

## Oxidative Coupling of Aldehydes & Imines I. An Entry to the Synthesis of 6,6,7,7-Tetraalkyl Tropane Alkaloid Analogs

by

John C. Leffingwell

Leffingwell & Associates, Canton, GA 30115 USA

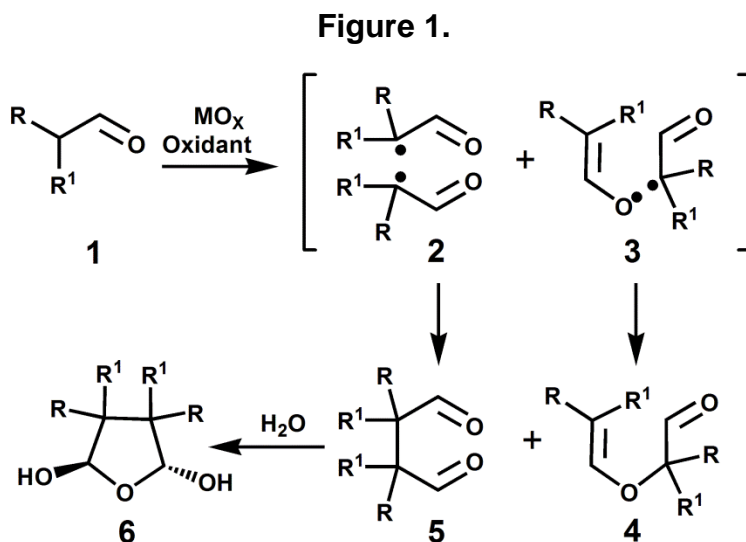
Email: [leffingwell@leffingwell.com](mailto:leffingwell@leffingwell.com)

### Abstract:

The oxidative coupling of selected aldehydes and imines with metal oxide oxidants, e.g.  $\text{MnO}_2$ , forms 2,2,3,3-tetraalkylsuccinaldehydes and aldimines to provide precursors for the synthesis of various novel 6,6,7,7-tetraalkyl tropane alkaloid analogs.

### Background:

The discovery that aldehydes, imines (and ketones) are easily coupled with metal oxide oxidants such as manganese dioxide to form products as shown in Figure 1. has been previously reported by us (1-5). Unpublished reports on this work are also referenced with links to the original research (6-10).



While such oxidative couplings were studied using lead dioxide, nickel peroxide and manganese dioxide, the latter was superior from a number of standpoints. As battery grade  $\text{MnO}_2$  from pyrolusite ore (containing 80-90%  $\text{MnO}_2$ ) is readily available, and inexpensive, it was the item of choice from a price standpoint as well as generally

providing better yields and less by-products. In addition, the reactivation of manganese dioxide can be done by treatment with various oxidizing agents such as ozone, chlorine, chloric acid or simply washing with hydrochloric acid (11-16).

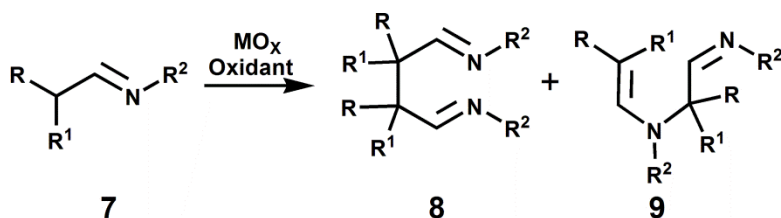
Table 1. provides a few examples. Towards the end of our exploratory research on the oxidative coupling of aldehydes, it was found that hydrocarbon solvents such as hexane provided optimum coupling results (6). Also, purification of the resulting aldehydic products is preferably done by steam distillation as the dialdehydes **5** form the water soluble tetrahydro-3,3,4,4-tetraalkylfuran-2,5-diols **6** which remain in the aqueous phase while the tetraalkyl-enolxyaldehydes **4** are separated in the steam distillate.

**Table 1.**

Aldehyde	Oxidant / Solvent	Yield	Product Ratio	
			<b>5</b>	<b>4</b>
R= -CH <sub>3</sub> , R <sup>1</sup> = -CH <sub>3</sub>	MnO <sub>2</sub> / Hexane	93%	49	: 51
R= -CH <sub>3</sub> , R <sup>1</sup> = -CH <sub>3</sub>	MnO <sub>2</sub> / THF	82%	44	: 56
R= -CH <sub>3</sub> , R <sup>1</sup> = -C <sub>2</sub> H <sub>5</sub>	MnO <sub>2</sub> / Dioxane	86%	44	: 56
R= -CH <sub>3</sub> , R <sup>1</sup> = -C <sub>2</sub> H <sub>5</sub>	NiOx / Dioxane	16%	33	: 67
R= -C <sub>2</sub> H <sub>5</sub> , R <sup>1</sup> = -C <sub>2</sub> H <sub>5</sub>	MnO <sub>2</sub> / Pyridine-Dioxane	86%	12	: 88
R= -C <sub>2</sub> H <sub>5</sub> , R <sup>1</sup> = -C <sub>2</sub> H <sub>5</sub>	MnO <sub>2</sub> / Dioxane	56%	21	: 79
R, R <sup>1</sup> = cyclohexane	PbO <sub>2</sub> / Dioxane	66%	45	: 55
R= -CH <sub>3</sub> , R <sup>1</sup> = -Ph	MnO <sub>2</sub> / Pyridine-Dioxane	56%	100	: --

Similarly, the metal oxide (e.g. MnO<sub>2</sub>) oxidation of dialkyl-aldimines provides an analogous mixture of coupling products as shown in Figure 2.

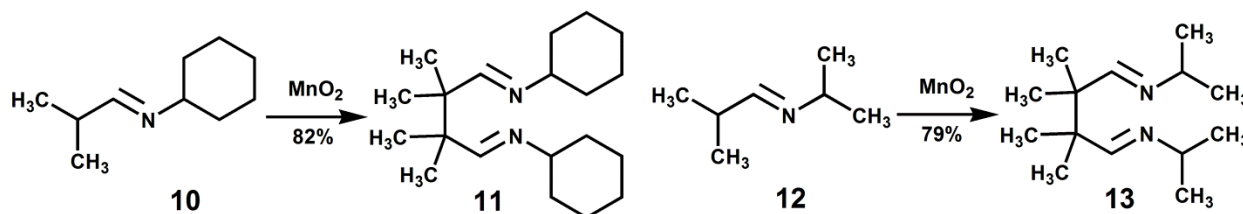
**Figure 2.**



\*Note – In the coupling of imine **7**, if R= alkyl and R<sup>1</sup>= H, the corresponding pyrrole is formed (**5**).

As with the aldehydes, initial studies utilized dioxane as the reaction medium, but it was also found that use of a hydrocarbon solvent such as hexane resulted in substantially higher yields of coupling products and reduced amounts of by-products. In this reaction when -R and -R<sup>1</sup> were methyl, the tetramethyl-succinaldimine coupling product **8** predominates with the pentaalkyl-enamine-imine **9** being significant only when the R<sup>2</sup> substituent was methyl (~17% **9**) or ethyl (~14% **9**). With larger R<sup>2</sup> groups, only <5% of the **9** isomer was formed. That the yields could be quite good was exemplified by an 82% yield in the coupling of the N-isobutyridenecyclohexylamine **10** to **11** and a 79% yield in the case of coupling the N-isobutyrideneisopropylamine **12** to form **13** (17). See Figure 3.

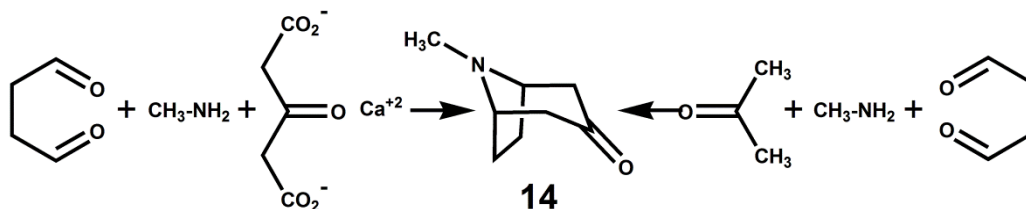
Figure 3.



### Classical methods for Tropane syntheses:

In 1917, Sir Robert Robinson devised a biomimetic synthesis of the tropane ring system in which he envisioned a retro-synthetic approach for the synthesis of tropinone. This involved two approaches – 1. addition of succinaldehyde + methylamine + acetone in water and – 2. addition of succinaldehyde + methylamine + acetone dicarboxylic acid (as the calcium salt) in water. Only traces of tropinone **14** were produced by the acetone procedure, but using acetone dicarboxylic acid was somewhat more efficient as shown in Figure 4. (18).

Figure 4 - Robinson's Tropinone Syntheses



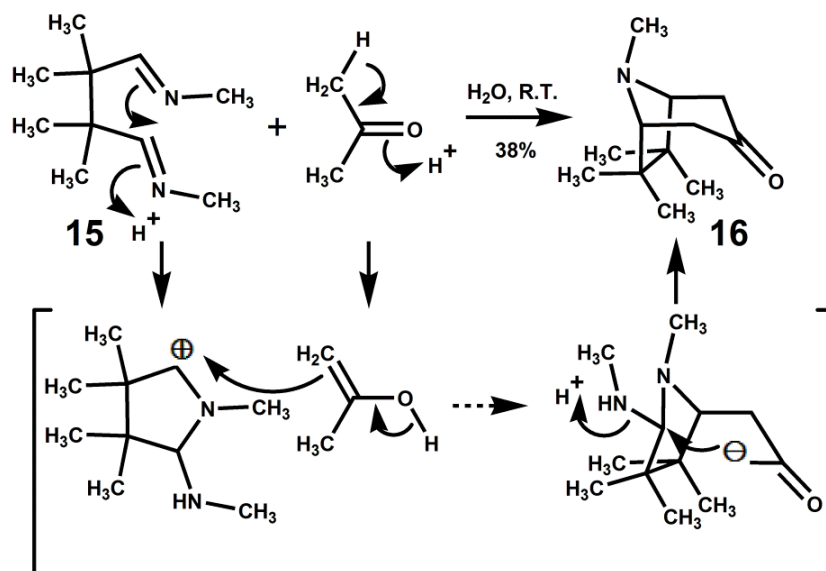
In 1937, Schöpf et al. were able to improve the yield to about 80% using acetone dicarboxylic acid at a physiological pH (19). In 1946, Keagle & Hartung modified Schöpf's procedure and reached tropinone yields of 83-90% by substituting succinaldehyde dioxime for succinaldehyde (20).

Following the suggestion that the tetraalkylsuccinaldehydes and aldimines were prime candidates for the synthesis of tropane analogs (8), R.F. Moates of our group undertook a study on the preparation of a number of 6,6,7,7-Tetramethyl-tropane type compounds (21).

**A. 6,6,7,7-Tetramethyltropinone (6,6,7,7,8-pentamethyl-8-azabicyclo-[3.2.1]octan-3-one) 16:**

In contrast to the Robinson's synthesis of tropinone using succinaldehyde, acetone and methylamine, the procedure for the preparation of 6,6,7,7-Tetramethyltropinone 16 using an excess of aqueous acetone with N,N<sup>1</sup>-dimethyl-2,2,3,3-tetramethylsuccindialdimine 15 gave a much better, 38% yield (21). The reaction undoubtedly proceeds in a tandem double Mannich reaction as shown in Figure 5.

**Figure 5.**

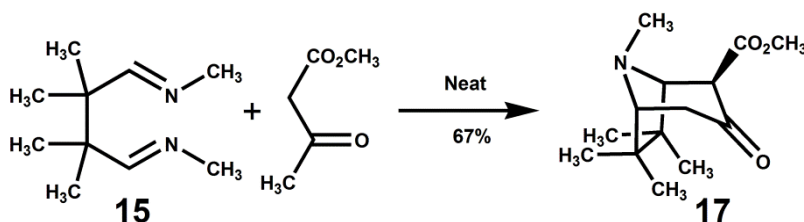


In addition, a dilute solution of the dialdimine 15 (< 2% in water) when reacted with ethyl acetotacetate for 72 hours at R.T. gave a 26% yield of 16, after extraction and distillation.

**B. 2-Carbomethoxy-6,6,7,7-tetramethyltropinone (Methyl 6,6,7,7,8-pentamethyl-3-oxo-8-azabicyclo[3.2.1]octane-2-carboxylate) 17:**

In contrast to the dilute reaction of dialdimine 15 in water with ethyl acetoacetate, direct addition of 15 to methyl acetoacetate (no solvent) gave an exothermic reaction. After 72 hours stirring at R.T., distillation gave 17 in 67% yield (Figure 6.).

**Figure 6.**

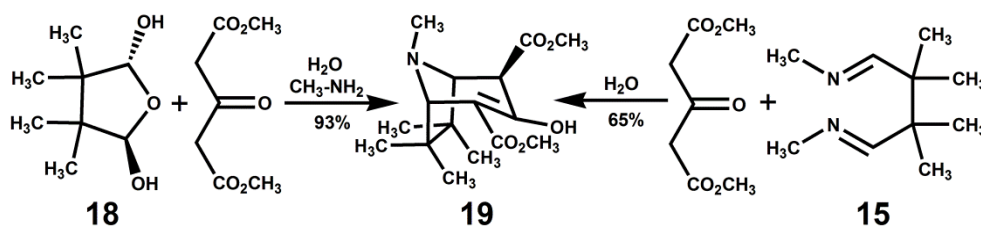


2-Carbomethoxy-6,6,7,7-tetramethyltropinone 17 is the 6,6,7,7-tetramethyl analog of 2-carbomethoxytropinone (Methyl ecgonone) which is the precursor for methylecgonine from which cocaine is produced. Moates did not assign the stereochemistry of the  $-\text{CO}_2\text{CH}_3$  group. However, from our conformational analysis using Chemaxon's conformer plugin, the axial conformation of both the  $\text{N}-\text{CH}_3$  group and the  $-\text{CO}_2\text{CH}_3$  are clearly thermodynamically favored. This is not as clear with 2-carbomethoxytropinone where Findley (22) found that "racemic 2-carbomethoxytropinone, as usually obtained, is a somewhat variable mixture of easily inter-convertible epimers or tautomers". He concluded from spectral evidence that this may be due to 2-carbomethoxytropinone existing in both enol and keto forms (which can lead to inter-conversion of the axial and equatorial configurations).

**C. 2,4-Carbomethoxy-6,6,7,7-tetramethyltropinone - enol form = 2,4-Dicarbomethoxy-6,6,7,7-tetramethyltrop-2-en-3-ol (2,4-Dimethyl 3-hydroxy-6,6,7,7,8-pentamethyl-8-azabicyclo[3.2.1]oct-2-ene-2,4-dicarboxylate) 19:**

This material was produced from both the tetramethylsuccinaldehyde hydrate (3,3,4,4-tetramethyltetrahydrofuran-2,5-diol) 18 and from the dialdimine 15 as shown in Figure 7 by reaction with Dimethyl-1,3-acetonedicarboxylate in water at room temperature.

Figure 7.

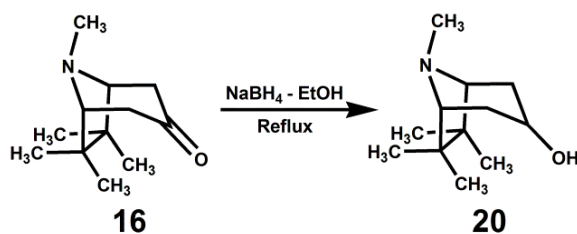


As with 2-carbomethoxy-6,6,7,7-tetramethyltropinone **17**, our conformational analysis shows the axial conformation of both the N-CH<sub>3</sub> group and the -CO<sub>2</sub>CH<sub>3</sub> are clearly thermodynamically favored. Moates determined that **19** was in the enol form by spectral analysis.

**D. Reduction of 6,6,7,7-tetramethyltropinone **16** to 6,6,7,7-tetramethyltropin-3-ol (6,6,7,7,8-pentamethyl-8-azabicyclo[3.2.1]octan-3-ol) **20** with NaBH<sub>4</sub>:**

The reduction of 6,6,7,7-tetramethyltropinone was accomplished by refluxing with an excess of NaBH<sub>4</sub> in ethanol for 6 hours to form **20**, isolated as the hydrate in 75% yield.

Figure 8.



While the hydrate melted over a fairly wide range, anhydrous material melted sharply at 162-163° C. indicating a single isomer. While Moates presumed this was the equatorial pseudo isomer,  $\psi$ -6,6,7,7-tetramethyltropine, the configuration was not rigorously determined. Our evaluation of the isomer actually produced is provided in the following section.

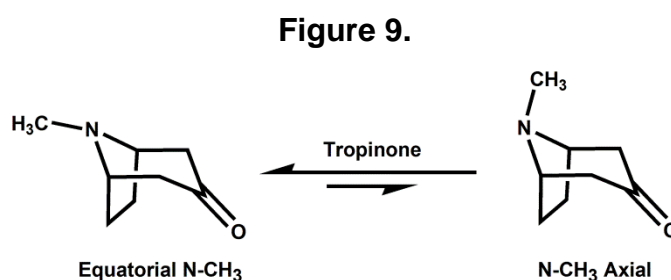
**E. Stereochemical and Thermodynamic Factors Affecting the Reduction of Tropinone **14** and 6,6,7,7-Tetramethyltropinone **16**:**

At the time of Moates's work, the axial or equatorial configuration of the 6,6,7,7-tetramethyltropin-3-ol **20** could presumably have been determined by reduction with sodium which would have led to the thermodynamically more favorable equatorial isomer, thus allowing comparison to the sample he isolated. Unfortunately this was not

done. Accordingly, we present here an analysis of our work on the preferred conformers and the reduction of tropinone and compare these results with what would be expected for the more sterically hindered tetramethyl analog **16**. See the supplementary section for details on conformation methodology and the energy minimization results for **14** and **16** done for this paper.

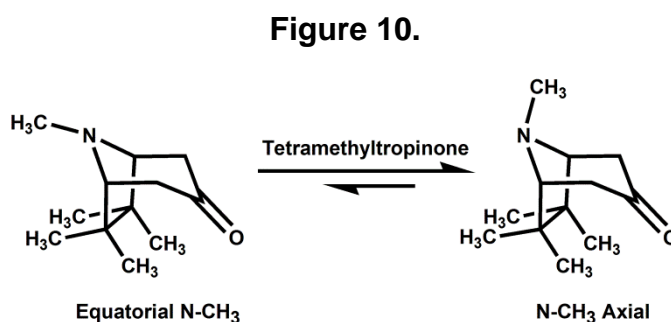
**a. The Conformations of Tropinone **14**:**

The preferred conformations of tropinone and a number of other Tropane alkaloids have been reported (23-29). In the case of Tropinone, there is agreement that the  $-N-CH_3$  group is primarily in the equatorial (or syn) configuration (Figure 9).



**b. The Conformations of 6,6,7,7-tetramethyltropinone **16**:**

As we suspected that the preferred conformation for the tetramethyltropinone analog could impact the results of the  $NaBH_4$  reduction because of the steric effects of the four methyl groups, a brief study was undertaken to determine the preferred conformer. From our results, it appears that the  $-N-CH_3$  group is primarily in the axial (or anti) configuration (Figure 10).

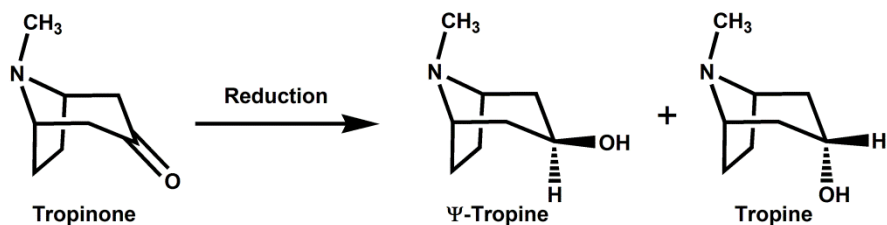


**c. The Reduction of Tropinone **14** and 6,6,7,7-tetramethyltropinone **16**:**

A considerable amount of literature exists on the stereospecificity of the reduction of tropinone with various reducing agents to give  $\psi$ -Tropine and Tropine. While much of

the literature indicates that reduction with  $\text{LiAlH}_4$  or  $\text{NaBH}_4$  gives predominately  $\psi$ -Tropine, it is worthwhile to review the original literature for exact details which indicates that the solvent employed can rather dramatically change the product ratio\*.

Figure 11.



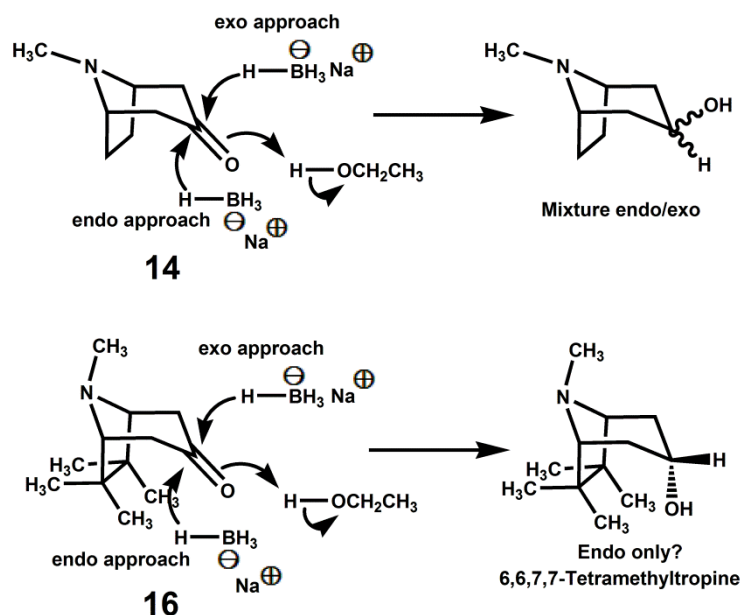
Reducing Agent	$\psi$ -Tropine	Tropine	Tropinone
$\text{LiAlH}_4$ / Ether	~56%	~44%	--
$\text{NaBH}_4$ / water	~70%	~30%	--
$\text{NaBH}_4$ / MeOH or EtOH	~51%	~49%	--
DIBAL-H / THF	3%	97%	--
$\text{H}_2$ / $\text{PtO}_2$ / EtOH	--	100%	--
$\text{H}_2$ / Raney-Ni / EtOH	--	~100%	--
$\text{H}_2$ / Raney-Ni / water	< 2%	> 98%	--
Na / iso-BuOH / toluene	~87%	~9%	~4%

\*See Supplemental Table 2. for details and references.

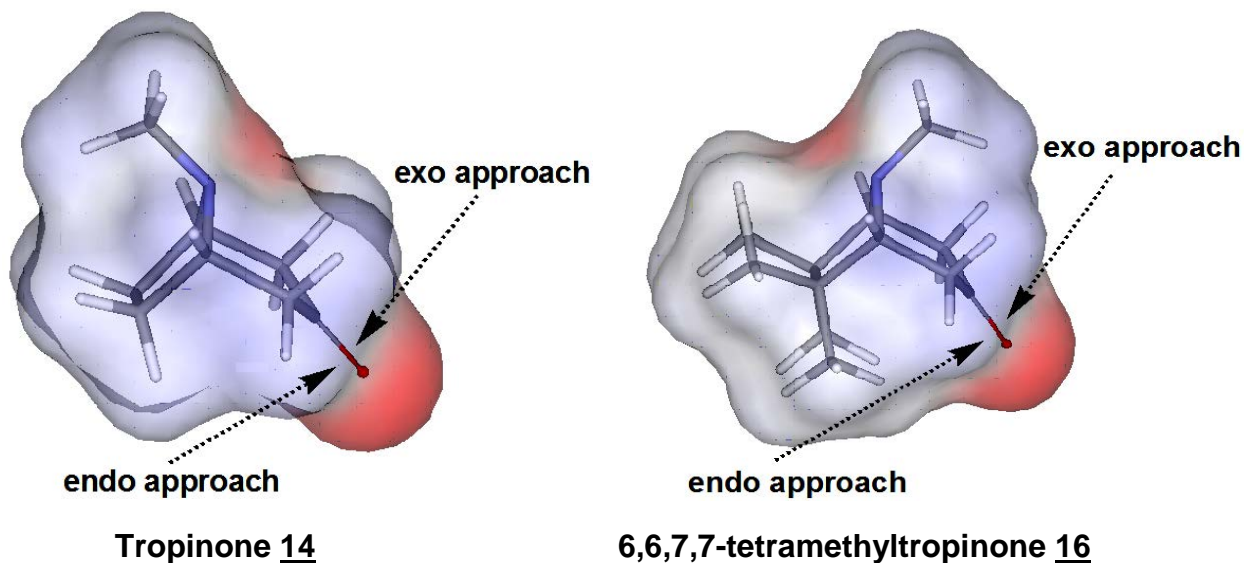
Thus reduction of tropinone, **14**, with  $\text{NaBH}_4$  in alcohol provides  $\psi$ -Tropine and tropine with little stereoselectivity. However, it is well known that the aluminos and borohydrides are sensitive to steric effects in the reduction of cyclo-ketones and generally provides the isomer with the  $-\text{OH}$  group on the face opposite to the hydride approach (38-39). As 6,6,7,7-tetramethyltropinone, **16**, is sterically hindered, it should give predominately more of the endo isomer, i.e. 6,6,7,7-tetramethyltropine. Figure 12 depicts this.



Figure 12.

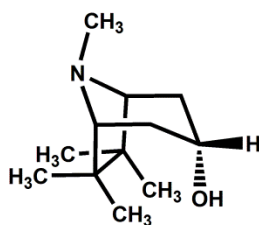


Visually, molecular models provides a better perspective view of the endo / exo approach and the relative steric hindrance.



As Moates only obtained a single isomer on reduction of **16** it can be reasonably assigned the endo alcohol structure **21** (Figure 13).

**Figure 13.**

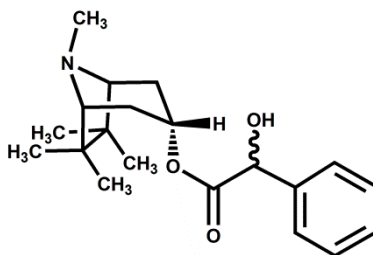


**21**

**6,6,7,7-Tetramethyltropine**

Final validation for structure **21** came from Moates's reported  $^1\text{H}$  NMR indicating the C3 equatorial  $-\text{H}$  shift at  $\delta$  4.00 ppm ( $J = 8.3$  Hz) which confirms this assignment; note that the C3 equatorial  $-\text{H}$  for tropine is also reported at  $\delta$  3.90-4.00 ppm (40-42) and is in agreement with the classical studies by Lemieux (43) and others for cyclohexanol equatorial alcohols  $-\text{H}$  shifts (e.g. *cis* & *trans*-*tert*-butylcyclohexanols). For pseudotropine the C3 axial  $-\text{H}$  is at  $\delta$  3.70 ppm (42).

In addition, Moates prepared a number of ester derivatives of **21** including what he thought was pseudo-6,6,7,7-tetramethylatropine, but was actually 6,6,7,7-tetramethylatropine **22**. We have confirmed this by comparing his  $^1\text{H}$  NMR data with that of atropine. The same types of equatorial vs. axial  $^1\text{H}$  NMR  $-\text{H}$  shifts occur for esters as alcohols. In these cases, the equatorial  $-\text{H}$  is at  $\delta$  4.98 ppm for 6,6,7,7-tetramethylatropine while it appears at  $\delta$  4.97-4.98 ppm for atropine (41-42).



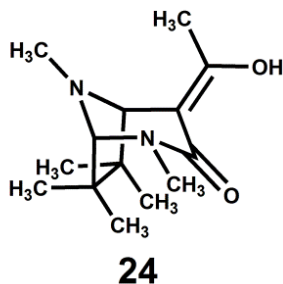
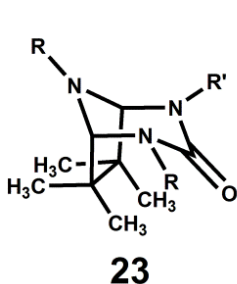
**22**

**6,6,7,7-Tetramethylatropine**

## **F. Additional work on the Synthesis of 6,6,7,7-Tetraalkyl Tropane Alkaloid Analogs**

In a future paper, we plan to provide a review detailing work on the syntheses of tropane alkaloid analogs prepared by the 1,4 dipolar addition of isocyanates and isothiocyanates to tetraalkylsuccinaldimines to form products such as the 2,4,8-trialkyl-

6,6,7,7-tetramethyl-2,4,8-triaza-bicyclo[3.2.1]octan-3-one **23** or the 4-(1-hydroxyethylidene)-2,6,6,7,7,8-hexamethyl-2,8-diazabicyclo[3.2.1]octan-3-one **24** produced by the reaction of diketene with N,N<sup>1</sup>-dimethyl-2,2,3,3-tetramethylsuccindialdimine.



## Supplemental Information

### a. Conformational analysis

The preferred conformations of compounds studied were done by first using Chemaxon's Marvin Sketch (Ver. 6.3.0) with the conformer calculator using both the MMFF4 and Dreiding force fields. Calculation time limit = 900 sec., Diversity limit = 0.1, No. of conformers set = 100, Optimization limit = Strict, Energy unit set to kcal/mole, Prehydrogenize set to ON, Hyperfine set to ON. From this the lowest energy conformers were determined. While such conformer searches do a good job in screening, the conformations need to be refined to determine more accurate relative energy values. Thus in a second step the conformers generated by the Chemaxon program were evaluated for lowest energy measurements by using the CambridgeSoft Chem3D (Ver. 8.0) program with MOPAC (using the AM1 and PM3 force fields), Mechanics Pro (using the MM2 and MM3 force fields) and also the MM2 module (Modified Allinger MM2 force field). Comparison of the relative energy values allows determination of the preferred (lowest energy) conformation. Tropinone and 6,6,7,7-tetramethyltropinone are relatively simple examples as only two conformations for each (where the -N-CH<sub>3</sub> group is primarily either in the axial or in the equatorial configuration) are being evaluated.

Supplemental Table 1. provides the results with the lowest energy for each force field being highlighted.

**Supplemental Table 1.**

	Chemaxon	Chemaxon	MOPAC	MOPAC	Mechanics Pro	Mechanics Pro	Allinger
Force Field	DREIDING	MMFF94	AM1	PM3	MM2	MM3	MM2
Tetramethyltropinone (-N-CH <sub>3</sub> equatorial)	66.02	56.50	-40.49	-62.74	41.34	53.82	19.57
Tetramethyltropinone (-N-CH <sub>3</sub> axial)	62.83	52.83	-40.62	-60.08	36.84	50.81	18.69
kcal/mole Difference	3.19	3.67	0.13	-2.66	4.5	3.01	0.88
Tropinone (-N-CH <sub>3</sub> axial)	32.02	11.73	-31.53	-46.27	24.63	32.45	9.54
Tropinone (-N-CH <sub>3</sub> equatorial)	31.38	9.71	-34.22	-48.79	23.75	31.25	7.83
kcal/mole Difference	-0.64	-2.02	-2.69	-2.52	-0.88	-1.2	-1.71

## a. Literature Reported Reductions of Tropinone

Supplemental Table 2.

Reduction	Temp.	Time (hr)	% $\psi$ -Tropine	% Tropine	% Tropinone	Ref.
Zn / HI	--	--	~29	~71	--	30
Electrolytic / (NH <sub>4</sub> ) <sub>2</sub> SO <sub>4</sub> / H <sub>2</sub> SO <sub>4</sub>	--	--	NA	~100?	--	32
H <sub>2</sub> / PtO <sub>2</sub> / EtOH	R.T.	--	--	100	--	20
H <sub>2</sub> / PtO <sub>2</sub> / EtOH	R.T.	--	--	99.4	0.6	32
H <sub>2</sub> / Raney-Ni / EtOH	R.T.	--	--	~100	--	33
H <sub>2</sub> / Raney-Ni / water	R.T.	--	< 2	> 98	--	34
DIBAL-H / THF	78°	17.3	3	97	--	35
LiAlH <sub>4</sub> / Ether	-10° to Reflux	--	100	0	--	36
LiAlH <sub>4</sub> / Ether	Reflux	0.5	54	45	1	37
LiAlH <sub>4</sub> / Ether	Reflux	5.0	54.5	45.5	--	37
LiAlH <sub>4</sub> / Ether (a)	Reflux	3.0	57	43	--	37
LiAlH <sub>4</sub> / Ether (b)	Reflux	1.0	56.5	41	2.5	37
LiAlH <sub>4</sub> / THF	Reflux	5.0	57	42	1	37
NaBH <sub>4</sub> / water	20°	2.0	65	34	1	37
NaBH <sub>4</sub> / water	20°	24.0	72	28	--	37
NaBH <sub>4</sub> / water	Reflux	48.0	69	30	1	37
NaBH <sub>4</sub> / water (c)	20°	2.0	70	29	1	37
NaBH <sub>4</sub> / 25% v/v MeOH	20°	7.0	68	32	--	37
NaBH <sub>4</sub> / 89% v/v MeOH	20°	16.0	60	40	--	37
NaBH <sub>4</sub> / 95% v/v MeOH	Reflux	6.0	51	49	--	37
NaBH <sub>4</sub> / 100% v/v MeOH	Reflux	6.0	48	52	--	37
NaBH <sub>4</sub> / MeOH	R.T.	~18	46.4	53.6	--	32
NaBH <sub>4</sub> / EtOH	Reflux	6.0	52	48	--	37
NaBH <sub>4</sub> / n-BuOH	Reflux	6.0	58	42	--	37
NaBH <sub>4</sub> / iso-PrOH	Reflux	2.25	67	33	--	37
KBH <sub>4</sub> / water	20°	24.0	66	34	--	37
KBH <sub>4</sub> / MeOH	Reflux	6.0	44	55	1	37
LiBH <sub>4</sub> / THF	Reflux	5.0	66	34	--	37
NaBH(OCH <sub>3</sub> ) <sub>2</sub> / water	20°	24.0	54	39	7	37
NaBH(OCH <sub>3</sub> ) <sub>2</sub> / water	Reflux	48.0	59	41	--	37

Reduction	Temp.	Time (hr)	% $\psi$ -Tropine	% Tropine	% Tropinone	Ref.
NaBH(OCH <sub>3</sub> ) <sub>2</sub> / MeOH	Reflux	6.0	37	59	--	37
Al(OPr <sub>iso</sub> ) <sub>3</sub> / iso-PrOH (d)	Reflux	2.5	34	65	1	37
Al(OPr <sub>iso</sub> ) <sub>3</sub> / iso-PrOH (d)	Reflux	1.5	29	71	--	37
Na / EtOH/ toluene	Reflux	3.0	85	11	4	37
Na / iso-BuOH/ toluene	Reflux	3.0	88	9	3	37
Na / iso-BuOH / toluene	0°	18.0	89	7	4	37
Na / iso-BuOH / toluene	0°	18.0	84	10	6	37
Al(OPr <sub>iso</sub> ) <sub>3</sub> Tropine equilibration (e)	Reflux	20	36	60	4	37
Al(OPr <sub>iso</sub> ) <sub>3</sub> Tropine equilibration (e)	Reflux	40	54	43	3	37
Al(OPr <sub>iso</sub> ) <sub>3</sub> Tropine equilibration (e)	Reflux	288	83.5	16	0.5	37
Al(OPr <sub>iso</sub> ) <sub>3</sub> Pseudotropine equilibration	Reflux	40	93	6	1	37
Al(OPr <sub>iso</sub> ) <sub>3</sub> Pseudotropine equilibration	Reflux	288	88	11	1	37
Na / n-C <sub>5</sub> H <sub>11</sub> OH / Tropine equilibration (e)	Reflux	12	91	8	1	37
Na / n-C <sub>5</sub> H <sub>11</sub> OH / Pseudo-Tropine equilibration (e)	Reflux	12	88	11	1	37
Na / iso-BuOH / Tropine equilibration	0°	18	14	81	5	37

## Notes:

- (a) 4 moles LiAlH<sub>4</sub> : 1 mole tropinone.
- (b) 0.25 mole LiAlH<sub>4</sub> : 1 mole tropinone.
- (c) Inverse addition.
- (d) Figures slightly higher than true value since slow equilibration occurs
- (e) "Tropine" containing 94% tropine and 6% pseudotropine.

## References:

- (1.) Leffingwell, John C., "The oxidative coupling of aliphatic aldehydes." *Journal of the Chemical Society D: Chemical Communications* 6 (1970): 357-358.
- (2.) Leffingwell, John C., "Preparation of monomeric or dimeric imines and pyrroles", U.S. Patent No. 3,598,827, issued August 10, 1971
- (3.) Leffingwell, John C., "Process of coupling aldehydes and ketones." U.S. Patent 3,609,193, issued September 28, 1971.
- (4.) Leffingwell, John C., " Treatment of 2-substituted aldehydes with lead dioxide." U.S. Patent No. 3,658,849, issued April 25, 1972.
- (5.) Leffingwell, John C., "Process for the preparation of dimeric imines and pyrroles." U.S. Patent 3,709,890, issued January 9, 1973.
- (6.) Leffingwell, John C., An improved process for the oxidative coupling of isobutyraldehyde - a method for the separation and purification of the two isomeric coupling products, RJRT Concept of Invention 1967, No. 1, January 20, 1967; accessed June 5, 2014 from <http://legacy.library.ucsf.edu/tid/aat58d00/pdf>
- (7.) Leffingwell, John C., The oxidative coupling of aldehydes with manganese dioxide, RJRT Concept of Invention 1966, No. 4, January 24, 1966; accessed June 5, 2014 from <http://legacy.library.ucsf.edu/tid/qlt58d00/pdf>
- (8.) Leffingwell, John C., The oxidative coupling of activated methylene compounds by metal oxides, RJRT Research Dept. Report 1966, No. 22, May 23, 1966; accessed June 5, 2014 from <http://legacy.library.ucsf.edu/tid/pll59d00/pdf>
- (9.) Leffingwell, John C., Oxidative coupling reactions in organic chemistry II. Oxidation of ketones, aldehydes and Schiff bases with lead dioxide, RJRT Research Dept. Report 1968, No. 5, January 23, 1968; accessed June 5, 2014 from <http://legacy.library.ucsf.edu/tid/aol59d00/pdf>
- (10.) Leffingwell, John C., Oxidation of aldehydes, ketones, amines and Schiff bases with lead peroxide, RJRT Concept of Invention 1967, No. 3, February 3, 1967; accessed June 5, 2014 from <http://legacy.library.ucsf.edu/tid/cat58d00/pdf>
- (11.) Shackelford R. E., Preparation of activated manganese dioxide, RJRT Research Dept. Memorandum 1966, No. 80, December 7, 1966; accessed June 9, 2014 from <http://legacy.library.ucsf.edu/tid/duw69d00/pdf>
- (12.) Boren, Richard M., and Charles F. Hammel. "Oxides of manganese processed in continuous flow reactors." U.S. Patent 7,419,637, issued September 2, 2008.

- (13.) Wang, Enoch I., and Francis Wang. "Alkaline cell with improved cathode." U.S. Patent 6,162,561, issued December 19, 2000.
- (14.) Cawfield, David W., and Leslie R. Ward. "Process for producing solid manganese dioxide." U.S. Patent 5,401,477, issued March 28, 1995.
- (15.) Brenet, Jean, and Peter Faber. "Process for making manganese dioxide." U.S. Patent 4,006,217, issued February 1, 1977.
- (16.) Shaabani, Ahmad, Peiman Mirzaei, Soheila Naderi, and Donald G. Lee. "Green oxidations. The use of potassium permanganate supported on manganese dioxide." *Tetrahedron* 60, no. 50 (2004): 11415-11420.
- (17.) Blum, H. J., The oxidative coupling of imines, RJRT Research Dept. Report 1968, No. 30, July 23, 1968; accessed June 5, 2014 from <http://legacy.library.ucsf.edu/tid/apl59d00/pdf>
- (18.) Robinson, Robert. "LXIII. - A synthesis of tropinone." *Journal of the Chemical Society, Transactions* 111 (1917): 762-768
- (19.) Schöpf, C., G. Lehmann and A. Arnold. "Die Synthese des Tropinons, Pseudopelletierins, Lobelanins und verwandter Alkaloide unter physiologischen Bedingungen." *Justus Liebigs Annalen der Chemie* 518, no. 1 (1935): 1-37.
20. Keagle, LeRoy C., and Walter H. Hartung. "Tropanone and its Homologs." *Journal of the American Chemical Society* 68, no. 8 (1946): 1608-1610.
- (21.) Moates, R. F., Synthetic tropane alkaloid analogs, RJRT Research Dept. Report 1969, No. 25, July 11, 1969; accessed June 5, 2014 from <http://legacy.library.ucsf.edu/tid/tql59d00/pdf>
- (22.) Findlay, Stephen P. "Concerning 2-Carbomethoxytropinone." *The Journal of Organic Chemistry* 22, no. 11 (1957): 1385-1394.
- (23.) Bishop, R. J., G. Fodor, A. R. Katritzky, F. Soti, L. E. Sutton, and F. J. Swinbourne. "The conformations of tropanes." *Journal of the Chemical Society C: Organic* (1966): 74-77.
- (24.) Carroll, F. Ivy, Michael L. Coleman, and Anita H. Lewin. "Syntheses and conformational analyses of isomeric cocaine: a proton and carbon-13 NMR study." *The Journal of Organic Chemistry* 47, no. 1 (1982): 13-19.
- (25.) Hrynychuk, Ronald J., Richard J. Barton, and Beverley E. Robertson. "The crystal structure of free base cocaine, C<sub>17</sub>H<sub>21</sub>NO<sub>4</sub>." *Canadian Journal of Chemistry* 61, no. 3 (1983): 481-487.



- (26.) Cocinero, Emilio J., Alberto Lesarri, Patricia Écija, Jens-Uwe Grabow, José A. Fernández, and Fernando Castaño. "N-Methyl stereochemistry in tropinone: the conformational flexibility of the tropane motif." *Physical Chemistry Chemical Physics* 12, no. 23 (2010): 6076-6083.  
See N-Methyl stereochemistry in tropinone - the conformational flexibility of the tropane motif.pdf
- (27.) Evangelisti, Luca, Alberto Lesarri, Michaela K. Jahn, Emilio J. Cocinero, Walther Caminati, and Jens-Uwe Grabow. "N-Methyl Inversion and Structure of Six-Membered Heterocyclic Rings: Rotational Spectrum of 1-Methyl-4-piperidone." *The Journal of Physical Chemistry A* 115, no. 34 (2011): 9545-9551. See this pdf.
- (28.) Demaison, Jean, Norman C. Craig, Emilio J. Cocinero, Jens-Uwe Grabow, Alberto Lesarri, and Heinz Dieter Rudolph. "Semiexperimental Equilibrium Structures for the Equatorial Conformers of N-Methylpiperidone and Tropinone by the Mixed Estimation Method." *The Journal of Physical Chemistry A* 116, no. 34 (2012): 8684-8692.
- (29.) Lazny, Ryszard, Artur Ratkiewicz, Aneta Nodzewska, Anna Wynimko, and Leszek Sergiejczyk. "Determination of the N-methyl stereochemistry in tropane and granatane derivatives in solution: a computational and NMR spectroscopic study." *Tetrahedron* 68, no. 31 (2012): 6158-6163.
- (30.) Willstätter, Richard, and Fritz Iglauer. "Reduction von Tropinon zu Tropin und Tropan." *Berichte der deutschen chemischen Gesellschaft*, 33, no. 1 (1900): 1170-1176.
- (31.) Verfahren zur Darstellung labiler unsymmetrischer Alkamine der cyclischen Acetonbasen auf elektrolytischem Wege, German Patent No. 96362 (Nov. 20, 1896) assigned to Chemische Fabrik Auf Actien (vorm. E. Schering).
- (32.) Yamaguchi, H., A. Numata, and K. Hokimoto. "Studies on the alkaloids of the root of *Physalis alkekengi*. II." *Yakugaku zasshi: Journal of the Pharmaceutical Society of Japan* 94, no. 9 (1974): 1115-1122.
- (33.) van de Kamp, Jacob and Meyer Sletzinger. "Production of tropine." U.S. Patent 2,366,760, issued January 9, 1945.
- (34.) Sachse, Rolf, and Albert Schaupp. "Process for the production of endotropine." U.S. Patent 6,005,110, issued December 21, 1999.
- (35.) Hayakawa, Yoshihiro, and Ryoji Noyori. "The Stereoselective Reduction of Tropinone to Tropine." *Bulletin of the Chemical Society of Japan* 47, no. 10 (1974): 2617-2617.
- (36.) Mirza, Rafat. "Reduction of Tropinone with Lithium Aluminium Hydride." *Nature*, 170 (1952): 630-630.

- (37.) Beckett, A. H., N. J. Harper, A. D. J. Balon, and T. H. E. Watts. "Stereochemistry of the reduction of tropinone." *Tetrahedron* 6, no. 4 (1959): 319-330.
- (38.) Carey, Francis A., and Richard J. Sundberg. *Advanced Organic Chemistry: Part B: Reactions and Synthesis*. Springer, 2007, pp. 407-409.
- (39.) Wigfield, Donald C. "Stereochemistry and mechanism of ketone reductions by hydride reagents." *Tetrahedron* 35, no. 4 (1979): 449-462.
- (40.) Sinnema, A., L. Maat, A. J. Van der Gugten, and H. C. Beyerman. "Configuration and conformation of all four cocaines from NMR spectra." *Recueil des Travaux Chimiques des Pays-Bas* 87, no. 9 (1968): 1027-1041.
- (41.) Do Pham, Duy D., Geoffrey F. Kelso, Yuanzhong Yang, and Milton TW Hearn. "One-pot oxidative N-demethylation of tropane alkaloids with hydrogen peroxide and a Fe III-TAML catalyst." *Green Chemistry* 14, no. 4 (2012): 1189-1195 (Supplementary Material).
- (42.) Cordell, Geoffrey A. *Introduction to alkaloids: A biogenetic approach*. New York: Wiley, 1981. p. 109.
- (43.) Lemieux, R. U., R. K. Kullnig, H. J. Bernstein, and W. G. Schneider. "Configurational Effects on the Proton Magnetic Resonance Spectra of Six-membered Ring Compounds<sup>1</sup>." *Journal of the American Chemical Society* 80, no. 22 (1958): 6098-6105.