CHEMISTRY LETTERS, pp. 1823-1826, 1987.

Conformations and Reactivities of Dimethyl 2,4-Dibromobicyclo[3.2.1]octane-6,7-dicarboxylates and Their 8-Oxa Analogs. A New Access to Tetracyclo[3.2.1.$0^{2,7}$.$0^{4,5}$]octane System

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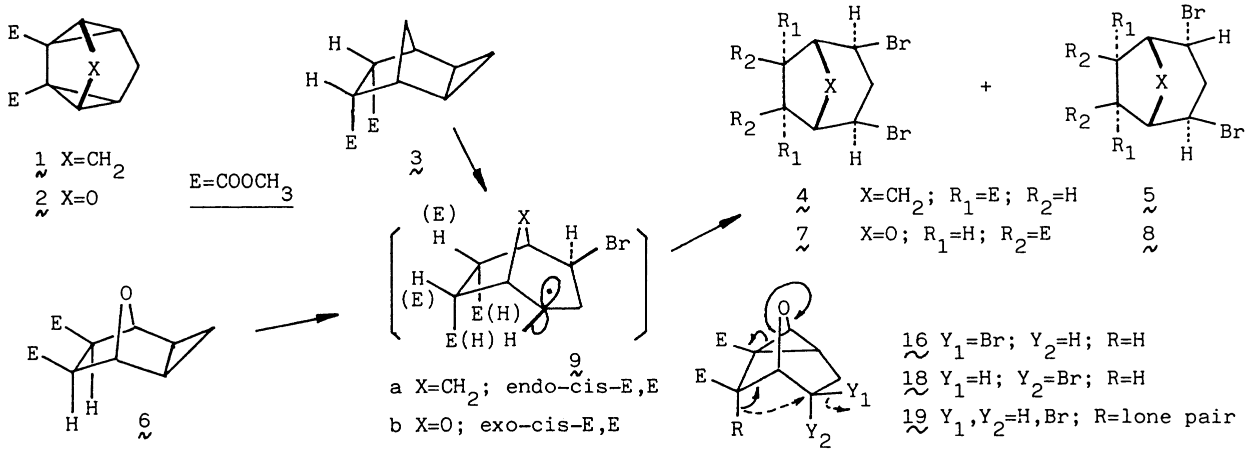
In solution, 6,7-disubstituted 2,4-dibromobicyclo[3.2.1]octanes and their 8-oxa analogs were deduced to exist preferentially in chair conformations of their 6-membered ring by comparing their J_{vic} with those calculated for the conformations obtained by MM2 method. Among them, the 2-exo,4-exo-dibromides on treatment with base gave readily tetracyclo[3.2.1.$0^{2,7}$.$0^{4,5}$]octane derivative and its 3-oxa analog by double 1,3-dehydrobromination.

exo-Tricyclo[3.2.1.$0^{2,4}$]octane derivative and its 8-oxa analog would be expected to undergo addition of bromine$^{1)}$ and may be transformed to 2,4-dibromobicyclo[3.2.1]octanes and their 8-oxa analogs, among which 2-exo,4-exo-dibromo compounds may be conformationally interesting because the less strained chair conformer$^{2)}$ in their 6-membered rings would suffer severe 1,3-diaxial interaction between two bromine atoms while the strained boat conformer$^{2)}$ would have no such interaction. Further, they may be used as precursors for the corresponding tetracyclooctane derivatives (1 and 2) if they have electron-withdrawing substituents on C_6 and C_7. These types of cage compounds had been obtained previously by intramolecular [2+2] addition under irradiation$^{3)}$ or under the influence of a transition metal complex$^{4)}$ but the above double cyclization approach with base has not been reported except in special cases,$^{5)}$ because it has been difficult to obtain the 2-exo,4-exo-dibromo compounds.

exo-Tricyclo[3.2.1.$0^{2,4}$]octane-6,7-endo-cis-dicarboxylate (3),$^{6)}$ obtained in 70% yield through cyclopropanation$^{7)}$ on the adduct of cyclopentadiene with maleic anhydride followed by methanolysis and esterification (CH_2N_2), was irradiated in dichloromethane$^{8)}$ (500W-HPL, Toshiba filter UV-39) for a short period of time in the presence of 2.5 equiv. mol of bromine$^{9)}$ to give 2-exo,4-exo-dibromobicyclo[3.2.1]octane-6,7-endo-cis-dicarboxylate (4)$^{10)}$(>90%) along with a slight amount of its 2-exo,4-endo-isomer (5).$^{10)}$ On the other hand, corresponding 8-oxa-6,7-exo-cis-dicarboxylate (6), similarly obtained in 73% yield from the adduct of furan with maleic anhydride, reacted under similar conditions in carbon tetrachloride$^{8)}$ rather slowly and gave a mixture (1:1) of 2-exo,4-exo-dibromo- (7)$^{10)}$ and 2-exo,4-endo-dibromo-8-oxabicyclo[3.2.1]octane-6,7-exo-cis-dicarboxylate (8)$^{10)}$ in quantitative yield. As the attack of bromine radical, formed by photolysis, on the bridgehead carbon in a three-membered ring, is to proceed with inversion of the stereochemistry,1) the exo-brominated radicals (9) must be initially formed and then they would attack on bromine molecule. In the case of 3, endo-ester groups might interfere the endo introduction of the 2nd bromine atom and 3 would give almost exclusively 4. In the case of 6, exo-standing ester groups might not interfere the introduction of the 2nd bromine atom from the endo side and a mixture of 7 and 8 might result. The preferred conformational structures of 4, 5, 7, and 8 were deduced from their ^{1}H-NMR spectra. Thus, comparison of the ^{1}H-^{1}H coupling constants obtained by successive decoupling experiments on 400 MHz ^{1}H-NMR spectra of these compounds with those calculated11) for preferred conformations of both chair and boat forms of 10, 11, 12, and 13, along with chair forms of 14 and 15, obtained by MM2 method clearly supports the preference of their chair conformations.12) The observed coupling constants shown in Table 1 of the cis and the trans dibromides (4, 7, 5, and 8) were very close to those calculated for the chair forms of 2-exo,4-exo- and 2-exo,4-endo-dibromides (10, 11, 12, and 13), respectively. The inconsistencies between calculated values of coupling constants, $J_{2,3exo}$ and $J_{2,3endo}$ for 14C and 15C, and those observed for 4 and 7 eliminate the endo-cis dibromo structures for these compounds.

On treatment with potassium t-butoxide (2.5 equiv. mol) in THF at -40 °C to -20 °C, 4 gave exclusively 1 (95%),10) but 7 gave 23) in rather low yield (29%). On the other hand, 7 with DBU (1.2 equiv. mol) in refluxing benzene gave tricyclic bromide 16 (90%),10) which was converted into 2 with potassium t-butoxide under the above conditions in 65% yield. The first cyclization step of 7 was found to be facile with DBU,13) but the second step with the same base was difficult; 16 gave 2 in 33% yield in addition to the lactonic ester (17)14)(23%). Treatment of the trans dibromide 8 with DBU gave the endo-monobromide (18) in 73% yield, but 18 resisted to further 1,3-dehydrobromination and gave only 17 in low yield (27%) on prolonged heating with a large excess of DBU. The formation of 17 can be rationallized as facile cyclopropane opening in the anion 19 by a push-pull mechanism.13,15) The ease of the first ring closure of 4 (93% with DBU) and 7 by base and probably the second cyclization by t-butoxide may be attributed to the stereoelectronic "3-exo-tetragonal" control16) as shown by the almost linear arrangement of bond Br-C$_2$ (or C$_4$) to C$_7$ (or C$_6$) on which anion is generated.



1 X=CH$_2$
2 X=O

E=COOCH$_3$

3

6

9
a X=CH$_2$; endo-cis-E,E
b X=O; exo-cis-E,E

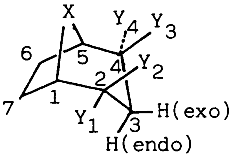
4 X=CH$_2$; R$_1$=E; R$_2$=H 5
7 X=O; R$_1$=H; R$_2$=E 8

16 Y$_1$=Br; Y$_2$=H; R=H
18 Y$_1$=H; Y$_2$=Br; R=H
19 Y$_1$,Y$_2$=H,Br; R=lone pair

Table 1. Dihedral Angles (φ) of Vicinal Protons, and Calculated (J_{calcd}) and Observed Values (J_{obsd}) of the Corresponding Coupling Constants[a)]

Compounds		H_1-H_2	H_5-H_4	H_2-H_{3exo}	H_4-H_{3exo}	H_2-H_{3endo}	H_4-H_{3endo}
10C	φ	57.9°	-57.8°	-71.6°	71.6°	41.3°	-41.3°
	J_{calcd}	3.20	3.22	1.95	1.95	5.48	5.48
10B	φ	88.9°	-104.6°	-153.7°	161.9°	-35.5°	46.2°
	J_{calcd}	0.79	1.49	9.74	10.81	7.26	5.62
14C	φ	-62.2°	62.2°	48.2°	-48.2°	165.2°	-165.2°
	J_{calcd}	2.68	2.68	5.31	5.31	11.10	11.10
4	J_{obsd}	+	+	0 Hz	0 Hz	5.8 Hz	5.8 Hz
11C	φ	62.4°	-62.3°	-72.5°	72.5°	41.2°	-41.2°
	J_{calcd}	1.75	1.76	1.88	1.88	5.50	5.50
11B	φ	96.3°	-114.6°	-157.6°	166.8°	-39.6°	49.2°
	J_{calcd}	1.29	3.14	10.29	11.29	6.65	5.15
15C	φ	-59.0°	59.0°	48.1°	-48.1°	166.0°	-166.0°
	J_{calcd}	3.60	3.60	5.33	5.33	11.22	11.22
7	J_{obsd}	1.7 Hz	1.7 Hz	1.3 Hz	1.3 Hz	5.6 Hz	5.6 Hz
12C	φ	56.6°	62.6°	-70.7°	-49.8°	44.0°	-165.3°
	J_{calcd}	3.39	2.63	2.04	5.05	5.05	11.15
12B	φ	110.5°	36.3°	-163.6°	28.15°	-49.1°	-86.8°
	J_{calcd}	2.09	6.49	10.99	7.50	5.16	1.18
5	J_{obsd}	5 Hz	2.2 Hz	0 Hz	5.4 Hz	4.6 Hz	12.7 Hz
13C	φ	60.0°	58.7°	-70.7°	-49.2°	45.0°	-165.0°
	J_{cacld}	1.97	3.64	2.04	5.15	4.89	11.13
13B	φ	119.3°	31.3°	-167.1°	30.5°	-51.2°	-85.8°
	J_{calcd}	3.78	6.97	11.31	7.15	4.83	1.20
8	J_{obsd}	1.7 Hz	3.8 Hz	1.7 Hz	5.4 Hz	4.9 Hz	11.9 Hz

a) The coupling constants were calculated by means of Altona's equation using parameter sets of D or E defined in the text.[11)] The following values of electronegativity differences for elements were used: $\Delta\chi_C$= 0.40; $\Delta\chi_{Br}$= 0.75; $\Delta\chi_O$= 1.30.

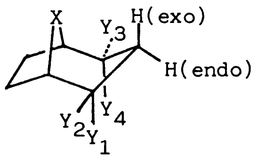


Chair (C)

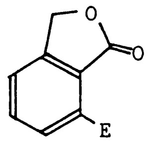
10 X=CH_2 11 X=O; Y_2=Y_3=Br; Y_1=Y_4=H

12 X=CH_2 13 X=O; Y_2=Y_4=Br; Y_1=Y_3=H

14 X=CH_2 15 X=O; Y_1=Y_4=Br; Y_2=Y_3=H



Boat (B)



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MM2 calculations were carried out using a program of Dr. Jun-Ichi Yoshida of our University which was presented by the courtesy of Professor Eiji Osawa of Hokkaido University. We want to express our gratitude to Professor Osawa and Dr. Yoshida for giving us permission to use it.

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8) The selection of the solvent was essential to clean photobromination.

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10) Physical Data. 4 mp 92-92.5 °C. 7 mp 189-191 °C. 8 mp 128-129 °C. 16 mp 131-133 °C. ^{1}H-NMR (400 MHz; $CDCl_3$) δ: 1 3.71 (s, 2OMe), 2.14 (t, J= 2.7 Hz), 2.05 (dt, J= 12.7, 2.7 Hz), 1.73 (d, J= 12.7 Hz). 2 4.52 (d, J= 6.1 Hz, 2CH-O), 3.74 (s, 2OMe), 2.24 (dm, J= 12.0 Hz), 1.96 (d, J= 12.0 Hz), 2.19 (t, J= 2.7 Hz). 4 4.88 (bs, H_2, H_4), 3.77 (dd, H_6, H_7), 3.68 (s, 2OMe), 3.14 (dm, J_{gem}= 18.3 Hz, H_{3endo}), 3.13 (d, J_{gem}= 12.9 Hz, H_{8syn}), 2.88 (bs, H_1, H_5), 2.40 (d, H_{3exo}), 1.57 (dm, H_{8anti}). 5 5.65 (H_2), 4.59 (H_4), 3.69 (OMe), 3.57 (OMe), 3.55 (H_6), 3.31 (H_{3endo}), 3.18 (H_7), 3.05 (H_5), 2.74 (H_1), 2.58 (H_{8syn}), 2.40 (H_{3exo}), 1.69 (H_{8anti}). 7 5.00 (s, H_1, H_5), 4.10 (bd, H_2, H_4), 3.70 (s, 2OMe), 3.23 (s, H_6, H_7), 2.57 (dt, H_{3exo}), 2.68 (H_{3endo}). 8 4.89 (b, H_5), 4.83 (bs, H_1), 4.58 (H_4), 4.11 (H_2), 3.72 (OMe), 3.70 (OMe), 3.68 and 3.27 (ABq, J= 9.8 Hz, H_6, H_7), 2.62 (dbt, H_{3exo}), 2.32 (dt, H_{3endo}). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 1 170.8 (s), 51.8 (q), 37.9 (s), 35.8 (d), 23.1 (t). 2 168.6 (s), 72.6 (d), 52.1 (q), 37.1 (s), 35.0 (d), 22.7 (t). 4 171.4 (s), 52.0 (q), 48.6 (d), 47.1 (d), 45.7 (d), 35.1 (t), 30.9 (t). 5 171.4 (s), 171.3 (s), 53.4 (q), 52.0 (q), 51.6 (d), 48.6 (d), 47.4 (d), 46.2 (d), 46.0 (d), 44.3 (d), 37.9 (t), 37.7 (t). 7 170.0 (s), 83.0 (d), 52.7 (q), 50.6 (d), 42.9 (d), 32.9 (t). 8 170.9 (s), 170.3 (s), 81.9* (d), 52.6* (q), 51.0 (d), 48.5 (d), 46.6 (d), 43.6 (d), 37.4 (t). 16 170.6 (s), 169.9 (s), 81.6 (d), 64.8 (d), 52.2 (q), 51.9 (q), 47.2 (d), 44.3 (d), 32.2 (s), 28.6 (t), 22.5 (d). 18 171.3* (s), 81.4 (d), 64.3 (d), 52.5 (q), 52.3 (q), 43.0 (d), 42.3 (d), 33.7 (s), 28.9 (t), 24.3 (d). The chemical shifts shown by asterisk may contain two similar carbon signals.

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(Received June 12, 1987)