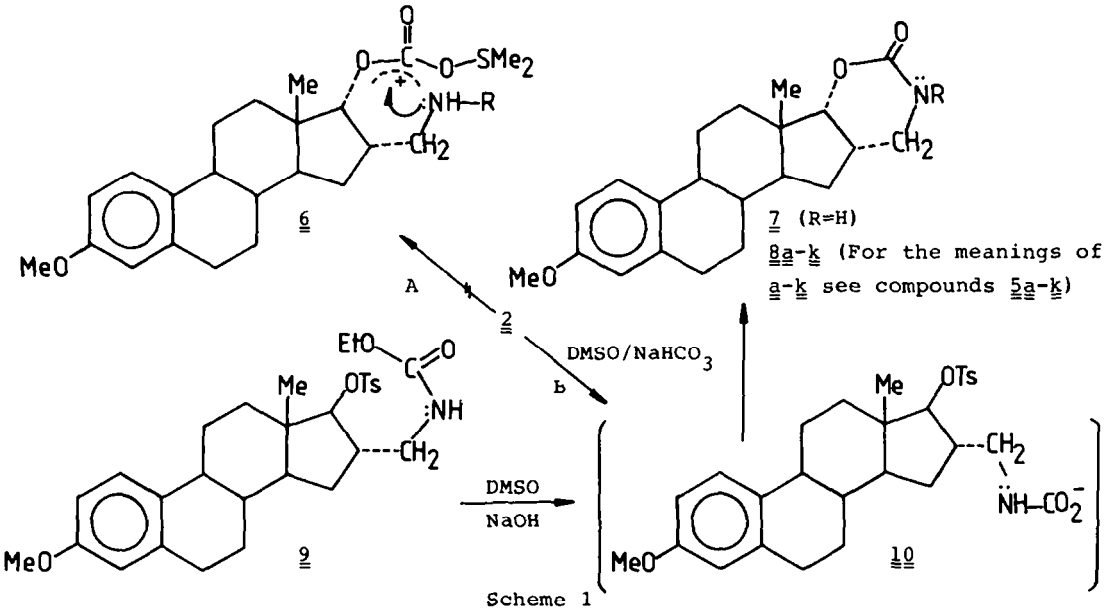
	C-1	C-2	C-3	C-4	C-5	C-6	C-7	C-8	C-9	C-10	C-11	C-12	C-13	C-14	C-15	C-16	C-17	C-18	OMe	CH_2(16)
1c	126.0	111.4	157.4	113.8	137.6	132.3	29.5	27.9[b]	38.4	43.4[c]	26.0	36.2	44.0	48.4	27.0[b]	43.7[c]	84.8	11.7	55.0	55.4
1d	126.1	111.5	157.6	113.8	137.6	132.0	29.5	27.8	38.4	43.4	25.9	36.1	44.1	48.0	26.9	41.2	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	38.5	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	125.9	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	38.8	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**: CH_3 = 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**: CH_3 and CH_2 lines of the ethoxy group in **5i**: 14.9 and 63.3, CH_3 and C=O lines of the acetyl group in **8d**: 24.0 and 167.0, NCH_3 : 40.5 (**5e**) and 40.3 (**8e**), NCH_2 (Assignments may be interchanged with 16-CH_2 for **5a-c,e,f,h**): 49.4-53.4 OCH_3 : 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[h] (**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 $CDCl_3$ 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 CH_2(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-effect[22] 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 CH_2(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 17β-tosyloxy group is replaced by the HCO_3^- 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).



Scheme 1

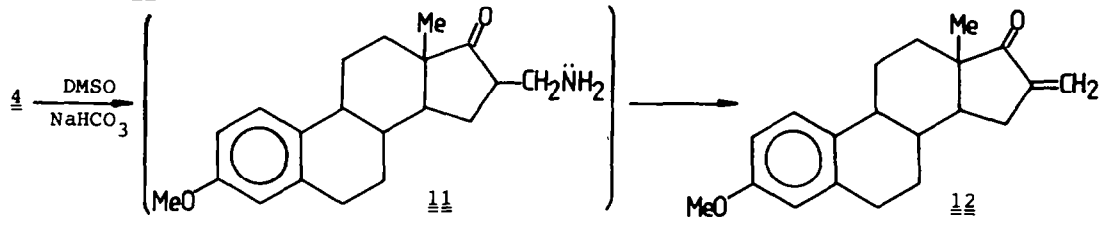
However, since 3-methoxy-17β-tosyloxyestra-1,3,5(10)-triene undergoes oxidation only very slowly under similar experimental conditions, and the C-17 tosyl esters participate in nucleophilic exchange only under vigorous experimental conditions,[23] the possibility of another mechanism was also considered.

In path B, the formation of free carbaminic acid was assumed in the $DMSO/NaHCO_3$ system, and its cyclization *via* intramolecular catalysis yields the corresponding tetrahydrooxazin-2-one relatively rapidly.

In order to verify this assumption 16α-ethoxycarbonylaminomethyl-17β-tosyloxy-3-methoxyestra-1,3,5(10)-triene (9) 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 Na_2CO_3/DMSO.[24]

16β-Aminomethyl-17β-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 16β-aminomethyl-3-methoxyestra-1,3,5(10)-trien-17-one (11) was formed *via* oxidation of the 17β-tosyl group, and then decom-

posed to 12 (Scheme 2).



Scheme 2

The strongly stereoselective conversion of the 16-aminomethyl-17β-tosyl epimers 3, 4 and 5a-k in the presence of DMSO and $NaHCO_3$ indicated the neighboring group participation in the case of the 16α-epimer. In the notation proposed by Winstein,[25] this process can be characterized by the symbol (R-NH-COO^--6).

Acknowledgements

The authors express their thanks to the G. Richter Works (Budapest) for supporting this project; to Mrs. K. L. Láng and Mrs. G. Bartók-Bozóki for the microanalytical measurements; and to Miss Cs. Horváth, Mrs. D. Fodor, Mrs. É. Mogyórósi-Párnay, Mrs. J. Csákvári, Mrs. M. Sipos and Mr. A. Fürjes for technical assistance.

Experimental

Melting points were measured on a Kofler block and are uncorrected. The specific rotation values were determined in $CHCl_3$, 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 $CDCl_3$ solution in 5 or 10 mm tubes at room temperature, on Bruker WM-250 (^1H) and WP-80SY (^{13}C) 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 (^{13}C) μs (∿20° and ∿30° 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 (^{13}C) Hz] and for the ^{13}C NMR spectra complete proton noise decoupling (∿1.5 W) was applied. The DEPT[26] spectra were run in a standard way,[27] using only the Θ = 135° pulse to separate CH/CH_3 and CH_2 lines phased "up and down", respectively. Typical acquisition data were: number of scans 128-12 K, relaxation delay for protons 3 s, 90° pulse width 10.8 and 22.8 μs for ^{13}C 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 °C for 15 minutes. The R_f values were determined in uv light of 365 nm. In the column chromatographic separation procedures, Al_2O_3 (standardized according to Brockmann) with an activity of III-IV was used.

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

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

General method

16α- or 16β-Tosyloxymethyl-3-methoxyestra-1,3,4(10)-trien-17β-ol[18] (4.7 g, 0.01 mol) was dissolved in DMF (30 mL), NaN_3 (3.2 g, 0.05 mol) was added, and the mixture was heated at 100 °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 Al_2O_3. The pure substance was eluted with a 1:1 mixture of benzene and petroleum ether.

16α- and 16β-Azidomethyl-3-methoxy-17β-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 °C for 6 h, and was then poured onto a mixture of cc. H_2SO_4 (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.

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

16α-Hydroxymethyl-3-methoxyestra-1,3,5(10)-trien-17β-ol[18] (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 °C for 6 h, and then allowed to stand at room temperature overninght. 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**

Compound	Formula	Mol. wt.	M. p. [°C]	/α/D	Rf [a]	Analysis (%) Calculated/Found C	H	N	Yield
1c	$C_{20}H_{27}O_2N_3$	341.46	83-86	+54	0.70	70.35/70.54	7.97/8.05	12.30/12.06	96
1d	$C_{27}H_{33}O_4N_3S$	495.65	115-117	+16	0.90	65.42/65.37	6.71/6.80	8.47/8.12	87
1e	$C_{27}H_{33}O_4SCl$	489.08	150-154	+5	0.95	66.30/66.45	6.80/6.65	- / -	76
2c	$C_{20}H_{27}O_2N_3$	341.46	134-135	+80	0.90	70.35/70.43	7.97/7.86	12.30/12.11	94
2d	$C_{27}H_{33}O_4N_3S$	495.65	115-116	+74	0.95	65.42/65.37	6.71/6.55	8.47/8.34	85
3	$C_{27}H_{35}O_4NS$	469.65	156-158	+13	0.20	69.05/69.18	7.51/7.45	2.98/3.05	70
4	$C_{27}H_{35}O_4NS$	469.65	155-158	+51	0.20	69.05/69.17	7.51/7.43	2.98/3.08	81
5a	$C_{34}H_{41}O_4NS$	559.77	144-147	+12	0.65	72.95/72.86	7.38/7.25	2.50/2.63	78
5b	$C_{35}H_{43}O_5NS$	589.80	144-146	+21	0.55	71.27/71.35	7.34/7.44	2.37/2.41	83
5c	$C_{34}H_{40}O_2NSCl$	594.22	145-149	+10	0.80	68.72/68.85	6.78/6.88	2.35/2.17	85
5d	$C_{36}H_{44}O_5N_2Sb$	653.29	198-203	+49	0.15	66.18/66.25	6.78/6.85	4.28/4.34	78
5e	$C_{36}H_{46}O_4N_2S$	602.85	93-95	+3	0.40	71.72/71.79	7.69/7.55	4.64/4.54	82
5f	$C_{34}H_{40}O_8N_2S$	604.77	144-147	+30	0.75	67.52/67.65	6.66/6.49	4.63/4.42	92
5g	$C_{34}H_{40}O_8N_2Sb$	641.23	153-158	+16	0.20	63.68/63.55	6.28/6.13	4.36/4.25	90
5h	$C_{37}H_{47}O_7NS$	649.85	137-139	+15	0.65	68.38/68.25	7.29/7.25	2.15/2.05	76
5i	$C_{38}H_{45}O_5NS$	613.91	132-134	+7	0.65	70.43/70.25	7.38/7.43	2.28/2.08	72
5j	$C_{34}H_{38}O_4SCl$ [b]	635.13	197-202	+24	0.80	64.29/64.52	6.03/6.14	2.20/2.34	68
5k	$C_{37}H_{47}O_7NS$	649.85	75-77	+19	0.70	68.38/68.45	7.29/7.37	2.15/2.26	80
7	$C_{21}H_{27}O_3N$	341.45	265-270	+35	0.45	73.86/73.72	7.97/8.04	4.10/4.15	85
8a	$C_{28}H_{33}O_3N$	431.58	155-158	-23	0.85	77.92/78.03	7.70/7.65	3.24/3.40	82
8b	$C_{29}H_{35}O_4N$	461.60	176-178	-37	0.85	75.45/75.58	7.64/7.54	3.03/3.16	86
8c	$C_{28}H_{32}O_3NCl$	466.03	204-209	-44	0.80	72.16/72.34	6.92/7.05	3.00/3.21	84
8d	$C_{30}H_{38}O_4N_2$	474.52	140-145	-36	0.40	73.74/73.56	7.42/7.52	5.73/5.45	73
8e	$C_{30}H_{28}O_3N_2$	464.57	224-226	-47	0.90	77.56/77.40	6.07/6.23	6.03/5.96	78
8f	$C_{28}H_{32}O_5N_2$	476.58	198-200	-11	0 80	70.56/70.43	6.76/6.79	5.87/5.65	85
8g	$C_{28}H_{32}O_5N_2$	476.58	162-163	-33	0.80	70.56/70.34	6.76/6.58	5.87/5.91	82
8h	$C_{28}H_{33}O_4N$	447.58	191-193	-36	0.80	75.13/75.25	7.43/7.33	3.12/3.26	76
8i	$C_{30}H_{37}O_4N$	475.63	154-156	-29	0.80	75.75/75.60	7.84/7.67	2.94/2.70	68
8j	$C_{28}H_{31}O_3NCl_2$	500.48	204-206	-8	0.95	67.19/67.30	6.24/6.15	2.79/2.92	82
8k	$C_{31}H_{38}O_6N$	521.66	75-77	-16	0.70	71.37/71.45	7.53/7.63	2.68/2.56	74
9	$C_{30}H_{39}O_6NS$	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

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

Compound 1e (4.89 g, 0.01 mol) was dissolved in DMF (30 mL), NaN_3 (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.

16α- and 16β-Aminomethyl-3-methoxy-17β-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 $N_2H_4 \cdot H_2O$ (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 Al_2O_3 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.

16α-(N-Benzyl- and substituted N-benzyl)-aminomethyl-3-methoxy-17β-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 $NaBH_4$ (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 $(NH_4)_2SO_4$, 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,j 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-(16α,17α-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.

16α-Ethoxycarbonylaminomethyl-3-methoxy-17β-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 (16α-17α-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; $[\alpha]_D$ = + 133 (c = 1, $CHCl_3$). Lit. m. p. 121-122 °C;[28] $[\alpha]_D$ = + 133.[29]

References

1. This paper forms Part 38 of the series Steroids and Part 10 of Neighboring Group Participation; Part 37/9: Gy. Schneider, L. Hackler and P. Sohár, Ann. Chem. (in press).
2. Preliminary communication: Gy. Schneider, L. Hackler and Gy. Dombi, J. Chem. Soc. Chem. Comm., 1980, 891.
3. D. M. Piatik and E. Caspi, J. Heterocyclic Chem., 4, 8 (1967).
4. J. Szmuszkovicz and L. L. Skaletzky, J. Org. Chem., 32, 3300 (1967).
5. T. Urbanski, Synthesis, 1974, 613.
6. W. Lwowski, Nitrenes. Intersciences Publishers, New York. 1970. p. 236.
7. O. E. Edwards and Z. Paryzek, Can. J. Chem., 51, 3866 (1973).
8. P. F. Alewood, M. Benn, J. Wong and A. J. Jones, Can. J. Chem., 55, 2510 (1977).
9. R. Adams and J. B. Segur, J. Am. Chem. Soc., 45, 785 (1923).
10. J. S. Pierce and R. Adams, J. Am. Chem. Soc., 45, 790 (1923).
11. F. L. Scott, E. R. Glick and S. Winstein, Experientia, 13, 183 (1957).
12. F. L. Scott and P. F. Fenton, Tetrahedron Letters, 1970, 685.
13. Gy. Schneider, L. Hackler and P. Sohár, Acta Chim. Hung., 111, 285 (1982).
14. N. Kornblum, W. J. Jones and G. J. Anderson, J. Am. Chem. Soc., 81, 4113 (1959).
15. N. Bosworth and P. D. Magnus, J. Chem. Soc. Chem. Comm., 1972, 257.

16. N. Bosworth, P. D. Magnus and R. Moore, J. Chem. Soc. Perkin Trans., I, 1973, 2694.

17. Gy. Schneider and I. W.-Vincze, Kémiai Közl., (In Hungarian) 44, 427 (1975).

18. Gy. Schneider, A. Vass, I. Vincze and P. Sohár, Ann. Chem. (in press).

19. S. Holly and P. Sohár, Theoretical and Technical Introduction to the Serie "Absorption Spectra in the Infrared Region" (Ed.'s L. Láng and W. H. Prichard), a) p. 124; b) pp. 82-83.

20. E. Pretsch, T. Clerc, J. Seib und W. Simon, Tabellen zur Strukturaufklärung organischer Verbindungen mit Spektroskopischen Methoden, Springer Verlag, Berlin, New York, 1976. p. H 5.

21. D. M. Grant and B. V. Cheney, J. Am. Chem. Soc., 89, 5315 (1967).

22. P.Sohár, Nuclear Magnetic Resonance Spectroscopy. CRC Press, Boca Raton, Florida, 1984. Vol. 2, pp. 152-153.

23. M. Davis, E. W. Parnell and D. Warburton, J. Chem. Soc. (C), 1966, 1968.

24. A. Hassner and S. S. Burke, Tetrahedron, 30, 2613 (1966).

25. S. Winstein, E. Allred, R. Heck and R. Glick, Tetrahedron, 3, 1 (1958).

26. D. T. Pegg, D. M. Doddrell and M. R. Bendall, J. Chem. Phys., 77, 2745 (1982).

27. M. R. Bendall, D. M. Doddrell, D. T. Pegg and W. E. Hull, High Resolution Multipulse NMR Spectrum Editing and DEPT. Bruker, Karlsruhe (1982).

28. S. Serini and H. Köster, Chem. Ber., 110, 75 (1977).

29. Gy. Schneider, I. Vincze, L. Hackler and Gy. Dombi, Synthesis, 1983, 665.