REGIO- AND STEREO-CONTROLLED DIELS-ALDER REACTION OF DIOXOPYRROLINES WITH ACTIVATED BUTADIENES: FACILE SYNTHESES OF RING D FUNCTIONALIZED ERYTHRINANS[1)]

Takehiro Sano*, Jun Toda, and Noriaki Kashiwaba
Showa College of Pharmaceutical Sciences, Setagaya-Ku, Tokyo 154, Japan
Yoshisuke Tsuda
Faculty of Pharmaceutical Sciences, Kanazawa University, Kanazawa 920, Japan
Yoichi Iitaka
Faculty of Pharmaceutical Sciences, University of Tokyo, Tokyo 113, Japan

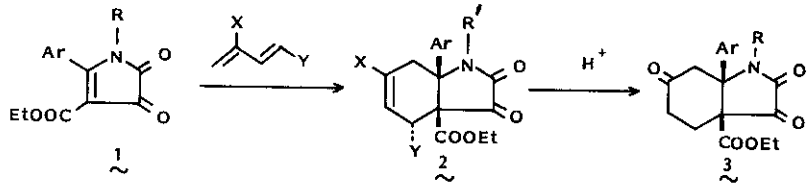
Diels-Alder reaction of Δ^2-pyrroline-4,5-diones with activated butadienes proceeds in regio- and stereo-selective manner. Thus, isoquinolinopyrrolinediones (prepared in 3 steps from β-arylethylamines) gave single erythrinan derivatives which are functionalized at ring D in acceptable yields. The structure and stereochemistry of the adducts were established by chemical and spectroscopic means and finally by X-ray analysis of the derived diacetate (19).

Hydroindole synthesis by Diels-Alder reaction of Δ^2-pyrroline-4,5-diones with butadiene exploited by Tsuda et al,[2)] prompted us to use of activated butadienes such as 1-methoxy-3-trimethylsilyloxybutadiene[3)] instead of butadiene, since it seems to promise yielding variously functionalized hydroindoles directly. In that case the regio- and stereo-chemistry of the product must be clarified. This communication treats this subject mainly.

Table 1 summarizes the present result on Diels-Alder reaction of 2-aryl-Δ^2-pyrrolinediones (1) with some previous results[2c)] for comparison. It indicates that 2-phenyl-Δ^2-pyrrolinedione is poorly reactive to butadiene unless the nitrogen is negatively substituted and 2-(3',4'-methylenedioxyphenyl) derivative is less reactive. However, with activated butadienes they are moderately reactive to yield single adduct suggesting that the reaction proceeds in regio- and stereo-selective manner (structures of the products are given on analogy with the results described below).

We therefore examined Diels-Alder reaction of isoquinolinopyrrolinediones (7), in which free rotation of an aromatic ring is prohibited by formation of a new

Table 1. Diels-Alder Reaction of 2-Aryl-Δ^2-pyrroline-4,5-diones (1) with Butadienes.



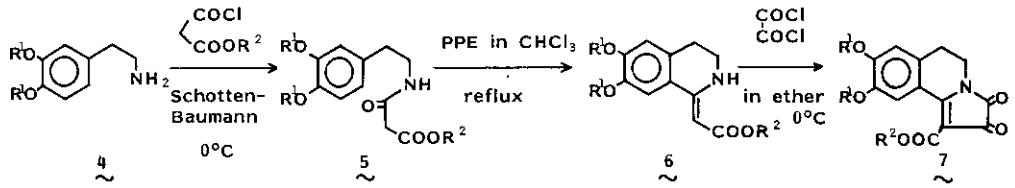
dienophiles (1)			reaction condition			products (2)				
Ar	R	diene	solvent	temp.	time	X	Y	R'	yield	mp
Ph	H	A	CH_2Cl_2	180°	28hr	H	H	H	10%[a]	228-230°[a]
Ph	H	A	Ac_2O	160°	8hr	H	H	Ac	60%[a]	164-166°[a]
Ph	H	C	toluene	150°	8hr	H	OTMS	H	11%[b]	(212-214°)[b]
Ph	H	D	toluene	160°	10min	OTMS	OMe	H	35%	146-150°
Ph	Me	A	CH_2Cl_2	160°	8hr	H	H	Me	10%[a]	158-160°[a]
Ph	Me	A	Ac_2O	160°	8hr	H	H	Me	10%	158-160°
Ph	Me	C	toluene	150°	7hr	H	OTMS	Me	15%[b]	(154-156°)[b]
3,4-$(OCH_2O)C_6H_3$	H	A	CH_2Cl_2	180°	28hr	H	H	H	c)	c)
3,4-$(OCH_2O)C_6H_3$	H	A	Ac_2O	160°	8hr	H	H	Ac	10%	gum

A: butadiene, C: 2-trimethylsilyloxybutadiene, D: 1-methoxy-3-trimethylsilyloxybutadiene.

a) see ref. 2c.

b) Isolated as the ketone 3 after acid hydrolysis.

c) Not isolable.



a: R^1=Me, R^2=Et; b: R^1=Me, R^2=Me; c: R^1-R^1=-CH_2-, R^2=Et; d, R^1-R^1=-CH_2-, R^2=Me

Chart 1

Table 2. Syntheses of Isoquinolinopyrrolinediones (7) (mp and yield %)

	5		6		7	
a	57-58°,	98%	82-85°,	90%	209-212°,	89%
b	75-76°,	99%	gum ,	90%	244-246°,	60%
c	98-100°,	86%	148-150°,	80%	219-223°,	94%
d	98-99°,	95%	138-141°,	80%	221-224°,	89%

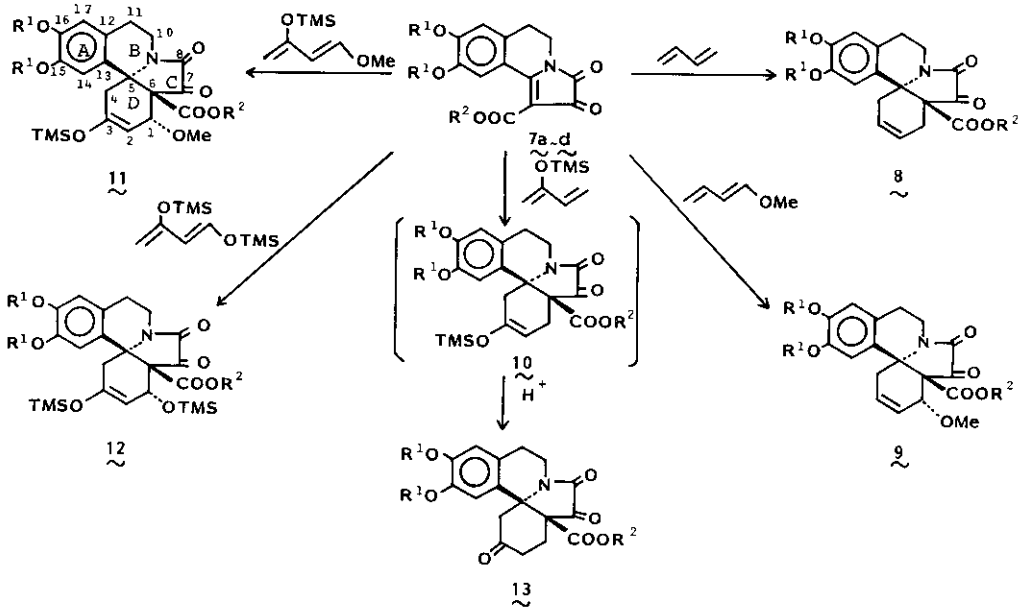


Chart 2

Table 3. Diels-Alder Reaction of 7 with Butadienes.

dienophile	diene	solvent	temp.	time(hr)	1,4-adduct	(mp)	yield(%)
7a	A	toluene	170°	30	8a	175-176°	6
	B	toluene	140°	9	9a	gum	80[b]
	C	toluene	160°	17	10a	a)	33
	D	neat	130°	3	11a	124-126°	58
	E	neat	140°	0.5	12a	142-145°	58
7b	D	dioxane	130°	1	11b	142-144°	82
	E	dioxane	130°	0.5	12b	141-143°	65
7c	A	toluene	170°	20	8c	c)	c)
	B	toluene	140°	5	9c	191-192°	36
	C	toluene	170°	13	10c	a)	23
	D	neat	130°	3	11c	176-179°	49
	E	neat	130°	2	12c	202-205°	76
7d	D	dioxane	120°	1	11d	174-177°	51
	E	neat	130°	2	12d	173-176°	64

A: butadiene. B: 1-methoxybutadiene. C: 2-trimethylsilyloxybutadiene.
D: 1-methoxy-3-trimethylsilyloxybutadiene. E: 1,3-bis(trimethylsilyloxy)butadiene.
a) Isolated as a keto compound (13) after acid hydrolysis.
b) Yield given as a crude gum.
c) Not isolable.

Table 4. IR and NMR Spectra of the Cycloadducts.

cycloadducts	IR (cm^{-1}) ν c=o absorptions	NMR ($CDCl_3$, δ) olefinic protons
8a	1770, 1730, 1715	5.57-6.27 (2H, m.)
9a	1770, 1740, 1710	5.68-6.48 (2H, m.)
9c	1775, 1740, 1715	5.91, 6.27 (each 1H, m.)
11a	1770, 1725, 1710	5.34 (1H, d., J=5 Hz)
11b	1780, 1745, 1720	5.38 (1H, d., J=5 Hz)
11c	1770, 1745, 1720	5.33 (1H, d., J=5 Hz)
11d	1766, 1720, 1710	5.31 (1H, d., J=5 Hz)
12a	1760, 1740, 1715	5.35 (1H, d., J=6 Hz)
12b	1760, 1740, 1715	5.38 (1H, d., J=6 Hz)
12c	1760, 1730, 1710	5.33 (1H, d., J=6 Hz)
12d	1765, 1740, 1720	5.31 (1H, d., J=5 Hz)

ring. The desired dienophiles, 7a~d were prepared as shown in Chart 1, which were obtained as red-reddish yellow crystals in yield of 60~80% starting from the β-arylethylamines (4) (Table 2).

Table 3 summarizes the result of Diels-Alder reaction of 7 with various butadienes: reaction conditions, products, and yields. 7a~d were more reactive to butadienes than 1 apparently due to gaining planarity in a dienophile. The reaction was again highly regio- and stereo-selective to give single 1,4-cycloadducts in acceptable yields (IR and NMR listed in Table 4). The adducts 10a and 10c were characterized as the corresponding ketones (13a), mp 223-225°, and (13c), mp 272-275°, after acid hydrolysis (2.5%HCl-THF).

The regiochemistry of the adducts was elucidated as shown in Chart 3 as follows. Treatment of 11c and 12c with acid (2.5%HCl-THF) caused not only cleavage of the O-Si bond but also opening of the ring D to give the same keto-aldehyde (16), mp 243-246°, δ 8.07 (1H, br s, CHO). Trituration of 11c with methanol again gave the ring D cleaved product, the enol-ether (17), mp 182-186°, δ 3.67 (3H, s, OCH_3), 5.45 and 7.47 (each 1H, d, J=12 Hz, olefinic protons). While on treatment with KF in THF, 11c and 12c gave the ketone (14) (52%), mp 210-213°, and (15) (54%), mp 208-211°, respectively , which changed into 16 and 17, respectively, on treatment with base (DBU at r.t.). Those ring opening reactions were rationalized in term of the reverse Michael reaction of a 1,5-diketo derivative. The above results indicate that the 1,4-cycloaddition of Δ^2-pyrrolinediones proceeds in a fashion acceptable from the ground state electron interaction of the diene and the dienophile.

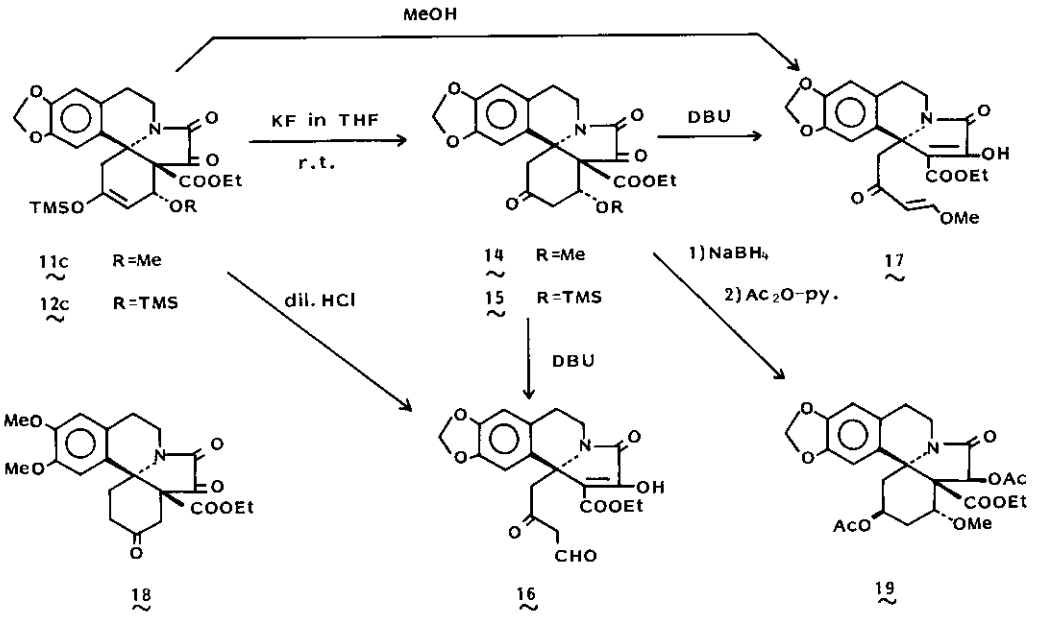
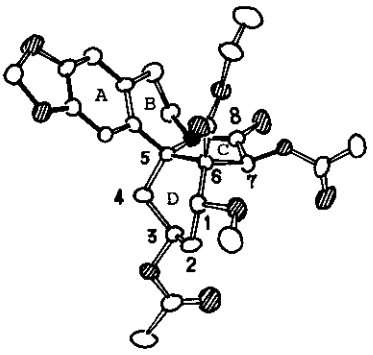


Chart 3



O:C ●:N ●:O

crystal data

monoclinic crystals

space group, $P2_1/a$

a=15.660, b=12.142, c=13.682Å

β=109.09°

Z= 4

Fig. 1 The computer-plotted structure of the diacetate (19)

The structure of the adduct(10) was elucidated as shown in Chart 2 based on the above consideration. In fact, the derived ketone (13a) was isomeric with 2-keto derivative (18) reported previously.[5)]

The structure of 11c including the stereochemistry of C_1-substituent was finally established by X-ray crystallographic analysis. The X-ray analysis was carried out for the diacetate (19), mp 242-244°, which was prepared by $NaBH_4$ reduction of the methoxy-ketone (14c) followed by acetylation. The intensity data were collected on a Philips PW-1100 diffractometer using graphite-monochromated Cu-Kα radiation. The structure was solved by direct methods with the MULTAN program.[6)] Block-diagonal least-squares refinements of positional and thermal parameters based on 1483 observed reflections reduced *R* value to 0.04. The resulting structure is shown in Fig. 1, which rigidly established not only the α-configuration of C_1-OMe but also the β-configurations of the C_3 and C_7-OAc. The latter asymmetric centers are newly produced by hydride reduction. Furthermore, it is worthwhile to note that both the ring B and D have boat conformation in the crystalline state.

The stereochemistry of 9 was assumed as shown in Chart 2 based on the above results, though rigid proof was not available.

The present method may provide a simple route to erythrina alkaloids, since 6-alkoxycarbonyl group is easily removable from the above prepared 6-alkoxycarbonyl-7,8-dioxoerythrinans.[7)]

Acknowledgement: A part of this work was supported by Grant-in-Aid for Special Project Research from the Ministry of Education, Sciences and Culture, Chemical Research in Development and Utilization of Nitrogen-Organic Resources, and Naito Research Grant, for which we are grateful.

References and Note

1. Dioxopyrrolines XXI. Syntheses of Erythrina and Related Alkaloids (4). Part XX: Y. Tsuda, Y. Sakai, M. Kaneko, K. Akiyama, and K. Isobe, Heterocycles, 16, in press.
2. a) Y. Tsuda, K. Isobe and A. Ukai, Chem. Comm., 1971, 1554.
   b) Y. Tsuda, Y. Horiguchi, and T. Sano, Heterocycles, 1976, 4, 1355.
   c) T. Sano and Y. Tsuda, Heterocycles, 1976, 4, 1361.
3. S. Danishefsky and T. Kitahara, J. Am. Chem. Soc., 1974, 96, 7807.
4. T. Ibuka, Y. Mori and Y. Inubushi, Tetrahedron Letters, 1976, 3169.
5. Y. Tsuda, Y. Sakai and T. Sano, Heterocycles, 1981, 15, 1097.
6. G. Germain, P. Main, and M. M. Woolfson, Acta Cryst., 1971, A27, 368.
7. Y. Tsuda and Y. Sakai, Synthesis, 1981, 118.

Received, 27th March, 1981