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OXABICYCLONONANE DERIVATIVES

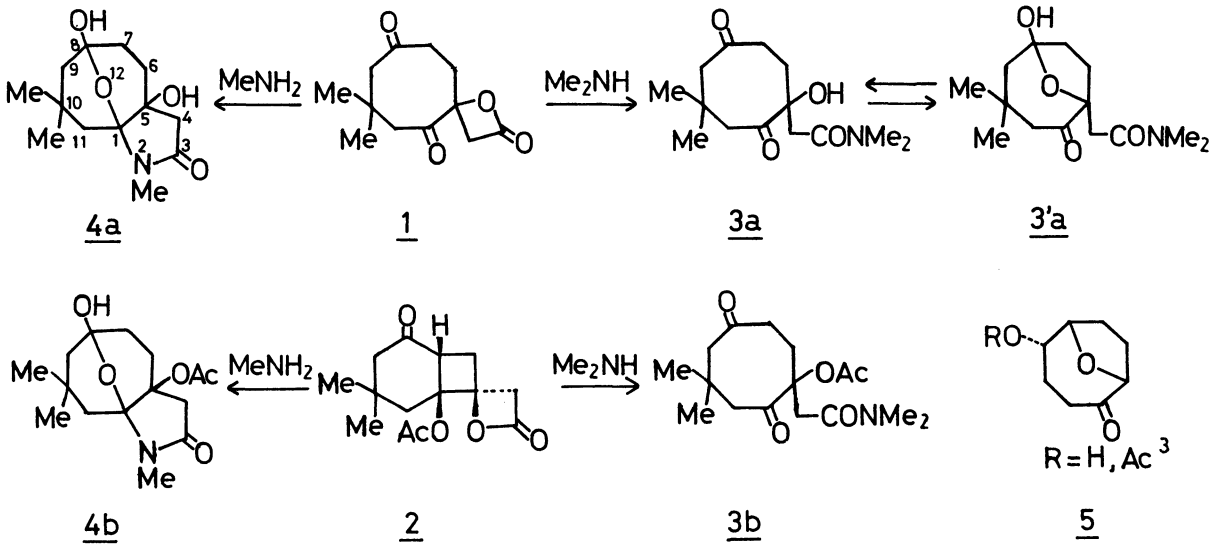
Tetsuzo KATO*, Masayuki SATO, and Yoshinori KITAGAWA
Pharmaceutical Institute, Tohoku University, Aobayama, Sendai 980

Reactions of 1-hydroxy-4,4-dimethylcyclooctane-2,6-dione-1-acetic acid β-lactone (1) and 6-acetoxy-7-hydroxy-4,4-dimethyl-cis-bicyclo[4.2.0]octan-2-one-7-acetic acid β-lactone (2) with methylamine give the oxabicyclononane derivatives (4a and 4b). Reaction of compound 1 with dimethylamine gives the amide (3a), whose transannular prototropic tautomerism is discussed.

Previously we have reported that cis-bicyclo[4.2.0]octan-2-one-7-acetic acid β-lactone (2) reacted with dimethylamine to give the cyclooctane derivative (3b)[1]. As a continuation of this study we investigated the reaction of 1-hydroxy-4,4-dimethylcyclooctane-2,6-dione-1-acetic acid β-lactone (1)[2]. The present communication reports the unique transannular prototropic tautomerism of the cyclooctane derivative (3a) and the synthesis of the novel heterocyclic ring system, 4a and 4b.

Compound 1 was allowed to react with 40% dimethylamine in $CHCl_3$ at room temperature for 2 hr to give the product, $C_{14}H_{23}NO_4$ (3a), in 59% yield, mp 111.5-113.5° (AcOEt-cyclohexane). The NMR spectrum in trifluoroacetic acid (TFA) was well consistent with the structure, 1-hydroxy-N,N,4,4-tetramethylcyclooctane-2,6-dione-1-acetamide (3a). NMR(TFA) δ 1.15(3H, s, CH_3), 1.21 (3H, s, CH_3), 1.82-2.80 (8H, m, $C_{3,5,7,8}$-methylene), 3.42, 3.61 (2H, ABq, J=17.5 Hz, α-methylene), 3.34 (6H, s, N-CH_3). However, the spectrum in pyridine and in $CDCl_3$ showed a little complicated signals suggesting the presence of its tautomers. For instance, in pyridine an AX type signal was observed at δ 2.25 and 4.12, which was assignable to the endo and exo protons of the C_3-methylene of the bicyclic structure (3'a) (Table 1). This assignment was made on the basis of the reported fact that the endo and exo protons of the C_3-methylene of 5-hydroxy(and 5-acetoxy)-9-oxabicyclo[4.2.1]nonan-2-one (5) exhibited great different chemical shifts giving the AX type signal[3]. The IR spectral data also supported this isomerization, i.e., the spectrum in $CHCl_3$ showed two

amide carbonyl peaks at 1640 and 1626 cm^{-1}, but that as a Nujol mull exhibited only one amide carbonyl peak at 1620 cm^{-1}.



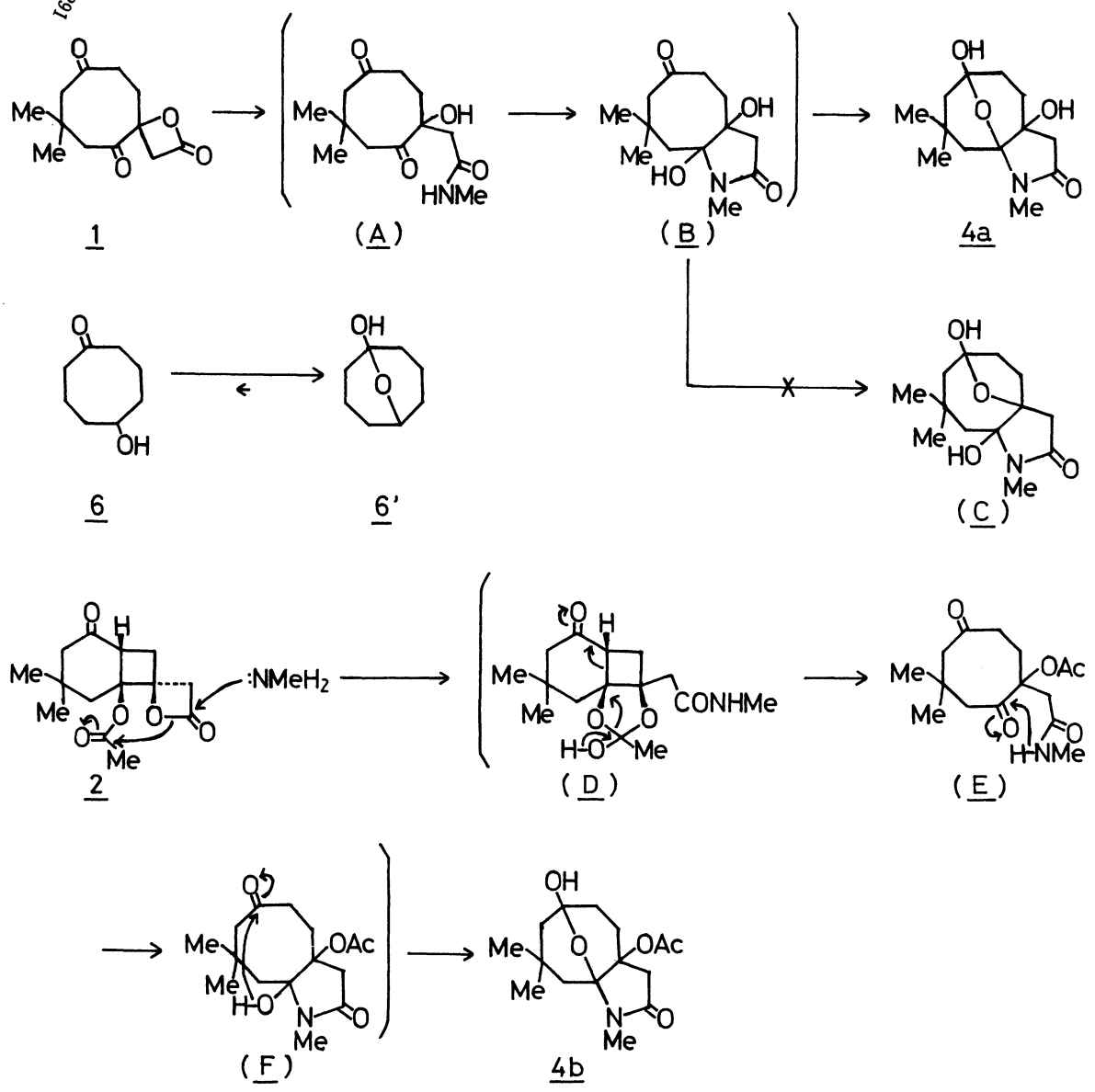
Similar tautomerisms were observed in case of 1-hydroxy-4,4-dimethylcyclooctane-2,6-dione-1-acetic acid (3c)[2] and its ester (3d)[2]. Namely, the NMR spectra of both compounds in TFA were consistent with the cyclooctanedione structures (3c and 3d). 3c: δ 1.20 (3H, s, CH_3), 1.23 (3H, s, CH_3), 2.20-2.75 (8H, m, $C_{3,5,7,8}$-methylene), 3.04, 3.48 (2H, ABq, J=17.0 Hz, α-methylene). 3d: δ 1.12 (3H, s, CH_3), 1.16 (3H, s, CH_3), 2.14-2.72 (8H, m, $C_{3,5,7,8}$-methylene), 2.96, 3.36 (2H, ABq, J=16.0 Hz, α-methylene), 3.79 (3H, s, OCH_3). On the other hand, their spectra in pyridine showed the similar pattern with that of 3a, i.e., an AX type signal was observed in both spectra (δ 2.35 and 4.00, J=11.5 Hz; 2.22 and 3.70, J=12.0 Hz) suggesting the endo and exo protons of the C_3-methylene of the bicyclo-isomers (3'c and 3'd) (Table 1).

Reaction of compound 1 with methylamine gave a sole product, $C_{13}H_{21}NO_4$ (4a)[5], in 78% yield, mp 182°(decomp.) (AcOEt). IR(KBr) 3490 (OH), 3260 (OH), 1675 (amide) cm^{-1}, NMR(pyridine) δ 1.04 (3H, s, CH_3), 1.44 (3H, s, CH_3), 1.76, 2.44 (2H, ABq, J=14.0 Hz), 1.80-2.24 (6H, m), 2.45, 3.04 (2H, ABq, J=16.0 Hz, C_4-methylene), 2.97 (3H, s, NCH_3), 4.86 (1H, br., OH). These data were consistent with the tricyclic structure (4a).

Compound 4b[5] was obtained in 55% yield by the reaction of 2 with methylamine, mp 176-177° (ether), $C_{15}H_{23}NO_5$. IR(Nujol) 3340 (OH), 1745 (ester), 1695 (lactam) cm^{-1}, NMR(pyridine) δ 1.10 (3H, s, CH_3), 1.46 (3H, s, CH_3), 1.66-3.15 (8H, m), 1.98 (3H, s, OAc), 3.00, 3.25 (2H, ABq, J=18.0 Hz, C_4-methylene), 3.05 (3H, s, NCH_3), 4.90 (1H, br., OH).

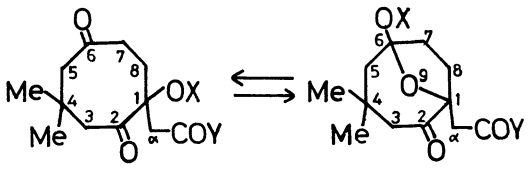
Although the precise mechanism of the formation of these products (4a and 4b)

remains obscure at present, the reaction is presumed as following: addition of methylamine to the oxetane carbonyl carbon of 1 gives the amide intermediate (A), which isomerizes to the cycloocta[b]pyrroridone derivative (B). Further cyclization of the intermediate B would give either the tricyclic hemiketal derivatives 4a or C. As mentioned above, the methylamide of 1 exsists in only one form in pyridine and in DMSO-d_6-$CDCl_3$ solution. Therefore, the 9-oxabicyclo[3.3.1]nonane structure (4a) is more stable compared with the 9-oxabicyclo[4.2.1]nonane system (C) because of the less steric strain of the structure. Such isomerization to the cyclic hemiketal had to be considered in view of the reported fact that 5-hydroxycyclooctanone (6) exsists almost exclusively in the hemiketal form, 1-hydroxy-9-oxabicyclo[3.3.1]-nonane (6')[4].



The formation of 4b can be explained as follows: addition of methylamine to 2 would give the tricyclic amide intermediate (D), acyl migration of which, accompanied with ring expansion, affords the cyclooctane derivative (E). Isomerization followed by cyclization gives the tricyclic hemiketal (4b) via the intermediate F.

Table 1 NMR Spectral Data of Compounds 3 and 3'*1



3a-d 3'a-d

a: X=H, Y=NMe_2 [5]
b: X=Ac, Y=NMe_2 [5]
c: X=H, Y=OH
d: X=H, Y=OMe

	Ratio (%)	4-CH_3	CH_2	N(O)-CH_3
3a	17	1.09, 1.12	1.94-3.30(10H, m)	2.62, 2.69
3'a	83	0.90, 1.01	2.83, 3.27(2H, ABq, J=16.0 Hz, α-CH_2), 2.25 (1H, d, J=11.5 Hz, endo-C_3-H), 4.12(1H, d, J=11.5 Hz, exo-C_3-H), 1.94-3.30(6H, m)	2.62, 2.69
3b	100	1.06, 1.32	3.46(2H, s, α-CH_2), 2.19(1H, d, J=13.0 Hz, $C_{3(5)}$-H), 3.40(1H, d, J=13.0 Hz, $C_{3(5)}$-H), 2.20-3.00(6H, m)	2.17, 2.78 2.82
3'b	0	- -	-	- -
3c	13	1.18, 1.29	2.00-3.53(10H, m)	
3'c	87	1.01, 1.10	2.92, 3.56(2H, ABq, J=16.0 Hz, α-CH_2), 2.35 (1H, d, J=11.5 Hz, endo-C_3-H), 4.00(1H, d, J=11.5 Hz, exo-C_3-H), 2.00-3.53(6H, m)	
3d	32	1.15, 1.24	2.84, 3.20(2H, ABq, J=15.0 Hz, α-CH_2), 1.90-3.03(8H, m)	3.50
3'd	68	1.00, 1.05	2.68, 3.30(2H, ABq, J=15.0 Hz, α-CH_2), 2.22 (1H, d, J=12.0 Hz, endo-C_3-H), 3.70(1H, d, J=12.0 Hz, exo-C_3-H), 1.90-3.03(6H, m)	3.54

*1 Spectra were taken on a JEOL-PS-100 instrument. Chemical shifts are given in parts per million relative to tetramethylsilane as an internal standard.

References

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5) Satisfactory elemental analyses were obtained.

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