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Synthesis of 11H-4b,10b-Dihydro[1]benzopyrano[4,3-c]isoquinoline-6,11(5H)-diones and 13H-6c,12b-Dihydronaphtho[1',2':5,6]-pyrano[4,3-c]isoquinoline-8,13(7H)-dione from Homophthalic Anhydride and N-(2-Hydroxyarylidene)alkylamines[1]

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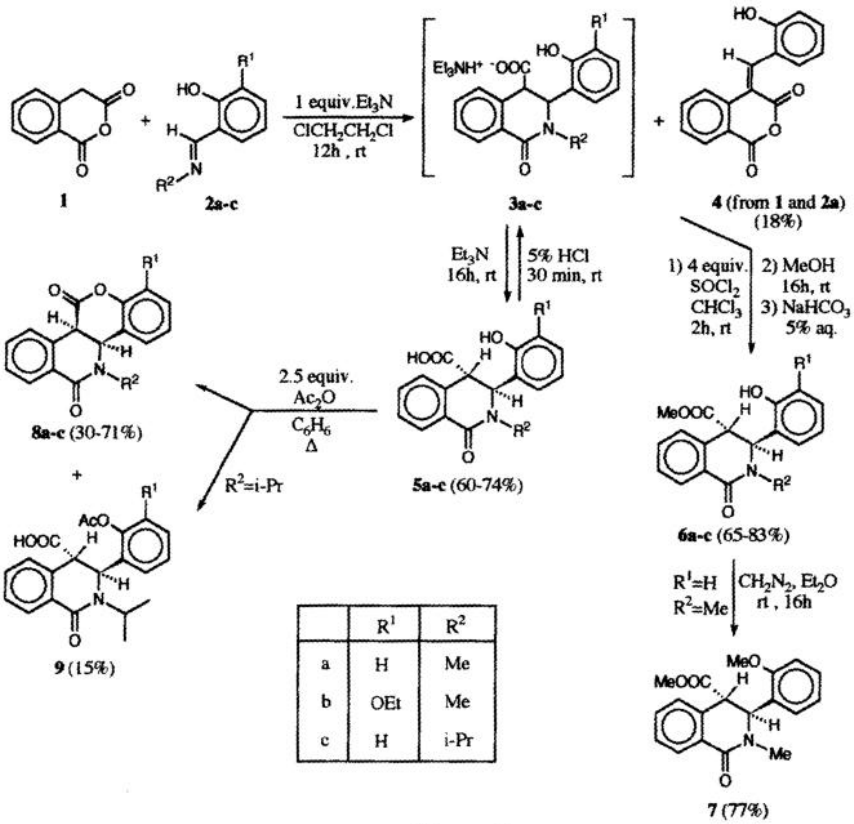
Abstract: 2-Alkyl-3-(2-hydroxyaryl)-3,4-dihydro-1(2H)-isoquinolinone-4-carboxylic acids (**5,13**) were prepared from homophthalic anhydride (**1**) and N-(2-hydroxyarylidene)alkylamines (**2,10**). The acids **5,13** showed a tendency towards cyclodehydration to give isoquinoline derivatives with fused [1]benzopyrane (**8**) or naphthopyrane (**12**) ring system. The relative configurations of the novel fused heterocyclic compounds **5,8,12,13** and related compounds were determined by NMR studies, and in the case of **13** also by means of X-ray analysis. Some MM2 force field molecular mechanics calculations on some selected fused heterocycles were executed. The naphtho[1',2':5,6]pyrano[4,3-c]-isoquinoline ring system incorporated in the lactone **12** is hitherto unreported.

Reactions of homophthalic anhydrides with imines were used previously for synthesis of heterocycles. Recently we showed that the reaction of homophthalic anhydrides with α-chloro-imines leads to the formation of furo[3,4-c]isoquinolinediones.[1] As a continuation of our studies on the preparation of isoquinolines with annelated lactone ring, we examined as a first stage the reaction of homophthalic anhydride **1** and N-(2-hydroxyarylidene)alkylamines **2a,c**[2,3] and the hitherto undescribed **2b** (Scheme 1). The extra hydroxyl functionality in the aromatic ring of the imine allows for a further elaboration toward lactones, resulting in tetracyclic heterocycles which are otherwise difficultly accessible. The reaction of **1** and **2** was conducted in 1,2-dichloroethane in the presence of triethylamine at room temperature and yields as main products the adducts **5a-c**, i.e. 2-alkyl-3-(2-hydroxyaryl)-3,4-dihydro-1(2H)-isoquinolinone-4-carboxylic acids. The reaction proceeds most favourably if reactants and triethylamine are used in

[1] Preliminary report presented at the XIVth International Congress of Heterocyclic Chemistry, Antwerp (Belgium), August 1-6, 1993.



	R^1	R^2
a	H	Me
b	OEt	Me
c	H	i-Pr

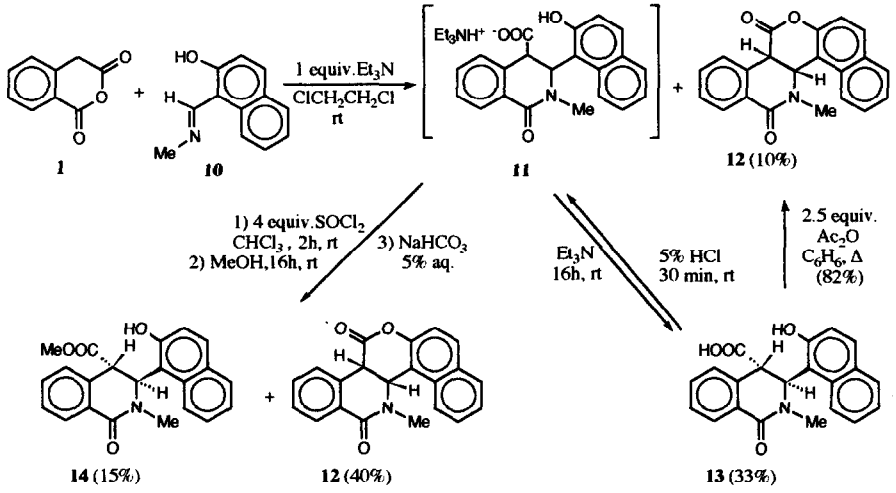
Scheme 1

equimolar amounts. In this case the acids **5** are precipitated as triethylammonium salts **3**, which are easily isolable. Besides the acid **5c**, the product **4** resulting from a Perkin type condensation was also isolated as a side product.

The acids **5a-c** were characterized as the corresponding methyl esters **6a-c** which were prepared via successive treatment of the triethylammonium salts **3a-c** with thionyl chloride and methanol. Treatment of the ester **6a** with diazomethane yielded the known methyl trans-3-(2-methoxyphenyl)-2-methyl-3,4-dihydro-1(2H)-isoquinolinone-4-carboxylate (**7**).[4]

Since the hydroxycarboxylic acids **5a-c** are suitably substituted by a phenolic hydroxyl function, they can be subjected to a heterocyclization through dehydration The acids **5a-c** were smoothly transformed into the corresponding lactones **8a-c** by heating with acetic anhydride in benzene. In the case of the acid **5c**, possessing a bulky substituent at nitrogen, the cyclization to the lactone **8c** is accompanied by a competitive acetylation of the phenolic hydroxyl to give the acetoxycarboxylic acid **9**. The [1]benzopyrano[4,3-a]isoquinoline ring system incorporated in compounds **8a-c** has been described only in one literature citation,[5] where a reaction of 3-phenyl-4-aminocoumarines with diphenylcarbonate at 300 °C was used for the preparation of such type of condensed heterocycles.

Homophthalic anhydride (1) reacts under the same conditions with N-(2-hydroxynaphthylmethylidene)methylamine 10[6] (Scheme 2) to give 3-(2-hydroxynaphthyl)-2-methyl-3,4-dihydro-1(2H)-isoquinolinone-4-carboxylic acid 13. Since the acid 13 is more prone to cyclodehydration, the corresponding lactone 12 is obtained from the reaction mixture as well in a yield of 10%. The pentacyclic lactone 12 is also obtained from the acid 13 by heating with acetic anhydride in benzene. In order to characterize the acid 13, similar to the characterization of the acids 5a-c, we attempted its transformation into its methyl ester under the conditions as described above. The successive treatment of the triethylammonium salt 11 with thionyl chloride and methanol gave the lactone 12 as a major product, and the ester 14 as a minor product. Up to the best of our knowledge, the naphtho[1',2':5,6]pyrano-[4,3-c]isoquinoline ring system, incorporated in the lactone 12, is hitherto unreported.

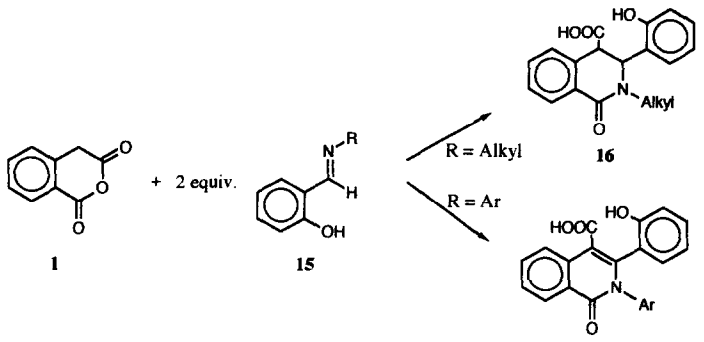


Scheme 2

Recently, an investigation on the reaction of homophthalic anhydride with N-(2-hydroxyarylidene)-arylamines was published (Scheme 3).[7] When a 1:2 molar ratio of anhydride 1 to imine 15 was used in the presence of catalytic amounts of triethylamine, 2,3-diaryl-1-isoquinolinone-4-carboxylic acids 17 were prepared. The formation of these compounds results from the oxidation of the intermediate 3,4-dihydro-1(2H)-isoquinolinone-4-carboxylic acids by the Schiff bases used in excess.[7]

We carried out a reaction of N-(2-hydroxybenzylidene)methylamine (2a) with homophthalic anhydride under the same conditions as described in the latter report but we obtained only the acid 5a. This result can be explained by the assumption that 2-alkyl-3-aryl-3,4-dihydroisoquinolinone-4-carboxylic acids of type 5 are less prone to aromatization than their 2,3-diaryl-substituted analogs. This result clearly distinguishes the chemical behavior of N-(2-hydroxyarylidene)amines with an N-aryl substituent from those with an N-aliphatic substituent.

The structure and stereochemistry of all compounds of types 5-9 and 12-14, isolated as single diastereoisomers, were determined on the basis of spectral data. The ^{1}H NMR spectra of the acids 5a-c and the corresponding esters 6a-c, as well as of 9 are very similar to each other. In all these cases the



Scheme 3

vicinal coupling constant $J_{3,4}$ is below 1.4 Hz. In accordance to the literature, trans-configuration and favoured solution conformation with di-pseudoaxially oriented substituents at C-3 and C-4 were attributed to all these compounds.[4,8] This assignment was also confirmed by the transformation of the methyl ester **6a** into the compound **7** with known relative configuration.[4]

The configurational assignment for compounds **13** and **14** presented some difficulties due to the much higher vicinal coupling $J_{3,4}$ observed (4-6 Hz), as compared to all other acids **5** and **9**, as well as the esters **6** and **7**. These higher values could be explained assuming that compounds **13** and **14** also possess the trans-configuration but in solution exist as mixtures of conformers with di-pseudoequatorial and di-pseudoaxial 3,4-substituents, both of them represented in significant amount. This assumption is supported by the results of MM2 force field molecular mechanics calculations.[9] The calculations showed that replacement of the 2-hydroxyphenyl substituent (compound **6a**) by a 2-hydroxynaphthyl group (**14**) significantly increased the energy of the di-pseudoaxial conformer as compared to that of the di-pseudoequatorial one. However, it should be pointed out that the possibility of compounds **13** and **14** possessing cis- rather than trans-configuration could not be fully excluded at that stage. According to the calculations, a cis-conformer of **14** with pseudoaxial 4-substituent and pseudoequatorial 3-substituent is of similar energy as the trans-form and exhibits a calculated[10] $J_{3,4}$ coupling constant of 3.8 Hz, in good agreement with the experimental data. The unequivocal configurational assignment of compounds **13** and **14** came from single X-ray diffraction analysis of compound **13** which confirmed the trans-configuration of the 3- and 4-substituents (Figure 1, Tables 1-3).

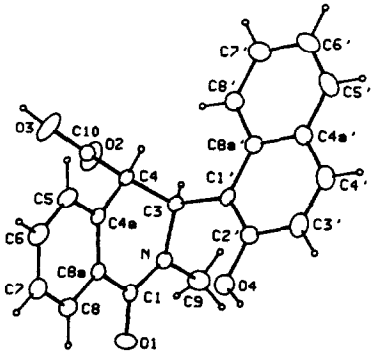


Fig. 1 : X-ray crystallographic picture of compound **13** showing the atom numbering system.

The crystal data of compound **13** are the following : orthorhombic, P $2_12_12_1$, a = 10.174(2), b = 11.981(4), c = 14.184(4)Å, V = 1729(1), Z = 4, D_x = 1.334 g cm^{-3}, λ(MoKα) = 0.71073, μ = 0.08 cm^{-1}, F(000) = 728, t = 292 K, R = 0.036 and R_w = 0.037 for 1038 observed reflections with I > 3σ(I).

The conformation of the pyridinone ring was determined as a half-chair (Q = 0.2989, Phi = 329.20, Theta = 121.80)[11,12], with puckering amplitude of 0.352 Å. The C-3 and C-4 atoms are displaced from the least-squares plane of C-1/N/C-4a/C-8a atoms (planarity ± 0.026(2) Å at 0.284(4) and 0.254(4) Å. The hydroxynaphthyl and carboxyl substituents are both in a pseudoaxial conformation. Dihedral angles between the plane of the pyridinone ring and the planes of the above groups are 93.6()° and 106.4(3)°, resp.

The molecules of **13** are packed in chains along the c-axis by short O3-HO3...O1(1/2-x,1-y,1/2+z) hydrogen bonds [HO3...O1 1.562(2), O3...O1 2.548(4) Å, O3-HO3...O1 163.5(2)°]. The chains are further interlinked by longer O4-HO4...O2(1-x,-1/2+y,1/2-z) hydrogen bonds [HO4...O2 1.989(3), O4...O2 2.834(4), O4-HO4...O2 177.8(2)°].

The ^{1}H NMR spectra of the lactones **8a-c,12** showed a vicinal coupling constant of 3.9-4.5 Hz for the protons at the adjacent carbons common for the dihydropyridinone and the dihydropyranone rings (C-4b/C-10b for **8a-c** and C-6c/C-12b for **12**, resp.). These values are indicative for cis-fusion of the rings specified. Thus, the cyclodehydration of the trans-3,4-dihydroisoquinolinone-carboxylic acids **5a-c** and **13** is accompanied by epimerization.

The ^{1}H NMR spectra of the lactones **8a,b**; taken at ambient temperature, showed strongly broadened signals for H-3 and N-CH_3, which sharpened at higher temperatures (60°C). This effect should be attributed to hindered conformational interconversion of the saturated part of the ring system (particularly the fragment O=C-N(CH_3)-CH) at room temperature which is typical for amides and lactams.[13]

The ^{13}C NMR data (see the experimental part) are in accordance with the structures assigned. Some of the ^{13}C signals (NCH_3, aromatic C, etc., as indicated) of the lactones **8a,b** are extremely broadened (or even missing), analogously to the ^{1}H signals and presumably on the same ground.

Experimental :

Melting points (mp, uncorrected) : microhot stage Boetius PHMK 0.5. TLC : Silicagel 60 F_{254} on aluminium sheets "Merck", layer thickness 0.2 mm. Solvent systems : ether/hexane 1:1 (1 part) and hexane/ethylacetate/methanol/ammonia 120:100:15:10, upper layer (1 part). Column chromatography : silicagel type 60 "Merck", particle size 0.2-0.063 mm. Mass spectra (MS) : m/z (rel. intensity)-Jeol JMS D-300, electron impact, 70eV, or chemical ionization (CI) where stated. IR-spectra : C. Zeiss-Jena Specord IR-71 (suspension in nujol if not stated otherwise). ^{1}H-NMR and ^{13}C-NMR spectra : Bruker Spectrospin WM-250 (250 MHz), Varian XL-300 (300 MHz), JEOL JNM EX 270 (270 MHz) ($CDCl_3$ as solvent if not stated otherwise). The DEPT sequence and in some cases also 2D H-C correlation spectroscopy was used for the ^{13}C-assignment.

X-ray structure determination. Crystals of **13** were obtained by slow evaporation of a solution in ethanol. A colourless prism-shaped crystal of 0.20 x 0.26 x 0.24 mm was investigated on a Enraf-Nonius CAD4 diffractometer (MoKα radiation, graphite monochromator; ω/29 scan mode, speed 5 to 7 deg/min, width = 0.80 + 0.40 tan θ. Cell constants from 22 reflections with 19.9<θ<21.40. For λ < 28° (h : 0 to 13, k : 0 to 15, l : -18 to 18) 4599 reflections measured. Three standard reflections measured every 2 hours, max intensity variation 0.7%. No decay correction. $R_{(int)}$ = 0.034 for 2365 unique reflec-

Table 1. Positional and Equivalent Isotropic Displacement Parameters (Å)

label	x	y	z	$U_{iso/eq}$
O1	0.2421(2)	0.3826(2)	0.1747(2)	0.03855(7)
O2	0.3649(3)	0.6239(2)	0.4366(2)	0.0535(8)
O3	0.3724(3)	0.4989(2)	0.5502(2)	0.0612(9)
O4	0.5597(2)	0.3024(2)	0.1829(2)	0.0473(8)
N	0.4082(3)	0.4793(2)	0.2402(2)	0.0260(7)
C1	0.3205(3)	0.3967(3)	0.2402(2)	0.0262(9)
C3	0.5137(3)	0.4906(3)	0.3115(2)	0.0248(9)
C4	0.4712(3)	0.4469(3)	0.4083(2)	0.027(1)
C4a	0.3942(3)	0.3397(3)	0.4020(2)	0.0260(9)
C5	0.3909(4)	0.2641(3)	0.4770(2)	0.036(1)
C6	0.3115(4)	0.1699(3)	0.4701(3)	0.043(1)
C7	0.2341(4)	0.1515(3)	0.3923(3)	0.041(1)
C8	0.2370(4)	0.2260(3)	0.3175(3)	0.033(1)
C8a	0.3178(3)	0.3202(3)	0.3230(2)	0.0253(9)
C9	0.4193(4)	0.5522(3)	0.1586(3)	0.048(1)
C10	0.3957(4)	0.5336(3)	0.4651(2)	0.032(1)
C1'	0.6474(3)	0.4445(3)	0.2817(2)	0.0253(9)
C2'	0.6659(4)	0.3556(3)	0.2213(3)	0.034(1)
C3'	0.7937(4)	0.3197(3)	0.1968(3)	0.048(1)
C4'	0.9010(4)	0.3690(4)	0.2345(3)	0.051(1)
C4a'	0.8886(4)	0.4569(3)	0.2997(3)	0.038(1)
C5'	0.9991(4)	0.5058(4)	0.3426(3)	0.056(1)
C6'	0.9886(4)	0.5882(4)	0.4062(3)	0.053(1)
C7'	0.8634(4)	0.6282(3)	0.4305(3)	0.046(1)
C8'	0.7534(4)	0.5840(3)	0.3900(3)	0.034(1)
C8a'	0.7604(4)	0.4959(3)	0.3236(2)	0.0297(9)
H3	0.5238	0.5690	0.3175	0.0506
H4	0.5509	0.4312	0.4405	0.0506
H5	0.4422	0.2769	0.5318	0.0506
H6	0.3115	0.1165	0.5196	0.0506
H7	0.1773	0.0886	0.3895	0.0506
H8	0.1835	0.2141	0.2635	0.0506
H91	0.4853	0.6065	0.1700	0.0506
H92	0.4423	0.5092	0.1047	0.0506
H93	0.3376	0.5884	0.1477	0.0506
H3'	0.8039	0.2598	0.1535	0.0506
H4'	0.9862	0.3460	0.2152	0.0506
H5'	1.0845	0.4813	0.3254	0.0506
H6'	1.0644	0.6178	0.4361	0.0506
H7'	0.8559	0.6878	0.4743	0.0506
H8'	0.6700	0.6134	0.4070	0.0506
HO4	0.5822	0.2479	0.1485	0.0506
HO3	0.3287	0.5568	0.5913	0.0506

Table 2. Interatomic Distances (Å) and Angles (°)

label 1	label 2	distance
O1	C1	1.236(4)
O2	C10	1.196(5)
O3	C10	1.298(5)
O4	C2'	1.368(5)
N	C1	1.333(4)
N	C3	1.481(4)
N	C9	1.454(5)
C1	C8a	1.490(5)
C3	C4	1.532(5)
C3	C1'	1.528(5)
C4	C4a	1.507(5)
C4	C10	1.522(5)
C4a	C5	1.398(5)
C4a	C8a	1.384(5)
C5	C6	1.391(6)
C6	C7	1.375(6)
C7	C8	1.386(5)
C8	C8a	1.398(5)
C1'	C2'	1.379(5)
C1'	C8a'	1.433(5)
C2'	C3'	1.413(5)
C3'	C4'	1.351(6)
C4'	C4a'	1.408(6)
C4a'	C5'	1.406(6)
C4a'	C8a'	1.427(5)
C5'	C6'	1.341(6)
C6'	C7'	1.403(6)
C7'	C8'	1.365(6)
C8'	C8a'	1.416(5)
O3	HO3	1.011(3)
O4	HO4	0.846(3)

label 1	label 2	label 3	angle
C1	N	C3	123.6(3)
C1	N	C9	119.9(3)
C3	N	C9	115.6(3)
O1	C1	N	122.2(3)
O1	C1	C8a	119.8(3)
N	C1	C8a	118.0(3)
N	C3	C4	112.2(3)
N	C3	C1'	115.1(3)
C4	C3	C1'	112.0(3)
C3	C4	C4a	112.6(3)
C3	C4	C10	112.6(3)
C4a	C4	C10	110.5(3)
C4	C4a	C5	121.3(3)
C4	C4a	C8a	119.0(3)
C5	C4a	C8a	119.5(3)
C4a	C5	C6	119.1(3)
C5	C6	C7	121.3(4)
C6	C7	C8	119.9(4)
C7	C8	C8a	119.3(3)
C1	C8a	C4a	121.6(3)
C1	C8a	C8	117.6(3)
C4a	C8a	C8	120.8(3)
O2	C10	O3	123.8(4)
O2	C10	C4	124.8(3)
O3	C10	C4	111.4(3)
C3	C1'	C2'	124.9(3)
C3	C1'	C8a'	116.4(3)
C2'	C1'	C8a'	118.7(3)
O4	C2'	C1'	120.0(3)
O4	C2'	C3'	119.1(3)
C1'	C2'	C3'	120.9(3)
C2'	C3'	C4'	120.9(4)
C3'	C4'	C4a'	121.0(4)
C4'	C4a'	C5'	121.7(4)
C4'	C4a'	C8a'	118.9(3)
C5'	C4a'	C8a'	119.4(4)
C4a'	C5'	C6'	122.3(4)
C5'	C6'	C7'	119.3(4)
C6'	C7'	C8'	120.5(4)
C7'	C8'	C8a'	121.9(4)
C1'	C8a'	C4a'	119.6(3)
C1'	C8a'	C8'	123.8(3)
C4a'	C8a'	C8'	116.6(3)

Table 3. Anisotropic Atom Displacement Parameters

label	U11	U22	U33	U12	U13	U23
O1	0.043(1)	0.041(1)	0.031(1)	-0.006(2)	-0.016(1)	0.006(1)
O2	0.085(2)	0.030(1)	0.045(2)	0.021(2)	0.025(2)	0.007(1)
O3	0.105(2)	0.045(2)	0.033(1)	0.019(2)	0.029(2)	0.002(1)
O4	0.044(2)	0.040(2)	0.058(2)	-0.004(2)	0.012(2)	-0.023(2)
N	0.028(2)	0.028(1)	0.022(1)	0.002(2)	-0.001(2)	0.010(1)
C1	0.024(2)	0.030(2)	0.025(2)	0.005(2)	0.005(2)	0.003(2)
C3	0.029(2)	0.022(2)	0.023(2)	0.002(2)	0.001(2)	-0.000(2)
C4	0.030(2)	0.031(2)	0.019(2)	0.003(2)	0.002(2)	0.000(2)
C4a	0.028(2)	0.025(2)	0.025(2)	0.006(2)	0.007(2)	-0.003(2)
C5	0.050(2)	0.034(2)	0.025(2)	0.000(2)	0.001(2)	0.006(2)
C6	0.064(3)	0.034(2)	0.030(2)	-0.006(2)	0.008(2)	0.009(2)
C7	0.048(2)	0.035(2)	0.040(2)	-0.005(2)	0.013(2)	-0.001(2)
C8	0.037(2)	0.029(2)	0.032(2)	-0.000(2)	0.001(2)	0.000(2)
C8a	0.027(2)	0.025(2)	0.024(2)	0.005(2)	0.004(2)	0.002(2)
C9	0.058(3)	0.048(2)	0.038(2)	-0.016(2)	-0.007(2)	0.018(2)
C10	0.034(2)	0.036(2)	0.026(2)	-0.010(2)	0.004(2)	-0.004(2)
C1'	0.032(2)	0.022(2)	0.021(2)	0.002(2)	0.006(2)	0.002(2)
C2'	0.036(2)	0.030(2)	0.036(2)	-0.003(2)	0.002(2)	-0.003(2)
C3'	0.045(2)	0.045(2)	0.055(3)	0.008(2)	0.019(2)	-0.014(2)
C4'	0.036(2)	0.057(3)	0.060(3)	0.005(3)	0.013(2)	-0.007(3)
C4a'	0.029(2)	0.046(2)	0.040(2)	0.004(2)	0.003(2)	0.004(2)
C5'	0.026(2)	0.074(3)	0.067(3)	-0.004(2)	-0.001(2)	0.010(3)
C6'	0.043(2)	0.063(3)	0.054(3)	-0.017(3)	-0.012(2)	0.004(3)
C7'	0.052(3)	0.041(2)	0.045(2)	-0.011(2)	-0.006(2)	0.003(2)
C8'	0.041(2)	0.029(2)	0.034(2)	-0.003(2)	0.002(2)	0.007(2)
C8a'	0.035(2)	0.028(2)	0.026(2)	-0.001(2)	-0.002(2)	0.006(2)

tions; 1038 reflections observed with $I > 3\sigma(I)$. Structure solved by MULTAN82 and refined by full-matrix least-squares on F's. Hydroxyl and carboxyl hydrogen atoms were localized on a difference Fourier map and the others were placed in calculated positions, all were refined using a riding model with a common isotropic thermal parameter, U_{iso} = 0.0506 Å. The absolute structure was not determined. Final R = 0.036, R_w = 0.037 and S = 1.026; weights $w = 1/[\sigma^2(F) + (0.014F)^2]$ were used. Max. and min. residual density 0.167 and -0.196 e A^{-3}. Atomic scattering factors and anomalous-dispersion coefficients as coded in SDP/PDP V3.0 (Enraf-Nonius, 1985). PDP11 computer with a locally modified CAD4/SDP software package (Enraf-Nonius, 1988) used.

1. N-(3-Ethoxy-2-hydroxybenzylidene)methylamine (2b) was synthesized from 3-ethoxy-2-hydroxybenzene-carbaldehyde and methylamine, analogously to the literature.[3] Yield 81%, mp 53.5-54.5°C (petroleum ether). MS : 164(100) [M^+-CH_3], 179(80) [M^+]. IR ($CHCl_3$) : 1580 (C=C, arom.), 1630 (C=N), 3000-3100 (=C-H, arom.). ^{1}H-NMR : 1.47 (3H, t, J=6.9, $C\underline{H}_3CH_2$), 3.47 (3H, d, J=1.2, NCH_3), 4.11 (2H, q, J=6.9, $CH_3C\underline{H}_2$), 6.73-7.26 (3H, m, arom.), 8.31 (1H, m, N=CH), 13.90 (1H, br s, OH, exchangeable with D_2O). Calcd for $C_{10}H_{13}NO_2$ (179.3) : C 67.02, H 7.31; found : C 66.81, H 7.25%.

2. Preparation of trans-2-alkyl-3-(2-hydroxyphenyl)-3,4-dihydro-1(2H)-isoquinolinone-4-carboxylic acids(5a-c)andtrans-3-(2-hydroxynaphthyl)-2-methyl-3,4-dihydro-1(2H)-isoquinolinone-4-carboxylicacid (13) (General Procedure).

To a solution of 2 mmol N-(2-hydroxyarylidene)alkylamine (**2a-c** or **10**) and 0.28 ml (2 mmol) dry triethylamine in 4 ml dry 1,2-dichloroethane, 2 mmol homophthalic anhydride (**1**) was added. The mixture was stirred for 6 hours and left at room temperature overnight. The precipitated triethylammonium salt (**3a-c**) was filtered and, without further purification, was stirred for 30 min with 8 ml 5% aq. HCl. It was then filtered and recrystallized from ethanol.

5a (from **1** and **2a**) : Yield of **3a** : 96%; yield of **5a** : 72%, mp 211-212°C. Mixed mp with an authentic sample[7] was undepressed. MS : 297 (100) [M^+], 252(21) [M^+-COOH]. $C_{17}H_{15}NO_4$ (297.3). IR : 1575, 1600 (C=C, arom.), 1630 (C=O, amide), 1710, 2400-3100 (COOH), 3360 (OH). ^{1}H-NMR : 3.13 (3H, s, NCH_3), 4.13 (1H, s, $J_{3,4}\leq 1.0$, H-4), 5.58 (1H, s, $J_{3,4}\leq 1.0$, H-3), 9.30 (1H, br s, OH, phenol), 6.55-7.39 (7H, m, arom. H), 8.8 (1H, m, H-8).

5b (from **1** and **2b**) : Yield of **3b** : 86%; yield of **5b** : 74%, mp 241-242°C. MS (CI) : 342(100) [MH^+]. IR : 1580, 1650 (C=C, arom.), 1640 (C=O), 1710, 2400-3100 (COOH), 3360 (OH, phenol). ^{1}H-NMR : 1.45 (3H, t, J=7.0, $C\underline{H}_3CH_2$), 3.16 (3H, s, NCH_3), 4.09 (2H, q, J=7.0, $CH_3C\underline{H}_2$), 4.20 (1H, d, $J_{3,4}$=1.3, H-4), 5.59 (1H, d, $J_{3,4}$=1.3, H-3), 5.97 (1H, s, OH, phenol, exchangeable with D_2O), 6.31-7.42 (6H, m, arom. H), 8.17 (1H, m, H-8). ^{13}C-NMR ($CDCl_3$+DMSO-d_6) : 14.6 $\underline{C}H_3CH_2$, 34.3 NCH_3, 47.8 C-4, 58.1 C-3, 64.3 $CH_3\underline{C}H_2$, 111.7, 117.4, 118.4, 124.5, 127.0, 127.5, 128.6, 129.6, 131.6, 133.9, 143.4, 146.5 arom. C and CH, 163.7 C-1, 172.3 COOH. Calcd. for $C_{19}H_{19}NO_5$ (341.4) : C 66.85, H 5.61; found : C 66.55, H 5.49%.

5c (from **1** and **2c**) : Yield of **3c** : 47%; yield of **5c** : 60%, mp 259-260°C. MS : 325(8) [M^+], 326(2) [M^++1]. $C_{19}H_{19}NO_4$ (325.4). IR : 1580, 1605 (C=C, arom.), 1630 (C=O), 1715, 3220 (COOH), 3460 (OH, phenol). ^{1}H-NMR ($CDCl_3$+DMSO-d_6) : 0.90 and 1.27 (each 3H, each d, J=7.0, $CH(C\underline{H}_3)_2$), 4.00 (1H, s, $J_{3,4}\leq 1.0$, H-4), 4.89 (1H, sept, J=7.0, $C\underline{H}(CH_3)_2$), 5.66 (1H, s, $J_{3,4}\leq 1.0$, H-3), 6.45-7.37 (7H, m, arom. H), 8.03 (1H, m, H-8), 9.52 (1H, br s, OH, phenol). ^{13}C-NMR ($CDCl_3$+DMSO-d_6) : 19.4, 20.3 $CH(\underline{C}H_3)_2$, 45.5 $\underline{C}H(CH_3)_2$, 48.8 C-4, 51.0 C-3, 115.1, 118.4, 126.5, 127.0, 127.2, 127.5, 128.0, 129.1, arom. CH, 130.3, 131.3, 133.7, 153.4, arom. C, 163.6 C-1, 172.4 COOH.

The filtrate of **3c** was concentrated in vacuo and 4 ml 10% aq. HCl was added. The mixture was stirred for 30 min then filtered and the residue was recrystallized. In this way, 4-(2-hydroxybenzylidene)-1H-[2]benzopyran-1,3-dione (**4**) was obtained. Yield 18%, mp 270-272°C (ethanol). MS : 266(100) [M^+], 267(16) [M^++1]. IR : 755, 950, 960 (HC=), 1600 (C=C, arom.), 1725, 1680 (CO-O-CO); ^{1}H-NMR ($CDCl_3$+DMSO-d_6) : 7.28-7.69 (7H, m, arom. H), 8.04 (1H, m, H-8), 9.68 (1H, s, OH, phenol). Calcd. for $C_{16}H_{10}O_4$ (266.2) : C 72.18, H 3.79; found : C 72.37, H 3.81%.

13 (from **1** and **10**) : Yield of **11** : 45%; yield of **13** : 33%, mp 224-225°C. MS : 346(3) [M^+-1], 345(8) [M^+-2], 319(63), 160(100). $C_{21}H_{17}NO_4$ (347.4). IR : 1580, 1600 (C=C, arom.), 1625 (C=O), 1720, 2450-3100 (COOH), 3300 (OH, naphthol). ^{1}H-NMR ($CDCl_3$+DMSO-d_6) : 2.58 (3H, s, NCH_3), 4.48 (1H, d, $J_{3,4}$=4.0, H-4), 6.14 (1H, d, $J_{3,4}$=4.0, H-3), 7.04-8.33 (9H, m, arom. H), 8.10 (1H, m, H-8), 9.20 (1H, s, OH, naphthol). ^{13}C-NMR ($CDCl_3$+DMSO-d_6) : 48.0, 57.5 C-3, C-4, 113.0, 119.3, 121.8, 122.6, 127.0, 127.4, 127.6, 128.8, 128.9, 129.7, 129.9, 131.1, 132.9, 134.7, 154.1, arom. C and CH, 164.9 C-1, 173.5 COOH.

The filtrate of **13** was evaporated in vacuo, the residue was column chromatographed using petroleum ether-ethyl acetate (90:10) as eluent and then recrystallized to give compound **12**, yield 10%, mp 194.5-195.5 °C (ethyl acetate). Mixed mp with a sample of the same product was undepressed and the compound showed identical spectral data as described below (procedure 3).

3. Preparation of cis-5-alkyl-11H-4b,10b-dihydro[1]benzopyrano[4,3-c]isoquinoline-6,11(5H)-diones (8a-c) and cis-7-methyl-13H-6c,12b-dihydronaphtho[1',2':5.6]pyrano[4.3-c]isoquinoline-8,13(7H)-dione (12) (General Procedure).

To a suspension of the acid **5a-c** or **13** (1 mmol) in dry benzene, acetic anhydride (0.24 ml, 2.5 mmol) was added and the reaction mixture was refluxed for 4-6 hours. After cooling at room temperature, water (5 ml) was added and the mixture was neutralized with solid $NaHCO_3$. The organic phase was separated, dried (Na_2SO_4) and, after solvent evaporation, the residue was recrystallized from ethyl acetate.

8a (from **5a**) : Yield 71%, mp 221-222 °C (ethyl acetate). MS : 280(28), 279(100) [M^+], 250(37). IR : 1590 (C=C, arom.), 1650 (C=O, amide), 1770 (C=O, lactone). ^{1}H-NMR : 3.20 (3H, br s, NCH_3), 4.4 (1H, br s, H-10b), 5.04 (1H, d, $J_{4b,10b}$=4.1, H-4b), 7.03-7.56 (7H, m, arom. H), 8.09 (1H, m, H-7). ^{13}C-NMR : 31 br NCH_3, 44.7, 56.4 C-10b, C-4b, 117.3, 125.2, 127 br, 128.6, 128.9, 130.5, 132.5 arom. C and CH, 155 br C-12a, 165 br C-6, 166.2 C-11. Calcd. for $C_{17}H_{13}NO_3$ (279.3) C 73.11, H 4.69; found : C 73.42, H 4.39%.

8b (from **5b**) : Yield 71%, mp 203-204 °C (ethyl acetate). MS(CI) : 356(4), 324(100) [MH^+]. IR : 1605 (C=C, arom.), 1655 (C=O, amide), 1770 (C=O, lactone). ^{1}H-NMR : 1.43 (3H, t, J=7.0, CH_3CH_2), 3.20 (3H, br s, NCH_3), 4.09 (2H, q, J=7.0, CH_3CH_2), 4.4 (1H, br s, H-10b), 5.01 (1H, d, $J_{4b,10b}$=4.3, H-4b), 6.65-7.55 (6H, m, arom. H), 8.05 (1H, m, H-7). ^{13}C-NMR : 14.7 CH_3CH_2, 36 br NCH_3, 44.7 C-4, 56.7 C-3, 64.9 CH_3CH_2, 114.5, 125.1, 128.6, 128.9, 132.5 arom. C and CH, 147.2 C-1 and/or C-12a, 165.9 C-6. Calcd. for $C_{19}H_{17}NO_4$ (323.3) : C 70.57, H 5.30; found : C 70.27 H 5.51%.

8c and **9** (from **5c**) : trans-3-(2-Acetoxyphenyl)-2-isopropyl-3,4-dihydro-1(2H)-isoquinolinone-4-carboxylic acid (**9**) was filtered and, after removal of solvent, the residue was column chromatographed with petroleum ether-ethyl acetate as eluent (90:10). The solid product obtained was recrystallized from ethyl acetate.

8c : Yield 30%, mp 186-188 °C (ethyl acetate). MS : 307(4) [M^+], 308(2) [M^++1]. IR : 1590, 1600, 1615 (C=C, arom), 1650 (C=O, amide), 1770 (C=O, lactone). ^{1}H-NMR : 1.37 (6H, d, J=6.0, $CH(CH_3)_2$), 4.90 (1H, d, $J_{4b,10b}$=4.5, H-10b), 5.18 (1H, d, $J_{4b,10b}$=4.6, H-4b), 5.26 (1H, m, J=6.0, $CH(CH_3)_2$), 6.91-7.38 (7H, m, arom. H), 7.96 (1H, d, H-7). ^{13}C-NMR : 19.5, 22.3 $CH(CH_3)_2$, 45.9, 46.4, 48.9 C-10b, C-4b, $CH(CH_3)_2$, 116.7, 124.9, 125.2, 126.3, 129.6, 129.9, 130.5, 132.5 arom. CH, 123.8, 128.7, 129.0 arom. C, 149.7 C-12a, 163.1 C-6, 166.8 C-11. Calcd. for $C_{19}H_{17}NO_3$ (307.3) : C 74.25, H 5.58; found : C 74.53, H 5.70%.

9 : Yield 15%, mp 235-236 °C (ethanol). MS : 367(54) [M^+], 368(58) [M^++1], 369(12) [M^++2]. IR : 1180, 1200 (C-O, acetate), 1605 (C=C, arom.), 1620 (C=O, amide), 1730, 2500 br (COOH), 1760 (C=O, acetate). ^{1}H-NMR ($CDCl_3$+DMSO-d_6) : 0.85 and 1.21 (each 3H, each d, J=7.0, $CH(CH_3)_2$), 2.47 (3H, s, CH_3CO), 3.83 (1H, d, $J_{3,4}$=1.2, H-4), 4.96 (1H, m, J=7.0, $CH(CH_3)_2$), 5.47 (1H, br s, H-3), 6.81-7.40 (8H, m, arom. H), 8.9 (1H, m, H-8). ^{13}C-NMR ($CDCl_3$+DMSO-d_6) : 19.2, 20.0, 20.7 $CH(CH_3)_2$, CH_3CO, 44.8, 49.6, 51.3 $CH(CH_3)_2$, C-4, C-3, 122.9, 125.6, 127.0, 127.2, 127.9, 128.5, 129.2, 132.8 arom. CH, 129.9, 131.6, 132.6, 147.1 arom. C, 163.1 C-1, 169.2, 171.9 CH_3CO, COOH. Calcd. for $C_{21}H_{21}NO_5$

(367.4) : C 68.65, H 5.76; found : C 68.07, H 5.63%.

12 (from **13**) : Yield 82%, mp 194.5-195.5°C (ethyl acetate). MS : 329(35) [M^+], 327(88), 312(100), 215(88). IR : 1580, 1605 (C=C, arom.), 1635 (C=O, amide), 1770 (C=O, lactone). ^{1}H-NMR : 2.75 (3H, s, NCH_3), 4.11 (1H, d, $J_{6c,12b}$=3.9, H-12b), 5.77 (1H, d, $J_{6c,12b}$=3.9, H-6c), 7.26-8.04 (9H, m, arom. H), 8.25 (1H, m, H-9). ^{13}C-NMR : 30.5 NCH_3, 44.4, 51.9 C-12b, C-6c, 117.5, 122.3, 125.8, 128.5, 128.8, 129.0, 129.2, 129.3, 132.3 arom. CH, 112.9, 128.5, 131.0, 131.7, 133.1 arom. C, 150.5C-14a, 165.2, 166.5 C-8, C-13. Calcd. for $C_{21}H_{15}NO_3$ (329.3) : C 76.58, H 4.59; found : C 76.31, H 4.89%.

4. Preparation of methyl trans-2-alkyl-3-(2-hydroxyphenyl)-3,4-dihydro-1(2H)-isoquinolinone-4-carboxylates(**6a-c**)andmethyltrans-3-(2-hydroxynaphthyl)-2-methyl-3,4-dihydro-1(2H)-isoquinolinone-4-carboxylate (**14**) (General procedure).

Triethylammonium salt **3a-c** or **11** (1 mmol) was dissolved in 12 ml dry chloroform with stirring and thionyl chloride 0.29 ml (4 mmol) was added to the solution. The mixture was stirred for 2 hours at room temperature. It was then concentrated in vacuo, dry methanol (2 ml) was added and the mixture was left at room temperature overnight. The solvent was evaporated in vacuo and the solid was stirred with 10 ml 5% aq. $NaHCO_3$ for 30 min. It was then filtered and recrystallized from ethanol.

6a (from **3a**) : Yield 65%, mp 254-255°C (ethanol). MS(CI) : 312 (71) [MH^+], 280 (10) [M^+-CH_3OH] IR : 1580, 1610 (C=C, arom.), 1650 (C=O, amide), 1735 (C=O, ester), 3200br (OH, Phenol). ^{1}H-NMR : 3.16 (3H, s, NCH_3), 3.70 (3H, s, $COOCH_3$), 4.13 (1H, d, $J_{3,4}$=1.3, H-4), 5.3 (1H, s, OH, phenol, exchangeable with D_2O), 5.59 (1H, d, $J_{3,4}$=1.4, H-3), 6.72-7.40 (7H, m, arom. H), 8.16 (1H, m, H-8). Calcd. for $C_{18}H_{17}NO_4$ (311.3) : C 69.44, H 5.50; found : C 69.59, H 5.37%.

6b (from **3b**) : Yield 83%, mp 193-194°C (ethanol). MS(CI) : 356 (100) [MH^+], 324 (50) [M^+-CH_3OH] IR ; 1650 (C=O, amide), 1740 (C=O, ester), 3250 br (OH, phenol). ^{1}H-NMR : 1.43 (3H, t, J=7.0, $C\underline{H}_3CH_2$), 3.16 (3H, s, NCH_3), 3.69 (3H, s, $COOCH_3$), 4.08 (2H, q, J=7, $CH_3C\underline{H}_2$), 4.14 (1H, s, $J_{3,4}$≤1.0, H-4), 5.58 (1H, s, $J_{3,4}$≤1, H-3), 6.01 (1H, s, OH, phenol), 6.29-7.38 (6H, m, arom.H), 8.16 (1H, m, H-8). Calcd. for $C_{20}H_{21}NO_5$ (355.4) : C 67.59, H 5.96; found C 67.77, H 6.06.

6c (from **3c**) : Yield 81%, mp 250-251°C (ethanol). MS : 339 (100) [M^+], 340 (29) [M^++1], 341 (5) [M^++2] IR : 1580, 1610 (C=C, arom), 1630 (C=O, amide), 1740 (C=O, ester), 3280 (OH, phenol) ^{1}H-NMR : 0.93 and 1.25 (each 3H, each d, J=7.0, $CH(C\underline{H}_3)_2$), 3.68 (3H, s, $COOCH_3$), 4.10 (1H, s, J≤1.0, H-4), 4.95 (1H, sept, $C\underline{H}(CH_3)_2$), 5.65 (1H, s, J≤1.0, H-3), 6.47-7.40 (7H, m, arom. H), 8.09 (1H, m, H-8), 9.36 (1H, s, OH, phenol). Calcd. for $C_{20}H_{21}NO_4$ (339.4) : C 70.78, H 6.24; found C 70.91, H 5.94.

14 and **12** (from **11**) : The mixture was separated by fractional recrystallization to give the **14** and **12**.

14 : Yield 15%, mp 242-243°C (ethanol). MS : 361 (63) [M^+], 302 (100) [M^+-$COOCH_3$]. IR : 1640 (C=O, amide). 1720 (C=O, ester), 3200 br (OH, naphtol). ^{1}H-NMR = 2.95 (3H, s, NCH_3), 3.68 (3H, s, $COOCH_3$), 4.62 (1H, d, $J^{3,4}$=5.7, H-4), 6.09 (1H, d, $J_{3,4}$=5.8, H-3), 7.08-7.75 (9H, m, arom. H), 8.05 (1H, m, H-8), 9.80 (1H, s, OH), naphthol. ^{13}C-NMR ($CDCl_3$+DMSO-d_6) : 32.4 NCH_3, 48.0, 51.9, C-3, C-4, 112.4, 118.5, 121.0, 122.1, 126.6, 127.0, 127.2, 128.1, 128.5, 129.0, 129.7, 130.9, 132.2, 133.7 arom. C and CH, 153.7C-10, 163.6 C-1, 171.1 $\underline{C}OOCH_3$. Calcd. for $C_{22}H_{19}NO_4$ (361.4) : C 73.11 H 5.30; found C 73.51 H5.52%.

Compound **12**, yield 40%, mp 194.5-195.5°C (ethyl acetate) showed identical mixed mp and spectral data with a sample of the same product, described above (procedure 3).

5. Preparation of methyl trans-3(2-methoxyphenyl)-2-methyl-3,4-dihydro-1(2H)-isoquinolinone-4-carboxylate (7).

6a (1 mol) was dissolved in methanol and chloroform (1:1), diazomethane (ether solution) was added and the mixture was left at room temperature overnight. The solution was concentrated and the crystals of 7 were filtered. Yield 77%, mp 126.5-127.5 °C (ethyl acetate); Lit. [4] mp 144-145 °C (methanol). MS(CI) : 326 (100) [MH^+] IR($CHCl_3$) : 1230 (C-O, ether), 1580, 1605 (C=C, arom), 1645 (C=O, amide, 1730 (C=O, ester). ^{1}H-NMR : 3.14 (3H, s, NCH_3), 3.70 (3H, s, $COOCH_3$), 3.91 (3H, s, OCH_3), 4.02 (1H, d, J=1.1, H-4), 5.57 (1H, d, J=1.4, H-3), 6.72-7.38 (7H, m, arom. H), 8.15 (1H, m, H-8). Calcd. for $C_{19}H_{19}NO_4$ (325.5): C 70.14, H 5.89; found C 70.42, H 6.05%.

IR- and ^{1}H-NMR spectra are in full agreement with those in the literature.[4]

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