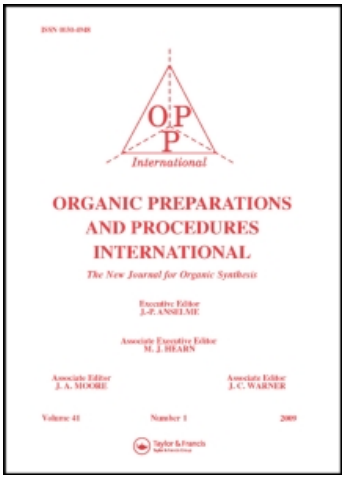

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A. Mahamoud[a]; J. -P. Galy[a]; J. Barbe[a]
[a] GERCTOP - URA CNRS 1411, Faculte de Pharmacie, Marseille Cedex 5, France

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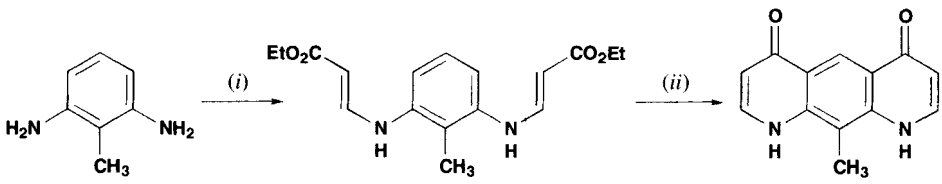
SYNTHESIS AND COMPETITIVE N- AND O-ALKYLATION OF 10-METHYLPYRIDO[3,2-g]QUINOLINE-4,6-DIONE†

Submitted by (10/29/93) A. Mahamoud, J.-P. Galy and J. Barbe*

GERCTOP - URA CNRS 1411, Faculte de Pharmacie
27 Boulevard Jean Moulin, 13385 Marseille Cedex 5, FRANCE

Within the scope of work devoted to DNA intercalating agents, we were interested in the pyridoquinolinedione series and 10-methylpyrido[3,2-g]quinoline-4,6-dione (**1**) was considered to be a convenient starting material. This compound is usually prepared in 65-70% yield, from the reaction



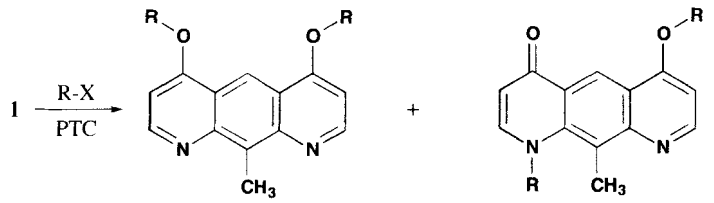
(1)

i) $HC{\equiv}CCO_2Et$, CH_3OH *ii*) Δ, Ph-O-Ph, N_2 **1**

of either ethyl (ethoxymethylene)malonate or acetylenic esters with 2,6-diaminotoluene by a multi-step procedure[1] involving one of the many variations of the Skraup method or Gould-Jacobs reaction. We now show that **1** can be obtained in near quantitative yield in a two-step procedure using ethyl propiolate.

In this approach, a double Michael-type addition is followed by thermal cyclization under nitrogen, in the presence of a large amount of high boiling point solvent (diphenyl ether) to prevent polymerization (Eq. 1). It should be noted that the yield for the one-step condensation-cyclization in diphenyl ether only approximates 40-50%.

Due to the ambident character of **1**, we have investigated its reactivity towards alkylation under phase transfer-catalysis (PTC) conditions. Alkylation of **1** led to the O,O-disubstituted isomers **2** as the main product while the O,N-disubstituted isomers **3** were the minor product **2**.



(2)

2 **3**

a) R = CH_3 b) R = CH_2CH_3 c) R = $CH(CH_3)_2$ d) R = $(CH_2)_3CH_3$

TABLE. Alkylation of 10-Methylpyrido[3,2-g]quinoline-4,6-dione (**1**)

Cmpd	Time (hrs)	Yield (%)	mp. (°C)	Elemental Analysis (Found) C	H	N	^{1}H NMR δ (ppm)[b] J (Hz)
2a	30	52	>265	71.08 (70.87)	5.50 (5.51)	10.05 (10.02)	3.35 (s, 3H, CH_3)*, 415 (s, 6H, O-CH_3)*, 6.70 (d, J = 4.9 Hz, 2H, Ar), 8.90 (d, J = 4.9 Hz, 2H, Ar), 9.05 (s, 1H, Ar)
2b	24	72	210-212	72.13 (72.34)	6.39 (6.38)	9.91 (9.93)	1.65 (t. J = 7Hz, 6H, CH_3), 3.35 (s, 3H, CH_3), 4.30 (q, J = 7 Hz, 4H, O-CH_2,) 6.65 (d, J = 5 Hz, 2H, Ar), 8.85 (d, J = 5 Hz, 2H, Ar), 9.00 (s, 1H, Ar)
2c	24	52	206-208	73.61 (73.55)	7.07 (7.09)	9.04 (9.03)	1.55 (d, J = 6 Hz, 12H, CH_3), 8.35 (s, 3H, CH_3), 4.90 (spt, J = 6Hz, 2H, O-CH), 6.65 (d, J = 5 Hz, 2H, Ar), 8.90 (d, J = 5 Hz, 2H, Ar), 9.00 (s, 1H, Ar)
2d	48	38	161-163	74.72 (74.55)	7.68 (7.69)	8.30 (8.28)	1.05 (t, J = 7.3Hz, 6H, CH_3), 1.65 (m, 4H. CH_2); 2.00 (m, 4H. CH_2), 3.35 (s, 3H, CH_3)**, 4.25 (t, J = 6.2 Hz, 4H, O-CH_2), 6.65 (d, J = 4.9 Hz, 2H, Ar), 8.90 (d, J = 4.9 Hz, 2H, Ar), 9.05 (s, 1H, Ar)**
3a[a]	30	20					3.10 (s, 3H, CH_3), 4.00 (s, 3H. N-CH_3)*, 4.10 (s, 3H, O-CH_3)*, 6.20 (d, J = 7.7 Hz, 1H, Ar), 6.70 (d, J = 5.1Hz, 1H, Ar), 7.60 (d, J = 7.7 Hz, 1H, Ar), 8.85 (d, J = 5.1Hz, 1H, Ar), 9.20 (s, 1H, Ar)*
3d[a]	48	10					1.00 (t, J = 7.3 Hz, 6H, CH_3), 1.55 (m, 4H, CH_2), 1.85 (m, 4H, CH_2); 2.95 (s, 3H, CH_3)**, 4.00 (t, J = 6.1Hz, 4H, N-CH_2), 4.30 (t, J = 6.2 Hz, 2H, O-CH_2, 6.20 (d, J = 4.9 Hz, 1H, Ar), 6.90 (d, J = 4.6 Hz, 1H, Ar), 7.90 (d, J = 4.5 Hz, 1H, Ar), 8.60 (d, J = 5 Hz, 1H, Ar), 9.20 (s, 1H, Ar)**

a) Compounds (**3a**) and (**3d**) were not isolated and their yields were estimated from the NMR spectrum. Peaks used for this purpose are marked with one asterisk (**3a** versus **2a**) or two asterisks (**3d** versus **2d**) b) Recorded on a Bruker AM 200 spectrometer.

Despite the fact that isomer **3** has never been isolated, the existence of isomeric mixtures was demonstrated by NMR spectroscopy. Indeed, while the ^1H NMR spectrum of **2** should show only one singlet (H-5) and two doublets for the aromatic moiety because **2** is a symmetrical, the spectrum of **3** should exhibit one singlet and four doublets, because the non-equivalence of the protons concerned. Further evidence for the OR/NR disubstitution was obvious from the comparison of the ^{13}C chemical shifts (in ppm) of methyl substituted derivatives **2a** and **3a** in CF_3CO_2D with those of homologous acridine derivatives.[2] The data on these compounds (Table) differ substantially from those previously obtained with 9-acridones,[3] alkylation of the latter under PTC conditions afforded a poorly stable O-R isomer only in a modest yield.

EXPERIMENTAL SECTION

Melting points were determined in open capillary tubes on a Büchi apparatus and are uncorrected. Elemental analyses were performed at the Service de Microanalyse (Faculté des Sciences et Techniques, Marseille, France). ^1H NMR and ^{13}C NMR spectra were recorded on a Bruker AM 200 spectrometer with TMS as the internal reference. All starting compounds were obtained from Aldrich-Chimie France.

10-Methylpyrido[3,2-g]quinoline-4,6-dione (1).- A mixture of 2,6-diaminotoluene (5 mmol), ethyl propiolate (11 mmol) and methanol (20 mL) was stirred for 24 hrs at room temperature. The resulting precipitate was collected and recrystallized from methanol to give 1.27g (80%) of 2,6-bis(2'-carboethoxyvinylamino)toluene, mp. 134-136°. ^1H NMR (200 MHz, $CDCl_3$/TMS): δ 10.05 (d, J= 12.4 Hz, 2H, NH), 7.25 (dd, J = 12.3- 8.3 Hz, 2H, CH), 7.15 (t, J = 8.1 Hz, 1H, Ar), 6.75 (d, J = 8.1 Hz, 2H, Ar), 4.90 (d, J = 8.2 Hz, 2H, CH), 4.20 (q, J = 7.1 Hz, 4H, CH_2), 2.25 (s, 3H), 1.30 (t, J = 7.1 Hz, 6H, CH_3). This compound was then added to diphenyl ether (125 mL) at 120° and the solution was then heated for 30 min at 250-260° under a nitrogen atmosphere. The desired product was precipitated as an orange solid by addition of 250-300 mL of petroleum ether. The solid was collected and washed with petroleum ether, methanol and acetone. No recrystallization solvent could be found.[4] However, the product was analytically pure, yield 0.88g (98%), mp. >265°. ^1H NMR (CF_3CO_2D/TMS): δ 10.0 (s, 1H, Ar), 9.1 (d, J = 6.7 Hz, 2H, Ar), 7.6 (d, J = 6.8 Hz, 2H, Ar), 3.3 (s, 3H, CH_3)].

Alkylation of 1.- A mixture of **1** (5 mmol), 12.5 mmol of alkylating agent (CH_3I, CH_3CH_2Br, $(CH_3)_2CHBr$ or $CH_3(CH_2)_2CH_2Br$), toluene (20 mL), 50% aqueous potassium hydroxide (10 mL) and tetrabutylammonium bromide (2.5 mmol) was refluxed under stirring for 24-48 hrs. The organic layer was separated, washed with water and dried over sodium sulfate. After evaporation of the solvent, the solid obtained was dissolved in methanol (10 mL) and precipitated three times with ether. Recrystallization of the resulting solid in methanol gave the predominant isomer **2**.

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† This work is incorporated in the European COST 81 5 ACRIVAL Program

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2. ^{13}C NMR (200 MHz, CF_3CO_2D) data: **2a** : δ 175.59 (C-4, C-6), 61.43 (OCH_3); **3a**: δ 175.49 (C-4), 174.09 (C-6), 61.37 (O-CH_3), 51.47 (N-CH_3); **9-OMe acridine**: δ 174.8 (C-9), 67.8 (O-CH_3); **N-Me-9-acridone**: δ 170.8 (C-9), 37.2 (N-CH_3)

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4. Diphenyl ether cannot be used as a co-solvent with the solvents mentioned, because of the poor solubility of **1** at low temperatures (<120°).

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A CONVENIENT PREPARATION OF 9*H*-FLUORENE-9-ACETIC ACID

Submitted by R. Richard Goehring
(12/03/93)

Scios Nova, Inc.
6200 Freeport Centre
Baltimore, MD 21224-6522

As part of a program for the synthesis of leukocyte recruitment inhibitors (leumedins)[1] we required substantial quantities of 9*H*-fluorene-9-acetic acid (**3a**). While **3a** is commercially available, we found the price to be prohibitively high.[2] A number of routes to **3a** have been described in the literature.[3] These include Reformatsky reaction with fluorenone (**1**),[3b,c] alkylation of diethyl malonate with 9-bromofluorene,[3d] alkylation of fluorene with glycolic acid,[3e] and ring opening of a cyclopropanone cyanohydrin.[3f] The preparation of **3a** from **1** held particular appeal due to analogs we had planned and the low cost of **1**. However, the Reformatsky-based approach proved to be undesirable due to modest yields, as well as synthetic incompatibility with other planned target molecules. We would like to describe a simple, high yielding alternate preparation of **3a** from fluorenone (**1**).