2-(3,4-Dichlorophenyl)-*N*-methyl-*N*-[2-(1-pyrrolidinyl)-1-substituted-ethyl]-acetamides: The Use of Conformational Analysis in the Development of a Novel Series of Potent Opioid κ Agonists

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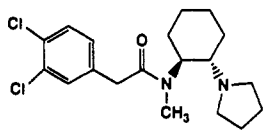
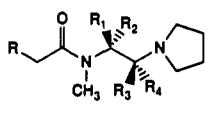
This paper describes the synthesis of a series of *N*-[2-(1-pyrrolidinyl)ethyl]acetamides (1), methylated at C1 and/or C2 of the ethyl linking group, and their biological evaluation as opioid κ agonists. Conformational analysis of corresponding desaryl analogues 2 suggested that only those compounds capable of occupying an energy minimum close to that of the known κ agonist *N*-[2-(1-pyrrolidinyl)cyclohexyl]acetamide U-50488 might possess κ agonist properties. Starting from chiral amino acids, other alkyl and aryl substituents were introduced at C1 of the ethyl-linking moiety, giving compounds capable of adopting the same conformation as U-50488. The most potent of these, 2-(3,4-dichlorophenyl)-*N*-methyl-*N*-[(1*S*)-1-phenyl-2-(1-pyrrolidinyl)ethyl]acetamide (8), was 146-fold more active than U-50488 in vitro in the mouse vas deferens model and exhibited potent naloxone-reversible analgesic effects (ED_{50} = 0.004 mg/kg sc) in an abdominal constriction model.

Since the existence of multiple subtypes of opioid receptors was first proposed,[1,2] it has become apparent that activation of κ receptors can give rise to centrally mediated analgesia, sedation, and diuresis.[3] In addition to a number of naturally occurring and synthetic peptides related to dynorphin,[4] three structurally dissimilar classes of compound, exemplified by ethylketocyclazocine (EKC),[5] tifluadom,[6] and U-50488,[7] have emerged as κ agonists ca-

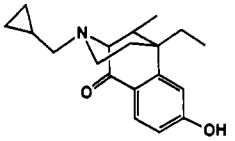


(-) U-50488



1 : R = 

2 : R = H



EKC

pable of producing analgesia in experimental models. The most selective of these, *N*-[2-(1-pyrrolidinyl)cyclohexyl]-acetamide U-50488, has relatively poor affinity but good selectivity for κ receptors labeled by [^{3}H]bremazocine[8] and represents a novel structure which offers considerable potential for modification. Other members of this class of compound include U-62066 (spiradoline),[9] which differs from U-50488 by the addition of a spirotetrahydrofuranyl substituent at C4 in the cyclohexane ring, and PD117302,[10] in which the 3,4-dichlorophenyl group of U-50488 has been replaced by a 4-benzo[*b*]thiophenyl substituent.

(-)-U-50488 is claimed to exhibit greater κ agonist activity than the (+)-enantiomer[11] and the patent literature[12] suggests that it has the 1*S*,2*S* configuration in which the pyrrolidine and amide groups are trans to each other. This has been confirmed more recently by an independent study which established the absolute configuration of the diaminocyclohexylamine precursor of (-)-U-50488.[13] The pyrrolidine nitrogen of U-50488, effectively protonated at physiological pH,[14] and the tertiary amide are prominent polar features. Their disposition, relative to each other and to the lipophilic 3,4-dichlorophenyl group, could be important for binding to the κ receptor and the subsequent expression of efficacy. The opportunity to study this aspect of structure/activity in this series per se is severely limited by the attachment of the principal functional groups to the cyclohexane ring.

The objective of the present study has been to explore the effect of changes in conformation resulting from replacement of the cyclohexane ring of U-50488 with an ethylene chain. It was envisaged that some degree of steric control over the conformation of the resulting *N*-(2-aminoethyl)acetamides could be achieved by methylation at C1 and/or C2 of the ethylene chain. In this paper we describe the synthesis of a series of 2-(3,4-dichlorophenyl)-*N*-[2-(1-pyrrolidinyl)ethyl]acetamides (1), methylated at C1 and/or C2, and their subsequent evaluation as κ agonists. Corresponding truncated analogues 2, lacking the 3,4-dichlorophenyl substituent, have been analyzed for their conformational preferences which have been related to the κ agonist activity of the compounds synthesized. In the later stages of the program, conformational analysis, in conjunction with the emerging structure/activity pattern, was used to aid the selection of C-methylated compounds for synthesis. The approach has been extended to include other alkyl and aryl sub-

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(14) U-50488 pK_a = 9.4, determined by potentiometry. Albert, A.; Sergeant, E. P. *The Determination of Ionization Constants. A Laboratory Manual*, 3rd ed.; Chapman and Hall: London, 1984.

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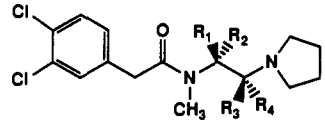
Table I. Biological Activity in K Binding, Mouse Vas Deferens, and Analgesic Assays for Compounds of the Generic Formula Shown



no	substituents R_1	R_2	R_3	R_4	K binding, IC_{50}, nM	mouse vas deferens: potency[a] vs EKC	mouse vas deferens: K_e naloxone,[b] nM	analgesia sc; ED_{50}, mg/kg
1a	H	H	H	H	6120 (3530–10600)	NA[c]	–	–
1b	CH_3	H	H	H	53.2 (30.8–91.7)	0.14 ± 0.02	17.3 ± 3.3	0.67 (0.54–0.8)[d]
1c	H	CH_3	H	H	~10000	NA[c]	–	–
1d	H	H	CH_3	H	1540 (796–2960)	0.002 ± 0.001	~25	>10
1e	CH_3	CH_3	H	H	2060 (1540–2750)	0.004 ± 0.001	–	>10
1f	CH_3	H	CH_3	H	84.6 (41–176)	0.013 ± 0.003	19.1 ± 5.1	4.4 (3.5–5.6)[d]
1g	CH_3	H	H	CH_3	3410 (1960–5930)	NA[c]	–	–
6	$(CH_3)_2CH$	H	H	H	6.3 (3.7–10.7)	4.3 ± 0.8	14.9 ± 2.7	0.05 (0.02–0.06)[d]
7	$(CH_3)_3C$	H	H	H	24.3 (13.0–45.4)	2.5 ± 0.1	10.8 ± 1.8	0.03 (0.01–0.06)[d]
	H	$(CH_3)_3C$	H	H				
8	Ph	H	H	H	6.9 (3.4–14.4)	16.1 ± 5.7	17.8 ± 3.6	0.004 (0.002–0.007)[d]
U-50488H					96 (64–143)	0.11 ± 0.02	15.5 ± 1.6	1.1 (0.6–2.2)[d]
morphine					2390 (2099–2721)	0.13 ± 0.03	4.2 ± 2.0	0.4 (0.3–0.6)[d]

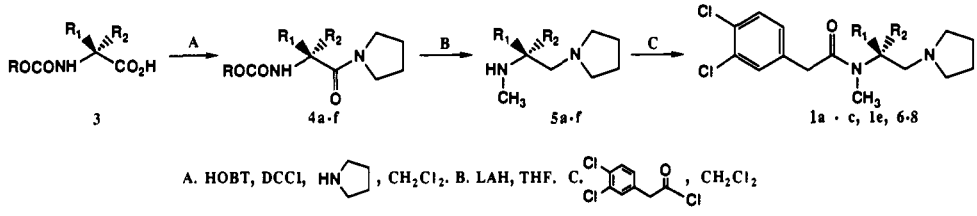
[a] Results expressed as the molar potency ratio to EKC assayed in the same tissues. The mean IC_{50} value for EKC = 64.2 ± 6.6 nM. [b] Values of approximately 15 nM are indicative of κ receptor antagonism.[8] [c] NA = not active, i.e. <0.002 × EKC. [d] Analgesia reversed by 3 mg/kg of naloxone, administered sc at the same time as the test agonist, in a separate experiment.

Table II. Physical Data for Carbamoylaminoamides **4a–e**

no.	R	R_1	R_2	mp, °C	$[\alpha]^{20}_D$,[a] deg	cryst solv	% yield	formula	anal.[b]
4a	$PhCH_2$	CH_3	H	128–131	−16.8[c]	EtOAc	82	$C_{15}H_{20}N_2O_3$	C,H,N
4b	$PhCH_2$	H	CH_3	128–130	+16.9[c]	EtOAc	92	$C_{15}H_{20}N_2O_3$	C,H,N
4c	$(CH_3)_3C$	$(CH_3)_2CH$	H	*d*	+9.2[e]		67	$C_{14}H_{26}N_2O_3$	*f*
4d	CH_3	Ph	H	129–130	+180.3[e]	EtOAc/petroleum ether (60–80)	74	$C_{14}H_{18}N_2O_3$	C,H,N
4e[g]	$(CH_3)_3C$	CH_3	CH_3	147–149		EtOAc	67	$C_{13}H_{24}N_2O_3$	C,H,N

[a] c = 1.0, solvent as indicated. [b] All analyses within ±0.4% of the theoretical value. [c] MeOH. [d] Viscous oil. [e] $CHCL_3$. [f] MS m/z M^+ 270. [g] Prepared by direct coupling of the 3,4-dihydro-3-hydroxy-4-oxo-1,2,3-benzotriazine Boc-aminoisobutyric acid ester with pyrrolidine.

Scheme I



stituents at C1, resulting in the discovery of several potent, selective κ agonists. Consideration of the most potent analogues has enabled an active conformation to be defined which is close to the X-ray conformation of U-50488. The most active analogue, **8**, is 146-fold more potent than U-50488 in vitro and exhibits potent analgesic activity (ED_{50} = 0.004 mg/kg) when administered sc in an abdominal constriction model in the mouse, in which U-50488 has an ED_{50} = 1.1 mg/kg.

Chemistry

Analogues in Table I with one chiral center of known absolute configuration were synthesized from suitably protected α-amino acid derivatives **3**. Two complementary strategies were adopted which enabled the original amino function to be transformed into either the *N*-methylamine or the pyrrolidine of the intermediate diamines **5a–d** and **11**, respectively.

In the first (Scheme I), the optically active urethane-protected amino acids **3** (R = $PhCH_2$, $(CH_3)_3C$ or CH_3) were converted to the carbamoylaminoamides **4a–d** (Table II) by DCC/HOBT (1-hydroxybenzotriazole) coupling with pyrrolidine. Two of these (**4a** and **4d**) had been prepared previously from the *p*-nitrophenyl esters[15] or mixed anhydrides[16] of the corresponding protected α-amino acids. Simultaneous reduction of both carbamoyl and amide functions of the intermediates **4a–d** using excess LAH gave the corresponding diamines **5a–d** in high yield. Similar procedures were used to convert the Boc-aminoisobutyric acid ester of 3,4-dihydro-3-hydroxy-4-oxo-1,2,3-benzotriazine and (*R,S*)-*N*-[(phenylmethoxy)carbonyl]-3-methylvaline to the corresponding optically inactive diamines **5e** and **5f** ($R_1 = R_2 = CH_3$ and R_1 = H, $R_2 = (CH_3)_3C$/$R_1 = (CH_3)_3C$, R_2 = H, respectively, Scheme I). The latter was obtained without isolation and characterization of the intermediate amide **4f**, which was obtained as a viscous oil in poor yield.

The second strategy afforded diamine **11**, in which the pyrrolidine ring was derived from the amino group of the starting material as shown in Scheme II. Thus, (*S*)-alanine methylamide (**9**) was reacted with 1,4-butanedial, prepared from 2,5-dimethoxytetrahydrofuran by acid hydrolysis, in

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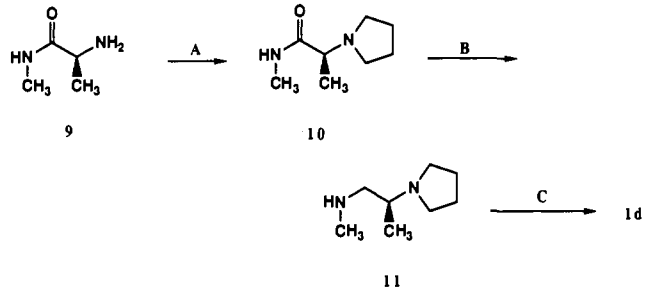
Table III. Physical Properties of 2-(3,4-Dichlorophenyl)-*N*-methyl-*N*-[2-(1-pyrrolidinyl)-1-substituted-ethyl]acetamides (**1a–g**), **6**, **7** and **8**)

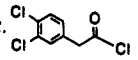
no.	mp, °C	$[\alpha]^{20}_D$,[a] deg	cryst solv	% yield[b]	formula	analysis[c]
1a	152–155		*i*-PrOH	12[d]	$C_{15}H_{20}Cl_2N_2O\cdot(CO_2H)_2$	C,H,N,Cl
1b	173–174	−55.7[e]	MeOH/EtOAc	64	$C_{16}H_{22}Cl_2N_2O\cdot HCl\cdot H_2O$	C,H,N,Cl,H_2O
1c	174–176	+56.5[e]	MeCN/Et_2O	55	$C_{16}H_{22}Cl_2N_2O\cdot HCl\cdot H_2O$	C,H,N,Cl,H_2O
1d	*f*	−7.7[g]		38[h]	$C_{16}H_{22}Cl_2N_2O\cdot 0.125H_2O$	C,H,N,Cl,H_2O
1e	176–180		MeOH/EtOAc	69	$C_{17}H_{24}Cl_2N_2O\cdot HCl$	C,H,N
1f	*i*	−50.0[e]	*j*	30	$C_{17}H_{24}Cl_2N_2O\cdot HCl\cdot 0.25H_2O$	C,H,N,H_2O
1g	*i*	−22.8[k]	*j*	20	$C_{17}H_{24}Cl_2N_2O\cdot HCl$	C,H,N,Cl,H_2O
6	174–175	−64.4[e]	MeOH/EtOAc	78	$C_{18}H_{26}Cl_2N_2O\cdot HCl\cdot 0.25H_2O$	C,H,N,Cl
7	215–217		MeOH/EtOAc	22[l]	$C_{19}H_{28}Cl_2N_2O\cdot HCl$	C,[m]*H*,N
8	233–235	+130.0[l]	MeOH/EtOAc	94	$C_{21}H_{24}Cl_2N_2O\cdot HCl$	C,H,N

[a] c = 1.0, solvent as indicated. [b] Combined yield for LAH reduction and acylation, except where indicated. [c] All analyses within ± 0.4% of the theoretical value, except where indicated. [d] From *N*-methylethylenediamine. [e] $CHCl_3$. [f] Viscous oil; HCl salt extremely hygroscopic. [g] MeOH containing 1 equiv of HCl. [h] Yield for acylation only. [i] Collapse of hygroscopic salt at 95 °C. [j] Suitable solvent for recrystallization of hygroscopic salts not found. [k] Free base in $CHCl_3$. [l] Overall yield from (*R*,*S*)-3-Methyl-*N*-[(Phenylmethoxy)carbonyl]valine.[27] [m] C: calc, 56.0; found, 55.5.

Scheme II



A. $(CH_2CHO)_2$, $NaBH_3CN$, pH5, EtOH / H_2O.

B. LAH, THF. C.  , CH_2Cl_2

the presence of sodium cyanoborohydride to give pyrrolidine **10**. This was reduced with lithium aluminum hydride, affording diamine **11**. The unsubstituted diamine **5g** (R_1 = R_2 = H, Scheme I) was prepared from *N*-methylethylenediamine by an analogous reductive alkylation with 1,4-butanedial.

The diamine diastereoisomers **16** and **17** were synthesized from nitrile **13**, derived from (*S*)-Boc-alanine amide (**12**) by treatment with methanesulfonyl chloride. A Grignard reaction, followed by selective reduction of the intermediate imino–magnesium complex and then reductive alkylation with 1,4-butanedial, as described above, afforded the Boc-protected diamines **14** and **15**. These were separated chromatographically then independently reduced with LAH as shown in Scheme III.

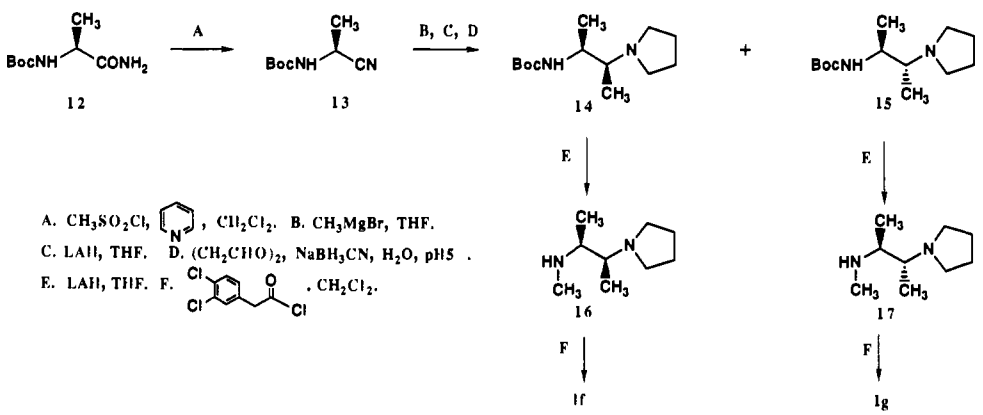
The penultimate diamines **5a–e** (Scheme I) were obtained as homogeneous oils, which were pure enough (TLC) to be used directly. Only the *tert*-butyl and unsubstituted diamines **5f** and **5g** appeared to contain significant impurities which were removed by chromatography after acylation. The use of 3,4-dichlorophenylacetyl chloride in CH_2Cl_2 for the final acylation was common to all three schemes. The products derived from Scheme I (**1b**,**c**,**e**, **6**, and **8**, Table I) conveniently afforded crystalline HCl salts, in high yield, on evaporation of the solvent. Products from Schemes II and III containing a methyl substituent on the carbon adjacent to the pyrrolidine (**1d** and **1f** + **1g**, respectively) proved more difficult to isolate. Their HCl salts were very hygroscopic and suitable solvents for crystallization were not identified, neither were alternative pharmaceutically acceptable salts found. While the microcrystalline HCl salts of **1f** and **1g** gave acceptable elemental analyses, satisfactory melting points were not observed and crystals suitable for X-ray studies were not obtained. The identity of the diastereoisomers **1f** and **1g** was established by using NMR techniques, subsequent to the biological evaluation of these compounds. The physical characteristics of all final products are summarized in Table III.

These synthetic sequences were expected to proceed with retention of configuration, as suggested by the opposite and near-equal optical rotations of the enantiomeric products **1b** and **1c** (see Table III). Rigorous proof of lack of racemization was not obtained, though the *R* isomer **1c** was inactive as a κ agonist while the *S* isomer **1b** was approximately equipotent with U-50488 (see Table I).

Conformational Studies

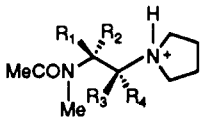
The cyclohexane ring of U-50488 acts to restrict the number and/or the extent of the low-energy conformations available to this molecule. Breaking the ring would be

Scheme III



A. CH_3SO_2Cl, , ClH_2Cl_2. B. CH_3MgBr, THF.
C. LAH, THF. D. $(CH_2CHO)_2$, $NaBH_3CN$, H_2O, pH5.
E. LAH, THF. F. , CH_2Cl_2.

Table IV. Population[a] of Energy Wells A–F by Truncated Analogues 2a–p



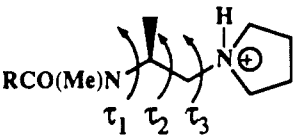
	substituents				conformations					
no.	R_1	R_2	R_3	R_4	A	B	C	D	E	F
2a	H	H	H	H	0	0	+	+	0	0
2b	Me	H	H	H	–	–	–	0	+	+
2c	H	Me	H	H	+	+	0	–	–	–
2d	H	H	Me	H	–	–	+	+	0	0
2e	Me	Me	H	H	–	+	+	+	+	–
2f	Me	H	Me	H	–	–	–	0	0	+
2g	Me	H	H	Me	–	–	+	+	–	–
2h	H	Me	Me	H	–	–	+	+	–	–
2i	H	Me	H	Me	+	0	0	–	–	–
2j	H	H	Me	Me	0	0	+	+	0	0
2k	H	H	H	Me	0	0	+	+	–	–
2l	Me	Me	Me	H	–	–	–	+	+	–
2m	Me	Me	H	Me	–	+	+	–	–	–
2n	Me	H	Me	Me	–	–	–	0	–	+
2o	H	Me	Me	Me	+	–	0	–	–	–
2p	Me	Me	Me	Me	–	+	–	–	–	–

[a] The populations of the six potential energy wells A–F (as depicted in Figure 3) for compounds of the above general formula. + denotes a high probability that the well is populated (within 3 kcal/mol of the global minimum); 0 denotes a low probability of occupation (3–6 kcal/mol); – indicates that the well is essentially unpopulated (above 6 kcal/mol).

expected to result in a significant increase in the conformational freedom of the functional groups which might be important for binding to or activation of the κ receptor. At an early stage, the unsubstituted analogue **1a** was shown to be devoid of activity (see Table I). Further analogues were therefore considered in which substituents were introduced on the carbons of the ethyl chain joining the amide to the pyrrolidine ring in an attempt to exert steric control over conformation. In order to simplify the conformational analysis, it was assumed that the (3,4-dichlorophenyl)methyl, though essential for the activity of U-50488, could be replaced by methyl with no significant effect on rotation about the three bonds linking the amide to the pyrrolidine ring. As the intention of this part of the study was to examine conformational effects alone, it was decided to employ methyl-group substitution at either or both of the carbons in the ethylene chain since this represents the smallest steric and electrostatic perturbation that might generate different conformational populations.

A total of fifteen theoretical possibilities exist which contain all combinations of one to four methyl groups as branches to the ethyl chain, including pairs of enantiomers (Table IV, **2b–p**). Conformational analysis was used in conjunction with the emerging structure/activity pattern to reduce the number of synthetic targets. In addition, the technique was used to aid interpretation of the structure/activity pattern which emerged from the screening of several other alkyl- and aryl-substituted analogues. A fast and routine method was required to screen the conformational minima available to the methylated derivatives of **2a**. Molecular mechanics (MM2)[17] is frequently used to calculate the conformational energy of flexible molecules. This allows full bond and angle deformation but is relatively demanding of computational time when used to search systematically for all the low-energy conformations. Thus a restricted force field was

Table V. The Conformational Effects of Truncation and the Exclusion of Hydrogen-Bond and Coulombic Terms for



	1b	2b	2b	2b	2b
charges	absent	absent	present	absent	present
H-bond term	absent	absent	absent	present	present
torsion[a] τ_1	−109	−106	−101	−106	−85
τ_2	76	77	76	70	78
τ_3	−172	−171	−172	−165	−158

[a] Angles (in degrees) corresponding to the torsions τ_1, τ_2, τ_3 at the global minimum for **1b** (R = Me) and **2b** (R = (3,4-dichlorophenyl)methyl).

used which contained only nonbonded potentials and the effect of excluding the electrostatic and explicit hydrogen bonding terms (eq 1) was studied. The *A*, *B*, *C*, and *D*

$$E = \sum_{ij} -\frac{A_{ij}}{R^6_{ij}} + \frac{B_{ij}}{R^{12}_{ij}} - \frac{C_{ij}}{R^{10}_{ij}} + \frac{D_{ij}}{R^{12}_{ij}} + \frac{Q_iQ_j}{R^2_{ij}} \qquad (1)$$

parameters used in eq 1 were taken from MM2[17] and modified to reproduce experimental lattice energies of crystalline organic molecules. The charges *Q* were calculated from MNDO[18] and a linearly dependent dielectric was chosen. R_{ij} refers to the interatomic distance between pairs of atoms *i* and *j* determined with standard bond lengths and angles obtained from the Cambridge crystallographic data base.[19] Initially, the full equation was used for compound **1b** and its methyl counterpart **2b** to examine the effect of this truncation on the torsional values τ_1, τ_2, and τ_3 (defined in Table V) at the global energy minimum. In addition, the effect of excluding the hydrogen bond and Coulombic terms on the calculated miminum energy conformation of **2b** was examined. The results are listed in Table V. Columns 1 and 2 confirm that truncation has very little effect on the torsion angles τ_1, τ_2, and τ_3. Columns 3–5 show that the exclusion of the hydrogen bond and Coulombic terms has small effects on τ_1–τ_3. There is a significant overhead in calculating meaningful atomic charges and the value of including the hydrogen-bonding term explicitly for charged molecules without correcting for solvation effects is questionable. In consequence, all further calculations were performed on the protonated species using the methyl truncation and excluding Coulombic and H-bonding terms.

An assumption often made in conformational analysis is that the bulk of a molecule remains rigid as a bond is rotated. This is reasonable for relatively rigid molecules but introduces artificial and sometimes misleading energy barriers for more flexible molecules. The methyl and pyrrolidine groups were therefore allowed to relax rotationally while simultaneously rotating the two torsions τ_1 and τ_2 in 10° increments from 0° to 350°. The effect of minimizing the energy for **2b** at each scan point is shown in Figures 1 and 2. The two energy wells become larger and change shape when the methyls and the pyrrolidine ring are allowed to relax, resulting in the removal of a false energy barrier at τ_2 = 180°. All further conformational

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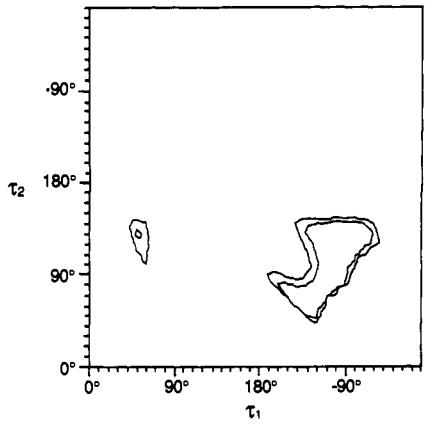

Figure 1. Conformational energy map for **2b**. τ_1 and τ_2 are rotated while the rest of the molecule is left rigid. Energy contours are at 3 and 6 kcal/mol above the global minimum.

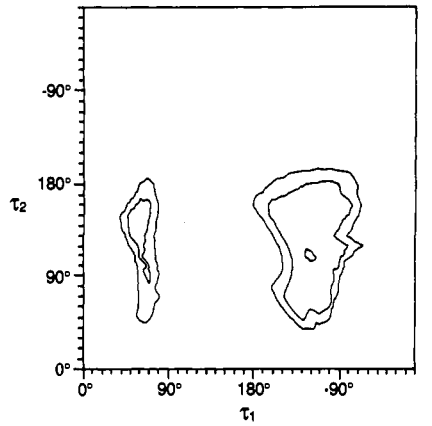

Figure 2. Conformational energy map for **2b**. τ_1 and τ_2 are rotated with simultaneous optimization of the 3 methyl groups and the pyrrolidinium ring. Energy contours are at 3 and 6 kcal/mol above the global minimum.

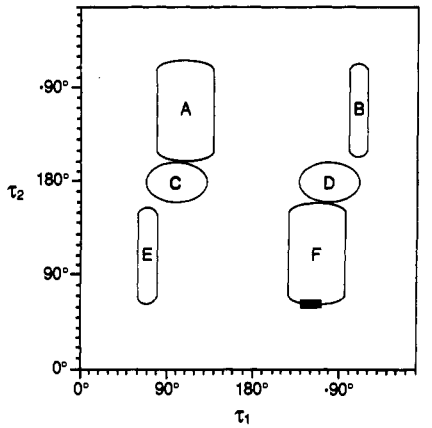

Figure 3. Conformational map illustrating the six conformations A–F populated by **2a–p**.

maps were calculated with simultaneous optimization of the rotatable groups as in Figure 2.

The use of eq 1 to calculate the conformational energy as a function of the two scan angles τ_1 and τ_2 while simultaneously optimizing the methyl and pyrrolidine torsions provides a fast and routine method for examining conformational minima in this series. Owing to the approximations inherent in eq 1, the method is used as a guide to conformations which might be populated rather than those which are definitely occupied, in keeping with the objectives of the study.

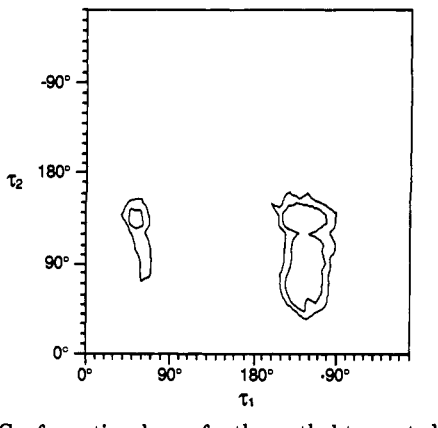

Figure 4. Conformational map for the methyl-truncated analogue of **6**. Energy contours are at 3 and 6 kcal/mol above the global minimum.

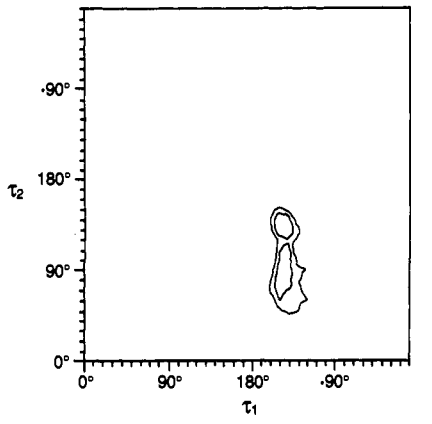

Figure 5. Conformational map for the methyl-truncated analogue of **7**. Energy contours are at 3 and 6 kcal/mol above the global minimum.

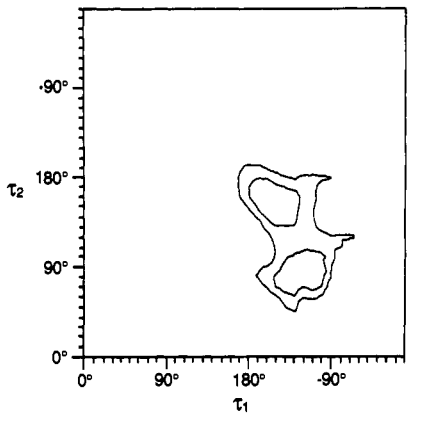

Figure 6. Conformational map for the methyl-truncated analogue of **8**. Energy contours are at 3 and 6 kcal/mol above the global minimum.

The results of the conformational analysis for the unsubstituted analogue **2a** and its C-methylated derivatives **2b–p** (Table IV) show that all can occupy one or more of six low-energy conformations (A–F) illustrated in Figure 3. Superimposed on this diagram is a short line at τ_2 = 58°, τ_1 = −110° to −130° indicating the low-energy conformation of (−)-U-50488. This result was obtained by setting τ_2 at the X-ray-determined value of 58° [23] and ro-

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tating τ_1 as described above. The calculated value for τ_1 agrees remarkably well with the X-ray value of −130°. Table IV lists those low-energy conformations, represented by A–F in Figure 3, which are accessible to each of the 16 molecules **2a–p**.

In addition, the same methodology was used to examine the effect on conformation of introducing bulky groups at C1, such as isopropyl, *tert*-butyl, and phenyl. The results are shown in Figures 4, 5, and 6 which depict the conformational energy maps for the methyl truncation analogues of **6**, the *S* enantiomer of **7**, and **8**, respectively.

Pharmacology

Binding. Opioid κ receptor affinities were determined by displacement of [^{3}H]bremazocine of specific activity 15–30 Ci/mmol using guinea pig brain membranes.[20] [D-Ala, D-Leu]enkephalin (DADLE) was included at a concentration of 3 μM to suppress binding to μ and δ sites. At concentrations above 1 μM, DADLE, normally considered to be δ selective, binds to both μ and δ receptors in guinea pig brain membranes. Results are expressed in Table I as IC_{50} values (nM) with 95% confidence intervals.

Mouse Vas Deferens. Agonist activity was determined on the field-stimulated mouse vas deferens preparation,[21] and antagonist K_e values (nM) were recorded with the standard opioid antagonist naloxone. Results are expressed in Table I as the molar potency ratio relative to the standard agonist EKC, which was used to calibrate each tissue. This assay provides a measure of efficacy in vitro, and as proposed,[8] K_e values for naloxone versus a test agonist of approximately 15 nM are characteristic of κ compounds while values of 1–4 nM are indicative of μ opioid effects.

Analgesia. Compounds were administered by the sc route to female mice of the Alderley Park strain. Antinociceptive activity was determined by using the acetic acid (0.4%) induced abdominal constriction assay, observed over a period of 30–45 min after dosing.[22] The results are expressed in Table I as ED_{50} values in mg/kg with 95% confidence intervals. The effects of all compounds active in this assay were abolished by naloxone administered at 3 mg/kg (sc) at the same time as the agonist, in a separate experiment.

Structure/Activity Relationships

In the discussion which follows, it has been assumed that all the 2-(3,4-dichlorophenyl)acetamides will have the same conformational preferences as their truncated acetamide counterparts **2a–l**, as has been demonstrated in the case of **1b** and **2b** (see Table V). Structure/activity relationships have been considered with respect to potency in the mouse vas deferens assay. Where naloxone K_e values are approximately 15 nM, indicative of κ affinity,[8] potency in the mouse vas deferens closely parallels results obtained in the binding assay (Table I). Further, compounds with good activity in vitro show potent naloxone-reversible analgesic effects in the mouse abdominal constriction model (Table I).

The unsubstituted analogue **1a** is, as expected, the most flexible molecule and can adopt all six conformations although it prefers an extended conformation (C and D). Its flexibility and consequently its high entropy appears to contribute to its relative lack of activity. Substitution of a methyl group at C1 in the *S* configuration (**1b**) restricts the conformations available to E and F. The global minimum of this compound lies close to that of (−)-U-50488, with which it is equipotent in vitro. In contrast, the *R* isomer **1c** can only adopt the A and B conformations and appears inactive as a κ agonist. Methylating at C2 in the *S* configuration (**1d**) favors conformations represented by C and D, although E and F are also accessible. Compound **1d** exhibits only trace activity. Similarly, 1,1-dimethyl analogue **1e**, which does not favor the F configuration, is virtually inactive. These results suggest that the compounds which prefer conformations lying within the energy well F are most likely to exhibit κ agonist activity.

Simultaneous methylation at C1 and C2 can give rise to four isomers, but only two compounds were selected for synthesis to test the predictive power of the method. Table IV suggests that **2h** and **2i**, which have the *R* configuration at C1, are unlikely to populate conformations E or F and were therefore not considered further. The 1*S*,2*S* isomer **2f**, which has the same absolute stereochemistry at C1 and C2 as (−)-U-50488, would be expected to occupy the energy well F, with some population of wells D and E. Thus the corresponding 3,4-dichlorophenyl analogue **1f** should be active. The 1*S*,2*R* diastereoisomer **2g** would be expected to be restricted to the conformations C and D and hence its 3,4-dichlorophenyl counterpart **1g** should be devoid of activity. At the time of preparation and testing, the absolute stereochemistry at C1 was known to be *S* by virtue of the synthesis of **1f** and **1g** from (*S*)-alanine. The stereochemistry at C2 was assigned later by NMR studies as *S* for **1f** and *R* for **1g**. The basis for this assignment was, firstly, the size of the coupling constants for the protons in the ethylene moiety linking amide to pyrrolidine, secondly, the NOEs observed in the proton spectrum, and finally, the steric effects observed in the carbon spectrum (see the supplementary material for further details). **1f** showed weak, though significant, κ agonist activity while **1g** was inactive, in vitro, consistent with the prediction of the conformational analysis.

In the later stages of the program a series of open-chain analogues was prepared in which the ethyl chain linking amide and pyrrolidine groups were substituted at C1 with more bulky groups such as isopropyl and phenyl in the *S* configuration and *tert*-butyl as the racemate. The purpose of these substitutions was to explore the effect of further restrictions in conformation caused by the steric bulk of groups larger than methyl at C1. The resulting compounds (**6**, **8**, and **7**, respectively) were significantly more potent in vitro and in the binding assay than the methyl analogue **1b** (Table I).

Conformational analysis of the corresponding truncated methyl compounds, in which the C1 substituent was in the *S* configuration, afforded the conformational energy maps illustrated in Figures 4–6 and revealed that all analogues can occupy the energy well F. As the size of the substituent is increased from methyl (Figure 2) through isopropyl (Figure 4) to *tert*-butyl (Figure 5), the potential energy wells E and F become smaller and deeper, and in the case of *tert*-butyl, the well E disappears altogether. The highly

(23) (−)-U-50488 was prepared by the method of Lahti[12] and converted with 1 equiv of maleic acid in Et_2O to its 1:1 maleate salt, which was subjected to X-ray crystallographic examination. Crystal data: $[C_{19}H_{27}Cl_2N_2O]^+[C_4H_3O_4]^-$, M = 485.40, orthorhombic, space group $P2_12_12_1$, a = 18.500 (3) Å, b = 11.661 (2) Å, c = 11.024 (2) Å, V = 2378.19 Å^3, Z = 4, F(000) = 1024, D_c = 1.355 g cm^{-3}, μ(Mo Kα) = 2.62 cm^{-1}. A total of 2358 unique reflections were collected in the range $3° < \theta < 25°$, on a Phillips PW1100 diffractometer using Mo Kα radiation (λ = 0.71069 Å), with a crystal of dimensions 0.34 × 0.26 × 0.13 mm and a θ–2θ scan mode. The data were corrected for Lorentz and polarization factors but not for absorption. The final R value was 0.0739. Tables of coordinates, bond lengths and angles and hydrogen atom coordinates have been deposited with the Crystallographic Data Centre, Cambridge University, Cambridge CB2 1EW.

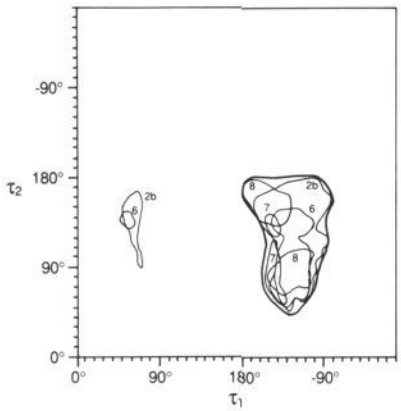

Figure 7. Union of the 3 kcal/mol contours for **2b** and the methyl-truncated analogues of **6**, **7**, and **8**, enclosed by the heavy line.

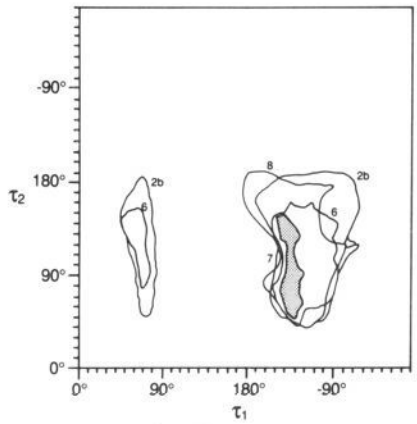

Figure 8. Intersection of the 6 kcal/mol contours for **2b** and the methyl-truncated analogues of **6**, **7**, and **8**, represented by the hatched area.

potent phenyl analogue **8** also favors the F configuration almost exclusively (Figure 6). Inevitably such changes will alter other parameters which might be expected to contribute to activity, for example by increasing log *P*, causing electrostatic perturbations, or introducing new binding entities. None-the-less, the relatively high activities of **6–8** are consistent with the hypothesis that a U-50488-like conformation is important for activity in this series. The selectivity of compounds **6** and **8** has been demonstrated in binding and in vitro assays in a comprehensive study previously reported.[8]

The conformational energy maps of the four most active compounds (**1b** and **6–8**) have been overlayed. This technique[24] provides a rough guide to the "active conformation", giving a necessary but not sufficient condition for activity. By studying the union of the energy contours, a range of conformations accessible to at least one of the active structures is defined, as shown in Figure 7. The intersection of the maps gives an "essential" conformation shown in Figure 8, available to all the structures. The "active conformation" probably lies somewhere between the two with approximate bounding torsion angles of $\tau_1 = -130° \pm 30°$ and $\tau_2 = 100° \pm 50°$.

In conclusion, this paper reports the utility of conformational analysis in defining one aspect of the structure/activity relationships in a series of *N*-[2-(1-pyrrolidinyl)ethyl]acetamides (**2**). A number of approximations were adopted which are justified provided the results are used as a guide to probable conformational preferences rather than to identify minima which are definitely occupied. In consequence, an "active conformation" has been defined which represents a *necessary, but not sufficient, criterion for agonism at the* κ receptor in this series. Thus, in the present study, no attempt has been made to relate the level of activity to a calculated conformation for individual compounds. Removal of the cyclohexane ring has enabled the facile introduction of substituents at C1 and C2 of the ethyl moiety linking the amide and pyrrolidine groups without excluding access to the "active conformation". As a result of this study, potent κ agonists have been discovered, of which **8** is 146-fold more effective than U-50488 in vitro.

Experimental Section

Melting points (uncorrected) were determined in open capillary tubes with a Büchi-Tottoli apparatus. Optical rotations were determined on a Perkin-Elmer 241 polarimeter. Proton NMR spectra were obtained with either a JEOL FX 90Q or a Bruker AM 200 spectrometer in $CDCl_3$, DMSO-d_6, or AcOH-d_4/DMSO-d_6. Chemical shifts are reported in δ values (ppm) relative to internal Me_4Si. Mass spectra were determined on Vacuum Generators VG 212 or VG 70-250SE instruments, giving molecular ions and fragmentation patterns consistent with the anticipated structures. Analytical TLC was performed on 0.25-mm silica gel plates (Merck, Kieselgel 60 F-254). Flash column chromatography was carried out with Merck Kieselgel 60 (230–400 mesh). Elemental analyses were performed by B. Crooks and his associates (ICI Pharmaceuticals).

Starting urethane-protected α-amino acids were obtained from commercial sources and used without further purification. (*S*)-Alanine methylamide was prepared by the method of Englefried,[25] (*S*)-Boc-alanine amide was prepared by the method of Ohashi,[26] and (*RS*)-(benzyloxycarbonyl)-3-methylvaline was synthesized from diethyl 2-(1,1-dimethylethyl)malonate (Aldrich) by the method of Miyazawa.[27] 3,4-Dichlorophenylacetyl chloride was prepared from the corresponding acid (Aldrich) with oxalyl chloride/DMF[28] and distillation of the product before use.

2-(3,4-Dichlorophenyl)-*N*-methyl-*N*-[2-(1-pyrrolidinyl)-ethyl]acetamide Oxalate (1a·Oxalate). A 1.5 N solution of 1,4-butanedial was prepared from 2,5-dimethoxytetrahydrofuran (19.8 g, 150 mmol) stored in 0.025 N HCl (65 mL) at 0 °C for 16 h, then adjusted to pH 6 with saturated $NaHCO_3$ solution, and diluted to 100-mL total volume with H_2O. An aliquot (8 mL, 12 mmol) was added to a solution of *N*-methylethylenediamine (0.765 g, 10.3 mmol) in EtOH (180 mL) plus glacial HOAc (1.2 mL) at 0 °C. $NaCNBH_3$ was added in portions over a period of 15 min, then further HOAc was added to attain pH 5. After 20 h at 20 °C the solution was cooled to 0 °C, basified by the addition of KOH pellets, and extracted with CH_2Cl_2 (3 × 100 mL). The combined extracts were dried (KOH) and concentrated to give the crude diamine (**5g**, $R_1 = R_2 = H$) as an orange oil. This was dissolved in CH_2Cl_2 (30 mL), 3,4-dichlorophenylacetyl chloride (2.43 g, 11 mmol) in CH_2Cl_2 (10 mL) was added to 0 °C, and the mixture was allowed to warm to 20 °C over 2.5 h. Water (20 mL) and then saturated $NaHCO_3$ (30 mL) were added, and the organic phase was separated, back-washed with brine (50 mL), and dried (Na_2SO_4). The viscous oil which remained after removal of the solvent was chromatographed on alumina (150 g, Woelm grade I, neutral), eluting with CH_2Cl_2/EtOAc (2/1) and collecting 20-mL fractions. Fractions 8–11 were combined and evaporated to give 0.4 g (12%) of **1a** as a colorless oil, which was treated with oxalic

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acid (0.11 g, 1.2 mmol) in EtOAc (20 mL), filtered and recrystallized (*i*-PrOH), affording white crystals of **1a**·oxalate: mp 152–155 °C; NMR (DMSO-d_6) δ 1.80–2.00 (m, 4 H, 2 CH_2CH_2N), 2.85 (s, 3 H, CH_3N, 17% minor rotamer), 3.05 (s, 3 H, CH_3N, 83% major rotamer), 3.15–3.35 (m, 6 H, 3 CH_2N), 3.64 (t, J = 6 Hz, 2 H, CH_2NCO), 3.65–3.80 (m, 2 H, CH_2CO), 7.15–7.60 (cmplx, 3 H, aromatic). Anal. ($C_{17}H_{22}Cl_2N_2O_5$) C, H, Cl, N.

(1*S*)-Benzyl *N*-[1-(1-Pyrrolidinylcarbonyl)ethyl]carbamate (4a). 1-Hydroxybenzotriazole (33.22 g, 246 mmol) was added to a solution of (*S*)-*N*-(benzyloxycarbonyl)alanine (50.0 g, 244 mmol) in dry CH_2Cl_2 (400 mL) while being stirred under an atmosphere of argon with ice-bath cooling. DCCI (50.89 g, 247 mmol) in dry CH_2Cl_2 (150 mL) was added at a fast drop rate and the reaction mixture was stirred for 1 h at 0 °C. Pyrrolidine (17.46 g, 246 mmol) was added and stirring was continued for a further 18 h at ambient temperature. DCU was removed by filtration and washed with a little CH_2Cl_2. On cooling to 0 °C, the combined filtrate afforded a second solid, which was filtered to give 32.2 g of crude product. The filtrate from this was evaporated under reduced pressure and the residue was dissolved in EtOAc (1.4 L), washed successively with saturated $NaHCO_3$ solution (2 × 300 mL), water (300 mL), 2 M HCl (2 × 300 mL), water (300 mL), and brine (300 mL), and then dried ($MgSO_4$). Evaporation of the solvent afforded a solid which was crystallized (EtOAc), combined with the first isolated product, and recrystallized (EtOAc) to give 41.97 g (68%) of **4a** as a white solid: mp 128–131 °C; NMR ($CDCl_3$) δ 1.3 (d, J = 8 Hz, 3 H, CH_3CH), 1.7–2.2 (m, 4 H, 2 CH_2CH_2N), 3.2–3.7 (m, 4 H, 2 CH_2N), 4.2–4.7 (m, 1 H, NHC*H*CO), 5.1 (s, 1 H, CH_2Ph), 5.7 (br d, J = 9 Hz, 1 H, N*H*CO), 7.3 (br s, 5 H, aromatic). Anal. ($C_{15}H_{20}N_2O_3$) C, H, N.

(2*S*)-1-[2-(Methylamino)propyl]pyrrolidine (5). A solution of **4a** (19.04 g, 69 mmol) in freshly distilled THF (400 mL) was added dropwise, over a period of 30 min, to a stirred suspension of LAH (7.85 g, 207 mmol) in freshly distilled THF (100 mL) at 0 °C. The mixture was stirred for 3.5 h at 20 °C and then a 3 N Na_2CO_3 solution was added cautiously until effervescence ceased. The mixture was filtered through Celite and the filter cake was washed thoroughly with Et_2O. The combined filtrate was concentrated to give an oil, which was dissolved in Et_2O (300 mL) and extracted with 2 N HCl (3 × 150 mL). The combined aqueous extracts were washed with Et_2O (2 × 200 mL), basified to pH > 11 with solid NaOH, and extracted with Et_2O (3 × 150 mL). After drying (K_2CO_3), the combined extracts were evaporated under reduced pressure to give 7.28 g (74%) of **5a** as a clear oil that was used without further purification: NMR ($CDCl_3$) δ 1.00 (d, J = 6 Hz, 3 H, CH_3CH), 1.70–1.83 (m, 4 H, 2 CH_2CH_2N), 2.11 (br s, 1 H, N*H*), 2.08–2.24 (m, 1 H, $CHCH_3$), 2.34–2.64 (cmplx, 6 H, 3 CH_2N), 2.43 (s, 3 H, CH_3N).

2-(3,4-Dichlorophenyl)-*N*-methyl-*N*-[(1*S*)-1-methyl-2-(1-pyrrolidinyl)ethyl]acetamide Hydrochloride (1b·HCl). A solution of 3,4-dichlorophenylacetyl chloride (1.73 g, 7.7 mmol) in dry CH_2Cl_2 (15 mL) was added to a solution of **5a** (1.0 g, 7 mmol) in dry CH_2Cl_2 (10 mL) and the mixture was left at 20 °C for 4 h. Evaporation under reduced pressure gave a pale yellow oil which solidified on trituration with Et_2O. Recrystallization from EtOAc/MeOH gave 1.87 g (73%) of **1b**·HCl as a white solid: mp 173–175 °C; $[\alpha]^{20}_D$ = −55.7° (c 1.0, $CHCl_3$); NMR (DMSO-d_6/HOAc-d_6) δ 1.10 (d, J = 6 Hz, 3 H, CH_3CH), 1.86–2.08 (m, 4 H, 2 CH_2CH_2N), 2.93 (s, 3 H, CH_3NCO), 2.96–3.55 (cmplx, 6 H, 3 CH_2N), 3.82 (AB q, J = 14 Hz, $\Delta\delta$ = 50 Hz, 2 H, CH_2Ar), 4.90–5.10 (m, 1 H, C*H*NCO), 7.21–7.58 (cmplx, 3 H, aromatic). Anal. ($C_{16}H_{23}Cl_3N_2O·H_2O$) C, H, N, H_2O.

(2*S*)-*N*-Methyl-2-(1-pyrrolidinyl)propionamide (10). A 1.5 N solution of 1,4-butandial (100 mL, 150 mmol), prepared as previously described for 1 above, was added to (*S*)-alanine methylamide (**9**) in EtOH (800 mL), and $NaCNBH_3$ (17.4 g, 275 mmol) was added at 0 °C. The reaction mixture was adjusted to pH 5 by the addition of glacial HOAc and stirred at 4 °C for 16 h. After concentration to low volume (50 mL), saturated Na_2CO_3 solution was added and the resulting mixture was extracted with EtOAc (3 × 200 mL). Combined extracts were backwashed with brine (200 mL), dried (Na_2CO_3), and evaporated under reduced pressure to give 16.4 g (84%) of **10** as an oily yellow solid, used directly in the next stage: NMR ($CDCl_3$) δ 1.3 (d, J = 4 Hz, 3 H, CH_3CH), 1.6–2.0 (m, 4 H, 2 CH_2CH_2N), 2.2–3.4 (cmplx, 8 H, 2 CH_2N + CHN + CH_3NH), 6.9 (br s, 1 H, N*H*CO).

(2*S*)-*N*-[2-[1-(Methylamino)propyl]]pyrrolidine (11). Amide **10** (16.4 g, 105 mmol) was dissolved in dry THF (250 mL) and added dropwise over a period of 15 min to a stirred suspension of LAH (8.0 g, 210 mmol) in THF (100 mL) under an argon atmosphere at 0 °C. After 48 h at 20 °C more LAH (2.0 g, 52.5 mmol) was cautiously added and the reaction mixture was heated to reflux for 24 h. Saturated Na_2CO_3 solution was added slowly at 0 °C with rapid stirring until effervescence ceased and the solid so formed was filtered through Celite. Concentration of the filtrate gave an oil which was dissolved in Et_2O (750 mL) and extracted with 2 N HCl (3 × 300 mL). The combined aqueous extracts were back-washed with Et_2O (2 × 200 mL), basified to pH 11 with KOH pellets at 0 °C, then extracted with Et_2O (3 × 300 mL), and dried (K_2CO_3). Evaporation under reduced pressure gave 9.7 g (65%) of **11** as a colorless oil, used without further purification: NMR ($CDCl_3$) δ 1.11 (d, J = 6 Hz, 3 H, CH_3CH), 1.65–1.84 (m, 4 H, 2 CH_2CH_2N), 2.45 (s, 3 H, CH_3NH), 2.50–2.72 (cmplx, 7 H, 2 CH_2N + $NHCH_2$ + CH_2CHN).

2-(3,4-Dichlorophenyl)-*N*-methyl-*N*-[(2*S*)-2-methyl-2-(1-pyrrolidinyl)ethyl]acetamide Hydrochloride (1d). Diamine **11** (0.7 g, 5 mmol) was dissolved in dry CH_2Cl_2 (20 mL), and 3,4-dichlorophenylacetyl chloride (1.12 g, 5 mmol) in dry CH_2Cl_2 (30 mL) was added dropwise with stirring over 10 min at 0 °C. After 1 h at 20 °C the reaction mixture was evaporated to dryness and the oily residue was partitioned between Et_2O (50 mL) and saturated $NaHCO_3$ (50 mL) and the aqueous phase was extracted with Et_2O (2 × 50 mL). Combined Et_2O extracts were evaporated and the resulting oil was subjected to flash chromatography on silica (60 g), eluting with a MeOH/CH_2Cl_2 gradient (5%–20% in 5% steps, 250 mL/step) and collecting 50-mL fractions. Evaporation of fractions 17–34 gave 0.63 g (38%) of **1d** as a pale yellow gum after high-vacuum drying: $[\alpha]^{20}_D$ = −7.7° (c 1.0, MeOH containing 1 equiv of HCl); NMR (DMSO-d_6/HOAc-d_4) δ 1.24 (d, J = 6.5 Hz, 3 H, CH_3CH), 1.80–2.03 (m, 4 H, 2 CH_2CH_2N), 2.87 (s, 3 H, CH_3N, 14% minor rotamer), 3.19–3.37 (m, 4 H, 2 CH_2N), 3.40–3.75 (cmplx, 3 H, $CHCH_3$ + $CONCH_2$), 3.8 (s, 2 H, CH_2CO), 7.18–7.60 (cmplx, 3 H, aromatic).

(1*S*)-*tert*-Butyl *N*-(1-Cyanoethyl)carbamate (13). A solution of (1*S*)-*tert*-butyl *N*-(1-carbamoylethyl)carbamate **12** (15 g, 80 mmol) in dry pyridine (50 mL) was cooled to 0 °C and methanesulfonyl chloride (11.0 g, 96 mmol) was added over 5 min with stirring. The reaction mixture was stirred at 20 °C overnight and the solid so formed was filtered off and washed with CH_2Cl_2 (2 × 10 mL). Concentration of the combined filtrates at 25 °C in vacuo gave a viscous oil which was dissolved in CH_2Cl_2 (100 mL), washed with 1 M aqueous citric acid (3 × 100 mL), saturated $NaHCO_3$ (2 × 75 mL), and then brine (100 mL), dried ($MgSO_4$), and evaporated to give an oily solid. Trituration with petroleum ether (60–80 °C) afforded **13** as a pale orange solid (10.7 g, 78.7%): mp 105–108 °C; NMR ($CDCl_3$) δ 1.3–1.8 (cmplx, 12 H, $(CH_3)_3C$ + CH_3CH), 4.4–5.0 (cmplx, 2 H, N*H*CO + $CHCH_3$). Anal. ($C_8H_{14}N_2O_2$) C, H, N.

(1*S*,2*S*)- and (1*S*,2*R*)-*tert*-Butyl *N*-[1-Methyl-2-(1-pyrrolidinyl)butyl]carbamate (14 and 15, Respectively). A 3 M solution of MeMgBr in Et_2O (65 mL, 195 mmol) was added to a solution of **14** (10.0 g, 59 mmol) in freshly distilled THF (300 mL) under an argon atmosphere over 10 min at 0 °C. The solution was stirred at 20 °C for 5 h and then cooled to 0 °C and LAH (2.22 g, 55 mmol) was added portionwise with stirring. After 2 h a further portion of LAH (1.1 g, 27 mmol) was added and the mixture was stirred at 20 °C for 2.5 h before pouring into 1 N monobasic sodium phosphate buffer (500 mL, pH 4). The resulting mixture was filtered through Celite and the pH was immediately adjusted to pH 5 with 1 M citric acid solution. A 1.5 N solution of 1,4-butandial (50 mL, 75 mmol), made immediately before use from 2,5-dimethoxytetrahydrofuran as described for **1a** above, was added to the above solution together with $NaCNBH_3$ (8.15 g, 130 mmol). The mixture was stirred for 16 h at 20 °C and then adjusted to pH 10.5 by the addition of solid Na_2CO_3 and was extracted with EtOAc (3 × 400 mL). The combined organic phase was back-washed with brine containing a little $NaHCO_3$ (2 × 200 mL), dried (Na_2CO_3), concentrated, and subjected to flash chromatography on silica (500 g), eluting with CH_2Cl_2/5 M NH_3 in MeOH (9/1) and collecting 100-mL fractions after a 5-L runoff. Fractions 4–28 (3.97 g) and 29–44 (2.13 g) were enriched in the higher and lower R_f components, respectively, total

recovery was 6.1 g (43%). Fractions 4–28 were flash chromatographed on silica (120 g), eluting with MeOH, affording pure higher R_f component **14** as a white, crystalline mass after evaporation (1.52 g, 11%): mp 54–55 °C; NMR (DMSO-d_6) δ 0.98 (d, J = 7 Hz, 3 H, CH_3CHN), 1.11 (d, J = 7 Hz, 3 H, CH_3CHNHCO), 1.46 (s, 9 H, $(CH_3)_3$C), 1.67–1.85 (m, 4 H, 2 CH_2CH_2N), 2.37–2.52 (m, 1 H, NC*H*), 2.52–2.68 (m, 4 H, 2 CH_2N), 3.58–3.81 (m, 1 H, C*H*NHCO), 4.83 (br m, 1 H, N*H*CO). Anal. ($C_{13}H_{26}N_2O_2$) C, H, N.

The impure lower R_f component from the second column (1.05 g) was combined with fractions 29–44 from the first column and chromatographed on silica (100 g) eluting with MeOH to give 1.26 g (9%) of the pure lower R_f component **15** as a viscous, colorless oil: NMR (DMSO-d_6) δ 1.02 (d, J = 7 Hz, 3 H, CH_3CHN), 1.15 (d, J = 7 Hz, 3 H, CH_3CHNHCO), 1.46 (s, 9 H, $(CH_3)_3$C), 1.68–1.83 (m, 4 H, 2 CH_2CH_2N), 2.24–2.39 (m, 1 H, C*H*N), 2.5–2.65 (m, 4 H, 2 CH_2N), 3.7–3.9 (m, 1 H, C*H*NHCO), 4.8 (br d, 1 H, N*H*CO).

2-(3,4-Dichlorophenyl)-*N*-methyl-*N*-[(1*S*,2*S*)-1,2-dimethyl-2-(1-pyrrolidinyl)ethyl]acetamide Hydrochloride (1f). A solution of **14** (1.2 g, 5 mmol) in freshly distilled THF (20 mL) was added dropwise over 10 min to a stirred suspension of LAH (0.285 g, 7.5 mmol) in dry THF (50 mL) at 0 °C under an argon atmosphere. The reaction mixture was allowed to attain 20 °C over a period of 1 h and was then heated to reflux for 1 h. After cooling to 0 °C, 2 N NaOH was added dropwise to give a granular, off-white precipitate which was filtered through Celite. The filtrate was concentrated in vacuo, redissolved in Et_2O, dried (Na_2CO_3), and evaporated to give 0.52 g (66%) of **16** as a pale yellow oil. This crude product (3.3 mmol) was dissolved in CH_2Cl_2 (30 mL), and 3,4-dichlorophenylacetyl chloride (0.81 g, 3.65 mmol) was added dropwise over 5 min at 0 °C. After 1 h at 20 °C the reaction mixture was concentrated and flash chromatographed on silica (50 g) eluting with CH_2Cl_2/5 M NH_3 in MeOH (9/1), with collection of 40-mL fractions. Fractions 23–37 were combined and evaporated under reduced pressure, affording a colorless oil 0.54 g which was treated with ethereal HCl to give 0.57 g (30%) of **1f**·HCl as a white, amorphous, hygroscopic solid: mp 95 °C, slow collapse; $[\alpha]^{20}_D$ = −50.0° (c 1.0, $CHCl_3$); NMR (DMSO-d_6) δ 1.11 (d, J = 7 Hz, 3 H, CH_3CH), 1.20 (d, J = 7 Hz, 3 H, CH_3CH), 1.80–2.05 (m, 4 H, 2 $CH_2CH_2N^+$), 2.93 (s, 3 H, CH_3N), 3.00–3.65 (cmplx, 5 H, 2 CH_2N^+ + CHN^+), 3.86 (AB q, J = 16 Hz, $\Delta\delta$ = 80 Hz, 2 H, CH_2Ar), 4.66–4.74 (m, 1 H, C*H*NCO), 7.24–7.55 (cmplx, 3 H, aromatic), 10.08 (br s, 1 H, NH^+). Anal. ($C_{17}H_{15}Cl_3N_2O$·0.25H_2O) C, H, N, H_2O.

2-(3,4-Dichlorophenyl)-*N*-methyl-*N*-[(1*S*,2*R*)-1,2-dimethyl-2-(1-pyrrolidinyl)ethyl]acetamide hydrochloride (1g) was prepared from **15** (0.91 g, 4 mmol) by a procedure analogous to that used for **1f** above, affording 0.4 g (65%) of the intermediate diamine **17**, which was acylated and purified by chromatography and then treated with etheral HCl, as above, to give 0.31 of **1g**·HCl as a white, amorphous, hygroscopic solid: mp 95 °C, slow collapse; $[\alpha]^{20}_D$ (free base) = −22.8° (c 1.0, $CHCl_3$); NMR (DMSO-d_6) δ 1.24 (d, J = 8 Hz, 3 H, CH_3CH), 1.28 (d, J = 8 Hz, 3 H, CH_3CH), 1.80–2.00 (m, 4 H, 2 $CH_2CH_2N^+$), 2.96 (s, 3 H, CH_3N), 2.90–3.90 (cmplx, 5 H, 2 CH_2N^+ + CHN^+), 3.86 (AB q, J = 16 Hz, $\Delta\delta$ = 78 Hz, 2 H, CH_2Ar), 4.60–4.80 (m, 1 H, C*H*NCO), 7.23–7.60 (cmplx, 3 H, aromatic), 10.34 (br s, 1 H, NH^+). Anal. ($C_{17}H_{15}Cl_3N_2O$·0.25H_2O) C, H, N, H_2O.

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Registry No. **1a**, 116763-50-9; **1a**·oxalate, 130013-80-8; **1b**, 115200-95-8; **1b**·HCl, 115199-66-1; **1c**, 130013-57-9; **1d**, 130013-58-0; **1e**, 130013-59-1; **1f**, 130013-60-4; **1g**, 130013-61-5; **2a**, 130013-65-9; **2b**, 130013-66-0; **2c**, 130013-67-1; **2d**, 130013-68-2; **2e**, 130013-69-3; **2f**, 130013-70-6; **2g**, 130013-71-7; **2h**, 130013-72-8; **2i**, 130013-73-9; **2j**, 130013-74-0; **2k**, 130013-75-1; **2l**, 130013-76-2; **2m**, 130013-77-3; **2n**, 130013-78-4; **2o**, 130031-68-4; **2p**, 130013-79-5; **4a**, 56439-36-2; **4b**, 130062-35-0; **4c**, 130013-62-6; **4d**, 130013-63-7; **4e**, 130013-64-8; **5a**, 115200-96-9; **5g**, 32776-22-0; **6**, 115199-69-4; **7**, 130062-34-9; **8**, 115199-84-3; **9**, 33194-35-3; **10**, 130013-81-9; **11**, 130013-82-0; **12**, 85642-13-3; **13**, 130013-83-1; **14**, 130013-84-2; **15**, 130013-85-3; **16**, 130013-86-4; **17**, 130013-87-5; $OHCCH_2CH_2CHO$, 638-37-9; $MeNHCH_2CH_2NH_2$, 109-81-9; 3,4-$Cl_2C_6H_3CH_2COCl$, 6831-55-6; Cbz-Ala-OH, 1142-20-7; (−)-U-50488·maleate, 67198-20-3; 2,5-dimethoxytetrahydrofuran, 696-59-3; pyrrolidine, 123-75-1; 3,4-dihydro-3-hydroxy-4-oxo-1,2,3-benzotriazine BOC-aminoisobutyric acid ester, 130013-88-6.

Supplementary Material Available: NMR data supporting the assignment of stereochemistry at C2 for **1f** and **1g**, including discussion of 400-MHz NOE and thermal experiments and ^{13}C NMR spectral data (13 pages). Ordering information is given on any current masthead page.