

May-Jun 1997 Methanetricarboxylates as Key Reagents for the Simple Preparation of Heteroarylcarboxamides with Potential Biological Activity. Part 1  
 Reaction of Methanetricarboxylates with Indoline and 1,2,3,4-Tetrahydroquinoline

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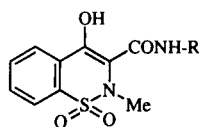
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The reaction of methanetricarboxylates **2a,b** with indoline as well as 1,2,3,4-tetrahydroquinoline yields tricyclic 4-hydroxy-2(1*H*)-quinolones with an ester group in position 3 (**3**, **8a,b**). These heterocyclic esters condense with primary aliphatic, aromatic, and heteroaromatic amines to give the corresponding amides **5a-e** and **10a-t**.

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Heterocyclic tricarbonylmethane derivatives are an important class of natural products. Moreover, some of their synthetic derivatives play an important part in agrochemistry [1]. Quite recently there has been a report on the potential antiinflammatory activity of amides of 4-hydroxy-2-quinolone-3-carboxylic acid of type **1** [2]. Some of them (with R = 2-thiazolyl) are quoted [2] to be more potent than sudoxicam. Other amides of type **1** show high antimicrobial and fungicidal [3], anticoagulant [4], or herbicidal activity [5].



SUDOXICAM  
 PIROXICAM  
 ISOXICAM

R = 2-thiazolyl  
 R = 2-pyridyl  
 R = 5-methyl-3-isoxazolyl

Figure 1

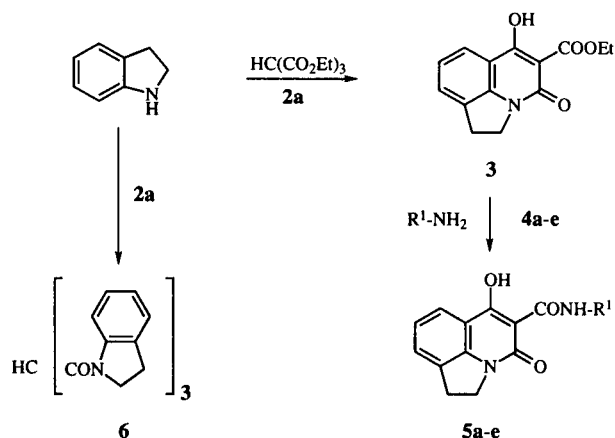
Our long lasting interest [6] in the synthesis of non-steroidal antiinflammatory agents has been also focused for some time [7] on derivatives of Sudoxicam, Piroxicam and Isoxicam [8]. The aforementioned papers of Ukrainets *et al.* [2-4] prompt us to report some of our results in this area.

The easiest way to obtain compounds of type **1** is the reaction of the 4-hydroxy-2(1*H*)-quinolone, unsubstituted in position 3, with isocyanates in the presence of a base, such as 1,8-diazabicyclo[5.4.0]undec-7-ene [9]. However, these starting compounds are, in many cases, only available through a multistep synthesis. A more general

approach is the synthesis of the corresponding esters, and their reaction with amines. The esters can be obtained in a simple manner from isatoic acids and their reaction with malonates [10], or, in a more general fashion, from alkyl anthranilates with malonates [11] or malonic acid chloride monoalkylester (RO<sub>2</sub>CCH<sub>2</sub>COCl) [12]. However, this approach depends on the availability of the anthranilates or isatoic acids.

We have previously demonstrated that alkyl tricarbonylates **2a,b** react with 1,2-dinucleophiles to yield 5-membered heterocycles [13], or with 1,3-dinucleophiles 6-membered heterocycles, containing an ester group between the two carbonyl moieties [7,14]. *N*-Substituted anilines react as 1,3-dinucleophiles in the same way. Thus, indoline and 1,2,3,4-tetrahydroquinoline yield the tricyclic esters **3** and **8a,b** if heated with an excess of methanetri-

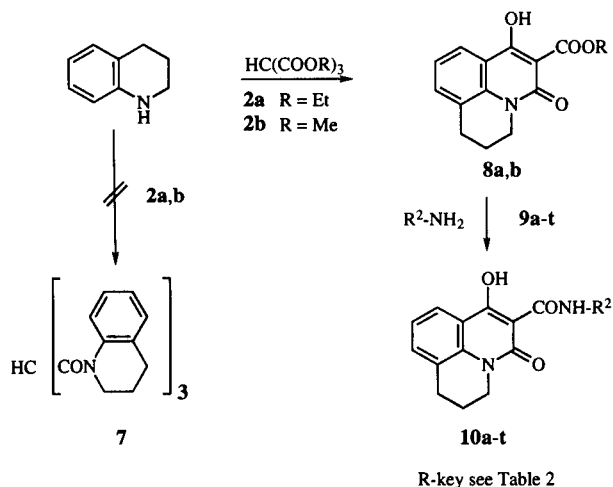
Scheme 1



R-key see Table 1

carboxylates. The excess of the esters is necessary to prevent the formation of amides of type **5** and **10**. The reaction of indoline with an equimolar amount of triethyl methanetricarboxylate resulted in the formation of the triamide **6**. However, the reaction with tetrahydroquinoline under the same conditions did not yield **7**.

Scheme 2



carbonyl bands in compounds **5** and **10** appear generally at  $1680-1660\text{ cm}^{-1}$  and  $1650-1640\text{ cm}^{-1}$ .

## EXPERIMENTAL

Melting points were obtained on a Gallenkamp Melting Point Apparatus, Model MFB-595 in open capillary tubes. The ir spectra were recorded on a Perkin-Elmer Model 298 infrared spectrophotometer, the nmr spectra were measured on a Varian Gemini 200 and a Bruker AM 360 spectrometer with tetramethylsilane as internal standard. Microanalyses were performed on a Carlo Erba 1106 Elemental analyzer.

Preparation of ethyl and methyl methanetricarboxylates **2a,b** were performed according to the literature [17].

General Procedure for the Preparation of Esters **3**, **8a,b**.

Indoline or 1,2,3,4-tetrahydroquinoline (5 mmoles) and esters **2a** or **2b** (10 mmoles) were heated to  $220^\circ$  for 15 minutes. The crude product was crystallized from diethyl ether or hexane.

Ethyl 1-Hydroxy-3-oxo-5,6-dihydro-3*H*-pyrrolo[3,2,1-*ij*]quinoline-2-carboxylate (**3**).

This compound was obtained in a yield of 90% as yellow needles, mp  $140^\circ$  (diethyl ether, lit [7] mp  $140-142^\circ$ ); ir (potassium bromide):  $3400, 2900$  (OH),  $1670, 1630, 1600$  (C=O, C=C)  $\text{cm}^{-1}$ ;

Table 1

Experimental, Physical and Analytical Data of Compounds **5**

No.	R <sup>1</sup>	Reaction Time (hours)	Yield (%)	Mp (°C) (Solvent)	Formula	Analysis Calcd./Found		
						C	H	N
<b>5a</b>	4-Me-Ph	36	59	220 (DMF)	C <sub>19</sub> H <sub>16</sub> N <sub>2</sub> O <sub>3</sub>	71.24 71.44	5.03 4.89	8.74 8.86
<b>5b</b>	4-Cl-Ph	36	62	242 (DMF)	C <sub>18</sub> H <sub>13</sub> ClN <sub>2</sub> O <sub>3</sub>	63.44 63.29	3.85 3.76	8.22 8.45
<b>5c</b>	3-CF <sub>3</sub> -Ph	30	59	204 (DMF)	C <sub>19</sub> H <sub>13</sub> F <sub>3</sub> N <sub>2</sub> O <sub>2</sub>	60.97 60.88	3.50 3.45	7.48 7.40
<b>5d</b>	2-Thiazolyl	12	88	268 (DMF)	C <sub>15</sub> H <sub>11</sub> N <sub>3</sub> O <sub>3</sub> S	57.50 57.31	3.54 3.71	13.41 13.26
<b>5e</b>	2-Benzothiazolyl	30	54	320 (DMF)	C <sub>19</sub> H <sub>13</sub> N <sub>3</sub> O <sub>3</sub> S	62.80 62.62	3.61 3.84	11.56 11.64

The conversion of the esters **3** and **8** to amides **5a-e** and **10a-r** was performed by heating the esters under reflux with an excess (40%) of the corresponding amine in boiling bromobenzene for the time given in Tables 1 and 2. The preparation of the hydrazides **10s,t** was accomplished in the same way by using *N,N*-dimethylhydrazine or phenylhydrazine, respectively.

The infrared absorption band for the esters **3** and **8** is at  $1670-1660\text{ cm}^{-1}$ . This rather low frequency for an ester carbonyl group is well known [15] and is caused by strong intramolecular hydrogen bonding [16]. The amide

<sup>1</sup>H nmr (deuteriochloroform):  $\delta$  1.50 (t, 3H, J = 7 Hz, CH<sub>3</sub>), 3.30 (t, 2H, J = 7 Hz, CH<sub>2</sub>-Ar), 4.40 (m, 4H, J = 7 Hz, NCH<sub>2</sub>, OCH<sub>2</sub>), 7.2 (m, 2H, aromatic), 7.7 (dd, 1H, J = 7 and 1 Hz, peri-H), 14.15 (s, 1H, OH).

Anal. Calcd. for C<sub>14</sub>H<sub>13</sub>N<sub>4</sub>O<sub>4</sub>: C, 64.86; H, 5.05; N, 5.40. Found: C, 64.95; H, 5.07; N, 5.39.

Ethyl 1-Hydroxy-3-oxo-6,7-dihydro-3*H*,5*H*-benzo[*ij*]quinolizine-2-carboxylate (**8a**).

This compound was obtained in a yield of 98% as yellow needles, mp  $101^\circ$  (hexane, lit [7] mp  $86.5-90.5^\circ$ , lit [7] yield 42%); ir (potassium bromide):  $3400, 2900$  (OH),  $1660, 1630, 1600, 1570$  (C=O, C=C)  $\text{cm}^{-1}$ ; <sup>1</sup>H nmr (hexadeuteriodimethyl sulfox-

Table 2  
Experimental, Physical and Analytical Data of Compounds 10

No.	R <sup>2</sup>	Reaction Time (hours)	Yield (%)	Mp (°C) (Solvent)	Formula	Analysis		
						Calcd./Found	C	H
10a	<i>n</i> -Hexyl	20	58	183 (Hexane)	C <sub>19</sub> H <sub>24</sub> N <sub>2</sub> O <sub>3</sub>	69.49 69.68	7.37 7.26	8.53 8.50
10b	Ph	16	55	179 (Xylene [a])	C <sub>19</sub> H <sub>16</sub> N <sub>2</sub> O <sub>3</sub>	71.24 71.44	5.03 5.27	8.74 8.81
10c	4-Me-Ph	15	66	207 (DMF)	C <sub>20</sub> H <sub>18</sub> N <sub>2</sub> O <sub>3</sub>	71.84 71.76	5.43 5.51	8.38 8.52
10d	CH <sub>2</sub> Ph	20	48	136 (Xylene [a])	C <sub>20</sub> H <sub>18</sub> N <sub>2</sub> O <sub>3</sub>	71.84 72.02	5.43 5.20	8.38 8.29
10e	4-Cl-Ph	48	50	192 (Xylene)	C <sub>19</sub> H <sub>15</sub> ClN <sub>2</sub> O <sub>3</sub>	64.32 64.49	4.26 4.39	7.90 7.82
10f	3-CF <sub>3</sub> -Ph	48	41	178 (DMF)	C <sub>20</sub> H <sub>15</sub> F <sub>3</sub> N <sub>2</sub> O <sub>3</sub>	61.86 61.99	3.89 3.92	7.21 7.49
10g	4-OH-PO	16	89	208 (Xylene [a])	C <sub>19</sub> H <sub>16</sub> N <sub>2</sub> O <sub>4</sub>	67.85 67.88	4.80 4.73	8.33 8.27
10h	3-MeO-Ph	23	80	175 (Xylene)	C <sub>20</sub> H <sub>18</sub> N <sub>2</sub> O <sub>4</sub>	68.60 68.60	5.18 5.20	8.00 7.93
10i	2-NH <sub>2</sub> -Ph	15	81	223 (Xylene)	C <sub>19</sub> H <sub>17</sub> N <sub>3</sub> O <sub>3</sub>	68.05 68.25	5.11 5.02	12.28 12.28
10j	2,4-Di-Cl-Ph	16	67	252 (DMF)	C <sub>19</sub> H <sub>14</sub> Cl <sub>2</sub> N <sub>2</sub> O <sub>3</sub>	58.63 58.46	3.63 3.89	7.20 7.03
10k	2,5-Di-MeO-Ph	19	92	254 (DMF)	C <sub>21</sub> H <sub>20</sub> N <sub>2</sub> O <sub>5</sub>	66.31 66.44	5.30 5.65	7.36 7.57
10l	1-Naphthyl	16	78	224 (DMF)	C <sub>23</sub> H <sub>18</sub> N <sub>2</sub> O <sub>3</sub>	74.58 74.49	4.90 4.95	7.56 7.82
10m	1-Adamantyl	15	82	220 (Xylene)	C <sub>23</sub> H <sub>26</sub> N <sub>2</sub> O <sub>3</sub>	72.99 73.23	6.92 7.23	7.40 7.17
10n	2-Pyridyl	20	69	214 (Xylene [a])	C <sub>18</sub> H <sub>15</sub> N <sub>3</sub> O <sub>3</sub>	67.28 67.56	4.71 4.81	13.08 12.83
10o	2-Pyrimidyl	10	65	240 (DMF)	C <sub>17</sub> H <sub>14</sub> N <sub>4</sub> O <sub>3</sub>	63.35 63.01	4.38 4.49	17.28 17.53
10p	2-Thiazolyl	14	79	217 (DMF)	C <sub>16</sub> H <sub>13</sub> N <sub>3</sub> O <sub>3</sub> S	58.71 58.47	4.00 4.26	12.84 12.69
10q	3-Pyrazolyl	12	97	260 (Xylene)	C <sub>16</sub> H <sub>14</sub> N <sub>4</sub> O <sub>3</sub>	61.93 61.80	4.55 4.84	18.06 17.92
10r	2-(1,2,3-Thiadiazolyl)	18	46	286 (DMF)	C <sub>15</sub> H <sub>12</sub> N <sub>4</sub> O <sub>3</sub> S	54.87 54.54	3.68 3.70	17.06 16.98
10s	NMe <sub>2</sub>	12	87	170 (Xylene [a])	C <sub>15</sub> H <sub>17</sub> N <sub>3</sub> O <sub>3</sub>	62.71 62.45	5.96 5.80	14.63 14.30
10t	NHPh	6	78	242 (DMF)	C <sub>19</sub> H <sub>17</sub> N <sub>3</sub> O <sub>3</sub>	68.05 68.35	5.11 5.07	12.53 12.76

[a] + Addition of Hexane.

ide):  $\delta$  1.45 (t, 3H, J = 7 Hz, CH<sub>3</sub>), 2.10 (m, 2H, -CH<sub>2</sub>-), 2.95 (t, 2H, J = 7 Hz, CH<sub>2</sub>-Ar), 4.15 (t, 2H, J = 7 Hz, NCH<sub>2</sub>), 4.5 (q, 2H, J = 7 Hz, OCH<sub>2</sub>), 7.10, 7.40 (m, 2H, aromatic), 8.0 (dd, 1H, J = 1.5 Hz, J = 8 Hz, peri-H), 13.9 (s, 1H, OH).

Anal. Calcd. for C<sub>15</sub>H<sub>15</sub>NO<sub>4</sub>: C, 65.92; H, 5.53; N, 5.13. Found: C, 65.81; H, 5.57; N, 4.98.

Methyl 1-Hydroxy-3-oxo-6,7-dihydro-3*H*,5*H*-benzo[*ij*]quinolizine-2-carboxylate (8*b*).

This compound was obtained in a yield of 66% as yellow needles, mp 142° (diethyl ether, lit [7] 139-142°); ir (potassium bromide): 3400, 2900 (OH), 1660, 1630, 1600, 1570 (C=O, C=C) cm<sup>-1</sup>; <sup>1</sup>H nmr (hexadeuteriodimethyl sulfoxide):  $\delta$  2.10 (m, 2H, J = 7 Hz, -CH<sub>2</sub>-), 3.05 (t, 2H, J = 7 Hz, CH<sub>2</sub>-Ar), 4.15 (m, 5H, NCH<sub>2</sub>, OCH<sub>3</sub>), 7.10, 7.45 (m, 2H, aromatic), 8.05 (dd, 1H, J = 1.5 Hz, J = 7 Hz, peri-H), 13.9 (s, 1H, OH).

Anal. Calcd. for C<sub>14</sub>H<sub>13</sub>NO<sub>4</sub>: C, 64.86; H, 5.05; N, 5.40. Found: C, 64.55; H, 5.01; N, 5.45.

General Procedure for Preparation of *N*-Substituted 1-Hydroxy-3-oxo-5,6-dihydro-3*H*-pyrrolo[3,2,1-*ij*]quinoline-2-carboxamides 5*a*-*e*, and 2-Aminocarbonyl-1-hydroxy-3-oxo-6,7-dihydro-3*H*,5*H*-benzo[*ij*]quinolizines 10*a*-*t*.

The appropriate esters 3, 8*a*,*b* (5 mmoles) and amines 4*a*-*e*, 9*a*-*t* (7 mmoles) in brombenzene (35 ml) were heated under reflux. The solvent was evaporated under reduced pressure. The crude amides and hydrazides were recrystallized from the solvents given in Tables 1 and 2.

Methanetri-*N*-(1-indolyl)carboxamide (6) [7].

The mixture of 2*a* (4.8 g, 4 mmoles) and indoline (7.6 g, 4 mmoles) were heated to 220° for 20 minutes. The crude product (3.2 g, 71%) was recrystallized from dimethylformamide to

yield 3.2 g (53%) of colorless prisms, mp 320° dec; ir (potassium bromide): 1650, 1595 1480  $\text{cm}^{-1}$ .

Anal. Calcd. for  $\text{C}_{28}\text{H}_{25}\text{N}_3\text{O}_3$ : C, 74.48; H, 5.58; N, 9.31. Found: C, 74.43; H, 5.56; N, 9.10.

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