fine needles: mp 148.5–149.5 °C. Anal. ($C_{16}H_{18}FNO_4$) C, H, N.

4-(2,5-Difluorophenyl)-1,2,3,6-tetrahydro-1-methylpyridine maleate (4) was prepared in a similar manner as 3 from 2 (2.3 g of the free base, 10 mmol). After 6 was removed by filtration, the aqueous filtrate was basified with concentrated ammonia and the liberated amine was extracted into ether. Treatment of the ether solution with ethereal maleic acid gave 1.6 g (50%) of 4, which was recrystallized from acetone–ether to give fine needles, mp 163–164 °C. Anal. ($C_{16}H_{17}F_2NO_4$) C, H, N.

1,3-Dihydro-1′-methyl-3-phenylspiro[benzo[*c*]thiophene-1,4′-piperidine] (21). Method C. A solution of sodium methylsulfinylmethide was prepared by heating 0.45 g of sodium hydride in 20 mL of anhydrous Me_2SO at 80–85 °C under N_2 for 30 min. The mixture was cooled to room temperature and to it, over 10–15 min, was added a solution of 5 (4.9 g of the free base, 15.6 mmol) in 10 mL of Me_2SO. The reaction mixture turned brownish red and, after stirring at room temperature for 1 h, it was poured onto 200 g of ice–water. The solid was filtered off, washed (H_2O), and air-dried. Recrystallization of the crude product from ether–hexane gave 3.1 g (67%) of **21** as colorless prisms. Properties of **21**, and of **22–34** prepared in a similar manner, are included in Table II.

1,3-Dihydro-1′-(phenoxycarbonyl)-3-phenylspiro[benzo[*c*]thiophene-1,4′-piperidine] (35). Method D. A mixture of **21** (2.3 g, 7.8 mmol), 1.4 g of phenyl chloroformate, and 0.5 g of sodium bicarbonate in 40 mL of CH_2Cl_2 was stirred at room temperature for 4 h. The inorganic salts were filtered, and the filtrate was washed with dilute NaOH (5%) and water and dried ($MgSO_4$). Removal of solvent under reduced pressure left an off-white solid, which was recrystallized from benzene–hexane to give 3.0 g (93%) of **35** as rosettes. Properties of **35**, and of **36–48** prepared in a similar manner, are included in Table II.

1,3-Dihydro-3-phenylspiro[benzo[*c*]thiophene-1,4′-piperidine] (49). Method E. A mixture of **35** (3.0 g, 7.5 mmol) and 8.5 g of 85% potassium hydroxide pellets in 50 mL of ethylene glycol was stirred at 155 °C for 30 min. The mixture was cooled, diluted with water, and extracted 3 times with $CHCl_3$ (100-mL portions). The combined organic solution was washed exhaustively with H_2O (to remove ethylene glycol) and dried over K_2CO_3. Removal of solvent under reduced pressure left a solid residue which was recrystallized from acetone–hexane to give 1.95 g (94%) of **49**. Properties of **49**, and of **50–61** prepared in a similar manner, are included in Table II.

Antagonism of Tetrabenazine-Induced Ptosis in Mice.[12] The test compound was administered per os or by intraperitoneal injection (ip) to male mice (Charles River CD-1), weighing 20 to 30 g, in groups of five. Tetrabenazine methansulfonate (40 mg/kg, ip) was administered 30 min after ip or 60 min after po administration, and after another 30 min the mice were placed in individual containers. Ptosis was then evaluated on a three-point scale: eyes closed = 2; eyes half-opened = 1; eyes open = 0. A linear-regression analysis of the ptosis scores was used to compute ED_{50} values and 95% confidence intervals.

5-Hydroxytryptophan Potentiation in Rats.[13a,b] Groups of six male Wistar rats weighing 150–200 g were used in this test procedure. Four hours prior to testing, pargyline hydrochloride was prepared and administered by subcutaneous injection at 75 mg/kg in 1% saline and at a dosage volume of 1.25 mL/kg. Thirty minutes before testing, drugs were prepared (distilled water and a few drops of Tween 80) and administered intraperitoneally at a dosage volume of 10 mL/kg. L-5-Hydroxytryptophan (1.0 mg/kg, ip) was administered in volumes proportional to 10 mL/kg, and 5 min after 5-HTP administration the animals were observed for 15 min. A compound was considered to potentiate 5-HTP activity if the animals exhibited head twitching accompanied by course tremors. Potentiation was expressed as normalized percent potentiation relative to vehicle control. Dose-range studies were performed in a similar manner, except that 10 animals per dose group were tested. ED_{50} values were calculated by a linear-regression analysis and presented with 95% confidence limits.

Physostigmine Lethality in Mice. Groups of ten male (Charles River CD-1) mice weighing 18–25 g were administered the test compound (ip or po) at the dosage volume of 10 mL/kg. Control group received vehicle (distilled water and a few drops of Tween 80). At 30, 60, and 120 min after administration of the test compound, an injection of physostigmine sulfate at 2.5 mg/kg, ip, was given to the individual animals. One hour after physostigmine administration, the drug group was checked for deaths. Surviving mice were considered protected. The time period with the greatest protection was the peak time of drug activity. A dose-range study was performed in a similar manner, except that all animals were tested at the peak time of drug activity and five groups of ten animals were employed (four drug groups and one vehicle control). ED_{50} values were calculated by a linear-regression analysis and presented with 95% confidence limits.

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(12) Binesova, O.; Nahunek, K. *Psychopharmacologia* 1971, 20, 337.

(13) (a) Shtee, L.; Saarnivaara, L. *J. Pharm. Pharmacol.* 1971, 23, 495. (b) Douglas, W. W. "The Pharmacological Basis of Therapeutics", Goodman, L. S.; Gilman, A., Eds.; McMillan: New York, 1975; p 613.

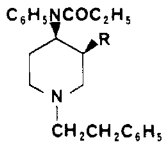
Synthesis and Stereochemistry of 7-Phenyl-2-propionanilidobenzo[*a*]quinolizidine Derivatives. Structural Probes of Fentanyl Analgesics

Bruce E. Maryanoff,* David F. McComsey, Russell J. Taylor, Jr., and Joseph F. Gardocki

Departments of Chemical, Biochemical, and Pharmacological Research, McNeil Laboratories, Fort Washington, Pennsylvania 19034. *Received May 9, 1980*

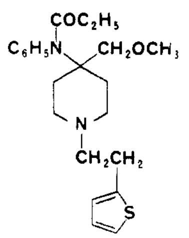
The four diastereomers of *N*-(1,3,4,6,7,11b-hexahydro-7-phenyl-2*H*-benzo[*a*]quinolizin-2-yl)-*N*-phenylpropanamide (**7c**, **7d**, **9c**, and **9d**), which are conformationally restricted analogues of fentanyl, were synthesized and separately tested for analgesic activity and affinity for the opiate receptor of rat brain. Stereochemical assignments for **7c**, **7d**, **9c**, and **9d** were deduced from NMR spectral analyses. Conformational analysis revealed that the 2α isomers (**7d** and **9d**) exist in solution as mixtures of cis- and trans-fused conformers with ca. 90 and 45% cis form, respectively. Other compounds (**12a**, **12b**, and 14) related to these propionanilides were also prepared, stereochemically characterized, and tested. Weak analgesic activity was observed for **7d**, and both **7d** and **9d** bound to the opiate receptor with an I_{50} of ca. 1100 and 1500 nM, respectively (ca. 0.5% of fentanyl and 2% of morphine). The analgesic activity of **7d** was abolished by the opiate antagonist naloxone.

The 4-propionanilidopiperidines represent a class of potent, morphine-like analgesics.[1–4] Fentanyl (**1a**),[2] its *cis*-(+)-3-methyl analogue (**1b**),[3a] and sufentanil (**2**)[4] are typical structures of this series with potent analgesic



1a R = H

1b R = CH_3



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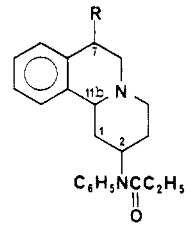


3a R = H

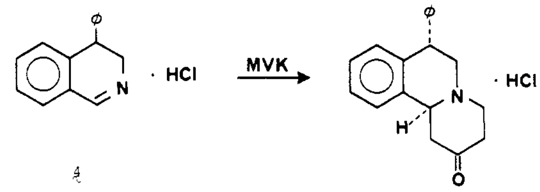
3b R = C_6H_5

properties. Beginning with the prototype, fentanyl (**1a**), structure–activity relationships (SAR) have mainly addressed the effect of substituents on the 2, 3, and 4 positions of the piperidine ring[3,4] and variation of the *N*-alkyl,[5a,b] *N*-phenyl,[5c] or *N*-acyl[2b] groups. Many of these changes retained or enhanced analgesic activity. On the contrary, conformational restriction of the propionanilide moiety, by connection of the acyl and phenyl portions[6a] or by connection of the phenyl and piperidine rings,[6b] abolished analgesic properties.

Given the loss of antinociceptive activity with conformational restriction at the propionanilide portion of **1a**, we became interested in conformational restriction of the piperidine nitrogen substituent. As a test system, we first considered benzo[*a*]quinolizidine **3a**, a structure which imposes a syn conformation on the 2-phenethyl moiety. The cis and trans isomers of **3a** had already been studied, and no analgesic activity was reported for either isomer.[7,8] One may argue that the lack of activity for **3a** is reasonable, since the more prevalent disposition of the 2-phenethyl side chain in fentanyl is expected to be the extended, anti conformation and/or since α substitution of the piperidine ring in fentanyl is known to attenuate activity.[3b] Thus, we decided to explore the effect of introducing a phenyl group into the 7 position of **3a** (viz., **3b**). This article describes the synthesis, stereochemistry, and biological properties of the four diastereomers of **3b**, which possess an extended, conformationally restrained phenethyl group, and of some compounds related to **3b**. The new compounds were evaluated for their analgesic and opiate-receptor binding properties in comparison to **1a**.

Results and Discussion

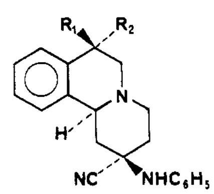
Chemistry. Amino ketone **5** was prepared from imine salt **4** and methyl vinyl ketone (MVK).[9] This condensa-



4 → 5·HCl

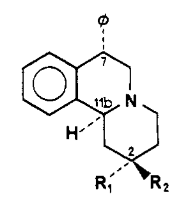
tion was completely stereoselective, giving the 7α,11bα relative configuration (see Stereochemistry Subsection). Preparation of the *N*-phenylimine of ketone **5** under typical conditions[3a,7a] worked in good yields, as judged by $NaBH_4$ reduction to anilines, but a mixture of all four diastereomeric anilines (**7a**, **7b**, **9a**, and **9b**) was obtained. Evidently, epimerization of the 7,11b positions had taken place during anil formation (see below).

Alternatively, ketone **5**·HCl was allowed to react with aniline and KCN in methanol to give only two anilinonitriles. However, the two diastereomers had structures **6a** and **6b** because of epimerization of the 7,11b positions



6a R_1 = H; R_2 = C_6H_5

6b R_1 = C_6H_5; R_2 = H



(7α,11bα SERIES)

7a R_1 = H; R_2 = C_6H_5NH

7b R_1 = C_6H_5NH; R_2 = H

7c R_1 = H; R_2 = $C_6H_5NC(O)C_2H_5$

7d R_1 = $C_6H_5NC(O)C_2H_5$; R_2 = H

but, interestingly, cyanide addition to the imine double bond was highly stereoselective. Subsequent elimination of hydrogen cyanide[10] with potassium *tert*-butoxide, followed by $NaBH_4$ reduction, again furnished a mixture of four diastereomeric anilines.

Reaction of $(C_6H_5)_3As{=}NC_6H_5$[11] with ketone **5** gave no desired anil.

Reductive amination of **5** by the procedure of Borch and co-workers[12] led not only to epimerization problems (which were anticipated), but also to significant formation of alcohol byproducts. Usually, the reduction of ketones to alcohols with $NaBH_3CN$ is much slower than reductive amination.[12] Modification of the Borch procedure (see Experimental Section), after much experimentation, reduced the undesired side reactions to a suitable minimum. By this optimized process, a mixture of two anilines, **7a** and **7b** (ca. 1:1 ratio), was obtained in good yield, and the mixture was propionylated (eq 1). Diastereomeric anilides

$$\mathbf{5} \xrightarrow[\text{NaBH}_3\text{CN},\ \text{H}^+]{\text{C}_6\text{H}_5\text{NH}_2} \mathbf{7a} + \mathbf{7b} \xrightarrow{\text{C}_2\text{H}_5\text{C(O)Cl}} \mathbf{7c} + \mathbf{7d} \qquad (1)$$

7c and **7d** were separated by fractional recrystallization (Table I).

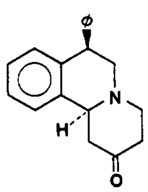
(1) P. A. J. Janssen and C. A. M. Van der Eycken in "Drugs Affecting the Central Nervous System", A. Burger, Ed., Marcel Dekker, New York, 1968, pp 51–54.
(2) (a) P. A. J. Janssen, *Br. J. Anaesth.*, **34**, 260 (1962); J. F. Gardocki, J. Yelnosky, W. F. Kuehn, and M. Gunster, *Toxicol. Appl. Pharmacol.*, **6**, 593 (1964); (b) P. A. J. Janssen, U.S. Patent 3 164 600 (1965).
(3) (a) W. F. M. Van Bever, C. J. E. Niemegeers, and P. A. J. Janssen, *J. Med. Chem.*, **17**, 1047 (1974); (b) T. N. Riley, D. B. Hale, and M. C. Wilson, *J. Pharm. Sci.*, **62**, 983 (1973); (c) T. N. Riley and J. R. Bagley, *J. Med. Chem.*, **22**, 1167 (1979).
(4) P. G. H. Van Daele, M. F. L. De Bruyn, J. M. Boey, S. Sanczuk, J. T. Agten, and P. A. J. Janssen, *Arzeim.-Forsch.*, **26**, 1521 (1976); W. F. M. Van Bever, C. J. E. Niemegeers, K. H. L. Schellekens, and P. A. J. Janssen, *ibid.*, **26**, 1548 (1976).
(5) (a) A. F. Casey, M. M. A. Hassan, A. B. Simmonds, and D. Staniforth, *J. Pharm. Pharmacol.*, **21**, 434 (1969); (b) P. A. J. Janssen, U.S. Patent 3 171 838 (1965); (c) A. Burkarts-Maier and E. Mutschler, *Arch. Pharm.*, **311**, 843 (1978).
(6) (a) W. Klein, W. Back, and E. Mutschler, *Arch. Pharm.* (*Weinheim, Ger.*), **308**, 910 (1975); *ibid.*, **307**, 360 (1974); (b) J. G. Berger, F. Davidson, and G. E. Langford, *J. Med. Chem.*, **20**, 600 (1977).
(7) (a) J. W. Van Dyke, Jr., H. J. Havera, R. D. Johnson, H. Vidrio, and A. Viveros, *J. Med. Chem.*, **15**, 91 (1972); (b) H. Vidrio, A. Viveros, and R. Vargas, *Arzeim.-Forsch.*, **21**, 941 (1971); (c) J. W. Van Dyke, Jr., U.S. Patent 3 634 431 (1972).
(8) However, the trans isomer of **3a** exhibited interesting antihypertensive activity.[7]
(9) R. Unger and H. Müller-Calgan, U.S. Patent 3 553 218 (1971); R. Unger, S. Sommer, E. Schorscher, and H. Müller-Calgan, U.S. Patent 3 393 198 (1968).
(10) J. S. Walia, L. Heindl, H. Lader, and P. S. Walia, *Chem. Ind.* (*London*), 155 (1968).
(11) P. Froyen, *Acta Chem. Scand.*, **27**, 41 (1973).
(12) R. F. Borch, M. D. Bernstein, and H. D. Durst, *J. Am. Chem. Soc.*, **93**, 2897 (1971).

Table I. Physical Properties and Biological Testing Data

compd	mp, °C[a]	formula[b]	Ach ED_{50}[c]	Haff[d]	binding I_{50}, nM[e]	LD_{50}, mg/kg[f]
7c	204-206	$C_{28}H_{30}N_2O$	>300		27500	>1000
7d	180.5-182	$C_{28}H_{30}N_2O$	10.8[g]	300[h]	1150[i]	~1000
9c	257-262	$C_{28}H_{30}N_2O{\cdot}HCl$	~100		20900	~300
9d	180-182	$C_{28}H_{30}N_2O$	~100		1480	~1000
12a	182-184	$C_{29}H_{32}N_2O$	>100		>100000	>1000
12b	211.5-215	$C_{29}H_{32}N_2O$	~75		100000	>1000
14	193.5-195	$C_{28}H_{28}N_2O$	>100		10500	>1000
fentanyl (1a)			0.4[j] (0.03 sc)	7.0[k] (0.5 sc)	8.0	62 sc
morphine			0.8 sc[l]	16 sc[m]	22[n]	530 sc
trans-3a					100000	
cis-3a	157.5-158				60000	
16	110-111		>100		24000	~650

[a] Corrected. [b] All new compounds were analyzed for C, H, and N, giving analytical values within ±0.3 of theory. [c] Acetylcholine writhing assay, ED_{50} (mg/kg); po unless otherwise noted; virtual inactivity is 100 mg/kg or higher. [d] Haffner tail-clip assay, ED_{50} (mg/kg); po unless otherwise noted. [e] Opiate-receptor binding assay (rat brain); concentration (nM) required to displace [^{3}H]naloxone by 50%. [f] po administration unless otherwise noted. [g] 95% confidence interval was 8.8-13.2. Subcutaneous administration gave a minimum active dose of only 50 mg/kg. [h] Inactive ip or sc. [i] I_{50} 5010 in the presence of 100 nM sodium ion; +Na/−Na = 3.5. [j] 95% confidence limits: 0.19-1.04. [k] 95% confidence limits: 4.3-11.4. [l] 95% confidence limits: 0.53-1.12. [m] 95% confidence limits: 11.3-23.1. [n] I_{50} 2130 in the presence of 100 nM sodium ion; +Na/−Na = 29.

When ketone **5** was heated in toluene at reflux with a trace of *p*-toluenesulfonic acid, epimerization occurred, affording an ca. 1:1 mixture of ketones **5** and **8**.[13,14] A sample of pure **8** was obtained by preparative high-performance LC. Reaction of **8** in our optimized reductive-amination process (modified Borch procedure) unfortunately resulted in a mixture of four anilines. Since use of pure **8**, which is apparently more sensitive to epimerization



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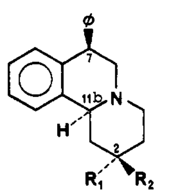


(7β,11bα SERIES)

9a R1 = H; R2 = C6H5NH

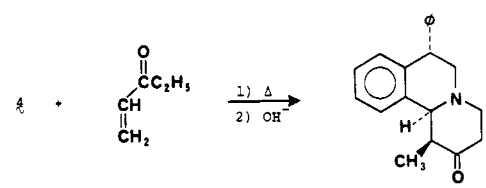
9b R1 = C6H5NH; R2 = H

9c R1 = H; R2 = C6H5NC(O)C2H5

9d R1 = C6H5NC(O)C2H5; R2 = H

than **5**, was not advantageous, we performed the reductive-amination reaction on the equilibrium mixture of epimeric ketones (ca. 1:1 ratio of **5** and **8**). The product, formed in excellent yield, contained all four anilines with 7β (**9a**, **9b**) to 7α (**7a**, **7b**) epimers in a ratio of 2:3 (GLC). Aniline **7b** was cleanly separated as a cyclohexylsulfamic acid salt by crystallization. The remaining three isomers were subjected to preparative high-performance LC to give a mixture of **9a** and **9b** and a sample greatly enriched in **7a**. The mixture (**9a** and **9b**) was propionylated and **9d** was separated by crystallization (Table I). The fourth isomer, **9c**, was isolated from the mother liquors as a hydrochloride salt (Table I).

Methylated analogues of **7** and **9** were also prepared (eq 2). Condensation of **4** with ethyl vinyl ketone gave a single



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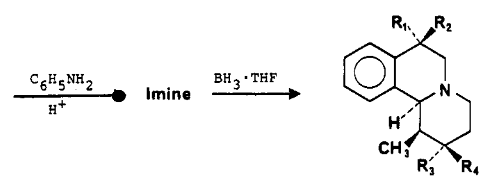
(2)



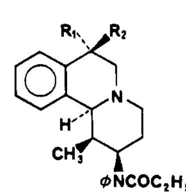
11

a R1 = C6H5; R2 = R4 = H; R3 = C6H5NH

b R1 = C6H5; R2 = R3 = H; R4 = C6H5NH

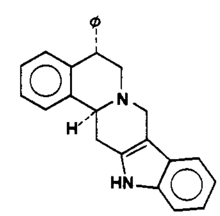
c R1 = R4 = H; R2 = C6H5; R3 = C6H5NH

d R1 = R3 = H; R2 = C6H5; R4 = C6H5NH



12a R1 = H; R2 = C6H5

12b R1 = C6H5; R2 = H



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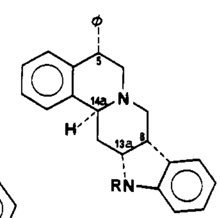


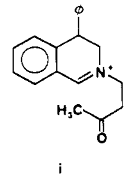
14a R = H

14b R = C(O)C2H5

diastereomer, **10**·HCl. The predominance of the 1β,11bα arrangement derives from severe steric interactions between the 1-methyl and fused benzene ring in the 1α,11bβ isomer.[15] Ketone **10** would not undergo reductive ami-

(13) Thus, the synthesis of only **5**·HCl in the MVK condensation is probably due to kinetic stereoselectivity, **5**·HCl being much less soluble in the reaction medium that **8**·HCl.

(14) The epimerizations observed for ketones **5** and **8** are acid catalyzed and probably proceeded by a reversed Mannich mechanism, **5** ⇄ **i** ⇄ **8**. For analogous observations see: H.



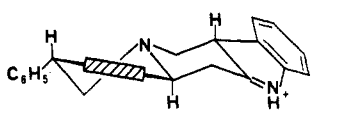
i

T. Openshaw and N. Whittaker, *J. Chem. Soc.*, 1461 (1963); W. Oppolzer, H. Hauth, P. Pfaffli, and R. Wenger, *Helv. Chim. Acta*, **60**, 1801 (1977).

(15) A. Buzas, F. Cossais, J. P. Jacquet, L. Novak, and C. Z. Szantay, *J. Heterocycl. Chem.*, **11**, 175 (1974); A. Buzas, R. Cavier, F. Cossais, J.-P. Finet, J.-P. Jacquet, G. Lavielle, and N. Platzer, *Helv. Chim. Acta*, **60**, 2122 (1977).

nation in our modified Borch procedure. Consequently, the anil was prepared despite the expected epimerization, which could scramble the relative stereochemistry of all three asymmetric centers. Reduction (BH_3·THF) of the anil afforded a mixture of four (of eight possible) diastereomeric anilines (**11a–d**), highly enriched in just two, **11b** and **11d**. Propionylation of this mixture, and subsequent fractional crystallization, gave **12a** and **12b** (Table I).

We also synthesized a compound with conformational rigidity at both the propionanilide and N-substituent segments of the fentanyl molecule (**14b**). Reaction of ketone **5** with phenylhydrazine, followed by treatment with polyphosphoric acid (PPA), generated one isomeric indole **13**, favored because of vicinal steric interactions in the alternative indole and location of the double bond opposite to the 6,6 ring fusion.[16] Reduction of indole **13** with borane–tetrahydrofuran (THF) and trifluoracetic acid (TFA)[17] gave one of three possible diastereomers in excellent yield. The indoline had the 8β,13aβ configuration (**14a**), so the reduction occurred cis as expected.[17] The 8β,13aβ stereochemistry derives from an equatorial preference for the phenyl bond (after protonation of **13**) and equatorial attack at the iminium carbon in **15**. Propionylation of indoline **14a** supplied **14b** (Table I).



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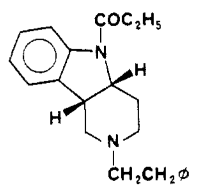
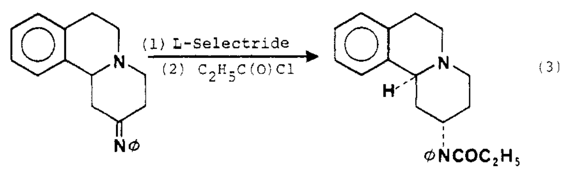


16

cis-Indoline **16**, described by Berger et al.,[6b] was obtained by reduction of the corresponding indole using borane–THF in TFA, followed by propionylation. *cis*-**3a** (2α,11bα)



was prepared by a 100% stereoselective reduction of anil **17**[7a] using lithium tri-*sec*-butylborohydride,[18] followed by propionylation (eq 3). A sample of *trans*-**3a** (2β,11bα) was obtained through the courtesy of Miles Laboratories.

Stereochemistry and Conformational Analysis. Configurational assignments for the 7 and 11b stereocenters in the 7-phenylbenzo[*a*]quinolizidine stuctures were established with the starting ketones **5** and **8**. Both ketones may assume one trans- and two cis-fused quinolizidine conformations (cf. eq 4), readily interconvertible under normal conditions.[19] The trans-fused quinolizidine conformer (Figure 1) will be strongly preferred in solution,

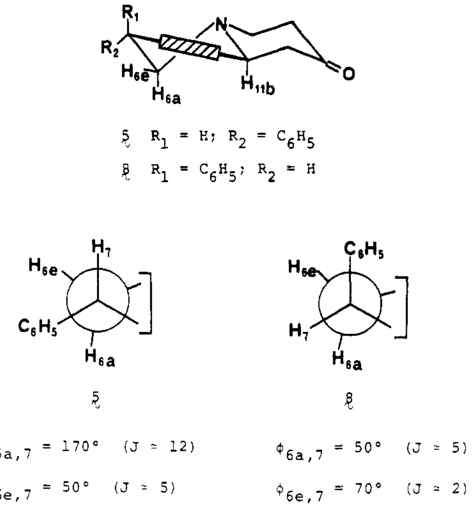


Figure 1. Preferred conformation of ketones **5** and **8**.

since structural features disfavoring this form are not present in **5** or **8**.[15,16,19,20] Examination of molecular (Dreiding) models supported the validity of this preliminary analysis. Furthermore, prominent absorption ("Bohlmann") bands in the IR spectrum (CCl_4) of **5** at 2745 and 2800 cm^{-1} and of **8** at 2755 and 2805 cm^{-1} indicated the prevalence of the trans-fused conformers in solution.[19]

With the preliminary conformational analysis in hand, configurational assignments for **5** and **8** were made by ^1H NMR spectrosocpy. Dreiding models furnished approximate dihedral angles for the C_6–C_7 segment (Figure 1, Newman projections), which assisted in relating the vicinal proton–proton coupling constants to structure.

The 90-MHz ^1H NMR spectrum of **5** in $CDCl_3$ exhibits a broadened doublet of doublets at δ 3.73 (H_{11b}) and a broadened doublet of doublets at δ 4.42 (H_7). Irradiation of the aromatic region at δ 7.15 sharpened these signals by eliminating "benzylic" coupling. Accordingly, the resonance at δ 3.7 clearly appeared as a doublet of doublet of doublets with J = 11.8, 3.3, and 1.3 Hz, and the resonance at δ 4.4 appeared as a doublet of doublet of doublets with J = 10.7, 5.3, and 1.3 Hz.[21] Irradiation of the downfield resonance (at δ 4.3) resulted in sharpening of the signal at δ 3.7, due to loss of J = 1.3 Hz,[21] and collapse of certain lines in the upfield aliphatic multiplet between δ 2.3 and 3.3. The splitting patterns for these decoupled, upfield aliphatic protons defined the AB portion of an ABX spin system, representing H_{6a} and H_{6e} (see Figure 1): δ 2.60 (J = 11.3 and 11.3 Hz) and 3.15 (J = 11.3 and 5.5 Hz), respectively. The vicinal coupling constants between protons on the C_6–C_7 unit correspond by the Karplus relation[22a] to dihedral angles, which are consistent with those derived from Drieding models (Figure 1), es-

(16) S. Gerszberg, P. Cueva, and A. R. Frasca, *An. Asoc. Quim. Argent.*, **60**, 331 (1972); *Chem. Abstr.*, **78**, 42785 (1973).
(17) B. E. Maryanoff and D. F. McComsey, *J. Org. Chem.*, **43**, 2733 (1978).
(18) We were able to employ this stereoselective reduction with L-Selectride to obtain directly **7b** and **9b** free of the 2β anilines (**7a** and **9a**). However, application of this reduction to the anil from **10** resulted in no reaction. (See paragraph at the end of this paper regarding supplementary material.)
(19) (a) M. Uskokovic, H. Bruderer, C. von Planta, T. Williams, and A. Brossi, *J. Am. Chem. Soc.*, **86**, 3364 (1964); (b) G. W. Gribble and R. B. Nelson, *J. Org. Chem.*, **38**, 2831 (1973).
(20) The nitrogen-containing ring of the tetrahydroisoquinoline fragment is reasonably assumed to prefer a half-chair conformation. See, e.g., (a) T. Kametani, K. F. Kumoto, M. Ihara, A. Ujiie, and H. Koizumi, *J. Org. Chem.*, **40**, 3280 (1975); (b) B. R. Lowry and A. C. Huitric, *ibid.*, **37**, 1316 (1972).
(21) One should take note of the relatively large long-range coupling ($^5J_{HH}$) between H_7 and H_{11b} in **5**, which can characterize the 7α,11bα relative configuration [A. C. Huitric, B. R. Lowry, A. E. Weber, J. E. Nemorin, and S. Sternhell, *J. Org. Chem.*, **40**, 965 (1975)]. Huitric et al. reported an ca. 1.8-Hz stereospecific homobenzylic coupling in a similar system, between trans pseudoaxial protons.
(22) (a) L. M. Jackman and S. Sternhell, "Applications of NMR Spectroscopy in Organic Chemistry", 2nd ed., Pergamon Press, London, 1969; (b) R. E. Sievers, Ed., "Nuclear Magnetic Resonance Shift Reagents", Academic Press, New York, 1973.

Table II. ^{1}H NMR Coupling Constants[a]

compd	$^3J_{6a,7}$	$^3J_{6e,7}$	$^2J_{6a,6e}$	$^5J_{7,11b}$	$^3J_{1a,11b}$	$^3J_{1e,11b}$
5[b]	10.7-11.3	5.3-5.5	11.3	1.3	11.8	3.3
8[b]	3.0-3.3	4.0-4.3	~11	0	11.7	3.1-3.3
7c[c]	10-11	5	11-12		11	~2
7d[c]	11.5	6.5	13		~4	~2
9c[d]	3.5	4.5			12	2
9d	4	6	12		6 (or 5)	5 (or 6)
12a	11	5-6	11			1-2
12b	2 (or 3)	3 (or 2)				1-2

[a] Absolute values in hertz. From 90-MHz spectra unless otherwise noted. [b] Precise values from expanded spectrum. [c] From 270-MHz spectra (see paragraph at end of paper regarding supplementary material). [d] 60 MHz.

Table III. ^{1}H NMR Chemical Shifts[a]

compd	H_{1e}	H_2	H_{6a}	H_{6e}	H_7	H_{11b}
5			2.60	3.15	4.42	3.73
8			3.0/3.1		4.17	3.58
7c	~2.4	5.03	~2.6	~3.0	4.30	3.51
7d	~2.7	4.67	3.13	3.27	4.32	4.39
9c		~5.0	2.9		4.07	3.48
9d	~2.3	4.94	2.84	3.08	3.92	3.49
12a	3.42	4.65	2.5	2.9	4.25	3.63
12b	3.46	4.63	~2.8		3.97	3.43

[a] In parts per million downfield from Me_4Si ($CDCl_3$ solutions).

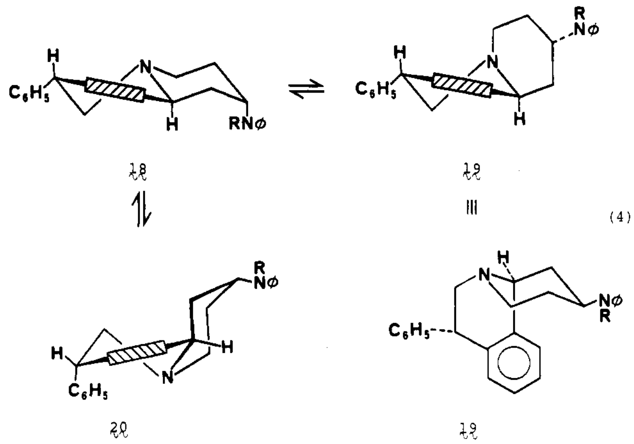
tablishing the 7α,11bα stereochemistry. A lanthanide-induced shift (LIS) study conducted with $Eu(fod)_3$[22b] rendered an almost complete analysis of the aliphatic protons of **5**, bolstering the configurational assignment (see paragraph at the end of this paper regarding supplementary material).

The 90-MHz ^{1}H NMR spectrum of **8** in $CDCl_3$ exhibits a broadened doublet of doublets at δ 3.58 (H_{11b}), J = 12 and 3 Hz, and a broadened triplet at δ 4.17 (H_7), J = 5 and 3 Hz (cf. Figure 1). Homonuclear decoupling experiments analogous to those performed with **5**, supplied additional spectral data (Table II) needed to affirm the 7β,11bα stereochemical assignment. A long-range coupling between H_7 and H_{11b} was not observed.[21]

The ketone equilibration experiment, mentioned earlier, shows that **5** and **8** have approximately the same thermodynamic stability. This result suggests that the free-energy difference (ΔG°) between a pseudoequatorial and pseudoaxial 7-phenyl substituent in the benzo[a]quinolizidin-2-one system (Figure 1) is negligible.

Ketones stereochemically related to **5** and **8** have been described in the syntheses of taclamine and butaclamol.[23] ^{1}H NMR coupling data led to analogous configurational assignments, which have been unambiguously confirmed by an X-ray crystallographic study on butaclamol.[23b]

The presence of new asymmetric centers at C_2 in **7** and **9** and at C_1 and C_2 in **11** and **12** necessitates additional stereochemical assignments. ^{1}H NMR spectral data (90 MHz) for aniline **7a** indicated pseudoequatorial 7-phenyl and equatorial 2-anilino substituents [H_7: δ 4.40 (J = 12 and 6 Hz); H_2: δ 3.4–3.9 ($w_{1/2}$ = ~35 Hz)], and data (90 MHz) for aniline **7b** indicated pseudoequatorial 7-phenyl and axial 2-anilino substituents [H_7: δ 4.42 (J = 12 and 6 Hz); H_2: δ 3.85 ($w_{1/2}$ = ~10 Hz)].[24] Both compounds strongly preferred a trans-fused quinolizidine conformation, as judged by Bohlmann bands and NMR resonances for H_{11b} [**7a**: δ 3.42 (J = ~11 and 2 Hz); **7b**: δ 3.70 (J = ~11 and 2 Hz)].[19] The axial 2-anilino group in **7b** did not impose sufficient strain to significantly populate a cis-fused quinolizidine.[25a] In eq 4, steric strain from the 2-axial



group in the trans-fused conformer **18** may be alleviated by conversion to conformer **19**, which is destabilized by an axial benzene group on a piperidine ring. The other cis-fused conformer **20**, which is unfavorable because of an axial *N*-alkyl group on the piperidine ring and two pseudoaxial substituents (7-phenyl and 11b-alkyl) on the tetrahydroisoquinoline, still retains the 2-axial group.[19,25b] Since the trans quinolizidine ring fusion is probably ~2.6 kcal/mol more stable than the cis ring fusion[19b] and since an anilino substituent probably has a conformational free energy (*A* value) of 1.0–1.1 kcal/mol,[25d] an axial anilino group (as in **7b**) will not induce a significant population of cis-fused conformer.[25b]

The corresponding propionylated compounds **7c** and **7d** showed different conformational properties. ^{1}H NMR data (60 and 270 MHz) for **7c** were consistent with the 2β,7α,11bα configuration with a trans-fused quinolizidine (see Tables II and III; Bohlmann bands at 2750 and 2800 cm^{-1}). The distinct resonance for H_2 was characteristic of

(23) (a) F. T. Bruderlein, L. G. Humber, and K. Pelz, *Can. J. Chem.*, **52**, 2119 (1974); F. T. Bruderlein, L. G. Humber, and K. Voith, *J. Med. Chem.*, **18**, 185 (1975); (b) P. H. Bird, F. T. Bruderlein, and L. G. Humber, *Can. J. Chem.*, **54**, 2715 (1976).

(24) (a) Approximate terminal values for $w_{1/2}$ are $w_{1/2}$ (ax H) = 30–34 Hz and $w_{1/2}$ (eq H) = 8–10 Hz. (b) Using these terminal values, one can *estimate* the amounts of cis- and trans-fused conformers according to the equation: % cis = $100[w_{1/2}(\text{observed}) - 9]/(32 - 9)$.

(25) (a) A compound related to **7b**, but lacking the 7-phenyl group, was suggested to populate both cis- and trans-fused conformations; however, no supportative data were supplied.[7a] (b) Conceivably, a nonchair (twist or boat) conformer could also serve to alleviate the strain of a 2-axial group in conformer **18**. However, the expected large free-energy difference between a nonchair and chair piperidine ring (>4 kcal/mol)[25c] and the lack of evidence for nonchair conformers in related compounds[19,26] diminishes the potential significance of nonchair forms. (c) G. M. Kellie and F. G. Riddell, *Top. Stereochem.*, 8, 225 (1974); M. Squillacote, R. S. Sheridan, O. L. Chapman, and F. A. L. Anet, *J. Am. Chem. Soc.*, **97**, 3244 (1975). (d) J. A. Hirsch, *Top. Stereochem.*, 1, 199 (1967).

an axial proton ($w_{1/2}$ = 30–31 Hz).[24] On the other hand, ^{1}H NMR data (270 MHz) for **7d** were indicative of a cis-fused conformer, namely, **19** (see Table II and III; *no* Bohlmann bands). Relief of strain from the axial propionanilido group outweighed the undesirable energetics associated with cis structure **19**. The isolated resonance for H_2 was again characteristic of an axial proton ($w_{1/2}$ = 29–30 Hz).[24] ^{1}H NMR data at 270 MHz for **7c** and **7d** permitted complete spectral analysis, affording chemical shifts and coupling constants for each aliphatic proton (see paragraph at end of paper regarding supplementary material). The vicinal coupling constants for **7c** and **7d** (270 MHz spectra) were completely consistent with the stereochemical assignments (**7c**/**7d**: $J_{1a,11b}$ = 11/4, $J_{1e,11b}$ = 2/2, $J_{1a,2}$ = 12/10, $J_{1e,2}$ = 2/2, $J_{2,3a}$ = 12/10, $J_{2,3e}$ = 2/2, $J_{3a,4a}$ = 12/12, $J_{3e,4a}$ = 2/2, $J_{3e,4e}$ = 2/2, $J_{6a,7}$ = 10.5/11.5, and $J_{6e,7}$ = 5/6.5 Hz); thus, a boat or twist (i.e., nonchair) conformation for the 4-propionanilidopiperidine ring, which would exhibit more averaged $^3J_{HH}$ values, is not prevalent.[25b] ^{13}C NMR spectral data for **7c** and **7d** (to be published elsewhere; available on request) reinforced the configurational and conformational assignments.[26]

Analogously, ^{1}H NMR data (90 MHz) for the 7β propionanilides **9c** and **9d** permitted structural assignments (Tables II and III). Also, ^{1}H NMR data for **9d** at 270 MHz (not shown) permitted a complete analysis of the aliphatic protons in **9d**, giving all of the coupling constants (double irradiation of H_2, H_{3a}, H_{4e}, and H_{11b}). The 2β,7β,11bα compound (**9c**) was exclusively trans-fused (Bohlmann bands at 2750 and 2800 cm^{-1}; $w_{1/2}$ for H_2 = ~32 Hz), but the 2α,7β,11bα analogue (**9d**) was not; **9d** was a mixture of trans-fused (Bohlmann bands at 2750 and 2805 cm^{-1}) and cis-fused ($w_{1/2}$ for H_2 = ~20 Hz).[24] Compound **9d** (~40–50% cis) does not favor a cis conformation as strongly as **7d** (~90% cis).[24] Distinguishing criteria for the conformational assignment of **9d** are as follows: (1) the chemical shifts for H_2 in **9c** and **9d** do not behave the same as the shifts in **7c** and **7d**; (2) the chemical shift of H_{11b} is not deshielded in going from **9c** to **9d**;[19] (3) the H_2 proton resonance for **9d** is a binomial pentet (1:4:6:4:1) with J = 6 Hz (average coupling) and $w_{1/2}$ is much smaller than that for an axial proton; (4) the two couplings between H_{11b} and H_1 for **9d** are not as small as those for **7d** (averaged values); (5) the four vicinal couplings between H_3 and H_4 (270-MHz spectrum) were averaged values. The ^{1}H NMR data for **9d** might also be interpreted in terms of a conformational equilibrium involving substantial amounts of nonchair piperidine conformations, but there is no compelling reason to promote this view.[25b] ^{13}C NMR data for **9c** and **9d** (to be published elsewhere; available on request) were consistent with the conformational analysis.[26] The apparent existence of **9d** as an ca. 55:45 mixture of trans- and cis-fused conformers in solution is explicable, in comparison with **7d** (trans/cis = 10:90), if one considers the 1,3-dipseudoaxial interactions (between the 5 and 7 positions) introduced into the tetrahydroisoquinoline segment of the cis conformer (**19**, with C_6H_5 and H exchanged on C_7).

We are not aware of any report of an *A* value for the propionanilide group or for a tertiary amide substituent. From our observations on **7c**/**7d** and **9c**/**9d** and from the analogous conformational behavior of 3-propionanilidotropanes,[3c,27a] the *A* value for the propionanilido group is probably in the range of 3.5–4.0 kcal/mol. The great steric requirement of the tertiary amide group, compared to a secondary amino group, is also illustrated by the conformational properties of fortimicins A and B.[27b]

^{1}H NMR data (90 MHz) for **12a** and **12b** (Tables II and III) and for **14b** (see Experimental Section, cf. ref 6b) were consistent with the configurational assignments. Amides **12a** and **12b** largely adopted trans conformations with equatorial 2-anilido groups ($w_{1/2}$ = 22 and 24 Hz, respectively; one large J is absent in each due to the axial CH_3 group). Indolinamide **14b** displayed a doublet of doublets for H_{14a} at δ 4.04 with J = 4 and 5 Hz, indicative mainly of a cis conformer which is not as predominant here as in **7d**. The 5α,8aβ,13aβ,14aα configurational assignment for **14b** was determined by analysis of the 90-MHz ^{1}H NMR spectrum of its indoline precursor **14a**, with the aid of homonuclear decoupling experiments (see Experimental Section).

Biological Evaluation. Antinociceptive activity for the propionanilides was assessed by employing the acetylcholine writhing test,[28] and active compounds were then tested in the Haffner tail-clip test[29] (Table I). Anilides **7c**, **9c**, **9d**, **12a**, **12b**, and **14** were weakly active in the writhing assay. By contrast, **7d** exhibited an ED_{50} of ~11 mg/kg (po) in this test (with activity falling off sharply for subcutaneous administration). The tail-clip assay showed weak but significant activity for **7d**. Both the antiwrithing and Haffner activity were eliminated by administration of the opiate antagonist naloxone. The analgesic activity of **7d** is much less than that demonstrated by fentanyl (4% of fentanyl, po).[30]

Since pharmacologic investigations with intact animals have intrinsic limitations (metabolism, pharmacodynamics, etc.) in structural correlations, we undertook a study of in vitro binding to opiate receptors. Opiate receptor affinities were determined by displacement of the radiolabeled ligand [^{3}H]naloxone from rat-brain homogenates, according to published methodology.[32] Affinities are

(26) G. W. Gribble, R. B. Nelson, J. L. Johnson, and G. C. Levy, *J. Org. Chem.*, **40**, 3720 (1975); Also, ref 20a.

(27) (a) J. R. Bagley and T. N. Riley, *J. Heterocycl. Chem.*, **14**, 599 (1977). For 3α- and 3β-propionanilidotropanes, the 3α isomer adopted a chair piperidine ring with an equatorial anilido group, but the 3β isomer largely adopted a nonchair piperidine conformation to relieve the strain of an otherwise bulky axial anilido group (chair–chair interconversion in this case was not possible). (b) R. S. Egan, R. S. Stanaszek, M. Cirovic, S. L. Mueller, J. Tadanier, J. R. Martin, P. Collum, A. W. Goldstein, R. L. DeVault, A. C. Sinclair, E. E. Fager, and L. A. Mitscher, *J. Antibiot.*, **30**, 352 (1977).

(28) H. O. J. Collier, L. C. Drunnen, C. A. Johnson, and C. Schneider, *Br. J. Pharmacol.*, **32**, 295 (1968).

(29) C. Bianchi and J. Franceschini, *Br. J. Pharmacol.*, **9**, 280 (1954).

(30) The compounds in Table I were tested for their effect on general behavior and for acute toxicity.[31] Behavioral effects were observed for approximately 1 h following intraperitoneal (ip) injection of several dose levels: 1, 3, 10, 30, 100, 300, and 1000 mg/kg. The estimated LD_{50} is based on the lethality count at 5 days following injection of the test compound. None of the compounds tested produced the characteristic gross behavioral profile observed with fentanyl or morphine in mice. Following ip doses of compounds **7c**, **12a**, and **12b** slight to moderate ataxia and decreased spontaneous motor activity were observed. Slight irritability to touch was seen following injection of compounds **7c**, **12a**, and **14**. No significant gross behavioral effects were seen at nonlethal doses of **9c** and **16**. Death, preceded by clonic convulsions, was observed within 15–30 min after ip or oral administration of **16** and within 90 min after ip injection of **9c**. The lethality observed following oral administration of **7d**, **9c**, and **9d** occurred 7 to 24 h after administration. Death, where observed, was attributed to respiratory depression.

(31) S. Irwin, *Psychopharmacologia*, **13**, 222 (1968).

presented as concentrations (nM) required for displacement of 50% of radioligand (Table I). Compounds **7c**, **9c**, **12a**, and **12b** had minimal binding properties, and **14** had a slight affinity for the receptor (0.08% of fentanyl). Anilides **7d** and **9d** successfully competed against [^{3}H]-naloxone with I_{50} values of ca. 1100–1500 nM [0.50–0.7% of fentanyl; 1.4–1.9% of (–)-morphine], weak but significant receptor affinities. Notably, the I_{50} values for these 2α,11bα diastereomers are independent of the C_7 stereochemistry, although pharmacologic activity is not (vide supra). The sodium/no sodium ratio for **7d** may reflect opiate agonist/antagonist character (Table I).[33]

For comparison purposes we also measured receptor affinities for *trans*-**3a**, *cis*-**3a**, and **16**,[34] which turned out to be relatively insignificant (Table I). Both **7d** and **9d** are configurationally related to *cis*-**3a** but differ structurally from *cis*-**3a** by a phenyl group on C_7. The 7-phenyl group is obviously important for binding to the opiate receptor, thus reinforcing the idea that an *anti*-2-phenethyl conformation in fentanyl and its congeners is the biologically active one.

The two compounds that bind to the opiate receptor, **7d** and **9d**, have a substantial proportion of cis conformer (see **19**; Stereochemistry Subsection) with an equatorial 2-anilido group (in $CDCl_3$). Further, **7d**, the compound which populates this form more strongly, almost exclusively, demonstrates analgesic activity. 4-Anilidopiperidines, such as fentanyl, strongly prefer chair conformers with the anilido group equatorial.[5a] However, an equatorial orientation for the 2-anilido group is not sufficient for activity in our series; we must also have the benzene ring α to the piperidine nitrogen in an axial orientation.

Our results serve to define SAR for fentanyl-type analgesics more completely. The reduction of activity for **7d** and **9d** relative to fentanyl may be related to steric crowding near the basic piperidine nitrogen, since 2-methylfentanyl shows greatly attenuated activity.[3b] The cis-fused conformation in **7d** and **9d** may be associated with a diminution of unfavorable steric interactions during complexation of the nitrogen binding site to the receptor. From our work, and the work of others,[3a,3c,6] it can be concluded that analgesic activity, or affinity for the opiate receptor, in the fentanyl series is very sensitive to stereochemical factors.

Experimental Section

General Procedures. Melting points were determined with a Thomas-Hoover melting point apparatus and are corrected. UV data were collected on a Cary 14 spectrophotometer. IR spectra were obtained using a Perkin-Elmer 521 or 283 spectrophotometer on free bases in KBr (pellets), unless otherwise noted. ^{1}H NMR spectra were measured with a Perkin-Elmer R-32 (90 MHz), (so noted) a Varian EM-360 (60 MHz), or Bruker HX-270 (270 MHz; performed at Florida State University) using $CDCl_3$ as solvent and $(CH_3)_4Si$ as an internal standard. NMR abbreviations used are as follows: s, singlet; d, doublet; t, triplet; dd, doublet of doublets; m, multiplet; ms, multiplets; br, broad. GLC analyses were performed on a Perkin-Elmer 3920B instrument (flame-ionization detector) equipped with a Hewlett-Packard Model 3352 data system and Hewlett-Packard 18652A A/D converter, employing an SE-30 glass column ($^1/_8$ in. × 6 ft, 3% SE-30 on Chromasorb Q). TLC separations were conducted using Analtech, Inc., silica gel GF 250-μm plates (visualized with UV and I_2 staining). Preparative high-performance LC separations were performed on a Waters Prep LC/System 500 instrument. Chemical microanalyses were determined by Atlantic Microlab, Inc., Atlanta, Ga.

3,4-Dihydro-4-phenylisoquinoline Hydrochloride (4). Styrene oxide (360 g, 3.0 mol) in 1500 mL of dimethylformamide was treated with benzylamine (516 g, 4.82 mol). The solution was heated at reflux for 15 h, cooled, and poured with stirring into a twofold volume of water. The mixture was filtered and the solid was mixed well with 500 mL of ether. An equal volume of petroleum ether (30–60 °C) was added and the pale yellow solid was collected by filtration. The yield of vacuum-dried α-[[(phenylmethyl)amino]methyl]benzenemethanol was 430 g (63%). A 5.0-g sample was recrystallized twice from methanol/ether to give white crystals (2.83 g), mp 101–102.5 °C (lit.[35] mp 102–103 °C).

Polyphosphoric acid (1 kg) was heated to 100 °C on a steam bath with mechanical stirring and the above amino alcohol (140 g, 0.705 mol) was added.[36] After 2 h at 100 °C, the reaction was cooled to about 50 °C and 800 mL of water was added slowly with stirring and ice-bath cooling. (The temperature was allowed to rise as high as 85 °C.) The mixture was cooled to 20 °C and a solution of KOH (530 g, 8.0 mol, 85% assay) in 450 mL of water was added slowly with stirring and ice-bath cooling (temperature kept under 45 °C). The precipitate was filtered, resuspended in 600 mL of water, and basified with 700 mL of 50% w/v aqueous KOH solution (cooling needed). To the cool solution was added 300 mL of ether, and the layers were separated. The aqueous layer was reextracted with 500 mL of CH_2Cl_2. The combined organic solutions were dried (Na_2SO_4) and concentrated to a viscous oil. Distillation afforded a 60–70% yield of colorless 1,2,3,4-tetrahydro-4-phenylisoquinoline (bp 145–150 °C) (0.6 torr).

The tetrahydroisoquinoline (42.1 g, 0.20 mole) was dissolved in dry CH_2Cl_2 (415 mL) and *N*-chlorosuccinimide (27.8 g, 0.21 mol) was added with stirring in portions over 15 min.[37] After 1.5 h, the mixture was washed with 3% HCl (210 mL) and then water (2 × 210 mL) and dried (Na_2SO_4). The solution was concentrated to about 175 mL (**not to dryness**) without application of heat (ambient water bath), cooled to 0–5 °C, and slowly treated with a solution of $NaOCH_3$ in methanol (from dissolution of 30 g of sodium in 350 mL of methanol), maintaining the temperature under 5 °C (30-min addition). After the solution was left standing for 45 min at room temperature, cracked ice (150 mL) was added. After the solution was stirred 30 min further, the layers were separated and the aqueous layer was extracted with 200 mL of CH_2Cl_2. The combined organic solutions were rinsed with 200 mL of saturated NaCl solution, dried (Na_2SO_4), and concentrated to a light brown oil (36 g). The dry oil was dissolved in anhydrous ether and treated with dry HCl gas. The solid was collected and recrystallized from a mixture of ethyl acetate and 2-propanol to furnish an off-white solid (30 g, 62%). Pure free base had mp 112–114 °C (from ether); ^{1}H NMR δ 3.8–4.3 (m, 3 H), 6.7–7.5 (m, 10 H, aromatic), 8.38 (s, H_1); UV (CH_3OH) λ_{max} 252 nm (ε 4890, sh), 257 (5100), 267 (3600, sh). Anal. Calcd for $C_{15}H_{13}N$: C, 86.92; H, 6.32; N, 6.76. Found: C, 86.71; H, 6.10; N, 6.94.

(7α,11bα)-1,3,4,6,7,11b-Hexahydro-7-phenyl-2*H*-benzo[*a*]quinolizin-2-one (5). Isoquinoline hydrochloride (**4**; 59.0 g, 0.242 mol) and methyl vinyl ketone (100 g, 1.43 mol) were combined and heated at reflux on a steam bath for 1.5 h. Acetone (25 mL) was added to the cooled reaction mixture and light tan, crystalline ketone **5**·HCl (59.5 g, 78.5%) was filtered, mp 190–195 °C (lit.[9] mp 211 °C). Free base **5** was recrystallized from acetone or methanol: mp 139–140 °C (lit.[9] mp 138 °C); ^{1}H NMR δ 2.3–3.4 (ms, 8 H, aliphatic), 3.74 (dd, H_{11b}), 4.44 (dd, H_7), 6.8–7.4 (m, 9 H, aromatic); IR ν_{max} 2805/2740 (Bohlmann bands), 1715 (C=O) cm^{-1}.

(32) G. W. Pasternak, H. A. Wilson, and S. H. Snyder, *Mol. Pharmacol.*, 11, 340 (1975); C. B. Pert and S. H. Snyder, *Proc. Natl. Acad. Sci. U.S.A.*, **70**, 2243 (1973).
(33) C. B. Pert and S. H. Synder, *Mol. Pharmacol.*, **10**, 868 (1974).
(34) Berger et al.[6b] were tempted to conclude that the lack of analgesic activity for **16** indicated the importance of stereochemical factors for activity in the fentanyl series. However, they noted that absorption, distribution, and metabolism could interfere with the SAR. Our opiate receptor binding data for **16** lay their doubts to rest.
(35) C. L. Browne and R. E. Lutz, *J. Org. Chem.*, 17, 187 (1952).
(36) T. J. Schwan, G. S. Lougheed, and S. E. Burrows, *J. Heterocycl. Chem.*, 11, 807 (1974), and references cited therein.
(37) J. Parello, *Bull. Soc. Chim. Fr.*, 1117 (1968); G. Ehrhart, *Chem. Ber.*, **88**, 883 (1955).

(7β,11bα)-1,3,4,6,7,11b-Hexahydro-7-phenyl-2*H*-benzo[*a*]quinolizin-2-one (8). Ketone 5 (42.0 g, 0.152 mol) was dissolved in 300 mL of toluene containing 0.5 g of *p*-toluenesulfonic acid, and the reaction was refluxed for 5.25 h. The solution was cooled rapidly by submersion ice-water, washed with cold 1 N NaOH, dried (K_2CO_3), and evaporated in vacuo to an oil (38.7 g) containing equal amounts of 5 and 8: TLC [ethyl acetate/heptane (1:1)] R_f 0.51 and 0.59. Ketone 8 was isolated using preparative high-performance LC [ethyl acetate/petroleum ether (1:2)] and recrystallized from acetone to give white crystals: mp 122.5–124 °C; ^{1}H NMR δ 2.1–3.2 (ms, 8 H, aliphatic), 3.68 (dd, H_{11b}), 4.17 (dd, H_7), 6.8–7.3 (m, 9 H, aromatic); IR ν_{max} 2805/2755/2710 (Bohlmann bands), 1718 (C=O) cm^{-1}. Anal. Calcd for $C_{19}H_{19}NO$: C, 82.28; H, 6.90; N, 5.05. Found: C, 82.14; H, 6.97; N, 5.03.

***N*-(2α,7α,11bα)- and *N*-(2β,7α,11bα)-(1,3,4,6,7,11b-Hexahydro-7-phenyl-2*H*-benzo[*a*]quinolizin-2-yl)-*N*-phenylpropanamide (7d and 7c).** Ketone 5 (34.6 g, 0.125 mol) was dissolved in 500 mL of dry THF containing 25 g of molecular sieves (Linde 4A). Aniline hydrochloride (17.5 g, 0.135 mol) was added, the mixture was cooled to ca. 0 °C, and $NaCNBH_3$ (7.85 g, 0.125 mol) was added slowly. After 30 min, 250 mL of H_2O was added; the solution was brought to pH ~2 by the addition of 12 M HCl, made alkaline (pH 12) by addition of 50% NaOH, and extracted with $CHCl_3$. The organic solution was washed with H_2O, dried (K_2CO_3), and evaporated in vacuo to furnish a mixture (ca. 3:2, GLC) of anilines 7a and 7b (42.7 g, 96%).[38] To this mixture of anilines (34.7 g, 0.098 mol) in 500 mL of dry CH_2Cl_2 was added propionyl chloride (10.2 g, 0.11 mol) in 25 mL of CH_2Cl_2 with ice-bath cooling. After the reaction stirred at room temperature for 16 h, the precipitate was filtered off and the filtrate was washed with 1 N NaOH, dried (K_2CO_3), and evaporated in vacuo to afford a mixture of propionanilides 7c and 7d (30.0 g, 75%). Crystallization of this mixture from acetonitrile gave 7c (8.5 g, 21%), recrystallization of which from ethyl acetate gave white crystals: mp 204–206 °C; ^{1}H NMR see text; IR ν_{max} 2820/2770 (Bohlmann bands), 1655/1650 (C=O) cm^{-1}. Anal. Calcd for $C_{28}H_{30}N_2O$: C, 81.91; H, 7.37; N, 6.83. Found: C, 81.70; H, 7.39; N, 6.90.

The filtrate from separation of 7c was evaporated in vacuo to an oil, which was redissolved in hot ethyl acetate, to afford 7d (6.0 g, 15%) on cooling. Recrystallization from ethyl acetate gave white crystals: mp 180.5–182 °C; ^{1}H NMR see text; IR ν_{max} 1655/1648 (C=O) cm^{-1}; Bohlmann bands absent. Anal. Calcd for $C_{28}H_{30}N_2O$: C, 81.91; H, 7.37; N, 6.83. Found: C, 81.83; H, 7.43; N, 6.81.

(2α,7α,11bα)- and (2β,7α,11bα)-1,3,4,6,7,11b-Hexahydro-*N*,7-diphenyl-2*H*-benzo[*a*]quinolizin-2-amine (7b and 7a). A mixture of anilines 7a and 7b (60.5 g, 84%) was prepared as above from ketone 5 (56.5 g, 0.204 mol), aniline hydrochloride (26.5 g, 0.204 mol), and $NaCNBH_3$ (12.8 g, 0.204 mol). To this mixture in 100 mL of 2-propanol was added 1 mol-equiv of cyclohexylsulfamic acid (30.4 g, 0.17 mol). The white, crystalline cyclohexylsulfamate salt of aniline 7b (18.6 g, 20%) was filtered and recrystallized from methanol: mp 201–203.5 °C; ^{1}H NMR (7b, D_2O added) δ 1.7–3.2 (ms, 8 H, aliphatic), 3.70 (dd, H_{11b}, J = ~11 and 2 Hz), 3.85 (m, H_2, $w_{1/2}$ = ~10 Hz), 4.42 (dd, H_7, J = 6 and 12 Hz), 6.5–7.4 (m, 14 H, aromatic); IR (7b, CCl_4) ν_{max} 2795/2745 (Bohlmann bands), 1598 cm^{-1}. Anal. Calcd for $C_{25}H_{26}N_2 \cdot C_6H_{13}NO_3S$: C, 69.76; H, 7.37; N, 7.87. Found: C, 69.83; H, 7.39; N, 7.86.

The filtrate from separation of the hexamate salt of 7b was evaporated in vacuo to an oil, which was partitioned between ether and 1 N NaOH. The ether layer was dried (K_2CO_3) and HCl gas was bubbled into it. The crude hydrochloride salt was filtered, stirred in 200 mL of boiling methanol for 10 min, filtered again (10.3 g, 14%), and recrystallized from methanol/water (20:1) to give crystals containing 93% 7a and 7% 7b (GLC): mp 275–285 °C; ^{1}H NMR (7a, D_2O added) δ 1.1–3.2 (ms, 8 H, aliphatic), 3.42 (dd, H_{11b}, J = ~11 and 12 Hz), 3.4–3.9 (br m, H_2, $w_{1/2}$ = ~35 Hz), 4.40 (dd, H_7, J = 12 and 6 Hz), 6.5–7.3 (m, 14 H, aromatic); IR (7a, CCl_4) ν_{max} 2795/2745 (Bohlmann bands), 1600 cm^{-1}. Anal. Calcd for $C_{25}H_{26}N_2 \cdot 2HCl$: C, 70.25; H, 6.60; N, 6.56. Found: C, 70.06; H, 6.61; N, 6.51.

***N*-(2α,7β,11bα)- and *N*-(2β,7β,11bα)-(1,3,4,6,7,11b-Hexahydro-7-phenyl-2*H*-benzo[*a*]quinolizin-2-yl)-*N*-phenylpropanamide (9d and 9c).** A mixture (ca. 1:1) of ketones 5 and 8 (22.6 g, 0.081 mol) was prepared as above from ketone 5 (24 g, 0.086 mol). This mixture was reacted in the usual manner with aniline hydrochloride (10.6 g, 0.082 mol) and $NaCNBH_3$ (5.2 g, 0.082 mol) to give four isomeric anilines, 7a, 7b, 9a, and 9b (27.7 g, 96%), in a ratio of 3:3:2:2 (GLC). Aniline 7b was isolated as a cyclohexylsulfamic acid salt (vide supra). The filtrate was evaporated in vacuo to an oil, which was partitioned between CH_2Cl_2 and 1 N NaOH. The organic solution was dried (K_2CO_3) and evaporated in vacuo to an oil (22.5 g) enriched in 7a, 9a, and 9b. This oil was separated using preparative high-performance LC [ethyl acetate/hexane (1:3)] to give a mixture [TLC (ethyl acetate/hexane, 1:2) R_f 0.75] of anilines 9a and 9b (5.6 g, 20%), which was reacted as above with propionyl chloride (1.61 g, 17.4 mmol), furnishing on workup an oily mixture of propionanilides 9c and 9d (5.8 g, 90%). This oil was crystallized from ethyl acetate to give 9d (1.8 g); recrystallization from ethyl acetate gave white crystals: mp 180–182 °C; ^{1}H NMR δ 1.05 (t, CH_3), 1.7–3.2 (ms, 10 H, aliphatic), 3.49 (dd, H_{11b}), 3.92 (dd, H_7), 4.93 (m, H_2), 6.8–7.5 (m, 14 H, aromatic); IR (CCl_4) ν_{max} 2795/2740 (Bohlmann bands), 1655 (C=O) cm^{-1}. Anal. Calcd for $C_{28}H_{30}N_2O$: C, 81.91; H, 7.37; N, 6.83. Found: C, 81.88; H, 7.39; N, 6.81.

The filtrate from separation of propionanilide 9d was evaporated in vacuo to an oil, which was dissolved in 25 mL of dry CH_2Cl_2 and treated with HCl gas until pH ~1. Ether was added to precipitate the hydrochloride salt of 9c (2.55 g), recrystallization of which from methanol/2-propanol afforded white crystals: mp 257–262 °C; ^{1}H NMR (9c, 60 MHz) δ 1.05 (t, CH_3), 1.3–3.1 (ms, 10 H, aliphatic), 3.47 (dd, H_{11b}), 4.05 (dd, H_7), 5.0 (m, H_2), 7.07–7.6 (ms, 14 H, aromatic); IR (9c, CCl_4) ν_{max} 2800/2750 (Bohlmann bands), 1658 (C=O) cm^{-1}. Anal. Calcd for $C_{28}H_{30}N_2O \cdot HCl \cdot 0.05C_3H_8O$: C, 75.13; H, 7.07; N, 6.23. Found: C, 75.17; H, 7.01; N, 6.25.

(1β,7α,11bα)-1,3,4,6,7,11b-Hexahydro-1-methyl-7-phenyl-2*H*-benzo[*a*]quinolizin-2-one (10). Isoquinoline hydrochloride (4; 40 g, 0.164 mol) was combined with ethyl vinyl ketone (50 g, 0.595 mol) and heated on a steam bath for 5 min. Methyl ethyl ketone (30 mL) was added to the ice-cooled mixture and 10·HCl (43.5 g, 81%) was filtered off. Free base 10 was recrystallized from acetone to afford white crystals: mp 120–122.5 °C; ^{1}H NMR δ 0.98 (d, CH_3), 2.1–3.3 (ms, 7 H, aliphatic), 3.78 (d, H_{11b}), 4.37 (dd, H_7), 6.7–7.4 (m, 9 H, aromatic); IR ν_{max} 2795/2742 (Bohlmann bands), 1598 cm^{-1}. Anal. Calcd for $C_{20}H_{21}NO$: C, 82.44; H, 7.26; N, 4.81. Found: C, 82.53; H, 7.34; N, 4.75.

(1β,2β,7α,11bα)- and (1β,2β,7β,11bα)-1,3,4,6,7,11b-Hexahydro-1-methyl-*N*,7-diphenyl-2*H*-benzo[*a*]quinolizin-2-amine (11b and 11d). Ketone 10 (23.2 g, 0.08 mol) and aniline (8.18 g, 0.088 mol) were combined in 200 mL of dry toluene containing 0.25 g of *p*-toluenesulfonic acid and the mixture was refluxed under a Dean–Stark trap for 16 h. With ice-bath cooling and stirring, 90 mL of 1 M $BH_3 \cdot THF$ was added over 25 min. After 2 h, an additional 30 mL of 1 M $BH_3 \cdot THF$ was added. The reaction was stirred at room temperature for 88 h, quenched with 2 mL of 12 M HCl (added slowly with cooling), and acidified with 1 N HCl until pH ~1. The solution was heated on a steam bath for 10 min, cooled, and brought to pH ~12 with 10% NaOH. The toluene layer was dried (K_2CO_3) and evaporated in vacuo to give a crude product containing 11a–11d, but enriched in anilines 11b and 11d (GLC). This mixture was dissolved in 400 mL of ether, and HCl gas was bubbled through the solution until pH 1. The crude HCl salt was filtered (35.4 g, 99%), stirred with 100 mL of boiling 2-propanol, and filtered again. This solid, after stirring with 100 mL of boiling methanol for 15 min, gave on filtration 11b·HCl (14.6 g, 41%). Free base 11b was recrystallized from CH_2Cl_2/methanol to furnish white crystals: mp 154–155.5 °C; ^{1}H NMR δ 0.71 (d, CH_3), 1.71–3.1 (ms, 7 H, aliphatic), 3.5 (d, H_{11b}), 3.6 (m, H_2), 4.31 (dd, H_7), 6.5–7.5 (m, 14 H, aromatic); IR ν_{max} 2790/2740 (Bohlmann bands), 1595 cm^{-1}. Anal. Calcd for

(38) Attempted stereoselective reduction under these reaction conditions gave the following ratios of products 7b/7a: 1:1 with Li(Et)$_3$BH, 2:1 with sodium diisopinocampheylcyanoborohydride, and >99:1 with Li(*sec*-Bu)$_3$BH (compared to 1:1 with $NaBH_3CN$). This trend in stereoselectivity is analogous to trends found for the reduction of *N*-methylimines [D. A. Evans, A. M. Golob, N. S. Mandel, and G. S. Mandel, *J. Am. Chem. Soc.*, **100**, 8170 (1978)].

$C_{26}H_{28}N_2$: C, 84.74; H, 7.66; N, 7.60. Found: C, 84.52; H, 7.75; N, 7.63.

The filtrates from the separation of **11b**·HCl were combined and evaporated in vacuo to an oil, which slowly deposited crystals of **11d**·HCl (7.35 g, 21%) from methanol/2-propanol. This salt was partitioned between CH_2Cl_2 and 1 N NaOH, and the organic layer was dried (K_2CO_3) and evaporated in vacuo to afford aniline **11d** (6.36 g): ^{1}H NMR (60 MHz) δ 0.78 (d, CH_3), 1.6–3.2 (ms, 7 H, aliphatic), 3.37 (d, H_{11b}), 3.67 (m, H_2), 4.05 (dd, H_7), 6.6–7.5 (m, 14 H, aromatic); IR (neat) ν_{max} 2800/2750 (Bohlmann bands) cm^{-1}. Anal. Calcd for $C_{29}H_{32}N_2O$: C, 82.04; H, 7.60; N, 6.60. Found: C, 81.90; H, 7.63; N, 6.61.

***N*-(1β,2β,7α,11bα)-(1,3,4,6,7,11b-Hexahydro-1-methyl-7-phenyl-2*H*-benzo[*a*]quinolizin-2-yl)-*N*-phenylpropanamide (12b).** Aniline **11b** (9.0 g, 24.4 mmol) was treated as above with propionyl chloride (2.48 g, 26.8 mmol) to afford on workup oily propionanilide **12b**, which was crystallized from ethyl acetate to give a powdery solid (7.85 g, 76%). Recrystallization from CH_2Cl_2/methanol gave white crystals: mp 211.5–215 °C; ^{1}H NMR δ 0.78 (d, C_1 CH_3), 1.04 (t, CH_3), 1.3–3.5 (ms, 9 H, aliphatic), 3.62 (d, H_{11b}), 4.25 (dd, H_7), 4.65 (m, H_2), 6.7–7.5 (m, 14 H, aromatic); IR ν_{max} 2805/2750 (Bohlmann bands), 1642 (C=O) cm^{-1}. Anal. Calcd for $C_{29}H_{32}N_2O$: C, 82.04; H, 7.60; N, 6.60. Found: C, 82.02; H, 7.62; N, 6.61.

(5α,8aβ,13aβ,14aα)-5,6,8,8a,13,13a,14,14a-Octahydro-13-(1-oxopropyl)-5-phenylbenz[*a*]indolo[3,2-*g*]quinolizine (14b). Phenylhydrazine hydrochloride (13.0 g, 0.09 mol) and sodium acetate (7.4 g, 0.09 mol) were dissolved in 120 mL of water and filtered. The filtrate was added to a refluxing solution of ketone **5** in 220 mL of ethanol, and heating was continued for 40 min. After the solution was boiled for an additional 10 min without a condenser, 300 mL of water was added and the solution was cooled in an ice bath for 1.5 h. The precipitate was filtered off (27.3 g, 99%) and dissolved in 275 mL of refluxing THF. Polyphosphoric acid (130 mL) was added and the reaction was heated on a steam bath, allowing the THF to evaporate out of the reaction mixture. Crushed ice (1.5 L) was added, followed by 60 mL of 12 M HCl with cooling and stirring. The solution was neutralized with aqueous KOH and extracted with ether. The ether layer was dried (K_2CO_3) and evaporated in vacuo to a solid (14.2 g, 54%), indole **13**. Recrystallization from ethyl acetate gave tan crystals, mp 192–197 °C.

Indole **13** (5.9 g, 17 mmol) was dissolved in 85 mL of trifluoroacetic acid under N_2 at 0 °C, 50 mL of 1 M BH_3·THF was stirred in over 15 min (0 °C), 20 mL of water was added, and the solution was stirred for 10 min.[17] After the solution was evaporated in vacuo to a volume of 35 mL, the residue was partitioned between $CHCl_3$ and 1 N NaOH. The organic layer was dried (K_2CO_3) and evaporated in vacuo to an oil (6.3 g). Crude indoline **14a** (6.1 g, 17.3 mmol) was reacted with propionyl chloride (2.77 g, 30 mmol) in the usual manner to give oily propionanilide **14b**, which crystallized from ethyl acetate (4.7 g, 66%). Recrystallization from ethyl acetate afforded white crystals: mp 193.5–195 °C; ^{1}H NMR δ 1.3 (t, CH_3), 2.3–3.6 (ms, 9 H, aliphatic), 4.04 (dd, H_{14a}), 4.45 (dd, H_5), 4.55 (m, H_{13a}), 6.8–7.8 (m, 13 H, aromatic); IR ν_{max} 1642 (C=O); absence of Bohlmann bands. Anal. Calcd for $C_{28}H_{28}N_2O$: C, 82.32; H, 6.91; N, 6.86. Found: C, 82.10; H, 6.94; N, 6.83.

(4aα,9bα)-2,3,4,4a,5,9b-Hexahydro-5-(1-oxopropyl)-2-(2-phenylethyl)-1*H*-pyrido[4,3-*b*]indole (16). 2-(2-Phenylethyl)-1,2,3,4-tetrahydropyrido[4,3-*b*]indole[39] (2.43 g, 8.8 mmol) was dissolved in 20 mL of trifluoroacetic acid under N_2 at 0 °C and 45 mL of 1 M BH_3·THF was added at 15 °C.[17] The reaction was stirred for 1.5 h at room temperature, 2 mL of water was added, and the solution was stirred for 1 h and then evaporated in vacuo to a solid. This solid was partitioned between CH_2Cl_2 and 1 N NaOH, and the organic layer was dried (K_2CO_3) and evaporated in vacuo to an oil, which was distilled by Kugelrohr [100–210 °C (0.6 torr)] to give the indoline intermediate (1.84 g, 75%). The indoline (1.84 g, 6.6 mmol) was dissolved in 20 mL of dry CH_2Cl_2 and reacted as above with propionyl chloride (0.925 g, 10 mmol). After 40 min, 15 mL of water was added and the solution was made alkaline with 10% NaOH. The organic phase was dried (K_2CO_3) and evaporated in vacuo to give oily propionanilide **16** (2.14 g, 97%), which crystallized from 2-propanol to give white crystalline **16** (1.52 g, 69%): mp 110–111 °C (lit.[6b] mp 109–110 °C); ^{1}H NMR δ 1.23 (t, CH_3), 1.4–3.7 (ms, 13 H, aliphatic), 4.4 (m, H_{4a}), 7.0–8.0 (m, 9 H, aromatic); IR ν_{max} 2800/2760/2740 (Bohlmann bands), 1660 (C=O) cm^{-1}.

***N*-(2α,11bα)-(1,3,4,6,7,11b-Hexahydro-2*H*-benzo[*a*]quinolizin-2-yl)-*N*-phenylpropanamide (*cis*-3a).** 1,3,4,6,7,11b-Hexahydro-2*H*-benzo[*a*]quinolizin-2-one[40] (0.50 g, 2.5 mmol) and aniline (0.256 g, 2.75 mmol) were dissolved in 5 mL of dry toluene containing 15 mg of *p*-toluenesulfonic acid and refluxed for 21 h under a Dean–Stark trap. The solution was cooled in an ice bath and 12 mL of 1 M L-Selectride was stirred in slowly. After 1.5 h, 1 mL of water was added, followed by 1 mL of 10% NaOH. The two-phase solution was stirred for 10 min. The toluene solution was dried (K_2CO_3) and evaporated in vacuo to an oil, which was stirred for 1.25 h with 2% NaOH. The mixture was extracted with CH_2Cl_2 and this organic phase was dried (K_2CO_3) and evaporated in vacuo to afford the intermediate aniline (0.60 g, 86%).

The aniline (0.60 g, 2.2 mmol) was reacted as described above with propionyl chloride (0.23 g, 2.5 mmol) to give *cis*-**3a** (0.56 g, 76%). Recrystallization from ethyl acetate afforded white crystals: mp 157.5–158 °C (lit.[7a] mp 157–158 °C); ^{1}H NMR (60 MHz) δ 4.15 (t, H_{11b}), 4.65 (m, H_{2ax}); IR ν_{max} 1642 (C=O) cm^{-1}; absence of Bohlmann bands.

Opiate Receptor Binding Assay. Male Wistar rats (Charles River, 150–200 g) were killed by cervical dislocation and their brains were removed. The cerebellums were excised and the remaining brain tissue was homogenized, according to Snyder.[32,33] The binding assay, was conducted in the manner of Snyder using [^{3}H]naloxone as the radioligand. Radioactivity was measured by liquid scintillation spectrometer, and the specific binding was determined as the difference in the mean counts per minute between the control sample and those containing levorphanol. Percent inhibition due to a test compound was determined by the percent lowering of the specific binding. Fifty-percent inhibition levels (I_{50} values) were calculated by linear least-squares regression using from 6 to 30 data points occurring between 15 and 85% inhibition.

Analgesic Activity. Two methods were used to evaluate the compounds presented in Table I for analgesic activity: (a) the acetylcholine bromide body-constriction-response assay and (b) the Haffner assay.

The acetylcholine bromide assay was similar to that described by Collier et al.[28] Twenty male albino mice of the Swiss Webster strain, weighing 18–24 g, were used per dosage level. Following administration of the test compound (pretreatment times and routes employed are in Table I), the mice were injected with 5.5 mg/kg ip of acetylcholine bromide. The presence of a single body-constriction response, during a 10-min period following the injection of acetylcholine bromide, was considered to be a positive nociceptive response. A group of 20 mice pretreated with saline (10 mL/kg, po) and injected with acetylcholine bromide served as controls for each daily experiment.

The Haffner assay was similar to the procedure described by Bianchi and Franceschini.[29] Ten male albino mice of the Swiss Webster strain, weighing 18–24 g, were used per dosage level. Four to six dosage levels were employed in the determination of each ED_{50} value (Table I). The ED_{50} values and 95% confidence limits were calculated using probit analysis.[41] Following administration of the test compound (pretreatment times and routes employed are in Table I), a small rubber-covered clip was placed approximately 1 cm from the base of the tail and the mouse was observed for a 30-s period. A positive nociceptive response was indicated by vigorous biting of the clip within 3–4 s following placement of the clip.

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(39) R. G. W. Spickett, *J. Med. Chem.*, 9, 436 (1966).
(40) D. Beke and C. Szantay, *Chem. Ber.*, 95, 2132 (1962).
(41) D. J. Finney, "Probit Analysis", 2nd ed., Cambridge University Press, London, 1962.

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Supplementary Material Available: ^{1}H NMR LIS data for 5 (at 90 MHz); chemical shifts and coupling constants derived therefrom for the aliphatic protons. ^{1}H NMR (270 MHz) data, chemical shifts and coupling constants, for the aliphatic protons of **7c** and **7d**. Additional experimental procedure for the stereoselective L-Selectride reduction of *N*-phenylimines (4 pages). Ordering information is given on any current masthead page.

1-Oxacephalosporins: Enhancement of β-Lactam Reactivity and Antibacterial Activity

Kazuhisa Murakami,* Mamoru Takasuka, Kiyoshi Motokawa, and Tadashi Yoshida

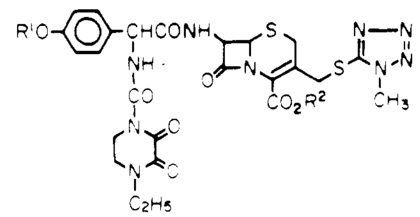
Shionogi Research Laboratories, Shionogi & Company, Ltd., Fukushima-ku, Osaka 553, Japan. *Received July 1, 1980*

The effect of replacement of sulfur in the cephem nucleus by oxygen upon the β-lactamase stability, infrared carbonyl frequency of the β-lactam ring, and antibacterial activity was investigated. The replacement reduced the stability of β-lactam compounds to β-lactamases, increased the IR frequencies, and enhanced the intrinsic antibacterial activity against bacterial strains without β-lactamase. The instability of 1-oxacephalosporins to β-lactamases, in other words, high reactivity to the enzymes, seemed to be due to the enhanced chemical reactivity of their β-lactam rings which was indicated by their higher IR β-lactam carbonyl frequencies. Based on a view that acylation of the enzyme by β-lactam compounds occurred in both cases of β-lactamase hydrolysis and target enzyme inhibition, the suggestion was made that one of the factors which conferred the higher intrinsic antibacterial activity on 1-oxacephalosporins was their high reactivity to the target enzyme(s), as was the case with β-lactamases.

Several reports have described the synthesis of 1-carba- and 1-oxacephalosporins.[1-5] Christensen and his coworkers reported that the 1-oxa analogue of cefamandole had higher antibacterial activity than cefamandole, although 1-oxa analogues of cephalothin and cefoxitin tended to reduce the activity.[4,5] Narisada and his colleagues published the synthesis of several 1-oxacephalosporins and showed that 1-oxa congeners, including 1-oxacephalothin and 1-oxacefamandole, had four- to eightfold more antibacterial potency against sensitive bacterial strains than the corresponding cephalosporins.[2,6]

In order to study in more detail the effect of substitution of the sulfur atom in cephalosporins with oxygen upon the biological activities, we selected several cephalosporins and their 1-oxa congeners and measured their β-lactamase stability and antibacterial activity. Morin et al. assumed that high infrared β-lactam carbonyl frequency indicated high acylating power, that is, high reactivity of the β-lactam ring.[7a] Thus, we compared the infrared carbonyl frequencies of 1-oxacephalosporins and 1-sulfur congeners and correlated them with the susceptibility to β-lactamases and antibacterial activity.

Synthesis of the New Compounds. Amine **10a** was acylated with succinimino trifluoromethylthioacetate to give **13a**, which was treated with trifluoroacetic acid in anisole to yield acid **4a** (Scheme I). Preparation of the starting oxacephems **10b**, **11**, and **12** has already been reported from our laboratories.[2,6] The amine **10b**[2] was converted similarly into acid **4b** via **13b**. Acylation of the amine **11**[6] with 1(1*H*)-tetrazolylacetyl chloride and subsequent treatment of the resulting **14** with trifluoroacetic acid in anisole yielded 1-oxacefazoline (**5b**). The amine **12**[6] was acylated with 4-bromo-2-oxobutyroyl bromide to give **15**, which on treatment with thiourea was converted into the aminothiazole derivative **16**. On treatment of the latter with trifluoroacetic acid in anisole, the desired acid **6b** was obtained. Acylation of the amine **12** with 2-[4-(mesylamino)phenyl]-2-(*Z*)-[(dichloroacetoxy)imino]acetyl chloride and subsequent hydrolysis yielded the oximino compound **17**, which was treated with trifluoroacetic acid and anisole to give the acid **7b**. Cefoperazone (**18**)[8] was



18, $R^1 = H$, $R^2 = H$ (cefoperazone)

19, $R^1 = H$, $R^2 = CHPh_2$

20, $R^1 = NH_2CO-$, $R^2 = CHPh_2$

8a, $R^1 = NH_2CO-$, $R^2 = H$

converted into benzhydryl ester **19**. Carbamoylation of the 4-hydroxy group of **19** proceeded smoothly to produce **20**, which on treatment with trifluoroacetic acid in anisole gave the acid **8a**.

Results

Susceptibility to β-Lactamase Hydrolysis. The susceptibility of nine pairs of cephalosporins and their 1-oxa congeners to six β-lactamases from Gram-negative bacteria was examined as shown in Table I. In most cases, 1-oxacephalosporins were more susceptible to β-lactamases

(1) R. N. Guthikonda, L. D. Cama, and B. G. Christensen, *J. Am. Chem. Soc.*, **96**, 7584 (1974).

(2) M. Narisada, H. Onoue, and W. Nagata, *Heterocycles*, **7**, 839 (1977).

(3) S. Wolfe, J.-B. Ducep, K.-C. Tin, and S.-L. Lee, *Can. J. Chem.*, **52**, 3996 (1974).

(4) L. D. Cama and B. G. Christensen, *J. Am. Chem. Soc.*, **96**, 7582 (1974).

(5) R. A. Firestone, J. L. Fahey, N. S. Maciejewicz, G. S. Patel, and B. G. Christensen, *J. Med. Chem.*, **20**, 551 (1977).

(6) M. Narisada, T. Yoshida, H. Onoue, M. Ohtani, T. Okada, T. Tsuji, I. Kikkawa, N. Haga, H. Satoh, H. Itani, and W. Nagata, *J. Med. Chem.*, **22**, 757 (1979).

(7) (a) R. B. Morin, B. G. Jackson, R. A. Mueller, E. R. Lavagnino, W. B. Scanlon, and S. L. Andrews, *J. Am. Chem. Soc.*, **91**, 1401 (1969); (b) R. M. Sweet and L. F. Dahl, *ibid.*, **92**, 5489 (1970).

(8) I. Saikawa, S. Takano, C. Yoshida, O. Takashima, K. Momonoi, S. Kuroda, M. Komatsu, T. Yasuda, and Y. Kodama, Belgian Patent 837682 (1976); *Chem. Abstr.*, **87**, 6002v (1977).

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