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SYNTHESIS OF γ-LYCORANE AND RELATED COMPOUNDS VIA PHOTOCYCLIZATION OF N-SUBSTITUTED β-ENAMINOKETONES

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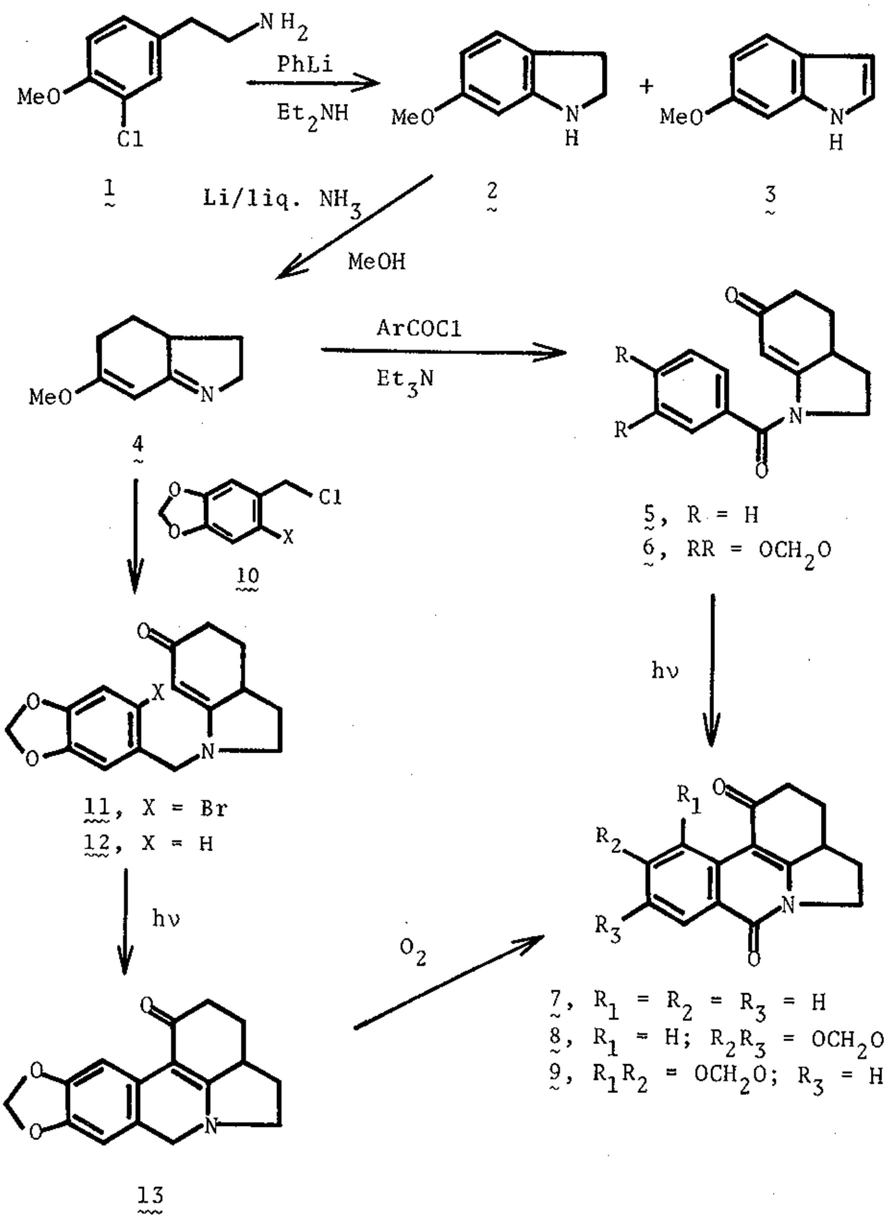
A new, facile synthesis of γ-lycorane and related compounds from a key intermediate 8 readily obtained by photocyclization of N-benzoyl and N-benzyl derivatives of 1,2,3,3a,4,5-hexahydroindol-6-one is described.

Recently we have developed[1] a convenient general procedure for the preparation of N-substituted β-enaminoketones by the reaction of a common intermediate, 3,3a,4,5-tetrahydro-6-methoxy-2H-indole (4), with acid chlorides or alkyl halides. We envisaged that photocyclization of these compounds would provide short, simple route to the pyrrolo[3,2,1-de]phenanthridine ring system.[1a,b] In this paper, we report an efficient intramolecular photoarylation of N-benzoyl and N-benzyl derivatives of 1,2,3,3a,4,5-hexahydroindol-6-one, and its application to the novel stereoselective synthesis of (±)-α-anhydrodihydrocaranine (15) and (±)-γ-lycorane (17) which have been derived from the Amaryllidaceae alkaloids lycorine or caranine.

As depicted in Scheme I, the preparation of requisite enaminoketone derivatives was achieved via a simple two-step procedure from 6-methoxyindoline: benzyne reaction of the phenethylamine 1 with phenyllithium and diethylamine in ether gave 6-methoxyindoline (2) in 42% yield, accompanied by a minor amount of 6-methoxyindole (3) (5% yield) as an oxidized product. Birch reduction of 2 with lithium in liquid ammonia and tetrahydrofuran in the presence of methanol afforded the iminoenol ether 4 in excellent yield (92%). Treatment of 4 with benzoyl chloride in the presence of triethylamine resulted in N-acylation and de-O-methylation *in situ* to give the enamidoketone 5 in 41% yield. Similarly, reaction of 4 with 3,4-methylenedioxybenzoyl chloride provided the enamidoketone 6 in 41% yield. On the other hand, heating 4 and 2-bromo-4,5-methylenedioxybenzyl chloride (10, X = Br) in refluxing toluene either in the presence or in the absence of base gave the bromoenaminoketone 11 in 51% yield.

Irradiation of the two enamidoketones 5 and 6 gave the corresponding oxidatively cyclized products 7 and 8 in 70% yields, presumably via concerted process. Stereomodels indicate that the alternative mode of cyclization to 9 is not favored because of serious non-bonded interaction between the 1-carbonyl group and the 11-ether oxygen atom. Hence the reaction appears to proceed regioselectively to give 8 as sole product. Irradiation of the bromoenaminoketone 11 in the presence of triethylamine also gave 8 (8% yield), together with the debrominated product (12) (26% yield), identical with a specimen prepared from the iminoenol ether 4 and 3,4-methylenedioxybenzyl chloride (10, X = H) in

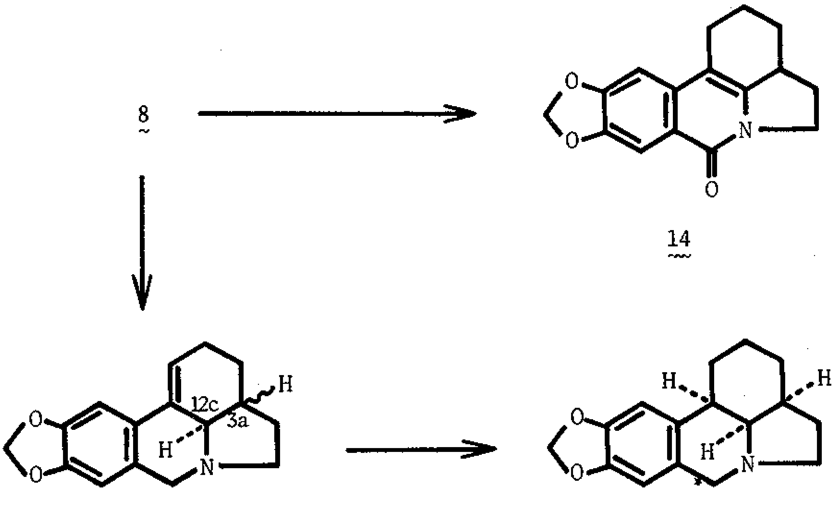
Scheme I


NH2
MeO
Cl
PhLi
Et2NH
MeO
N
H
+
MeO
N
H
1
2
3
Li/liq. NH3
MeOH
MeO
N
4
ArCOCl
Et3N
O
R
R
N
O
5, R = H
6, RR = OCH2O
O
O
Cl
X
10
O
O
O
X
N
11, X = Br
12, X = H
hν
hν
O
O
O
N
13
O2
R1
O
R2
R3
N
O
7, R1 = R2 = R3 = H
8, R1 = H; R2R3 = OCH2O
9, R1R2 = OCH2O; R3 = H

a similar manner for 11. The latter photochemical reaction may involve intramolecular arylation via photolysis, leading to the 1,2-dihydroisoquinoline 13, which occurs competitively with photoreduction to give 12; compound 13 is eventually oxidized by air to produce the stable isoquinolin-1-one 8.

Hydrogenation of 8 over Adams catalyst in acetic acid gave the deoxygenated product 14 via hydrogenolysis of the intermediate alcohol. Attempts to convert 14 to lycorane by catalytic reduction in acidic media or with lithium aluminum hydride were not successfull: most of the starting material was recovered unchanged or a complex mixture of unidentified products was obtained, respectively. Alternatively, treatment of 8 with lithium aluminum hydride in

Scheme II



14

15, α-H
16, β-H

17

tetrahydrofuran gave (±)-α-anhydrodihydrocaranine (15) in 32% yield. The stereochemical assignment of 15 was based on its UV spectrum, which agreed with that reported for the (-)-α-isomer 15,[2] but differed appreciably from that of the (-)-β-isomer 16.[2] Additional evidence for this assignment was provided by the NMR spectrum, in which the 12c-H–3aH coupling constant was 7.5 Hz, thus proving that the C/D ring junction is cis. Finally, hydrogenation of 15 over Adams catalyst in acetic acid gave (±)-γ-lycorane (17) in 47% yield; the mp (102—104 °C) of the product was consistent with that reported,[3] and its IR spectrum (in carbon disulfide) was identical with that of an authentic sample.[4]

REFERENCES AND NOTE

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(4) We are indebted to Dr. K. Kotera for the IR spectrum of (+)-γ-lycorane.