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14-AZASTEROIDS VIA HETEROCYCLOADDITION

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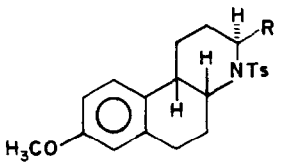
Abstract—Benzo[f]quinoline alcohol **1** has been converted into azasteroids **14** and **15** via a standard procedure and via application of the newly discovered 1.4 aryl radical rearrangement of α-halomethyl-N-arylsulfonylpiperidines. An intramolecular accelerating effect of an OH group on LAH reductions of N-tosylamides is described.

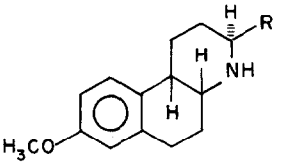
In preceding communications the stereoselective cycloaddition of N-trichloroethylidene-tosylamide to dienes[2] and the conversion of the CCl_3 group into a hydroxymethyl[3] have been described. The so-obtained benzo[f]quinoline **1** constitutes an important starting material for the synthesis of 14-azasteroids. The latter compounds contain both the physiologically important benzo[f]quinoline and indolizidine[4] fragments in one molecule.

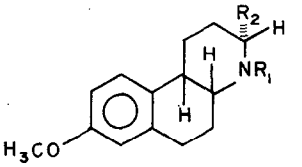
DMSO–Ac_2O oxidation[5] of **1** afforded the aldehyde **2** in 65% yield, which was shown to retain the C_3 stereochemistry[3] by LAH reduction of **2** producing **1** in return. Condensation of **2** with triethylphosphono acetate gave **3** which was hydrogenated over Pd/C (10%) to yield **4**. Surprisingly, upon LAH reduction of **4** at r.t. for 1 hr a 55/35 mixture of **6** and **11** was obtained. At 5° no detosylation was observed. In view of the inertness of sulfonamides[6] under these mild conditions some help from an intramolecular process seemed obligatory, which could happen in the form of a ligand exchange[7] as depicted in **16**. Support for the latter assumption was found in a comparison of the LAH rates of detosylation of **1** and **9**. In the former case detosylation to **10** is complete after 65 hr/r.t. while **9** is unaffected. After 72 hr/THF/reflux of **9** both dechlorination and detosylation had occurred leaving **12** which was isolated as its HCl-salt. This remarkable difference between **1** and **9** with respect to LAH reduction may be interpreted in a similar manner as for **4**. Treatment of **6** with conc./HCl/HOAc[8] did not give 14-azasteroid **14** but acetate **7**.

Ring closure of **11** however proceeded rapidly under influence of PBr_3 in benzene followed by treatment with $NaHCO_3$. The oily **14** was obtained as its HCl-salt. Since there were no configurational changes, the stereochemistry of **14** is most likely given as depicted with a *cis* C/D ring junction. Further support for the C_{13}-stereochemistry was obtained from the fact that no Bohlmann bands[9] were present in **14**.

In a second scheme for preparing 14-azasteroids starting from **1**, the newly discovered 1.4 aryl rearrangement of sulfonamides was chosen as the basic concept. As reported earlier[10] cyclic N-tosylamides substituted with an halomethyl group in an appropriate



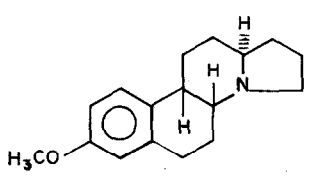




1. R= CH_2OH
2. R= CHO
3. R= $CH{=}CH{-}COOC_2H_5$
4. R= $CH_2CH_2COOC_2H_5$
5. R= $CHOHCH_2COOC_2H_5$
6. R= $CH_2CH_2CH_2OH$
7. R= $CH_2CH_2CH_2OAc$
8. R= $CHBrCH_2COOC_2H_5$

10. R= CH_2OH
11. R= $CH_2CH_2CH_2OH$
13. R= $CHCH_2COOC_2H_5$ (with $C_6H_4-CH_3-p$)

9. R_1=Ts , R_2=CH_2Cl
12. R_1=H , R_2=CH_3



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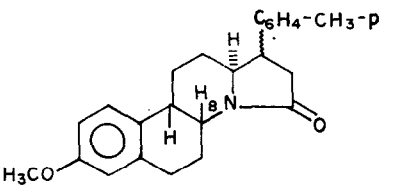

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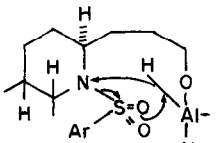

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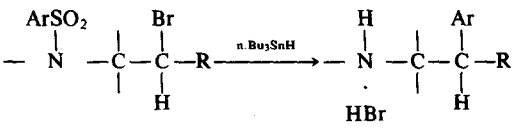
Scheme 1.

position undergo a reaction under influence of tri-(n-butyl) tinhydride of the type:



In this case R is containing additional functionality and further cyclization could be envisaged. This expectation was realized in a simple manner starting from aldehyde **2** which was condensed with bromo-acetic ester/Zn to **5**. PBr_3 treatment afforded the unstable bromo-ester **8** which was converted quantitatively to the HBr-salt of **13** upon refluxing in benzene/n-Bu_3SnH soln.[11] Although cyclisation of **13** proceeded sluggishly, the lactam **15** was formed in moderate yield upon refluxing in EtOH. The stereochemistry of azasteroid **15** B/C *cis*-H_8 eq. was concluded from an analysis of its PMR spectrum. The position of H_8 at δ 4.46 is in accordance with the marked deshielding of an equatorial proton by the amide CO as has been described for several types of quinolizidones.[12] Moreover, the splitting pattern of H_8 falls completely in line with earlier observations in this series and consists of a double triplet with J values 12.0 and 3.0 c/s respectively.

The presently described method can be considered as a synthetic attractive pathway for the construction of bridgehead nitrogen hererocyclics and additional applications are currently investigated.

EXPERIMENTAL

N - *Tosyl* - 3 - *formyl* - 1,2,3,4,4a,5,6,10b - *octahydro* - *benzo*(f)*quinoline* **2**. To a soln of **1** (0.62 mmol) in 20 ml DMSO, 1.2 ml Ac_2O was added. After 18 hr at r.t. ether and H_2O were added. The organic layer was worked up and the residue tritutated with ether, yield: 65%; m.p. (EtOH): 135–137°; IR($CHCl_3$): 1725 (s) C=O; 1335 (m), 1155 (s) SO_2 PMR δ ($CDCl_3$): 2.44 (s) $ArCH_3$; 3.74 (s) OCH_3; 4.19 (m) H_{4a}; 6.93 (d) H_{10} 7.33 (d) and 7.73(d) tosyl; 9.72 (d, J = 3 c/s) CHO. Mass: 399 (M) 1%; 91 100%. (Found: C, 66.1; H, 6.3; N, 3.5; S, 8.3. Calc. for $C_{22}H_{25}O_4NS$ (399.50): C, 66.14; H, 6.31; N, 3.51; S, 8.03%).

Ethyl - β - (N - *tosyl* - 8 - *methoxy* - 1,2,3,4,4a,5,6,10b - *octahydro* - *benzo*(f)*quinolinyl* - 3) - *acrylate* **3**. 10 mmol NaH (in 50% suspension of mineral oil) was washed with dimethoxyethane. After the addition of 10 ml dimethoxyethane and 2.50 mmol **2** a soln of 15 mmol triethylphosphono acetate in 5 ml dimethoxyethane was added dropwise. After 2.5 hr, H_2O was added and the organic layer was extracted with ether, yield: 75%; m.p. (EtOH): 123–125°; IR ($CHCl_3$): 1705 (s) C=C–COOEt; 1320 (m), 1150 (s) SO_2; PMR δ ($CDCl_3$): 1.25 (t, J = 7 c/s); 2.39 (s) $ArCH_3$; 3.74 (s) OCH_3; 4.0 (m) H_3; 4.13 (q, J = 7 c/s) OCH_2CH_3 4.55 (m) H_{4a}; 5.83 (d, J = 15 c/s) H_1; 6.73 (d) H_2; 6.94 (d) H_{10}; 7.24 (d) and 7.64 (d) tosyl. Mass: 469 (M) 3%; 424 (M–OEt) 5%; 314 (M-Ts) 100%; 91 15%. (Found: C, 66.4; H, 6.7; N, 2.9; S, 6.9. Calc. for $C_{26}H_{31}O_5NS$ (469.59): C, 66.50; H, 6.65; N, 2.98; S, 6.83%).

Ethyl - β - (N - *tosyl* - 8 - *methoxy* - 1,2,3,4,4a,5,6,10b - *octahydro* - *benzo*(f)*quinoline* **4**. A mixture of **3**, Pd/C 10% (equal quantity by weight) and EtOH was hydrogenated for 18 hr. The quantitatively formed oil **4** crystallized, yield: 70%; m.p. (EtOH): 134–134.5°; IR($CHCl_3$): 1720 (s) COOEt; 1315 (m), 1150 (s) SO_2; PMR δ ($CDCl_3$): 1.21 (t, J = 7 c/s); 2.39 (s) $ArCH_3$; 3.41 (m) H_3; 4.08 (q, J = 7 c/s); 4.42 (m) H_{4a}; 6.92 (d) H_{10}; 7.26 (d) and 7.74 (d) tosyl. Mass: 316 (M–Ts) 100%, 91 26%. (Found: C, 66.4; H, 7.1; N, 2.9; S, 6.9. Calc. for $C_{26}H_{33}O_5NS$ (471.60): C, 66.21; H, 7.05; N, 2.97; S, 6.80%).

N - *Tosyl* - 3 - (3' - *hydroxypropyl*) - 8 - *methoxy* - 1,2,3,4,4a,5,6,10b - *octahydro* - *benzo*(f)*quinoline* **6** *and* 3 - (3' - *hydroxypropyl*) - 8 - *methoxy* - 1,2,3,4,4a, 5,6,10b - *octahydro* - *benzo*(f)*quinoline* **11**. To a soln of **4** (1.03 mmol) in 40 ml THF, 5.3 mmol LAH_4 was added. After 1 hr, 0.2 ml H_2O, 0.2 ml 15% NaOH aq and 0.6 ml H_2O were added in 15 min intervals. After work-up **6** was isolated from the organic layer upon extraction with 2NHCl, yield: 55%; m.p. (EtOH): 143–145°; PMR δ ($CDCl_3$) 2.38 (s) $ArCH_3$; 3.4 (m) H_3; 3.44 (t, J = 6 c/s) CH_2OH; 3.73 (s) OCH_3; 4.43 (m) H_{4a}; 6.92 (d) H_{10}; 7.25 (d) and 7.71 (d) tosyl. Mass: 274 (M–Ts) 20%; 91 30%. (Found: C, 67.0; H, 7.4; N, 3.3; S, 7.6. Calc. for $C_{24}H_{31}O_4NS$(429.77): C, 67.07; H, 7.32; N, 3.26; S, 7.46%). The HCl-layer was neutralized and extracted with $CHCl_3$. From the $CHCl_3$-extract **11** was isolated, yield: 35%; m.p. (ether): 97–102°; IR: 3600–3100 (s) OH; NH.PMR δ (DMSO -d_6): 3.40 (t, J = 5.5 c/s) CH_2OH; 3.66 (s) OCH_3; 3.73 (s) OH and NH (exchangeable for D) 6.99 (d) H_{10}. **11**. HCl: m.p. (MeOH): 266–268°; IR($CHCl_3$): 3600–3200 (s) OH, $\overset{+}{N}H$; 2800–2300 (s) $\overset{+}{N}H$. Mass: 275 (M) 16%; 257 (M–H_2O) 10%. (Found: C, 65.5; H, 8.4; M, 4.5; $Cl^{\ominus}$ 11.4. Calc. for $C_{17}H_{26}O_2NCl$ (311.85): C, 65.47; H, 8.40; N, 4.49; $Cl^{\ominus}$ 11.37%).

N - *Tosyl* - 3 - (3' - *acetoxypropyl*) - 8 - *methoxy* - 1,2,3,4,4a,5,6,10b - *octahydro* - *benzo*(f)*quinoline* **7**. 0.047 mmol of **6** was dissolved in 2 ml HOAc and 2 ml conc HCl. After 2 hr **6** was completely converted, yield: 50%; m.p. (MeOH): 105.5–108°; PMR δ ($CHCl_3$): 1.98 (s) CH_3CO; 2.41 (s) $ArCH_3$; 3.35 (m) H_3; 3.74 (s) OCH_3; 3.96 (t, J = 6.0 c/s) CH_2OAc; 4.50 (m) H_{4a}; 6.95 (d) H_{10}; 7.24 and 7.73 (d) tosyl. UV λ_{max}^{EtOH}: 222 (15,500), 277 (2200); 287 (2000). Mass: 471 (M) 3%; 316 (M-Ts) 23%.

3 - *Methoxy* - 6,7,8,9,11,12,13,14,15,16 - *decahydro* - 14 - *azacyclopenta*(a)*phenanthrene* **14**. A mixture of **11** (0.95 mmol), 4.5 mmol PBr_3 and 10 ml C_6H_6 was boiled for 3 hr. After washing with sat. $NaHCO_3$ aq and further work-up an unstable oil **14** was obtained, yield: 50%; IR($CHCl_3$): 1610 (m), 1500 (s) arom.; PMR δ ($CHCl_3$): 3.73 (s) OCH_3; 7.01 (d) H_{10}. The HCl-salt of **14** was crystalline, yield: 35% (based on **11**); m.p. (CH_2Cl_2/EtOAc): 228.5–230.5°; PMR δ ($CDCl_3$): 3.74 (s) OCH_3; 7.02 (d) H_{10}; 11.95 (diff. s) $\overset{\oplus}{N}H$. UV λ_{max}^{EtOH}: 222 (8600); 278 (1950); 287 (1950). Mass: 257 (M) 100%; 168, 50%. (Found: C, 69.6; H, 8.4; N, 4.7; $Cl^{\ominus}$ 12.1. Calc. for $C_{17}H_{24}ONCl$ (293.81): C, 69.49; H, 8.23; N, 4.77; $Cl^{\ominus}$ 12.07%).

3β - *Hydroxymethyl* - 8 - *methoxy* - 1,2,3,4,4a,5,6,10b - *octahydro* - *benzo*(f)*quinoline* **10**. A soln of **1** (10 mmol) in THF (10 ml) and LAH (2.0 mmol) was stirred for 65 hr. After work-up and evaporation of the solvent **10** was semi-crystalline, yield: 50%; m.p. (CH_2Cl_2/ether): 149–151°; PMR δ ($CDCl_3$): 3.74 (s) OCH_3; 7.00 (d) H_{10}. UV λ_{max}^{EtOH}: 221 (8600); 278 (2100); 287 (2000). Mass: 247 (M) 7%. (Found: C, 72.8; H, 8.7; N, 5.7. Calc. for $C_{15}H_{21}O_2N$ (247.33): C, 72.84; H, 8.56; N, 5.66%).

3α - *Methyl* - 8 - *methoxy* - 1,2,3,4,4a,5,6,10b - *octahydro* - *benzo*(f)*quinoline* **12**. To a soln of **9** (2.38 mmol) in 25 ml THF, LAH (8.4 mmol) was added. After 65 hr at r.t. no reaction had occurred. After refluxing for 72 hr the product was worked up, yield: 75% (oil); PMR δ ($CDCl_3$) 0.95 (d, J = 6.5 c/s) CH_3; 1.3 (s) NH (exchangeable); 3.76 (s) OCH_3; 7.25 (d) H_{10}. The HBr-salt of **12** was obtained by adding a few drops of 48% HBr-solution to an ether soln of **12**, m.p. (CH_2Cl_2)/EtOAc): 204–207° PMR δ ($CDCl_3$): 1.32 (d, J = 6.0 c/s) CH_3; 3.74 (s) OCH_3; 7.11 (d) H_{10}. Mass: 231 (M) 100%. (Found: C, 57.7; H, 7.3; N, 4.5; Br, 25.6. Calc. for $C_{15}H_{22}ONBr$: C, 57.69; H, 7.10; N, 4.49; Br, 25.59%).

Ethyl - β - (N - *tosyl* - 8 - *methoxy* - 1,2,3,4,4a,5,6,10b - *octahydro* - *benzo*(f)*quinolinyl* - 3) - β - *hydroxypropionate* **5**. To a mixture of activated Zn, (1.5 mmol) **2** (0.50 mmol) and 3 ml C_6H_6, 1.5 mmol bromoacetic acid ethylester in 3 ml C_6H_6 was added dropwise. After addition of a few crystals I_2 and boiling for 1.5 hr the product was dissolved in $CHCl_3$/2 NHCl and worked up, yield: 70% (oil); IR($CHCl_3$): 3580 (m) OH; 1720 (m) COOEt; 1330 (m), 1155 (s) SO_2; PMR δ ($CDCl_3$): 1.25 (t, J = 7 c/s); 4.15 (q, J = 7 c/s).

3 - *Methoxy* - 15 - *keto* - 17 - (p)*tolyl* - 6,7,8,9,11,12,13,14,15,16 - *decahydro* - 14 - *azacyclopenta*(a)*phenanthrene* **15**. To **5** (0.82 mmol) dissolved in 15 ml C_6H_6, 1.6 mmol PBr_3 was added. After boiling for 1 hr the solvent was removed and the product was passed through a column (silanized silicagel, C_6H_{12}/C_6H_6 = 1/1).

Ethyl - β - *bromo* - β - (N - *tosyl* - 8 - *methoxy* - 1,2,3,4,4a,5,6,10b - *octahydrobenzo*(f)*chinolinyl*(- 3) - *propionate*

8 was isolated as an unstable oil, yield: 50%; IR($CHCl_3$): 1725 (s) ester; 1310 (m); 1150 (s) SO_2. 0.29 mmol **8** was reacted with a soln of 1.00 mmol nBu_3SnH in 36 ml C_6H_6 for 42 hr at 55°. After evaporation of the solvent the residue was passed through a column of (silanized) silicagel and successively eluted with C_6H_6/C_6H_{12} and EtOH to give **13** isolated as its HBr salt.

A soln of the HBr-salt in $CHCl_3$ was washed with a sat. $NaHCO_3$aq. The IR spectrum indicated a mixture of **13** and **15**. After boiling the mixture in EtOH for 65 hr **15** was obtained, yield: 35%; m.p. (ether/diisopropylether): 151–152°. PMR δ ($CDCl_3$): 2.28 (s) $ArCH_3$; 3.69 (s) OCH_3; 4.46 (m) H_{4a}; 6.85 (d) H_{10}; 7.06 (s) $C_6H_4CH_3$. UV λ_{max}^{EtOH}: 277 (2050), 287 (1900). Mass: 361 (M) 62%; 174 100%; 160 46%. (Found: C, 79.7; H, 7.6; N, 3.9. Calc. for $C_{24}H_{27}O_2N$ (361.46): C, 79.74; H, 7.53; N, 3.88%).

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