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A series of 4-aminomethyl-1,2,3,4-tetrahydroisoquinoline derivatives were prepared as potential CNS-agents acting *via* amino-acid neurotransmitter systems. The compounds were synthesized from 1,2,3,4-tetrahydro-1-oxoisoquinoline-4-carboxylic acids obtained by dipolar cycloaddition reactions of imines with homophthalic anhydride. Among the compounds tested **5c** and **5m** showed sub-micromolar affinity for the NMDA receptor and represent a structurally novel class of ligand for this site.

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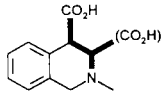
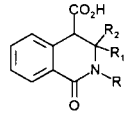
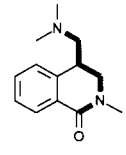
Considerable effort has been devoted over the past two decades to the study of amino-acid neurotransmission [1]. In particular, the involvement of γ-aminobutyric acid in anxiety and epilepsy [2-6], the physiological and pathophysiological role of glycine [7], and the importance of aspartic and glutamic acids in ischemic and neurodegenerative diseases [8-15] have been extensively studied. In the search for novel compounds acting on amino-acid neurotransmitter systems we were attracted to the readily-accessible isoquinolines of general formula **1** as potential precursors both of compounds related to structure **A**, containing an aspartic or β-alanine subunit, and of compounds related to structure **B**, which can be considered as inverse-amide analogs of γ-aminobutyric acid. In the present paper we describe the preparation of a number of 4-aminomethyl-1,2,3,4-tetrahydroisoquinolines derived from structure **B** as potential CNS-agents.



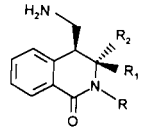
A



1



B



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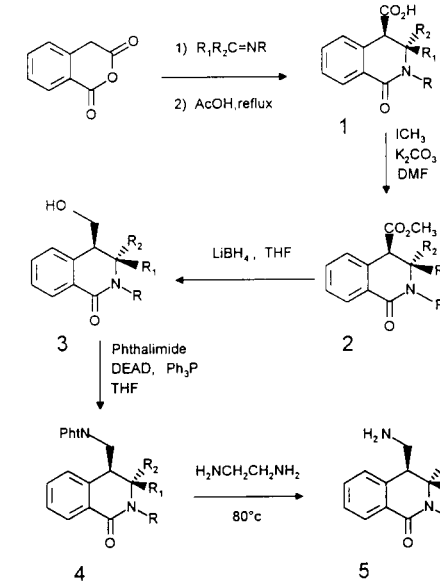
The synthetic route to primary 4-aminomethyl-1,2,3,4-tetrahydro-1-oxoisoquinolines **5** is shown in Scheme 1. The requisite starting materials **1** were obtained using the well-established cycloaddition reaction of imines with homophthalic anhydride [16]. Compounds where R_1 and R_2 are different possess two asymmetric centers and may exist as *cis* or *trans* diastereoisomers. In all the cases examined in the present work a mixture of isomers was obtained, the relative proportions being dependent on steric and electronic factors [17]. The crude cycloaddition products were therefore isomerized in acetic acid at reflux in order to obtain the thermodynamically more stable *trans* diastereoisomers. Acid **11**, which failed to epimerize under these conditions, was converted to the methyl ester and isomerized by treatment with sodium methoxide according to literature procedures [18].

Scheme 1

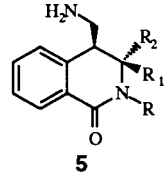


a, R=H,R_1=H,R_2=C_6H_5
b, R=CH_3,R_1=H,R_2=C_6H_5
c, R=C_2H_5,R_1=H,R_2=C_6H_5
d, R=n-C_3H_7,R_1=H,R_2=C_6H_5
e, R=c-C_6H_{11},R_1=H,R_2=C_6H_5
f, R=$C_6H_5CH_2$,R_1=H,R_2=C_6H_5
g, R=C_2H_5,R_1=H,R_2=n-C_3H_7
h, R=C_2H_5,R_1=H,R_2=i-C_3H_7
i, R=$C_6H_5CH_2$,R_1=H,R_2=i-C_3H_7
j, R=C_2H_5,R_1=R_2=CH_3
k, R=C_2H_5,R_1R_2=$(CH_2)_5$
l, RR_1=$(CH_2)_3$,R_2=CH_3
m, RR_1=$(CH_2)_3$,R_2=C_6H_5

The methyl esters **2**, obtained from **1** by reaction with iodomethane in the presence of potassium carbonate, were selectively reduced by lithium borohydride in tetrahydrofuran to afford the 4-hydroxymethyl derivatives **3**. Treatment of the alcohols **3** with phthalimide, triphenylphos-

Table 1

Analytical and Spectral Data of 4-Aminomethyl-1,2,3,4-tetrahydro-1-oxoisoquinolines **5a-m**



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Compound	R	R_1	R_2	Yield %	Mp°C (solvent)	Formula	Analysis (%) Calcd/Found C	H	N	IR (KBr) √ C=O cm^{-1}	NMR Chemical Shifts, δ ppm (solvent)
5a	H	H	C_6H_5	35	259-261 [a] (CH_3CN)	$C_{20}H_{20}N_2O_5$	65.21 65.20	5.47 5.48	7.60 7.68	1600 1650	(CD_3OD): δ 3.22 (m, 1H), 3.50 (m, 2H), 4.96 (s, 1H), 6.26 (s, 2H), 7.23 (m, 6H), 7.50 (m, 2H), 8.06 (m, 1H)
5b	CH_3	H	C_6H_5	42	183-185 [a] (EtOH/Et_2O)	$C_{21}H_{22}N_2O_5$	65.96 65.98	5.80 5.81	7.33 7.34	1605 1630	(D_2O): δ 3.15 (s, 3H), 3.27 (m, 1H), 3.55 (m, 2H), 5.00 (s, 1H), 6.25 (s, 2H), 7.04-7.24 (m, 6H), 7.50 (m, 2H), 8.03 (m, 1H)
5c	C_2H_5	H	C_6H_5	70	198-200 [a] (AcOEt)	$C_{22}H_{24}N_2O_5$	66.65 66.36	6.10 6.06	7.07 7.05	16 10 1645	(CD_3OD): δ 1.23 (t, 3H), 3.10 (m, 2 H), 3.40 (m, 1H), 3.61 (m, 1H), 4.05 (m, 1H), 5.02 (s, 1H), 6.28 (s, 2H), 7.03-7.28 (m, 6H), 7.50 (m, 2H), 8.10 (m, 1H)
5d	*n*-C_3H_7	H	C_6H_5	50	200-202 [b] (CH_3CN)	$C_{21}H_{24}N_2O_3$	71.57 71.30	6.86 6.70	7.95 8.08	1610 1645	(CD_3OD): δ 0.95 (t, 3H), 1.68 (m, 2 H), 2.98 (m, 2H), 3.37 (m, 2H), 3.94 (m, 1H), 5.05 (s, 1H), 6.69 (s, 1H), 7.17 (m, 6H), 7.45 (m, 2H), 8.07 (m, 1H)
5e	*c*-C_6H_{11}	H	C_6H_5	49	237-275 [c] (AcOEt)	$C_{22}H_{27}ClN_2O$	71.24 71.19	7.34 7.46	7 55 7.38	1625	(CD_3OD): δ 1.12-1.50 (m, 5H), 1.66-2.01 (m, 5H), 3.06 (dd, 1H), 3.31 (m, 1H), 3.60 (dd, 1H), 4.67 (m, 1H), 5.16 (s, 1H), 7.16 (m, 6H), 7.47 (m, 2H), 8.07(m, 1H)
5f	$C_6H_5CH_2$	H	C_6H_5	47	191-193 [c] (AcOEt/ Et_2O)	$C_{23}H_{23}ClN_2O$	72.91 73.23	6.12 6.08	7.39 7.34	1635	(D_2O): δ 2.88 (dd, 1H), 3.09 (dd, 1H), 3.38 (m, 1H), 3.82 (d, 1H), 4.86 (s, 1H), 5.43 (d, 1H), 7.03-7.53 (m, 13H), 8.10 (m, 1H)
5g	C_2H_5	H	*n*-C_3H_7	42	239-241 [b] (CH_3CN)	$C_{17}H_{24}N_2O_3$	67.08 67.26	7.95 8.00	9.20 9.25	1600 1620	(CD_3OD): δ 0.86 (t, 3H), 1.14-1.57 (m, 7H), 2.90-3.23 (m, 3H), 3.62 (m, 1H), 4.07 (m, 1H), 4.88 (s, 1H), 6.67 (s, 1H), 7.34 (d, 1H), 7.44-7.63 (m, 2H), 7.97 (d, 1H)
5h	C_2H_5	H	*i*-C_3H_7	65	158-160 [a] (CH_3CN)	$C_{19}H_{26}N_2O_5$	62.96 62.97	7.23 7.24	7.73 7.74	1610 1635	(CD_3OD): δ 0.78 (d, 3H), 0.97 (d, 3H), 1.26 (t, 3H), 1.80 (m, 1H), 2.97 (m, 2H), 3.32 (m, 3H), 4.20 (m, 1H), 6.26 (s, 2H), 7.36 (m, 1H), 7.44-7.63 (m, 2H), 7.96 (m, 1H)
5i	$C_6H_5CH_2$	H	*i*-C_3H_7	57	185-187 [c] (EtOH/Et_2O)	$C_{20}H_{25}ClN_2O$	69.25 69.60	7.31 7.24	8.12 8.13	1625	(CD_3OD): δ 0.78 (d, 3H), 1.05 (d, 3H), 1.86 (m, 1H), 2.46 (m, 1H), 2.63 (m, 1H), 3.30 (m, 1H), 3.41 (d, 1H), 3.98 (d, 1H), 5.62 (d, 1H), 7.33-7.63 (m, 8H), 8.04 (m, 1H)
5j	C_2H_5	CH_3	CH_3	49	237-239 [d] (CH_3CN)	$C_{18}H_{24}N_2O_5$	62.05 61.92	6.94 6.83	8.04 8.10	1620 1680	(CD_3OD): δ 1.17 (s, 3H), 1.26 (t, 3H), 1.62 (s, 3H), 2.86 (m, 1H), 3.01 (m, 1H), 3.48-3.75 (m, 3H), 6.67 (s, 2H), 3.37 (m, 1H), 7.47-7.65 (m, 2H), 8.01 (m, 1H)

Table 1 (continued)

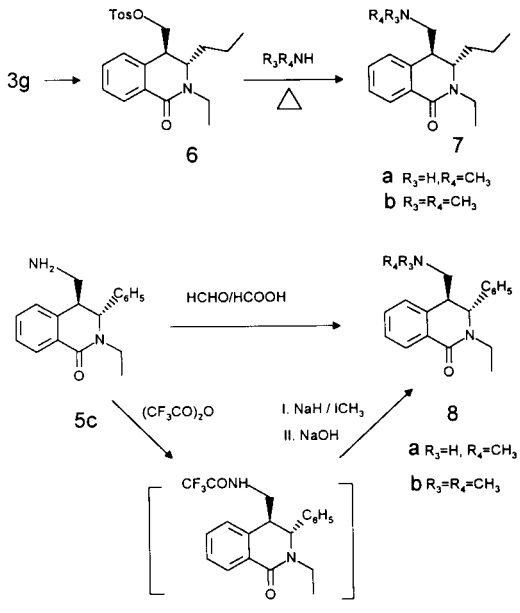
Compound	R	R_1	R_2	Yield %	Mp°C (solvent)	Formula	Analysis (%) Calcd/Found C	H	N	IR (KBr) √ C=O cm^{-1}	NMR Chemical Shifts, δ ppm (solvent)(10)
5k	C_2H_5	-$(CH_2)_5$-		47	>270 [c] (CH_3CN)	$C_{17}H_{25}ClN_2O$	66.11 66.31	8.16 8.19	9.07 9.12	1620	(CD_3OD): δ 1.25 (t, 3H), 1.45 (m, 5H), 1.66-2.21 (m, 5H), 2.85 (t, 1H), 3.42 (dd, 1H), 3.70 (m, 3H), 7.42 (m, 1H), 7.49-7.65 (m, 2H), 7.27 (m, 1H)
5l	-$(CH_2)_3$-	CH_3		55	250-252 [c] (CH_3CN)	$C_{14}H_{19}ClN_2O$	63.03 63.24	7.18 7.27	10.50 10.49	1625	(CD_3OD): δ 1.18 (s, 3H), 1.93-2.15 (m, 4H), 2.80 (dd, 1H), 3.32 (m, 1H), 3.52 (dd, 1H), 3.69 (m, 2H), 7.43-7.87 (m, 3H), 7.98 (m, 1H)
5m	-$(CH_2)_3$-	C_6H_5		46	>270 [c] (CH_3CN)	$C_{19}H_{21}ClN_2O$	69.40 69.30	6.44 6.43	8.52 8.57	1640	(CD_3OD): δ 1.56 (m, 1 H), 2.01 (m, 1H), 2.30 (m, 1 H), 2.55 (m, 1 H), 2.98 (dd, 1H), 3.69-3.93 (m, 4H), 7.08-7.24 (m, 6H), 7.38 (m, 2H), 7.96 (m, 1H)

[a] Maleate. [b] Hemifumarate. [c] Hydrochloride. [d] Fumarate.

phine, and diethyl azadicarboxylate according to the method described by Mitsunobu [19] gave the phthalimides **4** in moderate to good yield. The primary amines **5** were obtained by heating compounds **4** in ethylenediamine at 80°. The physical, analytical, and spectroscopic data for the isoquinolines **5** prepared are shown in the Table.

The 4-methylaminomethyl-1,2,3,4-tetrahydro-1-oxo-3-propylisoquinoline **7a** and the dimethylamino analogue **7b** were obtained by aminolysis of the tosylate **6**, as depicted in Scheme 2. Attempts to prepare the corresponding mono- and dimethylamines **8a** and **8b** *via* the tosylate were complicated by concomitant elimination. Therefore,

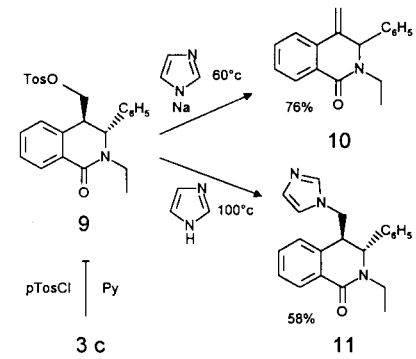
Scheme 2



8a was prepared from the primary amine **5c** by methylation of the trifluoroacetamide derivative followed by hydrolysis, and **8b** by exhaustive methylation using formaldehyde in formic acid (Scheme 2).

Tosylate **9** also underwent elimination on reaction with the anion derived from imidazole to give compound **10**. Product **11** was obtained, albeit in moderate yield, by heating **9** with excess imidazole in acetonitrile at reflux for 48 hours (Scheme 3).

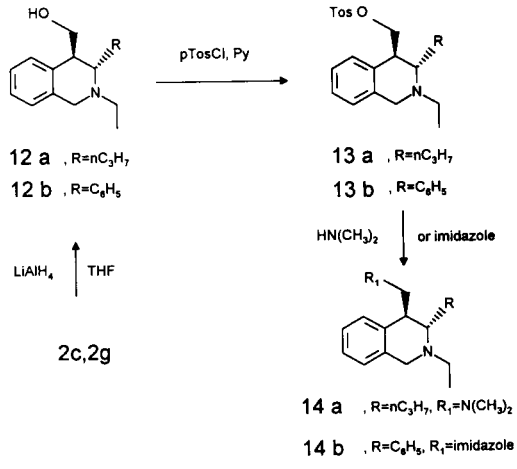
Scheme 3



In order to assess the importance of the 1-oxo group in terms of biological activity compounds **14a** and **14b** were prepared according to Scheme 4. Reduction of the 1-oxo esters **2c** and **2g** with lithium aluminum hydride gave alcohols **12a** and **12b** which were converted to the dimethylamino derivative **14a** or the imidazole **14b** *via* tosylates **13a** and **13b**.

Pharmacological screening of the compounds showed that **5c** and **5m** have sub-micromolar affinity for the NMDA subtype of glutamic acid receptors. The desoxo

Scheme 4



compounds **14a** and **14b** were inactive.

In conclusion, compounds of general formule **5**, as exemplified by **5c** and **5m**, represent a novel structural prototype for the elaboration of products capable of modulating glutaminergic activity.

EXPERIMENTAL

Melting point were determined using a Kofler block (Heizbank WME) and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Model 177 infrared spectrometer. The ^{1}H nmr spectra were recorded using a Bruker AC-200 spectrometer and chemical shifts (δ) are reported in ppm relative to tetramethylsilane. Ascending thin layer chromatography was performed on precoated plates of silica gel 60 F 254 (Merck) and the spots visualized using a uv lamp or iodine vapor. E. Merck silica gel 60 F (230-400 mesh) was used for column chromatography. The elemental analyses were carried out using a Carlo Erba Model 1106 elemental analyzer. The tetrahydro-1-oxoisoquinoline-4-carboxylic acids **1a-1f** and esters **2a-2f** were prepared as previously described [17, 20-22] and the requisite imines obtained using reported procedures [23-25].

General Procedure for the Preparation of 1,2,3,4-Tetrahydro-1-oxoisoquinoline-4-carboxylic Acids **1**.

Homophthalic anhydride (0.1 mole) was added in portions to a solution of the imine (0.1 mole) in chloroform (120 ml) and the solution stirred at room temperature for 15 hours. The solvent was evaporated under reduced pressure and the residual crystalline product was taken up in acetic acid (100 ml) and heated at reflux for 8 hours. Evaporation of the acetic acid followed by recrystallization gave the required acids **1**.

trans-2-Ethyl-1,2,3,4-tetrahydro-1-oxo-3-propylisoquinoline-4-carboxylic Acid (**1g**).

This compound was obtained as colorless crystals (diisopropyl ether) in 45% yield, mp 138-140°; ir (potassium bromide): ν 1620 and 1731 cm^{-1} (C=O); ^{1}H nmr (deuteriochloroform): δ 0.87 (t, 3H), 1.14 (t, 3H), 1.17-1.58 (m, 4H), 2.90 (m, 1H), 3.73 (d, 1H), 3.98 (m, 1H), 4.11 (m, 1H), 7.23-7.52 (m, 3H), 8.03-8.07 (m, 1H), 9.61 (s, 1H).

Anal. Calcd. for $C_{15}H_{19}NO_3$: C, 68.94; H, 7.33; N, 5.36. Found: C, 68.89; H, 7.39; N, 5.41.

trans-2-Ethyl-1,2,3,4-tetrahydro-1-oxo-3-isopropylisoquinoline-4-carboxylic Acid (**1h**).

This compound was obtained as colorless crystals (ethyl acetate-diisopropyl ether) in 86% yield, mp 180-182°; ir (potassium bromide): ν 1605 and 1730 cm^{-1} (C=O); ^{1}H nmr (deuteriochloroform): δ 0.75 (d, 3H), 0.93 (d, 3H), 1.10 (t, 3H), 1.80 (m, 1H), 4.78 (m, 1H), 3.71 (d, 1H), 3.84 (s, 1H), 4.24 (m, 1H), 7.20-7.48 (m, 3H), 8.02 (d, 1H), 11.15 (s, 1H).

Anal. Calcd. for $C_{15}H_{19}NO_3$: C, 68.94; H, 7.33; N, 5.36. Found: C, 69.26; H, 7.41; N, 5.42.

trans-2-Benzyl-1,2,3,4-tetrahydro-1-oxo-3-isopropylisoquinoline-4-carboxylic Acid (**1i**).

This compound was obtained in 45% yield as colorless crystals (ethyl acetate-diisopropyl ether), mp 179-181°; ir (potassium bromide): ν 1618 and 1726 cm^{-1} (C=O); ^{1}H nmr (deuteriochloroform): δ 0.69 (d, 3H), 0.98 (d, 3H), 1.93 (m, 1H), 3.78 (m, 2H), 4.08 (d, 1H), 5.43 (d, 1H), 7.05-7.51 (m, 8H), 8.12 (d, 1H), 10.83 (s, 1H).

Anal. Calcd. for $C_{20}H_{21}NO_3$: C, 74.28; H, 6.55; N, 4.33. Found: C, 74.30; H, 6.50; N, 4.39.

2-Ethyl-1,2,3,4-tetrahydro-3,3-dimethyl-1-oxoisoquinoline-4-carboxylic Acid (**1j**).

This compound was obtained in 41% yield as colorless crystals (ethyl acetate-diisopropyl ether), mp 178-180°; ir (potassium bromide): ν 1605 and 1715 cm^{-1} (C=O); ^{1}H nmr (deuteriochloroform): δ 1.15 (t, 3H), 1.21 (s, 3H), 1.57 (s, 3H), 3.40 (m, 1H), 3.59 (s, 1H), 3.68 (m, 1H), 7.17-7.45 (m, 3H), 6.04 (m, 1H), 8.47 (s, 1H).

Anal. Calcd. for $C_{14}H_{17}NO_3$: C, 68.00; H, 6.93; N, 5.66. Found: C, 67.80; H, 6.99; N, 5.74.

2-Ethyl-1,2,3,4-tetrahydro-1-oxo-3-spirocyclohexanylisoquinoline-4-carboxylic Acid (**1k**).

This compound was obtained in 72% yield as colorless crystals (ethyl acetate-diisopropyl ether), mp 220-222°; ir (potassium bromide): ν 1622 and 1714 cm^{-1} (C=O); ^{1}H nmr (deuteriochloroform): δ 1.14 (t, 3H), 1.17-1.42 (m, 4H), 1.50-1.95 (m, 5H), 2.11 (m, 1H), 3.42 (m, 1H), 3.71 (m, 1H), 4.14 (s, 1H), 7.15-7.38 (m, 4H), 7.96 (m, 1H).

Anal. Calcd. for $C_{17}H_{21}NO_3$: C, 71.06; H, 7.37; N, 4.87. Found: C, 71.07; H, 7.39; N, 5.00.

1,2,3,5,10,10a-Hexahydro-10a-methyl-5-oxopyrrolo[1,2-*b*]isoquinoline-10-carboxylic Acid (**1l**).

This compound was obtained as a mixture of *cis* and *trans* isomers which failed to epimerize under the above conditions. The mixture of acids was used without further purification for the following reaction.

trans-1,2,3,5,10,10a-Hexahydro-5-oxo-10a-phenylpyrrolo[1,2-*b*]-isoquinoline-10-carboxylic Acid (**1m**).

This compound was obtained in 50% yield as colorless crystals (methanol-diisopropyl ether), mp 253-255°; ir (potassium bromide): ν 1605 and 1715 cm^{-1} (C=O); ^{1}H nmr (dimethyl sulfoxide-d_6): δ 1.38 (m, 1H), 1.88 (m, 1H), 2.33 (m, 2H), 3.55 (m, 1H), 3.77 (m, 1H), 4.41 (s, 1H), 7.10-7.34 (m, 8H), 7.82 (m, 1H), 12.96 (s, 1H).

Anal. Calcd. for $C_{19}H_{17}NO_3$: C, 74.25; H, 5.58; N, 4.56. Found: C, 74.26; H, 5.49; N, 4.54.

General Procedure for the Preparation of Methyl 1,2,3,4-Tetrahydro-1-oxoisoquinoline-4-carboxylates **2**.

Iodomethane (0.1 mole) was added dropwise to a stirred suspension of potassium carbonate (0.05 mole) and acid **1** (0.05 mole) in dimethylformamide (50 ml). The reaction mixture was poured into ice-water after 15 hours agitation at room temperature and the crystalline product collected by filtration, dried, and recrystallized. In the case of oily esters purification was accomplished by flash-chromatography.

Methyl *trans*-2-Ethyl-1,2,3,4-tetrahydro-1-oxo-3-propylisoquinoline-4-carboxylate (**2g**).

This compound was obtained in 73% yield as a pale-yellow oil; ir (film): ν 1654 and 1734 cm^{-1} (C=O); ^1H nmr (deuteriochloroform): δ 0.87 (t, 3H), 1.19 (t, 3H), 1.25-1.57 (m, 4H), 2.90 (m, 1H), 3.62 (s, 3H), 3.72 (d, 1H), 3.98 (m, 1H), 4.18 (m, 1H), 7.25 (m, 1H), 7.36-7.50 (m, 2H), 8.05 (m, 1H).

Anal. Calcd. for $C_{16}H_{21}NO_3$: C, 69.79; H, 7.69; N, 5.09. Found: C, 69.43; H, 7.57; N, 4.90.

Methyl *trans*-2-Ethyl-1,2,3,4-tetrahydro-1-oxo-3-isopropylisoquinoline-4-carboxylate (**2h**).

This compound was obtained in 81% yield as colorless crystals (diisopropyl ether-hexane), mp 76-78°; ir (potassium bromide): ν 1633 and 1723 cm^{-1} (C=O); ^1H nmr (deuteriochloroform): δ 0.78 (d, 3H), 0.95 (d, 3H), 1.16 (t, 3H), 1.77 (m, 1H), 2.80 (m, 1H), 3.62 (s, 3H), 3.68 (dd, 1H), 3.85 (d, 1H), 4.32 (m, 1H), 7.19 (m, 1H), 7.35-7.47 (m, 2H), 8.04 (m, 1H).

Anal. Calcd. for $C_{16}H_{21}NO_3$: C, 69.79; H, 7.69; N, 5.09. Found: C, 69.81; H, 7.72; N, 5.09.

Methyl *trans*-2-Benzyl-1,2,3,4-tetrahydro-1-oxo-3-isopropylisoquinoline-4-carboxylate (**2i**).

This compound was obtained in 90% yield as colorless crystals (water), mp 146-148°; ir (potassium bromide): ν 1635 and 1742 cm^{-1} (C=O); ^1H nmr (deuteriochloroform): δ 0.75 (d, 3H), 1.02 (d, 3H), 1.91 (m, 1H), 3.15 (m, 3H), 3.76 (m, 2H), 3.84 (d, 1H), 5.66 (d, 1H), 7.12-7.49 (m, 8H), 8.14 (m, 1H).

Anal. Calcd. for $C_{21}H_{23}NO_3$: C, 74.75; H, 6.87; N, 4.15. Found: C, 74.59; H, 6.88; N, 4.19.

Methyl 2-Ethyl-1,2,3,4-tetrahydro-3,3-dimethyl-1-oxoisoquinoline-4-carboxylate (**2j**).

This compound was obtained in 42% yield as a pale-yellow oil; ir (film): ν 1641 and 1738 cm^{-1} (C=O); ^1H nmr (deuteriochloroform): δ 1.24 (m, 6H), 1.52 (s, 3H), 3.43 (m, 1H), 3.61 (s, 3H), 3.65 (s, 1H), 3.76 (m, 1H), 7.16 (m, 1H), 7.40 (m, 2H), 6.09 (m, 1H).

Anal. Calcd. for $C_{15}H_{19}NO_3$: C, 68.94; H, 7.33; N, 5.36. Found: C, 68.62; H, 7.42; N, 5.18.

Methyl 2-Ethyl-1,2,3,4-tetrahydro-1-oxo-3-spirocyclohexanylisoquinoline-4-carboxylate (**2k**).

This compound was obtained in 95% yield as colorless crystals (water), mp 109-111°; ir (potassium bromide): ν 1625 and 1725 cm^{-1} (C=O); ^1H nmr (deuteriochloroform): δ 1.20 (t, 3H), 1.34-1.77 (m, 8H), 1.93 (m, 2H), 3.47 (m, 1H), 3.56 (s, 3H), 3.83 (m, 1H), 4.26 (s, 1H), 7.19 (m, 1H), 7.37 (m, 2H), 8.06 (m, 1H).

Anal. Calcd. for $C_{18}H_{23}NO_3$: C, 71.73; H, 7.69; N, 4.65. Found: C, 71.91; H, 7.59; N, 4.70.

Methyl *trans*-1,2,3,5,10,10a-Hexahydro-10a-methyl-5-oxopyrrolo-[1,2-*b*]isoquinoline-10-carboxylate (**21**).

The previously obtained mixture of *cis* and *trans* acids was converted to the methyl esters according to the general procedure, and epimerization accomplished by treatment with sodium methoxide in refluxing methanol [18]. Compound **21** was obtained in 48% yield as colorless crystals (diisopropyl ether), mp 104-106°; ir (potassium bromide): ν 1648 and 1720 cm^{-1} (C=O); ^1H nmr (deuteriochloroform): δ 1.15 (s, 3H), 1.96 (m, 4H), 3.57 (s, 3H), 3.61-3.79 (m, 2H), 3.62 (s, 1H), 7.20 (m, 1H), 7.33-7.43 (m, 2H), 8.04 (m, 1H).

Anal. Calcd. for $C_{15}H_{17}NO_3$: C, 69.48; H, 6.61; N, 5.40. Found: C, 69.80; H, 6.63; N, 5.46.

Methyl *trans*-1,2,3,5,10,10a-Hexahydro-5-oxo-10a-phenylpyrrolo-[1,2-*b*]isoquinoline-10-carboxylate (**2m**).

This compound was obtained in 70% yield as colorless crystals (diisopropyl ether), mp 162-164°; ir (potassium bromide): ν 1640 and 1725 cm^{-1} (C=O); ^1H nmr (deuteriochloroform): δ 1.12 (m, 1H), 1.58 (m, 1H), 1.92 (m, 1H), 2.18-2.38 (m, 2H), 3.68 (s, 3H), 3.72-3.94 (m, 2H), 6.97 (m, 1H), 7.12-7.34 (m, 7H), 8.06 (m, 1H).

Anal. Calcd. for $C_{20}H_{19}NO_3$: C, 74.75; H, 5.96; N, 4.36. Found: C, 74.55; H, 6.01; N, 4.38.

General Procedure for the Preparation of *trans*-1,2,3,4-Tetrahydro-4-hydroxymethyl-1-oxoisoquinolines **3**.

A solution of ester **2** (0.05 mole) in tetrahydrofuran (150 ml) was added dropwise with stirring to a suspension of potassium borohydride (0.1 mole) and lithium chloride (0.1 mole) in tetrahydrofuran (100 ml). After the addition was complete the suspension was stirred at room temperature for 15 hours. The reaction mixture was concentrated under reduced pressure, poured into water, and extracted with ethyl acetate. The extracts were washed with water, dried (sodium sulfate), filtered, and evaporated to afford an oil which was crystallized using the solvents indicated.

trans-1,2,3,4-Tetrahydro-4-hydroxymethyl-1-oxo-3-phenylisoquinoline (**3a**).

This compound was obtained in 85% yield as colorless crystals (diisopropyl ether), mp 190-192°; ir (potassium bromide): ν 1654 and 1677 cm^{-1} (C=O); ^1H nmr (deuteriochloroform): δ 3.10 (m, 1H), 3.51-3.73 (m, 2H), 3.81 (s, 1H), 4.98 (m, 1H), 6.88 (d, 1H), 6.97-7.31 (m, 8H), 7.95 (m, 1H).

Anal. Calcd. for $C_{16}H_{15}NO_2$: C, 75.87; H, 5.97; N, 5.53. Found: C, 75.75; H, 5.99; N, 5.52.

trans-1,2,3,4-Tetrahydro-4-hydroxymethyl-2-methyl-1-oxo-3-phenylisoquinoline (**3b**).

This compound was obtained in 86% yield as colorless crystals (ethyl acetate-hexane), mp 148-150°; ir (potassium bromide): ν 1641 cm^{-1} (C=O); ^1H nmr (deuteriochloroform): δ 2.84 (m, 1H), 3.14 (s, 3H), 3.20 (m, 1H), 3.80 (m, 2H), 5.00 (s, 1H), 7.00-7.40 (m, 8H), 8.15 (m, 1H).

Anal. Calcd. for $C_{17}H_{17}NO_2$: C, 76.38; H, 6.41; N, 5.24. Found: C, 76.58; H, 6.41; N, 5.27.

trans-2-Ethyl-1,2,3,4-tetrahydro-4-hydroxymethyl-3-phenyl-1-oxoisoquinoline (**3c**).

This compound was obtained in 95% yield as colorless crystals (ethyl acetate-diisopropyl ether), mp 135-137°; ir (potassium bromide): ν 1625 cm^{-1} (C=O); ^1H nmr (deuteriochloroform): δ 1.24 (t, 3H), 2.29 (s, 1H), 2.90 (m, 1H), 3.19 (t, 1H), 3.78 (d, 2H), 4.22 (m, 1H), 5.08 (s, 1H), 6.98-7.41 (m, 8H), 8.16 (m, 1H).

Anal. Calcd. for $C_{18}H_{19}NO_2$: C, 76.84; H, 6.80; N, 4.98. Found: C, 77.05; H, 6.81; N, 4.96.

trans-1,2,3,4-Tetrahydro-4-hydroxymethyl-1-oxo-3-phenyl-2-propylisoquinoline (**3d**).

This compound was obtained in 88% yield as colorless crystals (diisopropyl ether), mp 135-137°; ir (potassium bromide): ν 1631 cm^{-1} (C=O); ^1H nmr (deuteriochloroform): δ 0.94 (t, 3H), 1.67 (m, 2H), 2.39 (s, 1H), 2.74 (m, 1H), 3.19 (t, 1H), 3.78 (d, 2H), 4.15 (m, 1H), 5.07 (s, 1H), 6.98-7.39 (m, 8H), 8.16 (m, 1H).

Anal. Calcd. for $C_{19}H_{21}NO_2$: C, 77.26; H, 7.17; N, 4.74. Found: C, 77.33; H, 7.25; N, 4.89.

trans-2-Cyclohexyl-1,2,3,4-tetrahydro-4-hydroxymethyl-1-oxo-3-phenylisoquinoline (**3e**).

This compound was obtained to 80% yield as colorless crystals (ethyl acetate-diisopropyl ether), mp 253-255°; ir (potassium bromide): ν 1627 cm^{-1} (C=O); ^1H nmr (deuteriochloroform): δ 0.99-1.33 (m, 4H), 1.57-1.80 (m, 5H), 3.01 (m, 1H), 3.35 (s, 1H), 3.39-3.53 (m, 2H), 4.56 (m, 1H), 5.16 (s, 1H), 5.23 (m, 1H), 7.02-7.39 (m, 8H), 7.94 (m, 1H).

Anal. Calcd. for $C_{22}H_{25}NO_2$: C, 78.77; H, 7.51; N, 4.18. Found: C, 78.56; H, 7.54; N, 4.26.

trans-2-Benzyl-1,2,3,4-tetrahydro-4-hydroxymethyl-1-oxo-3-phenylisoquinoline (**3f**).

This compound was obtained in 75% yield as colorless crystals (diisopropyl ether), mp 133-135°; ir (potassium bromide): ν 1627 cm^{-1} (C=O); ^1H nmr (deuteriochloroform): δ 1.74 (s, 1H), 3.09 (m, 1H), 3.45 (m, 2H), 3.57 (d, 1H), 4.88 (s, 1H), 5.84 (d, 1H), 6.95-7.41 (m, 13H), 8.23 (m, 1H).

Anal. Calcd. for $C_{23}H_{21}NO_2$: C, 80.44; H, 6.16; N, 4.08. Found: C, 79.96; H, 6.14; N, 4.12.

trans-2-Ethyl-1,2,3,4-tetrahydro-4-hydroxymethyl-1-oxo-3-propylisoquinoline (**3g**).

This compound was obtained in 81% yield as colorless crystals (diisopropyl ether), mp 77-79°; ir (potassium bromide): ν 1628 cm^{-1} (C=O); ^1H nmr (deuteriochloroform): δ 0.81 (t, 3H), 1.16-1.53 (m, 7H), 2.89 (m, 2H), 3.42 (s, 1H), 3.50-3.60 (m, 3H), 4.17 (m, 1H), 7.12-7.4 (m, 3H), 7.95 (m, 1H).

Anal. Calcd. for $C_{15}H_{21}NO_2$: C, 72.84; H, 8.56; N, 5.67. Found: C, 72.80; H, 8.43; N, 5.70.

trans-2-Ethyl-1,2,3,4-tetrahydro-4-hydroxymethyl-1-oxo-3-isopropylisoquinoline (**3h**).

This compound was obtained in 75% yield as colorless crystals (diisopropyl ether), mp 127-129°; ir (potassium bromide): ν 1623 cm^{-1} (C=O); ^1H nmr (deuteriochloroform): δ 0.73 (d, 3H), 0.93 (d, 3H), 1.20 (t, 3H), 1.81 (m, 1H), 2.79 (m, 1H), 2.98 (s, 1H), 3.08 (t, 1H), 3.48 (d, 1H), 3.62 (m, 2H), 4.30 (m, 1H), 7.13 (m, 1H), 7.26-7.42 (m, 2H), 7.97 (m, 1H).

Anal. Calcd. for $C_{15}H_{21}NO_2$: C, 72.84; H, 8.56; N, 5.66. Found: C, 73.13; H, 8.63; N, 5.65.

trans-2-Benzyl-1,2,3,4-tetrahydro-4-hydroxymethyl-1-oxo-3-isopropylisoquinoline (**3i**).

This compound was obtained in 69% yield as colorless crystals (diisopropyl ether-hexane), mp 118-120°; ir (potassium bromide): ν 1628 cm^{-1} (C=O); ^1H nmr (deuteriochloroform): δ 0.77 (d, 3H), 1.03 (m, 4H), 1.93 (m, 1H), 3.01 (m, 2H), 3.30 (m, 2H), 3.74 (d, 1H), 5.90 (d, 1H), 7.10 (m, 1H), 7.13-7.47 (m, 7H), 8.10 (m, 1H).

Anal. Calcd. for $C_{20}H_{23}NO_2$: C, 77.64; H, 7.49; N, 4.53. Found: C, 77.76; H, 7.46; N, 4.57.

2-Ethyl-1,2,3,4-tetrahydro-4-hydroxymethyl-3,3-dimethyl-1-oxoisoquinoline (**3j**).

This compound was obtained in 42% yield as colorless crystals (diisopropy ether), mp 128-130°; ir (potassium bromide): ν 1618 cm^{-1} (C=O); ^1H nmr (deuteriochloroform): δ 1.17 (s, 3H), 1.22 (t, 3H), 1.53 (s, 3H), 1.87 (s, 1H), 2.70 (m, 1H), 3.42 (m, 1H), 3.66 (m, 2H), 3.98 (m, 1H), 7.22 (m, 1H), 7.26-7.48 (m, 2H), 8.04 (m, 1H).

Anal. Calcd. for $C_{14}H_{19}NO_2$: C, 72.07; H, 8.21; N, 6.00. Found: C, 72.27; H, 8.46; N, 6.15.

2-Ethyl-1,2,3,4-tetrahydro-4-hydroxymethyl-1-oxo-3-spirocyclohexanylisoquinoline (**3k**).

This compound was obtained in 81% yield as colorless crystals (diisopropyl ether), mp 147-149°; ir (potassium bromide): ν 1626 cm^{-1} (C=O); ^1H nmr (deuteriochloroform): δ 1.16 (t, 3H), 1.29-1.87 (m, 9H), 2.13 (m, 1H), 2.31 (s, 1H), 3.34 (m, 1H), 3.46 (m, 2H), 3.70 (m, 1H), 3.88 (m, 1H), 7.19 (m, 1H), 7.26-7.43 (m, 2H), 7.96 (m, 1H).

Anal. Calcd. for $C_{17}H_{23}NO_2$: C, 74.69; H, 8.48; N, 5.12. Found: C, 74.82; H, 8.43; N, 5.19.

trans-1,2,3,5,10,10a-Hexahydro-10-hydroxymethyl-10a-methyl-5-oxopyrrolo[1,2-*b*]isoquinoline (**3l**).

This compound was obtained in 74% yield as colorless crystals (diisopropyl ether), mp 127-129°; ir (potassium bromide): ν 1622 cm^{-1} (C=O); ^1H nmr (deuteriochloroform): δ 1.15 (s, 3H), 1.80-2.07 (m, 3H), 2.11 (s, 1H), 2.39 (m, 1H), 2.98 (t, 1H), 3.52-3.73 (m, 3H), 3.89 (m, 1H), 7.24-7.72 (m, 3H), 8.00 (m, 1H).

Anal. Calcd. for $C_{14}H_{17}NO_2$: C, 72.70; H, 7.41; N, 6.06. Found: C, 72.55; H, 7.46; N, 6.05.

trans-1,2,3,5,10,10a-Hexahydro-10-hydroxymethyl-5-oxo-10a-phenylpyrrolo[1,2-*b*]isoquinoline (**3m**).

This compound was obtained in 73% yield as colorless crystals (diisopropyl ether), mp 164-166°; ir (potassium bromide): ν 1630 cm^{-1} (C=O); ^1H nmr (deuteriochloroform): δ 1.38 (m, 1H), 1.78 (m, 1H), 2.12 (m, 1H), 2.67 (m, 1H), 3.42 (m, 1H), 3.53-3.99 (m, 5H), 6.86-7.26 (m, 8H), 7.65 (m, 1H).

Anal. Calcd. for $C_{19}H_{19}NO_2$: C, 77.79; H, 6.53; N, 4.77. Found: C, 77.60; H, 6.57; N, 4.73.

General Procedure for the Preparation of 1,2,3,4-Tetrahydro-1-oxo-4-phthalimidomethylisoquinolines **4**.

A solution of diethyl azodicarboxylate (0.024 mole) in tetrahydrofuran (10 ml) was added over 10 minutes to a stirred suspension of alcohol **3** (0.023 mole), phthalimide (0.024 mole), and triphenylphosphine (0.024 mole) in tetrahydrofuran (60 ml). The suspension was stirred for 15 hours at room temperature. The tetrahydrofuran was evaporated under reduced pressure and the residual solid triturated with hexane, and then recrystallized from ethanol.

trans-1,2,3,4-Tetrahydro-1-oxo-3-phenyl-4-phthalimidomethylisoquinoline (**4a**).

This compound was obtained in 82% yield as colorless crystals, mp 226-228°; ir (potassium bromide): ν 1640, 1719 and 1767 cm^{-1} (C=O); ^1H nmr (deuteriochloroform): δ 3.29 (t, 1H), 3.54 (m, 1H), 3.85 (dd, 1H), 4.15 (dd, 1H), 4.67 (d, 1H), 6.89-7.13 (m, 6H), 7.29 (m, 2H), 7.66-7.81 (m, 4H), 8.07 (m, 1H).

Anal. Calcd. for $C_{24}H_{18}N_2O_3$: C, 75.38; H, 4.74; N, 7.33. Found: C, 75.34; H, 4.81; N, 7.38.

trans-1,2,3,4-Tetrahydro-2-methyl-1-oxo-3-phenyl-4-phthalimidomethylisoquinoline (**4b**).

This compound was obtained in the usual way and the crude product used directly in the following reaction.

trans-2-Ethyl-1,2,3,4-tetrahydro-1-oxo-3-phenyl-4-phthalimidomethylisoquinoline (**4c**).

This compound was obtained in 75% yield as colorless crystals, mp 197-199°; ir (potassium bromide): ν 1615, 1685 and 1750 cm^{-1} (C=O); ^1H nmr (deuteriochloroform): δ 1.29 (t, 3H), 3.19 (m, 1H), 3.51 (dd, 1H), 3.80 (dd, 1H), 3.96-4.25 (m, 2H), 4.70 (s, 1H), 6.93-7.04 (m, 3H), 7.13-7.20 (m, 3H), 7.27-7.41 (m, 2H), 7.76-8.19 (m, 4H), 8.21 (m, 1H).

Anal. Calcd. for $C_{26}H_{22}N_2O_3$: C, 76.08; H, 5.40; N, 6.83. Found: C, 75.72; H, 5.22; N, 6.76.

trans-1,2,3,4-Tetrahydro-1-oxo-3-phenyl-4-phthalimidomethyl-2-propylisoquinoline (**4d**).

This compound was obtained in 62% yield as colorless crystals, mp 143-145°; ir (potassium bromide): ν 1659, 1711 and 1769 cm^{-1} (C=O); ^1H nmr (deuteriochloroform): δ 0.96 (t, 3H), 1.72 (m, 2H), 3.05 (m, 1H), 3.51 (t, 1H), 3.80 (m, 2H), 4.15 (dd, 1H), 4.72 (s, 1H), 6.96 (m, 2H), 7.14-7.40 (m, 6H), 7.74-7.91 (m, 4H), 8.23 (m, 1H).

Anal. Calcd. for $C_{27}H_{24}N_2O_3$: C, 76.39; H, 5.70; N, 6.60. Found: C, 76.21; H, 5.71; N, 6.64.

trans-2-Cyclohexyl-1,2,3,4-tetrahydro-1-oxo-3-phenyl-4-phthalimidomethylisoquinoline (**4e**).

This compound was obtained in 48% yield as colorless crystals, mp 139-141°; ir (potassium bromide): ν 1625, 1705 and 1765 cm^{-1} (C=O); ^1H nmr (deuteriochloroform): δ 1.04-2.04 (m, 10H), 3.45 (t, 1H), 3.90 (m, 1H), 4.11 (m, 1H), 4.71 (m, 1H), 4.89 (s, 1H), 6.73 (d, 1H), 7.01-7.16 (m, 6H), 7.28 (m, 1H), 7.71-7.86 (m, 4H), 8.20 (d, 1H).

Anal. Calcd. for $C_{30}H_{28}N_2O_3$: C, 77.56; H, 6.08; N, 6.03. Found: C, 77.21; H, 6.24; N, 5.88.

trans-2-Benzyl-1,2,3,4-tetrahydro-1-oxo-3-phenyl-4-phthalimidomethylisoquinoline (**4f**).

This compound was obtained in 57% yield as colorless crystals, mp 188-190°; ir (potassium bromide): ν 1640, 1710 and 1770 cm^{-1} (C=O); ^1H nmr (deuteriochloroform): δ 3.45 (m, 1H), 3.61 (m, 1H), 3.78 (m, 2H), 4.65 (s, 1H), 5.75 (d, 1H), 6.67 (d, 1H), 7.00-7.40 (m, 12H), 7.67-7.87 (m, 4H), 8.30 (d, 1H).

Anal. Calcd. for $C_{31}H_{24}N_2O_3$: C, 78.79; H, 5.12; N, 5.93. Found: C, 78.60; H, 5.05; N, 6.18.

trans-2-Ethyl-1,2,3,4-tetrahydro-1-oxo-4-phthalimidomethyl-3-propylisoquinoline (**4g**).

This compound was obtained in the usual way and the crude product used directly in the following reaction.

trans-2-Ethyl-1,2,3,4-tetrahydro-1-oxo-4-phthalimidomethyl-3-isopropylisoquinoline (**4h**).

This compound was obtained in 69% yield as colorless crystals, mp 134-136°; ir (potassium bromide): ν 1644, 1719 and 1772 cm^{-1} (C=O); ^1H nmr (deuteriochloroform): δ 0.65 (d, 3H), 0.87 (d, 3H), 1.42 (t, 3H), 1.85 (m, 1H), 2.96 (m, 1H), 3.22 (d, 1H), 3.42 (m, 1H), 3.73 (dd, 1H), 3.99 (dd, 1H), 4.23 (m, 1H), 7.15 (m, 1H), 7.34 (m, 2H), 7.72-7.90 (m, 4H), 8.10 (m, 1H).

Anal. Calcd. for $C_{23}H_{24}N_2O_3$: C, 73.38; H, 6.43; N, 7.44. Found: C, 73.57; H, 6.55; N, 7.48.

trans-2-Benzyl-1,2,3,4-tetrahydro-1-oxo-4-phthalimidomethyl-3-isopropylisoquinoline (**4i**).

This compound was obtained in the usual way and the crude product used directly in the following reaction.

2-Ethyl-1,2,3,4-tetrahydro-3,3-dimethyl-1-oxo-4-phthalimidomethylisoquinoline (**4j**).

This compound was obtained in 65% yield as colorless crystals mp 193-195°; ir (potassium bromide): ν 1643, 1720 and 1766 cm^{-1} (C=O); ^1H nmr (deuteriochloroform): δ 1.19 (s, 3H), 1.33 (t, 3H), 1.67 (s, 3H), 3.10 (dd, 1H), 3.54 (m, 1H), 3.70-4.07 (m, 3H), 6.78 (d, 1H), 7.13 (m, 1H), 7.27 (m, 1H), 7.65-7.77 (m, 4H), 8.08 (m, 1H).

Anal. Calcd. for $C_{22}H_{22}N_2O_3$: C, 72.91; H, 6.12; N, 7.73. Found: C, 73.25; H, 6.00; N, 7.77.

2-Ethyl-1,2,3,4-tetrahydro-1-oxo-4-phthalimidomethyl-3-spirocyclohexanylisoquinoline (**4k**).

This compound was obtained in 68% yield as colorless crystals, mp 199-201°; ir (potassium bromide): ν 1645, 1716 and 1770 cm^{-1} (C=O); ^1H nmr (deuteriochloroform): δ 1.32 (t, 3H), 1.35 (m, 4H), 1.51 (m, 1H), 1.90 (m, 4H), 2.27 (m, 1H), 3.59-3.98 (m, 5H), 6.75 (d, 1H), 7.06 (t, 1H), 7.27 (m, 1H), 7.65-7.77 (m, 4H), 6.07 (m, 1H).

Anal. Calcd. for $C_{25}H_{26}N_2O_3$: C, 74.60; H, 6.51, N, 6.96. Found: C, 74.75; H, 6.49; N, 7.04.

trans-1,2,3,5,10,10a-Hexahydro-10a-methyl-5-oxo-10-phthalimidomethylpyrrolo[1,2-*b*]isoquinoline (**4l**).

This compound was obtained in the usual way and the crude product used directly in the following reaction.

trans-1,2,3,5,10,10a-Hexahydro-5-oxo-10a-phenyl-10-phthalimidomethylpyrrolo[1,2-*b*]isoquinoline (**4m**).

This compound was obtained in 65% yield as colorless crystals, mp 262-264°; ir (potassium bromide): ν 1650, 1717 and 1766 cm^{-1} (C=O); ^1H nmr (deuteriochloroform): δ 1.61 (m, 1H), 2.01 (m, 1H), 2.29 (m, 1H), 2.65 (m, 1H), 3.82-4.06 (m, 4H), 4.21 (m, 1H), 6.60 (d, 1H), 6.92 (m, 1H), 7.07-7.26 (m, 6H), 7.65-7.78 (m, 4H), 8.02 (m, 1H).

Anal. Calcd. for $C_{27}H_{22}N_2O_3$: C, 76.76; H, 5.25; N, 6.63. Found; C, 76.46; H, 5.20; N, 6.66.

General Procedure for the Preparation of 4-Aminomethyl-1,2,3,4-tetrahydro-1-oxoisoquinolines **5**.

The phthalimidomethyl compound **4** (0.01 mole) was heated with ethylenediamine (8 ml) at 80° for 2 hours with stirring. The reaction mixture was allowed to cool, poured into ice-water, and extracted with ethyl acetate. The extracts were washed with water, dried (sodium sulfate), and filtered. The solvent was evaporated under reduced pressure and the residue purified by flash-chromatography. The purified amines were converted to appropriate salts (Table) by standard techniques.

trans-2-Ethyl-1,2,3,4-tetrahydro-1-oxo-3-propyl-4-tosyloxymethylisoquinoline (**6**).

p-Toluenesulfonyl chloride (4.96 g, 0.026 mole) was added in portions, with stirring, to a solution of **3g** (4.30 g, 0.0174 mole) in pyridine (45 ml) maintained at −5°. The reaction mixture was allowed to warm to room temperature and stirring continued for a further 15 hours. The mixture was poured into ice-water and the crystalline product collected by filtration, washed with water, and

dried over phosphorus pentoxide to give 5.8 g (83%) of **6**, mp 64-66°; ir (potassium bromide): ν 1647 cm^{-1} (C=O); ^1H nmr (deuteriochloroform): δ 0.85 (t, 3H), 1.07 (t, 3H), 1.25-1.55 (m, 4H), 2.43 (s, 3H), 2.64 (m, 1H), 3.19 (m, 1H), 3.64 (m, 1H), 3.67-4.19 (m, 3H), 7.15 (d, 1H), 7.27-7.47 (m, 4H), 7.73 (d, 2H), 8.02 (m, 1H).

Anal. Calcd. for $C_{22}H_{27}NO_4S$: C, 65.81; H, 6.78; N, 3.49; S, 7.99. Found: C, 65.74; H, 6.89; N, 3.86; S, 8.05.

trans-2-Ethyl-1,2,3,4-tetrahydro-4-methylaminomethy-1-oxo-3-propylisoquinoline (**7a**).

A mixture of compound **6** (4.2 g, 0.011 mole) and an ethanolic solution of methylamine (16 ml of a 33% solution) was maintained at 100° in a closed pressure vessel for 15 hours. The cooled suspension obtained was concentrated, poured into decinormal sodium hydroxide solution, and extracted with ethyl acetate. The extracts were washed with water, dried (sodium sulfate), and filtered. The solvent was evaporated under reduced pressure and the residual oil purified by flash-chromatography using chloroform:methanol (97:3) as eluent. The amine obtained was treated with a solution of fumaric acid in ethanol to afford, after recrystallization from acetonitrile, 1.75 g (44%) of **7a** fumarate, mp 154-156°; ir (potassium bromide): ν 1640 and 1700 cm^{-1} (C=O); ^1H nmr (deuteriomethanol): δ 0.87 (t, 3H), 1.28 (t, 3H), 1.34-1.59 (m, 4H), 2.70 (s, 3H), 3.08 (m, 2H), 3.34 (m, 2H), 3.67 (m, 1H), 4.05 (m, 1H), 6.71 (s, 2H), 7.39-7.64 (m, 3H), 7.98 (m, 1H).

Anal. Calcd. for $C_{20}H_{28}N_2O_5$: C, 63.81; H, 7.50; N, 7.44. Found: C, 63.88; H, 7.40; N, 7.49.

trans-2-Ethyl-1,2,3,4-tetrahydro-4-dimethylaminomethyl-1-oxo-3-propylisoquinoline (**7b**).

The procedure described above for the preparation of **7a**, but using dimethylamine instead of methylamine, gave **7b** as the fumarate in 37% yield, mp 141-143°; ir (potassium bromide): ν 1635 and 1685 cm^{-1} (C=O); ^1H nmr (deuteriomethanol): δ 0.87 (t, 3H), 1.29 (t, 3H), 1.34-1.56 (m, 4H), 2.78 (s, 6H), 3.05 (m, 2H), 3.30 (m, 2H), 3.62 (m, 1H), 4.06 (m, 1H), 6.71 (s, 2H), 7.41-7.61 (m, 3H), 7.95 (d, 1H).

Anal. Calcd. for $C_{21}H_{30}N_2O_5$: C, 64.59; H, 7.74; N, 7.17. Found: C, 64.72; H, 7.66; N, 7.24.

trans-2-Ethyl-1,2,3,4-tetrahydro-4-methylaminomethyl-1-oxo-3-phenylisoquinoline (**8a**).

A solution of **5c** (3.0 g, 0.011 mole) and trifluoroacetic anhydride (6.05 ml, 0.043 mole) in methylene chloride (50 ml) was stirred at room temperature for 4 hours. The reaction mixture was washed twice with 10% aqueous sodium bicarbonate solution, with water, and then dried (sodium sulfate). Evaporation of the solvent under reduced pressure gave a crystalline product which was immediately taken up in acetone (30 ml) and treated with iodomethane (2.66 ml, 0.043 mole). The solution was heated to reflux and powdered potassium hydroxide (2.4 g, 0.043 mole) added. After a further 15 minutes at reflux the reaction mixture was allowed to cool and the solvent evaporated under reduced pressure. Water (50 ml) was added to the residue and the mixture heated at reflux for 1.5 hours. The reaction mixture was allowed to cool and the oily supernatent extracted with ethyl acetate. The extracts were washed with water, dried (sodium sulfate), and filtered. Evaporation of the solvent under reduced pressure gave an oil which was treated with oxalic acid to afford, after recrystallization from ethyl acetate, 1.48 g (35%) of **8a** as the oxalate, mp 260-262°; ir (potassium bromide): ν 1600 and 1625 cm^{-1} (C=O); ^1H nmr (DMSO-d_6): δ 1.13 (t, 3H), 2.63 (s, 3H), 3.00 (m, 2H), 3.44 (m, 2H), 3.92 (m, 1H), 5.14 (s, 1H), 6.1-7.4 (broad s, 3H), 7.03-7.45 (m, 8H), 7.95 (m, 1H).

Anal. Calcd. for $C_{21}H_{24}N_2O_5$: C, 65.61; H, 6.29; N, 7.29. Found: C, 65.28; H, 6.30; N, 7.24.

trans-2-Ethyl-1,2,3,4-tetrahydro-4-dimethylaminomethyl-1-oxo-3-phenylisoquinoline (**8b**).

Aqueous formaldehyde (3.34 ml of 37% solution, 0.041 mole) was added dropwise, with stirring and ice-bath cooling, to a mixture of **5c** (3.85 g, 0.014 mole) and 98% formic acid (2.6 ml, 0.069 mole). The solution was stirred for 1 hour at room temperature and then heated at 80° for 30 minutes. The reaction mixture was allowed to cool, basified with concentrated sodium hydroxide solution, and extracted with methylene chloride. The extracts were washed with water, dried (sodium sulfate), and the solvent removed under reduced pressure. The crude product was purified by flash-chromatography using chloroform:methanol (99:1) as eluent. The amine was converted to the hydrochloride and recrystallized from ethanol-diethyl ether to afford 1.15 g (24%) of **8b** hydrochloride, mp 263-265°; ir (potassium bromide): ν 1635 cm^{-1} (C=O); ^1H nmr (DMSO-d_6): δ 1.16 (t, 3H), 2.83 (d, 3H), 2.93 (d, 3H), 2.99-3.19 (m, 2H), 3.56 (m, 2H), 3.98 (m, 1H), 5.72 (s, 1H), 7.12-7.52 (m, 8H), 7.98 (m, 1H), 8.64 (broad s, 1H).

Anal. Calcd. for $C_{20}H_{25}ClN_2O$: C, 69.65; H, 7.31; N, 8.12. Found: C, 69.73; H, 7.25; N, 8.14.

trans-2-Ethyl-1,2,3,4-tetrahydro-1-oxo-3-phenyl-4-tosyloxymethyl-isoquinoline (**9**).

This compound was obtained by a procedure analogous to that described for **6**, yield 88%, mp 117-119° (diisopropyl ether); ir (potassium bromide): ν 1641 cm^{-1} (C=O); ^1H nmr (deuteriochloroform): δ 1.08 (t, 3H), 2.45 (s, 3H), 2.85 (m, 1H), 3.42 (t, 1H), 4.00-4.21 (m, 3H), 4.93 (s, 1H), 7.01 (m, 3H), 7.20 (m, 3H), 7.26-7.42 (m, 4H), 7.80 (d, 2H), 8.09-8.17 (m, 1H).

Anal. Calcd. for $C_{25}H_{25}NO_4S$: C, 68.95; H, 5.79; N, 3.22; S, 7.35. Found: C, 69.17; H, 5.77; N, 3.24; S, 7.30.

2-Ethyl-1,2,3,4-tetrahydro-1-oxo-3-phenylisoquinoline-4-ylidene (**10**).

A solution of **9** (4.35 g, 0.01 mole) in dimethylformamide (12 ml) was added dropwise to a mixture of imidazole (1.36 g, 0.02 mole) and sodium hydride (0.65 g of 80% suspension, 0.021 mole) in dimethylformamide (15 ml). The reaction mixture was heated at 60° with stirring for 2 hours, allowed to cool, and poured into ice-water. The crystalline product was collected by filtration, washed with water, and dried. Recrystallization from diisopropyl ether gave 1.98 g (76%) of **10**, mp 134-136° ir (potassium bromide): ν 1641 cm^{-1} (C=O); ^1H nmr (deuteriochloroform): δ 1.23 (t, 3H), 2.97 (m, 1H), 4.21 (m, 1H), 5.25 (s, 1H), 5.44 (s, 1H), 5.56 (s, 1H), 7.13-7.26 (m, 5H), 7.42 (m, 3H), 8.21 (m, 1H).

Anal. Calcd. for $C_{18}H_{17}NO$: C, 82.10; H, 6.51; N, 5.32. Found: C, 81.86; H, 6.42; N, 5.36.

trans-2-Ethyl-1,2,3,4-tetrahydro-4-(1-imidazolylmethyl)-1-oxo-3-phenylisoquinoline (**11**).

A mixture of **9** (2.28 g, 0.0052 mole) and imidazole (1.42 g, 0.021 mole) in acetonitrile (18 ml) was maintained at 100° in a closed vessel for 48 hours. The reaction mixture was allowed to cool, concentrated under reduced pressure, and poured into water. The product was extracted with ethyl acetate and the extracts washed with water. Extraction of the organic phase with 1*N*

hydrochloric acid (30 ml) followed by basification with potassium carbonate afforded the crude base which was collected by filtration. Purification by flash-chromatography using chloroform:-methanol (98:2) as eluent, treatment with gaseous hydrogen chloride and recrystallization from ethanol-ethyl acetate, gave 1.03 g (54%) of **11** as the hydrochloride, mp 239-241°; ir (potassium bromide): ν 1630 cm^{-1} (C=O); ^1H nmr (DMSO-d_6): δ 1.16 (t, 3H), 2.95 (m, 1H), 3.78 (m, 1H), 4.02 (m, 1H), 4.43 (m, 1H), 4.86 (m, 1H), 4.96 (s, 1H), 6.56 (d, 1H), 7.06-7.30 (m, 7H), 7.71 (s, 1H), 7.88 (s, 1H), 8.00 (dd, 1H), 9.01 (s, 1H), 14.8 (broad s, 1H).

Anal. Calcd. for $C_{21}H_{22}ClN_3O$: C, 68.56; H, 6.03; N, 11.42; Cl, 9.64. Found: C, 68.51; H, 6.10; N, 11.35; Cl, 9.70.

trans-2-Ethyl-1,2,3,4-tetrahydro-4-hydroxymethyl-3-propylisoquinoline (**12a**).

Lithium aluminum hydride reduction of **2g** according to the described procedure [22] gave **12a** as a pale-yellow oil in 85% yield; ^1H nmr (deuteriochloroform): δ 0.87 (t, 3H), 0.92-1.57 (m, 8H), 2.60-2.76 (m, 2H), 2.80 (s, 1H), 3.18 (d, 1H), 3.53 (d, 1H), 3.66-3.94 (m, 2H), 4.15 (m, 1H), 7.05 (m, 1H), 7.14-7.27 (m, 3H).

Anal. Calcd. for $C_{15}H_{23}NO$: C, 77.20; H, 9.94; N, 6.00. Found: C, 77.57; H, 10.05; N, 5.78.

trans-2-Ethyl-1,2,3,4-tetrahydro-4-hydroxymethyl-3-phenylisoquinoline (**12b**).

An analogous procedure to that described for **12a** but starting from **2c** afforded **12b** as colorless crystals in 80% yield, mp 103-105°; ^1H nmr (deuteriochloroform): δ 1.25 (t, 3H), 2.37 (m, 1H), 2.71 (m, 1H), 3.11 (s, 1H), 3.32 (d, 1H), 3.85-4.00 (m, 2H), 4.27 (m, 2H), 5.65 (broad s, 1H), 6.96-7.32 (m, 9H).

Anal. Calcd. for $C_{18}H_{21}NO$: C, 80.86; H, 7.92; N, 5.24. Found: C, 81.19; H, 7.98; N, 5.27.

trans-2-Ethyl-1,2,3,4-tetrahydro-4-dimethylaminomethyl-3-propylisoquinoline (**14a**).

Compound **12a** was converted to the tosylate **13a** according to the method described for the preparation of **6** and the crude product treated with dimethylamine as described for **7b**. The base obtained was treated with gaseous hydrogen chloride to afford **14a** as colorless crystals of the dihydrochloride in 42% yield, mp 260° (ethyl acetate); ^1H nmr (deuteriomethanol): δ 1.02 (t, 3H), 1.53 (m, 7H), 1.96 (m, 1H), 3.00 (s, 3H), 3.06 (s, 3H), 3.29-3.65 (m, 4H), 4.25 (m, 2H), 4.58 (m, 1H), 7.27-7.55 (m, 4H).

Anal. Calcd. for $C_{17}H_{30}Cl_2N_2$: C, 61.26; H, 9.07; N, 8.40; Cl, 21.27. Found: C, 61.61; H, 9.11; N, 8.42; Cl, 21.45.

trans-2-Ethyl-1,2,3,4-tetrahydro-4-(1-imidazolylmethyl)-3-phenylisoquinoline (**14b**).

The tosylate **13b** was prepared as described for **6** and the crude product treated with imidazole in the same way as for the preparation of **11**. The base obtained was treated with gaseous hydrogen chloride to afford **14b** as colorless crystals of the dihydrochloride in 60% yield, mp 232-234° (ethanol-ethyl acetate); ^1H nmr (deuterium oxide): δ 1.55 (t, 3H), 2.98 (q, 2H), 4.48-4.70 (m, 6H), 7.14 (d, 2H), 7.44 (m, 9H), 8.31 (s, 1H).

Anal. Calcd. for $C_{21}H_{25}Cl_2N_3$: C, 64.61; H, 6.46; Cl, 18.16; N, 10.76. Found: C, 64.13; H, 6.63; Cl, 17.81; N, 10.78.

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