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Note

Sodium artelinate : A potential antimalarial†

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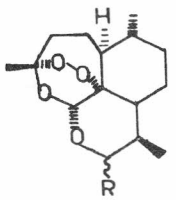
An economically viable process is developed for the synthesis of sodium artelinate, a potential antimalarial drug.



	R
1	=O
2	– OH
3a	β-$OCH_2C_6H_4COOCH_3$-p
3b	α-$OCH_2C_6H_4COOCH_3$-*p*
4a	β-$OCH_2C_6H_4COOH$
4b	α-$OCH_2C_6H_4COOH$
5a	β-$OCH_2C_6H_4COONa$
5b	α-$OCH_2C_6H_4COONa$

Artemisinin **1** is a sesquiterpene endoperoxide, a potent antimalarial agent[1-3] isolated in 1972 from the Chinese plant Qinghao (*Artemisia annua*) and used in the treatment of fever for over 2000 years as a herbal remedy for malaria[4]. The practical value of artemisinin however is impaired by its high rate of recrudesence, poor solubility in oil and water, short plasma half life and poor oral abilities[5]. Chemical modification of artemisinin has resulted in a number of analogs with improved efficacy and increased solubility in oil. Arteether and artemether are more lipophilic and more efective than artemisinin. A water soluble derivative sodium artesunate was prepared and found useful in the treatment of cerebral malaria but utility of sodium artesunate is impaired by its poor stability in aqueous solution due to the facile hydrolysis of the ester linkage and extremely short plasma half life (20-30 min)[6]. Sodium artelinate possesses comparable antimalarial activity *in vitro* as well as *in vivo* to artemether or arteether. Because of its encouraging chemical and biological properties, it is currently being subjected to preclinical testing and has been considered the best candidate among the available water soluble analogs[7].

Dihydroartemisinin **2**, prepared by reduction of artemisinin **1**, was converted into a mixture of α- and β-artelinic esters **3a** and **3b** which were separated by coloumn chromatography[8]. β-Isomer was hydrolysed to yield β-artelinic acid **4a** which inturn was converted into its sodium salt **5a**, a potent, stable and water soluble antimalarial agent. Similarly, an attempt was also made to prepare sodium α-artelinate **5b**. The overall advantage of this method lies in the initiation and completion of the reaction at room temperature without using inert atmosphere.

The ^{1}H NMR data of **3a**, **3b**,**4a** and **4b** were found to be similar with those available in literature[6,9], and we are reporting the ^{13}C NMR data of these derivatives for the first time (cf. **Table I**).

Experimental Section

General. Melting points were determined in open capillaries and are uncorrected. EI mass spectra were recorded on a Jeol D 300 mass spectrometer, FAB-mass on a Jeol SX - 102 mass spectrometer (10 KV accelerating potential) using 6 KV xenon beam. NBA was used as matrix. IR spectra was recorded on a Perkin-Elmer spectrometer in neat/KBr, ^{1}H NMR spectra on a Bruker WM (400 MHz) spectrometer and ^{13}C NMR spectra on a Bruker DRX-300 (300 Mhz FT NMR) spectrophotometer using TMS as internal reference. Solvent $CDCl_3$ and standard software were

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used for data acquisation. TLC was performed on 5 × 20 cm precoated silica gel glass plates.

Table I — ^{13}C NMR spectral data of compounds **3a,3b,4a** and **4b.**

	Artelinic ester		Artelinic acid	
Atom	**3b**	**3a**	**4a**	**4b**
No.	(α)	(β)	(α)	(β)
C-1	51.8	52.5	51.6	52.0
C-2	24.6	24.6	24.7	24.1
C-3	36.2	36.4	36.3	36.0
C-4	104.2	104.1	104.4	104.0
C-5	91.2	88.0	91.3	87.2
C-6	80.2	81.0	80.4	80.4
C-7	45.3	44.3	45.3	44.0
C-8	22.1	24.5	22.2	24.0
C-9	34.1	34.6	34.1	34.1
C-10	37.2	37.4	37.3	37.2
C-11	32.5	30.8	32.7	30.2
C-12	99.1	101.5	99.3	101.1
C-13	12.6	13.0	12.7	11.0
C-14	20.1	20.2	20.2	19.5
C-15	25.9	26.1	26.0	25.4
C-1′	69.1	69.1	69.2	68.2
C-2′	143.1	143.6	144.6	144.1
C-3′7′	127.1	126.8	127.2	126.4
C-4′6′	129.4	129.6	130.2	129.9
C-5′	129.1	129.2	128.3	128.0
OMe	51.6	51.9	–	–
CO	166.8	166.8	171.6	171.8

Dihydroartemisinin 2. Artemisinin (1) (10 g) in 40 ml methanol was cooled in an ice bath to 0-5 °C. To the cooled solution was added in small portions 0.25 g of sodium borohydride over a period of 30 minutes and the solution was stirred at 0-5 °C for 3 hrs. The reaction mixture was neutralized with 30% acetic acid/methanol and evaporated to dryness under reduced pressure. The white residue was extracted with ethyl acetate (3×50 ml). The ethyl acetate extracts were combined, filtered and evaporated to dryness to give white needles of dihydroartemisinin m.p. 153 °C, yield 8.5 g (85%).

Methyl *p*-[(12-dihydroartemisininoxy)methyl]-benzoate (artelinic esters 3a+3b. A solution of dihydroartemisinin (5g) in 80 mL benzene was treated with 5g of methyl *p*-hydroxymethylbenzoate. To this 1.2 mL of chlorotrimethylsilane (CTMS) was added in successive three portions of 0.4 mL each during 30 min with stirring. The reaction mixture was further stirred at room temperature for 2 hr. It was then washed successively with saturated solution of sodium acetate and water, dried over anhyd. sodium sulphate and evaporated to dryness under reduced pressure affording a viscous mass. Yield 8.5 g (85%); IR (Neat): 1720 cm^{-1} (O–C–O). The resultant viscous mass (**3a+3b**) was purified by column chromatography using silica gel as adsorbent (60-120 mesh). Elution was carried out using solvent systems with increasing percentage of ethyl acetate in hexane. Fractions (Fr No. 27-53) eluted from 6% ethyl acetate in hexane contained pure β-artelinic ester **3a**. It was a viscous liquid, yield 5.5g (60%); R_f 0.4 (in 10% ethyl acetate in hexane); ^1H NMR: δ 8.02 (d, 2H, *J*=9Hz, H-3′ and H-7′), 7.39 (d, 2H, *J*=9Hz, H-4′ and H-6′). 4.98 (d, 1H, *J*=12.5 Hz, H-1′), 4.92 (d, 1H, *J*=3.5 Hz, H-12), 4.95 (d, 1H, *J*=12.5 Hz, H-1′), 3.92 (s, 3H, COOMe); ^{13}C NMR data of **3a** are given in **Table I**; FABMS: 433 $(M+H)^+$.

Fractions (Fr.No 54-69) eluted from 7% ethyl acetate in hexane was the mixture of α- and β-artelinic esters yield 1g (11.8%).

Fractions (Fr No 70-73) eluted from 8% ethyl acetate contained pure α-artelinic ester **3b** as viscous mass, yield 120 mg (1.4%); R_f value 0.37 (in 10% ethyl acetate in hexane); ^1H NMR: δ 8.02 (d, 2H, *J*=9Hz, H-3′ and H-7′), 7.43 (d, 2H, *J*=9Hz, H-4′ and H-6′), 5.02 (d, 1H, *J*=12Hz, H-1′), 4.68 (d, 1H, *J*=12Hz, H-1′), 4.54 (d, 1H, *J*=9Hz, H-12), 3.92 (s, 3H, COOMe); ^{13}C NMR data of **3b** are reported in Table 1. FABMS: m/z 433 $(M+H)^+$.

***p*-[(12- β- Dihydroartemisinoxy) methyl]benzoic acid 4a. β-artelinic acid.** A solution of ester 3a (0.4g) in 10mL of 1.5% methanolic NaOH was allowed to stand at room temperature for 2 days. The solvent was evaporated to dryness under reduced pressure. The residue was dissolved in 10 mL water and the solution washed two times with an equal amount of ether. The aqueous layer was acidified with 5% acetic acid and extracted twice with solvent ether. The ether extracts were combined, dried over anhydrous sodium sulphate and evaporated to dryness to get a gummy mass which was crystallised from chloroform to give white crystals, m.p. 145 °C, yield 0.2g (55%); ^1H NMR: δ 8.09 (d, 2H, *J*=8.2 Hz, H-3′ and H-7′), 7.41 (d, 2H, *J*=8.2 Hz, H-4′ and H-6′), 4.98 (d, 1H, *J*=13.5Hz, H-1′) 4.92 (d, 1H, *J*=2.7 Hz, H-12), 4.59 (d, 1H, *J*=13.5 Hz, H-1′), 2.70 (m, 1H); ^{13}C NMR data of **4a** are given in Table I; FABMS: m/z 419 $(M+H)^+$.

Similarly 0.4g of **3b** in 10 mL 1.5% methanolic NaOH was allowed to stand at room temperature for 2 days. The procedure adopted to extract pure α-isomer **4b** from the reaction mixture was the same as described above, yield 0.21g (55.o%); ^1H NMR: δ 8.05 (d, 2H, *J*=8.2 Hz, H-3′ and H-7′), 7.45 (d, 2H, *J*=8.2 Hz, H-4′

and H-6′), 5.02 (d, 1H, *J*=13.2Hz, H-1′), 4.70 (d, 1H, *J*=13.2Hz, H-1′), 4.53 (d, 1H, *J*=9.3Hz, H-12), 2.57 (m, 1H); ^{13}C NMR data of **4b** are given in Table I; FABMS: m/z 419 $(M+H)^+$.

Sodium *p*-[(12-β-dihydroartemisininoxy-)methyl]-benzoate 5a (sodium-β-artelinate). β-Artelinic acid (0.5g) was dissolved in minimum quantity (2 mL) of methanol and loaded on a column (length 35 cm, diameter 1.5 cm), containing 35 g amberlite IR-120 Na^+ resin. The material was kept adsorbed on column for 2 hrs and then elution was carried out with distilled water. The process was repeated four times. Lastly, the column was washed with distilled water and washings were mixed with eluate and lyophillised to get a cream coloured solid, m.p. 160° (decomp), yield 4.5g (90%).

An attempt was also made to prepare sodium α-artelinate **5b** following the above procedure.

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