from methanol and dried in vacuo to give 77 mg (19%) of 1-^{13}C, mp 225–227 °C dec. Authentic unlabeled 1 had mp 226–227 °C dec.

In a similar manner 366 mg (1.56 mmol) of 2 and 199 mg (1.67 mmol) of 5-^{14}C in 1.70 mL of methanol gave, after recrystallization, 194 mg (51%) of 1-^{14}C, mg 224–226 °C dec.

The title compounds were characterized by their infrared spectra [(KBr) 3400, 1685, 1495, and 1100 cm^{-1}] which were identical with that of authentic, unlabeled 1, except minor differences in 1-6-^{13}C due to the high percentage of isotope composition. These compounds were also characterized by the GC retention time of their Me_3Si derivatives from reaction with *N,O*-bis(trimethylsilyl)trifluoroacetamide in acetonitrile on column a at 250 °C, which were identical with that of Me_3Si-1, and by the mass spectra of their Me_3Si derivatives. The latter gave major fragments at *m/e* (rel intensity) 245 (36), 217 (98), 147 (49), and 73 (100), as were the major ions of Me_3Si-1. No major ion contained the ^{13}C label. The ^{13}C NMR spectrum of 1 using natural ^{13}C abundance has been published.[13] Synthetic 1-^{13}C (0.15 M in H_2O–D_2O) showed a single chemical shift of 157.5 ppm for C-6 relative to Me_4Si (lit.[13] 157.5 ppm).

Drug Analysis. Thin-layer chromatographic separation of 1 from metabolites was performed by a modified published procedure.[6] Known volumes of biological fluids from radiolabeled 1-treated rabbits along with standards of 1 spiked into blank bile and urine were applied onto Eastman cellulose sheets (Rochester, N.Y.) which were subsequently developed in a solvent system consisting of isobutyric acid–triethylamine–water, 66:2:32. Visible spots under UV lamp (UV SL-25, San Gabriel, Calif.) corresponding to the R_f of 1 (0.72) were sectioned and transferred into liquid scintillation vials. In the case of low concentrations of 1 in the biological samples, a small amount of unlabeled 1 was added to increase visibility, and the spots were processed as before. These TLC materials were assayed for radioactivity using a standard liquid scintillation counting procedure with a Beckman 300 (Beckman, Fullerton, Calif.) liquid scintillation counter. The UV visible spots corresponding to 1 without isotopic dilution were pooled and the specific activity was examined via absorption at 254 nm and liquid scintillation counting. Comparable specific activity to the administered dose of 1 validated the TLC analysis.

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Synthesis of Some Conformationally Restricted Analogues of Fentanyl[1]

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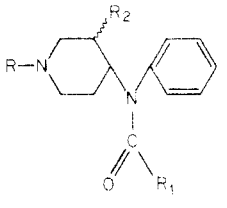
The preparation of *cis*- and *trans*-2,3,4,4a,5,9b-hexahydro-2-phenethyl-5-propionyl-1*H*-pyrido[4,3-*b*]indole is described. These compounds, which are conformationally restricted analogues of the potent analgesic fentanyl, were devoid of analgesic or CNS activity.

The 4-anilidopiperidines 1 as archetypified by fentanyl (R = $CH_2CH_2C_6H_5$; R_1 = C_2H_5; R_2 = H) have been shown to constitute a class of extremely potent short-acting morphine-like analgesics.[2] Previous efforts in delineating



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the structure–activity relationships in this series have focused on varying the nature and stereochemical relationships of the substituents R, R_1,[2,3] and R_2.[4] Most recently,[5] R_1 has been tied back to the ortho position of the aromatic ring.

The 4-anilidopiperidines are conformationally mobile, although recent ^1H NMR data suggest that the preferred conformers are piperidine chairs with the anilido group equatorially oriented.[3] In view of the nature of the previous studies, it was felt to be of interest to prepare some analogues of fentanyl where conformational mobility is restricted and to assess the effect of this upon biological activity.

Treatment of 2 with sodium cyanoborohydride in trifluoroacetic acid[6] gave 3 (Scheme I). Reaction of 2 with BH_3–THF followed by treatment with 37% HCl and

Scheme I

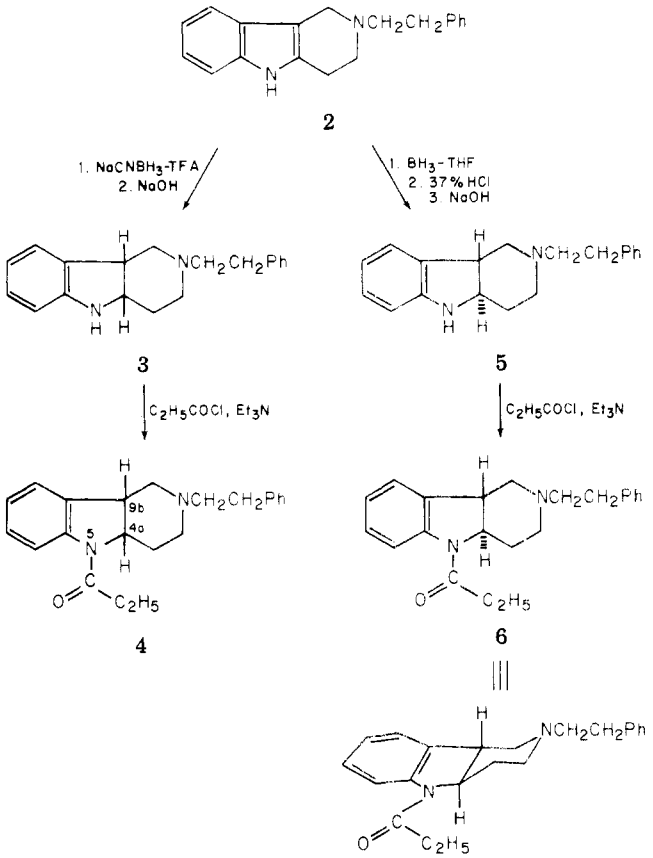


Table I. ^{13}C Chemical Shifts (ppm from Me_4Si) in $CDCl_3$

Compd	C-4a	C-9b
3	57.5	41.1
4	58.8	40.7
5	68.4	47.3
6	69.3	47.4

subsequent neutralization gave the diastereomeric **5**. Propionylation yielded **4** and **6**, respectively.

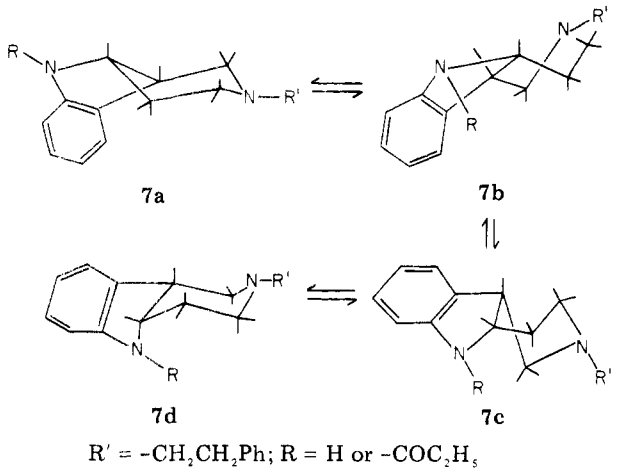
Although previous work in these laboratories has established that the BH_3 reduction procedure applied to compounds closely related to **2** gives rise to the trans-ring junction,[7] the configurational assignments can be unequivocally confirmed by means of ^{13}C NMR. Thus, the signals for C-4a and C-9b are shifted to much higher field in **3** and **4** as compared to **5** and **6** (Table I). This effect has been previously observed in the diastereomeric decalins[8] and decahydroquinolines[9] and is presumed due to γ-gauche interactions in the cis isomers.

The trans-ring junction demands a completely rigid "locked" conformation for compounds **5** and **6** in which the substituents on the piperidine ring are fused diequatorially. Therefore, **6** represents a conformationally fixed fentanyl. Cis compounds **3** and **4**, however, are conformationally mobile and may exist as conformers **7a–d** (Scheme II).

The 220-MHz ^1H NMR spectrum of **3** shows signals assigned to H-4a at δ 3.80 and 3.21 assigned to H-9b as doublets of triplets. By application of the INDOR[10] technique at 270 MHz, coupling constants for each proton on the piperidine ring may be unequivocally assigned (Table II).

These data appear uniquely interpretable in terms of conformation **7d**. The situation for **4**, however, is quite different. At 220 MHz at +68 °C, H-4a is observed at δ 4.43 as a quartet (line separations 8 Hz) of 24 Hz bandwidth and H-9b as a distorted triplet, bandwidth 15 Hz, at δ 3.42. These ^1H NMR assignments were confirmed by single-frequency proton decoupling of the ^{13}C NMR spectrum. The observed bandwidths are well accounted for by conformation **7a**, and the data closely parallel that recently reported for *N*-acetyl-*cis*-hexahydrocarbazole.[11] The twist–boat conformer **7b** may be ruled out in view of the narrow bandwidth of H-9b. It therefore seems that **4** is also conformationally analogous to fentanyl in that the anilido nitrogen is equatorial to a chair piperidine.

Scheme II



R' = $-CH_2CH_2Ph$; R = H or $-COC_2H_5$

Table II. Coupling Constants for Compound **3** (±0.5 Hz)

J	Hz	J	Hz
4a,9b	6.6	4ax,4eq	−13.8
4a,4ax	5.0	4ax,3ax	10.5
4a,4eq	4.0	4ax,3eq	5.0
9b,lax	9.7	4eq,3ax	3.3
9b,leq	6.3	4eq,3eq	4.5
lax,leq	−11.5	3ax,3eq	−11.0

Both **4** and **6**·HCl were inactive in the mouse phenylquinone writhing test[12] at doses of up to 130 mg/kg orally. Fentanyl was found to have an ED_{50} of 0.8 mg/kg in the same test at a peak time of 10 min after oral dosing. In addition, **4** and **6**·HCl showed no depression of locomotor activity (visual) in the mouse at doses up to 200 mg/kg orally.

In view of these results, it is tempting to conclude that analgesic activity in the fentanyl series is highly dependent on stereochemical factors. However, it should be kept in mind that differences in absorption, distribution, and metabolism may exist between these two series and may play an important role.

Experimental Section

Melting points were determined in open capillary tubes and are uncorrected. ^1H NMR spectra were determined on a Varian HR-220 spectrometer and on the Bruker HF-270 spectrometer at The University of Chicago. C-13 spectra were determined using a Bruker WH-90 spectrometer. IR spectra were recorded using a Perkin-Elmer 727 spectrometer. Analytical results were within ±0.4% of theory for the elements stated (Spang Microanalytical Lab, Ann Arbor, Mich.).

Compounds tested were administered as solutions or suspensions in 1% aqueous Methocel.

***cis*-2,3,4,4a,5,9b-Hexahydro-2-phenethyl-1*H*-pyrido[4,3-*b*]indole (3).** A freshly prepared solution of $Na(CN)BH_3$ (10.0 g, 0.16 mol) in 25 mL of methanol was added dropwise to a stirred solution of **2**[13] (9.0 g, 0.032 mol) in 100 mL of CF_3CO_2H at ice-bath temperature under a nitrogen atmosphere. Vigorous gas evolution resulted. Upon completion of the addition, the reaction mixture was stirred at room temperature for 1 h and then poured into 400 mL of water. The resulting mixture was stirred 15–20 min and

basified with 50% NaOH and the resulting mixture extracted twice with 200-mL portions of ether. The combined extracts were washed once with water and then extracted twice with 100-mL portions of 6 N HCl. The extracts were basified, and the oily product was reextracted into ether. After washing with water and drying over anhydrous K_2CO_3, the filtered solution was evaporated in vacuo to yield crude **3** (7.4 g) as a pale yellow oil which was distilled in a Kugelrohr apparatus. Two fractions were taken: bp 170–175 °C (bath) (0.05 mm) (3.7 g) and bp 147–153 °C (bath) (0.01 mm) (1.6 g). Both fractions were colorless viscous oils which crystallized on trituration with pentane: mp 70–71 °C; infrared (Nujol) 3350 cm^{-1} (NH); TLC R_f 0.53 (silica gel F_{254}; eluent, 8% Et_2NH in benzene). Anal. ($C_{19}H_{22}N_2$) C, H, N.

cis-**2,3,4,4a,5,9b-Hexahydro-2-phenethyl-5-propionyl-1*H*-pyrido[4,3-*b*]indole (4).** A solution of propionyl chloride (2.0 mL, 2.1 g, 0.023 mol) in 10 mL of $CHCl_3$ was added dropwise to a stirred solution of **3** (4.4 g, 0.016 mol) and triethylamine (3.5 mL, 0.025 mol) in 75 mL of $CHCl_3$. The reaction mixture was heated at reflux for 30 min, cooled, and washed twice with water. After drying over anhydrous K_2CO_3, evaporation in vacuo left a yellow oil which deposited crystals (3.4 g) from benzene–hexane: mp 105–108 °C. Recrystallization from ethanol gave pure **4** (2.1 g, 27% yield): mp 109–110 °C; infrared (Nujol) 1660 cm^{-1} (amide C=O).

trans-**2,3,4,4a,5,9b-Hexahydro-2-phenethyl-1*H*-pyrido[4,3-*b*]indole (5).** A warm solution of **2** (34.5 g, 0.125 mol) in 300 mL of dioxane was added dropwise to 500 mL of a stirred solution of 1 M BH_3 in THF (Alfa-Ventron) under a nitrogen atmosphere. Vigorous gas evolution was noted during addition. The resulting mixture was then heated at reflux for 3.5 h and then THF was slowly distilled from the mixture and replaced with dioxane until a pot temperature of 96 °C was attained. The resulting mixture was maintained at reflux overnight, then cooled in ice, and cautiously decomposed by addition of 300 mL of 37% HCl. The resulting mixture was heated at reflux for 2 h, cooled, and basified with excess 50% NaOH solution. Most of the volatile solvent was removed on a rotary evaporator, and the residue was then diluted with water to dissolve inorganic salts. It was then extracted with two 250-mL portions of ether, and the combined extracts were then washed with water and in turn extracted with two 250-mL portions of 3 N HCl. The combined acid extracts were washed once with ether and basified, and the precipitated oil was reextracted into ether. The ether solution was dried over anhydrous K_2CO_3, filtered, and evaporated in vacuo to give a solid product which was recrystallized twice from ether–hexane–benzene to give 15.2 g (44%) of **5**: mp 105–107 °C; infrared (Nujol) 3300 cm^{-1} (NH); TLC R_f 0.49 (silica gel F_{254}, 8% Et_2NH in benzene). Anal. ($C_{19}H_{22}N_2$) C, H, N.

trans-**2,3,4,4a,5,9b-Hexahydro-2-phenethyl-5-propionyl-1*H*-pyrido[4,3-*b*]indole (6).** Compound **5** (5.6 g, 0.02 mol) was propionylated in a manner identical with that used to prepare **4**. The crude product was obtained as a waxy solid which was taken up in 75 mL of ethanol and treated with dry HCl. On chilling a solid (3.5 g) separated which was filtered and recrystallized from 125 mL of H_2O to give 2.8 g (38%) of **6**·HCl: mp 280–282 °C dec. Anal. ($C_{22}H_{26}N_2O$·HCl) C, H, N, Cl.

The mother liquor from the above recrystallization was basified with 1 N NaOH and the precipitated oil extracted into ether. After drying over anhydrous K_2CO_3 and evaporation in vacuo, a yellow oil was obtained which was dissolved in 50 mL of pentane and allowed to stand overnight at 0–5 °C. The white crystals which formed were filtered and dried to give 0.25 g of free base: mp 96–98 °C; mmp with **4**, 86–100 °C; infrared (Nujol) 1660 cm^{-1} (amide C=O); ^1H NMR (270 MHz, $CDCl_3$) δ 1.29 (t, J = 6 Hz, 3 H, CH_3), 2.10 [q (J = 12.3 Hz) of d (J = 4.0 Hz), 1 H, H-4ax], 2.57 (q, J = 6 Hz, 2 H, $CHCH_3$), 2.71–2.93 (m, 5 H, overlapping H-3ax and CH_2CH_2), 3.13 [t (J = 12.3 Hz) of d (J = 2.0 Hz), 1 H, H-9b], 3.25 (d, J = 11.8 Hz, 1 H, H-3eq), 3.48 [t (J = 14.7 Hz) of d (J = 4.0 Hz), 1 H, H-4a], 3.60 [d (J = 12.0 Hz of d (J = 2.5 Hz), 1 H, H-leq]. Anal. ($C_{22}H_{26}N_2O$) C, H, N.

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Synthesis of Some Pentazocine Metabolites and Related Compounds

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The syntheses of the trans alcohol **2** and the trans acid **5**, metabolites of pentazocine (**1**), are described. These are essentially devoid of agonist and antagonist activities. Some related oxidation products were also prepared for comparison with products isolated during metabolism studies.

Early studies of the metabolism of pentazocine (**1**) in this Institute by Rosi and Merola[1] using mouse liver homogenates led to the isolation of a sufficient amount of the major metabolite as the acetate derivative to characterize by NMR. The data (see Experimental Section) showed that there was a loss of a side-chain methyl signal from pentazocine and the gain of a CH_2OAc group so that the compound was the acetate of either **2** or **3**, but in the absence of a sample of known configuration, no decision could be reached as to whether the cis alcohol **3** or trans alcohol **2** had been isolated. The present work was undertaken to provide a reference sample for comparison so