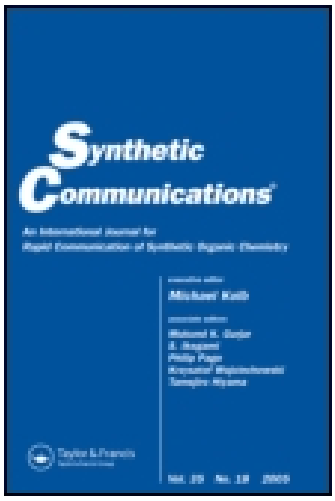

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One Step Synthesis of *N*-[1-(2-Diethylamino-ethylamino)-7-(*H* or methoxy)-9-oxo-9*H*-thioxanthen-4-ylmethyl]-formamides and, Acetamide from Their Corresponding Alcohols, Hycanthone, and 7-Methoxy-hycanthone

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ABSTRACT

N-[1-(2-Diethylamino-ethylamino)-7-(*H* or methoxy)-9-oxo-9*H*-thioxanthen-4-ylmethyl]-formamides and acetamide were synthesized from their corresponding alcohols, hycanthone and 7-methoxy-hycanthone, in one step procedure and 45% yield.

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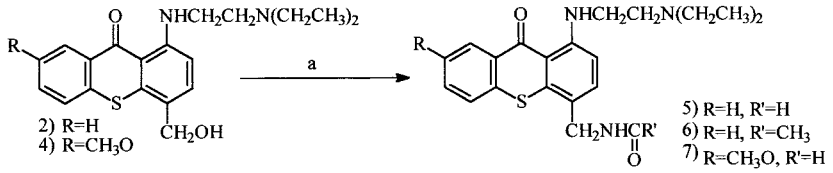
INTRODUCTION

Lucanthone (Miracil D) (**1**)[1–4] and hycanthone (Etrenol) (**2**)[5–8] belong to the thioxanthenone class and have been well known as antischistosomal and anticancer agents. Upon random screening of the Eastman Kodak and Sterling Winthrop compound collections, a new series of thioxanthenones,[9] e.g., WIN 33377 (**3**), related to lucanthone (**1**) and hycanthone (**2**), were identified to show curative anticancer activities. The discovery initiated a new round of preclinical and clinical trials.[10–13] During the course of our research to further explore thioxanthenones as anticancer agents, it was discovered that intermediate compounds, such as N-substituted formamides/acetamides (**5**), (**6**), and (**7**), could be synthesized in a one step procedure. These compounds were synthesized via a two step reaction sequence originally,[14] namely oxidation of the alcohols, hycanthone (**2**) /7-MeO-hycanthone (**4**) to the corresponding aldehydes and then reaction of the aldehydes with simple amides, formamide or acetamide, via the Leuckard reaction.[15,16] Here we report a convenient one step reaction, which bypasses the aldehyde intermediates, to synthesize compounds **5–7** in about 45% yield.

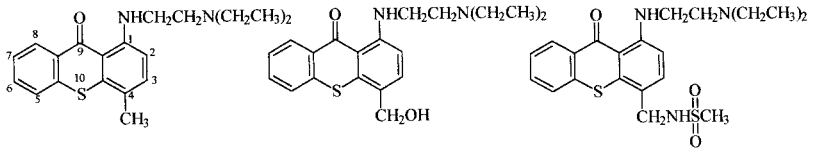
RESULTS AND DISCUSSION

Hycanthone (**2**) or 7-MeO-hycanthone (**4**) was allowed to react with acetamide or formamide in acetic acid with or without a small amount of sulfuric acid at 140°C with a vigorous stirring for ten minutes. The acidic condition was thought to activate the hydroxyl group in hycanthone (**2**)/7-MeO-hycanthone (**4**) and allow the hydroxyl group to be substituted by the nitrogen group of simple amides, viz., formamide/acetamide. Although both of the conditions gave the expected amides, the condition with a small amount of sulfuric acid produced higher yields (TLC). The structures were determined by ^{1}H and COSY NMR. The cross peaks in COSY spectrums between the benzylic proton doublets at around δ 4.5



Scheme 1. (a) Formamide or acetamide, acetic acid, 140°C, 10 min.

and a broad peak at around $\delta 6$ clearly confirmed the newly formed-CH_2NHCO-structure.



1 **2** **3**

EXPERIMENTAL SECTION

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and were uncorrected. ^{1}H NMR spectra were recorded on Bruker, 400 MHz instrument with tetramethylsilane as an internal standard. Chemical shifts are reported as δ values (ppm) downfield from tetramethylsilane. NMR abbreviations were used as follows: s (singlet), d (doublet), m (multiplet). IR spectra were recorded on FT-IR (Perkin Elmer Spectrum 1000) instrument. Silica GF plates (Analtech) were used for TLC (250 μm, 2.5 × 10 cm). Silica Gel (40 μm, Baker) was used for flash column chromatography. All organic reagents and solvents were reagent grade and purchased from commercial vendors.

***N*-[1-(2-Diethylamino-ethylamino)-9-oxo-9*H*-thioxanthen-4-ylmethyl]-formamide (5).** Twenty-five milliliters of formamide was warmed to 140°C in an oil bath. Five hundred milligrams (1.4 mmol) of hycanthone (**2**) was added. The mixture was stirred vigorously and 16 drops of sulfuric acid (0.21 mL, 4.01 mmol) in 6 mL of acetic acid was added. After 10 min, the reaction flask was cooled down by tap water. Fifty milliliters of water was added. The solution was then basified by addition of sodium carbonate, the mixture extracted with methylene chloride, dried over sodium sulfate and concentrated. The crude product was purified on a silica gel column using EtOAc/EtOH (1:1) as eluent to give 0.23 g (0.60 mmol, 43%) of pure product (**5**): m.p. 154–156°C (lit.[14] m.p. 154–155°C); TLC R_f 0.18 in EtOAc/TEA (19.5:0.5); R_f 0.21 in EtOH/EtOAc (1:1). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.10 (t, 6H, $J = 7.1$), 2.64 (q, 4H, $J = 7.09$), 2.81 (t, 2H, $J = 6.81$), 3.33 (dd, 2H, $J = 11.68$, 6.40), 4.56 (d, 2H, $J = 5.38$), 5.93 (b, 1H), 5.55 (d, 1H, $J = 8.64$), 7.36–7.61 (m, 4H), 8.28 (s, 1H), 8.49 (d, 1H, $J = 7.94$), 10.35 (b, 1H). IR (KBr): 3258.69, 2968.97, 2866.38, 1686.59, 1643.85, 1616.89, 1593.64, 1555.82, 1512.47, 1436.01, 1373.95, 1263.86, 1223.60, 1082.77, 812.66, 755.59, 660.84, 608.59 cm^{-1}.

***N*-[1-(2-Diethylamino-ethylamino)-9-oxo-9*H*-thioxanthen-4-ylmethyl]-acetamide (6).** Fifty grams (0.85 mol) of acetamide was heated to 140°C in an oil bath. One gram (2.8 mmol) of hycanthone (**2**) was added. The mixture was vigorously stirred and 32 drops of sulfuric acid (0.42 mL, 8.02 mmol) in 12 mL of acetic acid was added. After 10 min, the reaction flask was cooled down by tap water. Fifty milliliters of water was added. The solution was basified by addition of sodium carbonate, the mixture extracted with 3×35 mL of methylene chloride, dried over sodium sulfate and concentrated. The crude product was initially purified on a silica gel column using EtOAc/TEA (19.5:1) and EtOAc/EtOH (1:1) as eluent. The resulting product was further purified on a silica gel column using eluent EtOAc/EtOH (1:1) as eluent to give 48 mg (1.2 mmol, 43%) of pure product (**6**): m.p. 182–184°C (lit.[14] 182–183°C). TLC R_f 0.25 in EtOAc/TEA (19.5:0.5); R_f 0.13 in EtOH/EtOAc (1:1). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.10 (t, 6H, $J = 7.1$ Hz), 2.03 (s, 3H), 2.64 (q, 4H, $J = 7.1$ Hz), 2.81 (t, 2H, $J = 6.9$ Hz), 3.34 (dd, 2H, $J = 11.9$, 6.65 Hz), 4.51 (d, 2H, $J = 5.3$ Hz), 5.79 (b, 1H), 6.56 (d, 1H, $J = 8.7$ Hz), 7.36–7.54 (m, 4H), 8.49 (d, 1H, $J = 8.1$ Hz), 10.3 (b, 1H). IR (KBr): 3326, 2969, 1648, 1619, 1560, 1435, 1370, 1289, 1254, 1229, 1098, 810, 753 cm^{-1}.

***N*-[1-(2-Diethylamino-ethylamino)-7-methoxy-9-oxo-9*H*-thioxanthen-4-ylmethyl]-formamide (7).** The mixture of 2.11 g (5.46 mmol) of 7-methoxy-hycanthone (**4**) and 118 mL of formamide was warmed to 140°C in an oil bath. The mixture was vigorously stirred and 13 mL of acetic acid was added first, and followed by addition of 0.99 mL of sulfuric acid in 13 mL of acetic acid. After 10 min, the reaction mixture was immediately poured into ice water. The solution was basified by addition of sodium carbonate, the mixture extracted with methylene chloride, dried over sodium sulfate and concentrated. The crude product was purified on a silica gel column using EtOAc/EtOH (1:1) as eluent to give 1.15 g (2.77 mmol, 50.7%) of pure product (**7**): m.p. 108–110°C (lit.[14] 95–99°C). ^{1}H NMR ($CDCl_3$) δ 1.09 (t, 6H, $J = 7.13$), 2.64 (q, 4H, $J = 7.13$), 2.79 (t, 2H, $J = 6.86$), 3.30 (m, 2H), 3.88 (s, 3H), 4.53 (d, 2H, $J = 4.49$), 6.04 (b, 1H), 6.50 (m, 1H), 6.85 (m, 1H), 6.94 (m, 1H), 7.30 (m, 1H), 8.29 (s, 1H), 8.39 (m, 1H), 10.32 (s, 1H). IR (KBr): 3276.75, 2966.41, 1648.64, 1600.89, 1559.82, 1508.53, 1406.14, 1385.95, 1237.68, 1184.62, 1068.24, 1033.45, 801.21, 658.20 cm^{-1}.

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