Studies on Tetrahydroisoquinolines. Part 14.[1,2] A Synthesis of 4-Alkoxyaporphines

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(±)-4β-Acetoxythaliporphine (2) on dissolution in methanol is converted into (±)-4β-methoxyaporphine (4). While (2) reacted with primary alcohols (ethyl and benzyl alcohols) in the presence of boron trifluoride–ether to give the corresponding (±)-4β-alkoxythaliporphines (7) and (8) stereospecifically, reaction with secondary alcohols (isopropyl alcohol and cyclohexanol) and with neopentyl alcohol gave a mixture of the (±)-4α- (11), (12), and (14) and (±)-4β- (9), (10), and (13) alkoxyaporphines. However, in the case of reaction with t-butyl alcohol several (±)-4-alkenyl derivatives (15), (16), (19), and (21)—(23) were obtained.

DURING the course of synthetic studies on (±)-cataline (1)[3] we observed that (±)-4β-acetoxythaliporphine (2) was smoothly converted into the methoxyaporphine (4) on dissolution in methanol.[2] We report here on the structural determination of this product and on the acid-catalysed alkoxylation of (2).

Treatment of (2) with methanol at room temperature for 1 h afforded (4) in 86.2% yield. The (±)-4β-methoxythaliporphine structure (4), a regioisomer of (±)-cataline, was assigned on the basis of a one-proton broad singlet ($W_{\frac{1}{2}}$ 5.0 Hz) at δ 4.12 in its n.m.r. spectrum. The intermediacy of a *p*-quinone methide[4] in the above reaction is suggested by the fact that neither (±)-de-1-methylcataline (5) nor (±)-*O*-acetylcataline (6) reacted with methanol. Hydrogen bonding of methanol to the nitrogen atom of such an intermediate could be responsible for the stereoselective introduction of methoxy-group. Furthermore, no alkoxythaliporphine was formed when methanol was replaced by other alcohols such as ethyl, isopropyl, or benzyl alcohols. These results suggested that only methanol was acidic enough to eliminate the acetoxy-group of (2) and form the *p*-quinone methide. Confirmation of this role for methanol was obtained from treatment of (2) with a 1 : 1 mixture of methanol and ethanol, whereupon an approximately 1 : 1 mixture of (±)-4β-methoxythaliporphine (4) and the ethoxy-analogue (7) was obtained.

Employment of a suitable acid in a given alcohol was therefore expected to give rise to novel 4-alkoxythaliporphines. Thus, when stirred alcoholic solutions of (2) were treated with boron trifluoride–ether (15 min at room temperature) the results were as shown in Table 1.

TABLE 1

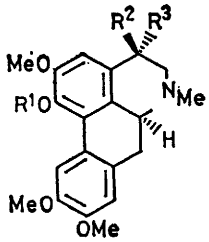
Alkoxylated products and their yields [%]

ROH	4β-RO-aporphine	4α-RO-aporphine
MeOH	(4) [86.2]	
EtOH	(7) [57.5]	
$PhCH_2OH$	(8) [47.3]	
Me_2CHOH	(9) [48.7]	(11) [6.3]
$C_6H_{11}OH$	(10) [28.7]	(12) [7.0]
Me_3CCH_2OH	(13) [23.2]	(14) [6.4]

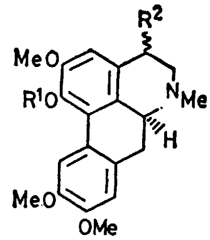
In contrast to the reaction of (2) with primary alcohols (EtOH and $PhCH_2OH$), where (±)-4β-alkoxythaliporphines (7) and (8) were obtained almost exclusively, reaction with secondary alcohols (Pr^iOH and cyclohexanol) afforded mixtures of the (±)-4β-alkoxythaliporphines (9) and (10) and the corresponding (±)-4α-alkoxy-derivatives (11) and (12), with the ratios 4β : 4α being 7.5 : 1 and 4.1 : 1 respectively. The stereochemistry of the (±)-4α-alkoxy-derivatives (11) and (12) was assigned on the basis of one-proton double doublets (*J* 10 and 6.3 Hz), at δ 4.75 and 4.78 respectively, in their n.m.r. spectra.

The formation of both 4α- and 4β-alkoxy-derivatives on treatment of (2) with secondary alcohols could be explained by weaker hydrogen bonding of such alcohols, as compared with primary alcohols, to the nitrogen of the intermediate *p*-quinone methide and/or hindrance of β-attack of the hydrogen-bonded secondary alcohol allowing α-attack by non-bonded alcohol. A trend of increasing yield of the 4α-isomer in relation to ' alcohol bulk ' is obvious from the aforementioned data. Thus the bulky primary alcohol neopentyl alcohol, on reaction with (2), also leads to a substantial yield of the 4α-isomer, the ratio of (±)-4β- (13) to (±)-4α- (14) neopentoxythaliporphine being 3.6 : 1.

However, in the case of reaction with t-butyl alcohol, alkenylthaliporphines rather than t-butoxy-derivatives were obtained. Thus treatment of (2) with t-butyl alcohol, in the manner already described, produced a crude product which was roughly separated into five fractions (I—V) by preparative t.l.c. Both fractions I and II were shown to be mixtures of two components, separation of which was attempted after acetylation. Although fraction II was readily separable into two acetates (see below), separation of fraction I was unsuccessful. From microanalytical and spectral data, particularly n.m.r., the acetylated fraction I is presumed to comprise two structural isomers, (±)-4-(2-neopentylprop-2-enyl)- (17) and (±)-4-(2,4,4-trimethylpent-2-enyl)-*O*-acetylthaliporphine (18), in the ratio 5 : 1. Thus, n.m.r. signals due to t-butyl protons were observed at δ 0.99 and 1.16 (5 : 1) while those due to olefinic protons appeared at δ 4.85, 4.94, and 5.28 (5 : 5 : 1). Also on the basis of spectral data, the structures of the two acetates separated from fraction II were determined to be (±)-4β-(2,4,4-trimethylpent-1-enyl)-*O*-acetylthaliporphine (19), a structural isomer of the former two and (±)-4-(2-methylprop-2-enyl)-*O*-



	R^1	R^2	R^3
(1)	Me	OH	H
(2)	H	OAc	H
(3)	H	H	H
(4)	H	OMe	H
(5)	H	OH	H
(6)	Me	OAc	H
(7)	H	OEt	H
(8)	H	OCH_2Ph	H
(9)	H	$OCHMe_2$	H
(10)	H	OC_6H_{11}	H
(11)	H	H	$OCH(Me)_2$
(12)	H	H	OC_6H_{11}
(13)	H	OCH_2CMe_3	H
(14)	H	H	$OCHCMe_3$
(19)	Ac	$CH{=}C(Me)CH_2CMe_3$	H
(21)	H	$CH{=}CMe_2$	H
(23)	Ac	H	$CH{=}CMe_2$
(24)	Ac	$CH{=}CMe_2$	H



	R^1	R^2
(15)	H	$CH_2C(=CH_2)CH_2CMe_3$
(16)	H	$CH_2C(Me){=}CHCMe_3$
(17)	Ac	$CH_2C(=CH_2)CH_2CMe_3$
(18)	Ac	$CH_2C(Me){=}CHCMe_3$
(20)	Ac	$CH_2C(Me){=}CH_2$
(22)	H	$CH_2C(Me){=}CH_2$

acetylthaliporphines, m.p. 169—171°, *m/e* 437 (M^+). However, the stereochemistry at the 4-position of compounds (17), (18), and (20) is undetermined. Recrystallization of fraction III afforded (±)-4β-(2-methylprop-1-enyl)thaliporphine (21), an isomer of (22). That the hydrogen at C-4 of this compound (21) had the α-configuration was demonstrated by the double resonance n.m.r. technique. Thus, irradiation at δ 3.55 (C-4 proton) caused the original broad doublet at δ 5.61 (C-1 proton of side-chain) to collapse to a broad singlet, and inverse irradiation, *i.e.* at δ 5.61, changed the original broad doublet into a broad triplet ($W_{\frac{1}{2}}$ 5.0 Hz). Further purification of fraction IV, a complex mixture, was not attempted due to its paucity. Separation of fraction V by preparative t.l.c. afforded two components. Although one of these remains uncharacterized the

TABLE 2

Mass spectral and microanalytical data of new compounds

Compound	M.p.[a]	Formula (mol. wt.)	Calc. (%) C	Calc. (%) H	Calc. (%) N	Found (%) C	Found (%) H	Found (%) N	*m/e* M^+	*m/e* B.p.[b]
(4)	198—199° [A]	$C_{21}H_{25}NO_5$ (371.42)	67.90	6.78	3.77	68.05	6.85	3.8	371	328
(7)	171—172° (dec.) [B]	$C_{22}H_{27}NO_5$ (385.44)	68.55	7.06	3.63	68.85	7.15	3.55	385	342
(8)	160—162° [B]	$C_{27}H_{29}NO_5$ (447.51)	72.46	6.53	3.13	72.2	6.75	3.15	447	337
(9)	125—127° [B]	$C_{23}H_{29}NO_5$ (399.47)	69.15	7.32	3.51	68.85	7.35	3.4	399	337
(10)	186—188° (dec.) [B]	$C_{26}H_{33}NO_5$ (439.24)	71.04	7.57	3.19	71.2	7.7	3.15	439	337
(11)	146—148° (dec.) [B]	$C_{23}H_{29}NO_5$ (399.47)	69.15	7.32	3.51	68.95	7.35	3.25	399	337
(12)	201.5—202.5° (dec.) [B]	$C_{26}H_{33}NO_5$		439.236			439.239 [c]			
(13) [d]	158—159° [C]	$C_{27}H_{35}NO_6$ (469.56)	69.06	7.51	2.98	68.95	7.6	3.05	427	337
(14)	213—214° (dec.) [B]	$C_{25}H_{33}NO_5$ (427.52)	70.23	7.78	3.28	70.25	7.85	3.2	427	384
(17 + 18)	147—148° [B]	$C_{30}H_{39}NO_5$ (493.62)	72.99	7.96	2.84	73.15	7.95	2.95	493	491
(19)	176—177° [D]	$C_{30}H_{39}NO_5$ (493.62)	72.99	7.96	2.84	72.95	7.9	2.8	493	491
(21)	169—171° [B]	$C_{26}H_{31}NO_5$		437.2202			437.2191 [c]		437	338
(22)	179—180° [B]	$C_{24}H_{29}NO_4$ (395.48)	72.88	7.39	3.54	73.0	7.4	3.5	395	352
(24)	180—181° [B]	$C_{26}H_{31}NO_5$ (437.52)	71.37	7.14	3.20	71.0	7.2	3.15		

[a] Solvent for recrystallization: A, benzene–n-hexane; B, ether–n-hexane; C, ether–light petroleum; D, ether–Pr^{i}OH. [b] Base peak. [c] High resolution mass spectral data. [d] Acetate of (13).

structure of the other, after acetylation, was shown to be (±)-4α-(2-methylprop-1-enyl)-*O*-acetylthaliporphine (23), a stereoisomer of (24).

This reaction with t-butyl alcohol can most readily be formulated as nucleophilic attack by isobutene or 2,4,4-trimethylpent-1-ene, generated from t-butyl alcohol, on the *p*-quinone methide, or attack by the alkenyl product (22) on isobutene.

EXPERIMENTAL

All melting points were measured on a Büchi melting point apparatus. N.m.r. spectra were taken with a JEOL model JNR-4H-100 spectrometer (100 MHz) for solutions in $CDCl_3$ (5—10%) with Me_4Si as internal standard. I.r. spectra were run on a Hitachi model 215 spectrometer for solutions in $CHCl_3$. Mass spectra were measured with a Hitachi model RMU-6E mass spectrometer. Preparative t.l.c. was performed on silica gel HF_{254} (Merck). Mass spectral and microanalytical data of all new compounds are shown in Table 2.

TABLE 3

I.r. and n.m.r. spectral data of 4-alkoxyaporphines

Compound	$\nu_{max.}$(OH)/ cm^{-1}	δ NMe	OMe	3-H	8-H	11-H	4α-H [a]	4β-H	Others
(4)	3 520	2.53	3.86 (9 H)	6.24 [b]	6.26 [b]	8.06	4.12		3.47 (3 H, s, 4β-OMe)
(7)	3 520	2.47	3.84 (9 H)	6.72 [b]	6.73 [b]	8.02	4.21		1.26 (3 H, t, *J* 6.3 Hz, OCH_2Me)
(8)	3 520	2.47	3.73 (3 H) 3.82 (6 H)	6.48	6.73	8.01	4.29		4.58 and 4.77 (each 1 H, d, *J* 12.5 Hz, OCH_2Ph)
(9)	3 500	2.48	3.84 (9 H)	6.70 [b]	6.72 [b]	7.99	4.24		1.22 and 1.27 (each 3 H, d, *J* 5.0 Hz, $OCHMe_2$)
(10)	3 500	2.51	3.87 (9 H)	6.75	6.75	8.03	4.36		1.2—2.1 (10 H, complex)
(11)	3 500	2.58	3.89 (9 H)	6.72	6.91	8.00		4.75 [c]	1.27 and 1.33 (each 3 H, d, *J* 6.3 Hz, $OCHMe_2$)
(12)	3 500	2.57	3.88 (9 H)	6.72	6.82	8.01		4.78 [c]	1.2—2.1 (10 H, complex)
(13)	3 520	2.51	3.87 (9 H)	6.72	6.78	8.00	4.28		0.95 (9 H, s, OCH_2CMe_3)
(14)	3 520	2.55	3.86 (9 H)	6.74	7.01	8.04		4.67 [d]	0.98 (9 H, s, OCH_2CMe_3)

[a] Broad t, $W_{\frac{1}{2}}$ 5.0 Hz. [b] Assignments may be interchanged. [c] dd, *J* 10 and 6.3 Hz. [d] dd, *J* 10 and 5.5 Hz.

(±)-4β-*Methoxythaliporphine* (4).—(±)-4β-Acetoxythaliporphine (2) [3] (122 mg), obtained from thaliporphine (3) (100 mg), was dissolved in MeOH (30 ml) and the solution stirred at room temperature for 1 h. Evaporation followed by usual work-up of the residue gave 4β-methoxythaliporphine (4) (94 mg, 86.2%).

General Procedure for the Reaction of (±)-4β-*Acetoxythaliporphine with Alcohol in the Presence of* BF_3–*Ether*.—(±)-4β-Acetoxythaliporphine (2) [3] obtained from thaliporphine (3) (100 mg) was dissolved in a mixture of CH_2Cl_2 (2 ml) and ethanol (0.1 ml), and BF_3–ether (0.5 ml) was slowly added to the stirred mixture at room temperature. Stirring was continued at the same temperature for 15 min and then the mixture was poured into ice–water. After basification with $NaHCO_3$(powder), the product was taken up in CH_2Cl_2. The CH_2Cl_2 layer was washed with brine and dried (K_2CO_3). Each residue obtained on evaporation of the solvent was subjected to preparative t.l.c. I.r. and n.m.r. spectral data for all products are shown in Table 3.

Reaction with Bu^tOH.—The residue (742 mg) obtained from (3) (500 mg) * was extracted with hot light petroleum. Evaporation of the solvent gave a pale brown amorphous mass (547 mg), which was separated into five fractions (I—V, moving rates; I > II > III > IV > V) by preparative t.l.c. (benzene–AcOEt, 3 : 4 v/v). Fraction I (121 mg) was purified by preparative t.l.c. ($CHCl_3$–MeOH 20 : 1 v/v) giving an amorphous mixture of (±)-4-(2-neopentylprop-2-enyl)thaliporphine (15) and (±)-4-(2,4,4-trimethylpent-2-enyl)thaliporphine (16) (110 mg), $\nu_{max.}$ 3 515 cm^{-1} (OH), δ 0.97 (9 H × 5/6, s, CMe_3), 1.13 (9 H × 1/6, s, CMe_3), 1.82 [3 H × 1/6, s, $CH_2C(Me)$=], 2.01 (2 H × 5/6, s, CH_2CMe_3), 2.48 (3 H, s, NMe), 3.85 (3 H, s, OMe), 3.89 (6 H, s, 2 × OMe), 4.85 and 4.96 (each 1 H × 5/6, br s, olefinic H), 5.30 (1 H × 1/6, br s, olefinic H), and 6.52, 6.75, and 8.05 (each 1 H, s, ArH). Acetylation [Ac_2O (0.5 ml) and pyridine (0.3 ml); overnight] of the mixture (110 mg) afforded a mixture of their acetates (17) and (18) (96 mg), $\nu_{max.}$ 1 760 cm^{-1} (OAc), δ 0.99 (9 H × 5/6, s, CMe_3), 1.16 (9 H × 1/6, s, CMe_3), 1.83 [3 H × 1/6, s, $CH_2C(Me)$=], 2.02 (2 H × 5/6, s, CH_2CMe_3), 2.29 (3 H, s, OAc), 2.43 (3 H, s, NMe), 3.81 (3 H, s, OMe), 3.88 (6 H, s, 2 × OMe), 4.85 and 4.94 (each 1 H × 5/6 br s, olefinic H), 5.28 (1 H × 1/6, br s, olefinic H), and 6.61, 6.75, and 7.51 (each 1 H, s, ArH). Fraction II (142 mg) was purified by preparative t.l.c. ($CHCl_3$–Pr^iOH 20 : 1 v/v) yielding an amorphous mass (134 mg), which was acetylated [Ac_2O (0.3 ml) and pyridine (0.5 ml); overnight] followed by separation on preparative t.l.c. [alumina HF_{254} (Merck); $CHCl_3$–benzene, 5 : 4 v/v] to afford (±)-4β-(2,4,4-*trimethylpent*-1-*enyl*)-O-*acetylthaliporphine* (19) (41 mg): $\nu_{max.}$ 1 760 cm^{-1} (OAc); δ 0.92 [9 H, s, CMe_3], 1.89 (3 H, s, =$CMeCH_2$), 1.97 (2 H, s, $CMeCH_2$), 2.28 (3 H, s, OAc), 2.45 (3 H, s, NMe), 3.61 (1 H, br d, *J* 10 Hz, 4-H), 3.77, 3.87, and 3.89 (each 3 H, s, OMe), 5.57 (1 H, d, *J* 10 Hz, olefinic H), and 6.58, 6.75, and 7.46 (each 1 H, s, aromatic H), and (±)-4-(2-*methylprop*-2-*enyl*)-O-*acetylthaliporphine* (20) (22 mg); $\nu_{max.}$ 1 765 cm^{-1} (OAc); δ 1.82 [3 H, s, $C(=CH_2)Me$], 2.28 (3 H, s, OAc), 2.44 (3 H, s, NMe), 3.81, 3.86, and 3.88 (each 3 H, s, OMe), 4.79 and 4.84 (each 1 H, br s, olefinic H), and 6.61, 6.74, and 7.49 (each 1 H, s, ArH). Recrystallization from ether–n-hexane of fraction III (107 mg), gave (±)-4β-(2-*methylprop*-1-*enyl*)*thaliporphine* (21); $\nu_{max.}$ 3 510 cm^{-1} (OH); δ 1.72 and 1.83 (each 3 H, s, –CH=CMe_2), 2.48 (3 H, s, NMe), 3.55 (1 H, br d, *J* 10 Hz, 4-H), 3.83 (3 H, s, OMe), 3.89 (6 H, s, 2 × OMe). 5.61 (1 H, br d, *J* 10 Hz, olefinic H), and 6.45, 6.75, and 8.03 (each 1 H, s, ArH). Fraction V (75 mg) was purified on preparative t.l.c. (AcOEt) and acetylated [Ac_2O (0.1 ml) and pyridine (0.2 ml); overnight] to afford an amorphous mass (36 mg), which on preparative t.l.c. (benzene : AcOEt = 3 : 1) gave (±)-4α-(4-*methylprop*-1-*enyl*)-O-*acetylthaliporphine* (23) (23 mg), $\nu_{max.}$: 1 760 cm^{-1} (OAc); δ 1.81 [6 H, s, –CH=CMe_2],

* CH_2Cl_2 (10 ml), Bu^tOH (1 ml), and BF_3–ether (2.5 ml) were used in the reaction.

2.28 (3 H, s, OAc), 2.49 (3 H, s, NMe), 3.78, 3.87, and 3.88 (each 3 H, s, OMe), 5.02 (1 H, br d, *J* 10 Hz, olefinic H), and 6.62, 6.74, and 7.46 (each 1 H, s, ArH).

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