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Synthesis and Reactions of 11-Azaartemisinin and Derivatives

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Abstract: 11-Azaartemisinin was prepared in 45% yield in a one pot, two-step sequence from the reaction of artemisinin with excess ammonia followed by acid treatment. Analogous reactions of artemisinin with primary alkylamines gave N-alkylazaartemisinins in similar yields.

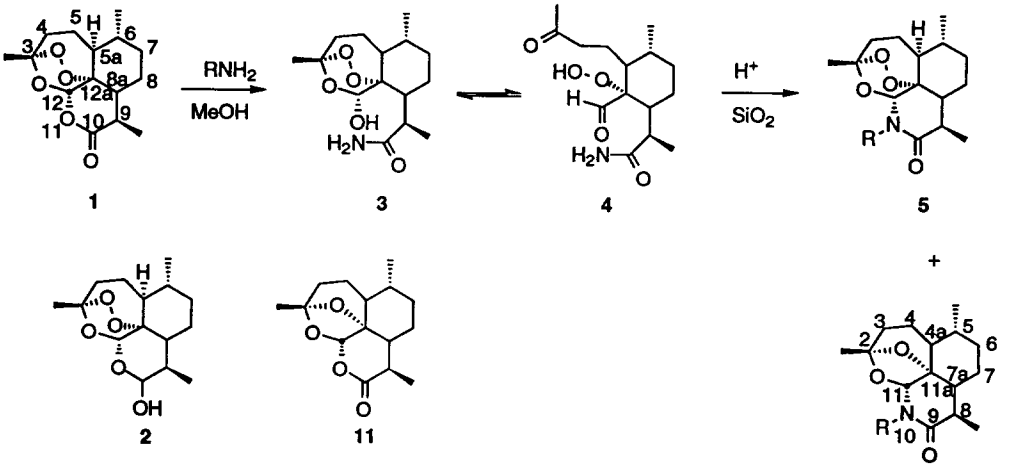
The discovery by Chinese researchers that artemisinin, **1**, a constituent of *Artemisia annua*, is an effective antimalarial drug against drug-resistant strains of *Plasmodium falciparum* [1] stimulated many groups to pursue research on this important lead compound.[2] The resulting studies revealed that the peroxide functionality is essential for the antimalarial activity of this class of compounds.[1a] The labile peroxide and facile hydrolysis of the lactone by acid or base restricted the reactions that could be employed to introduce new functional groups or to modify existing ones. The majority of derivatives prepared thus far have been esters, ethers, carbonates and urethanes of the free hydroxyl group of dihydroartemisinin, **2**.[1b,2] The rationale for employing **1** as a starting material is its availability from *A. annua*, grown in most tropical and semi-tropical regions, and the fact that derivatives could be prepared economically.

None of the reported reaction sequences starting with **1** open the tetracyclic ring system, modify the existing functionality and then reform the tetracyclic ring system. We describe here a short reaction sequence, compatible with the critical peroxide, in which the lactone of **1** is opened to produce an amide and the tetracyclic ring system is reformed in the process of converting the amide into a lactam. This reaction sequence was employed to prepare N-substituted 11-azaartemisinins by substituting primary amines for ammonia.

Reaction of **1** with methanolic ammonia produces a complex mixture, as determined by tlc. A ^{1}H nmr spectrum of the mixture was consistent with the presence of a methyl ketone, e.g. **4**. Longer reaction times resulted in a more complex mixture, with additional polar products being detected by tlc.[3] Although there is precedence for converting hydroxy-amides into lactams,[4] the presence of an equilibrium between the hemiacetal, **3**, and an aldehyde containing a hydroperoxide, **4**, introduced uncertainty as to which member of the equilibrium mixture would react. In many syntheses of **1** and its analogs, crude mixtures of hydroperoxides were treated with acid to form artemisinin or analogs, in respectable yields.[5] The reaction mixture from **1** was subjected to reaction conditions employed by

Avery *et al.*[5a] to synthesize artemisinin derivatives (silica gel, dilute sulfuric acid and BHT), to form a new product, **5**.[6] The product was isolated by flash chromatography on silica gel. Its structure was assigned based on spectroscopic data (^1H and ^{13}C nmr data (Tables 1 and 2))[7] and supported by data from CI-ms (NH_3), which indicated that its molecular weight was 1 dalton less than that of artemisinin. Additional spectroscopic data for the structural assignment was obtained by employing $^{15}NH_3$ in the synthesis. The ^1H nmr spectrum of the ^{15}N-containing product showed H-12 was coupled to ^{15}N (J=86.9 Hz).[8] The cmr spectrum showed ^{15}N coupled to C-12 (J=11.9 Hz) and C-10 (J=10.3 Hz). A two bond coupling to C-9 (J= 5.9 Hz) was also observed.

Fig. 1. Preparation of Azaartemnisinins



R	Azaartemisinins		Azadeoxyartemisinins	
		Yield(%)		Yield(%)
H	**5**	45	**6**	9
isobutyl	**7**	45	**8**	4
allyl	**9**	45	**10**	15

In addition to **5**, a second N-containing compound was isolated in 9% yield. It was slightly less polar; its molecular weight (CI-ms (NH_3)) was 16 daltons less than that of **5**. An analysis of its ^1H and ^{13}C nmr spectra (Tables 1 and 2)[9] suggested it was the deoxy compound **6**. The ^1H nmr spectrum of the ^{15}N-containing **6** showed a ^{15}N-H coupling(J=88.2 Hz) with H-11 and the cmr spectrum showed ^{15}N was coupled to C-11, C-9, and C-8 (11.7, 10.4 and 5.9 Hz, respectively). The expected metabolite from **5**[1b] is **6**, therefore its synthesis will facilitate biological studies with **5**.

Successful synthesis of **5** prompted us to extend this approach to the preparation of N-alkyl derivatives. When isobutyl or allyl amine was substituted for ammonia in the reaction with **1** followed by treatment of the reaction mixture with acid, N-alkyl-11-azaartemisinins, **7** and **9**, were obtained in

good yields, in addition to N-alkyl-10-azadeoxyartemisinins, **8** and **10**, which formed in low yields. This reaction sequence can thus be utilized to prepare a variety of N-alkyl derivatives by employing the appropriate primary amine.

In summary, a two step stereospecific synthesis of **5** and **6** is described and extended to prepare N-alkyl derivatives of both compounds. The syntheses demonstrate that ring D in **1** can be opened, the existing functionality modified and the tetracyclic system reformed with acid. The antimalarial properties of these new artemisinin derivatives are under investigation and the results will be published elsewhere.

Table 1. Select ^{1}H nmr Data.

Artemisinin Analogs					Deoxyartemisinin Analogs				
	δ (ppm)					δ (ppm)			
Proton	**1**	**5**	**7**	**9**	Proton	**6**	**8**	**10**	**11**
4α	2.44	2.34	2.41	2.41					
4β	2.03	1.92	1.98	1.98					
5α	2.07	1.96	2.02	2.02					
5β	1.45	1.37							
9	3.40	3.17	3.29	3.31	8	2.99	3.07	3.06	3.20
11		5.93			10	6.48			
12	5.86	5.33	5.25	5.22	11	5.09	5.04	5.08	5.69
3-Me	1.45	1.30	1.36	1.36	2-Me	1.43	1.45	1.44	1.52
6-Me	1.00	0.93	0.93	0.99	5-Me	0.88	0.92	0.91	0.99
9-Me	1.21	1.07	1.14	1.14	8-Me	1.09	1.14	1.15	1.12

Table 2. Summary of ^{13}C nmr Data and Assignments

Artemisinin analogs					Deoxyartemisinin analogs				
	δ (ppm)					δ (ppm)			
Carbon	**1**	**5**	**7**	**9**	Carbon	**6**	**8**	**10**	**11**
3	105.2	104.8	104.6	104.7	2	107.5	107.0	107.3	109.1
4	35.8	36.5	36.6	36.7	3	34.7	34.8	34.9	33.9
5	24.8	25.5	25.2	25.3	4	22.8	22.8	22.3	23.8
5a	49.9	51.0	51.4	51.4	4a	45.6	45.9	46.4	44.6
6	37.4	37.6	37.5	37.6	5	35.2	35.4	35.5	35.2
7	33.4	33.8	33.7	33.7	6	33.6	33.6	33.7	33.4
8	23.3	23.0	23.0	22.8	7	23.0	23.0	24.4	23.4
8a	44.8	46.0	45.3	45.8	7a	43.6	42.9	43.2	42.3
9	32.8	32.8	33.1	33.1	8	32.8	33.3	33.2	32.6
10	171.9	173.0	171.8	171.4	9	173.8	171.9	171.2	171.6
12	93.6	75.6	78.6	77.8	11	81.5	86.0	84.7	99.5
12a	79.4	79.9	80.1	80.2	11a	82.2	82.0	82.1	82.3
3-Me	25.1	25.1	25.0	25.1	2-Me	22.2	20.6	22.3	21.9
6-Me	19.7	19.7	19.7	19.8	5-Me	18.5	18.6	18.7	18.4
9-Me	12.5	12.1	13.1	12.8	8-Me	11.9	12.8	12.7	12.5
13			48.9	44.3	12		51.4	34.9	
14			26.3	133.0	13		29.4	132.9	
15,16			20.4	117.7	14		26.7,24.33	117.8	

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6. To a saturated solution of methanolic ammonia (12 mL) at rt was added artemisinin (1.128 g, 4 mmol). The reaction was stirred for 1.5 h and concentrated under reduced pressure to give a yellow solid. The solid was dissolved in CH_2Cl_2 (180 mL) and cooled to -78°C. BHT (80 mg, 0.36 mmol), 15% H_2SO_4 (0.8 ml), and silica gel (8.0 g) were added in succession. After stirring overnight with warming the reaction was filtered and the silica gel washed with CH_2Cl_2. The combined organics were concentrated under reduced pressure to afford the crude product **5**. Column chromatography with 8% acetone/CH_2Cl_2 and silica gel gave **5** (510 mg, 45%); mp 143-145°C; R_f = 0.40 (15% acetone/ CH_2Cl_2); $[\alpha]^{25}_D$ = -40.9° (*c* 0.127, CH_2Cl_2); IR ($CHCl_3$): 3313, 3223, 2928, 2873, 1668 cm^{-1}; CIMS (NH_3) 299 (M + NH_4^+,76%) 282 (M + H^+, 100%); ^1H NMR δ 0.93-1.01 (m, 2H), 0.93 (d, *J* = 5.5 Hz, 3H), 1.07 (d, *J* = 7.2 Hz, 3H), 1.30 (s, 3H), 1.25-1.42 (m, 3H), 1.61-1.70 (m, 2H), 1.71-1.77 (m, 1H), 1.92 (dm, *J* = 10.2 Hz, 2H), 2.34 (m, 1H), 3.17 (p, *J* = 6.8 Hz, 1H), 5.33 (s, 1H), 5.93 (bs, 1H); ^{13}C NMR δ 12.1, 19.7, 23.0, 25.1, 25.5, 32.8, 33.8, 36.5, 37.6, 46.0, 51.0, 75.6, 79.9, 104.8, 173.1. Further elution provided the slightly less polar 10-azadeoxyartemisinin (**6**) (120 mg, 9%); mp 169-171°C; R_f = 0.39 (15% acetone/CH_2Cl_2); $[\alpha]^{25}_D$ = -151.5° (*c* 0.033, CH_2Cl_2); IR ($CHCl_3$): 3250, 3325, 2936, 3050, 1681 cm^{-1}; CIMS (NH_3) 283 (M + NH_4^+,50%) 266 (M + H^+, 100%);^1H NMR δ 0.88 (d, *J* = 5.7 Hz, 3H), 0.95-1.08 (m, 2H), 1.08 (d, *J* = 7.5 Hz, 3H), 1.10-1.28 (m, 2H), 1.43 (s, 3H), 1.55-1.97 (m, 8H), 2.92-3.01 (m, 1H), 5.09 (d, *J* = 2.7 Hz, 1H), 6.49 (bs, 1H); ^{13}C NMR δ 11.9, 18.5, 22.2, 22.8, 24.2, 32.8, 33.6, 34.7, 35.2, 43.6, 45.6, 81.5, 82.2, 107.5, 173.4.
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