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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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].

1

SUDOXICAM R = 2-thiazolyl
PIROXICAM R = 2-pyridyl
ISOXICAM R = 5-methyl-3-isoxazolyl

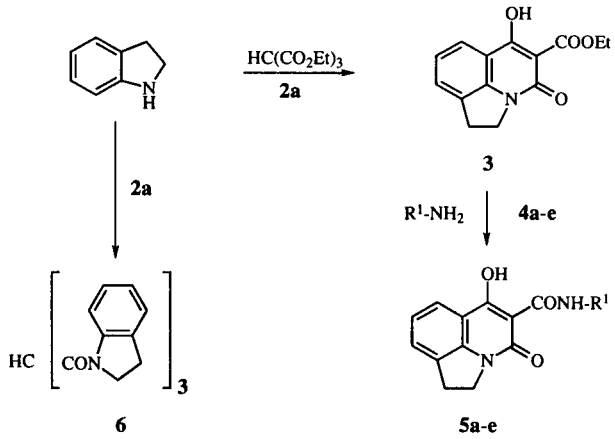
Figure 1

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_2CCH_2COCl) [12]. However, this approach depends on the availability of the anthranilates or isatoic acids.

We have previously demonstrated that alkyl tricarboxylates **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 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-

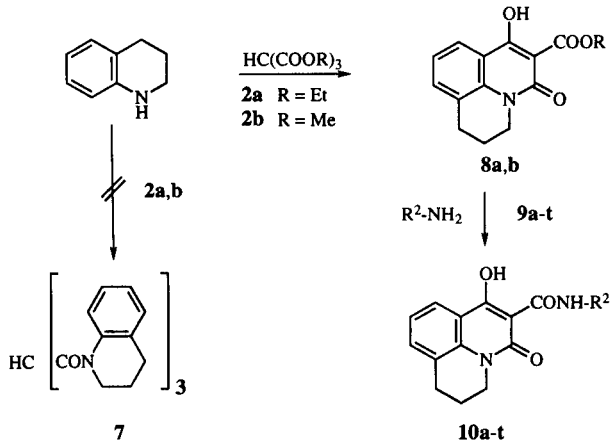
Scheme 1



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



R-key see Table 2

carbonyl bands in compounds **5** and **10** appear generally at 1680-1660 cm^{-1} and 1650-1640 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° 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° (diethyl ether, lit [7] mp 140-142°); ir (potassium bromide): 3400, 2900 (OH), 1670, 1630, 1600 (C=O, C=C) cm^{-1};

Table 1

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

No.	R^1	Reaction Time (hours)	Yield (%)	Mp (°C) (Solvent)	Formula	Analysis Calcd./Found C	H	N
5a	4-Me-Ph	36	59	220 (DMF)	$C_{19}H_{16}N_2O_3$	71.24 71.44	5.03 4.89	8.74 8.86
5b	4-Cl-Ph	36	62	242 (DMF)	$C_{18}H_{13}ClN_2O_3$	63.44 63.29	3.85 3.76	8.22 8.45
5c	3-CF_3-Ph	30	59	204 (DMF)	$C_{19}H_{13}F_3N_2O_2$	60.97 60.88	3.50 3.45	7.48 7.40
5d	2-Thiazolyl	12	88	268 (DMF)	$C_{15}H_{11}N_3O_3S$	57.50 57.31	3.54 3.71	13.41 13.26
5e	2-Benzothiazolyl	30	54	320 (DMF)	$C_{19}H_{13}N_3O_3S$	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 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

^1H nmr (deuteriochloroform): δ 1.50 (t, 3H, J = 7 Hz, CH_3), 3.30 (t, 2H, J = 7 Hz, CH_2-Ar), 4.40 (m, 4H, J = 7 Hz, NCH_2, OCH_2), 7.2 (m, 2H, aromatic), 7.7 (dd, 1H, J = 7 and 1 Hz, peri-H), 14.15 (s, 1H, OH).

Anal. Calcd. for $C_{14}H_{13}NO_4$: 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° (hexane, lit [7] mp 86.5-90.5°, lit [7] yield 42%); ir (potassium bromide): 3400, 2900 (OH), 1660, 1630, 1600, 1570 (C=O, C=C) cm^{-1}; ^1H nmr (hexadeuteriodimethyl sulfox-

Table 2

Experimental, Physical and Analytical Data of Compounds **10**

No.	R^2	Reaction Time (hours)	Yield (%)	Mp (°C) (Solvent)	Formula	Analysis Calcd./Found C	H	N
10a	*n*-Hexyl	20	58	183 (Hexane)	$C_{19}H_{24}N_2O_3$	69.49 69.68	7.37 7.26	8.53 8.50
10b	Ph	16	55	179 (Xylene [a])	$C_{19}H_{16}N_2O_3$	71.24 71.44	5.03 5.27	8.74 8.81
10c	4-Me-Ph	15	66	207 (DMF)	$C_{20}H_{18}N_2O_3$	71.84 71.76	5.43 5.51	8.38 8.52
10d	CH_2Ph	20	48	136 (Xylene [a])	$C_{20}H_{18}N_2O_3$	71.84 72.02	5.43 5.20	8.38 8.29
10e	4-Cl-Ph	48	50	192 (Xylene)	$C_{19}H_{15}ClN_2O_3$	64.32 64.49	4.26 4.39	7.90 7.82
10f	3-CF_3-Ph	48	41	178 (DMF)	$C_{20}H_{15}F_3N_2O_3$	61.86 61.99	3.89 3.92	7.21 7.49
10g	4-OH-PO	16	89	208 (Xylene [a])	$C_{19}H_{16}N_2O_4$	67.85 67.88	4.80 4.73	8.33 8.27
10h	3-MeO-Ph	23	80	175 (Xylene)	$C_{20}H_{18}N_2O_4$	68.56 68.60	5.18 5.20	8.00 7.93
10i	2-NH_2-Ph	15	81	223 (Xylene)	$C_{19}H_{17}N_3O_3$	68.05 68.25	5.11 5.02	12.28 12.28
10j	2,4-Di-Cl-Ph	16	67	252 (DMF)	$C_{19}H_{14}Cl_2N_2O_3$	58.63 58.46	3.63 3.89	7.20 7.03
10k	2,5-Di-MeO-Ph	19	92	254 (DMF)	$C_{21}H_{20}N_2O_5$	66.31 66.44	5.30 5.65	7.36 7.57
10l	1-Naphthyl	16	78	224 (DMF)	$C_{23}H_{18}N_2O_3$	74.58 74.49	4.90 4.95	7.56 7.82
10m	1-Adamantyl	15	82	220 (Xylene)	$C_{23}H_{26}N_2O_3$	72.99 73.23	6.92 7.23	7.40 7.17
10n	2-Pyridyl	20	69	214 (Xylene [a])	$C_{18}H_{15}N_3O_3$	67.28 67.56	4.71 4.81	13.08 12.83
10o	2-Pyrimidyl	10	65	240 (DMF)	$C_{17}H_{14}N_4O_3$	63.35 63.01	4.38 4.49	17.28 17.53
10p	2-Thiazolyl	14	79	217 (DMF)	$C_{16}H_{13}N_3O_3S$	58.71 58.47	4.00 4.26	12.84 12.69
10q	3-Pyrazolyl	12	97	260 (Xylene)	$C_{16}H_{14}N_4O_3$	61.93 61.80	4.55 4.84	18.06 17.92
10r	2-(1,2,3-Thiadiazolyl)	18	46	286 (DMF)	$C_{15}H_{12}N_4O_3S$	54.87 54.54	3.68 3.70	17.06 16.98
10s	NMe_2	12	87	170 (Xylene [a])	$C_{15}H_{17}N_3O_3$	62.71 62.45	5.96 5.80	14.63 14.30
10t	NHPh	6	78	242 (DMF)	$C_{19}H_{17}N_3O_3$	68.05 68.35	5.11 5.07	12.53 12.76

[a] + Addition of Hexane.

ide): δ 1.45 (t, 3H, J = 7 Hz, CH_3), 2.10 (m, 2H, -CH_2-), 2.95 (t, 2H, J = 7 Hz, CH_2-Ar), 4.15 (t, 2H, J = 7 Hz, NCH_2), 4.5 (q, 2H, J = 7 Hz, OCH_2), 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 $C_{15}H_{15}NO_4$: C, 65.92; H, 5.53; N, 5.13. Found: C, 65.81; H, 557; N, 4.98.

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

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^{-1}; ^1H nmr (hexadeuteriodimethyl sulfoxide): δ 2.10 (m, 2H, J = 7 Hz, -CH_2-), 3.05 (t, 2H, J = 7 Hz, CH_2-Ar), 4.15 (m, 5H, NCH_2, OCH_3), 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 $C_{14}H_{13}NO_4$: 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 **5a-e**, and 2-Aminocarbonyl-1-hydroxy-3-oxo-6,7-dihydro-3*H*,5*H*-benzo[*ij*]quinolizinones **10a-t**.

The appropriate esters **3**, **8a,b** (5 mmoles) and amines **4a-e**, **9a-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-indolinyl)carboxamide (**6**) [7].

The mixture of **2a** (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 cm^{-1}.

Anal. Calcd. for $C_{28}H_{25}N_3O_3$: C, 74.48; H, 5.58; N, 9.31. Found: C, 74.43; H, 5.56; N, 9.10.

REFERENCES AND NOTES

[1] Th. Kappe and B. Schnell, *J. Heterocyclic Chem.*, **33**, 663 (1996); and literature cited therein.

[2] I. V. Ukrainets, O. V. Gorokhova, S. G. Taran and A. V. Turov, *Khim. Geterosikl. Soedin.*, **10**, 1397 (1994).

[3] I. V. Ukrainets, O. V. Gorokhova, S. G. Taran, P. A. Bezuglyi, N. I. Filimonova and A. V. Turov, *Khim. Geterosikl. Soedin.*, **10**, 1400 (1994).

[4] P. A. Bezuglyi, V. I. Treskach, I. V. Ukrainets, Yu. F. Krylov, M. Yu. Ladinskaya, N. P. Moryakov and E. G. Lobanova, *Khim.-Farm. Zh.*, **24**, 31 (1990); *Chem. Abstr.*, **7** 113, 7050j, (1990).

[5] W. von Deyn, H. Theobald, C. Nuebling, U. Kardorf, H. Walter, K.-O. Westphalen, Th. Kappe and M. Gerber, BASF AG., German offen., DE 4,138,820 (1993); *Chem. Abstr.*, **119**, 160140z (1993).

[6] K. Faber, H. Stückler and Th. Kappe, *J. Heterocyclic Chem.*, **21**, 1177 (1984); K. Faber and Th. Kappe, *J. Heterocyclic Chem.*, **21**, 1881 (1984); K. Faber, H. Steininger and Th. Kappe, *J. Heterocyclic Chem.*, **22**, 1081 (1985); Th. Kappe and H. Wildpanner, *Monatsh. Chem.*, **119**, 727 (1988); Th. Kappe and F. Frühwirth, *J. Prakt. Chem.*, **332**, 475 (1990).

[7] H. Kraxner, Ph. D. Thesis, University of Graz, 1982, pp 27-47.

[8] J. G. Lombardino and E. H. Wiseman, *J. Med. Chem.*, **15**, 848 (1972); J. G. Lombardino, E. H. Wiseman and J. Chianti, *J. Med. Chem.*, **16**, 493 (1973); E. H. Wiseman, Y. H. Chang and J. G. Lombardino, *Arzneimittel-Forsch.*, **26**, 1300 (1976); J. G. Lombardino, E. H. Wiseman and W. M. McLamore, *J. Med. Chem.*, **14**, 1171 (1971); J. Chianti, E. H. Wiseman and J. G. Lombardino, *J. Med. Chem.* **14**, 1175 (1971); H. Zinnes, N. A. Lindo, F. R. Zuleski, A. N. Caro and J. Shavel, *J. Org. Chem.*, **30**, 2241 (1965); H. Zinnes, N. A. Lindo, J. C. Sircar, M. L. Schwartz and J. Shavel, *J. Med. Chem.*, **16**, 44 (1973); C. R. Rasmussen and D. L. Shaw, *J. Org. Chem.*, **39**, 1560 (1974); T. J. Carty, J. D. Eskra, J. G. Lombardino and W. W. Hoffman, *Prostaglandins*, **19**, 51 (1980); R. N. Brogden, G. S. Avery, R. C. Heel and T. M. Speight, *Drugs*, **22**, 165 (1981), **28**, 292 (1984); G. DiPasquale, C. Rassaert, R. Richter, P. Welaj, J. Gingold and R. Singer, *Agents Actions*, **5**, 256 (1975); **6**, 748 (1976); G. DiPasquale and D. Mellace, *Agents Actions*, **7**, 481 (1977); G. DiPasquale, C. Rassaert, P. Welaj, J. Gingold and E. Schwartz, *Res. Commun. Chem. Pharm. Pharmacol.*, **19**, 529 (1978); E. U. Kölle, H. Hengy and K. O. Vollmer, *Arzneimittel-Forsch.*, **33**, 582 (1983).

[9] R. Richter and H. Ulrich, *J. Org. Chem.*, **44**, 4877 (1979).

[10] G. M. Coppola and G. E. Hardtmann, *J. Heterocyclic Chem.*, **16**, 1605, (1979); L. A. Mitscher, G. W. Clark, T. Suzuki and M. S Bathalia, *Heterocycles*, **3**, 913 (1979); Th. Kappe and W. Stadlbauer, *Adv. Heterocyclic Chem.*, **28**, 127 (1981).

[11] G. Koller, *Chem. Ber.*, **60**, 1110 (1927); A. F. A. Khattab, Ph. D. Thesis, Menoufeia University, Egypt, 1990; S. Prattes, Diploma Thesis, University of Graz, 1996.

[12] I. V. Ukrainets, P. A. Bezuglyi, V. I. Treskach, A. V. Turov and S. V. Bodzyan, *Khim. Geterotsick. Soedin.*, **5**, 636 and 640 (1990).

[13] Th. Kappe and C. Kos, *Synthesis*, 629 (1989); C. Kos, Ph. D. Thesis, University of Graz, 1985.

[14] M. Jöbstl, Ph. D. Thesis, University of Graz, 1984.

[15] Th. Kappe, G. Baxevanidis and E. Ziegler, *Monatsh. Chem.*, **102**, 1392 (1971).

[16] P. E. Hansen, S. Bolvig and Th. Kappe, *J. Chem. Soc., Perkin Trans. 2*, 1901 (1995).

[17] H. Lund and A. Voigt, *Organic Synthesis, Coll. Vol.* **2**, 594; B. B. Corson and J. L. Sayre, *Organic Synthesis, Coll. Vol.* **2**, 596 (1943); G. R. Newkome and G. R. Baker, *Org. Prep. Proced. Int.*, **18**, 117 (1986).