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STUDIES ON THE STEREOSELECTIVE SYNTHESIS OF *cis*-3-METHYLFENTANYL

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The potent synthetic opiate fentanyl can be prepared by reduction of an intermediate Schiff base or by decyanation of a suitable alpha-aminonitrile. In the more potent 3-methyl-fentanyl series, the *cis*-isomer is more active than *trans*-isomer. Hence an attempt was made to develop an efficient stereoselective synthesis of the *cis*-isomer. Using sodium borohydride, Super-Hydride, Red-Al, and L-Selectride, the reduction of the appropiate Schiff base and the reductive decyanation of alpha-aminonitrile was studied. The ratio of the *cis* and *trans*-isomers formed in these reactions was determined by gas chromatograph. The *cis*-isomer predominated in all cases, with the selectivity being most pronounced for Selectride.

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PREFACE

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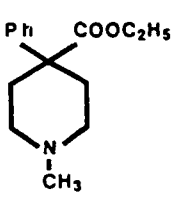
1. INTRODUCTION

A very significant further development in synthetic piperidine opiates since the discovery of meperidine (pethidine), 1-methyl-4-phenyl-4-piperidinecarboxylic acid ethyl ester,(1) by Eisleb and Schaumann in 1939, was the introduction of fentanyl, N-(1-phenethyl-4-piperidyl)-propionanilide,(2) by Janssen and his co-workers in 1964.[1]



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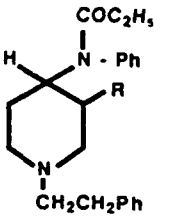
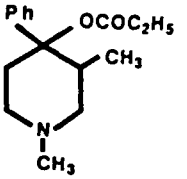


2, R = H
3, R = CH_3



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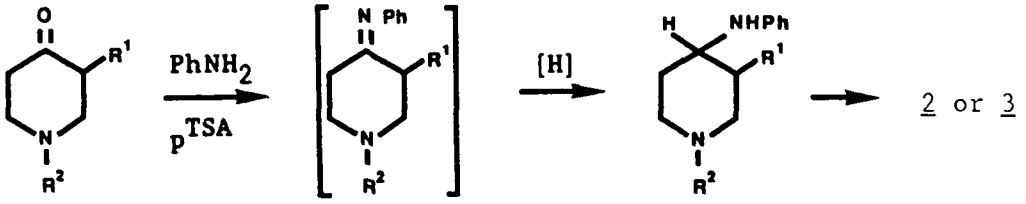
The preparation of fentanyl involves the condensation of an N-substituted 4-piperidone with aniline, followed by the reduction of the corresponding Schiff base by a variety of reducing agents, such as $LiAlH_4$[2,3,4], $NaBH_4$[5], Na/EtOH[3], and H_2/PtO_2[6,7], to yield the 4-anilino-piperidine. The latter then is acylated at the anilino moiety followed by introduction of the phenethyl group at the piperidine nitrogen to complete the fentanyl synthesis as shown in Scheme 1.

Scheme 1



5 6 7

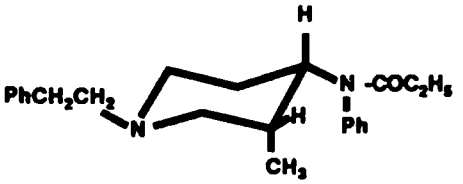
R^1 = H, CH_3
R^2 = $COOCH_3$, CH_2Ph, CH_2CH_2Ph

The superior analgesic properties of fentanyl, usually administered as its citrate salt (Sublimaze), relative to other piperidine

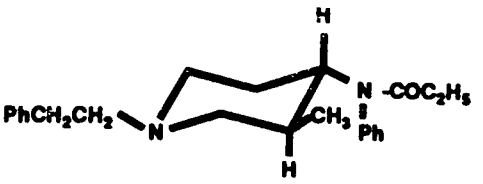
analgesics and morphine have been well summarized.[8] In the tail-withdrawal test in rats, it was found to have almost 600 times the potency of meperidine and more than 200 times that of morphine. Its onset time and duration of action are much shorter than that of morphine, and its therapeutic index (LD_{50}/ED_{50}) is over 100. The undesirable side effects parallel those of morphine, namely respiratory depression, cardiac depression, emesis, and dependence.

In 1973, Riley *et al.*[9] guided by the example of prodine (4), synthesized 3-methylfentanyl (3) from 4-anilino-3-methylpyridine. With the introduction of a methyl group into the piperidine ring of the symmetrical fentanyl, 3-methylfentanyl becomes an unsymmetrical molecule. The analgesic properties of 3 prepared by Riley were 10 times greater than fentanyl in the rat tail-flick assay.[9] The stereochemical configuration of Riley's 3-methylfentanyl was not established, however, from its melting point (HCl salt) and potency the compound is probably the *cis* diastereoisomer that was later described by Janssen's group.[5] Shortly thereafter, Janssen and his co-workers[5] published a more practical method of synthesizing 3 from 3-methyl-4-piperidone (5), which is analogous to the fentanyl synthesis as shown in Scheme 1.

With two chiral centers in the molecule 3, there are four possible stereoisomers, i.e. the two geometric isomers, 3a (*cis*) and 3b (*trans*), each of which has two enantiomers. The preferred conformation of *trans*-3-methylfentanyl (3b) should have both the methyl and anilino groups at equatorial positions. On the other hand, the *cis*-3 (3a) should have the anilino group at the equatorial and the methyl at the axial position based on the *A*-value of these group in the cyclohexane system.[10]



3a



3b

Pure samples of racemic *cis*- and *trans*-3-methylfentanyl were obtained by Janssen and co-workers.[5] They reduced Schiff base 6 with $NaBH_4$, obtaining 70% *cis* and 30% *trans* of 7 ($R^1 = CH_3$, $R^2 = COOCH_3$) which was then separated. The *cis*- and *trans*-7 were then successfully converted to the *cis*- and *trans*-3-methylfentanyl (3a and 3b). It was interesting but not too surprising to observe a difference of analgesic activity of these two stereoisomers. In the tail-withdrawal test, (±)-3a (*cis*) was found to be 8 times more active than the *trans*-(±)-isomer, which was equipotent to fentanyl. The enantiomers of the *cis*-isomer of the N-unsubstituted piperidine compound were then resolved by means of their tartrate salts, providing (+)- and (-)-3a. The analgesic activity of these two optical

isomers was tested in mice using the tail-withdrawal method. In this study, they found that the (+)-3a was the most potent isomer. The ED_{50} was 20 times lower than fentanyl and it was 100 times more potent than the (-)-3a. The (+)-3a was later assigned the absolute configuration 3*R*, 4*S*, i.e. (3*R*, 4*S*)-*cis*-(+)-3-methylfentanyl.[11]

In 1984 Borne *et al.*[12] prepared 1-benzyl-3-methyl-4-phenylamino-piperidine (7) ($R^1 = CH_3$, $R^2 = CH_2Ph$), also a precursor for the synthesis of 3, by Janssen's method (see Scheme 1). In his synthesis, the $NaBH_4$ reduction of the intermediate Schiff base, 6 ($R^1 = CH_3$, $R^2 = CH_2Ph$), yielded the *cis*- and *trans*-isomers in approximately a 2:1 ratio. Another synthetic approach used by Borne[12] was the one-step reductive amination of 5 ($R^1 = CH_3$, $R^2 = CH_2Ph$) with aniline and sodium cyanoborohydride, yielding a mixture of the two isomers in the same ratio. In view of the high potency of the *cis*-isomer of substituted fentanyls, we became interested in developing diastereoselective methods for their preparation. In this report we will discuss the results of our studies.

2. CHEMISTRY

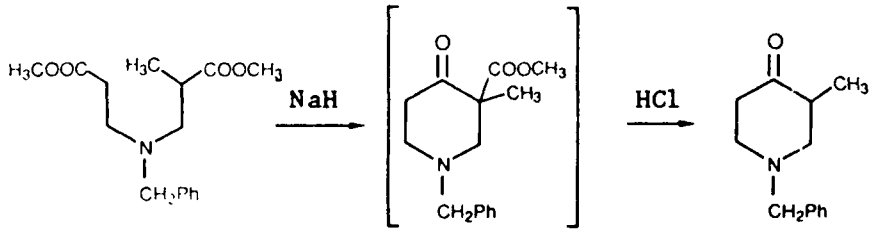
To study the stereoselective synthesis of *cis*-3-methylfentanyl (3), we employed two different approaches: A) bulky hydride reduction of the Schiff base; B) reductive decyanation of the α-aminonitrile.

A. Bulky Hydride Reduction of the Schiff Bases

Reviewing Janssen's synthesis of 3, we focused our attention on the reduction step because this step is decisive in determining the stereochemistry of the final product. It was rationalized that the bulky hydride reducing agents would deliver hydride ion to the C=N from the less hindered side or the opposite side to the 3-methyl group. This would produce a *cis* orientation of anilino and methyl group.

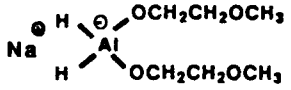
1-Benzyl-3-methyl-4-piperidone (5) was prepared according to the procedure reported by Carabateas and Grumbach[13] as shown in Scheme 2. Schiff base, 6 ($R^1 = CH_3$, $R^2 = CH_2Ph$), was prepared from 5 and aniline as described by Borne *et al.*[12]. Using xylene or toluene as the solvent, the formation of the Schiff base never totally reached completion which had not been specifically mentioned by these authors. The extent of completion was monitored by the appearance of the IR band at 1665 cm^{-1} (C=N) and the disappearance of the carbonyl band at 1720 cm^{-1}. There usually was a small amount of ketone left and this crude reaction product was used in the next step (reduction) without further purification. Because of this, we always observed a small amount of alcohol as the by-product from these hydride reductions.

Scheme 2

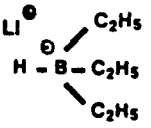


8 9 5

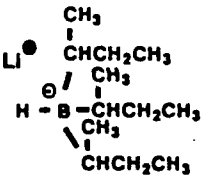
To study the stereoselective reduction of the Schiff base, several bulky reducing agents were employed: Super-Hydride (lithium triethylborohydride), Red-Al (sodium *bis*[2-methoxyethoxy]aluminum hydride), and L-Selectride (lithium tri-*sec*-butylborohydride). The known sodium borohydride reduction was also included in order that both geometric isomers, *cis*- and *trans*-7 (7a and 7b), were obtained for reference. These two isomers obtained separated by flash column chromatography on silica gel followed by distillation. The stereochemistry of the 7a and 7b was assigned from their NMR spectra and confirmed by comparison of the data for the oxalate salts reported by Borne.[12]



Red-Al

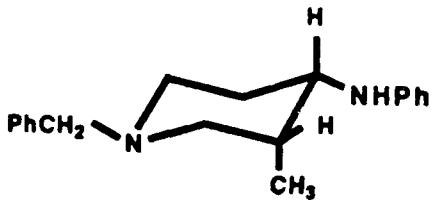


Super-Hydride

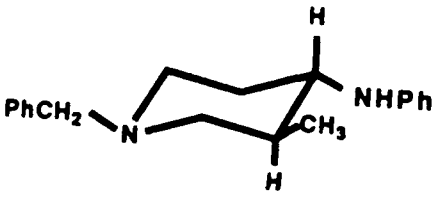


L-Selectride

For the NMR spectra, the chemical shift assignments were made by two-dimensional heteronuclear NMR (HETCOR) and COSY spectra. The spectrum of 7a showed signals at δ 1.72 (2H, m) for H_{5a} and H_{5e} (a = axial, e = equatorial) and at 2.14 (1H, m) for H_3. The other isomer, *trans*-7 (7b), showed signals at δ 1.36 (1H, m) assigned for H_{5a} and 1.64 (1H, m) for H_3. The highest-field signals at 1.36 from 7b and 1.72 from 7a were assigned to the protons at C-5. Since the signals of axial hydrogens in the chair conformation of cyclohexane-like rings generally appear upfield from these equatorial hydrogens[14], we tentatively assign the δ 1.64 signal to the *trans*-isomer (7b) which has an axial C-3 proton (H_{3a}), and the lower-field signal at 2.14 to the *cis*-isomer (7a) which has an equatorial C-3 hydrogen (H_{3e}).



7a



7b

These assignments were further confirmed by the R_f value of 0.45 for the *cis*-isomer 7a and 0.30 for the *trans*-isomer 7b (silica gel, solvents: chloroform with a small amount of methanol and aqueous ammonia); these relative values are in agreement with those reported by Borne[12].

The preparation of oxalate salts, although only successful in the case of the *cis*-isomer 7a, provided additional support. Depending on the amount of oxalic acid used, we obtained two oxalate salts of the *cis*-isomer 7a: the first oxalate had mp 177° C, corresponding to $C_{19}H_{24}N_2$ $C_2H_2O_4$, reported by Borne[12], and the second had mp 202° C, apparently of the composition $2(C_{19}H_{24}N_2)$ $C_2H_2O_4$ H_2O which was not previously reported. Our efforts to prepare the reported[12] oxalate mp 150-152° C of the *trans*-isomer 7b failed; instead we obtained precipitates which were difficult to crystallize, and had broad melting points in the range of 95-125° C. The relative ratios of the *cis*- and *trans*-isomers formed by hydride reduction of the Schiff base 6 (R^1 = CH_3, R^2 = CH_2Ph), were determined by gas chromatography of the crude reaction products and are listed in Table 1.

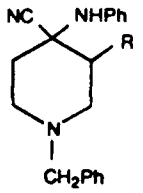
Table 1. Hydride Reduction of Schiff Base 6 (R^1 = CH_3, R^2 = CH_2Ph)

Hydride Reagent	Product 7a (*cis*) : 7b (*trans*)
$NaBH_4$	2.9 : 1
Red-Al	3.4 : 1
Super-Hydride	4.5 : 1
L-Selectride	14.5 : 1

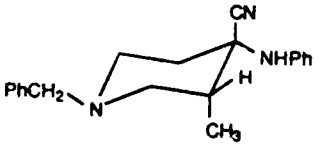
Red-Al and Super Hydride only produced a 3-4 fold excess of the *cis*-isomer 7a and were not more selective than $NaBH_4$.[5,12]. There was a distinctly greater stereoselectivity in the case of L-Selectride which formed a 14-15 fold excess of this desired isomer.

B. Reductive Decyanation of α-aminonitriles

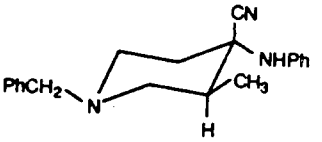
The reductive decyanation of α-aminonitriles is well-known. Reagents such as $LiAlH_4$[15], $NaBH_4$[16-21], and Na in liquid NH_3[22,23] have been employed. Among these, $NaBH_4$ has been successfully applied to the synthesis of many alkaloids of defined stereochemistry.[15-19] Compound 10 is an α-aminonitrile and a precursor in the syntheses of carfentanil and sufentanil.[24] The $NaBH_4$ reduction of 8 gave a high yield of decyanated product, 7 (R^1 = H, R^2 = CH_2Ph)[25], which was also obtained from the reduction of the Schiff base, 6. In view of the possibility of the stereoselective decyanation with bulky reducing agents, the reductive decyanation of the model compound, 10 with Red-Al, Super-Hydride, L-Selectride, and lithium tri-*tert*-butoxy-aluminohydride was attempted. The results were very promising. When 10 was treated with these reducing agents either in THF or toluene/THF at refluxing temperature a very clean conversion took place except in the case of tri-*tert*-butoxy-aluminohydride. This procedure was then applied to the 3-methyl series. The decyanation of 11 not only offered an alternate route to fentanyl compounds, but also provided interesting mechanistic information for this type of reaction.



10, R = H
11, R = CH_3



11a

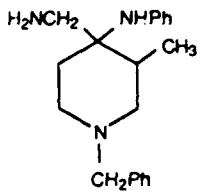


11b

Compound 11 was prepared by the Strecker synthesis as described by Van Daele *et al.*[24] The treatment of the piperidone, 5 (R^1 = CH_3, R^2 = CH_2Ph) with aniline and KCN for 2 days at room temperature in aqueous acetic acid gave a 30% yield of the *cis*- and *trans*-isomers (11a and 11b). The modified Strecker synthesis[26] using 2-propanol/acetic acid as the solvent system at reflux temperature improved the yield to 53%. NMR analysis of the product mixture obtained with both procedures indicated a 10:1 preponderance of the more stable *trans*-isomer, 11b in which both anilino and methyl groups are at equatorial. The two isomers were separated by flash column chromatography on silica gel. The faster moving, minor component, 11a (mp 136-8° C) has the following NMR characteristics: δ 1.99 (1H, m) assigned to H_{5a}, 2.40 (1H, m) for H_{5e} and 2.53 (1H, m) for H_3. The slower moving component, 11b (mp 117-8° C) had

signals at δ 1.72 (1H, td) for H_{5a}, 2.57 (1H, dt) for H_{5e}, and 2.07 (1H, m) for H_3. Using a similar NMR analysis as for compound 7a and 7b, we assign the δ 2.53 of 11a to H_{3e}, corresponding to the *cis*-isomer, and 2.07 of 11b to H_{3a}, corresponding to the *trans*-isomer.

It has been speculated that the reductive decyanation might proceed via dehydrocyanation of the α-monoaminonitrile to form the Schiff base followed by the hydride reduction. Another possibility for decyanation is an S_N2 mechanism. The stereochemistry of the product in each case will depend on the mechanism by which the replacement proceeds. Thus, the distribution of the isomeric products should elucidate the reaction mechanism. To test these mechanistic possibilities on the one hand and to develop an efficient synthesis of the *cis*-isomer, 7a on the other, we proceeded to study the ratio of the isomeric products 7a and 7b formed in the reductive decyanation of compounds 11a and 11b with the metal hydride reducing agents mentioned above. The reductive decyanation of 11a and 11b with sodium borohydride, Red-Al, Super-Hydride and L-Selectride produced a mixture of products 7a and 7b plus a minor product which was the primary amine, 12, derived from the reduction of the cyano group. The ratio of these isomers was determined by gas chromatography and is summarized in Table 2.



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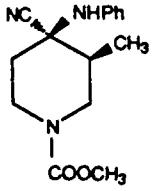
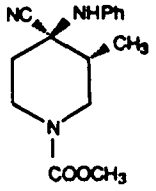


13a



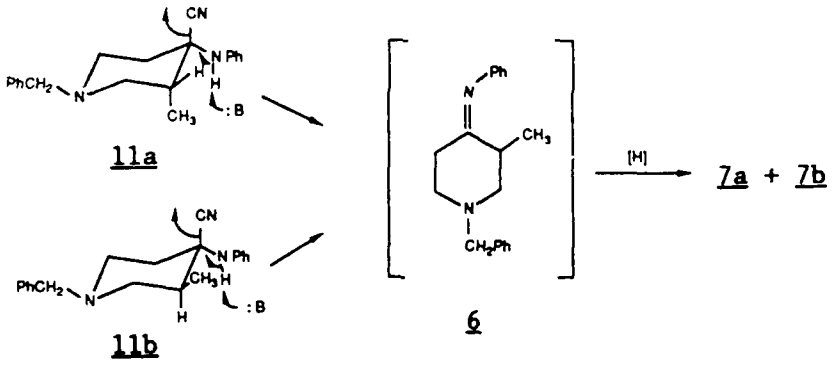
13b

Table 2. Reductive Decyanation of *cis*- and *trans*-11 (11a and 11b)

α-aminonitrile (11)	Reagent	Product ratio 7a (*cis*) : 7b (*trans*)
11a (*cis*)	$NaBH_4$	2.5 : 1
11b (*trans*)	$NaBH_4$	3.7 : 1
11a	Red-Al	3.2 : 1
11b	Red-Al	7.1 : 1
11a	Super-Hydride	4.3 : 1
11b	Super-Hydride	4.7 : 1
11a	L-Selectride	16.0 : 1
11b	L-Selectride	14.0 : 1

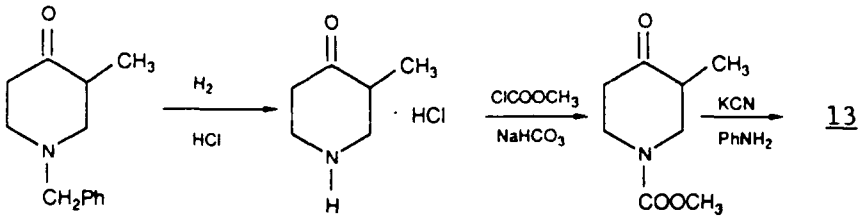
From this table it can be seen that in the reductive decyanations the isomer distribution is similar to that one obtained in the direct Schiff base reduction (see Table 1). Furthermore, the *cis*-isomer 7a was by far the predominant product in the decyanation of either the *cis*-α-aminonitrile 11a or the *trans*-isomer 11b. As in the case of the Schiff base reduction, L-Selectride was the most stereoselective reagent. It is reasonable to conclude, therefore, that the mechanism of the reaction of 11a and 11b probably proceeds through a common Schiff base intermediate as shown in Scheme 3. First, the metal hydride reagent acts as a base abstracting the elements of HCN from the starting α-aminonitrile producing the Schiff base. Next, the Schiff base is reduced by the hydride reagent as discussed above producing predominantly the *cis*-isomer in both cases.

Scheme 3



In a similar fashion as described for the synthesis of 11, 1-methoxycarbonylpiperidine α-aminonitrile, 13 was prepared from our common starting material, 5 (R^1 = CH_3, R^2 = CH_2Ph). N-Debenzylation of 5, followed by carbamylation and Strecker synthesis yielded a mixture of *cis*- and *trans*-13. Unlike N-benzyl derivative 13, the distribution of *cis*- and *trans*-isomers of 13 is about 3 : 4. The R_f values of both isomers is identical on silica gel TLC plates and separation by means of cnromatography becomes unrealistic. Fractional recrystallization of 13 from 2-propanol gave reasonably pure *cis*- and *trans*-13. Interestingly, the preparation of 13 by Janssen's group[24] did not mention formation of a mixture of isomers. The compound they reported was apparently the *trans*-isomer, with mp 106.5° C. We obtained *cis*-isomer, 13a: mp 144-145° C and *trans*-isomer, 13b: mp 105-108° C. The stereochemical configuration of 13a and 13b were analyzed and determined by 2D-NMR.

Scheme 4



5 14 15

3. EXPERIMENTATION

Melting points were determined using a Thomas-Hoover Uni-melt apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Model 1420 spectrophotometer. NMR spectra were recorded with a Varian XL-200 spectrometer using TMS as the internal standard. Chemical ionization (CI) mass spectra were obtained on a Finnigan 1015D spectrometer with a Model 6000 data collection system. GC analysis were obtained on a Hewlett-Packard 5880A instrument using a 12-m OV-1 capillary column, with a flame ionization detector. Elemental analyses were performed by the Analytical Division, CRDEC. The composition of of the reaction mixtures from various runs was monitored by TLC on silica gel GF plates (Analtech, Inc., Newark, DE). Flash column chromatography was performed on Merck silica gel 60, 230-400 mesh ASTM.

Reagents: L-Selectride (1M in THF), Super-Hydride (1M in THF), Red-Al (3.4M in toluene), tri-*tert*-butoxy-aluminohydride (powder) were purchased from Aldrich Chemical Co., WI.

3.1 1-Benzyl-3-methyl-4-piperidone (5)[13]

To a gray suspension of 50% NaH in mineral oil (120 g, 2.5 mol) in 4 L dry benzene under N_2, was added 4 mL of ethanol, followed by additions of 8 (356 g, 1.21 mol) over 1.5 hr. The mixture was refluxed for 24 hr. After cooling, the mixture was hydrolyzed with cautious addition of 500 mL H_2O and 400 mL concentrated HCl. The organic layer was separated and discarded. The yellow aqueous layer was diluted with 3 L H_2O and heated to reflux for 30 hr. After cooling, the tan solution was basified with solid Na_2CO_3, and extracted with benzene. The organic extracts were washed with H_2O, dried, and concentrated under vacuum. The oil was distilled twice to yield 175 g of colorless oil (96% pure by GC). The oil was then chromatographed over alumina, eluted with hexane, and concentrated under vacuum. A final distillation gave colorless oil, 5 (114.4 g, 46.5%): bp 111-115° C/0.2 mm (literature[13] bp 110-115° C/0.3 mm).

Anal. Calcd for $C_{13}H_{17}NO$: C, 76.81; H, 8.43; N, 6.89. Found: C, 76.73; H, 8.34; N, 6.83.

3.2 **1-Benzyl-3-methyl-4-phenyliminopiperidine** (6) (R^1 = CH_3, R^2 = CH_2Ph).[12]

A solution of 1-benzyl-3-methyl-4-piperidone (5) (2.0 g, 9.8 mmol) and aniline (0.6 g, 6.5 mmol) in 25 mL of toluene with several crystals of p-TsOH monohydrate was refluxed with azeotropic removal of the water for 4-5 hr. The mixture was cooled slightly, the second half (0.6 g, 6.5 mmol) of aniline and a few more crystals of p-TsOH monohydrate were added. The mixture was continued refluxing for an additional 18 hr. A few drops of the resulting deep orange-brown solution were evaporated on NaCl plates to estimate the progress of the reaction by IR. The intensity of the C=O band (1720 cm^{-1}) of the starting ketone was found to have decreased, but did not completely disappear even with a prolong refluxing. The Schiff base formation was detected from the strong absorption band at 1665 cm^{-1} (C=N). This solution was evaporated under vacuum and the crude Schiff base residue (brown oil) was used for the hydride reduction without further purification.

3.3 *cis*- and *trans*-**1-Benzyl-3-methyl-4-phenylaminopiperidine** (7a and 7b).[13]

The crude Schiff base, 6 (2.7 g, 9.8 mmol) was dissolved in 20 mL MeOH, and $NaBH_4$ (0.4 g, 10.6 mmol) was added in small portions with external cooling. The mixture was stirred for 18 hr at room temperature. Water (10 mL) was added slowly and the low boiling point solvents were evaporated and the resulting aqueous solution was then extracted with toluene. The toluene solution was washed with H_2O, dried, and evaporated to give 3.7 g of the crude mixture of *cis*- and *trans*-isomers 7a and 7b. GC of this brown oil indicated a *cis*- to *trans*-isomer ratio of 2.9 : 1 (Table 1). This crude mixture was flash-chromatographed over a silica gel and eluted with a solvent system containing 10 mL MeOH and 20 drops of NH_4OH per 600 mL of $CHCl_3$. The faster moving compound was concentrated to give 1.6 g of crude 7a (*cis* isomer) and the slower moving component yielded 0.8 g of crude 7b (*trans* isomer).

The crude 7a was distilled to yield 1 g of 7a: bp 170-180° C /0.05-0.1 mm. TLC and IR indicated the contamination of the starting ketone. Thus the oil was purified by converting to the oxalate salt and then regenerated to give the pure 7a: *Rf* = 0.45; IR (neat) 3420 cm^{-1} (NH); ^1H NMR ($CDCl_3$) δ 0.96 (d, 3H, CH_3, J = 7.1 Hz), 1.72 (m, 2H, CH_2), 2.14 (m, 1H, CH), 2.34 (m, 2H, CH_2), 2.55 (m, 1H, NH), 3.43 (d, 1H, CH_aH_bPh, J = 13.4 Hz), 3.47 (m, 3H), 3.49 (d, CH_aCH_bPh, J = 13.4 Hz), 6.55 (m, 3H, ArH), 7.09-7.34 (m, 7H, ArH); MS (CI/NH_3) m/e 281 (MH^+).

Compound 7a formed two different oxalate salts depending on the amount of oxalic acid dihydrate used as described in the following:

(a). To a solution of oxalic acid dihydrate (0.73 g, 5.8 mmol) in 5 mL EtOH was added dropwise a solution of 7a (0.32 g, 1.1 mmol) in 3 mL EtOH. The clear solution was concentrated to one half of its volume and ethyl ether was added to cloudiness. Scratching and cooling produced a fine white precipitate which as collected, washed with ether and recrystallized from EtOH to give 7a oxalate: mp 176-177° C (literature[12]: 176.5-177.5° C).

(b). To a solution of 7a (1.1 g, 3.9 mmol) in 13 mL EtOH was added dropwise a solution of oxalic acid dihydrate (0.5 g, 3.9 mmol) in 7 mL EtOH. A white precipitate formed immediately. After aging the slurry at room temperature for 3 hr, the fine, white precipitate was collected, washed with cold EtOH, and air dried to yield $(7a)_2$ oxalate (0.7 g, 50%): mp 195-198° C. Recrystallization from EtOH gave white crystals, mp 201-202° C.

Anal. Calcd for $2(C_{19}H_{24}N_2)\cdot C_2H_2O_4\cdot H_2O$: C, 71.82; H, 7.83; N, 8.38. Found: C, 72.28; H, 7.69; N, 8.14.

The crude 7b obtained from column chromatography (slower moving compound) was distilled to afford the pure 7b as a pale-yellow oil (0.6 g): bp 140-150° C/0.1 mm; R_f= 0.30; IR (neat) 3420 cm^{-1} (NH); ^1H NMR ($CDCl_3$) δ 0.94 (d, 3H, CH_3, J = 6.3 Hz), 1.36 (m, 1H), 1.64 (m, 1H, methine), 1.80 (t, 1H, J = 11.0 Hz), 2.05 (m, 2H), 2.87 (m, 3H), 3.29 (m, 1H, NH), 3.49 (s, 2H, CH_2Ph), 6.55 (d, 2H, ArH, J = 7.8 Hz), 6.63 (d, 1H, ArH, J = 7.3 Hz), 7.12 (t, 2H, ArH, J = 7.5 Hz), 7.30 (m, 5H, ArH); MS (CI/NH_3) m/e 281 (MH^+). Attempts to prepare an oxalate salt of 7b under the same conditions used for 7a produced jelly-like or gummy precipitates which on treatment with EtOAc gradually turned solid but had a broad melting point in the range of 95-125° C (literature[12] mp 150-152° C).

3.4 **General procedure for the reduction of 6 (R^1 = CH_3, R^2 = CH_2Ph) with L-Selectride, Super-Hydride, and Red-Al.**

The Schiff base 6 was prepared from 2.1 g (10.0 mmol) of 5 in toluene solution. To this solution was added dropwise the metal hydride reducing agent (30 mmol) under N_2 at room temperature with stirring. The mixture was refluxed for 2 hr, cooled and quenched with 10 mL H_2O. The mixture was extracted with 40 mL of 6N HCl. The acidic aqueous solution was washed with ether and then basified with cold concentrated NH_4OH. The milky mixture was extracted with $CHCl_3$ and the $CHCl_3$ solution was washed with H_2O, dried, and evaporated to give a brown oil. GC analysis was used to determine the ratio of 7a and 7b (see Table 1). The crude mixture could be separated by column chromatography or by fractional distillation. The relatively pure 7a or 7b was converted to the oxalate salt and then regenerated in pure form.

3.5 *cis*- and *trans*-1-Benzyl-3-methyl-4-(phenylamino)-4-piperidine-carbonitrile (11a and 11b)

Procedure A[24]. A solution of 5 (5.0 g, 24.6 mmol, and aniline (2.3 g, 24.7 mmol) in 17 mL of AcOH was cooled in an ice-water bath. To this solution was added a solution of KCN (1.8 g, 27.6 mmol) in 5 mL H_2O dropwise with stirring. The mixture was then stirred at room temperature for two days. The brown, turbid mixture was poured into a mixture of crushed ice (25 g) and concentrated NH_4OH (50 mL), and extracted with $CHCl_3$. The organic layer was washed with H_2O, dried and evaporated to yield 6.3 g of a brown oil. This crude oil, on trituration with isopropyl ether/petroleum ether (1:1) deposited 1.5 g (20%) of the crystalline isomeric mixture, 11a and 11b: mp 97-105° C. Two recrystallizations of this material from 2-propanol raised the melting point to 113-115° C, but did not lead to a complete separation of the isomers; the lower R_f was the major isomer.

Procedure B.[26] A mixture of 5 (5.0 g, 24.6 mmol), aniline (3.3 g, 35.4 mmol), KCN (2.3 g, 35.3 mmol), 2-propanol (50 mL), and AcOH (5 mL) was refluxed for 4 hr. On cooling to room temperature, the clear solution turned into a crystal slurry which was transferred into crushed ice (30 g) and concentrated NH_4OH (35 mL). The mixture was extracted with $CHCl_3$ and the organic layer was washed with H_2O and dried. Evaporation of the solvent left 8.1 g of oil. Addition of EtOH (15 mL) to the oil and cooling at 0° C produced a crystal slurry. The white crystals were collected, washed with cold EtOH and dried to yield the crude isomeric mixture 11a and 11b (4.0 g, 53%): mp 105-110° C. This crude product was flash chromatographed over silica gel and eluted with $CHCl_3$/MeOH/NH_4OH (1 L : 6 mL : 0.3 mL) to give the faster moving isomer, 11a (0.6 g) and the slower moving, major isomer, 11b (1.6 g). Both 11a and 11b were recrystallized from EtOH to yield the pure products. The stereochemistry of 11a and 11b was determined by 2-D NMR and 11a was assigned for *cis*-isomer and 11b was for *trans* isomer.

11a: mp 136-138° C; R_f = 0.75 (silica gel, $CHCl_3$: MeOH : NH_4OH = 40 mL : 1 mL : 1 drop); ^1H NMR ($CDCl_3$) δ 1.15 (d, 3H, CH_3, J = 6.6 Hz), 1.99 (m, 1H), 2.40 (m, 1H), 2.55 (m, 3H), 2.75 (dd, 1H, J = 13.3, 5.5 Hz), 3.51 (s, 1H, NH), 3.58 (s, 2H, CH_2Ph), 6.77-6.90 (m, 3H, ArH), 7.08-7.35 (m, 7H, ArH).

11b: mp 117.5-118.5° C; R_f = 0.55; ^1H NMR ($CDCl_3$) δ 1.22 (d, 3H, CH_3, J = 6.6 Hz), 1.72 (td, 1H, J = 11.5, 3.0 Hz), 2.07 (m, 1H, methine), 2.22 (dd, 1H, J = 10.0, 11.5 Hz), 2.39 (td, 1H, J = 11.5, 2.2 Hz), 2.57 (dt, 1H, J = 11.5, 3.0 Hz), 2.85 (m, 2H), 3.55 (s, 2H, CH_2Ph), 3.65 (s, 1H, NH), 6.85-6.98 (m, 3H, ArH), 7.22-7.35 (m, 7H, ArH).

3.6 General procedure for the decyanation of 11a and 11b with L-Selectride, Red-Al, and Super-Hydride

To a solution of carbonitrile (100 mg, 0.33 mmol) in 4 mL of dried THF was added the hydride reducing agent (2.0 mmol) under N_2 with stirring at room temperature. The mixture was refluxed for 20 hr. After cooling, H_2O (3 mL) and then 6N HCl (5 mL) was added dropwise to the solution and the mixture was washed with ether. The acidic aqueous layer was basified with concentrated NH_4OH and the milky mixture was extracted with $CHCl_3$. The $CHCl_3$ was washed with H_2O, dried, and evaporated to leave a brown oil. TLC analysis of the crude product showed a mixture of *cis*- and *trans*-isomers (7a and 7b) along with aniline and starting ketone (derived from the hydrolysis of the Schiff base intermediate). A small amount of polar material was also observed using TLC and was separated by preparative TLC and characterized by IR and MS. This by-product was the primary amine, 12, arising from the reduction of the cyano group: IR $CHCl_3$) 3400 cm^{-1} (NH_2); MS (CI/NH_3) m/e 310 (MH^+), 217 (M - NHC_6H_5). The GC analysis of the crude product was summaried in Table 2.

3.7 Decyanation of 11a and 11b with $NaBH_4$

Compound 11 (3 mg) was dissolved in several drops of 2-propanol and then treated with excess $NaBH_4$. The mixture was heated for 20 minutes and work up. TLC analysis of th crude products confirmed the presence of isomers 7a and 7b. The ratio of the isomeric mixture was determined by GC and was shown in Table 2.

3.8 3-Methyl-4-piperidone hydrochloride (14)

To a solution of 5 (10.0 g, 50 mmol) in 80 mL EtOH was added 1.0 g of 10% Pd/C and 5 mL of concentrated HCl. The mixture was hydrogenated at 35 psi at room temperature for 22 hr. The catalyst was filtered off and the filtrate was evaporated to give a white solid 14 (7.5 g).

3.9 Methyl 3-Methyl-4-oxo-1-piperidinecarboxylate (15)

A mixture of 14 (7.5 g, 50 mmol), $CHCl_3$ (80 mL), methyl chloroformate (6.0 g, 60 mmol), $NaHCO_3$ (18 g), and H_2O (100 mL) was stirred at room temperature for 20 hr. The $CHCl_3$ layer was separated, the aqueous layer re-extracted with $CHCl_3$, and the combined organic layers were washed with H_2O and dried. Evaporation of the solvent gave an oil (8.7 g). This crude product was distilled to yield the colorless oil, 15 (7.3 g, 87% from 5): bp 73-76° C/0.1 mm; IR (neat) 1680-1720 cm^{-1} (br, C=O).

3.10 *cis*- and *trans*-Methyl 4-Cyano-3-methyl-4-(phenylamino)-1-piperidinecarboxylate (13)[24]

Procedure A: To a solution of 15 (1.1 g, 6.4 mmol) and aniline (0.6 g, 6.4 mmol) in AcOH (4 mL) was added a solution of KCN (0.5 g, 7.6 mmol) in H_2O (1.8 mL). The mixture was stirred at room temperature for 48 hr. The light-brown mixture was poured into crushed ice and 13 mL of concentrated NH_4OH and extracted with $CHCl_3$. The $CHCl_3$ layer was washed

with H_2O, dried, and evaporated to yield a brown oil (2.0 g). Trituration with isopropyl ether at cold temperature gave 0.3 g of white crystals as the *cis*-isomer: mp 132-134° C. The filtrate was condensed and flash chromatographed over silica gel ($CHCl_3$) to give 0.1 g of white crystals as the *trans*-isomer: mp 105-107° C, plus 0.3 g of less pure material: mp 102-105° C. *cis*-Isomer was recrystallized from 2-propanol to give pure 13a: mp 144-145° C; ^1H NMR ($CDCl_3$) δ 1.09 (d, 3H, CH_3, J = 7.1 Hz), 1.91 (m, 1H), 2.27 (m, 1H), 2.49 (m, 1H, methine), 3.44-3.72 (m, 3H), 3.71 (s, 3H, $COOCH_3$), 6.95 (m, 3H, ArH), 7.26 (t, 2H, ,ArH, J = 9.0 Hz). *trans*-Isomer, 13b, was recrystallized from 2-propanol to yield : mp 105-108° C; ^1H NMR ($CDCl_3$) δ 1.24 (d, 3H, CH_3, J = 6.8 Hz), 1.56 (td, 1H, J = 13.0, 4.0 Hz), 1.92 (m, 1H, methine), 2.50 (dt, 1H, J = 13.0, 4.0 Hz), 2.96 (td, 1H, J = 14.4, 10.7 Hz), 3.16 (td, 1H, J = 13.0, 4.0 Hz), 3.61 (s, 1H, NH), 3.69 (s, 3H, $COOCH_3$), 4.08 (m, 1H), 6.94 (m, 3H, ArH), 7.25 (m, 2H, ArH).

Procedure B: A mixture of (1.0 g, 5.8 mmol), aniline (0.8 g, 8.7 mmol), KCN (0.54 g, 8.3 mmol), and 2-propanol (10 mL) was refluxed for 1 hr. On cooling, the mixture turned into a crystal slurry which was poured into crushed ice containing concentrated NH_4OH and extracted with $CHCl_3$. The $CHCl_3$ was washed with H_2O, dried, and evaporated to give 1.8 g of oil. Triturating with isopropyl ether at cold temperature afforded the *cis*-isomer, as white crystals (0.37 g). Recrystallization from 2-propanol yielded rather pure *cis*-isomer, 13a : mp 138-140° C, which was identical in all respect to the isomer obtained from procedure A. Condensation of the mother liquor to a small volume and cooling yielded an impure *trans*-isomer, (0.47 g, 30%): mp 110-113° C.

4. CONCLUSION

The L-Selectride was by far the most stereoselective reagent of all the metal hydrides used in both the Schiff base reduction and the reductive decyanations of α-aminonitrile, producing more than a 13-fold excess of the pharmacologically more active *cis*-isomer. The results indicate that the decyanation of 11a and 11b proceed through the same Schiff base intermediate. Thus, the diastereomeric mixture of *cis*- and *trans*-α-aminonitriles obtained in the Strecker synthesis can be reduced directly without separation.

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25. Modified procedure for a one-pot reductive amination developed by Dr. Harold D. Banks, U.S. Army, Chemical Research, Development & Engineering Center, Aberdeen Proving Ground, MD., 1986.

26. This procedure is the second part of the reductive amination procedure[25].