Synthesis of Some Novel Fused Tetracyclic Quinolonecarboxylic Acids *via* 7-Methyl-6,7,8,9-tetrahydro-3*H*-imidazo[4,5-*f*]quinoline and 6-Methyl-5,6,7,8-tetrahydro-1*H*-imidazo[4,5-*g*]quinoline

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A series of fused tetracyclic quinolonecarboxylic acids was prepared for biological evaluation. These compounds were synthesized by a route involving a regiospecific functionalization of 5-fluoro-2-methyl-1,2,3,4-tetrahydroquinoline to obtain a series of new substituted 7-methyl-6,7,8,9-tetrahydro-3*H*-imidazo[4,5-*f*]quinolines and 6-methyl-5,6,7,8-tetrahydro-1*H*-imidazo[4,5-*g*]quinolines as convenient precursors of quinolones.

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In recent years, antibacterial research has focused on discovery of agents which exhibit improved activity, particularly against resistant organisms such as *Staphylococcus aureus*, and decreased incidence of side effects, specially for the quinolone agents [1]. Certain structural features of quinolone-3-carboxylic acid family contribute significantly to their antibiotic efficacy [2a-b]. Among the different quinolone class of antibacterial agents there is a series of potent tricyclic compounds containing a three-atom bridge connecting the vicinal positions of quinolones. This series includes Oxolinic acid [3], Tioxacin [4], Flumequine [5], Ofloxacin [6], and different tricyclic quinolones which contain a three-atom bridge connecting the C2 and either N1 [7a-c] or C3 [7d]. In order to study the structure-activity relationships, we are interested in preparing novel fused tetracyclic quinolones candidates for biological evaluation.

In this paper we report first a synthesis of new 7-methyl-6,7,8,9-tetrahydro-3*H*-imidazo[4,5-*f*] and 6-methyl-5,6,7,8-tetrahydro-1*H*-imidazo[4,5-*g*]quinolines as precursors of quinolones, containing a benzo[*i,j*]quinolizine structure. These imidazo compounds are generally synthesized by a Skraup or Doebner-Miller reaction from an aminobenzimidazole [8]; but it is not always possible to obtain a selective cyclization, giving either 7-methyl-3*H*-imidazo[4,5-*f*]-quinoline or 6-methyl-1*H*-imidazo[4,5-*g*]quinoline.

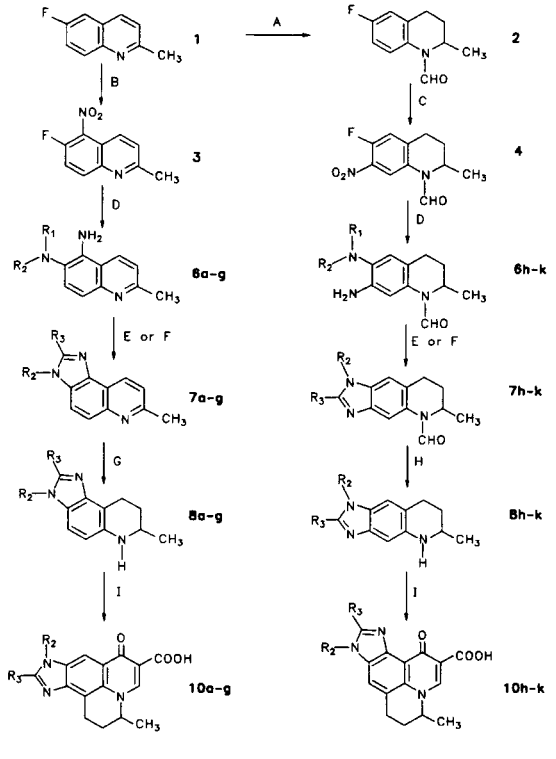
In the synthesis that we proposed it is first necessary to prepare the 6-fluoro-2-methyl-5-nitroquinoline and the 6-fluoro-1-formyl-2-methyl-7-nitro-1,2,3,4-tetrahydroquinoline. These two compounds were obtained by electrophilic substitution from corresponding 6-fluoro-2-methylquinoline and 6-fluoro-1-formyl-2-methyl-1,2,3,4-tetrahydroquinoline this last product itself synthesized in one step from the 6-fluoro-2-methylquinoline by a convenient reduction [9]. It is well known that substitution on 6-halogenated-2-methylquinolines gives a mixture of 5- and 5,8-substituted compounds [10]. But with special conditions described in the experimental part, we obtained the 5-nitro compound in 80% yield from **1** and the 7-nitro compound from **2** in about the same yield (Scheme 1B, C).

The nitro compounds **3** and **4** were aminated by nucleophilic substitution in position 6 with a primary or secondary amine, in the presence of potassium carbonate in order to increase the yields (Scheme 1D).

The reduction of the nitro group in a neutral medium such as ethanol, with stannous chloride [11] gives the *ortho*-diaminoquinolines **6a-g** in good yields.

It is important to note that, during this step, we already obtained some traces of 7-methyl-3*H*-imidazo[4,5-*f*]quinolines and 5-formyl-6-methyl-5,6,7,8-tetrahydro-1*H*-imidazo-

Scheme 1



A) 5HCOOH,2N$(C_2H_5)_3$, Pd/C; B) 1.oleum, HNO_3 2.NH_4OH; C) oleum, HNO_3
D) 1.K_2CO_3, R_1NHR_2 2.$SnCl_2$, C_2H_5OH; E) 1.H_2O_2, HCOOH 2.Na_2CO_3; F) $HC(OC_2H_5)_3$ reflux
G) 1.5HCOOH,2N$(C_2H_5)_3$, Pd/C 2.HCl, H_2O 3.NaOH; H) 1.HCl, H_2O 2.NaOH
I) 1.DEEM 2.PPE 3.NaOH 10% 4.HCl

Compounds 6, 7, 8, 10	R_1	R_2	R_3
a	$-CH_2CH_3$	$-CH_2CH_3$	$-CH_3$
b	$-(CH_2)_3CH_3$	$-(CH_2)_3CH_3$	$-(CH_2)_2CH_3$
c	$-(CH_2)_4-$	$-(CH_2)_3-$	
d	$-(CH_2)_5-$	$-(CH_2)_4-$	
e	$-CH_3$	$-CH_3$	H
f	$-CH(CH_3)(CH_2)_4-$	$-CH(CH_3)(CH_2)_3-$	
g	H	$-C_6H_5$	H
h	$-CH_2CH_3$	$-CH_2CH_3$	$-CH_3$
i	$-(CH_2)_4-$	$-(CH_2)_3-$	
j	$-(CH_2)_5-$	$-(CH_2)_4-$	
k	H	$-(CH_2)_3CH_3$	H

[4,5-*g*]quinolines in the case of compounds which correspond to the substitution of the fluorine atom by a secondary amine. This reaction that proceeds through the *tert*-amino effect [12] doesn't permit us to obtain the imidazoquinolines in good yield even with a longer reaction time or a different reducing agent. In this case the amino compounds have not been isolated but used directly in the next step.

The synthesis of the imidazole moiety is carried out according to methods A or B.

Method A, which proceeds with triethylorthoformate, is used when the condensed amine is primary (Scheme 1F).

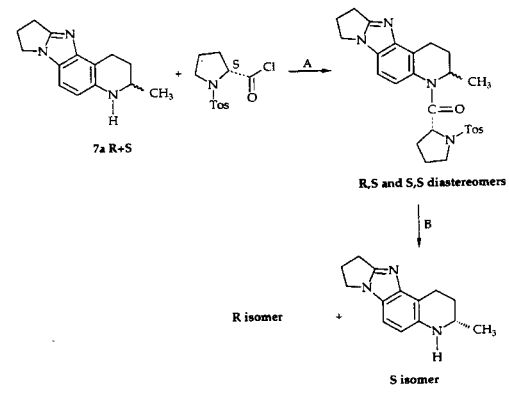
In the case of a secondary amine, we realized an oxidative cyclization (method B) [13], with performic acid, which is prepared *in situ* from formic acid and hydrogen peroxide. By this process, the ring closure between the primary amino group and an α-methylene of the secondary condensed amine cyclizes to the imidazo ring in good yields (Scheme 1E). When the secondary amines contain two heteroatoms, like morpholine or the *N*-methylpiperazine, the cyclization is unsuccessful [14].

The selective reduction of the 7-methyl-3*H*-imidazo-[4,5-*f*]quinolines, by triethylammonium formate with palladium on activated carbon as the catalyst [15] permits us to reduce only the pyridine ring. The compounds obtained are not isolated but directly deformylated to give the corresponding 7-methyl-6,7,8,9-tetrahydroimidazoquinolines (Scheme 1G).

In the same way, the hydrolysis by dilute hydrochloric acid of compounds **7h-k** gives the free amine (Scheme 1H).

Compounds **7a-k** were obtained as racemic mixtures and the stereoisomers can be separated according to the Gerster method [16]. Diastereomeric amides, prepared from compounds **7a-k** and *N*-tosyl-*S*-prolyl chloride, are separated by flash chromatography. Hydrolysis of the amides in refluxing 2*N* sodium ethoxide gives the *R* and *S* isomers. Only compounds **7c** *R* and *S* have been prepared by this route (Scheme 2).

Scheme 2



A) DIPEA, CH_2Cl_2
B) 1.Separation by flash chromatography 2.C_2H_5ONa

These tetrahydroimidazoquinolines permit us to obtain a new class of precursors of quinolone, that, according to the reaction of condensation of diethyl ethoxymethylenemalonate and a cyclization of the intermediate in polyphosphoric acid ethyl ester (PPE) gave quinolonecarboxylic acid esters which are hydrolysed in alkaline medium. The fused tetracyclic quinolonecarboxylic acids **9a-k** are recovered in the usual manner (Scheme 1I).

The biological testing data for these compounds are forthcoming and will be reported elsewhere.

EXPERIMENTAL

Melting points were determined on a Leitz 350 microscope hot stage and are uncorrected. The ^1H nmr spectra were recorded on a Brucker AM 300 W.B. (300.134 MHz). Chemical shifts are expressed in ppm (δ) relative to internal tetramethylsilane. The oils or the low melting products were purified by column chromatography on silica gel with chloroform/methanol or cyclohexane/acetone as the eluents.

6-Fluoro-1-formyl-2-methyl-1,2,3,4-tetrahydroquinoline (**2**).

A mixture of 16.1 g (0.1 mole) of **1**, 50 ml of triethylammonium formate and 0.3 g of (5%) palladium on charcoal is heated. The triethylamine formed is distilled during the reaction. The residue is dissolved in dichloromethane, the catalyst filtered and the organic layer washed twice with 20 ml of 10% hydrochloric acid and twice with water, then dried over magnesium sulfate. After evaporation of the solvent, compound **6** is crystallized from diisopropyl ether, yield 16.4 g (85%), mp 64-66°; ^1H nmr (deuteriochloroform): δ 1.1 (d, J = 6.0 Hz, 3H, CH_3), 1.3-2.3 (m, 2H, H3), 2.5-2.8 (m, 2H, H4), 4.5-4.9 (m, 1H, H2), 6.7-7.1 (m, 3H, Ar-H), 8.6 (s, 1H, HCO).

Anal. Calcd. for $C_{11}H_{12}FNO$: C, 68.38; H, 6.26; N, 7.25. Found: C, 68.43; H, 6.24; N, 7.23.

6-Fluoro-2-methyl-5-nitroquinoline (**3**).

To 80 ml of 20% sulfur trioxide fuming sulfuric acid is slowly added 16.1 g (0.1 mole) of **1**. The reaction mixture is cooled in an ice bath with stirring and 0.2 g of sodium nitrite (0.003 mole) and after 7 ml of 65% nitric acid were then slowly added. The temperature is maintained between 0° and 10° during the addition. The reaction mixture is warmed to room temperature and stirred during 2 hours. The mixture is poured onto ice. The solution is neutralized to *p*H 7 using concentrated ammonium hydroxide. The precipitate is filtered, dried by azeotropic distillation in cyclohexane and recrystallized from the same solvent, yield 16.5 g (80%), mp 113-115°; ^{1}H nmr (deuteriochloroform): δ 2.7 (s, 3H, CH_3), 7.3-8.3 (m, 4H, Ar-H).

Anal. Calcd. for $C_{10}H_7FN_2O_2$: C, 58.26; H, 3.42; N, 13.59. Found: C, 58.20; H, 3.41; N, 13.58.

6-Fluoro-1-formyl-2-methyl-7-nitro-1,2,3,4-tetrahydroquinoline (**4**).

To 81 ml of 20% sulfur trioxide fuming sulfuric acid is added first, below 15°, 7.7 ml of 65% nitric acid then 19.3 g (0.1 mole) of **2**. The reaction mixture is warmed to room temperature and stirred during 45 minutes. The mixture is poured onto ice (500 g). The solution is extracted with 400 ml of dichloromethane, then the organic layer is washed once with 100 ml of 5% sodium bicarbonate, once with 100 ml of water, dried over magnesium sulfate, filtered and flash distilled. The crude product is recrystallized from cyclohexane, yield 19 g (80%), mp 128-130°; ^{1}H nmr (deuteriochloroform): δ 1.2 (d, J = 6.6 Hz, 3H, CH_3), 1.7-2.2 (m, 2H, H3), 2.7-2.95 (m, 2H, H4), 4.8-4.9 (m, 1H, H2), 7.1 (d, J = 10.5 Hz, 1H, H5), 7.8 (d, J = 6.6 Hz, 1H, H8), 8.7 (s, 1H, HCO).

Anal. Calcd. for $C_{11}H_{11}FN_2O_3$: C, 55.46; H, 4.65; N, 11.76. Found: C, 55.36; H, 4.56; N, 11.68.

General Procedure for the Condensation of the Amines.

To cooled *N,N*-dialkylamine, *N*-alkylamine or arylamine (0.16 mole) is slowly added 8.2 g of **3** or **4** (0.04 mole), and 2.7 g of potassium carbonate (0.02 mole). The reaction mixture is stirred and refluxed during 2 hours. After cooling, the potassium carbonate is filtered and the filtrate evaporated *in vacuo*. The residue is dissolved in 100 ml of dichloromethane; the organic layer is washed twice with water and dried over anhydrous magnesium sulfate. The drying agent is discarded by filtration and the dichloromethane removed by flash distillation.

6-*N,N*-Diethylamino-2-methyl-5-nitroquinoline (**5a**).

The yield is 90%, oil; ^{1}H nmr (deuteriochloroform): δ 1.05 (t, J = 7.0 Hz, 6H, 2 ethyl CH_3), 2.7 (s, 3H, CH_3), 3.1-3.2 (m, 4H, 2 ethyl CH_2), 7.3 (d, J = 9.0 Hz, 1H, H3), 7.5 (d, J = 9.0 Hz, 1H, H7), 7.8 (d, J = 9.0 Hz, 1H, H4), 8.0 (d, J = 9.0 Hz, 1H, H8).

6-*N,N*-Dibutylamino-2-methyl-5-nitroquinoline (**5b**).

The yield is 95%, oil; ^{1}H nmr (deuteriochloroform): δ 0.9 (t, J = 7.0 Hz, 6H, 2 butyl CH_3), 1.25-1.35 (m, 4H, 2 butyl CH_2), 1.45-1.55 (m, 4H, 2 butyl CH_2), 2.7 (s, 3H, CH_3), 3.2 (t, J = 7.0 Hz, 4H, 2 butyl CH_2), 7.3 (d, J = 9.0 Hz, 1H, H3), 7.6 (d, J = 9.0 Hz, 1H, H7), 7.9 (d, J = 9.0 Hz, 1H, H4), 8.0 (d, J = 9.0 Hz, 1H, H8).

2-Methyl-5-nitro-6-pyrrolidinoquinoline (**5c**).

The yield is 71%, mp 181-183°; ^{1}H nmr (deuteriochloroform): δ 2.0-2.1 (m, 4H, 2 pyrrolidinyl CH_2), 2.7 (s, 3H, CH_3), 3.4-3.45 (m, 4H, 2 pyrrolidinyl CH_2), 7.3-7.4 (m, 2H, H3 and H7), 8.0 (d, J = 8.8 Hz, 1H, H4), 8.1 (d, J = 9.3 Hz, 1H, H8).

2-Methyl-5-nitro-6-piperidinoquinoline (**5d**).

The yield is 90%, mp 91-93°; ^{1}H nmr (deuteriochloroform): δ 1.7 (m, 6H, 3 piperidinyl CH_2), 2.7 (s, 3H, CH_3), 3.1-3.2 (m, 4H, 2 piperidinyl CH_2), 7.3 (d, J = 8.8 Hz, 1H, H3), 7.5 (d, J = 9.3 Hz, 1H, H7), 7.9 (d, J = 8.8 Hz, 1H, H4), 8.0 (d, J = 9.3 Hz, 1H, H8).

6-*N,N*-Dimethylamino-2-methyl-5-nitroquinoline (**5e**).

The yield is 80%, oil; ^{1}H nmr (deuteriochloroform): δ 2.6 (s, 3H, CH_3), 3.1 (s, 6H, 2 CH_3), 7.3 (d, J = 8.8 Hz, 1H, H3), 7.5 (d, J = 9.3 Hz, 1H, H7), 7.8 (d, J = 8.8 Hz, 1H, H4), 8.0 (d, J = 9.3 Hz, 1H, H8).

2-Methyl-5-nitro-6-(2-methylpiperidino)quinoline (**5f**).

The yield is 96%, oil; ^{1}H nmr (deuteriochloroform): δ 0.9 (d, J = 6.0 Hz, 3H, piperidinyl CH_3), 1.3-1.5 (m, 2H, piperidinyl CH_2), 1.6-1.8 (m, 4H, 2 piperidinyl CH_2), 2.7 (s, 3H, CH_3), 3.2-3.3 (m, 3H, CH_2 and piperidinyl CH), 7.4 (d, J = 8.8 Hz, 1H, H3), 7.7 (d, J = 9.3 Hz, 1H, H7), 7.9 (d, J = 8.8 Hz, 1H, H4), 8.1 (d, J = 9.3 Hz, 1H, H8).

2-Methyl-5-nitro-6-phenylaminoquinoline (**5g**).

The yield is 72%, mp 153-155°; ^{1}H (deuteriochloroform): δ 2.7 (s, 3H, CH_3), 7.5-8.8 (m, 9H, ArH), 10.0 (m, 1H, NH).

6-*N,N*-Diethylamino-1-formyl-2-methyl-7-nitro-1,2,3,4-tetrahydroquinoline (**5h**).

The yield is 93%, oil; ^{1}H nmr (deuteriochloroform): δ 1.1 (t, J = 7.3 Hz, 6H, 2 ethyl CH_3), 1.2 (d, J = 6.6 Hz, 3H, CH_3), 1.7-2.2 (m, 2H, H3), 2.5-3.0 (m, 2H, H4), 3.1-3.2 (m, J = 7.3 Hz, 4H, 2 ethyl CH_2), 4.8-4.9 (m, 1H, H2), 7.0-7.5 (m, 2H, Ar-H), 8.6 (s, 1H, HCO).

1-Formyl-2-methyl-7-nitro-6-pyrrolidino-1,2,3,4-tetrahydroquinoline (**5i**).

The yield is 95%, mp 152-154°; ^{1}H nmr (deuteriochloroform): δ 1.2 (d, J = 6.5 Hz, 3H, CH_3), 1.55-1.65 (m, 1H, 1H3), 1.85-2.05 (m, 4H, 2 pyrrolidinyl CH_2), 2.1-2.2 (m, 1H, 1H3), 2.6-2.8 (m, 2H, H4), 3.1-3.3 (m, 4H, 2 pyrrolidinyl CH_2), 4.7-4.8 (m, 1H, H2), 6.7-7.5 (2s, 2H, Ar-H), 8.5 (s, 1H, HCO).

1-Formyl-2-methyl-7-nitro-6-piperidino-1,2,3,4-tetrahydroquinoline (**5j**).

The yield is 93%, oil; ^{1}H nmr (deuteriochloroform): δ 1.2 (d, J = 6.6 Hz, 3H, CH_3), 1.5-1.8 (m, 8H, H3 and 3 piperidinyl CH_2), 2.6-2.9 (m, 2H, H4), 2.9-3.1 (m, 4H, 2 piperidinyl CH_2), 4.8-4.9 (m, 1H, H2), 6.9-7.6 (2s, 2H, Ar-H), 8.6 (s, 1H, HCO).

6-*N*-Butylamino-1-formyl-2-methyl-7-nitro-1,2,3,4-tetrahydroquinoline (**5k**).

The yield is 78%, mp 111-113°; ^{1}H nmr (deuteriochloroform): δ 1.0 (t, J = 7.3 Hz, 3H, butyl CH_3), 1.3 (d, J = 6.5 Hz, 3H, CH_3), 1.45-1.65 (m, 3H, 1H3 and butyl CH_2), 1.7-1.8 (m, 2H, butyl CH_2), 2.2-2.3 (m, 1H, 1H3), 2.6-2.8 (m, 2H, H4), 3.3 (t, J = 6.8 Hz, 2H, butyl CH_2), 4.7-4.8 (m, 1H, H2), 6.7-8.0 (2s, 2H, Ar-H), 8.6 (s, 1H, HCO).

General Procedure for the Reduction of the Nitro Group.

To a stirred and cooled (0°) solution of nitro derivatives, **5a-k** (0.03 mole) in ethyl alcohol (70 ml) is added 23 g (0.12 mole) of

stannous chloride. The temperature is maintained during the addition. The reaction mixture is then refluxed during 2 hours. After cooling and evaporation of the solvent, the residue is tritured with 30% aqueous sodium hydroxide and extracted with 100 ml of chloroform. The organic layer is then washed twice with 100 ml of water, dried over magnesium sulfate, filtered and flash distilled.

5-Amino-2-methyl-6-phenylaminoquinoline (**6g**).

The yield is 71%, mp 217-219°; ^{1}H nmr (deuteriochloroform): δ 1.75 (m, 1H, NH), 2.8 (s, 3H, CH_3), 4.4-5.3 (m, 2H, NH), 6.7-8.2 (m, 9H, ArH).

7-Amino-6-*N*-butylamino-1-formyl-2-methyl-1,2,3,4-tetrahydroquinoline (**6k**).

The yield is 91%, oil; ^{1}H nmr (deuteriochloroform): δ 1.0 (t, J = 7.3 Hz, 3H, butyl CH_3), 1.2 (d, J = 6.6 Hz, 3H, CH_3), 1.4-1.5 (m, 3H, 1H3 and butyl CH_2), 1.6-1.7 (m, 2H, butyl CH_2), 2.0-2.1 (m, 1H, 1H3), 2.5-2.8 (m, 2H, H4), 3.1 (t, J = 6.8 Hz, 2H, butyl CH_2), 3.7 (m, 3H, NH), 4.7-4.8 (m, 1H, H2), 6.45-6.55 (m, 2H, Ar-H), 8.5 (s, 1H, HCO).

General Procedure for the Cyclization with the Performic Acid (Method B).

To cooled formic acid (0.6 mole) are slowly added compounds **6a-f, 6h-j** (0.02 mole). The reaction mixture is stirred and refluxed during 5 minutes. After cooling in an ice bath, 30-32% hydrogen peroxide (0.12 mole) is slowly added. The reaction mixture is still refluxed during 1.5 hours. The solution is cooled and neutralized with potassium carbonate (0.3 mole). The mixture is extracted twice with 100 ml of chloroform. The organic layer is dried over magnesium sulfate, filtered and flash distilled.

2,7-Dimethyl-3-ethyl-3*H*-imidazo[4,5-*f*]quinoline (**7a**).

The yield is 69%, mp 149-151°; ^{1}H nmr (deuteriochloroform): δ 1.5 (t, J = 7.3 Hz, 3H, ethyl CH_3), 2.7 (s, 3H, CH_3), 2.8 (s, 3H, imidazole CH_3), 4.2-4.3 (m, 2H, ethyl CH_2), 7.4 (d, J = 8.4 Hz, 1H, H8), 7.7 (d, J = 8.9 Hz, 1H, H4), 7.95 (d, J = 8.9 Hz, 1H, H5), 8.85 (d, J = 8.4 Hz, 1H, H9).

3-Butyl-7-methyl-2-propyl-3*H*-imidazo[4,5-*f*]quinoline (**7b**).

The yield is 79%, oil; ^{1}H nmr (deuteriochloroform): δ 0.9 (t, J = 7.3 Hz, 3H, butyl CH_3), 1.05 (t, J = 7.4 Hz, 3H, propyl CH_3), 1.3-1.4 (m, 2H, butyl CH_2), 1.8-1.9 (m, 4H, propyl CH_2 and butyl CH_2), 2.7 (s, 3H, CH_3), 2.8 (t, J = 6.9 Hz, 2H, propyl CH_2), 4.1 (t, J = 7.4 Hz, 2H, butyl CH_2), 7.3 (d, J = 8.4 Hz, 1H, H8), 7.6 (d, J = 8.9 Hz, 1H, H4), 7.8 (d, J = 8.9 Hz, 1H, H5), 8.8 (d, J = 8.4 Hz, 1H, H9).

9,10-Dihydro-3-methyl-8*H*-pyrrolo[1′,2′:1,2]imidazo[4,5-*f*]quinoline (**7c**).

The yield is 79%, mp 259-261°; ^{1}H nmr (deuteriochloroform): δ 2.8-2.9 (m, 5H, pyrrolidinyl CH_2 and CH_3), 3.2 (t, J = 7.0 Hz, 2H, pyrrolidinyl CH_2), 4.25 (t, J = 7.0 Hz, 2H, pyrrolidinyl CH_2), 7.4 (d, J = 8.4 Hz, 1H, H2), 7.7 (d, J = 8.9 Hz, 1H, H6), 7.95 (d, J = 8.9 Hz, 1H, H5), 8.85 (d, J = 8.4 Hz, 1H, H1).

3-Methyl-8,9,10,11-tetrahydropyrido[1′,2′:1,2]imidazo[4,5-*f*]quinoline (**7d**).

The yield is 70%, mp 163-165°; ^{1}H nmr (deuteriochloroform): δ 2.0-2.2 (m, 4H, 2 piperidinyl CH_2), 2.75 (s, 3H, CH_3), 3.2 (t, J = 6.4 Hz, 2H, piperidinyl CH_2), 4.2 (t, J = 6.0 Hz, 2H, piperidinyl CH_2), 7.4 (d, J = 8.4 Hz, 1H, H2), 7.65 (d, J = 8.9 Hz, 1H, H6), 7.9 (d, J = 8.9 Hz, 1H, H5), 8.8 (d, J = 8.4 Hz, 1H, H1).

3,7-Dimethyl-3*H*-imidazo[4,5-*f*]quinoline (**7e**).

The yield is 50%, mp 171-173°; ^{1}H nmr (deuteriochloroform): δ 2.7 (s, 3H, CH_3), 4.0 (s, 3H, imidazole CH_3), 7.4 (d, J = 8.5 Hz, 1H, H3), 7.7 (d, J = 9.0 Hz, 1H, H4), 7.9-8.0 (m, 2H, H5 and imidazole H), 8.85 (d, J = 8.5 Hz, 1H, H9).

3,8-Dimethyl-9,10,11-trihydro[1′,2′:1,2]imidazo[4,5-*f*]quinoline (**7f**).

The yield is 60%, mp 139-141°; ^{1}H nmr (deuteriochloroform): δ 1.6 (d, J = 6.6 Hz, 3H, piperidinyl CH_3), 2.0-2.4 (m, 4H, 2 piperidinyl CH_2), 2.8 (s, 3H, CH_3), 3.1 (m, 2H, piperidinyl CH_2), 4.7-4.8 (m, 1H, piperidinyl CH), 7.4 (d, J = 8.8 Hz, 1H, H8), 7.7 (d, J = 8.8 Hz, 1H, H4), 7.9 (d, J = 8.8 Hz, 1H, H5), 8.8 (d, J = 8.8 Hz, 1H, H9).

2,7-Dimethyl-6-ethyl-1-formyl-1,2,3,4-tetrahydro-6*H*-imidazo[4,5-*g*]quinoline (**7h**).

The yield is 75%, mp 180-182°; ^{1}H nmr (deuteriochloroform): δ 1.2 (d, J = 6.5 Hz, 3H, CH_3), 1.4 (t, J = 7.2 Hz, 3H, ethyl CH_3), 1.5-1.6 (m, 1H, 1H3), 2.3-2.4 (m, 1H, 1H3), 2.5 (s, 3H, CH_3), 2.8-2.9 (m, 2H, H4), 4.1-4.2 (m, 2H, ethyl CH_2), 4.7-4.8 (m, 1H, H2), 7.0-7.4 (2s, 2H, H5 and H9), 8.6 (s, 1H, HCO).

1-Formyl-1,2,3,4,8,9-hexahydro-2-methyl-7*H*-pyrrolo[1′,2′:1,2]-imidazo[4,5-*g*]quinoline (**7i**).

The yield is 34%, mp 183-185°; ^{1}H nmr (deuteriochloroform): δ 1.2 (d, J = 6.4 Hz, 3H, CH_3), 1.5-1.6 (m, 1H, 1H3), 2.3-2.4 (m, 1H, 1H3), 2.7-2.8 (m, 2H, pyrrolidinyl CH_2), 2.8-2.9 (m, 2H, H4), 3.1 (t, J = 7.6 Hz, 2H, pyrrolidinyl CH_2), 4.1-4.2 (t, J = 7.0 Hz, 2H, pyrrolidinyl CH_2), 4.7-4.8 (m, 1H, H2), 7.0-7.4 (2s, 2H, H5 and H11), 8.6 (s, 1H, HCO).

1-Formyl-2-methyl-1,2,3,4,7,8,9,10-octahydropyrido[2′,1′:2,3]imidazo[4,5-*g*]quinoline (**7j**).

The yield is 82%, mp 170-172°; ^{1}H nmr (deuteriochloroform): δ 1.2 (d, J = 6.4 Hz, 3H, CH_3), 1.5-1.6 (m, 1H, 1H3), 2.0-2.1 (m, 4H, 2 piperidinyl CH_2), 2.3-2.4 (m, 1H, 1H3), 2.7-2.8 (m, 2H, H4), 3.1 (t, J = 6.3 Hz, 2H, piperidinyl CH_2), 4.0 (t, J = 6.0 Hz, 2H, piperidinyl CH_2), 4.7-4.8 (m, 1H, H2), 7.0-7.4 (2s, 2H, H5 and H12), 8.6 (s, 1H, HCO).

General Procedure for the Cyclization with the Triethylorthoformate (Method A).

To cooled triethylorthoformate (0.13 mole) the compounds **6g** and **6k** (0.02 mole) are added. The reaction mixture is stirred and refluxed during 2 hours. After cooling, the excess of triethylorthoformate is removed by flash distillation. The product is recrystallized from cyclohexane.

7-Methyl-3-phenyl-3*H*-imidazo[4,5-*f*]quinoline (**7g**).

The yield is 96%, mp 146-148°; ^{1}H nmr (deuteriochloroform): δ 2.8 (s, 3H, CH_3), 7.4-7.8 (m, 9H, Ar-H), 8.2 (s, 1H, imidazole H).

6-Butyl-1-formyl-2-methyl-1,2,3,4-tetrahydro-6*H*-imidazo[4,5-*g*]-quinoline (**7k**).

The yield is 96%, oil; ^{1}H nmr (deuteriochloroform): δ 1.0 (t, J = 7.3 Hz, 3H, butyl CH_3), 1.2 (d, J = 6.4 Hz, 3H, CH_3), 1.3-1.4 (m, 2H, butyl CH_2), 1.5-1.6 (m, 1H, 1H3), 1.8-1.9 (m, 2H, butyl CH_2), 2.3-2.4 (m, 1H, 1H3), 2.7-2.9 (m, 2H, H4), 4.1-4.2 (t, J = 7.0 Hz, 2H, butyl CH_2), 4.7-4.8 (m, 1H, H2), 7.1-7.5 (2s, 2H, H5 and H9), 7.9 (s, 1H, imidazole H), 8.6 (s, 1H, HCO).

General Procedure for the Reduction of the 2-Methylquinolines.

A mixture of compounds **7a-g** (0.015 mole), 20 ml of triethylammonium formate and 0.1 g of palladium (5%) is heated. The triethylamine formed is distilled during the reaction. The residue is distilled in dichloromethane, the catalyst filtered and the organic layer washed twice with 10 ml of 10% hydrochloric acid and twice with water. The organic layer is dried with magnesium sulfate, filtered and flash distilled to dryness.

General Procedure for the Preparation of the Free Base.

The compounds **8a-g** and **7h-k** are refluxed during 2 hours with 50 ml of 10% hydrochloric acid, cooled to 0° and filtered to provide the corresponding imidazo-2-methyl-1,2,3,4-tetrahydroquinoline hydrochloride. The free bases are obtained by stirring with 30% aqueous sodium hydroxide and extraction with dichloromethane.

2,6-Dimethyl-7-ethyl-1,2,3,4-tetrahydro-7*H*-imidazo[4,5-*f*]quinoline (**8a**).

The yield is 85%, mp 159-161°; ^{1}H nmr (deuteriochloroform): δ 1.2 (d, J = 6.2 Hz, 3H, CH_3), 1.3 (t, J = 7.3 Hz, 3H, ethyl CH_3), 1.6-2.0 (m, 2H, H8), 2.4 (m, 1H, NH), 2.6 (s, 3H, CH_3), 3.15-3.25 (m, 2H, H9), 3.3-3.4 (m, 1H, H7), 3.95-4.05 (m, 2H, ethyl CH_2), 6.5 (d, J = 8.5 Hz, 1H, H7), 6.9 (d, J = 8.5 Hz, 1H, H5).

Anal. Calcd. for $C_{14}H_{19}N_3$: C, 73.33; H, 8.35; N, 18.32. Found: C, 73.13; H, 8.27; N, 18.29.

7-Butyl-2-methyl-6-propyl-1,2,3,4-tetrahydro-7*H*-imidazo[4,5-*f*]-quinoline (**8b**).

The yield is 89%, oil; ^{1}H nmr (deuteriochloroform): δ 0.95 (t, J = 7.3 Hz, 3H, butyl CH_3), 1.05 (t, J = 7.4 Hz, 3H, propyl CH_3), 1.2 (d, J = 6.3 Hz, 3H, CH_3), 1.4-1.5 (m, 2H, butyl CH_2), 1.65-1.95 (m, 5H, 1H8, propyl CH_2 and butyl CH_2), 2.1-2.2 (m, 1H, 1H8), 2.85-2.95 (m, 2H, propyl CH_2), 3.3-3.4 (m, 2H, H9), 3.4-3.5 (m, 1H, H2), 3.9 (m, 1H, NH), 4.0 (t, J = 7.4 Hz, 2H, butyl CH_2), 6.5 (d, J = 8.4 Hz, 1H, H4), 6.95 (d, J = 8.4 Hz, 1H, H5).

Anal. Calcd. for $C_{18}H_{27}N_3$: C, 75.74; H, 9.53; N, 14.73. Found: C, 75.46; H, 9.34; N, 14.83.

2-Methyl-1,2,3,4,6,7-hexahydro-9*H*-pyrrolo[1′,2′:1,2]imidazo[4,5-*f*]quinoline (**8c**).

The yield is 89%, mp 259-261°; ^{1}H nmr (deuteriochloroform): δ 1.2 (d, J = 6.7 Hz, 3H, CH_3), 1.6-1.7 (m, 1H, 1H3), 1.85 (m, 1H, NH), 2.0-2.1 (m, 1H, 1H3), 2.6-2.7 (m, 2H, pyrrolidinyl CH_2), 3.0 (t, J = 7.0 Hz, 2H, pyrrolidinyl CH_2), 3.2-3.3 (m, 2H, H4), 3.3-3.4 (m, 1H, H2), 4.0 (t, J = 7.0 Hz, 2H, pyrrolidinyl CH_2), 6.5 (d, J = 8.5 Hz, 1H, H10), 6.9 (d, J = 8.4 Hz, 1H, H11).

Anal. Calcd. for $C_{14}H_{17}N_3$: C, 73.97; H, 7.54; N, 18.49. Found: C, 73.65; H, 7.74; N, 18.28.

2-Methyl-1,2,3,4,6,7,8,9-octahydropyrido[1′,2′:1,2]imidazo[4,5-*f*]-quinoline (**8d**).

The yield is 69%; mp 221-223°; ^{1}H nmr (deuteriochloroform): δ 1.2 (d, J = 6.7 Hz, 3H, CH_3), 1.6-1.7 (m, 1H, 1H3), 1.9-2.2 (m, 5H, 1H3 and 2 piperidinyl CH_2), 3.0 (t, J = 6.4 Hz, 2H, piperidinyl CH_2), 3.2-3.3 (m, 2H, H4), 3.3-3.4 (m, 1H, H2), 4.0 (t, J = 6.0 Hz, 2H, piperidinyl CH_2), 4.3 (m, 1H, NH), 6.5 (d, J = 8.5 Hz, 1H, H11), 6.8 (d, J = 8.4 Hz, 1H, H12).

Anal. Calcd. for $C_{15}H_{19}N_3$: C, 74.65; H, 7.94; N, 17.41. Found: C, 74.35; H, 7.81; N, 17.25.

2,7-Dimethyl-1,2,3,4-tetrahydro-7*H*-imidazo[4,5-*f*]quinoline (**8e**).

The yield is 80%, mp 93-95°; ^{1}H nmr (deuteriochloroform): δ 1.2 (d, J = 6.0 Hz, 3H, CH_3), 1.6-1.7 (m, 1H, 1H3), 2.0-2.1 (m, 1H, 1H3), 3.2-3.3 (m, 2H, H4), 3.35-3.45 (m, 1H, H2), 4.0 (s, 3H, imidazole CH_3), 4.9 (m, 1H, NH), 6.6 (d, J = 9.0 Hz, 1H, H8), 7.0 (d, J = 8.3 Hz, 1H, H9), 7.7 (s, 1H, imidazole H).

Anal. Calcd. for $C_{12}H_{15}N_3$: C, 71.61; H, 7.51; N, 20.88. Found: C, 71.37; H, 7.70; N, 20.60.

2-Methyl-7-phenyl-1,2,3,4-tetrahydro-7*H*-imidazo[4,5-*f*]quinoline (**8g**).

The yield is 50%, mp 59-61°; ^{1}H nmr (deuteriochloroform): δ 1.3 (d, J = 6.6 Hz, 3H, CH_3), 1.7-2.1 (m, 2H, H3), 2.7 (m, 1H, NH), 3.1-3.3 (m, 2H, H4), 3.4-3.5 (m, 1H, H2), 6.6 (d, J = 8.25 Hz, 1H, H8), 7.2 (d, J = 8.25 Hz, 1H, H9), 7.5-7.6 (m, 5H, Ar-H), 8.0 (s, 1H, imidazole H).

Anal. Calcd. for $C_{17}H_{17}N_3$: C, 77.54; H, 6.50; N, 15.96. Found: C, 77.32; H, 6.29; N, 15.69.

2,7-Dimethyl-6-ethyl-1,2,3,4-tetrahydro-6*H*-imidazo[4,5-*g*]quinoline (**8h**).

The yield is 75%, mp 135-137°; ^{1}H nmr (deuteriochloroform): δ 1.2 (d, J = 6.2 Hz, 3H, CH_3), 1.4 (t, J = 7.3 Hz, 3H, ethyl CH_3), 1.6-2.0 (m, 2H, H3), 2.6 (s, 3H, CH_3), 2.8-3.1 (m, 2H, H4), 3.3-3.4 (m, 1H, H2), 3.7 (m, 1H, NH), 4.0-4.1 (m, 2H, ethyl CH_2), 6.8-6.9 (2s, 2H, H5 and H9).

Anal. Calcd. for $C_{14}H_{19}N_3$: C, 73.33; H, 8.35; N, 18.32. Found: C, 73.13; H, 8.21; N, 18.19.

2-Methyl-1,2,3,4,8,9-hexahydro-7*H*-pyrrolo[1′,2′:1,2]imidazo[4,5-*g*]quinoline (**8i**).

The yield is 75%, mp 181-183°; ^{1}H nmr (deuteriochloroform): δ 1.2 (d, J = 6.2 Hz, 3H, CH_3), 1.6-2.0 (m, 2H, H3), 2.7-2.8 (m, 2H, pyrrolidinyl CH_2), 2.9-3.0 (m, 4H, H4 and pyrrolidinyl CH_2), 3.4-3.5 (m, 1H, H2), 3.7 (m, 1H, NH), 4.0 (t, J = 7.0 Hz, 2H, pyrrolidinyl CH_2), 6.8-6.9 (2s, 2H, H5 and H11).

Anal. Calcd. for $C_{14}H_{17}N_3$: C, 73.97; H, 7.54; N, 18.49. Found: C, 74.65; H, 7.31; N, 18.67.

2-Methyl-1,2,3,4,7,8,9,10-octahydropyrido[2′,1′:2,3]imidazo[4,5-*g*]-quinoline (**8j**).

The yield is 58%, mp 201-203°; ^{1}H nmr (deuteriochloroform): δ 1.2 (d, J = 6.3 Hz, 3H, CH_3), 1.6-1.7 (m, 1H, 1H3), 1.9-2.1 (m, 5H, 1H3 and 2 piperidinyl CH_2), 2.8-2.9 (m, 2H, H4), 3.0 (t, J = 6.3 Hz, 2H, piperidinyl CH_2), 3.35-3.45 (m, 1H, H2), 4.0 (t, J = 6.1 Hz, 2H, piperidinyl CH_2), 4.1 (m, 1H, NH), 6.8-6.9 (2s, 2H, H5 and H12).

Anal. Calcd. for $C_{15}H_{19}N_3$: C, 74.65; H, 7.94; N, 17.41. Found: C, 74.37; H, 7.84; N, 17.62.

6-Butyl-2-methyl-1,2,3,4-tetrahydro-6*H*-imidazo[4,5-*g*]quinoline (**8k**).

The yield is 32%, mp 119-121°; ^{1}H nmr (deuteriochloroform): δ 0.95 (t, J = 7.15 Hz, 3H, butyl CH_3), 1.25 (d, J = 6.6 Hz, 3H, CH_3), 1.3-1.4 (m, 2H, butyl CH_2), 1.6-1.7 (m, 1H, 1H3), 1.8-1.9 (m, 2H, butyl CH_2), 2.0-2.1 (m, 1H, 1H3), 3.2-3.3 (m, 2H, H4), 3.35-3.45 (m, 1H, H2), 4.1 (t, J = 7.15 Hz, 2H, butyl CH_2), 6.5-7.0 (2s, 2H, H5 and H9), 7.7 (s, 1H, imidazole H).

Anal. Calcd. for $C_{15}H_{21}N_3$: C, 74.03; H, 8.70; N, 17.27. Found: C, 74.23; H, 8.52; N, 17.17.

General Procedure for the Condensation of the *N*-Tosyl-*S*-prolyl Chloride with Compound **7c**.

To a stirred and cooled (0°) solution of compound **7c** (11.5 mmoles) and *N,N*-diisopropylethylamine (15 mmoles) in dichloromethane (30 ml) is added dropwise the *N*-tosyl-*S*-prolyl chloride (11.5 mmoles) in solution in dichloromethane (30 ml). The reaction mixture is stirred and refluxed during 1 hour. After cooling, the reaction mixture is washed twice with 20 ml of 0.1*N* hydrochloric acid, twice with 20 ml of 5% sodium hydrogen carbonate and once with 20 ml of water. The organic layer is dried over magnesium sulfate, filtered and flash distilled. A combine yield of 4.8 g (83%) of solid product is obtained, which showed two spots on tlc (eluent:dichloromethane/ethyl acetate/methyl alcohol; 5/5/0.5). The diastereomeric amides are separated by flash chromatography. A combine yield of 0.8 g of the *R,S* diastereomer, 1.8 g of the *S,S* diastereomer and 1.1 g of a mixture of both was obtained from the 4.8 g sample of the diastereomeric mixture.

S,S-Diastereomer.

This isomer had mp 114-116°; $[\alpha]_D$ +24.5° (c 0.1 g/10 ml ethyl alcohol); ^{1}H nmr (deuteriochloroform): δ 1.1 (d, J = 6.7 Hz, 3H, CH_3), 1.5-2.0 (m, 6H, H3 and 2 prolyl CH_2), 2.4 (s, 3H, Tos CH_3), 2.8-2.9 (m, 2H, pyrrolidinyl CH_2), 3.2-3.45 (m, 6H, H4, pyrrolidinyl CH_2 and prolyl CH_2), 4.25 (t, J = 7.0 Hz, 2H, pyrrolidinyl CH_2), 4.85-4.95 (m, 1H, H2), 5.15-5.25 (m, 1H, prolyl H), 7.3-7.6 (m, 4H, H10, H11 and Tos ArH), 7.85 (d, J = 8.1 Hz, 2H, Tos ArH).

Anal. Calcd. for $C_{26}H_{30}N_4O_3S$: C, 65.25; H, 6.32; N, 11.71. Found: C, 65.19; H, 6.28; N, 11.65.

R,S-Diastereomer.

This isomer had mp 107-109°; $[\alpha]_D$ −316° (c 0.1 g/10 ml ethyl alcohol); ^{1}H nmr (deuteriochloroform): δ 1.1 (d, J = 6.7 Hz, 3H, CH_3), 1.5-2.1 (m, 6H, H3 and 2 prolyl CH_2), 2.4 (s, 3H, Tos CH_3), 2.85-2.95 (m, 2H, pyrrolidinyl CH_2), 3.35-3.45 (m, 6H, H4, pyrrolidinyl CH_2 and prolyl CH_2), 4.3 (t, J = 7.0 Hz, 2H, pyrrolidinyl CH_2), 4.85-4.95 (m, 1H, H2), 5.1-5.2 (m, 1H, prolyl H), 7.3-7.75 (m, 4H, H10, H11 and Tos ArH), 7.85 (d, J = 8.1 Hz, 2H, Tos ArH).

Anal. Calcd. for $C_{26}H_{30}N_4O_3S$: C, 65.25; H, 6.32; N, 11.71. Found: C, 65.17; H, 6.29; N, 11.61.

General Procedure for the Hydrolysis of the Diastereomeric Amides.

To a stirred solution of sodium (24 mmoles) in ethanol (15 ml) is added the diastereomeric amide (2 mmoles). The reaction mixture is stirred and refluxed during 2 hours. After cooling, the precipitate is filtered and the filtrate is flash distilled. The residue is then dissolved in 20 ml of dichloromethane; the organic layer is washed twice with water and dried over anhydrous magnesium sulfate. The drying agent is removed by filtration and the dichloromethane removed by flash distillation.

General Procedure for the Condensation of the Diethyl Ethoxymethylenemalonate and Cyclization in Polyphosphoric Acid Ethyl Ester.

The imidazoquinolines (0.01 mole) are added to the diethyl ethoxymethylenemalonate (0.02 mole). The reaction mixture is stirred and refluxed during 2 hours. The ethyl alcohol formed is distilled under reduced pressure at the end of the reaction. The excess of diethyl ethoxymethylenemalonate is removed by a Kugelrorh apparatus. The compounds are after dissolved in polyphosphoric acid ethyl ester, stirred and warmed at 120° during 2 hours. The reaction mixture is poured into ice and neutralized with 30% aqueous sodium hydroxide. The mixture is extracted twice with 100 ml of dichloromethane. The organic layer is dried over magesium sulfate, filtered and flash distilled.

6,7-Dihydro-5,9-dimethyl-10-ethyl-1-oxo-10*H*-imidazo[4',5':8,9]-1*H*,5*H*-benzo[*i,j*]quinolizine-2-carboxylic Ethyl Ester (**9a**).

The yield is 30%, oil; ^{1}H nmr (deuteriochloroform): δ 1.35-1.45 (m, 6H, 2 ethyl CH_3), 1.5 (d, J = 6.2 Hz, 3H, CH_3), 2.2-2.3 (m, 2H, H6), 2.7 (s, 3H, CH_3), 3.5-3.6 (m, 2H, H7), 4.2-4.3 (m, 2H, imidazole CH_2), 4.35-4.45 (m, 2H, ethyl CH_2), 4.45-4.55 (m, 1H, H5), 8.4 (s, 1H, H11), 8.5 (s, 1H, H3).

10-Butyl-6,7-dihydro-5-methyl-9-propyl-1-oxo-10*H*-imidazo[4',5':-8,9]-1*H*,5*H*-benzo[*i,j*]quinolizine-2-carboxylic Acid Ethyl Ester (**9b**).

The yield is 48%, mp 189-191°; ^{1}H nmr (deuteriochloroform): δ 0.9 (t, J = 7.3 Hz, 3H, butyl CH_3), 1.0 (t, J = 7.4 Hz, 3H, propyl CH_3), 1.3-1.4 (m, 2H, propyl CH_2), 1.4-1.5 (m, 6H, CH_3 and ethyl CH_3), 1.7-1.8 (m, 2H, butyl CH_2), 1.9-2.0 (m, 2H, butyl CH_2), 2.1-2.2 (m, 2H, H6), 3.0 (t, J = 6.9 Hz, 2H, propyl CH_2), 3.2-3.3 (m, 2H, H7), 4.4-4.5 (m, 4H, ethyl CH_2 and butyl CH_2), 5.0-5.1 (m, 1H, H5), 8.4 (s, 1H, H11), 9.0 (s, 1H, H3).

5-Methyl-1-oxo-6,7,10,11-tetrahydropyrrolo[1'',2'':1',2']imidazo-[4',5':8,9]-1*H*,5*H*,12*H*-benzo[*i,j*]quinolizine-2-carboxylic Acid Ethyl Ester (**9c**).

The yield is 42%, mp 246-248°; ^{1}H nmr (deuteriochloroform): δ 1.45 (t, J = 7.1 Hz, 3H, ethyl CH_3), 1.5 (d, J = 6.7 Hz, 3H, CH_3), 2.2-2.3 (m, 2H, H6), 2.75-2.85 (m, 2H, pyrrolidinyl CH_2), 3.2 (t, J = 7.0 Hz, 2H, pyrrolidinyl CH_2), 3.4-3.5 (m, 2H, H7), 4.25 (t, J = 7.0 Hz, 2H, pyrrolidinyl CH_2), 4.35-4.45 (m, 2H, ethyl CH_2), 4.45-4.55 (m, 1H, H5), 8.4 (s, 1H, H14), 8.5 (s, 1H, H3).

5-Methyl-1-oxo-6,7,10,11,12,13-hexahydropyrido[1'',2'':1',2']imidazo[4',5':8,9]-1*H*,5*H*-benzo[*i,j*]quinolizine-2-carboxylic Acid Ethyl Ester (**9d**).

The yield is 45%, mp 239-241°; ^{1}H nmr (deuteriochloroform): δ 1.4 (t, J = 7.1 Hz, 3H, ethyl CH_3), 1.5 (d, J = 6.7 Hz, 3H, CH_3), 2.05-2.15 (m, 2H, H6), 2.2-2.3 (m, 4H, 2 piperidinyl CH_2), 3.2-3.3 (m, 2H, piperidinyl CH_2), 4.35-4.45 (m, 2H, ethyl CH_2), 4.6-4.7 (m, 1H, H5), 8.4 (s, 1H, H15), 8.8 (s, 1H, H3).

5,10-Dimethyl-6,7-dihydro-1-oxo-10*H*-imidazo[4',5':8,9]-1*H*,5*H*-benzo[*i,j*]quinolizine-2-carboxylic Acid Ethyl Ester (**9e**).

The yield is 16%, mp 247-249°; ^{1}H nmr (deuteriochloroform): δ 1.3 (t, J = 7.1 Hz, 3H, ethyl CH_3), 1.35 (d, J = 6.7 Hz, 3H, H5), 2.1-2.2 (m, 2H, H6), 3.35-3.45 (m, 2H, H7), 3.9 (s, 3H, CH_3), 4.2-4.3 (m, 2H, ethyl CH_2), 4.7-4.8 (m, 1H, H5), 8.3 (s, 1H, imidazole H).

5,13-Dimethyl-1-oxo-6,7,10,11-tetrahydropyrido[1'',2'':1',2']imidazo[4',5':8,9]-1*H*,5*H*,12*H*-benzo[*i,j*]quinolizine-2-carboxylic Acid Ethyl Ester (**9f**).

The yield is 69%, mp 106-108°; ^{1}H nmr (deuteriochloroform): δ 1.45 (t, J = 7.1 Hz, 3H, ethyl CH_3), 1.5 (d, J = 6.6 Hz, 3H, CH_3), 1.6 (d, J = 6.6 Hz, 3H, piperidinyl CH_3), 2.0-2.2 (m, 2H, H6), 2.25-2.45 (m, 4H, piperidinyl CH_2), 3.0-3.1 (m, 2H, piperidinyl CH_2), 3.55-3.65 (m, 2H, H7), 4.2-4.3 (m, 1H, piperidinyl CH), 4.5-4.6 (m, 2H, ethyl CH_2), 4.7-4.8 (m, 1H, H5), 8.4 (s, 1H, H15), 8.5 (s, 1H, H3).

6,7-Dihydro-5-methyl-1-oxo-10-phenyl-10*H*-imidazo[4',5':8,9]-1*H*,-5*H*-benzo[*i,j*]quinolizine-2-carboxylic Acid Ethyl Ester (**9g**).

The yield is 52%, mp 266-268°; ^{1}H nmr (deuteriochloroform): δ 1.5 (t, J = 7.1 Hz, 3H, ethyl CH_3), 1.6 (d, J = 6.8 Hz, 3H, CH_3),

2.3-2.5 (m, 2H, H6), 3.7-3.8 (m, 2H, H7), 4.4-4.5 (m, 3H, ethyl CH_3), 4.55-4.65 (m, 1H, H5), 7.5-7.7 (m, 5H, ArH), 8.4 (s, 1H, imidazole H), 8.6 (s, 1H, H11), 8.7 (s, 1H, H3).

6,7-Dihydro-5,10-dimethyl-9-ethyl-1-oxo-9*H*-imidazo[4',5':9,10]-1*H*,5*H*-benzo[*i,j*]quinolizine-2-carboxylic Acid Ethyl Ester (**9h**).

The yield is 60%, oil; ^{1}H nmr (deuteriochloroform): δ 1.3-1.4 (m, 6H, 2 ethyl CH_3), 1.5 (d, J = 6.7 Hz, 3H, CH_3), 2.2-2.4 (m, 2H, H6), 2.7 (s, 3H, CH_3), 3.0-3.3 (m, 2H, H7), 4.15-4.25 (m, 2H, imidazole CH_2), 4.3-4.4 (m, 2H, ethyl CH_2), 4.4-4.5 (m, 1H, H5), 7.4 (s, 1H, H8), 8.4 (m, 1H, H3).

5-Methyl-1-oxo-6,7,10,11-tetrahydropyrrolo[1'',2'':1',2']imidazo-[4',5':9,10]-1*H*,5*H*,12*H*-benzo[*i,j*]quinolizine-2-carboxylic Acid Ethyl Ester (**9i**).

The yield is 70%, mp 241-243°; ^{1}H nmr (deuteriochloroform): δ 1.4 (t, J = 7.1 Hz, 3H, ethyl CH_3), 1.5 (d, J = 6.7 Hz, 3H, CH_3), 2.1-2.35 (m, 2H, H6), 2.7-2.8 (m, 2H, pyrrolidinyl CH_2), 3.05-3.15 (m, 2H, H7), 3.25 (t, J = 7.7 Hz, 2H, pyrrolidinyl CH_2), 4.2 (t, J = 7.0 Hz, 2H, pyrrolidinyl CH_2), 4.45-4.55 (m, 1H, H5), 7.5 (s, 1H, H8), 8.4 (s, 1H, H3).

5-Methyl-1-oxo-6,7,10,11,12,13-hexahydropyrido[1'',2'':1',2']imidazo[4',5':9,10]-1*H*,5*H*-benzo[*i,j*]quinolizine-2-carboxylic Acid Ethyl Ester (**9j**).

The yield is 79%, mp 252-254°; ^{1}H nmr (deuteriochloroform): δ 1.4 (t, J = 7.1 Hz, 3H, ethyl CH_3), 1.5 (d, J = 6.6 Hz, 3H, CH_3), 2.0-2.2 (m, 2H, H6), 2.3-2.4 (m, 4H, 2 piperidinyl CH_2), 3.0-3.2 (m, 2H, H7), 3.3 (t, J = 6.3 Hz, 2H, piperidinyl CH_2), 4.1 (t, J = 6.1 Hz, 2H, piperidinyl CH_2), 4.35-4.45 (m, 2H, ethyl CH_2), 4.5-4.6 (m, 1H, H5), 7.4 (s, 1H, H8), 8.4 (s, 1H, H3).

9-Butyl-6,7-dihydro-5-methyl-1-oxo-9*H*-imidazo[4',5':9,10]-1*H*,5*H*-benzo[*i,j*]quinolizine-2-carboxylic Acid Ethyl Ester (**9k**).

The yield is 87%, mp 129-131°; ^{1}H nmr (deuteriochloroform): δ 0.95 (t, J = 7.1 Hz, 3H, butyl CH_3), 1.3-1.4 (m, 2H, butyl CH_2), 1.45 (t, J = 7.1 Hz, 3H, ethyl CH_3), 1.5 (d, J = 6.6 Hz, 3H, CH_3), 1.8-1.9 (m, 2H, butyl CH_2), 2.1-2.3 (m, 2H, H6), 3.15-3.35 (m, 2H, H7), 4.2 (t, J = 7.1 Hz, 2H, butyl CH_2), 4.35-4.45 (m, 1H, H5), 7.5 (s, 1H, H8), 8.05 (s, 1H, imidazole H), 8.4 (s, 1H, H3).

General Procedure for the Hydrolysis of the Quinolonecarboxylic Acid Esters.

The quinolonecarboxylic acid esters (5 mmoles) are dissolved in 10 ml of 10% aqueous sodium hydroxide. The reaction mixture is stirred and refluxed during 1.5 hours. The mixture is cooled and acidified with hydrochloric acid. The quinolones are filtered and recrystallized from dimethylformamide.

6,7-Dihydro-5,9-dimethyl-10-ethyl-1-oxo-10*H*-imidazo[4',5':8,9]-1*H*,5*H*-benzo[*i,j*]quinolizine-2-carboxylic Acid (**10a**).

The yield is 28%, mp 284-286°; ^{1}H nmr (DMSO-d_6): δ 1.45 (t, J = 7.3 Hz, 3H, ethyl CH_3), 1.5 (d, J = 6.2 Hz, 3H, CH_3), 2.2-2.3 (m, 2H, H6), 2.7 (s, 3H, CH_3), 3.5-3.6 (m, 2H, H7), 4.2-4.3 (m, 2H, ethyl CH_2), 4.45-4.55 (m, 1H, H5), 8.4 (s, 1H, H11), 8.5 (s, 1H, H3), 15.5 (s, 1H, COOH); ms: m/z 325 (M^+), 281 (M^+-CO_2).

Anal. Calcd. for $C_{18}H_{19}N_3O_3$: C, 66.45; H, 5.88; N, 12.91. Found: C, 66.15; H, 5.65; N, 12.72.

10-Butyl-6,7-dihydro-5-methyl-9-propyl-1-oxo-10*H*-imidazo[4',5':-8,9]-1*H*,5*H*-benzo[*i,j*]quinolizine-2-carboxylic Acid (**10b**).

The yield is 47%, mp 289-291°; ^{1}H nmr (DMSO-d_6): δ 0.9 (t, J = 7.3 Hz, 3H, butyl CH_3), 1.0 (t, J = 7.4 Hz, 3H, propyl CH_3), 1.3-1.4 (m, 2H, propyl CH_2), 1.4 (d, J = 6.3 Hz, 3H, CH_3), 1.7-1.8 (m, 2H, butyl CH_2), 1.85-1.95 (m, 2H, butyl CH_2), 2.1-2.2 (m, 2H, H6), 3.0 (t, J = 6.9 Hz, 2H, propyl CH_2), 3.15-3.25 (m, 2H, H7), 4.4 (t, J = 7.4 Hz, 2H, butyl CH_2), 4.95-5.05 (m, 1H, H5), 8.4 (s, 1H, H11), 9.0 (s, 1H, H3), 15.6 (s, 1H, COOH); ms: m/z 381 (M^+), 337 (M^+-CO_2).

Anal. Calcd. for $C_{22}H_{27}N_3O_3$: C, 69.27; H, 7.13; N, 11.01. Found: C, 69.01; H, 6.95; N, 10.79.

5-Methyl-1-oxo-6,7,10,11-tetrahydropyrrolo[1'',2'':1',2']imidazo-[4',5':8,9]-1*H*,5*H*,12*H*-benzo[*i,j*]quinolizine-2-carboxylic Acid (**10c**).

The yield is 40%, mp 286-288°; ^{1}H nmr (DMSO-d_6): δ 1.5 (d, J = 6.7 Hz, 3H, CH_3), 2.2-2.3 (m, 2H, H6), 2.75-2.85 (m, 2H, pyrrolidinyl CH_2), 3.2 (t, J = 6.7 Hz, 2H, pyrrolidinyl CH_2), 3.4-3.5 (m, 2H, H7), 4.25 (t, J = 7.0 Hz, 2H, pyrrolidinyl CH_2), 4.45-4.55 (m, 1H, H5), 8.4 (s, 1H, H14), 8.5 (s, 1H, H3), 15.6 (s, 1H, COOH); ms: m/z 323 (M^+), 279 (M^+-CO_2).

Anal. Calcd. for $C_{18}H_{17}N_3O_3$: C, 66.86; H, 5.30; N, 12.99. Found: C, 66.52; H, 5.01; N, 12.65.

5-Methyl-1-oxo-6,7,10,11,12,13-hexahydropyrido[1'',2'':1',2']imidazo[4',5':8,9]-1*H*,5*H*-benzo[*i,j*]quinolizine-2-carboxylic Acid (**10d**).

The yield is 41%, mp 288-290°; ^{1}H nmr (DMSO-d_6): δ 1.5 (d, J = 6.7 Hz, 3H, CH_3), 2.05-2.15 (m, 2H, H6), 2.2-2.3 (m, 4H, 2 piperidinyl CH_2), 3.2-3.3 (m, 2H, piperidinyl CH_2), 3.6-3.7 (m, 2H, H7), 4.2-4.3 (m, 2H, piperidinyl CH_2), 4.6-4.7 (m, 1H, H5), 8.4 (s, 1H, H15), 8.6 (s, 1H, H3), 12.1 (s, 1H, COOH); ms: m/z 337 (M^+), 293 (M^+-CO_2).

Anal. Calcd. for $C_{19}H_{19}N_3O_3$: C, 67.64; H, 5.68; N, 12.45. Found: C, 67.52; H, 5.34; N, 12.36.

5,10-Dimethyl-6,7-dihydro-1-oxo-10*H*-imidazo[4',5':8,9]-1*H*,5*H*-benzo[*i,j*]quinolizine-2-carboxylic Acid (**10e**).

The yield is 30%, mp 294-296°; ^{1}H nmr (DMSO-d_6): δ 1.4 (d, J = 6.7 Hz, 3H, CH_3), 2.2-2.3 (m, 2H, H6), 3.35-3.45 (m, 2H, H7), 4.0 (s, 3H, CH_3), 4.9-5.0 (m, 1H, H5), 8.4 (s, 1H, H imidazole), 8.6 (s, 1H, H11), 8.9 (s, 1H, H3), 12.2 (s, 1H, COOH); ms: m/z 297 (M^+), 253 (M^+-CO_2).

Anal. Calcd. for $C_{16}H_{15}N_3O_3$: C, 64.64; H, 5.08; N, 14.13. Found: C, 64.38; H, 4.95; N, 13.99.

5,13-Dimethyl-1-oxo-6,7,10,11-tetrahydropyrido[1'',2'':1',2']imidazo[4',5':8,9]-1*H*,5*H*,12*H*-benzo[*i,j*]quinolizine-2-carboxylic Acid (**10f**).

The yield is 90%, mp 289-291°; ^{1}H nmr (DMSO-d_6): δ 1.4 (d, J = 6.6 Hz, 3H, CH_3), 1.5 (d, J = 6.6 Hz, 3H, piperidinyl CH_3), 1.9-2.05 (m, 2H, H6), 2.1-2.3 (m, 4H, 2 piperidinyl CH_2), 3.4-3.5 (m, 4H, piperidinyl CH_2 and H7), 4.9-5.1 (m, 2H, piperidinyl CH and H5), 8.4 (s, 1H, H15), 9.0 (s, 1H, H3), 14.9 (s, 1H, COOH); ms: m/z 351 (M^+), 307 (M^+-CO_2).

Anal. Calcd. for $C_{20}H_{21}N_3O_3$: C, 68.36; H, 6.02; N, 11.96. Found: C, 68.27; H, 5.85; N, 11.69.

6,7-Dihydro-5-methyl-1-oxo-10-phenyl-10*H*-imidazo[4',5':8,9]-1*H*,-5*H*-benzo[*i,j*]quinolizine-2-carboxylic Acid (**10g**).

The yield is 27%, mp 303-305°; ^{1}H nmr (DMSO-d_6): δ 1.7 (d, J = 6.8 Hz, 3H, CH_3), 2.4-2.5 (m, 2H, H6), 3.7-3.8 (m, 2H, H7), 5.2-5.3 (m, 1H, H5), 7.75-8.0 (m, 5H, ArH), 8.55 (s, 1H, imidazole H), 9.2 (s, 1H, H11), 9.3 (s, 1H, H3), 14.3 (s, 1H, COOH); ms: m/z 360 (M^+), 316 (M^+-CO_2).

Anal. Calcd. for $C_{21}H_{17}N_3O_3$: C, 70.18; H, 4.77; N, 11.69.

Found: C, 69.82; H, 4.53; N, 11.37.

6,7-Dihydro-5,10-dimethyl-9-ethyl-1-oxo-9*H*-imidazo[4',5':9,10]-1*H*,5*H*-benzo[*i,j*]quinolizine-2-carboxylic Acid (**10h**).

The yield is 42%, mp 298-303° dec; ^{1}H nmr (DMSO-d_6): δ 1.3 (t, J = 7.3 Hz, 3H, CH_3), 1.45 (d, J = 6.6 Hz, 3H, CH_3), 2.2-2.3 (m, 2H, H6), 2.7 (s, 3H, CH_3), 3.4-3.5 (m, 2H, H7), 4.2-4.3 (m, 2H, ethyl CH_2), 4.4-4.5 (m, 1H, H5), 8.45 (s, 1H, H8), 9.1 (s, 1H, H3), 11.8 (s, 1H, COOH); ms: m/z 325 (M^+), 281 (M^+-CO_2).

Anal. Calcd. for $C_{18}H_{19}N_3O_3$: C, 66.45; H, 5.88; N, 12.91. Found: C, 66.17; H, 5.52; N, 12.67.

5-Methyl-1-oxo-6,7,10,11-tetrahydropyrrolo[1'',2'':1',2']imidazo-[4',5':9,10]-1*H*,5*H*,12*H*-benzo[*i,j*]quinolizine-2-carboxylic Acid (**10i**).

The yield is 45%, mp 289-291°; ^{1}H nmr (DMSO-d_6): δ 1.45 (d, J = 6.7 Hz, 3H, CH_3), 2.15-2.25 (m, 2H, H6), 2.7-2.9 (m, 2H, pyrrolidinyl CH_2), 3.1-3.4 (m, 4H, H7 and pyrrolidinyl CH_2), 4.4 (t, J = 7.0 Hz, 2H, pyrrolidinyl CH_2), 5.0-5.1 (m, 1H, H5), 8.2 (s, 1H, H8), 9.1 (s, 1H, H3), 14.9 (s, 1H, COOH); ms: m/z 323 (M^+), 279 (M^+-CO_2).

Anal. Calcd. for $C_{18}H_{17}N_3O_3$: C, 66.86; H, 5.30; N, 12.99. Found: C, 66.50; H, 5.02; N, 12.73.

5-Methyl-1-oxo-6,7,10,11,12,13-hexahydropyrido[1'',2'':1',2']imidazo[4',5':9,10]-1*H*,5*H*-benzo[*i,j*]quinolizine-2-carboxylic Acid (**10j**).

The yield is 47%, mp 302-307° dec; ^{1}H nmr (DMSO-d_6): δ 1.45 (d, J = 6.6 Hz, 3H, CH_3), 2.0-2.3 (m, 6H, H6 and 2 piperidinyl CH_2), 3.25-3.4 (m, 4H, H7 and piperidinyl CH_2), 4.4 (t, J = 6.1 Hz, 2H, piperidinyl CH_2), 5.05-5.15 (m, 1H, H5), 8.35 (s, 1H, H8), 9.15 (s, 1H, H3), 15.0 (s, 1H, COOH); ms: m/z 337 (M^+), 293 (M^+-CO_2).

Anal. Calcd. for $C_{19}H_{19}N_3O_3$: C, 67.64; H, 5.68; N, 12.45. Found: C, 67.52; H, 5.47; N, 12.33.

9-Butyl-6,7-dihydro-5-methyl-1-oxo-9*H*-imidazo[4',5':9,10]-1*H*,5*H*-benzo[*i,j*]quinolizine-2-carboxylic Acid (**10k**).

The yield is 27%, mp 327-332° dec; ^{1}H nmr (DMSO-d_6): δ 0.9 (t, J = 7.1 Hz, 3H, butyl CH_3), 1.3-1.4 (m, 2H, butyl CH_2), 1.5 (d, J = 6.6 Hz, 3H, CH_3), 1.8-1.9 (m, 2H, butyl CH_2), 2.1-2.3 (m, 2H, H6), 3.15-3.35 (m, 2H, H7), 4.3-4.4 (m, 2H, butyl CH_2), 5.1-5.2 (m, 1H, H5), 8.3 (s, 1H, H8), 9.2 (s, 1H, H3), 9.25 (s, 1H, H imidazole), 15.9 (s, 1H, COOH); ms: m/z 339 (M^+), 295 (M^+-CO_2).

Anal. Calcd. for $C_{19}H_{21}N_3O_3$: C, 67.24; H, 6.24; N, 13.38. Found: C, 66.19; H, 6.18; N, 12.32.

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