Substituted Benzamides with Conformationally Restricted Side Chains. 1. Quinolizidine Derivatives as Selective Gastric Prokinetic Agents

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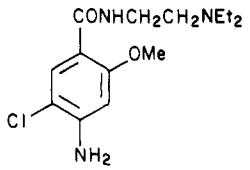
The gastric prokinetic action of metoclopramide may not be primarily due to its dopamine antagonist activity. The present aim was to obtain a selective gastric prokinetic agent lacking dopamine antagonist activity by conformationally restricting the side chain of metoclopramide. In a series of quinolizidinylbenzamides, only compounds with the benzamide moiety at position 2 of the quinolizidine ring retain gastric activity. Of these 2-substituted compounds, the 2α,9aα isomer has potent selective gastric prokinetic activity with only weak dopamine antagonist properties. Spectroscopic data show that the quinolizidine ring preferentially adopts a trans chair–chair conformation with an axial benzamide moiety. However, energy calculations indicate that, at nondopaminergic receptors controlling gastric motility, an alternative cis chair–chair conformation with an equatorial benzamide moiety cannot be ruled out.

Metoclopramide (1) is a substituted benzamide that is used clinically as a stimulant of upper gastrointestinal motility and as an antiemetic.[1] Although it is a dopamine



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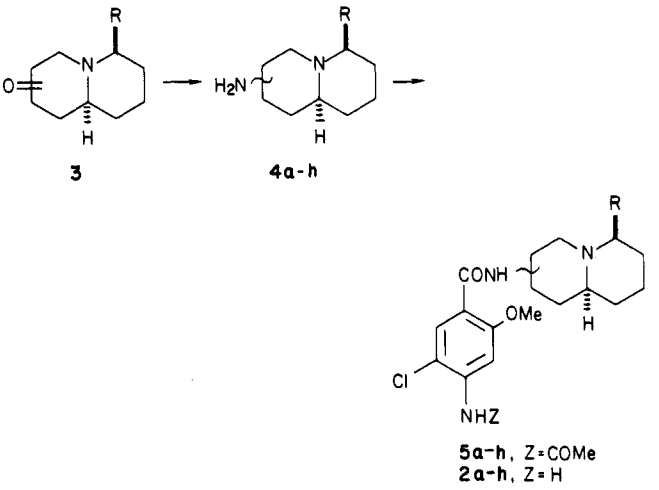
receptor antagonist in both the central nervous system and the periphery, its gastrointestinal stimulant activity cannot be fully explained by its ability to block the inhibitory control by dopamine on the gut. Potentiation of cholinergic effects on the gut muscle, possibly mediated by a stimulatory effect at neuronal 5-hydroxytryptamine receptors, may be of more importance.[2,3] Its stimulatory effect on gastric motility may contribute to its antinauseant action.

The aim of the present work was to discover a gastric prokinetic agent lacking dopamine receptor antagonist activity. Such activity in the pituitary gland results in elevated serum prolactin levels, whereas in the central nervous system it can give rise to extrapyramidal side effects, although for metoclopramide their incidence is low.

It was considered that compounds with a more selective profile than metoclopramide might be obtained by conformationally restricting its (diethylamino)ethyl side chain. The analogues selected, compounds **2a–h**, incorporate a quinolizidine ring in place of the (diethylamino)ethyl side chain, with the benzamide moiety at the 1-, 2-, or 3-position (Table I). In each case, both diastereoisomers were prepared. Thus, a range of compounds was obtained in which the presumed important structural features for receptor binding, namely the benzamide moiety and the bridgehead nitrogen atom, differed in their separations and relative orientations.

Chemistry. The quinolizidinyl benzamides **2a–h** were prepared (Scheme I) by reaction of the respective aminoquinolizidines **4a–h** with 4-(acetylamino)-5-chloro-2-methoxybenzoyl chloride, followed by selective base hydrolysis of the 4-acetylamino group. The aminoquinolizidines **4a–h** were obtained as diastereoisomeric mixtures

Scheme I



from the corresponding quinolizidinones **3** by conversion to the oximes followed by reduction with lithium aluminum hydride. Separation of the diastereoisomers was delayed until after conversion to the benzamides, as the latter were more amenable to separation by fractional crystallization or chromatography.

Stereochemical assignments were made spectroscopically. Compounds **2a–h** showed Böhlmann bands in their IR spectra between 2700 and 2800 cm^{-1} indicative of trans-fused quinolizidine rings.[4]

In the NMR spectra of **2c**, **2e**, and **2f**, the proton at the amide-substituted carbon appeared at δ 4.01–4.18 as a double triplet of triplets (J = 8, 12, 5 Hz) which simplified to a triplet of triplets (J = 12, 5 Hz) after exchange of the amidic proton with deuterium. These data indicate that the proton is axial, it being coupled to two equivalent pairs of vicinal axial and equatorial protons.[5] Consequently, these compounds have an equatorial benzamide moiety. The same is true for **2a** where the respective proton appeared at δ 3.93 as a doublet of triplets (J = 12, 5 Hz) after exchange with deuterium. The reduced multiplicity is a consequence of there being only one vicinal equatorial proton.

In contrast, the equivalent proton in **2b**, **2d**, **2g**, and **2h** appeared at δ 4.06–4.37 as a poorly resolved doublet of multiplets that simplified, after deuterium exchange, to a poorly resolved quintet for **2d**, **2g**, and **2h** and to a broad singlet for **2b**. These multiplets had much narrower signal

(1) Harrington, R. A.; Hamilton, C. W.; Brogden, R. N.; Linkewich, J. A.; Romankiewicz, J. A.; Heel, R. C. *Drugs* **1983**, *24*, 451.
(2) Ebong, O. O.; Bateman, D. N.; Zar, M. A. *Gut* **1982**, *23*, 66.
(3) Kilbinger, H.; Kruel, R.; Pfeuffer-Friederich, I.; Wessler, I. *Naunyn Schmiedeburg's Pharmacol.* **1982**, *319*, 231.
(4) Bohlmann, F. *Chem. Ber.* **1958**, *91*, 2157.
(5) Huitric, A. C.; Carr, J. B.; Trager, W. F.; Nist, B. J. *Tetrahedron* **1963**, 2145.

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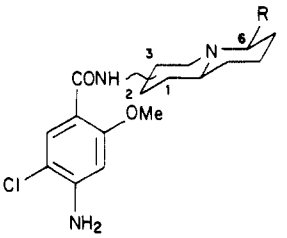
Table I. Structures of 2a-h and Pharmacological Data



no.	pos of benzamide	isomer[a]	R	ED_{50}, mg/kg sc (95% CL) stimulation of intragastric pressure:[b]	antiapomorphine climbing:[b]
1	metoclopramide			1.0 (0.30-2.7)	0.75 (0.62-0.90)
2a	1	E	H	1.0-50 (inact)	>50
2b	1	A	H	1.0-50 (inact)	0.40 (0.16-1.0)
2c	3	E	H	1.0-50 (inact)	12 (10.0-14.4)
2d	3	A	H	1.0-10 (inact)	10 (5.6-18.0)
2e	2	E	H	4.0 (2.3-7.0)	7 (3.7-13.3)
2f	2	E	Me	1.0-50 (inact)	>50
2g	2	A	H	0.80 (0.35-1.8)	25 (14.7-42.5)
2h	2	A	Me	0.80 (0.30-2.1)	25 (20.7-30.3)

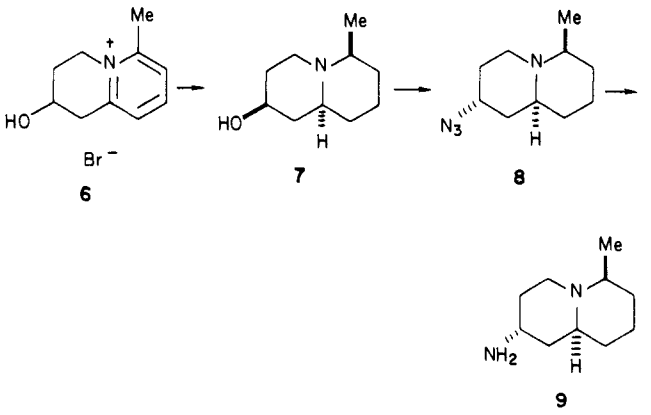
[a] E = equatorial, A = axial. [b] See the Experimental Section.

widths and were at lower field strengths than for the axial protons in **2a**, **2c**, **2e**, and **2f**. These data are consistent with **2b**, **2d**, **2g**, and **2h** having an axial benzamide moiety.[6] Additionally, the amidic proton in these benzamides appeared at lower field strengths (δ 8.05–8.65) than in the equatorial benzamides **2a**, **2c**, **2e**, and **2f** (δ 7.4–7.55). These findings are similar to those reported for related acetamides.[7]

The orientation of the 6-methyl substituent of **2f** and **2h** was assigned by spectral comparison with the desmethyl analogues **2e** and **2g**. By analogy with quinolizidine,[8] the two-proton multiplet at δ 2.8–2.92 in the NMR spectrum of **2e** can be assigned to the equatorial C-4 and C-6 protons. Similarly for **2g** these protons appeared as multiplets at δ 2.69–2.78 and 2.82–2.91. For **2f** and **2h**, however, only a one proton signal was evident at δ 3.31 and 3.12–3.24, respectively, indicating that these compounds have an equatorial 6-methyl substituent. This was confirmed both from the lower field position of the remaining C-4 equatorial proton[9] and from the ^{13}C NMR spectrum of **2h**. The 6-methyl substituent appeared as a quartet at δ 20.66, similar to the chemical shift (δ 20.8) for the equatorial methyl in the 4-methylquinolizidin-2-one epimyrtine and very different from the chemical shift (δ 11.0) for the axial methyl in the C-4 epimer myrtine.[10]

The axial stereochemistry of the benzamide moiety in **2h** was also confirmed by stereospecific synthesis (Scheme II). Hydrogenation of the hydroxypyridinium salt **6** over platinum oxide gave the 2-hydroxyquinolizidine **7**[11] with the hydroxy group predominantly (85% by ^1H NMR) equatorial. Conversion of **7** to the axial azide **8** was effected using triphenylphosphine, diethyl azodicarboxylate, and diphenylphosphoryl azide, a method reported to proceed with inversion of configuration.[12] The axial

Scheme II



orientation of the azide was confirmed by the appearance of the C-2 proton in the NMR spectrum at δ 3.80 as a quintet (J = 4 Hz). Reduction with lithium aluminum hydride afforded the axial amine **9** which, after benzoylation and hydrolysis, gave a compound that was identical to **2h**, obtained by the nonstereospecific route. By an identical procedure, **2g** was obtained from the analogue of **6** lacking the methyl group.

Results and Discussion

The gastric prokinetic activity of **2a–h** and metoclopramide was determined by their ability to increase basal intragastric pressure in rats (Table I).[13] Activity in this screen is thought to indicate that the compound stimulates gastric motility by a nondopaminergic mechanism. Compounds like domperidone, which can reverse the inhibitory effect of dopamine on gastric motility,[14] are inactive in this screen.[15] Central dopamine antagonist activity was as-

(6) Franklin, N. C.; Feltkamp, H. *Angew. Chem., Int. Ed. Engl.* **1965**, *4*, 774.
(7) Lichtenthaler, F. W. *Chem. Ber.* **1963**, *96*, 2047.
(8) Hamlow, H. P.; Okuda, S.; Nakagawa, N. *Tetrahedron Lett.* **1964**, 2553.
(9) Bohlmann, F.; Schumann, D.; Schulz, M. *Tetrahedron Lett.* **1964**, 173.
(10) Slosse, P.; Hootelé, C. *Tetrahedron* **1981**, *37*, 4287.
(11) Boekelheide, V.; Gall, W. G. *J. Am. Chem. Soc.* **1954**, *76*, 1832.
(12) Lal, B.; Pramanik, B. N.; Manhas, M. S.; Bose, A. K. *Tetrahedron Lett.* **1977**, 1977.
(13) McClelland, C. M.; McRitchie, B.; Turner, D. H. *Br. J. Pharmacol. Proc. Supp.* **1983**, *80*, 569P.
(14) Van Nueten, J. M.; Ennis, C.; Helsen, L.; Laduron, P. M.; Janssen, P. A. J. *Life Sci.* **1978**, *23*, 453.
(15) McRitchie, B.; McClelland, C. M.; Cooper, S. M.; Turner, D. H.; Sanger, G. J. In "Mechanisms of Gastrointestinal Motility and Secretion"; Bennett, A., Velo, G.P., Eds.; Plenum Press: New York, 1984; p 287.

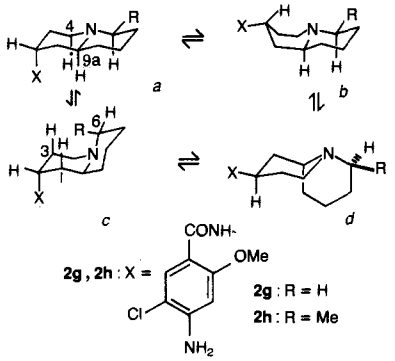


Figure 1. Possible conformations of **2g**, **2h**, and related model compounds.

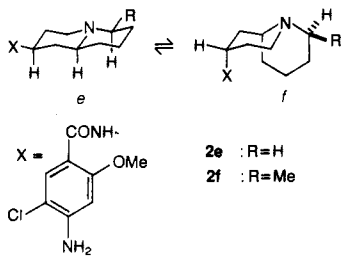


Figure 2. Possible conformations of **2e** and **2f**.

sessed by their ability to antagonize apomorphine-induced climbing behavior in mice.[16]

Benzamides **2a–d**, in which there is a two-carbon separation between the benzamide and bridgehead nitrogen atoms as in metoclopramide, exhibited no gastric prokinetic activity. In contrast, **2e** and **2g**, in which there is a three-carbon separation, did show such activity. The equatorial isomer **2e** was less potent than metoclopramide and showed little improvement in separation of gastric prokinetic and central dopamine antagonist potencies. However, the axial isomer **2g** had comparable gastric prokinetic potency to metoclopramide and yet was over 30-fold less potent as a central dopamine antagonist.

It has been reported that, in a series of centrally active benzamides, the central dopamine antagonist potency can be reduced by steric bulk in the vicinity of the basic nitrogen atom.[17] It is interesting to compare this finding with our own concerning the effect of introducing a methyl substituent at C-6 into **2e** and **2g**. The equatorial isomer **2f** showed no gastric stimulatory or central dopamine antagonist activity in the dose ranges used. However, the axial isomer **2h** retained both the potency and gastric selectivity of **2g**. Its low dopamine antagonist potency was confirmed by its lack of effect on plasma prolactin levels in rats at subcutaneous doses below 10 mg/kg.[13] Further details of pharmacological and biochemical studies on the hydrochloride salt (BRL 20627) of **2h** have been reported elsewhere.[13,18]

It is intriguing to consider whether the shapes of **2g** and **2h** give any information on the nature of nondopaminergic receptors mediating gastric prokinetic activity. Spectral evidence, discussed earlier, indicates that in **2g** and **2h** the quinolizidine ring preferentially adopts a trans chair–chair conformation with an axial benzamide moiety (Figure 1, a). However, a molecule does not necessarily bind to a receptor in its lowest energy conformation. Some other possible conformations (b–d) are shown in Figure 1. Normally the relatively large energy difference between chair and boat conformations would preclude consideration of the latter. However, the interactions between the benzamide moiety X and the axial protons at C-4 and C-9a in a are relieved in the boat–chair conformation b. Alternatively, the nitrogen atom can be inverted to give a *cis*-quinolizidine ring as in c, but this still has an axial benzamide moiety and the R substituent at C-6 is in a particularly crowded environment, due to interactions with axial protons at C-1 and C-3. However, inspection of molecular models reveals an alternative cis chair–chair conformation d, in which these interactions are absent and both benzamide and C-6 substituents are equatorially orientated.

Table II. Energies (kJ mol^{-1}) of Conformations b–d above Those of Conformation a for Model Compounds Related to **2g** and **2h** (See Figure 1)

		X		
conformn	R	Me	CH_2=CH	MeCONH
b	H	18		
	Me	15	16	25
c	H	16		
	Me	32	35	31
d	H	5.4		
	Me	2.7	2.4	12

Energy calculations have been performed on conformations a–d for model compounds where the benzamide moiety X in **2g** and **2h** has been replaced by methyl, vinyl, and acetylamino (Table II). The molecular mechanics program MM2[19] was used with partial charges for the input calculated by the semiempirical molecular orbital method INDO.[20] Boat conformations were relaxed to minimize "bowsprit–flagpole" and other interactions.

Conformation c is very unlikely to be adopted at a receptor as it is of particularly high energy when R is methyl, and benzamides **2g** (R = H) and **2h** (R = Me) are equipotent. The same is probably true for conformation b because the model compound where X is acetylamino, structurally closest to the benzamide moiety, is of fairly high energy.

However, conformation d cannot be ruled out on energy grounds and must be considered as an alternative receptor binding conformation to a. A receptor model also should explain the activity but lower potency of the equatorial benzamide **2e**. In its lowest energy conformation e (Figure 2), it can overlap well on d, assuming that the key structural features involved in receptor binding are the bridgehead nitrogen atom and the benzamide moiety. Its lower potency and also the inactivity of **2f** (R = Me) could be a consequence of steric interactions of the R-substituted ring with the receptor. Alternatively, if a is the receptor-binding conformation of **2g**, the only feasible way that **2e** can be overlapped well is for it to adopt conformation f, in which the quinolizidine ring is in a cis chair–chair conformation with an axial benzamide substituent. The energy of this conformation is presumably higher than that of e and this could explain the lower potency of **2e**.

The weak central dopamine antagonist potency of all the quinolizidinylbenzamides with the exception of **2b** probably reflects their low affinity for central dopamine receptors (e.g., IC_{50} = 2.5 μM for **2h** for displacement of [^{3}H]spiroperidol from rat striatal tissue)[21] rather than lack

(16) Protais, P.; Constentin, J.; Scwartz, J. C. *Psychopharmacology* **1976**, *50*, 1.
(17) Iwanami, S.; Takashima, M.; Hirata, Y.; Hasegawa, O.; Usuda, S. *J. Med. Chem.* **1981**, *24*, 1224.
(18) McClelland, C. M.; Sanger, G. J. *Br. J. Pharmacol. Proc. Suppl.* **1983**, *80*, 568P.
(19) Allinger, N. L.; Yuh, Y. H. *QCPE* **1977**, *395*.
(20) Dobosh, P. A. *QCPE* **1969**, *141*.
(21) Riley, G., unpublished results.

of central penetration. This could be due to either steric or conformational factors.

Experimental Section

Chemistry. Melting points and boiling points are uncorrected. The elemental analyses indicated were within 0.4% of the theoretical values. ^{1}H NMR spectra were recorded on a Perkin-Elmer R12B or a JEOL GX270 spectrometer using Me_4Si as internal standard. ^{13}C NMR spectra were recorded on a Bruker WM 250 spectrometer. IR and mass spectra were recorded on a Perkin-Elmer 197 and an AEI MS9 (79eV) spectrometer, respectively. All evaporations of solvent were carried out under reduced pressure, and organic solvents were dried over K_2CO_3, unless specified otherwise. For column chromatography, the silica gel used was Merck Kieselgel 60, and the alumina, Camag grade 1. Light petroleum refers to the fraction boiling between 60 and 80 °C. The octahydro-2*H*-quinolizin-1-one,[22] -2-one,[23] and -3-one[24] were prepared by literature procedures.

General Procedure for Preparation of Amines 4a–h. A solution of the appropriate octahydro-2*H*--quinolizinone **3** (0.1 mol), hydroxylamine hydrochloride (14 g, 0.14 mol), and pyridine (15 mL) in EtOH (200 mL) was heated under reflux for 1 h. After evaporation, the residue was treated with EtOAc (300 mL) and aqueous NaOH (2.5 M, 60 mL). The organic layer was separated, dried and evaporated to give the crude oxime (ca. 0.09 mol) as a mixture of isomers. This oxime was placed in an extraction thimble of a Soxhlet apparatus in which a stirred suspension of $LiAlH_4$ (6.5 g, 0.17 mol) and Et_2O (500 mL) was heated under reflux. After 24 h, aqueous NaOH (2.5 M, 10 mL) followed by H_2O (20 mL) were added, and the mixture was filtered. Evaporation of the filtrate afforded amines **4a–h** as diastereoisomeric mixtures, sufficiently free of other impurities to be converted directly to the benzamides.

General Procedure for Preparation of 4-(Acetylamino)-benzamides 5a–h. A solution of 4-(acetylamino)-5-chloro-2-methoxybenzoyl chloride (2.6 g, 0.01 mol), Et_3N (4 mL), and the appropriate amine, **4a–h** (0.01 mol), in toluene (100 mL) was stirred at 0 °C for 30 min. Aqueous NaOH (2.5 M, 10 mL) was added and the product extracted into EtOAc (3 × 10 mL). Evaporation of the dried extracts afforded 4-(acetylamino)-benzamides **5a–h** as diastereoisomeric mixtures.

(1α,9aα)-4-Amino-5-chloro-2-methoxy-*N*-(octahydro-2*H*-quinolizin-1-yl)benzamide (2a) and (1β,9aα)-4-Amino-5-chloro-2-methoxy-*N*-(octahydro-2*H*-quinolizin-1-yl)benzamide (2b). The mixture **5a,5b** of the 1-α and 1-β isomers was chromatographed on alumina deactivated with 10% H_2O. Elution with CH_2Cl_2 containing progressively increasing amounts of $CHCl_3$ afforded initially the 1-β isomer **5b** [1.4 g (37%), mp 173–174 °C], followed by the 1-α isomer **5a** [2.4 g (63%), mp 219–220 °C]. A solution of **5b** (1.4 g, 3.7 mmol) and NaOH (0.32 g, 8 mmol) in EtOH (50 mL) and H_2O (20 mL) was heated under reflux for 2 h. After evaporation, the residue was extracted into EtOAc (3 × 100 mL) and dried. Evaporation and recrystallization (EtOAc/light petroleum) gave **2b**: 1.05 g (67%); mp 176–178 °C. Anal. ($C_{17}H_{24}ClN_3O_2$) C, H, N, Cl. ^{1}H NMR ($CDCl_3$): δ 8.32 (br d, 1), 4.06 (dm, 1), 2.74–2.85 (m, 2). Similar deacetylation of **5a** gave **2a**: 1.34 g (61%); mp 176–178 °C. Anal. ($C_{17}H_{24}ClN_3O_2$) C, H, N, Cl. ^{1}H NMR ($CDCl_3$): δ 7.40 (br d, 1), 3.93 (ddt, 1, J = 8, 12, 5 Hz), 2.76–2.93 (m, 2).

(3α,9aα)-4-Amino-5-chloro-2-methoxy-*N*-(octahydro-2*H*-quinolizin-3-yl)benzamide (2c) and (3β,9aα)-4-Amino-5-chloro-2-methoxy-*N*-(octahydro-2*H*-quinolizin-3-yl)benzamide (2d). The mixture of **5c** and **5d** was triturated with EtOAc and the insoluble 3-α isomer, **5c**, collected: 1.82 g (48%); mp 211–212 °C. Deacetylation as previously described for **5b** afforded **2c**: 1.0 g (62%); mp 207–208 °C. Anal. ($C_{17}H_{24}ClN_3O_2$), C, H, N, Cl. ^{1}H NMR ($CDCl_3$): δ 7.44 (br, 1), 4.18 (dtt, 1, J = 8, 12, 5 Hz), 3.14 (dm, 1), 2.82 (dm, 1). The EtOAc filtrate was evaporated and the residue chromatographed on silica. Elution with EtOAc containing 3% MeOH afforded the 3-β isomer, **5d**: 1.37 g (36%); mp 147–149 °C. Deacetylation as previously described afforded **2d**: 0.8 g (65%); mp 211–213 °C. Anal. ($C_{17}H_{24}ClN_3O_2$) C, H, N, Cl. ^{1}H NMR ($CDCl_3$) δ 8.65 (br d, 1), 4.28 (dquin, 1), 2.69 (m, 2).

(2β,9aα)-4-Amino-5-chloro-2-methoxy-*N*-(octahydro-2*H*-quinolizin-2-yl)benzamide (2e) and (2α,9aα)-4-Amino-5-chloro-2-methoxy-*N*-(octahydro-2*H*-quinolizin-2-yl)benzamide (2g). The mixture of **5e** and **5g** was triturated with a 1:1 mixture of EtOAc/light petroleum and the insoluble **5e** collected: 1.33 g (35%); mp 205 °C. Deacetylation as previously described afforded **2e**: 0.89 g (75%); mp 175–178 °C. Anal. ($C_{17}H_{24}ClN_3O_2$) C, H, N, Cl. ^{1}H NMR ($CDCl_3$) δ 7.55 (br d, 1), 4.01 (dtt, 1, J = 8, 12, 5 Hz), 2.85 (dm, 2). The filtrate was evaporated to afford an oil containing mainly **5g**, 1.82 g (48%). Deacetylation as previously described afforded **2g**: 0.9 g (55%); mp 178–179 °C. Anal. ($C_{17}H_{24}ClN_3O_2$) C, H, N, Cl. ^{1}H NMR ($CDCl_3$): δ 8.08 (br d, 1), 4.42 (m, 3), 2.86 (dm, 1) 2.73 (dm, 1).

(2β,6β,9aα)-4-Amino-5-chloro-2-methoxy-*N*-(octahydro-6-methyl-2*H*-quinolizin-2-yl)benzamide (2f) and (2α,6β,9aα)-4-Amino-5-chloro-2-methoxy-*N*-(octahydro-6-methyl-2*H*-quinolizin-2-yl)benzamide (2h). The mixture of **5f** and **5h** was triturated with Et_2O and the insoluble **5f** collected: 1.7 g (43%); mp 205–207 °C. Deacetylation as previously described gave **2f**: 0.6 g (40%); mp 188–189 °C. Anal. ($C_{18}H_{26}ClN_3O_2$) C, H, N, Cl. ^{1}H NMR ($CDCl_3$) δ 7.54 (br d, 1), 4.01 (dtt, 1, J = 8, 12, 5 Hz), 3.31 (dt, 1, J = 12, 4 Hz), 1.12 (d, 3). The Et_2O filtrate was evaporated to afford an oil containing mainly **5h**, 2.0 g (50%). Deacetylation as previously described afforded **2h**: 0.35 g (20%); mp 243–244 °C ($CHCl_3$/light petroleum). Anal. ($C_{18}H_{26}ClN_3O_2$) C, H, N, Cl. ^{1}H NMR ($CDCl_3$): δ 8.05 (br d, 1), 4.35 (m, 1), 2.24–3.12 (m, 1), 1.14 (d, 3). ^{13}C-NMR ($CDCl_3$) δ 20.66 (q).

(2β,6β,9aα)-Octahydro-6-methyl-2*H*-quinolizin-2-ol (7). A suspension of 2-hydroxy-6-methyl-1,2,3,4-tetrahydroquinolizinium bromide[25] (**6**; 12 g, 0.05 mol) in EtOH (200 mL) was shaken with PtO_2 (0.5 g) and H_2 at atmospheric pressure until 3 mol equiv of H_2 had been absorbed. Removal of the catalyst by filtration and evaporation afforded an oily residue that was treated with H_2O (20 mL) and saturated with K_2CO_3. Extraction with EtOAc (5 × 100 mL), evaporation, and distillation of the residue afforded **7** [7.1 g (80%); bp 88–92 °C (0.1 mm)] containing ca. 15% of the 2α isomer. ^{1}H NMR ($CDCl_3$): δ 4.08 (quin, 0.15, J = 4 Hz), 3.59 (tt, 0.85, J = 11, 5 Hz), 3.28 (dt, 0.85, J = 12, 4 Hz), 3.04 (ddd, 0.15, J = 12, 5, 3Hz), 1.11 (d, 3, J = 6 Hz). Phenylurethane mp 144–145 °C. Anal. ($C_{17}H_{24}N_2O_2$) C, H, N. ^{1}H NMR ($CDCl_3$): δ 4.70 (tt, 1, J = 11, 5 Hz), 3.32 (dt, 1, J = 12, 4 Hz), 1.12 (d, 3, J = 6 Hz).

Stereospecific Synthesis of (2α,6β,9aα)-4-Amino-5-chloro-2-methoxy-*N*-(octahydro-6-methyl-2*H*-quinolizin-2-yl)benzamide (2h). To a stirred solution of Ph_3P (3.7 g, 0.014 mol) and diethyl azodicarboxylate (2.44 g, 0.014 mol) in dry THF (50 mL) at 0 °C was added **7** (2.37 g, 0.014 mol). After 10 min, diphenyl phosphorylazide (3.85 g, 0.014 mol) was added. After 48 h, the reaction mixture was diluted with EtOAc (100 mL) and the product extracted into aqueous HCl (5 M, 20 mL). This extract was basified with solid K_2CO_3 and extracted with EtOAc (2 × 100 mL). The EtOAc extract was dried and evaporated to afford an oil that was chromatographed on silica gel. Elution with EtOAc gave **8**: 1.63 g (60%); IR ν_{N_3} 2100 cm^{-1} (film); ^{1}H NMR ($CDCl_3$) δ 3.80 (quin, 1, J = 4 Hz). A solution of **8** (1.55 g, 8 mmol) in dry Et_2O (10 mL) was added to a stirred suspension of $LiAlH_4$ (0.6 g, 16 mmol) in Et_2O (100 mL). After 12 h, aqueous NaOH (2.5 M, 1 mL) followed by H_2O (2 mL) was added and the mixture filtered. Distillation of the filtrate afforded **4h**: 1.2 g (90%); bp 65 °C (0.5 mm); mass spectrum m/e 168 (M^+). The amine, **4h** (1.2 g, 7.1 mmol), was converted to **2h** [1.9 g (75%); mp 243–244 °C] by a procedure identical with that previously described for the amine mixture (**4f, 4h**).

Pharmacology. Activity on gastric motility was determined in male Wistar rats (200–500 g) in which a chronic gastric fistula had previously been established.[26] The rats were fasted overnight

(22) Clemo, G. R.; Ramage, G. R. *J. Chem. Soc.* **1931**, 437.
(23) Leonard, N. J.; Fulmer, R. W.; Hay, A. S. *J. Am. Chem. Soc.* **1956**, *78*, 3457.
(24) Clemo, G. R.; Morgan, W. M.; Paper, R. *J. Chem. Soc.* **1935**, 1743.
(25) Bockelheide, V.; Ross, J. M. *J. Am. Chem. Soc.* **1955**, *77*, 5691.
(26) Brodie, D. A. In "Pathophysiology of Peptic Ulcer"; Skoryna, S. C., Ed.; Lippincott: Philadelphia, 1963; p 403.

and then individually restrained in Bollman cages for the duration of the experiment. Gastric motility was assessed from the mean amplitude of pressure waves (mean motility index of Bech et al.[27]) recorded via the gastric fistula for four 10-min periods before and after subcutaneous administration of compound. Pressure was monitored by a Bell and Howell 4-422 transducer that, after suitable amplification, was displayed on a hot-wire pen recorder. Only rats with a low pretreatment basal motility (mean amplitude <4 mmHg) were used. Usually four groups of 10 such rats were treated with either a graded dose of test compound or vehicle.

Antagonism of apomorphine-induced climbing behavior was assessed by a modification of the method of Protais et al.[16] Usually four groups of 10 male CD-1 mice (20–25 g) were treated subcutaneously with either a graded dose of test compound or vehicle, 30 min before administration of a submaximal dose of apomorphine hydrochloride (1 mg/kg sc). The degree of antagonism was determined 10, 20, and 30 min later.

ED_{50} values and 95% confidence limits were calculated by the method of Litchfield and Wilcoxon.[28]

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Registry No. **2a**, 67092-55-1; **2b**, 67092-54-0; **2c**, 98482-26-9; **2d**, 98482-27-0; **2e**, 98482-28-1; **2f**, 98482-29-2; **2g**, 98482-30-5; **2h**, 98482-31-6; **3a**, 10447-21-9; **3a** (oxime), 80220-51-5; **3c**, 27257-46-1; **3c** (oxime), 80220-49-1; **3e**, 23581-42-2; **3e** (oxime), 34893-58-8; **3f**, 67092-64-2; **3f** (oxime), 80220-55-9; **4a**, 98482-32-7; **4b**, 98482-33-8; **4c**, 98482-34-9; **4d**, 98482-35-0; **4e**, 98482-36-1; **4f**, 98482-37-2; **4g**, 98482-38-3; **4h**, 98482-39-4; **5a**, 67092-53-9; **5b**, 67092-52-8; **5c**, 98482-40-7; **5d**, 98482-41-8; **5e**, 98482-42-9; **5f**, 98482-43-0; **5g**, 98482-44-1; **5h**, 98482-45-2; **6**, 98482-46-3; **7**, 98482-47-4; **8**, 98482-48-5; 4-(acetylamino)-5-chloro-2-methoxybenzoyl chloride, 4516-32-9; (2β,9aα)-octahydro-2-methyl-2*H*-quinolizine, 5581-90-8; (2β,6α,9aβ)-octahydro-2,6-dimethyl-2*H*-quinolizine, 98482-49-6; (2β,6α,9aβ)-octahydro-2-ethenyl-6-methyl-2*H*-quinolizine, 98482-50-9; (2β,6α,9aβ)-octahydro-2-(methylcarbonylamino)-6-methyl-2*H*-quinolizine, 98482-51-0.

(27) Bech, K.; Hovendal, C. P.; Anderson, D. *Scand. J. Gastroenterol.* **1982**, *17*, 103.

(28) Litchfield, J. T.; Wilcoxon, F. *J. Pharmacol. Exp. Ther.* **1949**, *96*, 99.

Synthesis and LTD_4 Antagonist Activity of 2-Norleukotriene Analogues

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A series of structural analogues of 4(*R*)-hydroxy-5(*S*)-cysteinylglycyl-6(*Z*)-nonadecenoic acid ((4*R*,5*S*,6*Z*)-2-nor-LTD_1 (**10b**), SK&F 101132) has been synthesized and pharmacologically characterized. (4*R*,5*S*,6*Z*)-2-nor-LTD_1 significantly antagonized LTD_4-induced contractile responses on isolated guinea pig trachea. The cis double-bond geometry appears to be critical for antagonist activity, whereas the trans isomer **17** exhibited weak contractile activity. Replacement of the cysteinylglycyl moiety with cysteine afforded **20**, which retained significant antagonist activity, while lengthening or shortening the lipid tail by five methylene groups resulted in complete loss of activity. The eicosanoid amide **15**, glycinamide **14**, and C-1 carbinol **18** analogues all possessed antagonist activity, whereas the diol derivative **19** exhibited increased intrinsic agonist activity.

Leukotriene C_4, D_4, and E_4 comprise a family of closely related eicosanoic acids derived from arachidonic acid via the 5-lipoxygenase pathway. These leukotrienes possess most of the biological activity attributed to slow-reacting substance of anaphylaxis (SRS-A).[1-4] Released upon antigen provocation of sensitized human and animal lung tissue,[5,6] they induce potent bronchoconstriction, increased microvascular permeability,[7-9] and altered mucus production and transport[10] and have been implicated as important mediators of anaphylaxis.[11] It follows that the discovery of selective leukotriene receptor antagonists may provide new therapeutic approaches to the treatment of allergic asthma and other immediate hypersensitivity diseases.

Structure–activity studies[12-14] on the natural agonist, LTD_4, suggested that the eicosanoid carboxyl region of the molecule was critical for agonist activity on the airway smooth muscle. To define the structural requirements in this region on agonist and antagonist activity, we examined the effect of altering the chain length between the C-1 carboxyl and C-5 hydroxyl groups on intrinsic activity. This study, utilizing the hexahydro analogues of LTD_4 to improve chemical stability and ease of synthesis, resulted in the identification of 2-nor-LTD_1 (**10b**, SK&F 101132) as a chemically stable, selective LTD_4 antagonist. The structure–activity relationship of a series of (4*R*,5*S*,6*Z*)-2-nor-LTD_1 analogues was explored with particular em-

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(1) Hammarstrom, S.; Murphy, R. C.; Samuelsson, B.; Clark, D. A.; Mioskowski, C.; Corey, E. J. *Biochem. Biophys. Res. Commun.* **1979**, *91*, 1266.
(2) Lewis R. A.; Austen, K. F.; Drazen, J. M.; Clark, D. A.; Marfat, A.; Corey, E. J. *Proc. Natl. Acad. Sci. U.S.A.* **1980**, *77*, 3710.
(3) Morris, H. R.; Taylor, G. W.; Piper, P. J.; Samhoun, M. N.; Tippins, J. R. *Prostaglandins* **1980**, *19*, 185.
(4) Murphy, R. C.; Hammarstrom, S.; Samuelsson, B. *Proc. Natl. Acad. Sci. U.S.A.* **1979**, *76*, 4275.
(5) Dahlen, S. E.; Hedquist, P.; Hammarstrom, S.; Samuelsson, B. *Nature* **1980**, *288*, 484.
(6) Peck, M. J.; Piper, P. G.; Williams, T. J. *Prostaglandins* **1981**, *21*, 315.
(7) Woodward, D. F.; Weichman, B. M.; Gill, C. A.; Wasserman, M. A. *Prostaglandins* **1983**, *25*, 131.
(8) Marom, Z.; Shelhamer, J. H.; Bach, M. K.; Morton, D. R.; Kaliner, M. *Am. Rev. Respir. Dis.* **1982**, *126*, 449.
(9) Gleason, J. G.; Ku, T. W.; McCarthy, M. E.; Weichman, B. M.; Holden, D.; Osborn, R. R.; Zabko-Potapovich, B.; Berkowitz, B.; Wasserman, M. A. *Biochem. Biophys. Res. Commun.* **1983**, *117*, 732.
(10) Weichman, B. M.; Wasserman, M. A.; Holden, D. A.; Osborn, R. R.; Woodward, D. F.; Ku, T. W.; Gleason, J. G. *J. Pharmacol. Exp. Ther.* **1983**, *227*, 700.
(11) (a) Brocklehurst, W. E. *J. Physiol.* **1960**, *151*, 416. (b) Austin, K. F.; Orange, R. P. *Am. Rev. Respir. Dis.* **1975**, *112*, 423.
(12) Lewis, R. A.; Drazen, J. M.; Austen, K. F.; Toda, M.; Brion, F.; Marfat, A.; Corey, E. J. *Proc. Natl. Acad. Sci. U.S.A.* **1981**, *78*, 4579.

0022-2623/85/1828-1847$01.50/0