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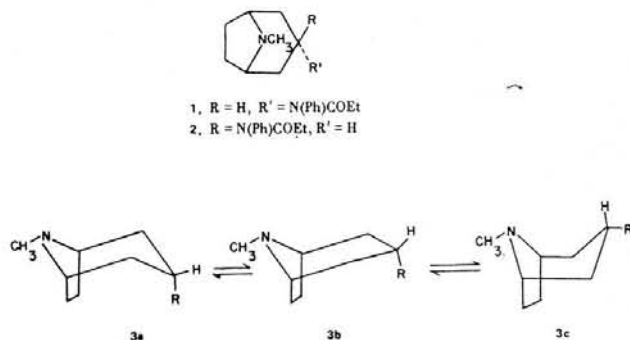
The isomeric 3-anilino and 3-propananilidotropanes have been synthesized and obtained in isomerically pure form. The configurations and solute conformations of these isomers were studied *via* glc and nmr analysis. The 3 $\beta$ -isomers have been shown to exist in the normal piperidine chair conformation whereas the 3 $\alpha$ -anilino tropane exists in a flattened piperidine chair conformation and the 3 $\alpha$ -propananilidotropane isomer preferentially exists in a conformation in which the piperidine ring system is a boat.

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In a study of conformational influences on the analgetic activities of the 4-anilidopiperidines we had occasion to synthesize and conformationally analyze the 3 $\alpha$ - and 3 $\beta$ -propananilidotropane isomers, **1** and **2**, respectively. Conformational analyses of several 3-substituted tropane derivatives have indicated that the 3 $\beta$ -substituted isomers exist predominantly in the piperidine ring chair conformation while the 3 $\alpha$ -substituted isomers exhibit varying degrees of conformational distortion of the piperidine ring as a result of repulsive interactions between the 3 $\alpha$ -substituent and the hydrogen atoms of the 6,7-bimethylene bridge (1-5). The degree of distortion of the piperidine ring conformation in the 3 $\alpha$ -monosubstituted tropanes has been found to vary from the normal chair conformation (**3a**) to slight flattening of the C-2,3,4 plane (**3b**) to adoption of a boat conformation (**3c**). It would appear that the degree of conformational distortion is a function of the size of the 3 $\alpha$ -substituent.

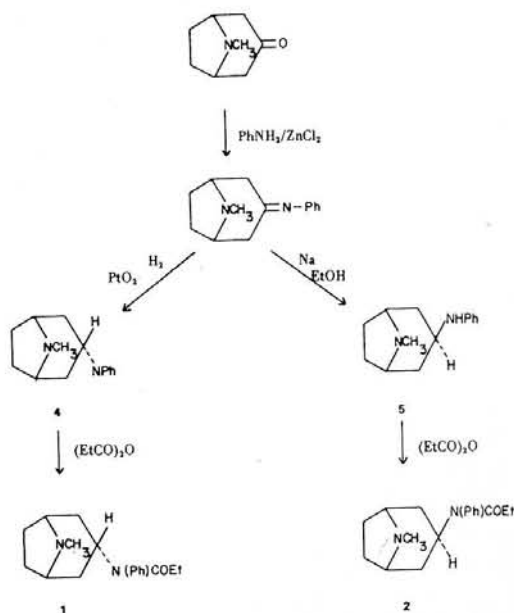
The isomers of 3-propananilidotropane (**1** and **2**) were synthesized as illustrated in Scheme I. Catalytic (platinum oxide) reduction of tropananil provided an isomerically pure product as evidence by glc analysis (Table I). Sodium-alcohol reduction of tropananil provided a 70:30 mixture of 3-anilino tropane isomers (**4** and **5**). The minor component of this mixture exhibited a glc retention time identical to that of the isomer prepared by catalytic reduction. Fractional crystallization of the isomeric mixture from petroleum ether readily provided the major component in pure form. The 3-anilino tropane isomers were then refluxed in propionic anhydride to provide the desired 3 $\alpha$ - and 3 $\beta$ -propananilidotropane isomers.

The relative configurations of the 3-anilino tropane isomers were tentatively assigned on the basis of the reported stereoselectivity of catalytic and sodium-alcohol reductions of both tropinone and tropanimines (6-8). Hence the product of catalytic reduction was assigned the  $\alpha$ -configuration whereas the major component of the mixture obtained from sodium-alcohol reduction was assigned the  $\beta$ -configuration. The behavior of the 3-anilino tropane isomers in glc analysis was consistent with this assignment of configuration. In the case of 3-monosubstituted tropane



derivatives, axial orientation of a polar function results in a lower dipole moment whereas equatorial orientation provides a higher dipole moment (2). Hence, the shorter retention time of the 3-anilino tropane isomer formed from catalytic reduction is consistent with the assignment of the  $\alpha$ -configuration for this compound. Further, one would anticipate less facile adsorption of this isomer to the polar stationary phase of the chromatographic column due to shielding of the axial-anilino moiety by the hydrocarbon

Scheme I



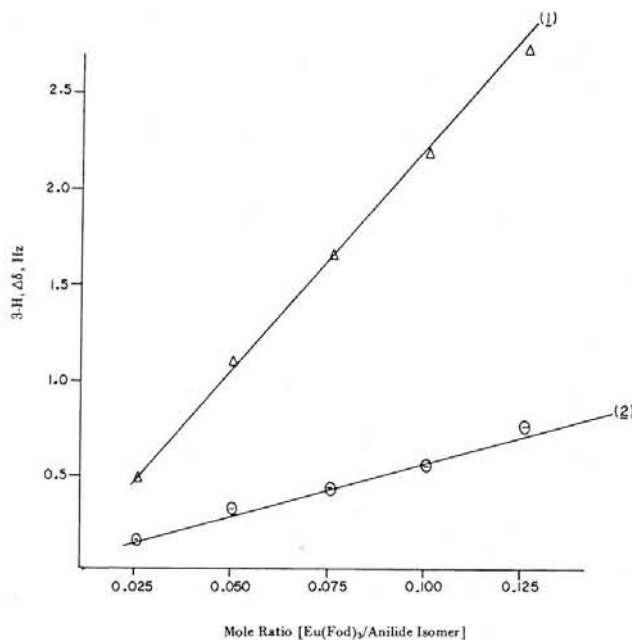


Figure 1. The effect of  $\text{Eu}(\text{fod})_3$  on the chemical shift of the 3-H of the  $\alpha$ -anilide (1) and the  $\beta$ -anilide (2).

residues of the tropane ring (9). Conversely, the longer retention time of the 3-anilidotropane isomer predominantly formed *via* sodium-alcohol reduction is consistent with the assignment of the  $\beta$ -configuration. One would also expect greater adsorption of this isomer to the chromatographic column because of greater accessibility of the equatorial anilino moiety. While the relative configurations of the 3-propanilidotropane isomers were made obvious by their synthesis from the 3-anilidotropanes of established configurations *via* synthetic reactions that would not be expected to alter the stereochemistry at C3, their nearly identical retention times upon glc analysis suggested possible abnormalities in the conformations of these isomers.

Elucidation of the preferred conformations of the 3-anilino and 3-propanilidotropane isomers prepared in this study primarily involved analyses of the nmr spectra of these compounds (Table II). The splitting patterns of the 3-H and the halfbandwidths (HBW) of the bridgehead [1(5)-H] protons were of greatest diagnostic value in this study. The N-Me group in these isomers is assumed to exist predominantly in the equatorial orientation as indicated by conformational studies of other tropanes (2).

The appearance of a septet signal in the nmr spectrum of **5** for the 3- $\alpha$ H was consistent with the assignment of a normal piperidine chair conformation for this isomer. However, a triplet signal ( $J = 6$  Hz) for the 3- $\beta$ H of **4** suggested a flattened piperidine chair conformation for this isomer. A normal piperidine chair conformation for this compound would require a quintet signal for the 3- $\beta$ H with  $J = 2.5$  Hz. The halfbandwidths of the bridgehead proton signals (broad multiplets from which  $J$  values could

not be abstracted) for both 3-anilidotropane isomers were essentially identical. Examination of molecular models of the piperidine chair conformation of **5** and of the flattened chair conformation of **4** indicate similar dihedral angles between the bridgehead protons and the 2(4)methylene protons of these isomers. The additional coupling of the bridgehead protons with the 6(7)bimethylene bridge protons is unaffected by distortion of the piperidine ring conformation as found for **4**.

As expected, the nmr spectrum of the  $\beta$ -anilide (**2**) was consistent with a normal piperidine chair conformation with the 3- $\alpha$ H appearing as a nonet and a bridgehead proton signal having a halfbandwidth of 9 Hz (Table II). The 3- $\beta$ H signal in the nmr spectrum of **1** appeared as a clear nonet having an apparently anomalous chemical shift downfield relative to the 3- $\alpha$ H of **2**. The halfbandwidth of the bridgehead proton signal for **1** was significantly larger (17 Hz) than the corresponding value for **2**. The nonet pattern for the 3- $\beta$ H signal in the nmr spectrum of the  $\alpha$ -anilide isomer can be explained in terms of a boat conformation for the piperidine ring of this isomer in which the 3- $\beta$ H is placed in an axial-axial and axial-equatorial relationship with the 2(4)methylene protons. A chair conformation of the  $\alpha$ -anilide isomer would require a triplet signal for the 3- $\beta$ H while a flattened piperidine chair conformation would require a quintet signal. The larger HBW for the bridgehead protons of **1** are also indicative of a boat conformation for this isomer in that near eclipsing of these protons with the 2(4)- $\beta$ H generates a large coupling constant. The anomalous shielding of the 3- $\beta$ H of **1** can perhaps be explained in terms of a projection of this proton into the shielding cone of the tertiary amino nitrogen atom as a result of the adoption of a boat conformation for **1**. Further, a slowing of the pyramidal inversion of the tertiary amine in **1** is evidenced by the appearance of a pair of singlets for the N-CH<sub>3</sub> moiety. Apparently the existence of non-bonded interactions between the N-CH<sub>3</sub> and C3- $\beta$ H of the boat conformation is responsible for this effect. The dual singlet signal was observed to collapse to a singlet when the temperature of the nmr samples was raised to 75°. In this regard, the N-CH<sub>3</sub> signal in the nmr spectrum of **2** was found to be the expected singlet.

Further support for the proposed conformations of the 3-anilidotropane isomers prepared in this study was obtained through the analysis of pseudo-contact deshielded nmr spectra of these compounds. Chappell, *et al.*, have studied deshielded spectra of  $\alpha$ - and  $\beta$ -tropines and tropinones and concluded that a distorted chair form predominates for the piperidine ring of these isomers (10). Treatment of deuteriochloroform solutions of **1** and **2** with the lanthanide shift reagent  $\text{Eu}(\text{fod})_3$  provided the results illustrated in Figure 1. The reasonable assumption is made in the interpretation of these data that the tertiary amine

Table I

GLC Retention Times for Tropane Isomers (a)

Isomer	R <sub>t</sub> (minutes)
α-Anilino (4)	5.0
β-Anilino (5)	5.7
α-Propanilido (1)	13.4
β-Propanilido (2)	13.2

(a) Column (5.5 ft. x 0.24 in.) of Carbowax 20M (4%) on 80/100 Anakrom ABS at 185°.

Table II

NMR Characteristics of Isomeric 3-Anilinetropanes and 3-Propanilidotropanes

## 3-Anilinetropanes

Assignments	α-Isomer (4)	β-Isomer (5)
N-CH <sub>3</sub>	s, δ 2.27	s, δ 2.27
H <sub>1</sub> , H <sub>5</sub>	m, δ 3.12, HBW = 10 Hz	m, δ 3.17, HBW = 10 Hz
H <sub>3</sub>	t, δ 3.63, J = 6 Hz	septet, δ 3.55 J = 5 Hz, 10 Hz
N-C <sub>6</sub> H <sub>5</sub>	m, δ 6.82	m, δ 6.83

## 3-Propanilidotropanes

Assignments	α-Isomer (1)	β-Isomer (2)
N-CH <sub>3</sub>	s, δ 2.10, s, δ 2.12	s, δ 2.13
H <sub>1</sub> , H <sub>5</sub>	m, δ 3.17 HBW = 17 Hz	m, δ 3.15 HBW = 9 Hz
H <sub>3</sub>	nonet, δ 4.60, J = 8 Hz, 11 Hz	nonet, δ 4.98, J = 7 Hz, 10 Hz
N-C <sub>6</sub> H <sub>5</sub>	m, δ 7.20	m, δ 7.17

moiety is the primary site of complexation between substrate and Eu(fod)<sub>3</sub> (11). This assumption is supported by the finding of nearly identical rates of deshielding of both the N-CH<sub>3</sub> signals and the anilide signals in the two isomers studied. As can be seen in Figure I, the 3-βH of the α-anilide isomer is deshielded at a much greater rate than the 3-αH of the β-anilide. These results are readily explained in terms of a boat conformation for the piperidine ring system of 1 which places the 3-βH in close proximity to the site of complexation of the lanthanide shift reagent. In comparison, the induced shift of the 3-βH of 4 (distorted chair conformation) is 7 times less than for the 3-βH of 1 at equivalent Eu(fod)<sub>3</sub>:substrate concentrations. The results of this study serve to confirm the assignment of both configuration and preferred solute conformation for the tropane isomers prepared for this report.

With regard to the similarity of retention times of the 3-anilidotropane isomers upon glc analysis (Table I), examination of molecular models of the preferred conformations

of these isomers indicates a similarity in the spatial disposition of the propanilido moieties relative to the tropane ring system. It is presumably this similarity that accounts for the behavior of these isomers in glc analysis.

Studies of the HBW for the bridgehead protons in the nmr spectra (deuterium oxide) of 1·HCl and 2·HCl, 16 and 10 Hz respectively, suggests conformations for the salt forms that are similar to those found for the free bases. Analysis of the splitting pattern of the 3-H signals for these isomers was of no value in conformational analysis since they were obscured by the HOD signal.

## EXPERIMENTAL

All melting points are uncorrected and were determined with a Mel-Temp apparatus. Infrared spectra were determined with a Beckman IR-33 spectrophotometer. Mass spectra were measured with a Dupont 21-492 mass spectrograph. Nmr spectra were taken on a Jolco C-60HL spectrophotometer using deuteriochloroform as solvent and TMS as internal standard. In the lanthanide shift reagent studies tris(6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionato)europium [Eu(fod)<sub>3</sub>] was purchased from Pierce Chemicals. Additions of 0.10 M, 0.05 M, and 0.025 M solutions of Eu(fod)<sub>3</sub> in deuteriochloroform were employed. All volume measurements were made with a calibrated syringe. Elemental analyses were performed by Galbraith Laboratories, Knoxville, TN.

## 3α-Anilino-1αH,5αH-tropane (4).

A solution of 30.0 g. (0.215 mole) of tropinone and 40.0 g. (0.520 mole) of aniline in toluene (250 ml.) was refluxed with stirring over 90 g. of 4A molecular sieves for 24 hours. The solution was cooled, filtered and concentrated *in vacuo* yielding a thick, dark oil which was shown to be the tropanil intermediate ( $\nu$  C=N 1660 cm<sup>-1</sup>). A solution of tropanil in 100 ml. of absolute ethanol was treated with 0.8 g. of platinum oxide and the mixture hydrogenated at 3 atmospheres until the calculated amount of hydrogen was consumed. The mixture was filtered and concentrated *in vacuo* and the resulting oil was distilled to provide 14.4 g. (31%) of 4, 132-141° (0.6 mm). The distilled oil solidified upon standing and recrystallized from pet ether, m.p. 68-71°, glc showed a single component (R<sub>t</sub> 5.0 minute); mass spectrum: M<sup>+</sup> 216, m/e 124 (base); ir (potassium bromide): 3300 cm<sup>-1</sup> (N-H).

Anal. Calcd. for C<sub>14</sub>H<sub>20</sub>N<sub>2</sub>: C, 77.78; H, 9.26; N, 12.76. Found: C, 77.98; H, 9.43; N, 12.85.

## 3β-Anilino-1αH, 5αH-tropane (5).

A solution of tropanil, prepared as described above from 9.9 g. (0.071 mole) tropinone and 18.0 g. (0.194 mole) of aniline, was dissolved in 100 ml. of absolute ethanol and 6.6 g. (0.280 g-atom) of Na pieces were added over a 10 minute period. The reaction was then refluxed for 3.5 hours. The reaction was cooled and poured into 100 ml. of ice water and extracted with 2 x 100 ml. portions of ether. The ethereal solution was dried (magnesium sulfate), concentrated *in vacuo* and the residual oil distilled from 130-135° (1.0 mm.). The distillate solidified upon standing yielding 3.2 g. (21%) of a mixture of isomers. Glc showed a 70:30 mixture of the β-isomer (R<sub>t</sub> 5.7 minute) and the α-isomer (R<sub>t</sub> 5.0 minute). Recrystallization of the isomer mixture from pet ether yielded 1.8 g. (12%) of pure 5, m.p. 105-107°; mass spectrum: M<sup>+</sup> 216, m/e 124 (base); ir (potassium bromide): 3300 cm<sup>-1</sup> (N-H).

Anal. Calcd. for C<sub>14</sub>H<sub>20</sub>N<sub>2</sub>: C, 77.78; H, 9.26; N, 12.96. Found: C, 77.65; H, 9.11; N, 12.79.

3 $\alpha$ -(*N*-Propananilido)-1 $\alpha$ H,5 $\alpha$ H-tropane (1).

A solution of 1.0 g. (0.0046 mole) of 4 in 13 ml. of propionic anhydride was refluxed for 24 hours. The reaction was cooled, diluted with 200 ml. of ether and treated with 10% sodium hydroxide for 15 minutes. The ether layer was separated, dried (magnesium sulfate), concentrated *in vacuo* and the residual oil distilled, b.p. 170-175° (0.10 mm) providing 0.97 g. (77%) of 1. Glc showed a single peak ( $R_t$  13.4 minutes); ir: 1650  $\text{cm}^{-1}$  (C=O). The hydrochloride salt of 1 (ethanol-ether) was prepared, m.p. 196-197°, mass spectrum:  $M^+$  272,  $m/e$  124 (base); ir: 1658  $\text{cm}^{-1}$  (C=O).

*Anal.* Calcd. for  $C_{17}H_{24}N_2O \cdot HCl$ : C, 66.13; H, 8.10; N, 9.07. Found: C, 65.97; H, 8.16; N, 8.96.

3 $\beta$ -(*N*-Propananilido)-1 $\alpha$ H,5 $\alpha$ H-tropane (2).

Treatment of 1.0 g. (0.0046 mole) of 5 with 13 ml. of propionic anhydride as described above provided 0.83 g. (66%) of 2, b.p. 220-222° (0.5 mm). Glc showed a single peak ( $R_t$  13.2 minutes), ir: 1650  $\text{cm}^{-1}$  (C=O). The hydrochloride salt of 2 (ethanol-ether), m.p. 172-173°; mass spectrum:  $M^+$  272,  $m/e$  124 (base); IR: 1658  $\text{cm}^{-1}$  (C=O).

*Anal.* Calcd. for  $C_{17}H_{24}N_2O \cdot HCl$ : C, 66.13, H, 8.10; N, 9.07. Found: C, 65.90, H, 8.14; N, 8.95.

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