HETEROCAGE COMPOUND [IV][1] SYNTHESIS OF DIOXACAGE TRICYCLIC SYSTEMS: DIOXABRENDANE AND DIOXAISOTWISTANE SKELETON WITH AN AMINO FUNCTION

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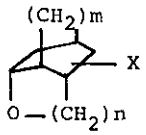
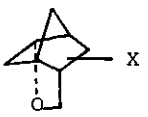
Abstract--- A series of dioxacage tricyclic systems with an amino function was synthesized in order to examine their chemical, physicochemical and biological properties.

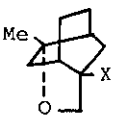
In our previous papers[1a,b], we have described the synthesis of various oxacage tricyclic systems with amino functions as represented by the general formula(1a, 1b and 1c) and also their interesting biological activities. The oxacage tricycles obtained there were found to show a significant antiviral (influenza A) activity similar to amantadine[2], but weaker CNS effects compared to amantadine.[3] This has prompted us to synthesize a series of dioxacage tricyclic systems in which two ether linkages are included in the cage tricyclic skeletons.
Here we wish to report synthesis of dioxabrendane(2) and dioxaisotwistane(3) with an aminomethyl group.[4]



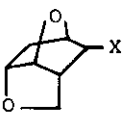
1a(m,n:1-2)



1b



1c



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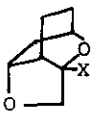


3

Dioxabrendane

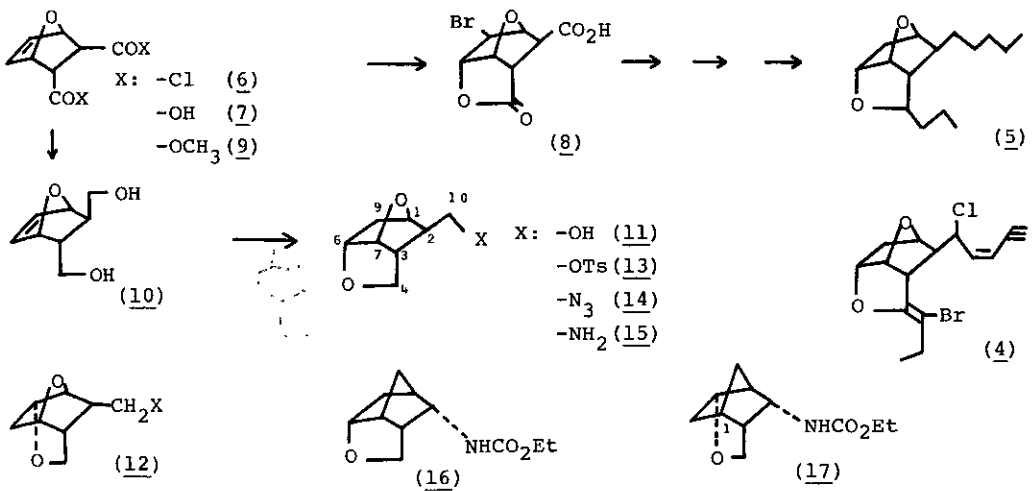
The dioxabrendane ring system has recently received particular attention since cis-maneonene-A(4) and their geometrical isomers which had been isolated from Hawaiian marine alga(Laurencia nidifica) were shown to contain the dioxabrendane system.[5] The synthesis of their reduction products(5) was also reported by Raithby et al.[6] starting from furan through the sequence (6→7→8→5) shown below.

We utilized the same diene adduct(6) as an intermediate. Thus, the product obtained by the reaction of furan and fumaryl chloride was treated with methanol to give the methyl ester(9). The diol(10) obtained by reduction of 9 with $LiAlH_4$ was subjected in situ[7] to cyclization with $Hg(OCOCCl_3)_2$, followed by treatment with $NaBH_4$ in dil. NaOH to give the methanol derivative(11) with the target dioxabrendane system, in 31 % yield from 9.

In the ^{1}H-NMR spectrum ($CDCl_3$) of 11, the methine proton signal at the 6-position (C-6) appeared at 4.37 as a double doublet ($J_{7,6}$=5.0 Hz, $J_{9exo,6}$=7.5 Hz), and the coupling constants for ($J_{2,1}$, $J_{1,9endo}$ and $J_{9endo,6}$) were found to be 0 in agreement with those of cis-maneonene-A in which their dihedral angles are 90°.

The splitting of the peak suggests the skeleton of 11 to be a dioxabrendane, and not to be a dioxatwistbrendane(12) based on the data of the corresponding pairs of oxabrendane(16) and oxatwistbrendane(17).

Thus, in the former oxabrendane series, the signal of the methine proton appeared as a triplet (J=7 Hz) while that in the latter oxatwistbrendane series appeared as a triplet (J=6 Hz) with further small splitting (J=2 Hz) due to the long-range coupling with the C-1-methine proton.

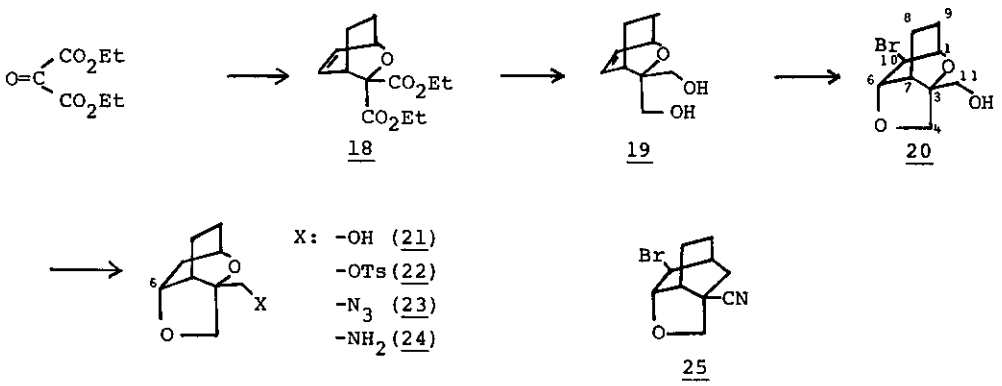


Treatment of 11 with p-TsCl and pyridine gave the tosylate(13), which was reacted with NaN_3 in dimethylformamide at 100°C to give the azide(14). Reduction of 14 with $LiAlH_4$ yielded the target dioxabrendane-methylamine(15).[8]

Dioxaisotwistane

Dimethyl 3-oxabicyclooctene-dicarboxylate(18)[9], prepared by the reaction of 1,3-cyclohexadiene and diethyloxo-malonate was reduced with $LiAlH_4$ to yield the 3-oxabicyclooctene-dimethanol(19) in a good yield.

Ring closure of 19 into a tricyclic system was attempted by treatment of 19 with N-bromosuccinimide in chloroform at room temperature for 24 h. The product thus obtained in 72 % yield from 19 was assumed to be the bromo ether(20) with a target dioxaisotwistane system, a novel cage system. Reduction of 20 with Bu_3SnH yielded the dioxaisotwistane-methanol(21), which was then converted into the tosylate (22). Treatment of 22 with NaN_3 in dimethylformamide yielded the azide(23) quantitatively, which was then reduced with $LiAlH_4$ to give the target methylamine (24)[8].



The ring structure assingment of these compounds was supported by their spectral data, especially by those of ^{1}H-nmr and ^{13}C-nmr. Thus, in the ^{1}H-nmr spectrum ($CDCl_3$) of 20, C-6-methine proton signal appeared at 4.51 as a doublet (J=5.6 Hz), the chemical shift and its splitting pattern of which are in agreement with the data for the corresponding oxaisotwistane derivatives obtained previously [for example 4.43(d,J=5.6 Hz) for 25].

Triplet peaks (around 4.3, J=5 Hz) for C-6-protons observed in the ^{1}H-nmr spectra ($CDCl_3$) of 21, 23 and 24 provided further supports to the structure assignment based on the data obtained in the corresponding oxaisotwistane derivatives.

^{13}C-nmr Data

The ^{13}C-nmr spectral data of both 11 and 20 are presented in Table 1. The interpretation of data has been done by using off-resonance techique and specific hydrogen-carbon decoupling(SEL) technique.

Table 1

^{13}C-nmr data for compounds 11 and 20

Compound	1	2	3	4	5	6	7	8	9	10	11
11 δc,ppm	*77.0 (d)	53.7 (d)	42.2 (d)	71.2 (t)	-	*76.9 (d)	82.4 (d)	-	40.5 (t)	63.6 (t)	-
20 δc,ppm	67.1 (d)	-	81.3 (s)	76.0 (t)	-	83.9 (d)	36.4 (d)	*20.8 (t)	*12.1 (t)	49.8 (d)	63.5 (t)

Multiplicity: s-singlet, d-doublet, t-triplet from off-resonance H.

* The assignments of two carbons are interchangeable for their nearly same chemical shifts of ^{13}C and ^{1}H-nmr.

EXPERIMENTAL

Melting points are uncorrected. IR spectra were measured by a HITACHI 260-10 spectrometer. NMR spectra were obtained with a Varian T-60, Varian XL-200 and JEOL FX-100 spectrometer in $CDCl_3$ with Me_4Si as an internal standard. MS spectra were recorded on a Shimadzu LKB-9000 instrument. High resolution mass spectra was recorded on a Hitachi M-80 instrument.

exo-3,6-Epoxy-Δ^4-tetrahydrophthalic(trans) dimethyl ester (9) A solution of an excess of furan (13.3 g, 0.196 mole) and fumaryl chloride(10 g, 65.4 mmole) in 100 ml of benzene was stirred in a sealed tube at room temperature. After 48 h, the reaction mixture was added into a mixture of methanol(5.2 g, 162 mmole) and triethylamine(16.6 g, 164 mmole) in 200 ml of ether at 10°C. After stirring for 30 min, the resulting mixture was extracted with Et_2O and the extract was washed with water, brine and dried over $MgSO_4$. After removal of the solvent, the residue was purified by column chromatography on silica gel to give the diester(9) as white crystals(4.2 g, 19.8 mmole, 30 %): mp 92-93.5°C(Lit.[10] 90-91°C); IR(KBr) 1740, 1220, 1180 cm^{-1}; NMR(δ): 6.35(2H,dd), 5.15(2H,d), 3.70(3H,s), 3.62(3H,s), 3.55(1H, dd), 2.80(1H,d).

2-Hydroxymethyl-5,8-dioxabrendane (11) $LiAlH_4$(LAH, 389 mg, 10 mmole) was suspended in THF(7.8 ml) and the mixture was stirred at 0°C for 10 min. A THF solution of the diester 9(1.0 g, 4.1 mmole) was added dropwise to the hydride suspension and the mixture was then stirred for 30 min at 25°C. Excess hydride was quenched by cautious addition of H_2O, and the mixture was then acidified with AcOH. To a stirred solution of trichloroacetic acid(1.34 g, 8.2 mmole) and mercuric oxide(888 mg, 4.1 mmole) in 11.1 ml of water was added the reaction mixture all at once. The mixture was stirred for 24 h at room temperature. To

the mixture was added an aq. solution of NaOH(656 mg, 16.4 mmole in 5 ml water), and then $NaBH_4$(156 mg, 4.1 mmole) in small portions, and stirring was continued for 1.5 h. The solution was decanted from Hg, concentrated to half-volume under reduced pressure, and extracted with three 30 ml portions of $CHCl_3$. The combined $CHCl_3$ phase was washed twice with 20 ml portions of water and dried ($MgSO_4$). Removal of the solvent in vacuo left an oil, which was purified by silica gel column chromatography using a mixture of $CHCl_3$ and MeOH(10:1) as an eluent to give 11(210 mg, 31 %) as a colorless liquid: IR(film) 3400, 2950, 2880, 1060, 1040 cm^{-1}; NMR(XL-200)(δ): 4.88(1H,t,J=5.0 Hz), 4.40(1H,t,J=5.0 Hz), 4.37(1H,dd,J=5.0, 7.5 Hz), 3.87(2H,m), 3.56(1H,m), 2.40(1H,br-s), 2.20(1H,m), 1.85(2H,m), 1.47(1H,d, J=13.2 Hz); MS m/e 156.0773(M^+), $C_8H_{12}O_3$ calculated: 156.0784.

2-p-Toluenesulfonyloxymethyl-5,8-dioxabrendane (13) To a stirred solution of 11 (780 mg, 5.0 mmole) and p-TsCl(1.24 g, 6.5 mmole) in benzene(7.8 mml) was added pyridine(2.14 g, 27 mmole) dropwise under ice cooling. The mixture was stirred for 24 h at room temperature. The reaction mixture was worked up in an usual manner and purified by column chromatography on silica gel to give 13(1.23 g, 81.3 %) as white crystals: mp 64-65°C; IR(film) 2980, 1600, 1360, 1245, 1190 cm^{-1}; NMR(δ): 7.79(2H,d,J=8 Hz), 7.33(2H,d,J=8 Hz), 4.85(1H,t,J=5 Hz), 4.35(2H,d,J=5 Hz), 4.05(1H,d,J=2 Hz), 3.85(3H,d,J=4 Hz), 2.50(3H,s), 2.06(2H,s), 1.2-1.9(2H,m); MS m/e 310(M^+), 138(base peak). Anal. Calcd. for $C_{15}H_{18}SO_5$: C,58.05; H,5.85; S,10.33. Found: C,58.12; H,5.94; S,10.08.

2-Azidomethyl-5,8-dioxabrendane (14) A mixture of 13(1.4 g, 4.5 mmole), NaN_3 (1.32 g, 20 mmole) and DMF(14 ml) was stirred for 3.5 h at 100°C. After cooling, the reaction mixture was diluted with water and extracted with ether. The extract was washed with brine and dried ($MgSO_4$). Removal of the solvent gave the azide(14, 440 mg, 54 %): IR(film) 2975, 2940, 2100, 1340, 1260, 1085, 1035 cm^{-1}.

2-Aminomethyl-5,8-dioxabrendane (15) LAH(138 mg, 3.64 mmole) was suspended in THF(2.8 ml) and the mixture was stirred at 0°C for 5 min. A THF solution(8.8 ml) of the azide 14(440 mg, 2.43 mmole) was added dropwise to the hydride suspension and the mixture was then stirred for 30 min at 25°C. Excess hydride was quenched by cautious addition of H_2O, followed by 0.14 ml of 15 % aq. KOH. The organic layer was dried on Na_2SO_4. Concentration led to the crude amine as a colorless liquid: mp 248-249.5°C(as a HCl salt, 530 mg, 61 %); IR(film) 3370, 3000, 1080, 1020 cm^{-1}; NMR(δ): 4.73(1H,t,J=6 Hz), 4.26(2H,dd,J=3, 6 Hz), 3.70(2H,d,J=3 Hz), 2.59(2H,dd,J=7, 3 Hz), 2.10(m,1H), 1.66(m,1H), 1.46(s,2H), 1.10(s,2H); MS m/e

155(M^+), 30(base peak). Anal. Calcd. for $C_8H_{13}NO_2$.HCl: C,50.11; H,7.37; N,7.31. Found: C,50.08; H,7.43; N,7.36.

2-Oxa-3,3-dicarboethoxybicyclo[2.2.2]oct-5-ene (18) Adduct 18 was prepared according to the method of the literature[9] in 85 % yield, bp 125-130°C/1.5 mmHg (Lit. 120°C/0.8 mmHg): IR(film) 2990, 1745, 1260, 1220 cm^{-1}.

2-Oxa-3,3-bis-hydroxymethylbicyclo[2.2.2]oct-5-ene (19) LAH(360 mg, 9.5 mmole) was suspended in ether(10 ml) and the mixture was stirred at 0°C for 10 min. An ethereal solution(10 ml) of the diester 18(1.21 g, 4.76 mmole) was added dropwise to the hydride suspension and the mixture was then stirred at 0°C for 3 h. Excess hydride was quenched by cautious addition of H_2O, and the contents were extracted with ether. The organic layer was washed with water and dried over $MgSO_4$. Concentration led to the crude dialcohol 19(790 mg, 87 %), which was recrystallized from isopropyl ether to give analytically pure 19 as white needles: mp 92-93.5 °C; IR(KBr) 3420, 3330, 2950, 1050, 1030, 1010 cm^{-1}; NMR(δ): 6.45(2H,m), 4.40(1H, m), 3.70(1H,m), 3.35(4H,d); MS m/e 170(M^+), 139(base peak). Anal. Calcd. for $C_9H_{14}O_3$: C,63.51; H,8.29. Found: C,63.50; H,8.60.

2,5-Dioxa-3-hydroxymethyl-10-exo-bromo-isotwistane (20) To a stirred solution of 19(170 mg, 1 mmole) in $CHCl_3$(10 ml) was added N-bromosuccinimide(178 mg, 1 mmole) under ice cooling. The mixture was stirred for 48 h at room temperature. The reaction mixture was treated with 10 % aq. sodium thiosulfate, and extracted with $CHCl_3$. The extract was washed with brine and dried over $MgSO_4$. Removal of the solvent in vacuo left an oil, which was purified by column chromatography on silica gel using $CHCl_3$ as an eluent to give 20(180 mg, 72 %) as white needles: mp 111-113°C; IR(KBr) 3350, 2970, 1460, 1303 cm^{-1}; NMR(XL-200)(δ): 4.51(1H,d,J=5.6 Hz), 4.04(2H,s), 3.6(4H,m), 2.05-2.25(3H,m), 1.75-1.95(3H,m); MS m/e 248, 250(M^+), 123(base peak). Anal. Calcd. for $C_9H_{13}O_3Br$: C,43.49; H,5.26; Br,32.08. Found: C,43.58; H,5.41; Br,32.36.

2,5-Dioxa-3-hydroxymethyl-isotwistane (21) To a stirred solution of Bu_3SnH(4.8 mmole) in ether(50 ml) was added the bromide 20(600 mg, 2.4 mmole) at room temperature in the presence of a catalytic amount of AIBN(10 mg). The mixture was stirred for 48 h at room temperature. Removal of the solvent in vacuo left an oil, which was purified by column chromatography on silica gel using a mixture of n-hexane and AcOEt(1:2) as an eluent to give 21(340 mg, 83 %) as a colorless liquid: IR(film) 3430, 2950, 1060, 990, 820 cm^{-1}; NMR(δ): 4.30(1H,t,J=5 Hz), 3.70 (1H,d,J=4 Hz), 3.65(2H,d,J=3 Hz), 3.60(2H,s); MS m/e 170(M^+), 124(base peak).

Anal. Calcd. for $C_9H_{14}O_3$: C,63.51; H,8.29. Found: C,63.14; H,8.50.

2,5-Dioxa-3-p-toluenesulfonyloxymethyl-isotwistane (22) The tosylate 22 was obtained in the same manner as described for the tosylate 13 in 68 % yield as a colorless liquid: IR(film) 2950, 2880, 1600, 1360, 1190 cm^{-1}; NMR(δ): 7.70(2H,d, J=8 Hz), 7.33(2H,d,J=8 Hz), 4.35(1H,t,J=5 Hz), 4.06(2H,s), 3.80(1H,m), 3.62(1H,d, J=2 Hz), 2.38(3H,s), 1.6-2.3(8H,m); MS m/e 324(M^+), 169(base peak). Anal. Calcd. for $C_{16}H_{20}SO_5$: C,59.24; H,6.21. Found: C,59.68; H,6.29.

2,5-Dioxa-3-azidomethyl-isotwistane (23) The azide 23 was obtained in the same manner as described for the azide 14 in a quantitative yield as a colorless liquid: IR(film) 2950, 2870, 2100, 1090, 1070 cm^{-1}.

2,5-Dioxa-3-aminomethyl-isotwistane (24) The amine 24 was obtained in the same manner as described for the amine 15 in 52 % yield as a HCl salt: mp 285°C (sublimed); IR(free base, film) 3370, 3300, 2940, 1050 cm^{-1}; NMR(δ): 4.33(1H,td,J= 5, 1 Hz), 3.85(1H,m), 3.75(2H,s), 2.8(2H,d,J=4 Hz) 1.3-2.0(9H,m); MS m/e 169(M^+), 30(base peak). Anal. Calcd. for $C_9H_{15}NO_2$.HCl: C,52.55; H,7.84; N,6.81. Found: C,52.60; H,7.87; N,6.75.

ACKNOWLEDGMENT: The anthors are grateful to Mr. Fujio Antoku for his excellent technical assistance.

REFERENCES AND NOTES

1) a) Part I of this series; Heterocycles, 1982, 19, 1419; b) Part III; Heterocycles, 1983, 20, 13.

2) 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.

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

4) In this paper, semi-trivial names are adopted for easy understanding instead of the names following the IUPAC organic nomenclature rules. The correlation between them is shown below.
dioxabrendane------5,8-dioxatricyclo[4.2.1.$0^{3,7}$]nonane
dioxaisotwistane---2,5-dioxatricyclo[4.3.1.$0^{3,7}$]decane

5) S. M. Waraszkiewicz, H. H. Sun and K. L. Erickson, J. Org. Chem., 1978, 43, 3194.

6) C. L. D. Jennings-White, A. B. Holmes and P. R. Raithby, J. Chem. Soc. Chem. Comm., 1979, 542.

7) The diol(10) was hard to be extracted from water layer due to its strong hydrophilic property.

8) The antiviral activities of the present dioxacage tricycles(15 and 24) were found to be reduced in comparison to those of the corresponding mono-oxacage-tricycles.

9) R. Bonjouklian and R. A. Ruden, J. Org. Chem., 1977, 42 4095.

10) T. A. Eggelte, H. de Koning and H. O. Huisman, Tetrahedron, 1973, 29, 2491.

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