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

by

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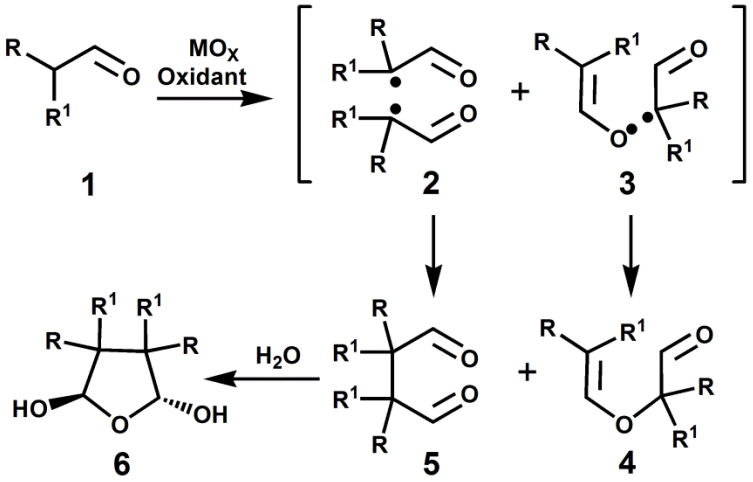
Abstract:

The oxidative coupling of selected aldehydes and imines with metal oxide oxidants, e.g. MnO_2, forms 2,2,3,3-tetraalkylsucinnaldehydes 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 Unpublished reports on this work are also referenced with links to the original research (6-10).

Figure 1.



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 MnO_2 from pyrolusite ore (containing 80-90% 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).

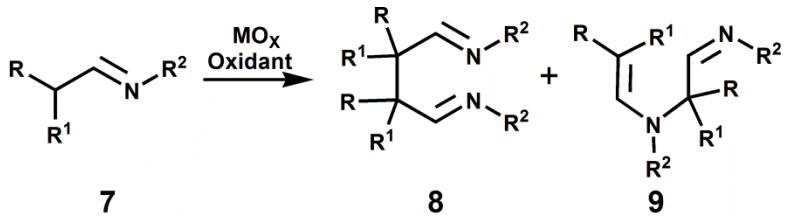
Table 1. provides a few examples. Towards the end of our exploratory research on the oxidative coupling of aldehydes, it was found that hydrocarbon solvents such as hexane provided optimum coupling results (6). Also, purification of the resulting aldehydic products is preferably done by steam distillation 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-enoloxyaldehydes **4** are separated in the steam distillate.

Table 1.

Aldehyde	Oxidant / Solvent	Yield	Product Ratio 5 : 4
R= $-CH_3$, R^1= $-CH_3$	MnO_2 / Hexane	93%	49 : 51
R= $-CH_3$, R^1= $-CH_3$	MnO_2 / THF	82%	44 : 56
R= $-CH_3$, R^1= $-C_2H_5$	MnO_2 / Dioxane	86%	44 : 56
R= $-CH_3$, R^1= $-C_2H_5$	NiOx / Dioxane	16%	33 : 67
R= $-C_2H_5$, R^1= $-C_2H_5$	MnO_2 / Pyridine-Dioxane	86%	12 : 88
R= $-C_2H_5$, R^1= $-C_2H_5$	MnO_2 / Dioxane	56%	21 : 79
R, R^1= cyclohexane	PbO_2 / Dioxane	66%	45 : 55
R= $-CH_3$ R^1= -Ph	MnO_2 / Pyridine-Dioxane	56%	100 : --

Similarly, the metal oxide (e.g. MnO_2) oxidation of dialkyl-aldimines provides an analogous mixture of coupling products as shown in Figure 2.

Figure 2.

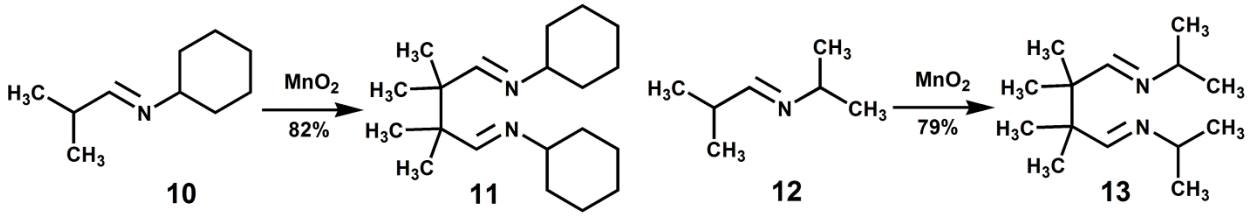


7 8 9

***Note – In the coupling of imine 7, if R= alkyl and R^1= 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^1 were methyl, the tetramethyl-succinaldimine coupling product **8** predominates with the pentaalkyl-enamine-imine **9** being significant only when the R^2 substituent was methyl (~17% **9**) or ethyl (~14% **9**). With larger R^2 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-isobutylidenecyclohexylamine **10** to **11** and a 79% yield in the case of coupling the N-isobutylideneisopropylamine **12** to form **13** (17). See Figure 3.

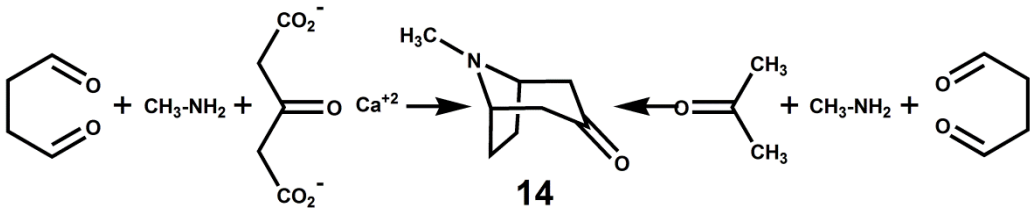
Figure 3.



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



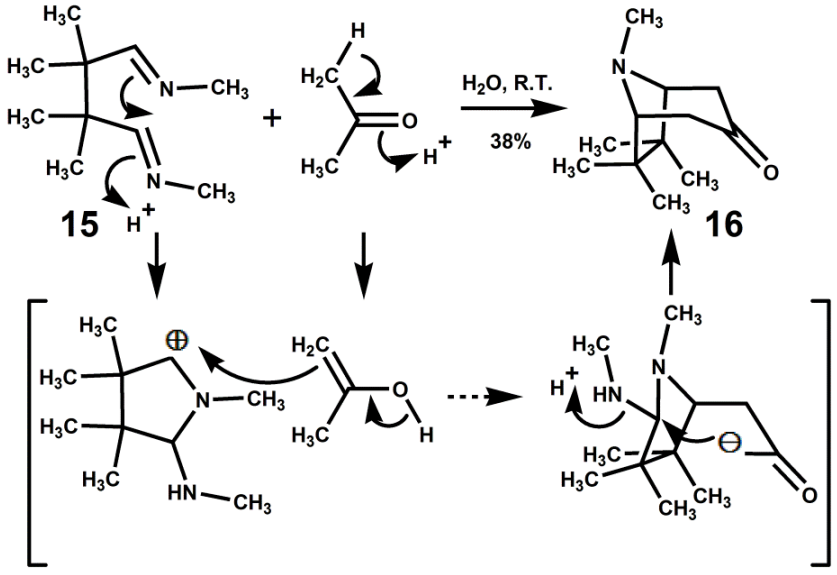
In 1937, Schöpf et al. were able to improve the yield to about 80% using acetone dicarboxylic acid at a physiological pH (19). In 1946, Keagle & Hartung modified Schöpf's procedure and reached tropinone yields of 83-90% by substituting succinaldehyde dioxime for succinaldehyde (20).

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[1]-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.

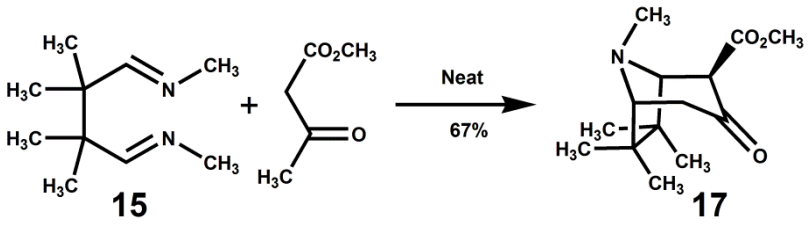


In addition, a dilute solution of the dialdimine **15** (< 2% in water) when reacted with ethyl acetotacetate for 72 hours at R.T. gave a 26% yield of **16**, after extraction and distillation.

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.

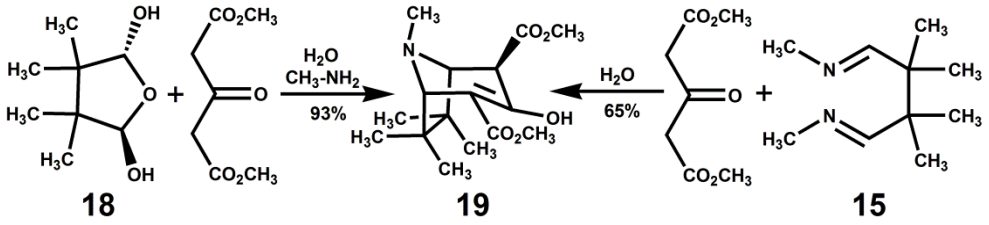


2-Carbomethoxy-6,6,7,7-tetramethyltropinone **17** is the 6,6,7,7-tetramethyl analog of 2-carbomethoxytropinone (Methyl ecgonone) which is the precursor for methylecgonine from which cocaine is produced. Moates did not assign the stereochemistry of the $-CO_2CH_3$ group. However, from our conformational analysis using Chemaxon's conformer plugin, the axial conformation of both the N-CH_3 group and the $-CO_2CH_3$ 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.



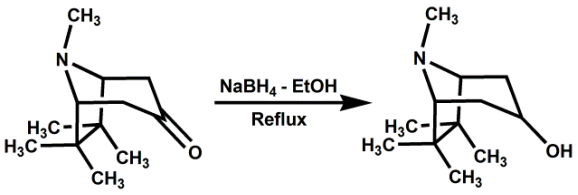
18 **19** **15**

As with 2-carbomethoxy-6,6,7,7-tetramethyltropinone **17**, our conformational analysis shows the axial conformation of both the N-CH_3 group and the -CO_2CH_3 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 $NaBH_4$:

The reduction of 6,6,7,7-tetramethyltropinone was accomplished by refluxing with an excess of $NaBH_4$ in ethanol for 6 hours to form **20**, isolated as the hydrate in 75% yield.

Figure 8.



16 **20**

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, ψ-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:

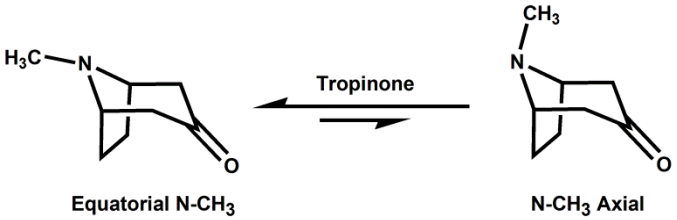
At the time of Moates's work, the axial or equatorial configuration of the 6,6,7,7-tetramethyltropin-3-ol **20** could presumably have been determined by reduction with sodium which would have led to the thermodynamically more favorable equatorial isomer, thus allowing comparison to the sample he isolated. 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).

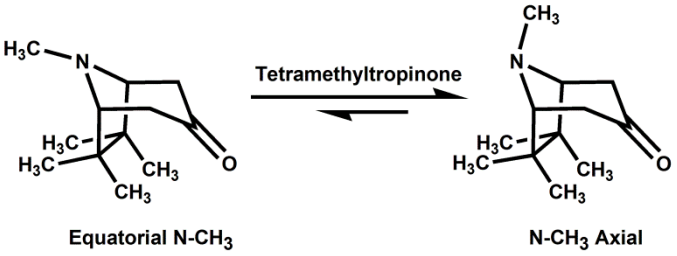
Figure 9.



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).

Figure 10.

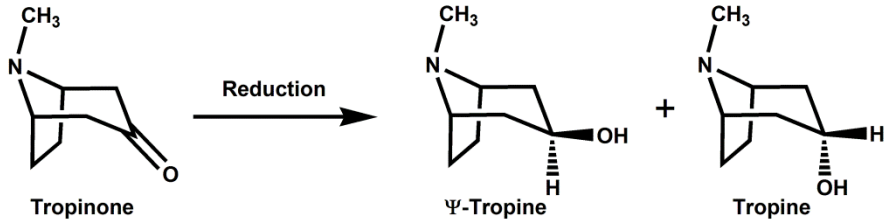


c. The Reduction of Tropinone 14 and 6,6,7,7-tetramethyltropinone 16:

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

the literature indicates that reduction with LiAlH4 or NaBH4 gives predominately ψ-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.

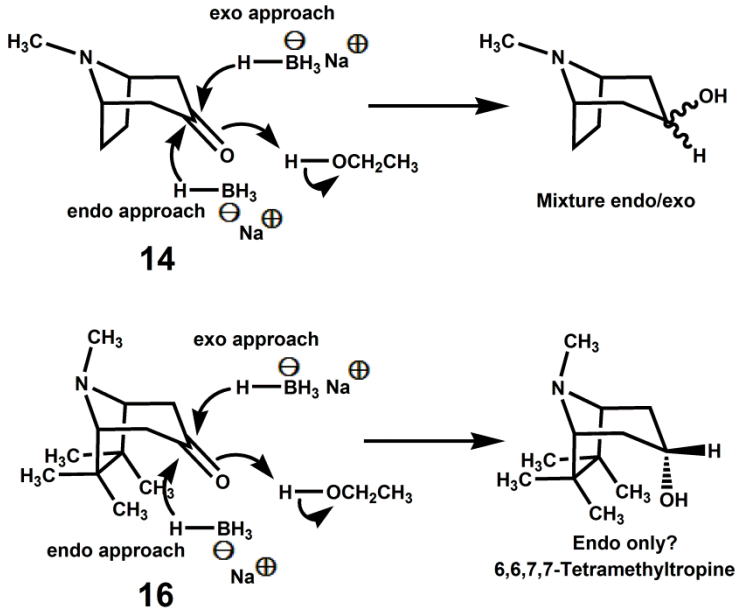


Reducing Agent	ψ-Tropine	Tropine	Tropinone
$LiAlH_4$ / Ether	~56%	~44%	--
$NaBH_4$ / water	~70%	~30%	--
$NaBH_4$ / MeOH or EtOH	~51%	~49%	--
DIBAL-H / THF	3%	97%	--
H_2 / $Pt0_2$ / EtOH	--	100%	--
H_2 / Raney-Ni / EtOH	--	~100%	--
H_2 / Raney-Ni / water	< 2%	> 98%	--
Na / iso-BuOH / toluene	~87%	~9%	~4%

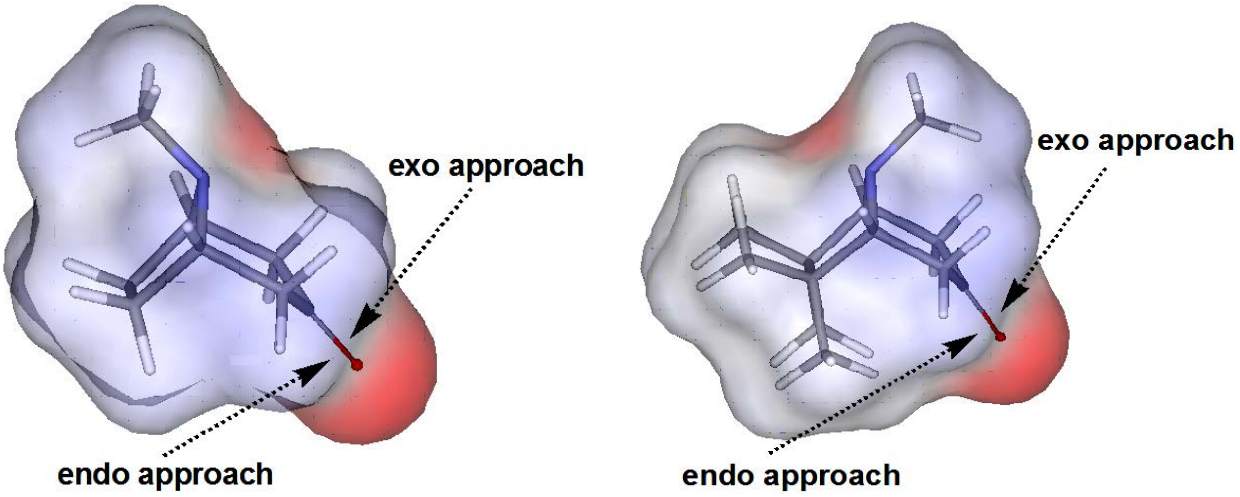
*See Supplemental Table 2. for details and references.

Thus reduction of tropinone, **14**, with $NaBH_4$ in alcohol provides ψ-Tropine and tropine with little stereoselectivity. However, it is well known that the alumino and borohydrides are sensitive to steric effects in the reduction of cyclo-ketones and generally provides the isomer with the –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.



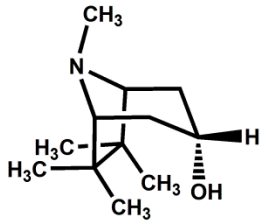
Visually, molecular models provides a better perspective view of the endo / exo approach and the relative steric hindrance.



Tropinone <u>14</u> **6,6,7,7-tetramethyltropinone <u>16</u>**

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

Figure 13.

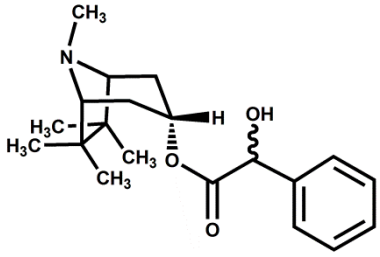


21

6,6,7,7-Tetramethyltropine

Final validation for structure **21** came from Moates's reported 1H NMR indicating the C3 equatorial –H shift at δ 4.00 ppm (J = 8.3 Hz) which confirms this assignment; note that the C3 equatorial –H for tropine is also reported at δ 3.90-4.00 ppm (40-42) and is in agreement with the classical studies by Lemieux (43) and others for cyclohexanol equatorial alcohols –H shifts (e.g. cis & trans-tert-butylcyclohexanols). For pseudotropine the C3 axial –H is at δ 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 1H NMR data with that of atropine. The same types of equatorial vs. axial 1H NMR –H shifts occur for esters as alcohols. In these cases, the equatorial –H is at δ 4.98 ppm for 6,6,7,7-tetramethylatropine while it appears at δ 4.97-4.98 ppm for atropine (41-42).



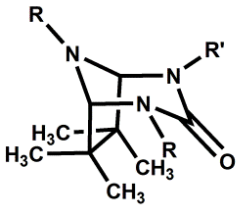
22

6,6,7,7-Tetramethylatropine

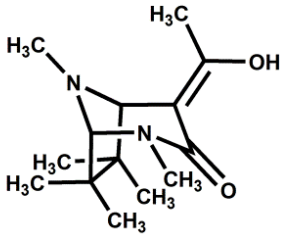
F. Additional work on the Synthesis of 6,6,7,7-Tetraalkyl Tropane Alkaloid Analogs

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[1]-dimethyl-2,2,3,3-tetramethylsuccindialdimine.



23



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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_3 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_3 equatorial)	66.02	56.50	-40.49	-62.74	41.34	53.82	19.57
Tetramethyltropinone (-N-CH_3 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_3 axial)	32.02	11.73	-31.53	-46.27	24.63	32.45	9.54
Tropinone (-N-CH_3 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)	% ψ-Tropine	% Tropine	% Tropinone	Ref.
Zn / HI	--	--	~29	~71	--	30
Electrolytic / $(NH_4)_2SO_4$ /H_2SO_4	--	--	NA	~100?	--	32
H_2 / $Pt0_2$ / EtOH	R.T.	--	--	100	--	20
H_2 / $Pt0_2$ / EtOH	R.T.	--	--	99.4	0.6	32
H_2 / Raney-Ni / EtOH	R.T.	--	--	~100	--	33
H_2 / Raney-Ni / water	R.T.	--	< 2	> 98	--	34
DIBAL-H / THF	78°	17.3	3	97	--	35
$LiAlH_4$ / Ether	-10° to Reflux	--	100	0	--	36
$LiAlH_4$ / Ether	Reflux	0.5	54	45	1	37
$LiAlH_4$ / Ether	Reflux	5.0	54.5	45.5	--	37
$LiAlH_4$ / Ether (a)	Reflux	3.0	57	43	--	37
$LiAlH_4$ / Ether (b)	Reflux	1.0	56.5	41	2.5	37
$LiAlH_4$ / THF	Reflux	5.0	57	42	1	37
$NaBH_4$ / water	20°	2.0	65	34	1	37
$NaBH_4$ / water	20°	24.0	72	28	--	37
$NaBH_4$ / water	Reflux	48.0	69	30	1	37
$NaBH_4$ / water (c)	20°	2.0	70	29	1	37
$NaBH_4$ / 25% v/v MeOH	20°	7.0	68	32	--	37
$NaBH_4$ / 89% v/v MeOH	20°	16.0	60	40	--	37
$NaBH_4$ / 95% v/v MeOH	Reflux	6.0	51	49	--	37
$NaBH_4$ / 100% v/v MeOH	Reflux	6.0	48	52	--	37
$NaBH_4$ / MeOH	R.T.	~18	46.4	53.6	--	32
$NaBH_4$ / EtOH	Reflux	6.0	52	48	--	37
$NaBH_4$ / n-BuOH	Reflux	6.0	58	42	--	37
$NaBH_4$ / iso-PrOH	Reflux	2.25	67	33	--	37
KBH_4 / water	20°	24.0	66	34	--	37
KBH_4 / MeOH	Reflux	6.0	44	55	1	37
$LiBH_4$ / THF	Reflux	5.0	66	34	--	37
$NaBH(OCH_3)_2$ / water	20°	24.0	54	39	7	37
$NaBH(OCH_3)_2$ / water	Reflux	48.0	59	41	--	37

Reduction	Temp.	Time (hr)	% ψ-Tropine	% Tropine	% Tropinone	Ref.
$NaBH(OCH_3)_2$ / MeOH	Reflux	6.0	37	59	--	37
$Al(OPr_{iso})_3$ / iso-PrOH (d)	Reflux	2.5	34	65	1	37
$Al(OPr_{iso})_3$ / 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
$Al(OPr_{iso})_3$ Tropine equilibration (e)	Reflux	20	36	60	4	37
$Al(OPr_{iso})_3$ Tropine equilibration (e)	Reflux	40	54	43	3	37
$Al(OPr_{iso})_3$ Tropine equilibration (e)	Reflux	288	83.5	16	0.5	37
$Al(OPr_{iso})_3$ Pseudotropine equilibration	Reflux	40	93	6	1	37
$Al(OPr_{iso})_3$ Pseudotropine equilibration	Reflux	288	88	11	1	37
Na / n-$C_5H_{11}OH$ / Tropine equilibration (e)	Reflux	12	91	8	1	37
Na / n-$C_5H_{11}OH$ / 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 $LiAlH_4$: 1 mole tropinone.

(b) 0.25 mole $LiAlH_4$: 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.

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