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NOVEL RING TRANSFORMATION REACTIONS OF XANTHINE DERIVATIVES[1)]

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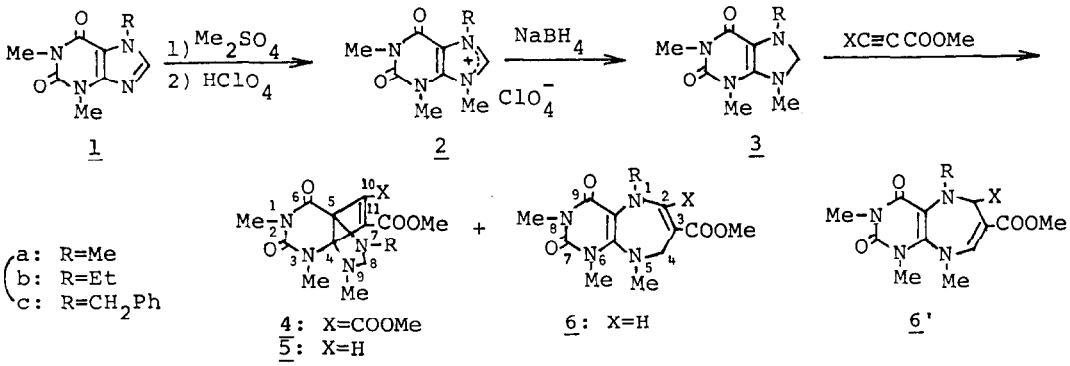
Summary: The novel ring transformation reactions were found in the reactions of 1,3,7,9-tetraalkyl-8,9-dihydroxanthines and acetylenic compounds. The reaction of the dihydroxanthine with DMAD gave a propellane type compound and with methyl propiolate afforded the similar type compound and a pyrimido[4,5-b]diazepine derivative. The mechanism of these reactions was also discussed.

Xanthine derivatives have potent biological activities of phosphodiesterase inhibition and vasodilation.[2)] There have been many reports on their synthesis, alkylation reactions[3)] and biological activities. However, the chemistry of 8,9-dihydroxanthine derivatives was little known.[4)] On the other hand, the reactions using acetylenic compounds[5)] are now remarkable in the heterocyclic synthesis. Now, we wish to report here the novel ring transformation reactions of 1,3,7,9-tetraalkyl-8,9-dihydroxanthines 3 with acetylenic compounds.

The 1,3,7,9-tetraalkylxanthinium perchlorates 2 were prepared by known procedures[6)] and quantitatively converted to the corresponding dihydroxanthines 3[3)] by reduction with sodium borohydride in water at ice bath temperature and then room temperature.

Compounds 3 reacted with 1.5 eq of acetylenic compounds in dry solvents under nitrogen atmosphere at room temperature for 1-2 days to give ring-transformed products 4-7. The reaction results were summarized in Table I.



Scheme I

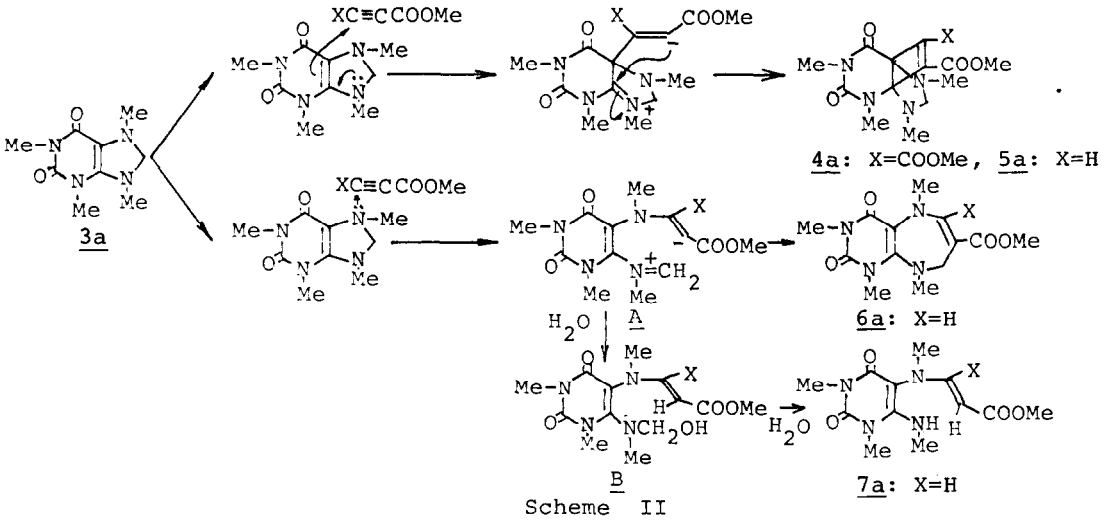
Table I : Reactions of 3 with Acetylenic Compounds

Dihydro-xanthines	Acetylenic Compounds [a]	Solvents	Time (days)	Products (Yields %)
3a	A	C_6H_6	2	4a (21)
3a	A	MeCN	1	4a (76)
3a [b]	A	MeCN	1	4a (70)
3a [c]	A	C_6H_6	2	4a (25)
3a	B	MeCN	2	5a (25), 6a (25)
3b	B	MeCN	2	5b (31), 6b (20)
3c	B	MeCN	2	5c (40)
3a	B	MeCN+H_2O	0.5	6a (9), 7a (42)

a) A is dimethyl acethylenedicarboxylate. B is methyl propiolate. b) All operations were done in the dark. c) added 2,6-di-tert-butyl-p-cresol.

The structure of the propellane type compound 4a[7] was determined by ^{1}H-NMR, ^{13}C-NMR and so on. In the ^{1}H-NMR spectrum, one of the C_8-methylene protons was observed at δ 3.31 (d, J_{gem}= 7.0Hz) by the shielding effect of C_{10}-C_{11} double bond. In the ^{13}C-NMR spectrum, signals of two sp^2 carbons (C_4 and C_5) of 3a were disappeared, and signals of two tertiary sp^3 carbons (C_4, δ 83.0 and C_5, δ 71.8) were observed. Other characteristic signals were as follows: two sp^2 carbons, C_{10}, C_{11} (δ 141.6, 142.4) and a methylene carbon, C_8 (δ 77.0). On the other hand, the structure of the ring-enlarged compound 6a[8] was determined based on the nuclear Overhauser effect (NOE). The irradiation of 6a at the frequency of the 1-methyl signal (δ 3.32) [9] increased the intensity of the olefinic proton (δ 7.41) by ca. 20%. On the contrary, in the case of the irradiation at the frequency of the olefinic proton signal, the NOE was not clear because of the overlap of signals (δ 3.32) for two methyl groups (1- and 8-methyls). Further, the irradiation of methylene protons (δ 3.84) increased the intensity of 5-methyl signal (δ 2.68) by ca. 18%, whereas the irradiation at the frequency of 5-methyl was of no effect. These NOE experiments exclude the possibility of 6a' for the structure of the ring-enlarged compound.

Although the reaction of 3a with dimethyl acetylenedicarboxylate (DMAD) afforded only a propellane type cycloadduct 4a, the reaction with methyl propiolate gave the ring enlarged pyrimido[4,5-b]diazepine derivative 6a in addition to the propellane type compound 5a.[10] The mechanism for the formation of 4a and 5a, in which either stepwise or concerted cycloaddition is considered, was clarified by the following reactions. The yield of 4a in dry benzene was very low, but in dry acetonitrile much improved up to 76%. The reaction without light, which accelerates the concerted [2+2] cycloaddition, or the addition of 2,6-di-tert-butyl-p-cresol as a radical scavenger exerted no influence on the yield of 4a (Table I). These results indicate that this reaction may proceed by an ionic cycloaddition of acetylenic compounds to an enamine moiety of 3a. On the other hand, the reaction mechanism for 6a may be explained as shown in Scheme II. Methyl propiolate initially attacks on N_7, followed by the cleavage of the N_7-C_8 bond, and resulting iminium salt intermediate A gives 6a. In the presence of water



Scheme II

A leads to 7a[11] via an intermediate B in 42% yield.

DMAD, which is bulkier than methyl propiolate, did not afford the ring-expanded compound. Moreover, the dihydroxanthines 3b and 3c having the bulkier group (ethyl or benzyl) at N_7, were less transformed to ring-expanded compounds than 3a (Table I). Therefore, the ratio of the propellane type compounds 4 and 5, and the ring-expanded compound 6 may be affected by the bulkiness of dihydroxanthines and acetylenic compounds . That is, acetylenic compounds react mainly on C_5 more than on N_7, if bulky acetylenic compounds are used or bulky group is substituted on N_7 (Scheme II).

Further work on the other reactions of 3a is now in progress.

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7) 4,5,8,9-tetrahydro-4,5-(dimethoxycarbonyletheno)-1,3,7,9-tetramethylxanthine (4a): mp 110°. ^{1}H-NMR ($CDCl_3$) δ: 2.53, 2.67, 3.24, 3.27 (each 3H, each s, 4 X N-Me), 3.31 (1H, d, J=7.0Hz, C_8-H), 3.86, 3.92 (each 3H, each s, 2 X O-Me), 4.02 (1H, d, J=7.0Hz, C_8-H). ^{13}C-NMR ($CDCl_3$) δ: 28.7, 32.3, 34.9, 37.2 (4 X N-Me), 53.1 (2 X O-Me), 71.8 (C-5), 77.0 (C-8), 83.0 (C-4), 141.6, 142.4 (C-10, 11), 152.1 (C-2), 161.7, 162.6 (2 X COOMe), 165.8 (C-6). MS m/e: 351 (M^+-1), 210 (base peak).

8) 4,5-dihydro-3-methoxycarbonyl-1,5,6,8-tetramethyl-7,9-dioxopyrimido[4,5-b]1H-1,5-diazepine (6a): mp 136°. ^{1}H-NMR ($CDCl_3$)δ: 2.68, 3.32, 3.32, 3.45 (each 3H, each s, 4 X N-Me), 3.69 (3H, s, O-Me), 3.84 (2H, bs, C_4-H_2), 7.41 (1H, s, C_2-H). ^{13}C-NMR ($CDCl_3$)δ: 28.5, 29.8, 37.8, 43.1 (4 X N-Me), 51.1 (O-Me), 52.6 (C-4), 97.8 (C-3), 117.7 (C-9a), 145.9 (C-2), 150.8 (C-5a), 151.9 (C-7), 159.9 (COOMe), 168.1 (C-9). MS m/e: 294 (M^+), 209 (base peak).

9) These assignments were determined by ^{1}H-NMR spectrum of 6a, which is substituted by 5-CD_3 instead of 5-CH_3.

10) 4,5,8,9-tetrahydro-4,5-(11-methoxycarbonyletheno)-1,3,7,9-tetramethylxanthine (5a): mp 93-95°. ^{1}H-NMR ($CDCl_3$)δ: 2.51, 2.57, 3.19, 3.31 (each 3H, each s, 4 X N-Me), 3.31 (1H, d, J= 6.6Hz, C_8-H), 3.80 (3H, s, O-Me), 3.98 (1H, d, J=6.6Hz, C_8-H), 7.13 (1H, s, C_{10}-H). MS m/e: 293 (M^+-1), 210 (base peak).

11) 5-(trans-2-methoxycarbonylvinyl)methylamino-6-methylamino-1,3-dimethyluracil (7a): ^{1}H-NMR ($CDCl_3$)δ: 2.95 (3H, d, J=6.0Hz, NH-Me), 3.06, 3.30, 3.45 (each 3H, each s, 3 X N-Me), 3.62 (3H, s, O-Me), 4.62 (1H, d, J=13.2Hz, olefinic H), 4.90-5.20 (1H, br, NH), 7.42 (1H, d, J= 13.2Hz, olefinic H). MS m/e: 282 (M^+), 209 (base peak).

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