

A PRACTICAL ROUTE TO SPIRO-TYPE HETEROCYCLES RELATED TO ERYTHRINAN¹

Yoshisuke Tsuda*, Yuki Sakai, Mari Kaneko, and Yukie Ishiguro

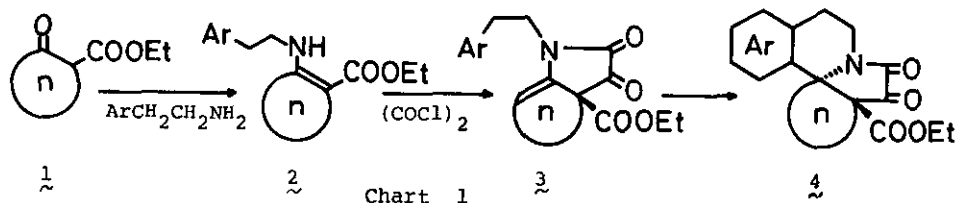
Faculty of Pharmaceutical Sciences, Kanazawa University, Kanazawa 920, Japan

Kimiaki Isobe, Jun-ichi Taga, and Takehiro Sano

Showa College of Pharmaceutical Sciences, Setagaya-ku, Tokyo 154, Japan

A new method of synthesizing spiro-type heterocycles by intramolecular cyclization of 3,3-disubstituted dioxopyrrolines was presented. The method is particularly useful in synthesizing erythrinans and has the following advantages: 1) it is of short steps with high yield (one-pot reaction is possible), 2) an activating group at ring A is not necessary, and 3) the procedure can be carried out without protection of phenolic hydroxyl groups. Wide applicability of this method was also shown by synthesizing *C*-nor and *C*-homomerythrinans, and other variants which carry heterocycles at ring A instead of benzenoids.

Dioxopyrrolines show high electrophilicity at C₂.² The 3,3-disubstituted analogues are expected as well. In this communication we report a simple and high yield conversion of cyclic β -ketoesters, via intramolecular nucleophilic cyclization to 3,3-disubstituted dioxopyrrolines, into various erythrinans, the alkaloids of this skeletal group being remarkable in their strong curare-like action.³



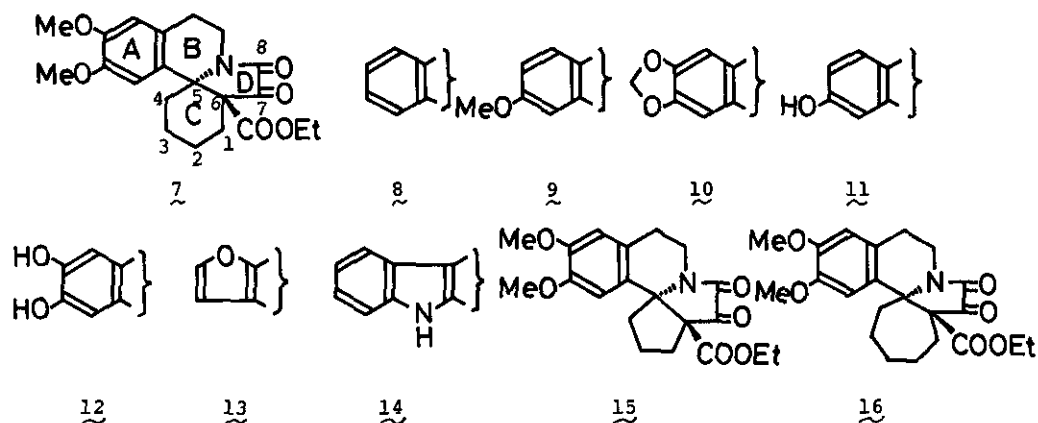
The reaction scheme is shown in Chart 1. Heating of 2-ethoxycarbonylcycloalkanone **1** with β -arylethylamine gave an enaminone **2** which was condensed with oxalyl chloride to afford a 3,3-disubstituted dioxopyrrolone **3**. Treatment of **3** with PPA or an appropriate Lewis acid yielded a spiro-type compound **4** in high

Table 1 Synthesis of Various Erythrinans and Related Heterocycles.

Product	Reagent	Cyclization Condition		Yield(%) (overall) ^{a)}	mp. (°C)
<u>7</u>	anhy. H ₃ PO ₄ ^{b)}	r.t.	1.5 hr.	90(86)	177-179
	PPE	90°	1.5 hr.	100	
	BF ₃ ·Et ₂ O in CH ₂ Cl ₂	r.t.	3 hr.	100	
	AgClO ₄ in benzene	80°	10 min	100	
<u>8</u>	PPA ^{c)}	80°	30 min	96(93)	184-185
<u>9</u>	PPA	80°	3 hr.	82(78)	171-173
<u>10</u>	anhy. H ₃ PO ₄	50°	30 min	60	228-230
<u>11</u>	anhy. H ₃ PO ₄	80°	1.5 hr.	31(30)	292-295
<u>12</u>	BF ₃ ·Et ₂ O in CH ₂ Cl ₂	reflux	2 hr.	56(28)	229-233
<u>13</u>	PPE	50°	2 hr.	85	145-147
<u>14</u>	_____	_____	_____	(20) ^{d)}	300-303
<u>15</u>	anhy. H ₃ PO ₄	r.t.	50 min	(62)	153-156
<u>16</u>	anhy. H ₃ PO ₄	50°	2 hr.	(63)	222-224

a) Parenthetical data indicate overall yield from β -ketoesters.b) Prepared from 85% H₃PO₄ 15 g and P₂O₅ 5 g, 110°, 6 hr.c) Prepared from 85% H₃PO₄ 33 g and P₂O₅ 25 g, 110°, 6 hr.

d) Concomitant formation upon oxalylolation.



yield. Although the intermediate enaminone 2 and the dioxopyrroline 3 can sometimes be isolated and characterized spectroscopically, it is not necessary to isolate them. A general procedure of one-pot reaction is as follows.

General Procedure (for 7): 2-Ethoxycarbonylcyclohexanone (1 g) and homoveratrylamine (1.2 g, 1.1 mol eq.) in ethanol (8 ml) were heated in a sealed tube at 100° for 2 hr, then the solvent was evaporated to leave the enaminone 5.⁴ To a stirred solution of 5 in benzene (10 ml) oxalyl chloride (0.8 g, 1.1 mol eq.) was added dropwise at 0-5°. After 0.5-1 hr's stirring the solvent was evaporated in vacuo and the residue 6⁵ stirred with a large excess of anhydrous phosphoric acid at room temp. for 1.5 hr. The mixture was poured into ice-water and extracted with CHCl_3 . Concentration of the dried extract gave 15,16-dimethoxy-7,8-dioxo-6-ethoxycarbonylerythrinan 7 (1.9 g, 86%). Alternatively, the dioxopyrroline 6 in CH_2Cl_2 (20 ml) was stirred with 2-3 mol eq. of $\text{BF}_3 \cdot \text{Et}_2\text{O}$ at room temp. for 3 hr. Decomposition of the excess reagent with ice-water followed by usual work-up gave 7 in quantitative yield. It crystallized in almost colorless needles from MeOH. mp 177-179°. IR; see Table 2.

Table 2 Spectral Data of Various Erythrins and Related Heterocycles.

Compound	IR(cm^{-1}) C=O	NMR(in CDCl_3) $-\text{COOCH}_2\text{CH}_3$
<u>7</u>	1770, 1740, 1700	δ 0.70
<u>8</u>	1765, 1730, 1700	0.63
<u>9</u>	1765, 1745, 1705	0.67
<u>10</u>	1765, 1740, 1710	0.77
<u>11</u>	1765, 1735, 1685	f)
<u>12</u>	1765, 1740, 1705	e)
<u>13</u>	1766, 1739, 1717	0.85
<u>14</u>	1770, 1740, 1700	f)
<u>15</u>	1765, 1732, 1717	0.62
<u>16</u>	1765, 1740, 1705	0.70

e) hardly soluble in CDCl_3 . Diacetate(mp. 200-201°) showed the peak at δ 0.73.

f) hardly soluble in CDCl_3 .

NMR(δ): 6.70(1H, s, Ar-H), 6.60(1H, s, Ar-H), 4.5-4.7(1H, N-CH₂), 3.78(3H, s, OCH₃), 3.86(3H, s, OCH₃), 3.61(2H, q, J=7 Hz, COOCH₂CH₃), 0.70(3H, t, J=7 Hz, COOCH₂CH₃).

The 7,8-dioxo-6-ethoxycarbonylerythrinans thus prepared are assembled in Table 1. Usually they are highly crystalline compounds and well characterized by IR and NMR spectra (Table 2). The IR spectra exhibited three well separated carbonyl absorptions at 1770-1700 cm⁻¹, and in the NMR spectra the methyl proton signal of the ethyl ester appeared at unusually high field (δ 0.6-0.8 ppm). Comparing to the signal in the compound before cyclization, it shifted up-field by 0.4-0.5 ppm. This indicated that the methyl group is placed in the shielding region of the aromatic nucleus (ring A) showing the C/D cis configuration of the product 4.

This assignment of the stereochemistry was supported by an alternative synthesis of 7 as shown in Chart 2. Hydrogenation of the Diels-Alder product 18⁶ of an isoquinolinopyrrolinedione 17 and butadiene gave the compound identical with 7.

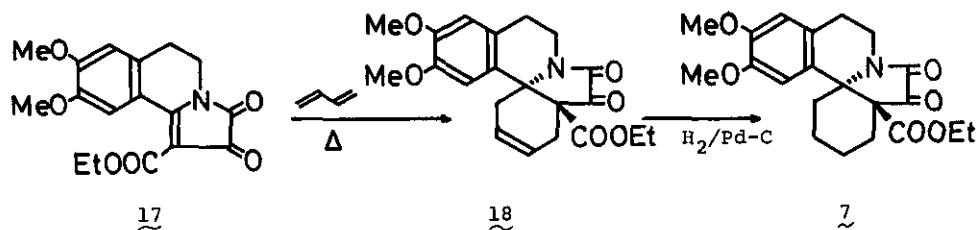


Chart 2

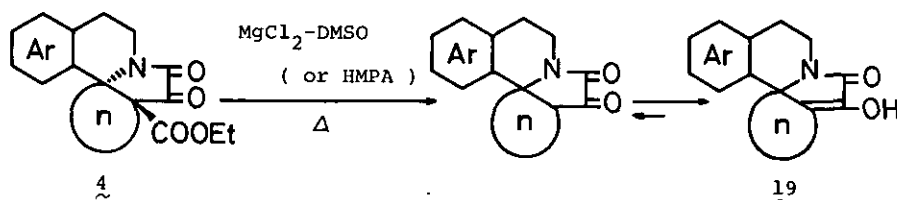
As a cyclizing reagent, PPA and anhydrous H₃PO₄ were most widely applicable which cyclized not only the compound p-activated but also the compounds which do not carry activating group in aromatic nucleus (eg. 8, 9⁷). PPE, BF₃·Et₂O in CH₂Cl₂, and AgClO₄ in benzene were effective only to the compounds which carry p-activating group (eg. 7, 10, 12), but were sometimes superior to PPA or H₃PO₄ in the yield and easiness of work-up.

POCl₃, H₃PO₄-MeOH-H₂O⁸, AgBF₄ in benzene, and AlCl₃ in Me₂S were moderately effective for cyclization of 6 to give 7 in 61, 35, 40, and 41 % yield, respectively. 10 % HCl-MeOH did not give any characterizable product.

C-Nor and C-homoerythrinans were also easily prepared by this method. Thus 2-ethoxycarbonylcyclopentanone and 2-ethoxycarbonylcycloheptanone gave 15 and 16

in overall yield 62 and 63 %, respectively. Easiness of cyclization relative to the size of ring C was $n=5 > 6 > 7$.

Another generalization of this method is the synthesis of the erythrinan variants which carry heterocycles at ring A instead of benzenoid. Thus starting from 2-furylethylamine and 2-ethoxycarbonylcyclohexanone, 13 was prepared in 85 % yield by use of PPE. Tryptamine gave directly the spiro-compound 14 upon reaction of the enaminone with oxalyl chloride, though the overall yield was 20 %.

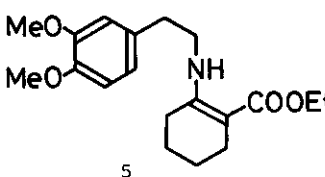
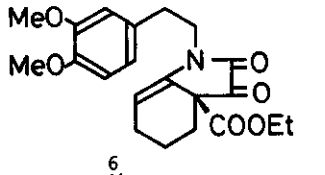


Since 6-ethoxycarbonyl group in the above compound 4 was easily removed by heating them with NaCN-HMPA or MgCl_2 -DMSO (or HMPA)⁹ giving rise to the compound 19, the above method provides a new practical route to erythrinan-type spiro-compounds. Particularly it has the following advantages.

- i) The procedure is of short steps and high yield, starting from easily available α -ketoesters.
- ii) The method is widely applicable synthesizing all type of erythrinans, not only those of ring A activated but also those of non-activated, and the variants of rings A and C.
- iii) Phenolic erythrinans can be synthesized without protection of the phenolic hydroxyl groups. For the water-soluble product (eg. 12) PPA is not recommended as a cyclizing reagent. Cyclization with Lewis acid (eg. $\text{BF}_3 \cdot \text{Et}_2\text{O}$ in CH_2Cl_2) and direct chromatography of the reaction mixture made possible pure separation of the product.

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References and Notes

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3. L. E. Craig, " The Alkaloids " vol. V, ed. by R. H. F. Manske, p. 265(1955), Academic press.
4.  Colorless needles from EtOH. mp 60-61°.
IR(cm^{-1}): 1640, 1585, 1515. NMR(CDCl_3): δ 8.92(1H, bs, -NH-), 6.72(3H, s, ArH), 4.07(2H, q, $J=7.8$ Hz, OCH_2CH_3), 3.81(6H, s, $\text{OCH}_3 \times 2$), 3.29(2H, bt, $J=6.8$ Hz, NHCH_2CH_2), 2.73(2H, t, $J=6.8$ Hz, $-\text{CH}_2\text{Ar}$), 1.22(3H, t, $J=7.8$ Hz, OCH_2CH_3).
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5.  Yellow prisms from benzene-ether. mp 113-116°.
IR(cm^{-1}): 1770, 1715. NMR(CDCl_3): δ 6.73(3H, s, ArH), 5.23(1H, diffused t, $J=3.8$ Hz, $\text{C}=\text{CH}-$), 3.83(3H, s, OCH_3), 3.81(3H, s, OCH_3), 4.07(2H, q, $J=7.1$ Hz, OCH_2CH_3), 1.18(3H, t, $J=7.1$ Hz, $-\text{OCH}_2\text{CH}_3$).
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6. T. Sano, J. Toda, and Y. Tsuda: unpublished result which will be published soon.
7. See Table 1, footnote b), c).
8. A. Mondon, Liebigs Ann. Chem., 628, 123(1959).
9. Y. Tsuda and Y. Sakai, Synthesis, to be submitted.

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