

2-Carboxytetrahydroquinolines. Conformational and Stereochemical Requirements for Antagonism of the Glycine Site on the NMDA Receptor

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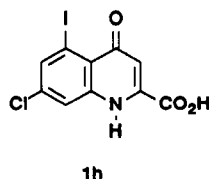
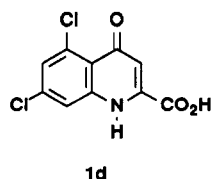
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2-Carboxy-1,2,3,4-tetrahydroquinoline derivatives, derived from kynurenic acid, have been synthesized and evaluated for in vitro antagonist activity at the glycine site on the NMDA receptor. 2,3-Dihydrokynurenic acids show reduced potency relative to the parent lead compounds (Table I) possibly as a result of conformational effects. Removal of the 4-oxo group results in further reduced potency, but introduction of a *cis*-carboxymethyl group to the 4-position restores antagonist activity (Tables III and IV). Replacement of the keto group of 5,7-dichloro-2,3-dihydrokynurenic acid with other alternative H-bonding groups, for example *cis*- and *trans*-benzyloxycarbonyl and *cis*- and *trans*-carboxamido (Table V), gives comparable activity, but there is negligible stereoselectivity. A significant increase in potency and stereoselectivity is seen within the 4-acetate series (Table VI). The *trans*-4-acetic acid is significantly more potent than the corresponding lead kynurenic acid and has 100-fold greater affinity than the *cis* isomer. The results are consistent with a requirement in binding for a pseudoequatorially placed 2-carboxylate and clearly demonstrate the importance for binding of a correctly positioned hydrogen-bond-accepting group at the 4-position. The high-affinity binding of an anionic group in the 4-substituent binding pocket suggests that the glycine site and the neurotransmitter recognition (NMDA) site may have some features in common.

Introduction

Overactivation of the *N*-methyl-D-aspartate (NMDA) subtype of excitatory amino acid receptors has been implicated in several neurodegenerative disorders including epilepsy, stroke, and Alzheimer's disease.¹ As a result, NMDA antagonists may be of therapeutic benefit, since these compounds have been shown to be neuroprotective and anticonvulsant in a variety of animal models. The receptor complex consists of distinct binding regions,² including a neurotransmitter (probably glutamate) recognition site; a strychnine-insensitive glycine site; a site-recognizing phencyclidine, MK-801, and related molecules; sites for zinc and magnesium ions; and a polyamine site.³ Competitive NMDA antagonists such as [3-(2-carboxypiperazin-4-yl)propyl]phosphonic acid⁴ (CPP), which act at the neurotransmitter binding site, and uncompetitive NMDA antagonists, for example (+)-5-methyl-10,11-dihydro-5H-dibenzo[*a,d*]cyclohepten-5,10-imine⁵ (MK-801), which act by blockade of the open state of the ion channel, both show undesirable in vivo behavioural effects.⁶ Since the discovery of the role of glycine^{7,8} in promoting NMDA receptor activation, compounds which would block the effect of glycine have been sought as potentially superior NMDA antagonists.⁹ We have previously reported on the optimization of the lead compound kynurenic acid (1a),¹⁰ where studying the effect of aromatic substitution resulted in potent 5,7-disubstituted derivatives (1d, 1h). We

the glycine/NMDA site was the 4-keto-1-amino form as illustrated by 1d and 1h. In this paper we have tested the model by modifications of the heterocyclic ring and 4-substituents of the kynurenic acid nucleus (compounds 1-18). 4-Substituted-2-carboxytetrahydroquinolines in

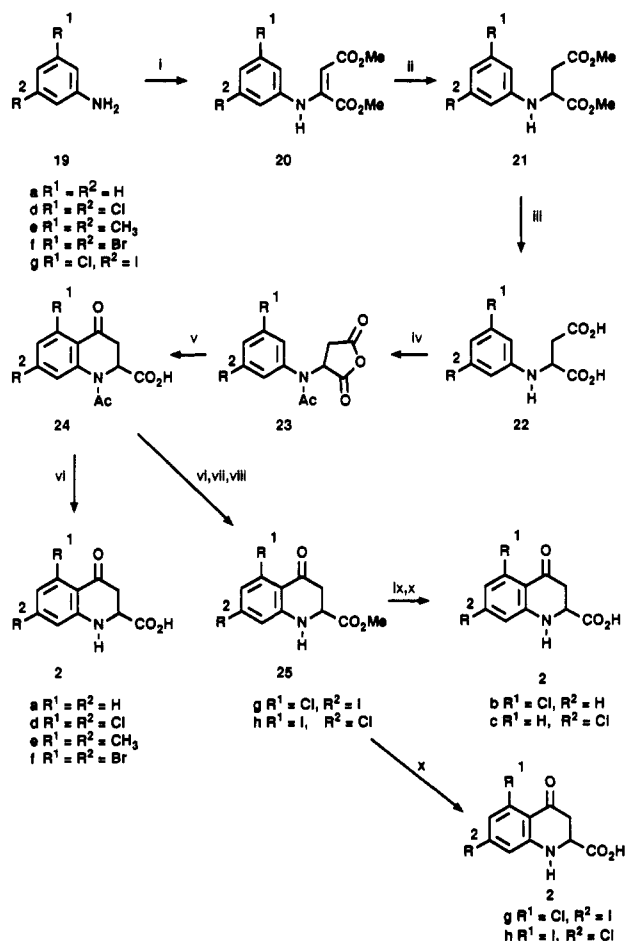


proposed a model¹⁰ to account for glycine-site NMDA receptor antagonist binding which comprised (a) size-limited, hydrophobic binding of the benzene ring, (b) hydrogen-bond acceptance by the 4-oxo group, (c) hydrogen-bond donation by the 1-amino group, and (d) a Coulombic attraction of the 2-carboxylate. We proposed that the tautomer of the kynurenates which was recognized by

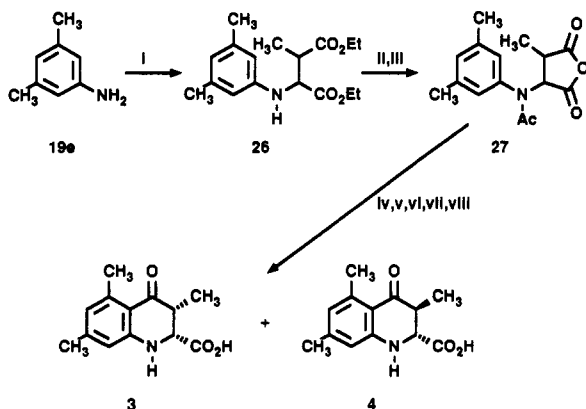
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Scheme I^a

^a Reagents: (i) $MeO_2CC\equiv CCO_2Me$, MeOH, reflux; (ii) H_2 -Pd, C, EtOAc or H_2 -Pt-S, C, EtOH; (iii) NaOH, aqueous MeOH; (iv) $(CH_3CO)_2O$, 80 °C; (v) $AlCl_3$, 160 °C; (vi) 3 N HCl, 100 °C; (vii) MeOH, HCl; (viii) silica chromatography; (ix) H_2 , Pd, C, MeOH; (x) LiOH, THF.

Scheme II^a

^a Reagents: (i) $EtO_2CCO-CH(CH_3)CO_2Et$, H_2 , Pd, C, EtOH; (ii) NaOH, aqueous MeOH; (iii) Ac_2O , 80 °C; (iv) $AlCl_3$, 160 °C; (v) 3 N HCl, 100 °C; (vi) MeOH, HCl; (vii) silica chromatography; (viii) NaOH, aqueous MeOH.

particular are shown to have improved glycine-site antagonist potencies and provide the first details of the stereochemical and conformational requirements for antagonist binding.¹¹ The overall structure-activity requirements fully support the proposed model for glycine-site antagonist binding and indicate that a variety of 4-substituents can be tolerated.

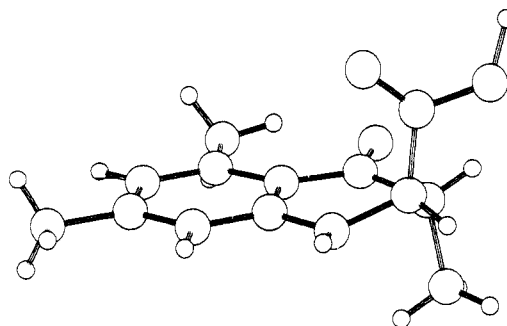
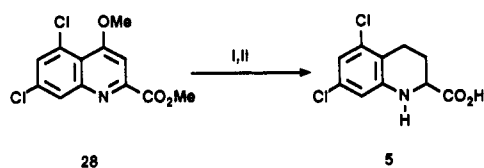


Figure 1. The structure and conformation of 4 as determined by X-ray crystallography.

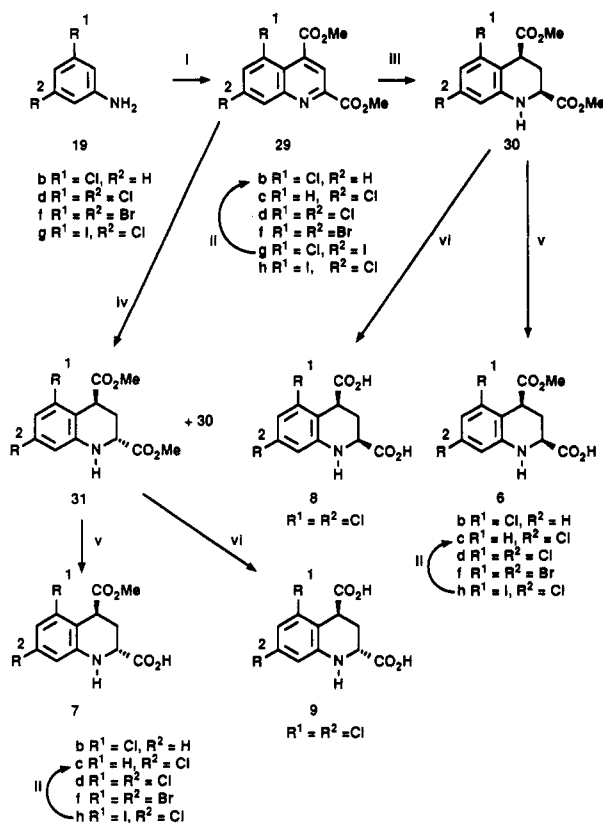
Synthesis

The 2,3-dihydrokynurenic acid analogues 2a-h were prepared by the route shown in Scheme I. The appropriate aniline 19a-d-g and dimethyl acetylenedicarboxylate were heated together in methanol to give the corresponding enamines 20,¹² which were hydrogenated over palladium on carbon catalyst to produce the reduced amino diesters 21. In the cases of 20f and 20g, sulfided platinum on carbon was used as the hydrogenation catalyst in order to prevent dehalogenation. Saponification of 21 gave the *N*-arylaspartic acid derivatives 22, which upon treatment with acetic anhydride at 80 °C produced the *N*-acetyl anhydrides 23. Intramolecular Friedels-Crafts acylation using neat aluminum chloride at 160 °C in the melt according to the conditions of Tokuyama et al.¹³ produced the cyclic ketones 24 in yields ranging from 15 to 41%. Removal of the acetyl group to give the required compounds 2 was accomplished by treatment with 3 N HCl at reflux.¹³ The iodo and chloro disubstituted compounds 2g and 2h were obtained by esterification of the crude mixture produced after deacetylation of 24, followed by chromatographic separation to give the intermediate esters 25g and 25h, which were subsequently saponified. 5-Chloro and 7-chloro derivatives 2b and 2c were made by deiodination and hydrolysis of 25g and 25h, respectively. The 3-methyl-2,3-dihydrokynurenic acid analogues 3 and 4 were prepared as outlined in Scheme II. 3,5-Dimethylaniline and diethyl oxalpropionate were heated together in ethanol over 4A molecular sieves for several days, and then the reaction mixture was hydrogenated over palladium on carbon catalyst to give diester 26. Basic hydrolysis followed by treatment with acetic anhydride at 80 °C produced anhydride 27, which was cyclized under the previously described conditions to give, after deprotection and separation, the *cis*- and *trans*-3-methyl isomers 3 and 4. The relative stereochemistries of these com-

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Scheme III^a

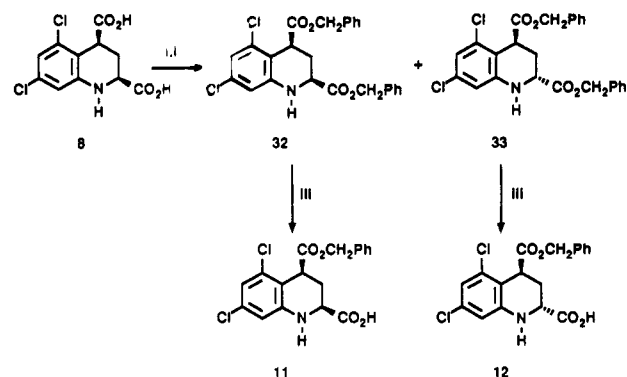
^aReagents: (i) H₂, PtO₂, MeOH; (ii) NaOH, aqueous MeOH.

Scheme IV^a

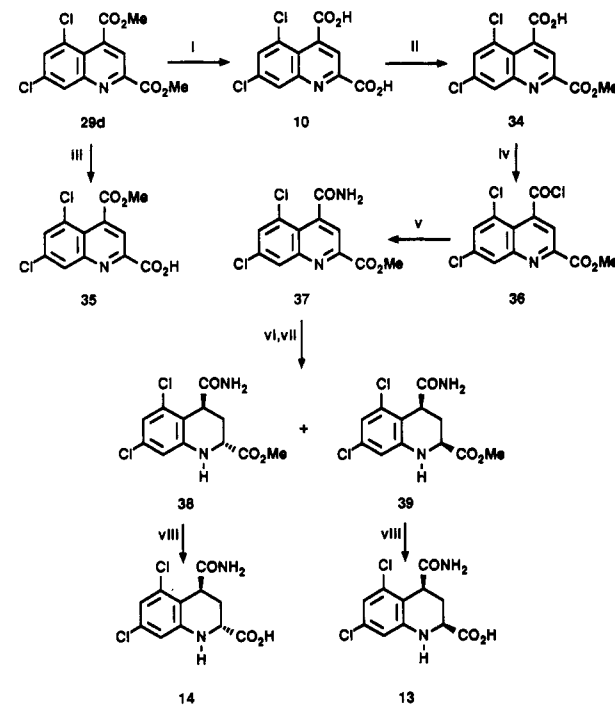
^aReagents: (i) MeO₂CCOCH=CHCO₂Me, HCl, CH₂Cl₂; (ii) H₂, Pd, C, MeOH; (iii) H₂, PtO₂, MeOH; (iv) NaCNBH₃, AcOH, 50 °C; (v) 1 equiv NaOH, aqueous (CH₃)₂CO; (vi) excess NaOH, aqueous MeOH, reflux, 14 h.

pounds followed from X-ray crystallographic analysis of the 2,3-trans derivative (4) (Figure 1). The 4-unsubstituted tetrahydroquinoline 5 was prepared by hydrogenation of 4-methoxyquinoline 28,¹⁰ followed by saponification (Scheme III).

The *cis*- and *trans*-2-carboxy-4-methyl ester tetrahydroquinolines 6b-d,f,h and 7b-d,f,h, and the *cis*- and *trans*-2,4-dicarboxytetrahydroquinolines 8 and 9 were prepared as described in Scheme IV. Anilines 19 were stirred with excess dimethyl glutaconate in dichloromethane for several hours and then treated with a catalytic amount of dry hydrogen chloride or boron trifluoride etherate to give quinolines 29.¹⁴ In the case of 3-chloroaniline (19b) the major product was 7-chloroquinoline 29c, 5-chloro isomer 29b being formed only in trace amounts. Sufficient quantities of the 5-chloro isomer were obtained by deiodination of the 5-chloro-7-iodo compound 29g (the major isomer [1.7:1] of cyclizing 19g) via hydrogenation

Scheme V^a

^aReagents: (i) K₂CO₃, DMF, BnBr; (ii) silica chromatography; (iii) 1 equiv NaOH, aqueous MeOH.

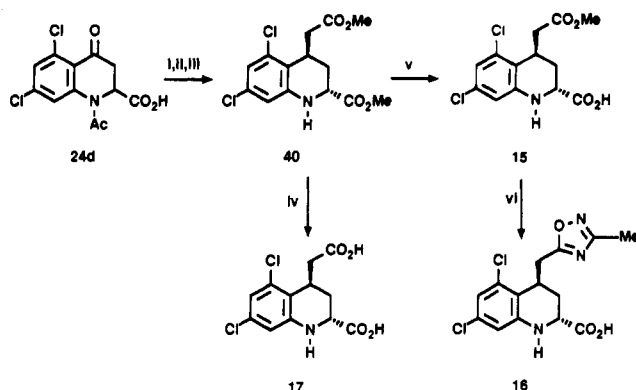
Scheme VI^a

^aReagents: (i) excess NaOH, aqueous MeOH, reflux, 14 h; (ii) MeOH, HCl, 2 h; (iii) 1 equiv NaOH, room temperature; (iv) SOCl₂, 60 °C; (v) NH₃, THF; (vi) NaCNBH₃, AcOH, 50 °C; (vii) silica chromatography; (viii) NaOH, aqueous MeOH.

over palladium on carbon catalyst. Hydrogenation of 29b-d and 29f over platinum oxide produced *cis*-diesters 30b-d and 30f exclusively, but deiodination occurred with 29h. To overcome this problem, and to prepare the corresponding *trans* isomers 31, quinolines 29 were reduced by reaction with sodium cyanoborohydride in acetic acid at 50 °C.¹⁵ Typically, formation of the *trans* isomers was favored by a factor of approximately 2:1. Treatment of compounds 30 and 31 with 1 equiv of sodium hydroxide resulted in selective cleavage of the 2-ester group to give 2-carboxylates 6 and 7. The origin of this selectivity probably lies with a peri shielding effect of the 4-ester by the 5-chloro substituent. Treatment of compounds 30 and 31 with excess base at room temperature gave incomplete reaction, and more forcing conditions had to be employed to form dicarboxylates 8 and 9. The regiochemistry of 6h and 7h was proven to be 5-iodo-7-chloro by deiodination to produce 7-chloro derivatives 6c and 7c, respectively.

The *cis*- and *trans*-4-benzyl ester 2-carboxytetrahydroquinolines 11 and 12 were prepared by reaction of *cis*-

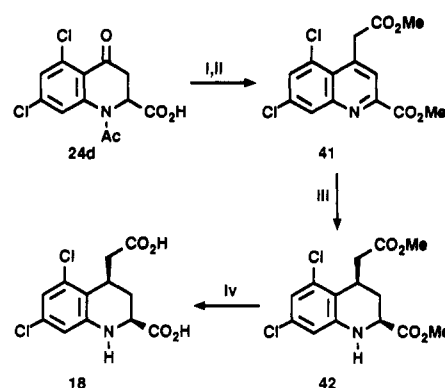
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Scheme VII^a

^aReagents: (i) $\text{MeO}_2\text{CCH}_2\text{P}(\text{O})(\text{OMe})_2$, NaNH_2 , THF; (ii) H_2 , PtO_2 , MeOH, 60 h. (iii) MeOH, HCl; (iv) excess NaOH, aqueous MeOH; (v) 1 equiv NaOH, aqueous MeOH; (vi) $\text{CH}_3=\text{N}(\text{OH})\cdot\text{NH}_2$, NaH, THF.

2,4-dicarboxylate 8 with benzyl bromide in dimethylformamide in the presence of potassium carbonate, followed by chromatographic separation of the isomers 32 and 33 and subsequent treatment with 1 equiv of sodium hydroxide (Scheme V). The *cis*- and *trans*-4-carboxamides (13 and 14) were synthesized by the route described in Scheme VI. Quinoline diester 29d was hydrolyzed under forcing conditions to give quinolinediacid 10, and treatment of this compound with methanolic hydrogen chloride for 2 h resulted in selective ester formation at the 2-position to give 34. The regiochemistry of compound 34 was confirmed since treatment of 29d with 1 equiv of sodium hydroxide cleanly produced the isomeric mono ester 35, which was significantly different from 34 according to ^1H NMR spectra and reverse-phase HPLC. Reaction of 34 with thionyl chloride at 60 °C produced acid chloride 36, which underwent reaction with dry ammonia in tetrahydrofuran to give amide 37. Reduction of the heterocyclic ring was accomplished with sodium cyanoborohydride in acetic acid¹⁵ at 50 °C to give an approximately equal amount of the *cis*- and *trans*-esters 38 and 39, and the required final compounds 13 and 14 were obtained by simple basic hydrolysis.

trans-4-Acetate derivatives 15–17 were prepared as outlined in Scheme VII. Treatment of 24d with the anion of trimethyl phosphonoacetate (preformed with sodium amide¹⁶) gave a crude mixture of olefins which was hydrogenated over platinum then treated with methanolic hydrogen chloride to give *trans*-diester 40. Basic hydrolysis under forcing conditions gave diacid 17, and milder conditions mono acid 15. Methyloxadiazole derivative 16 was prepared by reaction of the anion of acetamide oxime¹⁸ with 4-mono ester 15. The synthesis of *cis*-4-acetic acid 18 was carried out by the route described in Scheme VIII. Treatment of ketone 24d with the anion of trimethyl phosphonoacetate gave the same crude mixture of alkenes described previously. This was dissolved in methanol which had been presaturated with dry hydrogen chloride and stood at room temperature for several days. Quinoline 41 was isolated and then hydrogenated over platinum in

Scheme VIII^a

^aReagents: (i) $\text{MeO}_2\text{CCH}_2\text{P}(\text{O})(\text{OMe})_2$, NaNH_2 , THF; (ii) H_2 , PtO_2 , MeOH, 42 days; (iii) H_2 , PtO_2 , MeOH; (iv) excess NaOH, aqueous MeOH.

methanol to produce *cis*-diester 42, which was hydrolyzed under standard conditions to yield the required compound.

Biology

Compounds were evaluated in *in vitro* assays predictive for activity at the NMDA receptor, and details of the methodologies used have been published.^{10,19,20} Affinities for the glycine binding site were determined by displacement of [^3H]glycine binding to membranes prepared from rat cerebral cortex and hippocampus. The concentrations of test compounds required to inhibit 50% of the specific binding (IC_{50} 's) of [^3H]glycine were indicative of affinities for the glycine/NMDA site. Functional antagonist potency was assessed by determination of the apparent dissociation constants (K_b 's) of test compounds for antagonism of the depolarizations induced by NMDA and α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) in a rat cortical slice preparation.

The IC_{50} 's from the radioligand binding assay are the means of at least three experiments (except where stated) and the maximum variance (geometric mean) was 60%. The K_b values from the cortical slice assay are means from at least three experiments; the maximum variance (geometric mean) was 15%. Generally, IC_{50} 's of compounds in the [^3H]glycine binding assay are around 10-fold lower than apparent K_b 's for *N*-methyl-D-aspartate antagonism in the cortical slice. The lower activity in the functional assay is probably a consequence of competition with high levels of endogenous glycine present in the cortical slice preparation. The potencies of selected compounds as antagonists of glycine-induced NMDA currents in isolated cultured neurones, where glycine concentrations can be adjusted, were fully consistent with their affinities for the [^3H]glycine site.^{19,21}

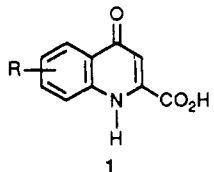
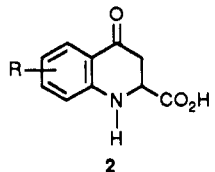
Results and Discussion

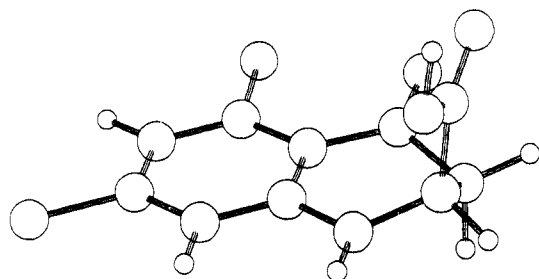
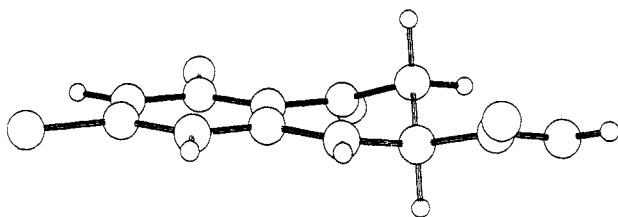
The effect of reduction at the 2,3-double bond of kynurenic acid and its more potent substituted derivatives is summarized in Table I. The dihydro analogues 2a–h

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Table I. Kynurenic Acids and 2,3-Reduced Kynurenic Acids

 1				 2			
R	no.	IC ₅₀ (μM) vs [³ H]Gly ¹⁰	K _b (μM) vs NMDA ¹⁰	no.	IC ₅₀ (μM) vs [³ H]Gly	K _b (μM) vs NMDA	
H	1a	41	154	2a	>100	473	
5-Cl	1b	5.2	37	2b	6.96		
7-Cl	1c	0.56	7	2c	2.36	39	
5,7-Cl ₂	1d	0.20	3	2d	2.31	14	
5,7-Me ₂	1e	0.54	7	2e	1.86	57	
5,7-Br ₂	1f	0.086	1.6	2f	1.29	12	
5-Cl,7-I	1g	0.65	10	2g	3.84	60	
5-I,7-Cl	1h	0.032	0.41	2h	0.36	2.5	

Figure 2. The 2-pseudoaxial conformer of 2d energy minimized (3.43 kcal) using AMF (Advanced Modeling Facility).²²Figure 3. The 2-pseudoequatorial conformer of 2d energy minimized (2.73 kcal) using AMF.²²

generally show reduced potency, but the rank order of activity reflects that of the lead compounds, and thus, 5-iodo-7-chloro substitution still optimal. The maintenance of activity in the dihydrokynurenates, which cannot tautomerize, provides further evidence that the 4-oxo tautomer of compounds 1a–h is required for receptor recognition. The relative reduction in potency observed with the 2,3-reduced kynurenic acids may be attributable to the preferred existence in solution of the pseudoaxial 2-carboxylate conformation (Figure 2). This follows from the absence of a large vicinal coupling in the ¹H NMR spectrum for 2d, where the observed coupling constants for H_A are only 6.8 and 6.2 Hz. The less preferred pseudoequatorial conformer (Figure 3) is clearly a better mimic of the planar kynurenic acid and is almost certainly the conformation needed for binding. Further evidence for this argument is provided by the data summarized in Table II. 2,3-Dihydro-5,7-dimethyl analogue 2e is approximately 1 order of magnitude less potent than the corresponding kynurenic acid 1e. *cis*-3-Methyl derivative 3 is equipotent in the functional assay with 2e while *trans*-3-methyl compound 4 is essentially inactive. In the case of the *trans* compound 4, the energy difference between the 2-pseudoaxial and 2-pseudoequatorial conformation is increased by vicinal repulsion between the 2- and 3-substituents (to obtain a dihedral angle of 180°) and so reduced potency is seen. The 2,3-diaxial relationship of compound 4 has

been confirmed by X-ray crystallographic analysis (Figure 1). In the case of *cis* compound 3, 2,3-substituent gauche interactions are unavoidable in both 2-pseudoaxial and 2-pseudoequatorial conformers, the two conformers are consequently in competition, and so potency is retained.

The reduction in potency seen with the 1,2,3,4-tetrahydroquinoline 5 relative to the corresponding 2,3-dihydrokynurenic acid 2d (Table III) indicates the importance of the 4-keto group, which is probably acting as a hydrogen-bond acceptor.¹⁰ Further evidence for this hypothesis is the finding that addition of a methoxycarbonyl group to the 4-position of the molecule results in increased potency in both the *cis* (6d) and the *trans* (7d) isomers (Table IV). The effect of aromatic substitution in the *trans* series (compounds 7b–d,f,h) is different from that observed in the kynurenic acid and reduced kynurenic acid series since the 5,7-dichloro (7d), 5,7-dibromo (7f), and 5-iodo-7-chloro (7h) derivatives are essentially equipotent. ¹H NMR (*J*[H_A–H_B] = 11.7 Hz) and molecular modeling studies indicate that the preferred conformation of *trans* compounds 7 is probably 4-pseudoaxial 2-pseudoequatorial (Figure 4). In the *cis* series (compounds 6b–d,f,h), 5,7-dichloro analogue 6d is actually the most potent compound and 5-iodo-7-chloro derivative 6h is markedly less potent. This finding can again be rationalized by consideration of conformational arguments since the size of the 5-substituent is likely to influence conformational preference within the *cis* series. Steric interaction between 4- and 5-substituents results in the 4-substituent adopting a pseudoaxial arrangement and the degree to which this occurs is likely to depend on the relative sizes of both groups. With the *cis* isomers (6b–d,f,h), ¹H NMR studies in DMSO (*J*[H_A–H_B] = 7.1 Hz) show that the preferred conformation is indeed 2,4-diaxial (Figure 5), and since the pseudoequatorial 2-carboxylate is likely to be preferred for receptor binding, this finding would account for the decrease in potency observed as the size of the 5-substituent increases. 5-Iodo-7-chloro derivative 6h is less potent than 7-chloro compound 6c even though the latter compound lacks the usually beneficial effect of a size-limited hydrophobic substituent at the 5-position. This is attributable, again, to an increase in the population of the receptor-active di-pseudoequatorial conformation (Figure 6).

The 5,7-dichloro 2,4-dicarboxylate derivatives (8 and 9, Table V) both show a marked reduction in potency relative to the corresponding parent 4-methyl ester derivatives (6d and 7d). 2,4-Dicarboxyquinoline 10 is essentially inactive, providing further evidence of the need for a hydrogen-bond donor at the 1-position.^{10,23} The *cis*- and *trans*-4-benzyl esters 11 and 12 are equipotent and both compounds are significantly more active than corresponding acids 8 and

Table II. Reduced and Methylated Derivatives of 5,7-Dimethylkynurenic Acid

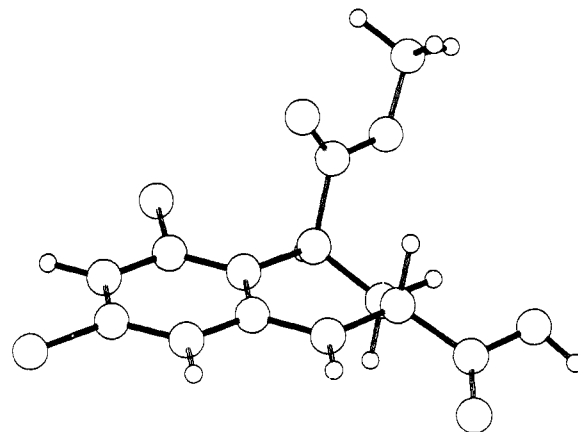
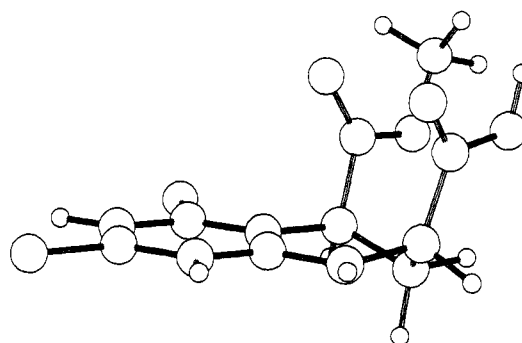
no.	structure	IC ₅₀ (μM) vs [³ H]Gly	K _d (μM) vs NMDA
1e		0.54 ¹⁰	7.0 ¹⁰
2e		1.86	57
3		13.7	62
4		>100	>100

Table III. Reduced Derivatives of 5,7-Dichlorokynurenic Acid

no.	structure	IC ₅₀ (μM) vs [³ H]Gly	K _d (μM) vs NMDA
1d		0.20 ¹⁰	3 ¹⁰
2d		2.31	14
5		6.39	84

9, and this result suggests bulk tolerance on the receptor adjacent to the 4-position. The *cis*- and *trans*-4-carboxamides 13 and 14 are also essentially equipotent (in the functional assay), and the general lack of stereoselectivity exhibited throughout Table V indicates that the hydrogen-bonding groups and/or their relative positions are probably not optimal.

Homologation at the 4-position of *trans*-methyl ester 7d gives methyl acetate derivative 15 (Table VI), which shows a 5-fold improvement in functional potency and is approximately equipotent with the best 4-carboxylic ester analogue 6d. Methyloxadiazole 16 has only 4-fold reduced potency and is clearly an acceptable replacement for a methyl ester.²⁴ A marked increase in activity occurs with

**Figure 4.** The 4-pseudoaxial-2-pseudoequatorial conformer of 7d energy minimized (12.812 kcal) using AMF.²²**Figure 5.** The 2,4-di-pseudoaxial conformer of 6d energy minimized (14.654 kcal) using AMF.²²

trans-4-acetic acid derivative 17, which is more potent than the corresponding lead 5,7-dichlorokynurenic acid (1d). Compound 17 is also very selective (K_b vs AMPA > 100 μM; K_b vs NMDA, 1.2 μM) and the high activity of 17 is in agreement with other recent results^{23,25} showing that an anionic group is tolerated in the 4-position binding pocket of the glycine receptor. This suggests that the glycine site may have some features in common with the neurotransmitter recognition sites on NMDA and AMPA receptors since the majority of antagonists and agonists (including glutamate itself) that bind to these sites are also α-amino acids which contain remote anionic functionality.⁴ The >100-fold binding affinity of 17 relative to *cis* isomer 18 and the lower acid homologues 8 and 9 may be explained by optimal positioning in 17 of the 4-substituent carboxyl group. The difference in potency between the two isomers 17 and 18 can again be rationalized by conformational analysis. ¹H NMR evidence shows *cis* compound 18 to exist in the 2,4-pseudoaxial (receptor-inactive) conformation ($J[H_A-H_B] < 7.0$ Hz) while the *trans* compound 17 exists in the 4-pseudoaxial, 2-pseudoequatorial conformation ($J[H_A-H_B] = 12.4$ Hz), which we propose is required for receptor recognition.

Conclusions

The results of these studies are consistent with the model we proposed previously for high-affinity binding of antagonists to the glycine site of the NMDA receptor.¹⁰ The need for a hydrogen-bond-accepting group at the

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Table IV. 4-(Methoxycarbonyl)-2-carboxytetrahydroquinolines

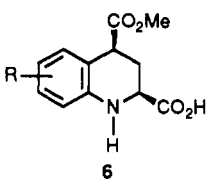
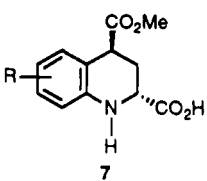
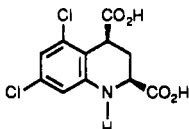
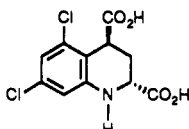
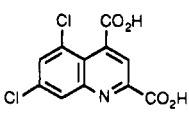
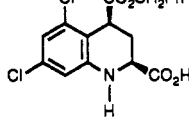
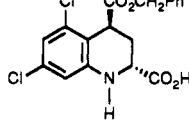
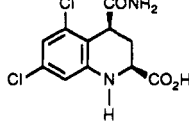
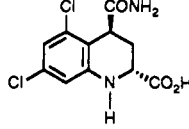
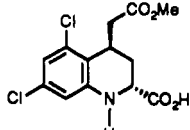
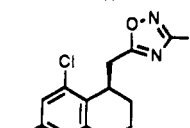
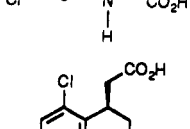
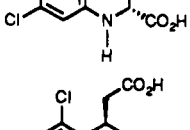
							
R	no.	IC ₅₀ (μM) vs [³ H]Gly	K _b (μM) vs NMDA	no.	IC ₅₀ (μM) vs [³ H]Gly	K _b (μM) vs NMDA	
5-Cl	6b	26.1	128	7b	176	~300	
7-Cl	6c	5.02	19	7c	16.9	75	
5,7-Cl ₂	6d	1.21	5.2	7d	2.47	23	
5,7-Br ₂	6f	2.05	10	7f	2.89	16	
5-I,7-Cl	6h	4.18	28	7h	3.09	15	

Table V. 5,7-Dichloro-4-carboxytetrahydroquinoline Derivatives

no.	structure	IC ₅₀ (μM) vs [³ H]Gly	K _d (μM) vs NMDA
8		31.4	214
9		20 (n = 1)	>10
10		>100	>100
11		2.33	42
12		1.05	44
13		3.44	27
14		0.72	19

4-position of the quinoline ring has been proven by both removal of the 4-oxo group, resulting in reduced potency, and replacement with alternative 4-substituents, realizing increased activity. The requirement of a hydrogen-bond-donating group at the 1-position independently indicated by Leeson et al.¹⁰ and Harrison et al.²³ is supported by the generally high activity seen with the 2-carboxytetrahydroquinolines described in this paper. This finding supports the view that the active tautomer of the kynurenic acid (1) series has the 4-keto-1-amino structure. Conformational arguments, which place the 2-carboxylic acid pseudoaxial as opposed to pseudoequatorial, can account for the differences in biological activity seen with

Table VI. 5,7-Dichloro-4-methylenetetrahydroquinoline Derivatives

no.	structure	IC ₅₀ (μM) vs [³ H]Gly	K _b (μM) vs NMDA
15		0.603	5.6
16		2.53	20
17		0.134	1.2
18		15.0	105

the tetrahydroquinoline stereoisomers. The comparable affinities of benzyl esters 11 and 12 with methyl esters 6d and 7d indicate probable bulk tolerance at the receptor adjacent to the 4-substituent. The high potency observed with *trans*-4-acetic acid 17 suggests optimal positioning of the 4-substituent and indicates that the glycine site may have some features in common with the neurotransmitter recognition site on the NMDA receptor. These results clearly extend current views of structural requirements and tolerance for binding to the glycine site on the NMDA receptor.

Experimental Section

General directions have appeared previously.²⁶

2-Carboxy-5,7-dichloro-4-oxo-1,2,3,4-tetrahydroquinoline (2d). 3,5-Dichloraniline (19d) (104 g, 0.62 mol) and dimethyl acetylenedicarboxylate (79 mL, 0.63 mol) were dissolved in dry methanol (100 mL) and heated under reflux for 14 h. On cooling a yellow solid crystallized out and this was collected by filtration. The mother liquors were concentrated under vacuum to leave a

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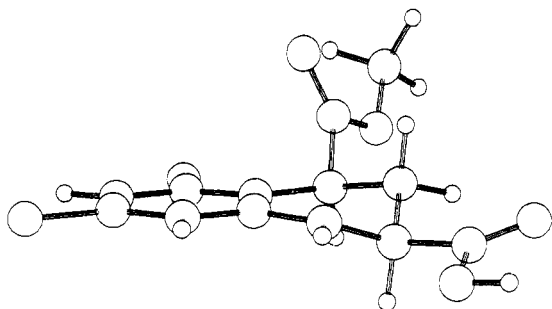


Figure 6. The 2,4-di-pseudoequatorial conformer of **6d** energy minimized (14.371 kcal) using AMF.²²

residue from which a second crop of product was obtained by recrystallization from diethyl ether/petroleum ether (bp 60–80 °C throughout). From the combined crops (167.5 g, 87%) a portion of this material (105 g) was dissolved in ethyl acetate (100 mL) and hydrogenated over 10% palladium on carbon catalyst (4 g) for 40 h. The catalyst was removed by filtration and the solvent was evaporated under vacuum to leave a residue which was recrystallized from diethyl ether/petroleum ether to give diester **21d** as a white crystalline solid (84.8 g, 80%): mp 66–67 °C; NMR δ (CDCl₃) 2.88 (2 H, m, CH₂CH₂H₂CO), 3.71 (3 H, s, CH₃), 3.78 (3 H, s, CH₃), 4.36 (1 H, t, J = 5.4 Hz, CH₂CH₂H₂CO), 4.71 (1 H, br, s, NH), 6.51 (2 H, d, J = 1.8 Hz, 2-*H* and 6-*H*), 6.73 (1 H, t, J = 1.8 Hz, 4-*H*); MS (EI) m/e 305 [M⁺]. Anal. (C₁₂H₁₂Cl₂NO₄) C, H, N. Diester **21d** (131.4 g, 0.43 mol) was dissolved in methanol (800 mL) with sodium hydroxide (51.5 g, 1.29 mol, in 600 mL of water) and stirred at room temperature for 5 h. The methanol was removed under vacuum and the residual solution was acidified to pH 1 by the cautious addition of concentrated hydrochloric acid. After extraction with ethyl acetate (2 × 600 mL), the combined organic layers were dried (MgSO₄), filtered, and concentrated in vacuo to give **22d** as a white solid (116 g, 97%): mp 217 °C dec; NMR δ (NaOD) 2.47 (1 H, dd, J = 15.1 and 10.1 Hz, CH₂CH₂H₂C), 2.73 (1 H, dd, J = 15.1 and 3.8 Hz, CH₂CH₂H₂C), 4.06 (1 H, dd, J = 10.1 and 3.8 Hz, CH₂CH₂H₂C), 6.62 (2 H, d, J = 1.5 Hz, 2-*H* and 6-*H*), 6.79 (1 H, t, J = 1.5 Hz, 4-*H*); MS (EI) m/e 277 [M⁺]. Anal. (C₁₀H₈Cl₂NO₄) C, H, N. A portion of **22d** (80 g, 0.29 mol) was dissolved in acetic anhydride (600 mL), heated at 80 °C for 2 h, and then allowed to cool to room temperature. A white solid was collected by filtration, and the mother liquors were concentrated under vacuum and triturated with diethyl ether to give a second crop. The combined crops were dried under high vacuum to give **23d** (82.6 g, 92%): NMR δ (CDCl₃) 1.97 (3 H, s, NCOCH₃), 3.27 (2 H, m, CH₂CH₂H₂C), 4.44 (1 H, dd, CH₂CH₂H₂C, J = 9.4 and 7.0 Hz), 7.30 (2 H, d, J = 1.6 Hz, 2-*H* and 6-*H*), 7.46 (1 H, t, J = 1.6 Hz, 4-*H*). A portion of this material (60 g, 0.19 mol) and finely ground aluminum trichloride (168 g, 1.26 mol) was blended together and heated at 160 °C for 30 min. The reaction mixture was poured onto aluminum foil and allowed to cool to room temperature, and the solid mass was ground to a powder and cautiously poured into ice-cold 1 N HCl. After effervescence had ceased, the aqueous layer was decanted and the residual solid was triturated with absolute ethanol to give **24d** as a white solid (10.2 g, 17%): mp 212–213 °C; NMR δ (DMSO) 2.32 (3 H, s, NCOCH₃), 3.04 (1 H, dd, J = 17.4 and 1.7 Hz, CH₂CH₂H₂C), 3.21 (1 H, dd, J = 17.4 and 6.6 Hz, CH₂CH₂H₂C), 5.59 (1 H, m, CH₂CH₂H₂C), 7.54 (1 H, d, J = 2.0 Hz, 6-*H* or 8-*H*), 7.81 (1 H, d, J = 2.0 Hz, 6-*H* or 8-*H*); MS (EI) m/e 301 [M⁺]. Anal. (C₁₂H₉Cl₂NO₄) C, H, N.

24d (21.17 g, 0.07 mol) was suspended in 3 N HCl (500 mL), heated under reflux for 14 h, and then cooled and extracted with ethyl acetate (3 × 300 mL), washed with brine (1 × 300 mL), dried (MgSO₄), filtered, and concentrated in vacuo to give **2d** as a yellow solid (17.45 g, 96%): mp 218–219 °C; NMR δ (DMSO) 2.73 (1 H, dd, J = 15.7 and 6.8 Hz, CH₂CH₂H₂C), 2.92 (1 H, dd, J = 15.7 and 6.2 Hz, CH₂CH₂H₂C), 4.36 (1 H, m, CH₂CH₂H₂C), 6.67 (1 H, d, J = 2.0 Hz, 6-*H* or 8-*H*), 6.96 (1 H, d, J = 2.0 Hz, 6-*H* or 8-*H*), 7.62 (1 H, br s, NH); MS (FAB) m/e 260 [MH]⁺. Anal. (C₁₀H₇Cl₂NO₃) C, H, N.

Compounds **2e** and **2f** were prepared in the same way as described for **2d** starting with the appropriate anilines.

2-Carboxy-5,7-dimethyl-4-oxo-1,2,3,4-tetrahydroquinoline (2e): mp 154–155 °C; NMR δ (DMSO) 2.14 (3 H, s, CH₃), 2.40 (3 H, s, CH₃), 2.65 (1 H, dd, J = 15.9 and 6.7 Hz, CH₂CH₂H₂C), 2.79 (1 H, dd, J = 15.9 and 6.2 Hz, CH₂CH₂H₂C), 4.18 (1 H, ddd, J = 6.7, 6.2, and 2.1 Hz, NHCH₂CH₂H₂C), 6.21 (1 H, s, 6-*H* or 8-*H*), 6.54 (1 H, s, 6-*H* or 8-*H*), 6.83 (1 H, br s, NH); MS (FAB) m/e 220 [MH]⁺. Anal. (C₁₂H₁₃NO₃·0.8H₂O) C, H, N.

2-Carboxy-5,7-dibromo-4-oxo-1,2,3,4-tetrahydroquinoline (2f): mp 213–216 °C; NMR δ (DMSO) 2.74 (1 H, dd, J = 15.7 and 6.4 Hz, CH₂CH₂H₂C), 2.93 (1 H, dd, J = 15.7 and 6.4 Hz, CH₂CH₂H₂C), 4.36 (1 H, dt, J = 6.4 and 2.0 Hz, NHCH₂CH₂H₂C), 6.98 (1 H, d, J = 1.7 Hz, 6-*H* or 8-*H*), 7.16 (1 H, d, J = 1.7 Hz, 6-*H* or 8-*H*), 7.59 (1 H, d, J = 2.0 Hz, NH), 13.15 (1 H, br s, CO₂H); MS (EI) m/e 349 M [M⁺]. Anal. (C₁₀H₆Br₂O₃) C, H, N.

2-Carboxy-5-chloro-4-oxo-1,2,3,4-tetrahydroquinoline (2b). A mixture of **24g** and **24h** (4.0 g, 0.012 mol) (which was obtained from 3-chloro-5-iodoaniline (20 g) by the same sequence of reactions described for the preparation of **24d**) was dissolved in 3 N HCl and heated under reflux for 3 h. After cooling, extraction into ethyl acetate, drying (Na₂SO₄), filtration and evaporation, a crude mixture (3.19 g, 89%) of **2g** and **2h** was obtained. Treatment of the mixture with methanolic hydrogen chloride (20 mL) for 3 h, evaporation, and silica gel chromatography using 10% hexane in dichloromethane as eluent gave **25h** (0.3 g, 9%, mp 176–177 °C) as the less polar isomer and **25g** (0.7 g, 21%, mp 208–209 °C) as the more polar isomer. **25g** (0.3 g, 0.82 mmol) was dissolved in methanol (50 mL) and hydrogenated under atmospheric pressure over 10% palladium on carbon catalyst for 8 h. After filtration and evaporation, the residue obtained was purified by silica gel chromatography using 10% hexane in dichloromethane as eluent to give a product (0.069 g) which was dissolved in THF (30 mL) and treated with 0.5 N lithium hydroxide solution (0.58 mL, 0.35 mmol). After 2 h, the solvent was removed under vacuum and the residue was dissolved in water (40 mL) and acidified to pH 1 with 1 N HCl. After extraction into ethyl acetate (2 × 40 mL), washing with brine (1 × 40 mL), drying (Na₂SO₄), filtration, and evaporation, the residue was recrystallized from methanol to give **2b** as a yellow solid (0.042 g, 26% from **25g**): mp 166–167 °C; NMR δ (DMSO) 2.72 (1 H, dd, J = 15.5 and 6.6 Hz, CH₂CH₂H₂C), 2.91 (1 H, dd, J = 15.5 and 6.2 Hz, CH₂CH₂H₂C), 4.30 (1 H, dt, J = 6.4 and 3.1 Hz, CH₂CH₂H₂C), 6.60 (1 H, dd, J = 8.0 and 0.7 Hz, 6-*H* or 8-*H*), 6.85 (1 H, dd, J = 8.0 and 0.7 Hz, 6-*H* or 8-*H*), 7.18 (1 H, t, J = 8.0 Hz, 7-*H*), 7.53 (1 H, br s, NH), 13.0 (1 H, br s, CO₂H); MS (CI) m/e 226 [MH]⁺. Anal. (C₁₀H₈ClNO₃·0.4H₂O) C, H, N.

2-Carboxy-7-chloro-4-oxo-1,2,3,4-tetrahydroquinoline (2c). Treatment of **25h** under the conditions described for the conversion of **25g** to **2b** gave **2c**, as a yellow solid: mp 232–233 °C dec; NMR δ (DMSO) 2.73 (1 H, dd, J = 16.5 and 7.0 Hz, CH₂CH₂H₂C), 2.86 (1 H, dd, J = 16.5 and 6.0 Hz, CH₂CH₂H₂C), 4.34 (1 H, m, CH₂CH₂H₂C), 6.12 (1 H, dd, J = 8.0 and 1.9 Hz, 6-*H*), 6.99 (1 H, d, J = 1.9 Hz, 8-*H*), 7.30 (1 H, s, NH), 7.53 (1 H, d, J = 8.0 Hz, 5-*H*), 13.0 (1 H, br s, CO₂H); MS (EI) m/e 225 [M⁺]. Anal. (C₁₀H₈ClNO₃·0.1H₂O) C, H, N.

2-Carboxy-5-chloro-7-iodo-4-oxo-1,2,3,4-tetrahydroquinoline (2g). Compound **25g** (0.15 g, 0.41 mmol) was dissolved in THF (30 mL) and 0.5 N lithium hydroxide solution (0.984 mL, 1.2 molar equiv) was added. After stirring at room temperature for 3 h, the solvent was removed under vacuum and the residue produced was dissolved in water (50 mL). The aqueous solution was acidified to pH 1 with 1 N HCl, extracted into ethyl acetate (2 × 40 mL), washed with brine (1 × 40 mL), dried (Na₂SO₄), filtered, and concentrated under vacuum. The product obtained was recrystallized from ethyl acetate/hexane to give **2g** as a yellow solid (0.095 g, 67%): mp 232 °C; NMR δ (DMSO) 2.71 (1 H, dd, J = 15.7 and 6.3 Hz, CH₂CH₂H₂C), 2.91 (1 H, dd, J = 15.7 and 6.2 Hz, CH₂CH₂H₂C), 4.33 (1 H, dt, J = 6.3 and 2.8 Hz, CH₂CH₂H₂C), 6.93 (1 H, d, J = 1.5 Hz, 6-*H* or 8-*H*), 7.31 (1 H, d, J = 1.5 Hz, 6-*H* or 8-*H*), 7.51 (1 H, d, J = 2.1 Hz, NH), 13.11 (1 H, br s, CO₂H); MS (EI) m/e 351 [M⁺]. Anal. (C₁₀H₇ClINNO₃·0.1H₂O) C, H, N.

2-Carboxy-7-chloro-5-iodo-4-oxo-1,2,3,4-tetrahydroquinoline (2h). Treatment of **25h** under the conditions described for the conversion of **25g** to **2g** produced **2h** as a yellow solid: mp 239–240 °C; NMR δ (DMSO) 2.76 (1 H, dd, J = 15.8 and 6.7 Hz, CH₂CH₂H₂C), 2.93 (1 H, dd, J = 15.8 and 6.2 Hz, CH₂CH₂H₂C),

4.36 (1 H, dt, $J = 6.5$ and 2.6 Hz, $\text{CH}_A\text{CH}_B\text{H}_C$), 7.03 (1 H, d, $J = 2.0$ Hz, 6- H or 8- H), 7.19 (1 H, d, $J = 2.0$ Hz, 6- H or 8- H), 7.54 (1 H, d, $J = 2.0$ Hz, NH), 13.1 (1 H, br s, CO_2H); MS (EI) m/e 351 [M^+]. Anal. ($\text{C}_{10}\text{H}_7\text{ClINO}_3$) C, H, N.

trans- and cis-2-Carboxy-4-oxo-3,5,7-trimethyl-1,2,3,4-tetrahydroquinoline (3 and 4). 3,5-Dimethylaniline (19e) (24.2 g, 0.2 mol) and diethyl oxalpropionate (40.4 g, 0.2 mol) were dissolved in ethanol (800 mL) and crushed 4A sieves (10 g) added. The reaction mixture was heated under reflux for 10 days, cooled, and filtered and the residue obtained was purified by silica gel chromatography (40% CH_2Cl_2 in petroleum ether) to give an oil (32 g). This was dissolved in ethanol (200 mL) and hydrogenated at 50 psi over 10% palladium on carbon catalyst for 14 h to give a crude oil (26) as product (24.2 g, 39% from 19e): NMR δ (CDCl_3) 1.24 (9 H, m, $2 \times \text{CH}_3\text{CH}_2\text{O}$ and $\text{CH}_A\text{CH}_B\text{CH}_3$), 2.22 (6 H, s, $2 \times \text{CH}_3\text{Ar}$), 2.99 (1 H, m, $\text{CH}_A\text{CH}_B\text{CH}_3$), 4.16 (4 H, m, $2 \times \text{CH}_3\text{CH}_2\text{O}$), 4.43 (1 H, m, $\text{CH}_A\text{CH}_B\text{CH}_3$), 6.32 (2 H, br, s, 2- H and 6- H), 6.41 (1 H, br s, 4- H). 26 (24.2 g, 0.079 mol) was dissolved in 50% aqueous methanol with sodium hydroxide (20 g, 0.5 mol), stirred at room temperature for 14 h, and then concentrated under vacuum. The residue was dissolved in water (300 mL) and washed with diethyl ether (2×200 mL), and then the aqueous layer was acidified to pH 1 with 5 N HCl and the solid produced was collected by filtration, dried under high vacuum, and then heated in acetic anhydride (450 mL) at 80°C for 2 h. After evaporation of the solvent, the residue was triturated with diethyl ether, and an off white solid (27) (21 g, 97%) was collected by filtration: NMR δ (CDCl_3) 1.45 (3 H, d, $J = 7.5$ Hz, CH_3CH), 1.93 (3 H, s, COCH_3), 2.36 (6 H, s, $2 \times \text{CH}_3\text{Ar}$), 3.59 (1 H, m, CH_3CH), 4.24 (1 H, m, NCH), 6.94 (2 H, br s, 2- H and 6- H), 7.06 (1 H, br s, 4- H); MS (EI) m/e 275 [M^+]. 27 (20 g, 0.073 mol) and AlCl_3 (58.2 g, 0.44 mol) were blended together and then heated at 160°C for 20 min. The cooled reaction mixture was poured into ice-cold 1 N HCl, and after effervescence had ceased the solution was decanted off and the residue was triturated with hot diethyl ether to produce a white solid which was collected by filtration (2.82 g, 14%). The white solid (1.5 g, 5.5 mmol) was treated with 3 N HCl (60 mL) at reflux for 2 h, cooled, extracted into EtOAc (2×40 mL), dried (Na_2SO_4), filtered, and concentrated in vacuo to give a mixture of 3 and 4 (1.18 g, 92%). Recrystallization of the residue from diethyl ether gave 4 as yellow needles (0.22 g, 17%): mp $156\text{--}157^\circ\text{C}$; NMR δ (CDCl_3) 1.35 (3 H, d, $J = 7.2$ Hz, $\text{CH}_3\text{CH}_2\text{CH}_A$), 2.23 (3 H, s, CH_3Ar), 2.54 (3 H, s, CH_3Ar), 2.97 (1 H, m, $\text{CH}_3\text{CH}_2\text{CH}_A$), 3.97 (1 H, d, $J = 4.9$ Hz, $\text{CH}_3\text{CH}_2\text{CH}_A$), 6.40 (2 H, br s, 6- H and 8- H); MS (EI) m/e 233 [M^+]. Anal. ($\text{C}_{13}\text{H}_{15}\text{NO}_3$) C, H, N. The mother liquor (a 0.6-g portion, 2.5 mmol) was dissolved in a solution of methanol that had been presaturated with HCl gas and stood at room temperature for 14 h. After removal of the solvent in vacuo, the residue was chromatographed on silica gel with 20% hexane in dichloromethane as eluent. The less polar material (0.13 g) was dissolved in 50% aqueous methanol (60 mL) with 1 N sodium hydroxide solution (1.58 mL, 3 molar equiv) and stirred at room temperature for 2 h. Standard workup gave 3 as a green oil (0.09 g, 30%): NMR δ (CDCl_3) 1.17 (3 H, d, $J = 7.2$ Hz, $\text{CH}_3\text{CH}_2\text{CH}_A$), 2.24 (3 H, s, CH_3Ar), 2.57 (3 H, s, CH_3Ar), 2.95 (1 H, dq, $J = 7.2$ and 4.0 Hz, $\text{CH}_3\text{CH}_2\text{CH}_A$), 4.43 (1 H, d, $J = 4.0$ Hz, $\text{CH}_3\text{CH}_2\text{CH}_A$), 4.90 (1 H, br s, NH), 6.40 (1 H, s, 6- H or 8- H), 6.42 (1 H, s, 6- H or 8- H); MS (EI) m/e 233 [M^+]. Anal. ($\text{C}_{13}\text{H}_{15}\text{NO}_3 \cdot 0.4\text{H}_2\text{O}$) C, H, N. The relative stereochemistries of 3 and 4 could not be determined by NMR studies, but X-ray crystallography showed 4 to be 2,3-*trans*.

2-Carboxy-5,7-dichloro-1,2,3,4-tetrahydroquinoline (5). Compound 28¹⁰ (1 g, 3.5 mmol) was dissolved in methanol (200 mL) and hydrogenated at atmospheric pressure over platinum oxide (0.1 g) for 3 h. After filtration and evaporation, the residue was purified by silica gel chromatography using 10% ethyl acetate in hexane as eluent to give a product which was dissolved in 50% aqueous acetone and treated with sodium hydroxide (0.1 g) for 2 h. Standard workup produced a residue which was purified by preparative plate chromatography using 2% methanol/1% acetic acid in dichloromethane as eluent, followed by recrystallization from dichloromethane to give 5 as a white solid (0.039 g, 5% from 28): mp 143°C dec; NMR δ (DMSO) 1.99–2.02 (2 H, m, $\text{NCH}_2\text{CH}_2\text{H}_C\text{CH}_D\text{H}_E$), 2.45–2.53 (1 H, m, $\text{NCH}_2\text{CH}_2\text{H}_C\text{CH}_D\text{H}_E$), 2.67–2.74 (1 H, m, $\text{NCH}_2\text{CH}_2\text{H}_C\text{CH}_D\text{H}_E$), 3.95–3.99 (1 H, m, $\text{NCH}_2\text{CH}_2\text{H}_C\text{CH}_D\text{H}_E$), 6.60 (1 H, d, $J = 2.1$ Hz, 6- H or 8- H), 6.64

(1 H, d, $J = 2.1$ Hz, 6- H or 8- H), 12.74 (1 H, br s, CO_2H); MS (EI) m/e 245 [M^+]. Anal. ($\text{C}_{10}\text{H}_5\text{Cl}_2\text{NO}_3$) C, H, N.

cis-2-Carboxy-5,7-dichloro-4-(methoxycarbonyl)-1,2,3,4-tetrahydroquinoline (6d). Compound 19d (75.35 g, 0.465 mol) and dimethyl glutaconate (100 g, 0.058 mol) were dissolved in dichloromethane (800 mL) and stirred at room temperature for 36 h. $\text{BF}_3 \cdot \text{OEt}_2$ (100 mL) was added and the solution stirred 2 days further. The reaction mixture was quenched with saturated NaHCO_3 solution and the organic layer was separated, washed with brine, then dried (MgSO_4), filtered, and concentrated in vacuo. Chromatography on silica gel with 15% ethyl acetate in hexane and recrystallization from methanol gave 29d as a colorless solid (28 g, 19%): mp $116\text{--}118^\circ\text{C}$; NMR δ (CDCl_3) 4.04 (3 H, s, CH_3), 4.10 (3 H, s, CH_3), 7.77 (1 H, d, $J = 2.2$ Hz, 6- H or 8- H), 8.19 (1 H, s, 3- H), 8.31 (1 H, d, $J = 2.2$ Hz, 6- H or 8- H); MS (EI) m/e 313 [M^+]. Anal. ($\text{C}_{13}\text{H}_9\text{Cl}_2\text{NO}_4$) C, H, N. 29d (1 g, 3.2 mmol) was dissolved in methanol (100 mL) and hydrogenated over platinum oxide (0.1 g) at atmospheric pressure for 1 h. Filtration, evaporation, and silica gel chromatography with dichloromethane as eluent gave *cis*-diester 30d (0.79 g, 78%): mp $152\text{--}153^\circ\text{C}$; NMR δ (DMSO) 2.28 (1 H, ddd, $J = 14.0$, 7.1, and 5.4 Hz, $\text{CH}_A\text{CH}_B\text{H}_C\text{CH}_D$), 2.80 (1 H, dt, $J = 14.0$ and 3.5 Hz, $\text{CH}_A\text{CH}_B\text{H}_C\text{CH}_D$), 3.64 (3 H, s, CH_3), 3.67 (3 H, s, CH_3), 3.94 (1 H, dd, $J = 7.0$ and 3.1 Hz, $\text{CH}_A\text{CH}_B\text{H}_C\text{CH}_D$), 4.06 (1 H, dd, $J = 5.4$ and 3.6 Hz, $\text{CH}_A\text{CH}_B\text{H}_C\text{CH}_D$), 6.63 (1 H, d, $J = 1.8$ Hz, 6- H or 8- H), 6.67 (1 H, d, $J = 1.8$ Hz, 6- H or 8- H); MS (EI) m/e 317 [M^+]. Anal. ($\text{C}_{13}\text{H}_{13}\text{Cl}_2\text{NO}_4$) C, H, N. 30d (0.7 g, 2.2 mmol) was dissolved in 50% aqueous methanol (60 mL), and sodium hydroxide (0.097 g, 2.4 mmol) was added. After stirring at room temperature overnight, the solvents were removed under vacuum, and the residue was dissolved in water and washed with diethyl ether. The aqueous layer was acidified to pH 1 with 1 N HCl, extracted into diethyl ether, dried (Na_2SO_4), filtered, and concentrated under vacuum to give an oil which was purified by silica gel chromatography using 2.5% methanol/0.5% acetic acid/97% dichloromethane as eluent. 6d was obtained as a white solid (0.53 g, 80%): mp $154\text{--}156^\circ\text{C}$; NMR δ (DMSO) 2.23 (1 H, ddd, $J = 13.9$, 7.1, and 5.3 Hz, $\text{CH}_A\text{CH}_B\text{H}_C\text{CH}_D$), 2.66 (1 H, dt, $J = 13.9$ and 4.0 Hz, $\text{CH}_A\text{CH}_B\text{H}_C\text{CH}_D$), 3.57 (3 H, s, CH_3), 3.86 (1 H, dd, $J = 7.1$ and 4.0 Hz, $\text{CH}_A\text{CH}_B\text{H}_C\text{CH}_D$), 3.91 (1 H, br m, $\text{CH}_A\text{CH}_B\text{H}_C\text{CH}_D$), 5.74 (1 H, br, s, NH), 6.56 (1 H, d, $J = 1.9$ Hz, 6- H or 8- H), 6.58 (1 H, d, $J = 1.9$ Hz, 6- H or 8- H); MS (EI) m/e 303 [M^+]. Anal. ($\text{C}_{12}\text{H}_{11}\text{Cl}_2\text{NO}_4$) C, H, N.

Compounds 6b, 6c, 6f, and 6h were prepared in the same way as described for 6d starting with the appropriate anilines.

cis-2-Carboxy-5-chloro-4-(methoxycarbonyl)-1,2,3,4-tetrahydroquinoline (6b): mp $190\text{--}193^\circ\text{C}$; NMR δ (DMSO) 2.20 (1 H, m, $\text{CH}_A\text{CH}_B\text{H}_C\text{CH}_D$), 2.56 (1 H, dm, $J = 13.8$ Hz, $\text{CH}_A\text{CH}_B\text{H}_C\text{CH}_D$), 3.55 (3 H, s, CH_3), 3.91 (1 H, dd, $J = 7.1$ and 3.3 Hz, $\text{CH}_A\text{CH}_B\text{H}_C\text{CH}_D$), 3.98 (1 H, m, $\text{CH}_A\text{CH}_B\text{H}_C\text{CH}_D$), 6.53 (1 H, br s, NH), 6.58 (1 H, d, $J = 7.8$ Hz, 6- H or 8- H), 6.64 (1 H, d, $J = 8.3$ Hz, 6- H or 8- H), 6.98 (1 H, t, $J = 8.0$ Hz, 7- H). Anal. ($\text{C}_{12}\text{H}_{12}\text{ClNO}_4$) C, H, N.

cis-2-Carboxy-7-chloro-4-(methoxycarbonyl)-1,2,3,4-tetrahydroquinoline (6c): mp $176\text{--}178^\circ\text{C}$; NMR δ (DMSO) 2.44 (2 H, m, $\text{CH}_A\text{CH}_B\text{H}_C\text{CH}_D$), 3.62 (3 H, s, CH_3), 3.87 (1 H, dd, $J = 7.0$ and 6.8 Hz, $\text{CH}_A\text{CH}_B\text{H}_C\text{CH}_D$), 3.97 (1 H, m, $\text{CH}_A\text{CH}_B\text{H}_C\text{CH}_D$), 6.34 (1 H, br s, NH), 6.48 (1 H, dd, $J = 8.2$ and 2.2 Hz, 6- H), 6.72 (1 H, d, $J = 2.2$ Hz, 8- H), 6.85 (1 H, d, $J = 8.2$ Hz, 5- H); MS (EI) m/e 269 [M^+]. Anal. ($\text{C}_{12}\text{H}_{12}\text{ClNO}_4$) C, H, N.

cis-2-Carboxy-5,7-dibromo-4-(methoxycarbonyl)-1,2,3,4-tetrahydroquinoline (6f): mp $171\text{--}173^\circ\text{C}$; NMR δ (DMSO) 2.15 (1 H, m, $\text{CH}_A\text{CH}_B\text{H}_C\text{CH}_D$), 2.59 (1 H, dm, $J = 13.9$ Hz, $\text{CH}_A\text{CH}_B\text{H}_C\text{CH}_D$), 3.53 (3 H, s, CH_3), 3.82 (1 H, m, $\text{CH}_A\text{CH}_B\text{H}_C\text{CH}_D$), 4.00 (1 H, m, $\text{CH}_A\text{CH}_B\text{H}_C\text{CH}_D$), 6.89 (3 H, br m, 6- H , 8- H and NH); MS (EI) m/e 393 [M^+]. Anal. ($\text{C}_{12}\text{H}_{11}\text{Br}_2\text{NO}_4$) C, H, N.

cis-2-Carboxy-7-chloro-5-iodo-4-(methoxycarbonyl)-1,2,3,4-tetrahydroquinoline (6h): mp 188°C dec; NMR δ (DMSO) 2.29 (1 H, m, $\text{CH}_A\text{CH}_B\text{H}_C\text{CH}_D$), 2.92 (1 H, dm, $J = 14.2$ Hz, $\text{CH}_A\text{CH}_B\text{H}_C\text{CH}_D$), 3.65 (3 H, s, CH_3), 3.91 (1 H, dd, $J = 6.4$ and 3.4 Hz, $\text{CH}_A\text{CH}_B\text{H}_C\text{CH}_D$), 4.10 (1 H, dd, $J = 6.1$ and 3.3 Hz, $\text{CH}_A\text{CH}_B\text{H}_C\text{CH}_D$), 6.66 (1 H, d, $J = 2.0$ Hz, 6- H or 8- H), 7.26 (1 H, d, $J = 2.0$ Hz, 6- H or 8- H); MS (EI) m/e 395 [M^+]. Anal. ($\text{C}_{12}\text{H}_{11}\text{ClINO}_4 \cdot 0.4\text{H}_2\text{O}$) C, H, N.

trans-2-Carboxy-5,7-dichloro-4-(methoxycarbonyl)-1,2,3,4-tetrahydroquinoline (7d). Compound 29d (2 g, 6.4 mmol) was dissolved in glacial acetic acid (15 mL), and sodium cyanoborohydride (2.4 g, 0.0384 mol) was added in portions over a period of 15 min. The reaction mixture was heated at 50 °C for 1 h and then stirred at room temperature overnight. After dilution with dichloromethane (30 mL), ice-cold 50% NaOH solution was added until a pH of 14 was attained, and the two-phase mixture was stirred vigorously for 2 h, after which time more dichloromethane (50 mL) was added. The two layers were separated, and the organic layer was washed with brine, dried (Na₂SO₄), filtered, and concentrated under vacuum to give a residue which was purified by silica chromatography using 70% dichloromethane in hexane and then neat dichloromethane as eluents. 31d was obtained as a white solid (1.3 g, 64%); mp 113–114 °C; NMR δ (CDCl₃) 1.88 (1 H, ddd, J = 13.4, 12.2, and 5.9 Hz, CH_ACH_BH_CCH_D), 2.67 (1 H, dt, J = 13.4 and 2.6 Hz, CH_ACH_BH_CCH_D), 3.74 (3 H, s, CH₃), 3.82 (3 H, s, CH₃), 4.04 (1 H, dd, J = 12.2 and 3.2 Hz, CH_ACH_BH_CCH_D), 4.06 (1 H, m, CH_ACH_BH_CCH_D), 4.74 (1 H, br s, NH), 6.56 (1 H, d, J = 2.0 Hz, 6-H or 8-H), 6.73 (1 H, d, J = 2.0 Hz, 6-H or 8-H); MS (EI) m/e 317 [M⁺]. Anal. (C₁₃H₁₃Cl₂NO₄) C, H, N. Treatment of 31d (1.13 g, 3.6 mmol) with 1.1 equiv of sodium hydroxide under the same conditions as described for the conversion of 30d to 6d gave 7d (0.85 g, 78%); mp 160 °C dec; NMR δ (DMSO) 1.91 (1 H, ddd, J = 13.4, 11.7, and 6.0 Hz, CH_ACH_BH_CCH_D), 2.41 (1 H, dm, J = 13.4 Hz, CH_ACH_BH_CCH_D), 3.65 (3 H, s, CH₃), 3.79 (1 H, dd, J = 11.7 and 3.2 Hz, CH_ACH_BH_CCH_D), 3.96 (1 H, dd, J = 6.0 and 2.5 Hz, CH_ACH_BH_CCH_D), 6.66 (1 H, d, J = 2.1 Hz, 6-H or 8-H), 6.83 (1 H, d, J = 2.1 Hz, 6-H or 8-H); MS (EI) m/e 303 [M⁺]. Anal. (C₁₂H₁₁Cl₂NO₄) C, H, N.

Compounds 7b, 7c, 7f, and 7h were prepared in the same way as described for 7d starting with the appropriate aniline.

trans-2-Carboxy-5-chloro-4-(methoxycarbonyl)-1,2,3,4-tetrahydroquinoline (7b): mp 159–161 °C; NMR δ (DMSO) 1.93 (1 H, m, CH_ACH_BH_CCH_D), 2.39 (1 H, dm, J = 13.4 Hz, CH_ACH_BH_CCH_D), 3.65 (3 H, s, CH₃), 3.74 (1 H, dd, J = 11.6 and 3.1 Hz, CH_ACH_BH_CCH_D), 3.96 (1 H, dd, J = 6.1 and 2.7 Hz, CH_ACH_BH_CCH_D), 6.30 (1 H, br s, NH), 6.59 (1 H, d, J = 7.7 Hz, 6-H or 8-H), 6.72 (1 H, d, J = 8.2 Hz, 6-H or 8-H), 6.99 (1 H, t, J = 8.0 Hz, 7-H); MS (EI) m/e 269 [M⁺]. Anal. (C₁₂H₁₂ClNO₄) C, H, N.

trans-2-Carboxy-7-chloro-4-(methoxycarbonyl)-1,2,3,4-tetrahydroquinoline (7c): mp 122–124 °C; NMR δ (DMSO) 1.88 (1 H, m, CH_ACH_BH_CCH_D), 2.33 (1 H, dm, J = 13.5 Hz, CH_ACH_BH_CCH_D), 3.65 (3 H, s, CH₃), 3.75 (1 H, t, J = 5.0 Hz, CH_ACH_BH_CCH_D), 3.99 (1 H, dd, J = 9.5 and 3.8 Hz, CH_ACH_BH_CCH_D), 6.37 (1 H, br s, NH), 6.49 (1 H, dd, J = 8.2 and 2.2 Hz, 6-H), 6.74 (1 H, d, J = 2.2 Hz, 8-H), 6.94 (1 H, d, J = 8.2 Hz, 5-H); MS (EI) m/e 269 [M⁺]. Anal. (C₁₂H₁₂ClNO₄) C, H, N.

trans-2-Carboxy-5,7-dibromo-4-(methoxycarbonyl)-1,2,3,4-tetrahydroquinoline (7f): mp 175–176 °C; NMR δ (DMSO) 1.90 (1 H, dt, J = 13.4 and 5.7 Hz, CH_ACH_BH_CCH_D), 2.41 (1 H, dm, J = 13.4 Hz, CH_ACH_BH_CCH_D), 3.66 (3 H, s, CH₃), 3.76 (1 H, dd, J = 11.9 and 3.1 Hz, CH_ACH_BH_CCH_D), 3.92 (1 H, dd, J = 4.5 and 1.0 Hz, CH_ACH_BH_CCH_D), 6.65 (1 H, br s, NH), 6.91 (1 H, d, J = 1.8 Hz, 6-H or 8-H), 7.02 (1 H, d, J = 1.8 Hz, 6-H or 8-H); MS (EI) m/e 393 [M⁺]. Anal. (C₁₂H₁₁Br₂NO₄) C, H, N.

trans-2-Carboxy-7-chloro-5-iodo-4-(methoxycarbonyl)-1,2,3,4-tetrahydroquinoline (7h): oil; NMR δ (DMSO) 1.95 (1 H, ddd, J = 14.2, 12.2, and 5.6 Hz, CH_ACH_BH_CCH_D), 2.72 (1 H, dm, J = 14.4 Hz, CH_ACH_BH_CCH_D), 3.76 (3 H, s, CH₃), 3.98 (1 H, dd, J = 5.6 and 2.1 Hz, CH_ACH_BH_CCH_D), 4.09 (1 H, dd, J = 12.2 and 3.4 Hz, CH_ACH_BH_CCH_D), 6.64 (1 H, d, J = 1.9 Hz, 6-H or 8-H), 7.20 (1 H, d, J = 1.9 Hz, 6-H or 8-H); MS (EI) m/e 395 [M⁺]. Anal. (C₁₂H₁₁ClINO₄) C, H, N.

cis-2,4-Dicarboxy-5,7-dichloro-1,2,3,4-tetrahydroquinoline (8). Compound 30d (0.2 g, 0.66 mmol) was dissolved in 50% aqueous methanol (200 mL) with sodium hydroxide (0.3 g, 0.0075 mol) and heated under reflux for 14 h. After cooling and evaporation of the solvents, the residue was partitioned between water and diethyl ether. The aqueous layer was acidified to pH 1 with 1 N HCl and extracted into ethyl acetate, dried (Na₂SO₄), filtered, and concentrated under vacuum. The crude solid obtained was

recrystallized from diethyl ether/hexane to give 8 as a white solid (0.095 g, 53%); mp 225–227 °C; NMR δ (DMSO) 2.19 (1 H, m, CH_ACH_BH_CCH_D), 2.53 (1 H, dt, 13.9 and 3.5 Hz, CH_ACH_BH_CCH_D), 3.76 (1 H, dd, J = 7.3 and 3.5 Hz, CH_ACH_BH_CCH_D), 3.98 (1 H, m, CH_ACH_BH_CCH_D), 6.64 (1 H, d, J = 2.1 Hz, 6-H or 8-H), 6.70 (1 H, d, J = 2.1 Hz, 6-H or 8-H), 6.80 (1 H, br s, NH), 12.48 (2 H, br s, 2 × CO₂H); MS (EI) m/e 289 [M⁺]. Anal. (C₁₁H₉Cl₂NO₄) C, H, N.

trans-2,4-Dicarboxy-5,7-dichloro-1,2,3,4-tetrahydroquinoline (9). Treatment of 31d (0.2 g, 0.66 mmol) under the conditions described for the conversion of 30d to 8 gave 9 (0.02 g, 11%); mp 135 °C; NMR δ (DMSO) 1.84 (1 H, ddd, J = 13.4, 11.9, and 5.8 Hz, CH_ACH_BH_CCH_D), 2.44 (1 H, dm, J = 13.4 Hz, CH_ACH_BH_CCH_D), 3.77 (1 H, dd, J = 11.9 and 3.0 Hz, CH_ACH_BH_CCH_D), 3.84 (1 H, dd, J = 5.8 and 2.1 Hz, CH_ACH_BH_CCH_D), 6.58 (1 H, br s, NH), 6.63 (1 H, d, J = 2.0 Hz, 6-H or 8-H), 6.81 (1 H, d, J = 2.0 Hz, 6-H or 8-H); MS (FAB) m/e 290 [MH]⁺. Anal. (C₁₁H₉Cl₂NO₄) C, H, N.

2,4-Dicarboxy-5,7-dichloroquinoline (10). Treatment of 31d (0.3 g, 0.96 mmol) under the conditions described for the conversion of 30d to 8 gave 10 as a white solid (0.098 g, 36%); mp 246 °C; NMR δ (DMSO) 8.09 (1 H, s, 3-H), 8.13 (1 H, d, J = 2.2 Hz, 6-H or 8-H), 8.32 (1 H, d, J = 2.2 Hz, 6-H or 8-H); MS (EI) m/e 285 [M⁺]. Anal. (C₁₁H₇Cl₂NO₄·H₂O) C, H, N.

cis-4-(Benzyloxycarbonyl)-2-carboxy-5,7-dichloro-1,2,3,4-tetrahydroquinoline (11). Compound 8 (0.47 g, 1.63 mmol) was dissolved in DMF (30 mL) with potassium carbonate (1.12 g, 8.1 mmol) and benzyl bromide (0.43 mL, 3.6 mmol). After stirring for 14 h, the solvent was evaporated under vacuum and the residue was partitioned between water and dichloromethane. The organic layer was dried (Na₂SO₄), filtered, and concentrated in vacuo then purified by silica gel chromatography using 70% dichloromethane in hexane as eluent to give as colorless solids 32 [(0.23 g, 30%) mp 112–114 °C; NMR δ (CDCl₃) 2.43 (1 H, dd, J = 13.9, 7.2, and 5.1 Hz, CH_ACH_BH_CCH_D), 2.80 (1 H, dt, J = 13.9 and 4.4 Hz, CH_ACH_BH_CCH_D), 4.01 (1 H, dd, J = 7.2 and 4.4 Hz, CH_ACH_BH_CCH_D), 4.05 (1 H, m, CH_ACH_BH_CCH_D), 4.64 (1 H, br s, NH), 5.04 (4 H, m, 2 × PhCH₂), 6.56 (1 H, d, J = 2.0 Hz, 6-H or 8-H), 6.77 (1 H, d, J = 2.0 Hz, 6-H or 8-H), 7.31 (10 H, m, 2 × Ph); MS (EI) m/e 469 [M⁺].] and 33 [(0.35 g, 46%) mp 150–152 °C; NMR δ (CDCl₃) 1.89 (1 H, ddd, J = 13.5, 11.2, and 5.0 Hz, CH_ACH_BH_CCH_D), 2.68 (1 H, dm, J = 13.5 Hz, CH_ACH_BH_CCH_D), 4.02 (1 H, dd, J = 12.2 and 3.1 Hz, CH_ACH_BH_CCH_D), 4.09 (1 H, dd, J = 5.9 and 2.1 Hz, CH_ACH_BH_CCH_D), 4.72 (1 H, br s, NH), 5.16 (2 H, s, PhCH₂), 5.21 (2 H, s, PhCH₂), 6.54 (1 H, d, J = 1.9 Hz, 6-H or 8-H), 6.72 (1 H, d, J = 1.9 Hz, 6-H or 8-H), 7.35 (10 H, m, 2 × Ph); MS (EI) m/e 469 [M⁺].] Treatment of 32 (0.23 g, 0.49 mmol) under the conditions described for the conversion of 30d to 6d gave 11 as a white solid (0.027 g, 15%); mp 144 °C dec; NMR δ (CDCl₃) 2.35 (1 H, m, CH_ACH_BH_CCH_D), 2.81 (1 H, dm, J = 13.9 Hz, CH_ACH_BH_CCH_D), 4.03 (2 H, m, CH_ACH_BH_CCH_D), 5.07 (2 H, s, PhCH₂), 6.57 (1 H, d, J = 1.5 Hz, 6-H or 8-H), 6.77 (1 H, d, J = 1.5 Hz, 6-H or 8-H), 7.32 (5 H, m, Ph); MS (EI) m/e 379 [M⁺]. Anal. (C₁₈H₁₈Cl₂NO₄) C, H, N.

trans-4-(Benzyloxycarbonyl)-2-carboxy-5,7-dichloro-1,2,3,4-tetrahydroquinoline (12). Treatment of 33 (0.35 g, 0.75 mmol) under the conditions described for the conversion of 30d to 6d gave 12 as a white solid (0.045 g, 16%); mp 124–126 °C; NMR δ (CDCl₃) 1.95 (1 H, m, CH_ACH_BH_CCH_D), 2.71 (1 H, dm, J = 12.6 Hz, CH_ACH_BH_CCH_D), 4.08 (1 H, dd, J = 12.3 and 3.1 Hz, CH_ACH_BH_CCH_D), 4.13 (1 H, dd, J = 5.8 and 2.0 Hz, CH_ACH_BH_CCH_D), 5.19 (2 H, s, PhCH₂), 6.56 (1 H, d, J = 1.8 Hz, 6-H or 8-H), 6.75 (1 H, d, J = 1.8 Hz, 6-H or 8-H), 7.33 (5 H, m, Ph); MS (CI⁺) m/e 380 [M + H]⁺. Anal. (C₁₈H₁₈Cl₂NO₄) C, H, N.

cis-4-(Aminocarbonyl)-2-carboxy-5,7-dichloro-1,2,3,4-tetrahydroquinoline (13). Compound 10 (19.5 g, 0.0684 mol) was dissolved in methanol (500 mL) which had been saturated with HCl gas and stood at room temperature for 1 h. The volume was reduced to approximately 100 mL by evaporation under vacuum and the white solid that was produced was collected by filtration to give 34 (18.5 g, 90%); mp 260–262 °C; NMR δ (DMSO) 3.98 (3 H, s, CH₃), 8.11 (1 H, s, 3-H), 8.15 (1 H, d, J = 2.1 Hz, 6-H or 8-H), 8.36 (1 H, d, J = 2.1 Hz, 6-H or 8-H); MS (EI) m/e 299 [M⁺]. Anal. (C₁₂H₇Cl₂NO₄·0.2H₂O) C, H, N. 34

(15.2 g, 0.051 mol) was dissolved in thionyl chloride (300 mL) and the reaction mixture was heated at 60 °C for 3 h. The solvent was removed under vacuum and the residue dried under high vacuum for 14 h to give **36** as a white solid (16.5 g, 102%): NMR δ (CDCl₃) 4.12 (3 H, s, CH₃), 7.83 (1 H, d, J = 1.9 Hz, 6-H or 8-H), 8.25 (1 H, s, 3-H), 8.35 (1 H, d, J = 1.9 Hz, 6-H or 8-H); MS (EI) m/e 317 [M⁺]. **36** (1.5 g, 0.0047 mol) was dissolved in dry THF (20 mL) at 0 °C and an ice-cold solution of THF (150 mL), which had been presaturated with dry ammonia, was added in one portion. After stirring at room temperature for 30 min, the white solid that precipitated was collected by filtration and dried (1.4 g, **37** contaminated with ammonium chloride). A portion of this solid (1 g) was suspended in glacial acetic acid (20 mL), and sodium cyanoborohydride (1.3 g, 0.02 mol) was added in portions. When the addition was complete, the reaction mixture was heated at 50 °C for 2 h, cooled, and stirred at room temperature for 14 h. The solution was diluted with dichloromethane (80 mL) and ice-cold 50% NaOH was added cautiously until a pH of 14 was attained. The organic layer was separated and the aqueous layer was extracted twice with dichloromethane. The combined organic layers were washed with brine, dried (Na₂SO₄), filtered, and concentrated in vacuo to give a residue which was purified by silica gel chromatography, using 2% methanol in dichloromethane as eluent to give as white solids **38** [(0.15 g, 11% from **36**) mp 227–229 °C; NMR δ (DMSO) 1.83 (1 H, m, CH₃CH₂H₂CH₂), 2.32 (1 H, dm, J = 13.2 Hz, CH₃CH₂H₂CH₂), 3.72 (3 H, s, CH₃), 3.78 (1 H, dd, J = 5.8 and 2.0 Hz, CH₃CH₂H₂CH₂), 4.01 (1 H, dd, J = 12.2 and 2.1 Hz, CH₃CH₂H₂CH₂), 6.63 (1 H, d, J = 2.1 Hz, 6-H or 8-H), 6.66 (1 H, br s, NH), 6.78 (1 H, d, J = 2.1 Hz, 6-H or 8-H), 7.02 (1 H, br s, NH), 7.51 (1 H, br s, NH); MS (EI) m/e 302 [M⁺]. Anal. (C₁₂H₁₂Cl₂N₂O₃) C, H, N.] and **39** [(0.14 g, 10% from **37**) mp 203–204 °C; NMR δ (DMSO) 2.05 (1 H, m, CH₃CH₂H₂CH₂), 2.52 (1 H, m, CH₃CH₂H₂CH₂), 3.54 (3 H, s, CH₃), 3.71 (1 H, dd, J = 7.2 and 3.4 Hz, CH₃CH₂H₂CH₂), 4.11 (1 H, dd, J = 5.2 and 3.2 Hz, CH₃CH₂H₂CH₂), 6.61 (1 H, d, J = 2.1 Hz, 6-H or 8-H), 6.70 (1 H, d, J = 2.1 Hz, 6-H or 8-H), 6.84 (2 H, br s, CONH₂), 7.20 (1 H, br s, NH); MS (CI) m/e 303 [MH]⁺. Anal. (C₁₂H₁₂Cl₂N₂O₃) C, H, N. Treatment of **39** (0.12 g, 0.4 mmol) under the conditions described for the conversion of **30d** to **6d** gave **13** (0.082 g, 71%): mp 220–222 °C; NMR δ (DMSO) 2.28 (2 H, m, CH₃CH₂H₂CH₂), 3.71 (1 H, m, CH₃CH₂H₂CH₂), 3.89 (1 H, m, CH₃CH₂H₂CH₂), 6.62 (1 H, d, J = 2.1 Hz, 6-H or 8-H), 6.64 (1 H, br s, NH), 6.74 (1 H, d, J = 2.1 Hz, 6-H or 8-H), 6.81 (1 H, br s, NH), 7.26 (1 H, br s, NH); MS (FAB) m/e 289 [MH]⁺. Anal. (C₁₁H₁₀Cl₂N₂O₃·0.4H₂O) C, H, N.

trans-4-(Aminocarbonyl)-2-carboxy-5,7-dichloro-1,2,3,4-tetrahydroquinoline (14). Treatment of **38** (0.12 g, 0.4 mmol) under the conditions described for the conversion of **30d** to **6d** gave **14** (0.104 g, 86%): mp 168–170 °C; NMR δ (DMSO) 1.79 (1 H, m, CH₃CH₂H₂CH₂), 2.35 (1 H, dm, J = 13.4 Hz, CH₃CH₂H₂CH₂), 3.78 (1 H, m, CH₃CH₂H₂CH₂), 3.89 (1 H, dm, J = 11.8 Hz, CH₃CH₂H₂CH₂), 6.55 (1 H, br s, NH), 6.61 (1 H, d, J = 2.0 Hz, 6-H or 8-H), 6.81 (1 H, d, J = 2.0 Hz, 6-H or 8-H), 7.02 (1 H, s, NH), 7.49 (1 H, s, NH); MS (FAB) m/e 289 [MH]⁺. Anal. (C₁₁H₁₀Cl₂N₂O₃·0.4H₂O) C, H, N: calcd, 9.45; found, 8.95.

trans-2-Carboxy-4-[(methoxycarbonyl)methyl]-5,7-dichloro-1,2,3,4-tetrahydroquinoline (15). Trimethyl phosphonoacetate (32.4 mL, 0.2 mol) was dissolved in dry THF (700 mL) with sodamide (7.8 g, 0.2 mol), heated at 60 °C for 1.5 h, and then cooled to 0 °C. **24d** (16 g, 0.062 mol) was added and the reaction mixture was allowed to warm to room temperature and stirred for 14 h. After quenching with glacial acetic acid (10 mL) and evaporation of the solvents, the residue obtained was dissolved in saturated NaHCO₃ solution (800 mL) and washed with ethyl acetate (4 × 500 mL). The aqueous layer was acidified to pH 1 with 1 N HCl and extracted with ethyl acetate (2 × 500 mL). The combined organic layers were washed with water (4 × 300 mL), dried (Na₂SO₄), filtered, and concentrated in vacuo. The residue (~16 g) was dissolved in methanol (1400 mL) and hydrogenated under atmospheric pressure over platinum oxide (10 g) for 60 h. After filtration and evaporation, the oily residue was dissolved in methanol (1000 mL) which had been presaturated with dry HCl and stood at room temperature for 8 days. The solvent was removed under vacuum and the oil obtained was purified by silica gel chromatography using 20% hexane in dichloromethane as eluent to give as a white solid **40** (6.53 g, 32%): mp 131 °C; NMR

δ (DMSO) 1.69 (1 H, ddd, J = 13.4, 12.3, and 4.0 Hz, CH₃CH₂H₂CH₂), 2.16 (1 H, dm, J = 13.4 Hz, CH₃CH₂H₂CH₂), 2.52 (2 H, m, CH₂CO₂CH₃), 3.46 (1 H, m, CH₃CH₂H₂CH₂), 3.65 (3 H, s, CH₃), 3.72 (3 H, s, CH₃), 4.11 (1 H, dd, J = 12.3 and 2.9 Hz, CH₃CH₂H₂CH₂), 6.64 (1 H, d, J = 1.9 Hz, 6-H or 8-H), 6.71 (1 H, br s, NH), 6.80 (1 H, d, J = 1.9 Hz, 6-H or 8-H); MS (EI) m/e 331 [M⁺]. Anal. (C₁₄H₁₅Cl₂NO₄) C, H, N. Treatment of **40** (0.4 g, 1.2 mmol) under the conditions described for the conversion of **30d** to **6d** gave **15** (0.26 g, 63%): mp 181–182 °C; NMR δ (CDCl₃) 1.72 (1 H, ddd, J = 13.3, 12.5, and 4.0 Hz, CH₃CH₂H₂CH₂), 2.36 (1 H, dm, J = 13.3 Hz, CH₃CH₂H₂CH₂), 2.39 (1 H, dd, J = 16.0 and 11.2 Hz, CH₂CH₂CO₂CH₃), 2.72 (1 H, dd, J = 16.0 and 3.5 Hz, CH₂CH₂CO₂CH₃), 3.66 (1 H, m, CH₃CH₂H₂CH₂CH₂CH₂CO₂CH₃), 3.73 (3 H, s, CO₂CH₃), 3.99 (1 H, dd, J = 12.5 and 5.1 Hz, CH₃CH₂H₂CH₂CH₂CH₂CO₂CH₃), 5.15 (1 H, br s, NH), 6.56 (1 H, d, J = 2.0 Hz, 6-H or 8-H), 6.62 (1 H, d, J = 2.0 Hz, 6-H or 8-H); MS (EI) m/e 317 [M⁺]. Anal. (C₁₃H₁₃Cl₂NO₄) C, H, N.

trans-2-Carboxy-5,7-dichloro-4-[(3-methyl-1,2,4-oxadiazol-5-yl)methyl]-1,2,3,4-tetrahydroquinoline (16). Acetamide oxime (0.22 g, 2.8 mmol) was dissolved in THF (30 mL) with sodium hydride (0.11 g of an 80% dispersion in oil, 2.8 mmol) and heated at 60 °C for 2 h. **15** (0.317 g, 1.0 mmol) was added and the reaction mixture was heated at 60 °C for a further 2 h, then cooled, poured into 1 N HCl (30 mL), and extracted into diethyl ether. After drying (Na₂SO₄), filtration, and evaporation, the residue obtained was purified by silica gel chromatography using 2% methanol and 0.5% acetic acid in dichloromethane as eluent to give **16** as a white solid (0.12 g, 35%): mp 191–192 °C; NMR δ (CDCl₃) 1.75 (1 H, ddd, J = 13.5, 12.6, and 4.4 Hz, CH₃CH₂H₂CH₂CH₂CH₂CH₂), 2.29 (1 H, dm, J = 13.5 Hz, CH₃CH₂H₂CH₂CH₂CH₂CH₂), 2.41 (3 H, CH₃), 2.96 (1 H, dd, J = 15.6 and 11.1 Hz, CH₃CH₂H₂CH₂CH₂CH₂CH₂), 3.23 (1 H, dd, J = 15.6 and 3.8 Hz, CH₃CH₂H₂CH₂CH₂CH₂CH₂), 3.75 (1 H, m, CH₃CH₂H₂CH₂CH₂CH₂CH₂), 4.05 (1 H, dd, J = 12.6 and 3.6 Hz, CH₃CH₂H₂CH₂CH₂CH₂CH₂), 5.25 (1 H, br s, NH), 6.60 (1 H, d, J = 1.9 Hz, 6-H or 8-H), 6.65 (1 H, d, J = 1.9 Hz, 6-H or 8-H); MS (CI) m/e 343 [MH]⁺. Anal. (C₁₄H₁₃Cl₂N₃O₃) C, H, N.

trans-2-Carboxy-4-(carboxymethyl)-5,7-dichloro-1,2,3,4-tetrahydroquinoline (17). Treatment of **40** (0.4 g, 0.2 mmol) under the conditions described for the conversion of **30d** to **8** gave **17** as a white solid (0.24 g, 66%): mp 229–231 °C; NMR δ (DMSO) 1.63 (1 H, ddd, J = 13.3, 12.4, and 4.0 Hz, CH₃CH₂H₂CH₂CH₂CH₂CH₂), 2.20 (1 H, dm, J = 13.3 Hz, CH₃CH₂H₂CH₂CH₂CH₂CH₂), 2.40 (2 H, m, CH₃CH₂H₂CH₂CH₂CH₂CH₂), 3.39 (1 H, m, CH₃CH₂H₂CH₂CH₂CH₂CH₂), 3.98 (1 H, dd, J = 12.4 and 3.3 Hz, CH₃CH₂H₂CH₂CH₂CH₂CH₂), 6.57 (1 H, br s, NH), 6.61 (1 H, d, J = 2.0 Hz, 6-H or 8-H), 6.80 (1 H, d, J = 2.0 Hz, 6-H or 8-H); MS (FAB) m/e [MH]⁺. Anal. (C₁₂H₁₁Cl₂NO₄) C, H, N.

cis-2-Carboxy-4-(carboxymethyl)-5,7-dichloro-1,2,3,4-tetrahydroquinoline (18). Trimethyl phosphonoacetate (16.2 mL, 0.1 mol) was dissolved in dry THF (350 mL) with sodamide (3.90 g, 0.1 mol), heated at 60 °C for 2 h and then cooled to 0 °C and **24d** (8 g, 0.031 mol) added. The reaction mixture was stirred at room temperature for 14 h and then quenched with glacial acetic acid (10 mL) and concentrated under vacuum. The residue was dissolved in saturated NaHCO₃ solution and washed several times with ethyl acetate. The aqueous solution was acidified to pH 1 with 5 N HCl and extracted into ethyl acetate. The organic layer was washed several times with water and then brine, dried (Na₂SO₄), filtered, and concentrated under vacuum. The residue was dissolved in methanol (500 mL) which had been saturated with dry HCl and stood at room temperature for 42 days. The solid which slowly precipitated was collected by filtration and recrystallized from methanol/water to give, as an off-white solid, **41** (2.4 g, 24%): mp 140–142 °C; NMR δ (CDCl₃) 3.73 (3 H, s, CH₃), 4.08 (3 H, s, CH₃), 4.50 (2 H, s, CH₂), 7.70 (1 H, d, J = 2.1 Hz, 6-H or 8-H), 8.01 (1 H, s, 3-H), 8.29 (1 H, d, J = 2.1 Hz, 6-H or 8-H); MS (CI) m/e 328 [MH]⁺. **41** (2.2 g, 6.7 mmol) was dissolved in methanol (150 mL) and hydrogenated at atmospheric pressure over platinum oxide (0.3 g) for 2.5 h. Filtration and evaporation produced a residue which was purified by silica gel chromatography using 25% ethyl acetate in petroleum ether as eluent to give, as a white solid, **42** (0.61 g, 28%): mp 128–129 °C; NMR δ (CDCl₃) 2.16 (2 H, m, CH₃CH₂H₂CH₂CH₂CH₂CH₂), 2.60 (1 H, dm, J = 14.5 Hz, CH₃CH₂H₂CH₂CH₂CH₂CH₂), 2.72 (1 H, dd, J

= 16.7 and 3.3 Hz, $\text{CH}_\text{A}\text{CH}_\text{B}\text{H}_\text{C}\text{CH}_\text{D}\text{CH}_\text{E}\text{H}_\text{F}$), 3.64 (1 H, m, $\text{CH}_\text{A}\text{CH}_\text{B}\text{H}_\text{C}\text{CH}_\text{D}\text{CH}_\text{E}\text{H}_\text{F}$), 4.07 (1 H, dd, $J = 6.6$ and 2.5 Hz, $\text{CH}_\text{A}\text{CH}_\text{B}\text{H}_\text{C}\text{CH}_\text{D}\text{CH}_\text{E}\text{H}_\text{F}$), 4.59 (1 H, br s, NH), 6.51 (1 H, d, $J = 1.9$ Hz, 6-*H* or 8-*H*), 6.72 (1 H, d, $J = 1.9$ Hz, 6-*H* or 8-*H*); MS (CI) m/e 331 $[\text{MH}]^+$. Treatment of 42 (0.3 g, 0.91 mmol) under the conditions described for the conversion of 30d to 8 gave 18 as a white solid (0.045 g, 16%): mp 203–204 °C; NMR δ (DMSO) 1.98 (1 H, m, $\text{CH}_\text{A}\text{CH}_\text{B}\text{H}_\text{C}\text{CH}_\text{D}\text{CH}_\text{E}\text{H}_\text{F}$), 2.19 (1 H, dd, $J = 17.2$ and 11.7 Hz, $\text{CH}_\text{A}\text{CH}_\text{B}\text{H}_\text{C}\text{CH}_\text{D}\text{CH}_\text{E}\text{H}_\text{F}$), 2.41 (2 H, m, $\text{CH}_\text{A}\text{CH}_\text{B}\text{CH}_\text{C}\text{CH}_\text{D}\text{CH}_\text{E}\text{H}_\text{F}$), 3.39 (1 H, m, $\text{CH}_\text{A}\text{CH}_\text{B}\text{H}_\text{C}\text{CH}_\text{D}\text{CH}_\text{E}\text{H}_\text{F}$), 4.03 (1 H, br s, $\text{CH}_\text{A}\text{CH}_\text{B}\text{H}_\text{C}\text{CH}_\text{D}\text{CH}_\text{E}\text{H}_\text{F}$), 6.62 (1 H, s, 6-*H* or 8-*H*), 6.64 (1 H, s, 6-*H* or 8-*H*), 6.84 (1 H, br s, NH), 12.49 (2 H, br s, $2 \times \text{CO}_2\text{H}$); MS (EI) m/e 303 $[\text{M}]^+$. Anal. ($\text{C}_{12}\text{H}_{11}\text{Cl}_2\text{NO}_4 \cdot 0.25\text{H}_2\text{O}$) C, H, N.

- (27) The following library of crystallographic programs was used: SHELXS-86, G.M. Sheldrick, University of Göttingen, West Germany (1986); PLUTO, W.D.S. Motherwell and W. Clegg, University of Cambridge, England (1978); a version of SDPV.3, Enraf-Nonius, Delft, The Netherlands (1985), locally modified for a Sun Microsystems computer.

Crystallography Data. Crystals of 4 ($\text{C}_{13}\text{H}_{15}\text{NO}_3$) formed in space group $2_1/n$ with $a = 10.414$ (1) Å, $b = 8.392$ (1) Å, $c = 13.960$ (1) Å, $\beta = 103.65$ (1)° for $Z = 4$, and a calculated density of 1.307 g/cm³. An automatic four-circle diffractometer equipped with Cu K α radiation ($\lambda = 1.5418$ Å) was used to measure 2248 potential diffraction peaks of which 1474 were observed ($I > 3\sigma I$). Application of a multisolution tangent formula approach to phase solution gave an initial model for the structure²⁷ which was subsequently refined with least squares and Fourier methods. Anisotropic temperature parameters were refined for the non-hydrogen atoms while isotropic temperature factors were applied to the hydrogens but were not refined. The function $\sum \omega(|F_o| - |F_c|)^2$ with $\omega = 4F_o^2/\sigma^2(F_o^2)$ was minimized with full matrix least squares to give an unweighted residual of 0.056.

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