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REACTIONS OF α-CHLOROIMINES WITH HOMOPHTHALIC ANHYDRIDES. SYNTHESIS AND MOLECULAR STRUCTURE OF 3,3a-DIHYDROFURO[3,4-c] ISOQUINOLINE-1,5(4H,9bH)-DIONES, FURO[3',4':9,9a]-8,9,16,16a-TETRAHYDRO-1H,3H,11H-DIBENZO[a,g]QUINOLIZINE-1,11-DIONES AND RELATED COMPOUNDS[1]

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Abstract

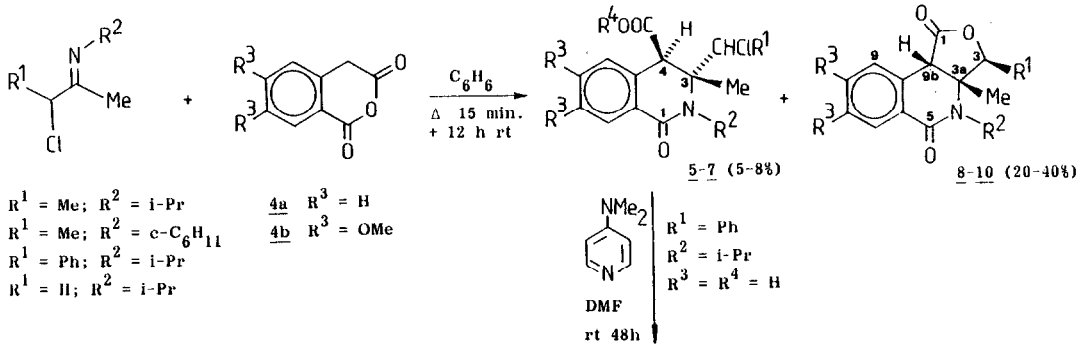
The reaction of α-chloroimines 1-3, resp. 11 with homophthalic anhydrides 4 leads to the formation of the isoquinoline ring system incorporated in furo[3,4-c]isoquinolinediones 8-10, resp. 13a-(chloromethyl)-8H-dibenzo[a,g]-quinolizine-8-one-13-carboxylic acids 12. The latter compounds were converted into furo[3',4':9,9a]dibenzoquinolizinediones 13 under basic conditions. NMR studies provided information concerning the relative configuration and the solution conformation of the various heterocycles obtained. The molecular structure of 8b and 12b was determined by X-ray analysis.

α-Chloroimines are bifunctional reagents which are suitable building blocks for the synthesis of a wide range of heterocyclic compounds.[2] Homophthalic anhydrides react with imino compounds to give substituted 1(2H)-isoquinolinones or heteropolycyclic compounds containing the 1(2H)-isoquinolinone fragment.[3] When the imino carbon atom is carrying a polar group, which may act as a leaving group (e.g., imidoyl halides and related compounds), the initial reaction step with homophthalic anhydrides is considered to be a C-C bond formation by means of the CH-acidic center of the anhydride.[4] In the absence of such a leaving group, the iminolysis of the

anhydride, i.e. C-N bond formation is accepted as initial step.[5] The reaction of homophthalic anhydrides with imines has been utilized for the preparation of a variety of alkaloids[3,6] and their analogs.[7]

We attempted the investigation of reactions of open-chain and cyclic α-chloroimines with homophthalic anhydrides aiming the synthesis of 1(2H)-isoquinolinones and related compounds possessing the chloro atom in the side chain as a potential leaving group, appropriate for a further elaboration of the molecular structure.

N-(3-chloro-2-butylidene)- (1), N-(3-chloro-3-phenyl-2-propylidene)- (2), and N-(1-chloro-2-propylidene)alkylamines (3), synthesized by reaction of the corresponding α-chloroketones with primary amines in the presence of titanium(IV) chloride,[8] reacted with homophthalic anhydrides 4 in aprotic solvents (benzene, short reflux; 1,2-dichloroethane, room temperature). The expected 3-(α-chloroalkyl)-3,4-dihydro-1(2H)-isoquinolinone-4-carboxy-



1a R^1 = Me; R^2 = i-Pr
1b R^1 = Me; R^2 = c-C_6H_{11}
2 R^1 = Ph; R^2 = i-Pr
3 R^1 = H; R^2 = i-Pr

4a R^3 = H
4b R^3 = OMe

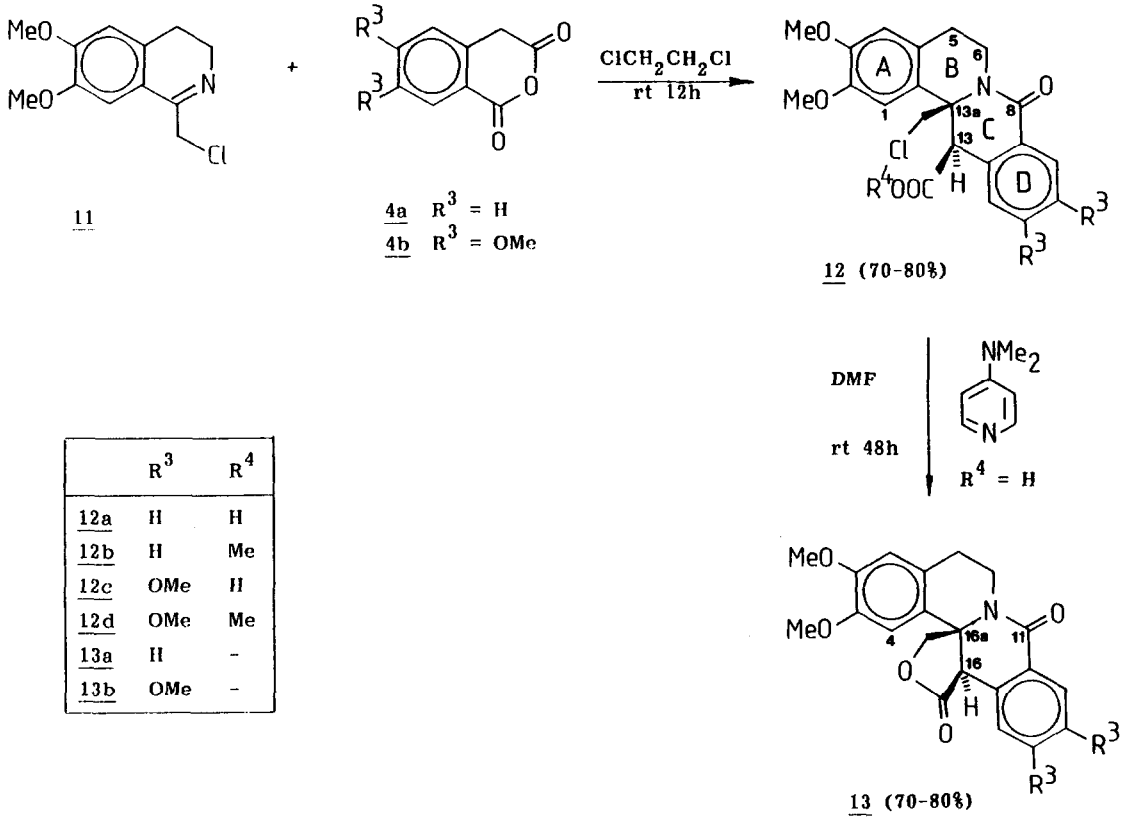
R^1 = Ph
R^2 = i-Pr
R^3 = R^4 = H

	R^1	R^2	R^3	R^4
5a	Me	i-Pr	H	Me
5b	Me	i-Pr	OMe	Me
5c	Me	i-C_6H_{11}	H	Me
6a	Ph	i-Pr	H	H
6b	Ph	i-Pr	H	Me
7	H	i-Pr	H	Me
8a	Me	i-Pr	H	-
8b	Me	i-Pr	OMe	-
8c	Me	c-C_6H_{11}	H	-
8d	Me	c-C_6H_{11}	OMe	-
9	Ph	i-Pr	H	-
10	H	i-Pr	H	-

Scheme 1

lic acids 5-7 (R^4 = H) were formed as minor products and were isolated and characterized as their respective methyl esters 5-7 (R^4 = Me), with the exception of the sparingly soluble acid 6a, which crystallizes from the reaction mixture (Scheme I). The corresponding 3,3a-dihydrofuro[3,4-c]isoquinoline-1,5(4H,9bH)-diones (8-10) were obtained as major products, in addition to 5-7 (Scheme I). These compounds incorporate the hitherto rarely reported[9,10] furo[3,4-c]isoquinoline ring system.

The 1-(chloromethyl)-6,7-dimethoxy-3,4-dihydroisoquinoline 11[11] reacted with homophthalic anhydrides 4 to yield the expected 13a-(chloromethyl)-5,6,13,13a-tetrahydro-8H-dibenzo[a,g]quinolizine-8-one-13-carboxylic acids 12 (R^4 = H) in 70-80% yield. The latter compounds were also converted to the corresponding methyl esters 12 (R^4 = Me) by reaction with diazomethane (Scheme II).



	R^3	R^4
12a	H	H
12b	H	Me
12c	OMe	H
12d	OMe	Me
13a	H	-
13b	OMe	-

Scheme II

All compounds from types 5-8, 10 and 12 were isolated as single diastereoisomers (for 9, see below). Their structure and stereochemistry were elucidated on the basis of spectral data, mainly detailed ^{1}H-NMR spectroscopy.

The similarity of the ^{1}H-NMR parameters for the chloro-compounds 5-7 leads to the conclusion that the acids and the methyl esters possess the same relative configuration. Difference NOE experiments performed for 5a permitted a tentative assignment of the configuration of compounds 5-7. Irradiation of Me-3 led to signal enhancements for H-4, CHCl and CH of the isopropyl group (R^2 = i-Pr). Assuming the most probable conformation for 5-7 to be close to a half-chair, the latter result indicates a pseudo-equatorial orientation of Me-3. On the other hand, irradiation of H-4 increased the intensity of Me-3, MeCCl (R^1 = Me) and H-5, which is in agreement with a pseudo-equatorial orientation of H-4 as well. Thus, the NOE results are supporting a configuration with trans-oriented Me-3 and H-4. Similar NMR studies of lactones 8-10 indicated that all compounds, prepared directly from homophthalic anhydrides and α-chloroimines, possess a configuration with Me-3a, H-9b and R^1 cis to each other. This was proven by the mutual NOE enhancements of all these signals. Irradiation of H-9b enhanced also H-9, indicating the pseudo-equatorial position of the former hydrogen. On the other hand, there was no NOE observed for H-3 upon irradiation of H-9b and vice versa. NOE effects were also observed in appropriate cases for the i-Pr and ortho-Ph-3 protons, also in agreement with the proposed configuration. The stereochemistry thus established was fully supported by the X-ray data for 8b (see below).

Thus, the chloro-derivatives 5-7 possess a configuration at C-3,4 different from that at C-3a,9b for the lactones 8-10. Nevertheless, the acid 6a was transformed into a lactone 9' under basic conditions [dimethylformamide, 4-(dimethylamino)pyridine, room temperature]. The ^{1}H NMR spectra of 9 (prepared as 8 and 10) and 9' differ significantly and suggest that their configuration is not the same. Indeed, the NOE experiments for 9' indicated mutual signal enhancement of Me-3a, H-9b and H-3, whereas the interactions with the latter proton were absent in the case of 9. This evidence shows that 9' retains the cis-annelation of the 2-furanone ring but differs from the lactones 8-10 in the configuration at C-3, the substituent R^1 being trans-oriented with respect to Me-3a and H-9b. This conclusion is also supported by the strong deshielding of Me-3a as well as by the shielding and the much larger nonequivalence of the Me groups in the isopropyl moiety observed for 9' as compared to 9, the effects being attributed to the phenyl group anisotropy.

The stereochemistry of the dibenzoquinolizine derivatives 12 was determined on the basis of the X-ray analysis of 12b (see below). Some information about the solution conformation was extracted from the ^{1}H NMR data. The values of the vicinal coupling constants between the four 5,6 protons support their axial/equatorial orientation and indicate that the favoured conformation of ring B is a twist-boat. In the NOE experiments performed for 12b, irradiation of H-1 led to enhancement of one of the protons of the chloromethyl group at the 13a-position, whereas irradiation of H-13 increased the intensity of the H-12 signal, but had no effect on H-5,6. This result is compatible with a nearly equatorial orientation (with respect to ring B) of the $ClCH_2$-group which exists in a strongly favoured conformation with nonequivalent CH_2 protons. The proposed stereochemistry for 12 is in agreement with the possibility to achieve a ring closure between the CH_2Cl and the COOH group, which was demonstrated by the smooth conversion of the acids 12a,c into the corresponding furo-[3',4':9,9a]-8,9,16,16a-tetrahydro-1H,3H,11H-dibenzo[a,g]quinolizine-1,11-diones (13a,b) under basic conditions. The structure of compounds 13 was confirmed by their spectral data. Compound 13a includes solvent upon crystallization which led to unsatisfactory analytical data. The similarity of the ^{1}H NMR parameters for compounds 12 and 13 indicates that their

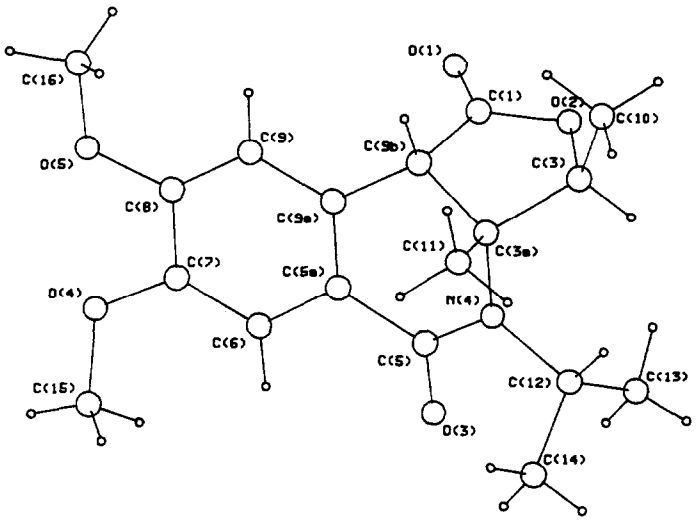


Fig. 1. X-ray structure of (3SR,3aRS,9bSR)-7,8-dimethoxy-3,3a-dimethyl-4-(iso-propyl)-3,3a-dihydrofuro[3,4c]isoquinoline-1,5(4H,9bH)-dione (8b).

stereochemistry is very close : the furanone ring in 13 is again cis-fused and the conformation of ring B is a twist-boat. An additional proof for the furanone ring closure in 13 is the decrease (in absolute value) of the geminal coupling constant of the CH_2-3 protons as compared to that in compounds 12. Up to our knowledge, compounds 13 are the first example of compounds possessing a furo[3',4':9,9a]-1H,3H,11H-dibenzo[a,g]quinolizine ring system.

The molecular structures of 8b and 12b were determined by the X-ray crystallographic data.

Crystal data for 8b : monoclinic, P $2_1/c$, a = 19.586(7), b = 7.690(1), c = 13.907(2) Å, β = 121.9(3)°, V = 1778(1) $Å^3$, Z = 4, D_x = 1.241 $g.cm^{-3}$, λ(MoKα) = 0.71073 Å, μ = 0.8 cm^{-1}, F(000) = 708, T = 292 K, R = 0.041 for 2394 observed reflections with $I > 3\sigma(I)$.

The B-ring of 8b has a conformation close to a half-chair type[12] (puckering parameters[13] Q = 0.3687, Φ = 81.96, Θ = 113.3°) with C-3a and C-9b atoms out of the least-squares plane through the other four atoms at -0.182(2) and 0.477(2) Å resp. The C-ring is envelope-shaped with folding of 32.3(1)° along the C-3...C-9b line (planarity of the four-atom fragment

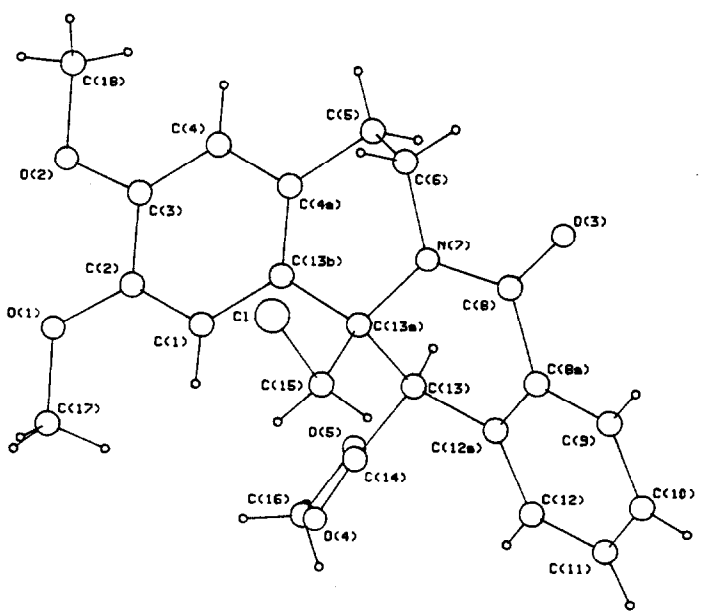


Fig. 2. X-ray structure of the methyl ester of (13RS,13aRS)-(chloromethyl)-2,3-dimethoxy-5,6,13,13a-tetrahydro-8H-dibenzo[a,g]quinolizine-8-one-13-carboxylic acid (12b).

within 0.001(1) Å), C-3a being 0.525(1) Å out of the plane. These two rings are cis-annelated with Me-3, Me-3a and H-9b cis-oriented to each other, in agreement with the NMR results. The axial position of Me-3 deduced from the NMR data is also confirmed.

Crystal data for 12b : monoclinic, P $2_1/c$, a = 9.532(2), b = 23.186(3), c = 9.444(2) Å, β = 99.036(1)°, V = 2061(1) $Å^3$, Z = 4, D_x = 1.340 $g.cm^{-3}$, λ(MoKα) = 0.70930 Å, μ = 2.1 cm^{-1}, F(000) = 872, T = 292 K, R = 0.040 for 2328 observed reflections with I > 3σ(I).

The puckering parameters[13] Φ = 102.8/103.5 and Θ = 115.3/112.4° show a non-standard conformation between half-chair and skew-boat[12] for both B- and C-rings. The corresponding puckering amplitudes 0.5284 and 0.5465 are greater than the 0.3687 value for the B-ring in 8b. In the B-ring C-6 and C-13a are displaced from the least-squares plane of C-4a,C-5,N-7,C-13b (planarity ± 0.027(2) Å at -0.686(2) and 0.233(2) Å resp. Analogously in the C-ring C-13a and C-8 are at -0.716(2) and 0.241(2) Å from its planar (within 0.007(2) Å) part. The COOMe and CH_2Cl groups are cis-positioned and in a gauche-conformation with respect to the C-13/C-13a bond (torsion angle 62.8(2)°). The former substituent is pseudo-equatorial while the latter one is axial in relation to the C-ring.

Experimental

Melting points (mp, uncorrected) : microhot stage Boetius PHMK 05. TLC : Silicagel $60F_{254}$ on aluminium sheets "Merck", layer thickness 0.2 mm. Solvent systems : ether/hexane 1:1 (1 part), and hexane/ethyl acetate/methanol/ammonia 120:100:15:10, upper layer (1 part). Column chromatography : silicagel type 60 "Merck", particle size 0.2-0.063 mm. IR spectra : C. Zeiss-Jena Specord IR-71 (nujol). ^1H NMR : Bruker WM-250 (250 MHz), ^{13}C NMR : Varian FT-80 (20 MHz) ($CDCl_3$ as solvent if not stated otherwise). Mass spectra (MS) : JEOL JMS D-300, chemical ionization if not stated otherwise.

X-ray structure determination :

Crystals of 8b were obtained by slow evaporation of a solution in ethanol. A transparent colourless prism-shaped crystal with sizes 0.2 x 0.16 x 0.2 mm was investigated. D_m was not determined. Enraf Nonius CAD4 diffractometer (graphite monochromator, MoKα radiation); $\omega/2\theta$ scan : speed 5 to 7°/min, width = 1.5 + 0.400 tan(θ). Cell constants from least squares of 22 reflections with 19.95 < θ < 21.78°. 8893 reflections measured in the range of $\sin(\theta)/\lambda$ < 0.660 (h : 0 to 18, k : -10 to 10, l : -22 to 21). Three standard reflections (monitored every 4 hrs), intensity variations < 0.1%. No decay correction. Lorentz and polarization correction; no ab-

sorption correction. 4591 unique reflections with $R_{(int)}$ = 0.020; 3067 reflections considered unobserved [$I < 3\sigma(I)$]. Structure solved by MULTAN82 and refined by full matrix least squares on F's. H-atoms refined isotropically. Final R = 0.0411, R_w = 0.0520 and S = 1.6421; weight w defined as $4F_o^2/[\sigma(F_o)^2]^2$. Max. (Δ/p) = 0.025; max. residual density 0.18 e.A^{-3}. Empirical correction for secondary extinction, $F_{(corr)} = F/(1+gI)$ with g = 0.811E-06. Atomic scattering factors and anomalous-dispersion coefficients from IT(1974). PDP11 computer with a locally modified CAD4/SPD software package used.

Crystals of 12b were obtained by slow evaporation of a chloroform solution. A transparent colourless prism-shaped crystal with sizes 0.1 x 0.17 x 0.14 mm was investigated. Scan speed 2 to 10°/min, width = 0.7 + 0.400 tan(θ). Cell constants from least squares of 22 reflections with 20.06 < θ < 21.06°. 6878 reflections measured in the range of $\sin(\theta)/\lambda < 0.572$ (h : 0 to 10, k : -26 to 26, l : -10 to 10). Three standard reflections (monitored every 2 hrs), intensity variation < 0.1%. 3217 unique reflections with $R_{(int)}$ = 0.015; 1115 reflections considered unobserved. H-atoms included in refinements as riding atoms except the methyl ones. Final R = 0.038, R_w = 0.051 and S = 1.7316, Max. (Δ/p) = 3.140; max. residual density 0.31 e.A^{-3}. $F_{(corr)}$ with g = 0.327E-06.

Preparation of (3RS,4SR)-3-(α-chloroalkyl)-3,4-dihydro-1(2H)-isoquinolinone-4-carboxylic acids and their methyl esters (5-7), and (3SR,3aRS,9bSR)-3,3a-dihydrofuro[3,4-c]isoquinoline-1,5(4H,9bH)-diones (8-10) (General Procedure).

Homophthalic anhydride 4 (2 mmol) and 4 ml dry benzene were added to the α-chloroketimine 1-3 (2 mmol). After 15 min of reflux the mixture was left overnight at ambient temperature, diluted with chloroform and extracted with 3 x 5 ml 10% aqueous $NaHCO_3$. After drying the organic layer, solvent evaporation and recrystallization, the neutral products 8-10 were obtained. The alkaline extract was acidified with hydrochloric acid, the precipitated acidic products were filtered off, dissolved in 4 ml MeOH/CH_2Cl_2 (1:1) mixture and treated with a solution of diazomethane in ether, prepared from nitrosomethylurea.[14] After solvent evaporation, the residue was chromatographed on a silica gel column using mixtures of ether/hexane in varying ratios as eluents. In this way the following compounds were obtained :

5a (from 1a and 4a) : Yield 4%; mp 127-129°C (ether). MS : 324 (MH^+). IR : 1655 (C=O amide), 1745 (C=O ester) cm^{-1}. ^1H NMR : 1.37 (3H,bd,J=6.1), CH_3CHCl-3; 1.60 (3H,s), Me-3; 1.52 (3H,d,J=6.7) and 1.72 (3H,d,J=6.6),

($C\underline{H}_3)_2CH$; 4.00 (1H,sept,J=6.7), $C\underline{H}(CH_3)_2$; 3.77 (3H,s), COOMe; 4.22 (1H,bs), H-4; 4.68 (1H,q,J=6.7), $CH_3C\underline{H}Cl$-3; 6.97 (1H,m), H-5; 7.36 (1H,m), H-7; 7.40 (1H,m), H-6; 8.03 (1H,m), H-8.

8a (from 1a and 4a) : Yield 39%; mp 253.5-254°C (ethanol). MS (electron impact, 70 eV) : 273 (M^+). IR : 1650 (C=O amide), 1785 (C=O, 5-membered lactone). ^1H NMR : 1.47 (3H,s), Me-3a; 1.48 (3H,d,J=6.9), Me-3, 1.58 (3H,d,J=6.9) and 1.59 (3H,d,J=6.5), ($C\underline{H}_3)_2CH$; 3.51 (1H,sept,J=6.8), $C\underline{H}(CH_3)_2$; 3.76 (1H,s), H-9b; 5.05 (1H,q,J=6.8), H-3; 7.36 (1H,dd,J=7.3, 1.1), H-9; 7.58 (1H,td,J=7.5,1.5), H-8; 7.48 (1H,td,J=7.5, 1.5), H-7; 8.10 (1H,dd,J=7.7,1.6), H-6. ^{13}C NMR : 20.2q, 20.6q and 49.1d, $(CH_3)_2CH$; 17.2q and 20.2q, Me-3 and Me-3a; 50.2d, C-9b, 67.4s, C-3a; 80.1d, C-3; 128.2d, 128.8d(2C) and 132.4, C-6,7,8,9; 128.6s and 128.7s, C-5a,9a; 162.5s, C-5; 172.9s, C-1. Calcd. for $C_{16}H_{19}NO_3$ (273.3) : C 70.31, H 7.01; found : C 70.77, H 7.45.

5b (from 1a and 4b) : Yield 6%; mp 170-172°C (ethanol); IR : 1650 (C=O,amide), 1740 (C=O,ester). ^1H NMR : 1.55 (3H,d,J=6.6), $C\underline{H}_3CHCl$-3; 1.60 (3H,s), Me-3; 1.50 (3H,d,J=6.7) and 1.71 (3H,d,J=6.4), ($C\underline{H}_3)_2CH$; 3.75 (1H,m), $C\underline{H}(CH_3)_2$; 3.73 (3H,s), COOMe; 3.89 (3H,s) and 3.93 (3H,s), MeO-6,7; 4.05 (1H,bs), H-4; 4.60 (1H,q,J=6.6), $CH_3C\underline{H}Cl$-3; 6.48 (1H,s), H-5; 7.58 (1H,s), H-8. Calcd. for $C_{19}H_{26}ClNO_5$ (383.8) : C 59.45, H 6.78; found : C 59.80, H 6.88%.

8b (from 1a and 4b) : Yield 37%; mp 254-255.5°C (ethanol). MS : 334 (MH^+). IR : 1645 (C=O amide), 1780 (C=O, 5-membered lactone). ^1H NMR : 1.47 (3H,s), Me-3a; 1.47 (3H,d,J=6.5), Me-3; 1.57 (3H,d,J=6.7) and 1.59 (3H,d,J=6.6), ($C\underline{H}_3)_2CH$; 3.50 (1H,sept,J=6.7), $C\underline{H}(CH_3)_2$; 3.67 (1H,s), H-9b; 4.99 (1H,q,J=6.7), H-3; 3.93 (3H,s) and 3.96 (3H,s), MeO-7,8; 6.81 (1H,s), H-9; 7.60 (1H,s), H-6. ^{13}C NMR : 20.8q, 21.0q and 48.8d, $(CH_3)_2CH$; 17.1q and 20.2q, Me-3 and Me-3a; 56.1q and 56.2q, MeO-7,8; 50.0d, C-9b; 67.5s, C-3a; 80.2d, C-3; 110.5d and 110.9d, C-6,9; 121.7s and 122.1s, C-5a,9a; 149.7s and 152.8s, C-7,8; 162.5s, C-5; 173.2, C-1. Calcd. for $C_{18}H_{23}NO_5$ (333.4) : C 64.85, H 6.95; found : C 64.59, H 6.85%.

5c (from 1b and 4a) : Yield 5%; mp 166-168°C (ethanol-hexane). MS : 364 (MH^+). IR : 1655 (C=O amide), 1730 (C=O ester). ^1H NMR : 1.65 (3H,d, J=6.5),$C\underline{H}_3CHCl$-3; 1.50 (3H,s), Me-3; 1.2-2.0 (8H,m) and 2.5-3.0 (3H,m), c-C_6H_{11}; 3.70 (3H,s), COOMe; 3.98 (1H,s), H-4; 4.75 (1H,q,J=6.5), $CH_3C\underline{H}Cl$-3; 7.1-7.5 (3H,m), H-5,6,7; 8.07 (1H,m), H-8.

8c (from 1b and 4a) : Yield 40%; mp 241-243°C (ethanol). MS : 314 (MH^+). IR : 1650 (C=O amide), 1790 (C=O, 5-membered lactone). ^1H NMR : 1.44 (3H,s), Me-3a; 1.48 (3H,d,J=6.7), Me-3; 1.2-1.9 (8H,m) and 2.5-3.0 (3H,m), c-C_6H_{11}; 3.73 (1H,s), H-9b; 4.97 (1H,q,J=6.7), H-3; 7.36 (1H,bd, J=7.4), H-9; 7.56 (1H,bt,J=7.4), H-8; 7.46 (1H,bt,J=7.5), H-7; 8.09 (1H,bd, J=7.7), H-6. ^{13}C NMR : 59.5d, 25.3t, 26.7t, 26.8t, 29.8t and 30.4t, c-C_6H_{11}; 17.3q and 20.3q, Me-3 and Me-3a; 49.1d, C-9b; 67.5s, C-3a; 128.3d, 128.6s, 128.8 (2C)s+d, aromatic C; 80.1d, C-3; 162.5s, C-5; 172.8s, C-1. Calcd. for $C_{19}H_{23}NO_3$ (314.4) : C 72.82, H 7.40; found : C 73.11, H 7.24%.

8d (from 1b and 4b) : Yield 33%; mp 202-204°C (ethanol). MS : 374 (MH^+). IR : 1650 (C=O amide), 1790 (C=O, 5-membered lactone). ^1H NMR : 1.45 (3H,s), Me-3a; 1.47 (3H,d,J=8.0), Me-3; 1.2-1.9 (8H,m) and 2.5-3.0 (3H,m), c-C_6H_{11}; 3.66 (1H,s), H-9b; 4.93 (1H,q,J=6.6), H-3; 3.92 (3H,s) and 3.95 (3H,s), MeO-7,8; 6.80 (1H,s), H-9; 7.59 (1H,s,H-6). ^{13}C NMR : 59.3d, 25.4t, 26.8 (2C)t, 30.0t and 30.5t, c-C_6H_{11}; 17.2q and 20.3q, Me-3 and Me-3a; 48.8d, C-9b; 67.4s, C-3a; 56.1q and 56.2q, MeO-7,8; 80.2d, C-3; 110.5d and 110.8d, C-6 and C-9; 121.7s and 122.0s, C-5a and C-9a; 149.6s and 152.7s, C-7 and C-8; 162.6s, C-5; 173.2s, C-1. Calcd. for $C_{21}H_{27}NO_5$ (373.4) : C 67.40, H 7.43; found : C 67.54, H 7.29%.

6a (from 2 and 4a) : Yield 8%; mp 170-172° (ethanol). IR : 1620 (C=O amide), 1720 (C=O acid). ^1H NMR : 1.85 (3H,bs), Me-3; 1.55 (3H,d,J=6.7) and 1.91 (3H,d,J=6.5), $(C\underline{H}_3)_2CH$; 4.23 (1H,sept,J=6.5), $C\underline{H}(CH_3)_2$; 4.35 (1H,bs), H-4; 5.82 (1H,bs), PhC$\underline{H}$Cl; 6.8-7.5 (8H,m), Ph, H-5,6,7; 7.95 (1H,m), H-8. Calcd. for $C_{21}H_{22}ClNO_3$ (371.8) : C 67.82, H 5.96; found : C 67.76, H 5.69%.

6b (from 2 and 4a) : Yield 9%; mp 165-168° (ethanol). IR : 1650 (C=O amide), 1740 (C=O ester). ^1H NMR : 1.77 (3H,bs), Me-3; 1.56 (3H,d,J=6.7) and 1.91 (3H,d,J=6.5), $(C\underline{H}_3)_2CH$; 4.21 (1H,sept,J=6.6), $C\underline{H}(CH_3)_2$; 4.35 (1H,bs), H-4; 3.88 (3H,s), COOMe; 5.78 (1H,bs), PhC$\underline{H}$Cl; 6.5-7.5 (9H,m), Ph, H-5,6,7,8. Calcd. for $C_{22}H_{24}ClNO_3$ (385.9) : C 68.47, H 6.27; found : C 68.77, H 6.21%.

9 (from 2 and 4a) : Yield 25%; mp 198-199°C (ether). MS : 336 (MH^+). IR : 1660 (C=O amide), 1790 (C=O, 5-membered lactone). ^1H NMR : 1.12 (3H,s), Me-3a; 1.63 (3H,d,J=6.6) and 1.70 (3H,d,J=6.8), $(C\underline{H}_3)_2CH$; 3.75 (1H,sept,J=6.6), $C\underline{H}(CH_3)_2$; 3.78 (1H,s), H-9b; 5.90 (1H,s), H-3; 7.2-7.6 (8H,m), Ph, H-7,8,9; 8.12 (1H,m), H-6. ^{13}C NMR : 20.6q, 21.2q and 21.8q, $(\underline{C}H_3)_2CH$ and Me-3a, 48.8d and 50.7d, $\underline{C}H(CH_3)_2$ and C-9b; 68.8s, C-3a; 84.9d,

C-3; 125.8, 128.1, 128.4, 128.7, 128.8, 129.0, 129.2, 132.4 and 139.9, aromatic C; 162.6s, C-5; 173.7, C-1.

7 (from 3 and 4a) : Yield 7%; oil. MS : 310 (MH^+). IR : 1660 (C=O amide), 1745 (C=O ester). ^1H NMR : 1.43 (3H,s), Me-3; 1.54 (3H,d,J=6.6) and 1.64 (3H,d,J=6.6), $(CH_3)_2CH$; 3.70 (1H,m), $CH(CH_3)_2$; 3.69 (3H,s), COOMe; 3.91 (1H,d,J=11.1) and 4.16 (1H,d,J=11.1), CH_2Cl; 4.08 (1H,s), H-4; 7.20 (1H,m), H-5; 7.3-7.6 (2H,m), H-6,7; 8.02 (1H,m), H-8.

10 (from 3 and 4a) : Yield 20%; mp 218-221°C (ethanol). MS : 260 (MH^+). IR : 1640 (C=O amide), 1780 (C=O, 5-membered lactone). ^1H NMR : 1.51 (3H,s), Me-3a; 1.55 (3H,d,J=6.9) and 1.60 (3H,d,J=6.5), $(CH_3)_2CH$; 3.53 (1H,sept,J=6.7), $CH(CH_3)_2$; 3.67 (1H,s), H-9b; 4.12 (2H,d,J=10.5) and 4.79 (2H,d,J=10.5), CH_2-3; 7.35 (1H,dd,J=7.2,1.1), H-9; 7.57 (1H,td,J=7.3,1.4), H-8; 7.48 (1H,td,J=7.5,1.4), H-7; 8.10 (1H,dd,J=7.5,1.4), H-6. Calcd. for $C_{15}H_{17}NO_3$ (259.3) : C 69.48, H 6.61; found : C 69.95, H 6.84%.

Preparation of (13RS,13aRS)-13a-(chloromethyl)-5,6,13,13a-tetrahydro-8H-dibenzo[a,g]quinolizine-8-one-13-carboxylic acids (12a,c) and their methyl esters (12b,d) (General Procedure).

1-(Chloromethyl)-6,7-dimethoxy-3,4-dihydroquinolinium perchlorate (mp 173-176°C; 4.1 mmol)[11] was suspended in dichloromethane and the mixture was treated with 10% aqueous sodium carbonate. The organic layer was dried, decanted and the solvent was evaporated in vacuo below 30°C. After addition of the homophthalic anhydride 4 (4 mmol) and dichloroethane (8 ml) the mixture was left overnight and the precipitated acid was filtered off and recrystallized. The methyl esters were prepared by treatment of the solution of the acid in 10 ml methanol/chloroform (1:1) with diazomethane[14] in ether. In this way the following compounds were prepared :

12a (from 11 and 4a) : Yield 78%, mp 196-199° (ethanol). MS : 402 (MH^+). IR : 1630 (C=O amide), 1730 (C=O acid), 3100 (broad, OH). ^1H NMR ($CDCl_3$/DMSO-d_6 3:1) : 2.84 (1H,m), H-5e; 2.91 (1H,m), H-5a; 3.25 (1H,m), H-6a; 5.12 (1H,m), H-6e; 3.87 (3H,s) and 3.89 (3H,s), MeO-2,3; 3.97 (1H,d, J=12.3) and 4.79 (1H,d,J=12.3), CH_2-13a; 4.25 (1H,s), H-13; 6.79 (1H,s) and 7.00 (1H,s), H-1,4; 7.16 (1H,m), H-12; 7.47 (1H,m), H-10; 7.54 (1H,m), H-11; 8.10 (1H,m), H-9. Calcd. for $C_{21}H_{20}ClNO_5$ (401.8) : C 62.76, H 5.02, Cl 8.80; found : C 62.95, H 4.85, Cl 8.84%.

12b (from 12a) : Mp 239-240° (ethanol). MS : 416 (MH^+). IR : 1645 (C=O amide), 1730 (C=O ester). ^1H NMR : 2.83 (1H,m,$J_{5e,5a}$=15.4,

$J_{5e,6a}$=3.2), H-5e; 2.93 (1H,m,$J_{5a,6a}$=11.5), H-5a; 3.29 (1H,m), H-6a; 5.21 (1H,ddd,$J_{6e,6a}$=12.8,$J_{6e,5a}$=4.3,$J_{6e,5e}$=2.2), H-6e; 3.74 (3H,s), COOMe; 3.87 (3H,s), MeO-2; 3.92 (3H,s), MeO-3; 4.00 (1H,d,J=12.5) and 4.74 (1H,d, J=12.5), CH_2-13a; 4.33 (1H,s), H-13; 6.75 (1H,s), H-4; 6.77 (1H,s), H-1; 6.94 (1H,m), H-12; 7.48 (1H,m), H-10; 7.50 (1H,m), H-11; 8.18 (1H,m), H-9. Calcd. for $C_{22}H_{22}ClNO_5$ (415.8) : C 63.53, H 5.33, Cl 8.52; found : C 63.86, H 5.28, Cl 8.79%.

12c (from 11 and 4b) : Yield 75%, Mp 210-213° (ethanol). MS : 462 (MH^+). IR : 1630 (C=O amide), 1730 (C=O acid). ^1H NMR : 2.83 (1H,m), H-5e; 2.90 (1H,m), H-5a; 3.28 (1H,m), H-6a; 5.15 (1H,m), H-6e; 3.88 (3H,s) and 3.90 (3H,s), MeO-2,3; 3.92 (3H,s) and 3.98 (3H,s), MeO-10,11; 4.09 (1H,d,J=12.4) and 4.70 (1H,d,J=12.4), CH_2-13a; 4.32 (1H,d,J=0.9), H-13; 6.52 (1H,s), H-12; 7.68 (1H,s), H-9; 6.75 (1H,s) and 6.88 (1H,s), H-1,4. Calcd. for $C_{23}H_{24}ClNO_7$ (461.9) : C 59.8, H 5.24; found : 59.72, H 4.93%.

12d (from 12c) : Mp 192-194° (ethanol). MS : 476 (MH^+). IR : 1650 (C=O amide), 1735 (C=O ester). ^1H NMR : 2.83 (1H,m), H-5e; 2.92 (1H,m), H-5a; 3.28 (1H,m), H-6a; 5.16 (1H,ddd,$J_{6e,6a}$=12.5,$J_{6e,5a}$=4.1,$J_{6e,5e}$=2.0), H-6e; 3.73 (3H,s), COOMe; 3.87 (3H,s) and 3.89 (3H,s), MeO-2,3; 3.92 (3H,s) and 3.98 (3H,s), MeO-10,11; 4.10 (1H,d,J=12.4) and 4.69 (1H,d,J=12.4), CH_2-13a; 4.27 (1H,d,J=0.9), H-13; 6.34 (1H,s), H-12; 7.67 (1H,s), H-9; 6.74 (1H,s) and 6.76 (1H,s), H-1,4. Calcd. for $C_{24}H_{26}ClNO_7$ (475.9) : C 60.05, H 5.50; found : C 60.11, H 5.50%.

Preparation of the 3,3a-dihydrofuro[3,4-c]isoquinoline-1,5(4H,9bH)dione 9' and furo[3',4':9,9a]-8,9,16,16a-tetrahydro-1H,3H,11H-dibenzo[a,g]quinolizine-1,11-diones 13a,b.

To a solution of the acid 6a, 12a,c (0.5 mmol) in 1 ml dimethylformamide, 4-(dimethylamino)pyridine (0.061 g, 0.5 mmol) was added and the mixture was left 48 hrs at room temperature. After dilution with chloroform, washing with brine, aq. HCl (1:4) and drying, the solvent was evaporated and the residue was chromatographed on silica gel using mixtures of ether and hexane in varying ratios as eluents (in the case of 9') or recrystallized from ethanol (for 13a,b).

9' (from 6a) : Yield 19%, mp 162-164°C (ether-hexane). MS : 336 (MH^+). IR (nujol, cm^{-1}) : 1650 (CO amide), 1790 (CO, five-membered lactone). ^1H NMR : 1.91 (3H,s), Me-3a; 0.90 (3H,d,J=6.5) and 1.39 (3H,d,J=6.6), $(CH_3)_2CH$; 3.21 (1H,sept,J=6.5), $CH(CH_3)_2$; 3.97 (1H,s), H-9b; 5.43 (1H,s), H-3; 7.75 (1H,bd,J=7.7), H-9; 7.59 (1H,td,J=7.5,1.4), H-8; 7.44 (1H,td,

J=7.6,1.0), H-7; 8.00 (1H,dd,J=7.7,1.3), H-6, 7.01 (2H,dd,J=7.6,1.4), o-Ph; 7.2-7.3 (3H,m), m,p-Ph.

13a (from 12a) : Yield 70%, mp 178-179° (ethanol). IR : 1645 (C=O amide), 1780 (C=O, 5-membered lactone). ^{1}H NMR : 2.68 (1H,m), H-8e; 3.18 (1H,m), H-8a; 3.37 (1H,m), H-9a; 4.91 (1H,m), H-9e; 3.85 (3H,s) and 3.87 (3H,s), MeO-5,6; 4.41 (1H,s), H-16; 4.46 (1H,d,J=9.8) and 4.74 (1H,d, J=9.8), CH_2-3; 6.62 (1H,s) and 6.78 (1H,s), H-4,7; 7.4-7.6 (3H,m), H-13,14, 15; 8.20 (1H,m), H-12.

13b (from 12c) : Yield 81%, mp 245-246° (ethanol). IR : 1650 (C=O amide), 1780 (C=O, 5-membered lactone). ^{1}H NMR : 2.70 (1H,m), H-8e; 3.10 (1H,m), H-8a; 3.33 (1H,m), H-9a; 4.86 (1H,m), H-9e; 3.86 (3H,s), 3.88 (3H,s), 3.93 (3H,s) and 3.97 (3H,s), MeO-5,6,13,14; 4.29 (1H,s), H-16; 4.49 (1H,d,J=9.4) and 4.67 (1H,d,J=9.4), CH_2-3; 6.64 (1H,s) and 6.76 (1H,s), H-4,7; 7.04 (1H,s), H-15; 7.67 (1H,s), H-12. Calcd. for $C_{23}H_{23}NO_7$ (425.4) : C 64.93, H 5.45; found : C 65.20, H 5.60.

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