Tetrahedron Vol. 35, pp. 267–272
© Pergamon Press Ltd., 1979. Printed in Great Britain

0040-4020/79/0115-0267/$02.00/0

SYNTHESIS AND CONFORMATIONAL ANALYSIS OF *EXO*- AND *ENDO*-7-SUBSTITUTED-3-AZABICYCLO[3.3.1]NONANES

TH. REINTS BOK and W. N. SPECKAMP*
Laboratory for Organic Chemistry, University of Amsterdam, 1000 HE Amsterdam, P.O. Box 20241, The Netherlands

(*Received in UK 20 July 1978; accepted for publication 7 August 1978*)

Abstract—The synthesis of some 7-substituted-3-azabicyclo[3.3.1]nonanes is described. Routes followed were the debenzoylation of the 7-benzoyl derivative **7** and the decarboxylation of the 7-carboxy compounds **21** and **27**. The so-obtained 7-oxo-N-tosyl-3-azabicyclo[3.3.1]nonanes **8** and **11** show an extremely low reactivity towards a series of nucleophilic reagents. From analysis of the ^{1}H NMR spectral data of a series of derivatives, the twin-chain conformation for the 7-*exo* compounds and the chair-boat conformation for the 7-*endo* compounds is indicated.

Incorporation of an N atom in a carbocyclic cage compound frequently leads to pronounced alterations in chemical behaviour. In addition the investigation of physicochemical phenomena associated with the rigidity of the heterocyclic cage is of general interest.[1] The facile synthesis of 1-azaadamantanes[1] via ring closure of 3-azabicyclo[3.3.1]nonanes[2] initiated the investigation of synthetic routes towards the corresponding 3-azanoradamantanes. The latter goal could be realized by chemical transformation of suitable azabicyclic starting materials of types **A** and **B** (Fig. 1).

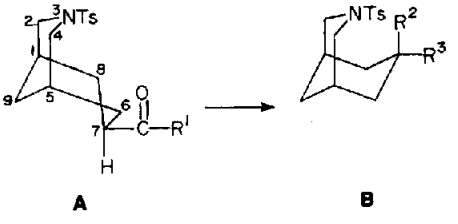


Fig. 1.

Two general routes were followed: conversion of carboxylic acids **A** (R^1=OH) via lead tetraacetate decarboxylation yielded chlorides or alcohols **B** (R^2=, R^3=OH, Cl), while ketones **A** (R^1=C_6H_5) were transformed oxidatively into ketones **B** (R^2R^3=O). In addition to the synthetic work some observations on the conformational behaviour of the latter azabicyclics and the steric influence of the toluenesulfonamide moiety on the reactivity are also discussed.

Synthesis

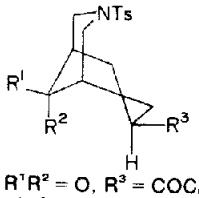
The benzoyl derivative **1a** was obtained via α,α'-annelation of enamine **3** with 2 - benzoyl - 1,3 - dichloropropane.[3] Its C_7-*endo* configuration was proven via LAH reduction of **1a** to a C_9-*anti*/*syn*† mixture of diols **4a** and **4b** (ratio 3:2), which was directly converted by refluxing in conc HCl/HOAc into the corresponding 1-azaadamantanes **5a** and **5b**. Ag_2CO_3/celite oxidation of the latter mixture provided 4 - oxo - 8 - phenyl - 1 - azaadamantane **6**, synthesized before via an independent route.[4]

†With respect to the piperidine ring.

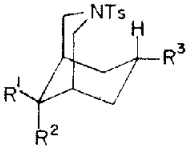
The degradation of the C_7-benzoyl substituent was best performed after protection of the C_9-oxo function as a ketal by oxidation of the C_7-anion. During acetalization of **1a** in MeOH an epimerization at C_7 took place, leading to the C_7-*exo*-benzoyl derivative **7**. The latter compound was shown to possess the twin-chair conformation contrary to **1a**, which existed in the chair-boat form (*vide infra*). Reaction of **7** with O_2 in presence of 1.1 equivalent of tBuOK/tBuOH (1:1) in HMPA afforded **8** in 58% yield. Surprisingly, a corresponding reaction of the C_9-unsubstituted **10** failed to give any of the C_7-oxo product **11**. The starting material **10** was obtained by thioketalization of **1a** at 0°, affording the *exo*-epimer **9** and subsequent Ra–Ni treatment of **9**. Oxidation of **10** gave a variety of products, presumably arising from over-oxidation. This observation indicates a marked difference in reactivity between **8** and **11**.

The steric inhibition of reactions at C_7 by the C_3-methylene group[5] or the tosyl substituent[6] has been established with certainty. For example, the steric influence of the sulfonamide group is evident from the monoacetalization in MeOH of **1a** yielding **7** as sole product. In contrast to the carbocyclic analogue[3] no trace of a benzoyl ketal is found. The difference in reactivity between **8** and **11** may be attributed to the steric hindrance by an additional axial substituent at C_9. The presence of a C_9-*anti*-OMe substituent presumably lowers the accessibility of the C_7-oxo function, thus allowing the isolation of ketone **8**. As described in the sequel other findings also support this conclusion. For instance a $NaBH_4$ reduction of ketone **11**-prepared in a different manner—at r.t. for 16 hr affords the alcohol **12a** possessing an *endo* C_7–OH function, albeit in a slow reaction. On the contrary, **8** does not react under the latter conditions with $NaBH_4$, while upon treatment with LAH at r.t. both detosylation and reduction occurred to the amino alcohol **13**.[7] Upon LAH reduction at −20° a quantitative yield of alcohol **14** was obtained. Similar reactions of **11** with LAH at −20° gave *endo*-product **12a** while at 40° the amino alcohol **15** was formed exclusively. The unusually facile detosylation reactions in presence of properly oriented OH groups have been observed before[8] and are probably due to a favorable coordination process between the sulfon O-atoms and the central Al atom (Fig. 2).

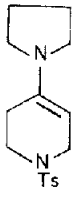
Several other experiments with **8** and **11** gave negative results. Reaction with methylenephosphorane left the



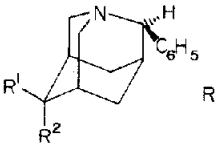
1a: $R^1R^2 = O$, $R^3 = COC_6H_5$
2: $R^1R^2 = O$, $R^3 = COOEt$
4a: $R^1 = H$, $R^2 = OH$, $R^3 = CHOHC_6H_5$
4b: $R^1 = OH$, $R^2 = H$, $R^3 = CHOHC_6H_5$
12a: R^1, $R^2 = H$, $R^3 = OH$
14: R^1, $R^2 = OMe$, $R^3 = OH$
21: R^1, $R^2 = O$, $R^3 = COOH$
26: R^1, $R^2 = H$, $R^3 = COOEt$
28: R^1, $R^2 = O$, $R^3 = OH$



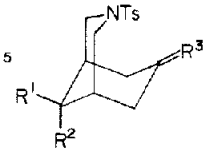
1b: R^1, $R^2 = O$, $R^3 = COC_6H_5$
7: R^1, $R^2 = OMe$, $R^3 = COC_6H_5$
9: $R^1 - R^2 = (SCH_2)_2$, $R^3 = COC_6H_5$
10: R^1, $R^2 = H$, $R^3 = COC_6H_5$
12b: R^1, $R^2 = H$, $R^3 = OH$
22: R^1, $R^2 = O$, $R^3 = Cl$
24: R^1, $R^2 = O$, $R^3 = OAc$
27: R^1, $R^2 = H$, $R^3 = COOH$



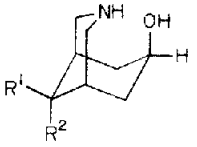
3



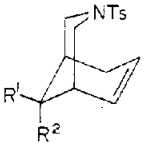
5a: $R^1 = H$, $R^2 = OH$
5b: $R^1 = OH$, $R^2 = H$
6: R^1, $R^2 = O$



8: R^1, $R^2 = OMe$, $R^3 = O$
11: R^1, $R^2 = H$, $R^3 = O$
16: R^1, $R^2 = OMe$, $R^3 = CHCOOMe$
17: R^1, $R^2 = H$, $R^3 = CHCOOMe$
18: R^1, $R^2 = OMe$, $R^3 = N—NH—Ts$
19: R^1, $R^2 = H$, $R^3 = N—NH—Ts$



13: R^1, $R^2 = O$
15: R^1, $R^2 = H$



20: R^1, $R^2 = H$
23: R^1, $R^2 = O$

Scheme 1.

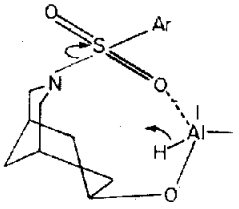


Fig. 2.

starting material unchanged, while upon treatment of **8** or **11** at −20° with Me- or Ph–Li non-identifiable products were formed. Reaction with MeMgI also failed to yield C_7-addition or reduction products. After a period of 5 days at 50° 3% of **16** and 15% of **17** were obtained in the reactions of **8** and **11** with the anion of trimethylphosphonacetate.

Hydrazones **18** and **19**, however, could be prepared via reactions with tosylhydrazide; decomposition of **19** in alkaline medium (n-Buli in tetramethylethylene diamine) afforded the known olefine **20**, no trace of the desired unsaturated aldehyde being formed.[9] In conclusion all of the aforementioned results indicate the unusually low reactivity of the C_7-oxo function. In view of the detosylation results found in the hydride reductions a steric blocking by the neighbouring tosyl group seems the most plausible explanation.

A second possibility for the synthesis of C_7-substituted bicyclo[3.3.1]nonanes is the decarboxylation of the acid **21**, easily obtained by acid hydrolysis of the bicyclic ketoester **2**.[2] Decarboxylation of **21** with $Pb(OAc)_4$ and 1 eq LiCl in benzene gives the C_7-*exo* chloride **22** (60%). Decarboxylation of **21** in absence of an external anion ($Pb(OAc)_4$/pyridine) gave rise to the formation of olefin **23** (14%) together with the C_7-*exo* acetate **24** (18%). The latter compound upon hydrolysis afforded a mixture of two epimeric alcohols **25a** and **25b** (*vide infra*).

The ester **2** also is a suitable precursor for the C_7-oxo compound **11**. Thioketalization and subsequent Ra–Ni treatment gives the ester **26**; combined base-catalyzed isomerization and hydrolysis of **26** yields the C_7-*exo*-substituted acid **27**.[10] Decarboxylation with $Pb(OAc)_4$/pyridine in benzene and hydrolysis of the crude mixture gives in contrary to the decarboxylation of the acid **21** in reasonable yield the unsaturated compounds **20** (16%) and the C_7-*exo* alcohol **12b** (47%). In the $Pb(OAx)_4$ oxidation of acids **21** and **27** the approach of the nucleophile occurs from the steric more favourable *exo*-side, yielding products with a C_7-*exo* substituent. Oxidation of **11a** with pyridinium chlorochromate affords the desired compound **11** (80%).

Table 1. ^{1}H NMR spectra of 7 - substituted - N - tosyl - 3 - azabicyclo[3.3.1]nonanes[a] (chemical shifts in ppm)

compound	conf	$H_{2,4}^{eq}$	$H_{2,4}^{ax}$	$H_7(W_{\frac{1}{2}})^b$
1a	cb	3.95	2.75	3.24 (23)
1b	cc	4.28	2.96	5.27 (23)
2	cb	3.96	±2.50[c]	±2.60[c]
4a	cb	3.65	±2.40[c]	±2.00[c]
4b	cb	3.40	±2.40[c]	±2.00[c]
7	cc	3.84	2.94	4.82 (20)
9	cc	3.95	3.12	4.78 (27)
10	cc	3.92	2.50	4.85 (24)
12a	cb	3.65	2.45	3.90 (20)
12b	cc	3.74	2.40	4.89 (20)
14	cb	3.50	2.75	3.83 (15)
21	cb	4.06	±2.70[c]	±2.70[c]
22	cc	4.08	±2.70[c]	5.43 (22)
24	cc	4.01	2.75	5.92 (19)
25a	cb	3.67	2.70	4.24 (10)
25b	cc	4.00	2.70	5.08 (20)
26	cb	3.68	2.26	±2.50[c]
27	cc	3.92	2.51	3.96 (20)
28	cb	4.00	2.63	3.80 (20)

[a]In $CDCl_3$, except **21** and **28** (C_5D_5N).
[b]$W_{1/2}$ in Hz.
[c]The indicated protons are obscured by other absorptions. The probable region is given.

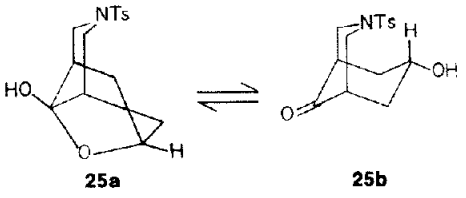
Spectral analysis

The ^{1}H NMR data of the N–CH_2 protons and H_7 and the preferred conformation (twin-chair or chair-boat) for the N-tosyl-3-azabicyclo[3.3.1]nonanes are compiled in Table 1. The chemical shifts and the geminal coupling of the N-methylene protons indicate the chair conformation for the piperidine ring.[10] Owing to the deshielding of the tosyl group the absorption of H_7-*endo* in the chair form of the cyclohexane ring is shifted considerably downfield, compared with the absorption of H_7-*exo* in the boat form and is an important indication for the conformation of the bicyclo[3.3.1]nonanes. Substitution of the C_7-*endo* hydrogen increases the conformational energy of the twin-chair, thus favouring the chair-boat form.

The C_7-*endo* configuration of **1a** is also proven by chemical methods. The ^{1}H NMR data indicate an axial H_7 ($W_{1/2}$ = 28 Hz), compatible with the chair-boat conformation of **1a**. Epimerization of **1a** with EtONa/EtOH gives a new compound **1b**, possessing the more stable twin-chair conformation. The absorption of H_7ax ($W_{1/2}$ = 23 Hz) is shifted two ppm downfield (5.27 ppm), as result of the deshielding of the tosyl group. Reaction with acid also leads to epimerization of **1a**; acetalization with MeOH gives **7** possessing a low-field absorption of H_7ax (4.82 ppm). Additional evidence for the twin-chair conformation of **7** is obtained by acetalization of **1b** yielding **7** as the sole product. Compounds **9** and **10**, obtained by respective thioketalization and Ra–Ni treatment of **1a**, also possess the twin-chair conformation, as can be deduced from the absorption of H_7ax at 4.78 ppm and 4.85 ppm. Reduction of **8** and **11** with LAH gives the products **14** and **12a**. Both compounds show an ^{1}H NMR an absorption of an axial H_7 at 3.83 ppm and 3.90 ppm respectively, indicating the chair-boat conformation. Steric interaction with the tosyl group results in the approach of the aluminium-hydride-anion from the less hindered *exo*-side, yielding one isomer in the chair-boat form with C_7–OH *endo*. In reverse this result also supports the twin-chair form of **8** and **11**.

Decarboxylation of **21** and **27** gave rise to olefins together with C_7-*exo* substituted bicyclo[3.3.1]nonanes **22** or **24** and **12b** respectively. The ^{1}H NMR spectra of these compounds show a marked shift to lower field of H_7ax, indicating the twin-chair conformation.

Hydrolysis of **24** yields a mixture of **25a** and **25b** (Fig. 3) characterized by the following ^{1}H NMR data: H_7eq at 4.34 ppm and H_7ax at 5.08 ppm. These data differ markedly from the data of the C_7-*endo* isomer **28** with H_7ax at 3.80 ppm, obtained by hydrolysis of **14**. The existence of a conformational equilibrium between the two isomers **25a** and **25b** was proved by ^{13}C NMR.[11] **25a** possesses the chair-boat conformation stabilized by a hemi-acetal formation, while in **25b** the twin-chair con-



25a 25b

Fig. 3.

formation with the OH group *exo* is preferred.

The reductions of **8** and **11** with LAH and the decarboxylation reactions of **21** and **27** give rise to isomers with a different configuration at C_7 and allow the unambiguous determination of the conformation of the various stereo-isomers. These results are in good agreement with the ^{13}C NMR data of the bicyclic compounds.[12]

EXPERIMENTAL

All m.ps are uncorrected. Analyses were carried out by H. Pieters of the Micro-analytical Department of this laboratory. IR spectra were recorded on an Unicam SP-200. Absorptions are given in cm^{-1}. ^1H NMR spectra were measured on a Varian Associates HA-100 instrument. Chemical shifts are reported in ppm relative to TMS.

N - Ts - 3 - *Aza* - 7 - *benzoyl* - 9 - *oxo* - *bicyclo*[3.3.1]*nonane* **1a**. 2 - Benzoyl - 1,3 - dichloropropane[3] (1.085 g; 5 mmol) in dry acetonitrile (10 ml) was added dropwise with stirring at r.t. in N_2 to **3** (1.53 g; 5 mmol) and triethylamine (0.606 g; 6 mmol) in dry acetonitrile (20 ml). After 2 hr water (10 ml) was added and the soln was stirred for 1 hr. After evaporation of the solvent, water was addeded and the aqueous soln was extracted with $CHCl_3$. The extracts were washed with 2N HCl, sat $NaHCO_3$aq and dried over $MgSO_4$. Evaporation of solvent yielded 1.47 g (74%) of **1a**, m.p. (EtOAc/cyclohexane) 183–185°. IR($CHCl_3$): 1725 and 1685 (C=O); 1360 and 1170 (Ts). ^1H NMR ($CDCl_3$): 3.95 (d, N–CH_2eq); 3.24 ($W_{1/2}$ = 28 Hz, H_7ax); 2.75 (d, N–CH_2ax). (Found: C, 66.3; H, 6.0; N, 3.6; S, 8.1. Calc. $C_{22}H_{23}O_4N_1S_1$ (M = 397.47): C, 66.49: 5.83; N, 3.52; S, 8.06%).

N - Ts - 3 - *Aza* - 7 - *benzoyl* - 9 - *oxo* - *bicyclo*[3.3.1]*nonane* **1b**. **1a** (100 mg, 0.25 mmol) was stirred 1 hr at 0° with Na (0.1 g) in MeOH (25 ml). 2N HCl was added till pH = 7. MeOH was evaporated and the soln extracted with $CHCl_3$. The $CHCl_3$ soln was dried over $MgSO_4$ and evaporated, yielding 73 mg (73%) of **1b**, m.p. (EtOAc/pentane) 204–206°. IR($CHCl_3$): 1730 and 1680 (C=O); 1360 and 1160 (Ts). ^1H NMR ($CDCl_3$): 5.27 ($W_{1/2}$ = 23 Hz, H_7ax); 4.28 (d, N–CH_2eq); 2.96 (d, N–CH_2ax). (Found: C, 66.4; H, 5.8; N, 3.5; S, 8.0. Calc. $C_{22}H_{23}O_4N_1S_1$ (M = 397.47): C, 66.49; H, 5.83; N, 3.52; S, 8.06%).

N - Ts - 3 - *Aza* - 7 - *carboethoxy* - 9 - *oxo* - *bicyclo*[3.3.1]*nonane* **2**[10] was obtained as described.

N - Ts - 4 - *Pyrrolidinyl* - 1,2,3,6 - *tetrahydropyridine* **3**[10] was obtained as described.

N - Ts - 3 - *Aza* - 7 - *hydroxybenzyl* - 9 - *hydroxy* - *bicyclo*[3.3.1]*nonanes* **4a + 4b**. **1a** (795 mg, 2 mmol) in THF (20 ml) was added dropwise to LAH (152 mg, 4 mmol) in THF (20 ml). After 4 hr stirring at 50° EtOAc and Na_2SO_4 aq were added dropwise. After filtration and evaporation of the solvent, the residue was dissolved in $CHCl_3$ and the soln washed with 2N HCl, sat $NaHCO_3$ aq, dried over $MgSO_4$ and evaporated. Yield: 760 mg (95%) of **4a + 4b** (mixture: 60/40). IR($CHCl_3$): 3500 (OH); 1360 and 1160 (Ts). ^1H NMR ($CDCl_3$): 4.32 (0.6 H, J = 8 Hz, CHOHC$_6$H$_5$ **4a**); 4.20 (0.4 H, J = 7 Hz, CHOHC$_6$H$_5$ **4b**); 3.70 (0.4 H, H_9 **4b**); 3.65 (1.2 H, N–CH_2eq **4a**); 3.45 (0.6 H, H_9 **4a**); 3.40 (0.8 H, N–CH_2eq **4b**). (Found: C, 65.8; H, 6.8; N, 3.5; S, 8.0. Calc. $C_{22}H_{27}O_4N_1S_1$ (M = 401.50): C, 65.82; H, 6.85; N, 3.49; S, 7.97%).

4 - *Oxo* - 8 - *phenyl* - 1 - *azatricyclo*[3.3.1.1.^{3,7}]*dekaan* **6**. **4a + 4b** (460 mg, 1.14 mmol) were heated at reflux for 5 hr in conc HCl (20 ml) and HOAc (20 ml). After evaporation of the solvent, 2N HCl was added and the soln washed with $CHCl_3$ (5x). After evaporation of the acid layer, water (5 ml) and some pellets of KOH were added and the soln extracted with $CHCl_3$ and dried over $MgSO_4$. Evaporation of the solvent yielded 160 mg (60%) of **5a + 5b** as an oil. IR($CHCl_3$): 3400 (OH); 1600 (phenyl). ^1H NMR ($CDCl_3$): 4.10 (s, 80%, H_2 **5a**); 4.00 (t, 80%, H_6 **5a**); 3.30 (AB, H_9); 3.00 (AB, H_8). Mass measurements 229.1472, confirming $C_{15}H_{19}O_1N_1$. Ag_2CO_3/celite (3 g, 5 mmol) was added to **5a + 5b** (70 mg, 0.3 mmol) in xylene (50 ml) and heated at reflux. After 10 min the soln became black. After filtration the solvent was evaporated, yielding 68 mg (98%) of **6**, m.p. (cyclohexane) 114–115°. IR($CHCl_3$): 1700 (C=O). ^1H NMR ($CDCl_3$): 7.45 (5 H, C_6H_5); 4.30 (s, H_2); 3.50 (3 H, H_8, H_9); 2.90 (d, H_8). (Found: C, 79.1; H, 7.6; N, 6.1. Calc. $C_{15}H_{17}O_1N_1$ (M = 227.29): C, 79.26; H, 7.54; N, 6.16%).

N - Ts - 3 - *Aza* - 7 - *benzoyl* - 9,9 - *dimethoxy* - *bicyclo*[3.3.1]*nonane* **7**. **1a** (5.59, 13.8 mmol) was heated at reflux in dry MeOH (200 ml) and 1 ml conc H_2SO_4 for 2 hr in a D.S. apparate. The soln was cooled and 1 N NaOH was added till pH = 10. MeOH was evaporated and the soln was extracted with $CHCl_3$. The organic layers were dried over $MgSO_4$ and the solvent was evaporated yielding 5.65 g (95%) of **7**, m.p. (EtOAc/pentane) 161–163°. IR($CHCl_3$): 1680 (C=O); 1340 and 1160 (Ts). ^1H NMR ($CDCl_3$): 4.82 ($W_{1/2}$ = 20 Hz, H_7); 3.84 (d, N–CH_2eq); 3.15 and 3.04 (s, OMe). (Found: C, 64.8; H, 6.4; N, 3.2; S, 7.2. Calc. $C_{24}H_{29}O_5N_1S_1$ (M = 443.54): C, 65.00; H, 6.59; N, 3.16; S, 7.22%).

N - Ts - 3 - *Aza* - 7 - *oxo* - 9,9 - *dimethoxy* - *bicyclo*[3.3.1]*nonane* **8**. **7** (26.5 g, 60 mmol) was added with stirring to tBuOK/tBuOH (1/1) (12.6 g, 67 mmol) in tBuOH (20 ml) and HMPA (100 ml) in an O_2 atmosphere. After 30 min the soln was poured in icewater and extracted with benzene/THF. The organic layers were washed with sat NaClaq and dried over $MgSO_4$. Evaporation of solvent and column chromatography (silicagel) of the oil with EtOAc/cyclohexane (1/2) yielded 2 g (7.5%) of **7** and 12.3 g (58%) of **8**, m.p. (EtOAc) 207–209°. IR($CHCl_3$): 1710 (C=O); 1360 and 1160 (Ts). ^1H NMR ($CDCl_3$): 3.48 (d, N–CH_2eq); 3.21 and 3.11 (s, OME); 2.75 (d, N–CH_2ax). (Found: C, 57.6; H, 6.6; N, 3.9; S, 8.9. Calc. $C_{17}H_{23}O_5N_1S_1$ (M = 353.42): C, 57.78; H, 6.56; N, 3.96; S, 9.01%).

N - Ts - 3 - *Aza* - 7 - *benzoyl* - 9,9 - *dithioethylene* - *bicyclo*[3.3.1]*nonane* **9**. **1a** (1.19 g, 3 mmol), ethanedithiol (0.314 ml, 3.75 mmol) in dry $CHCl_3$ (15 ml) was added dropwise to $BF_3O(Et)_2$ (0.6 ml) at −5° and the soln was stirred for 16 hr at 0°. The organic layer was washed with cold 1N NaOH (3x), cold NaClaq (3x), dried over Na_2SO_4 and evaporated. Yield 1.2 g (85%) of **9**, m.p. (EtOAc/pentane) 162–164°. IR($CHCl_3$): 1680 (C=O); 1360 and 1160 (Ts). ^1H NMR ($CDCl_3$): 4.78 (m, $W_{1/2}$ = 27 Hz, H_7ax); 3.95 (d, (N–CH_2eq); 3.15 (s, CH_2–S); 3.12 (d, N–CH_2ax). (Found: C, 60.7; H, 5.7; N, 3.1; S, 20.1. Calc. $C_{24}H_{27}O_3N_1S_3$ (M = 473.64): C, 60.88; H, 5.75; N, 2.96; S, 20.28%).

N - Ts - 3 - *Aza* - 7 - *benzoyl* - *bicyclo*[3.3.1]*nonane* **10**. **9** (100 mg, 0.21 mmol) was heated at reflux in EtOH (50 ml) with 2 g of desactivated RaNi for 18 hr. After filtration the soln was evaporated, yielding 80 mg (100%) of **10**, m.p. (EtOAc/pentane) 162–164°. IR($CHCl_3$): 1680 (C=O). ^1H NMR ($CDCl_3$): 4.85 (m, $W_{1/2}$ = 24 Hz, H_7ax); 3.92 (d, N–CH_2eq); 2.60 (d, N–CH_2ax).. (Found: C, 69.0; H, 6.4; N, 3.5; S, 8.2. Calc. $C_{22}H_{25}O_3N_1S_1$ (M = 383.49): C, 68.91; H, 6.57; N, 3.65; S, 8.34%).

N - Ts - 3 - *Aza* - 7 - *oxo* - *bicyclo*[3.3.1]*nonane* **11**. To pyridinium chlorochromate (215 mg, 1 mmol) in dry CH_2Cl_2 (10 ml) was added **12b** (100 mg, 0.3 mmol) in dry CH_2Cl_2 (5 ml). After 2 hr the reaction was complete; CH_2Cl_2 and ether were added and the soln was passed through a column of Florisil, yield: 85 mg (85%) of **11**, m.p. (EtOAc/pentane) 154–155°. IR($CHCl_3$): 1690 (C=O); 1360 and 1150 (Ts). ^1H NMR ($CDCl_3$): 3.64 (d, N–CH_2eq); 2.55 (d, N–CH_2ax). (Found: C, 61.3; H, 6.4; N, 4.6; S, 11.1. Calc. $C_{15}H_{19}O_3N_1S_1$ (M = 293.37): C, 61.43; H, 6.53; N, 4.78; S, 10.92%).

N - Ts - 3 - *Aza* - 7 - *hydroxy* - *bicyclo*[3.3.1]*nonane* **12a** *and* 7 - *hydroxy* - 3 - *azabicyclo*[3.3.1]*nonane* **15**. **11** (100 mg, 0.34 mmol) in THF (10 ml) was added to LAH (38 mg, 1 mmol) in THF (5 ml) and the soln was stirred for 16 hr. EtOAc and Na_2SO_4aq were added dropwise. After filtration the solvent was evaporated, 2N HCl was added and the soln extracted with

$CHCl_3$ (5x). The organic layer was dried over $MgSO_4$ and evaporated, yielding 52 mg (50%) of **12a**, m.p. (isopropanol/diisopropylether) 125–126°. IR($CHCl_3$): 3500 (OH); 1360 and 1160 (Ts). ^{1}H NMR ($CDCl_3$): 3.90 (m, $W_{1/2}$ = 20 Hz, H_7ax); 3.65 (d, N–CH_2eq); 2.45 (d, N–CH_2ax). (Found: C, 60.8; H, 7.3; N, 4.9; S, 10.8. Calc. $C_{15}H_{21}O_3N_1S_1$ (M = 295.39): C, 61.00; H, 7.19; N, 4.74; S, 10.84%). The acid waterlayer was evaporated and the residue was purified via ion exchange (IRA 400), yielding: 20 mg (41%) of amine **15**. ^{1}H NMR (D_2O): 4.20 ($W_{1/2}$ = 10 Hz, H_7eq); 3.25 (s, N–CH_2); 2.25–1.75 (8 H). Mass measurement 141.1150, confirming $C_8H_{15}O_1N_1$.

N - Ts - 3 - *Aza* - 7 - *hydroxy* - *bicyclo*[3.3.1]*nonane* **12b** *and* N - Ts - 3 - *azabicyclo*[3.3.1]*non* - 6 - *ene* **20**. **27** (1.7 g, 5.26 mmol) and $Pb(OAc)_4$ (3 g, 6.8 mmol) were heated under reflux in C_6H_6 (76 ml) and pyridine (2.16 ml) for 7 hr. After filtration, the soln was washed with 10% $Na_2S_2O_3$aq, 2N HCl, sat $NaHCO_3$aq, dried over Na_2SO_4 and evaporated, yield: 1.23 g. The oil was treated for 16 hr with a 3% KOH soln in MeOH (50 ml) and water (10 ml). 2N HCl was added till pH = 7, MeOH was evaporated and the water layer was extracted with $CHCl_3$. The organic soln was dried over Na_2SO_4 and evaporated. Column chromatography (silicagel) of the oil with EtOAc/cyclohexane (1/1) yielded 3 products: 229 mg (16%) of **20**, 100 mg (6%) of **27** and 730 mg (47%) of **12b**.

Compound **12b**. M.p. (benzene) 145–147°. IR($CHCl_3$): 3500 (OH); 1360 and 1160 (Ts). ^{1}H NMR ($CDCl_3$): 4.89 ($W_{1/2}$ = 20 Hz, H_7ax); 3.74 (d, N–CH_2eq); 2.40 (N–CH_2ax). (Found: C, 61.1; H, 7.1; N, 4.7; S, 10.7. Calc. $C_{15}H_{21}O_3N_1S_1$ (M = 295.39): C, 61.00; H, 7.17; N, 4.74; S, 10.84%).

Compound **20**. M.p. (isopropanol) 95–97°. IR($CHCl_3$) 1340 and 1160 (Ts). ^{1}H NMR ($CDCl_3$): 5.78 (t, H–C=C–H); 3.61 (N–CH_2eq); 2.48 (N–CH_2ax). (Found: C, 65.1; H, 6.8; N, 5.0; S, 11.7. Calc. $C_{15}H_{19}O_2N_1S_1$ (M = 277.37): C, 64.96; H, 6.91; N, 5.05; S, 11.54%).

7 - *Hydroxy* - 9 - *oxo* - 3 - *azabicyclo*[3.3.1]*nonane* **13**. **8** (176 mg, 0.5 mmol) in THF (20 ml) was added dropwise to LAH (70 mg, 1.75 mmol) in THF (20 ml) and the soln was stirred for 16 hr at r.t. EtOAc and Na_2SO_4aq were added dropwise. After filtration the solvent was evaporated, 2N HCl was added and the soln washed with $CHCl_3$ (5x). The acid waterlayer was evaporated and the residue was purified via ion exchange (IRA 400), yielding 43 mg (55%) of **13**. ^{1}H NMR (D_2O) (HCl salt): 4.20 (t, $W_{1/2}$ = 8 Hz, H_7-eq); 3.40 (AB, N–CH_2); 2.40 (A_2B_2, $H_{6,8}$); 2.20 (s, $H_{1,5}$). Mass measurement 155.0931, confirming $C_8H_{13}O_2N_1$.

N - Ts - 3 - *Aza* - 7 - *hydroxy* - 9,9 - *dimethoxy* - *bicyclo*[3.3.1]*nonane* **14**. **8** (100 mg, 0.20 mmol) in THF (15 ml) was added dropwise to LAH (38 mg, 1 mmol) in THF (10 ml) at −20°. After 40 hr at −20° EtOAc, sat Na_2SO_4aq was added, the soln was filtered and evaporated. The residue was dissolved in $CHCl_3$ and the soln washed with 2N HCl, sat $NaHCO_3$aq, dried over $MgSO_4$ and evaporated. Yield: 100 mg (99%) of **14**, m.p. (EtOAc/pentane) 177–179°. IR($CHCl_3$): 3500 (OH); 1160 (Ts). ^{1}H NMR ($CDCl_3$): 3.83 ($W_{1/2}$ = 15 Hz, H_7ax); 3.50 (d, N–CH_2eq); 3.10 and 2.99 (s, OMe); 2.75 (d, N–CH_2ax). (Found: C, 57.3; H, 7.0; N, 3.8; S, 8.9. Calc. $C_{17}H_{25}O_5N_1S_1$ (M = 355.44): C, 57.45; H, 7.09; N, 3.94; S, 9.00%).

Methyl N - Ts - 3 - *aza* - 9,9 - *dimethoxy* - *bicyclo*[3.3.1]*nonane* - 7 - *ylideneacetate* **16**. Trimethylphosphonoacetate (1.365 g, 7.5 mmol) in THF (10 ml) was added dropwise with stirring to a slurry of 55% NaH (330 mg, 7.5 mmol) in THF (10 ml). After 1 hr **8** (530 mg, 1.5 mmol) in THF (30 ml) was added dropwise and the soln was stirred for 5 days at 50–60°. Water was added, THF evaporated and the soln extracted with $CHCl_3$. The organic layers were dried over Na_2SO_4 and evaporated. Column chromatography (silicagel) with EtOAc/cyclohexane (1/1) yielded 20 mg (3%) of **16**, m.p. (EtOAc/cyclohexane) 184–187°. IR($CHCl_3$): 1705 (C=O); 1640 (C=C); 1160 (Ts). ^{1}H NMR ($CDCl_3$): 5.59 (C=CH); 3.72 (s, OMe); 3.50 (N–CH_2eq); 3.14 and 3.05 (s, OMe); 2.75 (d, N–CH_2ax). (Found: C, 58.7; H, 6.7; N, 3.2; S, 7.8. Calc. $C_{20}H_{27}O_6N_1S_1$ (M = 409.48): C, 58.67; H, 6.65; N, 3.42; S, 7.82%).

Methyl N - Ts - 3 - *azabicyclo*[3.3.1]*nonane* - 7 - *ylideneacetate* **17**. Trimethylphosphonoacetate (1.365 g, 7.5 mmol) in THF (10 ml) was added dropwise with stirring to a slurry of 55% NaH (330 mg, 7.5 mmol) in THF (10 ml). After 1 hr **11** (440 mg, 1.5 mmol) in THF (20 ml) was added dropwise and the soln was stirred for 5 days at 50–60°. Water was added, THF evaporated and the soln extracted with $CHCl_3$. The organic layers were dried over Na_2SO_4 and evaporated. Column chromatography (silicagel) with EtOAc/cyclohexane (1/1) yielded 78 mg (15%) of **17** and 310 mg (70%) of **11**.

Compound **17**. M.p. (EtOAc/cyclohexane) 112–115°. IR($CHCl_3$): 1710 (C=O); 1650 (C=C); 1150 (Ts). ^{1}H NMR ($CDCl_3$): 5.60 (C=CH); 3.70 (N–CH_2eq); 3.66 (s, OMe); 2.50 (N–CH_2ax). (Found: C, 61.8; H, 6.8; N, 4.0: S, 9.3. Calc. $C_{18}H_{23}O_4N_1S_1$ (M = 349.43): C, 61.88; H, 6.64; N, 4.01; S, 9.16%).

N - Ts - 3 - *Aza* - 7 - *tosylhydrazone* - 9,9 - *dimethoxy* - *bicyclo*[3.3.1]*nonane* **18**. **8** (176 mg, 0.5 mmol) and tosylhydrazide (186 mg, 1 mmol) were stirred for 60 hr at 60° in MeOH (20 ml). After 24 hr tosylhydrazide (186 mg, 1 mmol) was added. The solvent was evaporated and the residue dissolved in $CHCl_3$. The $CHCl_3$ soln was washed with 2N HCl (3x), sat $NaHCO_3$aq, dried over $MgSO_4$ and evaporated. Column chromatography (silicagel) with EtOAc/cyclohexane (2/1) yielded 195 mg (75%) of **18**, m.p. (MeOH) 191–193°. IR($CHCl_3$): 1360 and 1160 (Ts). ^{1}H NMR (CD_3OD/DMSO-d_6): 3.40 (d, N–CH_2eq); 3.13 and 3.05 (s, OMe); 2.70 (N–CH_2ax); 2.43 and 2.39 (s, $CH_3C_6H_5$). (Found: C, 55.4; H, 6.0; N, 8.1; S, 12.1. Calc. $C_{24}H_{31}O_6N_3S_2$ (M = 521.63): C, 55.27; H, 5.99; N, 8.06; S, 12.27%).

N - Ts - 3 - *Aza* - 7 - *tosylhydrazone* - *bicyclo*[3.3.1]*nonane* **19**. **11** (146 mg, 0.5 mmol) and tosylhydrazide (186 mg, 1 mmol) were stirred for 60 hr at 60° in MeOH (20 ml). The solvent was evaporated and the residue dissolved in $CHCl_3$. The organic soln was washed with 2N HCl (3x), sat $NaHCO_3$aq, dried over $MgSO_4$ and evaporated, yield: 165 mg (72%) of **19**, m.p. (MeOH) 228–230°. IR($CHCl_3$): 1360 and 1160 (Ts). ^{1}H NMR (DMSO-d_6): 3.40 (d, N–CH_2eq); 2.36 and 2.31 (s, $CH_3C_6H_5$). (Found: C, 57.1; H, 5.7; N, 9.0; S, 13.9. Calc. $C_{22}H_{27}O_4N_3S_2$ (M = 461.58): C, 57.26; H, 5.90; N, 9.11; S, 13.87).

N - Ts - 3 - *Aza* - 7 - *carboxy* - 9 - *oxo* - *bicyclo*[3.3.1]*nonane* **21**[10] was prepared as described.

N - Ts - 3 - *Aza* - 7 - *chloro* - 9 - *oxo* - *bicyclo*[3.3.1]*nonane* **22**. $Pb(OAc)_4$ (8.85 g, 20 mmol) was added under N_2 to **21** (5.05 g, 15 mmol) in C_6H_6 (150 ml). The mixture was stirred at r.t. until homogeneous LiCl (635 mg, 15 mmol) was added and the mixture was immediately flushed with N_2. The mixture was placed in an oil bath (81°). After 3 hr the soln was cooled, filtered and washed with 10% $Na_2S_2O_3$aq, sat $NaHCO_3$aq, dried over $MgSO_4$ and evaporated, yield: 2.94 g (60%) of **22**, m.p. (EtOAc/pentane) 170–172°. IR($CHCl_3$): 1730 (C=O); 1360 and 1160 (Ts). ^{1}H NMR ($CDCl_3$): 5.43 ($W_{1/2}$ = 22 Hz, H_7ax); 4.08 (d, N–CH_2eq); 2.70 (N–CH_2ax). (Found: C, 55.1; H, 5.6; N, 4.2; S, 9.6; Cl, 10.7. Calc. $C_{15}H_{18}O_3N_1S_1Cl_1$ (M = 327.82): C, 54.95; H, 5.53; N, 4.27; S, 9.78; Cl, 10.82%).

N - Ts - 3 - *Aza* - 9 - *oxo* - *bicyclo*[3.3.1]*non* - 6 - *ene* - **23** *and* N - Ts - 3 - *aza* - 7 - *acetoxy* - 9 - *oxo* - *bicyclo*[3.3.1]*nonane* **24**. A soln of **21** (2 g, 6 mmol), $Pb(OAc)_4$ (6 g, 13.6 mmol) and pyridine (2 ml) in C_6H_6 (76 ml) was heated at reflux for 7 hr. The soln was cooled, filtered and washed with 10% $Na_2S_2O_3$aq, 2N HCl, sat $NaHCO_3$aq, dried over $MgSO_4$ and evaporated.

Column chromatography (silicagel) of the oil (1 g) with EtOAc/cyclohexane (2/1) yielded 240 mg (14%) of **23**, m.p. (i-PrOH) 143–145° and 380 mg (18%) of **24**, m.p. (i-PrOH) 214–216°.

Compound **23**. IR($CHCl_3$): 1725 (C=O); 1650 (C=C); 1360 and 1160 (Ts). ^{1}H NMR ($CDCl_3$): 5.98 and 5.64 (m, C=CH); 3.97 (N–CH_2eq); 2.80 (N–CH_2ax). (Found: C, 61.8; H, 6.0; N, 4.7; S, 11.1. Calc. $C_{15}H_{17}O_3N_1S_1$ (M = 291.35): C, 61.85; H, 5.88; N, 4.81; S, 10.98%).

Compound **24**. IR($CHCl_3$): 1720 (C=O); 1350 and 1160 (Ts). ^{1}H NMR ($CDCl_3$): 5.92 ($W_{1/2}$ = 19 Hz, H_7ax); 4.01 (d, N–CH_2eq); 2.75 (d, N–CH_2ax); 2.02 (s, $MeCO_2$). (Found: C, 58.0; H, 6.0; N, 3.9; S, 9.2. Calc. $C_{17}H_{21}O_5N_1S_1$ (M = 351.41): C, 58.11; H, 6.02; N, 3.99; S, 9.10%).

N - Ts - 3 - *Aza* - 7 - *hydroxy* - 9 - *oxo* - *bicyclo*[3.3.1]*nonanes* **25a** + **25b**. **24** (380 mg; 1.08 mmol) was treated with 3% KOH in MeOH (50 ml) and water (10 ml) for 16 hr. 2N HCl was added till pH = 7, MeOH evaporated and the soln was extracted with $CHCl_3$. The $CHCl_3$ soln was dried over $MgSO_4$ and evaporated,

yield: 300 mg (90%) of **25a** + **25b**, m.p. (benzene) 170–173°. IR($CHCl_3$): 3500 (OH); 1730 (C=O); 1340 and 1160 (Ts). ^{1}H NMR ($CDCl_3$): 5.06 ($W_{1/2}$ = 20 Hz, H_7ax of **25b**); 4.24 ($W_{1/2}$ = 10 Hz, H_7eq of **25a**); 4.00 (d, N–CH_2eq of **25b**); 3.67 (d, N–CH_2eq of **25a**); 2.70 (d, N–CH_2ax). (Found: C, 58.3; H, 6.3; N, 4.5; S, 10.5. Calc. $C_{15}H_{19}O_4N_1S_1$ (M = 309.37): C, 58.24; H, 6.19; N, 4.53; S, 10.35%).

N - Ts - 3 - *Aza* - 7 - *carboethoxy* - *bicyclo*[3.3.1]*nonane* **26**[10] was obtained as described.

N - Ts - 3 - *Aza* - 7 - *carboxy* - *bicyclo*[3.3.1]*nonane* **27**[10] was obtained as described.

N - Ts - 3 - *Aza* - 7 - *hydroxy* - 9 - *oxo* - *bicyclo*[3.3.1]*nonane* **28**. **14** (170 mg, 0.48 mmol) was heated at reflux 3 hr in 2N HCl (15 ml) and MeOH (15 ml). MeOH was evaporated and the waterlayer extracted with $CHCl_3$. The organic soln was washed with sat $NaHCO_3$aq, dried over Na_2SO_4 and evaporated, yield: 140 mg (94%) of **28**, m.p. (EtOAc) 220–223°. IR($CHCl_3$): 3500 (OH); 1730 (C=O); 1160 (Ts). ^{1}H NMR (C_5D_5N): 4.00 (d, N–CH_2eq); 3.80 ($W_{1/2}$ = 20 Hz, H_7ax); 2.63 (d, N–CH_2ax). (Found: C, 58.3; H, 6.3; N, 4.5; S, 10.4. Calc. $C_{15}H_{19}O_4N_1S_1$ (M = 309.37): C, 58.24; H, 6.19; N, 4.53; S, 10.35%).

REFERENCES

[1]A. W. J. D. Dekkers, J. W. Verhoeven and W. N. Speckamp, *Tetrahedron* **29**, 1691 (1973).
[2]W. N. Speckamp, J. Dijkink and H. O. Huisman, *Chem. Commun.* 197 (1970).
[3]H. Stetter, K. Rämsch and K. Elfert, *Liebigs Ann.* 1322 (1974).
[4]C. van Lenten, unpublished results.
[5]T. Momose, S. Atarashi and O. Muraoka, *Tetrahedron Letters* 3697 (1974).
[6]Th. Reints Bok and W. N. Speckamp, *Tetrahedron* **33**, 787 (1977).
[7]R. T. Wall, *Ibid.* **26**, 2107 (1970).
[8]R. Loven, Ph.D. Thesis, University of Amsterdam (1973).
[9]P. C. Traas, H. Boelens and H. J. Takken, *Tetrahedron Letters* 2287 (1976).
[10]W. N. Speckamp, J. Dijkink, A. W. J. D. Dekkers and H. O. Huisman, *Tetrahedron* **27**, 3143 (1971).
[11]Th. Reints Bok and W. N. Speckamp, *Tetrahedron Letters* 657 (1978).
[12]Th. Reints Bok, H. van Oosterhout and W. N. Speckamp, to be published.