A ROUTE FOR TOTAL SYNTHESIS OF ERGOT ALKALOIDS
SYNTHESIS OF THE DESPYRROLE ANALOGS OF METHYL LYSERGATE, ISOLYSERGOL, AND ISOFUMIGACLAVINE A.

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Abstract ——— A general and potential synthetic route involving reductive photocyclization of enamide followed by the formation of glycols and their cleavage for total synthesis of ergot alkaloids was developed using the model compounds (3,6,7, and 13).

Although the potentiality of reductive photocyclization of enamides for the construction of nitrogen-containing heterocyclic compounds has been convincingly demonstrated[1,2], there remains the equally important task for us on the application of this new methodology to the total synthesis of natural alkaloids. Within this context and also as an extension of our work on the synthesis[3,4] of ergot alkaloids, we report here a simple synthetic route to the despyrrole analogs (11), (12b), and (14) of methyl lysergate[5], isofumigaclavine A[6], and isolysergol[5] by applying reductive photocyclization of the enamide (1) which carries a furan ring[7] and ring opening of the dihydrofuran moiety of the photocyclized lactam (3).

Acylation of the 2-tetraloneimine with 3-furoyl chloride in the presence of triethylamine afforded the enamide (1) in 71 % yield. Reductive photocyclization of the enamide (1) in the presence of sodium borohydride at 4-5 °C afforded a mixture of two hydrogenated lactams (2 and 3) with different ratios depending on the solvent used as summarized in the Table I. The stereochemistry of these lactams (2) and (3) was deduced from their n.m.r. spectra which firmly established the B/C-trans ring junction of (3) and the cis-structure of (2).

Conversions of the stable trans-lactam (3) into the target compounds, which lack only a pyrrole ring from the parent ergot alkaloids, were carried out as follows.

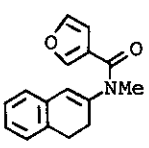
Attempts to cleave the dihydrofuran ring in the lactam (3) via the corresponding glycols were not successful probably due to the susceptibility to dehydration and oxidation of intermediates thus giving only the dehydrolactam (4). Therefore, the lactam (3) was reduced with lithium aluminum hydride to give the corresponding amine (5). Then osmylation of the amine (5) with osmium tetroxide[8] followed by usual workup with hydrogen sulfide afforded a mixture of two cis-glycols (6a and b) in 52 % combined yield from (3). The ratio of isomers was 2 : 1 in favor of the β-glycol (6a). Without separation, cleavage of these glycols (6a and b) with sodium metaperiodate in methanol-water afforded an unstable and inseparable mixture of epimeric hydroxy-aldehydes (7), which were then dissolved in methanol-acetone and treated with chromic trioxide in sulfuric acid[8] at 0° for 30 mins to give a 1 : 1 mixture of the corresponding hydroxy-esters (8) and (9) in 20 % respective yields, which were separated by preparative t.l.c.

According to the method described by Horii and coworkers[9], dehydration of the hydroxy-esters (8) and (9) was achieved by heating with phosphorus oxychloride-phosphoric acid in pyridine to afford a mixture of the unsaturated esters (10) and (11) with almost identical ratios of 1 : 2 in about 35 % yields respectively, each of which was assigned as the despyrrole analogs[9,10] of methyl lysergate and methyl isolysergate by thorough comparisons of their n.m.r. spectra.[11,12]

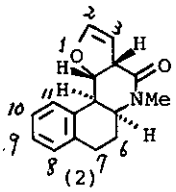
Wolff-Kishner reduction of the above hydroxy-aldehydes (7) afforded the C_2-methyl derivative (12a) in 24 % yield which was then converted by acetylation into the despyrrole analog (12b) of isofumigaclavine A[6].

On the other hand, glycol cleavage of a mixture of the amines (6a and b) with periodic acid in dry tetrahydrofuran afforded the C_1-O-formate (13) as a major product together with small amounts of the C_2-epimer of (13) and the hydroxy-aldehydes (7). The C_1-O-formate (13) was then converted into the cis-hydroxy-ester (8) by oxidation with chromic trioxide and hydrolysis as in the case of (7). The C_1-O-formate (13) was then treated with sodium borohydride in methanol to afford the unsaturated methylol (14), the despyrrole analog of isolysergol[5], in 25 % yield.

Thus, the route presented above for the synthesis of the despyrrole analogs (11), (12b), and (14) offers a great possibility for the total synthesis of a group of ergot alkaloids, which is now under progress.



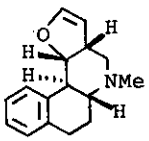
(1)



(2)

Table I

Solvent	Yield	Ratio (3)/(2)
C_6H_6-MeOH (10:1)	82%	1
MeCN-MeOH (10:1)	72%	4



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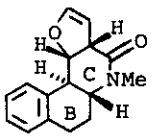

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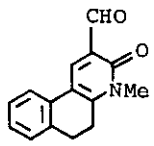

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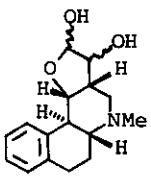
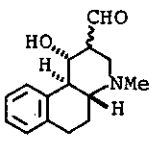


(6a) β-glycol
(6b) α-glycol



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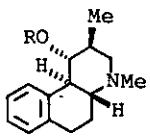
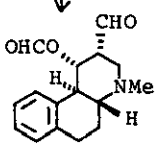


(12a) R=H
(12b) R=Ac



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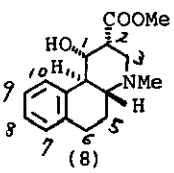

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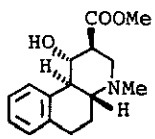

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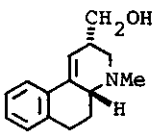

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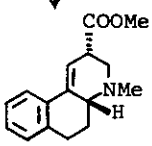

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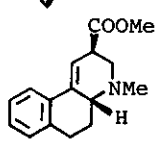

(11)

Table II ^{1}H nmr Data For Benzo[f]furo[2,3-a]quinoline Derivatives.

Compds.	2-H	3-H	3a-H	5a-H	11-H	11b-H	11c-H	NMe
(2)	6.42(t, J=2.5)	5.33(t, J=2.5)	3.87(dt, J=10, 2.5)	3.51(ddd, J=13, 6, 4)	7.30 (m)	3.21-2.88(m)*	4.77(dd, J=11, 10)	3.08 (s)
(3)	6.46(t, J=2.5)	5.18(t, J=2.5)	3.76(br,d, J=11)	3.48(ddd, J=12, 11, 3)	7.83 (m)	3.20-2.80(m)*	4.85(dd, J=11, 10)	3.08 (s)
(6a)**	5.38(d, J=4.5)	4.46-4.22(m)*	2.58-2.28(m)*		7.96 (m)	2.66(t, J=11)	4.46-4.22(m)*	2.40 (s)
(6b)**	5.28(d, J=4.5)				8.03 (m)	3.01(t, J=11)		

Table III ^{1}H nmr Data For Benzo[f]quinoline Derivatives.

Compds.	1-H	2-H	3ax-H	3eq-H	10-H	10b-H	NMe	others
(8)	4.03 (m)	3.08 (q, J=3.5)	2.28 (dd, J= 12, 3.5)	3.34 (dd, J= 12, 3.5)	7.91 (m)	3.02 (br.t, J=10)	2.22 (s)	3.81 (s, COOMe) 3.84 (br.s, OH)
(9)	4.23 (t, J=10)	2.96 (m)	2.26 (t, J=12)	3.19 (dd, J= 12, 4)	7.87 (m)	2.68 (t, J=10)	2.32 (s)	3.80 (s, COOMe) 3.32 (br.s, OH)
(10)	6.39 (m)	***	***	***	7.59 (m)	----	2.50 (s)	3.74 (s, COOMe)
(11)	6.42 (br.s)	3.66 (m)	2.56 (t, J=11.5)	3.22 (dd, J= 11.5, 6)	7.64 (m)	----	2.53 (s)	3.78 (s, COOMe) 2.80 (br.d, J=12, 4a-H)
(12a)	3.58 (t, J=10)	2.16-1.80(m)*		2.95-2.76(m)*	7.76 (m)	2.68 (t, J=10)	2.34 (s)	1.13 (d, J=6, 2-Me)
(12b)	5.14 (t, J=10)	2.30-1.80(m)*		2.95-2.75(m)*	7.22-7.16 (m)*	2.91 (t, J=10)	2.34 (s)	2.12 (s, OAc) 0.98 (d, J=6, 2-Me)
(14)	6.29 (br.d, J=5.5)	2.60-2.46 (m)*	2.71 (dq, J= 12, 2)	3.04-2.88(m)*	7.57 (m)	----	2.49 (s)	3.99(dd, J=10, 3) 3.82(dt, J=10, 2.5) 2-CH_2OH 2.80 (br.d, J=13, 4a-H)

* Splitting patterns assigned to those protons are ambigous due to their overlapping to other protons.

** Measured in $CDCl_3$-CD_3OD (5:1).

*** Signals for these protons are ambigous due to the co-presence of epimer (11).

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^{1}H n.m.r. spectral data for the compounds described in this paper were measured in $CDCl_3$ at 200 MHz unless otherwise mentioned and collected in the Tables II and III.

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