

PHOTOCYCLIZATION OF 4-SUBSTITUTED ISOQUINOLINONE.
 AN APPROACH TO THE SYNTHESIS OF PHENANTHRIDINE ALKALOIDS

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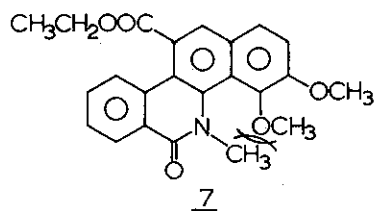
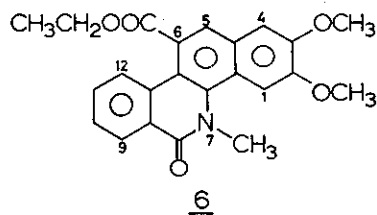
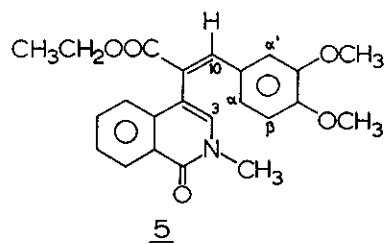
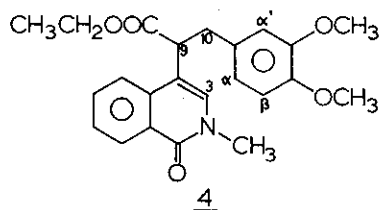
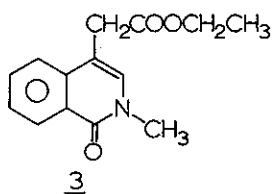
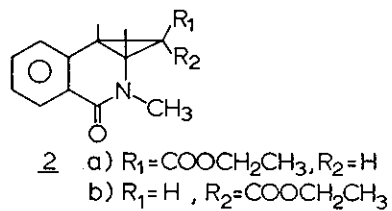
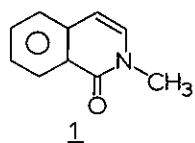
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A facile conversion of N-methylisoquinolinone to phenanthridine derivatives is described.

Phenanthridine alkaloids have received a great amount of attention in view of their antileukemic activity properties 2a,b,c. Several approaches to the synthesis of this class of alkaloids have been recently reported^{2b,c,3}. In connection with our interests in the reactivity pattern of functionalized enamines⁴, we have examined the reaction of carbenes (carbenoids) with 2-substituted isoquinolinone. The addition products (2a,b) of ethyl diazoacetate with 2-methylisoquinolinone 1 can be transformed to 4-substituted isoquinolinone 3 in high yield. The latter product can be conveniently converted to benzophenanthridine derivatives 6 and 7 via a sequence involving a photocyclization step. The facile availability of 3 makes the overall conversion to 6 and 7 a potentially useful practical approach to phenanthridine alkaloids.



Dedicated to Prof. S. Sugasawa on his 80th birthday.



Reactions of 1 with ethyl diazoacetate in the presence of a copper catalyst afforded a mixture of the exo-adduct (2a, 50%), the endo-adduct (2b, 40%) and 4(carboethoxymethyl)isoquinolino-
ne (3, 4%), which could be separated on a silicagel column. Iso-
merization of 2a and 2b to 3 was accomplished in quantitative
yields by refluxing solutions of either of the isomers in
EtOH/HCl for 16 hours.

The anion of 3 generated by reaction with Lithium di-isopro-
pylamide in THF, at -78° , was alkylated with veratrylbromide in
THF/HMPT at -50° to give 4 in 84% yield; m.p. $116-117^{\circ}\text{C}$. PMR⁶ δ
1.08 t (3H, $\text{COOCH}_2\text{CH}_3$), 3.03 AA'B, $J_{AA'}=14$ Hz, $J_{AB}=6$ Hz (1H,
 $\text{C}_{10}\text{-H}_a$), 3.35 AA'B, $J_{AA'}=14$ Hz, $J_{A'B}=9$ Hz, (1H, $\text{C}_{10}\text{-H}_b$), 3.56 s
(3H, N-CH₃), 3.77 and 3.81 $2 \times s$ (6H, $2 \times \text{OCH}_3$), 3.95 - 4.50 m
(3H, $\text{COOCH}_2\text{CH}_3$, $\text{C}_9\text{-H}$), 6.55 - 6.80, (3H, $\text{C}_\alpha\text{-H}$, $\text{C}_\alpha'\text{-H}$, $\text{C}_\beta\text{-H}$),
7.08 s (1H, $\text{C}_3\text{-H}$), 7.27 - 7.85 m (3H, $\text{C}_5\text{-H}$, $\text{C}_6\text{-H}$, $\text{C}_7\text{-H}$), 8.43 -
8.60 m (1H, $\text{C}_8\text{-H}$). IR⁶: 1600, 1620, 1640 and 1725 cm^{-1} ; UV⁶:
204 (4.638) shoulders at 228, 245 and 253, 285 (3.917) and
327 nm (3.594).

When 4 was treated with 6 eq. of DDQ, in refluxing decalin,
a single dehydro product (5) was isolated. PMR spectrum of the
compound exhibited vinyl protons at 8.10 (s, $\text{C}_{10}\text{-H}$) and 7.07
(s, $\text{C}_3\text{-H}$). The dehydro product can possess either the E or Z
configuration. In the absence of the second isomer, the follow-
ing information throws light upon the configuration of the
product. In a series of cinnamic acid derivatives the Z-isomers
show the β -proton (analogous to $\text{C}_{10}\text{-H}$) in the range δ 6.80 -
6.96 while the same proton in the corresponding E-isomers

resonate at a significantly lower field (δ 7.55 - 7.75⁷). Furthermore, in a system closely related to 5, Onda and co-workers^{3d} have isolated both the Z and E isomers. The Z-isomer has been shown to be photo-labile and upon photolysis undergoes transformation to the E-isomer. The dehydro product obtained in our work is not converted to the second isomer upon photolysis. On the basis of the aforementioned the oxidation product of 4 is tentatively assigned the E-configuration 5.

Photolysis of a benzene solution of 5, in the presence of iodine, afforded, after chromatographic separation, phenanthridones 6 (22%, m.p. 167/168° and 7 (63%, isolated as an oil). Their structures were confirmed by the following spectral data: 6 PMR 1.32 t (3H, COOCH₂CH₃), 3.99 s (3H, N-CH₃), 4.03 s (6H, 2 × OCH₃), 4.44 q (2H, COOCH₂CH₃), 7.19 s (1H, C₁-H), 7.49 s (1H, C₄-H), 7.84 s (1H, C₅-H), 7.40 - 7.80 m (3H, C₁₀-H, C₁₁-H, C₁₂-H), 8.45 - 8.58 m (1H, C₉-H); IR 1620, 1635 and 1705 cm⁻¹; UV: 217 (4.305), 288 (4.685), 322 (4.088), 364 (3.378) and 378 nm (3.405). 7 PMR 1.28 t (3H, COOCH₂CH₃), 3.47 s (3H, N-CH₃), 3.73 s (3H, C₁-OCH₃), 4.02 s (3H, C₂-OCH₃), 4.43 q (2H, COOCH₂-CH₃), 7.35 AB, J_{AB}=9 Hz (1H, C₃-H), 7.65 AB, J_{AB}=9 Hz (1H, C₄-H), 7.81 s (1H, C₅-H), 7.50 - 7.75 m (C₁₀-H, C₁₁-H, C₁₂-H), 8.47 - 8.63 m (1H, C₉-H); IR 1645 and 1705 cm⁻¹.

Particularly revealing in the PMR spectrum of 7 are the up-field shifts of the N-CH₃ ($\Delta\delta$ 0.55 ppm) and the C₁-OCH₃ ($\Delta\delta$ 0.30 ppm) relative to 6. These upfield shifts can be accounted for in terms of steric hindrance between the N-CH₃ and the O-CH₃ groups which forces these to lie above and below the

plane of the aromatic system. This is borne out by inspection of molecular models.

The abovementioned synthesis affords, in five steps, the phenanthridones 6 and 7 in an overall yield of 8.8% and 25%, respectively.

Acknowledgement. This work was carried out in part under auspices of the Netherlands Foundation for Chemical Research (S.O.N.) and with financial support from the Netherlands Organization of Pure Research (Z.W.O.).

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Received, 4th July, 1977