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A FACILE SYNTHESIS OF MONO-OXA- AND -AZA-BIRD-CAGE COMPOUNDS *VIA* TRANSANNULAR CYCLIZATION (1)

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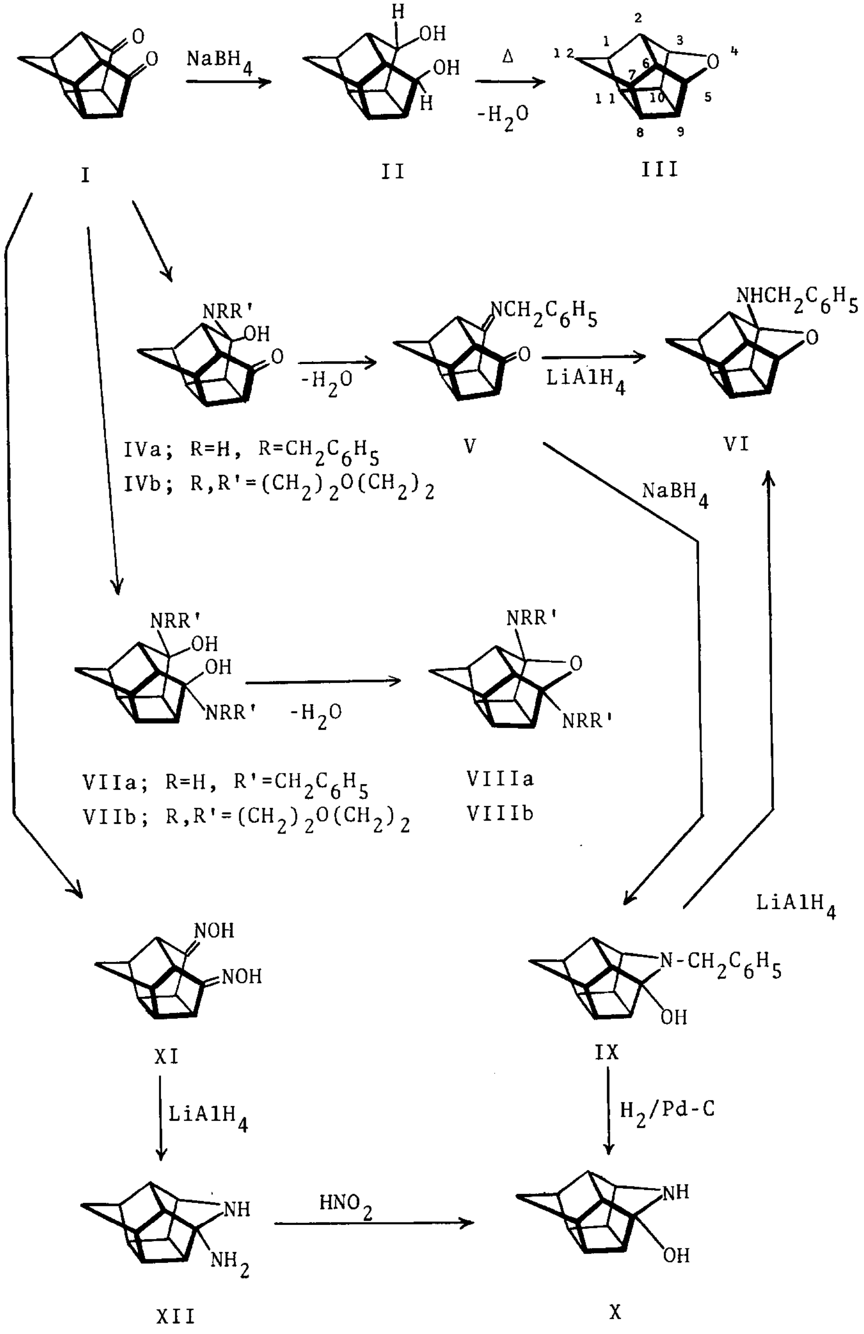
Tadashi Sasaki, Shoji Eguchi, and Tsutomu Kiriyama
Institute of Applied Organic Chemistry, Faculty of Engineering,
Nagoya University, Furo-cho, Chikusa-ku, Nagoya, 464, Japan

In a continuation of our studies on the synthesis and reactions of hetero-cage compounds (2,3), we wish to report a facile synthesis of mono-oxa- and -aza analogues of the so-called bird-cage compounds (4) by the transannular cyclization of the suitable materials.

As the starting material, we selected pentacyclo$[6.2.1.0^{2,7}.0^{4,10}.0^{5,9}]$-undecan-3,6-dione (I) which is easily obtained from the Diels-Alder adduct of cyclopentadiene and *p*-benzoquinone by $\pi 2s + \pi 2s$ intramolecular photocycloaddition (5).

Unsubstituted monooxabird-cage compound III (4-oxahexacyclo$[5.4.1.0^{2,6}.0^{3,10}.0^{5,9}.0^{8,11}]$dodecane) was obtained easily from a glycol II (5) on heating at its mp, followed by sublimation in 60% yield, mp 190-191° (sealed tube); *m/e* 160 (M^+); $\tau(CDCl_3)$ 5.27 (s, 2, CHOCH), 7.0-7.8 (m, 8, bridgehead protons), and 8.29 (AB-q, *J*=11 Hz, $J/\Delta\tau$=0.416, 2, CH_2)(6).

The additions of an equimolar amount of benzylamine and of morpholine to I in THF gave the corresponding 1:1 adducts, IVa, mp 95-97°dec; *m/e* 281 (M^+); ν (KBr) 3355, 3000-2400 and 1745 cm^{-1}, in 80% yield (7), and IVb, mp 186-189°dec; ν(KBr) 3250 and 1690 (8) cm^{-1}, in 56% yield, respectively. Both adducts were unstable; IVa was easily dehydrated to an oily Schiff base V, $\nu(CHCl_3)$ 1755, 1685 and 1603 cm^{-1}, which was characterized as trifluoroacetate salt, mp 123-125°; $\tau(CF_3COOH)$ 2.80 (m, 5, C_6H_5), 5.41 (d, *J*=4.5 Hz, 2, $=\overset{+}{N}HC\underline{H}_2$), 6.10-7.80 (m, 8, bridgehead protons), and 8.15 (AB-q, *J*=12 Hz, $J/\Delta\tau$=0.667, 2, CH_2). IVb


NaBH4
Δ
-H2O
1
2
3
4
5
6
7
8
9
10
11
12
I
II
III
NRR'
OH
-H2O
NCH2C6H5
LiAlH4
NHCH2C6H5
IVa; R=H, R=CH2C6H5
IVb; R,R'=(CH2)2O(CH2)2
V
VI
NaBH4
NRR'
-H2O
VIIa; R=H, R'=CH2C6H5
VIIb; R,R'=(CH2)2O(CH2)2
VIIIa
VIIIb
LiAlH4
NOH
N-CH2C6H5
OH
XI
IX
LiAlH4
H2/Pd-C
NH
NH2
HNO2
XII
X

dissociated rapidly to I and morpholine in chloroform solution.

$LiAlH_4$ reduction of V in ether gave 3-benzylamino-4-oxabird-cage compound VI in 30% yield, mp 116-117°; m/e 265 (M^+); ν(KBr) 3200 and 1605 cm^{-1}; τ($CDCl_3$) 2.78 (s, 5, C_6H_5), 4.42 (broad s, 1, NH), 6.29 (s, 2, NCH_2), 6.35 (broad s, ca. 1, CH-O), 7.1-7.9 (m, 8, other bridgehead protons), and 8.66 (AB-q, J=10.5 Hz, J/Δτ=0.300, 2, CH_2).

Treatment of I with two molar equivalent benzylamine under ice-cooling and then at room temperature gave 3,5-dibenzylamino derivative VIIIa in 72% yield, mp 94-95°; m/e 370 (M^+, very weak); τ($CDCl_3$) 2.55-3.00 (m,10), 6.05 (broad s, 4), 7.38 (s, 8), 7.75 (broad s, 2, disappeared on deuteration), and 8.35 (AB-q, J=11 Hz, J/Δτ=0.517, 2). Similarly, 3,5-dimorpholino derivative VIIIb was obtained in 85% yield, mp 232-233°dec; m/e 330 (M^+); τ($CDCl_3$) 6.05-6.45 (m, 8), 6.86-7.70 (m, 16), and 8.30 (AB-q, J=10 Hz, J/Δτ=0.429, 2). These 3,5-disubstituted oxabird-cage compounds are considered to be produced by a transannular dehydration of the corresponding bis-adducts VIIa and VIIb, because no transannular cyclization of the monoadducts IVa and IVb could be observed, and the OH absorption of the unstable bisadduct VIIb at 3400 cm^{-1} disappeared gradually on its recrystallization from n-hexane-CH_2Cl_2, affording VIIIb.

$NaBH_4$ reduction of V in THF-EtOH afforded 3-hydroxy-4-benzyl-4-azahexacyclo[$5.4.1.0^{2,6}.0^{3,10}.0^{5,9}.0^{8,11}$]dodecane (IX) in 36.5% yield (based on I), mp 77-78°; m/e 265 (M^+); ν(KBr) 3290 and 1603 cm^{-1}; τ(CCl_4) 2.5-3.0 (m, 5, C_6H_5), 5.50 (t, J=4.5 Hz, 1, CH-N), 6.13 (s, 2, N-CH_2), 7.0-7.8 (m, 8, other bridgehead protons), 8.05 (broad s, 1, OH), and 8.33 (AB-q, J=10.5 Hz, J/Δτ=0.467, 2, CH_2). Catalytic hydrogenation of IX over 10%Pd-C in EtOH gave 3-hydroxy-4-azabird-cage compound X in 70% yield, mp 138-140°; m/e 175 (M^+); ν(KBr) 3320, and 3060 cm^{-1}; τ($CDCl_3$) 5.41 (t, J=5.2 Hz, 1, CH-N), 6.9-7.9 (m, ca. 8, other bridgehead protons), 7.80 (s, 2, OH and NH), and 8.30 (AB-q, J=10.5 Hz, J/Δτ=0.439, 2, CH_2). IX was converted to VI in 86% yield on refluxing in THF in the presence of excess $LiAlH_4$.

On the other hand, treatment of I with hydroxylamine gave exclusively bisoxime XI in 85% yield, mp 302°dec, contrary to the report by Cookson et al (5) who described the formation of 3,5-dihydroxylamino-4-oxabird-cage compound instead of XI. Reduction of XI with $LiAlH_4$ gave 3-amino-4-azabird-cage compound XII in 40% yield, mp 192-195°; m/e 174 (M^+); ν(KBr) 3240 and 3120 cm^{-1}; τ($CDCl_3$) 5.58 (broad s, NH and NH_2), 6.32 (t, J=4.5 Hz, 1, CH-N), 6.5-7.9 (m, 8, other bridgehead protons), and 8.41 (AB-q, J=12 Hz, $J/\Delta\tau$=0.615, 2, CH_2), which on deamination with $NaNO_2$ in 75%HCOOH-AcOH at 5°, afforded also X in 80% yield.

References and footnotes

1. Studies on Hetero-Cage Compounds. Part III. Part II: T. Sasaki, S. Eguchi, and T. Kiriyama, submitted to Bull. Chem. Soc. Japan.
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3. T, Sasaki, S. Eguchi, and T. Kiriyama, J. Amer. Chem. Soc.,**91**, 212 (1969); Tetrahedron, **27**, 893 (1971).
4. For carbocyclic analogues, see R. J. Stedman, L. S. Miller, L. D. Davis, and J. R. E. Hoover, J. Org. Chem., **35**, 4169 (1970) and its preceding papers.
5. R. C. Cookson, E. Grundwell, R. R. Hill, and J. Hudec, J. Chem. Soc., 3062 (1964).
6. For this compound, cf., G. R. Underwood and B. Ramamorthy, Chem. Commun., 12 (1970).
7. All new compounds had satisfactory analyses. Mps are uncorrected.
8. In $CHCl_3$, the carbonyl absorption of IVb appeared at 1735 cm^{-1}, though some dissociation of IVb to I and morpholine was accompanied: The carbonyl absorption of I appeared at 1753 cm^{-1} as a shoulder after 10 min, which became stronger gradually on standing.