Methyl 3-Furoyl-3-(3-furoyl-4-methoxycarbonyl-2-tosyl-1-pyrrolyl)acrylate (16c)——Using method A described above for the preparation of **16a**, the reaction of **7** (234 mg, 1.2 mmol), methyl 3-(2-furoyl)propiolate (**14c**)[14] (427 mg, 2.4 mmol), and DBU (182 mg, 1.2 mmol) in 5 ml of DMF afforded 450 mg (68%) of **16c**; colorless needles from DMF/MeOH (4: 1), mp 248—250°. *Anal.* Calcd. for $C_{27}H_{21}NO_{10}S$: C, 58.80; H, 3.84; N, 2.54. Found: C, 58.75; H, 3.65; N, 2.59. IR ν_{max}^{KBr} cm^{-1}: 1740 and 1670 (C=O), 1630 (C=C), 1150 and 1320 (SO_2). UV λ_{max}^{EtOH} nm (log ε): 224 (4.51) and 300 (4.52). NMR (DMSO-d_6) δ: 2.20 (3H, s, phenyl-CH_3), 3.82 and 3.84 (each 3H, each s, nuclear and side-chain esters $-CH_3$), 6.72—8.10 (10H, m, nuclear and side-chain furyl groups 3-, 4-, and 5-H, phenyl 2-, 3-, 5-, and 6-H), 8.02 (1H, s, vinyl-H), and 8.24 (1H, s, pyrrolyl 5-H). MS (*m/e*): 551 (M^+), 520 (M^+-OCH_3).

Methyl 3-Benzoyl-3-(3-benzoyl-4-methoxycarbonyl-2-tosyl-1-pyrrolyl)acrylate (16d)——Using method A described above for the preparation of **16a**, the reaction of **7** (584 mg, 3 mmol), methyl 3-benzoylpropiolate (**14d**)[15] (1.13 g, 6 mmol), and DBU (456 mg, 3 mmol) in 10 ml of DMF afforded 441 mg (25%) of **16d**; colorless needles from DMF/MeOH (4: 1), mp 193—194°. *Anal.* Calcd. for $C_{31}H_{25}NO_8S$: C, 65.14; H, 4.41; N, 2.54. Found: C, 65.15; H, 4.27; N, 2.42. IR ν_{max}^{KBr} cm^{-1}: 1735 and 1675 (C=O), 1645 (C=C), 1150 and 1320 (SO_2). UV λ_{max}^{EtOH} nm (log ε): 236 (4.48) and 3.80 (4.39). NMR (DMSO-d_6) δ: 2.16 (3H, s, phenyl-CH_3), 3.74 and 3.80 (each 3H, each s, nuclear and side-chain esters $-CH_3$), 7.08—7.92 (14H, m, nuclear and side-chain phenyl groups), 7.82 (1H, s, vinyl-H), and 8.18 (1H, s, pyrrolyl 5-H). MS (*m/e*): 540 (M^+-OCH_3). No parent peak was observable.

14) H. Saikachi and T. Kitagawa, *Yakugaku Zasshi*, **91**, 454 (1971).
15) A.W. Nineham and R.A. Raphael, *J. Chem. Soc.*, **1949**, 118.

[Chem. Pharm. Bull. 27(11)2861—2864(1979)]

UDC 547.791.9.04 : 547.442.3.04

Triazolo[4,5-*d*]pyrimidines. III.[1] The Transformation of 3-Substituted 3*H*-1,2,3-Triazolo[4,5-*d*]pyrimidines into 3-Substituted 3*H*-1,2,3-Triazolo[4,5-*b*]pyridines

Takeo Higashino,[2a] Tatsuhiko Katori,[2b] and Eisaku Hayashi[2a]

Shizuoka College of Pharmacy[2a] and Central Research Laboratory, S S Pharmaceutical Co., Ltd.[2b]

(Received May 14, 1979)

Treatment of 3-substituted 3*H*-1,2,3-triazolo[4,5-*d*]pyrimidines (I) with active methylene compounds, such as 1,3-dicarbonyl compounds (A-1 to A-2), aliphatic ketones (A-3 to A-4), and cyclic ketones (A-5 to A-6), in the presence of dilute sulfuric acid gave the 3-substituted 3*H*-1,2,3-triazolo[4,5-*b*]pyridines (IIIm-1 to IIIm-2, IIIm-5 to IIIm-6, and IIIp-1 to IIIp-6).

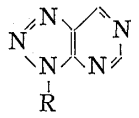
The mechanism of the transformation is discussed.

Keywords——triazolopyrimidines; triazolopyridines; active methylene compounds; ketones; ring transformation; mechanism

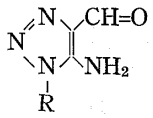
In the previous paper,[1] we reported that 3-substituted 3*H*-1,2,3-triazolo[4,5-*d*]pyrimidines (I) in dilute sulfuric acid easily undergo ring fission to give 1-substituted 5-amino-1*H*-1,2,3-triazole-4-carboxaldehydes (II). It was expected that the presence of active methylene compounds (A) in the reaction system might lead to a type of Friedlaender synthesis between the resulting II and A. In fact, we found that I reacted with A in dilute sulfuric acid and was transformed into 3-substituted 3*H*-1,2,3-triazolo[4,5-*b*]pyridines (III) in moderate yields.

The molar ratio of I to A was set at 1: 2.5. Thus, 3-methyl-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidine (Im) reacted with 2,4-pentanedione (A-1) in dilute sulfuric acid at room temperature

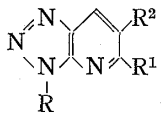
1) Part II: T. Higashino, T. Katori, and E. Hayashi, *Chem. Pharm. Bull.* (Tokyo), **27**, 2431 (1979).
2) Location: *a) 2-2-1 Oshika, Shizuoka-shi, 422, Japan; b) 1143 Nanpeidai, Narita-shi, 286, Japan.*



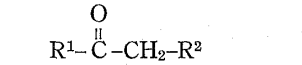
I R
Im: CH_3
Ip: C_6H_5



II R
IIm: CH_3
IIp: C_6H_5



III R R^1 R^2
IIIm-1: CH_3 CH_3 $COCH_3$
IIIm-2: CH_3 CH_3 $COOC_2H_5$
IIIm-5: CH_3 $(CH_2)_3$
IIIm-6: CH_3 $(CH_2)_4$
IIIp-1: C_6H_5 CH_3 $COCH_3$
IIIp-2: C_6H_5 CH_3 $COOC_2H_5$
IIIp-3: C_6H_5 CH_3 H
IIIp-4: C_6H_5 C_6H_5 H
IIIp-5: C_6H_5 $(CH_2)_3$
IIIp-6: C_6H_5 $(CH_2)_4$



A R^1 R^2
A-1: CH_3 $COCH_3$
A-2: CH_3 $COOC_2H_5$
A-3: CH_3 H
A-4: C_6H_5 H
A-5: $(CH_2)_3$
A-6: $(CH_2)_4$

Chart 1

to give 3,5-dimethyl-3*H*-1,2,3-triazolo[4,5-*b*]pyridin-6-yl methyl ketone (IIIm-1). Similarly, the reaction of Im with ethyl acetoacetate (A-2), cyclopentanone (A-5), and cyclohexanone (A-6) resulted in the formation of the corresponding 3-methyl-3*H*-1,2,3-triazolo[4,5-*b*]pyridines (IIIm-2, IIIm-5, and IIIm-6) as indicated in Table I.

A similar reaction was found to take place between 3-phenyl-3*H*-1,2,3-triazolo[4,5-*d*]-pyrimidine (Ip) and A (A-1 to A-6) in dilute sulfuric acid–dimethyl sulfoxide at room temperature affording the corresponding 3-phenyl-3*H*-1,2,3-triazolo[4,5-*b*]pyridines (IIIp-1 to IIIp-6) (see Table I).

The structures of the triazolo[4,5-*b*]pyridines (III) were suggested by their exact mass measurements (EMM) and confirmed by their infrared absorption (IR) and nuclear magnetic resonance (NMR) spectra, as shown in Tables I and II.

It has been reported that quinazoline (IVa)[3a] and its 3-oxide (IVb),[3b,c] on treatment with A in the absence of a catalyst or solvent, were transformed into quinolines (V), and the generality of this transformation has been shown by its application to many kinds of condensed pyrimidines, such as pyrido[2,3-*d*]pyrimidine,[3d,e,i] 1-methyl- and 1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidines,[3f,g] purine[4a] and pteridine.[4c] During the course of investigation of the transformation we proposed a mechanism involving sequential addition, ring fission and ring closure, as shown in Chart 2.[3] We showed that the intermediates derived from IVa by addition of A, such as 3,4-dihydro-4-quinazolinylmethyl alkyl ketones (VI), were the precursors of the ring-opened intermediates.[3h]

The mechanism of the transformation of I in dilute sulfuric acid is different from that of IVa mentioned above, and involves ring fission, followed by a type of Friedlaender synthesis reaction between the resulting II and A to form III, since I easily underwent ring fission in dilute sulfuric acid at room temperature, resulting in the formation of II in good yield,[1] and even in dilute sulfuric acid a type of Friedlaender synthesis between IIm and A-1 occurred, affording IIIm-1. Moreover, the reaction of Im with A-1 in the absence of a

3) *a*) T. Higashino, H. Ito, and E. Hayashi, *Chem. Pharm. Bull.* (Tokyo), **20**, 1544 (1972); *b*) T. Higashino, Y. Nagano, and E. Hayashi, *ibid.*, **21**, 1943 (1973); *c*) T. Higashino, K. Suzuki, and E. Hayashi, *ibid.*, **23**, 746 (1975); *d*) T. Higashino and E. Hayashi, *ibid.*, **21**, 2643 (1973); *e*) T. Higashino, K. Suzuki, and E. Hayashi, *ibid.*, **23**, 2939 (1975); *f*) T. Higashino, Y. Iwai, and E. Hayashi, *ibid.*, **25**, 535 (1977); *g*) *Idem*, *ibid.*, **24**, 3120 (1976); *h*) T. Higashino, K. Suzuki, and E. Hayashi, *ibid.*, **26**, 3485 (1978); *i*) *Idem*, *ibid.*, **26**, 3242 (1978).

4) *a*) A. Albert and W. Pendergast, *J. Chem. Soc.* Perkin I, **1973**, 1794; *b*) A. Albert and H. Mizuno, *ibid.*, **1973**, 1615.

Table I. Reaction of I with A in Dilute Sulfuric Acid

A	I	Reaction time (hr)	Product III	%	mp (°C)	EMM (m/e): M^+ Observed	Error[a]	Formula C	H	N	O	IR ν_{max}^{KBr} cm^{-1} =C=O
A-1	Im	8	IIIm-1	75	151—152	190.0853	−0.1	9	10	4	1	1695
A-2	Im	8	IIIm-2	72	102—103	220.0974	1.3	10	12	4	2	1710
A-5	Im	48	IIIm-5	78	139—140	174.0898	−0.8	9	10	4	—	—
A-6	Im	48	IIIm-6	82	124—125	188.1033	−2.9	10	12	4	—	—
A-1	Ip	48	IIIp-1	50	150—151	252.1015	0.2	14	12	4	1	1685
A-2	Ip	48	IIIp-2	48	102—103	282.1135	1.7	15	14	4	2	1720
A-3	Ip	48	IIIp-3	30	112—113	210.0896	−0.9	12	10	4	—	—
A-4	Ip	48	IIIp-4	21	124—125	272.1049	−1.3	17	12	4	—	—
A-5	Ip	48	IIIp-5	47	117—118	236.1080	1.5	14	12	4	—	—
A-6	Ip	48	IIIp-6	68	111—112	250.1225	0.4	15	14	4	—	—

a) Difference from the theoretical value in millimass units.

Table II.[a] NMR Spectra fo III

III	NMR (in $CDCl_3$) ppm 7-H[s]	3-CH_3[s]	3-C_6H_5[m]	Other (J=8 Hz)
IIIm-1	8.72	4.32	—	2.90[s] (5-CH_3), 2.71[s] (6-$COCH_3$)
IIIm-2	8.79	4.29	—	2.97[s] (5-CH_3), 4.41[q], 1.44[t] (-OCH_2CH_3)
IIIm-5	7.98	4.30	—	2.0—3.4[m] (-$(CH_2)_3$-)
IIIm-6	7.91	4.26	—	1.6—3.4[m] (-$(CH_2)_4$-)
IIIp-1	8.73	—	7.2—8.5	2.90[s] (5-CH_3), 2.71[s] (6-$COCH_3$)
IIIp-2	8.94	—	7.3—8.5	2.99[s] (5-CH_3), 4.45[q], 1.42[t] (-OCH_2CH_3)
IIIp-3	8.35[b),d]	—	7.3—8.5	7.22[b),d] (6-H), 2.72[s] (5-CH_3)
IIIp-4	8.42[b),d]	—	7.3—8.6	7.82[b),d] (6-H), 7.3—8.6[c),m] (5-C_6H_5)
IIIp-5	8.10	—	7.3—8.4	2.0—3.3[m] (-$(CH_2)_3$-)
IIIp-6	7.90	—	7.3—8.5	1.6—3.2[m] (-$(CH_2)_4$-)

a) The numbering used in this Table is that of the 3*H*-1,2,3-triazolo [4,5-*b*]pyridine ring system.
b) J_{6-7}=8 Hz.
c) Overlapping with hydrogens of the 3-phenyl group.
d: doublet; m: multiplet; q: quartet; s: singlet; t: triplet.

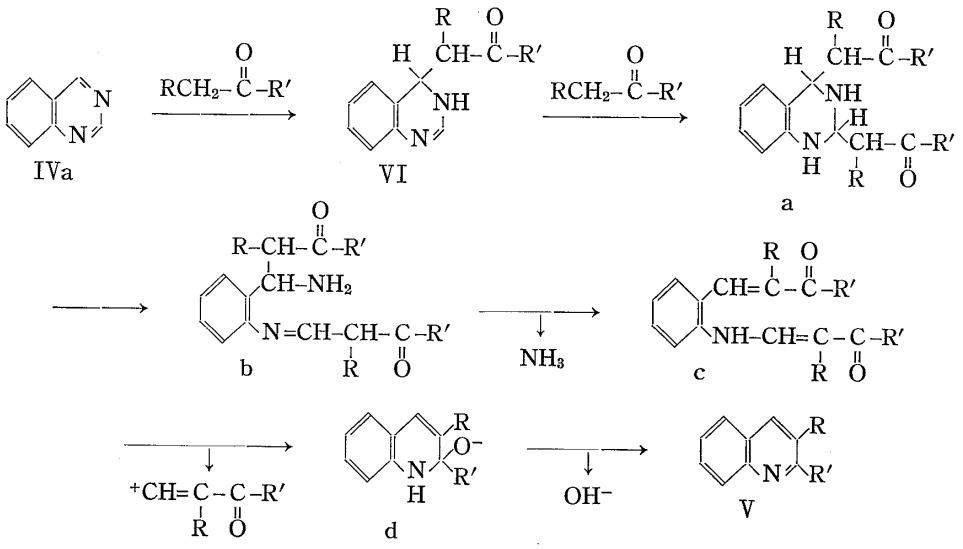


Chart 2

catalyst did not give any product, and resulted in recovery of the starting material (Im). Thus, II appears to be the precursor of the ring transformation product (III).

Experimental[5]

IR spectra were recorded on a Jasco IRA-1 grating infrared spectrophotometer. NMR spectra were measured in $CDCl_3$ at 60 Mc and at 23° on a Hitachi R-24 high resolution NMR spectrometer, using tetramethylsilane as an internal standard. EMM was carried out on a JEOL JMS-01SG-2 mass spectrometer combined with a JEC-6 spectrum computer. Samples were vaporized in a direct inlet system.

Reaction of Im with A in 20% H_2SO_4——A mixture of Im (300 mg, 2.2 mmol) and A (5.5 mmol) in 20% H_2SO_4 (1.5 ml) was stirred at room temperature for the time indicated in Table I. The separated crystalline solid was extracted with benzene and the benzene extract was dried over Na_2SO_4. The residue, obtained by evaporation of benzene from the extract, was recrystallized from petr. ether to give IIIm. The yields, melting points, EMM, and IR spectra of IIIm are shown in Table I, and their NMR spectra in Table II.

Reaction of Ip with A in 20% H_2SO_4-Dimethyl Sulfoxide——H_2SO_4 (20%, 0.5 ml) was added to a solution of Ip (200 mg, 1.0 mmol) and A (2.5 mmol) in dimethyl sulfoxide (5.0 ml), and the mixture was allowed to stand at room temperature for the time indicated in Table I. The reaction mixture was then poured into H_2O (10.0 ml). The separated crystalline solid was collected by suction and extracted with $CHCl_3$. The $CHCl_3$ extract was dried over Na_2SO_4 and chromatographed on a column of alumina using $CHCl_3$ as an eluent. The first fraction gave IIIp as colorless needles (from petr. ether). The yields, melting points, EMM, and IR spectra of IIIp are shown in Table I, and their NMR spectra in Table II.

Reaction of IIm with A-1 in 20% H_2SO_4——A mixture of IIm (277 mg, 2.2 mmol) and A-1 (550 mg, 5.5 mmol) in 20% H_2SO_4 (1.5 ml) was stirred at room temperature for 8 hr. The separated crystalline solid was extracted with benzene and dried over Na_2SO_4. The crystals, obtained by removal of benzene from the extract, were recrystallized from petr. ether to give IIIm-1 in 69% yield (288 mg).

Acknowledgement We are greatly indebted to the Ministry of Education Science and Culture, Japan, for a Grant-in-Aid for Scientific Research (D) and a grant for Special Project Research in 1978.

Our thanks are also due to Dr. M. Uchida of this college for exact mass measurement.

5) Melting points are uncorrected.