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CONFIGURATIONAL AND CHEMICAL STUDIES ON (-)-6,8-DIBROMOBORNANE-2-ONE

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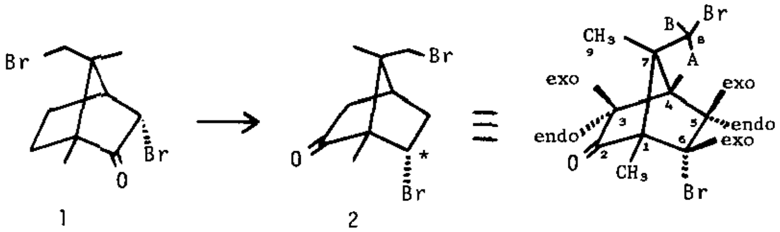
Abstract ——— The absolute configuration of C_6-bromine in (-)-6,8-dibromobornane-2-one (2) was confirmed by the spectral data. Condensation of 2 with hydrazine hydrate gave diazatricyclo[4,4,$0,0^{5,9}$]dec-7-one (7) which provided Diels-Alder adducts (9a,b) with dienes.

We have recently prepared a series of optically active (4*S*,7*R*)-4,7-methanoindazoles, and elucidated their appreciable pharmacological activities.1) In continuation of our work, the synthetic studies on the analogous heterocyclic compounds having two nitrogens in the tricyclic ring are considered to be useful for the development of the new pharmacologically effective compounds.

Nishikawa2) has reported an unusual reaction that (1*R*,3*S*,4*R*)-(+)-3,8-dibromobornane-2-one (1) rearranges to (1*S*,4*S*)-(-)-6,8-dibromobornane-2-one (2) in cold fuming sulfuric acid, however, the spectral and stereochemical studies concerned with the configuration of C_6-bromine in compound 2 were not described.

In this paper we report the absolute configuration about chiral center (*) and the chemical transformation of 2 to the new diazatricycle (7) and related compounds (9a,b).



1 2

Treatment of 1 with 30 % fuming sulfuric acid for 1 hr on cooling gave (1*S*,4*S*,6*S*)-6,8-dibromobornane-2-one [(2), mp 153-155° (lit.[2]) 152°); $[\alpha]_D^{25}$ -85.1° (*c*=0.308, EtOH); IR (nujol) cm^{-1} 1760 (CO); ^{1}H-NMR ($CDCl_3$) δ 1.94 (1H, dd, $J_{5en-5ex}$=16Hz, $J_{5en-6ex}$=3Hz, 5-Hen), 2.04 (1H, d, $J_{3en-3ex}$=18Hz, 3-Hen), 2.45 (1H, dd, $J_{3ex-3en}$=18Hz, J_{3ex-4}=4Hz, 3-Hex), 2.62 (1H, t, J_{4-5ex}=J_{4-3ex}=4Hz, 4-H), 2.76 (1H, sept, $J_{5ex-5en}$=16Hz, $J_{5ex-6ex}$=12Hz, J_{5ex-4}=4Hz, 5-Hex), 4.21 (1H, dd, $J_{6ex-5ex}$=12Hz, $J_{6ex-5en}$=3Hz, 6-Hex); M^+ 310]. Although the structure of 2 was assigned on the basis of the ^{1}H-NMR and ^{13}C-NMR as shown in Fig. 1 and Table 2 respectively, these spectral data and the nuclear magnetic resonance technique could not clearly establish the absolute configuration of the chiral center, so that we investigated the chemical shifts of C_8-protons on the related compounds (1, 3, 4 and 5) in order to examine the correlation between a substituent at C_5 and bromomethyl protons.

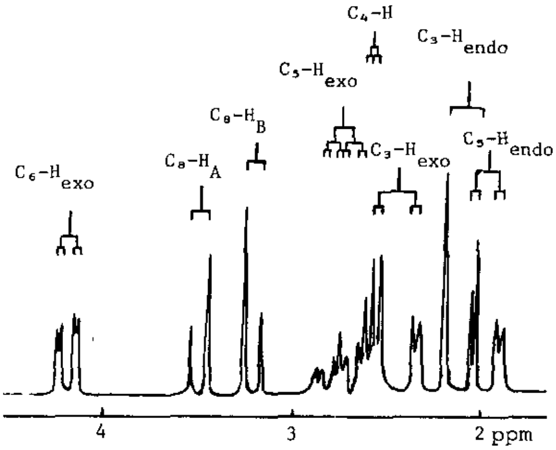
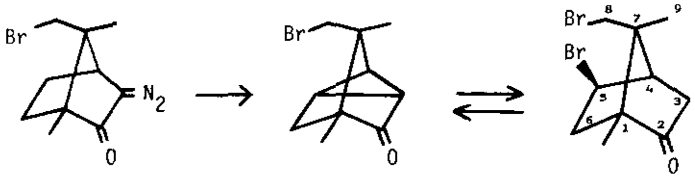


Fig. 1. ^{1}H-NMR of compound 2

For the purpose of this investigation, we carried out the synthesis of (1*R*,4*R*,5*R*)-5,8-dibromobornane-2-one (5) which has the *exo* C_5-bromine and probably shows a downfield shift of bromomethyl protons according to the strong deshielding effect by the *exo* bromine.

Compound 5 was prepared starting from 3 as follows; monotosylhydrazone of (1*R*,4*S*)-



3 4 5

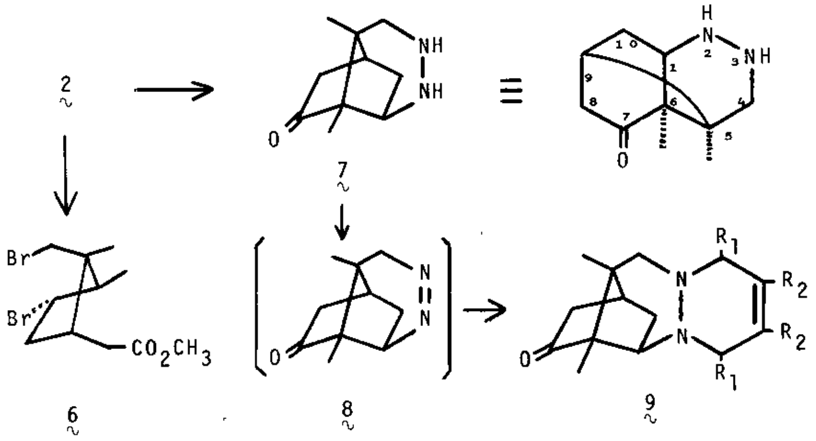
8-bromobornane-2,3-dione[3)] was dissolved in chloroform and passed through a basic alumina (Woelm) column to provide (1*R*,4*S*)-8-bromo-3-diazobornane-2-one [(3), mp 51-54°; Yield 84 %; ^{1}H-NMR ($CDCl_3$) δ 3.32 (1H, d, J=3Hz, 4-H)]. Pyrolysis of 3 with copper powder (Merck) at 130° gave (1*R*,4*R*)-7-bromomethyl-4,7-dimethyltricyclo-[2,2,1,$0^{2,6}$]heptan-3-one [(4), colorless oil; Yield 87 %; ^{1}H-NMR ($CDCl_3$) δ 2.27 (1H, t, J=4Hz, bridgehead proton)]. Subsequent substitution of bromine in 4 was achieved by treatment with hydrogen bromide in acetic acid to yield (1*R*,4*R*,5*R*)-5,8-dibromobornane-2-one [(5), mp 98-100°; Yield 68 %; $[\alpha]_D^{25}$ +43.8° (c=1.274, EtOH); ^{1}H-NMR ($CDCl_3$) δ 1.89 (1H, d, $J_{3en-3ex}$=19Hz, 3-Hen), 2.44 (1H, dd, $J_{3ex-3en}$=19Hz, J_{3ex-4}=5Hz, 3-Hex), 2.87 (1H, d, J_{4-3ex}=5Hz, 4-H), 4.09 (1H, t, $J_{5en-6en}$=$J_{5en-6ex}$=6Hz, 5-Hen); M^+ 310]. The ^{1}H-NMR of 5 showed the C_4-bridgehead proton as a doublet at δ 2.87 attributable to coupling with the adjacent *exo* C_3-proton. This observation provided an evidence that the configuration of C_5-bromine is *exo* , because the bridgehead proton is known[4)] to couple with only adjacent *exo* proton, but not *endo* proton.

As summarized in Table 1, the H_A and H_B protons of 2, as well as 1, 3 and 4, appeared as an AB quartet over a range of δ 3.63-3.19. In contrast, the H_A proton of 5 showed a considerable downfield shift (δ 4.30) which might apparently arised from deshielding effect by *exo* C_5-bromine. From these results, the absolute configuration of C_6-bromine in 2 was confirmed to be *endo*.

Table 1. Chemical Shifts and Coupling Constants of C_8-H_A and H_B (δ, $CDCl_3$)

Compd.	1	2	3	4	5
H_A	3.63	3.57	3.44	3.52	4.30
H_B	3.25	3.23	3.19	3.28	3.42
J(Hz)	11	11	11	10	11

Irradiation (100W, high pressure mercury lamp, Pyrex) of 2 in methanol-tetrahydrofuran containing sodium bicarbonate resulted in the cleavage of the bornane skeleton to provide methyl (1*S*,2*S*,3*S*,4*S*)-4-bromo-2-bromomethyl-2,3-dimethylcyclopentane acetate [(6), bp_1 105°; Yield 91 %; $[\alpha]_D^{23}$ -25.0° (c=0.72, EtOH); IR (nujol) cm^{-1} 1755 (CO_2CH_3); ^{1}H-NMR ($CDCl_3$) δ 0.98 (3H, s, C_2-CH_3), 3.39 (2H, s, CH_2Br), 3.68 (3H, s, OCH_3)]. The ^{1}H-NMR of 6 showed the bromomethyl protons as a singlet



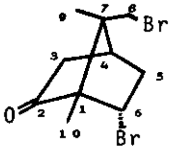
which means the cleavage of the rigid bornane ring.

Compound 2 was refluxed with hydrazine hydrate for 4 hr. After removal of hydrazine dihydrobromide, the resulting oily substance was repeatedly purified by alumina column to give (1*R*,5*S*,6*R*,9*S*)-5,6-dimethyl-2,3-diazatricyclo[4,4,0,$0^{5,9}$]dec-7-one [(7), mp 137-139°; Yield 74 %; $[\alpha]_D^{24}$ -45.3° (*c*=0.322, EtOH); IR ($CHCl_3$) cm^{-1} 3260 (NH), 1643 (CO); ^1H-NMR ($CDCl_3$) δ 4.40-4.72 (2H, br, NH-NH); M^+ 180]. ^{13}C-NMR (Table 2) of 7 was accorded with the proposed structure, though ^1H-NMR was too complicated to assign all of the protons. Similar condensation of 5 with hydrazine hydrate, however, resulted in dehydrobromination to provide a hydrazone of 4.

The azotricyclic compound 8 formed *in situ* by the oxidation of 7 with lead tetraacetate in methylenechloride would be expected to furnish Diels-Alder adducts with dienes. In order to examine the reactivity of this ring system, compound 7 was allowed to react with a variety of dienes of different reactivities.

Adducts, (1*R*,9*S*,10*R*,13*S*)-4,5,9,10-tetramethyl-2,7-diazatetracyclo[8,4,0,$0^{2,7}$,$0^{9.13}$]-tetradec-4-ene [(9a: R_1=H, R_2=CH_3), mp 96-99° (dec.); Yield 55 %; IR (nujol) cm^{-1} 1750 (CO), 1665 (C=C); ^1H-NMR ($CDCl_3$) δ 2.06 (4H, s, 2(CH_2-C=C)), 2.16 (6H, s, 2(CH_3-C=C)); M^+ 260] and (1*R*,9*S*,10*R*,13*S*)-9,10-dimethyl-3,6-diphenyl-2,7-diazatetracyclo[8,4,0,$0^{2,7}$,$0^{9,13}$]tetradec-4-ene [(9b: R_1=phenyl, R_2=H), mp 128-131° (dec.); Yield 51 %; $[\alpha]_D^{24}$ +17.4° (*c*=0.172, EtOH); IR (nujol) cm^{-1} 1750 (CO), 1660 (C=C); ^1H-NMR ($CDCl_3$) δ 7.18-7.60 (12H, m, olefinic and aromatic protons); M^+ 382] were obtained on the reaction with two reactive dienes such as 2,3-dimethyl-

Table 2. ^{13}C-NMR of 2 and 7 (ppm from TMS, $CDCl_3$)



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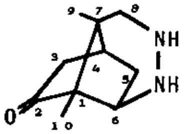

7

Compd.	C_1	C_2	C_3	C_4	C_5	C_6	C_7	C_8	C_9	C_{10}
2	64.1	210.8	37.9	40.5	39.1	42.0	48.2	49.3	17.7	7.9
7	59.6	160.9	33.7	40.3	42.7	49.9	47.9	55.7	20.8	9.1

1,3-butadiene and 1,4-diphenyl-1,3-butadiene. On the other hand, unidentified products were obtained when 7 was reacted with other dienes.

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