Tetrahedron Letters,Vol.26,No.40,pp 4903-4906,1985 0040-4039/85 $3.00 + .00
Printed in Great Britain

SYNTHESIS OF ORELLANINE, THE LETHAL POISON OF A TOADSTOOL

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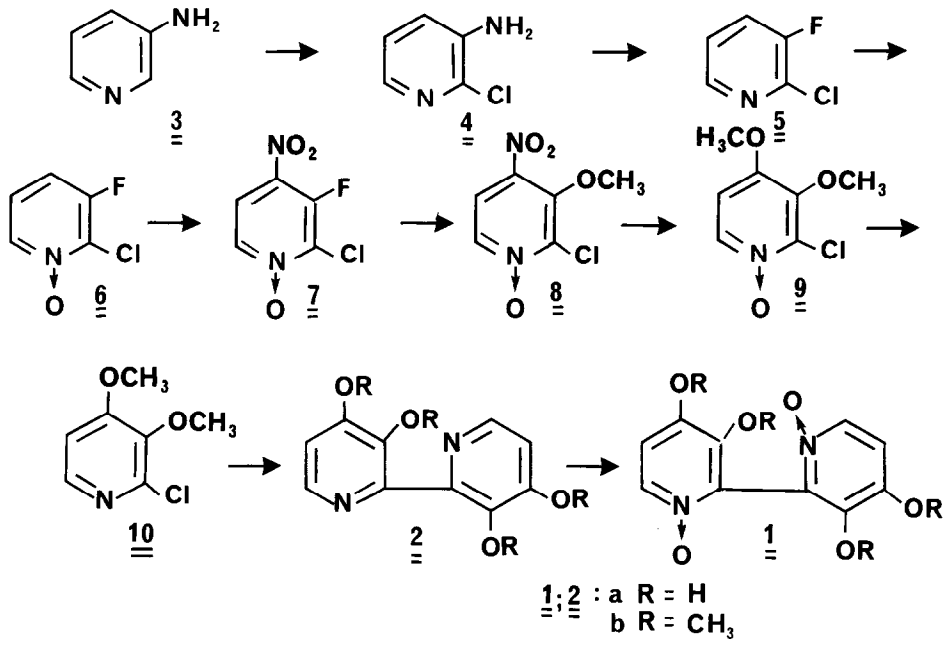
Abstract: *A ten step synthesis of the structure of orellanine, 3,3',4,4'-hydroxy-2,2'-bipyridyl-bis-N-oxide (1a), is described which proves the identity of the natural product.*

The mushroom Cortinarius orellanus Fries was considered edible until 1952, when a mass poisoning of 135 persons (including 19 deaths) in Poland caused attention. Analysis of the incident was complicated by the latency period of 3 to 20 days between consumption of the toadstools and the appearance of symptoms[1]. The first separation of the poisonous principle, named orellanine, led to a mixture apparently[2]. Antkowiak and Gessner[3] isolated a single compound to which they assign the structure of 3,3',4,4'-tetrahydroxy-2,2'-bipyridyl-bis-N-oxide (1a). Decomposition of 1a on heating gives oxygen[4] and non-toxic orelline (2a). Moser et al. seem to have isolated 1a as well[5]. Although the nephrotoxicity of this compound and other bipyridyls is well established[6], recent work from another group implies that the C. orellanus toxins might be peptides[7]. In view of the unusual structure, a synthesis of 1a seemed desirable.

Several synthetic routes towards 1b were attempted in vain. All experiments were futile in particular which used substituted bipyridyls as early intermediates. Ultimately, the process shown in the scheme was developed. The chlorination 3 ⟶ 4 (15% H_2O_2 in concentrated HCl) was executed in 82% yield[8]. 38% 5 was obtained from 4 in a Schiemann reaction[9]. Oxidation of 5 with acetic anhydride/30% H_2O_2 gave 54% of 6[10]. Nitration (100% HNO_3/100% H_2SO_4 containing 10% SO_3) of 6 led 42% 7 and 2% of 2-chloro-3-fluoro-6-nitro-



pyridine-N-oxide (11). The structure of 7 as a 4-nitro compound becomes apparent from the NMR signals of the isomers 7 and 11 (Table 1). Selective substitution by a molar amount of methoxide in methanol at room temperature gave 8 (84%), whereas the action of two equivalents of methoxide yielded 9 which could also be obtained from 8 in a stepwise manner. The attempted isolation of 9 resulted in a violent decomposition sometimes, and therefore the immediate PCl_3 reduction of raw 9 to 10 is preferred (62% from 7).

The bipyridyl coupling was achieved with the help of the nickel(0)-triphenylphosphine complex using the method of Tiecco et al.[11]. 10 was added to the freshly prepared complex in DMF and stirred at 50°C for 4 hours. 2b was obtained in 25% yield. It exhibits the expected MS and NMR signals[12]. Oxidation of 2b (Ac_2O/H_2O_2) gave 1b in 41% yield. Interestingly, the mass spectrum of 1b[13] shows the loss of the two oxygen atoms in seperate steps so that the [1.5] oxygen shift mechanism proposed for 1a[4] cannot apply here.

Refluxing 2b or 1b in 33% HBr/HOAc for 4 h yielded 46% 2a or ca. 30% 1a, respectively. Comparison of physical data of these compounds with the published ones (Table 2) established the identity of the natural product[14].

Constant support by Fonds der Chemischen Industrie is acknowledged.

Table 1. Melting Points and ^1H NMR Data of New Compounds

Comp.	m.p. [°C]	Signals (Δ) H-4	H-5	H-6	OCH_3		Coupling Constants (Hz) $J_{4,5}$	$J_{4,6}$	$J_{5,6}$	$J_{F,4}$	$J_{F,5}$	$J_{F,6}$
1b	235-6 (dec.)	—	7.24 (d)	8.13 (d)	3.70	3.93	—	—	7.3	—	—	—
2b	186-7	—	7.15 (d)	8.23 (d)	3.58	3.92	—	—	5.5	—	—	—
6	145-7	7.52 (ddd)	7.46 (d"t")	8.37 (dt)	—	—	8.8	1.6	6.4	7.0	6.4	1.6
7	176-8	—	8.01 (dd)	8.27 (dd)	—	—	—	—	7.5	—	8.0	1.8
11	95-6	7.27 (dd)	7.72 (dd)	—	—	—	9.3	—	—	6.0	6.0	—
8	104-5	—	7.82 (d)	8.21 (d)	4.11	—	—	—	7.4	—	—	—
9	99-100	—	6.76 (d)	8.17 (d)	3.93	3.95	—	—	7.5	—	—	—
10	43-4	—	6.81 (d)	8.04 (d)	3.89	3.93	—	—	5.6	—	—	—

Table 2. Comparison of Constants for Synthetic and Natural 1a and 2a.

Constant	Synthetic 2a	Lit.[3]	Synthetic 1a	Lit.[3]
m.p.	slow decomp. > 320°C	—	slow decomp. > 150°C explosively 267°C	same
UV (MeOH)	219, 343, 390	219, 344, 390	218, 248, 279, 350	219, 248, 282, 352
(0.1nNaOH)	217, 242, 258 282, 384, 406	243, 260, 285 385, 407	221 (sh), 234, 292 317	234, 292, 319
(0.1nHCl)	213, 248, 304	213, 250, 305	205 (sh), 213, 265 290	213, 265, 290
MS	220	220	(CI) 253, 237, 221	(EI) 252, 236, 220
NMR (DMSO-d_6)	7.93, 6.94 (J=5.6)	7.9, 6.9 (J=5.6)	*a)	8.6, 7.5 (J=7.0)
IR*b) (KBr)	1596, 1507, 1443, 1433, 1314, 1277, 1211, 1090, 973, 907, 832, 795, 775	1575, 1512, 1430, 1410, 1305, 1275, 1210, 1075, 986, 900, 816, 795, 765	1617, 1458, 1398, 1349, 1311, 1252, 1186, 1147, 1070, 1028, 988, 877, 836, 755	1620, 1460, 1380, 1342, 1305, 1254, 1177, 1150, 1075, 1033, 995, 877, 833, 765

*a) very dependent on concentration, H_2O, and acid traces, 7.13, 8.23 (J=7.0) (neutral), 7.33, 8.37 (J=7.0) presence of a drop aq. HCl

*b) Lit.-IR values extrapolated from published spectrum[3]

References and Footnotes

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[12] MS (EI): 277 (M^++H), 261, 245, 231. UV (CH_3OH) 269, 216 nm.

[13] MS (CI): 309 (M^++H), 293 [(M^++H)-O], 277 [(M^++H)-2O]; UV (CH_3OH): 311 (sh), 274, 226, 213 (sh).

[14] Diazomethane treatment is known to give one orelline and three orellanine tetramethyl derivatives[3]. Unfortunately, Antkowiak and Gessner give no data so that a comparison is not possible at the stages of 2b and 1b.

(Received in Germany 17 June 1985)