HETEROCAGE COMPOUND [I]. SYNTHESIS OF OXACAGE TRICYCLIC SYSTEMS: OXABRENDANE, OXAHOMOBRENDANE, OXAISOTWISTANE, OXAHOMOISOTWISTANE AND OXATWISTBRENDANE SKELETON WITH AN AMINO FUNCTION

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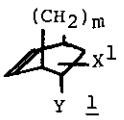
Abstract--- A series of various oxacage tricyclic systems with versatile functional groups including an amino function were synthesized in order to examine their chemical, physicochemical and biological properties.

The synthesis was based on the principle in which construction of the tricyclic systems was conducted by subjecting bicyclo[2.2.1]heptene or bicyclo[2.2.2]octene derivatives with an *endo*-hydroxyalkyl substituent to intramolecular cyclization.

As an extension of our previous research program to synthesize prostaglandins and their analogs using appropriately substituted bicycloheptene(1, m:1), readily accessible Diels-Alder reaction products, as key intermediates,[1,2] our research interest has next been focussed on synthesizing a series of functionalized heterocage tricyclic systems of the general formula(2 or 3, Z:O, S or NH) using the same type of bicycloheptene or bicyclooctene derivatives(1, m:1-2) as key intermediates.



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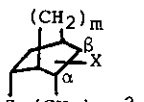

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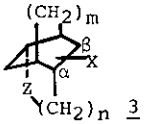

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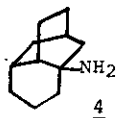

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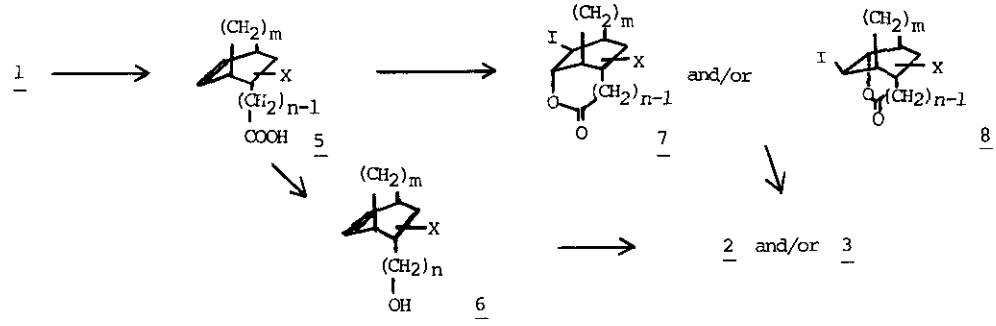
In fact, systematic studies on heterocage polycyclics have still been scarce and synthesis of this type of heterocage tricyclic systems has not been so extensively studied[3] although considerable attention has recently been paid to the synthesis and chemistry of heterocage polycyclics as well as to those of cage carbopolycyclics.[4] In our study, synthesis and biological evaluation of the heterocage tricyclic systems with an amino function has particularly been pursued since some cage carbocyclics with an amino function such as amino-adamantane(amantadine[5]) or amino-homoisotwistane(4)[6] have already been reported to have both an antiviral activity and central nervous system(CNS) effects.[7]

Here we wish to report the synthesis of oxabrendane(2, m,n:1, Z:O), oxahomobrendane(2, m:1,n:2, Z:O), oxaisotwistane(2, m:2,n:1, Z:O), oxahomoisotwistane(2, m,n:2, Z:O) and oxatwistbrendane(3, m,n:1, Z:O) skeleton with an amino function (X:-NH_2) at α- or β-position.[8]

Our synthetic route is outlined in Scheme 1. In this synthesis, the bicyclic system with an *endo*-hydroxyalkyl group(6) was cyclized with an assist of N-bromosuccinimide(NBS) or mercuric trichloroacetate to give the objective tricyclic systems. Alternatively, the bicyclic system with a carboxy or carboxymethyl group (5) was subjected to iodolactonization, and the resulting lactone linkage was then transformed into an ether one. Introduction of the amino function from X^1(carboxy group) was conducted by applying the Curtius or the Hofmann rearrangement before or after the formation of the tricyclic systems.



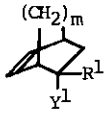
Scheme 1

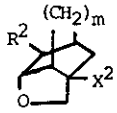
During this study, our attention was directed toward the following points; (1) how to distinguish the two substituents(X^1 and Y), (2) whether the direction of the cyclization *via* etherization or lactonization would be "frontwise" to yield 2 or 7, or "crosswise" to yield 3 or 8, and (3) whether cationic rearrangement would accompany or not. In such polycyclic systems there have been considerable difficulty in structure elucidation and also pronounced tendency to undergo cationic rearrangement, which would sometimes lead to serious misassignment.[9]

α-Substituted Oxabrendane and Oxaisotwistane

A mixture of the diene adducts(9a and 9b) obtained from *cyclopentadiene and* methyl α-cyanoacrylate nearly quantitatively(9a:9b=7:3) was reduced with $Ca(BH_4)_2$ to give the corresponding cyano-methanol(10a and its *exo*-isomer), which was cyclized with NBS in chloroform at 0°C to give the bromo ether(11, 71% from 9a after separation, mp 45-46.5°C). Debromination of 11 with tributyltinhydride(Bu_3SnH) yielded the nitrile(12), which was then partially hydrolyzed with H_2O_2-NaOH to

give the amide(13, 86% from 11, mp 138-139.5°C). The Hofmann rearrangement of 13 with aq. sodium hypobromite gave the objective α-amino-oxabrendane[14, 55%, nmr ($CDCl_3$): 4.3(1H,t), 3.6(2H,d); HCl salt, mp(with decomposition)[10] 305-310°C].





R^1	Y^1	m:1	m:2
-CN	$-CO_2CH_3$	9a	15a
$-CO_2CH_3$	-CN	9b	15b
-CN	$-CH_2OH$	10a	16a
$-CO_2H$	$-CH_2CO_2H$	21	28

X^2	R^2	m:1	m:2
-CN	-Br	11	17
-CN	-H	12	18
$-CONH_2$	-H	13	19
$-NH_2$	-H	14	20

By similar procedures as described above were obtained the corresponding homologs, bicyclooctene and oxaisotwistane derivatives. That is, a mixture of the diene adducts(15a:15b=93.2:6.8) obtained from cyclohexadiene and methyl α-cyanoacrylate nearly quantatively was reduced with $Ca(BH_4)_2$ to give the cyano-methanol (16a), which was cyclized with NBS to give the bromo ether(17, 59% from 16a, mp 108.5-109°C). The structure assignment of 17 was carried out by ^{1}H-nmr, ^{13}C-nmr and also X-ray crystallography.[11] In its ^{13}C-nmr spectrum, all the peaks could be attributed to all the constituent carbon atoms, and such ^{13}C-nmr analysis proved to be effective for structure assignment of the present oxatricyclic systems.

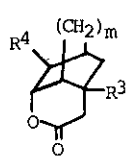
Debromination of 17 with Bu_3SnH gave the nitrile(18, mp 166.5-167.5°C), which was then hydrolyzed to give the amide(19). The Hofmann rearrangement of 19 with aq. sodium hypobromite gave the objective α-amino-oxaisotwistane[20, 50% from 19, nmr($CDCl_3$): 4.2(1H,m), 3.6(2H,s); HCl salt, mp(decomp.) 240-250°C].

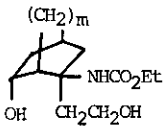
α-Substituted Oxahomobrendane and Oxahomoisotwistane

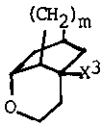
According to the method of Auken[12], the carboxy-iodolactone(22) was obtained in good yield from the dicarboxylic acid(21) by iodolactonization. Transformation of 22 into an acyl azide *via* a mixed anhydride by the reaction with ethyl chloroformate and sodium azide in acetone, followed by heating in benzene-ethanol(the Curtius rearrangement) gave the ethoxycarbonylamino-iodolactone(23, 62% from 22,mp 112-114°C). Deiodination of 23 with Bu_3SnH gave the lactone(24, 63%, mp 90-92°C).

Reduction of 24 with $Ca(BH_4)_2$ in ethanol gave the diol(25), which was then cyclized by treatment with p-toluenesulfonyl chloride(p-TsCl) and pyridine to give the ethoxycarbonylamino-oxahomobrendane[26, 32% from 24, nmr($CDCl_3$): 4.4(1H,m),3.8 (2H,m)]. The objective amine was obtained by heating of 26 in KOH-ethylene glycol

at 120°C for 7 h[27, 83%, nmr($CDCl_3$): 4.3(1H,m), 3.8(2H,d); HCl salt, mp(decomp.) 290-315°C].







R^3	R^4	m:1	m:2
$-CO_2H$	-I	22	29
$-NHCO_2Et$	-I	23	30
$-NHCO_2Et$	-H	24	31

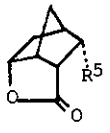
25(m:1)

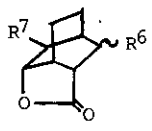
32(m:2)

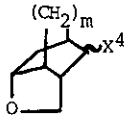
X^3	m:1	m:2
$-NHCO_2Et$	26	33
$-NH_2$	27	34

The cyano-methanol(16a) described above was methanesulfonylated, followed by cyanation with NaCN to give the dinitrile, which was hydrolyzed by aq. NaOH to give the dicarboxylic acid(28, 18% from 16a). Iodolactonization of 28 gave the carboxy-iodolactone(29, 50%), which was then transformed into the objective oxa-homoisotwistane system in a similar manner as described in the corresponding oxa-homobrendane series. The direction of lactonization of 28 was assigned by the lactone carbonyl streching frequency(1735cm^{-1}) of ir spectrum(30).[13] The Curtius rearrangement of 29 afforded the ethoxycarbonylamino-iodolactone(30, mp 140-144°C), which was then treated with Bu_3SnH to give the lactone(31, 75%, mp 118-120°C). Reduction of 31 with $Ca(BH_4)_2$, followed by treatment of the resulting diol(32) with p-TsCl/pyridine gave the ethoxycarbonylamino-oxahomoisotwistane[33, 28%, mp 87-88.5°C, nmr($CDCl_3$): 4.2(1H,m), 3.8(2H,m)]. The objective amine was obtained from 33 by heating in KOH-ethylene glycol at 120°C for 15 h[34, 26%; HCl salt, mp (decomp.) 320-330°C].

β-Substituted Oxabrendane and Oxaisotwistane







R^5	
$-CO_2H$	35
$-NHCO_2Et$	36

R^6	R^7	*endo*	*exo*
$-CO_2H$	-I	39	44
$-NHCO_2Et$	-I	40	45
$-NHCO_2Et$	-H	41	46

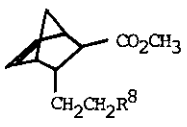
X^4	m:1	m:2
endo-$NHCO_2Et$	37	42
endo-NH_2	38	43
exo-$NHCO_2Et$		47
exo-NH_2		48

The carboxy-lactone(35) obtained previously[1f] was converted *via* a mixed anhydride into an acyl azide by the reaction with ethyl chloroformate and sodium azide, and followed by the Curtius rearrangement in ethanol at 80°C to give the ethoxycar-

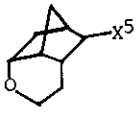
bonylamino-lactone(36, 40% from 35, mp 120-121°C). Reduction of 36 with $Ca(BH_4)_2$ in ethanol, followed by treatment with p-TsCl/pyridine yielded the β-*endo*-ethoxycarbonylamino-oxabrendane[37, 90% from 36, mp 68-69°C, nmr($CDCl_3$): 4.3(1H,m), 3.6 (2H,s)]. The objective amine was obtained from 37 by hydrolysis with KOH-ethylene glycol at 120°C for 7 h(38, 66%; HCl salt, mp 233-239°C). The *endo*-carboxy-iodolactone(39) was obtained from bicyclo[2.2.2]oct-5-ene 2,3-dicarboxylic acid[14] in 77% yield by iodolactonization with I_2-KI-$NaHCO_3$-H_2O[mp 191-193°C, ir(KBr): 1790, 1770,1730,1710 cm^{-1}]. Conversion of 39 into the ethoxycarbonylamino-iodolactone (40, mp 158-159°C) by the Curtius rearrangement was carried out in a similar manner as described above. Deiodination of 40 with Bu_3SnH gave the lactone(41, 52%, mp 157-159°C). Reduction of 41 with $Ca(BH_4)_2$ in ethanol, followed by treatment with p-TsCl/pyridine yielded the β-ethoxycarbonylamino-oxaisotwistane[42, 26% from 41, mp 83-84°C, nmr($CDCl_3$):4.1(2H,q), 3.8(2H,d)]. The objective amine was obtained from 42 by hydrolysis with KOH-ethylene glycol at 120°C for 9 h[43, 51%; HCl salt, mp(decomp) 248-256°C].

In a similar manner as described above for the *endo*-series, were obtained a series of the corresponding *exo*-compouds: The *exo*-carboxy-iodolactone[44, 79%, mp 182-185°C, ir(KBr): 1790,1760,1740,1715 cm^{-1}] was obtained by iodolactonization of bicyclo[2.2.2]oct-5-ene 2,3-*endo*,*exo*-dicarboxylic acid, and starting from 44, the following compounds were obtained; the ethoxycarbonylamino-iodolactone(45, 52% from 44, mp 90-91°C), the ethoxycarbonylamino-lactone(46, 47%, mp 156-159°C), the *exo*-ethoxycarbonylamino-oxaisotwistane[47, 32%, mp 133-135°C; nmr($CDCl_3$): 4.2(1H,m),3.7 (2H,s)] and the objective amine[48, 38%; HCl salt mp(decomp.) 265-275°C].

β-Substituted Oxahomobrendane



R^8
-Cl (49)
-OH (50)



X^5
$-CO_2CH_3$ (52)
$-NHCO_2Et$ (53)
$-NH_2$ (54)

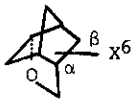
The adduct(49) obtained as a minor isomer by the Diels-Alder reaction of methyl 5-chloro-2-*trans*-pentenoate and cyclopentadiene was acetoxylated by sodium acetate in benzene, followed by methanolysis in the presence of Na_2CO_3 to give the corresponding alcohol(50). Intramolecular oxymercuration-demercuration was effected by treatment of 50 with mercuric trichloroacetate in water and then $NaBH_4$-NaOH to give the objective oxahomobrendane system(52). Hydrolysis of 52 gave its carboxylic acid, which was subjected to the Curtius rearrangement to give the ethoxycarbonyl-

amino-oxahomobrendane[53, 38%, nmr($CDCl_3$): 4.3(1H,m), 3.6(2H,m)]. The objective amine was obtained by hydrolysis of 53 with KOH-ethylene glycol at 120°C for 7 h[54, 15%; HCl salt, mp(decomp.) 270°C].

Direction of Cyclization and α- or β-Substituted Oxatwistbrendane

In our studies described above, there could be detected neither the cyclized product in "crosswise" nor the product formed by Meerwein type rearrangement.

In order to obtain the crosswise-cyclized products, the Kropp's procedure[15] was applied to bicyclo[2.2.1]heptene or bicyclo[2.2.2]octene derivatives with an *endo*-hydroxymethyl group(6, m:1-2, n:1), however only oxatwistbrendane system could be obtained in very poor yields from the former bicyclic system by irradiation with a high pressure mercury lamp in benzene at room temperature for 100 h; the nitrile (55) from the cyano-methanol(16a) in 5% yield, and the urethane(57) from the corresponding bicycloheptene(6, m,n:1, X: β-*endo*-$NHCO_2Et$) in 3% yield with recovered starting materials.



X^6: α-CN (55) β-*endo*-$NHCO_2Et$ (57)
α-CH_2NH_2 (56) β-*endo*-NH_2 (58)

Reduction of 55 with $LiAlH_4$ gave the aminomethyl-oxatwistbrendane[56, HCl salt, mp(decomp.) 255-260°C]. Hydrolysis of 57 with KOH-ethylene glycol at 120°C for 2 h yielded the β-*endo*-amino-oxatwistbrendane[58, 50%; HCl salt, mp(sublime) 180-200°C]

In comparative ^{13}C-nmr study of the oxatwistbrendane(55 and 57) with the corresponding oxabrendane series(12 and 37, respectively), there could be detected some characteristic spectrum pattern indicative of the direction of cyclization.[16]

Properties of the Substituted Oxacage Tricyclic Systems

The substituted oxacage tricyclic compounds obtained in this study were found to be fairly stable since they could stand without decomposition on treatment under ordinary storage conditions and even under aq. or nonaq. basic, or aq. acidic media. The objective amines obtained in this study(free bases) were all volatile oily substances and their hydrochloride salts were all powdery substances which tended to sublime at higher temperature. Further investigation of their chemical and physicochemical properties are now underway. As for their biological activities, these oxatricyclic systems with amino functions were found to show an antiviral(influenza A) activity similar to amantadine,[5] but interestingly much less CNS effects compared to amantadine.[17]

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

REFERENCES AND NOTES

1) J. Katsube and H. Shimomura et al., a) Agr. Biol. Chem., 1971, 35, 1828; b) ibid., 1972, 36, 1997; c) ibid., 1975, 39, 657; d) ibid., 1978, 42, 131; e) Tetrahedron Lett., 1976, 4099; f) ibid., 1979, 2607.

2) A. Mitra, "The Synthesis of Prostaglandins", Wieley-Interscience, 1977, p.190.

3) As for the synthesis of the oxacage tricyclic systems(2 and/or 3, Z:O), those of the following compounds have been recorded in the literatures: a) Oxabrendane and oxatwistbrendane: M. Nakazaki, K. Naemura and Y. Kondo, J. Org. Chem., 1976, 41, 1229; b) Oxaisotwistane(without data): M. Nakazaki and K. Naemura, J. Synth. Org. Chem. Japan, 1977, 35, 893; c) Oxahomoisotwistane(without data): H. W. Whitelock jr., J. Am. Chem. Soc., 1962, 84, 3412; d) Oxabrendane with a hydroxy or an acetoxy group: R. M. Moriarty and K. Kapadia, Tetrahedron Lett., 1964, 1165.

4) Interest is based on their characteristic features due to conformationally rigid structure, and they are useful in studies pertaining to stereochemistry and intramolecular interactions. For reviews of this subject, see a) L. N. Ferguson and J. C. Nadi, J. Chem. Educ., 1965, 42, 529; b) I. Tabuse, J. Synth. Org. Chem. Japan, 1969, 27, 403; c) C. Jr. Fort Raymond, "Adamantane", Marcel Dekker, 1976, and the description for heterocage compounds, p.267; e) T. Sasaki, Kagakunoryōiki, 1971, 25, 835 and ibid., 1979, 33, 147 and Heterocycles, 1979, 13, 531.

5) Amantadine is now clinically used in the United States as both an antiviral(influenza A) agent and an agent for treatment of Parkinson's disease; see, a) Merck Index, 9th ed., p.50(No. 377); b) J. S. Oxford and A. Galbraith, Pharmacol. Ther., 1980, 11, 181.

6) K. Aigami, Y. Inamoto, N. Takaishi and Y. Fujikura, J. Med. Chem., 1976, 19, 536.

7) CNS effects of amantadine have limited its wide use as an antiviral agent.

8) In this paper, semi-trivial names and the designation "α- or β-" are adopted for easy understanding instead of the names and the position numbering following the IUPAC organic nomenclature rules. The correlation between them is shown below.

oxabrendane---------	5-oxatricyclo[4.2.1.$0^{3,7}$]nonane	α:-3	β:-2
oxahomobrendane-----	6-oxatricyclo[5.2.1.$0^{3,8}$]decane	-3	-2

oxaisotwistane------	5-oxatricyclo[4.3.1.$0^{3,7}$]decane	-3	-2
oxahomoisotwistane--	6-oxatricyclo[5.3.1.$0^{3,8}$]undecane	-3	-2
oxatwistbrendane----	4-oxatricyclo[5.3.0.$0^{3,8}$]nonane	-6	-7

9) Some typical examples reported in the literatures are shown below. a) A rearrangement which occurred during the course of bromolactonization of bicyclo-[2.2.1]hept-5-ene-2-acetic acid(1, m:1, Y:-CH_2COOH, X^1:H) with $Br_2/NaHCO_3/H_2O$: D. I. Davies, M. D. Dowle and R. F. Kenyon, Synthesis, 1979, 990; b) A rearrangement which occurred in the acid catalyzed lactonization of *exo*- and *endo*-2-methyl-norbornene-2-carboxylic acid(1, m:1, Y:-COOH, X^1:-CH_3 or Y:-CH_3, X^1: -COOH): R. M. Moriarty, C. C. Chien and T. B. Adams, J. Org. Chem., 1979, 44, 2206; c) Competitive formation of γ- and δ-lactone(*via* frontwise and crosswise cyclization, respectively) by the electrophile addition to dimethyl *endo, endo*-bicyclo[2.2.2]oct-5-ene-2,3-dicarboxylate(1, m:2, X^1, Y:*endo* -$COOCH_3$): D. G. Garratt, M. D. Pyan and P. L. Beauliev, J. Org. Chem., 1980, 45, 839, e) A rearrangement which occurred by treatment of hydroxy-oxahomoadamantane derivatives in acetic media: H. Duddeck, V. Wiskanp and D. Rosenbaum, J. Org. Chem., 1981, 46, 5332.

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

11) X-ray crystallography analysis was performed by Mr. M. Minobe of the Central Research Institute of Sumitomo Chem. Co., Ltd.

12) R. K. Hill and T. V. van Auken, J. Org. Chem., 1958, 23, 626.

13) Measured in $CHCl_3$: The halo-δ-lactone(23), an analog to 30, was found to show the carbonyl stretching frequency at 1745 cm^{-1}.

14) H. Stockmann, J. Org. Chem., 1961, 26, 2025.

15) P. J. Kropp and H. J. Krauss, J. Am. Chem. Soc., 1969, 91, 7466.

16) The methylene carbon bound to oxygen in brendane system such as 12 and 37 resonated at lower magnetic field than those of twistbrendane systems such as 55 and 57, respectively. The detailed data will be reported in future.

17) Biological evaluation was conducted by Messrs. H. Okajima, T. Yamaoka, H. Awata, S. Aono and Dr. S. Ogino of the same department. The detailed data will be reported in future.

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