New Syntheses of Maculosidine and Pteleine

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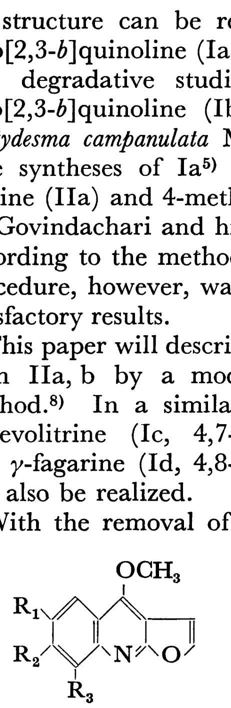
2,3-Dihydromaculosidine and 2,3-dihydropteleine were obtained from 2,4-dimethoxy- and 4-methoxy-aniline by condensation with diethyl β-benzyloxyethylmalonate, followed by methylation and subsequent cyclodebenzylation with polyphosphoric acid. The dehydrogenation of the dihydro compounds with 2,3-dichloro-5,6-dicyanobenzoquinone gave maculosidine (4,6,8-trimethoxyfuro[2,3-*b*]quinoline) and pteleine (4,6-dimethoxyfuro[2,3-*b*]quinoline) in relatively high yields. Similarly, evolitrine (4,7-dimethoxyfuro[2,3-*b*]quinoline) and γ-fagarine (4,8-dimethoxyfuro[2,3-*b*]quinoline) were also prepared.

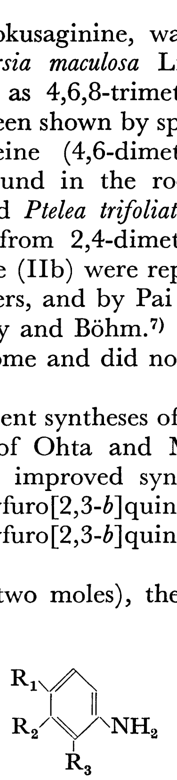
Maculosidine, together with kokusaginine, was isolated from the leaves of *Flindersia maculosa* Lindl.[1] Its structure can be represented as 4,6,8-trimethoxyfuro[2,3-*b*]quinoline (Ia), as has been shown by spectral and degradative studies.[2] Pteleine (4,6-dimethoxyfuro[2,3-*b*]quinoline (Ib)) was found in the roots of *Platydesma campanulata* Mann[3] and *Ptelea trifoliata* L.[4] The syntheses of Ia[5] and Ib[6] from 2,4-dimethoxyaniline (IIa) and 4-methoxyaniline (IIb) were reported by Govindachari and his co-workers, and by Pai *et al.*, according to the method of Tuppy and Böhm.[7] This procedure, however, was troublesome and did not give satisfactory results.

This paper will describe convenient syntheses of Ia, b from IIa, b by a modification of Ohta and Mori's method.[8] In a similar manner, improved syntheses of evolitrine (Ic, 4,7-dimethoxyfuro[2,3-*b*]quinoline) and γ-fagarine (Id, 4,8-dimethoxyfuro[2,3-*b*]quinoline) can also be realized.

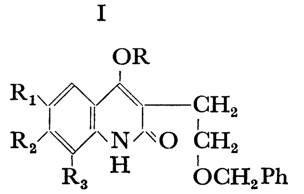
With the removal of ethanol (two moles), the condensation of aniline derivatives (IIa—d) and diethyl β-benzyloxyethylmalonate in diphenyl ether gave the 4-hydroxy-2-quinolone derivatives (IIIa—d), which were then easily methylated with diazomethane into the 4-methoxy compounds (IVa—d). While the IR spectra of IVa—d indicated the absence of the hydroxyl group, which was present in those of IIIa—d (*ca.* 3200—3500 cm^{-1}) (Table 1), the NMR spectra[9] of IVa—d exhibited signals for three protons (δ *ca.* 3.93s ppm) (Table 2) of the methoxy group. IVa—d gave positive color reactions with ferric chloride in ethanol (*e.g.*, IVa (reddish brown)), suggesting the presence of a keto-enol tautomerism of the amide group. The cyclodebenzylation of IVa—d with polyphosphoric acid yielded 2,3-dihydrofuro[2,3-*b*]quinoline derivatives (Va—d). The structures of Va—d were assigned on the basis of the NMR spectra, which showed signals at δ *ca.* 3.5t and 4.5t attributable to two methylene protons of a dihydrofuran ring system (Table 3). Difficulty had been experienced in the dehydrogenation of the dihydro derivatives of furoquinoline alkaloids (*e.g.*, dihydroacronycidine[10] and dihydrokokusaginine[11,12]) by treatment with *N*-bromosuccinimide, followed by dehydrobromination. The dehydrogenation of Va—d with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ), however, gave furo[2,3-*b*]quinoline derivatives (maculosidine (Ia),[1] pteleine (Ib),[3,4] evolitrine (Ic),[13]



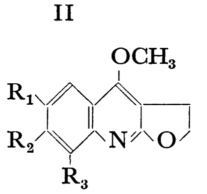
I



II



III R=H
IV R=CH_3



V

a) $R_1=R_3=OCH_3$, $R_2=H$ c) $R_2=OCH_3$, $R_1=R_3=H$
b) $R_1=OCH_3$, $R_2=R_3=H$ d) $R_3=OCH_3$, $R_1=R_2=H$

Table 1. IR spectral data of the compounds (I, III, IV, and V)

	III[a] (cm^{-1})	IV[a] (cm^{-1})	V[a] (cm^{-1})	I[b] (cm^{-1})
a	3360, 1655	1605	1615, 1520	1625, 1520
b	3200, 1670	1660	1630, 1526	1630, 1510
c	3500, 1640	1650	1630, 1520	1620, 1530
d	3360, 1640	1640	1630, 1520	1625, 1520

a) Nujol b) KBr

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1) R. F. Brown, P. T. Gilham, G. K. Hughes, and E. Ritchie, *Aust. J. Chem.*, **7**, 181 (1954).

2) R. H. Prager, E. Ritchie, and W. C. Taylor, *ibid.*, **13**, 380 (1960).

3) F. Werny and P. J. Sheuer, *Tetrahedron*, **19**, 1293 (1963).

4) V. I. Frolova, A. D. Kuzovkov, and P. N. Kibal'chich, *Zh. Obshch. Khim.*, **34**, 3499 (1964); *Chem. Abstr.*, **62**, 2800 (1965).

5) T. R. Govindachari and S. Prabhakar, *Indian J. Chem.*, **1**, 17 (1963).

6) B. R. Pai, S. Prabhakar, P. S. Santhanam, M. Seetha, and V. Sudarsanam, *ibid.*, **2**, 491 (1964).

7) H. Tuppy and F. Böhm, *Monatsh. Chem.*, **87**, 720 (1956).

8) T. Ohta and Y. Mori, *Tokyo Yakka Daigaku Kenkyu Nempo*, **10**, 100 (1960); *Chem. Abstr.*, **56**, 4806 (1962).

9) The NMR spectra in this paper were measured with a Hitachi R-20 spectrometer (60 MHz), using tetramethylsilane as the internal standard (δ value in $CDCl_3$); s singlet; bs broad singlet; d doublet; t triplet; m multiplet.

10) T. R. Govindachari, B. R. Pai, S. Prabhakar, P. S. Santhanam, and V. Sudarsanam, *Indian J. Chem.*, **3**, 71 (1965).

11) T. Ohta and Y. Mori, *Yakugaku Zasshi*, **82**, 549 (1962).

12) Y. Kuwayama, *ibid.*, **82**, 703 (1962).

13) R. G. Cooke and H. F. Haynes, *Aust. J. Chem.*, **7**, 273 (1954), **11**, 225 (1958); T. Sato and T. Ohta, This Bulletin, **31**, 161 (1958); T. Ohta and Y. Mori, *Yakugaku Zasshi*, **78**, 446 (1958).

TABLE 2. NMR SPECTRAL DATA OF 3-(2-BENZYLOXYETHYL)-4-METHOXY-2-QUINOLONES (IVa—d)[9]

	IVa	IVb	IVc	IVd
$C\underline{H}_3$-O	3.85s 3.93s (6H)	3.83s 3.94s	3.88s 3.98s	 3.92s (6H)
β-$C\underline{H}_2$-CH_2	3.05t (J=7.2 Hz)	3.08t (J=7.2 Hz)	3.17t (J=7.2 Hz)	3.01t (J=7.2 Hz)
α-$C\underline{H}_2$-O	3.80t (J=7.2 Hz)	3.83t (J=7.2 Hz)	3.86t (J=7.2 Hz)	3.77t (J=7.2 Hz)
$C_6H_5C\underline{H}_2$	4.54s	4.55s	4.61s	4.52s
N$\underline{H}$	9.12bs	12.50bs	12.40bs	9.20bs

TABLE 3. NMR SPECTRAL DATA OF 2,3-DIHYDROFURO[2,3-*b*]QUINOLINES (Va—d) AND FURO[2,3-*b*]QUINOLINES (Ia—d)[9]

	Va	Vb	Vc	Vd
β-$C\underline{H}_2$-CH_2	3.53t (J=7.8 Hz)	3.55t (J=7.8 Hz)	3.82t (J=7.8 Hz)	3.57t (J=7.8 Hz)
α-$C\underline{H}_2$-O	4.53t (J=7.8 Hz)	4.56t (J=7.8 Hz)	4.64t (J=7.8 Hz)	4.56t (J=7.8 Hz)
$C\underline{H}_3$-O	3.83s 3.93s 4.12s	3.86s 4.15s	3.92s 4.24s	3.94s 4.13s
Arom. H	6.61d(J=2.5 Hz) 6.86d (J=2.5 Hz)	7.1—7.75m (3H)	6.86—7.60m (3H)	6.85—7.65m (3H)
	Ia	**Ib**	**Ic**	**Id**
$C\underline{H}_3$-O	3.88s 4.02s 4.36s	3.90s 4.38s	3.90s 4.33s	4.07s 4.40s
Arom. H	6.68d (J=2.5 Hz) 6.97d (J=2.5 Hz) 7.03d (J=2.5 Hz) 7.56d (J=2.5 Hz)	7.0—8.0m (5H)	6.94—7.20m (5H)	7.0—7.9m (5H)

TABLE 4. 3-(2-BENZYLOXYETHYL)-4-HYDROXY-2-QUINOLONES (IIIa—d)

Compounds	Mp (°C)	Cryst. form	Yield (%)	Formula	Analysis (%) Found C H N	Analysis (%) Calcd C H N	UV λ_{max} mμ(log ε)	
IIIa	235.5—237.5	Colorless[a] needles	90	$C_{20}H_{21}O_5N$	67.66 5.94 3.98	67.59 5.96 3.94	228sh (4.43) 251 (4.50) 280 (4.00)	290 (3.97) 338 (3.77) 353sh (3.70)
IIIb	172—174	Pale yellow[b] needles	39	$C_{19}H_{19}O_4N$	69.98 5.94 4.18	70.14 5.89 4.31	231.5 (4.62) 275.5 (3.96) 285.5 (3.89)	324sh (3.79) 336 (3.90) 353sh (3.81)
IIIc	156.5—158	Colorless[a] plates	57	$C_{19}H_{19}O_4N$	70.18 5.89 4.40	70.14 5.89 4.31	222 (4.78) 242sh (4.17) 249 (4.08) 272sh (3.91)	282 (3.94) 301.5 (4.01) 314 (4.22) 328 (4.22)
IIId	148—149.5	Colorless[b] plates	66	$C_{19}H_{19}O_4N$	70.05 6.06 4.56	70.14 5.89 4.31	244 (4.46) 251 (4.44) 270sh (3.89) 279 (3.96)	289.5 (3.95) 320 (3.59) 334sh (3.44)

a) from ethanol b) from ethyl acetate sh shoulder

and γ-fagarine (Id)[14]) in *ca.* 50% yields. The properties of synthetic samples of Ia—d were identical with those recorded for natural specimens.[1,3,4,13,14]

Experimental[15]

3-(2-Benzyloxyethyl)-4-hydroxy-2-quinolones (IIIa—d). A mixture of 2,4-dimethoxyaniline (IIa (6.4 g)) or monomethoxy derivatives (IIb—d (5.4 g)) and diethyl β-benzyloxyethylmalonate (14.5 g)[16] in diphenyl ether (30 ml) was heated under stirring at 250°C for about 30 min, by which time 5 ml (2 mol equivalent) of ethanol had been distilled

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14) B. Berinzaghi, A. Muruyabal, and V. Deulofeu, *J. Org. Chem.*, **10**, 181 (1945).

15) All the melting points are uncorrected; the UV spectra of the compounds were measured in ethanol.

16) G. M. Bennett and A. L. Hock, *J. Chem. Soc.*, **1927**, 472: W. R. Kirner and G. H. Richter, *J. Amer. Chem. Soc.*, **51**, 2503 (1929).

TABLE 5. 3-(2-BENZYLOXYETHYL)-4-METHOXY-2-QUINOLONES (IVa—d)

Compounds	Mp (°C)	Cryst. form	Yield (%)	Formula	Analysis (%) Found C H N	Analysis (%) Calcd C H N	UV λ_{max} mμ (log ε)	
IVa	105—106	Pale yellow[a]	quant.	$C_{21}H_{23}O_5N$	68.44	68.28	232 (4.34)	290sh (3.80)
		leaves			6.37	6.28	255 (4.37)	347 (3.75)
					3.80	3.79	279 (3.91)	363sh (3.66)
IVb	157—158	Pale yellow[a]	68	$C_{20}H_{21}O_4N$	70.62	70.78	234 (4.62)	329sh (3.71)
		needles			6.36	6.24	261.5 (3.89)	343.5 (3.89)
					4.08	4.13	271.5 (3.91)	360.5sh (3.78)
							282sh (3.82)	
IVc	132.5—134	Colorless[b]	82	$C_{20}H_{21}O_4N$	70.78	70.78	238sh (4.55)	309 (4.01)
		needles			6.09	6.24	255 (3.84)	323 (4.24)
					4.31	4.13	283 (3.82)	
IVd	68.5—69.5	Colorless	96	$C_{20}H_{21}O_4N$	70.95	70.78	235.5 (4.34)	329 (3.55)
		needles			6.38	6.24	252 (4.45)	343sh (3.37)
					4.11	4.13	279 (3.95)	

a) from ethanol b) from dilute ethanol.

TABLE 6. 2,3-DIHYDROFURO[2,3-*b*]QUINOLINES (Va—d)

Compounds	Mp (°C) Found/Lit.	Cryst. form	Yield (%)	Formula	Analysis (%) Found C H N	Analysis (%) Calcd C H N	UV λ_{max} mμ(log ε)	
Va	188—191	Colorless[a]	83	$C_{14}H_{15}O_4N$	64.24	64.36	220 (4.44)	276 (3.40)
		plates			5.86	5.79	247 (4.56)	326 (3.63)
					5.34	5.36	266 (3.80)	342 (3.64)
Vb	169.5—160.5	Colorless[a]	35	$C_{13}H_{13}O_3N$	67.33	67.52	230 (4.66)	311sh (3.42)
		plates			5.67	5.67	260.5 (3.77)	325 (3.71)
					5.87	6.06	268.5 (3.77)	339 (3.72)
							279sh (3.62)	
Vc	135—136	Colorless[a]	39	$C_{13}H_{13}O_3N$	67.32	67.52	225.5 (4.72)	300sh (3.78)
	136—137[12]	needles			5.88	5.67	243sh (4.20)	306sh (3.92)
					6.04	6.06	251sh (3.88)	313.5 (4.05)
							276 (3.64)	319.5 (4.05)
							287 (3.71)	327 (4.02)
Vd	171—172	Colorless[a or b]	46	$C_{13}H_{13}O_3N$	67.32	67.52	248 (4.60)	290 (3.70)
	168—170[17]	plates			5.96	5.67	268sh (3.73)	314 (3.42)
					6.03	6.06	279 (3.79)	326 (3.43)

a) from ethanol b) from methanol

off. The solution was then poured into 300 ml of petroleum benzine, and the mixture was allowed to stand overnight. The solvent was decanted, and the residual oily precipitate was dissolved in chloroform. The chloroform solution was extracted with five 100 ml portions of a 5% sodium hydroxide solution. Washed with chloroform, the alkaline solution was acidified with an aqueous acetic acid solution (1: 1). The acidic solution was extracted with chloroform. After the solvent had been evaporated, the residue was triturated with ether and recrystallized to give IIIa—d (Tables 1, 4).

3-(2-Benzyloxyethyl)-4-methoxy-2-quinolones (IVa—d). A solution of IIIa—d (5.0 g) in chloroform (70 ml) was treated with an ethereal diazomethane solution, and then the mixture was allowed to stand overnight. After a usual work-up, the product was recrystallized to give IVa—d (Tables 1,2,5), which gave a light brown or a reddish brown color with ferric chloride in ethanol.

*2,3-Dihydrofuro[2,3-*b*]quinolines (Va—d).* A mixture of IVa—d (0.7 g) and polyphosphoric acid (13 g) was heated at 120—130°C for 1.5—3 hr. The cooled mixture was poured into water, and the insoluble materials were filtered off. The aqueous solution was neutralized with diluted aqueous ammonia. The precipitate was collected, washed with water, and recrystallized to give Va—d (Tables 1,3,6).

*Furo[2,3-*b*]quinolines (Ia—d).* To a solution of Va—d (1.0 g) in dry benzene (150 ml), DDQ (1.0 g) was added, the mixture was then stirred under reflux for 8 hr in an atmosphere of nitrogen. The reaction mixture was filtered, and the solvent was evaporated *in vacuo*. The residue was dis-

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[17] M. F. Grundon and N. J. McCorkindale, *J. Chem. Soc.*, **1957**, 2177.

TABLE 7. FURO[2,3-*b*]QUINOLINES (Ia—d)

Compounds	Mp (°C) Found/Lit.	Cryst. form	Yield (%)	Formula	Analysis (%) Found C H N	Analysis (%) Calcd C H N	UV λ_{max} mμ(log ε)	
Ia	183—185	Pale yellow[a,b]	55	$C_{14}H_{13}O_4N$	65.01	64.86	247 (4.76)	305 (3.72)
	182—184[1]	plates			5.13	5.05	283sh (3.78)	337 (3.43)
					5.30	5.40	293 (3.83)	353 (3.42)
Ib	134—136	Pale yellow[a]	60	$C_{13}H_{11}O_3N$	68.11	68.11	236.5 (4.69)	294 (3.97)
	134—135[3,4]	needles			4.90	4.84	249 (4.59)	307 (4.02)
					5.96	6.11	268 (3.70)	332 (3.75)
							285sh (3.83)	347.5 (3.72)
Ic	110—112	Pale yellow[a]	49	$C_{13}H_{11}O_3N$	68.30	68.11	245.5 (4.79)	307 (3.98)
	114—115[13]	needles			4.88	4.84	255sh (4.29)	318 (3.96)
					5.94	6.11	289sh (3.76)	332 (3.88)
							299sh (3.89)	
Id	137—139	Colorless[a]	53	$C_{13}H_{11}O_3N$	68.11	68.11	223 (4.21)	270sh (3.87)
	138—140[14]	needles			4.83	4.84	240sh (4.53)	310 (3.26)
					6.01	6.11	246 (4.64)	323 (3.22)
							253sh (4.54)	

a) from petroleum benzine b) from benzene

solved in chloroform, and the solution was extracted with dilute hydrochloric acid. After the aqueous solution had been neutralized with dilute aqueous ammonia, the resulting precipitate was collected and recrystallized to give Ia—d (Tables 1,3,7). The product was purified by means of chromatography on alumina (300 mesh, chloroform–2% ethanol).

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