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A NEW PATHWAY TO 1,3,4(2H)-ISOQUINOLINETRIONES AND SUBSTITUTED ISOINDOLINONES

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Abstract—A new synthesis in the isoquinoline series is discussed: the reaction of appropriate benzamides and oxalyl chloride affords isoquinolinetriones along N-aroyloxamoyl chlorides. The solvent effect, the acid catalysis and the isomer distribution are accounted for. On the other hand 1 - hydroxy - 3 - oxoisoindoline - 1 - carboxylates may be obtained by acid-catalyzed ring closure of N-aroyloxamates. Both cyclizations require an activating group.

Because of our interest in the preparation of isoquinoline derivatives related to natural alkaloids, we looked for a synthesis of versatile isoquinoline compounds. According to their approach, the large number of isoquinoline syntheses may be divided into four groups as visualized in Scheme 1. A first group (type a) contains modifications of bicyclic compounds: transformation of isocoumarines,[1] ring expansion of indenones,[2] indanone oximes[3] or phtalimides[4] and especially interconversions within the isoquinoline series.[5] In an approach of type b, substituted benzene derivatives incorporating both ring junctions are needed.[6] The Bischler–Napieralski[7] and the Pictet–Spengler[8] reactions, leading to 3,4-dihydro- respectively 1,2,3,4-tetrahydroisoquinolines, are typical representatives for group c. The Pomeranz–Fritsch reaction[9] and Bobbitt's modification[10] are very important ring closure reactions of group d. This group also includes some photochemical preparations of isoquinoline derivatives.[11,12]

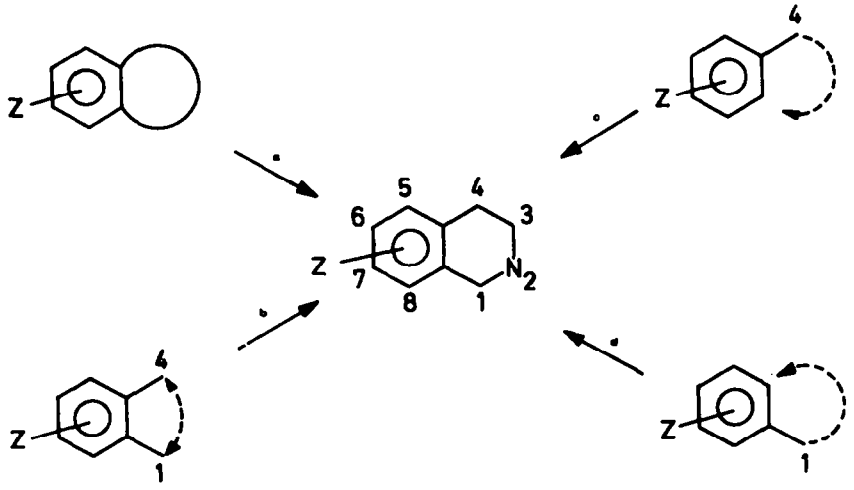
The predominant occurrence in nature of 6,7- and 7,8-dialkoxy-substituted isoquinoline alkaloids[13] and the difficult accessibility of precursors needed for ways a and b, made an approach of type d strongly preferable. Regarding the difficulties on preparing 1,4-dihydro-3(2H)- and 1,3-dihydro-4(2H)-isoquinolinones[14] and taking into account the necessity of further functionalization, 3,4(1H, 2H)-isoquinolinediones or 1,3,4(2H)-isoquinolinetriones became our products of choice.

In contrast with the synthesis of isatine from 2 - hydroxyimino - N - phenylacetamide,[15] no cyclization of hydroxyimino derivative **1** could be realized (Scheme 2). Friedel-Crafts reaction of N - 3 - methoxybenzyl - N - methyloxamoyl chloride (**2**) leads to the isoquinolinetriones **3a** and **3b** in poor yield. The latter probably result from an oxidation of the expected 3,4(1H, 2H)-isoquinolinediones; a comparable oxidation of 1,4-dihydro-3(2H)-isoquinolinones is observed.[16,17]

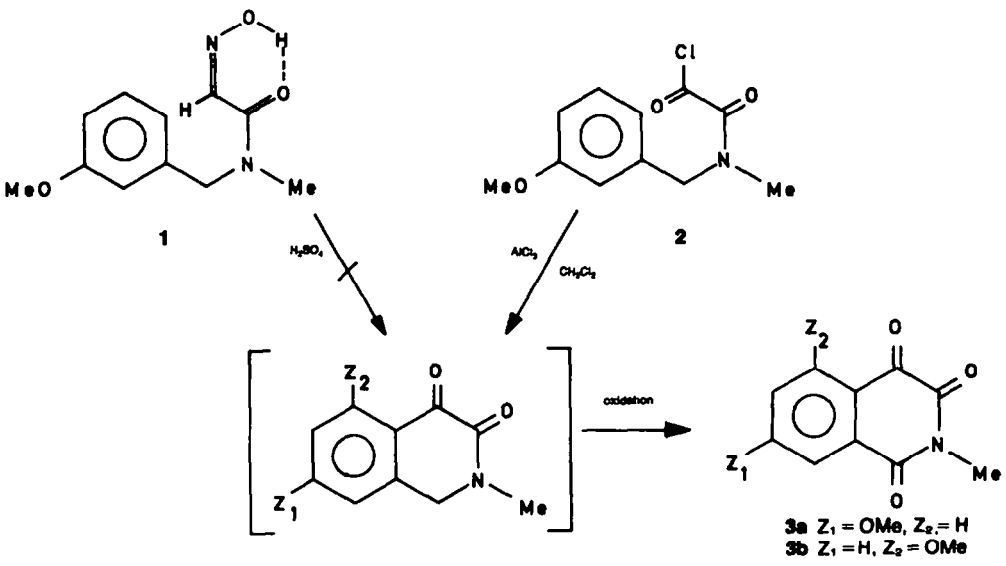
As the CO group at position 4 turned out to be very reactive, allowing further functionalization,[18] we directed our attention to the synthesis of 1,3,4(2H)-isoquinolinetriones. These compounds are only known as oxidation products of other isoquinoline derivatives.[16,17,19]

As shown in Table 1, action of oxalyl chloride on the secondary benzamides **4–13** in an appropriate solvent at 60° in most cases leads to N-aroyloxamoyl chlorides. These isolable intermediates may undergo cyclization on raising the temperature.

From Table 1 it is obvious that our synthetic method, which is characterized by very simple reactants and performance, also has some limitations. Starting from the commercial benzoic acids, the overall yields of isoquinolinetriones **3**, **14–18** vary from 20 to 80%. The method is limited to alkoxy-substituted N-alkylisoquinolinetriones, but fortunately in nature almost only alkoxy-substituted isoquinoline derivatives are found.

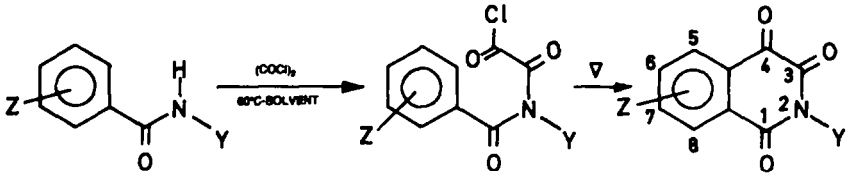


Scheme 1.



Scheme 2.

Table 1. 1,3,4(2H)-Isoquinolinetriones from benzamides and oxalyl chloride



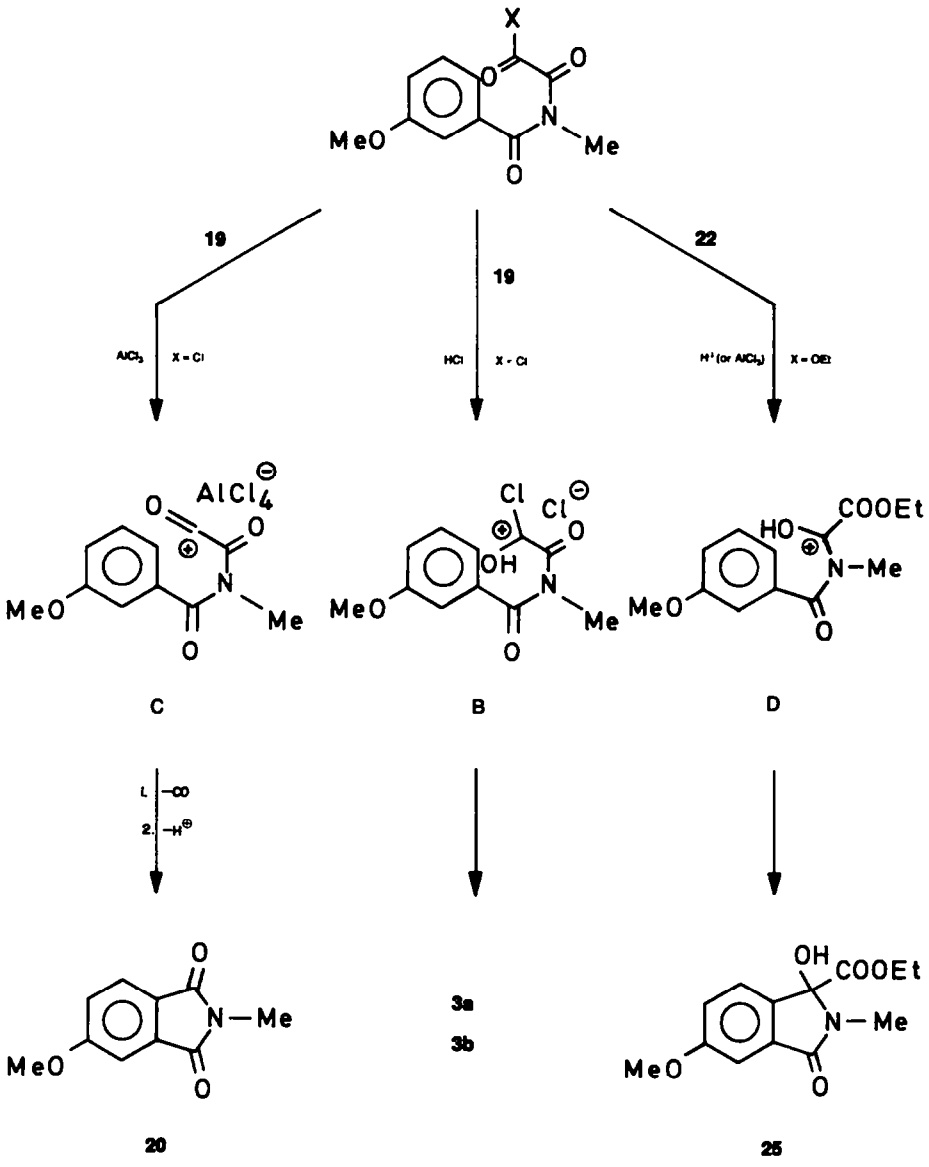
4-13 3, 14-18

No.	benzamide Z	Y	solvent	temp. °C	time hr	isoquinolinetrione No.	yield[a] %	ortho/para
4	3-OMe	Me	decaline	190	4	3	25	0.10
			ODCB[b]	180	2		41	0.11
			ODCB	150	4		72	0.12
			$C_6H_5NO_2$	135	2		74	0.16
			sulfolane	110	4		90	0.80
			no	120	1		74	0.25
5	H	Me	sulfolane	180	6		0	-
6	3-Me	Me	$C_6H_5NO_2$	200	4		0	-
7	2,3-diOMe	Me	$C_6H_5NO_2$	135	4	14	39	-
8	3,4-OCH_2O	Me	ODCB	175	6	15	17	0.17
			$C_6H_5NO_2$	140	6		26	0.24
			sulfolane	125	4		25	0.56
9	3,5-diOMe	Me	ODCB	85	2	16	96	-
10	3,4,5-triOMe	Me	ODCB	85	2	17	97	-
11	3-OMe	t.Bu					-[c]	
12	3-OMe	COOEt					-[c]	
13	3-OMe	CH_2COOEt	ODCB	180	8	18	46	0.11
			no	140	2		73	0.20

a. the yield is calculated with regard to the benzamide

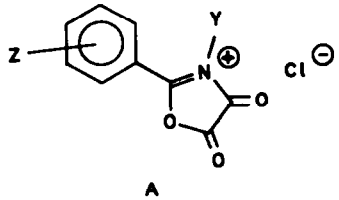
b. ODCB = ortho-dichlorobenzene

c. no oxamoyl chloride is formed



Scheme 3.

According to literature data[20] O-acylated amides may rearrange to oxamoyl derivatives along a cyclic intermediate such as A; however if Y represents a H atom, an acyl isocyanate results.[21] We also have observed the formation of isocyanate for Y = t-Bu. On the other hand N-carbethoxy derivative **12** fails to react with oxalyl chloride in comparable circumstances. Nevertheless the cyclization is not restricted to N-Me derivatives: also an N-carbethoxymethyl group has been introduced. Qualitative experiments have shown that N-phenyl- and N - cyclohexyl - 1,3,4(2H) - isoquinolinetriones arise in the same conditions.



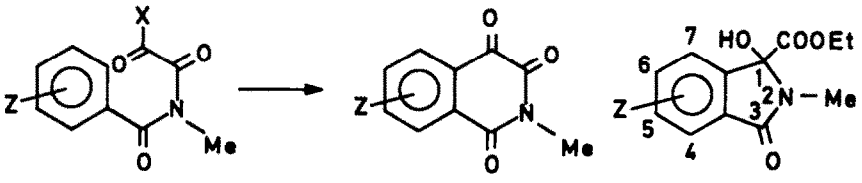
A

At all events a high yield of isoquinolinetrione is connected with a low reaction temperature: on heating oxamoyl chlorides, especially above 140°, we have noticed decomposition into benzonitriles, probably along benzoyl isocyanates.[22] This explains the almost quantitative formation of triones **16** and **17** starting from amides **9** and **10** and the decomposition, instead of cyclization, of the oxamoyl chlorides derived from **5** and **6**.

In order to account for the enhanced reactivity in more polar solvents and for the increased *ortho*:*para* ratio on changing the solvent from decaline to sulfolane, we suggest for this cyclization reaction an ion of type B as "reactive species" rather than an acylium ion (Scheme 3). If *ortho*-dichlorobenzene (ODCB) is replaced by a more polar solvent, probably ion pairing is reduced; this may result in a more reactive and less selective species, which favours the formation of the *ortho*-isomer.

The catalytic effect of hydrogen chloride is reasonable because cyclization of **19** proceeds faster in the presence of trifluoromethanesulfonic acid or in polyphosphoric acid (PPA) as shown in Table 2. With aluminum chloride

Table 2. Effect of the catalyst and of substituent X on the course of the cyclization



Z	X
19 3-OMe	Cl
21 3-OMe	Br
22 3-OMe	OEt
23 2,3-diOMe	OEt
24 3,5-diOMe	OEt

Z
3a 7-OMe
3b 5-OMe
14 7,8-diOMe
16 5,7-diOMe

Z
25 5-OMe
26 4,5-diOMe
27 5,7-diOMe

oxamoyl deriv. No.	solvent	temp. °C	catalyst	time hr	isoquinoline-trione No.	isoquinoline-trione yield(%)	isoindolinone No.	isoindolinone yield %
19	ODCB	70	CF_3SO_3H	6	3	58	-	
	PPA	50	PPA	4	3	35	-	
	CH_2Cl_2	0	$AlCl_3$	12	- [a]		-	
21	CCl_4	77	—	4	3	41	-	
22	ODCB	180	—	4	-		-	
	PPA	50	PPA	2	3	5	25 [b]	75
	CH_2Cl_2	25	$AlCl_3$	2	3	< 1	25 [b]	56
23	PPA	70	PPA	2	14	1	26	12
	CH_2Cl_2	25	$AlCl_3$	8	14	< 1	26	33
24	PPA	25	PPA	1	16	47	27	51
	CH_2Cl_2	-10	$AlCl_3$	2	16	3	27	76

a : 33% 5-methoxy-2-methyl-1H-isoindole-1,3(2H)-dione(20) is isolated with identical characteristics as described[23].

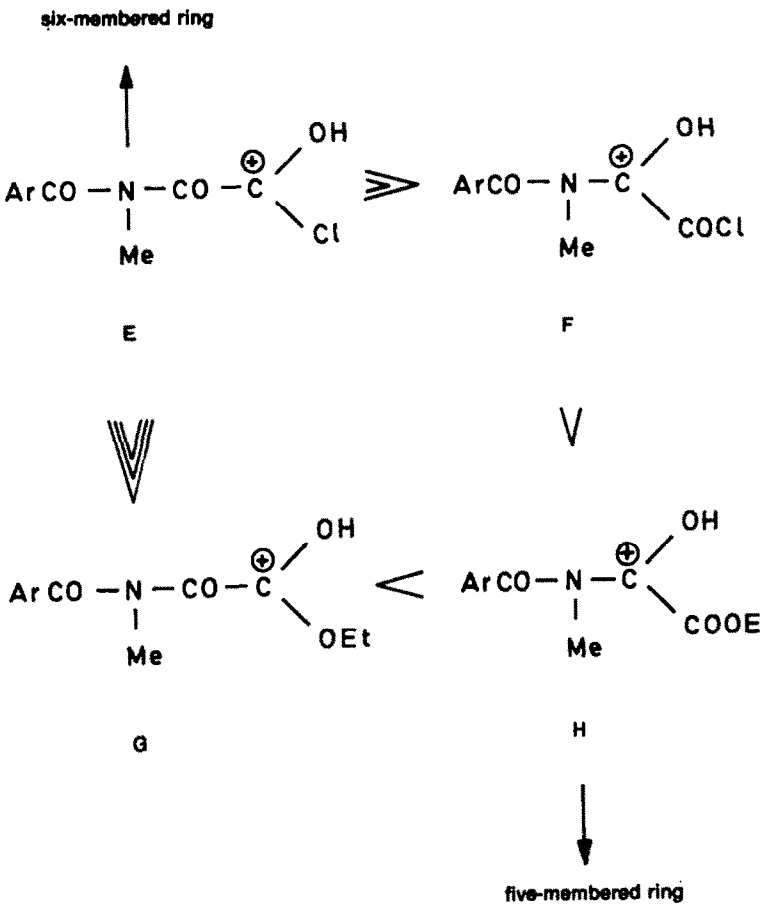
b : no trace of the ortho-isomer is observed.

the reaction of **19** proceeds at low temperature but probably is going through acylium intermediate C (Scheme 3). On losing carbon monoxide, a very selective intermediate is formed which leads to phtalimide **20** as the sole cyclization product. As mentioned earlier N-3-methoxybenzyl derivative **2** is partially transformed into isoquinolinetrione **3** in the presence of aluminum chloride: this is apparently due to its more reactive benzene nucleus.

In another series of experiments (Table 2) we investigated the influence of a change of substituent X on the course of the reaction. Radicalar cleavage of the oxamoyl bromide **21** is responsible for the lower yield in spite of the low reaction temperature. With **22–24** (X=OEt) no cyclization occurs without the addition of a catalyst; in PPA smaller quantities of isoquinolinetriones **3**, **14** and **16** are formed, but the major cyclization products prove to be the isoindolinones **25–27**. From Table 2 it is obvious that the preference for 5-membered ring formation is more pronounced with aluminum chloride than with PPA. It is remarkable that no *ortho*-isomer of isoindolinone **25** is formed; apparently steric factors have a greater impact here than in the reaction of oxamoyl chlorides to isoquinolinetriones. The isoindolinones probably arise from an ion of type D (Scheme 3). The ring size of the cyclization products may be related to the electrophilicity of the proposed intermediates E–H (Scheme 4). E is more electrophilic than F: this can account for 6-membered ring formation with oxamoyl chlorides. In contrast with the presumed 6-membered ring intermediates E and G, the electrophilicity of the 5-membered ring intermediates F and H is only slightly affected by substituent X: so intermediate H intervenes more in cyclization than intermediate G.

So we can conclude that $AlCl_3$-catalyzed cyclization of alkoxy-activated ethyl N-aroyloxamates leads almost exclusively to ethyl 1 - hydroxy - 3 - oxoisoindoline - 1 - carboxylates, whereas only traces of 6-membered ring compounds are formed.

N-aroyloxamoyl chlorides on the contrary lose CO in the presence of $AlCl_3$ but turn out to be excellent precursors in the ring closure-without the addition of a catalyst- to alkoxy-substituted 1,3,4(2H)-isoquinolinetroines. On changing the solvent system, the isomer distribution varies: in the very polar sulfolane the *ortho*:*para* ratio approaches 1, while in ODCB, a



Scheme 4.

solvent allowing an easy work-up, the *para*-isomer strongly predominates. The separation of the isomers *a* and *b* can easily be achieved by chromatography on silica gel. The ability to prepare also considerable amounts of the *ortho*-isomer, means that our synthetic method offers the possibility to obtain all substitution patterns on the benzene nucleus if sufficiently activated.

EXPERIMENTAL

All m.ps are uncorrected. UV spectra have been recorded with a Perkin Elmer 124 and IR spectra with a Perkin Elmer 257 spectrophotometer. Mass spectra have been taken on a AEI-MS-12 (ionization energy: 70 eV) and NMR spectra on a Varian XL-100 or a Jeol JNM-MH-100 spectrometer.

(A) *Substituted benzamides*

Most benzamides result from the reaction of an aroyl chloride on a cooled solution of a primary amine according to known procedures.[24] Depending on the solubility of these benzamides, the reactions are carried out in diethyl ether (**4–7, 10, 11, 13**) or in CH_2Cl_2 (**8, 9**). In contrast with a procedure for comparable substances,[25] urethane **12** is formed in good yield only if the disodium salt of urethane is allowed to react at low temperature with the acid chloride.

N-Methyl-3-methoxybenzamide (**4**)[24,26] yield: 95%; m.p.: 65°(CCl_4); ν_{max}($CHCl_3$)cm^{-1}: 3480, 3340(NH), 1665, 1530 (CONH); δ($CDCl_3$): 2.93(3H, d, J = 5 Hz, NMe), 3.76 (3H, s, OMe), 7.00 (1H, dxtr, J = 8 × 2 Hz, 4–H), 7.15 (1H, broad, NH), 7.35 (2H, m, 2–H, 5–H), 7.40 (1H, d × tr, J = 8 × 2 Hz, 6–H).

N-Methylbenzamide (**5**), yield: 82.5%; m.p.: 79° (CCl_4); ν_{max} ($CHCl_3$)cm^{-1}: 3480, 3340 (NH), 1655, 1535 (CONH); δ($CDCl_3$): 2.88 (3H, d, J = 5 Hz, NMe), 7.3 (3H, m, 3–H, 4–H, 5–H), 7.5 (1H, broad, NH), 7.78 (2H, d × d, J = 8 × 2 Hz, 2–H, 6–H).

N-Methyl-3-methylbenzamide (**6**), yield: 91%; m.p.: 45° (CCl_4); ν_{max}($CHCl_3$)cm^{-1}: 3460, 3350(NH), 1660, 1530 (CONH); δ($CDCl_3$): 2.25(3H, s, ArMe), 2.89 (3H, d, J = 5 Hz, NMe), 7.20 (2H, m, 4–H, 5–H), 7.6 (2H, m, 2-H, 6-H), 7.6 (1H, broad, NH).

N-methyl-2,3-dimethoxybenzamide (**7**), yield: 97%; m.p.: 80° (CCl_4); ν_{max} ($CHCl_3$) cm^{-1}: 3400 (NH), 1660, 1540 (CONH); δ($CDCl_3$): 2.97 (3H, d, J = 5 Hz, NMe), 3.85 (3H, s, OMe), 3.86 (3H, s, OMe), 7.01 (1H, d × d, J = 8 × 2 Hz, 4–H), 7.10 (1H, tr, J = 8 Hz, 5–H), 7.65 (1H, d × d, J = 8 × 2 Hz, 6–H), 7.9 (1H, broad, NH).

N-Methyl - 1,3 - benzodioxole - 5 - carboxamide (**8**),[27] yield: 95%; m.p.: 135° ($CHCl_3$); ν_{max}($CHCl_3$)cm^{-1}: 3480, 3340 (NH), 1660, 1530 (CONH); δ($CDCl_3$): 2.94 (3H, d, J = 5 Hz, NMe), 5.97 (2H, s, OCH_2O), 6.73 (1H, d, J = 9 Hz, 5–H), 6.8 (1H, broad, NH), 7.3 (2H, m, 2–H, 6–H).

N-Methyl-3,5-dimethoxybenzamide (**9**), yield: 91%; m.p.: 117° ($CHCl_3$); ν_{max}($CHCl_3$)cm^{-1}: 3460, 3340 (NH), 1665, 1525 (CONH); δ($CDCl_3$): 2.92 (3H, d, J = 5 Hz, NMe), 3.78 (6H, s, 3–OMe, 5–OMe), 6.56 (1H, tr, J = 2.5 Hz, 4–H), 6.7 (1H, broad, NM), 6.92 (2H, d, J = 2.5 Hz, 2–H, 6–H).

N-Methyl-3,4,5-trimethoxybenzamide (**10**),[28] yield: 84%; m.p.: 138° (CCl_4); ν_{max}($CHCl_3$)cm^{-1}: 3460, 3350 (NH), 1660, 1530 (CONH); δ($CDCl_3$): 2.91 (3H, d, J = 5 Hz, NMe), 3.77 (6H, s, 3–OMe, 5–OMe), 3.83 (3H, s, 4–OMe), 7.10 (2H, s, 2–H, 6–H), 7.5 (1H, broad, NH).

N-t-butyl-3-methoxybenzamide (**11**), yield: 82%; m.p.: 106°

(CCl_4); $\nu_{max}(CHCl_3)cm^{-1}$: 3420, 3320 (NH), 1650, 1505 (CONH); $\delta(CDCl_3)$: 1.46 (9H, s, Nt, Bu), 3.80 (3H, s, OMe), 6.2 (1H, broad, NH), 6.95 (1H, m, 4–H), 7.23 (3H, m, 2–H, 5–H, 6–H).

Ethyl N-3-*methoxybenzoylcarbamate* (12), yield: 68%; m.p.: 74° (CCl_4); $\nu_{max}(CHCl_3)cm^{-1}$: 3430, 3300 (NH), 1785 (COOEt), 1715 (CONH); $\delta(CDCl_3)$: 1.26 (3H, tr, J = 7 Hz, ester), 3.77 (3H, s, OMe), 4.20 (2H, q, J = 7 Hz, ester), 7.02 (1H, d × tr, J = 8 × 2 Hz, 4–H), 7.29 (1H, tr, J = 8 Hz, 5–H), 7.4 (2H, m, 2–H, 6–H), 8.8 (1H, s, NH).

Ethyl N-3-*methoxybenzoylglycinate* (13), yield: 72%; oil; $\nu_{max}(CHCl_3)cm^{-1}$: 3440, 3370 (NH), 1735 (COOEt), 1660, 1515 (CONH); $\delta(CDCl_3)$: 1.30 (3H, tr, J = 7 Hz, ester), 3.83 (3H, s, OMe), 4.21 (2H, d, J = 5 Hz, NCH_2), 4.25 (2H, q, J = 7 Hz, ester), 6.95 (1H, broad, NH), 7.00 (1H, d × tr, J = 8 × 2 Hz, 4–H), 7.3–7.4 (3H, m, 2–H, 5–H, 6–H).

(B) *Oxamoyl derivatives*

N-3-Methoxybenzyl-N-methyloxamoyl chloride (2)—(a) N-*methyl-3-methoxybenzylamine* (28). A hot soln of 4 (20.5 g, 0.124 mole) in 150 ml dry benzene was treated with LAH (8.0 g, 0.21 mole) in small portions. The mixture was further refluxed during 4 hr. After cooling, 8 g water was added dropwise, followed by 25 ml of 15% NaOH aq. The organic layer was isolated, while the aqueous suspension was extracted with CH_2Cl_2. The combined organic layers were treated with 4 M HCl (125 ml) and to the separated aqueous phase was added 40 g solid NaOH at 0°. Finally a new extraction with CH_2Cl_2 and evaporation of the solvent under reduced pressure, gave 16.5 g of a slightly yellow liquid, characterized as the expected amine 28. $\nu_{max}(CHCl_3)cm^{-1}$: 1615, 1605, 1595, 1585 (C–N, C=C); $\delta(CDCl_3)$: 1.94 (1H, broad, NH), 2.41 (3H, s, NMe), 3.62 (2H, s, CH_2), 3.73 (3H, s, OMe), 6.85 (3H, m, 2–H, 4–H, 6–H), 7.26 (1H, tr, J = 8 Hz, 5–H).

(b) N-*Methyl-3-methoxybenzylammonium chloride* (29). The amine 28 was dissolved in 150 ml dry ether. A white solid precipitated by conducting gaseous dry HCl through the soln. After suction filtration, washing with dry ether and drying 17.5 g 29 (m.p. 126°) was left. The yield, calculated from amide 4, was 76%.

(c) N-3-*Methoxybenzyl*-N-*methyloxamoyl chloride* (2). In a 100 ml flask equipped with a $CaCl_2$-drying-tube, a magnetic stirrer and a reflux condenser, 29 (9.37 g; 0.05 mole), oxalyl chloride (21.5 ml; 0.25 mole) and 45 ml CCl_4 were mixed. On warming and stirring HCl was liberated and a clear soln resulted. The reaction was complete after refluxing for 2 hr. The excess oxalyl chloride was removed under reduced pressure. The residual slightly yellow oil had all characteristics of the desired compound 2. $\nu_{max}(CCl_4)cm^{-1}$: 1780, 1680 (C=O); $\delta(CCl_4)$: 2.80 and 2.85 (3H, s, NMe), 3.76 (3H, s, OMe), 4.36 and 4.49 (2H, s, CH_2), 6.8 (3H, m, 2–H, 4–H, 6–H), 7.20 (1H, tr × d, J = 8 × 2 Hz, 5–H). Due to hindered rotation around the amidic bond, 2 isomers were visible in the NMR spectrum. *Remark*: In contrast with salt 29, the free base 28 invariably reacted with oxalyl chloride to the symmetrical N,N' - dimethyl - N,N' - di - 3 - methoxybenzyloxamide.[29]

N-3-*Methoxybenzoyl*-N-*methyloxamoyl chloride* (19). Solid 4 (20 g; 0.12 mole) was added in small portions to a warm soln of oxalyl chloride (17 ml; 0.20 mole) in 135 ml CCl_4. When the liberation of HCl ceased, the soln was refluxed during 1 hr. Removal of the excess oxalyl chloride and the solvent *in vacuo* yielded 30 g of 19 (96%). The slightly yellow product, which crystallized on standing, had consistent IR and NMR spectra. $\nu_{max}(CCl_4)cm^{-1}$: 1840, 1770, 1720 (C=O); $\delta(CCl_4)$: 3.03 (3H, s, NMe), 3.85 (3H, s, OMe), 7.0–7.5 (4H, m, aryl).

Ethyl N-3-*methoxybenzoyl*-N-*methyloxamate* (22). To a suspension of 4 (8.25 g; 0.05 mole) in 80 ml CCl_4 was added ethyl chlorooxoacetate (10.2 g; 0.075 mole). The temp was raised. After 4 hr of reflux the solvent and the excess ethyl chlorooxoacetate were removed *in vacuo*. The crude residue was purified over silica gel using CCl_4–EtOAc-mixtures. 22 was obtained in almost quantitative yield (13.0 g 98%). $\nu_{max}(CHCl_3)cm^{-1}$: 1750, 1715, 1675 (C=O); *m/e* 265 (M^+, 25%), 192 (2%), 135 (100%); $\delta(CDCl_3)$: 1.21 (3H, tr, J = 7 Hz, ester), 3.26 (3H, s, NMe), 3.83 (3H, s, OMe), 4.13 (2H, q, J = 7 Hz, ester), 7.05–7.5 (4H, m, aryl).

Ethyl N-2,3-*dimethoxybenzoyl*-N-*methyloxamate* (23). 23 was prepared from 7 in the same way as 22. $\nu_{max}(CHCl_3)cm^{-1}$: 1750, 1715, 1670 (C=O); *m/e* 295 (M^+, 17%), 222 (2%), 165 (100%); $\delta(CDCl_3)$: 1.33 (3H, tr, J = 7 Hz, ester), 3.16 (3H, s, NMe), 3.88 (3H, s, OMe), 3.90 (3H, s, OMe), 4.25 (2H, q, J = 7 Hz, ester), 6.85–7.20 (3H, m, aryl).

Ethyl N-3,5-*dimethoxybenzoyl*-N-*methyloxamate* (24). 24 was prepared from 9 in the same way as 22. $\nu_{max}(CHCl_3)cm^{-1}$: 1750, 1715, 1675 (C=O); *m/e* 295 (M^+, 20%), 222 (1%), 165 (100%); $\delta(CDCl_3)$: 1.24 (3H, tr, J = 7 Hz, ester), 3.30 (3H, s, NMe), 3.85 (6H, s, OMe), 4.15 (2H, q, J = 7 Hz, ester), 6.62 (1H, tr, J = 2 Hz, 4–H), 6.73 (2H, d, J = 2 Hz, 2–H, 6–H).

(C) *Isoquinolinetriones*

7-Methoxy- and 7 - methoxy - 2 - methyl - 1,3,4(2H) - isoquinolinetrione (3a *and* 3b)—*Method a* (*Starting from the isolated* 19). If no solvent was used or a catalyst had to be added (CF_3SO_3H, $AlCl_3$, PPA) the oxamoyl chloride had to be isolated. For example, 19 (5.11 g; 0.02 mole) was heated without solvent at 120°. HCl was formed and removed under reduced pressure. According to IR spectra (disappearance of 1840 and 1780 cm^{-1} peaks, appearance of 1730 and 1685 cm^{-1} peaks), the reaction was complete after 1 hr. The crude mixture (4.1 g) was chromatographed over silica gel. Using a gradient from CCl_4 to $CHCl_3$ the major product (3a) was eluted first; 3b was the more polar minor product. After crystallization from AcOH 3a (2.58 g; 59%) and 3b (0.66 g; 15%) 3b were obtained.

Method b (*directly starting from the amide* 4). To a warm stirred mixture of oxalyl chloride (106 ml; 1.25 mole) in 700 ml ODCB was added dropwise a soln of 4 (165 g; 1 mole) in 1000 ml ODCB. The temp. was kept at 60° until the formation of HCl ceased. Then the temp. was raised to 140–150°. The progress of the reaction was followed by IR spectroscopy. When the reaction was complete (± 4 hr), the dark red soln was allowed to cool, and afforded crystallization of the major compound (3a). The ppt was isolated by suction filtration, washed with ODCB and CCl_4 and chromatographed quickly over silica gel with $CHCl_3$. In this way 125 g very pure 3a was obtained. The mother liquor was evaporated under reduced pressure. The residue was chromatographed over silica gel, using CCl_4–$CHCl_3$ mixtures. After evaporation of the fractions containing cyclization product and after crystallization from AcOH another 15 g of 3a and also 17.5 g 3b were isolated. The total yield of the *para*-isomer (3a) was 140 g (64%) and of the *ortho*-isomer (3b) 17.5 g (8%). 3a: (Found: C, 60.30; H, 4.09; N, 6.39. $C_{11}H_9NO_4$ requires: C, 60.28; H, 4.14; N, 6.39%); *m/e* 219 (M^+, 31%), 191 (100%); exact mass: 219.051 ± 0.002, calculated 219.0531. 3b: (Found: C, 60.32; H, 4.14; N, 6.36. $C_{11}H_9NO_4$ requires: C, 60.28; H, 4.14; N, 6.39%); *m/e* 219 (M^+, 47%), 134 (100%); exact mass: 219.052 ± 0.002, calculated: 219.0531. Other physical constants are collected in Table 3.

Other isoquinolinetriones. Apart from 18 the other isoquinolinetriones are prepared according to method b. Unless otherwise stated the following standard procedure was used: (1) a soln of 0.05 mole of a benzamide in 50 ml ODCB was added to a mixture of 0.0625 mole (5.3 ml) oxalyl chloride and 35 ml of the same solvent at 60°; (2) when no further formation of HCl was observed, the temp. was raised in order to accomplish cyclization; (3) at the end of the reaction the solvent was removed under reduced pressure, the chromatographic separation was carried out on silica gel with $CHCl_3$–MeCN (9:1) (v:v) as eluens and the important fractions were evaporated. Most physical constants are collected in Table 3.

7,8 - Dimethoxy - 2 - methyl - 1,3,4(2H) - isoquinolinetrione (14). The cyclization was realized on heating at 165° during 4 hr. After chromatography and crystallization from AcOH, 14 (4.5 g; 36%) was obtained. (Found: C, 57.62; H, 4.38; N, 5.60. $C_{12}H_{11}NO_5$ requires: C, 57.83; H, 4.45; N, 5.62%); *m/e* 249 (M^+, 100%) exact mass: 249.062 ± 0.002, calculated: 249.0637.

6 - Methyl - 1,3 - dioxolo[4,5-g]isoquinoline - 5,7,8(6H) - trione (15a) *and 7 - methyl - 1,3 - dioxolo[4,5 - f]isoquinoline - 6,8,9(7H) - trione* (15b). The reaction was carried out in nitrobenzene. The cyclization was complete after 6 hr at 140°. Column chromatography resulted in 2 important fractions, which after evaporation and crystallization from $CHCl_3$ gave 2.45 g (21%) 15a and 0.55 g

Table 3. Physical constants of the prepared 1,3,4(2H)-isoquinolinetriones

no.	IR ($CHCl_3$)(cm^{-1}) C=O	C=C	UV (EtOH) λ_{max} in nm	m.p. °C	hR_f [a]
3a	1735,1700,1685	1601	350	175	29
3b	1734,1700,1684	1596	374	190	12
14	1731,1704,1688	1579	360	200	14
15a[17]	1732,1701,1682	1610,1598	378	232	25
15b	1730,1709,1683	1625,1598	400	265	16
16	1734,1694,1683	1606,1574	375	267	08
17	1730,1695,1680	1620,1585	349	210	14
18a	1740,1734,1694	1596	350	150	32
18b	1746,1736,1688	1594	374	166	15

a : stationary phase : silica gel;mobile phase : $CHCl_3$-MeCN (9:1)(v:v)

no.	NMR ($CDCl_3$) (δ in ppm) 5-H	6-H	7-H	8-H	$-OCH_2O-$	OMe	NMe
3a	8.17(d) 8.5Hz	7.29(dxd) 8.5x2.5Hz	—	7.75(d) 2.5Hz	—	4.00(s)	3.45(s)
3b	—	7.36(dxd) 8x2Hz	7.85(tr) 8Hz	7.99(dxd) 8x2Hz	—	4.03(s)	3.43(s)
14	8.07(d) 8.5Hz	7.30(d) 8.5Hz	—	—	—	3.98(s) 4.05(s)	3.44(s)
15a[17]	7.73(s) (or 7.58)	—	—	7.58(s) (or 7.73)	6.25(s)	—	3.45(s)
15b	—	—	7.25(d) 8Hz	8.02(d) 8Hz	6.38(s)	—	3.45(s)
16	—	6.80(d) 2.5Hz	—	7.56(d) 2.5Hz	—	4.02(s) (6H)	3.45(s)
17	—	—	—	7.68(s)	—	3.95(s) 3.97(s) 4.07(s)	3.43(s)
18a	8.20(d) 8.5Hz	7.31(dxd) 8.5x2.5Hz	—	7.75(d) 2.5Hz	—	4.02(s)	— [b]
18b	—	7.38(dxd) 8x2Hz	7.86(tr) 8Hz	8.00(dxd) 8x2Hz	—	4.04(s)	— [c]

b :18a also : 1.29(3H,tr,J=7Hz,ester), 4.24(2H,9,J=7Hz,ester), 4.78(2H,s,NCH_2)

c :18b also : 1.29(3H,tr,J=7Hz,ester), 4.24(2H,9,J=7Hz,ester), 4.77(2H,s,NCH_2)

(5%) **15b**. **15a**: (Found: C, 56.81; H, 3.13; N, 5.90. $C_{11}H_7NO_5$ requires: C, 56.66; H, 3.03; N, 6.01%); *m/e* 233 (M^+, 91%), 148 (100%); exact mass: 233.031 ± 0.002, calculated: 233.0324. **15b**: (Found: C, 56.38; H, 3.20; N, 5.93. $C_{11}H_7NO_5$ requires: C, 56.66; H, 3.03; N, 6.01%); *m/e* 233 (M^+, 100%); exact mass 233.030 ± 0.002, calculated: 233.0324.

5,7 - *dimethoxy* - 2 - *methyl* - 1,3,4(2H) - *isoquinolinetrione* (**16**). Solid **9** was added in small portions to a soln. of 5.3 ml oxalyl chloride in 85 ml ODCB at 60°. The cyclization took place at 85°: the reaction product precipitated. After 2 hr the suspension was cooled and filtered. Crystallization of the residue from AcOH yielded **16** (11.9 g; 96%). (Found: C, 57.57; H, 4.32; N, 6.57. $C_{12}H_{11}NO_5$ requires: C, 57.83; H, 4.45; N, 5.62%); *m/e* 249 (M^+, 100%); exact mass: 249.063 ± 0.002, calculated: 249.0637.

5,6,7 - *Trimethoxy* - 2 - *methyl* - 1,3,4(2H) - *isoquinolinetrione* (**17**). The cyclization was complete after 2 hr at 85°. Column chromatography and crystallization from toluene yielded 13.5 g (97%) of **17**. (Found: C, 55.99; H, 4.70; N, 4.94. $C_{13}H_{13}NO_6$ requires: C, 55.92; H, 4.69; N, 5.02%); *m/e* 279 (M^+, 100%); exact mass: 279.074 ± 0.002, calculated: 279.0742.

7 - *Methoxy* - 2 - *carbethoxymethyl* - 1,3,4(2H) - *isoquinolinetrione* (**18a**) *and* 5 - *methoxy* - 2 - *carbethoxymethyl* - 1,3,4(2H) - *isoquinolinetrione* (**18b**). These triones were prepared according to method a. After heating the oxamoyl chloride without solvent at 140° during 2 hr, the reaction was complete. Chromatography with CCl_4–EtOAc mixtures afforded 2 important fractions. By crystallization of the major fraction from CCl_4 8.8 g (61%) **18a** was obtained. A more polar minor fraction yielded 1.8 g (12%) of the corresponding *ortho*-isomer **18b**. **18a**: (Found: C, 58.01; H, 4.48; N, 4.78. $C_{14}H_{13}NO_6$ requires: C, 57.73; H, 4.50; N, 4.81%); *m/e* 291 (M^+, 8%), 190 (100%); exact mass: 291.074 ± 0.001, calculated: 291.0742. **18b**: (Found: C, 57.61; H, 4.58; N, 4.75. $C_{14}H_{13}NO_6$ requires: C, 57.73; H, 4.50; N, 4.81%); *m/e* 291 (M^+, 11%), 206 (100%); exact mass: 291.075 ± 0.002, calculated: 291.0742.

(D) *Isoindolinones*

Ethyl 1 - *hydroxy* - 5 - *methoxy* - 2 - *methyl* - 3 - *oxoisoindoline* - 1 - *carboxylate* (**25**). A stirred mixture of **22** (1 g; 3.7 mmole) and 30 g PPA was kept at 50°. After 2 hr, ice-water (300 ml) was added and the aqueous layer extracted with CH_2Cl_2. The organic layer was washed with 1% $NaHCO_3$, dried over Na_2SO_4 and evaporated *in vacuo*. The residue was purified by chromatography over silica gel using a mixture $CHCl_3$–MeCN (9:1) (v:v). In this way 0.75 g (75%) of a pure colourless oil was isolated. The spectra are in agreement with structure **25**. ν_{max}($CHCl_3$)cm^{-1}: 3485 (OH), 2835 (OMe), 1735 (COOEt), 1705 (lactam), 1622, 1604 (aryl); *m/e* 265 (M^+, 1%), 192 (100%); exact mass: 265.095 ± 0.001, calculated for $C_{13}H_{15}NO_5$: 265.0950; δ($CDCl_3$): 1.18 (3H, tr, J = 7 Hz, ester), 2.92 (3H, s, NMe), 3.84 (3H, s, OMe), 4.25 (2H, m, ester), 5.01 (1H, s, OH), 7.07 (1H, d × d, J = 8.5 × 2 Hz, 5–H), 7.21 (1H, d, J = 2 Hz, 4–H), 7.41 (1H, d, 8.5 Hz, 7–H).

Ethyl 1 - hydroxy - 4,5 - dimethoxy - 2 - methyl - 3 - oxoisoindoline - 1 - carboxylate (**26**). A soln of **23** (1.18 g; 4 mmole) in 50 ml CH_2Cl_2 was treated with $AlCl_3$ (0.71 g, 5.33 mmole) at room temp. After 4 hr the mixture was worked up as in the preparation of **25**. Chromatography over silica gel with $CHCl_3$–MeCN (9:1) (v:v) afforded 385 mg (33%) **26** (m.p. 124°). $\nu_{max}(CHCl_3)cm^{-1}$: 3495 (OH), 2835 (OMe), 1735 (COOEt), 1710 (lactam); *m/e* 295 (M^+, 2%) 222 (100%); exact mass 295.105 ± 0.001, calculated for $C_{14}H_{17}NO_6$: 295.1056; $\delta(CDCl_3)$: 1.20 (3H, tr, J = 7 Hz, ester), 2.88 (3H, s, NMe), 3.85 (3H, s, 5-OMe), 4.01 (3H, s, 4-OMe), 4.24 (2H, m, ester), 4.98 (1H, s, OH), 6.95 (1H, d, J = 8 Hz), 7.17 (1H, d, J = 8 Hz).

Ethyl 1 - hydroxy - 5,7 - dimethoxy - 2 - methyl - 3 - oxoisoindolenine - 1 - carboxylate (**27**). This was prepared from **24** according to the same procedure as **26**. $AlCl_3$ was added at −50°, while the reaction was carried out at −10° during 2 hr. Benzene–EtOAc (1:1) (v:v) was used for the chromatographic separation. 905 mg **27** (colourless oil) (76%) and 30 mg **16** (yellow crystals) (3%) were obtained. $\nu_{max}(CHCl_3)cm^{-1}$: 3495 (OH), 2840 (OMe), 1736 (COOEt), 1705 (lactam), 1626, 1617 (C=C); *m/e* 295 (M^+, 1%), 222 (100%); exact mass: 295.105 ± 0.001, calculated for $C_{14}H_{17}NO_6$: 295.1056; $\delta(CDCl_3)$: 1.19 (3H, tr, J = 8 Hz, ester), 2.92 (3H, s, NMe), 3.84 (3H, s, OMe), 3.88 (3H, s, OMe), 4.24 (2H, q, J = 7 Hz, ester), 4.73 (1H, s, OH), 6.55 (1H, d, J = 2 Hz, 6-H), 6.85 (1H, d, J = 2 Hz, 4-H).

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