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SYNTHESIS OF SUBSTITUTED 3-AZA-BICYCLO[3.3.1]NONANES*

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Abstract—The synthesis of 3-azabicyclo[3.3.1]nonanes is described via the addition of α-bromomethylacrylate **1** to N-tosylpiperidone enamine **4** and subsequent transformation of these adducts. A brief discussion is given on some mechanistic aspects of the addition. NMR-investigation of the various compounds showed a fair correlation between structure and conformation of the adducts and the observed chemical shifts of C<u>H</u>-COOR and N-C<u>H</u>$_2$ protons.

ALTHOUGH several 3-aza-bicyclo[3.3.1]nonanes have been synthesized[1] and some of the chemical[2] and conformational[3] properties studied, knowledge of the specific influence which the introduction of a nitrogen atom in reactions of these and similar systems must have is still rather restricted. This is in sharp contradiction with the vast amount of information on the properties of the bicyclo[3.3.1]nonane itself, which serves as a substrate for a variety of reactions among which the bridgehead alkenes,[4] hydride migrations,[5] carbene[6] and photochemical reactions[7] are of great current interest.

In the course of our work on the steric[8] and electronic[9] influence of the sulfonamide moiety in some base-catalyzed condensation reactions of piperidones and quinolones, it became of interest to synthesize a number of N-tosyl-3-aza-bicyclo[3.3.1]nonanes and to examine some of the reactions connected with these systems. As a second objective could conceivably follow the conversion of 3-aza-bicyclo[3.3.1]nonanes into 1-aza-adamantanes, systems for which a great variety of application might be considered, both as a useful model in estimating the influence of the nitrogen atom on some of the carbonium[10] and radical[11] reactions, well known in adamantane itself, as well as introducing a novel heterocyclic ring system in the synthesis of compounds of possible biological interest.

The procedure selected for the synthesis of 3-aza-bicyclo[3.3.1]nonanes was the α,α′-annelation[12] of cyclic ketones, in which an alkyl α-bromomethylacrylate **1**[13] or its precursor the corresponding β,β′-dibromoisobutyrate **2**[14] is condensed with the enamine of a N-arylsulfonyl-piperidone§.

N-Tosylpiperidone **3**, for which the preparation was considerably improved via the acetic anhydride-pyridine cyclization[15] of N-tosyl-(β,β′-dicarboxyethyl)-amine,

* A preliminary communication of this work has appeared. *cf* ref. 22.

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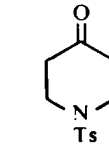
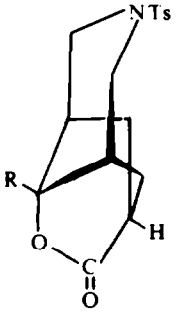
‡ Part of the forthcoming thesis of A. W. J. D. Dekkers, University of Amsterdam.

§ A number of sulfonyl-piperidone enamines, e.g. N-*p*-toluene, N-Ph- and N-methylsulfonyl compounds have been annelated, and were found to give more or less comparable results. Only those of the first series will be reported here.

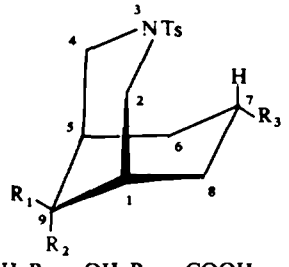
which in turn was prepared by HCl–EtOH treatment of N-tosyl-(β,β′-dicyanoethyl)-amine, was converted in high yield to the pyrrolidine enamine **4** (δ($CDCl_3$) 4·07 = C<u>H</u>) in the usual manner. Reaction of enamine **4** with bromoester **1** in MeCN gave rise to predominant formation of the α-alkylation product **5**, which was also obtained as the major product when EtOH was used as a cosolvent. The alkylation product **5** could not be cyclized to the bicyclic system **6** under alkaline conditions or by repeated treatment with pyrrolidine.



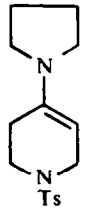
3 R = H
5 R = CH_2—C(COOEt)=CH_2



11 R = H
14 R = Me



18 R_1 = H R_2 = OH R_3 = COOH
19 R_1 = OH R_2 = H R_3 = COOH
32 R_1R_2 = (—$S(CH_2)_2S$—) R_3 = COOH
33 R_1 = R_2 = H R_3 = COOH



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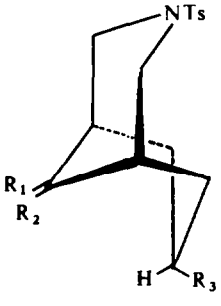
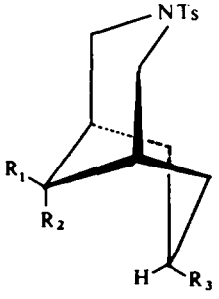
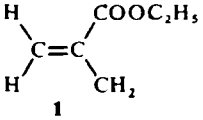


6 R_1R_2 = O R_3 = COOEt
22 R_1R_2 = (—SCH_2—CH_2S—)R_3 = COOEt
24 R_1R_2 = NOH_1R_3 = COOEt
29 R_1R_2 = O R_3 = $CON(C_2H_5)_2$
31 R_1R_2 = O R_3 = COOH



7 R_1 = H R_2 = OH R_3 = COOEt
8 R_1 = OH R_2 = H R_3 = COOEt
9 R_1 = H R_2 = OAc R_3 = COOEt
10 R_1 = OAc R_2 = H R_3 = COOEt
12 R_1 = Me R_2 = OH R_3 = COOH
13 R_1 = Me R_2 = OH R_3 = COOMe
15 R_1 = Ph R_2 = OH R_3 = COOH
16 R_1 = OMe R_2 = PH R_3 = COOMe
17 R_1 = H R_2 = OH R_3 = COOH
20 R_1 = H R_2 = OAc R_3 = COOH
21 R_1 = R_2 = —OCH_2CH_2Cl R_3 = COOEt
23 R_1 = R_2 = H R_3 = COOEt
25 R_1 = NH_2 R_3 = COOEt
26 R_1 = H R_2 = OH R_3 = CH_2OH
27 R_1 = R_2 = H R_3 = CH_2OH
28 R_1 = NH_2 R_2 = H R_3 = CH_2OH
30 R_1 = R_2 = H R_3 = CHO



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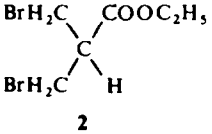

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On the contrary, when the reaction was carried out via addition of the bromoester **1** in EtOH to a refluxing solution of enamine **4** in MeCN the N-tosyl-3-aza-bicyclo [3.3.1]nonane **6** was produced in 58% yield. Alternatively, reaction of enamine **4** and dibromoester **2** in MeCN to which 2·2 eq. of Et_3N was added, gave the ring-closed product **6** in 80% yield.* In this reaction the use of EtOH as a cosolvent lowered the yield of **6** considerably. presumably because of prior HBr-elimination from the ester before cyclization.

Recent information on this type of enamine-addition in the carbocyclic series[16] indicates a preferred reaction pathway: alkylation, followed by isomerization of the intermediate imminium salt to the enamine and subsequent cyclization via Michael-addition. which in view of the necessary protonation in the last step always leads to the formation of the *endo*-adduct.[17] The experimental evidence in heterocycles. however, points to at least two mechanisms being operative, their difference being found in the amount of tertiary amine necessary to complete the reaction.

A rationale for the observed experimental differences could be the following: while it is generally accepted that the addition of an electron deficient species to monocyclic enamines leads to a chairlike imminium form,[18] incidental reports have suggested also other possible conformations[19] for this intermediate. Unfortunately. a major problem in the ascertainment of the stereochemical course in the formation of bicyclo[3.3.1]nonanes is the lack of knowledge about the actual shape of substituted derivatives (*vide infra*). When it is supposed that the crucial step in this addition is the establishment of an imminium ⇌ enamine equilibrium, conformational factors may have a strong influence on the position of this equilibrium. In this respect the influence of the N-tosyl function might favor the imminium form.† Even more important is the fact that a boatlike form for the imminium structure could be strongly favored via secondary attractive forces between the electronrich sulfonyl-group and the electron deficient imminium centre.‡ This extra stabilization of the imminium form will render spontaneous loss of a proton and concomitant double bond isomerization more difficult, unless proton abstraction could be facilitated via the help of a proton-acceptor.[20] When acrylate **1** adds in a Michael way, the carbanion could act as such a species. Upon alkylation as the first step, however, the use of an external base will be necessary to accomplish the proton transfer. Therefore the dissimilarity in behaviour between esters **1** and **2** upon addition to enamine **4** can be rationalized in terms of a different addition step, (Fig 1 where the structures of the two adducts I and II are given).

In intermediate I the carbanion abstracts a proton from the α′-position with back formation of an enamine. In adduct II enamine isomerization does not occur via internal proton abstraction and has to be accomplished by external base.§ Presumably, after loss of HBr in the first route, in both cases the following steps, ie

* In large-scale preparations an average yield of 67% was obtained in crystallization of the crude reaction mixture. Chromatography of the mother liquor afforded an additional crop of **6** (13%).

† Conformational studies of 4-substituted N-tosylpiperidines show a preference for boatlike structures in these compounds, P. P. M. Rijsenbrij and W. N. Speckamp, to be published.

‡ A similar role of the oxygen atoms of a sulfongroup has been suggested in the reaction of enamines with vinylsulfones.[21]

§ In the mesaconate series the use of Et_3N was also shown to be necessary. A. W. J. D. Dekkers, to be published.

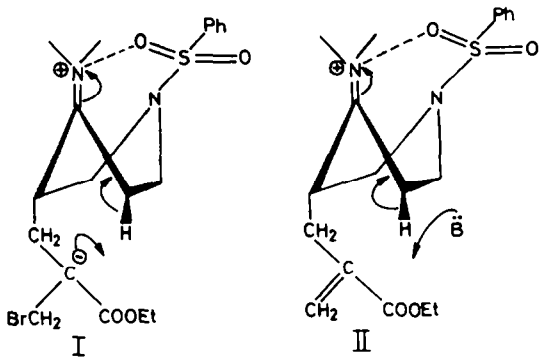


FIG 1

Michael addition and C_7-*endo*-protonation of the resulting bicycloadduct, are the same. An earlier suggestion according[22] to which a stereochemically directed alkylation of the intermediate enamine was supposed to be responsible for the observed *endo*-selectivity could not be proven.

To obtain additional information about the reactivity and conformation of 3-aza-bicyclo[3.3.1]nonanes a series of conversions of adduct **6** were carried out. On treatment of **6** with $NaBH_4$ the hydroxyesters **7** and **8** were formed in a ratio of 85:15. The major isomer could be purified via fractional crystallization, after which a further separation was effected by acetylation of the remaining mixture to the acetoxy-esters **9** and **10**. The *endo*-position of the ester function was proven in the ultimate conversion of **7** into 4-hydroxy-1-aza-adamantane. The *anti**-configuration of the C_9-OH group follows from the easy lactonization giving lactone **11** upon base-catalyzed isomerization of ester **7**. The second isomer **8** should have necessarily a C_9 *syn*-OH function.

The large preference in the $NaBH_4$ reduction[23] for a *syn*-attack reflects the presence of a sterical barrier in the molecule, most likely a boatform for ring B.* Further evidence, in line with the proposed reduction course, is obtained via the Grignard additions of **6** to MeMgBr and PhMgBr. In the first reaction the C_9-methyl-hydroxy acid **12** was formed which after esterification gave the ester **13**. Isomerization (Na–EtOH) produced the Me-lactone **14**, which confirms the predominant formation of the C_9-*anti*-OH compound, no evidence being found for the presence of the *syn*-isomer. The corresponding C_9-Ph-OH acid **15** could also be esterified, however, it was simultaneously converted to the isomeric Me-ether **16** upon treatment with CH_3OH—HCl, presumably via H^+ catalyzed isomerization of the Ph-substituent. Both Grignard-reactions are congruent with preferred *syn*-approach of the reagent. The facile isomerization of the C_9-Ph group is understandable in view of the severe 1,3-diaxial interactions in the piperidine chair, which are relieved upon isomerization. The possible 1,4 interaction in the boat form of the carbocyclic part is more easily removed by alteration of this ring into a twist-boat.

Of the four possible hydroxy-acids three could be obtained in crystalline state. Acid hydrolysis of **7** gave **17**, while KOH-ring opening of the lactone **11** produced

* With respect to the piperidine ring *anti* and *syn* prefixes are used for substituents at the C_9-bridge carbon atom. The piperidine part and the carbocyclic part are denoted respectively as ring A.

the second isomer **18**. The third one **19** was obtained on NaOEt treatment of keto-ester **6**. The latter reaction gave a mixture of lactone **11** and acid **19** thus demonstrating a facile hydride transfer from both sides of the C_9 bridge. Because of the concomitant ester isomerization the *syn*-attack is no longer preferred, provided both halves of the molecule are in a chair conformation. This evidence is the first indication for the geometrical form of the molecule after base-catalyzed isomerization of the ester-function.

Another series of experiments was carried out to investigate the introduction of different substituents at C_9. Catalytic hydrogenation (H_2/Pt/AcOH) did not affect the C_9-carbonyl, which was also unreactive towards ketalization. Appliation of the recently developed method for sterically hindered ketones[24] did give the dichloro-ether **21**. Treatment with $BF_3/(CH_2SH)_2$ afforded the thioketal **22** which was smoothly desulfurized (Ra–Ni) to the methylene ester **23**. Via reaction with H_2NOH–HCl the oxim **24** was obtained which, contrary to the ketone **6**, could be reduced catalytically to the amine **25**.

Finally, transformations of some of the aforementioned esters were carried out, in order to obtain the necessary starting materials for the synthesis of 1-aza-adamantanes. $LiAlH_4$-reduction* of hydroxyester **7** gave diol **26** in moderate yield, presumably as a result of secondary N–Ts cleavage. In the same manner the esters **23** and **25** were reduced to alcohols **27** and **28**. Keto-amide **29** and aldehyde **30** were prepared via the usual pathways: the first compound upon treatment of the acid chloride of **31** with Et_2NH, **31** being obtained upon HCl–AcOH hydrolysis of ester **6**; DMSO/DCC oxidation of alcohol **27** gave aldehyde **30**.

Spectral analysis

To elucidate or confirm the stereochemistry of the different adducts an extensive NMR-analysis was carried out, the results of which are given in Table 1.

Prior to a discussion of the data reported herein, some remarks on the role of the solvent have to be made. The varying solubilities of the different compounds necessitated the use of $CDCl_3$ and C_5D_5N, of which the latter solvent is known to induce variations in chemical shift. From compounds **6**, **10**, **11**, **22**, **23** and **33** a C_5D_5N (respectively $CDCl_3$) spectrum was also taken, the results of which, given in the Experimental, are fully comparable with the data from Table 1. The absence of significant solvent effects therefore allows the comparison of spectra taken in different solvents insofar the absorptions reported in Table 1 are under consideration. From these data several points of interest both about the configuration of the different substituents as well as the conformation of rings A and B can be taken. Two important areas which are of value for discussion are δ 2–3, covering most of the protons present in the system and δ 3–5, which part protons connected to a heteroatom, or an electron-attracting group are found.

$N—CH_2$

The N-methylene protons in the rigid 3-aza-bicyclo[3.3.1]nona system constitute an AA'BB' system, in which the low-field A part comprises the equatorial protons

* A complicating factor in some of these reactions was the competing hydrolysis or reductive removal of the N-Ts group, which rendered the use of hydride donors in higher boiling solvents (THF, dioxane) undesirable.

TABLE 1. NUCLEAR MAGNETIC RESONANCE SPECTRA OF 3-AZA-BICYCLO[3.3.1]NONANES

Compound	Solvent[a]	Chemical shift in ppm					
		$H_{2,4}$ ax	$H_{2,4}$ eq	H_7	H_9-*anti*	H_9-*syn.*	Δ^b
6	C	2·4–2·8[c]	3·96	2·6	—	—	1·2–1·6
7	P	2·41	3·87	2·83	—	3·58	1·46
8	P	3·10	3·68	2·5–2·9	3·80	—	0·58
9	C	2·3–2·7	3·77	2·5–3·0	—	4·44	1·1–1·5
10	C	2·4–2·9	3·54	2·4–2·9	4·68	—	0·6–1·1
11	C	1·9–2·4	3·72	2·64	—	4·13	1·3–1·8
13	C	2·3–2·7	3·65	2·3–2·7	—	–	1·0–1·4
14	C	2·54	3·64	2·65	—	—	1·10
15	P	2·17	3·97	2·5–3·1	—	—	1·80
16	C	2·94	3·61	2·4–2·7	—	—	0·67
17	P	2·46	4·00	3·12[d]	—	3·63	1·54
18	P	3·14	4·03	3·9–4·3	—	3·76	0·89
19	P	3·34	3·85	4·12[e]	3·96	—	0·51
20	C	2·50	3·82	2·65	4·47	—	1·32
22	C	2·7–3·0	3·72	2·3–2·9	—	—	0·7–1·0
23	C	2·26	3·68	2·3–2·7	1·58	1·17[f]	1·42
24	P	2·3–2·7	3·92	2·81	—	—	1·2–1·4
25	C	2·5–2·9	3·44	2·5–2·9	—	2·5–2·9	0·5–0·9
29	C	2·69	3·92	2·1–2·7	—	—	1·23
30	C	2·29	3·66	—	—	--	1·37
31	P	2·5–2·9	4·06	2·5–2·9	—	—	1·1–1·5
32	P	3·22	4·08	3·9–4·2	—	—	0·86
33	P	2·51	3·92	3·96	1·49	1·22	1·41

[a] C = $CDCl_3$, P = C_5D_5N

[b] $\Delta = \Delta(\delta H_{2,4\,eq} - \delta H_{2,4\,ax})$

[c] In a number of spectra the signals of the indicated protons are obscured by other absorptions. In such a case the probable region is given.

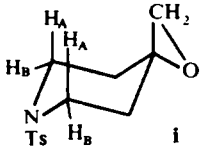
[d] Broadened septet. width 30 cps.

[e] Broadened signal. width 30 cps.

[f] Assigned on the basis of decoupling experiments.

and the high-field B part the axial ones. The equatorial protons which are in the N—S=O plane are shifted downfield considerably as a result of the deshielding of the S=O functions.* Thus the equatorial protons are found between δ 3·5–4·0, while the axial ones absorb around δ 2·5–3·5, leading to a difference Δ of 0·5–1·4 for the two halves of the AA'BB' system. The variation in Δ is an important criterium in the

* In the 2-substituted N-tosyl piperidine series similar deshielding effects were established. (P. P. M. Rijsenbrij. to be published). Furthermore a complete analysis of the spectrum of i showed $\Delta\delta H_B - \delta H_A$ as 0·64 p.p.m. The splitting pattern evidenced the equatorial position for H_B.



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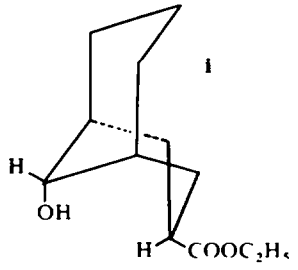

i

assignment of the stereochemistry. Similar deshielding effects are known in the spectra of N-acylpiperidines, and are attributed to a hindered rotation around the N—C bond.[25] In view of the presence of two symmetrical N—S═O moieties no time-dependent variations are expected for rigid N-sulfonyl compounds.

CHCOOR

For this proton, which occasionally is separately visible, variable δ values are found which could be correlated with conformational features. Mostly the absorptions are at higher field ($\delta < 3$).

DISCUSSION

Possible conformations for bicyclo[3.3.1]nonanes include twin-chair, boat-chair and twin-boat forms.* In general the twin-chair is preferred when the C_3—C_7 interactions are of the hydrogen type[26] or if one or both C_3—C_7 methylenes are replaced by N—H or N—CH_3 groups.[27] Also beyond doubt is the fact that substitution of one of the C_3—C_7 *endo*-hydrogens results in raising the conformational energy of the twin-chair, thus the boat-chair being favoured,[28] although novel experimental results indicate the existence of conformational mobility in bicyclo[3.3.1]nonanes.[29] The *endo*-C_7-ester function in the adducts not equilibrated by base treatment is most likely in the equatorial position with the boatform for ring B. The corresponding H_3 absorption in these compounds is generally found at δ 2·3–2·9. Unfortunately the splitting pattern cannot always be identified because of overlap with other signals. In the spectra of ester **7** (Fig 2) and acid **17**, however, separate H_7-absorptions are

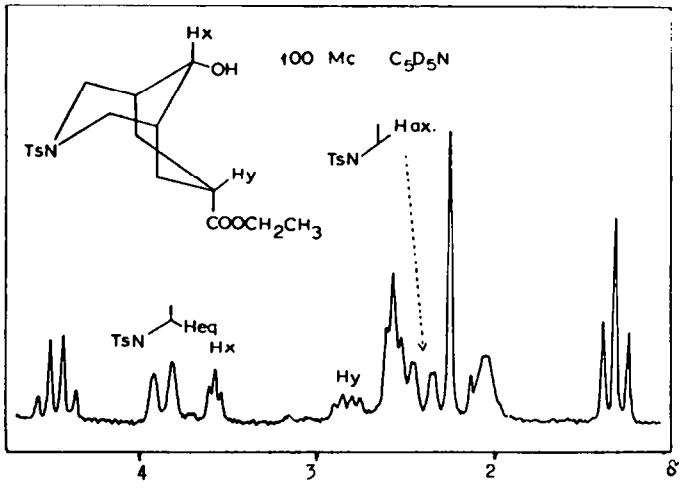

FIG 2

* Deviations from the ideal representations will be ignored in the discussion, although one must bear in mind that in most cases twist boat-forms or flattened chair-forms will more conform to the actual shape of the molecule.

found; a multiplet (width ≈ 28 c/s) for ester **7**† and a broadened septet (width ≈ 30 c/s) for acid **17**. The latter values correspond to similar lineshapes in the NMR spectra of *endo*-3-OH-bicyclo[3.3.1]nonanes[30] and *endo*-3-carbethoxy-bicyclo[3.3.1] nonane, systems which have been shown to exist in the boat-chair conformation.

A second point of interest is the extremely low-field absorption of H_7 in acids **18** and **19**, both resulting from base-catalyzed isomerization experiments. This conspicuous deshielding effect is rationalized by assuming a chair conformation for ring B in which H_7 is situated in the plane of the O═S═O group, symmetrically with respect to the oxygen atoms. This effect accounts well for the observed shift difference and can be used as a characteristic for all N-arylsulfonyl-3-aza-bicyclo[3.3.1]nonanes with *exo*-ester substituents in the carbocyclic ring.* Additional proof was taken from base-catalyzed conversion of *endo* esters **22** and **23** into the corresponding *exo*-acids **32** and **33**. Both acids displayed low-field H_7 absorptions.

A third and very important effect is the variation in separation of the N—CH_2 protons in the spectra, (denoted by Δ). The normally observed value of ≈1·4 ppm is greatly changed in the spectra of compounds **8**, **10**, **16**, **19**, **22** and **25**. In this series the substitution at C_9 has occurred from the *anti*-direction leading to *syn*-substituents such as OR, NH_2 and SR functions. With respect to ring A, these should be in axial position, which gives rise to the known 1,3 diaxial deshielding phenomena in cyclohexane-chair compounds.[31] The decreased Δ value thus is indicative for an axial C_9-substituent with respect to ring A†. A second conclusion is the indirect proof for a chairform of ring A in the aforementioned compounds because no axial deshielding effect would be expected in case of a different stereochemistry. For compound **19** the combined evidence thus indicates a twin-chair form, which is substantiated from the analysis of the H_7 splitting pattern, in which the presence of two diaxial J values of ≈12 c/s agree well for a chairform for ring B. For its stereoisomer **18** the lowfield absorption of H_7 corresponds best with a chairform of ring B and—in view of the SO_2 deshielding effect—also with a chairlike ring A.

In conclusion three NMR criteria for the conformational assignments of N-arylsulfonyl-3-aza-bicyclo[3.3.1]nonanes can be summarized: (a) a signalwidth of ~30 c/s and a lineshape as a broadened septet (partly overlapping triplet of triplets) H_7 axial. (b) low field position of H_7 (generally around δ ≈ 4): twin-chair conformation. (c) separation of axial and equatorial RSO_2—N—CH_2 of 0·5–0·7 ppm:

syn substituent at C_9 and a chairform for the piperidine ring. These characteristics also serve in the analysis of other substituted 3-aza-bicyclo[3.3.1]nonanes.

EXPERIMENTAL

All m.ps are uncorrected. Analyses were carried out by Messr. H. Pieters of the Micro-analytical Department of this laboratory. IR and Mass spectra were recorded on Unicam SP 200 and AEI MS3–9 spectrometers, respectively. NMR spectra were measured on a Varian Associates HA-100 instrument.

† For 3-carbethoxy-9-hydroxy-bicyclo[3.3.1]nonane i the H_3 absorption was found at δ 3·25. signalwidth ≈ 30 c/s.

* In the mesaconate series the same observation was made. A. W. J. D. Dekkers, private communication.

† A similar deshielding effect is found in the spectrum[32] of N-methyl-3-aza-syn-9-hydroxy-bicyclo-[3,3,1]nonane.

N-*Ts*-4-*piperidone* (**3**). A: β,β'-*Dicyano diethylamine*. 200 g. (3·77 mol) acrylonitrile were added in 15 min. with stirring. to 150 ml. of 25% NH_4OH. The mixture was stirred at 35° (slight cooling) till it became clear (2½ hr). Water was evaporated and the residue distilled. Yield: 179·45 g (77·2%). B.p.: 132–135/0·2 mm. n_D^{20}: 1·4620. IR (NaCl) C≡N: 2300 cm^{-1}; NH 3400 cm^{-1}.

B: N-*Ts*-β,β'-*dicyanodiethylamine*. To a solution of 80·2 g (0·652 mole) of β,β'-dicyanodiethylamine in dry pyridine (200 ml), was added, in 25 min, dropwise with stirring. 134·2 g. (0·652 mole + 8%) TsCl in benzene (130 ml). The mixture was stirred for 15 min at rt. 30 min at 75° and for 1 min at reflux. After cooling ice (300 g) and conc. HCl (200 ml) were added. The resulting mixture was extracted with $CHCl_3$. Extracts were washed with 1 N HCl, sat. $NaHCO_3$ aq. sat. NaCl aq. evaporation of solvent and recrystallization from EtOAc gave 171·9 g (94·2%) m.p. 105–107° IR ($CHCl_3$) C≡N: 2300 cm^{-1}; Ts: 1160 and 1360 cm^{-1} NMR ($CDCl_3$). δ 7·55 q (4 aromatic H). 3·45 t (4 H. C$\underline{H}_2$-CN). 2·75 t (4 H. C$\underline{H}_2$-N) 2·42 s (—CH_3).

C: N-*Ts*-β,β'-*dicarbomethoxydiethylamine*. 100 g (0·36 mole) of N-Ts-β,β'-dicyanodiethylamine in dry MeOH/HCl (600 ml) (3·6 mole HCl) was stirred and heated at reflux for 3 hr. After cooling. the solid product was collected and washed with MeOH. The filtrate was evaporated and residue neutralized with ice and K_2CO_3. The aqueous solution was extracted with $CHCl_3$. Evaporation of solvent yielded 115·5 g as an oil. (93%) IR ($CHCl_3$). C=O: 1720 cm^{-1}.

D: N-*Ts*-β,β'-*dicarbohydroxydiethylamine*. 24·8 g. (0·0725 mole) of N-Ts-β,β'-dicarbomethoxydiethylamine in THF (80 ml) and 4N HCl (30 ml) was heated at reflux for 4½ hr. The THF was evaporated and the resulting solution extracted with $CHCl_3$. The combined extracts were extracted with a cold 5% NaOH. The alkaline solution was cooled (< 10°) and acidified, yielding 20·1 g (89·7%) of solid. m.p. 171–174°. IR (KBr). COOH: 2500–3500 cm^{-1}; C=O: 1700 cm^{-1}; Ts: 1150 and 1330 cm^{-1}.

N-*Ts*-4-*piperidone* (**3**). 9·33 g. (30 mmole) of N-Ts-β,β'-dicarbohydroxydiethylamine. of Ac_2O (40 ml) and 5·06 ml. (60 mmole + 5%) of dry pyridine were refluxed for 8 hr. Solvents were evaporated and residue dissolved in ½N HCl (20 ml) and refluxed for 1 hr. The solution was neutralised with K_2CO_3. extracted with $CHCl_3$ and combined extracts washed with a 3% aq. K_2CO_3 1N HCl and sat. $NaHCO_3$ aq. Evaporation of solvent and recrystallization from THF/diisopropylether afforded 4·72 g. (62%). m.p.: 128–131°. IR($CHCl_3$). C=O: 1715 cm^{-1}; Ts: 1160 and 1340 cm^{-1}. NMR ($CDCl_3$) δ 7·40 q (4 aromatic H). 3·35 t (4H. C$\underline{H}_2$-C=O). 2·3–2·7 m (7H. including --CH_3 at δ = 2·35).

N-*Ts*-4-*pyrrolidinyl*-1,2,4,5-*tetrahydropyridine* (**4**). 5·57 g of **3** (0·022 mole). 4·69 g. (0·066 mole) of pyrrolidine and 0·2 g. *p*-TsOH in dry C_6H_6 (50 ml) were stirred and heated at reflux in a Dean Stark apparatus. over mol-sieve 3A. for 30 min in N_2. After cooling. the solvent was evaporated and MeOH (50 ml) added. The solid product was collected on a filter in N_2 at. Yield: 96%. m.p.: 132–136°. IR (KBr). C=C—N: 1640 cm^{-1}; Ts: 1160 and 1340 cm^{-1}.

N-*Ts*-3-[3'(2-*carboethoxypropene*-1)]-*piperidone*-4 (**5**). In N_2 5·37 g. (19·6 mmole) of ethyl-β,β'-dibromo-isobutyrate in dry MeCN (20 ml) was added (20 min) dropwise with stirring to 6·02 g. (19·6 mmole) of the enamine **4**. 2·17 g (21·5 mmole) of Et_3N and a trace of hydroquinone in MeCN (50 ml). During the addition the reaction-mixture was slowly heated to reflux for 2·5 hr. The solvent was evaporated and EtOH (50 ml) and H_2O (25 ml) added. The resulting solution was stirred for 1 hr at r.t. EtOH evaporated and to the resulting aqueous solution 2N HCl was added till pH = 1. The solution was extracted with $CHCl_3$ (60 ml). The combined extracts were washed with 1N HCl (10 ml). sat $NaHCO_3$ aq (15 ml) and sat NaCl aq. (15 ml). After evaporation a yellow oil was obtained. Crystallization from EtOAc yielded 0·5 g. (7%) of the keto-ester **6**.

A part of the resulting oil. (3 g) was passed through a column of aluminium oxide with EtOAc/cyclohexane = 2/3 as an eluant. 11 fractions of 25 ml. were collected. Fractions 1 and 2 were ethyl-α-(bromomethyl) acrylate. fractions 3 and 4 yielded 1·36 g of **5** (colourless oil). IR($CHCl_3$). C=O: 1700–1720 cm^{-1}; C=CH: 1625 cm^{-1}. NMR ($CDCl_3$), 7·5 q (4 aromatic H): 6·25 s (=C$\underline{H}$): 5·65 s (=C$\underline{H}$): 4·2 q (O—C$\underline{H}_2$): 2·2–3·9 m (12H): 1·25 t(O—CH_2—C$\underline{H}_3$). Mass: *m/e*: M^+ = 365 (6%); M^+ − Ts = 210 (100%).

Fractions 5 and 6 yielded **5** and some of **3** (NMR). Fractions 7–11, almost completely **3**.

N-*Ts*-3-*aza*-7-*carboethoxy*-9-*oxo*-bicyclo-3.3.1-*nonane* **6**. A: 15·4 g (0·08 mole) of ethyl-α-(bromomethyl) acrylate in EtOH (200 ml) were added in 45 min (N_2) to a refluxing solution of 24·5 g (0·08 mol) of **4** in MeCN (200 ml). containing some hydroquinone.

The mixture was stirred and heated at reflux for 5 hr. solvent evaporated and $EtOH_2$ (50 ml) and H_2O (50 ml) added and the solution stirred for 1 hr. The EtOH was evaporated and the resulting aqueous solution extracted with $CHCl_3$. the chloroform-solution washed with 2N HCl and with sat $NaHCO_3$ aq. Evaporation of solvent yielded 30·2 g crude product. from which pure **6** (55·5%) was obtained (EtOAc mp.: 156–159°. IR (KBr). C=O: 1710 and 1720 cm^{-1}; Ts: 1160 and 1340 cm^{-1}. NMR (C_5D_5N) δ: 4·02.

NCH (eq); 2·3–2·8, NCH_2(ax); 2·3–2·8, C_7-H. (Found: C, 59·03; H, 6·35; N, 4·01; S, 8·80%. $C_{18}H_{23}O_5N_1S_1$ (M = 365·45). Calc.: C, 59·16; H, 6·30; N, 3·83; S, 8·79%).

B: Under N_2, 0·91 g (3·3 mmole) of ethyl-β,β-dibromoisobutyrate in MeCN (5 ml) was added in 20 min dropwise with stirring to 1·02 g (3·3 mmole) of the enamine **4**, 0·73 g (72 mmole) of Et_3N and a trace of hydroquinone in MeCN (10 m). Meanwhile the mixture was slowly heated to reflux, then stirred and heated at reflux for 3·5 hr. solvent evaporated, and H_2O (5 ml) and EtOH (10 ml) added. The resulting solution was stirred for 1 hr at r.t. the solid product collected and washed with ether. Yield 0·6 g. From the filtrate, the EtOH was evaporated and resulting aqueous solution acidified with 2N HCl and extracted with $CHCl_3$. The combined extracts were washed with 1N HCl, sat $NaHCO_3$ aq and sat NaCl aq. Evaporation of solvent and recrystallization from EtOAc yielded 0·2 g product. Total yield: 0·8 g 66·1%.

N-*Ts*-3-*aza*-7-*carboethoxy*-9-*hydroxy*-*bicyclo*-3.3.1-*nonane* (**7**) *and* (**8**). A mixture of 7·30 g (20 mmole) of **6** and 4·39 g (116 mmole) of $NaBH_4$ in EtOH (300 ml) and H_2O (20 ml) was stirred for 18 hr at r.t. The mixture cooled and AcOH added slowly to 5. solvents were evaporated and water added. The aqueous mixture was extracted with $CHCl_3$ and combined extracts washed with sat. $NaHCO_3$ aq. Evaporation of solvent yielded 7·11 g (96·8%) of a mixture of **7** and **8**. Recrystallization from EtOH yielded 4·52 g. (61·5%) of **7**. mp.: 204–211°. After a second recrystallization. mp.: 211–214°. IR(KBr). OH: 3580 cm^{-1}; C=O: 1710 cm^{-1}; Ts: 1160 and 1360 cm^{-1}. (Found: C. 59·02; H. 7·11; N. 3·78; S. 8·74% $C_{18}H_{25}O_5N_1S_1$. (M = 367·45) Calc.: C. 58·63; H. 6·86; N. 3·81; S. 8·72%.)

N-*Ts*-3-*aza*-7-*carboethoxy*-9-*acetoxy*-*bicyclo*-3.3.1-*nonane* (**9**) *and* (**10**). 2·51 g of the resulting mixture of the hydroxy-esters **7** and **8** in Ac_2O (25 ml) was stirred and heated at reflux for 2 hr. After evaporation of solvent, the residue was dissolved in $CHCl_3$ and the solution washed with sat. $NaHCO_3$ aq. Evaporation of solvent gave 2·92 g. By recrystallization from EtOAc products **9** and **10** isolated. Product **10** yielded 0·585 g, mp.: 175–181°. (After a second recrystallization 183–185°) IR ($CHCl_3$), C=O: 1715 cm^{-1}; Ts: 1160 and 1340 cm^{-1}. NMR (C_5D_5N) δ 3·65, NCH_2(eq); 2·5–2·83, NCH_2(ax); 2·5–2·83, C_7-H; 4·76, C_9H. (Found: C, 58·85; H, 6·48; N, 3·52; S, 7·80%. $C_{20}H_{27}O_6N_1S_1$. (M = 409·43). Calc. C, 58·68; H, 6·63; N, 3·42; S, 7·83%). Product **9**, yield 0·368 g, m.p.: 190–192° IR ($CHCl_3$), C=O: 1710 cm^{-1}; Ts.: 1160 and 1350 cm^{-1}.

N-*Ts*-3-*aza*-7-*carboethoxy*-9-*hydroxy*-*bicyclo*-3.3.1-*nonane*-δ-*lactone* (**11**).

N-*Ts*-3-*aza*-7-*carbohydroxy*-9-*ol*-*bicylo*-3,3,1-*nonane* (**18**). 0·551 g (1·5 mmole) of the hydroxy-ester **7** in a solution Na (300 mg) in dry EtOH (30 ml) was stirred and heated in (70°) for 65 hr under N_2.

After cooling 2N HCl was added till pH 1 to 2. The EtOH was evaporated and the resulting solution extracted with $CHCl_3$. The combined extracts were washed with sat. $NaHCO_3$ aq. Evaporation gave 0·371 g. Recrystallization from THF/di-isopropylether yielded 0·267 g (55%) of the lactone **11**, m.p.: 243–244°. IR ($CHCl_3$), C=O: 1770 cm^{-1}; Ts.: 1160, 1350 cm^{-1}. NMR (C_5D_5N) δ 3·77, NCH_2 (eq); 1·0–2·5, NCH_2 (ax); 2·54, C_7CH; 4·17 C_9-H. (Found: C, 59·68; H, 6·06; N, 4·49; O, 20·02; S, 10·20% $C_{16}H_{19}O_4N_1S_1$. (M = 321·39) Calc. C, 59·79; H, 5·92; N, 4·36; O, 19·93; S, 10·00%). After acidification of the $NaHCO_3$-layer, 0·057 g (11%) of the hydroxy-acid **18** could be collected. The reaction mixture was acidified with AcOH till pH 5 to 6 (temperature <10°) and the EtOH is evaporated at r.t. till 10 ml of solvent is left. This solution is poured into H_2O, yielding 93% of the acid **18**, m.p.: 241–243°. (Upon fast heating the lactone **11** is formed). IR (KBr), OH: 3400 cm^{-1}; C=O: 1680, 1700; Ts.: 1160, 1350 cm^{-1}. (Found: C, 56·73; H, 6·33; N, 3·99; S, 9·59%. $C_{16}H_{21}O_5N_1S_1$. (M = 339·40) Calc. C, 56·63; H, 6·23; N, 4·13; S, 9·45%).

N-*Ts*-3-*aza*-7-*carbohydroxy*-9-*methyl*-9-*hydroxy*-*bicyclo*-3.3.1-*nonane* (**12**). To a freshly prepared solution of 40 mmole CH_3MgBr in THF (50 ml) was added in 20 min a solution of 1·348 g (4 mmole) of the keto-acid **31** in THF (50 ml). A white precipitate developed. The mixture was stirred and heated at reflux for 4 hr. cooled, poured into ice (200 g), acidified with 2N HCl till pH 3, and THF evaporated at r.t. Crystals formed. Yield: 1·025 g (72%). Recrystallization from EtOH/H_2O. m.p.: 254–255°. IR (KBr). OH: 3450 cm^{-1}; C=O: 1710 cm^{-1}; Ts.: 1165, 1340 cm^{-1}. (Found: C, 57·63; H, 6·58; N, 3·79%; S, 9·11. $C_{17}H_{23}O_5N_1S_1$. (M = 353·43). Calc. C, 57·78; H, 6·56; N, 3·96; S, 9·07%).

N-*Ts*-3-*aza*-7-*carbomethoxy*-9-*methyl*-9-*hydroxy*-*bicyclo*-3.3.1-*nonane* (**13**). 0·500 g (1·43 mmole) of the methyl-hydroxy-acid **12** in MeOH (25 ml) sat with HCl, was heated at reflux for 3 hr. After cooling and evaporation of solvent the product was neutralized with sat K_2CO_3 aq, extracted with $CHCl_3$, and extracts washed with sat NaCl aq. Evaporation of solvent yielded 0·477 g (90%) of the crude product. Recrystallization from THF/di-isopropylether yielded 0·335 g, m.p. 215–220°. Upon recrystallization from MeOAc 0·139 g of pure material m.p. 222–226°. IR ($CHCl_3$), C=O: 1710 cm^{-1}; Ts.: 1160, 1340 cm^{-1}. (Found: C, 58·53; H, 6·68%; $C_{18}H_{25}O_5N_1S_1$. (M = 367·471) Calc. C, 58·83; H, 6·86%.

N-*Ts*-3-*aza*-7-*carbohydroxy*-9-*methyl*-9-*hydroxy*-*bicyclo*-3.3.1-*nonane*, δ *lactone* (**14**). 100 mg (0·272

mmole) of the hydroxy-methyl-ester **13** in a solution of Na (100 mg) in dry EtOH (25 ml) was kept at 70° for 65 hr. After cooling, 2N HCl was added till pH 1 to 2 and the EtOH evaporated. The resulting aqueous solution was extracted with $CHCl_3$ the extracts washed with 5% K_2CO_3 aq and sat NaCl aq. Evaporation of solvent yielded 90 mg (97%) of product, recrystallized from EtOH, m.p. 200–204°. IR ($CHCl_3$). C=O: 1740 cm^{-1}; Ts.: 1340, 1360, 1060 cm^{-1}. (Found: C, 59·86; H, 6·11% $C_{17}H_{21}O_4N_1S_1$. (M = 235·43) Calc.: C, 60·88; H, 6·31%).

N-*Ts*-3-*aza*-7-*carbohydroxy*-9-*phenyl*-9-*hydroxy*-*bicyclo*-3.3.1-*nonane* (**15**). To a freshly prepared solution of 20 mmole C_6H_5MgBr in THF (40 ml) was added a solution of 1·348 g (4 mmole) of the keto-acid **31** in THF (125 ml). The mixture was heated at reflux for 4 hr and poured on 500 g of ice. 2N HCl was added till pH 3. THF evaporated and in the resulting aqueous solution the product crystallized. Yield: 1·283 g (77%). Recrystallization from EtOH/H_2O gave pure material. M.p. 234–237°. IR (KBr). OH: 3400–3500 cm^{-1}; C=O: 1690 cm^{-1}; Ts: 1340, 1260 cm^{-1}. (Found: 63·75; H, 6·16; N, 3·17; S, 7·92%. $C_{22}H_{25}O_5N_1S_1$. (M = 415·49) Calc. C, 63·78; H, 6·07; N, 3·37, S, 7·72%).

N-*Ts*-3-*aza*-7-*carbomethoxy*-9-*phenyl*-9-*hydroxy*-*bicyclo*-3.3.1-*nonane* (**16**). 500 mg (1·21 mmole) of acid **15**, in MeOH (25 ml) sat. with HCl was stirred and heated at reflux for 3 hr. After evaporation of solvent, the residue was neutralized with sat. K_2CO_3 aq. $CHCl_3$ extraction and work-up gave 521 mg (100%) of crude product, which after recrystallization from MeOAc afforded pure material, m.p.: 206–208°. IR (KBr). C=O: 1710 cm^{-1}; Ts.: 1340, 1610 cm^{-1}. (Found: C, 65·05; H, 6·51% $C_{24}H_{29}O_5N_1S_1$. (M = 443·57) Calc.: C, 64·98; H, 6·59%).

N-*Ts*-3-*aza*-7-*carbohydroxy*-9-*hydroxy*-*bicyclo*-3.3.1-*nonane* (**17**). 3·30 g (9 mmole) of the hydroxy-ester **7**, dissolved in a mixture of EtOH (25 ml) and 10% NaOH aq (25 ml) was heated at reflux for 1 hr. After cooling H_2O (50 ml) was added, evaporation of EtOH and the aqueous solution was adicified to pH 1. Crystallization resulted. Yield: 2·90 g (95%). m.p.: 245–251°. IR (KBr). OH: 3500 cm^{-1}; C=O: 1720 cm^{-1}; Ts.: 1160, 1340 cm^{-1}. (Found: C, 56·73; H, 6·30; N, 3·96; S, 9·45% $C_{16}H_{21}O_5N_1S_1$. (M = 321·42) Calc. C, 56·63; H, 6·23; N, 4·13; S, 9·45%).

N-*Ts*-3-*aza*-7-*carbohydroxy*-9-*hydroxy*-*bicyclo*-3.3.1-*nonane* (**19**). 1·460 g (4 mmole) of keto-ester **6**, in a solution of Na (920 mg) in EtOH (50 ml) was heated (70°) for 65 hr. After cooling 2N HCl was added to pH 3. By filtration 0·135 g of decomposition-products could be removed. After evaporating EtOH and extracting the aqueous solution with $CHCl_3$, the latter solution was treated with sat NaCl aq and the solvent removed.

Crystallization from EtOH and recrystallization from THF/di-isopropylether yielded 0·205 g of the lactone **11**. The mother liquor afforded a residue (0·511 g) which was crystallized from EtOH/H_2O: m.p. 248–252°. IR (KBr), OH: 3500 cm^{-1}; C=O: 1720 cm^{-1}; Ts.: 1160, 1330 cm^{-1}. Mass: M^+ = 339 (½%); $M^+ - Ts.$ = 184 (100%).

N-*Ts*-3-*aza*-7-*carbohydroxy*-9-*acetoxy*-*bicyclo*-3.3.1-*nonane* (**20**). 100 mg of ester **7** in 2 ml. HBr/glacial-AcOH, was heated at reflux for 4 hr. After cooling, the mixture was poured into H_2O (10 ml). The solid product was collected and washed with H_2O. Yield: 36·2 mg, m.p. 226–230°. IR (KBr). C=O: 1700, 1725 cm^{-1}; OH: 2000–3500 cm^{-1}; Ts.: 1165, 1360 cm^{-1}.

N-*Ts*-3-*aza*-7-*carboethoxy*-9,9'-*di*-(β-*Chloroethoxy*)-*bicylo*-3.3.1-*nonane* (**21**). 5·477 g of the keto-ester **6** was dissolved in chloroethanol (20 ml). After 18 hr the solution was poured into a mixture of EtOH (100 ml) and 10% aqueous KOH (100 ml). The solid product was collected and washed with H_2O and Et_2O. Yield: 3·95 g. Recrystallization from THF/di-isopropylether yielded 3·45 g, mp.: 148–150°. IR (KBr). C=O: 1720 cm^{-1}. (Found: C, 51·96; H, 6·25; O, 18·89; S, 6·58; N, 2·90%. $C_{22}H_{31}O_6N_1S_1Cl_2$. (M = 508·46) Calc. C, 51·67; H, 6·10; O, 18·89; S, 6·32; N, 2·76%).

N-*Ts*-3-*aza*-7-*carboethoxy*-9,9'-*dithioethylene*-*bicyclo*-3.3.1-*nonane* (**22**). To a cooled (5–10°) solution of 58·4 g (0·16 mole) of the keto-ester **6** in 20 ml of ethanol-1,2-dithiol and $CHCl_3$ (200 ml), was added in 20 min, dropwise with stirring, 15 ml of freshly distilled BF_3-etherate. The solution was stirred for 15 min at 5°, and for 1 hr at r.t. and washed with a cold solution of 1N NaOH and sat. NaCl aq.

Evaporation of the solvent yielded 75·5 g product, triturated with MeOH. Yield: 65·7 g (92·9%). After recrystallization from EtOAc, m.p.: 190–192°. IR ($CHCl_3$), C=O: 1715 cm^{-1}; CH: 2900, 2970 cm^{-1}; Ts.: 1160, 1350 cm^{-1}. NMR (C_5D_5N) δ 3·88 ($NC\underline{H}_2$ cq); 2·8–3·1 ($NC\underline{H}_2$ ax); 2·8–3·1 C<u>H</u> COOR. (Found: C, 54·58; H, 6·25; N, 3·04; S, 21·76%. $C_{20}H_{27}O_4N_1S_3$. (M = 441·62). Calc. C, 54·40; H, 6·16; N, 3·17; S, 21·78%).

N-*Ts*-3-*aza*-7-*carboethoxy*-*bicyclo*-3.3.1-*nonane* (**23**). 2·207 g (5 mmole) of thio-ketal **22** Raney Ni (22 ml) and EtOH (200 ml) were heated at reflux for 18 hr. After filtration the solvent was evaporated. Yield: 1·665 g. Recrystallization from EtOAc/cyclohexane, m.p.: 133–134°. IR (KBr). C=O: 1720 cm^{-1}; CH: 2870, 2929 cm^{-1}; Ts.: 1160, 1340 cm^{-1}. NMR (C_5D_5N) δ; 3·73 ($NC\underline{H}$ cq); 2·25 $NC\underline{H}_2$ ax), 2·3–2·7 ($C_7\underline{H}$).

(Found: C, 61·67; H, 7·28; N, 3·87; S, 9·23%. $C_{18}H_{25}O_4N_1S_1$. (M = 351·45) Calc. C, 61·52; H, 7·17; N, N, 3·99; S, 9·12%).

N-*Ts*-3-*aza*-7-*carboethoxy*-9-*oxo*-*bicyclo*-3.3.1-*nonane*-*oxime* (**24**). A solution of 8·34 g (120 mmole) of $NH_2OH \cdot HCl$ and 16·32 g of $NaOAc \cdot 3H_2O$ in H_2O (50 ml) was added in 10 min, dropwise with stirring to a solution of 5·48 g (15 mmole) of the keto-ester **6** in THF (55 ml). After addition of EtOH (50 ml) a clear solution was formed which crystallized. The mixture was stirred at r.t. for 16 hr. The solvents evaporated and water (100 ml) added. The solid product was collected, washed with water and dried. Recrystallization from EtOH yielded 5·07 g (88·4%) m.p. 230–233°. IR (KBr), OH: 3500 cm^{-1}; =C: 1600 cm^{-1}; C=O: 1700 cm^{-1}; Ts.: 1160, 1340 cm^{-1}. (Found: C, 56·68; H, 6·47; N, 7·17; S, 8·52%. $C_{18}H_{24}O_5N_2S_1$. (M = 380·47). Calc.: C, 56·82; H, 6·36; N, 7·36; S, 8·43%).

N-*Ts*-3-*aza*-7-*carboethoxy*-9-*amino*-*bicyclo*-3.3.1-*nonane* (**25**). A mixture of 1·386 g (3·64 mmole) of ketoxime **24** and Pt (0·237 g PtO_2) in AcOH (50 ml) and concentrated HCl (2 ml) was shaken for 16 hr in a Parr-apparatus at 37 p.s.i. The catalyst was filtered, the solvent evaporated and the residue dissolved in H_2O. To the aqueous solution was added K_2CO_3 to pH 9. This solution was extracted with $CHCl_3$ and the latter evaporated to yield 1·214 g of product, from EtOH, m.p.: 169–174°. IR (KBr), C=O: 1720 cm^{-1}; Ts.: 1160 and 1340 cm^{-1}. (Found: C, 59·11; H, 7·37; N, 7·61; S, 8·71%. $C_{18}H_{26}O_4N_2S_1$. (M = 366·48). Calc. C, 58·99; H, 7·15; N, 7·64; S, 8·75%).

N-*Ts*-3-*aza*-7-*hydroxymethyl*-9-*hydroxy*-*bicyclo*(3.3.1)-*nonane* (**26**). 1·838 g (5 mmole) of hydroxy-ester **7** dissolved in dry THF (200 ml) was added, dropwise with stirring, to 0·379 g (10 mmole) of $LiAlH_4$ in dry THF (25 ml), and kept at 75° for 3 hr. After cooling EtOAc and sat Na_2SO_4 aq were added and the white precipitate collected and washed with THF. The filtrate was evaporated, the residue dissolved in $CHCl_3$ and this solution washed with 1N HCl sat $NaHCO_3$ aq. Evaporation yielded 1·341 g (81·5%) m.p. 172–175°. Recrystallization from isopropanol/diisopropylether, m.p. 174–176°. IR (KBr), OH: 3350 cm^{-1}; Ts.: 1160, 1340 cm^{-1}. (Found: C, 59·01; H, 7·14; N, 4·13; S, 9·98%. $C_{16}H_{23}O_4N_1S_1$ (M = 325·42) Calc. C, 59·08; H, 7·12; N, 4·30; S, 9·86%).

N-*Ts*-3-*aza*-7-*hydroxymethyl*-*bicyclo* 3.3.1-*nonane* (**27**). 12·01 g (34·2 mmole) of methylene-ester **23** in THF (100 ml), were added in 10 min, dropwise with stirring, to 2·21 g (68·4 mmole) $LiAlH_4$ in 20 ml THF and kept at 70–75° for 3 hr. After cooling EtOAc and sat. Na_2SO_4 aq were added, the solid product collected and washed with THF. Evaporation of the filtrate and recrystallization from isopropanol/di-isopropylether yielded 8·24 g (78%) of the desired product, m.p. 140–143°. IR (KBr), OH: 3600 cm^{-1}; CH: 2880, 2950 cm^{-1}; Ts.: 1160, 1340 cm^{-1}. (Found: C, 62·20; H, 7·70; N, 4·17; S, 9·88% $C_{16}H_{23}N_1O_3S_1$. (M = 309·12) Calc. C, 62·13; H, 7·50; N, 4·53; S, 10·35%).

N-*Ts*-3-*aza*-7-*hydroxymethyl*-9-*amino*-*bicyclo*3.3.1-*nonane* (**28**). 0·472 g (1·28 mmole) of amino-ester **25**, dissolved in 50 ml THF, was added, to 0·0975 g (2·56 mmole) $LiAlH_4$ in 10 ml THF. The mixture was heated at reflux for 3 hr. Further as in the synthesis of **27**. Yield of crude product 0·476 g. Recrystallization from EtOH, m.p.: 173–175°. IR (KBr), NH, OH: 3000–3500 cm^{-1}; Ts.: 1160, 1340 cm^{-1}.

N-*Ts*-3-*aza*-7-*carboxy*-*diethylamino*-9-*oxo*-*bicyclo*-3.3.1-*nonane* (**29**). 3·033 g (9 mmole) of acid **31** and 50 ml $SOCl_2$ were kept at r.t. for 18 hr, after which the solvent was evaporated. After repeated addition and evaporation of C_6H_6 the residue was finally dissolved in benzene (50 ml). This solution was cooled in an ice-bath and 10 ml diethylamine added. The solution was kept at r.t. for 2 hr, and finally shaken with 50 ml cold 4N HCl. After separation of the aqueous layer, and extracting with C_6H_6, the combined extracts were washed sat. $NaHCO_3$ aq. Evaporation of the solvent yielded 3·21 g from EtOH, m.p. 177–180°. IR (KBr), C=O: 1720 cm^{-1}; NC=O: 1640 cm^{-1}; Ts: 1165, 1345 cm^{-1}. (Found: C, 61·12; H, 7·18; N, 7·00; S, 8·00%. $C_{20}H_{28}O_4N_2S_1$ (M = 392·56) Calc.: C, 61·18; H, 7·21; N, 7·14; S, 8·17%).

N-*Ts*-3-*aza*-7-*carbohydrogen* *bicyclo*-3.3.1-3-*aza*-*nonane* (**30**). 0·103 g (0·33 mmole) of alcohol **27**, in 0·67 ml Ac_2O and 10 ml DMSO stirred at r.t. for 18 hr. The mixture was poured into H_2O and the solution extracted with ether. The combined extracts were washed with sat. $NaHCO_3$ aq and sat. NaCl aq. Evaporation of solvent and crystallization from THF/di-isopropylether yielded 0·028 g of solid. (28%) m.p. 118–123°. IR (KBr), C=O: 1720 cm^{-1}; Ts: 1160, 1345 cm^{-1}.

N-*Ts*-3-*aza*-7-*carbohydroxy*-9-*oxo*-*bicyclo*-3.3.1-*nonane* (**31**). 0·658 g of ester **6**, in 10 ml glacial AcOH and 5 ml conc. HCl was refluxed for 2 hr. The mixture was diluted with 75 ml H_2O and the solid product collected and dried. Yield: 0·526 g (90·2%). Recrystallization from $EtOH/H_2O$, m.p.: 251–353°. IR (KBr), COOH: 2600–3400 cm^{-1}; C=O: 1700, 1720 cm^{-1} Ts: 1160, 1340 cm^{-1}. (Found: C, 57·09; H, 5·81; N, 4·01; S, 9·39%. $C_{16}H_{19}O_5N_1S_1$. (M = 337·40). Calc.: C, 56·98; H, 5·68; N, 4·15; S, 9·50%).

N-*Ts*-3-*aza*-7-*carbohydroxy*-9,9'-*dithioethylene*-*bicyclo* 3.3.1-*nonane* (**32**). 0·0675 g (0·15 mmole of **22** in a solution of 48 mg Na in 4·8 ml EtOH heated at 70° for 17·5 hr. After cooling 2N HCl added till pH 1

to 2. The pure product was collected, washed with H_2O and dried, m.p.: dec. > 260°. Yield: 0·0544 g (87·7%) IR (KBr). C=O: 1700 (v.s.), 1720 (w) cm^{-1}; Ts: 1160cm^{-1}. (Found: C, 52·37; H, 5·49; N, 3·54; S, 23·19. $C_{18}H_{23}O_4N_1S_3$. (M = 413·60) Calc.: C, 52·27; H, 5·62; N, 3·39; S, 23·21).

*N-Ts-3-aza-7-carbohydroxy-bicyclo*3.3.1-*nonane* (**33**). 0·1758 g (0·5 mmole) of the methylene-ester **23** in a solution of 160 mg Na in 16 ml EtOH was heated at 70° for 18 hr. After cooling 2N HCl added till pH 1. The EtOH evaporated and product crystallized. After filtration, washing with H_2O and drying, 0·1536 g (94·9%) of product was obtained, from EtOH, m.p.: 208–210°. IR (KBr). C=O: 1700, 1720 (shoulder) cm^{-1}. Ts: 1160, 1340 cm^{-1}; COOH: 2500–3500 cm^{-1}. NMR ($CDCl_3$) δ 3·80 ($C\underline{H}_2$Neq); 2·52 ($C\underline{H}_2$Nax); 3·76 ($C_7\underline{H}$). (Found: C, 59·49; H, 6·45; N, 4·38; S, 9·90%. $C_{16}H_{21}O_4N_1S_1$. (M = 323·44) Calc.: C, 59·41; H, 6·56; N, 4·33; S, 9·91%).

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