A SYNTHESIS OF APORPHINE DERIVATIVES

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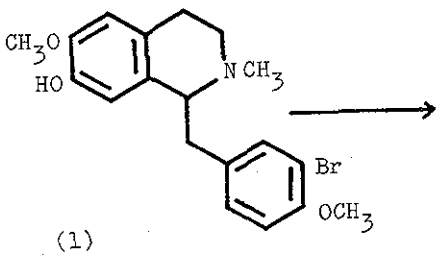
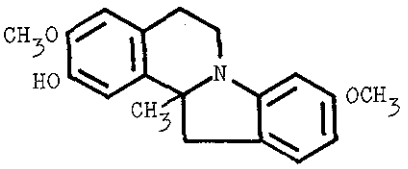
A variety of 1-hydroxyaporphines have been synthesized via 6a,7-dehydroaporphines, obtained by the reaction between a series of 1-halogenobenzyl-3,4-dihydro-2-methylisoquinolinium iodides and dimsylsodium.

We have studied the benzyne reaction of 1-(3-bromo-4-methoxybenzyl)-1,2,3,4-tetrahydro-7-hydroxy-6-methoxy-2-methylisoquinoline (1) using dimsylsodium as a base to give 12a-methyldibenz[b,g]indolizine (2). In this reaction, formation of niether the aporphine (3) nor the morphinandienone (4) was observed[1]. We widely investigated a synthesis of aporphine derivatives via 6a,7-dehydroaporphines, obtained by the reaction of 1-halogenobenzyl-3,4-dihydro-2-methylisoquinolinium salts with dimsylsodium, as an extension of the previous works[1,2], although a synthesis of the 6a,7-dehydroaporphine (5) was studied[3].

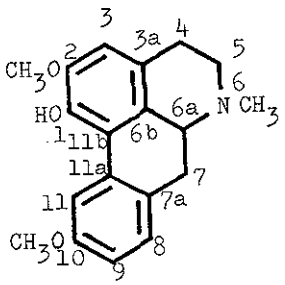
1-(2-Bromo-4,5-methylenedioxybenzyl)-3,4-dihydro-7-hydroxy-6-methoxy-2-methylisoquinolinium iodide (6) was treated with dimsylsodium in DMSO at room temperature to give the 6a,7-dehydroaporphine (7), mp 178-179° (from methanol), in 25 % yield. Reduction of (7)


CH3O
HO
N CH3
Br
OCH3

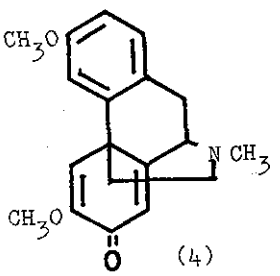
(1)


CH3O
HO
N
CH3
OCH3

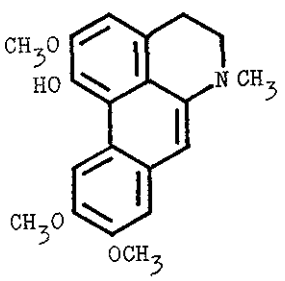
(2)


3
3a
4
5
2
6
CH3O
6a
N CH3
HO
1
11b
6b
11a
7
11
7a
CH3O
10
8
9

(3)


CH3O
N CH3
CH3O
O

(4)

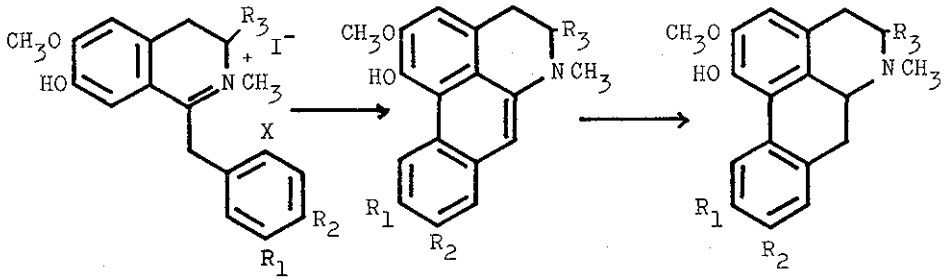

CH3O
HO
N CH3
CH3O
OCH3

(5)

with zinc amalgam in a mixture of 50 % acetic acid and conc. hydrochloric acid (1:1) yielded (±)-domesticine (8), mp 185-186° (lit.[4] mp 186-187°), in quantitative yield, which was identical with the authentic specimen[4]. Similarly, the reaction of 1-(3-bromo-4-methoxybenzyl)-3,4-dihydro-7-hydroxy-6-methoxy-2-methylisoquinolinium iodide (9) with dimsylsodium, followed by reduction of (10) with zinc amalgam, afforded the aporphine (3), mp 199-200° (from methanol), which showed δ ($CDCl_3$), 2.50 (NCH_3), 3.88, 3.92 (6H, 2xOCH_3), 6.50 (3-H), 6.78 (d,d, J=2, 11 Hz, 10-H), 7.22 (d, J=11 Hz, 8-H), 8.08 (d, J=2 Hz, 11-H), m/e 311 (M^+, $C_{19}H_{21}NO_3$), 310, 294. Gibson[5] also examined the benzyne reaction of (1) to obtain (3) by the use of sodium amide, but unsuccessful.

Furthermore, the aporphine derivatives possessing a substituent at the 5-position were synthesized by the same methods. The reaction of the quaternary salts (11), (12), (13) with dimsylsodium, followed by reduction of the dehydroaporphines (14), (15), (16) yielded the corresponding 5-methylaporphines (17), mp 165-167° (from methanol-ether) [δ ($CDCl_3$) 0.93 (d, J=6 Hz, 5-CH_3), 2.52 (NCH_3), 3.80, 3.85, 3.88 (9H, 3xOCH_3), 6.45 (3-H), 6.73 (8-H), 8.07 (11-H), m/e 355 (M^+, $C_{21}H_{25}NO_4$), 354, 338], (18), mp 196-198° (from methanol) [δ ($CDCl_3$) 0.98 (d, J=6 Hz, 5-CH_3), 2.55 (NCH_3), 3.90 (OCH_3), 5.93 (OCH_2O), 6.52 (3-H), 6.73 (8-H), 7.95 (11-H), m/e 339 (M^+, $C_{20}H_{21}NO_4$), 338, 322], and (19), mp 182-183° (from methanol) [δ ($CDCl_3$) 0.97 (d, J=6 Hz, 5-CH_3), 2.57 (NCH_3), 3.87, 3.90 (6H, 2xOCH_3), 6.58 (3-H), 6.78 (d,d, J=2, 11 Hz, 9-H), 7.20 (d, J=11 Hz, 8-H), 8.87 (d, J=2 Hz, 11-H), m/e 325 (M^+, $C_{20}H_{23}NO_3$), 324, 308], respectively.

Since the aporphine (17) synthesized by this method was identical



(6) $R_1=R_2=-OCH_2O-$, $R_3=H$, X=Br

(7) $R_1=R_2=-OCH_2O-$, $R_3=H$

(8) $R_1=R_2=-OCH_2O-$, $R_3=H$

(9) $R_1=Br$, $R_2=OCH_3$, $X=R_3=H$

(10) $R_1=OCH_3$, $R_2=R_3=H$

(17) $R_1=R_2=OCH_3$, $R_3=CH_3$

(11) $R_1=R_2=OCH_3$, $R_3=CH_3$, X=Br

(14) $R_1=R_2=OCH_3$, $R_3=CH_3$

(18) $R_1=R_2=-OCH_3$, $R_3=CH_3$

(12) $R_1=R_2=-OCH_2O-$, $R_3=CH_3$, X=Br

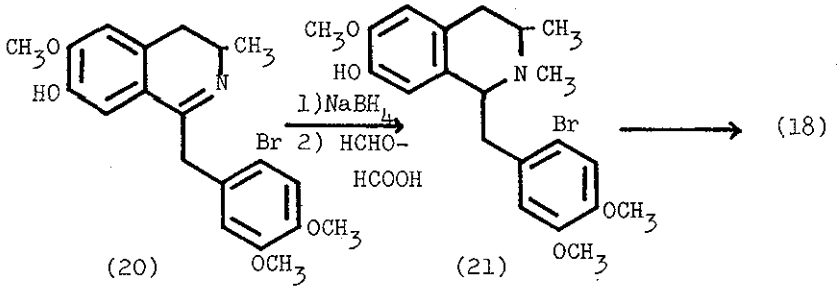
(15) $R_1=R_2=-OCH_2O-$, $R_3=CH_3$

(19) $R_1=OCH_3$, $R_2=H$, $R_3=CH_3$

(13) $R_1=Br$, $R_2=OCH_3$, X=H, $R_3=CH_3$

(16) $R_1=OCH_3$, $R_2=H$, $R_3=CH_3$

(22) $R_1=R_2=OCH_3$, $R_3=H$



(20)

(21)

(18)

with the product obtained by photolysis[6] of (21) which was prepared from the 3,4-dihydroisoquinoline (20) by Gal's method[7], the relative configuration of 5-CH_3 and 6a-H would be trans.

In the carbon-13 nmr spectroscopies of these aporphines in deuteriochloroform, the assignments of the chemical shifts, based on splitting patterns recorded under off-resonance decoupled conditions and on the comparison of the spectra[8], are showen in Table 1. The C_{6a} and NCH_3 signals shifted to the higher region by introducing a substituent at the 5-position.

Table 1 Carbon-13 Chemical Shifts of Aporphines[9]

(All shifts are in parts per milion from TMS)

	Compound				
Carbon	(8)	(17)	(18)	(19)	(22)[3]
C-1	140.73	140.79	140.86	141.32	140.86
C-2	145.83	146.23	145.89	146.03	146.03
C-3	109.73	109.67	109.67	110.33	109.01
C-3a	123.64	122.38	122.38	122.38	123.64
C-4	28.81	35.30	34.83	35.23	29.01
C-5	53.31	55.63	55.43	55.63	53.64
N-$\underline{C}H_3$	43.91	40.86	40.53	40.79	44.04
C-6a	62.45	54.44	54.44	54.24	62.78
C-7	34.94	34.30	34.57	34.64	34.70
C-7a	125.76	125.17	126.03	127.35	125.10
C-8	108.74	112.65	109.27	128.34	112.58
C-9	145.83	147.81	146.09	112.52	147.81
C-10	145.83	147.35	146.09	158.34	147.35
C-11	108.15	111.26	108.34	114.11	111.26
C-11a	130.20	129.54	130.60	133.31	129.01
C-11b	127.22	126.49	126.49	128.94	127.35
C-6b	119.47	119.54	119.40	119.43	119.74
5-$\underline{C}H_3$		10.07	10.20	9.93	
O$\underline{C}H_3$	56.03	56.03(x3)	56.09	56.03(x2)	55.96 56.16(x2)
O$\underline{C}H_2$O	100.73		100.79		

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9. The spectra were taken in deuteriochloroform with Varian NV-14 spectrometer operating at 15.1 MHz.

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