SYNTHESIS AND STRUCTURAL STUDY OF NEW DERIVATIVES OF 6,8-DIARYL-3-THIA-7-AZABICYCLO[3.3.1]NONANE SYSTEMS

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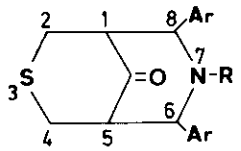
Abstract- The synthesis and structural analysis of new derivatives of the 6,8-diaryil-3-thia-7-azabicyclo[3.3.1]nonane systems were studied. The high reactivity and stereoselectivity presented by this type of system demonstrates the rigid special arrangement acquired by this type of molecule. Nucleophilic attack on the carbonyl group of 6,8-diaryl-3-thia-7-azabicyclo[3.3.1]nonan-9-one (Grignard and Reformatsky reactions) exclusively produce β-isomers, unlike the Bucherer-Bergs reaction which produced a mixture of isomeric hydantoins. The percentage of isomers and the configuration at C-9 was determined by ^{1}H-NMR spectroscopy. An IR study of solid state association in this type of molecule is presented.

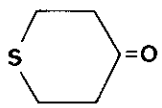
There has been a considerable interest in systems derived from 3,7-diheterobicyclo[3.3.1]nonanes from a theoretical point of view and their potential biological activity [1-2]. Similar nitrogen containing systems derived from 3-azabicyclo[3.3.1]nonane have been studied [3-6]. However, there are very few data about systems which have a sulfur atom in the 3 position [7-8]. In this work the synthesis and structural analysis of some 6,8-diaryl-3-thia-7-azabicyclo[3.3.1]nonanes are studied.

The 6,8-diaryl-3-thia-7-azabicyclo[3.3.1]nonan-9-ones 1 are obtained by the Mannich condensation of tetrahydro-4H-thiapyran-4-one 2 with an aromatic aldehyde (benzaldehyde or p-methoxybenzaldehyde) and ammonium acetate in ethanol produced the thia-azaketones 1a and 1c. Their N-methyl derivatives 1b and 1d were produced by treating these with dimethyl sulfate in acetone, (Scheme I).

Systems of bicyclo[3.3.1]nonanes exist in one of the three following structures: chair-chair, chair-boat and boat-boat. In the most cases, the chair-chair structure with slight flattening in the rings is favored [9]. However, the probability

Scheme I





1 a : R : H Ar : C_6H_5

b : R : CH_3 Ar : C_6H_5

c : R : H Ar : $pCH_3OC_6H_4$

d : R : CH_3 Ar : $pCH_3OC_6H_4$

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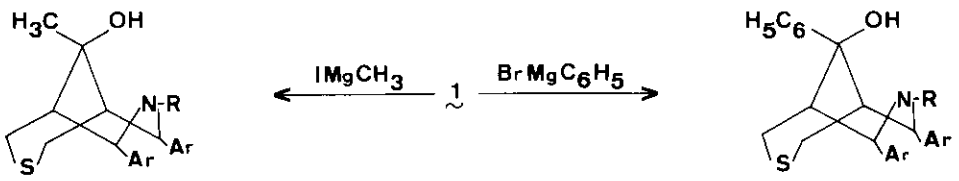
of the existence of the boat structure for one of the heterocyclic rings derived from bicyclo[3.3.1]nonane increased for derivatives of 1 where there are heteroatoms in positions 3 and 7 as suggested by Zefirov [10]. The presence of the sulfur atom at position 3 has the greatest effect on the conformation that the system assume which explains the results obtained by comparing the analogs of cyclohexanone and thiacyclohexan-4-one [8]. In the same manner, the X-ray diffraction analysis of 2,4,6,8-tetraphenyl-3-thia-7-azabicyclo[3.3.1]nonan-9-one [11] shows that the ring containing the sulfur atom and the ring containing the nitrogen are in chair-boat conformation and a rigidity indicates that there is little equilibrium between other conformers.

The ^{1}H-NMR analysis of the 1a-1d is based on the effects of the electronegativities of the heteroatoms. The chemical shifts for H-6 and H-8 are consistant with an axial arrangement since they resonate at a higher field than that expect if they were in equatorial position [12]. In the same manner, the hydrogens H-6 and H-8 suffer a dispersion of about 0.70 ppm which is observed in the N-methyl products 1b and 1d. This attributed to the substitution of the hydrogen on the nitrogen by a methyl group which adopts an equatorial configuration observed in the ^{1}H-NMR as an increase in the coupling constant $J_{8,1}$ of about 4 Hz. Alcohols 3-6 and 3a-6a are obtained by reacting the corresponding ketones 1a-d with the appropiate organomagnesium compound. The results of adding methylmagnesium iodide and phenylmagnesium bromide to the ketones 1a-d (Scheme II) demonstrate how the attack of the organometallic compounds occurs from the exo face (with respect to the piperidine ring) which produces the alcohol with the ß structure (the ß product has the hydroxil group endo to the piperidine ring),

unlike homologous systems lacking the sulfur atom in the 3 position [13], where in some cases isomeric alcohol mixtures are obtained.

Scheme II



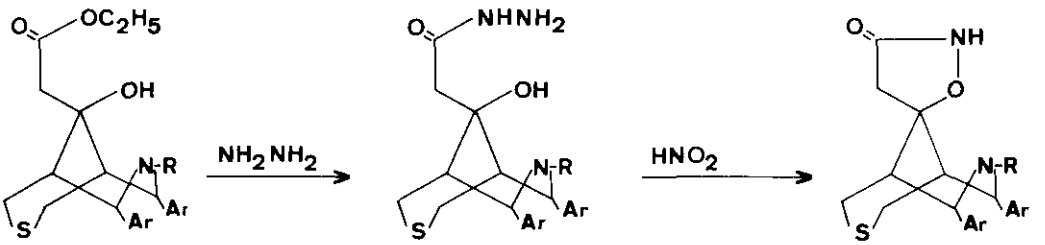
3	R: H	Ar: C_6H_5	3a	R: H	Ar: C_6H_5
4	R: CH_3	Ar: C_6H_5	4a	R: CH_3	Ar: C_6H_5
5	R: H	Ar: $pCH_3OC_6H_4$	5a	R: H	Ar: $pCH_3OC_6H_4$
6	R: CH_3	Ar: $pCH_3OC_6H_4$	6a	R: CH_3	Ar: $pCH_3OC_6H_4$

The structure represented by alcohols 3-6 and 3a-6a must be in the chair-boat conformation by analogy with that one presented by the initial ketones [8]. This structure is responsible to a great extent for the high stereoselectivity observed in the additions to the carbonyl at C-9. The chair arrangement acquired by the ring which carries the sulfur atom allows the ease of approach of the nucleophile to that side of the molecule, whereas, the approach to the other side is clearly hindered by: a) the adoption of the boat conformation by the diarylpiperidine ring, b) the presence of aromatic substituents at C-6 and C-8 and c) the sustitution of the amine hydrogen by a magnesium halide in the course of the Grignard reaction. On the other hand, the data we have obtained completely agree with that obtained by Eliel [8], who used ^{13}C-NMR to confirm the conformation of 6,8-diphenyl-3-thia-7-azabicyclo[3.3.1]nonan-9-ol. Another test confirming the assignment of a β-configuration for these alcohols consists of a transition of resonance for the C-9 methyl group in alcohols 3,4,5 and 6, which is located at 1.20 ppm. The signal is not affected by the paramagnetic influence which would be induced by the aromatic groups at C-6 and C-8 if the C-9 methyl group were situated in the β position. A diamagnetic displacement of the order of 0.70 ppm was observed for the hydrogens H-6 and H-8 in the N-methyl series, which can be attributed to the nitrogen methyl adopting an equatorial position which gives rise to a Bohlman band [14] at a frequency lower than 2800 cm^{-1}. There is a considerable diamagnetic displacement of the order of 1.00 ppm which is suffered by the bridge-head hydrogens H-1 and H-5 when there

is a phenyl group at C-9. This is due to the fact that the phenyl group assumes a position perpendicular to the symmetry plane of the molecule.

The high stereoselectivity presented by the nucleophilic additions of the Grignard reagents with ketones 1a-d has been used more widely than the Reformatsky reaction. The β-hydroxyesters 7,8,9 and 10 are obtained by treating the corresponding ketones 1a-d with zinc and ethyl bromoacetate (Scheme III).

Scheme III



7 R: H	Ar: C_6H_5	11 R: H	Ar: C_6H_5	15 R: H	Ar: C_6H_5
8 R: CH_3	Ar: C_6H_5	12 R: CH_3	Ar: C_6H_5	16 R: CH_3	Ar: C_6H_5
9 R: H	Ar: $pCH_3OC_6H_4$	13 R: H	Ar: $pCH_3OC_6H_4$	17 R: H	Ar: $pCH_3OC_6H_4$
10 R: CH_3	Ar: $pCH_3OC_6H_4$	14 R: CH_3	Ar: $pCH_3OC_6H_4$	18 R: CH_3	Ar: $pCH_3OC_6H_4$

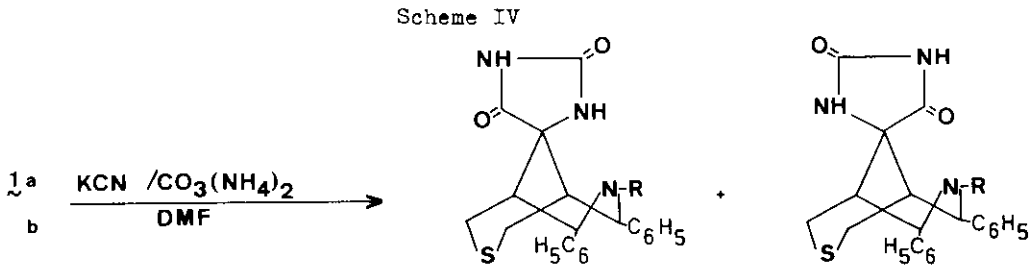
We have assigned the configuration at C-9 for these systems according to the ^{1}H-NMR parameters presented by those which have very nearly the values for H-6 and H-8 with respect to those found for the β-isomers of the preceeding alcohols obtained by the Grignard reaction. This data agree with products arising from the attack of the nucleophile from the exo face. A diamagnetic effect of the order of 0.80 ppm is observed for the N-methyl series with respect to those esters which are unsubstituted. This is again confirmed by the presence of a Bohlman band. The type of association presented by the hydroxyesters in solid state is exclusively intramolecular, the association being established between the hydroxyl group and the nitrogen atom of the diarylpiperidine ring.

By treating with hydrazine hydrate in ethanol, the hydroxyesters produce the corresponding hydrazides 11,12,13 and 14, which by treating with nitrous acid, the oxazolidinones 15,16,17 and 18 are obtained (Scheme III). The ^{1}H-NMR signals for the methylene groups in the oxazolidinone heterocycle suffer a para-

magnetic displacement of the order of 0.85 ppm and appear as a singlet at 3.45 ppm confirming that the spirooxazolidinones have a single configuration which is the β-configuration. The α-configuration would be indicated by the variations in the observed chemical shift for the methylene group due to effects of the aromatic rings at the C-6 and C-8 positions.

The spirohydantoins 19a-b and 20a-b are prepared by the treating the corresponding ketones 1a and 1b with potassium cyanide and ammonium carbonate in N,N-dimethylformamide [15]. The reaction is continued for four days to obtain a mixture of isomeric hydantoines whose ^{1}H-NMR spectrum shows a 70% to 30% mixture of α:β isomers (Scheme IV). By making a molecular model of the compound in the chair-boat conformation it is easily seen how the axial hydrogens at C-6 and C-8 are

Scheme IV



19a R: H β(30%) 19b R: H α(70%)

20a R: CH_3 β(20%) 20b R: CH_3 α(80%)

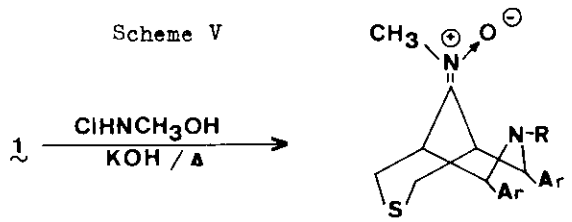
placed near to the $C_{4'}$ carbonyl thus appearing at 4.20 ppm in the α isomer. Whereas, in the β isomer these protons appear at 3.80 ppm. The N-methyl series are produced in a slightly different ratio α:β= 80%:20%. The protons H-6 and H-8 appear at 3.70 ppm for β and 3.90 ppm for α. The diamagnetic diamagnetic displacement for these protons compared to the unmethylated compounds is due to the methyl group assuming an equatorial position. This effect was also observed in the initial ketones.

The infrared spectra indicates strong intramolecular hydrogen bonding. This may occur between the N-H of the hydantoin and the amine nitrogen or the carbonyl of the hydantoin. These interactions will be studied further by X-ray diffraction techniques and will be reported later.

Finally, we took advantage of the excellent reactivity of the carbonyl group of this system to obtain the N-oxides (Nitrones) 21,22,23 and 24 (Scheme V).

These compounds are very useful in dipolar cycloaddition reactions offering a wide diversity of chemistry. By treating ketones 1a-d with N-methylhydroxylammonium chloride in base the corresponding nitrones were obtained. These compounds were characterized by ^{1}H-NMR and IR spectroscopy. The quaternary nitrogen gives rise to a singlet at 3.60 ppm corresponding to the methyl group.

Scheme V



21 R: H Ar: C_6H_5

22 R: CH_3 Ar: C_6H_5

23 R: H Ar: p$CH_3OC_6H_4$

24 R: CH_3 Ar: p$CH_3OC_6H_4$

The N→O bond is observed in the IR by a very intense band at 1180 cm^{-1}. The utility of these compounds in further chemistry will be reported later.

EXPERIMENTAL

The tetrahydro-4H-thiapyran-4-one 2 was prepared according to the Johnson method [16] with a yield of 40%. The ketones 1a,1b,1c and 1d were prepared according to literature [7].

6,8-Diphenyl-3-thia-7-azabicyclo[3.3.1]nonan-9-one 1a

(43%), mp 207-208°C; $C_{19}H_{19}NOS$ (309.2) (benzene)
calc: C, 73.98; H, 6.20; N, 4.54; S, 10.39.
found: C, 73.86; H, 6.34; N, 4.59; S, 10.35.

IR (KBr): ν = 3305, 3040, 2920, 2900, 2860, 1730 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: 7.5 7.1 (m, 10H); 5.0 (d, 2H, J 1Hz); 3.5-3.3 (m, 2H); 2.9 (d, 4H, J 1Hz); 1.70 ppm (s, 1H).

6,8-Diphenyl-7-methyl-3-thia-7-azabicyclo[3.3.1]nonan-9-one 1b

(35%), mp 155-156°C; $C_{20}H_{21}NOS$ (323.2) (methanol)
calc: C, 74.26; H, 6.54; N, 4.33; S, 9.91.
found: C, 74.16; H, 6.66; N, 4.28; S, 9.96.

IR (KBr): ν = 3060, 3040, 2960, 2910, 2840, 2790, 1725 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: 7.5-7.1 (m, 10H); 4.3 (d, 2H, J 4Hz); 3.5-3.2 (m, 2H); 2.9 (d, 4H, J 1Hz); 1.75 ppm (s, 3H).

6,8-Bis(p-methoxyphenyl)-3-thia-7-azabicyclo[3.3.1]nonan-9-one 1c

(40%), mp 188-189°C; $C_{21}H_{23}NO_3S$ calc: C, 68.26; H, 6.27; N, 3.79; S, 8.76.
(methanol) (369.1) found: C, 68.34; H, 6.36; N, 3.70; S, 8.80.

IR (KBr): ν = 3300, 3040, 3020, 2960, 2900, 2840, 1720 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: 7.3(d, 4H, J 9Hz); 6.8 (d, 4H, J 4Hz); 4.9 (d, 2H, J 1Hz); 3.7 (s, 6H); 3.6-3.2 (m, 2H); 3.0-2.5 (m, 4H); 1.9 ppm (s, 1H).

6,8-Bis(p-methoxyphenyl)-7-methyl-3-thia-7-azabicyclo[3.3.1]nonan-9-one 1d

(38%), mp 150-152°C; $C_{22}H_{25}NO_3S$ calc: C, 68.90; H, 6.57; N, 3.65; S, 8.35.
(methanol) (383.1) found: C, 68.79; H, 6.68; N, 3.57; S, 8.38.

IR (KBr): ν = 3060, 3030, 2960, 2900, 2790, 1720 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: 7.4-7.1 (m, 4H); 6.8 (d, 4H, J 9Hz); 4.2 (d, 2H, J 3Hz); 3.7 (s, 6H); 3.6-3.1 (m, 2H); 3.0-2.7 (m, 4H); 1.7 ppm (s, 3H).

General Procedure for Synthesis of Alcohols 3-6 and 3a-6a

A solution of the corresponding carbonyl compound in benzene (20 mmol of ketone in 60 ml of benzene) was added to a suspension of the organomagnesium compound (0.20 m), in ether (100 ml). The mixture was stirred 24 h at room temperature, 100 ml of the saturated ammonium chloride solution was added to the mixture, and the pH of the solution was adjusted to 10 with 20% aqueous sodium hydroxide. The organic layer was decanted and the aqueous solution was extracted with ether (50 ml). The organic extracts are washed with water (50 ml) and dried on anhydrous magnesium sulfate. The solvent is evaporated under reduced pressure and the residue is purified by recrystallization.

6,8-Diphenyl-9-methyl-3-thia-7-azabicyclo[3.3.1]nonan-9β-ol 3

(75%), mp 228-230°C; $C_{20}H_{23}NOS$ calc: C, 73.80; H, 7.12; N, 4.30; S, 9.85.
(methanol) (325.2) found: C, 73.74; H, 7.19; N, 4.27; S, 9.82.

IR (KBr): ν = 3320, 3260, 3060, 2980, 2860, 2830 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: 7.5-7.1 (m, 10H); 4.2 (d, 2H, J 2Hz); 3.3-3.1 (m, 2H); 2.4-2.0 (m, 6H); 1.3 ppm (s, 3H).

6,8-Diphenyl-7,9-dimethyl-3-thia-7-azabicyclo[3.3.1]nonan-9β-ol 4

(70%), mp 221-223°C; $C_{21}H_{25}NOS$ calc: C, 74.18; H, 7.41; N, 4.11; S, 9.42.
(methanol) (339.2) found: C, 74.22; H, 7.50; N, 4.14; S, 9.46.

IR (KBr): ν = 3270, 3060, 3030, 2980, 2960, 2850, 2780 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: 7.4-7.0 (m, 10H); 3.9 (d, 2H, J 5Hz); 3.4-3.3 (m, 2H); 2.5-2.1 (m, 5H); 1.8 (s, 3H); 1.2 ppm (s, 3H).

6,8-Bis(p-methoxyphenyl)-9-methyl-3-thia-7-azabicyclo[3.3.1]nonan-9β-ol 5

(68%), mp 206-207°C; $C_{22}H_{27}NO_3S$ calc: C, 68.54; H, 7.05; N, 3.63; S, 8.31.
(benzene) (385.1) found: C, 68.49; H, 7.11; N, 3.58; S, 8.35.

IR (KBr): ν = 3340, 3260, 3080, 3040, 2980, 2950, 2860 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ : 7.4 (d, 4H, J 9Hz); 6.9 (d, 4H, J 9Hz); 4.2 (d, 2H, J 2Hz); 3.7 (s, 6H); 3.3-3.2 (m, 2H); 2.6-2.2 (m, 6H); 1.2 ppm (s, 3H).

6,8-Bis(p-methoxyphenyl)-7,9-dimethyl-3-thia-7-azabicyclo[3.3.1]nonan-9β-ol 6

(76%), mp 188-189°C; $C_{23}H_{29}NO_3S$ calc: C, 69.14; H, 7.31; N, 3.50; S, 8.02.
(benzene) (399.1) found: C, 69.19; H, 7.39; N, 3.46; S, 8.07.

IR (KBr): ν = 3260, 3060, 3040, 2980, 2960, 2900, 2840, 2780 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ : 7.5-7.0 (m, 4H); 6.7 (d, 4H, J 9Hz); 3.7 (s, 6H); 3.5-3.3 (m, 2H); 2.5-2.1 (m, 5H); 1.8 (s, 3H); 1.2 ppm (s, 3H).

6,8,9-Triphenyl-3-thia-7-azabicyclo[3.3.1]nonan-9β-ol 3a

(73%), mp 240-242°C; $C_{25}H_{25}NOS$ calc: C, 77.48; H, 6.50; N, 3.62; S, 8.27.
(methanol) (387.5) found: C, 77.40; H, 6.58; N, 3.57; S, 8.31.

IR (KBr): ν = 3320, 3200, 3080, 3060, 2960, 2920, 2860 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ : 7.6-7.1 (m, 15H); 4.4 (d, 2H, J 1Hz); 3.4-3.1 (m, 6H); 2.3-2.1 ppm (m, 2H).

6,8,9-Triphenyl-7-methyl-3-thia-7-azabicyclo[3.3.1]nonan-9β-ol 4a

(77%), mp 231-233°C; $C_{26}H_{27}NOS$ calc: C, 77.77; H, 6.77; N, 3.48; S, 7.98.
(benzene) (401.5) found: C, 77.68; H, 6.85; N, 3.52; S, 8.06.

IR (KBr): ν = 3190, 3060, 3040, 3020, 2950, 2900, 2850, 2780 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ : 7.6-7.0 (m, 15H); 4.1 (d, 2H, J 3Hz); 3.5-3.2 (m, 5H); 2.3-2.0 (m, 2H); 1.8 ppm (s, 3H).

6,8-Bis(p-methoxyphenyl)-9-phenyl-3-thia-7-azabicyclo[3.3.1]nonan-9β-ol 5a

(70%), mp 214-216°C; $C_{27}H_{29}NO_3S$ calc: C, 72.42; H, 6.32; N, 3.14; S, 7.18.
(benzene) (447.5) found: C, 72.46; H, 6.39; N, 3.19; S, 7.22.

IR (KBr): ν = 3330, 3240, 3080, 3060, 2980, 2950, 2860 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ : 7.5 (d, 9H, J 8Hz); 6.9 (d, 4H, J 9Hz); 4.4 (d, 2H, J 1Hz); 3.7 (s, 6H); 3.5-3.2 (m, 6H); 2.3-2.1 ppm (m, 2H).

6,8-Bis(p-methoxyphenyl)-7-methyl-9-phenyl-3-thia-7-azabicyclo[3.3.1]nonan-9β-ol 6a

(68%), mp 203-204°C; $C_{28}H_{31}NO_3S$ calc: C, 72.85; H, 6.77; N, 3.04; S, 6.95.
(benzene) (461.5) found: C, 72.76; H, 6.85; N, 2.99; S, 7.02.

IR (KBr): ν = 3180, 3070, 3040, 2970, 2940, 2860, 2780 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ : 7.6-7.2 (m, 9H); 6.8 (d, 4H, J 8Hz); 4.0 (d, 2H, J 3Hz); 3.7 (s, 6H); 3.5-3.1 (m, 5H); 2.4-2.2 (m, 2H); 1.8 ppm (s, 3H).

General Procedure for Hydroxyesters 7-10

A solution of the corresponding ketone (25 mmol) dissolved in benzene (25 ml), was added to a suspension of the organozinc derivative (50 mmol). The mixture was stirred 12 h at room temperature, 50 ml of cold acetic acid was added to the mixture. An equal volume of water was added and the mixture was made alkaline with 22% aqueous ammonium hydroxide to pH 10. The organic layer was separated and the aqueous solution was extracted with benzene (75 ml). The organic extracts were dried on anhydrous magnesium sulfate. The solvent is evaporated under reduced pressure and the residue is purified by recrystallization.

6,8-Diphenyl-9ß-hydroxy-3-thia-7-azabicyclo[3.3.1]nonan-9-ethyl Acetate 7

(80%), mp 137°C (methanol); $C_{23}H_{27}NO_3S$ (397.5); calc: C, 69.49; H, 6.84; N, 3.52; S, 8.06. found: C, 69.40; H, 6.88; N, 3.48; S, 8.09.

IR (KBr): ν = 3320, 3260, 3090, 3060, 2980, 2860, 1740 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ : 7.6-7.1 (m, 10H); 4.6 (d, 2H, J 1Hz); 4.1 (q, 2H); 3.3-3.1 (m, 2H); 2.6 (s, 2H); 2.4-2.2 (m, 4H); 1.3 (t, 3H); 1.1 ppm (s, 2H).

6,8-Diphenyl-7-methyl-9ß-hydroxy-3-thia-7-azabicyclo[3.3.1]nonan-9-ethyl Acetate 8

(75%), mp 133°C (methanol); $C_{24}H_{29}NO_3S$ (411.1); calc: C, 70.03; H, 7.10; N, 3.40; S, 7.78. found: C, 70.10; H, 7.19; N, 3.46; S, 7.83.

IR (KBr): ν = 3220, 3080, 3030, 2970, 2930, 2780, 1740 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ : 7.5-7.0 (m, 10H); 4.1 (q, 2H); 3.8 (d, 2H, J 4Hz); 3.3-3.1 (m, 2H); 2.6 (s, 2H); 2.4-2.2 (m, 4H); 1.7 (s, 3H); 1.3 (t, 3H); 1.0 ppm (s, 1H).

6,8-Bis(p-methoxyphenyl)-9ß-hydroxy-3-thia-7-azabicyclo[3.3.1]nonan-9-ethyl Acetate 9

(77%), mp 130°C (methanol); $C_{25}H_{31}NO_5S$ (426.1); calc: C, 65.62; H, 6.82; N, 3.06; S, 7.00. found: C, 65.56; H, 6.91; N, 3.09; S, 7.04.

IR (KBr): ν = 3330, 3210, 3080, 2960, 2930, 2840, 1740 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ : 7.5 (d, 4H, J 8Hz); 6.8 (d, 4H, J 8Hz); 4.8 (s, 6H); 4.4 (d, 2H, J 1Hz); 4.1 (q, 2H); 3.3-3.1 (m, 2H); 2.6 (s, 2H); 2.3-2.0 (m, 4H), 1.3 (t, 3H); 1.1 ppm (s, 1H).

6,8-Bis(p-methoxyphenyl)-7-methyl-9ß-hydroxy-3-thia-7-azabicyclo[3.3.1]nonan-9-ethyl Acetate 10

(70%), mp 141°C (methanol); $C_{26}H_{33}NO_5S$ (440.1); calc: C, 66.21; H, 7.05; N, 2.96; S, 6.79. found: C, 66.13; H, 7.12; N, 2.92; S, 6.81.

IR (KBr): ν = 3240, 3080, 3060, 3020, 2980, 2900, 2840, 2780, 1740 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: 7.6-7.2 (m, 4H); 6.8 (d, 4H, J 8Hz); 4.8 (s, 6H); 4.1 (q, 2H); 3.8 (d, 2H, J 3Hz); 3.3-3.1 (m, 2H); 2.6 (s, 2H); 2.4-2.1 (m, 4H); 1.8 (s, 3H); 1.7 (s, 3H); 1.1 ppm (s, 1H).

General Synthetic Procedure of Hydrazides 11-14

Hydrazine hydrate (100%, 60 mmol) is added to a suspension of the corresponding hydroxyester (30 mmol) in benzene (200 ml). Absolute ethanol is added to the solution in a quantity enough to homogenize the warm mixture. The reaction is stirred for 48 h at reflux. The solvent is evaporated under reduced pressure and the residue is purified by recrystallization.

6,8-Diphenyl-9ß-hydroxy-3-thia-7-azabicyclo[3.3.1]nonan-9-acetohydrazide 11

(80%), mp 241-243°C; $C_{21}H_{25}N_3O_2S$ (383.4) (methanol) calc: C, 65.77; H, 6.57; N, 10.96; S, 8.36. found: C, 65.86; H, 6.66; N, 11.03; S, 8.31.

IR (KBr): ν = 3310-3210, 3080, 3060, 2960, 2900, 2840, 1650 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: 7.5-7.0 (m, 10H); 4.3 (d, 2H, J 1Hz); 3.4-3.2 (m, 2H); 2.5-2.1 (m, 6H); 8.3; 6.8; 2.0; 1.6 ppm (s, 4H, signals dissapeared after adding D_2O).

6,8-Diphenyl-7-methyl-9ß-hydroxy-3-thia-7-azabicyclo[3.3.1]nonan-9-acetohydrazide 12

(85%), mp 231-233°C; $C_{22}H_{27}N_3O_2S$ (397.5) (methanol) calc: C, 66.47; H, 6.85; N, 10.57; S, 8.07. found: C, 66.55; H, 6.91; N, 10.60; S, 8.10.

IR (KBr): ν = 3360-3240, 3060, 3020, 2980, 2920, 2780, 1640 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: 7.6-7.1 (m, 10H); 3.8 (d, 2H, J 3Hz); 3.3-3.2 (m, 2H); 2.6-2.0 (m, 6H); 1.7 (s, 3H); 8.4; 6.7; 1.9 ppm (s, 3H, signals dissapeared after adding D_2O).

6,8-Bis(p-methoxyphenyl)-9ß-hydroxy-3-thia-7-azabicyclo[3.3.1]nonan-9-acetohydrazide 13

(82%), mp 253-255°C; $C_{23}H_{29}N_3O_4S$ (443.5) (benzene) calc: C, 62.28; H, 6.59; N, 9.47; S, 7.23. found: C, 62.21; H, 6.68; N, 9.50; S, 7.26.

IR (KBr): ν = 3310-3220, 3070, 3040, 2960, 2860, 1650 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: 7.6 (d, 4H, J 9Hz); 6.8 (d, 4H, J 9Hz); 4.2 (d, 2H, J 1Hz); 3.7 (s, 6H); 3.4-3.2 (m, 2H); 2.7-2.2 (m, 6H); 8.3; 6.7; 2.0; 1.3 ppm (s, 4H, signals dissapeared after adding D_2O).

6,8-Bis(p-methoxyphenyl)-7-methyl-9β-hydroxy-3-thia-7-azabicyclo[3.3.1]nonan-9-acetohydrazide 14

(78%), mp 257-258°C; $C_{24}H_{31}N_3O_4S$ (457.5) (benzene) calc: C, 62.99; H, 6.83; N, 9.18; S, 7.01. found: C, 62.92; H, 6.88; N, 9.24; S, 6.97. IR (KBr): ν = 3320-3230, 3080, 3040, 2960, 2840, 2780, 1630 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ : 7.6-7.0 (m, 4H); 6.8 (d, 4H, J 9Hz); 3.7 (s, 6H); 3.3-3.1 (m, 2H); 2.7-2.3 (m, 6H); 1.7 (s, 3H); 8.3; 6.8; 1.5 ppm (s, 3H, signals dissapeared after adding D_2O).

General Synthetic Procedure for Oxazolidinones 15-18

The hydrazide (10 mmol) was dissolved in 2N hydrochloric acid (20 ml). The acid solution was then covered with a layer of petroleum ether (bp 65-90°C). The mixture was cooled to 5°C and a solution of sodium nitrite (4 g) in water (40 ml) was then added slowly and with stirring. After 45 min, urea (2 g) was added to the mixture. Afterwards, the solution was heated to 60°C for 2 h. The reaction was allowed to warm to room temperature and was stirred for 12 h. The solution was made alkaline with 22% aqueous ammonium hydroxyde solution and was extracted with benzene (100 ml). The organic extracts were dried on anhydrous magnesium sulfate. The solvent is evaporated under reduced pressure and the residue is purified by recrystallization.

6,8-Diphenyl-3-thia-7-azabicyclo[3.3.1]nonane-9β-spiro-5'-oxazolidin-2'-one 15

(45%), mp 267-269°C; $C_{21}H_{22}N_2O_2S$ (366.4) (methanol) calc: C, 68.82; H, 6.59; N, 7.65; S, 8.25. found: C, 68.73; H, 6.66; N, 7.70; S, 8.19. IR (KBr): ν = 3300, 3260, 3060, 3030, 2960, 2840, 1740 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ : 7.8-7.5 (m, 5H); 7.4-7.1 (m, 5H); 6.3 (s, 1H); 4.3 (d, 2H, J 1Hz); 3.4 (s, 2H); 3.1-2.8 (m, 2H); 2.6-2.2 ppm (m, 5H).

6,8-Diphenyl-7-methyl-3-thia-7-azabicyclo[3.3.1]nonane-9β-spiro-5'-oxazolidin-2'-one 16

(48%), mp 284-286°C; $C_{22}H_{24}N_2O_2S$ (380.4) (methanol) calc: C, 69.44; H, 6.36; N, 7.36; S, 8.43. found: C, 69.53; H, 6.39; N, 7.30; S, 8.38. IR (KBr): ν = 3400, 3080, 3050, 2970, 2900, 2860, 2780, 1740 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ : 7.8-7.4 (m, 5H); 7.4-7.0 (m, 5H); 5.6 (s, 1H); 3.9 (d, 2H, J 3Hz); 3.4 (s, 2H); 2.9-2.7 (m, 2H); 2.4-2.1 (m, 4H); 1.7 ppm (s, 3H).

6,8-Bis(p-methoxyphenyl)-3-thia-7-azabicyclo[3.3.1]nonane-9ß-spiro-5'-oxazolidin-2'-one 17

(40%), mp 255-257°C; $C_{23}H_{26}N_2O_4S$ calc: C, 64.76; H, 6.15; N, 6.57; S, 7.52.
(methanol) (426.5) found: C, 64.82; H, 6.22; N, 6.63; S, 7.48.

IR (KBr): ν = 3300, 3240, 3080, 3060, 2980, 2840, 1740 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: 7.5 (d, 4H, J 9Hz); 7.2 (d, 4H, J 9Hz); 6.0 (s, 1H); 4.2 (d, 2H, J 1Hz); 3.8 (s, 6H); 3.4 (s, 2H); 3.0-2.8 (m, 2H); 2.5-2.2 (m, 4H); 1.9 ppm (s, 1H).

6,8-Bis(p-methoxyphenyl)-7-methyl-3-thia-7-azabicyclo[3.3.1]nonane-9ß-spiro-5'-oxazolidin-2'-one 18

(44%), mp 274-276°C; $C_{24}H_{28}N_2O_4S$ calc: C, 65.43; H, 6.41; N, 6.36; S, 7.28.
(methanol) (440.5) found: C, 65.38; H, 6.39; N, 6.41; S, 7.32.

IR (KBr): ν = 3360, 3090, 3060, 2960, 2950, 2840, 2790, 1740 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: 7.8-7.4 (m, 4H); 7.1 (d, 4H, J 9Hz); 5.4 (s, 1H); 3.7 (s, 6H); 3.4 (s, 2H); 3.0-2.7 (m, 2H); 2.4-2.1 (m, 4H); 1.7 ppm (s, 3H).

General Synthetic Procedure for Hydantoines 19a-20a & 19b-20b

Ketone 1a or 1b (8 mmol), potassium cyanide (8 mmol) and ammonium carbonate (12 mmol) in N,N-dimethylformamide (60 ml) were placed in a 250 ml flask. The reaction mixture was maintained at 60°C for 4 days. The solution was then washed with water (400 ml) and filtered under vacuum. The solid obtained was washed with ether (100 ml) and purified by recrystallization.

6,8-Diphenyl-3-thia-7-azabicyclo[3.3.1]nonane-9-spiro-5'-hydantoin 19a & 19b

(50%), mp 288-289°C; $C_{21}H_{21}N_3O_2S$ calc: C, 66.46; H, 5.57; N, 11.07; S, 8.44.
(n-butanol) (379.1) found: C, 66.39; H, 5.53; N, 11.02; S, 8.41.

IR (KBr): ν = 3310, 3060, 3030, 2980, 2890, 2740, 1755, 1730 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: 10.6 (s, 2H); 9.8 (s, 1H); 8.9 (s, 1H); 7.7-7.1 (m, 10H); 5.4 (s, 1H); 4.2 (d, 2H, J 1Hz); 3.9-3.7 (m, 2H); 2.5-2.0 (m, 4H); 1.8-1.6 ppm (m, 2H).

6,8-Diphenyl-7-methyl-3-thia-7-azabicyclo[3.3.1]nonane-9-spiro-5'-hydantoin 20a & 20b

(52%), mp 280-281°C; $C_{22}H_{23}N_3O_2S$ calc: C, 67.15; H, 6.02; N, 10.67; S, 8.14.
(methanol) (393.1) found: C, 67.21; H, 6.07; N, 10.72; S, 8.09.

IR (KBr): ν = 3080, 3060, 2960, 2880, 2760, 1780, 1710 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: 10.5 (s, 2H); 9.2 (s, 1H); 8.1 (s, 1H); 7.5-7.0 (m, 10H); 3.9 (d, 2H, J 4Hz); 3.8-3.6 (m, 2H); 2.6-2.3 (m, 4H); 2.2-2.0 (m, 2H); 1.7 ppm (s, 3H).

General Synthetic Procedure for Nitrones 21-24

Ketone 1 (10 mmol) was added to a solution of N-methylhydroxylammonium chloride (30 mmol) and potassium hydroxide (40 mmol) in methanol (130 ml). The reaction was refluxed with stirring for 48 h. The reaction was quenched with water (200 ml) and the mixture was extracted with methylene chloride (200 ml). The organic extract were dried on magnesium sulfate. The solvent is evaporated under reduced pressure and the residue is purified by recrystallization.

N-[6,8-Diphenyl-3-thia-7-azabicyclo[3.3.1]nonanilydene-9]-methylamine N-Oxide 21

(70%), mp 197-198°C; $C_{20}H_{22}N_2OS$ (338.2) (pentane) calc: C, 70.97; H, 6.55; N, 8.27; S, 9.47. found: C, 70.89; H, 6.60; N, 8.24; S, 9.45.

IR (KBr): ν = 3300, 3080, 3060, 2960, 2840, 2740, 1180 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ : 7.6-7.1 (m, 10H); 4.6 (d, 2H, J 1Hz); 3.6 (s, 3H); 3.1-2.9 (m, 2H); 2.7-2.3 (m, 4H); 1.6 ppm (s, 1H).

N-[6,8-Diphenyl-7-methyl-3-thia-7-azabicyclo[3.3.1]nonanilydene-9]-methylamine N-Oxide 22

(75%), mp 207-209°C; $C_{21}H_{24}N_2OS$ (352.2) (pentane) calc: C, 71.55; H, 6.86; N, 7.94; S, 9.09. found: C, 71.49; H, 6.93; N, 7.96; S, 9.12.

IR (KBr): ν = 3060, 3040, 3010, 2960, 2840, 2730, 1180 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ : 7.7-7.0 (m, 10H); 4.0 (d, 2H, J 4Hz); 3.6 (s, 3H); 3.0-2.8 (m, 2H); 2.8-2.3 (m, 4H); 1.7 ppm (s, 3H).

N-[6,8-bis(p-Methoxyphenyl)-3-thia-7-azabicyclo[3.3.1]nonanilydene-9]-methylamine N-Oxide 23

(68%), mp 210-212°C; $C_{22}H_{26}N_2O_3S$ (398.1) (pentane) calc: C, 66.30; H, 6.37; N, 7.03; S, 8.04. found: C, 66.22; H, 6.43; N, 7.10; S, 8.01.

IR (KBr): ν = 3300, 3060, 3010, 2970, 2900, 2840, 2750, 1170 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ : 7.5 (d, 4H, J 8Hz); 6.9 (d, 4H, J 8Hz); 4.6 (d, 2H, J 1Hz); 3.7 (s, 9H); 3.0-2.8 (m, 2H); 2.7-2.4 (m, 4H); 1.4 ppm (s, 1H).

N-[6,8-bis(p-Methoxyphenyl)-7-methyl-3-thia-7-azabicyclo[3.3.1]nonanilydene-9]-methylamine N-Oxide 24

(73%), mp 221-223°C; $C_{23}H_{28}N_2O_3S$ (412.1) (pentane) calc: C, 66.96; H, 6.84; N, 6.79; S, 7.77. found: C, 66.89; H, 6.93; N, 6.72; S, 7.82.

IR (KBr): ν = 3080, 3050, 2980, 2950, 2840, 2780, 1180 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ : 7.8-7.0 (m, 4H); 6.8 (d, 4H, J 9Hz); 4.1 (d, 2H, J 3Hz); 3.7 (s, 9H); 3.0-2.7 (m, 2H); 2.7-2.4 (m, 4H); 1.7 ppm (s, 3H).

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