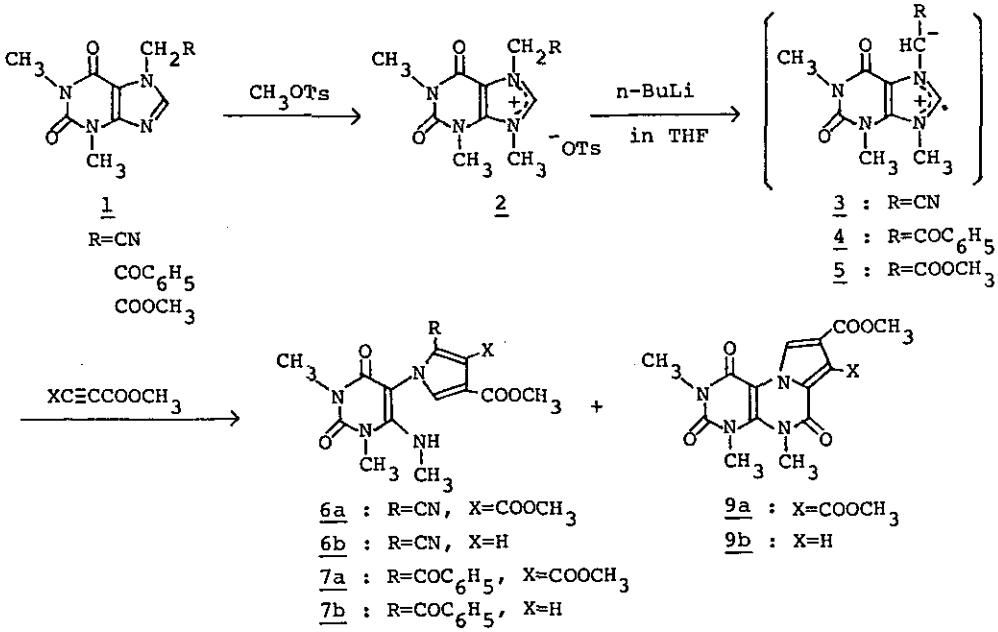
RING TRANSFORMATION REACTIONS OF NOVEL XANTHINIUM YLIDES[1)]

Mikio Hori*, Tadashi Kataoka, Hiroshi Shimizu, Eiji Imai,
Yukiharu Matsumoto, and Masanori Kawachi
Gifu College of Pharmacy, 5-6-1, Mitahora-higashi, Gifu 502,
Japan

Abstract --- The novel xanthinium ylides were generated and reacted with acetylenic compounds to give the ring transformed products, 5-pyrrolouracil derivatives and/or pyrrolo[1,2-f] pteridine derivatives. The mechanism of these reactions was also discussed.

Xanthine derivatives are widely distributed in nature and have potent biological activities[2)]. Many reports concerned with alkylated xanthines have appeared in recent years. Although these investigations have dealt with the syntheses of substituted xanthines and with the effects of reaction conditions on sitespecific alkylation, the less substantial work on the chemistry of the individual alkylated compounds have been reported.[3)]

Scheme I.



1 R=CN, COC_6H_5, $COOCH_3$

2

3 : R=CN
4 : R=COC_6H_5
5 : R=$COOCH_3$

6a : R=CN, X=$COOCH_3$
6b : R=CN, X=H
7a : R=COC_6H_5, X=$COOCH_3$
7b : R=COC_6H_5, X=H

9a : X=$COOCH_3$
9b : X=H

We investigated the ring transformation reactions of the novel xanthinium ylides to uracil and/or pteridine derivatives.

The precursors of the ylides, 1,3,7,9-tetraalkylxanthinium p-toluenesulfonates (2) were prepared quantitatively by the conventional method[4]. And they were converted to the corresponding xanthinium ylides 3 - 5 by deprotonation with n-butyllithium in THF. Then the solutions turned to yellow. These ylides were stable in the solution below -50°C, but unstable above -30°C.

Ylides 3 and 4 reacted in situ with 1 eq. of acetylenic compounds, such as dimethyl acetylenedicarboxylate (DMAD) or methyl propiolate (MP), to give the ring-cleaved compounds 6 and 7, in contrast 5 gave the ring-transformed products 9. The results were summarized in Table I.

Table I. Reactions of Xanthinium Ylides 3, 4, and 5 with Acetylenic compounds.

Xanthinium Ylides	Acetylenic compounds a)	Temp. (°C)	Time (hr)	Products	(Yield %)
3	DMAD	-70 ⟶ -10	12	6a	(65)
3	MP	-70 ⟶ -10	12	6b	(39)
4	DMAD	-50 ⟶ +10	6	7a	(41)
4	MP	-50 ⟶ +10	6	7b	(37)
5	DMAD	-70 ⟶ -10	12	9a	(81)
5	MP	-70 ⟶ -10	12	9b	(51)

a) DMAD is dimethyl acetylenedicarboxylate. MP is methyl propiolate.

The structure of the ring-cleaved compounds (6 and 7) was determined by mass, ^{1}H-NMR, and IR spectra. The mass spectra showed the molecular ion peaks of 1:1 adducts of the ylides and acetylenic compounds. In the ^{1}H-NMR spectra, the presence of the $-NHCH_3$ groups at the 6-position of the uracil ring was confirmed by two coupled signals of δ 5.13-5.74 (1H, q, NH) and δ 2.42 - 2.57 (3H, d, $NHCH_3$). And the pyrrole ring protons were observed at δ 7.20 - 7.50. In the case of 6b and 7b, coupling of two aromatic protons on the pyrrole ring was also observed. Moreover, the IR absorptions at about 3360 and 2230 cm^{-1} indicated the presence of NH and C≡N groups, respectively.

On the other hand, the structure of the ring-transformed products (9) was determined as follows : The mass spectra showed the molecular ion peaks, which were 32 less than those of the corresponding 1:1 adducts. In the ^{1}H-NMR spectra, lack of one $-OCH_3$ peak of the 1:1 adducts was observed. Furthermore, the ^{13}C-NMR spectrum[5]

Table II. Mass Spectra, Melting Points and ^{1}H-NMR Data of Products.

Products	MS m/e : (M^+)	mp (°c)	NMR δ : [a]
6a	375	110-113	2.49(3H, d, J=4.8Hz, $NHC\underline{H}_3$), 3.33 and 3.48 (each 3H, each s, 2 x NCH_3), 3.82 and 3.93 (each 3H, each s, 2 x OCH_3), 5.42(1H, q, J=4.8Hz, $N\underline{H}CH_3$), 7.40(1H, s, pyrrolo H).
6b	317	93- 96	2.42(3H, d, J=4.8Hz, $NHC\underline{H}_3$), 3.30 and 3.43 (each 3H, each s, 2 x NCH_3), 3.82(3H, s, OCH_3), 5.74(1H, q, J=4.8Hz, $N\underline{H}CH_3$), 7.29 and 7.46 (each 1H, each d, J=1.5Hz, 2 x pyrrolo H).
7a	454	139-141	2.57(3H, d, J=4.8Hz, $NHC\underline{H}_3$), 3.26 and 3.38 (each 3H, each s, 2 x NCH_3), 3.18 and 3.80 (each 3H, each s, 2 x OCH_3), 5.18(1H, d, J=4.80Hz, $N\underline{H}CH_3$), 7.42(1H, s, pyrrolo H), 7.20 - 7.86(5H, m, ArH).
7b	396	143-145	2.50(3H, d, J=4.8Hz, $NHC\underline{H}_3$), 3.28 and 3.44 (each 3H, each s, 2 x NCH_3), 3.82(3H, s, OCH_3), 5.13(1H, q, J=4.8Hz, $N\underline{H}CH_3$), 7.20 and 7.50 (each 1H, each d, J=1.5Hz, 2 x pyrrolo H). 7.20 - 7.94(5H, m, ArH).
9a	376	262-265	3.62(3H, s, NCH_3), 3.79(6H, s, 2 x NCH_3), 4.07 and 4.19(each 3H, each s, 2 x OCH_3), 9.40(1H, s, pyrrolo H).
9b	318	287-288.5	3.65(3H, s, NCH_3), 3.80(6H, s, 2 x NCH_3), 4.09 (3H, s, OCH_3), 7.91 and 9.41(each 1H, each d, J=1.5Hz, 2 x Pyrrolo H).

a) solvents --- 6 and 7 : $CDCl_3$, 9 : CF_3COOH

assigned by comparison with that of pyrroloquinoxaline[6] supported this structure. The mechanism for the formation of 6, 7, and 9 may be considered as follows : At first, 1,3-dipolar cycloaddition may occur to give the intermediate 10, and the tautomeric shift of an acidic proton results in the formation of 6, 7, and 8. In the case of 6 and 7, the reaction ceases in this stage. In the case of 8, however, the recyclization takes place with the elimination of methanol to afford 9 (Scheme II).

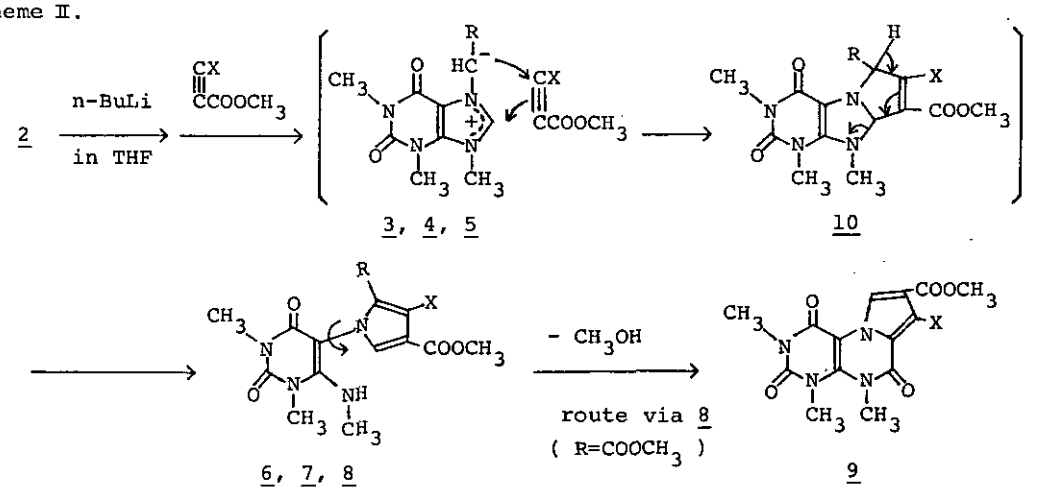
Generally, amino groups at the 6-position of uracils have low reactivity because of the enaminone component. But the $NHCH_3$ groups of 8 reacted with the methoxy-

carbonyl moiety smoothly beyond expectation.

Since the structure of 9 is somewhat similar to that of 5,10-methylenetetrahydrofolic acid, which participates in one carbon transfer reaction in vivo, interest may be aroused in these new pyrrolo[1,2-f]pteridines.

Further work on xanthinium ylides is now in progress.

Scheme II.



REFERENCES AND FOOTNOTES

1) A part of this work was presented at 102nd Annual Meeting of Pharmaceutical Society of Japan, Osaka, Japan, Apr., 1982, Abstracts of Papers, p.464.

2) M. Hori, Y. Matsumoto, M. Kuwayama, and N. Ito, Ann. Proc. Gifu Coll. Pharm., 30, 1 (1981). [C.A., 96, 122657x (1982)].

3) M. Hori, T. Kataoka, H. Shimizu, E. Imai, Y. Matsumoto, and I. Miura, Tetrahedron Lett., 22, 1259 (1981).

4) H. Bredereck, G. Kupsch, and H. Wieland, Chem. Ber., 92, 566 (1959). H. Bredereck, O. Christmann, W. Koser, P. Schellenberg, and R. Nast, Chem. Ber., 95, 1812 (1962).

5) 3,4-Dimethoxycarbonylpyrrolo[1,2-f]1,3,9-trimethylpteridin-2,4,7-trione (9a) ^{13}C-NMR(CF_3COOH) : 30.5, 38.8, and 41.2(3 x $N\underline{C}H_3$), 54.8 and 56.0(2 x $O\underline{C}H_3$), 104.4(C-9a), 119.6(C-3a), 121.8(C-3), 122.3(C-2), 128.0(C-1), 145.7, 159.8, and overlapped signal on others(5a, 7, and 9), 154.7(C-4), 167.4 and 170.7(2 x $\underline{C}OOCH_3$)

6) O. Meth-Cohn, Tetrahedron Lett., 413 (1975).

Received, 17th June, 1982