ATTEMPTED SYNTHESIS OF APORPHINE SKELETON BY PHOTOCYCLIZATION OF 4,5-DIARYL-4-OXAZOLIN-2-ONES

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Irradiation of 4,5-diaryl-4-oxazolin-2-ones (1a-f) with substituents on a benzene ring and nitrogen afforded various types of phenanthrenes (2a-h). Attempted synthesis of aporphines was undertaken by applying the photocyclization of 4-oxazolin-2-ones (1b,d,e, and f) and (4a and b).

Photocyclizations of 4,5-diaryl-4-oxazolin-2-one and 4,5-diaryloxazole in the presence of iodine as an oxidizing agent have recently been reported by Tsuge[1a], Neumeyer[1b], Hakimelahi[1c], Wasserman[1d], and Maeda[1e]. We now report studies on the photocyclization of various types of 4,5-diaryl-4-oxazolin-2-ones with

substituents on the benzene ring and nitrogen and on our unsuccessful attempts of its application to the synthesis of aporphine alkaloids which involve the formation of ring B of the alkaloid skeleton as the last step of the construction.

Treatment of the benzoins, prepared from various benzaldehydes, with ethyl carbamate[1c] or carbamoyl chloride[2] afforded 4,5-diaryl-4-oxazolin-2-ones which were converted into the corresponding N-alkyl derivatives (1a-f) in 20-40 % yields from the benzoins.

Under the essentially same condition reported by Hakimelahi[1c], irradiation of a methanolic solution (4 mmole) of the 4-oxazolin-2-ones (1a-f) in the presence of I_2 (1.4 mmole) and $CuCl_2.2H_2O$ (0.12 mmole) with a high pressure mercury lamp at room temperature for 5-12 hrs. afforded the photocyclized phenanthrenes (2a-h), precipitated as it formed. Bubbling of nitrogen into the solution during the course of irradiation was required to prevent ready photooxygenation[1a] of the oxazoline ring thus reducing yields. The structures of the photocyclized products (2a-h) were readily established from their n.m.r. spectra which showed peaks of protons at C-4, -7, -8, and -11 in low fields (δ 9.00-8.20) due to steric hindrance arising from the phenanthrene structure and the loss of two aromatic protons present in the starting materials.

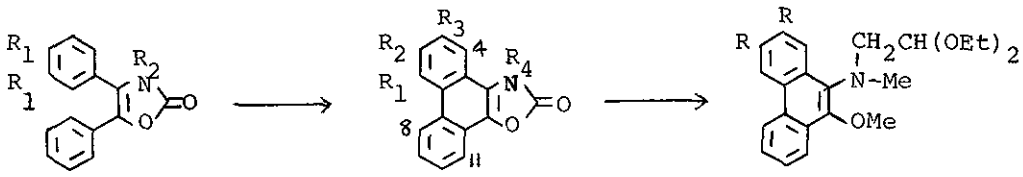
As an extension and application of this cyclization, the construction of aporphine skeleton by cyclization of ring B was attempted.

The Friedel-Crafts reaction of the carboxylic acids, which were prepared from (2b and e) by hydrolysis with hydrochloric acid gave no isoquinolones even under various conditions. Inspection of the Dreiding model of (2b and e) showed that the ester group is situated far away from the C-4 position for cyclization to occur due to the presence of an oxazoline ring which intervenes access of the ester group to the cyclizing position on the benzene ring.

Therefore, to overcome this situation, the oxazolin-2-one ring was subjected to cleavage by hydrolysis with KOH-H_2O-THF, but the product was 9,10-phenanthrenequinone. However, reduction of (2d and h) with lithium aluminum hydride followed by methylation with MeI afforded the aminomethyl ether (3a and b) in good yields respectively. The Pomeranz-Fritsch reaction of (3a and b) to prepare the isoquinoline skeleton in the presence of BF_3[3], 6N-HCl[4], and H_2SO_4[5] was also unsuccessful.

Since the synthesis of aporphine skeleton including an oxazolin-2-one moiety by the Pschorr reaction has been succeeded[6], the photocyclization of the oxazolin-2-one (4a), which has rings A and B in its structure, was attempted. Irradiation of (4a) under various conditions gave no photocyclized product but the imide (5) in 50 % yield, which was formed presumably by photooxygenation[1a] of (4a) in the presence of air, thus forming a dioxetane, which would undergo ring cleavage by splitting CO_2 as suggested by Tsuge[1a]

Since non-oxidative photocyclization of cis-stilbene having ortho-methoxy group to phenanthrene was reported by Giles[7]

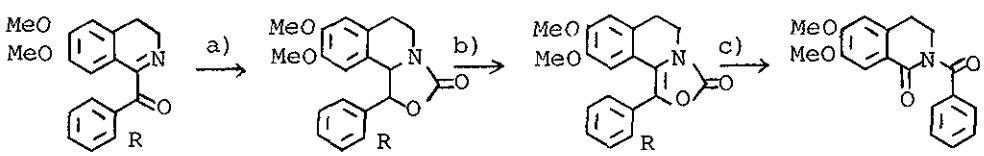


(1a-f) (2a-h) (3a and b)

a: R=H

b: R+R= OCH_2O

(1)	R_1	R_2	(2)	R_1	R_2	R_3	R_4	Yield (%) in MeOH
a	H	Me	a	H	H	H	Me	84
b	H	CH_2COOEt	b	H	H	H	CH_2COOEt	85
c	H	$CH_2CH=CH_2$	c	H	H	H	$CH_2CH=CH_2$	89
d	H	$CH_2CH(OEt)_2$	d	H	H	H	$CH_2CH(OEt)_2$	60
e	OCH_2O	CH_2COOEt	e	$-OCH_2O-$		H	CH_2COOEt	20
			f	H	$-OCH_2O-$		CH_2COOEt	30
f	OCH_2O	$CH_2CH(OEt)_2$	g	$-OCH_2O-$		H	$CH_2CH(OEt)_2$	17
			h	H	$-OCH_2O-$		$CH_2CH(OEt)_2$	33



(4a and b) (5)

a: R=H

b: R=OMe

a) i $LiAlH_4$; ii ClCOOEt; iii KOH. b) DDQ. c) hν/air

the photocyclization of the ortho-methoxy derivative (4b) under non-oxidative conditions, was attempted but the expected aporphine derivative was not detected in the reaction mixture.

Thus, attempts to prepare an aporphine skeleton by constructing ring B as the last step of the synthesis were so far unsuccessful presumably due to the intervention of severe steric hindrance. Work to overcome this hindrance is now under progress.

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