HETEROCAGE COMPOUND [II][1) SYNTHESIS OF THIACAGE TRICYCLIC SYSTEMS: THIABRENDANE AND THIAISOTWISTANE SKELETON WITH AN AMINO FUNCTION AND THEIR S-OXIDE DERIVATIVES

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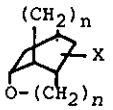
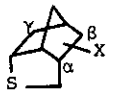
Abstract--- A series of thiacage tricyclic systems with amino functions were synthesized in order to examine their chemical, physicochemical and biological properties. Their S-oxide derivatives were also synthesized.

In the preceding paper of this series, synthesis of a series of oxacage tricyclic systems with versatile functional groups(1) was reported. As an integral part of our research program, synthetic study on the corresponding thia-series has been undertaken.



1(m,n:1-2)



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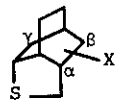


3

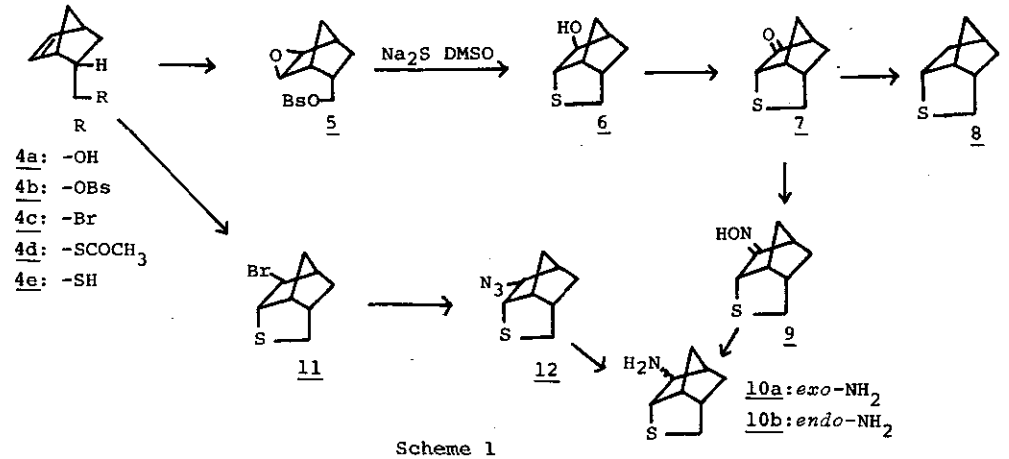
Here we wish to report synthesis of thiabrendane(2) and thiaisotwistane system (3) with versatile functional groups including amino functions at α-, β- or γ-position and also that of their S-oxide derivatives.[2,3] Investigation of their biological activities is thought to be of particular interest since the corresponding oxacage compounds were found to have an antiviral(influenza A) activity with weak CNS effects.[4]

The synthesis employed in this study involved intramolecular cyclization of bicyclo[2.2.1]heptene or bicyclo[2.2.2]octene derivatives with *endo*-sulfhydrylmethyl substituent as a key step for construction of the objective thiacage tricyclic systems.

γ-Amino-thiabrendane

The first synthesis of thiabrendane(8) was perfomed by C. R. Johnson et al.[2] according to the sequence(4a → 4b → 5 → 6 → 7 → 8) shown in Scheme 1.

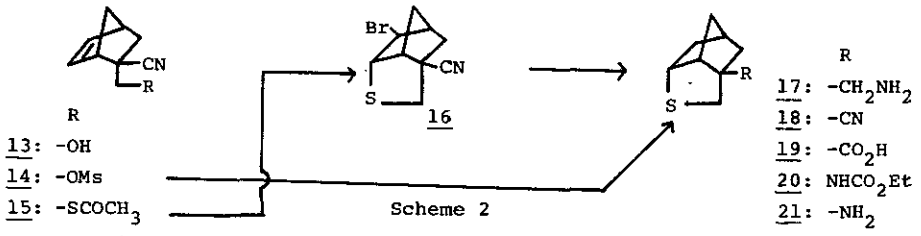
Attempt was then made to synthesize the objective γ-amino-thiabrendane using the Johnson's thiabrendanone(7) as an intermediate: An oxime(9, a *syn-anti* mixture)



Scheme 1

obtained by treatment of 7 with NH_2OH-HCl/Na_2CO_3/H_2O-EtOH at 80°C for 6 h, was reduced with $LiAlH_4$ in THF at 55°C for 1.5 h to give an *exo-endo* mixture of amine (4:1)[5] in 32% yield. The structure of the main diastereoisomer is considered to be γ-*exo*-amino-thiabrendane[10a, nmr($CDCl_3$): 3.1(m,1H), ir: 3350, 3270; HCl salt, mp(with decomposition)[6] 260-265°C]. The configuration was confirmed by synthesizing the *endo*-amine(10b) *via* an alternative route. That is, 5-norbornene-2-methanol(4a) was brominated, followed by acetothionation with potassium thioacetate($KSCOCH_3$) to give the thiolester(4d), which was then hydrolyzed by Na_2CO_3/CH_3OH in N_2 stream to give the thiol(4e, 47% from 4a). 5-Norbornene-2-methanthiol(4e) was subjected to intramolecular cyclization with bromine to give the objective bromo-thioether[11, 69%, nmr($CDCl_3$): 4.0(s,1H), 3.6(m,1H)]. S_N2-reaction of 11 with NaN_3/95%-EtOH at 80°C for 7 h yielded the azide(12, ir: 2100) in a nearly quantative yield, which was reduced with $LiAlH_4$ in ether at 30°C for 4.5 h to give the *endo*-amine[10b, HCl salt, mp(decomp.) 230°C], which was identical with the minor diastereoisomer obtained above. This result also indicates that direction of the cyclization was not crosswise, but frontwise.

α-Substituted Thiabrendane

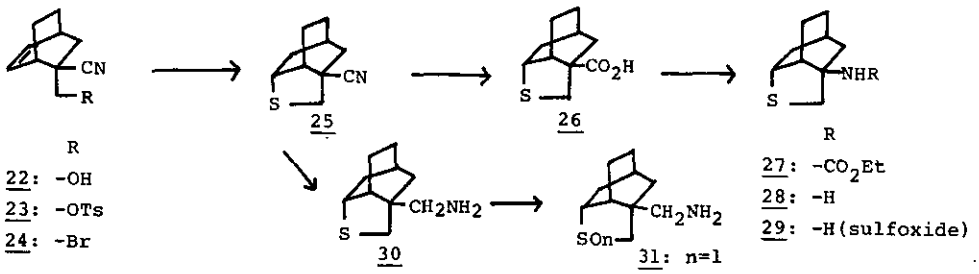


Scheme 2

2-*exo*-Cyano-2-*endo*-hydroxymethyl-bicyclo[2.2.1]hept-5-ene(13) obtained before[1] was treated with CH_3SO_2Cl/pyridine to give the mesylate(14, oil), which was then treated with $KSCOCH_3$/acetone at 60°C for 12 h, followed by methanolysis and bromination with bromine to give the bromo-thioether[16, 6.2% from 13, mp 106-108°C, nmr($CDCl_3$): 3.9(s,1H), 3.7(d,1H), 3.3(s,1H), 3.0(m,2H)]. Reduction of 16 with $LiAlH_4$ yielded the α-aminomethyl-thiabrendane[17, 52%, nmr($CDCl_3$): 3.4(m,1H), HCl salt, mp(decomp.) 270-280°C].

Debromination of 16 with tributyltin hydride(Bu_3SnH) in ether at room temperature yielded the nitrile[18, 90%, nmr($CDCl_3$): 3.4(d,2H), 3.1(m,2H)], which was hydrolyzed with KOH-ethylene glycol at 180°C for 15 min to give the carboxylic acid[19, 59%, nmr($CDCl_3$): 3.4(d,2H), 3.0(m,2H), mp 112-113°C]. Direct thiabrendane ring formation[7] could be achived by reacting the mesylate(14) with NaSH/DMF-DMSO at 80°C for 3 h, althoufh the yield was low(6%). Transformation of 19 into an acyl azide *via* a mixed anhydride by the reaction with ethyl chloroformate and NaN_3 in acetone, followed by heating in benzene-ethanol(the Curtius rearrangement) gave the ethoxycarbonylamino-thiabrendane[20, 95%, nmr($CDCl_3$): 3.2(s,2H), 2.6(m,1H), mp 75-77°C]. The objective amine was obtained by hydrolysis in KOH-ethylene glycol at 180°C for 30 min[21, nmr($CDCl_3$): 3.6(s,1H), 3.3(m,1H), 3.0(s,2H); HCl salt, mp (decomp.) 260°C].

α-Substituted Thiaisotwistane



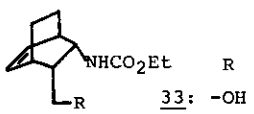
Scheme 3

2-*exo*-Cyano-2-*endo*-hydroxymethyl-bicyclo[2.2.2]oct-5-ene(22)[1] was converted *via* its p-toluenesulfonate(23, mp 95-96.5°C) into the bromide[24, 96%, oil, nmr ($CDCl_3$): 3.2(s,2H)]. Direct thiaisotwistane ring formation[7] could be achieved by treatment of 24 with NaSH/DMF-DMSO at room temperature for 8 h, although the yield was low[25, about 10%, mp 138°C, nmr($CDCl_3$): 3.4(m,1H), 3.2 and 2.8(dd,2H)].

Hydrolysis of 25 with KOH-ethylene glycol at 120°C for 15 min under N_2 yielded

the carboxylic acid(26, 60%, mp 108-113°C, ir: 3000, 2800, 1700). The acid(26) was converted *via* a mixed anhydride into an acyl azide, followed by the Curtius rearrangement in ethanol at 80°C to give α-ethoxycarbonylamino-thiaisotwistane[27, quantitatively, mp 73-76°C, nmr($CDCl_3$): 3.2(m,1H), 3.0(s,2H)]. The objective amine was obtained by heating in KOH-ethylene glycol at 120°C for 15 min under N_2 [28, 78%; HCl salt, mp(decomp.) 280°C]. The sulfide amine(28) was oxidized with potassium meta-periodate in aq. methanol to give an isomeric mixture[8] of the sulfoxide amine[29; nmr($CDCl_3$): 3.6, 3.4(d,1H), ir: 1040, 1010]. Reduction of 25 with $LiAlH_4$ gave the α-aminomethyl-thiaisotwistane[30, mp 75-77°C, nmr($CDCl_3$): 3.2 (m,1H), 2.7(m,2H)]. The sulfide amine(30) was oxidized to an isomeric mixture of sulfoxide amine by treatment with potassium meta-periodate in aq. methanol(31, 59%, ir: 3380, 3300, 1040, 1020). Oxidation of 30 into the sulfone(32) was found to proceed with potassium permanganate in acetic acid[32, 56%, ir: 3400, 3320, 1100; HCl salt, mp(decomp.) 265-268°C]. The use of other oxidizing reagents resulted in the decomposition of the substrate.

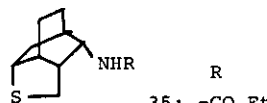
β-Amino Thiaisotwistane



R

33: -OH

34: -OTs



R

35: $-CO_2Et$

36: -H

2-*endo*-Hydroxymethyl-3-*endo*-ethoxycarbonylamino-bicyclo[2.2.2]oct-5-ene(33)[1] was converted into its tosylate(34, 48%), which was reacted with NaSH/DMF-DMSO at 90°C for 5 h to give the cyclized compound[7] [35, 64%, nmr($CDCl_3$): 3.3(m,1H), 2.7 (d,3H)]. The objective amine was obtained by heating in KOH-ethylene glycol at 120°C for 15 min under N_2 [36, 57%; HCl salt, mp(decomp.) 275°C].

Biological Properties of Thiabrendane and Thiaisotwistane with Amino Functions[9]

The sulfide amines obtained here were all found to possess both an antiviral activity and CNS effects, and their selectivities between both activities were found to be poor. Their biological activity was reduced by S-oxidation.

ACKNOWLEDGEMENT: The authors are grateful to Mr. Fujio Antoku for his excellent technical assistance.

REFERENCES AND NOTES

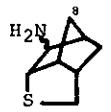
1) Part I of this series; Heterocycles, 1982, 19, 1419.

2) As for the synthesis of the thiacage tricyclic systems(2 and/or 3), those of the following compounds have been recorded in the literatures: a) Thiabrendanes with a methyl moiety at β-position: P. Wilder, Jr., J. Org. Chem., 1970, 35, 3295; b) Thiabrendane and thiaisotwistane with or without a hydroxy or an oxo moiety at γ-position: C. R. Johnson and W. D. Kingsbury, J. Org. Chem., 1973, 38, 1803.

3) In this paper, semi-trivial names and the designation "α,β or γ-: are adopted instead of the names and the position numbering following IUPAC nomenclature rule. The correlation between them is shown below.
α or β-Substituted thiabrendane: 5-thiatricyclo[4.2.1.$0^{3,7}$]nonane (α:3-, β:2-)
γ-Substituted thiabrenadne: 4-thiatricyclo[4.2.1.$0^{3,7}$]nonane (γ:2-)
α or β-Substituted thiaisotwistane: 5-thiatricyclo[4.3.1.$0^{3,8}$]decane (α:3-; β:2-)

4) Amantadine(amino-adamantane), only one markted antiinfluenza A viral agent in the United States, has potent CNS effects as well as its antiviral activity, and those CNS effects have limited the wide use of amantadine as an antiviral agent.

5) The epimeric isomers could be distinguished by ^{13}C-NMR, and their configuration was also assigned based on their ^{13}C-NMR($CDCl_3$): The peak of C_8-carbon of the *exo*-isomer(10a: δ^C, 29.0, t) appeared at higher field than that of the *endo*-isomer(10b: δ^C, 34.5, t) on account of steric compression effect due to the *exo*-amino substituent.



10a:*exo*-NH_2
10b:*endo*-NH_2

6) Melting points of all the amino-thiacage tricyclic derivatives(HCl salt) were measured by using sealed capillary tubes.

7) Such direct ring formation(thioetherization under basic media) would be due to the strong nucleophilicity of sulfhydryl moiety.

8) *exo-endo* Isomers concerning S→O bond could be detected by ^{13}C-NMR.

9) Biological evaluation was conducted by Messrs. H. Okajima, T. Yamaoka, H. Awata, S. Aono and Dr. S. Ogino of the same department.

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