A PRACTICAL ROUTE TO SPIRO-TYPE HETEROCYCLES RELATED TO ERYTHRINAN[1]

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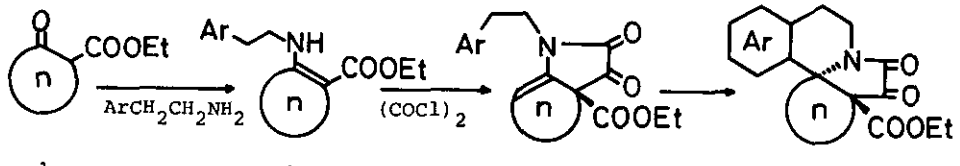
A new method of synthesizing spiro-type heterocycles by intramolecular cyclization of 3,3-disubstituted dioxopyrrolines was presented. The method is particularly useful in synthesizing erythrinans and has the following advantages: 1) it is of short steps with high yield (one-pot reaction is possible), 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-homoerythrinans, and other variants which carry heterocycles at ring A instead of benzenoids.

Dioxopyrrolines show high electrophilicity at C_2.[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]



1 2 3 4

Chart 1

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 dioxopyrroline 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.

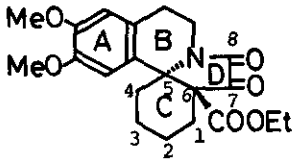
Product	Reagent	Cyclization Condition		Yield(%) (overall)[a]	mp.(°C)
7	anhy. H_3PO_4[b]	r.t.	1.5 hr.	90(86)	177-179
	PPE	90°	1.5 hr.	100	
	$BF_3 \cdot Et_2O$ in CH_2Cl_2	r.t.	3 hr.	100	
	$AgClO_4$ in benzene	80°	10 min	100	
8	PPA[c]	80°	30 min	96(93)	184-185
9	PPA	80°	3 hr.	82(78)	171-173
10	anhy. H_3PO_4	50°	30 min	60	228-230
11	anhy. H_3PO_4	80°	1.5 hr.	31(30)	292-295
12	$BF_3 \cdot Et_2O$ in CH_2Cl_2	reflux	2 hr.	56(28)	229-233
13	PPE	50°	2 hr.	85	145-147
14	———	———		(20)[d]	300-303
15	anhy. H_3PO_4	r.t.	50 min	(62)	153-156
16	anhy. H_3PO_4	50°	2 hr.	(63)	222-224

a) Parenthetical data indicate overall yield from β-ketoesters.

b) Prepared from 85% H_3PO_4 15 g and P_2O_5 5 g, 110°, 6 hr.

c) Prepared from 85% H_3PO_4 33 g and P_2O_5 25 g, 110°, 6 hr.

d) Concomitant formation upon oxalylation.



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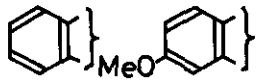

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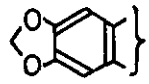

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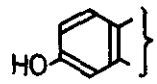

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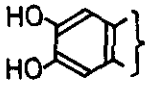

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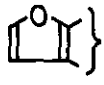

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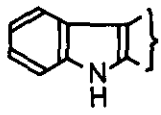

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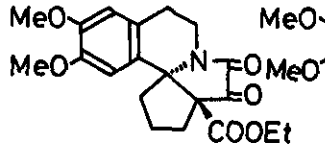

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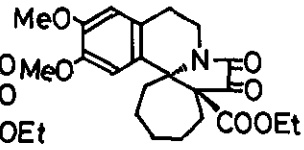

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yield. Although the intermediate enaminone 2 and the dioxopyrroline 3 can sometimes be isolated and characterized spectroscopically, it is not necessary to isolate them. A general procedure of one-pot reaction is as follows.

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 residure 6[5] 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 $BF_3 \cdot Et_2O$ 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 Erythrinans and Related Heterocycles.

Compound	IR(cm^{-1}) C=O	NMR(in $CDCl_3$) $-COOCH_2CH_3$
7	1770, 1740, 1700	δ 0.70
8	1765, 1730, 1700	0.63
9	1765, 1745, 1705	0.67
10	1765, 1740, 1710	0.77
11	1765, 1735, 1685	f)
12	1765, 1740, 1705	e)
13	1766, 1739, 1717	0.85
14	1770, 1740, 1700	f)
15	1765, 1732, 1717	0.62
16	1765, 1740, 1705	0.70

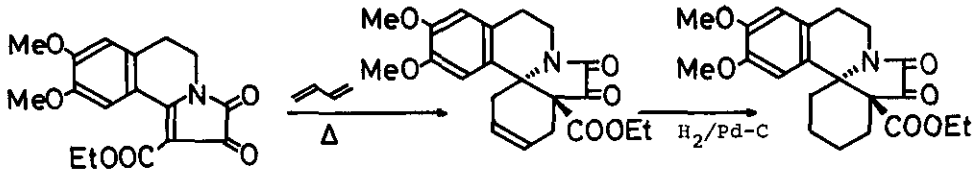
e) hardly soluble in $CDCl_3$. Diacetate(mp. 200-201°) showed the peak at δ 0.73.

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-CH_2), 3.78(3H, s, OCH_3), 3.86(3H, s, OCH_3), 3.61(2H, q, J=7 Hz, $COOCH_2CH_3$), 0.70(3H, t, J=7 Hz, $COOCH_2CH_3$).

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 18[6] of an isoquinolinopyrrolinedione 17 and butadiene gave the compound identical with 7.



17 18 7

Chart 2

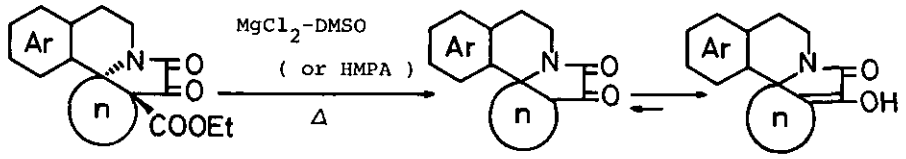
As a cyclizing reagent, PPA and anhydrous H_3PO_4 were most widely applicable which cyclized not only the compound p-activated but also the compounds which do not carry activating group in aromatic nucleus (eg. 8, 9[7]). PPE, $BF_3 \cdot Et_2O$ in CH_2Cl_2, and $AgClO_4$ in benzene were effective only to the compounds which carry p-activating group (eg. 7, 10, 12), but were sometimes superior to PPA or H_3PO_4 in the yield and easiness of work-up.

$POCl_3$, H_3PO_4-MeOH-H_2O[8], $AgBF_4$ in benzene, and $AlCl_3$ in Me_2S 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 generallization 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 %.



4 19

Chart 3

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 ω-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. $BF_3 \cdot Et_2O$ 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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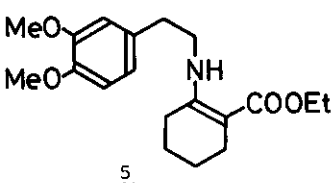
4. 

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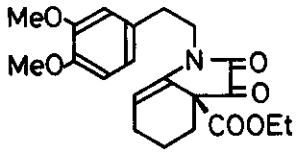
Colorless needles from EtOH. mp 60-61°. IR(cm^{-1}): 1640, 1585, 1515. NMR($CDCl_3$): δ 8.92(1H, bs, -NH-), 6.72(3H, s, ArH), 4.07 (2H, q, J=7.8 Hz, $OC\underline{H}_2CH_3$), 3.81(6H, s, OCH_3 x 2), 3.29(2H, bt, J=6.8 Hz, $NHC\underline{H}_2CH_2$), 2.73(2H, t, J= 6.8 Hz, $-CH_2Ar$), 1.22(3H, t, J=7.8 Hz, $OCH_2C\underline{H}_3$).
5. 

6
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, C=CH-), 3.83(3H, s, OCH_3), 3.81(3H, s, OCH_3), 4.07(2H, q, J=7.1 Hz, $OC\underline{H}_2CH_3$), 1.18(3H, t, J=7.1 Hz, $-OCH_2C\underline{H}_3$).
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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