

REACTIONS OF 1,2,3,3a,4,5-HEXAHYDRO-N-(3,4-DIMETHOXYPHENYL-
ACETYL)INDOL-6-ONE WITH ACIDS AND PHOSPHORYL CHLORIDE:
A SYNTHESIS OF THE ERYTHRINAN-TYPE COMPOUND

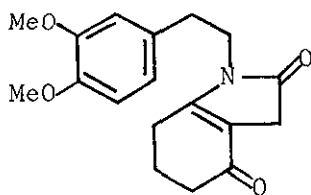
Hideo Iida,* Sakae Aoyagi, Kensuke Kohno, Norio Sasaki,
and Chihiro Kibayashi
Tokyo College of Pharmacy
Horinouchi, Hachioji, Tokyo 192-03, Japan

Some reactions of 1,2,3,3a,4,5-hexahydro-N-(3,4-dimethoxyphenylacetyl)indol-6-one (4), which was obtained from the iminoenol ether (5) and the acid chloride, with acids and electrophiles were investigated, and intramolecular cyclization to the erythrinan derivative (10) was achieved on treatment with phosphoryl chloride in acetonitrile.

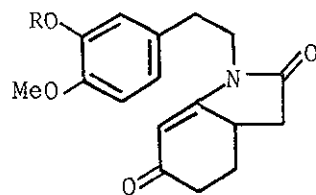
It has been proved in recent years that in acid-catalyzed cyclization enamido ketones can serve as important intermediates for the synthesis of the erythrinan skeleton.¹⁻⁴ However, the enamido ketones by the use of which cyclization was successfully accomplished have been limited to the keto lactam series [(1),² (2),³ and (3)⁴], and the preparations of them have been somewhat

troublesome. We report here some of the reactions of the enamido ketone (4) possessing the exocyclic amide group and a potential route to the erythrinan system.

The desired enamido ketone (4) was readily obtained via two-step reaction from 6-methoxyindoline in good yield: the iminoenol ether (5),⁵ prepared by Birch reduction of 6-methoxyindoline in quantitative yield, was treated with 3,4-dimethoxyphenylacetyl chloride in chloroform in the presence of triethylamine to give the product (4) (65% yield) [mp 143–144°; ν_{\max}

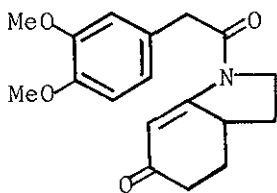


(1)

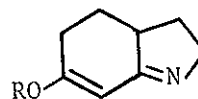


(2) R = H

(3) R = Me

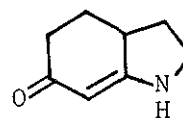


(4)



(5) R = Me

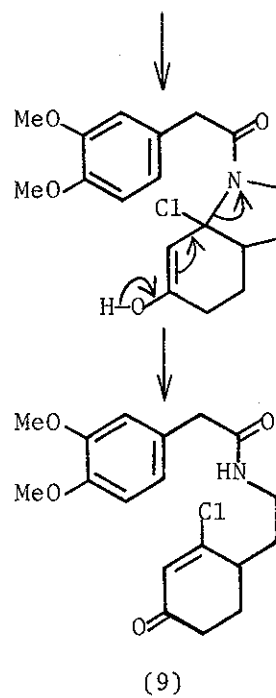
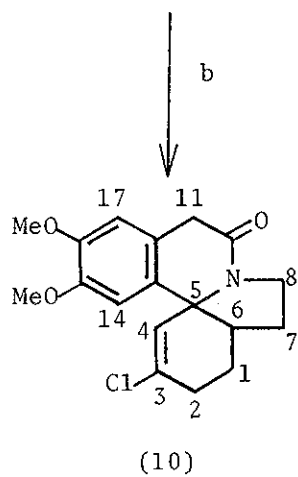
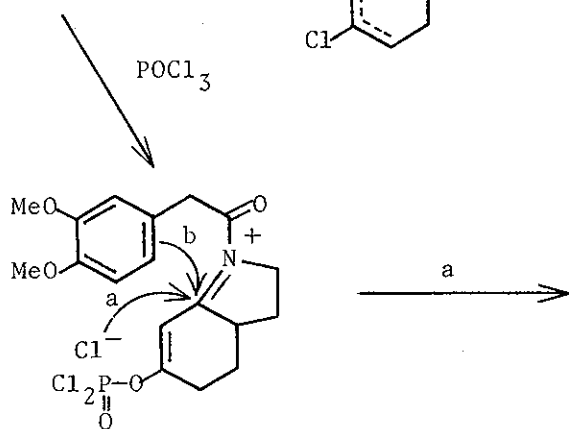
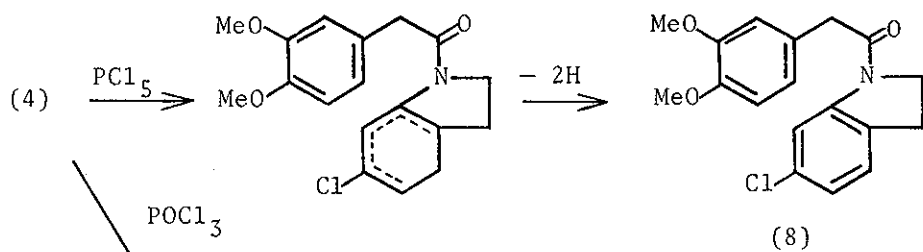
(6) R = Et



(7)

(CHCl₃) 1685, 1640, and 1600 cm⁻¹; δ (CDCl₃) 3.74 (2H, s, ArCH₂), 3.86 (6H, s, 2 x OMe), and 6.77 (4H, m, vinyl and aromatic H)].

Gentle heating of the enamido ketone (4) in 85% phosphoric acid or ethanolic hydrochloric acid gave no cyclized product and caused cleavage of the amide group yielding 1,2,3,3a,4,5-hexahydroindol-6-one (7), identical with an authentic sample,⁵ or the iminoenol ether (6), respectively. In order to avoid cleavage of the amide linkage, the reaction was then carried out under nonaqueous condition using aprotic electrophiles. Thus (4) was treated in dry chloroform (or acetonitrile) with phosphorus pentachloride at room temperature for 1 h to give the indoline derivative (8) (73%) [mp 136–137°; ν_{\max} (CHCl₃) 1665 (C=O) cm⁻¹; M⁺ at m/e 331 and 333 (36.5% of 331)], whose NMR spectrum [δ (CDCl₃) 3.07 (2H, t, J = 8 Hz, 2-H₂), 3.82 (2H, t, J = 8 Hz, 3-H₂), 6.86 (1H, dd, $J_{5,4}$ = 8 and $J_{5,7}$ = 2 Hz, 5-H), 6.97 (1H, d, $J_{4,5}$ = 8 Hz, 4-H), and 8.21 (1H, d, $J_{5,7}$ = 2 Hz, 7-H)] showed the presence of the 6-substituted indoline moiety. On the other hand, heating (4) with phosphoryl chloride in dry chloroform under reflux for 30 min gave the ring-opened product (9) (47%) [pale yellow liquid; ν_{\max} (CHCl₃) 3410 (NH), 1680 (ketone C=O), 1660 (amide C=O), and 1610 (C=C) cm⁻¹; δ (CDCl₃) 2.68 (2H, m, COCH₂CH₂), 3.26 (2H, q, J = 2 Hz, NCH₂), 3.44 (2H, s, ArCH₂), 3.84 (6H, s, 2 x OMe), and 6.08 (1H, d, J = 1 Hz, vinyl H)]; M⁺ at m/e 351 and 353 (35.9% of 351)]. When the above reaction using phosphoryl chloride was carried out in dry acetonitrile intramolecular cyclization (path b) leading to 3-chloro-3,4-



dehydro-15,16-dimethoxyerythrinan-10-one (10), albeit in low yield (4%) [mp 220–222°; ν_{\max} (CHCl₃) 1632 (C=O) cm⁻¹; δ (CDCl₃) 3.53 (2H, m, 8-H), 3.43 and 3.67 (2H, AB type q, 11-H₂), 3.83 (6H, s, 2 x OMe), 5.63 (1H, s, 4-H), 6.57 (1H, s, 17-H), and 6.81 (1H, s, 14-H); M⁺ at m/e 333 and 335 (36.6% of 333)] proceeded in competition with ring-opening (path a) yielding (9) (16%).

REFERENCES

- 1 K. Ito, M. Haruna, and H. Furukawa, "Symposium Papers of the 19th Symposium on the Chemistry of Natural Products, Hiroshima, Japan, 1975", p. 38.
- 2 A. Mondon and K. Böttcher, Chem. Ber., 1970, 103, 1512.
- 3 K. Ito, M. Haruna, and H. Furukawa, J. Chem. Soc. Chem. Comm., 1975, 681.
- 4 T. Oh-ishi, I. Iijima, N. Itoh, and S. Sugawara, Chem. and Pharm. Bull. (Japan), 1975, 23, 2573.
- 5 H. Iida, S. Aoyagi, and C. Kibayashi, J. Chem. Soc. Perkin I, 1975, 2502.

Received, 10th September, 1976