Potent Antipsoriatic Agents: A Facile Preparation of Acylated Derivatives from Dithranol in a Mild Basic Reaction

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Treatment of dithranol **1** with various equivalents of acetyl chloride and Et_3N in THF at room temperature afforded the corresponding acylated derivatives, such as 1-acetyloxy- and 1,8-diacetyloxy-9(10*H*)-anthracenones, **6a**, and **6b**, as well as 1,8,9-triacetyloxyanthracene **7a**, and 1,8,9-triacetyloxy-10-acetylanthracene **7b**. 1,8-Bis(trimethylacetyloxy)-9(10*H*)-anthracenone **6c** was also obtained in high yield by using pivaloyl chloride during the mild acylation.

Keywords: Dithranol; Anthralin; Psoriasis; Acylation; 1,8-Dihydroxy-9(10*H*)-anthracenone.

INTRODUCTION

Dithranol **1** (also called anthralin, IUPAC nomenclature: 1,8-dihydroxy-9(10*H*)-anthracenone) is the most effective agent for the treatment of psoriasis.[1] However, it is limited by its undesirable side effects such as irritation and staining of the skin. Dithranol is not quite stable, and it undergoes spontaneous oxidation enhanced by day-light, ultraviolent (UV)-light, exposure to air and molecular oxygen, temperature increases, the presence of trace metals or tar, alkaline solutions, etc. Intermediate products, such as dithranol anions **1a** and **1b**, dithranol radicals **1c**, and oxygen radicals are thought to be responsible for both the antipsoriatic effect and dithranol dermatitis,[2] whereas the brown staining is due to the anthraquinone dimers **4** and polymers,[1,3] and both danthron (1,8-dihydroxyanthraquinone) **2** and dithranol dimer **3** are not active for the treatment of psoriasis, although they have no inflammatory effect of the skin.[4] Fig. 1 illustrates the topical oxidation process of dithranol. Consequently, efforts are being made to understand the molecular basis of the proinflammatory and staining properties so that dithranol may be modified structurally to remove these unpleasant effects.

Dithranol exists almost totally in the ketonic form (anthrone) in the inert hydrocarbon solvents. In alkaline solutions such as triethylamine and pyridine, it changes to its tautomeric enolic form (anthranol).[5] One of the first derivatives of dithranol was triacetyloxyanthracene (dithranol triacetate) **7a**.[6] The relative absence of inflammatory reactions and staining of the skin during the treatment with triacetyloxyanthracene was unfortunately accompanied by a slower response and a lower antipsoriatic effect in comparison to dithranol.[7] The analogues of dithranol with partial substitution of the hydrogen atoms at the C10 position present an attractive alternative. When both hydrogen atoms were replaced, the new molecule lost not only its irritative and staining properties, but also the antipsoriatic activity of the parent compound. When only one of the two hydrogen atoms was replaced with an acetyl group, the new molecule retained most of the properties of dithranol.[8] Employing alkaline amines in the prescription can also help to inactivate dithranol by facilitating its oxidation and inhibit dithranol-induced inflammation by up to 96%.[9] Thus, syntheses and biological activities of 10-acyl substituted dithranol derivatives have been intensively studied recently.[10] We report herein the mild acylation method by treatment of dithranol **1** with acetyl chloride (AcCl) or pivaloyl chloride (PivCl, trimethylacetyl chloride) in the presence of triethylamine (Et_3N) in tetrahydofuran (THF) at room temperature.

RESULTS AND DISCUSSION

Our initial attempts to repeat the O-acetylation of **1**, according to the literature procedures demonstrated by van Duuren et al.,[11] either by using AcCl (1.2 equiv), pyridine (1.3 equiv.) in benzene at reflux for 20 h or by using acetic anhyhride (Ac_2O) at reflux afforded the corresponding 10-acetyl-1,8-dihydroxy-9(10*H*)-anthracenone **5** and 1,8-diacetoxy-9(10*H*)-anthracenone **6a**, respectively. However, although both reactions always gave the reaction mixtures, they not only contained the various acetyl derivatives including the corresponding desired products **6a** and **6b**, but also many side-products such as 1,8-dihydroxyanthraquinone **2** and dithranol dimer **3**. No desired corresponding 10-acetyl

derivative **5** was observed; instead, 1,8,9-triacetyloxyanthracene **7a** and 10-acetyl-1,8,9-triacetyloxyanthracene **7b** were obtained mainly in low yields. Formation of side-products **2** and **3** may result from the vigorous reaction conditions, i.e. at reflux for a long time. Thus, a mild acylation method should be employed for the preparation of acylated dithranol analogues.

Treatment of **1** with AcCl and Et_3N in THF at room temperature afforded the corresponding 1-acetyloxyanthracenone **6a**, 1,8-diacetyloxyanthracenone **6b**, 1,8,9-triacetyloxyanthracene **7a**, and 10-acetylanthracene triacetate **7b**, accompanied with a trace of 1-acetyloxydanthron **8** as shown in Fig. 2 and Table 1. Table 1 illustrates that isolated yields of the corresponding acetylation products were dependent upon the equivalents of AcCl and Et_3N being employed in the reactions and a period of the reaction time (from entry 2 to entry 4). While 1.0 equiv. of AcCl and 2.0 equiv. of Et_3N being used for the acetylation of **1** only mono-acetylated **6a** and di-acetylated **6b** were obtained in 88% combined yields, in which the former is predominate and the latter is minor (in entry 1); whereas excess of AcCl (6.0 equiv.) and Et_3N (7.2 equiv.) being used for the acetylation of **1** after 2 h, 1,8,9-triacetyloxyanthracene **7a** and 10-acetylanthracenone triacetate **8b** were obtained in 84% combined yields, as well as a trace amounts of 1-acetyloxyanthraquinone **9** (in entry 5). It is worth noting that the formation of **7b**, via Fredel-Craft acylation in the absence of Lewis acid as catalyst, might be clarified by that the greater reactivity of **7a** is enhanced by three activated acetyloxy groups located on 1-, 8-, and 9-positions of the anthracene molecule. All reactions took place at room temperature without heating and at an atmosphere pressure of N_2 to avoid the formation of side-products, such as danthron **2** and dithranol dimer **3**. It should be noted that the reaction conditions must be controlled to be basic, i.e. Et_3N being used should be 2.0 equiv. to AcCl, whereas in an acidic condition the reaction was running very slowly.

Bulky acylating agents such as benzoyl chloride and p-hydroxybenzoyl chloride were also employed to the acylation of dithranol, thus the corresponding 1,8-dibenzoyloxy-9-anthrone and 10-benzoyl-1,8,9-tribenzoyloxyanthracene were obtained in the high yields reported by Müller et al.[10] In our laboratories pivaloyl chloride was also employed in this

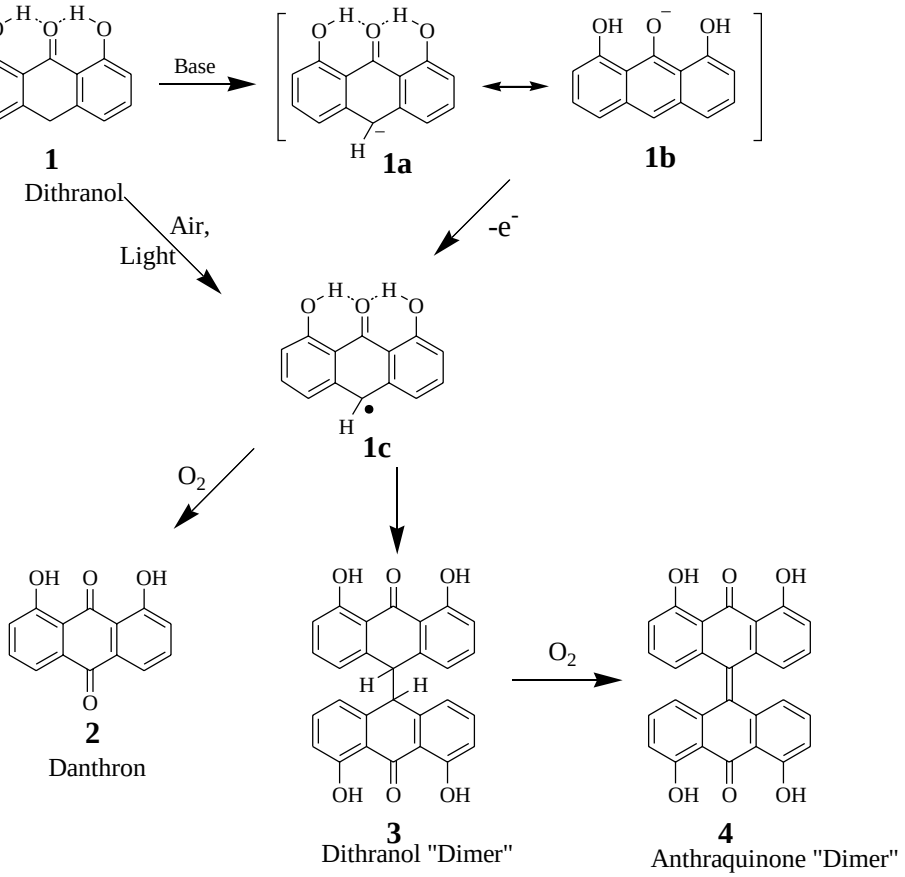

Fig. 1. Autooxidation process of dithranol.

Table 1. Acetylation of Dithranol[a]

Entry	AcCl (equiv.)	Et_3N (equiv.)	Reaction Time	Isolated Yields (%)				
				6a	**6b**	**7a**	**7b**	**8**
1	1.0	2.0	20 min	76	12	-	-	-
2	3.0	6.0	20 min	52	20	15	12	-
3	4.0	8.0	60 min	18	32	30	22	trace
4	4.0	8.0	120 min	-	26	36	36	trace
5	6.0	12.0	120 min	-	-	12	72	trace

[a] All reactions were carried out at room temperature in about 0.1 M of dry THF.

mild acylation method described above, by treatment of **1** with 3.0 equiv. of pivaloyl chloride and 3.6 equiv. of Et_3N, 1,8-bis(trimethylacetyloxy)anthracenone **6c** was obtained exclusively in 85% yield, even though excess amounts of pivaloyl chloride and Et_3N were applied, no expected 10-acylated derivatives were observed. The outcome of this reaction implied that pivaloyloxyl groups are much more bulky rather than acetyloxyl and benzoyloxyl groups resulting in the steric congestion located on the 1-, 8-, and 9-positions of anthracene molecule, hence, the expected 1,8,9-tripivaloyloxyanthracene and 10-pivaloylanthracene derivatives were not easily obtained by this mild acylation method.

CONCLUSION

In conclusion, the corresponding acetylated dithranol analogues, **6a**, **6b**, **7a**, and **7b**, were easily prepared in a mild basic reaction condition, in which the corresponding products were obtained according to how many equivalents of AcCl and Et_3N were employed and a period of reaction time. 1,8-Bis(trimethylacetyloxy)anthracenone **6c** was also obtained in high yield by using this mild acylation method. All

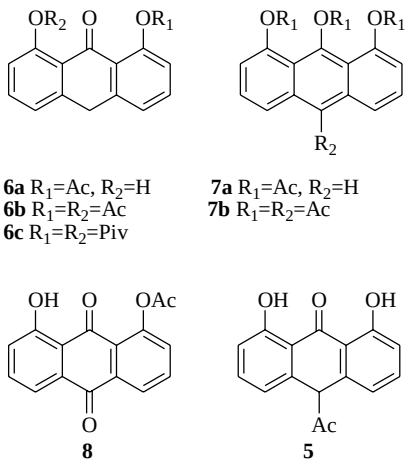

Fig. 2. Acylated derivatives from dithranol **1**.

acylated derivatives obtained starting from dithranol were further examined for the clinically therapeutic treatment of psoriasis.

EXPERIMENTAL SECTION

^1H NMR spectroscopic data for compounds, **6a**, **6b**, **6c**, **7a**, **7b**, and **8**, obtained from the acylation as well as starting material **1**, side-products **2** and **3** are listed in Table 2. HRMS and IR spectroscopic data for compounds **6a**, **6b**, **6c**, **7a**, and **7b** are listed in Table 3. ^1H NMR spectra were recorded with a Bruker AC-250 spectrometer (250 MHz), and were referenced to chloroform (δ 7.26 ppm) or tetramethylsilane (δ 0.00 ppm). Perkin-Elmer Model 883 or JASCO spectrometer was used for IR spectra. High resolution mass values were obtained on a JEOL JMS-SX/SX 102A mass spectrometer at the Department of Chemistry, National Chung-Hsing University. For thin-layer chromatography (TLC) analysis, Merck precoated TLC plates (Kieselgel 60 F_{254}, 0.2 mm) were used. Column chromatography was performed by using Merck Kieselgel 60 (70-230 mesh) as the stationary phase.

General Procedure for the Acylation of Dithranol 1

To a solution of **1** (1 mmol) in 10 mL of dry THF was added Et_3N followed by AcCl or PivCl at room temperature under N_2. The reaction mixture was monitored by TLC until

Table 2. ^1H NMR (250 MHz, $CDCl_3$) Spectroscopic Data

Compd	δ (ppm)
1	4.35 (s, 2H), 6.90 (d, *J* = 8 Hz, 4H), 7.49 (t, *J* = 8 Hz, 2H), 12.30 (s, 2H)
2	7.32 (d, *J* = 8 Hz, 2H), 7.71 (t, *J* = 8 Hz, 2H), 7.85 (d, *J* = 8 Hz, 2H), 12.10 (s, 2H)
3	4.60 (s, 2H), 6.38 (d, *J* = 8 Hz, 4H), 6.91 (d, *J* = 8 Hz, 4H), 7.39 (t, *J* = 8 Hz, 4H), 11.70 (s, 4H)
6a	2.46 (s, 3H), 4.35 (s, 2H), 6.84-6.89 (m, 2H), 7.05 (d, *J* = 8 Hz, 1H), 7.32 (d, *J* = 8 Hz, 1H), 7.43 (t, *J* = 8 Hz, 1H), 7.59 (t, *J* = 8 Hz, 1H), 12.80 (s, 1H)
6b	2.48 (s, 6H), 4.32 (s, 2H), 6.96 (d, *J* = 8 Hz, 4H), 7.28 (t, *J* = 8 Hz, 2H), 7.54 (d, *J* = 8 Hz, 2H)
6c	1.45 (s, 18H), 4.30 (s, 2H), 6.95 (d, *J* = 8 Hz, 4H), 7.28 (t, *J* = 8 Hz, 2H), 7.52 (d, *J* = 8 Hz, 2H)
7a	2.43 (s, 9H), 7.14 (d, *J* = 8 Hz, 2H), 7.44 (t, *J* = 8 Hz, 2H), 7.90 (d, *J* = 8 Hz, 2H), 8.43 (s, 1H)
7b	2.42 (s, 9H), 2.81 (s, 3H), 7.17 (d, *J* = 8 Hz, 2H), 7.51 (t, *J* = 8 Hz, 2H), 7.71 (d, *J* = 8 Hz, 2H)
8	2.45 (s, 6H), 7.41 (d, *J* = 8 Hz, 2H), 7.76 (t, *J* = 8 Hz, 2H), 8.22 (d, *J* = 8 Hz, 2H)

Table 3. HRMS and IR Spectroscopic Data

Compd	Molecular Formula	HRMS		IR (KBr)
		Calcd	Found	cm^{-1} (functional group, rel. intensity)
6a	$C_{16}H_{12}O_4$	268.0736	268.0730	3450 (OH, vs), 1740 (C=O of OAc, vs), 1610 (OH-O=C, vs)
6b	$C_{18}H_{14}O_5$	310.0841	310.0848	1760 (C=O of OAc, vs), 1660 (C=O, s)
6c	$C_{24}H_{26}O_5$	394.1781	394.1788	1750 (C=O of PivO, vs), 1650 (C=O, s)
7a	$C_{20}H_{16}O_6$	352.0947	352.0942	1750 (C=O of OAc, vs)
7b	$C_{22}H_{18}O_7$	394.1052	394.1056	1750 (C=O of OAc, vs), 1650 (C=O of Ac, s)

the reaction was finished, poured into water, then extracted with dichloromethane (3 × 10 mL). The combined organic layers were washed with 10% aq. $NaHCO_3$ solution, water, and brine, dried over anhydrous $MgSO_4$, filtered, and evaporated in vacuo. The resulting residue was purified by column chromatography on silica gel eluting with EtOAc/hexane to afford the corresponding products.

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