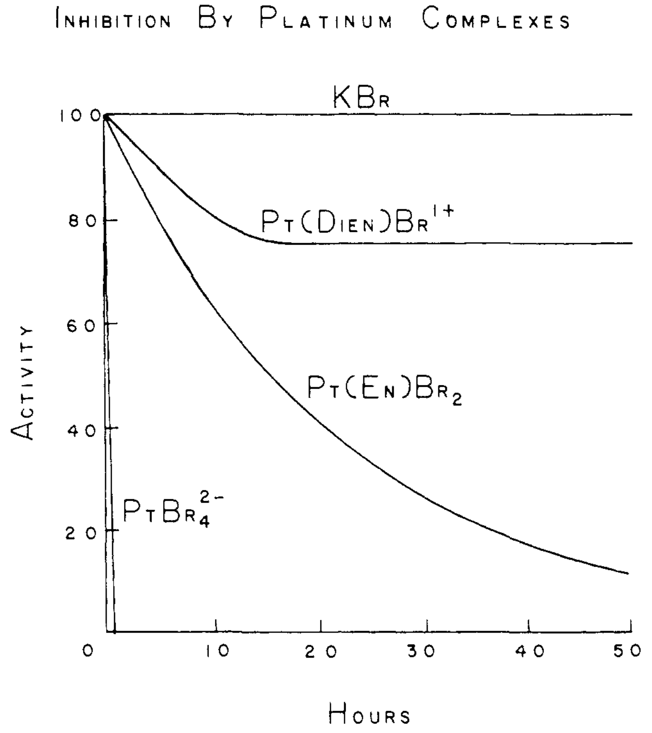

Figure 2.—Inhibition of Pt complexes. Four flasks containing 0.05 *M* $MgCl_2$, 0.025 *M* barbital buffer, pH 8.0, 20 μl of enzyme and the Pt complex or KBr standard, were placed in 37° water bath and aliquots were removed at various times and added to the assay vessel containing 0.05 *M* $MgCl_2$, 0.025 *M* barbital buffer, pH 8.0, and 0.01 *M* leucinamide.

(Dien)Br^+, which only contains a single Br^- ligand, did not deactivate the enzyme completely under the experimental conditions. It is well known that bidentate ligands, which are bound to the metal through two nucleophilic sites, are much more stable than comparable monodentate ligands. Thus, ethylenediamine complexes of Cu(II) have considerably larger formation constants than NH_3 complexes.[7] It is possible, therefore, that only Pt complexes which have at least 2 replaceable groups can be bound strongly to the enzyme with resultant deactivation. Nonbiological reactions in which a molecule containing cis nucleophilic groups displaces 2 halide ligands in a Pt(II) complex to produce a stable product have been reported.[8] It is also noticeable that all of the Pt complexes which have been shown to possess tumor-inhibiting properties by Rosenberg, *et al.*,[2] contain labile cis dihalide ligands. Mechanistic similarities between the enzyme-inhibition, tumor-inhibition, and inorganic substitution reactions are quite possible.

Experimental Section

Rubidium Tetrabromoplatinate(II).—K_2PtBr_6 was prepared by dissolving Pt wire in aqua regia, evaporating the resultant soln almost to dryness after the addition of excess HBr, and precipitating the hexabromoplatinate (IV) ion in the form of its K salt by the addition of sufficient K_2CO_3 to neutralize the remaining acid. A soln of K_2PtBr_4 was obtained by reduction of K_2PtBr_6 with an equivalent quantity of an aq oxalic acid. The sparingly sol Rb_2PtBr_4 was pptd from this soln by addn of excess RuBr. *Anal.*[9] ($Rb_2PtBr_4.H_2O$): Rb 24.3, Pt 27.7. Found: Rb 24.7; Pt 27.7.

Dibromo(ethylenediamine)platinum(II).—Pt(En)Br_2, was prepared by the direct reaction of equiv amounts of $Rb_2PtBr_4 \cdot H_2O$ and En in aq solution at pH 9. The experimentally determined Pt content of the complex (46.7%) was in good agreement with the theoretical value (47.0%).

Bromo(diethylenetriamine)platinum(II) bromide, [Pt(Dien)-Br]Br, was prepared and analyzed as described in a previous publication.[10]

Leucine Aminopeptidase.—The method of Moseley and Melius[3] was employed to prepare aq enzyme soln. Protein contents of enzyme prepns were estimated by the colorimetric procedure of Miller.[11] Assays of enzyme activity were performed by titrating NH_3 liberated from the hydrolysis of L-leucinamide using a Radiometer titrator, Type III 1e with a Titrigraph, Type SBR2C and syringe buret as a pH-Stat. All assays were carried out at pH 8.0 and 37°. A unit of enzyme activity hydrolyzed 1 equiv of L-leucinamide/min at a 0.01 *M* substrate concn.

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Some Pyrrolidine Derivatives as Antispasmodics

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Potent analgetic activity has been reported in *N*-substituted-4-aminopiperidine derivatives,[1-3] in which the basic heterocyclic N is separated from an acylated anilino group by 3 C atoms. It was considered pertinent to prepare a series of *N*-(substituted phenyl)-*N*′-(1-phenethyl-3-pyrrolidinyl)acetamides (**1**) having this structural feature.

The amides **1** were prepared by a 4-stage synthesis (Scheme I) described in the Experimental Section. None of the compounds examined showed any analgetic activity, but they had potent antispasmodic activity in the Konzett-Rossler test.[4] Fifteen compounds of type 1 were tested against AcCh, histamine, and 5-HT in anesthetized guinea pigs; the results are presented in Table I.

Potent activity is found in compounds where R_1 is an unsubstituted aromatic ring. Substitution of the aromatic ring reduced the antispasmodic activity, electron-donating groups producing a less marked reduction in activity than electron-withdrawing groups. The nature of the alkyl group R_2 influenced the toxicity as well as the activity of the compounds. When R_2 was Me, activity was maximal and toxicity minimal; the reverse was true when R_2 was Et. The other groups tested at R_2 showed intermediate levels of toxicity and activity.

The phenethyl side chain was selected in view of the associations with potent analgetic activity.[3] All the compounds **1** showed significantly greater activity

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TABLE I

N-(SUBSTITUTED PHENYL)-*N'*-(1-PHENETHYL-3-PYRROLIDENYL)AMIDES

								Percentage reduction in response[a]		
No.	R_1	R_2	Yield (%)	Mp or bp (°C) (mm)	Formula[d]	Method	Dose (mg/kg iv)	AcCh	Histamine	5-Hydroxytryptamine
1	C_6H_5	C_6H_5	78	146–147	$C_{28}H_{30}N_2O_5$[b]	A	5	100	100	100
							2.5	8	0	31
2	C_6H_5	C_2H_5	45	118–119	$C_{24}H_{30}N_2O_5$[c]	A	5	Animal died		
							2.5	100	100	95
3	$C_6H_5(CH_2)_2$	CH_3	58	175 (2.5)	$C_{23}H_{30}N_2O$	B	10	15	93	100
4	4-ClC_6H_4	CH_3	41	220 (3)	$C_{21}H_{25}ClN_2O$	B	10	2	83	90
5	C_6H_5	$C_6H_5CH_2$	42	220 (2)	$C_{27}H_{30}N_2O$	A	10 (i.p.)	0	38	0
6	4-Cl-2-$CH_3C_6H_3$	CH_3	50	240 (3)	$C_{22}H_{27}ClN_2O$	B	5	0	4	11
7	4-$CH_3C_6H_4$	CH_3	45	210 (0.4)	$C_{22}H_{28}N_2O$	B	5	76	83	100
8	C_6H_5	CH_3	60	210 (4)	$C_{21}H_{26}N_2O$	B	5	100	100	100
							2.5	100	100	100
							0.1	28	0	28
9	4-$OC_2H_5C_6H_4$	CH_3	60	210 (1.5)	$C_{23}H_{30}N_2O$	B	5	83	100	100
							1	0	67	42
10	2-$OCH_3C_6H_4$	CH_3	62	220 (2)	$C_{22}H_{28}N_2O$	B	5	51	76	100
11	4-$ClC_6H_4CH_2$	CH_3	42	190 (6)	$C_{22}H_{27}ClN_2O$	B	5	0	68	70
12	C_6H_5	$(C_2H_5)_2N$	46	180 (7)	$C_{24}H_{33}N_3O$	A	5	83	74	100
							1	20	12	87
13	$C_6H_5(CH_2)_2$	$(C_2H_5)_2N$	60	240 (5)	$C_{27}H_{37}N_3O$	A	5	Animal died		
							1	0	9	74
14	$C_6H_5(CH_2)_2$	C_2H_5	45	230 (3)	$C_{24}H_{32}N_2O$	A	5	20	90	100
15	$C_6H_5(CH_2)_2$	$C_6H_5CH_2$	39	240 (3)	$C_{29}H_{34}N_2O$	A	5	Animal died		
							1	0	13	60

[a] Konzett–Rossler test. [b] Isolated as the oxalate, recrystd from EtOH–Et_2O. [c] Isolated as the oxalate, recrystd from EtOH–*i*-PrOH. [d] All compounds were analyzed for C, H, N.

TABLE II

N-PHENETHYL-5-OXO-3-PYRROLIDINYLCARBOXAMIDES

R	Yield (%)	Mp or bp (°C) (mm)	Formula[a]	Method	Recrystn solvent
C_6H_5	87	150–151	$C_{19}H_{20}N_2O_2$	B	MEK
4-ClC_6H_4	53	151–152	$C_{19}H_{19}ClN_2O_2$	B	Me_2CO
4-Cl-2-$CH_3C_6H_3$	63	132–133	$C_{20}H_{21}ClN_2O_2$	B	EtOH
4-$CH_3C_6H_4$	68	154–155	$C_{20}H_{22}N_2O_2$	B	MeOH-MEK
4-$OC_2H_5C_6H_4$	81	159–160	$C_{20}H_{24}N_2O_3$	B	$CHCl_3$–petr ether (bp 40–60°)
2-$OCH_3C_6H_4$	53	240 (1.5)	$C_{20}H_{21}N_2O_3$	B	
4-$ClC_6H_4CH_2$	62	109–110	$C_{20}H_{21}ClN_2O_2$	A	Me_2CO-H_2O
$C_6H_5(CH_2)_2$	40	14–17	$C_{21}H_{24}N_2O_2$	A	Petr ether (bp 40–60°)

[a] See footnote *d*, Table I.

against histamine and 5-HT than against AcCh. Compounds **2**, **13**, and **15** were exceptionally toxic within this series, toxicity being manifest as respiratory depression. Antispasmodic activity and respiratory depression have been noted as side effects of meperidine.[5]

In an attempt to explain the absence of analgetic activity in the amides **1**, molecular models were made of some related known analgetics.[3] These models showed a substantial degree of coplanarity between the basic heterocyclic N and the aromatic ring attached to the amido group. This feature was absent in the models of amides **1**. Beckett and Casy[6] postulated that it was essential for the basic center and the aromatic ring to be coplanar for the molecule to have meperidine type analgetic activity.

In comparing the amides **1** with analgetics based on 4-aminopiperidine it is evident that reducing the size of the heterocyclic ring from 6 to 5 members, while maintaining the same number of C atoms between the basic center and the aromatic ring, abolishes analgetic activity.

Experimental Section

Uv, ir (Nujol), and nmr (Me_4Si) spectra were measured for all compounds and were as expected. Melting points were taken on a Büchi apparatus and are uncorrected.

***N*-Phenethyl-5-oxo-3-pyrrolidinylcarboxylic acid** (**2**) was prepared by the method of Paytash, *et al.*,[7] from itaconic acid (1.3 g, 0.01 mole) and phenethylamine (1.3 g, 0.01 mole), recrystd from aq DMF: mp 187–188°; yield 1.97 g (97%). *Anal.* ($C_{13}H_{15}NO_3$) C,H,N.

***N*-Phenethyl-5-oxo-3-pyrrolidinylcarboxamides** (**3**).—*N*-Phen-

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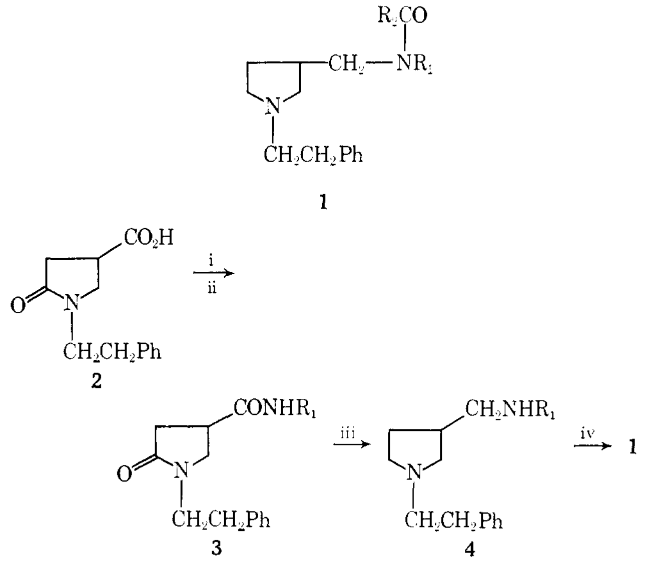
SCHEME I



4a, $R_1 = Ph$
4b, $R_1 = PhCH_2CH_2CH_2$

Reagents: i = $SOCl_2$, ii = R_2NH_2, iii = LAH, iv = R_2COCl

ethyl-5-oxo-3-pyrrolidinylcarboxylic acid (126 g, 0.5 mole) in $CHCl_3$ (200 ml) was added to freshly distd $SOCl_2$ (250 g, 2.1 mole). The reaction mixture was heated under reflux for 2 hr. The solvent and unreacted $SOCl_2$ were evapd under reduced pressure and the residual oil used without further purification.

Preparation of Amides. Method A.—Amines and *N*-phenethyl-5-oxo-3-pyrrolidinylcarbonyl chloride in equimolar quantities were allowed to react in an excess of 2% NaOH. A solid sepd on cooling, this was collected, washed (H_2O), and recrystd.

Method B.—Amines (2.0 moles) and *N*-phenethyl-5-oxopyrrolidinylcarbonyl chloride (1.0 mole) were allowed to react in dry $CHCl_3$ at −60°. A solid, which sepd on storage, was collected and washed ($CHCl_3$) and the washings were added to the filtrate. The combined washings were dried (Na_2SO_4) and evapd. The residual oils solidified on cooling and were recrystd. For details see Table II.

***N*-Phenethyl-3-pyrrolidinylmethylamines (4).**—LAH (4.7 g, 0.15 mole) was suspended in dry dioxane (150 ml) in a Soxhlet apparatus. *N*-Phenethyl-5-oxo-3-pyrrolidinylcarboxamides (0.1 mole) were packed into the thimble and extracted. The products were worked up in the usual way and purified as such or characterized as acyl derivatives.

***N*-Phenethyl-3-pyrrolidinylmethylaniline (4a)** was redistilled under reduced pressure, the fraction boiling at 190° (1.5 mm) was collected: yield 14.75 g (52%). *Anal.* ($C_{19}H_{24}N_2$) C,H,N.

***N*-Phenethyl-3-pyrrolidinylphenethylamine · 2HBr (4b)** was recrystd from EtOH–Et_2O: mp 255–256°; yield 31.95 g (68%) *Anal.* ($C_{21}H_{30}Br_2N_2$) C,H,N.

***N*-(Substituted phenyl)-*N'*-(1-phenethyl-3-pyrrolidinyl)acetamides (1). Method A.**—*N*-Phenethyl-3-pyrrolidinylmethylamines (0.1 mole) in dry $CHCl_3$ (100 ml) were added to anhyd $NaHCO_3$ (0.15 mole). The suspension was cooled to 0° and the appropriate acid chloride (0.2 mole) added. The reaction mixture was heated under reflux for 5 hr and filtered hot. The filtrate was dried (Na_2SO_4) and evapd. The residual oils were distd under reduced pressure.

Method B.—*N*-Phenethyl-3-pyrrolidinylmethylamines (0.1 mole) in dry $CHCl_3$ (100 ml) were treated with the appropriate acid chloride (0.3 mole) and the reaction mixture was heated under reflux for 2 hr. Excess acid chloride and solvent was distd off under reduced pressure. The residue was basified by addn of 36% KOH and the base extd with Et_2O (4 × 25 ml). The products were isolated as in method A. Compound **4** was insol in Et_2O.

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2,2'-Dialkoxybenzhydrylamides and 2,2'-Dialkylbenzhydryl Esters of N,N-Disubstituted α-Amino Acids. Synthesis and Pharmacological Evaluation

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Isomers of lidocaine which do not have two Me groups ortho to the anesthesiophore group differ markedly in anesthetic properties.[1] Obviously the considerable steric hindrance plays an important role in this pharmacological activity. Moreover, the replacement of a functional NH by O can lead to isosteric compounds of similar properties.[2,3]

The title compounds were chosen for study because they contain a key structural feature of lidocaine: steric hindrance; moreover, we were interested in studying what effect replacement of NHCO by OCO in this type of molecules would have on the activity profile.

The synthesis of the intermediate halo esters was achieved under mildly basic conditions. Attempts to prepare them by boiling di-*o*-tolylcarbinol and $ClCOCH_2Cl$ were unsuccessful, di-*o*-tolylchloromethane[4] was obtained.

An attempt was made to correlate local anesthetic potency with the bond order of the CO linkage as measured by the CO stretching frequency. A previous correlation of this type has been reported.[5,6] Examination of Table I shows there is no correlation between the CO absorption frequency and the local anesthetic potency. Direct comparison of esters and amides perhaps should not be made, particularly with the hindered amides reported here, since amides in general are representatives of a lower absorption frequency.

Biological Results.—Compounds **1**–**28** were tested for their local anesthetic activity and the results of the observations are summarized in Table I. Potency and duration of local anesthetic activity were assessed by the Bülbring and Wajda technique.[7] Aliquots of 0.25% solns of **1**–**20** in distd H_2O were injected intradermally in guinea pigs. Compounds **21**–**28**, because of instability in H_2O, were injected at a dose level of 0.25% in propyleneglycol. Local anesthesia was indicated by the absence of a flinching response when the treated site was pricked at 5, 10, 15, 30, 60, 120, and 180 min after injection. Lidocaine was used for comparison throughout the experiments.

It is apparent from these primary results that **3** is somewhat more active than lidocaine itself. However, the injection site was inflamed and edematous. Twenty-four hours after the experiment the animals

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